National Library
of Canada

Acquisitions and
Bibliographic Services Branch

395 Wellington Street
Ottawa, Ontario
K1A 0N4

Bibliothèque nationale
du Canada

Direction des acquisitions et
des services bibliographiques

395, rue Wellington
Ottawa (Ontario)
K1A 0N4

Your file Votre référence

Our file Notre référence

NOTICE

The quality of this microform is heavily dependent upon the quality of the original thesis submitted for microfilming. Every effort has been made to ensure the highest quality of reproduction possible.

If pages are missing, contact the university which granted the degree.

Some pages may have indistinct print especially if the original pages were typed with a poor typewriter ribbon or if the university sent us an inferior photocopy.

Reproduction in full or in part of this microform is governed by the Canadian Copyright Act, R.S.C. 1970, c. C-30, and subsequent amendments.

AVIS

La qualité de cette microforme dépend grandement de la qualité de la thèse soumise au microfilmage. Nous avons tout fait pour assurer une qualité supérieure de reproduction.

S'il manque des pages, veuillez communiquer avec l'université qui a conféré le grade.

La qualité d'impression de certaines pages peut laisser à désirer, surtout si les pages originales ont été dactylographiées à l'aide d'un ruban usé ou si l'université nous a fait parvenir une photocopie de qualité inférieure.

La reproduction, même partielle, de cette microforme est soumise à la Loi canadienne sur le droit d'auteur, SRC 1970, c. C-30, et ses amendements subséquents.

Canada

National Library
of Canada

Acquisitions and
Bibliographic Services Branch

395 Wellington Street
Ottawa, Ontario
K1A 0N4

Bibliothèque nationale
du Canada

Direction des acquisitions et
des services bibliographiques

395, rue Wellington
Ottawa (Ontario)
K1A 0N4

Your file Votre référence

Our file Notre référence

ISBN 0-315-96009-4

Canada

UNIVERSITÉ D'OTTAWA
UNIVERSITY OF OTTAWA

# Acknowledgments.

I am thankful to Dr. H. Alper for his constant attention, understanding and support during this research.

I am thankful to the Department of Chemistry, University of Ottawa for Teaching Assistantships.

I am grateful to V. Grushin for most helpful discussions and advices.

# Table of contents.

1.Introduction

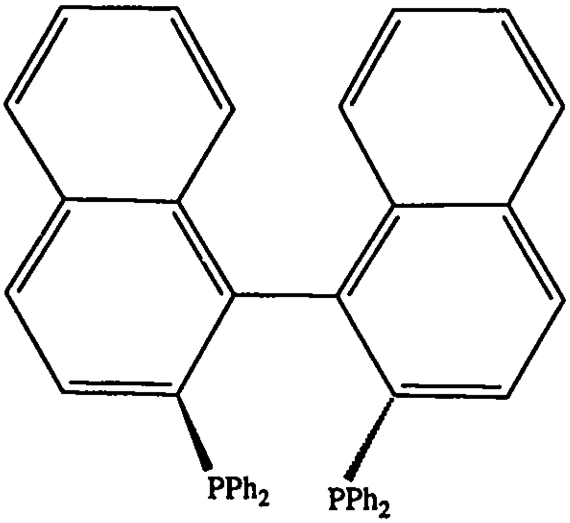
2.Results and discussion.

## List of tables.

List of abbreviations.

DIOP - 2,3-O-isopropylidene-2,3-dihydroxy-
1,4-bis(diphenyphosphino)-butane

BINAP - 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl



R-BINAP

COD - 1,5-cyclooctadiene

NBD - norbornadiene

BDPP - 2,4-bis(diphenylphosphino)pentane

# *1. INTRODUCTION*

## *1.1 Asymmetric hydrogenation of C=C, C=O and C=N functionalities.*

One of the most useful applications of transition metals in asymmetric synthesis is the asymmetric homogeneous hydrogenation of unsaturated prochiral substrates with the best studied and most successfully employed substrates being olefins and carbonyl compounds.

The first result on asymmetric homogeneous catalytic hydrogenation was reported in 1968. A rhodium complex of optically pure methylphenylpropylphosphine was used by Horner and coworkers to hydrogenate 2-phenylbutene[1]. Although the enantioselectivity was only 8%, this result supported the concept of homogeneous asymmetric hydrogenation.

Later Dang and Kagan[2] showed that the chiral phosphine ligand need not have chirality on the phosphorus. This was done using a phosphine derivative of tartaric acid, DIOP, reducing Z-($\alpha$)-acetamidocinnamic acid and producing N-acetylphenylalanine in 95% yield and 75% optical purity[2]. Since then, efficient methods for the hydrogenation of hundreds of different olefinic substrates have been developed, including derivatives of acetamidocinnamic acid, substituted enamides, and derivatives of acrylic acid with the optical purity of products being close to 100%. For example, a number of natural amino acids can be produced in high enantiomeric excess: leucine (100% ee), phenylalanine (95% ee), alanine (99% ee), tyrosine (98% ee), l-dopa (96% ee).

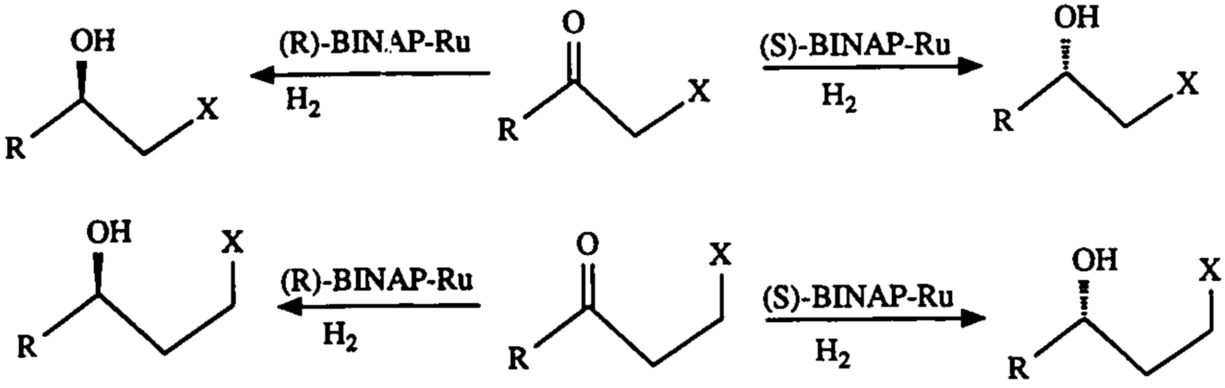
Although the asymmetric hydrogenation of ketones has also been examined for many years, the results achieved in this field were not impressive until recently. Introduction in 1990 of a ruthenium-BINAP (BINAP=2,2'-bis(diphenylphosphino)- 1,1'-binaphthol) catalysts[3,4] for the hydrogenation of carbonyl compounds resulted in high enantioselectivities and reaction rates for that reaction.

Different ketones have been effectively hydrogenated using Ru-BINAP catalysts with very high enantioselectivity. α and β-Functionalized ketones have been hydrogenated with synthetically useful enantioselectivities and in a predictable manner using $RuHal_2BINAP$ (Hal= Cl, Br, I) [3] (Scheme 1)

Carbonyl compounds are hydrogenated (40-100 atm. $H_2$) at room temperature, in 95-98% enantiomeric excesses.

It has been shown [5,6,7] that the key factor in the enantiofacial differentiation is the simultaneous coordination of the carbonyl oxygen and heteroatom X to the ruthenium atom forming a five or six-membered chelate ring (X is some nitrogen or oxygen containing directive group including dialkylamino, siloxy, keto, alkoxycarbonyl, dialkylaminocarbonyl, carboxyl). Halogen atoms were also shown to facilitate the carbonyl hydrogenation and to influence the stereochemical outcome of the process.

Asymmetric hydrogenation of prochiral β-keto esters gives rise to β-hydroxy carboxylic



X= dialkyamino, siloxyl, keto, alkoxycarbonyl, halogen.

Scheme 1.

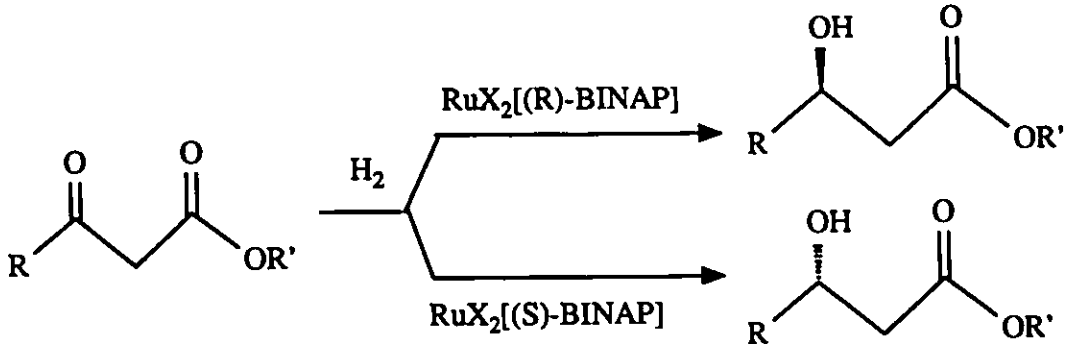
esters which are important intermediates for natural products synthesis. A variety of β-ketoesters have been hydrogenated in nearly quantitative yields and with high (up to 100%) enantioselectivities (Scheme 2)[4].

When prochiral symmetrical β-diketones were subjected to the ruthenium-catalyzed hydrogenation, mixtures of *dl* and *meso* 1,3-diols were formed (eq 1)[5].

The *dl* isomers were formed in high optical purity (up to 100% ee) .

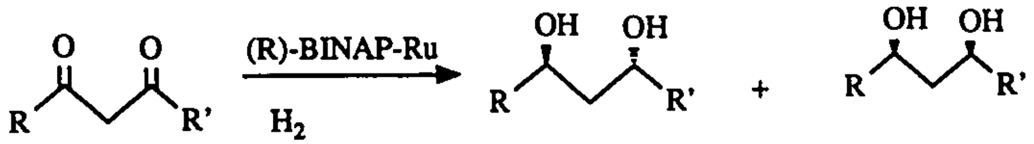
Diastereoselective hydrogenation of N-protected γ-amino-β-ketoesters catalyzed by $RuBr_2$(R)-BINAP provides an entry to γ-amino-β-hydroxy esters of the statine family (eq. 2)[8].

In substrates of this type, having an asymmetric center in the molecule, the stereochemical outcome of the reaction may depend strongly on the presence of the chiral center. It has been



R=Alk, X=Cl, Br, I

Scheme 2.



(eq 1)

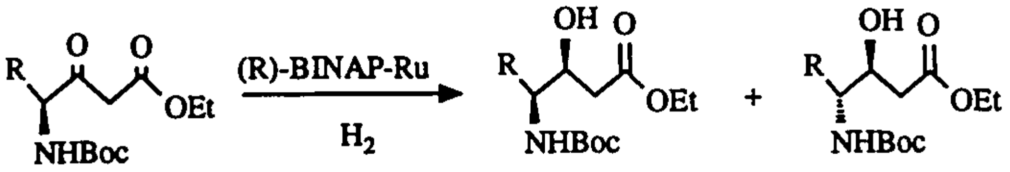
100% ee
for l form

*dl/meso* 99:1

R, R'= alkyl, aryl.

found that the γ-stereogenic center in the substrates significantly affect the degree of the stereoselectivity. In the case of asymmetric hydrogenation of γ-amino-β-ketoesters the efficiency of the catalyst/substrate chirality transfer (catalyst control) appears to cooperate with substrate induced chiral induction to form the natural threo series with high stereoselectivity.

The Ru-BINAP-catalyzed hydrogenation allows efficient resolution of certain chirally labile α-substituted β-ketoesters[9,10]. Dynamic kinetic resolution (transformation of racemic



(eq. 2)

threo:erythro 99:1, ee 99-100%

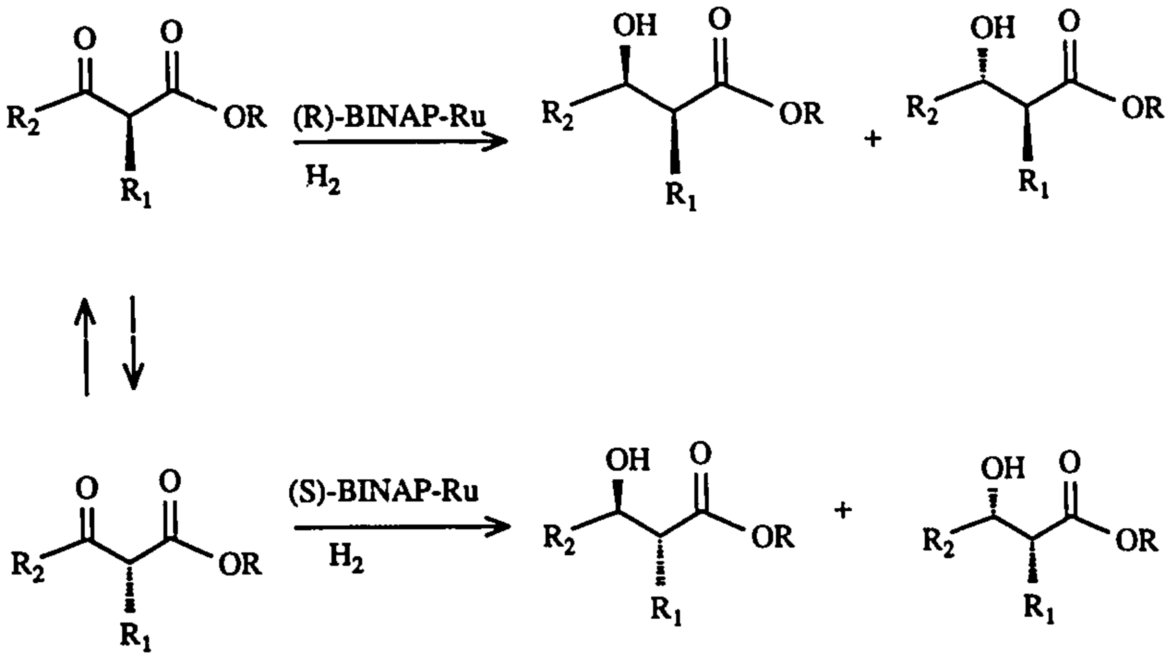
R=$CH_2Ph$, cyclohexylmethyl

compounds possessing a chirally labile asymmetric center into one major stereoisomer) have been revealed in that case. This provides an opportunity to obtain one stereoisomer among four possible in a diastereo and enantioselective manner (Scheme 3).

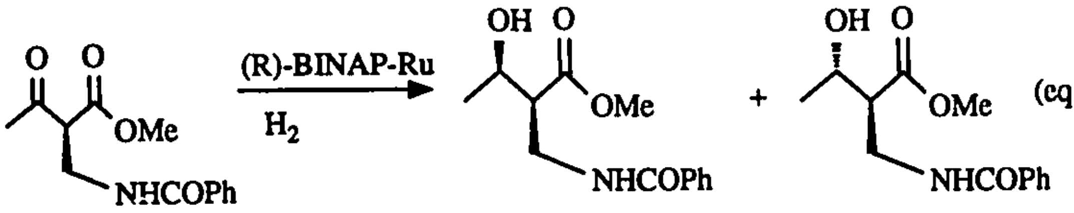
It was shown that when [$RuCl(C_6H_6)$(R)-BINAP]Cl was applied as a catalyst the steric course of hydrogenation is markedly influenced by the structures of substrates and reaction conditions including choice of solvent. Diastereoselective hydrogenation of methyl-2-benzamidomethyl-3-oxo-butanoate that affords methyl (2S,3R)-2-benzamidomethyl-3-hydroxybutanoate, an intermediate for the synthesis of β-lactam antibiotics (eq.3)[11]has been accomplished by using Ru[{(R)-BINAP}-{p-cymene}]I .

An example of an asymmetric hydrogenation of γ-oxo-carbocylic esters was recently reported [12]. Chiral γ-lactones have been obtained in enantiomerically pure form after acid-catalyzed cyclization of the resulting hydroxy esters (eq. 4)

It has been found that the catalyst, formed in situ by the addition of two equivalents of HCl to Ru(BINAP)$(OAc)_2$, is the most active in this reaction.

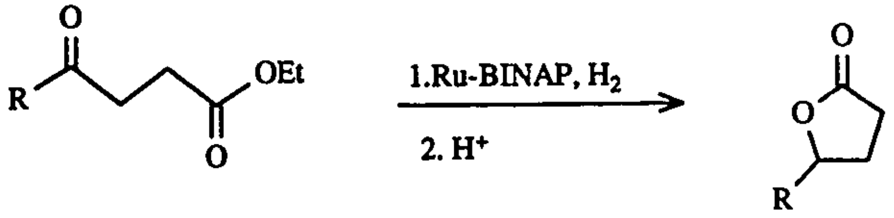


Scheme 3.



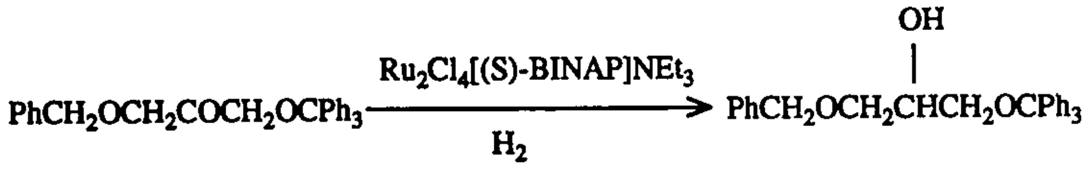
(eq. 3)

Another type of chiral phosphine-ruthenium complexes, which has been used for the enantioselective hydrogenation of ketones, is $Ru_2Cl_4(BINAP)NR_3$[13]. Asymmetric hydrogenation of β-ketoesters with $Ru_2Cl_4(BINAP)NEt_3$ was reported by Taber et al.[14] Different types of



(eq. 4)

β-ketoesters, including those having carbon-carbon double bonds, were reduced to β-hydroxyesters in 80-90% yields and enantiomeric excesses up to 98%. Optically active 1,3-glycerylesters, which are versatile building blocks for the synthesis of many of biologically important compounds were prepared via stereoselective hydrogenation of prochiral 1,3-disubstitued derivatives of dihydroxyacetone using $Ru_2Cl_4[(S)\text{-BINAP}]NEt_3$[15](eq. 5).



$$PhCH_2OCH_2COCH_2OCPh_3 \xrightarrow[H_2]{Ru_2Cl_4[(S)\text{-BINAP}]NEt_3} PhCH_2OCH_2\overset{\overset{OH}{|}}{C}HCH_2OCPh_3$$

(eq. 5)

The product was obtained in 70% yield and 90% enantioselectivity.

Asymmetric hydrogenation of carbon-carbon and carbon-oxygen double bonds, catalyzed by transition metal phosphine complexes is one of the best studied and the most widely used reaction among a large variety of transition metal catalyzed asymmetric reactions. However, until recently there were a few examples of asymmetric hydrogenation of carbon-nitrogen double bonds. Both chemical yields and enantiomeric inductions in these reactions were so far relatively modest as compared with those achieved in carbon-carbon bond hydrogenations.

In general, the catalytic hydrogenation of C=N bonds is considerably more difficult than the reduction of C=C and C=O double bonds, possibly due to:

a. The low stability and accordingly small number of complexes between transition metal hydrides and organic compounds, containing a C=N functionality.

b. the ability of the hydrogenation products (amines) to act as ligands[16].

Homogenous catalytic hydrogenation of carbon-nitrogen double bonds usually requires more drastic conditions (higher temperatures and pressures) than olefin hydrogenations. Since the asymmetric induction often decreases with increasing temperature[17] one can conclude *a priori* that it is a much more difficult task to achieve high asymmetric induction in the case of the hydrogenation of a carbon-nitrogen double bond than in case of olefins and ketones.

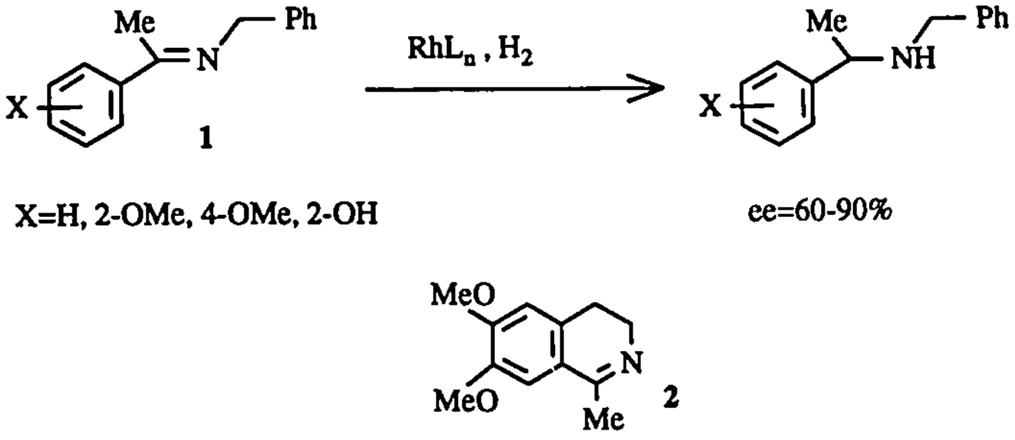
Until recently, only a few publications on the enantioselective hydrogenation of C=N double bonds have appeared. All publications in this field have been devoted to the hydrogenation of Schiff bases, mostly derived from benzylamine or aromatic amines. Catalysts used for these reactions were phosphine complexes of rhodium and iridium.

The enantioselective hydrogenation of Schiff bases derived from acetophenone and benzylamine was carried out using a Rh(I) complex, generated in situ from $[Rh(NBD)Cl]_2$ (NBD=norbornadiene) and (-)-(2S,4S)-2,4-bis(diphenylphosphino)pentane (BDPP)in the presence of triethylamine, as well as using the cationic complex $[Rh(S,S)\text{-}BDPP(COD)]BF_4$ [18]. It was shown that the composition of the solvent mixture and the reaction temperature have a marked influence on the enantioselectivity. These effects are thought to be related to the enhanced coordination flexibity of six-membered rings when simple substrates without functional groups are coordinated to the rhodium. The best optical yields were achieved in polar solvents (e.g. methanol) and were quite high (up to 85% ee). The optical yield of the reaction depended strongly on the temperature . The R-enantiomer in the product predominates at lower, and the S-species at higher temperatures. This was rationalized on the basis of the different stabilities of λ- and δ-conformers of the $Rh^I$-BDPP complex at different temperatures with the λ-skew conformation being more stable at high temperature and the δ-skew conformation having greater stability at low temperature.

A convenient procedure for the asymmetric hydrogenation of several types of imines (**1, 2**) using a catalyst, generated in situ from $[Rh(NBD)Cl]_2$ and (R)-1,2-bis(diphenylphosphino)-1-cyclohexylethane have been reported by James and co-workers[19,20] (Scheme 4). Optical yields of up to 91% were achieved by using low temperature and high $H_2$ pressure (more than 1000 psi). The presence of iodine as a cocatalyst is necessary to achieve high enantioselectivity in the reaction.

The mechanism of imine hydrogenation catalyzed by rhodium complexes with chiral phosphines[20] (Scheme 5), includes imine coordination through the nitrogen lone pairs to the square-planar $Rh^I$ complex as a first stage of the reaction.

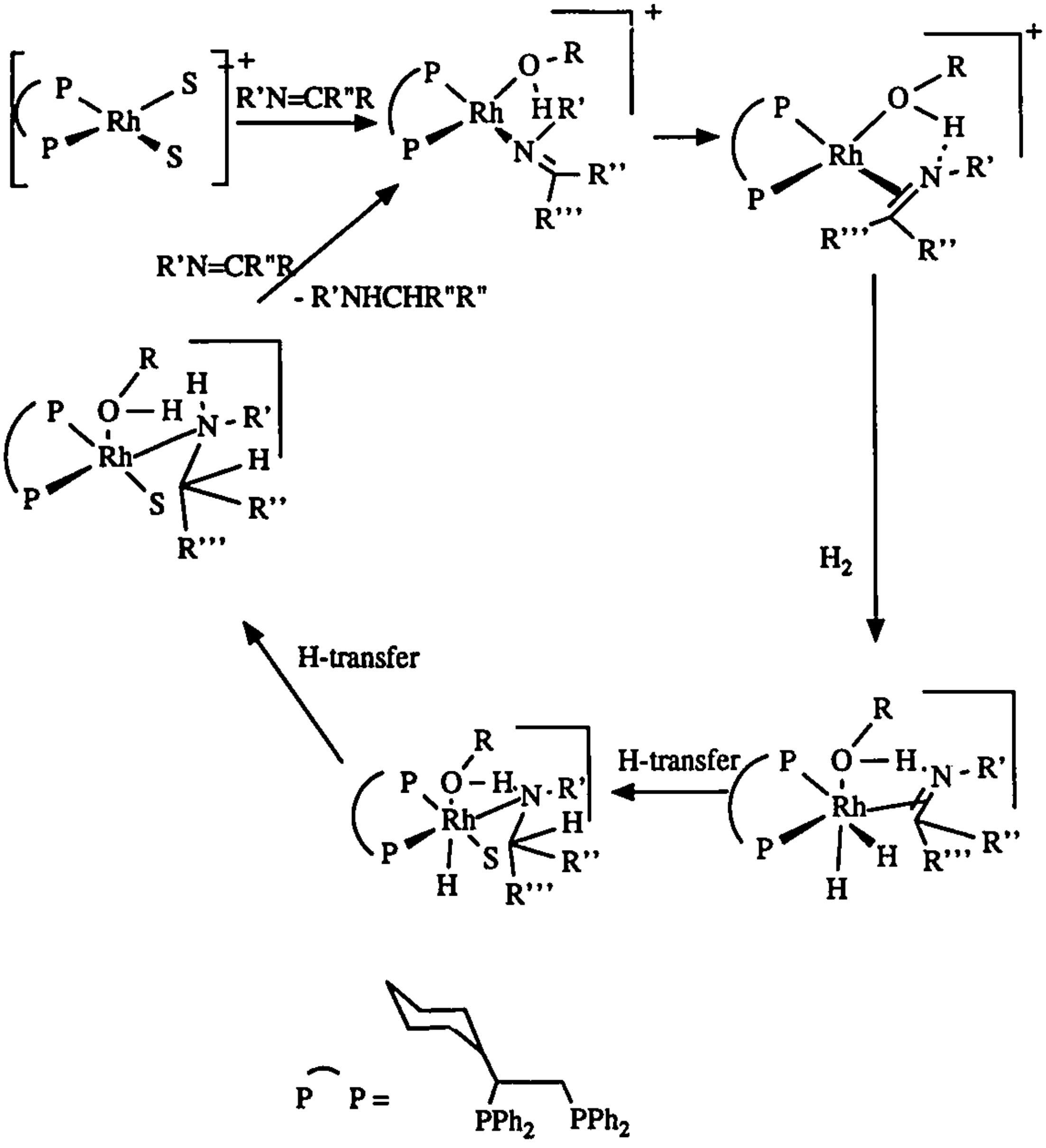
The subsequent transformation of the $\eta^1$-bonded imine to $\eta^2$-(C=N) species is facilitated by hydrogen bonding between the imine nitrogen and rhodium coordinated to an alcohol. Oxidative addition of dihydrogen with the formation of $Rh(III)(H)_2$ species, hydrogen transfer from the metal to the coordinated imine and displacement of amine with solvent or another molecule of substrate completes the catalytic cycle.



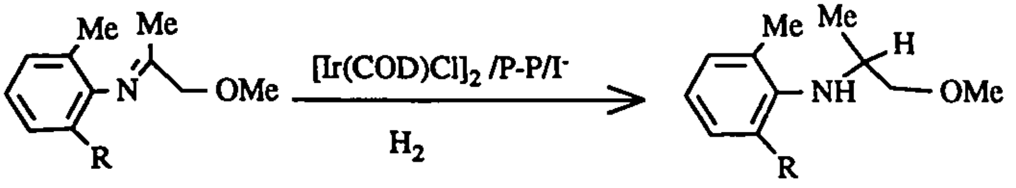
Scheme 4.

In situ generated diphosphinoiridium complexes have been used for the enantioselective hydrogenation of some N-arylketimines[21] (eq. 6). Good activities and enantioselectivities are obtained with chiral ligands which can form a conformationally flexible six- or seven-membered ring metallacycle (BDPP, DIOP, or BPPM) . A strong halogen effect was observed: the halogen free catalytic system $[Ir(COD)Cl]_2$/(2S,3S)-DIOP yields the (R)-enantiomer of the amine in only 4% ee, whereas addition of 1 equivalent of iodide leads to a considerably more active catalyst producing the (S)-enantiomer in 68% ee. The best enantioselectivities were achieved in the range of 70-85%. The secondary amines obtained are useful intermediates for the synthesis of herbicides.

The catalysts were obtained by treating $[Ir(COD)Cl]_2$ with chiral diphosphine and iodide-ion. Good activities and enantioselectivities have been obtained with chiral diphosphine ligands which can form conformationally flexible six- or seven membered metallocycles (DIOP, BDPP),(eq 6). Chiral 1,2-diphosphino compounds (CHIRAPHOS, NORPHOS) gave catalysts with



Scheme 5.



(eq. 6)

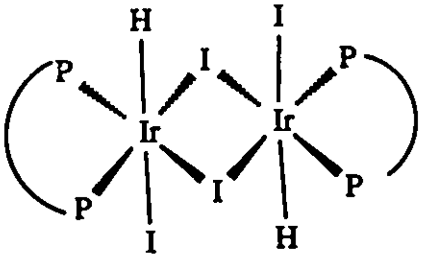
R=Et, Me

low activity. The highest enantiomeric excesses obtained with BDPP as a ligand was up to 85%.

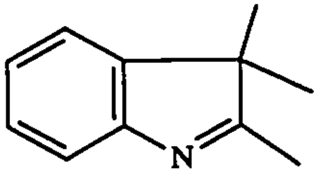
Chiral iridium(III)-diphosphine-monohydrido complexes (**3**) are useful for asymmetric hydrogenation of different imines (**4**,**5**,**6**) with good enantioselectivities[22] (Figure 1).
The catalytically active species are thought to be monomeric iridium complexes which are in eqiulibria with a dimer in the reaction mixture.

In two recent publications Burk and Feaster[23], as well as Willoughby and Buchwald[24], reported new transition metal catalysts for homogeneous asymmetric hydrogenation in which optically active amines can be obtained in high enantiomeric excesses.

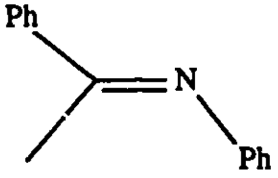
Following the investigation of the enantioselective hydrogenation of functionalized olefins with chiral bis(phospholane)rhodium(I) complexes, Burk and Feaster have then used the new transition metal catalysts for the asymmetric synthesis of primary amines. With 0.1 mol% of the catalyst system (Et-duphos)Rh$^{I}$ (Rh-7$^{+}$) , N-aroylhydrazones **8** of alkyl aryl ketones are reduced under mild reaction conditions(20$^{0}$C, 1-4 atm $H_2$, 1-36h) to give the corresponding optically active



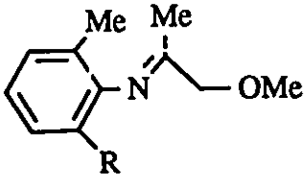
3



4



5



6

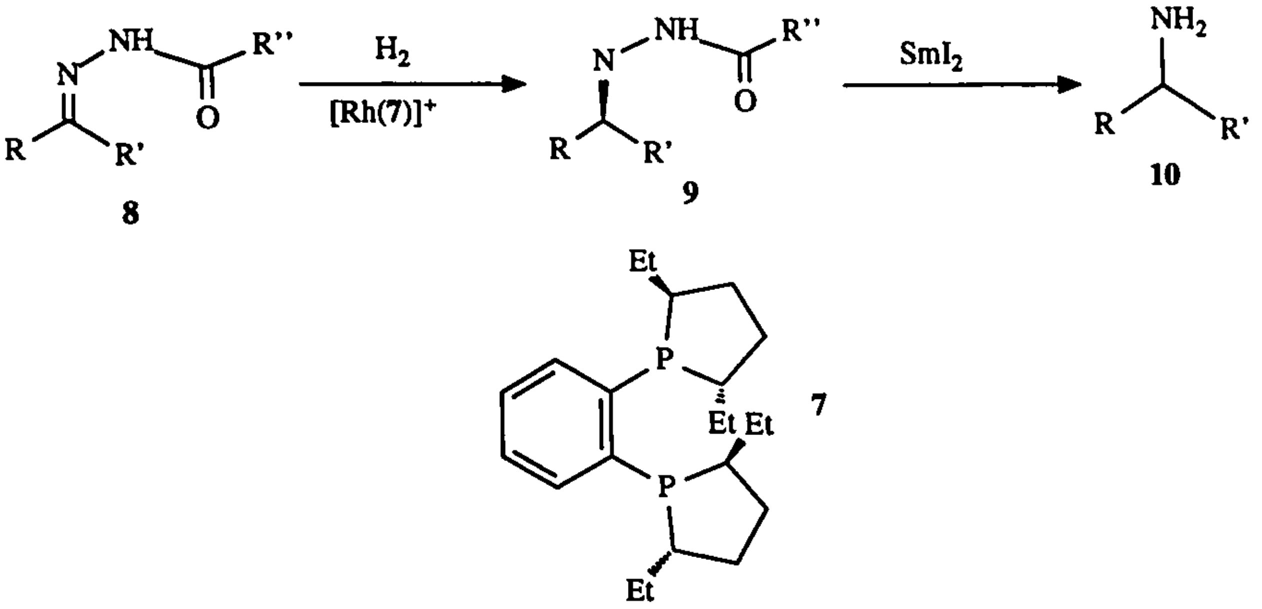
P-P= DIOP, BDPP, BINAP.

Figire 1.

N-aroylhydrazines **9** (Scheme 6).

Enantioselectivities of up to 97% ee were achieved for the enantioselective hydrogenation of N-aroylhydrazones with **7**. If aroylhydrazines are allowed to react with samarium iodide , the N-N bond can be cleaved and the corresponding amines **10** are obtained with no loss of optical purity. Thus, synthetically valuable primary amines are obtained as reaction products. The chiral α-hydrazino acid derivatives are of particular interest. These derivatives are obtained from α-keto esters and their hydrogenolysis leads to the optically active amino acids.

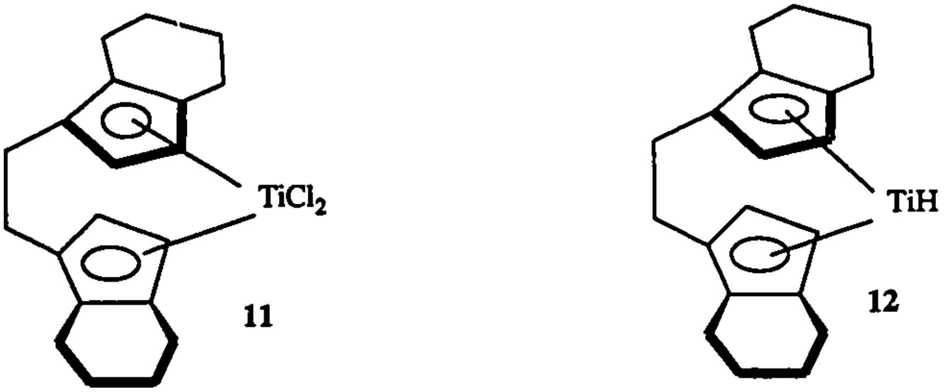
Willoughby and Buchwald have investigated[24] a fundamentally different catalyst system for



Scheme 6.

the asymmetric reduction of C=N bonds. If 2-10 mol % of the chiral ansa-titanocene **11** (Figure 2) is used as the catalyst for the hydrogenation of cyclic imines with molecular hydrogen excellent enantioselectivities (up to 98% ee ) are achieved. In contrast, the reactions of acyclic compounds with C=N bonds occur less selectively; starting with from N-benzylimines the products are only obtained with ee values between 58 and 87%. Steric factors in the formation of diastereomeric transition states and competitive hydrogenations of stereochemically different substrate/catalyst complexes are thought to be responsible for this.

The authors assume that the hydridotitanium(III) complex **12** is the active form of the catalyst. Complex **12** is prepared by the reaction of the stable complex **11** with n-butyllithium in situ and stabilized by phenylsilane. The hydrogenation of the ketimines occurs in THF at 65°under



11

12

Figure 2.

increased hydrogen pressure (ca 135 atm).

Most of the publications on the enantioselective hydrogenation of substrates with a carbon-nitrogen double bond are those dealing with the hydrogenation of imines. There is only one paper in the literature concerning the asymmetric hydrogenation of oximes . Botteghi et al.[25] have reported the use of the chiral ruthenium catalyst, $H_4Ru_4(CO)_8[(-)\text{-DIOP}]_2$, for the asymmetric hydrogenation of the oximes of 3-buten-2-one, 1-phenyl-1-ethanone and 1-phenyl-2,2-dimethylpropanone, with enantioselectivities in the 4-10 percent range. The best result (14% ee) was achieved for 1-phenyl-2,2-dimethylpropanone oxime. Severe conditions (100 atm. pressure and temperature up to 130°) were required to fulfill the reaction.

### *1.2. Asymmetric reduction of carbonyl group.*

### *1.2.1. Asymmetric Hydrogen Transfer Reduction of Ketones.*

The reduction of multiple bonds with the aid of a hydrogen donor in the presence of a catalyst is known as hydrogen-transfer reduction or transfer hydrogenation. The process entails hydrogen abstraction from the reagent (hydrogen donor) by means of the catalyst, followed by hydrogen addition to the unsaturated functional group of the substrate (hydrogen acceptor).

In hydrogen-transfer reactions the hydrogen source must be different from dihydrogen. Most of the reagents employed are organic molecules: unsaturated hydrocarbons such as cyclohexene or cyclohexadiene, primary or secondary alcohols like methanol, benzyl alcohol or propan-2-ol, and formic acid have been successfully used for this purpose. The use of hydrogen donors have some advantages over the use of molecular hydrogen since it avoids the risks and the constraints associated with these reagents as well as the necessity of pressure vessels. Additionally the rate and selectivity of the reaction can be favorably affected by selecting the most appropriate hydrogen donor.

There are two basic ways by which enantioselective hydrogen transfer can be achieved: enantioface selection by means of a chiral catalyst on achiral substrates or kinetic resolution of a chiral racemic compound.

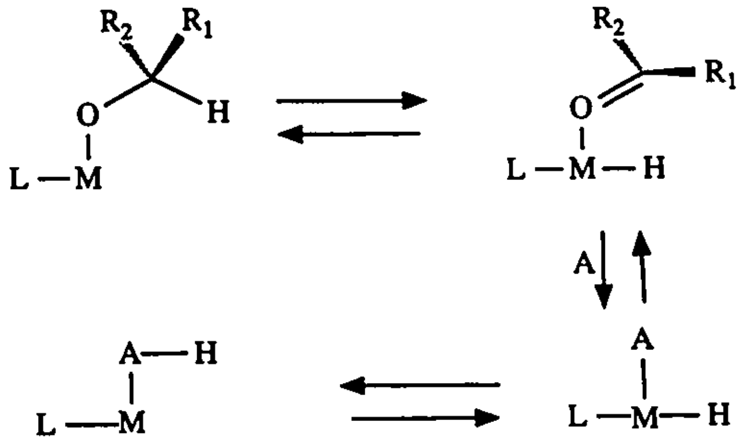
From a mechanistic point of view, two general reaction paths can be envisaged for hydrogen transfer[26] : a stepwise process, called the "hydridic route" and a concerted process, called direct hydrogen transfer (Scheme 7). The "hydridic route" involves the intermediate formation of a metal hydride derivative by interaction of the catalyst with the hydrogen donor, followed by hydride transfer from the metal to the substrate. The "direct hydrogen transfer" implies that hydrogen is transferred to the substrate in a concerted process where both the H-donor and H-acceptor are held together in close proximity by the catalyst. A cyclic transition state such as the one proposed for Meerwein-Pondorf-Verley reduction may be involved.

As for the catalyst, both mono- and polynuclear Ru(II), Rh(I), and Ir(I) complexes with chiral phosphorus and nitrogen ligands have been successfully employed to promote enantioselective H-transfer reactions.

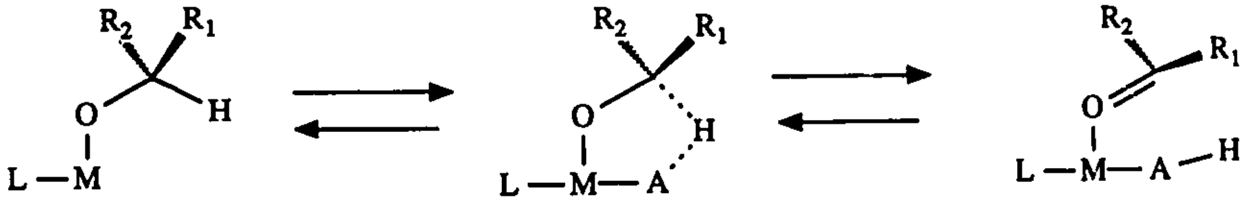
The chiral ligands employed in the asymmetric H-transfer reaction are basically the same as those able to effect high enantioselectivities in asymmetric hydrogenation. Chiral phosphines are the most popular ligands in asymmetric catalysis, and they have been employed in H-transfer since the very beginning with ruthenium, rhodium and iridium catalysts. Chelating diphosphines like DIOP, CHIRAPHOS, and BINAP have been mainly used in these reactions.

It should be noted, however, that unlike asymmetric hydrogenation, in the field of enantioselective H-transfer reactions, the most used chiral auxiliaries contain nitrogen, not phosphorus, as the donor atom.

Chiral bidentate nitrogen ligands used so far in enantioselective hydrogen transfer reactions belong to four different categories: chiral alkyl substituted bipyridines **13-15** (Figure 3) and phenanthrolines **16-19** (Figure 4)[27], alkyl-substituted tetrahydrobioxazoles (Figure 5)[28], chiral



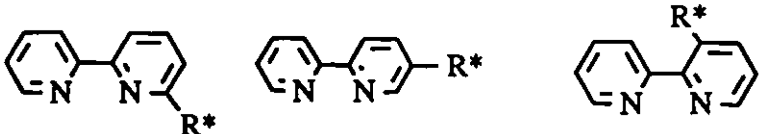
"hydridic route"



"direct hydrogen route"

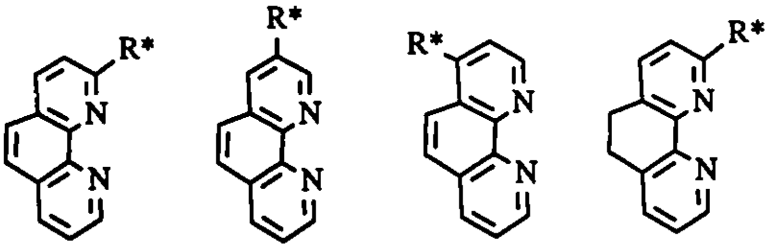
Scheme 7.

2-[[N-alkyl- and N-(arylalkyl)-imino]methyl]pyridines (Figure 6)[29] and chiral alkyl- and (arylalkyl)(2-pyridilmethyl)amines (Figure 7)[30]. Most of them have been employed in the enantioselective transfer hydrogenation of acetophenone in the presence of Rh(I) catalysts. These ligands have been prepared by multistep processes and different synthetic schemes have been used, depending on the position and the structure of the chiral alkyl substituent. All the schemes rely upon the same synthetic strategy involving the synthesis of the substituted pyridine ring through a racemization-free reaction path, starting from an optically active substrate.



**13** **14** **15**

Figure 3.



**16** **17** **18** **19**

Figure 4.

Alkyl-substituted tetrahydro-bis(oxazolyl)methanes and tetrahydrobioxazoles **20, 21** (Figure 5) have been introduced in enantioselective H-transfer by Pfalts[28]

**20** **21**

Figure 5.

Good to excellent enantioselectivities have been obtained in the reduction of alkyl aryl ketones in the presence of a Ir(I) catalyst. These ligands are readily prepared from easily available chiral β-aminoalcohols and are characterized by $C_2$-symmetry of the stereogenic centers in close proximity to the coordination site[27]. When the ligand coordinates to the metal, the substituents at the stereogenic centers provide an efficient shielding to the metal ion from two opposite directions and should therefore have a distinct effect on the stereochemical course of the reaction occurring within the coordination sphere.

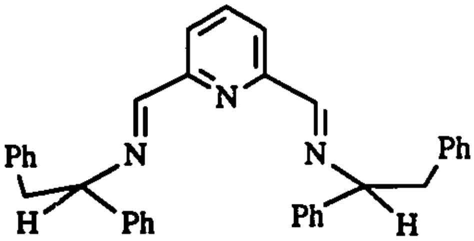
Chiral 2-[[N-alkyl and N-(arylalkyl)imino]methyl]pyridines **22** (Figure 6) can be readily obtained in both enantiomeric forms by condensation of 2-pyridinecarboxyaldehyde with the appropriate optically active primary amine[29].

**22** **23**

Figure 6.

They are similar to tetrahydrobioxazoles in that the stereogenic center is quite close to the reactive site of the catalyst , but, unlike tetrahydrobioxazoles, they are devoid of a $C_2$-symmetry axis. They have been successfully employed both with Rh(I) and Ir(I) catalysts. Chiral alkyl and (arylalkyl)(2-pyridylmethyl)amines **23** can be prepared by hydrogenation of the corresponding 2-[[N-alkyl and N-(arylalkyl)imino]methyl]pyridines **22** in the presence of a Pt/C catalyst[30]. Ir(I) complexes with these ligands display high catalytic activities and fair to excellent enantioselectivities in the hydrogen transfer reduction of ketones with isopropanol .

The potentially tetradentate Schiff base 2,6-bis[N-(1,2-diphenylmethyl)imino] methyl]pyridine **23a** (Figure 7) having two equivalent chiral substituents and a $C_2$-symmetry axis, have been recently prepared by condensation of pyridine 2,6-dialdehyde with (R)- or (S)-1,2-diphenylmethylamine. The corresponding Ir(I) complex displayed high chemo and enantioselectivities in the transfer reduction of 4-phenyl-3-butene-2-one in isopropanol[31].



**23a**

Figure 7.

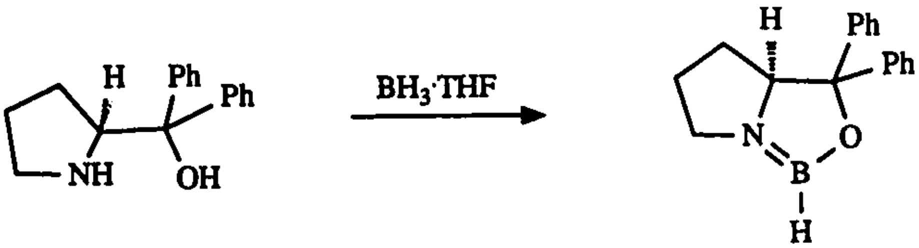
Most of the publications on the enantioselective hydrogen transfer reduction of ketones employ rhodium and iridium complexes as hydrogen transfer catalysts. Little has been achieved thus far using ruthenium complexes for the asymmetric hydrogen-transfer reduction of ketones, an exception being that of Botteghi et al[32] who applied the $[H_4Ru_4(CO)_8((-)\text{-DIOP}_2]$ cluster for the enantiofacial transfer hydrogenation of ketones using isopropanol or benzyl alcohol as hydrogen donors at 120°. Alkyl aryl ketones gave consistently better optical yields than dialkyl substrates, the best result being observed with phenyl isobutyl ketone (enantiomeric excess 10% ) Another report on enantioselective hydrogen-transfer reduction of ketones with $Ru_2Cl_4((-)\text{-DIOP})$[18] claims 10% ee for the reduction of acetophenone with isopropanol.

### *1.2.3. Reduction with complex metal hydrides.*

Reduction of unsaturated compounds with complex metal hydrides is a procedure, widely used in synthetic organic chemistry. Chiral modification of the corresponding hydrides leads to an enantioselective process with broad synthetic application. Considerable success in obtaining high asymmetrical inductions have been achieved in these process, particularly with modified lithium aluminum hydride reagents. Chiral ligands which were used to modify the hydride including 1,2, 1,4 and 1,5-diols, monoamines, primary, secondary and tertiary 1,2 and 1,4-diamines, 1,2 and 1,3-aminoalcohols. Probably the most efficient asymmetric diol-lithium aluminum hydride reagent (2,2'-binaphthol-lithium aluminum hydride complex ) have been reported by Noyori[33]. High ee values (more than 90%) have been reported for the reduction of several ketones. In the reduction of butyrophenone 100% ee was achieved. Series of (S)-(-)N-(*O*-substituted benzyl)-2-phenylethylamines was tested as lithium aluminum hydride modifiers by Yamaguchi[34]. The best result (42%) was achieved with (S)-(-)N-(o-dimethylamine benzyl)-2-phenylethylamine. (R)-2,2'-diamino-6,6'-dimethylbiphenyl-lithium aluminum hydride reagent was used for the reduction of a variety of substrates by Suda[35]. The highest asymmetric yield (54%) was achieved for the reduction of phenyl-tert-butyl ketone. Application of (S)-2-(N-substituted aminomethyl)pyrrolidines with alkyl and aryl substituents for the same reaction was tested for a large variety of aminomethylpyrrolidines[36]. (S)-2-(2,6-Xylidinomethyl)pyrrolidine was shown to be the most efficient reagent. Propiophenone was reduced in 90% yield and 96% ee using this modifier.

### *1.2.4. Asymmetric oxaborolidines catalyzed ketones reduction with boranes.*

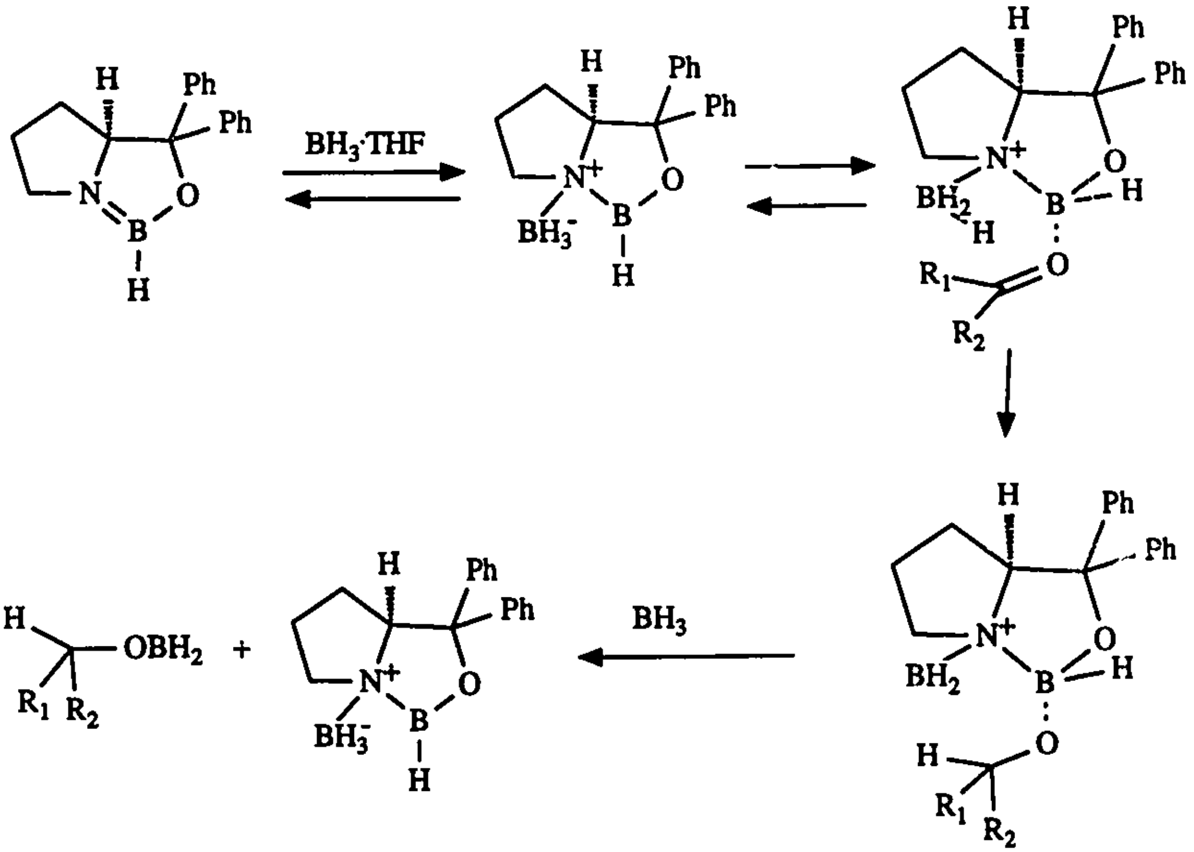
An approach for the asymmetric synthesis of alcohols based on oxaborolidines catalyzed ketones reduction with boranes has been developed by Corey[37-39]. Oxaborolidines are prepared from chiral aminoalcohols and borane. Very effective catalyst for the reduction of ketones was synthesized starting from (S)-diphenylprolinol[37] (Scheme 8).



Scheme 8.

The mechanism of ketone reduction with borane catalyzed by oxaborolidine are shown on Scheme 9. In $BH_3$ solution oxaborolidine coordinates $BH_3$ molecule via nitrogen atom. Subsequent coordination of ketonic carbonyl with electrophilic ring boron and hydrogen transfer from the $NBH_3^-$ unit to the carbonyl carbon affords reduced product.

Small amount (2.5-10%) of oxaborolidine catalyses asymmetric reduction of a large variety of ketones with high enantioselectivity (80-97%).



Scheme 9.

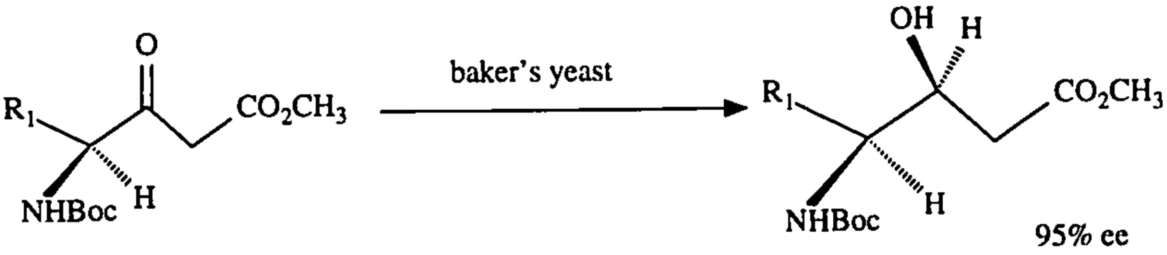
### *1.2.5. Enzymatic reduction of ketones.*

Enzymatic reduction of ketones, particularly β-keto esters have been well investigated. Enzymatic approach to the asymmetric ketone reduction allows to achieve high optical purity of product. There must be, however, careful selection of particular enzyme used, and the selection of experimental conditions.

Reduction of acyclic ketones by baker's yeast[40] was examined for the series of ketones with all combinations the substituents: methyl, ethyl, n-propyl, n-butyl and phenyl. With the exception of the alcohol derived from butyl methyl ketone, there R-configuration is preferred the secondary alcohols posses S-configuration. The more sterically hindered ketones such as, for example n-butyl n-propyl ketone were not reduced by yeast. For the rest of ketones tested, enantioselectivity of the reduction vary significantly. Optical purity of product depended on the relative bulkiness of the ketone substituents. Reduction of acetophenone (95% ee) and methyl t-butyl ketone (97% ee) occurs with high enantioselectivity. At the same time, reduction of methyl ethyl ketone afforded product with 32% ee.

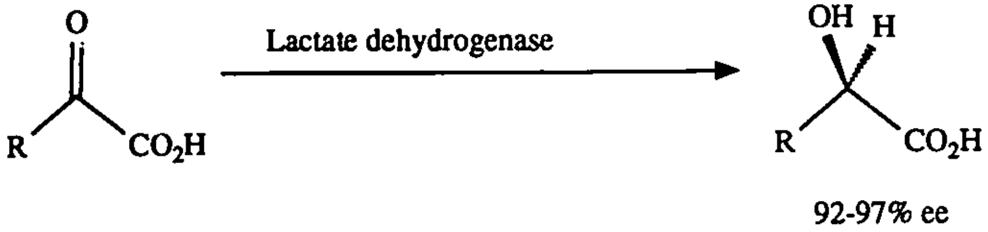
The asymmetric reduction of ketoesters by baker's yeast is a well established method for the preparation of hydroxo esters, valuable chiral building blocks[40]. The yield (60-90%) and the optical purity of the product (60%- 99%) vary depending on the procedure used. The most critical factor which affects the enantioselectivity of this reaction is the substrate concentration, because of the presence of competing enzymes of opposite chirality in baker's yeast. The optical purity of the product drops significantly when the concentration of substrate is greater then 5 g/L. The enantioselectivity of the reduction of ketocarbonyl compounds by east is also strongly influenced by changes in the carbonyl substituents. Among a homologous series of $C_1$to $C_{12}$-esters of 4-chloroacetic acid as substrates, a dramatic shift in the stereochemistry of the alcohol product was observed as the size of the ester group was enlarged[40].

Enzymatic reduction of carbonyl compounds which have an additional chiral center in the molecule is usually a difficult task because of the influence of an already existing asymmetric center. The reduction of statine precursor (Scheme 10) required particular kind of baker's yeast, which was selected from thirty different variations[41].



Scheme 10.

Reduction of carbonyl compounds with baker's yeast is the most developed and synthetically useful procedure for the enzymatic carbonyl reduction. In certain cases another alternatives can, however, be also quite useful. L-lactate dehydrogenase, an inexpensive enzyme that appears to possess broad substrate specifity and high enantioselectivity accepts a series of unnatural 2-oxoacids as substrates and with NADH it converts α-carbonyl acids into hydroxy acids[42] (Scheme 11).



Scheme 11.

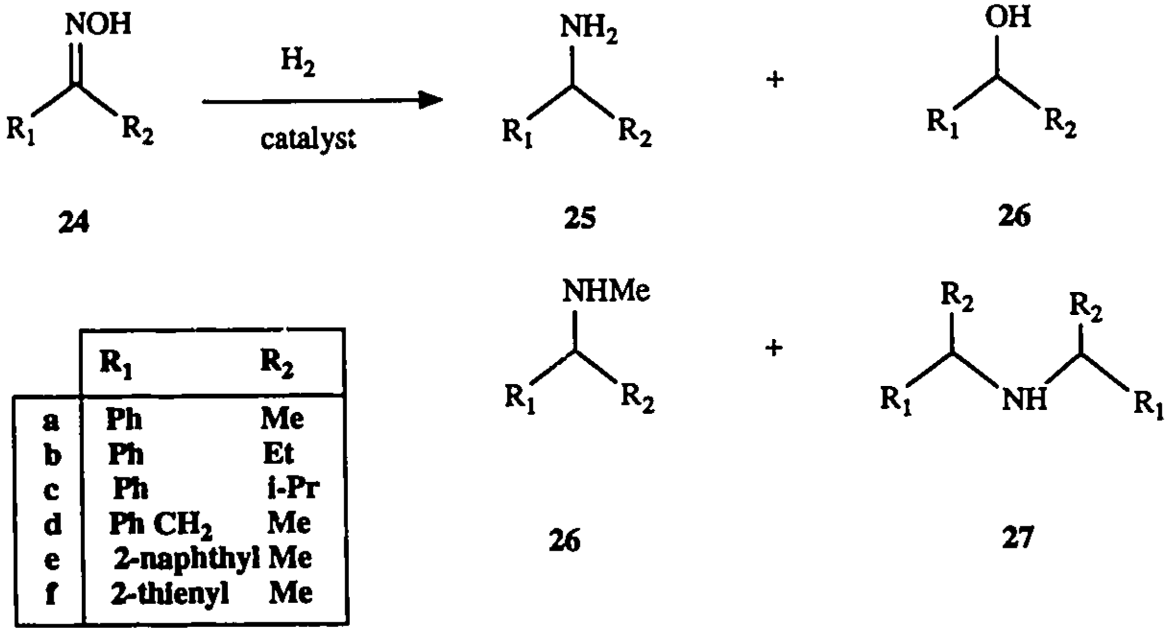
## *2. RESULTS AND DISCUSSION.*

### *2.1 Asymmetric Hydrogenation of Oximes with {RuX(arene)[(R)-BINAP]}X Complexes.*

The hydrogenation of oximes was carried out in alcohol (methanol or ethanol) - benzene mixtures at 90° C and 1300 psi of hydrogen using 1 molar percent of catalyst. The complexes ({(benzene)RuCl[(R)-BINAP]}Cl) were prepared *in situ* from $[RuX_2(arene)]_2$ (X= Cl, I) and (R)-BINAP . The prochiral ketoximes **24a-f**, were synthesized from the corresponding ketones, without separation of *Z* and *E*-isomers.

The hydrogenation reaction proceeds according to Scheme 12 affording primary amines in good chemical and moderate optical yields. Several by-products, i.e. alcohols **26** and secondary amines **27, 28** were formed in the reactions. When the reaction was carried out under optimized conditions, secondary amines were not detected. The conditions are discussed below.

When the reaction was completed solvents were evaporated and the products (alcohol-amine mixtures) were isolated using bulb to bulb distillation. As an example $^1H$ NMR spectra of reaction products of acetophenone oxime hydrogenation and 1-propiophenoone oxime hydrogenation are



|  | **R$_1$** | **R$_2$** |
|---|---|---|
| **a** | **Ph** | **Me** |
| **b** | **Ph** | **Et** |
| **c** | **Ph** | **i-Pr** |
| **d** | **Ph CH$_2$** | **Me** |
| **e** | **2-naphthyl** | **Me** |
| **f** | **2-thienyl** | **Me** |

Scheme 12.

shown on Figures 8 and 9. To determine the optical yields of the hydrogenation reaction, products (mixtures of **25** and **26** ) were transformed into α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) derivatives[43]. and enantiomeric ratios were measured by 300 MHz $^1$H NMR. For all the mixtures of the corresponding diastereomeric esters and amides distinct separation of the methoxy group signals were observed. Methoxy group signals of amides were located in the region of 3.34-3.44 ppm and those of esters at 3.45-3.59 ppm. Selected $^1$H NMR spectra ( 3-4 ppm regions, $CH_3O$ group signals) of (R)-MTPA derivatives of alcohol-amine mixtures are shown on Figures 10, 11 and 12.

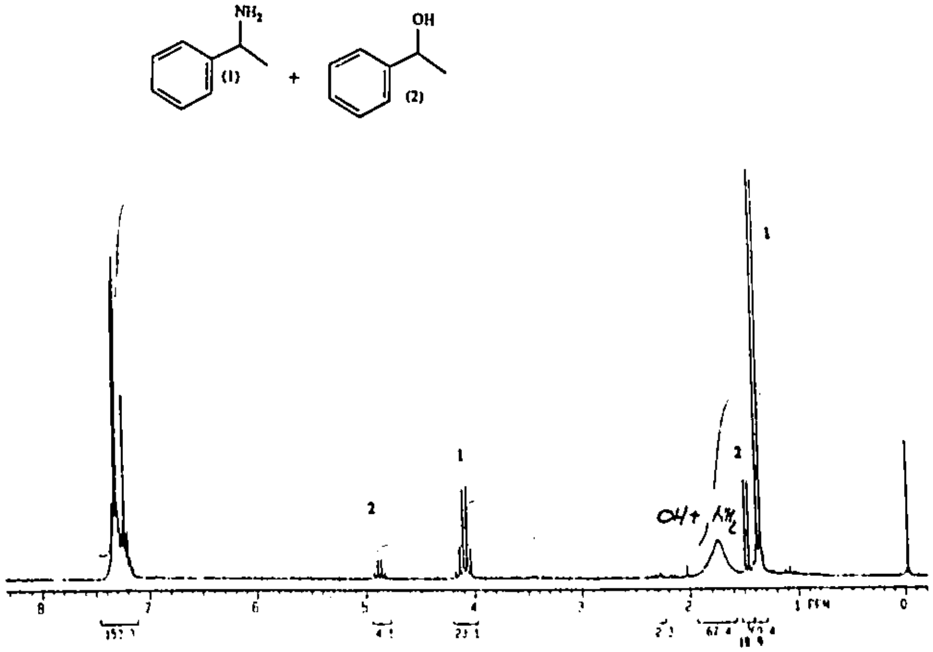


Figure 8. ¹H NMR spectrum of acetophenone oxime hydrogenation products.

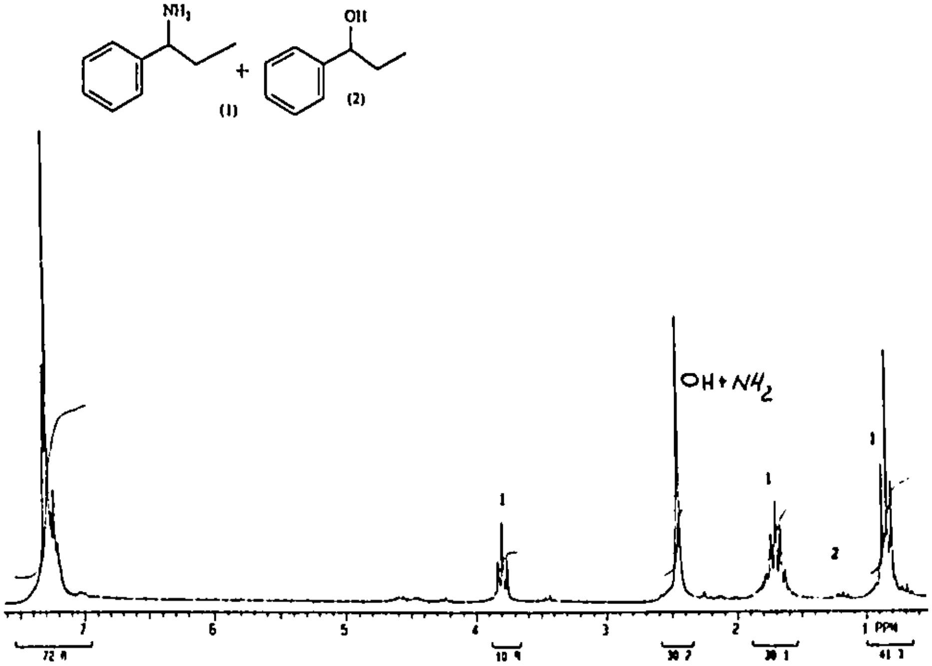


Figure 9. ¹H NMR spectrum of 1-propanone oxime hydrogenation products.

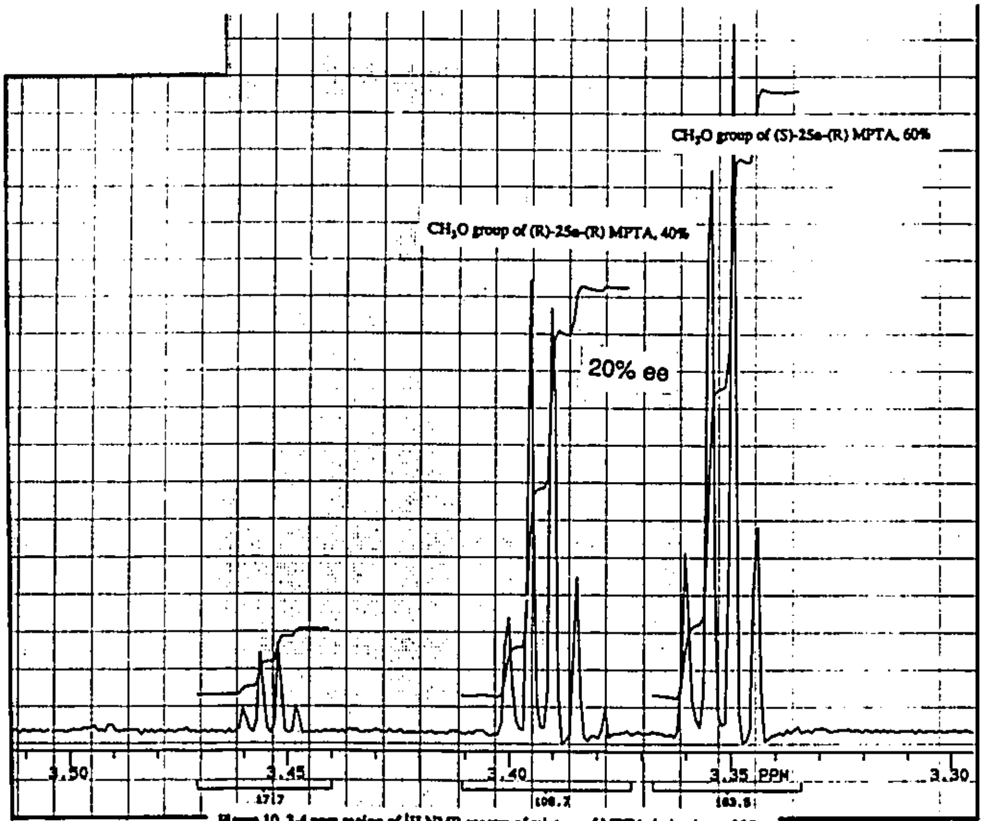


Figure 10. 3-4 ppm region of $^1$H NMR spectra of mixture of MPTA derivatives of 25a and 26a.

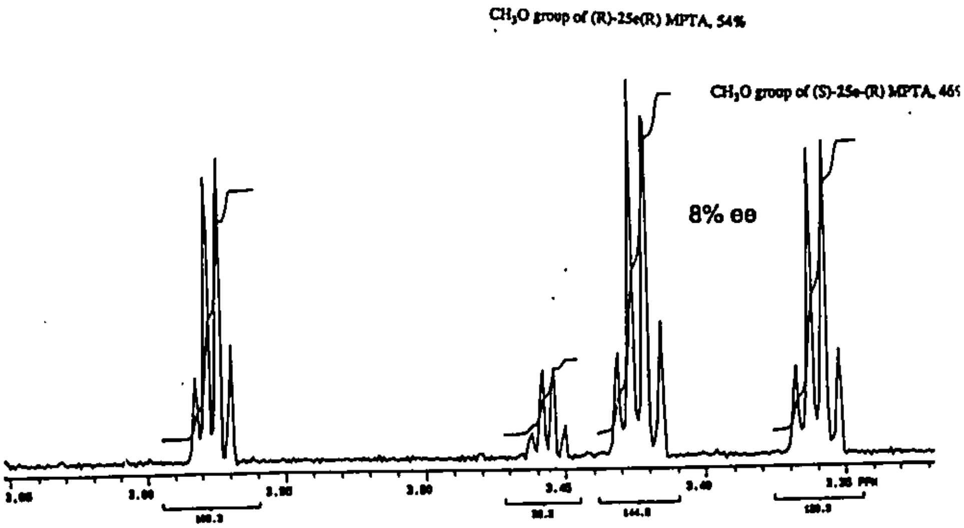


Figure 11. 3-4 ppm region of $^1$H NMR spectra of mixture of MPTA derivatives of 25e and 26e.

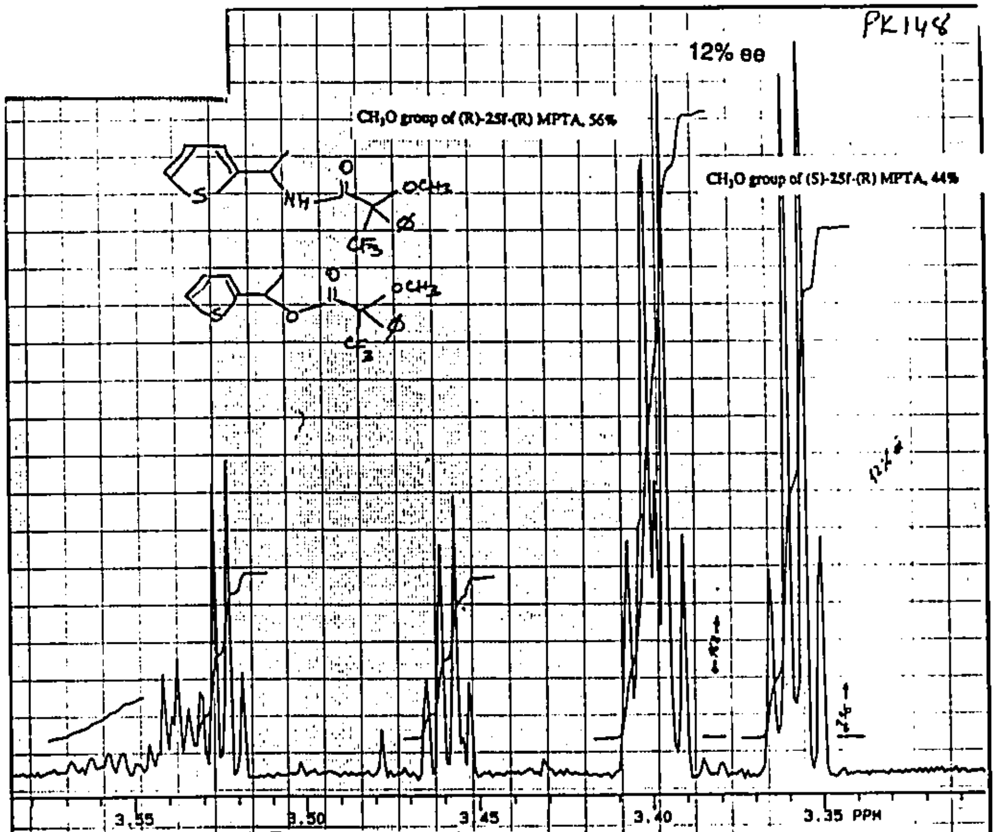


Figure 12. 3-4 ppm region of $^1$H NMR spectra of mixture of MPTA derivatives of 25f and 26f.

The alcohols **26** may result from hydrogenation of the corresponding ketones which can be produced by the hydrolysis of **24**. The beneficial effect of water on the catalytic process is discussed below. The secondary amines **27** likely arise from the hydrogenation of imines, formed in the reaction of formaldehyde with amines **25**. The formaldehyde can in turn be formed by transition metal catalyzed dehydrogenation of methanol[44]. The secondary amines **28** could be generated by the ruthenium catalyzed alkyl group exchange reactions[45] of primary amines **25**. Another path for the formation of **28**, namely by the hydrogenation of imines, generated in the reaction of amines **25** with ketones **26**, can be excluded, since under the reaction conditions reduction is very sluggish even for less hindered imines. For example, no reaction was observed when the Schiff base of acetophenone and benzylamine was treated under the same conditions for 48h.

The activity of the catalysts and the reaction path depend significantly on the amount of water in the reaction mixture. When prepared under anhydrous conditions the catalyst, {(benzene)RuCl[(R)-BINAP]}Cl (**29**), showed modest activity ( 40 percent conversion after 24h) (Table 1, run 1) and only the secondary amines, **27d** and **28d**, were detected. When {(benzene)RuCl[(R)-BINAP]}Cl was generated in the presence of water 100 percent conversion of the starting material to the mixture of primary amine **25d** and alcohol **26d** took place after 24h. The composition of the mixture depended on the amount of water added. Application of the catalyst, generated in the presence of water and then dried under vacuum resulted in the formation of a one to one mixture of **25d** and **26d**. When the same reaction was carried out in the reaction media containing 0.3% of water, 1-phenylpropanol-2 (**26d**) was the major product of the reaction and 1-phenyl-2-aminopropane (**25d**) was detected only in trace amounts (Table 1, runs 2,3).

Table 1. The effect of water on the hydrogenation of the oxime of 1-phenyl-2-propanone(**24d**) with (**29**)[a].

| Run No | Reaction media<br>$MeOH:C_6H_6:H_2O$ | Conversion (%) | Products(%)<br>**25** | **26** | **27** | **28** |
|---|---|---|---|---|---|---|
| 1 | 8.7 : 0.3 - | 40 | - | - | 16 | 8 |
| 2[b] | 8.7 : 0.3 - | 100 | 42 | 49 | - | - |
| 3 | 8.7 : 0.3 : 0.3 | 100 | 5 | 94 | - | - |

[a] Reaction conditions : 90°C, 24h, 1300 psi of hydrogen. Substrate concentration 0.22M, 1 mol% of catalyst.

[b] The catalyst was prepared from a $MeOH-C_6H_6-H_2O$ (5:1:0.5) mixture and then dried under vacuum.

For all the subsequent reactions a small amount of water (0.1 percent or less ) was added to the reaction mixture. Molecular sieves (3A°) were added to the reaction mixture in order to avoid an undesirable excess of water. The only by-products formed were the alcohols **26**, secondary amines **27** and **28** were detected in trace amounts in all cases. As 1-phenyl-2-aminopropane **25d** is of commercial importance, the hydrogenation of its precursor, 1-phenyl-2-propanone oxime **24d**, was chosen as the model reaction. The influence of different factors on the conversion of 1-phenyl-2-propanone oxime **24d** to 1-phenyl-2-aminopropane **25d** and the optical yield is discussed below.

### *(a) Catalyst.*

The results of the hydrogenation of 1-phenyl-2-propanone oxime (**24d**) are listed in Table 2. The catalysts were prepared *in situ* from [Ru(arene)$X_2$]$_2$, (arene= benzene, p-cymene; X=Cl,I) and BINAP, with {RuCl(benzene)[(R)-BINAP]}Cl (**29**) being the most effective catalyst for the asymmetric reduction of oximes (1-phenyl- 2-aminopropane was formed in 29 percent enantiomeric excess and 76 percent yield using 1 mol percent of catalyst). Increase in the catalyst/substrate ratio to 2 mol percent resulted in a similar chemical yield and enantioselectivity for product formation. The presence of an excess of added BINAP (1.5 molar equivalents of BINAP per one mole of ruthenium) reduced both the yield and % ee. Application of {RuI(p-cumene)[(R)-BINAP]}I for the same reaction gave rise to decreased chemical (60%) and optical (18%) yields in comparison with those obtained using {RuCl(benzene)[(R)-BINAP]}Cl.

### *(b) Solvent composition.*

A methanol-benzene mixture (8.7-0.3) containing 0.006 vol% of water was found to be the

Table 2. Asymmetric hydrogenation of 1-phenyl-2-propanone oxime (**24d**) catalyzed by {RuCl(benzene)-(R)-BINAP}Cl (**29**) and {RuI(p-cymene)[(R)-BINAP]}I (**30**).[a]

| Catalyst | Yield of 1-phenyl-2-propylamine[b] % | % ee[c] |
|---|---|---|
| **29** | 76 | 29 |
| **29**[d] | 75 | 25 |
| **29**[e] | 57 | 22 |
| **30**[f] | 60 | 18 |

[a] Reaction conditions: 90°C, 24h., 1300 psi of hydrogen in MeOH-$C_6H_6$-$H_2O$ (8.7: 0.2: 0.006), in the presence of 3A° molecular sieves. Substrate concentration 0.22 M.

[b] Isolated yield.

[c] Determined by $^1H$ NMR for mixture of MTPA derivatives of **25d** and **26d**.

[d] 2 mol % of catalyst.

[e] Catalyst was prepared using a 1:3 ratio of $[RuCl_2(benzene)]_2$ and BINAP.

[f] Solvent MeOH-dichloroethane-$H_2O$ (8.7:0.3:0.06).

MTPA= α-methoxy-α-(trifluoromethyl)phenylacetic acid

best solvent mixture for the hydrogenation of 1-phenyl-2-propanone oxime (**24d**).The decrease in the polarity of the media (ethanol is used instead of methanol, or the methanol-benzene ratio is increased) resulted in a somewhat lower yield of the desired product without a significant effect on the ee values. (Table 3).

Table 3. Effect of solvent on the hydrogenation of 1-phenyl-2-propanone oxime (**24e**) with **29**.[a].

| Solvent composition | Yield of **2e** (%)[b] | %ee [c]. |
|---|---|---|
| MeOH-$C_6H_6$-$H_2O$ (8.7:0.3:0.006) | 76 | 29 |
| EtOH-$C_6H_6$-$H_2O$ (8.7:0.3:0.006) | 68 | 18 |
| MeOH-$C_6H_6$-$H_2O$ (1 : 8 : 0.006) | 54 | 27 |

[a] Reaction conditions: 90°C, 24h., 1300 psi of hydrogen in the precence of 3A°molecular sieves. Conversions: 100%. Substrate concentration 0.22M, 1 mol% of catalyst.

[b] Isolated yield.

[c] Determined by $^1H$ NMR for MTPA derivatives of a mixture of **2e** and **3e**.

### *(c) Temperature.*

The hydrogenation reactions were typically carried out at 90 degrees. Unlike rhodium-catalyzed asymmetric hydrogenation reactions, where lower reaction temperatures afford higher optical yields [17], for the {RuCl(benzene)[(R)-BINAP]}Cl catalyzed asymmetric hydrogenation of oximes temperature does not effect significantly the optical yield. When the hydrogenation of 1-phenyl-2-propanone oxime was carried out at 75°, 1-phenyl-2-aminopropane was formed in 64% yield. Enantiomeric excess for the reaction was also slightly lower (20%). Only traces of 1-phenyl-2-aminopropane were detected after 48 hours at 45° (Table 4). The optical purity of the product was not determined because of the low yield.

Table 4. Influence of the temperature on the hydrogenation of 1-phenyl-2-propanone oxime (**24d**) with **29** [a]

| Temperature | Reaction time (h) | Yield of **25d** (%)[b] | % ee[c] |
|---|---|---|---|
| 90 | 24 | 76 | 29 |
| 75 | 48 | 64 | 20 |
| 45 [d] | 48 | 5 | - |

[a] Reaction condituons: 1300 psi of hydrogen , substrate concentration 0.22M, 1 mol% of catalyst ,in the presence of 3A° molecular sieves . 100% conversion, unless otherwise specified.

[b] Isolated yield.

[c] Determined by $^1$H NMR for MTPA derivatives of a mixture of **25d** and **26d**.

[d] Conversion: 34%.

Having optimized conditions for the asymmetric hydrogenation, we successfully hydrogenated a number of aryl alkyl oximes. The highest chemical yields (76-89%) were obtained for phenyl alkyl oximes. Optical yields for these oximes were moderate (20-29%) except for the oxime of phenyl isopropyl ketone (12%). Oximes of 2-naphthyl and 2-thienyl ketones were hydrogenated in lower chemical yields (64 and 48 percent respectively) and low optical yield (8% and 12%, respectively).

Table 5. Asymmetric hydrogenation of alkyl aryl oximes with **29**.[a]

| Substrate | Reaction time (h) | Yield of amine (%)[b] | % ee[c] (Configuration) |
|---|---|---|---|
| **24a** | 48 | 85 | 20(S) |
| **24b** | 48 | 89 | 25(S) |
| **24c** | 76 | 78 | 12(R) |
| **24d** | 24 | 76 | 29(S) |
| **24e** | 80 | 64 | 8(R) |
| **24f**[d] | 48 | 48 | 12(S) |

[a] Reactions conditions : 90°C and 1300 psi of hydrogen , in the presence of 3A° molecular sieves. Substrate (O.22M), 1 mol.% of catalyst. Conversion was 100% in all cases.

[b] Isolated yield.

[c] Determined by $^1$H NMR for MPTA derivatives

[d] Reaction temperature 110°.

From the data (Table 5) one can conclude that the asymmetric hydrogenation of oximes, catalyzed by Ru-BINAP catalysts, is very sensitive to the changes in the structure of the substrate. These changes affect both the chemical yield and the extent of asymmetric induction. It is noteworthy that the enantiomeric excess does not correlate directly with the steric bulk of alkyl substituents, and this may be due to the fact that *E/Z* ratios for oximes also depend on the same parameter[37].

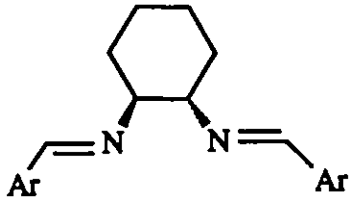
In conclusion, although the enantiomeric excesses are modest, the chemical yields are good for the hydrogenation of oximes, and **29** is the best catalyst found thus far for the asymmetric process.

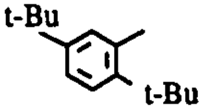
## *2.2 Schiff Bases as Added Chiral Ligands for the $[Ru(\eta^6-C_6H_6)Cl_2]_2$ Catalyzed Hydrogen Transfer Reduction of Ketones with Isopropanol.*

The asymmetric hydrogen-transfer reduction of alkyl aryl ketones was carried out using isopropanol as a hydrogen donor and ruthenium complexes, with chiral Schiff base ligands of (1R,2R)-diaminocyclohexane and aromatic aldehydes (Scheme 13), as catalysts in the presence of a base (potassium hydroxide or potassium carbonate).These ligands were synthesized in one step by condensation of (1R,2R)-diaminocyclohexane and an appropriate aldehyde. The relative bulkiness of the ligand can be easily modified by varying the aryl unit of the aldehyde.

The catalysts used for the hydrogen transfer hydrogenation were synthesized *in situ* from $[Ru(C_6H_6)Cl_2]_2$ and the corresponding chiral ligand and then activated in refluxing isopropanol in the presence of base. The reaction of $[Ru(Arene)Cl_2]_2$ with chelating imines[46] gives rise to the displacement of a chlorine atom in the coordination sphere of ruthenium by imine nitrogen with cleavage of the dimeric complex and formation of a cationic complex with two imine nitrogens, chlorine and arene coordinated to ruthenium. Therefore, it is likely that the catalyst precursors in this reaction are ruthenium-Schiff base complexes of the type $[Ru(C_6H_6)(N\hat{}N)Cl]Cl$ which, in refluxing isopropanol and in the presence of base, are then converted into the catalytically active species. No reaction was observed in the absence of base even after a prolonged reaction.

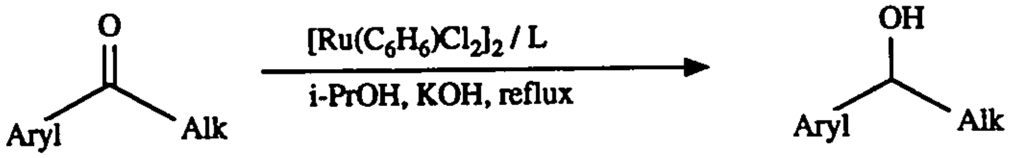
L=



| Ar | L |
|---|---|
| Ph | **30** |
| 2MeO-$C_6H_4$ | **31** |
|  | **32** |
|  | **33** |
| 1-naphthyl | **34** |
| 9-anthranyl | **35** |
| ferrocenyl | **36** |

Scheme 13.

Aryl alkyl ketones are reduced in refluxing isopropanol in the presence of 1 mol % of catalyst (1-10 h depending on the chiral ligand and substrate) affording the corresponding alcohols in 80-90% yields (eq. 7). The resulting alcohols were isolated using bulb to bulb distillation. Selected ${}^1$H NMR spectra of alcohols are shown on figures 13 and 14. The optical purity of the alcohol was determined by comparison of the specific rotation of the product with that of an optically pure authentic sample, and by 300 MHz ${}^1$H NMR for α-methoxy-α-(trifluoromethyl)phenylacetic acid derivatives[43]. Selected ${}^1$H NMR spectra (3-4 ppm region) of MPTA derivatives are shown on figures 15,16,17.



(eq. 7)

Acetophenone was chosen as a model substrate to examine the influence of steric bulk and coordination properties of the ligand on the outcome of the reaction. Application of $[Ru(C_6H_6)Cl_2]_2$/**30** (Scheme 9, Ar=Ph) for the hydrogen transfer reduction of acetophenone affords 1-phenylethanol in low optical purity (8% ee, Table 6). Introduction of a methoxy substituent which is able to provide an additional coordination to ruthenium in the 2-position of the aromatic ring of the aldehyde ( L=**31**) results in an increase of the optical yield of the reaction to 20% ee . When ligand **32**, similar to **31** but with increased conformational rigidity ( aromatic rings are connected in a 2-position with a propylenedioxy bridge), is used for the same reaction, the stereoselectivity of the reaction is lower (16 % ee). A diimine ligand derived from an aromatic aldehyde with a more bulky ortho substituent ( L=**34**, aryl=1-naphthyl) gives rise to a catalyst with increased stereoselectivity (ee=28%). However, a further increase in the bulkiness of the diimine ligand ( L=**33**) (tert-butyl group in the ortho position of aromatic ring), reduce the optical yield of the reaction (ee=22%). The best results in asymmetric hydrogen-transfer hydrogenation were achieved with catalysts derived from L=**34** (aryl=naphthyl) and L=**36** (aryl=anthranyl). This can be explained by the ability of the second aromatic ring of the naphthyl or anthranyl substituent to coordinate to ruthenium providing additional rigidity to the catalyst.

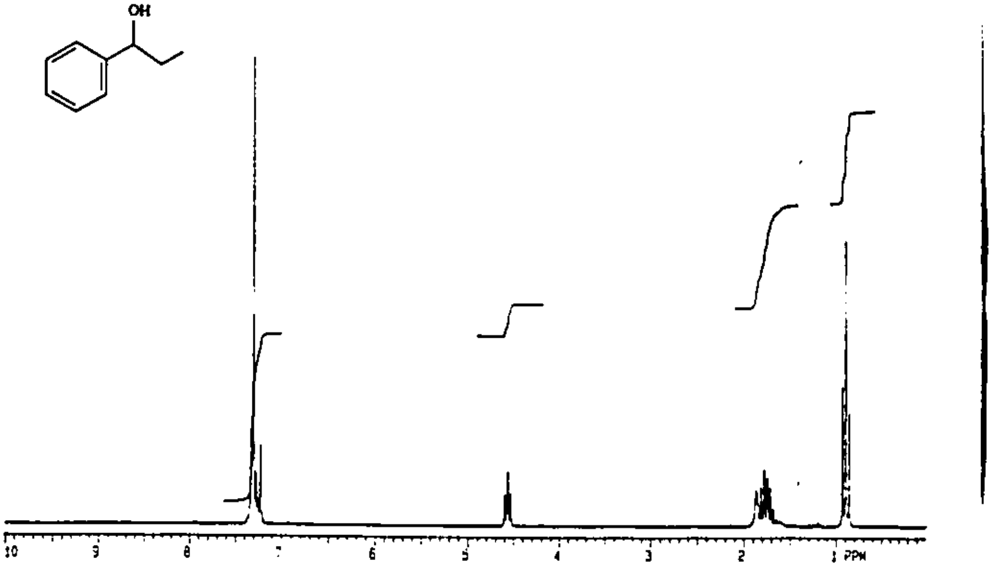


Figure 13. ¹H NMR spectrum of 1-phenylpropanol-1.

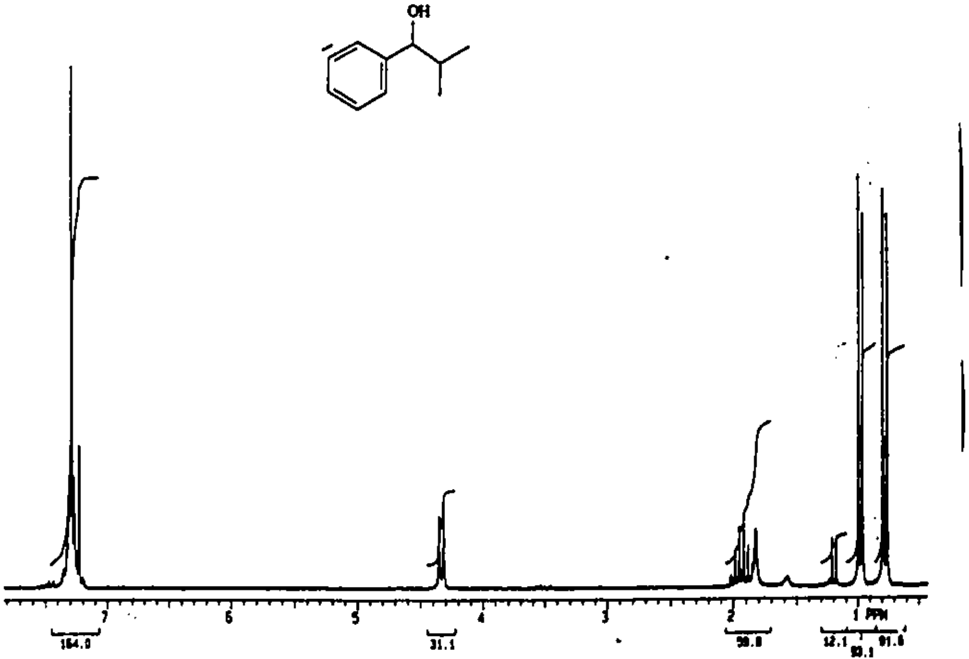


Figure 14. ¹H NMR spectrum of 1-phenyl-2-methylpropanol-1.

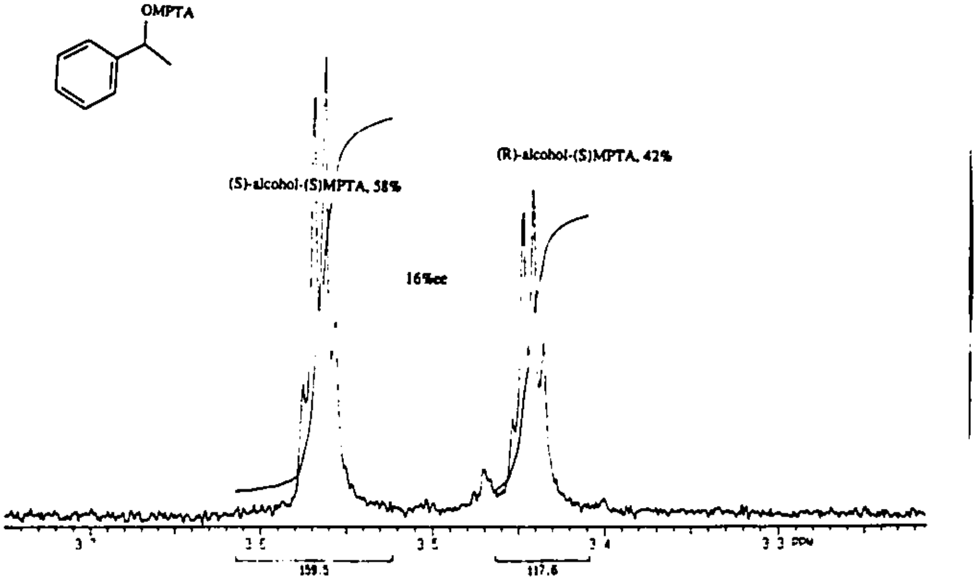


Figure 15. Asymmetric hydrogen transfer reduction of acetophenone with Ru-32, 3-4

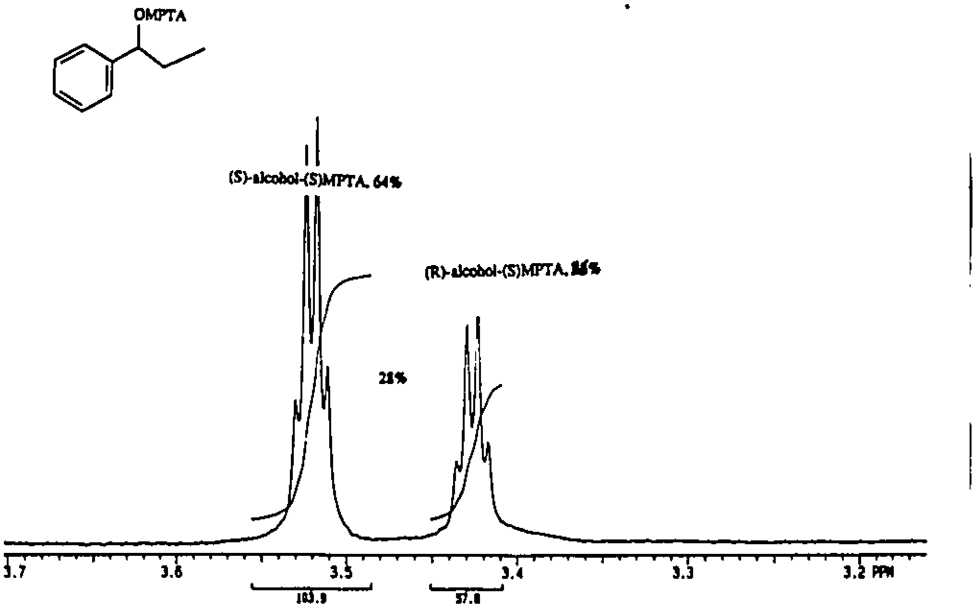


Figure 16. Asymmetric hydrogen transfer reduction of 1-propiophenone with Ru-34, 3-4

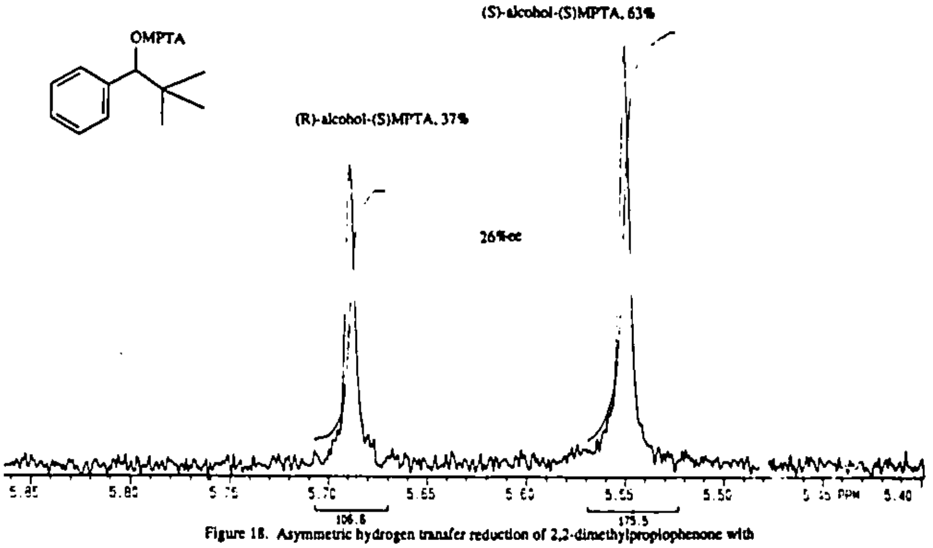


Figure 18. Asymmetric hydrogen transfer reduction of 2,2-dimethylpropiophenone with Ru-34 . 5.4-58 ppm region of $^1$H NMR spectra of MPTA derivative (CH groups

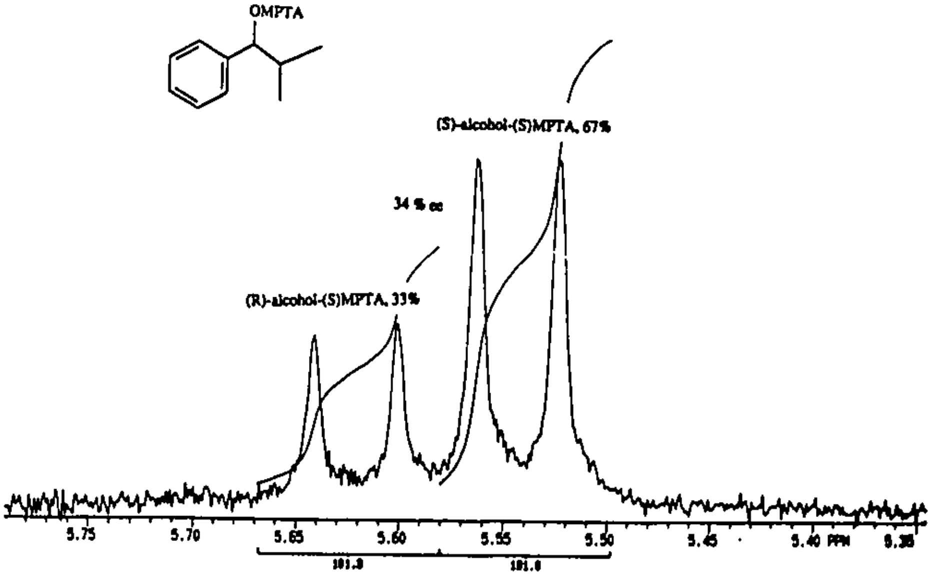


Figure 17. Asymmetric hydrogen transfer reduction of 2-methylpropiophenone with Ru-35. 5.3-5.7 ppm region of $^1$H NMR spectra of MPTA derivative (CH groups

Table 6. Asymmetric hydrogen-transfer reduction of acetophenone catalyzed by $[Ru(C_6H_6)Cl_2]_2$ / L complexes.

| Ligand | Chemical yield[a] | % ee (Configuration)[b] |
|---|---|---|
| **30** | 82 | 8(S) |
| **31** | 91 | 20(S) |
| **32** | 85 | 16(S) |
| **33** | 84 | 22(S) |
| **34** | 81 | 28(S) |
| **35** | 87 | 25(S) |
| **36** | 69 | 23(S) |

[a] isolated yield..

[b] determined by 300MHz $^1$HNMR for α-(methoxy)-α-(trifluoromethyl)phenyacetic acid derivatives.

The catalyst precursor generated from $[Ru(C_6H_6)Cl_2]_2$ and (1R,2R)-bis-1-naphthyliminocyclohexane (**34**) was found to be the most effective for asymmetric hydrogen-transfer reduction of alkyl aryl ketones. The dependence of the enantiomeric excess on the reaction parameters (temperature, amount and type of the base, amount of water in the reaction mixture) was then studied. The hydrogen transfer reduction of acetophenone, when carried out in refluxing isopropanol (83°C), affords 1-phenylethanol in 28 percent enantiomeric excess (Table 7).

Table 7. Temperature dependence of the optical purity of 1-phenylethanol in the hydrogen transfer hydrogenation of acetophenone with isopropanol catalyzed by **Ru-34**

| Temperature (°C) | Reaction time(h) | Conversion(%) | ee%[a] |
|---|---|---|---|
| 83 | 2 | 100 | 28 |
| 73 | 6 | 95 | 25 |
| 63 | 10 | 65 | 29 |

[a] Determined by $^1$H NMR for MPTA derivatives.

At lower temperatures the reaction rate slows down considerably without substantial changes in the optical purity of the product. 1-Phenylethanol of almost the same optical purity (25% and 29% ee) was obtained when the reaction was performed at 73°C and 63°C, respectively.

The presence of water in the reaction mixture gives rise to a sharp decrease in the optical yield. When the hydrogen transfer hydrogenation of acetophenone was carried out under anhydrous conditions, the highest enantioselectivity (1-phenylethanol in 28% enantiomeric excess) was observed. Addition of only 50 µl of water reduces the percent ee by a factor of two (15% ee). When the reaction mixture contains larger amount of water (250 µl) the reaction affords almost racemic product (4% ee) (Table 8).

Table 8. Effect of the amount of water on the optical purity of 1 -phenylethanol in the hydrogen transfer hydrogenation of acetophenone catalysed by Ru-(34)

| amount of water (µl) added | ee(%)[a] |
|---|---|
| 0 | 28 |
| 50 | 15 |
| 250 | 4 |

[a] determined by $^1H$ NMR with MPTA derivative.

A catalytic amount of base is required for the reaction. No reaction takes place in the absence of base (Table 9). In the presence of 0.5 molar eqv. of base per one eqv. of the catalyst (Ru-34), 1-phenylethanol was obtained in 7% optical yield. A two fold excess of the base affords 1-phenylethanol in 28% enantiomeric excess. Further increase in the base/catalyst ratio does not improve the optical yield of the reaction. When $K_2CO_3$ or $K_2CO_3$ together with KOH is used as a base,the enantiomeric excess of the reaction is similar to that obtained with KOH.

Table 9. Effect of the base on the % ee of 1-phenylethanol in the hydrogen transfer hydrogenation of acetophenone catalysed by Ru-(34)

| Base | Amount [base(eqv)/Ru-34(eqv)] | ee(%)[a] |
|---|---|---|
| KOH | 0 | no reaction |
| KOH | 0.5 | 7 |
| KOH | 2 | 28 |
| KOH | 4 | 25 |
| $K_2CO_3$ | 2 | 22 |
| $K_2CO_3$/KOH | 2/2 | 23 |

[a] determined by $^1H$ NMR with MPTA derivative.

It was shown that for many asymmetric hydrogen transfer hydrogenation processes, the metal to ligand ratio has a pronounced influence on the enantioselectivity of the reaction[29]. The dependence of the % ee on the ruthenium-chiral ligand ratio in the hydrogen transfer hydrogenation of acetophenone with isopropanol was studied for the metal-ligand ratios ranging from 1:1 to 1:4 (Table 10). For all the metal-ligand ratios the optical yield of the reaction remains essentially the same ( enantiomeric excesses of 25-29 percent). Interestingly, the chemical yields and reaction rates also remain unchanged with increasing ligand concentration This may be accounted for by the formation of only one ruthenium-Schiff base species with only one imine ligand coordinated to the ruthenium atom during the reaction, with very weak coordination of other ligands.

Table 10. Effect of the metal/ligand ratio on the optical yield of the hydrogen transfer hydrogenation of acetophenone catalyzed by Ru-(**34**)

| $[Ru(C_6H_6)Cl]_2$ / **34** | ee(%)[a] |
|---|---|
| 1 | 28 |
| 1.5 | 29 |
| 2 | 25 |
| 4 | 25 |

[a] Determined by $^1$H-NMR for MPTA derivatives.

The ruthenium-imine complexes which are formed in the reaction mixture before the activation stage can be isolated and characterized . The cationic ruthenium complex of **34** was prepared by stirring $[Ru(C_6H_6)Cl_2]_2$ with 1 eqv. of **34** in methanol at 60° for 1h with subsequent anion exchange using a saturated solution of $NaBF_4$ in water. The $^1$H-NMR spectra shows a singlet corresponding to the six protons at 5.2 ppm ( benzene coordinated to ruthenium ) along with the signals of (1R,2R)-bis-1-naphthyliminocyclohexane (**34**). Some of the signals due to **34** are doubled ( 3.5 ppm, the two protons of cyclohexyl ring connected with nitrogen, and 8.5 ppm, the imine protons), that is typical for chiral $C_2$-symmetrical ligands, coordinated to the metal[46]. It is therefore likely that the Ru-**34** complex has the structure depicted in Figure 19.

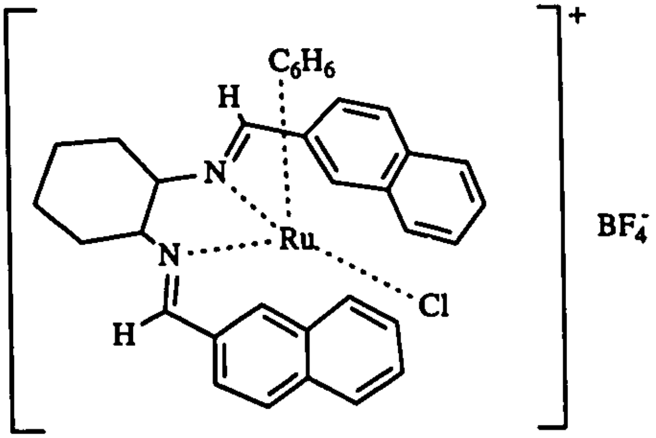


Figure 19.

This cationic complex is then transformed to the catalytically active hydride species. A "hydridic route" (i.e. participation of metal-hydride species) was suggested for the ruthenium catalyzed hydrogen transfer hydrogenation of alcohols with isopropanol by Zassinovich[29]. The formation of a ruthenium-hydride species is likely to occur through the coordination of isopropanol to ruthenium with subsequent deprotonation of the coordinated alcohol by base and β-hydrogen elimination. As the KOH solution in isopropanol has a low concentration of alkoxide ion , an alternative route which entails attack of alkoxide ion on the metal is less likely. The protonation of the ruthenium-hydride intermediate affords a ruthenium-dihydride complex, which acts as a reducing agent for the ketonic substrate.

All subsequent reactions were carried out under anhydrous conditions in refluxing isopropanol using 2 equivalents KOH per 1 equivalent of catalyst.

The hydrogen-transfer reduction of various alkyl aryl ketones using Ru-**34** as the catalyst (Table 11) affords the corresponding alcohols in high chemical yields. The % enantiomeric excess in the reaction are modest ( 16-40% ). While hydrogen transfer reduction of acetophenone and 1-propiophenone gives rise to alcohols with very similar optical purities (28 percent and 29 percent, respectively), 2-methylpropiophenone was reduced with 40% enantiomeric excess, which is the highest enantioselectivity achieved for the alkyl aryl ketones . Surprisingly, the hydrogen transfer reduction of 2,2-dimethylpropiophenone with a bulkier alkyl group affords the alcohol in lower optical purity (26% ee). The reduction of 1-acetonaphthone and α-tetralone gave alcohols in 20% enantiomeric excess.

The application of Ru-**34**, Ru-**35** and Ru-**36** complexes for the hydrogen transfer hydrogenation of acetophenone affords 1-phenylethanol with similar enantiomeric purity ( 28, 25 and 23%, respectively ). To distinguish the stereodifferential ability of these ligands, ruthenium complexes of **34, 35** and **36** were used for the hydrogen transfer reduction of 2-methylpropiophenone (Table 12). As for the reduction of acetophenone, the highest enantioselectivity was realized using

Table 11. Hydrogen transfer reduction of alkyl aryl ketones catalysed by $[Ru(C_6H_6)Cl_2]_2$ -**34**

| Ketone | Chemical yield[a] | % ee (configuration)[b]. |
|---|---|---|
| acetophenone | 89 | 28(S) |
| 1-propiophenone | 85 | 29(S) |
| 2-methylpropiophenone | 85 | 40(S) |
| 2,2-dimethylpropiophenone | 82 | 26(S) |
| 1-acetonaphthone | 74 | 16(S) |
| α-tetralone | 75 | 20(S) |

[a] isolated yield.

[b] determined by 300 MHz $^1H$ NMR for α-methoxy-α-(trifluoromethyl)phenyacetic acid derivatives.

**34** as the chiral ligand.

In conclusion, the application of ruthenium complexes with Schiff bases (**30-36**) for the hydrogen transfer hydrogenation of alkyl aryl ketones afforded enantiomerically enriched alcohols ( 16-40% ee). Although the enantiomeric excesses obtained lower than those achieved using rhodium

Table 12 Hydrogen transfer reduction of 2-methylpropiophenone catalysed by $[Ru(C_6H_6)Cl_2]_2$ -**34**,**35**,**36**

| L | Chemical yield[a] | % ee(configuration)[b] |
|---|---|---|
| **34** | 85 | 40(S) |
| **35** | 84 | 35(S) |
| **36** | 86 | 28(S) |

[a] isolated yield.

[b] determined by 300MHz $^1H$ NMR for α-methoxy-α-(trifluoromethyl)phenylacetic acid derivatives.

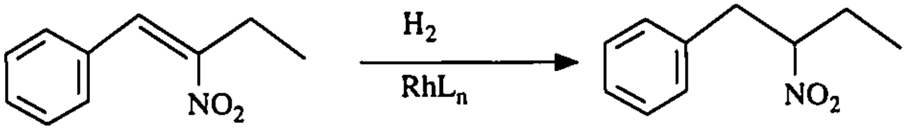
and iridium complexes[29,31, 32], the ruthenium Schiff base complexes are the best among all ruthenium complexes used for this purpose.

### *2.3 Selective Hydrogenation of α-Nitroolefins to Nitroalkanes.*

The selective reduction of the double bond in nitroolefins is a challenging problem. Nitrostyrenes can be successfully hydrogenated to the saturated nitro compounds using $RhCl(PPh_3)_3$[47] or $RhCl_3$/aliquat-336 in a two phase system[48]. The selective hydrogenation of the double bond in substituted nitrostyrenes however, did not receive any attention.

It was of interest to examine the hydrogenation of substituted nitroolefins catalysed by rhodium and iridium complexes.

The nitrostyrenes were synthesized by base catalyzed condensation of aromatic aldehydes with nitroalkanes. Selected spectra of the nitrocompounds are shown on Figures 20-23. 1-Phenyl-2-nitro-1-butene (**37**) was chosen as a model substrate for the reaction (eq. 8).



**37** **38**

(eq. 8)

Drastic conditions (pressures up to 1000 psi, 70-90°, prolonged reaction times) are required to achieve hydrogenation of **37** with rhodium catalysts such as $RhCl(PPh_3)_3$.

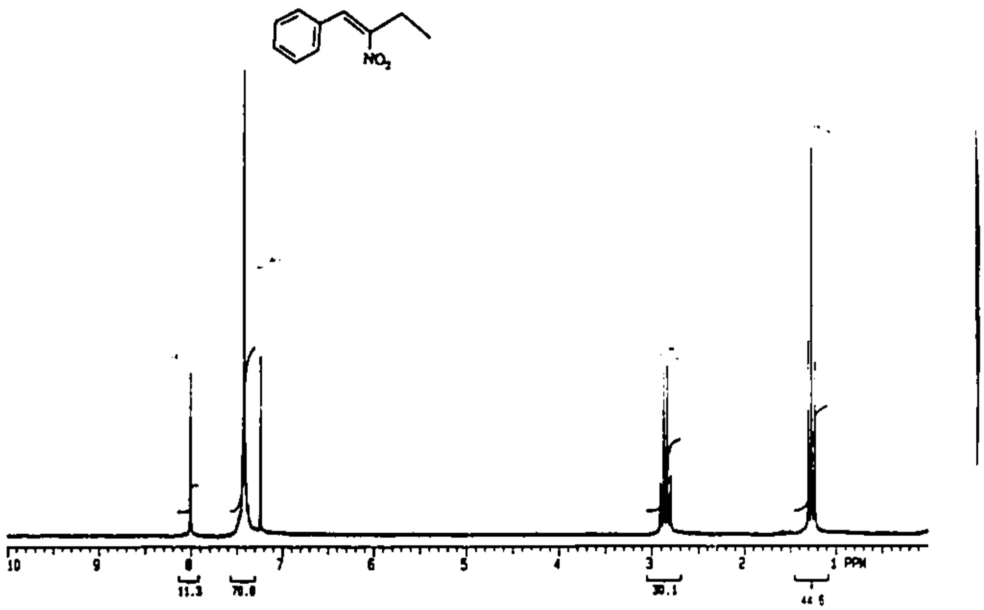


Figure 20. ¹H NMR spectrum of 1-phenyl-2-nitrobutene-1.

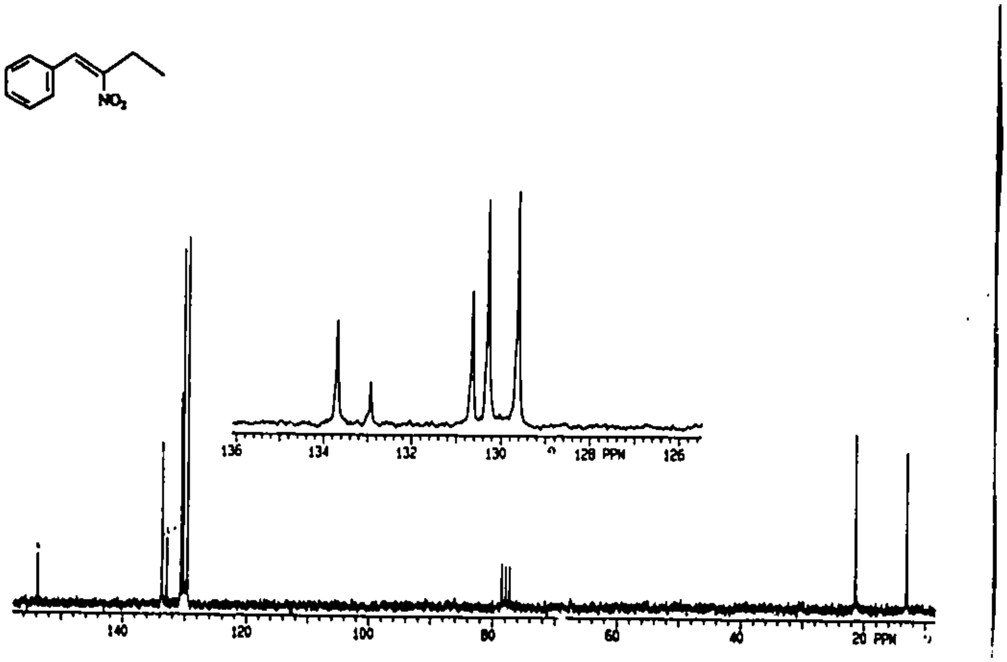


Figure 21. ¹³C NMR spectrum of 1-phenyl-2-nitrobutene-1.

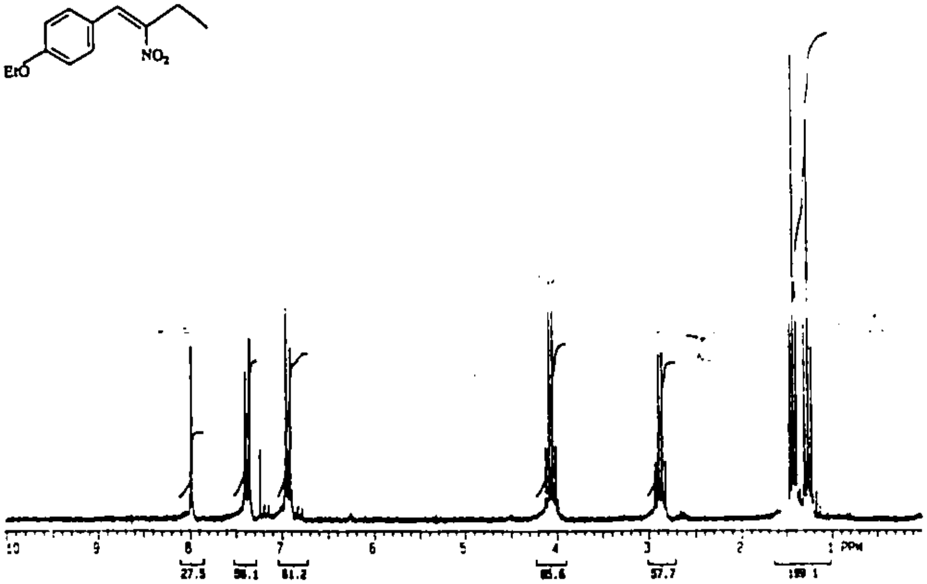


Figure 22. $^1$H NMR spectrum of 1-(4-ethoxyphenyl)- 2-nitrobutene-1.

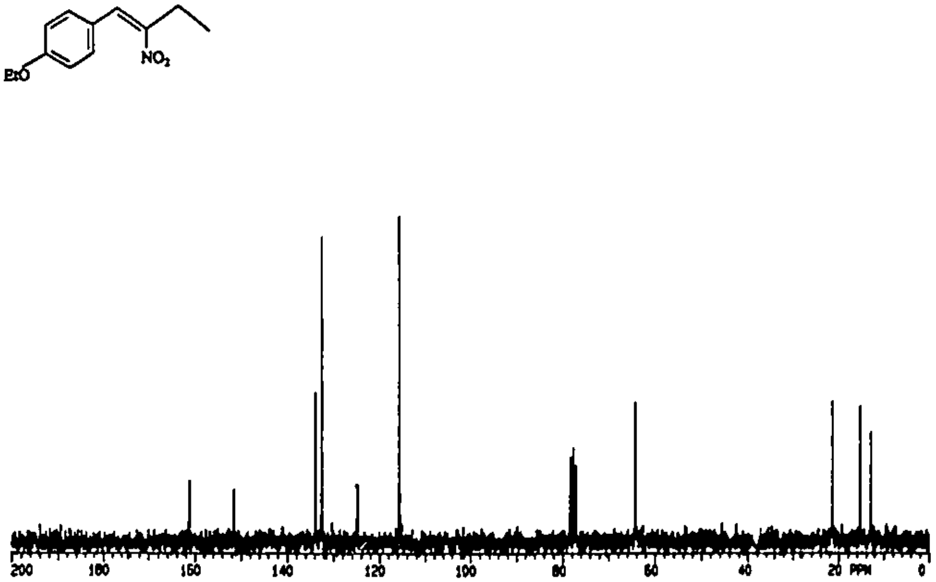


Figure 23. $^{13}$C NMR spectrum of 1-(4-ethoxyphenyl)- 2-nitrobutene-1.

$[Rh(NBD)(phosphine)]BF_4$ or in situ generated catalysts from $[Rh(NBD)Cl]_2$ and a tertiary phosphine. In a number of cases yields are relatively low, since under this conditions the substrate polymerizes (Table 13). Application of in situ Rh-BINAP catalyst for the hydrogenation of 37 affords optically active 1-phenyl-2-nitrobutane ($[\alpha]^{25}_D = 5.3°$). Subsequent attempts to determine the optical purity of the product using chiral shift reagents were unsuccessful. Reduction of nitro group with Pd/C-ammonuim formate afforded racemic product.

Table 13. Hydrogenation of 1-phenyl-2-nitro-1-butene using rhodium catalysts[a].

| Catalyst | Temperature(° C) | Reaction(h) time | Yield [b,c](%) |
|---|---|---|---|
| $RhCl(PPh_3)_3$ | 80 | 78 | -[d] |
| $[Rh(NBD)Cl]_2$/BINAP | 60 | 64 | 75 |
| $[Rh(NBD)Cl]_2$ /dppm | 95 | 48 | 20 |
| $[Rh(NBD)(PPh_3)_2]BF_4$ | 90 | 48 | 22 |
| $[Rh(NBD)Cl]_2$ / $Cy_3P$ | 90 | 14 | 57 |

[a] Reaction conditions 1000 psi of $H_2$, methanol/benzene 5:1., 1 mol % of catalyst.

[b] Isolated yield

[c] 100% conversion, unless specified otherwise

[d] 5% conversion

Similar results were obtained with catalysts derived from $[Ir(COD)Cl]_2$ and phosphines.

Prolonged reaction times and drastic conditions were required to achieve hydrogenation of the nitroolefin double bond. Chemical yields, obtained under these conditions, were low to moderate.

When Crabtree's catalyst[49] ( [Ir(COD)($Cy_3P$)(pyridine)]$PF_6$), which is very effective for the hydrogenation of hindered (tri and tetrasubstituted) olefins, was used for the same reaction, only 2% conversion of the starting material was detected after 10 minutes at room temperature and atmospheric pressure of hydrogen. At that point the reaction stopped and no further conversion of the substrate was detected. It was shown by Crabtree[49], that the catalyst can become inactive owing to its dimerization. To suppress the dimerization, a weak ligand ($I^-$) was added to the reaction mixture, however the conversion of the substrate was still low. In situ generated [Ir$(COD)_2$]$BF_4$/phosphine/LiI (phosphine =$Cy_3P$, dppb, triphenylphosphine ) catalysts did not show any catalytic activity under an atmospheric pressure of hydrogen. The reaction conditions required for the hydrogenation of **37** with these catalysts were again drastic ( 1000 psi of hydrogen, temperature 90-100°, 24-48h) and the yields were modest to good (25-60%). However, if [Ir$(COD)_2$]$BF_4$ and LiI without added phosphine are used in the reaction, **37** can be reduced to 1-phenyl-3-nitrobutane **38** in high yield using milder conditions (Table 14). Nitrobutane **38** was isolated in 70% yield after hydrogenation of **37** catalyzed by [Ir(COD)Cl$]_2$/ LiI at 500 psi and 90° for 0.5 h using only 0.5% of the catalyst.

The catalyst is not stable under the applied conditions and at the end the reaction mixture always contains iridium metal. However, it is reasonable to propose that the iodide ion stabilizes the iridium(I) species in solution during the reaction. When performed under the same conditions, but without the LiI, hydrogenation of **37** affords large amount of 1-phenyl-2-propanone oxime along

Table 14. Hydrogenation of **37**with $[Ir(COD)_2]BF_4$/LiI.

| Pressure of $H_2$(psi) | Reaction time (h) | Yield of **38**(%)[a,b] |
|---|---|---|
| 1000 | 1 | 76 |
| 1000 | 0.5 | 74 |
| 1000 | 0.5 | 60[c,d] |
| 500 | 0.5 | 70[e] |
| 500 | 3.5 | 50[f,j] |

[a] 100% conversion

[b] GC yields, unless otherwise specified

[c] the reaction was carried out in the abcence of LiI

[d] 10% of 1-phenyl-2-propanone oxime

[e] isolated yield

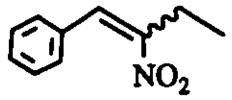
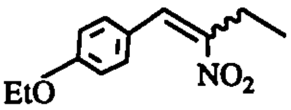
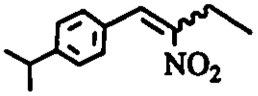
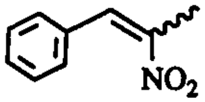
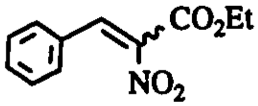
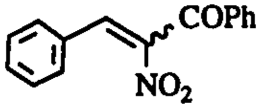
[f] 0.1molar % of catalyst was used

[j] 20% of 1-phenyl-2-propanone oxime

with **38** (Table 14).

These conditions (500 psi of hydrogen, 90°, 0,5h) were applied for the hydrogenenation of a number of nitroolefins (Table 15). When the reaction was completed, solvent was evaporated and the product was isolated using bulb to bulb distillation. In several cases (hydrogenation of 1-phenyl-2-nitropropene-1, 1-(4-ethoxyphenyl)-2-nitrobutene-1, 1-nitro-1-benzoylstyrene) the product was additionally purified chromatographically. Prepared alkyl[56] and functionally[53]

Table 15. Hydrogenation of nitroolefins to nitroalkanes using $[Ir(COD)_2]BF_4$ /LiI[a,b].

| Substrate | Yield of nitroalkane (%)[c]. |
|---|---|
|  | 70 |
|  | 82 |
|  | 72 |
|  | 50[d] |
|  | 74 |
|  | 54 |

---

[a] Reaction conditions: 500 psi of hydrogen, 90°, 0.5 h, in MeOH:$CH_2Cl_2$, 0.5 mol% of catalyst.

[b] 100% conversion.

[c] Isolated yield

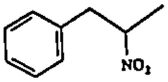
[d] The oxime of 1-phenylpropanone was (25%) isolated as a by-product.

product was additionally purified chromatographically. Prepared alkyl[56] and functionally[53] substituted nitro compounds were identified using $^1H$ NMR. All the compounds synthesised possess a characteristic pattern consisting of a multiplet at 4.8 ppm due to the proton of CH group adjacent to $NO_2$ and two symmetrical multiplets at 2.9-3.5 ppm due to the benzylic $CH_2$ group. Selected spectra of the hydrogenation products are shown in Figures 24, 25.

Good chemical yields of the corresponding nitroalkanes were obtained in all cases. Slightly lower yields of the saturated products obtained from 1-phenyl-2-nitro-1-propene (**39**) and 1-nitro-1-benzoylstyrene (**40**) are due to further hydrogenation of the nitro group of **39** (1-phenylpropanone oxime (25%) was isolated) and hydrogenation of the carbonyl group in **40** . Small amounts of the corresponding oximes were detected ($^1H$ NMR) as by-products in nearly all the hydrogenation reactions.

In conclusion the catalystic system ( $[Ir(COD)_2]BF_4$/LiI) provides an easy access to a large variety of saturated nitro compounds via hydrogenation of substituted nitrostyrenes under relatively mild conditions.

333



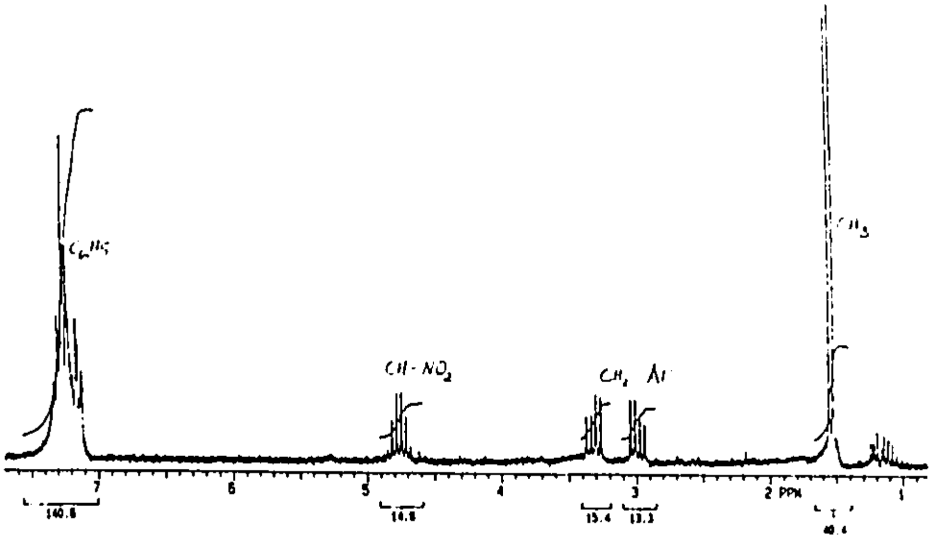
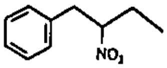


Figure 24. $^1$H NMR spectrum of 1-phenyl-2-nitropropane.



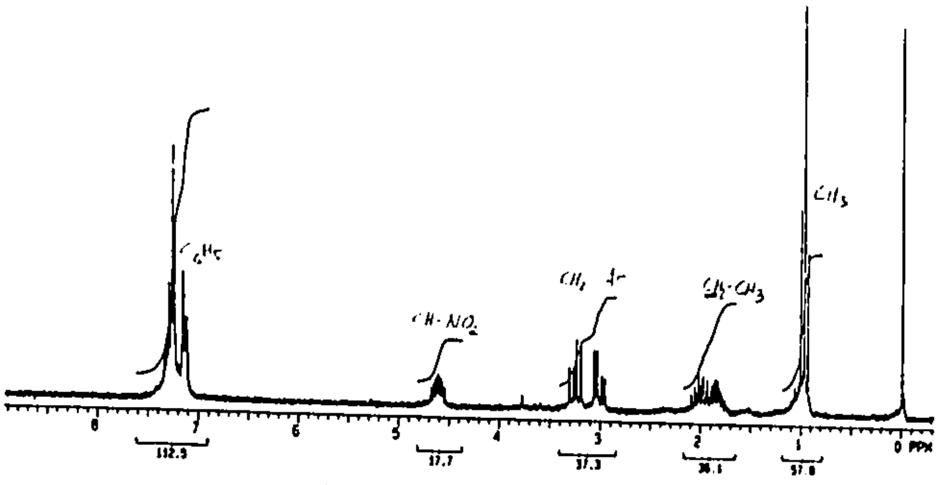


Figure 25. $^1$H NMR spectrum of 1-phenyl-2-nitrobutane.

## *3.EXPERIMENTAL SECTION.*

General. Gas chromatographic analyses were carried out on a Varian 3400 GC equipped with a FID detector and an OV-17 (1.5m×1mm, 1.5% of OV-17 on chromosorb) column. $^1$H NMR spectra were recorded on a Varian XL 300 or a Gemini 200 MHz spectrometer using $CDCl_3$ as a solvent. Melting point determinations were made using a Fisher-Johns apparatus and uncorrected values are reported. Elemental analyses were carried out by MHW Laboratories, Phoenix, AZ. GC determination of chemical yield in the reaction of 1-phenyl-2-nitro-butene-1 was carried out using 1.3.5-tert-butylbenzene as an internal standard. $[Ru(benzene)Cl_2]_2$, (1R,2R)-(-)1,2-diaminocyclohexane, alkyl aryl ketones and aromatic aldehydes were purchased from Aldrich Chemical Co. (R)-BINAP was purchased from (Strem Chemicals, Inc.). All the chemicals were used as received. The oximes were synthesized from the corresponding ketones and hydroxylamine liberated from hydroxylammonium chloride[50]. 2,5-Bis-*tert*-butylbenzaldehyde was prepared by formylation of 1,4-bis-*tert*-butylbenzene[51]. Alkyl[52] and functionally[53] substituted nitrostyrenes were synthesized according to the methods, published in literature. The hydrogen-transfer reduction experiments were carried out under nitrogen.

The optical purities of alcohols and amines were determined by 300 MHz $^1$H-NMR for α-methoxy-α-(trifluoromethyl)phenylacetic acid derivatives[43].

Preparation of oximes[50]. Ketone (0.03 mol) and hydroxylamine hydrochloride (2.76 g, 0.04 mol) were dissolved in EtOH (100 ml). Sodium hydroxide (8 ml of 5M sodium hydroxide solution in water, 0.04 mol) was added. The reaction mixture was stirred for 10h at room temperature. Then solvent was evaporated, and water (100 ml) was added. The reaction mixture was then extracted with dicloromethane (3×25 ml), solvent was evaporated, and the residue was distilled in vacuo. The following oximes were synthesized using this method: **24a**, m.p. 81-82°C (lit.[55] m.p. 81-83°C); **24b**, m.p. 52° (lit.[55] m.p. 53-54°C); **24c** m.p. 91°C [lit.[55] m.p. 90°C (Z-form)]; **24d** m.p. 68-69°C (lit[55]. m.p. 68-70°C); **24e** m.p. 117°C (lit.[55] m.p. 118°C); **24f** m.p. 114-115°C (lit.[55] m.p. 112-113°C).

Preparation of alkyl substituted Nitrostyrens[52]. Aromatic aldehyde (0.05 mmol), nitrocompound [ nitroethane for the 1-phenyl-2-nitro-1-propene, 1-nitropropane for 1-phenyl-2-nitrobutene-1, 1-(4-ethoxyphenyl)-2-nitro-1-butene, 1-(4-isopropylphenyl)-2-nitro-1-butene)] (0.05 mmol) and n-bytulamine were dissolved in ethanol (100 ml). The reaction mixture was refluxed overnight. Then the solvent was evaporated and the product was distilled in vacuo. This method was used for the preparation of 1-phenyl-2-nitro-1-pronene (m.p. 65-66$^0$, lit[52] m.p. 64°), 1-phenyl-2-nitro-1-butene (b.p. 124-126$^0$ (9mm), lit[52] b.p. 121$^0$ (6mm)), 1-(4-ethoxyphenyl)-2-nitro-1-butene (m.p. 73°C, lit[52] m.p. 74°C), 1-(4-isopropylphenyl)-2-nitro-1-butene (b.p. 145° (8mm), lit[52] b.p. 147-150$^0$ (6 mm)). Liquid products were additionally characterized by $^1H$ and $^{13}C$ NMR spectra: 1-phenyl-2-nitro-1-butene: $^1H$ NMR 1.23t(3H, $CH_3$), 2.84q (2H, $CH_2$), 7.43m (5H, $C_6H_5$), 8.0s, (1H, CH); $^{13}C$ NMR 13.1, 21.6, 129.6, 130.1, 130.7, 132.9, 133.7, 154.0; 1-(4-ethoxyphenyl)-2-nitro-1-butene: $^1H$ NMR 1.27t (3H, $CH_3$), 1.48t (3H, $CH_3$), 2.83q (3H, $CH_3$), 3.94q, (3H, $CH_3$), 6.98m (2H, $C_6H_4$), 7.4m (2H, $C_6H_4$), 8.0s (1H, CH); $^{13}C$ NMR 12.9, 15.3, 21.4, 64.3, 115.6, 124.9, 132.4, 133.9, 151.6, 161.3 1-(4-isopropylphenyl)-2-nitrobutene-1: 1.2d (6H, $CH_3$), 1.25t(3H, $CH_3$), 2.84q (2H, $CH_2$), 2.95m (1H, CH), 7.44q (4H, $C_6H_4$), 8.0s (1H, CH); $^{13}C$ NMR 13.5, 14.2, 21.6, 54.2, 130.4, 130.6, 134.9, 140.4, 141.2, 161,7.

Preparation of functionally substituted nitrostyrens[53]. N-benzylideneaniline (1g, 0.012 mol) was heated with corresponding nitrocompound (0.012 mol) and acetic anhydride (5 ml) at 40°C for 4h. Then the reaction mixture was diluted with hot (80°) water and stirred for 10 min. After that the reaction mixture was cooled down and extracted with $CCl_4$. Tetrachloromethane solution was washed with water, and dried with magnesium sulfate. The solvent was evaporated and the residue was distilled in vacuo (for the preparation of 1-nitro-1-carbethoxystyrene, fraction with b.p. 130-140°C (5 mm) was collected, m.p. 55-56°C (lit.[53] m.p. 57-58°C )), of purified chromatographically (for the preparation of 1-nitro-1-benzoylstyrene, $SiO_2$, 30×2 column, $CH_2Cl_2$:hexane, 3:1, m.p. 124-125$^0$C, lit[53] m.p. 125°C).

### *3.1 Asymmetric hydrogenation of oximes.*

Typical hydrogenation procedure. A suspension of $[Ru(benzene)Cl_2]_2$ (5 mg, 0.01 mmol) and

BINAP (12 mg, 0.0204 mmol) in 2 ml MeOH-$C_6H_6$-$H_2O$ (5:1:0.018)[54] was degassed by three freeze-pump-thaw cycles and then stirred for 40 min at 60-65°C under nitrogen. A solution of oxime (2 mmol) in 7 ml of degassed methanol[54] was added and the reaction mixture was transferred by syringe to a stainless steel autoclave, containing 1g of 3A° molecular sieves under a blanket of nitrogen. The autoclave was sealed, flushed three times with hydrogen by pressurizing to the specified reaction pressure and venting the gas back to just above atmospheric pressure, and finally charged with hydrogen to the specified pressure. The hydrogenation was performed under conditions specified in Tables 1-5. Conversions (Table 1) were determined by GLC using tetradecane as internal standard. The hydrogenation products (mixtures of **25** and **26** ) were isolated from the catalyst by distillation (Tables 2-5). Identification of products and determination of alcohol/amine ratios was based on the $^1$H NMR spectra. $^1$H NMR data are given in the Table 16. The optical yields were measured by 300 MHz $^1$H NMR for α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) derivatives[40] of mixtures of **25** and **26**.

### *3.2 Asymmetric hydrogen transfer reduction of ketones.*

<u>Synthesis of Schiff base ligands</u>: A mixture of (1R,2R)-(-)1,2-diaminocyclohexane (100 mg,

Table 16. $^1$H NMR spectra of the products of hydrogenation **24a-f**.

| Starting material | $^1$HNMR spectra of producrts (δ, ppm)[a] |
|---|---|
| **24a** | 1.35d (**25a** $CH_3$), 1.45d (**26a** $CH_3$), 1.76s (OH, $NH_2$), 4.1q (**25a** CH), 4.85q (**26a**, CH), 7.15-7.3 (ArH) |
| **24b**[b] | 0.84t ($CH_3$ ), 1.7m ($CH_2$), 1.45s ($NH_2$), 3.78t (CH), 7.1-7.4m(ArH) |
| **24c**[b] | 0.72d($CH_3$), 0.94d ($CH_3$) , 1.51 ($NH_2$), 1.81 m(CH), 3.55d (CH) |
| **24d** | 1.1d (**25d**, $CH_3$) , 1.22d(**26d**, $CH_3$), 1.45s (OH, $NH_2$), 2.4-2.8m ($CH_2$) 3.13m (**25d**, CH), 4.0m (**26d**, CH), 7.0-7.3 (Ar-H) |
| **24e** | 1.45d (**25e**, $CH_3$), 1.54d (**26e**, $CH_3$), 1.76s (OH, $NH_2$), 4.25q (**25e**, CH) 5.05q(**26e**, CH), 7.35-7.56m (ArH), 7.7-7.9m (ArH). |
| **24f** | 1.43d (**25f**, $CH_3$), 1.57d (**26f**, $CH_3$), 1.8s ( $NH_2$ ,OH), 4.32q(**25f**, CH), 5.1q (**26f**, CH), 6.8-6.95m(ArH), 7.0-7.21m(ArH), 7.54-7.7m(ArH) |

[a] $CDCl_3$ as a solvent.

[b] only amines **25b** and **25c** were detected.

0.88 mmol) and aromatic aldehyde ( 1.96 mmol) in $CH_2Cl_2$(2 ml) was stirred in the presence of 3A° molecular sieves for 12h. The molecular sieves were removed by filtration and the filtrate was concentrated by rotary evaporation. The residue was crystallized from hexane (**31**, **33**),hexane:benzene (**30**, **33**), or hexane: $CH_2Cl_2$ (**30**, **34**). The following compounds were prepared by this procedure:

(1R,2R)-Bis-diphenylaminocyclohexane (**30**), 91% yield, white solid, m.p. 99-100°; $^1H$ NMR 1.4-1.6 (m, 2H), 1.7-2.0 (m, 6H), 3.3-3.5 (m, 2H), 7.2-7.4 (m, 6H), 7.5-7.65 (m,4H), 8.2 (s,2H); $[\alpha]_D^{25}$-263°(c 0.19, methanol), Found: C 83.04, H 7.72, $C_{20}H_{22}N_2$ requires C 82.72, H 7.64.

(1R,2R)-Bis-2-methoxyphenyliminocyclohexane(**31**),89% yield, white solid, m.p.105-106°;$^1H$ NMR 1.4-1.6(m,2H), 1.7-2.0 (m,6H), , 3.3-3.5 (m,2H), 3.7(s, 6H), 6.7-6.9(m,4H), 7.15-7.35 (m,2H), 7.7-7.8 (m,2H), 8.1(s,2H); $[\alpha]_D^{25}$-69.2°(c 0.5, methanol), Found: C 75.79, H 7.75, $C_{22}H_{26}O_2N_2$ requires C 75.40, H 7.46.

(1R,2R)-Bis-1-naphthyliminocyclohexane (**34**), 87% yield, white solid, m.p. 131-132°, $^1H$ NMR: 1.45-1.76(m,4H), 1.8-2.5(m, 4H), 3.5-3.75 (m,2H), 7,1-7.25(m,2H), 7.1-7.25(m,4H), 7.6-7.8(m,6H), 8.55 (d,2H), 8.90(s,2H), $[\alpha]_D^{25}$-202°(c 0.25,$CH_2Cl_2$); Found C 86.27, H 6.71, $C_{28}H_{26}N_2$ requires C 86.61, H 6.71.

(1R,2R)-Bis-2,5-di-tert-butylphenyliminocyclohexane(33), 92% yield, white solid, m.p. 189-190°, $^1$H NMR 0.95 (s,18H), 1.3(s,18H), 1.45-1.6 (m,2H), 1.6-1.75 (m,2H), 1.75-2.0(m,4H), 3.4-3.6 (m,2H), 7.15 (s,4H), 7.35(s, 2H), 9.05(s,1H), $[\alpha]_D^{25}$-254° (c 0.3, methanol): Found: C 84.31, H 10.25, $C_{36}H_{54}N_2$ requires C 83.99, H 10.25.

(1R,2R)-Bis-9-anthranyliminocyclohexane(35), 85% yield, yellow crystalline solid, m.p. 239-241°, $^1$H NMR: 1.6-1.8(m,2H), 2.0-2.15(m,2H), 2.15-2.3(m,4H), 3.9-4.0(m,2H), 6.7-6.9(m,4H), 7.1-7.3(m,4H), 7.85 (d 5Hz,4H), 8.15(d, 4H), 8.4(s,2H), 9.35 (s,2H), $[\alpha]_D^{25}$+283°(c 0.3, $CH_2Cl_2$); Found C 88.13, H 5.80, $C_{36}H_{30}N_2$ requires C 88.13, H 6.16.

(1R,2R)-Bis-ferrocenyliminocyclohexane(36), 89% yield, red crystalline solid, m.p. 193-195°, 1.3-1.5(m,2H), 1.5-1.75 (m,4H), 1.8-1.9(m,2H), 3.95(s,10H), 4.2(s,4H), 4.5 (s,2H), 4.6(s,2H), 8.1(s,2H), $[\alpha]_D^{25}$-114°, (c 0.32, $CH_2Cl_2$), Found C 65.90, H 6.21, $C_{28}H_{30}N_2Fe$ requires C 66.43, H 5.97.

Ligand **32** was prepared in situ as a ruthenium complex starting from (1R,2R)-diaminocyclohexane and bis-(2-formylphenyloxy)propane. A mixture of $[Ru(C_6H_6)Cl_2]_2$ ( 10 mg , 0.020 mmol) , (1R,2R)-1,2-diaminocyclohexane (4.6 mg, 0.04 mmol) and bis-(2-formylphenyloxy)propane (11.5 mg, 0.04 mmol) in EtOH (2 ml) was stirred under nitrogen at 60° for 0.5 h. The solvent was then evaporated under reduced pressure and the newly synthesized ruthenium complex was used for the hydrogen-transfer reduction.

Hydrogen-transfer reduction.

a. Typical procedure: A suspension of $[Ru(C_6H_6)Cl_2]_2$ (5mg, 0.01 mmol) and the Schiff base ligand (0.02 mmol) in i-PrOH (2 ml) was degassed and then heated under reflux for 0.5 h. To the reaction mixture (through a rubber septum) was added 0.04 mmol of KOH (0.02M solution in i-PrOH, 2ml) and reaction mixture was refluxed for an additional 0.5h. The ketone (2 mmol) was then added, and when reaction was complete (2-8h, monitored by GC ), the solvent was evaporated and the residue was then subjected to bulb to bulb distillation. The reduction products were identified by their $^1H$ NMR spectra.

b. Optimization of reaction parameters:

*i. Reaction in the presence of water:* the reaction was carried out as in *a*, and water (Table 8) was added to the reaction mixture prior to activation stage.

*ii. Base:* The amount of base used in the reaction is indicated in Table 9. When potassium hydroxide was used as a base, it was introduced to the reaction mixture with $[Ru(C_6H_6)Cl_2]_2$ and the Schiff base ligand.

### *3.3 Selective hydrogenation of nitroolefins.*

$[Ir(COD)_2]BF_4$ (5 mg, 0.01 mmol) and LiI (8 mg, 0.06 mmol) were dissolved in 1ml of MeOH:$CH_2Cl_2$ (1:1). A solution of the nitroolefin (2 mmol) in MeOH (5 ml) was added, and resulting solution was transferred into an autoclave. The autoclave was flushed three times with hydrogen and then pressurized to 500 psi. After reaction for 0.5h at 90°, the solvent was evaporated and the product was isolated from the catalyst by bulb to bulb distillation. If the isolated nitro compound had an admixture of oxime, it was further purified by chromatography ($SiO_2$,20×2 column, 1:1 $CH_2Cl_2$/hexane as eluant). The nitrocompounds were identified by their $^1H$ NMR spectra[53,56]. $^1H$ NMR spectral data of the products are given as follows. 1-Phenyl-2-nitropropane: 1.54d,3H ($CH_3$), 2.91-3.05m, 1H($CH_2$), 3.28-3.39m, 1H($CH_2$), 4.75,1H (CH), 7.05-7.4m, 5H (ArH); 1-phenyl-2-nitrobutane: 0.96t,3H($CH_3$), 1.75-2.1m, 2H,($\underline{CH_2}CH_3$), 2.96-2.05m,1H ($CH_2$-Ar), 3.15-3.37m, 1H ($CH_2$-Ar), 4.53-4.7,1H (CH), 7.05 7.4m, 5H, (ArH); 1-(4-isopropylphenyl)-2-nitrobutane: 0.9t, 3H,($CH_3$), 1.2, 6H ($CH_3$), 1.7-2.15m, 2H,($\underline{CH_2}$-$CH_3$), 2.78-2.9m, 1H (CH-$CH_3$), 2.9-3.0m, 1H, ($CH_2$), 3.15-3.29m, 1H, ($CH_2$), 4.5-4.68m, 1H,(CH-$NO_2$), 7.0-7.2m, 4H,(ArH); 1-(4-ethoxyphenyl)-2-nitrobutane: 0.96t, 3H, ($CH_3$), 1.34t, 3H,($CH_3$), 1.7-2.15 ($CH_2$), 2.89-3.0m, 1H, ($CH_2$), 3.18-3.23m, 1H, ($CH_2$), 3.95q, 2H, ($CH_2$), 4.47-4.6,1H,(CH), 6.7-6.85, 6.94-7.1, 4H, (ArH), 1-phenyl-2-nitro-2-carbethoxyethane: 1.42t, 3H,($CH_3$), 2.83-2.96m, 1H, ($CH_2$), 3.1-3.23m, 1H, ($CH_2$), 4.05,2H,($CH_2$), 4.94-5.01, 1H (CH), 7.08-7.34m, 5H, (ArH); 1-phenyl-2-nitro-2-benzoylethane: 2.75-2.88m, 1H, ($CH_2$), 3.09-3.37m, 1H,($CH_2$), 4.83-5.02, 1H

## *4. REFERENCES.*

1. Horner L.; Siegel, H.; Buthe B. *Angew. Chem. Int. Ed.Engl.*, **1968**, *7*, 1968.

2. Dang, T.P.; Kagan, H.B. *J. Chem. Soc., Chem. Commun.* **1971**, 481.

3. Noyori, R.; Ohkuma,T.; Kutamura, M., Takaya, H; Sayo, N.; Kimobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856.

4. Kitamura, M.; Ohkuma, T.; Inoue, S.; Sayo, N.; Kimobayashi, H.; Akutagawa, S.; Ohta, T.; Noyori, R. *J.Am.Chem.Soc.*, **1988**, *110*, 629. .

5. Noyori, R. *Chem. Soc. Rev.* **1989**, *18*, 187.

6. Noyori, R. in *"Modern Synthetic Methods"*, **1989**, *15*, 115; Scheffold, R., Ed; Springer-Verland; Berlin, Heidelberg, New-York, Tokyo.

7. Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345.

8. Nishi, H.; Kitamura, T.; Ohkuma, T.; Noyori, R. *Tetrahedron Lett.* **1990**, *29*, 6327.

9. Kitamura, M.; Ohkuma, T.; Tokinaga, M.; Noyori, R. *Tetrahedron:Asymmetry* **1990**, *1*, 13.

10. Noyori, R.; Ikeda, T.; Ohkuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Akutagawa S. *J. Am. Chem. Soc.* **1989**, *111*, 9134.

11. Mashima, Y.; Matsumura, Y.; Rusano, K.; Kumobayshi, H.; Sayo, H.; Noyori, R. *J. Chem. Soc., Chem. Commun.* **1991**, 609.

12. Ohkuma, T.; Kitamura, M.; Noyori, R. *Tetrahedron Lett.* **1989**, *31*, 5509.

13. Ikariya, T.; Ishii, Y.; Kawano, Y.; Arai, T.; Saburi, T.; Akutagava, S. *J. Chem. Soc., Chem. Commun.* **1985**, 922.

14. Taber, D.F.; Siveberg, L.J. *Tetrahedron Lett.* **1991**, *32*, 4227.

15. Sesarotti, S.; Mari, A.; Havicini, M.P.; Villa, L. *Tetrahedron Lett.* **1991**, *32*, 4381.

16. Heil, B.; Marko, L.; Toros, S. in *"Homogenous Catalysis with Metal Phosphine Complexes";* Pignolet, L.D., Ed; Plenum Press, New York, London, 1983.

17. *Asymmetric Synthesis;* Morrison, J.D., Ed.; Vol. 5, Chiral Catalysis; Academic Press: Orlando, FL, 1985.

18. Bacos, J.; Toth, I.; Heil, B.; Szalontai, G.; Parcanyi, L.; Fulop, Y. *J. Organomet. Chem.* **1989**, *370*, 263.

19. Kang, G.; Cullen, W.R.; Fryzuk, M.; James. B.R. *J. Chem. Soc., Chem. Commun.* **1988**, 1466.

20. Kang, G.; Cullen, W.R.; Fryzuk, M.; James. B.R. *Inorg. Chem.* **1991**, *30*, 5002.

21. Spindler, F.; Bugin, B.; Blaser. H. *Angew. Chem. Int. Ed. Ingl.* **1990**, *29*, 558.

22. Chan, Y.N.; Osborn J.A. *J.Am. Chem. Soc.* **1990**, 112,9400.

23. Bark, M.J.; Feaster J.F.; *J. Am. Chem. Soc.* **1992**, *114*, 6266.

24. Willoughby, C.A.; Buchwald, S.L. *J. Am. Chem. Soc.* **1992**, *114*, 7562.

25. Botteghi, C.; Bianchi, M.; Benedetti, E.; Matteoli, U. *Chimia* **1975**, *29*, 256-258.

26. Sasson,O.; Blum. J. *J. Org Chem.* **1975**, *40*, 1887.

27. Gladiali, S.; Chelussi, G.; Delogu, G. *J.Organomet. Chem.* **1989**, *370*, 285.

28. Weber, B.; Pfaltz. A. *Helv. Chim. Acta*, **1991**, *74*, 232.

29. Zassinovich, G.; Betella, R.; Mestroni, G. *J. Organomet. Chem.* **1989**, *370*, 187.

30. Kaschig, J. European Patent 0,251,994, A1, 1988.

31. Bianchi, M.; Mattenoli, U.; Mechi, G.; Frediani,P.; Pratesi, S.; Piacenti, F.; Botteghi, G. *J.*

*Organomet. Chem.* **1980**, *198*, 73.

32. Mandal, S.K.; Chakravarty, A.R.; *Polyhedron* **1992**, *11*, 147.

33. Noyori, R.; Tomino, I.; and Nishizava, M. *J. Am. Chem. Soc.* **1979**, *101*, 5843.

34. Yamaguchi, S.; and Kabuto, K. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 3033.

35. Suda, H.; Motor, M.; Fujii, M.; Kanok, S. *Tetrahedron. Lett.* **1979**, 4565.

36. Asami, M.; Mikaiyama, T. *Heterocycles*, **1979**, *12*, 499.

37. Corey, E.J.; Bakshi, R.K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*,, 5551.

38. Corey, E.J.; Bakshi, R.K.; Singh, V.K. *J.Am. Chem. Soc.* **1987**, *109*, 7925.

39. Corey, E.J., Link, J.O. *J. Am. Chem. Soc.*, **1992**, *114*, 1906.

40. Sih, J.; Chen, G.-S. *Angew. Chem. Int. Ed. Ingl.* **1984**, *23*, 570.

41. Raddata, P.; Radung, H.-E. *Angew. Chem. Int. Ed. Ingl.*, **1988**, *27*, 426.

42. Hirschbein, B.L.; Whitides, G.M. *J.Am. Chem. Soc.* **1982**, *104*, 4458.

43. Dale, J.A.; Dull, D.L.; Mosher, H.S. *J. Org. Chem.* **1969**, *34*, 2543-2549.

44. Strathdee, G.; Given,R. *Can. J. Chem.* **1974**, *52*, 2216.

45 (a) Murahashi, S.-I.; Yoshimura, N.; Tsumiyama,T.; Kojima, T. *J. Am. Chem. Soc.* **1983**, *105*, 5002-5011. (b) Jung, C.W.; Fellman, J.D.; Garrou, P.E. *Organometallics* **1983**, *2*, 1042-1045.

46. Mandal, S.K.; Chakravarty, A.R. *Polyhedron*, **1992**, *11*, 147.

47. Harmon, R.E.; Parsons, J.L.; Cooke, D.W.; Gupta,.K. *J. Org. Chem.*, **1969**, *34*, 3684.

48. Amer,I., Blum, J., *Tetrahedron Lett.*,**1987**, *28*, 1321.

49. Crabtree R., *Acc. Chem. Res.* **1979**, *12*,331

50. Sandler S.R., Karo W., in *"Organic Functional Group Preparations,"* Second edition. Academic Press, 1983.

51. *Organic Synth,* **1960-1969**, *5*, 49; Baumgarten, H., Ed.; John Willey and Sons: New-York, London, Sidney, Toronto.

52. Hass, H.B.; Susie, A.G.; Heider, R.L. *J.Org.Chem.*, **1950**, *15*, 8.

53. Latov, E.P.; Belikov, V.M. *Zh. Org. Chim.* **1973**, 1770.

54. Solvent ratios (Tables 1-5) were obtained by recalculation to the total volume of solution after addition of methanol.

55. *Dictionary of Organic Compounds*, J.Buckingham, Ed.; Fifth edition, Chapman and Hall, 1982.

56. Chikashita,H., Nishida,S., Niyazaki,M., Morita,Y., Itoh,K., *Bull. Chem. Soc. Jpn.* **1987**, *60*, 737-46.