UNIVERSITY OF DICLE

INSTITUTE OF NATURAL AND APPLIED SCIENCES

DEPARTMENT OF CHEMISTRY

SYNTHESIS OF IMINE GROUP CONTAINING CHIRAL BIS(PHOSPHINITE) LIGANDS AND Ru(II) COMPLEXES: INVESTIGATION OF THEIR CATALYTIC ACTIVITY IN THE ASYMMETRIC TRANSFER HYDROGENATION OF KETONES

Najmuldain Abdullah SALEH

M.Sc. Thesis

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CONTENTS

ABSTRACT

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Transfer hydrogenation processes are attracting considerable attention in synthetic chemistry due to their operational simplicity. Asymmetric transfer hydrogenation of simple ketones by using chiral catalysts is one of the most significant ways to obtain chiral alcohols in organic synthesis. The most popular ligands employed in asymmetric catalysis are phosphorus containing ones. The common feature of the ligands used for this purpose is to have a C_2 symmetry axis. Although there have been many reports on these type ligands and their transition metal complexes, to the best of our knowledge, there are few studies on imine containing bis(phosphinites) and their catalytic activity in asymmetric transfer hydrogenation.

In the present study, firstly, 1-({[(1R,2R)-2-{[(2-hydroxynaphthalen-1-yl)methylidene] amino}cyclohexyl]imino}methyl)naphthalen-2-ol was prepared as precursors for phosphinites according to a literature procedure. Then, new chiral C_2-symmetric bis(phosphinite) ligands were synthesized the corresponding 1-({[(1R,2R)-2-{[(2-hydroxynaphthalen-1-yl)methylidene]amino}cyclohexyl] imino} methyl)naphthalen-2-ol and two equivalents of $(Cy)_2PCl$, PPh_2Cl or $P(i-Pr)_2Cl$ in high yields. Ru(II) metal complexes of the chiral phosphinite ligands were synthesized by treating of $[Ru(\eta^6-p\text{-cymene})(\mu\text{-Cl})Cl]_2$ with the phosphinites in 1:1 molar ratio in CH_2Cl_2 and their catalytic activity in asymmetric transfer hydrogenation were investigated in the reaction of acetophenone derivatives with isopropyl alcohol.

Keywords: Asymmetric transfer hydrogenation, Phosphinite, Catalysis, Ruthenium, Chirality

IV

TABLE LIST

FIGURE LIST

SCHEME LIST

APPENDICES LIST

^{31}P NMR SPECTRA

SYMBOLS AND ABBREVIATIONS

Ar	Aryl
ATH	Asymmetric Transfer Hydrogenation
$CDCl_3$	Chloroform-d_1
CH_2Cl_2	Dichlorometane
Cod	1,5-cyclooctadiene
Cy_2PCl	Monochlorodicyclohexylphosphine
min	Minute
DEPT	Distortionless Enhancement by Polarization Transfer
DMF	N,N'-Dimetylformamide
DMSO-d_6	Dimethyl sulfoxide-d_6
Con.	Conversion
ee	Enantiomeric excess
Et_3N	Triethylamine
GC	Gas Chromatography
HETCOR	Heteronuclear correlation (^{13}C-^1H)
IR	Infrared
J	Coupling constant
NMR	Nuclear Magnetic Resonance
Ph_2PCl	Monochlorodiphenylphosphine
^iP_2PCl	Monochlorodiisopropylphosphine
ppm	Part Per Million
R	Alkyl
TH	Transfer Hidrojenasyon
THF	Tetrahydrofuran
h	Hour
υ	Frequency (cm^{-1})
δ	Chemical shift

1.INTRODUCTION

Asymmetric transfer hydrogenation is a remarkable method to obtain optically active alcohols and it is one of the most important developments in catalytic asymmetric synthesis. Chiral alcohols are very important synthetic intermediates and building blocks in many fields such as pharmaceutical industry and organic synthesis. Catalytic reduction has a preference to stoichiometric reduction for large-scale industrial processes including ketone hydrogenations (Dong et al. 2005).

Transfer hydrogenation of ketones is a highly effective tool for the synthesis of chiral alcohols, because its fractional yields of side products are lower and product yields and enantiomeric excess are higher. On the other hand, its reaction conditions are milder and lower cost owing to its operational simplicity. Therefore, development of new chiral catalysts tailored to the transfer hydrogenation of prochiral ketones has been widely studied. Recently, this field has been advanced fast, mainly due to Noyori's work In ruthenium(II)-catalyzed transfer hydrogenation of simple amino alcohols, one of the highest catalytic activities so far was attained. However, diamines and chiral phosphorus and nitrogen ligands led to lower yields (Petra et al. 1999).

Ligands containing phosphorus atoms have been attracting great interest throughout inorganic and organic chemistry. These ligands have been investigated for the last several decades and are of great attention because they have a variety of uses in organometallic chemistry for the improvement of industrial transformations including a numerous catalytic reactions (Zuburi and Woollins, 2003).

Phosphines and phosphinites are important phosphorous-containing ligands in organometallic chemistry because of their electronic and steric features. These ligands have extensive applications in asymmetric transformation performed by transition metal catalysis. Phosphinites have also been stuied extensively, because they have different structural, electronic and chemical features than phosphines. Therefore, they provide copious opportunities to design novel ligands for asymmetric catalysis (Galka et al. 2003). From a practical perspective, developing very efficient chiral phosphinite ligands for asymmetric catalysis is of significant concern (Chan et al. 1997).

Asymmetric hydrogenation is one of the most valuable reactions and it has been explored in numerous reports. This reaction has been used for industrial applications

since its early years, due to its noticeable catalytic activity and chiral recognition ability. Asymmetric hydrogenation is usually promoted by a transition metal catalyst such as Rh, Ru, or Ir. We selected Ru due to its excellent catalytic performances. Furthermore, cost of Ru is lower than other metals, such as Ir (Shimuzu et al. 2005).

Transfer hydrogenation catalyzed by ruthenium complexes is an increasingly beneficial instrument in organic synthesis since its discovery, because this reaction enables transformations otherwise very tough and even almost impossible. This process, has gained considerable importance since the milder conditions are often necessary, and it is essential in the use of ruthenium complexes in asymmetric transfer hydrogenations (Ceron-Camacho et al. 2006). The use of chiral *p*-aminoalcohols as ligands in different fields of asymmetric synthesis has appealed pronounced consideration over recent years and prompted their application as chiral auxiliaries in the enantioselective transfer hydrogenation of prochiral ketones (Aitali et al. 2000).

2.LITERATURE SURVEY

2.1.Organophosphorus Ligands

Ligands containing phosphorus atoms have been attracting great interest throughout inorganic and organic chemistry. These ligands have been investigated for the last several decades and are of great attention because they have a variety of uses in organometallic chemistry for the improvement of industrial transformations including a numerous catalytic reactions (Zuburi and Woollins, 2003).

2.2.Phosphines

Synthesis of optically active hydroxy compounds and amino acids by asymmetric hydrogenation of prochiral ketones and dehydroamino acids is of great importance in organometallic catalysis. Similarly, considerable attention has been directed toward the synthesis of bisphosphine ligand for the catalytic hydrogenation of various functionalized ketones. Thus, innumerable chelating phosphines having a C_2-symmetry axis and the corresponding catalysts have been prepared, such as BINAP, BIPHEMP and TunaPhos, BPE and DUPHOS, and f-binaphane (Figure 2.1) (Gong et al. 2007).
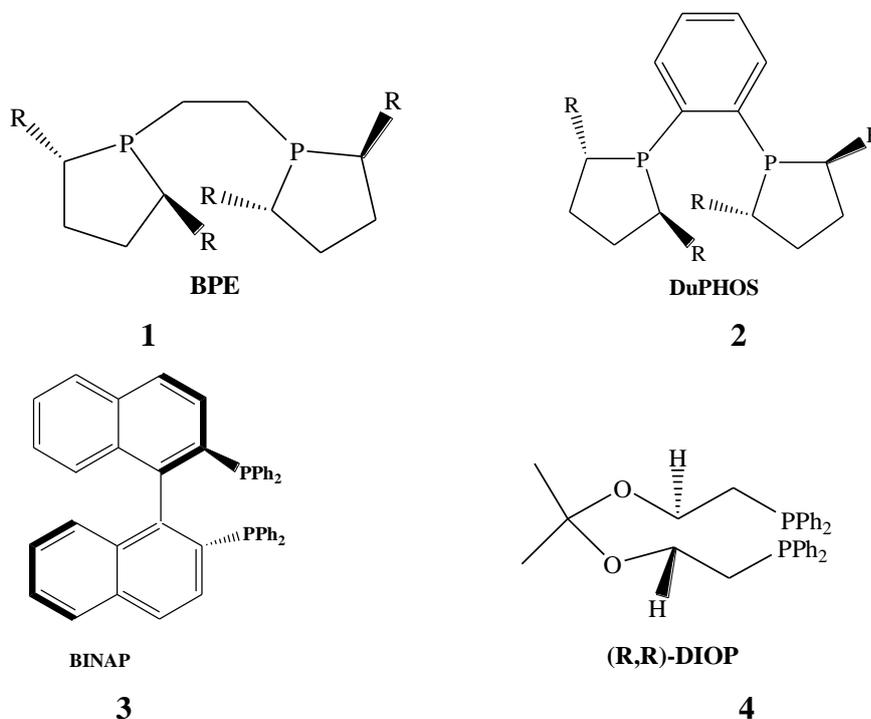
Figure 2.1 Several important examples of chiral phosphines

2.3.Phosphinites

Although both phosphines and phosphinites are useful in asymmetric reactions, phosphinites are better ligands, because they have different structural, electronic and chemical features than phosphines. Therefore, they provide copious opportunities to design novel ligands for asymmetric catalysis (Galka et al. 2003). For instance, metal-phosphorus bond is usually stronger in phosphinites than phosphines, since the presence an electron-withdrawing P-OR group exists. Moreover, the vacant σ∗-orbital of the phosphinite $P(OR)R_2$ becomes more stable, rendering the phosphinite a better acceptor (Aydemir et al. 2010). Easy synthesis of phosphinites is their most significant advantage over phosphines (Chan et al. 1997).

Noyori et al. proposed that the highly skewed position of the naphthyl rings in BINAP was the determining factor for the ligand to be so active in asymmetric catalytic reactions. When structure of BINAP is compared with the less-effective BINAPO [2,2'-bis(diphenylphosphinoxy)-1,1'-binaphthyl] (Figure 2.2), one can easily see that there seems to two possible reasons for this difference. (1) The oxygen atoms in BINAPO cause to an increase in the distance between the chiral binaphthyl and the PPh_2 groups, which in turn decrease the impact of the binaphthyl functionality on the stereopositions of the phenyl rings of the PPh_2 group. Subsequently, there is less control of stereoselectivity in the catalyst-substrate interaction. (2) The flexibility of the backbone substantially increases due to existence of the C-O-P bond in BINAPO, which decreases the enantioselectivity of the catalyst (Chan et al. 1997).
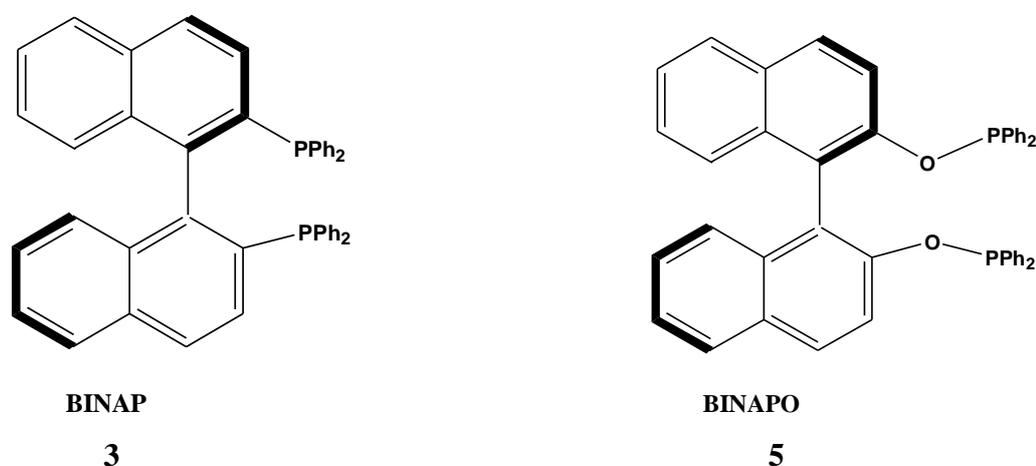
Figure 2.2 Structures of BINAP and BINAPO ligands

2.4.Hydrogenation

Hydrogenation is an important type of reaction especially for unsaturated organic compounds such as alkenes, alkynes, ketones and nitryles, and refers to the addition of hydrogen (H_2) to a species (Gladiali and Alberico. 2006).

2.4.1.Transfer Hydrogenation

The asymmetric reduction of unsaturated compounds offers good opportunities for the simultaneous introduction of new functionalities and new stereogenic elements into the structure of organic compounds. Hence, this transformation has become one of the most common tools in asymmetric synthesis and has been used in the preparation of various organic products having biological interest and featuring diverse functional groups. Recently, among the methods used for this aim, transfer hydrogen reduction has attained a noticeable position as to be rated second in order of importance immediately behind asymmetric hydrogenation with molecular hydrogen (Clapham et al. 2004). This method is increasingly successful since it is operationally simple and have less risks related with the employing of a facile inflammable and high diffusible gas, because hydrogen gas has substantial safety risks particularly for large-scale processess. Employing of a solvent which can donate hydrogen overcome these drawbacks. These extensive investigations struggles have caused to important progresses in the design of new catalysts having higher activity and/or selectivity; to gain insight the reaction mechanisms, especially as to the Ru-catalyzed reactions; in discovering unconventional methodologies driven by green chemistry principles (Gladiali and Alberico, 2006).

$$\text{H-D-H} + \text{A} \xrightleftharpoons{\text{Catalyst}} \text{D} + \text{H-A-H}$$

Scheme 2.1 "Hydride transfer from the H-donor DH_2 to the substrate A"

Hydride transfer from the H-donor DH_2 to the substrate A (Scheme 1) may happen in relation to two limiting mechanisms: a metal-templated concerted process (direct H-transfer) or a metal hydride mediated multi-step process (hydridic route) (Samec et al. 2006).
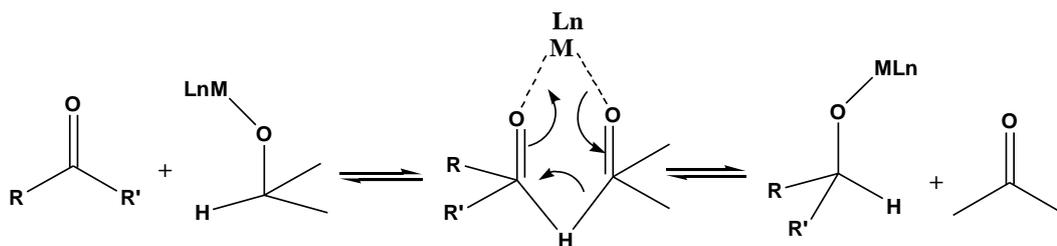
Scheme 2.2 Metal-templated concerted process (direct H-transfer)

The direct H-transfer (Scheme 2.2) advances via a complex in which both the donor and the acceptor are bound to the metal and are held in close proximity. Upon coordination to the metal, the substrate is activated towards the nucleophilic attack of the hydride. The metal acts as a template providing the reactants with the correct orientation for a concerted shift of hydride to be achievable.

The hydridic route includes the intermediate formation of a discrete metal hydride by interaction of the catalyst with the H-donor, followed by hydride transfer from the metal hydride to the substrate. Thus, the donor and the acceptor interact independently with the metal at different phases of the reaction. Transition metals most commonly catalyze the hydridic mechanism. A proposed mechanism for transfer hydrogenation is given in Scheme 2.3 (Gladiali and Alberico, 2006).
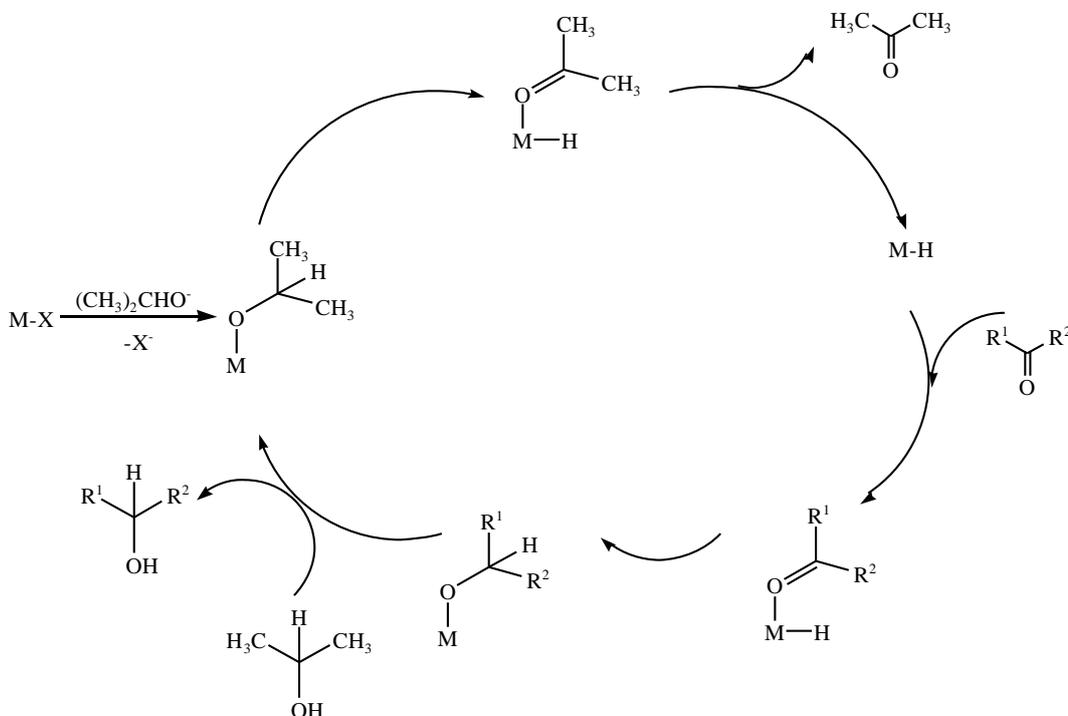
Scheme 2.3 A proposed mechanism for asymmetric transfer hydrogenation

2.4.2.Hydrogen sources in transfer hydrogenation

Isopropanol and formic acid/triethylamine are certainly the most employed sources of hydrogen in transfer hydrogenation. Isopropanol is a popular reactive solvent for transfer hydrogenation transformations because it is facile to handle (bp 82 $^{\circ}$C) and is relatively nontoxic, environmentally benign, and inexpensive. During the reaction, isopropanol is oxidized to acetone (Scheme 2.4). This makes the reduction of ketones by isopropanol a reversible process where the equilibrium is regulated by the oxidation potentials of the relevant carbinol/ketone couples. To shift the equilibrium towards the wanted product, isopropanol is most commonly employed as the solvent of the reaction. As the life-time of many metal catalysts in isopropanol solution is usually reasonably long even at reflux temperature, this allows for most reactions to be driven to high conversions (Gladiali and Alberico, 2006).
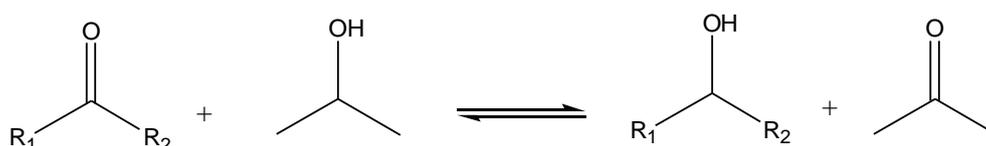
Scheme 2.4 Isopropanol as a source of hydrogen

When isopropanol is the hydrogen donor, a base is often necessary to activate the starting complex. Sodium or potassium carbonates, hydroxides or alkoxides at various concentrations are used for this aim (Noyori et al. 2001). Isopropanol is environmentally friendly and easy to handle, yet, the reversibility of the reaction is still a major disadvantage in transfer hydrogenation. The reaction is kinetically controlled and the stereoselectivity may be high at low conversions. When the conversion increases, the rate of the reverse reaction becomes higher and the ratio of enantiomers falls under thermodynamic control with gradual loss of the enantiomeric purity of the product. This restriction can be overcome by continuously distilling off acetone as soon as it is formed or by operating the reaction in dilute solution (Gladiali and Alberico, 2006).
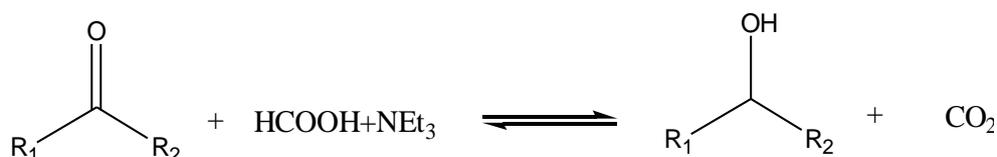
Scheme 2.5 Formic acid as a source of hydrogen

Formic acid and its salts are better hydrogen donors than isopropanol since their dehydrogenation in open systems is considerably irreversible due to the evolution of CO_2 (Scheme 2.5) (Koike and Ikariya, 2004). An azeotropic 5:2 mixture of HCOOH and NEt_3 is most commonly used as reducing agent. This gives a single phase at room temperature; it is miscible with many solvents at 20–60 ^{o}C; it allows for high substrate concentrations and brings about high conversions without back-reaction and racemization.

However, there exist some limitation to the use of formic acid. Several complexes undergo fast decomposition on attempted dissolution in formic acid and some other ones lose entirely their catalytic activity, perhaps since the acid inhibites one of the steps of the activation process promoted by the base (Gladiali and Alberico, 2006).

2.5.Asymmetric Synthesis

Asymmetric synthesis includes the formation of one or more chiral centers from a prochiral starting material under the impact of a chiral substrate, which may be used as a reagent, catalyst or as an auxiliary. Three different approaches: 1) employing chiral auxiliaries, 2) chiral reagents and 3) chiral catalysis are defined. Asymmetric synthesis is an alternative to resolution technology for the fabrication of chiral compounds. It is important to distinguish asymmetric synthesis from resolution both on mechanistic grounds and from an operational point of view. Resolution methods can be regarded as physical methods developed to separate previously synthesized enantiomers, whereas asymmetric synthesis consists of formation of one or more chiral centers from prochiral substrates. Enantiomeric excess (ee) is a measure of the effectiveness of an asymmetric synthesis (Kotha, 1994).

2.5.1.Asymmetric Synthesis Using Chiral Catalysts

Synthesis of optically pure compounds via transition metal mediated chiral catalysis is very beneficial from an industrial perspective. One can form substantial amounts of chiral compounds with the use of tiny quantities of a chiral source. The advantage of transition metal catalyzed asymmetric transformations is that the possibility of improving the catalysts by modification of the ligands (Hagen, 1999).

2.5.2.Asymmetric Hydrogenation (AH)

Catalytic asymmetric hydrogenation is a fairly developed transformation in terms of other asymmetric transformation accomplished today. There are several milestones which contributed to this state-of-the-art technology. The journey started with the discovery of Wilkinson's catalyst. Later on, both Homer and Knowles independently reported the practicability of asymmetric hydrogen transfer with the help of optically active Wilkinson type catalysts. Although they obtained low optical yields, the lessons learned from their research laid a solid foundation for the success of Monsanto's asymmetric synthesis of the anti-Parkinson's drug L-DOPA. In 1971 Kagan disclosed an important result with DIOP bi-dentate ligand (first ligand with C_2-symmetry axis) purposed at improving the stereoselectivity of the asymmetric process by restricting the conformational mobility around the metal atom. In the same year, Morrison designed an interesting neomenthyl diphenylphosphine ligand, which has no chiral phosphorous atom. Early lessons learned in asymmetric hydrogenation paved the way to some of the new asymmetric catalytic processes. Many of the successful chiral ligands employed for transition metal catalyzed asymmetric catalysis in general are chelating phosphines having a C_2-symmetry axis, the existence of which serves the important function of reducing the number of likely diastereomeric transition states (Hagen, 1999).

Upon first inspection, it may appear that the introducing a symmetry element within a chiral auxiliary would be antithetical to the stated aim of accomplishing asymmetric induction in a chemical conversion. Actually, the enantioface differentiation almost universally relied upon to provide asymmetric induction entails only that the assisting lack mirror or inversion symmetry and, therefore, need not be asymmetric, only dissymmetric. In the majority of scenarios for absolute stereochemical control, the presence of a C_2 symmetry axis within the chiral auxiliary may serve the very important function of intensely reducing the number of possible competing, diastereomeric transition states (Whitecell, 1989). Care is especially warranted in the field of absolute stereochemical control where there are generally only two possible consequences (either R or S), and any transition-state model has, a priori, a 50% probability of being consistent with the observed outcome. Nonetheless, it is almost universally observed

that auxiliaries with C_2 symmetry elements perform in their capacity as stereochemical directors to provide higher levels of absolute stereochemical control as compared to those totally lacking in symmetry. Therefore, generally, the most successful chiral ligands employed in asymmetric hydrogenation reactions are rigid chelating diphosphines owing a C_2-symmetry axis thus reducing the number of diastereomeric transition states. Furthermore, most of them carry at least two aryl substituents on their phosphorus atoms. If one analyzes the structures of these ligands, several design principles can be identified which may result in good enantiocontrol. Generally speaking, these measures form the required flexibility of the ligand to impart high turnover rates and give adequate rigidity to control stereoselectivity. It has to be emphasized that there are always examples where just the opposite is true. A ligand is more probably to induce high enantioselectivity if it has a C_2 symmetry (first example: diop) or is very strongly unsymmetrical (e.g., josiphos) in order to decrease the number of possible isomeric catalyst–substrate complexes (Whitecell, 1989).

3.PREVIOUS STUDIES

Gao et al. (1996) were synthesized and characterized "trans-Ru^{II}Cl$_2$ complexes with N,N'-bis[o-(diphenylphosphino)benzylidene]cyclohexane-1,2-diamine and N,N'-bis[o-(diphenylphosphino)-benzyl]cyclohexane-1,2-diamine ligands" (Figure 3.1). They reported that "the C$_2$-symmetric diphosphine/diamine based Ru complex acted as an excellent catalyst precursor in asymmetric transfer hydrogenation of acetophenone in a 0.1 M 2-propanol solution, affording to 2-phenylethanol in 97% ee and in 93% yield after 7 h at 45 °C."

6

7
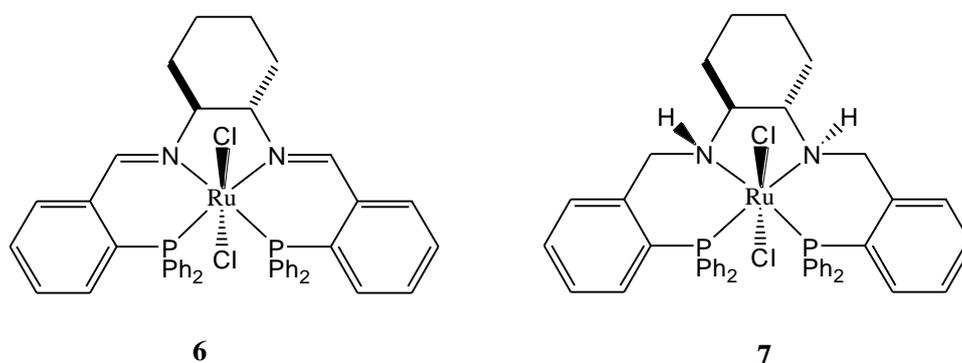
Figure 3.1 P$_2$N$_2$- and P$_2$(NH)$_2$-Ru^{II} complexes (6-7)

Guo et al. (2005) synthesized "a series of trans-ruthenium hydride borohydride complexes with chiral phosphinite and diamine ligands (Scheme 3.1) and used them in the asymmetric transfer hydrogenation of aryl ketones (Table 3.1), to obtain chiral alcohols in moderate to good enantioselectivities (up to 94% ee)." They reported that "these complexes were are efficient catalysts for the Michael addition of malonates to enones with enantioselectivities of up to 94%, and that this kind of catalyst allowed a one-pot tandem Michael addition/H$_2$ hydrogenation protocol to build structures with multiple chiral centers."
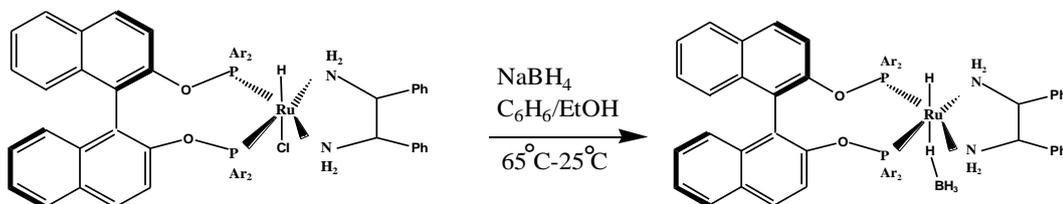
Scheme 3.1 "Reaction of *trans*-RuHCl(diphosphinite)(diamine) complexes with NaBH$_4$"

Table 3.1 "Transfer hydrogenation results of ketones catalyzed by 8-11**.**"
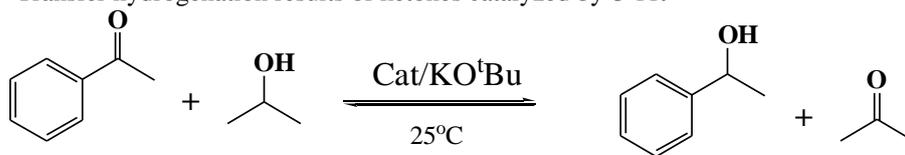
Catalyst	Time(h)	Conversion(%)	ee (%)
8	6	92	80
9	6	94	49
10	8	80	94
11	8	91	60

As seen in Table 3.1, they employed "complexes **8-11** in the asymmetric transfer hydrogenation of aryl ketones and found that the highest enantioselectivity (94 % ee) was obtained with complex **10**."

In their another study, Guo et al. (2005) prepared "ruthenium hydrido chloro complexes **12**-**15** with diamine and diphosphinite ligand modules (Figure 3.2) and employed them as catalysts in the asymmetric transfer hydrogenation of ketones to give chiral alcohols in good yield and enantioselectivity."
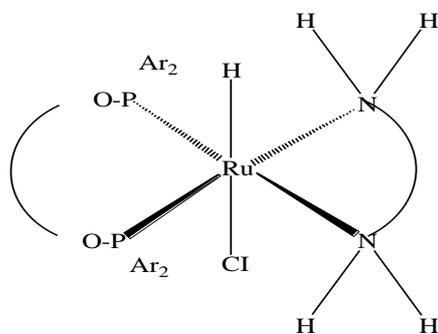
12, diphosphinite = (R)-BINOP   diamine = (R,R)DPEN

13, diphosphinite= (R)-BINOP   diamine = (S,S)-DPEN

14, diphosphinite = (R)-xyIBINOP   diamine = (R,R)-DPEN

15, diphosphinite =(R)-xyIBINOP   diamine=(S,S)-DPEN

Figure 3.2 "Trans-RuHCl(diphosphinite)(diamine) complexes, **12**-**15**"

They employed "complexes **12**-**15** precatalysts in the asymmetric transfer hydrogenation of acetophenone by 2-propanol in the presence of KOtBu (Table 3.2)" and they reported that "these complexes exhibited slightly higher activity than Noyori's

system RuCl$_2$((R)-BINAP)((R,R)-DPEN)/base/^{i}PrOH for the transfer hydrogenation of ketones and the TOF was more than 30 h^{-1} at 20 ^{o}C."

Table 3.2"Transfer hydrogenation results of ketones catalyzed by **12-15.**"
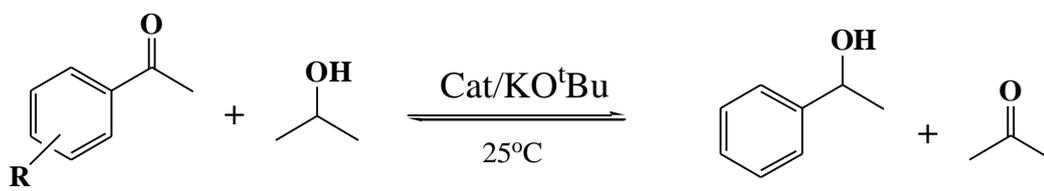
Catalyst	Time (h)	Conversion(%)	ee (%)
12	3	96	79
13	3	95	47
14	3	97	92
15	3	96	63

They found that "complex **14** with the more rigid and crowded phosphinite ligand (R)-xylBINOP and matching diamine (R,R)-DPEN afforded the best enantioselectivity (up to 92% ee) with the product in the R configuration (Table 3.2, entry 3)."

Ceron-Camacho et al. (2006) reported that "the reaction of pincer type ligand [C$_6$H$_4$-1,3-(OPPh$_2$)$_2$] with [(η6-p-cymene)RuCl$_2$]$_2$ gave the bimetallic species [C$_6$H$_4$-1,3-(OPPh$_2$\{Ru(η6-p-cymene)Cl$_2$\})$_2$] **(16)** possessing a phosphinite PCP ligand as a bridging ligand between the two ruthenium centers, which was proved to be an efficient catalyst in the transfer hydrogenation reaction of ketones in the presence of Pr^{i}OH and NaOH." They found that "several attempts, including the change of the ruthenium starting material (e.g. [(η6-benzene)RuCl$_2$]$_2$) and reflux conditions to enable the coordination of the diphosphinite [C$_6$H$_4$-1,3-(OPPh$_2$)$_2$] in a tridentate PCP pincer fashion failed." They tested "complex [C$_6$H$_4$-1,3-(OPPh$_2$\{Ru(η6-p-cymene)Cl$_2$\})$_2$] in the transfer hydrogenation of ketones."

16

17
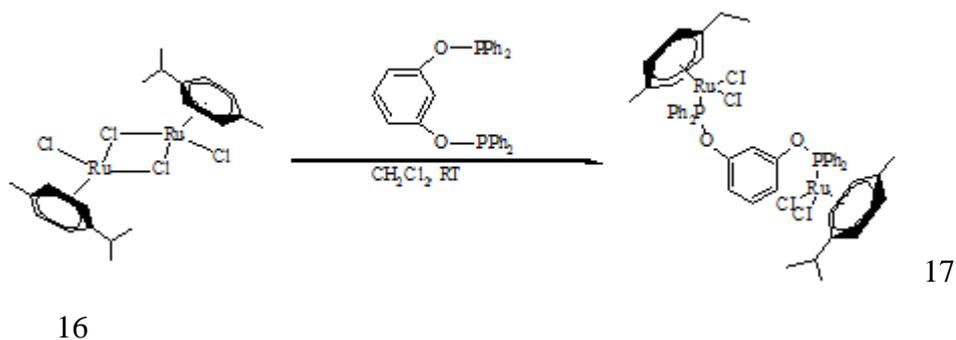
Scheme 3.2 "Synthesis of [C_6H_4-1,3-(OPPh$_2$\{Ru(η^6-p-cymene)Cl$_2$\})$_2$] (16)"

Table 3.3 "Reduction of ketones by [C_6H_4-1,3-(OPPh$_2$\{Ru(η^6-p-simen)RuCl$_2$\})$_2$]$_2$ in Pr^{i}OH"
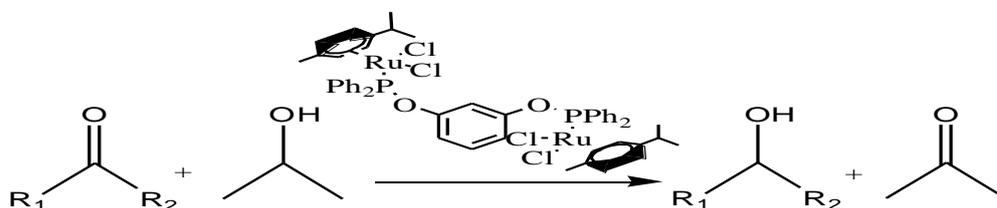
Entry	Substrate	Product	Conversion (%)
1			91
2			84
3			34
4			17
5			34

"Reaction conditions: Complex **17** (11.0 mg, 0.005 mmol), NaOH (0.5 mg, 0.012mmol) and ketone (0.5 mmol) isopropanol (2.5 ml) 10 h reflux"

14

Reetz and Li (2006) reported that "BINOL-derived diphosphonites are proper for asymmetric transfer hydrogenation of aryl/alkyl and alkyl/alkyl ketones." They investigated "2-propanol-based transfer hydrogenation of acetophenone using [RuCl$_2$(p-cymene)]$_2$ in the presence of ligands **18**-**20** and a base such as NaOH or potassium tert-butoxide." They found that "only the xanthene derived ligand **19** gave acceptable conversion (Table 3.4, entry 2)," while they obtained "very poor conversions with <20% ee using ligands **18**-**20** (Table 3.4, entries 1, 3, and 4). Optimization of Ru/2 showed that the ligand/Ru ratio played a crucial role in obtaining high enantioselectivity, a ratio of about 2.5 being optimal. The nature of the base appeared to be less important, KOtBu or NaOH being equally effective. Hydrogenation using H$_2$ was less successful."
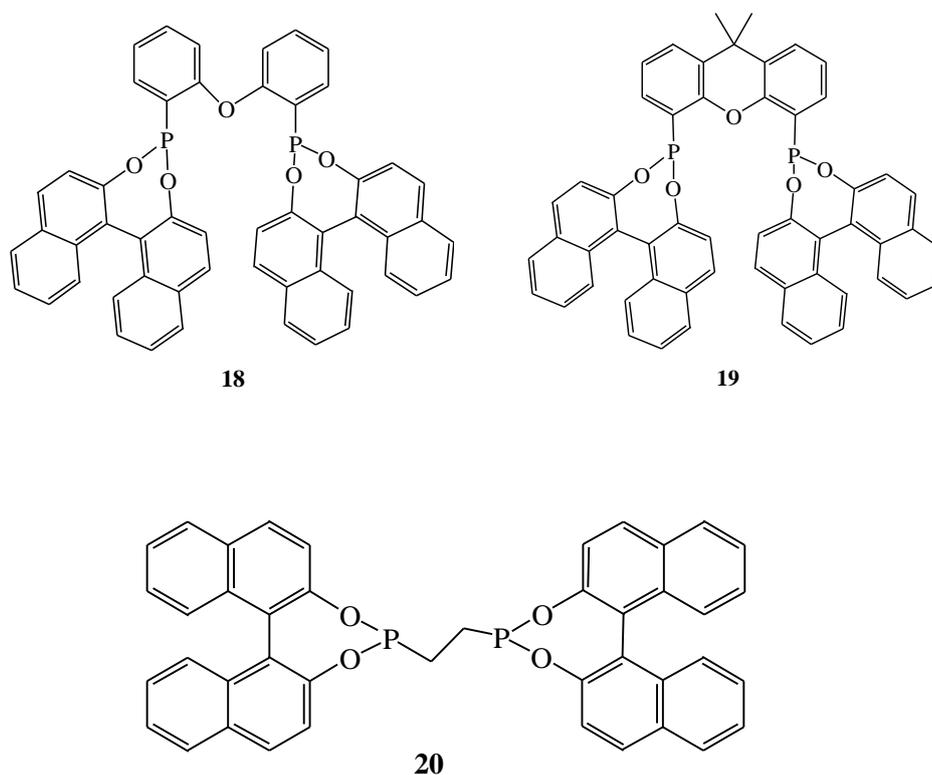
Figure 3.3 Binol derivatives diphosphonite ligands (18-20)

Table 3. 4 Transfer hydrogenation of acetophenone by 18-20 ligands
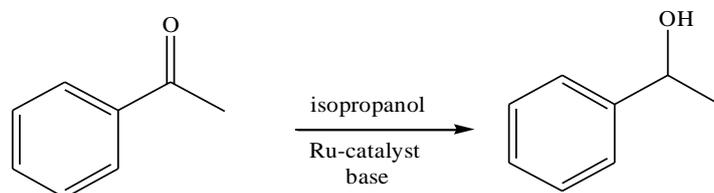
Ligand	Ligand:Ru	Base	Conversion (%)	ee (%)
18	1	KO^{t}Bu	5	17 (R)
19	1	KO^{t}Bu	95	54 (R)
20	1	KO^{t}Bu	5	5 (R)
19	2/5	KO^{t}Bu	90	93 (R)
19	2/5	NaOH	88	97(R)

"The reaction was carried out in isopropanol at 40 °C for 20 h."
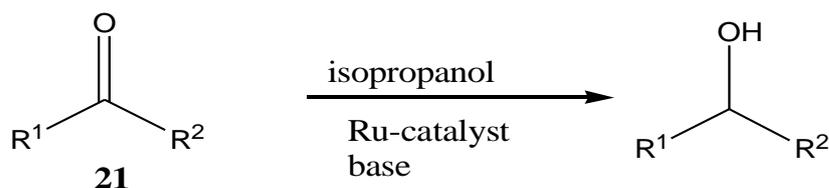
a	R^1=C$_6$H$_5$; R^2 =CH$_3$	**h**	R^1=p-CF$_3$C$_6$H$_4$; R^2=CH$_3$
b	R^1=o-ClC$_6$H$_4$; R^2=CH$_3$	**i**	R^1=C$_6$H$_5$; R^2 =CH$_2$CH$_3$
c	R^1=m-MeOC$_6$H$_4$; R^2=CH$_3$	**j**	R^1= 2-naphthyl; R^2 =CH$_3$
d	R^1=p-MeC$_6$H$_4$; R^2=CH$_3$	**k**	R^1= 3,5-(CF$_3$)$_2$C$_6$H$_3$; R^2 =CH$_3$
e	R^1= m-BrC$_6$H$_4$; R^2=CH$_3$	**l**	R^1=o-C$_6$H$_{11}$; R^2=CH$_3$
f	R^1= m-ClC$_6$H$_4$; R^2=CH$_3$	**m**	R^1=CH(CH$_3$)$_2$; R^2 =CH$_3$
g	R^1=p-ClC$_6$H$_4$; R^2=CH$_3$	**n**	R^1= n-C$_6$H$_{13}$; R^2 =CH$_3$

Table 3.5 "Asymmetric transfer hydrogenation of ketones (**21a**-**21n**) by ligand **19**."

Entry	Ketone	Ligand:Ru	Base	Time(h)	Conversion(%)	ee (%)
1	**21a**	4	KO^{t}Bu	28	91	97 (R)
2	**21a**	2.5	NaOH	20	88	97 (R)
3	**21a**	2.5	NaOH	40	93	98 (R)
4	**21b**	2.5	NaOH	26	83	99 (R)
5	**21b**	2.5	NaOH	40	90	99 (R)
6	**21c**	2.5	NaOH	40	63	93 (R)
7	**21c**	2.5	NaOH	96	91	93 (R)
8	**21d**	2.5	NaOH	26	65	95 (R)
9	**21e**	4	KO^{t}Bu	28	100	96 (R)
10	**21e**	2.5	NaOH	16	100	96 (R)
11	**21f**	4	KO^{t}Bu	22	96	96 (R)
12	**21f**	2.5	NaOH	16	98	95 (R)
13	**21g**	2.5	NaOH	26	98	95 (R)
14	**21h**	2.5	NaOH	16	100	97 (R)
15	**21i**	2.5	NaOH	26	65	93 (R)
16	**21j**	4	KO^{t}Bu	22	56	93 (R)
17	**21k**	2.5	NaOH	6	99	98 (R)
18	**21l**	2.5	NaOH	22	97	99 (R)
19	**21m**	2.5	NaOH	22	99	99 (R)
20	**21n**	2.5	NaOH	16	96	90 (R)

They applied "the general protocol for transfer hydrogenation to ketones **21a-q**, and as seen in Table 3.5," found that "the catalyst system was surprisingly versatile. The notoriously difficult alkyl/alkyl ketones **21l** and **21m** were reduced with essentially complete enantioselectivity (ee = 99%). 2-Octanone **21n** was even more challenging as a substrate, yet it reacted selectively (ee = 90%; entry 20)."

Gong et al. (2007) **"**focused on the construction of optically active C_2-symmetric AMPP ligand to increase rigidity of AMPP." For this purpose, they "designed bicyclic compounds and a four cyclic compound (**22**-**25**) bearing nitrogen and oxygen to make these new ligands not only electron-rich but also C_2 symmetric from readily available amino alcohols." They found that "Rh complexes with these ligands were highly

enantioselective catalysts for asymmetric hydrogenation of N-benzoyldehydroamino acid derivatives and α-functionalized ketones in 99% and 98% ee, respectively." They also reported that "this new class of (R,*R*)-BDOPPE (1,2-bis{di[(*R,R*)-1,3,2-oxaphosphilidine]phosphino}ethane) (**22**-**25**) gave much more effectivity and enantionselectivity than their corresponding non-C$_2$-asymmetric aminophosphine phosphinite."
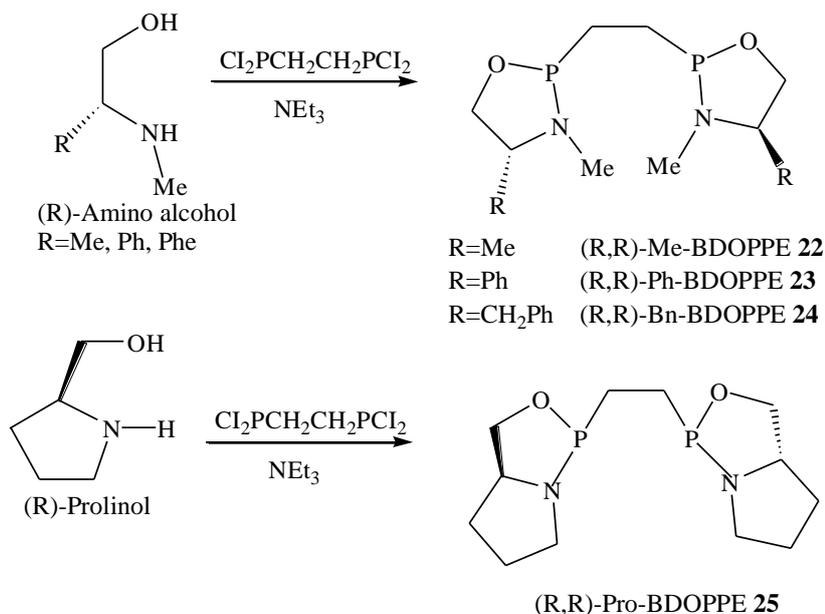
Scheme 3.3 Synthesis of (R,R)-BDOPPEs
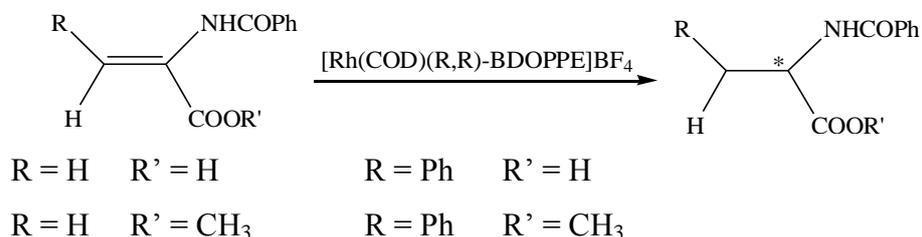
Scheme 3.4 Asymmetric hydrogenation of *N*-benzoyl- dehydroaminoacids catalyzed by Rh complexes
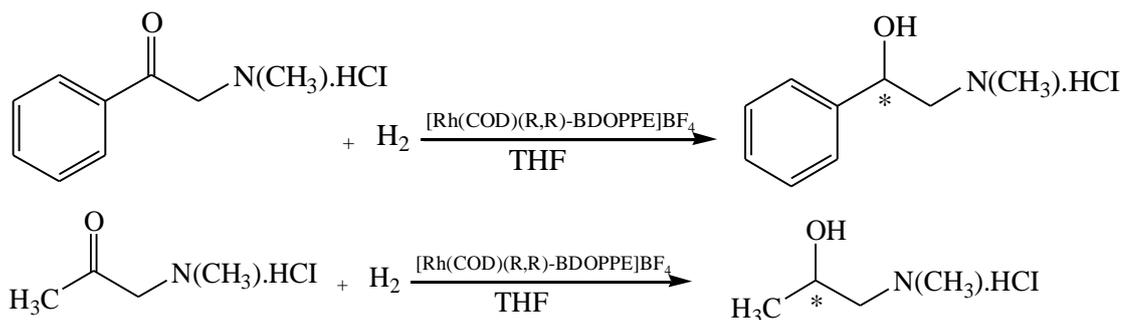
Scheme 3.5 "Asymmetric hydrogenation of α-functionalized ketones catalyzed by Rh-BPEBOP complexes"

Aydemir et al. (2009) reported that "the dimeric starting material [(η^6-p-cymene)RuCl$_2$]$_2$ reacted with N3,N3'-bis(diphenylphosphino)-2,2'-bipyridine-3,3'-diamine, **26** and P,P'-diphenylphosphinous acid-P,P'-[2,2'-bipyridine]-3,3'-diyl ester, **27** ligands to give bridged dinuclear complexes [C$_{10}$H$_6$N$_2${NHPPh$_2$-Ru(η^6-p-cymene)Cl$_2$}$_2$], **28** and [C$_{10}$H$_6$N$_2${OPPh$_2$-Ru(η^6-p-cymene)Cl$_2$}$_2$], **29** in quantitative yields." They found that "these bis(aminophosphine) and bis(phosphinite) based Ru(II) complexes served as active catalyst precursors for the transfer hydrogenation of acetophenone derivatives in 2-propanol and especially **29** acted as a good catalyst, giving the corresponding alcohols in 99% yield in 20 min (TOF < 280 h^{-1})."

Furthermore, they "employed these complexes in transfer hydrogenation of substituted acetophenones and obtained 93-99% conversions."
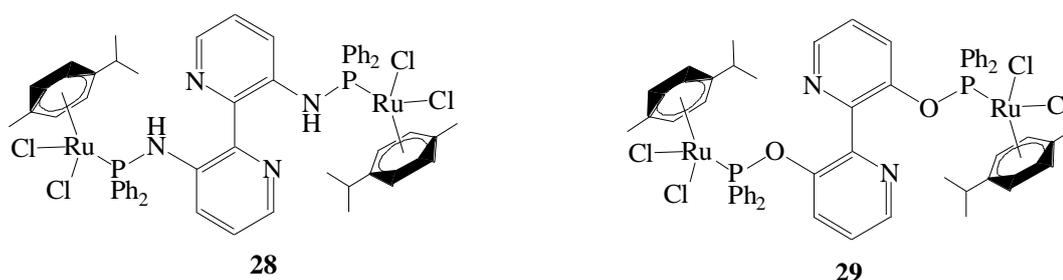
Figure 3.4 "[C$_{10}$H$_6$N$_2${NHPPh$_2$-Ru(η^6-p-cymene)Cl$_2$}$_2$], 28 and [C$_{10}$H$_6$N$_2${OPPh$_2$-Ru(η^6-p-cymene)Cl$_2$}$_2$], 29 catalysts"

Aydemir et al. (2010) in their another study "prepared the new chiral C$_2$-symmetric ligands N,N'-bis-[(1S)-1-sec-butyl-2-O-(diphenylphosphinite) ethyl]ethanediamide, **30** and N,N'-bis-[(1S)-1-phenyl-2-O-(diphenylphosphinite) ethyl]ethanediamide, **31** and the corresponding ruthenium complexes **32** and **33** and

elucidated their structures by a combination of multi-nuclear NMR spectroscopy, IR spectroscopy, and elemental analysis." They used "^{1}H–^{31}P NMR, DEPT, ^{1}H–^{13}C HETCOR, or ^{1}H–^{1}H COSY correlation experiments to confirm the spectral assignments." They also "studied the catalytic activity of complexes **32** and **33** in transfer hydrogenation of acetophenone derivatives by iso-PrOH." They reported that "these chiral ruthenium complexes served as catalyst precursors for the asymmetric transfer hydrogenation of acetophenone derivatives in iso-PrOH and acted as excellent catalysts under optimized conditions, giving the corresponding chiral alcohols in 99% yield and up to 75% ee. This transfer hydrogenation was characterized by low reversibility under these conditions."
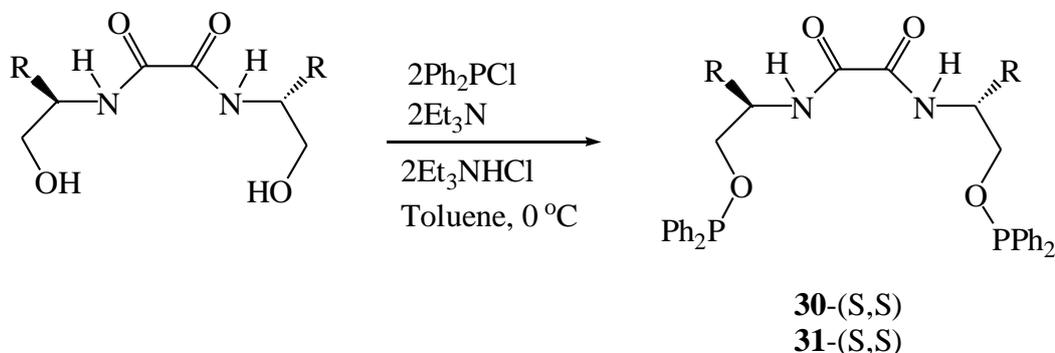
Scheme 3.6 "Preparation of *N,N′*-bis-[(1*S*)-1-*sec*-buthyl-2-*O*-(diphenylphosphinite) ethyl]ethanediamide, **30** and *N,N′*-bis-[(1*S*)-1-phenyl-2-*O*-(diphenylphosphinite) ethyl]ethanediamide, **31**"

They prepared "Ru(II) complexes by the reactions between Ru(II) precursor and bis(phosphinite) ligands," and they reported that "these reactions were not affected by the molar ratio of [(η^{6}-*p-cymene*)RuCl$_2$]$_2$ as well as the steric and electronic properties of the donor phosphorus atoms. The initial color change, that is, from clear orange to deep red, can be attributed to the dimer cleavage most probably by the bis(phosphinite) ligand. The complexes were isolated as indicated by singlets in the ^{31}P–{^{1}H} NMR spectra at 115.69 and 116.28 ppm, respectively." They remarked that "^{31}P–{^{1}H} NMR signals of ligands and complexes did not differ significantly."
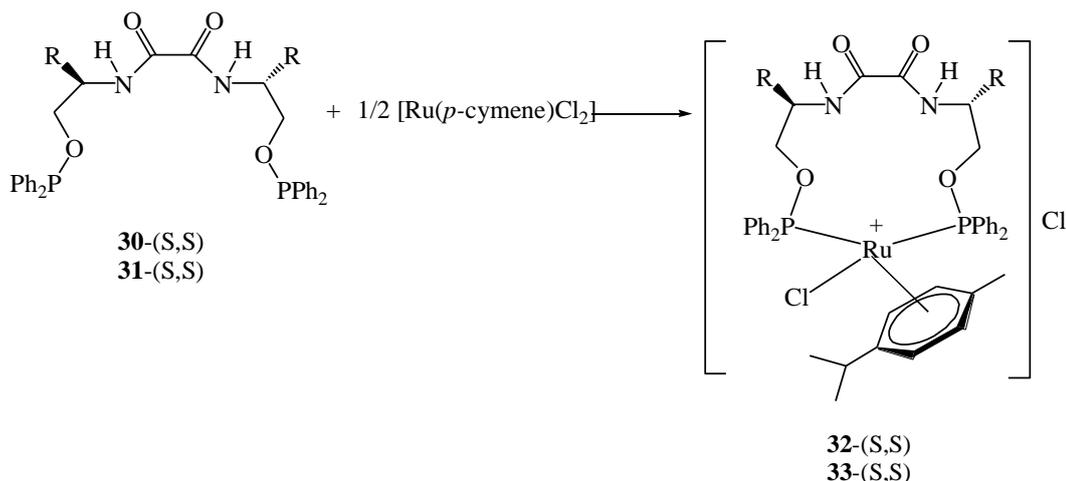
Scheme 3.7 "Synthesis of [Ru{chloro(*p*-cymene)(*N,N'*-bis[(1*S*)-1-*sec*-buthyl-2-*O*(diphenylphosphinite) ethyl]-ethanediamide)}]chloride, **32** and [Ru{chloro(*p-cymene*)(*N,N'*-bis[(1*S*)-1-phenyl*O* (diphenyl-phosphinite)ethyl]ethanediamide)}] chloride **33**"

Aydemir et al. (2010) "synthesized a novel Schiff base N3,N3'-di-2-hydroxybenzylidene-[2,2']bipyridinyl-3,3'-diamine, **34** from condensation of salicylaldehyde with 3,3'-diamino-2,2'-bipyridine." They reported that "the reaction of 1 with two equivalents of PPh$_2$Cl in the presence of Et$_3$N proceeded in toluene to afford N3,N3'-di-2-(diphenylphosphino)benzylidene-[2,2']bipyridinyl-3,3'-diamine, **35** in quantitative yield, and that ruthenium(II) dimers [Ru(η^6-arene)(-Cl)Cl]$_2$ readily reacted with phosphinite ligand [(Ph$_2$PO)$_2$-C$_{24}$H$_{16}$N$_4$], **35** in toluene at room temperature, to give the neutral derivatives [C$_{24}$H$_{16}$N$_4${OPPh$_2$–Ru(η^6-arene)Cl$_2$}$_2$] {arene: benzene **36**, p-cymene, **37**}." They "fully characterized all complexes by analytical and spectroscopic methods. ^{31}P–{^{1}H} NMR, ^{1}H–^{13}C HETCOR or ^{1}H–^{1}H COSY correlation experiments were used to confirm the spectral assignments." They also "determined molecular structure of Schiff base, **34** by X-ray single crystal diffraction study." They "tested the catalytic activity of complexes **36** and **37** in the transfer hydrogenation of acetophenone derivatives and found that stable ruthenium(II)–phosphinite complexes were efficient catalysts in the transfer hydrogenation of aromatic ketones in excellent conversions up to 99% (up to 530 per hour) in the presence of iso-PrOH/KOH (Scheme 13)."
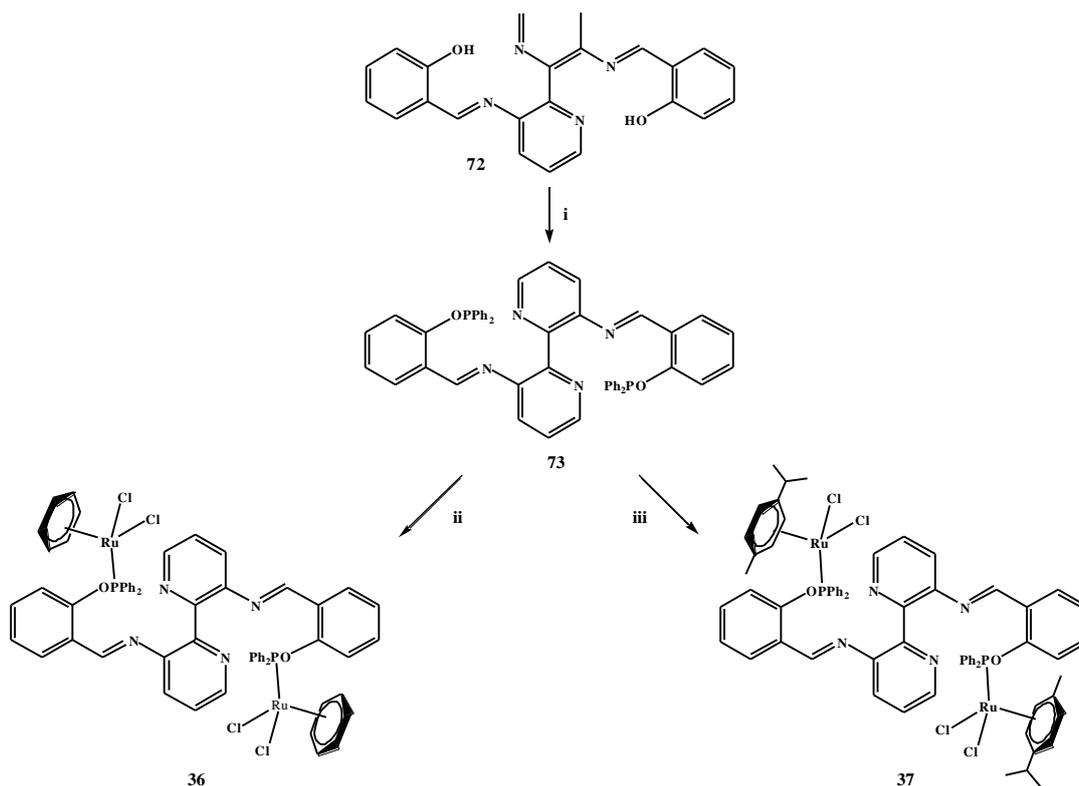
Scheme 3.8 "Synthesis of [(Ph$_2$PO)$_2$-C$_{24}$H$_{16}$N$_4$], **35**, [C$_{24}$H$_{16}$N$_4$\{OPPh$_2$-Ru(η^6-benzene)Cl$_2$\}$_2$], **36** and [C$_{24}$H$_{16}$N$_4$\{OPPh$_2$-Ru(η^6-p-cymene)Cl$_2$\}$_2$], **37** (i) 2 equiv. of Ph$_2$PCl, 2 equiv. of Et$_3$N, toluene, 0 °C; (ii) 1 equiv. [Ru(η^6-benzene)(μ-Cl)Cl]$_2$, toluene, room temperature; (iii) 1 equiv. [Ru(η^6-p-cymene)(μ-Cl)Cl]$_2$, toluene, room temperature."

They said that "they paid particular attention to arene ligands, because (i) the spectator ligands automatically occupy three adjacent coordination sites of Ru in an octahedral coordination environment, leaving three facial sites for other functions, (ii) arene ligands that are relatively weak electron donors may provide a unique reactivity on the metallic center, and (iii) the substitution pattern on the ring is flexible."

Aydemir et al. (2010) synthesized "a new chiral phosphinite compound N,N'-bis[(1S)-1-benzyl-2-O-(diphenylphosphinite)ethyl]ethanediamide (**38**) by the reaction of chlorodiphenylphosphine with N,N'-bis[(1S)-1-benzyl-2-hydroxyethyl] ethanediamide under argon atmosphere." They reported that "the oxidation of **38** with aqueous hydrogen peroxide, elemental sulfur or grey selenium in toluene gave the corresponding oxide **38a**, sulfide **38b** and selenide **38c**, respectively." They obtained "Pd, Pt and Ru complexes by the reaction of **38** with [MCl$_2$(cod)] (M: Pd **38d**, Pt **38e**) and [Ru(p-cymene)Cl$_2$]$_2$ **38f**, respectively." They characterized "all these new complexes by using NMR, FT-IR spectroscopies and microanalysis." They reported that

"the outstanding catalytic performance of phosphinite based transition metal complexes in the asymmetric hydrogenation prompted them to develop new chiral phosphinite based ruthenium(II) complex." Therefore, "as a demonstration of their catalytic reactivity, they tested the ruthenium complex **38f** as catalyst in the asymmetric transfer hydrogenation reactions of acetophenone derivatives with iPrOH." They selected "2-propanol as the conventional hydrogen source because of its well-known advantages: (i) having stable, (ii) easy to handle, (iii) nontoxic, (iv)environmentally benign, (v) inexpensive, (vi) dissolves in many organic solvents."

They observed that "the reaction of acetophenone, p-fluoroacetophenone, p-chloroacetophenone, p-bromoacetophenone, p-methoxyacetophenone, o-methoxyacetophenone with iPrOH gave high yields within 1 h in the absence of induction time period by using **1f** under the optimized conditions."

3.PREVIOUS STUDIES

4.MATERIALS AND METHODS

4.1.Chemicals

1.	Dichloromethane	**12.**	Benzophenone
2.	Chlorodiphenylphosphine	**13.**	Sodium
3.	Chlorodiisopropylphosphine	**14.**	Potassium hydroxide
4.	Chlorodicyclohexylphosphine	**15.**	Acetone
5.	Triethylamine	**16.**	2-Propanol
6.	"[Ru(η^6-*p*-cymene)(μ-Cl)Cl]$_2$"	**17.**	Acetophenone
7.	Chloroform-*d*	**18.**	4-Fluoroacetophenone
8.	Toluene	**19.**	4-Bromoacetophenone
9.	Hexane	**20.**	4-Chloroacetophenone
10.	Petroleum ether	**21.**	4-Methoxyacetophenone
11.	Diphosphorpentaoxide	**22.**	2-Methoxyacetophenone

These reagents and solvents were purchased from Merck, Fluka ve Aldrich.

4.2.Instrument Used For Characterization

1. FT-IR Spectrometer (Mattson 1000 ATI UNICAM)

2. Elemental analysis (Fisons EA 1108 CHNS-O)

3. NMR Spectrometer (Bruker AV400)

4. Gas chromatograph (Shimadzu GC 2010 Plus)

5. Melting points (Gallenkamp MPD 350 BM 2.5)

6. Polarimeter (Perkin Elmer 341)

4.3.Method

The study can be outlined with three main titles:

   i.   Synthesis of phosphinite ligands,

  ii.   Synthesis of Ru(II) complexes of these ligands,

 iii.   Application of Ru(II) complexes as catalyst in transfer hydrogenation reactions
        and determining their catalytic activity.

The Schiff base compounds were prepared in terms of a reported study (Ambroziak et
al. 2002). All experimental studies, i.e. synthesis of cyclohexyl based C_2-symmetric
phosphinites and their Ru(II) complexes, and use of them in catalytic investigations
were accomplished according to the literature (Aydemir et al. 2010).

4.3.1. 1-({[(1R,2R)-2-[({2-[(diphenylphosphanyl)oxy]naphthalen-1-yl} methylidene)amino]cyclohexyl]imino}methyl)naphthalen-2-yl diphenyl phosphinite (1)
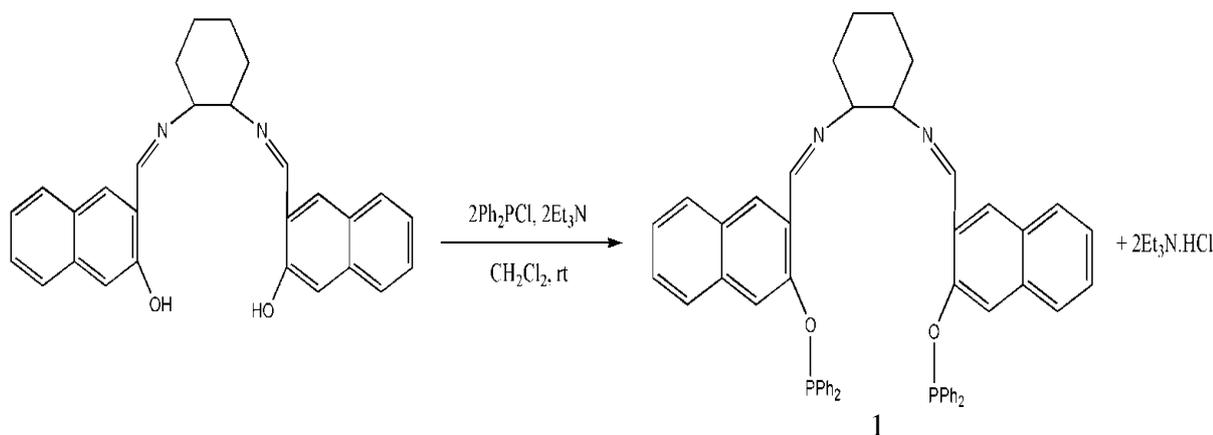
Yield: 100 mg, (84 %). ^{1}H NMR (CDCl$_3$, ppm): δ 9,07 (s, 2H, -N=C$\underline{H}$) 6.88-7.84 (m,
32 H, aromatic protons), 3.78 (br, 2H, C$\underline{H}$ of Cy), 1.87 (br, 4H, -C$\underline{H_2}$ of Cy), 1.31-1.37
(m, 4H, -C$\underline{H_2}$ of Cy). ^{13}C NMR (CDCl$_3$, ppm): δ 158.08 (d, J=44,3 Hz, i-$\underline{C}_6$H$_5$PO),
157.86 (-N=$\underline{C}$H), 135.32 (d, J=20,2 Hz, o-$\underline{C}_6$H$_5$PO), 130.95 (p-$\underline{C}_6$H$_5$PO), 130.57 (d,
J=10,1 Hz m-$\underline{C}_6$H$_5$PO), 176.02, 136.91, 133.97, 128.58, 127.83, 127.49, 124.51,
122.46, 118.77, 106.46, 68.00 (-$\underline{C}$H), 32.26 (-$\underline{C}$H$_2$ of Cy), 24.64 (-$\underline{C}$H$_2$ of Cy) "^{31}P-{^{1}H}
NMR (CDCl$_3$, ppm): δ 114.09" (s, O$\underline{P}$Ph$_2$). "IR (KBr pellet in cm^{-1})" υ (N-H): 3331,
(C=C-Cp): 1436, (O-P): 1020, (C-H): 3068, 3028, 2922, 2862. Anal. calcd. for

$C_{52}H_{44}N_2O_2P_2$ (790.884 g/mol): C, 78.97; H, 5.61; N, 3.54, "found: C", 78.41; H, 5.02; N, 3.38 %.

4.3.2. 1-({[(1R,2R)-2-{[(2-{[bis(propan-2-yl)phosphanyl]oxy}naphthalen-1-yl)methylidene]amino}cyclohexyl]imino}methyl)naphthalen-2-yl bis(propan-2-yl)phosphinite (2)
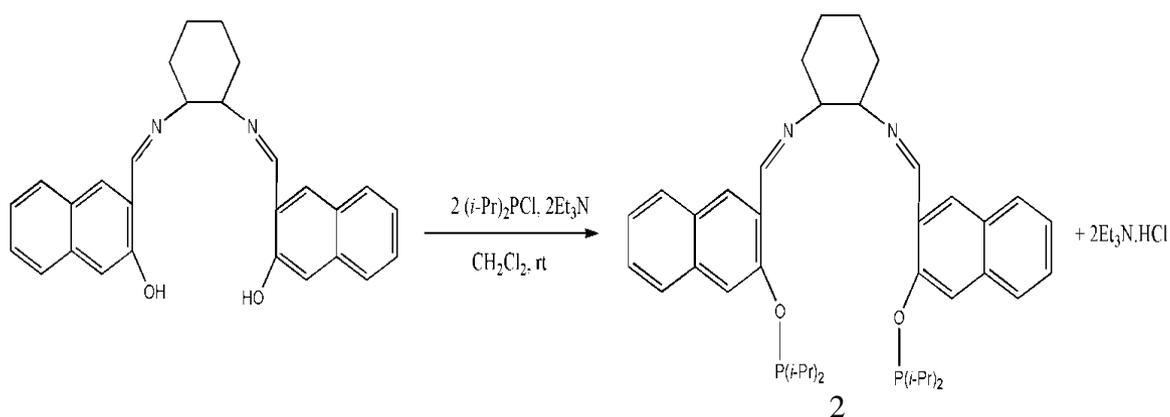
Yield: 85 mg, (86.7 %). ^{1}H NMR (CDCl$_3$, ppm):): δ 9.02 (s, 2H, -N=C**H**), 6.95-7.82 (m, 12 H, aromatic protons), 3.76 (s, 2H, -NC**H**), 1.85-1.87 (m, 2H,-C**H** iPr), 0.90-1,42 (m, 32H, -C**H₃** iPr + -C**H₂**Cy). ^{13}C NMR (CDCl$_3$, ppm): δ 172.3, 136.79, 133.18, 129.00, 127.78, 126.60, 122.80, 122.74, 118.39, 107.17 (aromatic carbons), 159.22 (-N=C**H**), 67.98 (-C**H**Cy), 32.71 (-C**H₂**Cy), 29.71 (-C**H** iPr), 24.70 (-C**H₂**Cy), 17.35, 17.53 (-C**H₃**iPr). ^{31}P-{^{1}H} NMR (CDCl$_3$, ppm): δ 150.62 (s, O**P**CH(CH$_3$)$_2$). "IR (KBr pellet in cm^{-1})" υ (N-H): 3233, (P-CH(CH$_3$): 1454, (O-P): 1039, (C-H): 2963, 2870. "Anal.calcd. for $C_{40}H_{52}N_2O_2P_2$ (654.816 g/mol): C, 73.37; H, 8.0; N, 4.28, found: C, 73.17; H, 7.90; N, 4.08 %, $[\alpha]_D^{20}$ = -4.2^o (c = 2, CHCl$_3$)."

4.3.3. 1-({[(1R,2R)-2-[({2-[(dicyclohexylphosphanyl)oxy]naphthalen-1-yl} methylidene)amino]cyclohexyl]imino}methyl)naphthalen-2-yl dicyclohexyl phosphinite (3)

3
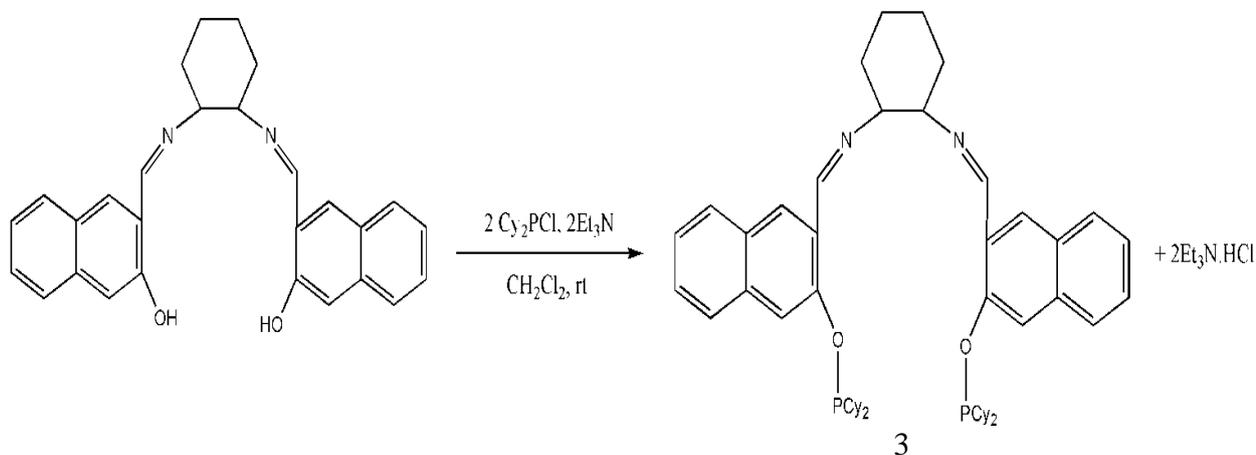
Yield: 110 mg, (90.2 %). ^{1}H NMR (CDCl$_3$, ppm): δ 9.19 (s, 2H, -N=C**H**), 7.05-7.82 (m, 12 H, aromatic protons), 3.75-3.78 (m, 2H, -C**H**Cy), 1.87-1.97 (m, 4H, C**H$_2$**Cy), 1.22-1.78 (m, 48H, protons of cyclohexyls). ^{13}C NMR (CDCl$_3$, ppm): δ 172.22, 136.42, 133.39,128.84, 127.78, 126.53, 123.36, 122.82, 118.62, 107.16 (aromatic carbons), 157.89 (-N=**C**H), 67.98 (-**C**HCy), 37.02 (-**C**HCy), 24.95, 26.23, 26.40, 26.52, 26.75, 26.97, 29.71, 32.71 (-**C**H$_2$Cy). ^{31}P-{^{1}H} NMR (CDCl$_3$, ppm): δ 146.24 (s, O**P**(Cy)$_2$). "IR (KBr pellet in cm^{-1}) υ (N-H): 3233, (P-CH(CH$_3$): 1454, (O-P): 1039, (C-H): 2963, 2870. Anal.calcd. for C$_{52}$H$_{68}$N$_2$O$_2$P$_2$ (815.076 g/mol): C, 76.63; H, 8.41; N, 3.44, found: C, 76.47; H, 8.29; N, 3.32 %, [α]$_D^{20}$ = +2.0° (c = 0.65, CHCl$_3$)."

4.3.4. 1-({[(1R,2R)-2-[({2-[(diphenylphosphanyl)oxy]naphthalen-1-yl} methylidene) amino]cyclohexyl]imino}methyl)naphthalen-2-yldiphenyl phosphinite(bis(dichloro-η^6-p-cymeneruthenium(II))(4)

(1)   (4)
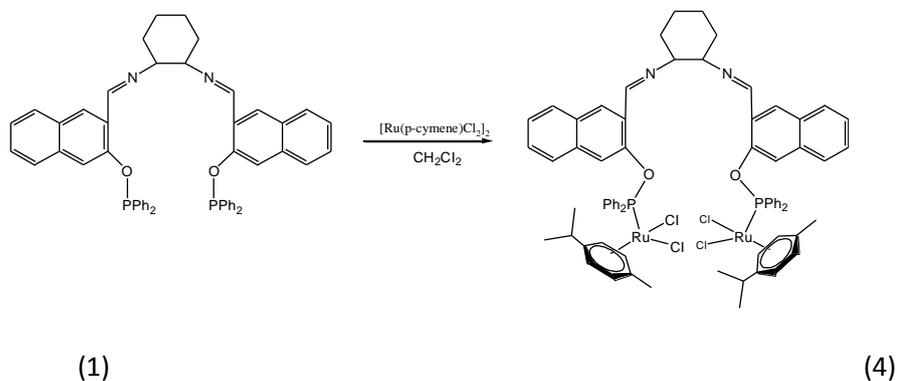
"Yield: 180 mg, 86 %, m.p: 120-122 °C. ^{1}H NMR (CDCl$_3$, ppm): δ 9,16 (br, 2H, -N=C**H**), 7.27-8.03 (m, 32 H, aromatic protons), 5.06-5.41 (m, 8H, aromatic protons of *p*-cymene), 3.10 (br, 2H, -C**H** of Cy), 2.47 (m, 2H, -C**H**(CH$_3$)$_2$ of *p*-cymene), 1,81 (br, 4H, -C**H$_2$** of Cy), 1.66 (s, 6H, -C**H$_3$**, of *p*-cymene), 1,32 (br, 4H, -C**H$_2$** of Cy), 0.85-0.87 (m, 12H, -C**H**(CH$_3$)$_2$). ^{13}C NMR (CDCl$_3$, ppm): δ 171.11, 136.94, 133.78, 128.65, 128.27, 128.17, 124.36, 122.72, 121.37, 110.41 (aromatic carbons), 158.87 (-N=**C**H), 135.17, 132.07, 129,81 (*o-, p-, m-*C$_6$H$_5$), 111.62, 96.72 (ipso *p*-cymene), 87.47, 87.54, 92.02, 92.07 (aromatic of *p*-cymene), 66.95 (**C**H of Cy), 30.16 (-**C**H(CH$_3$)$_2$ of *p*-cymene), 29.82 (-**C**H$_2$ of Cy), 24.24 (-**C**H$_2$ of Cy), 21.31 (-CH(**C**H$_3$)$_2$), 17.36 (-**C**H$_3$, of *p*-cymene). ^{31}P-{^{1}H} NMR (CDCl$_3$, ppm): δ 118.18 (s, O**P**Ph$_2$). IR (KBr pellet in cm^{-1}): υ (N H): 3313, (CH): 3054, 3015, 2907, 2855, (C-C-Cp): 1426, (O-P): 1008; Anal. Calc. for [C$_{72}$H$_{72}$N$_2$O$_2$P$_2$Ru$_2$Cl$_4$] (1403.274 g/mol): C 61.63, N 2.00, H 5.17; found: C 61.49, N 1.92, H 4.98 %, [α]$_D^{20}$ = +8.3° (c = 1, CHCl$_3$)."

4.3.5. 1-({[(1R,2R)-2-{[(2-{[bis(propan-2-yl)phosphanyl]oxy}naphthalen-1-yl)methyl idene]amino}cyclohexyl]imino}methyl)naphthalen-2-ylbis(propan-2-yl)phosphinite(bis(dichloro-ɳ^6-*p*-cymeneruthenium(II)) (5)


(2)   [Ru(p-cymene)Cl$_2$]$_2$ CH$_2$Cl$_2$ **(5)**
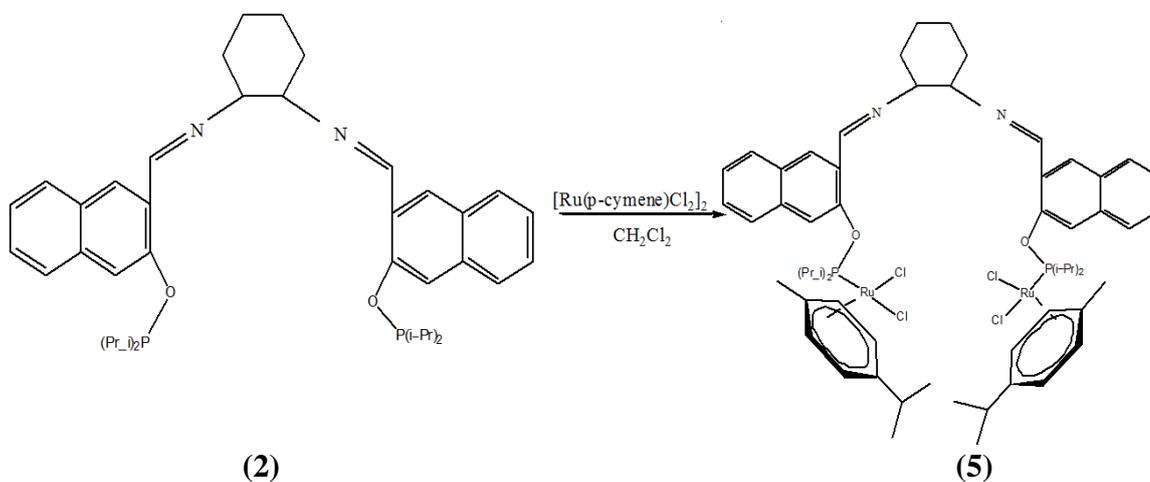
"Yield: 170 mg, 89.5 %, m.p: 120-122 °C. ^{1}H NMR (CDCl$_3$, ppm): δ 9,28 (s, 2H, -N=C**H**), 7.28-7.78 (m, 12 H, aromatic protons), 5.31-5.54 (m, 8H, aromatic protons of *p*-cymene), 3.82 (s, 2H, -C**H**N), 2.06-2.30(m, 2H, -C**H**(CH$_3$)$_2$ of *p*-cymene), 1.84-1.98 (m, 2H, -C**H** of Cy), 1.72 (s, 6H, -C**H$_3$**, of *p*-cymene), 1.11-1.45 (m, 32H, -CH(C**H$_3$**)$_2$ + -C**H$_2$** of Cy), 0.85-0.89 (m, 12H, -CH(C**H$_3$**)$_2$ of p-cymene).^{13}C NMR (CDCl$_3$, ppm): δ 173.3, 137.20, 133.61, 129.50, 127.81, 126.73, 124.54, 122.60, 118.66, 111.63

(aromatic carbons), 160.13 (-N=$\underline{C}$H), 111.31, 99.51 (ipso *p*-cymene), 88.79, 88.74, 86.50, 85.64 (aromatic of *p*-cymene), 68.05 ($\underline{C}$H of Cy), 32.07(-$\underline{C}$H$_2$ of Cy), 30.44 (-$\underline{C}$H(CH$_3$)$_2$ of *p*-cymene), 29.79 (-CH($\underline{C}$H$_3$)$_2$), 24.74 (-$\underline{C}$H$_2$ of Cy), 22.11(-CH($\underline{C}$H$_3$)$_2$ of *p*-cymene), 18.20, 18.51(-CH($\underline{C}$H$_3$)$_2$), 17.42 (-$\underline{C}$H$_3$, of *p*-cymene). ^{31}P-{^{1}H} NMR (CDCl$_3$, ppm): δ 160.84 (s, O$\underline{P}$CH(CH$_3$)$_2$). IR (KBr pellet in cm^{-1}): υ (N H): 3313, (CH): 3054, 3015, 2907, 2855, (C-C-Cp): 1426, (O-P): 1008; Anal. Calc. for [C$_{60}$H$_{80}$N$_2$O$_2$P$_2$Ru$_2$Cl$_4$] (1267.206 g/mol): C 56.87, N 2.21, H 6.36; found: C 56.42, N 2.09, H 6.12 %, [α]$_D^{20}$ = -10.3^o (c = 1, CHCl$_3$)."

4.3.6. 1-({[(1R,2R)-2-[({2-[(dicyclohexylphosphanyl)oxy]naphthalen-1-yl} methylidene)amino]cyclohexyl]imino}methyl)naphthalen-2-yldicyclohexyl phosphinite(bis(dichloro-η ^{6}-*p*-cymeneruthenium(II)) (6)


(3)   (6)
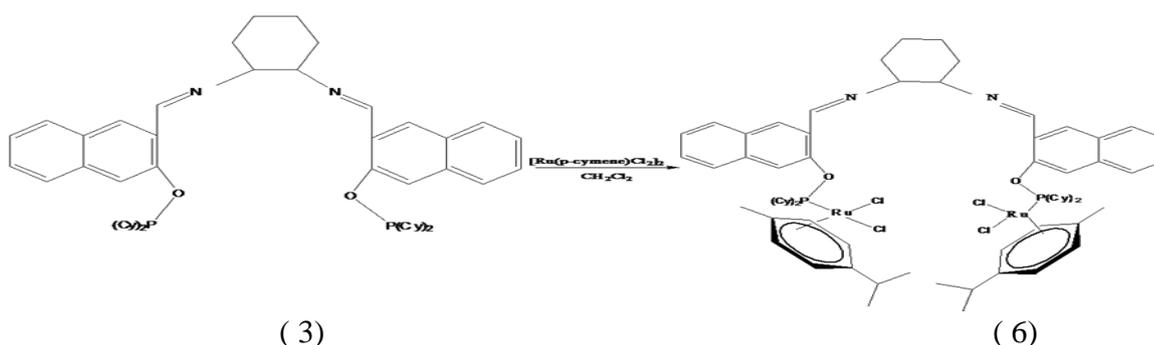
"Yield: 190 mg, 88.8 %, m.p: 120-122 ^{o}C. ^{1}H NMR (CDCl$_3$, ppm): δ 9,16 (s, 2H, -N=C$\underline{H}$), 7.10-7.81 (m, 12 H, aromatic protons), 5.29-5.55 (m, 8H, aromatic protons of *p*-cymene), 3.80-3.85 (m, 2H, -C$\underline{H}$N), 2.10-2.30(m, 2H, -C$\underline{H}$(CH$_3$)$_2$ of *p*-cymene), 1.96-2.06 (m, 4H, -C$\underline{H_2}$ of Cy), 1.82 (s, 6H, -C$\underline{H}_3$, of *p*-cymene), 1.24-1.80 (m, 48H, cyclohexyl protons) 0.80-0.92 (m, 12H, -CH(C$\underline{H}_3$)$_2$ of p-cymene).^{13}C NMR (CDCl$_3$, ppm): δ 172.10, 136.62, 133.40, 128.28, 127.80, 126.55, 123.30, 122.80, 118.50, 107.20 (aromatic carbons), 158.03 (-N=$\underline{C}$H), 110.98, 97.51 (ipso *p*-cymene), 88.70, 87.98, 87.74, 86.48 (aromatic of *p*-cymene), 68.00 ($\underline{C}$H of Cy), 37.10 (-$\underline{C}$H$_2$ of Cy), 30.35 (-$\underline{C}$H(CH$_3$)$_2$ of *p*-cymene), 29.73, 26.96, 26.70, 26.55, 26.35, 26.21 (-$\underline{C}$H$_2$ of Cy), 22.15 (-CH($\underline{C}$H$_3$)$_2$ of *p*-cymene), 17.44 -$\underline{C}$H$_3$ of *p*-cymene). ^{31}P-{^{1}H} NMR (CDCl$_3$, ppm): δ 155.42 (s, O$\underline{P}$(Cy)$_2$). IR (KBr pellet in cm^{-1}): υ (N H): 3215, (CH): 3073, 3053, 2960,

2823, (PPh): 1436, (O-P): 1024; Anal. Calc. for $[C_{72}H_{96}N_2O_2P_2Ru_2Cl_4]$ (1427.466 g/mol): C 60.58, N 1.96, H 6.78; found: C 60.35, N 1.53, H 6.49 %, $[\alpha]_D^{20} = +9.0^o$ (c = 0.65, $CHCl_3$)."

4.3.7. Catalytic Results

Within the scope of this thesis, catalytic activities of ruthenium complexes **4-6** in asymmetric transfer hydrogenation reactions of acetophenone and its derivatives were investigated and the results are shown in Tables 4.1 and 4.2.

Table 4.1 "Transfer hydrogenation of acetophenone with *iso*-PrOH catalyzed by Ru(II)-phosphinite complexes (**4**, **5** and **6**)."

Entry	Catalyst	S/C /KOH	Time	Conversion(%)[f]	ee(%)	TOF(h^{-1})[d]
1	4[a]	100:1:5	1	98	44(R)	98
2	5[a]	100:1:5	4	97	22(R)	25
3	6[a]	100:1:5	3	99	23(R)	32
4	4[b]	100:1	24	trans------	------	--------
5	5[b]	100:1	24	trans------	--------	--------
6	6[b]	100:1	24	trans------	--------	--------
7	4[c]	100:1:5	72	<10	60(R)	<10
8	5[c]	100:1:5	72	<10	34(R)	<10
9	6[c]	100:1:5	72	<10	37(R)	<10
10	4[d]	100:1:5	2	96	40(R)	48
11	5[d]	100:1:5	6	98	25(R)	16
12	6[d]	100:1:5	5	95	28(R)	19
13	4[e]	500:1:5	20	97	38(R)	<10
14	5[e]	500:1:5	24	98	17(R)	<10
15	6[e]	500:1:5	24	96	19(R)	<10

"**Reaction conditions:**

[a] Refluxing in *iso*-PrOH; acetophenone/Ru/KOH, 100:1:5; [b] Refluxing in *iso*-PrOH; acetophenone/Ru, 100:1, in the absence of base; [c] At room temperature; acetophenone/Ru/KOH, 100:1:5; [d] Refluxing the reaction in air; [e] Refluxing in *iso*-PrOH; acetophenone/Ru/KOH, 500:1:5; [f] Determined by GC (three independent

catalytic experiments); [g] Referred at the reaction time indicated in column; TOF= (mol product/mol Ru(II)Cat.)x h^{-1}."

Table 4.2 "Transfer hydrogenation results for substituted acetophenones catalyzed Ru(II)-phosphinite complexes (**4**, **5** and **6**)."

Entry	R	Time	Conversion(%)[b]	ee (%)	TOF(h^{-1})[c]
Cat: Ru(II) complex, **4**					
1	4-F	30 min	99	45 (R)	198
2	4-Cl	30 min	97	49 (R)	194
3	4-Br	45 min	97	42 (R)	129
4	2-MeO	3 h	98	60(R)	33
5	4-MeO	2 h	96	57 (R)	48
Cat: Ru(II) complex, **5**					
6	4-F	2 h	98	23	49
7	4-Cl	2 h	97	24	49
8	4-Br	2 h	96	21	48
9	2-MeO	3 h	92	32	31
10	4-MeO	3 h	96	29	32
Cat: Ru(II) complex, **6**					
11	4-F	3 h	98	24	33
12	4-Cl	3 h	97	23	32
13	4-Br	3 h	94	20	31
14	2-MeO	3 h	92	28	31
15	4-MeO	3 h	90	25	30

"**Reaction conditions:**
[a] Catalyst (0.005 mmol), substrate (0.5 mmol), *iso*-PrOH (5 mL), KOH (0.025 mmol %), 82 °C, respectively, the concentration of acetophenone derivatives is 0.1 M; [b] Purity of compounds is checked by NMR and GC (three independent catalytic experiments), yields are based on methyl aryl ketone; [c] TOF = (mol product/mol Cat.) x h^{-1}."

5.RESULTS AND DISCUSSION

5.1.Synthesis of new ligands (1-3) and their Ru(II) complexes

In the present work, firstly, 1-({[(1R,2R)-2-{[(2-hydroxynaphthalen-1-yl)methylidene] amino}cyclohexyl]imino}methyl)naphthalen-2-ol was synthesized as precursors for phosphinites (Ambroziak et al. 2002). Then, new chiral C_2-symmetric bis(phosphinite) ligands were prepared the corresponding 1-({[(1R,2R)-2-{[(2-hydroxynaphthalen-1-yl)methylidene]amino} cyclohexyl]imino}methyl) naphthalen-2-ol and two equivalents of $(Cy)_2PCl$, PPh_2Cl or $P(i\text{-}Pr)_2Cl$, which were characterized by the $^{31}P\text{-}\{H\}$ NMR spectroscopy. At the beginning of the reactions, the resonances of the starting materials were at δ= 81.0, 133.8 and 127.58 ppm for PPh_2Cl, $P(i\text{-}Pr)_2Cl$ and $(Cy)_2PCl$, respectively, which vanished and new singlets obtained in downfield corresponding to the phosphinites at 114.09, 150.62-149.91, 146.75-146.24 ppm for compounds **1**, **2** and **3**, respectively.

Then, the dinuclear ruthenium complexes **4-6** were synthesized as orange-red crystalline solids in good yields by treatment of $[Ru(\eta^6\text{-}p\text{-cymene})(\mu\text{-Cl})Cl]_2$ with phosphinites **1-3** in 1:1 molar ratio. They were obtained as shown by singlet resonances in the $^{31}P\text{-}\{H\}$ NMR spectra at 118.18, 160.84 and 156.32 ppm for **4-6**, respectively. The ^1H, $^{13}C\text{-}\{^1H\}$ NMR, IR spectroscopic data and the elemental analysis data of the complexes were in aggree with the expected compounds.

5.2. Transfer Hydrogenation Studies

Ruthenium complexes **4-6** were tested as catalysts in the transfer hydrogenation of the acetophenone to the corresponding chiral alcohol by *iso*-PrOH/KOH as a reducing system. As expected, they promoted the reduction of acetophenone to corresponding alcohol ((*R*), *(S)*-1-phenylethanol). At room temperature, transfer hydrogenation of acetophenone occurred considerably sluggishly and its conversion was too low (<10 % after 72h, Table 4.1, Entries 7-9) in all the reactions. However, when the temperature was increased to 82 ^{o}C, its yield became high enough. During the reaction, the color of the reaction solution altered from orange to deep red. When the base was added, the reaction begins instantly without any induction time. The range of conversions was between 90 to 99 % after 1-4 h for **4-6**. Furthermore, it is significant

that the reactivity of the complexes is different, as seen in Table 4.1, which implies that the reaction with **5**, **6** progressed more slowly and with less enantioselectivity than that with **4**. The selection of base, such as KOH and NaOH, had little effect on the conversion and enantioselectivity. "The base facilitates the formation of ruthenium alkoxide by abstracting proton of the alcohol and subsequently alkoxide undergoes β-elimination to give ruthenium hydride, which is an active species in this reaction (Raja et al. 2010)." This is the mechanism suggested by some researchers on the works of ruthenium catalyzed transfer hydrogenation reaction by metal hydride intermediates. Additionally, optimization studies exhibited that good catalytic activity was gained with a base/cat. ratio of 5:1.

Encouraged by the enantioselectivities attained in these initial studies, we next extended our researchs to involve asymmetric hydrogenation of substituted acetophenone derivatives. The findings in Table 4.2 demonstrate that a variety of acetophenone derivatives can be hydrogenated with good to high enantioselectivities. Thus, all acetophenone derivatives were tested under the conditions optimized for acetophenone. Complex **4** showed considerable high activity for the most of the ketones. As expected, we found that the introduction of electron withdrawing substituents, such as F, Cl and Br to the *p-* position of the aryl ring of the ketone decreased the electron density of the C=O bond so that the activity was enhanced leading to easier hydrogenation. An electron-withdrawing group such as fluoro group to the *p*-position was useful to achieve excellent conversion and enantioselectivity (up to 45% ee, Table 4.2), while the introduction of an electron-donating substituent such as methoxy group to the *p*-position caused to lower enantioselectivity while sustaining good activity. The position and electronic assets of the ring substituents also affected hydrogenation results. The introduction of an electron-donating group such as methoxy group to the *p*-position slows down the reaction, but that to the *o*-position increases the rate and improves the enantioselectivity (Table 4.2). The best result was acquired in the reduction of *o*-methoxyacetophenone among all selected ketones affording 60% ee (Table 7, Entry 4). The data in Table 7 clearly displayed that a strong electron-withdrawing substituents, such as fluoro, chloro, bromo were able to cause higher conversion but with slightly lower enantiomeric purity. On the contrary, the most electron donating substituent ($-OCH_3$) resulted in higher conversion and higher ee. [31]P-

{^{1}H}-NMR spectrum was obtained immediately after the catalytic reaction to probe the evolution of the catalyst. The single resonance at 21.6 ppm in the spectrum is corresponding to hydrolysis product diphenylphosphinous acid, $Ph_2P(O)H$.

5.RESULTS AND DISCUSSION

6.CONCLUSIONS

In conclusion, three new efficient ruthenium (II) complexes **4-6** were developed from C_2 symmetric phosphinite ligands (**1**-**3**), and they were used in Asymmetric Transfer Hydrogenation of acetophenone derivatives. In the catalytic reaction, high conversion and moderate to good enantioselectivity were attained. Therefore, the performance of these catalysts was good. I hope this study will reveal further studies to go on. Future works will focus on increasing the enantioselectivity of the catalytic system.

APPENDICES

³¹P NMR Spectra of the Ligands and the Complexes

Spectrum 1. 1-({[(1R,2R)-2-[({2-[(diphenylphosphanyl)oxy]naphthalen-1-yl}methylidene)amino]cyclohexyl]imino}methyl)naphthalen-2-yl diphenylphosphinite (**1**)

Spectrum 2. 1-({[(1R,2R)-2-{[(2-{[bis(propan-2-yl)phosphanyl]oxy}naphthalen-1-yl)
methylidene]amino}cyclohexyl]imino}methyl)naphthalen-2-yl bis(propan-2-yl)phosphinite (**2**)

Spectrum 3. 1-({[(1R,2R)-2-[({2-[(dicyclohexylphosphanyl)oxy]naphthalen-1-yl}methylidene)amino]cyclohexyl]imino}methyl)naphthalen-2-yl dicyclohexylphosphinite (**3**)

Spectrum 4. 1-({[(1R,2R)-2-[({2-[(diphenylphosphanyl)oxy]naphthalen-1-yl}methylidene)amino]
cyclohexyl]imino}methyl)naphthalen-2-yldiphenylphosphinite(bis(dichloro-ɳ 6-p-cymene ruthenium(II))
(**4**)

Spectrum 5. 1-({[[(1R,2R)-2-{[(2-{[bis(propan-2-yl)phosphanyl]oxy}naphthalen-1-yl)
methylidene]amino}cyclohexyl]imino}methyl)naphthalen-2-ylbis(propan-2-yl)phosphinite(bis (dichloro-
η⁶-p-cymeneruthenium(II)) (**5**)

Spectrum 6. 1-({[(1R,2R)-2-[({2-[(dicyclohexylphosphanyl)oxy]naphthalen-1-yl}methylidene)amino]cyclohexyl]imino}methyl)naphthalen-2-yldicyclohexylphosphinite(bis (dichloro-η 6-p-cymeneruthenium(II)) **(6)**
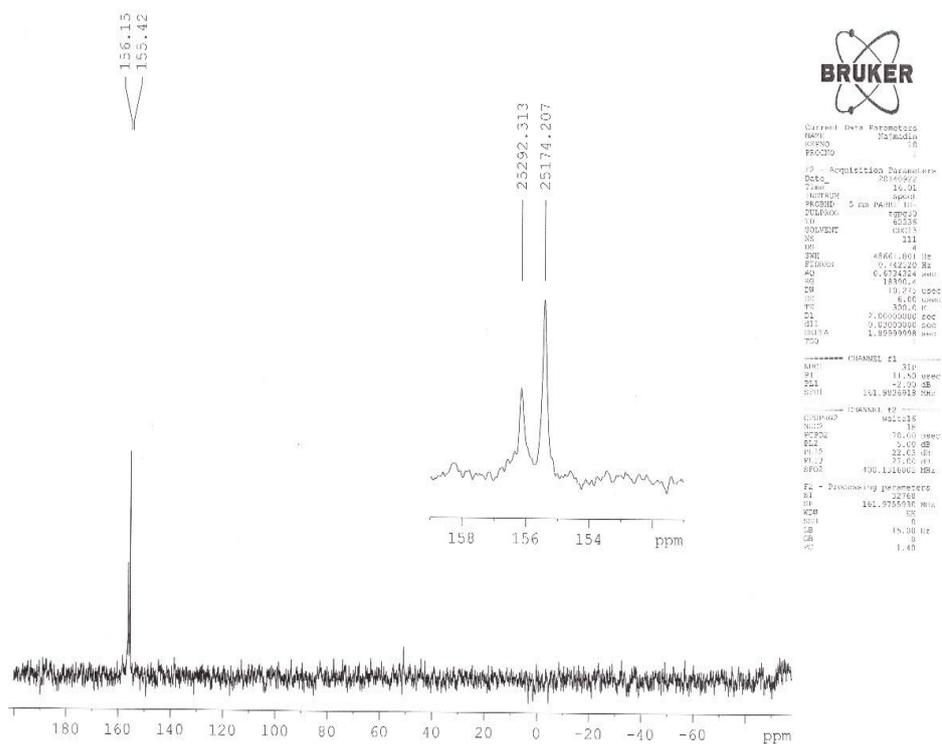
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CURRICULUM VITAE

:

Name, Surname   : Najmuldain Abdullah SALEH

Birth Place   : Musul/Naynawa

Date of Birth   : 2/5/1971

Marital Status   : Married

Country   : Iraq

Education (Institute and Year)

High School: Preparatory Al-zoohor for Boys 1987-1990

Graduate   : Mosul University College of Education, Department of Chemistry, 1991-1997

Master   : University of Dicle Institute of Natural and Applied Sciences Department Of Chemistry 2013-2015.