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ABSTRACT

Aromatic and aliphatic vinyl sulfones and sulfoxides have been hydroformylated with CO/H_2 in the presence of the zwitterionic rhodium complex, 1,5-cyclooctadiene rhodium(I) tetraphenylborate, $(1,5\text{-}(COD)Rh^{+}(\eta^{6}\text{-}C_6H_5)B(C_6H_5)_3^{-})$, to give previously unknown aldehydic sulfones and sulfoxides in excellent yields and regioselectivities. The hydroformylation of phenyl vinyl sulfoxide in the presence of $1,5\text{-}(COD)Rh^{+}(\eta^{6}\text{-}C_6H_5)B(C_6H_5)_3^{-}$ and the chiral phosphine ligand, BINAP, demonstrated considerable stereodifferentiating ability (up to 50% de). The hydroesterification of vinyl esters with CO/MeOH/bis(triphenylphosphine)palladium(II) dichloride, $((PPh_3)_2PdCl_2)$, has been studied. The critical necessity of catalytic amounts of acid, such as H_3PO_4 (1 mol % relative to substrate), was revealed. This reaction is also catalyzed by the cationic palladium(II) hydrido complex, $[(Cy_3P)_2Pd(H)(H_2O)]^{+}BF_4^{-}$. Lactic acid derivatives can be synthesized with modest ee's (up to 30%) using $[(Cy_3P)_2Pd(H)(H_2O)]^{+}BF_4^{-}$ in the presence of BINAP. Design and synthesis of new chiral borate ligands and their rhodium complexes have been undertaken.

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Finally I would like to thank my parents for always believing that I could make it.

CHAPTER 1

INTRODUCTION

CHAPTER 2

ZWITTERIONIC RHODIUM COMPLEX CATALYZED HYDROFORMYLATION OF VINYL SULFONES AND SULFOXIDES

CHAPTER 3

PALLADIUM CATALYZED HYDROESTERIFICATION OF VINYL ESTERS

CHAPTER 4

DESIGN AND ATTEMPTED SYNTHESIS OF NEW CHIRAL RHODIUM COMPLEXES FOR ASYMMETRIC HYDROFORMYLATION

CHAPTER 5

EXPERIMENTAL

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

DPPB	1,4-bis(diphenylphosphino)butane
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
ee	enantiomeric excess
de	diastereomeric excess
COD	cyclooctadiene
$Eu(hfc)_3$	tris[(3-heptafluoropropylhydroxy-methylene)-(+)-camphorato]europium (III)
l-DOPA	[3-(3,4-dihydroxyphenyl)-L-alanine
DIPAMP	1,2-ethanediylbis[(o-methoxyphenyl)-phenylphosphine
DIOP	2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
CHIRAPHOS	2,3-bis(diphenylphosphino)butane
DIPT	diisopropyltartrate
BPBP	2,2'-bis(diphenylphosphino)-1,1'-biphenyl
BPPFA	N,N-dimethyl-1-[1',2-bis(diphenyl-phosphino)ferrocenyl]ethylamine
DIPHOL	2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(dibenzophosphole)
L*	chiral ligand
acac	acetylacetonate
BPPM	N-butoxycarbonyl-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine

BINAPHOS	1,1'-binaphthyl-2,2'-diyl hydrogen phosphate
Ln	ligand
Cy	cyclohexyl
PTC	phase transfer catalysis
TBHP	t-butyl hydroperoxide

CHAPTER 1

INTRODUCTION

1. GENERAL INTRODUCTION

1.1 ASYMMETRIC SYNTHESIS AND CATALYSIS

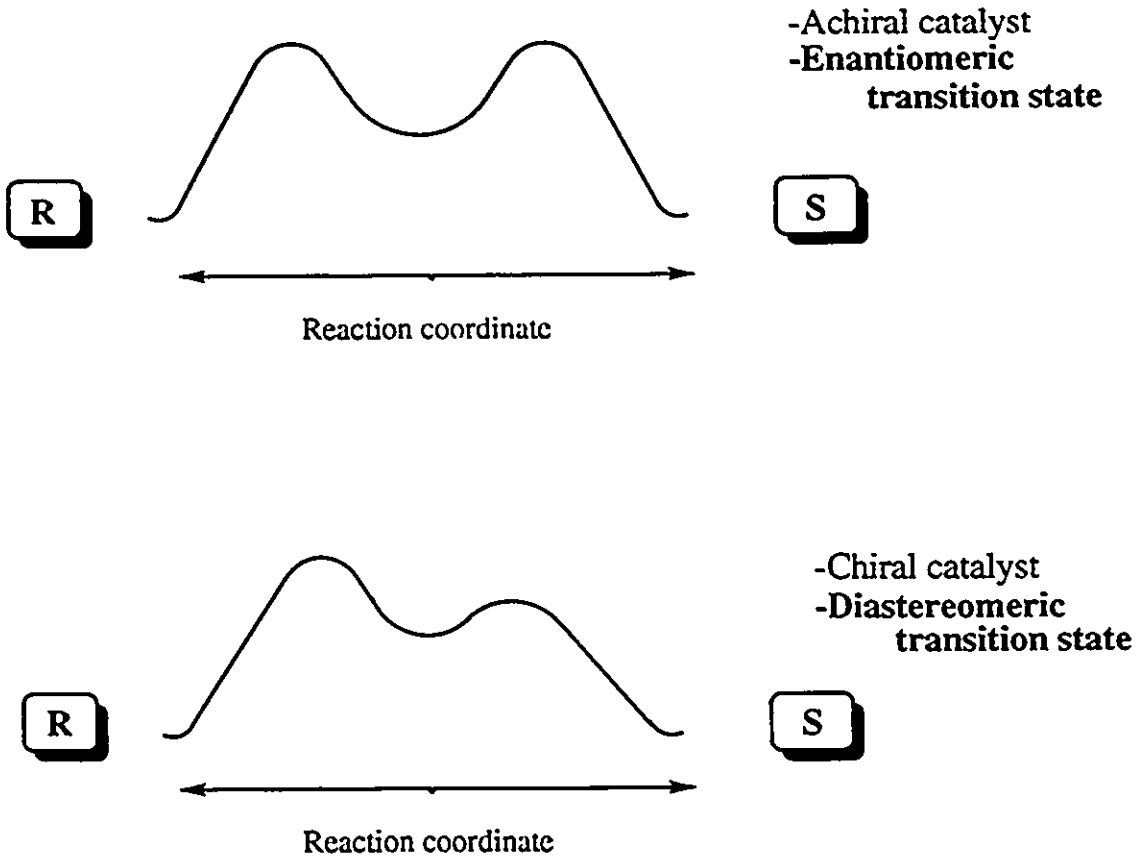
Homogeneous, transition metal catalyzed organic transformations are of interest for inorganic and organic chemists, from both a fundamental and applications perspective.[1-7] Transformations occurring on the metal template offer unique, alternative and/or facile pathways to a wide variety of products. These transformations can be selective or specific in terms of chemo-, regio- and stereo(enantio)differentiation. Remarkable success has been reached in solving the first two problems. However, the achievements in solving the third problem, which still remains a great challenge, have been rather modest.

Before embarking on a discussion of stereodifferentiating catalysis, it is important to clarify the terminology. Throughout this thesis, the stereochemical terminology will follow the rules outlined by Izumi and Tai.[8] Since all catalytic transformations discussed involve prochiral substrates, the term, enantiodifferentiating, refers to reactions which produce one enantiomer in excess of the other as a consequence of using an optically active catalyst. The differentiating ability is the measure of the ratio of product enantiomers produced. Generally, the numerical value quoted for the differentiating ability, is reported as an enantiomeric excess which is the ratio of the difference over the sum of the two enantiomers.

There are several methods for producing optically active materials. The oldest is optical resolution. The major disadvantage of this method is that even in the best case only a 50% yield of optically pure product can be recovered. A second approach is to begin with an optically active substrate and affect a chemical change which produces an additional chiral centre on the same molecule. Thus, some degree of differentiation is produced due to the diastereomeric nature of the transition state. Similar to the case of chiral resolution, this method is limited to only one mole of chiral substrate producing one mole of chiral product. The final, and most attractive method is chiral amplification. That is, to begin with a prochiral substrate, subject it to a chiral environment, e. g., asymmetric catalyst, and produce potentially infinite amounts of optically pure product. This transformation necessitates an optically active catalyst because if the catalyst is achiral, the transition state will be enantiomeric, producing the two enantiomers in equal amounts. In contrast, if the catalyst is chiral, the transition state will be diastereomeric having unequal energies. (see Scheme 1.1)

Asymmetric catalysis is a most desirable and challenging goal. An ideal catalyst would be one which mimics the naturally occurring enzymes in terms of their selectivity and efficiency. Enzymes, despite being the best known stereodifferentiating systems are restricted to very specific substrates and reactions and are not easily modified. Synthetic catalysts have the flexibility (in theory) to facilitate numerous reactions by choosing the right combination of ligand and

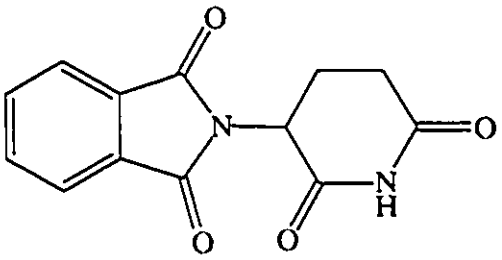
metal. Since the early 1970's, there has been a great deal of attention dedicated to this effort.[9-14]



Scheme 1.1

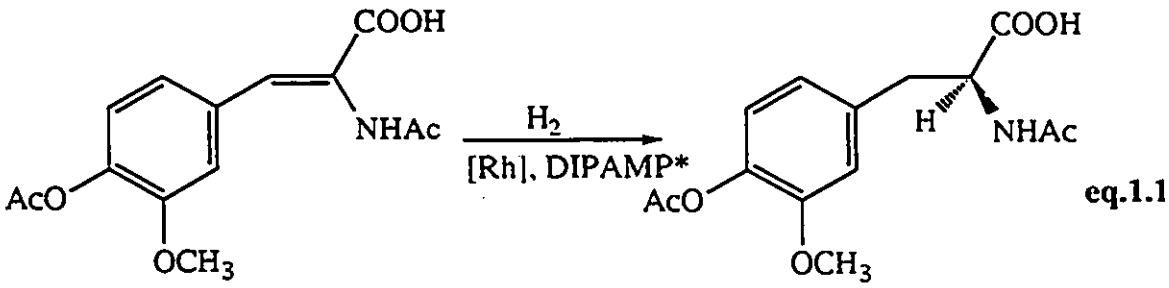
An historical example which has prompted the translation of academic interest in asymmetric catalysis to industrially applied syntheses is given by the production and sale of racemic thalidomide, **1.1**.[15] One enantiomer of thalidomide was an effective pain reliever used by pregnant women. Unfortunately the opposite enantiomer did

not remain an innocent partner, but rather caused extensive fetal deformities. This has necessitated that future pharmaceutical production of compounds containing chirality be produced in optically pure form.



1.1 THALIDOMIDE

Perhaps the most famous success story to this end is the Monsanto production of *l* -DOPA, a drug used for the treatment of Parkinson's disease (eq. 1.1).[16] Catalytic asymmetric hydrogenation of a cinnamic acid derivative resulted in the production of l-DOPA in 95% ee.



eq.1.1

l-DOPA 95% ee

* see Fig. 1.2 for structure of DIPAMP

Since this time, many other companies have incorporated homogeneous asymmetric catalysis into their processes.[15] Thus, there is a continuous demand for new and improved chiral complexes which can function efficiently in a variety of stereoselective transformations.

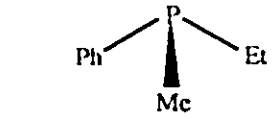
1.2 CHIRAL CATALYSTS

Numerous efficient achiral catalytic systems form the foundation for the design and production of chiral catalysts. It is from this data bank that modifications of the existing complexes can be focused in an effort to incorporate elements of chirality. There are two general methods for the incorporation of asymmetry into transition metal complexes. One is direct synthesis of chiral catalysts. This method, although successful, is sometimes encumbered by sophisticated and labour-consuming synthesis. A more popular and simplified method is the *in situ* generation of a chiral catalyst by the addition of an optically active ligand and a soluble transition metal complex. Independent of the method used to generate the complex, the requirement is to incorporate some element of asymmetry.

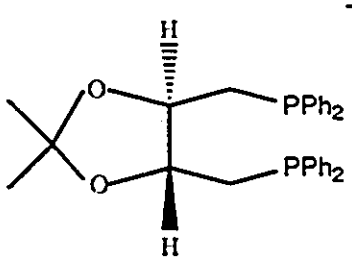
The chirality of the transition metal complex can be located on the metal itself or on one of its associated ligands. It should be noted that chiral complexes with the chirality centered on the metal have been studied and used for stoichiometric asymmetric transformations.[14] However, this class of chiral complexes are rarely employed in enantioselective catalysis. This is not surprising since, in

most cases, it is necessary during a catalytic cycle to have facile ligand exchange which in turn would not guarantee a rigid stereochemical environment for the substrate. In contrast however, there are numerous examples of transition metal complexes which have ligands containing either centres or elements of asymmetry.

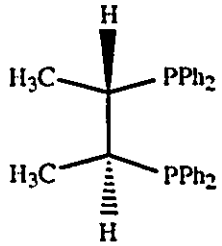
Centres of chirality can be either on the heteroatom directly attached to the metal or further removed from the metal, i. e., located several bonds away. From the numerous examples known, a few selected representations are shown in Figure 1.1.[17-21] These chiral ligands can be obtained from the readily available "chiral pool" or through synthetic means. A second and very important class of chiral ligands, are those containing an axis of symmetry, namely a C_2 symmetry axis.[17] It is not necessary that the ligand be asymmetric, only dissymmetric (lacking mirror or inversion symmetry). Kagan's introduction of DIOP as a C_2-symmetric auxiliary for the very successful introduction of asymmetry marked the beginning of this trend.[18] Since then, it has become almost universally observed that chiral auxiliaries having a C_2 axis of symmetry are very successful as stereochemical directors, yielding some of the highest levels of stereodifferentiation. The best results to date of asymmetric catalysis have been demonstrated in hydrogenation reactions using the dissymmetric ligand 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, BINAP.[23]



- monodentate phosphine
- chirality at the phosphorus[17]

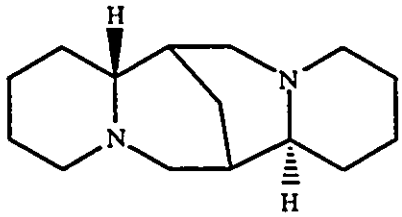


R,R-DIOP[18]



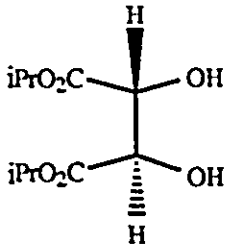
(S,S)-CHIRAPHOS[19]

-bidentate phosphine
-chirality on the carbon atoms



Sparteine[20]

-bidentate nitrogen
-chirality on the carbons



DIPT[21]

-bidentate oxygen
-chirality on the carbons

Figure 1.1 Selected examples of asymmetric ligands containing centres of chirality

The important features and characteristics of BINAP (Figure 1.2) which cause it to function as a very efficient chiral inducing ligand for a variety of transition metals are four-fold. First, it is fully aromatic which allows it to stabilize low oxidation state transition metals. The C1-C1' pivot allows sufficient flexibility to accommodate different sized metal centres. Despite this welcomed flexibility, it is at the same time structurally rigid due to the fact that all of the carbons are sp^2-hybridized. Finally, it contains only an axial element of chirality which results in halving the possible number of conformations at the diastereomeric transition state. Additionally, both R(+) and S(-) BINAP are available which allows the potential to generate both R and S products. With the realization of the value of C_2-symmetry and the subsequent success of BINAP as an optical inducing ligand, many other ligands have been developed with this in mind.[9]

Very recently, a novel strategy for the generation of chiral catalysts has been developed.[24] This new approach utilizes a racemic complex followed by selective poisoning of one hand of the chiral catalyst with an inexpensive chiral poison. The promising feature of this approach is that the sometimes cumbersome synthetic routes to optically pure ligands can be avoided.

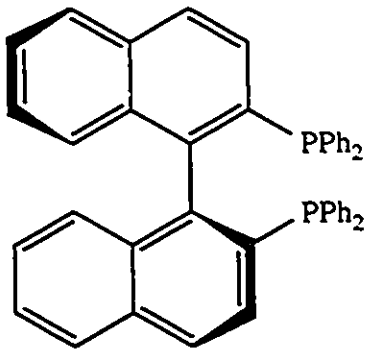
1.3 SELECTED ASYMMETRIC CATALYZED REACTIONS

1.3.1 ASYMMETRIC HYDROGENATIONS

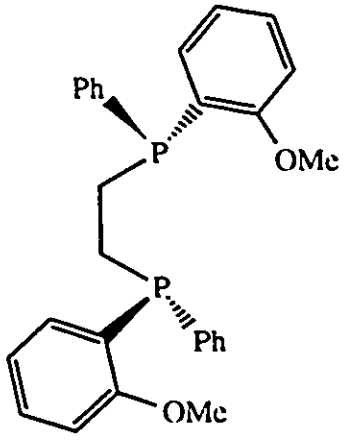
The most significant advancements in the application of asymmetric transition metal complexes to organic transformations have been in the area of homogeneous hydrogenation reactions. The first example of enantioselectivity arose with the modification of Wilkinson's rhodium complex, incorporating a chiral monodentate phosphine ligand.[25] Significant improvements in optical induction was achieved soon after through the use of chiral bidentate phosphines (Figure 1.2).[26] Since this time, extensive research in many different laboratories have resulted in optical induction as high as 100% for a variety of olefin/ligand/transition metal combinations. Selected examples are shown in Table 1.1.[25-27]

The nature of the substrate plays a significant role in the final outcome of the optical yield. Those olefins containing functionality (coordinating polar groups) adjacent to the double bond can help to direct the reaction thus affecting higher optical yields. This is demonstrated in Fig 1.3 for the hydrogenation of (Z)-α-acetamidocinnamate.[28,29] For less functionalized substrates, the ligands required become more complex.[12] In addition to carbon-carbon double bonds, asymmetric catalytic hydrogenations have been very successfully applied to unsymmetric ketones with enantiomeric excesses reaching 100% for the resulting secondary alcohols.[30] Asymmetric hydrogenation reactions are still an active area of

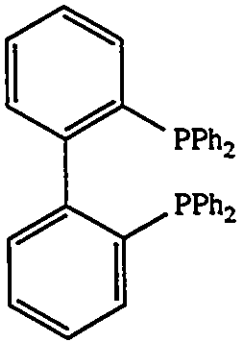
research, but a new challenge is to achieve similarly high optical activity for asymmetric carbon-carbon bond forming reactions.



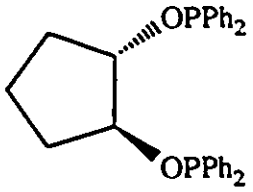
BINAP



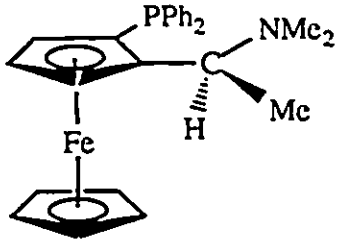
DIPAMP



BPBP



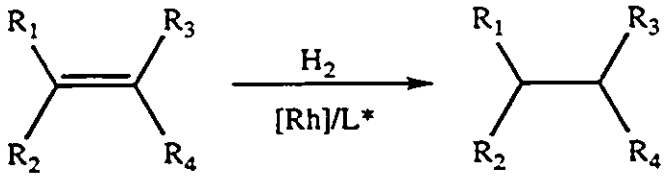
BDDCP



BPPFA

Figure 1.2. Bidentate chiral phosphines used in asymmetric hydrogenation and their abbreviations.

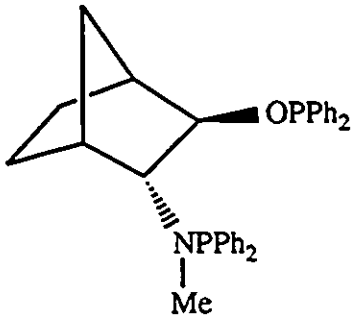
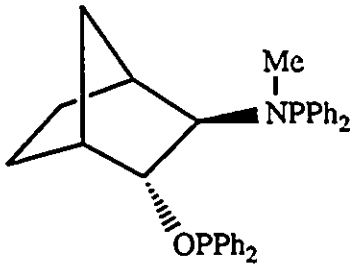
Table 1.1 Asymmetric Catalytic Hydrogenation of Olefins.



R_1, R_2 = H, Ph

R_3 = CO_2H, CO_2Me

R4 = NHCOMe, NHCOPh

L*	% ee (config.)	Ref.
(+) 	87 ± 2 (R)	27
(-) 	87± 2 (S)	27
(R)-BINAP	100 (S)	23
(S)-BINAP	98 (R)	23

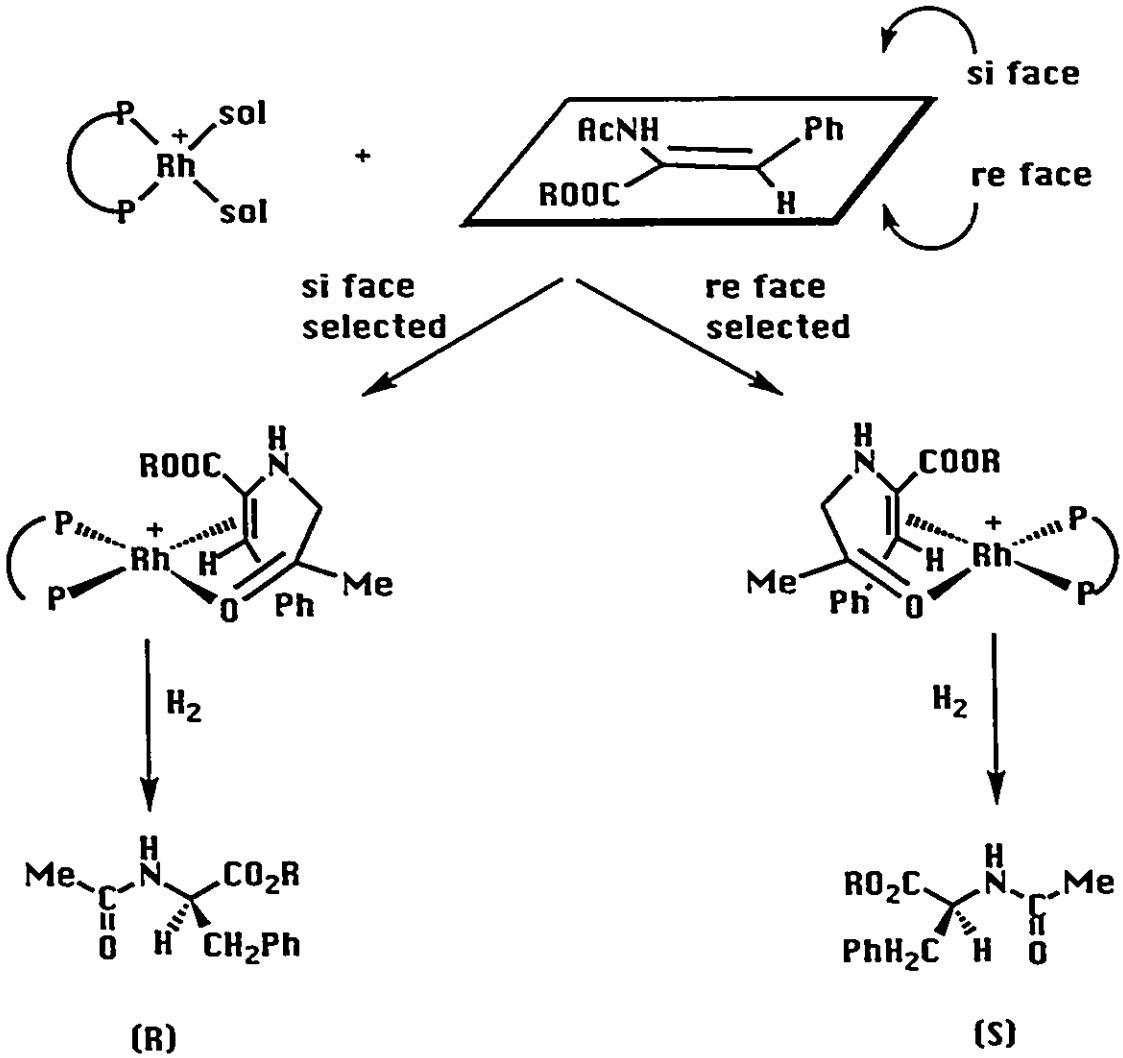


Figure 1.3 Two pathways for the asymmetric hydrogenation of (Z)-(α)-acetamidocinnamate catalyzed by a rhodium complex containing a chiral bidentate ligand.[28]

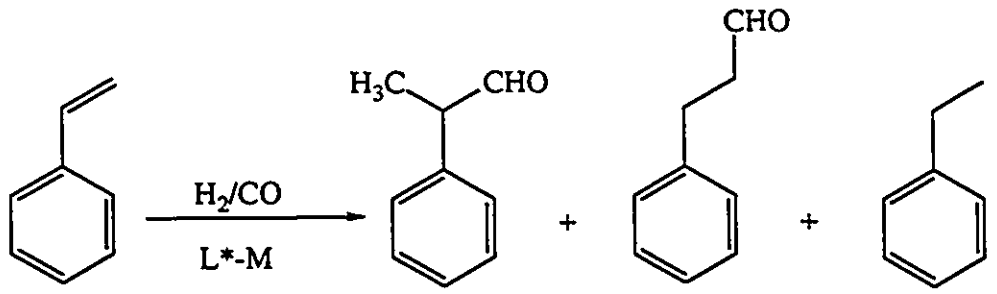
1.3.2 ASYMMETRIC HYDROCARBONYLATION REACTIONS

Unlike the wealth of results available for catalytic asymmetric hydrogenation reactions, those for catalytic asymmetric hydrocarbonylation are much more limited.[3] The challenge remains in developing a catalytic system to synthesize optically pure products

while simultaneously making a new carbon-carbon bond. In accordance with the objectives of our research (see below), only developments in asymmetric hydroformylation and hydroesterification will be considered.

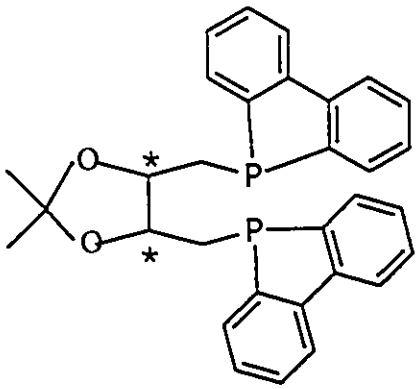
1.3.2.1 ASYMMETRIC HYDROFORMYLATION

The first successful asymmetric hydroformylation results were reported in 1972 with enantiomeric excesses of 1-2%.[31, 32] Extensive investigations followed this discovery but seldom have high enantioselective hydroformylation reactions catalyzed by chiral metal complexes been attained.[33] The substrate for most of this early work was styrene, which produced, in addition to the desired branched aldehyde, (2-phenylpropanal), the linear aldehyde, (3-phenylpropanal), and ethylbenzene (eq. 1.2).



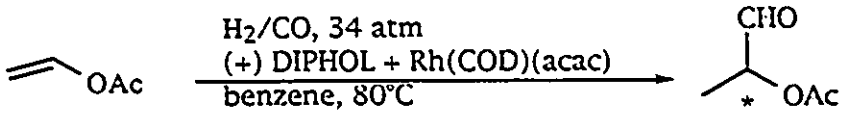
eq.1.2

Optical purities as high as 73% were obtained using rhodium and platinum based complexes with the chiral ligand DIPHOL, **1.2**.[34] However, the selectivity for 2-phenylpropanal remained low.



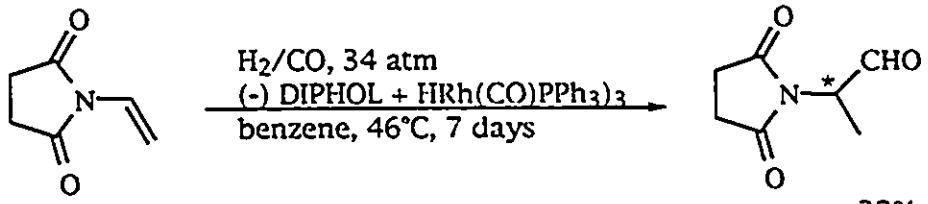
DIPHOL
1.2

The asymmetric hydroformylation of some functionalized olefins yielded modest optical induction, with correspondingly low chemical yields (eq. 1.3 & 1.4).[35, 36]



51% ee (R)

eq. 1.3



32% yield

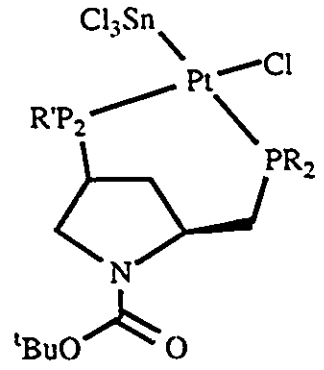
41% ee

eq. 1.4

Extension to other functionalized olefins containing oxygen and nitrogen heteroatoms yielded poor or no optical induction.

More recently, attention has again focused on styrene as a substrate but with a platinum/tin complex containing the chiral ligand

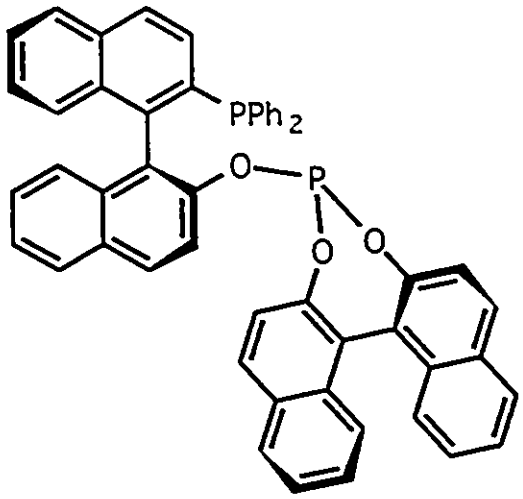
(2S,4S)-4-(diphenylphosphino)-2-[diphenylphosphino)methyl] pyrrolidine, [(-)BPPM]$PtCl_2$•$SnCl_2$, **1.3**.[37, 38]



1.3 [(-)BPPM] $PtCl_2$.$SnCl_2$

Optical purities as high as 96% were obtained when the aldehyde was trapped with triethyl orthoformate. The branched to linear ratio of aldehydes was sometimes as high as ten, but unfortunately, the reaction itself was only 40% selective for aldehyde with the hydrogenated olefin being produced as a significant side product. An efficient homogeneous asymmetric hydroformylating system which will result in high optical purities as well as producing the desired branched aldehydes in high overall yields, remains to be discovered.

It should be noted that very recently high enantioselective hydroformylation of selected olefins was realized using a new phosphinephosphite-Rh(I) complex.[39] This mixed bidentate ligand (**1.4**) was prepared via a multi-step synthesis beginning with readily available 1,1'-binaphthol.



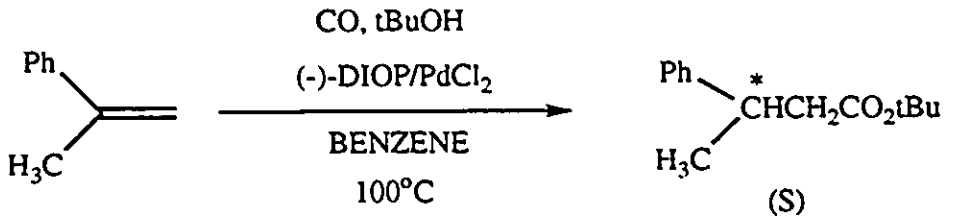
(R,S)BINAPHOS

1.4

$Rh(acac)(CO)_2$ in combination with BINAPHOS was an efficient system for the catalytic hydroformylation of olefins such as vinyl acetate, styrene, and N-vinyl-phthalimide to the corresponding branched aldehydes in 75-95% ee.

1.2 ASYMMETRIC HYDROESTERIFICATION

The results published to date on catalytic asymmetric hydroesterification is even more limited than that for hydroformylation. The first successful example for catalytically producing optically enriched esters appeared in 1973 using (-)-DIOP/$PdCl_2$ as the chiral catalyst.[40] The asymmetric hydroesterification of α-methylstryene (eq. 1.5) has been studied extensively.[41] Some of these early results are summarized below. (Table 1.2)

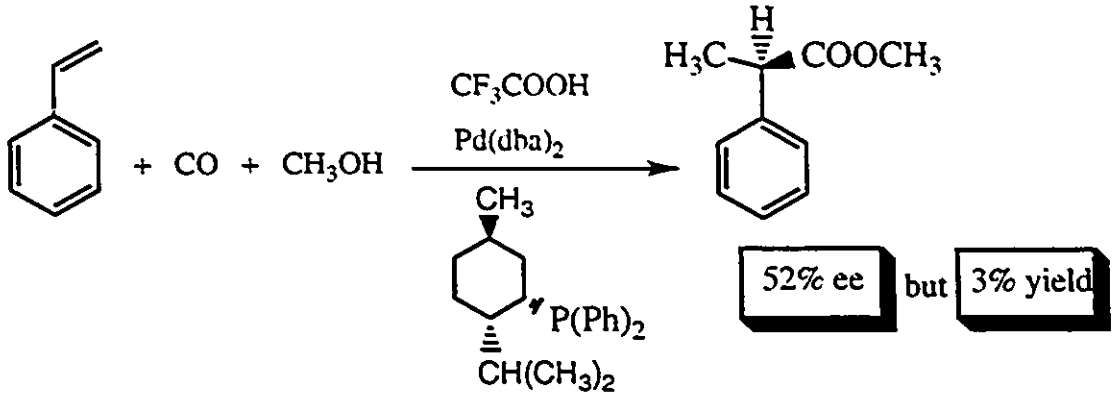


eq. 1.5

Table 1.2 Hydroesterification of α-methylstyrene in the presence of DIOP/PdCl2

$DIOP/PdCl_2$	P_{CO}(atm)	%ee
2	50	3.5
2	400	37
2	700	50
1	400	48
0.4	400	59

Perhaps the most significant advance in this area was reported in 1982. Styrene was hydroesterified at low pressure (1-2 atm, CO) in the presence of a palladium catalyst and the bulky chiral phosphine ligand, neomenthyldiphenylphosphine (eq. 1.6). 2-Phenylpropionate was produced with 52%ee but in only 3% yield.



eq. 1.6

With respect to synthetic utility, the reaction is not practical in light of the low yield.[42]

1.4 OBJECTIVES

Analysis of the results on asymmetric synthesis published to date shows that impressive achievements have been realized. Nevertheless, the most significant contributions are limited to asymmetric hydrogenations. The objectives of this thesis are to examine the possibility of further developing asymmetric catalysis in hydroformylation and hydroesterification reactions.

First, catalytic hydroformylation of functionally substituted olefins will be explored, in particular, with a series of aromatic and aliphatic vinyl sulfones and sulfoxides. There were no literature examples published prior to the initiation of this project on this subject. The expected aldehydic sulfones and sulfoxides were previously unknown. These bifunctional molecules have potential synthetic

utility. A closer look at asymmetric differentiation in the hydroformylation of phenyl vinyl sulfoxides will be examined.

Secondly, asymmetric hydroesterification of vinyl esters will be conducted to produce the corresponding optically enriched lactic acid derivatives. These lactic acid derivatives, if produced in optically active form, have obvious practical importance. In addition, both a conventional neutral palladium complex and a new cationic palladium-hydrido complex are applied to the asymmetric hydroesterification reactions.

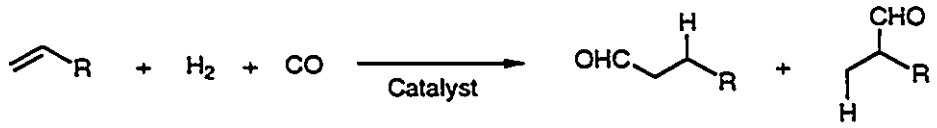
Finally, design and attempted synthesis of new optically active ligands and complexes as catalysts for asymmetric hydroformylation reactions are described.

CHAPTER 2

ZWITTERIONIC RHODIUM COMPLEX CATALYZED HYDROFORMYLATION OF VINYL SULFONES AND SULFOXIDES

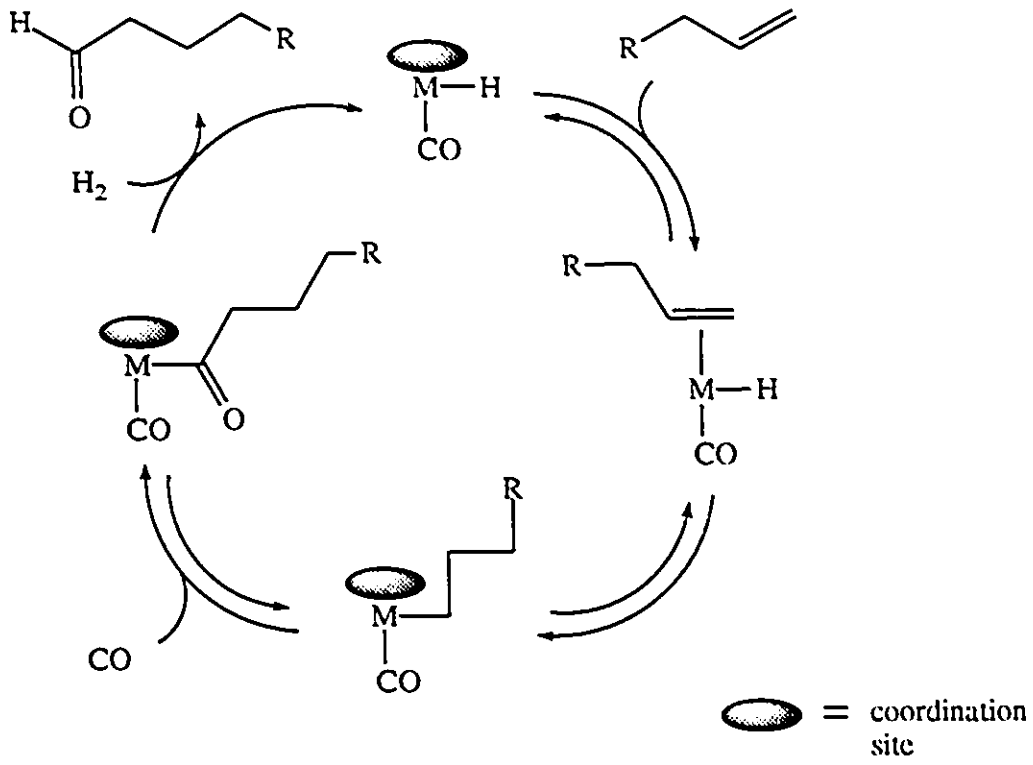
2.1 INTRODUCTION

Hydroformylation, also known as the "oxo process" was discovered in the late 1930's by Roelen.[43,44] Since this time it has become one of the most important industrial processes involving homogeneous catalysis and is a very intensely studied area of research. Hydroformylation, as its name suggests, is the addition of a hydrogen and a formyl group to an alkene or alkyne. This is accomplished by a series of coordination, activation and elimination steps involving carbon monoxide, dihydrogen and an unsaturated hydrocarbon with a transition metal catalyst (**eq. 2.1**). The resulting aldehydes are formed in varying regiochemical proportions.[3,5,45-50]



eq. 2.1

Early hydroformylation reactions utilized $Co_2(CO)_8$ as the catalyst precursor.[43,44] This was later expanded to include many other cobalt-based precursors including modifications with phosphine ligands.[45,47,50] These species showed remarkable reactivity and selectivity resulting in applications to industry.[50] A general mechanistic scheme is shown below for the generation of aldehydes from alkenes.[46]



Scheme 2.1

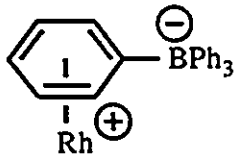
Many details of this scheme are not well understood, and therefore, it is only used to serve as a working model for the reaction. The metal hydrido carbonyl complex which must be generated *in situ* by oxidative addition of dihydrogen forms a vacant coordination site by dissociation of a weakly bound ligand. The olefin is then free to coordinate first η^2 and then η^1 by insertion into the metal hydride bond. This is the step which ultimately determines the branched to linear ratio of the product aldehydes. Following this is either alkyl migration to the carbonyl or migratory insertion of CO into the metal carbon bond. Reductive elimination of the acyl component yields the aldehyde while simultaneously regenerating the active catalyst. Both electronic and steric factors dictate the regiochemistry of insertion thus making

predictions difficult. As a result, regioselectivity strongly depends on the type of substrate, metal, ligand and conditions employed.[45,47,50] Many processes, for example the industrial scale hydroformylation of propene, require the formation of only linear aldehyde (formation of n-butanal for the ultimate reduction to alcohol). In many specialized syntheses, such as, the synthesis of pharmaceuticals, it is often desirable to form the branched analogue.[33] In doing so, for prochiral olefinic substrates, a chiral carbon center results. Thus, the search for an efficient catalytic system to specifically generate branched aldehydes is worth pursuing in the eventual goal of obtaining enantiomeric enrichment. The primary disadvantage of the cobalt-based systems towards achieving stereospecific or stereoselective products is the high temperatures and pressures required for the *in situ* generation of $HCo(CO)_4$.

Since the discovery of hydroformylation using cobalt complexes, much activity has expanded in searching for a more active and/or selective catalytic system. Although many transition metal catalysts were studied, only rhodium and cobalt show high reactivities. Iridium and ruthenium have reasonable reactivity but generally poor selectivity. Recently, hydridic platinum complexes containing a trichlorostannate ligand, have been successfully shown to hydroformylate olefins under very mild conditions. The other group VII, IX and X transition metals show only poor catalytic activity.[45,47,50]

To date, rhodium has been proven to be amongst the most reactive catalysts.[45,47,50] Wilkinson and co-workers discovered that the well known complex, $[RhCl(PPh_3)_3]$, readily reacts with carbon monoxide to form $[RhCl(CO)(PPh_3)_2]$.[51] This complex showed excellent hydroformylation ability, particularly in the presence of excess PPh_3. When rhodium catalysts are introduced into the reaction with excess phosphine, the hydroformylation of olefins occurs under very mild conditions with increased reactivity and selectivity. The complex $[RhH(CO)(PPh_3)_3]$ was isolated from the reaction mixture and subsequently shown to be an even better catalyst precursor. Because of their high reactivity, many examples of neutral and cationic rhodium complexes containing a wide variety of ligands have been studied.[45,47,50]

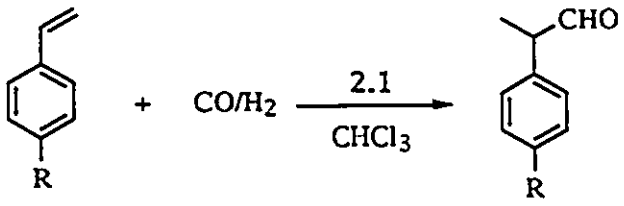
It has recently been reported that the zwitterionic rhodium η^6-tetraphenylborate complex[52], **2.1**, is a most efficient catalyst for the hydroformylation of alkenes.[53]



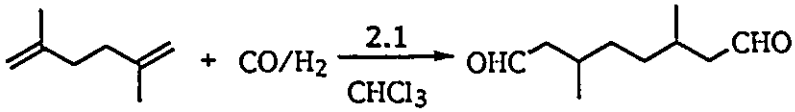
2.1

Hydroformylation reactions with this complex are highly regioselective, resulting in the formation of mainly branched or linear aldehydes depending on the nature of the reactant. For example, styrenes (**eq.**

2.2) afford the branched chain aldehydes as the predominant or exclusive product while the straight chain dialdehyde is obtained from 2,5-dimethyl-1,5-hexadiene (**eq. 2.3**).[53]

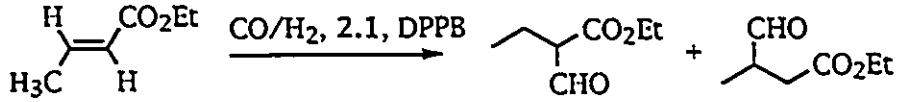


eq. 2.2



eq. 2.3

α,β-Unsaturated esters also show high regioselectivity, giving almost exclusively α-formyl derivatives (**eq. 2.4**).[54]



eq. 2.4

In addition to simple aryl and alkyl olefins, many alkenes containing other functionalities can be easily hydroformylated provided reaction with the functionality does not take place, poisoning of the catalyst does not occur or that the functional group does not react with the newly formed aldehyde. If the functionality is remote from the double bond, the hydroformylation proceeds as though the substrate is a simple alkyl or aryl alkene. The hydroformylation results may be altered however if the functionality is near the site of unsaturation. The result can be alkene isomerization or alteration and even complete reversal of regiochemistry. Functionalities such as alcohols, ether,

acetals and ketals are easily tolerated as well as conjugated and unconjugated double bonds. Because of the mild conditions available, even more active functionalities such as nitro and acylamido groups can be tolerated.[49]

Catalytic transformations of sulfur containing substrates have proven to be a challenging problem, as poisoning of the catalyst itself may result. It is well known that organosulfur compounds form stable complexes with late transition metals.[55] Application of the hydroformylation reaction to organic sulfur compounds, particularly sulfones and sulfoxides is very important from a synthetic standpoint. Molecules containing a sulfone moiety are useful for chain extension reactions due to the good leaving group ability of the RSO_2 unit.[56] Sulfoxides are often used in aldol-type condensations to make chain extensions enroute to the synthesis of natural products. For example, Corey's total synthesis of (-)-maytansine, a potent antileukemic agent, exploits such a method.[57] In addition, the asymmetric nature of sulfoxides can be used in catalytic transformations.[58,59] Stereoselectivity of the newly formed carbon-carbon bond may also be enhanced by coordination of the sulfoxide group of the substrate to the metal centre through the oxygen or sulfur atoms.[60,61]

This chapter describes the efficient catalytic hydroformylation of a series of vinylsulfones and sulfoxides, utilizing the rhodium zwitterionic complex, **2.1**, resulting in the generation of new bifunctional compounds. In addition, the asymmetric hydroformylation

of phenyl vinyl sulfoxide has been examined, serving as a good model for diastereoselective hydroformylation and a source of diastereomerically enriched derivatives. Amongst the known procedures for asymmetric catalysis (see chapter 1, section 1.2) we have chosen one of the most facile methods for the *in situ* generation of an optically active catalyst, namely the combination of complex **2.1** and an added chiral ligand. Recently, the combination of complex **2.1** and (-)-sparteine, was used for the hydrosilylation of prochiral ketones resulting in moderate (20-40%) enantiomeric excesses of the corresponding alcohols.[62] To our knowledge, the hydroformylation of vinyl sulfones/sulfoxides is the first synthesis of branched chain aldehydes containing the sulfone/sulfoxide functionality, attached to the carbon atom bearing the aldehyde unit.

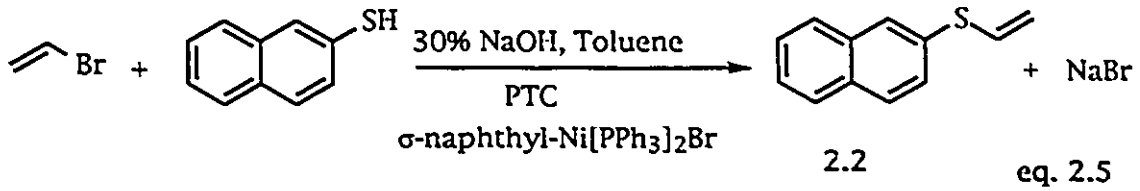
2.2 RESULTS AND DISCUSSION

2.2.1 HYDROFORMYLATION OF VINYL SULFONES

2.2.1.1 SYNTHESIS OF 2-NAPHTHYL VINYL SULFONE

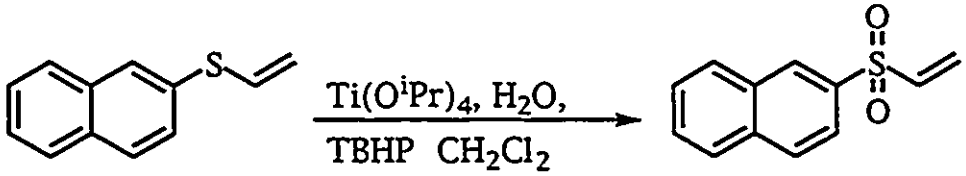
Many vinyl sulfones are readily available from commercial sources (e. g. methyl, ethyl and phenyl vinyl sulfones). In the case of 2-naphthyl vinyl sulfone, an extension of a known[63] phase transfer and metal-complex catalyzed S-vinylation technique was employed for the

synthesis of the sulfide, followed by oxidation to yield the sulfone. The synthesis of vinyl sulfides by the reaction of the thiol with acetylene at high pressures and temperatures[64] was found to be unsuitable. In addition, vinyl halides are not reactive towards nucleophiles, therefore aryl vinyl sulfides could not be synthesized by traditional nucleophilic substitution. Aryl sulfide, 2.2, was prepared by reacting vinyl bromide and 2-naphthalene thiol under biphasic conditions in the presence of hexadecyltributylphosphonium bromide as the phase transfer agent and σ-naphthyl-Ni[PPh_3]$_2$Cl[65] as the metal catalyst (**eq. 4**).



2.2 eq. 2.5

The original procedure utilizing the phase transfer technique for the synthesis of aryl vinyl sulfides did not include any unsubstituted vinyl sulfides. The modification of this procedure employs the direct addition of vinyl bromide to naphthalene thiol for the synthesis of naphthyl vinyl sulfide (see experimental section 4.5.7). Following formation and isolation of the sulfide, oxidation to the sulfone was accomplished by an oxidation technique developed by Kagan et al.[65] using a modified Sharpless procedure (**eq. 2.6**).

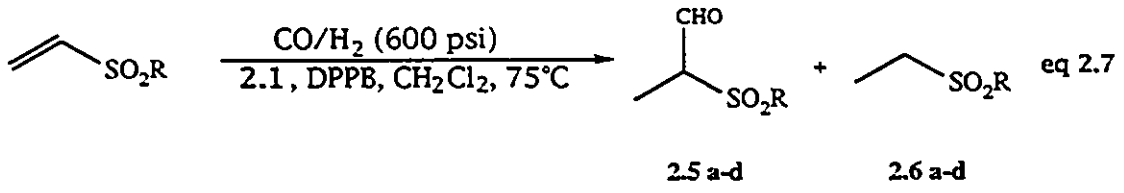


2.2 2.3 **eq. 2.6**

The resulting product mixture contained the starting sulfide, sulfoxide and desired sulfone. Separation was successfully accomplished by preparative TLC on silica using 30% ethyl acetate in hexane as the mobile phase.

2.2.1.2 HYDROFORMYLATION OF ALKYL AND ARYL VINYL SULFONES

A series of vinyl sulfones, **2.4 a-d**, were subjected to hydroformylation conditions shown in **eq. 2.7**, in the presence of **2.1**, to give only branched chain aldehydes, **2.5 a-d**, in high yields (Table 2.1).



The original hydroformylation conditions[53] using the rhodium zwitterionic complex (100:1 ratio of substrate/catalyst precursor), were significantly improved by the addition of two mole equivalents (relative to the rhodium catalyst) of 1,4-bis(diphenylphosphino)-butane (DPPB). The presence of the latter resulted in a notable increase in the conversion of starting material as well as in the chemo- and regioselectivities. In the absence of DPPB, the results were much less satisfactory, i.e., the conversions were low and the products were a mixture of branched aldehyde, **2.5 a-d**, and hydrogenated olefin, **2.6**

a-d. For example, in the case of ethyl vinyl sulfone, **2.4b**, a conversion of 53% was achieved with 29% branched aldehyde, **2.5b**, and 24% hydrogenated olefin, **2.6b**, the remaining 47% being starting material.

In all cases, the hydroformylation of vinyl sulfones, in the presence of two equivalents of DPPB relative to **2.1**, resulted in complete conversion of the starting material with the major product being branched aldehyde (Table 2.1). The branched chain aldehydic sulfones, **2.5a & b**, were formed in nearly quantitative yield from ethyl and methyl vinyl sulfones. Replacement of aryl for alkyl substituted vinyl sulfones, **2.4c & d**, gave high yields of the aromatic sulfones, **2.5c & d**, with small amounts of the saturated sulfone, **2.6c & d**, obtained as a by-product. This is the first synthesis of branched chain aldehydes containing the sulfone functionality attached to the carbon atom bearing the aldehyde unit.

Table 2.1 Hydroformylation of Unsaturated Sulfones Catalyzed by **2.1** and DPPB

	Yield / %[a,b]		
Substrate	**2.5**	**2.6**	**2.4**
ethyl vinyl sulfone	98 (29)	0 (24)	0 (47)
methyl vinyl sulfone	98 (21)	0 (27)	0 (52)
2-naphthyl vinyl sulfone	83 (-)	17 (-)	0 (-)
phenyl vinyl sulfone	83 (5)	17 (13)	0 (82)

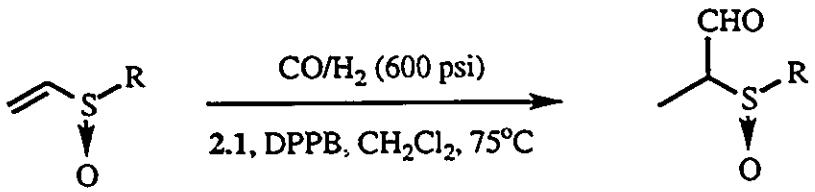
[a]NMR yields based on ferrocene as internal standard;

[b]Value in brackets for reaction in absence of DPPB

2.2.1 HYDROFORMYLATION OF PHENYL VINYL SULFOXIDE

2.2.2.1 STUDY OF REACTION CONDITIONS

Although the hydroformylation of phenyl vinyl sulfoxide, **2.7**, was not as facile as the vinyl sulfones, the corresponding branched aldehyde, **2.8**, was obtained regiospecifically in as much as 50 percent yield (**eq. 2.8**).



2.7 **2.8** eq. 2.8

The reaction conditions, however, were much more sensitive, particularly to time, temperature and the amount of added phosphine. Figure **2.1** shows that at room temperature, (20°C), the conversion of starting material proceeds slowly (50% after 2 days) but is completely regiospecific, affording only the branched chain aldehyde. The reaction then stops, possibly due to the poisoning of the catalyst.

At 75°C (Figure 2.2), the rate of conversion is much higher with 50 percent conversion of starting material resulting in two hours. The feature to note, however, is that the concentration of aldehyde decreases if the reaction is maintained at 75°C for more than two hours.

In addition, only **2.8**, the branched aldehyde, was present in the first two hours of reaction, while traces of linear aldehyde were detected on extended reaction. Under such conditions, an undesirable side reaction occurs, converting the branched aldehyde, **2.8**, to diphenyldisulfide, **2.9**, which was isolated and identified by comparison with an authentic sample. A plausible pathway is outlined in Scheme 2.2.

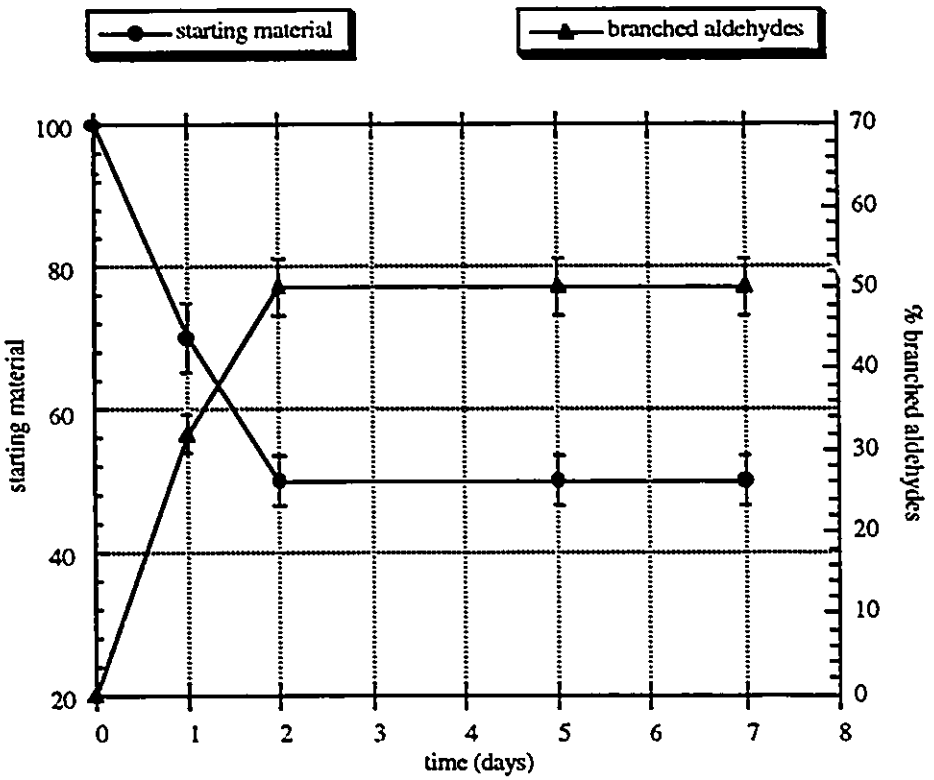


Figure 2.1 Hydroformylation of Phenyl Vinyl Sulfoxide at Room Temperature.

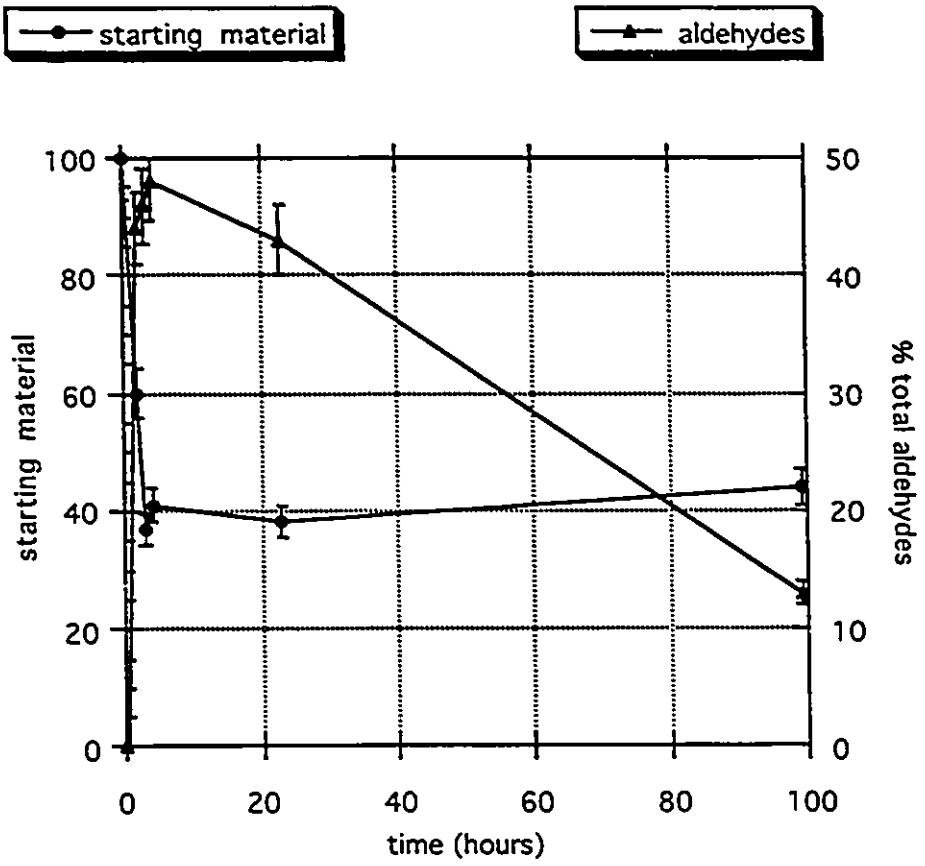
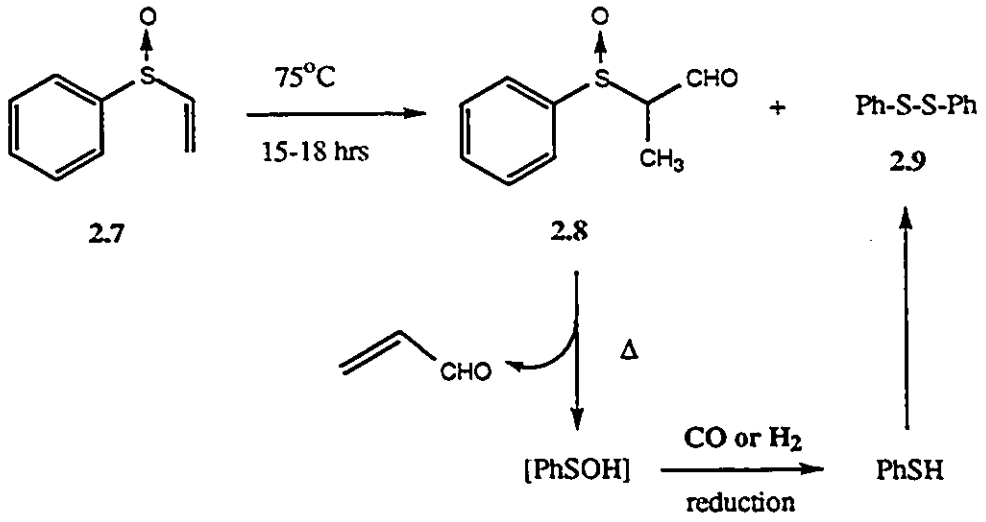


Figure 2.2 Hydroformylation of Phenyl Vinyl Sulfoxide at 75°



Scheme 2.2

In contrast to the hydroformylation of vinyl sulfones, phenyl vinyl sulfoxide is much more sensitive to the amount of added phosphine ligand. Using the optimum conditions realized from Figure 2.2, (75°C, 2 hours), phenyl vinyl sulfoxide was hydroformylated in the presence of varied ratios of DPPB to **2.1** (Table 2.2). In the complete absence of any added ligand, the reaction produced only a trace amount of the product aldehydes. To achieve 50 percent conversion, four equivalents of DPPB (relative to **2.1**) was used, with complete conversion realized using ten equivalents of bidentate phosphine.

From this study, the optimum conditions for the hydroformylation of phenyl vinyl sulfoxide was found to be 75°C for two hours using four equivalents of DPPB.

Table 2.2 Effect of Added DPPB on the Conversion of Phenyl VinylSulfoxide.

DPPB[a]	Conversion (2.7) %
0	<2
2	30
4	50
10	100

a) equivalents relative to **2.1**

2.2.2.2 DIASTEREOSELECTIVITY

Since the catalyst system under investigation exhibits such high regioselectivity for the hydroformylation of vinyl sulfones and sulfoxides, we chose to explore the possibility of inducing chirality. One way to do this is to replace the DPPB ligand with a chiral ligand. This allows exploration of the ability of the catalytic system to effect asymmetric induction. The achiral phosphine, DPPB, was substituted by optically pure 2,2'-bis-(diphenylphosphino)-1,1'-binaphthyl (BINAP). The results for the hydroformylation of phenyl vinyl sulfoxide in the presence of R-, S-, or R/S-BINAP are presented in Table 2.3.

The chiral ligand BINAP indeed was successful for inducing chirality in the product as can be seen from entries 1,2 and 3 of Table 2.3. Comparison of the 'H NMR spectra for entries 1,2 and 3 (Figure 2.3)

reveals that the same diastereomer is in excess regardless of which antipode of optically pure BINAP is used.

Table 2.3 Hydroformylation of phenyl vinyl sulfoxide with **2.1** and BINAP

Entry	L*	% Yield	% dc[a]	% ec[c]
1	R-(+)-BINAP	27	40	18
2	S-(-)-BINAP	22	50	21
3	S/R-(±)-BINAP[b]	43	46	0
4	DPPB	50	0	0

[a] Measured directly from ^{1}H NMR spectra; [b] Racemic BINAP;
[c] Resolved using Eu(hfc)3

As a blank test, the diastereomeric excess was measured when the achiral phosphine ligand, DPPB, was used (Figure 2.4). The two sets of diastereomers have clearly resolved methyl doublets at 1.40 and 1.25 ppm having equal intensity as would be expected (entry 4, Table 2.3).

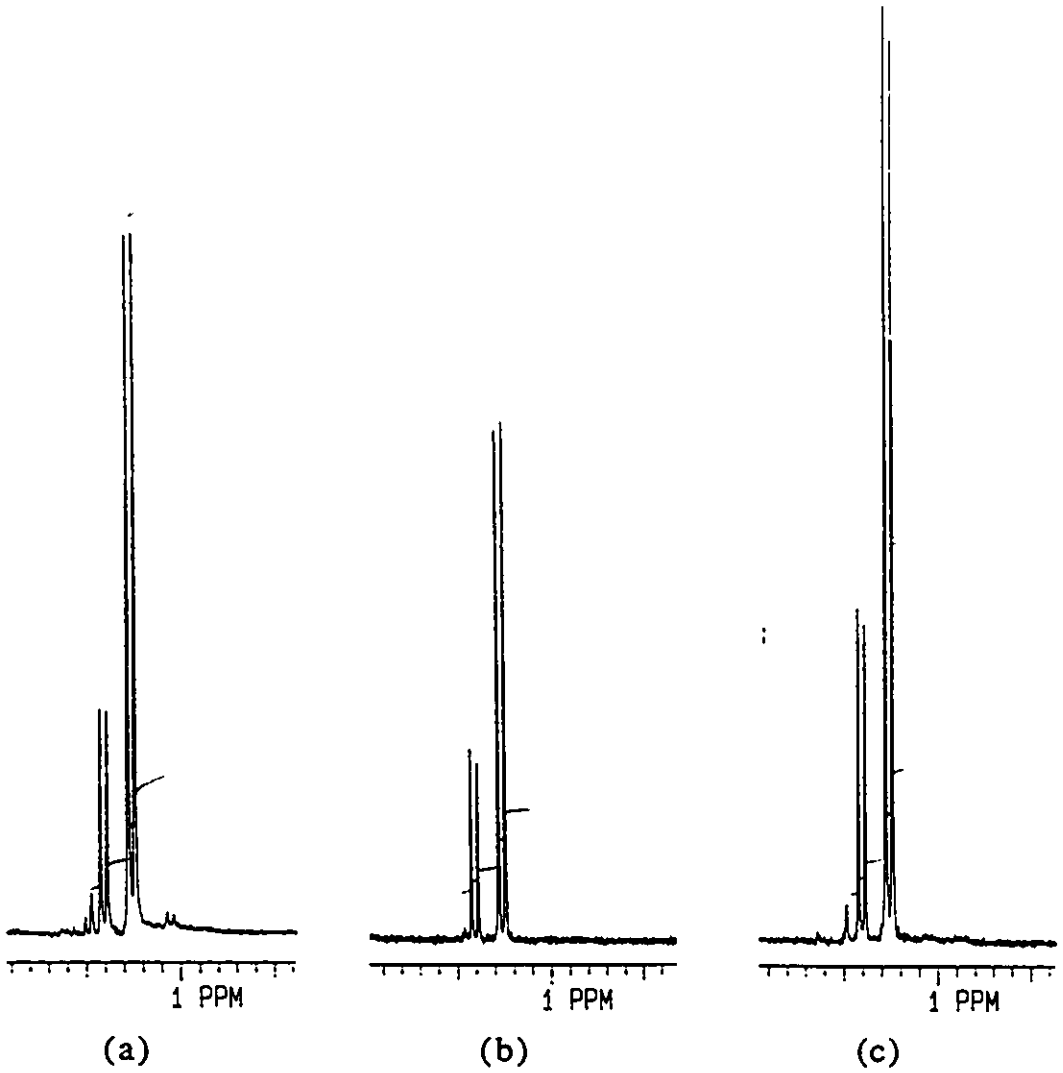


Figure 2.3 ^{1}H NMR of diastereomeric methyl resonances for the product of hydroformylation of phenyl vinyl sulfoxide in the presence of (a) (S)-(-)-BINAP; (b) (R)-(+)-BINAP; and (c) racemic BINAP

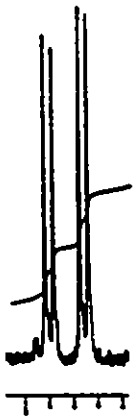
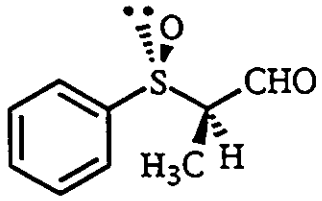
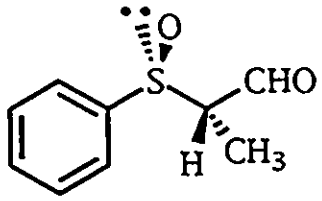


Figure 2.4 ^{1}H NMR of diastereomeric methyl resonances for the product of hydroformylation of phenyl vinyl sulfoxide with added DPPB.

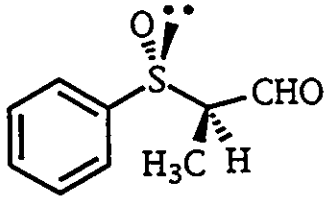
Each of the two diastereomers can conceivably consist of a pair of enantiomers as depicted in scheme 2.3. Therefore, chiral shift experiments were performed to resolve the enantiomeric pairs of each diastereomer. In each experiment, milligrams of the isomeric mixture was diluted in an NMR tube with $CDCl_3$. After recording the original spectrum, 1-2 mg of tris[3-(heptafluoropropyl hydroxymethylene)-(+)-camphorato] europium (III), ($Eu(hfc)_3$), was dissolved into the solution and the resulting spectrum recorded. Addition of $Eu(hfc)_3$ was continued, usually two to three times until the signals gradually shifted downfield revealing all four isomers. The resulting spectrum is shown in Figure 2.5, and show equal intensity for all four stereoisomers.



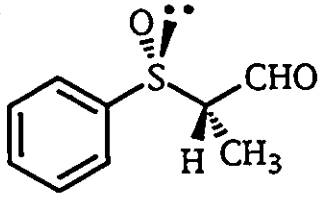
SR



SS



RR



RS

Scheme 2.3 Four stereoisomers of **2.8**

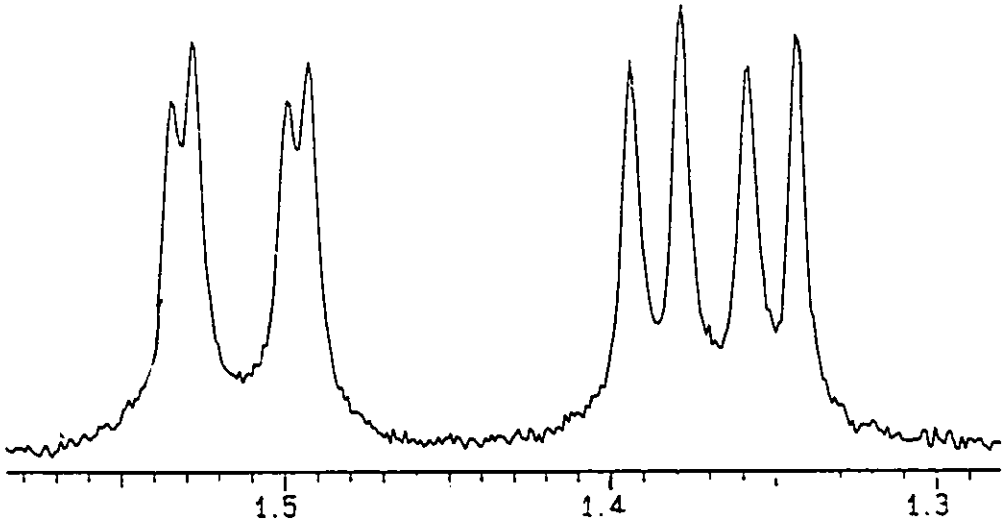


Figure 2.5 $Eu(hfc)_3$ resolution of racemic aldehydes obtained in presence of DPPB

The diastereomer, having its methyl resonance at 1.25 ppm shifts down field to a much greater extent than the diastereomer at 1.40 ppm when exposed to $Eu(hfc)_3$. As a consequence, the resolution obtainable is much better for the upfield signals. This becomes more significant in the case when enantiomeric enrichment occurs.

The same diastereomeric excess is achieved for hydroformylation with added R-(+)-, S-(-)-, and racemic BINAP. In addition, the ^1H NMR shows that the same diastereomer (the methyl resonance at 1.25 ppm) is in excess each time (Figure 2.3).

At first glance, these results appear rather unconventional in the sense that one would not expect opposite antipodes of the chiral inducing ligand to transfer the same direction of optical activity to the

product. The situation is even more peculiar when the chiral ligand is racemic yet continues to deliver the same amount of diastereomeric excess to the newly formed products. The events occurring in the reaction become more obvious upon resolution of the enantiomers which are associated with each diastereomer.

The preliminary NMR experiments, utilizing $Eu(hfc)_3$ as the resolving agent, resulted in separation of the enantiomer at 1.25 ppm but not those further downfield at 1.40 ppm. As mentioned earlier, for a racemic sample, the relative chemical shifts of the two enantiomers at 1.40 ppm is small compared with those at 1.25 ppm. When some amount of enantiomeric excess is expected, the result is a slight shoulder which is only detectable as peak broadening and therefore quantitation is impossible. To confirm, however, that all four isomers were indeed present, the same chiral shift experiment was conducted, but the ^{13}C NMR spectrum was recorded. Quantitation of course is not possible, but the resolution was better, allowing for verification that all four isomers are present (Figure 2.6). As a result, quantitation of the enantiomeric excesses can only be measured for the diastereomer having its methyl resonance at 1.25 ppm. Figures 2.7 and 2.8 show the resolution of enantiomers when the hydroformylation was conducted using R-(+)- and (S)-(-)-BINAP respectively.

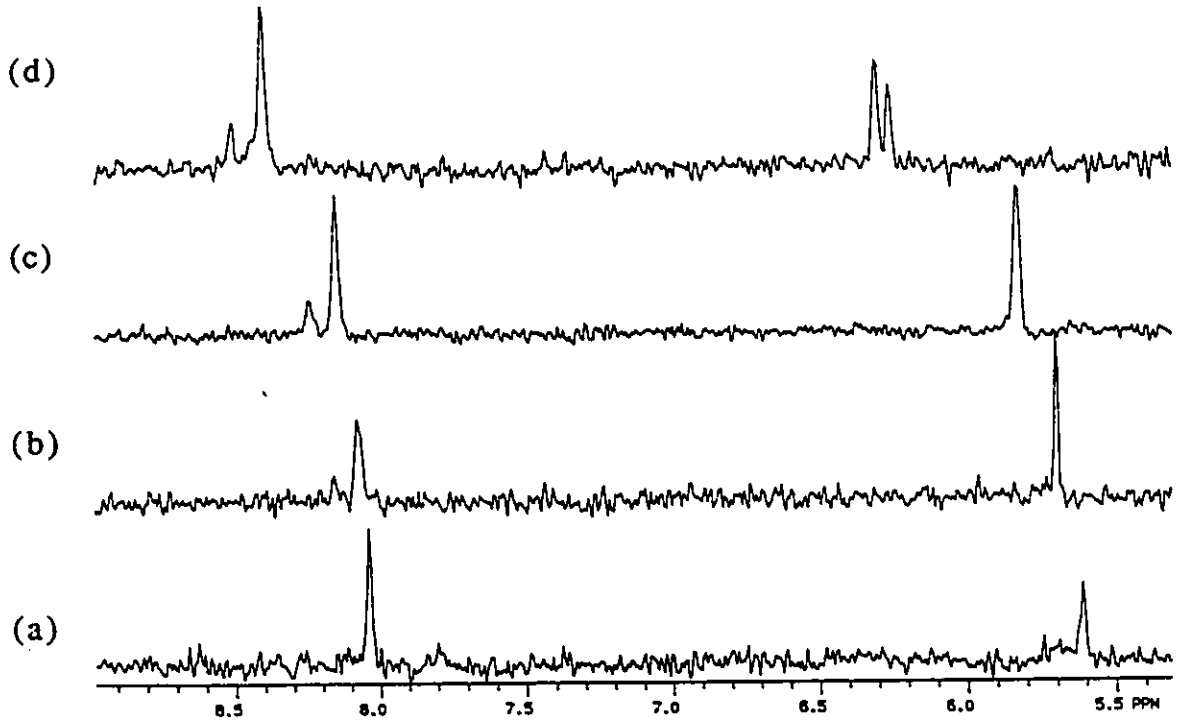


Figure 2.6 ^{13}C NMR spectra of **2.8** in the presence of $Eu(hfc)_3$: (a) isomeric mixture (no $Eu(hfc)_3$); (b) - (d) successive addition of $Eu(hfc)_3$. (R)-(+)-BINAP was use as chiral inducing ligand.

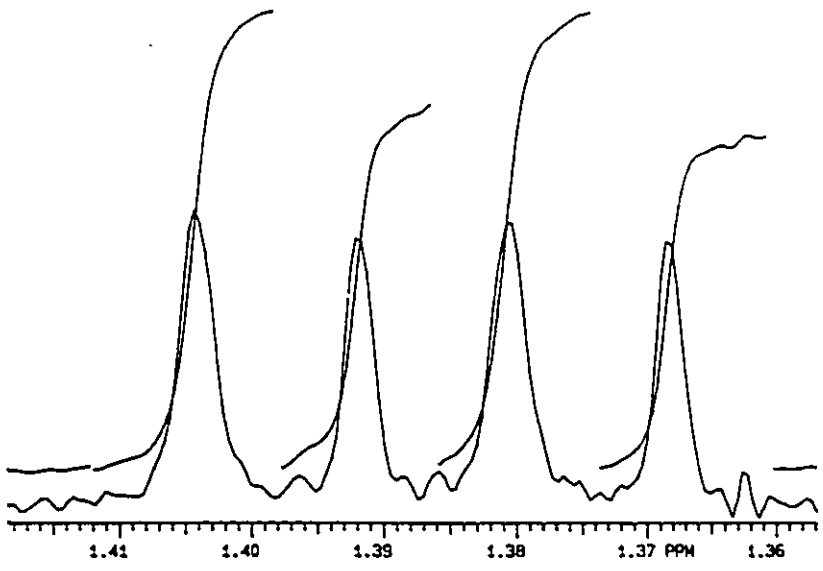


Figure 2.7 $Eu(hfc)_3$ resolved ^1H NMR of **2.8** generated in the presence of (R)-(+)-BINAP; enantiomeric excess = 18%

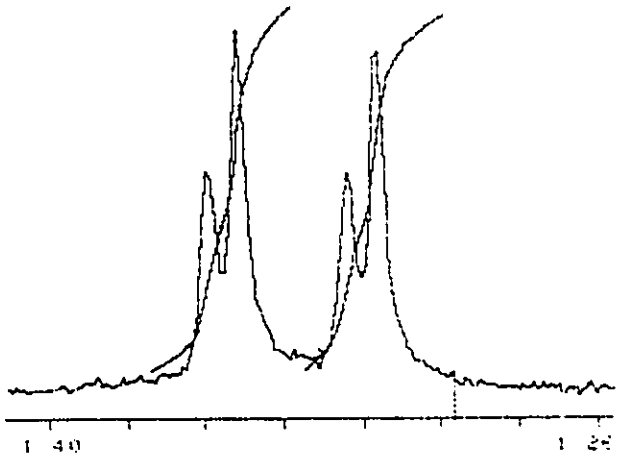


Figure 2.8 $Eu(hfc)_3$ resolved ^1H NMR of **2.8** generated in the presence of (S)-(-)-BINAP; enantiomeric excess = 21%

The percent enantiomeric excesses were determined from the integrations and found to be 18% and 21% respectively. The difference between the two values is within experiment error. However, it is now clear that the difference between the two reactions is that opposite isomers are produced in excess, which is what one would expect in changing from one optically pure ligand to its enantiomer. Figure 2.9 shows the result of resolving the enantiomers produced when the hydroformylation was carried out in the presence of racemic BINAP. As would be predicted, the enantiomeric excess is clearly zero.

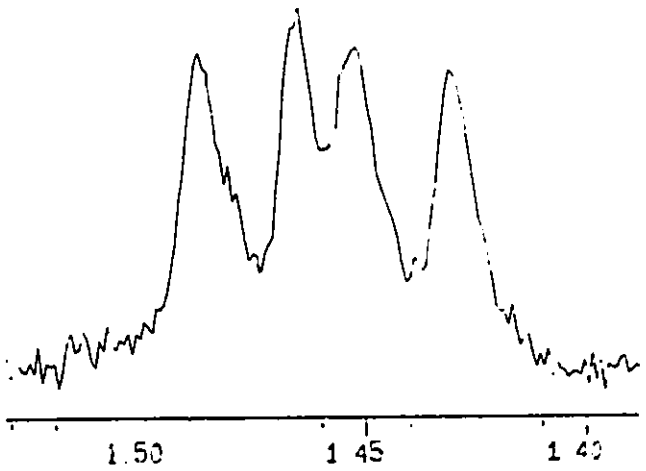


Figure 2.9 $Eu(hfc)_3$ resolved ^1H NMR of **2.8** generated in the presence of racemic BINAP; enantiomeric excess = 0%

The following rationale accounts for these observations. Hydroformylation of racemic phenyl vinyl sulfoxide, as described above, afforded diastereomeric branched aldehydes. The different chemical shifts of the diastereomers were well resolved in the NMR. Consideration of the hydroformylation products of racemic phenyl vinyl sulfoxide yields two possible sets of diastereomers, RS/SR and RR/SS. By definition, different pairs of diastereomers are chemically different, having different physical properties, and can therefore have different chemical shifts in an NMR spectrum. However, the diastereomeric pairs RR/SS and RS/SR are non-superimposable mirror images (enantiomers) differing only in their "handedness". As a consequence, they have identical chemical and physical properties.

The simplest result to explain is entry 4 in Table 2.3. The ligand DBBP is achiral and consequently cannot induce any optical activity in the new product. Additionally, the intermediate must be enantiomeric in nature thereby yielding no diastereomeric excess. This is confirmed by the generation of equal quantities of the four stereoisomers. (Figure 2.4 and 2.5) The result of entry 1 can best be interpreted by consideration of the following scheme.

$$\underset{\text{Racemic Starting Material}}{\text{R/S}} \xrightarrow{\text{R-BINAP}} \underset{(1-n)}{\text{RR}} + \underset{n}{\text{SR}} + \underset{n}{\text{RS}} + \underset{(1-n)}{\text{SS}}$$

For each of the four possible stereoisomers, the first letter represents the configuration at the sulfur atom and the second letter designates the configuration of the newly formed carbon center. If one assumes that the R-BINAP catalyst complex prefers to generate the new chiral center in the R configuration, then the isomers RR and SR will be equal and present in the amount denoted by x. The remainder, RS and SS would have the amount (1-x). The second factor which must also be considered is the interaction between the chiral starting material and the active catalyst to form the diastereomeric intermediates. If R-starting material forms a complex to yield the RS product in amount n, then S-starting material would from a complex to yield the SR product also in amount n. The remaining combinations, SS and RR would be formed in the amount (1-n).

From this, one can determine the relative quantities of each stereoisomer [RR=x(1-n); SS(1-x)(1-n); RS=n(1-x); SR=xn]. Since the isomers RR and SS are enantiomers, they occur at the same chemical shift and would correspond to the amount (1-n). By using the same assumptions with the S-(-)-BINAP (prefers in this case to produce the S product) and again with the racemic BINAP ligand, the end result is the same. That is, in each case, the SS/RR pair will be formed in the amount (1-n) and the RS/SR pair will be present in the amount, n. This analysis is in excellent agreement with the observation that each diastereomer is formed in the same excess irrespective of the antipode of ligand used (Figure 2.3). Using the same analysis, the enantiomers are predicted to occur with an excess but in addition, the opposite isomer will exist if the

opposite antipode of BINAP is used. In addition, when racemic BINAP is applied to the catalyst, there will be no enantiomeric excess. Again, this prediction is borne out by the experimental results presented in Table 2.3.

In conclusion, the zwitterionic rhodium(I) complex, **2.1**, together with DPPB, is an active and a regiospecific catalytic system for the hydroformylation of vinyl sulfones and sulfoxides. The previously unknown branched chain aldehydic sulfones and sulfoxides are prepared in good to excellent yields. Moderate diastereoselectivities and enantioselectivities resulted in the hydroformylation of racemic phenyl vinyl sulfoxide using the betaine - like rhodium(I) complex and optically active BINAP.

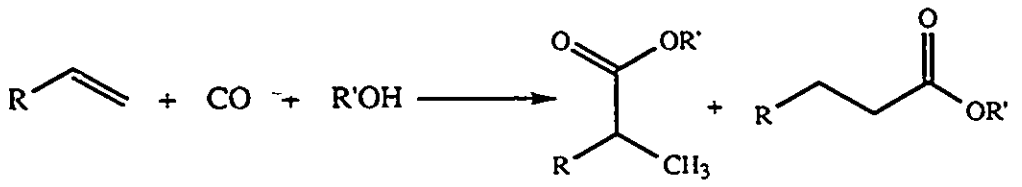
CHAPTER 3

PALLADIUM CATALYZED HYDROESTERIFICATION OF VINYL ESTERS

3.1 INTRODUCTION

3.1.1 CATALYTIC HYDROESTERIFICATION OF UNSATURATED MOLECULES

Hydroesterification is the transition metal catalyzed addition of carbon monoxide and an alcohol to an alkene to form esters (eq. 3.1).[66-71]



eq. 3.1

R = alkyl, aryl; R' = alkyl

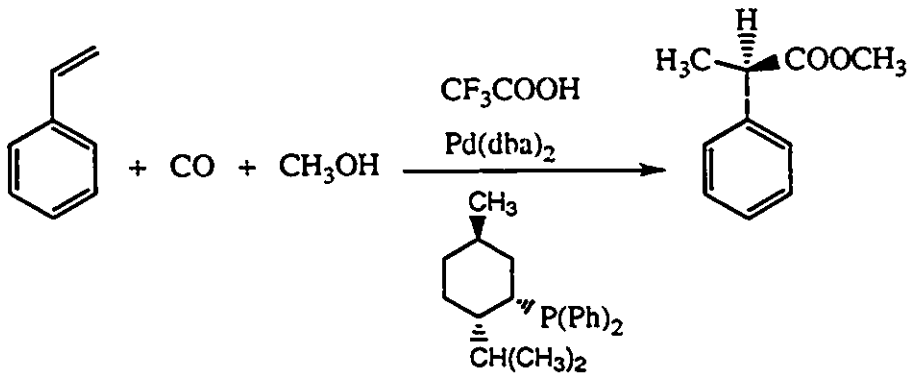
For terminal olefins, the esters produced can have either branched or linear regiochemistry. The regioselectivity of the reaction strongly depends on the catalytic system chosen and to a lesser extent on the substrate. The reaction is of practical importance because esters are extensively used as solvents, fragrances, and specialty chemicals.[72] Thus, the search for an efficient catalytic system that will allow the predictable production of regiospecific esters is of great general interest.[73]

Amongst the wealth of readily available transition metal catalysts, those capable of hydrocarboxylation include nickel, cobalt, platinum and

palladium complexes plus the less effective carbonyls of rhodium, iridium, iron, osmium and ruthenium. Nickel catalysts require the addition of an activator such as a hydrogen halide or halide ion to effect the transformation.[68] Cobalt complexes, in contrast, are effective catalysts and do not require the addition of activators. They can be used either as metallic cobalt, cobalt salts or as $Co_2(CO)_8$. In the presence of carbon monoxide it is believed that the catalytically active species is the cobalt tetracarbonyl anion. The reaction conditions are relatively drastic requiring a CO pressure of 100 - 200 atmospheres and temperatures from 140 - 170°C.[70] Platinum catalysts (e.g. chloroplatinic acid), together with $SnCl_2$ are active catalysts at pressures up to 200 atmospheres and temperatures between 80 - 90°C.[68] However, platinates are generally less reactive and are much more expensive. In contrast, palladium catalysts are frequently used because of their high activity at relatively mild conditions, tolerance to a large variety of substrates as well as their relatively low cost.[67] Additionally, in the presence of phosphines, palladium catalysts show increased activity, thus allowing for greater flexibility with respect to modification of the system to predict regio- and stereochemistry. The other group VIII transition metals are only marginally effective hydrocarboxylation catalysts and thus are seldom used.

With the large number of studies published thus far concerning the hydroesterification of a variety of olefinic substrates, the challenge still remains in affecting high optical inductions for branched esters. The only significant advance in stereocontrolled hydroesterification reactions has been the low pressure palladium(0) catalyzed

carbomethoxylation of vinyl aromatics in the presence of the chiral ligand neomenthyldiphenylphosphine (eq. 3.2)[42]. With this system, the highest asymmetric induction for the hydroesterification of styrene was 52% ee. A major disadvantage of this system was that the branched ester, methyl 2-phenylpropionate, was only obtained in 3% chemical yield.



eq. 3.2

For the past ten years, improvements with respect to chiral induction in these carbon - carbon bond forming reactions have not come to fruition. Thus, the need to investigate and find a more suitable catalytic system is obvious.

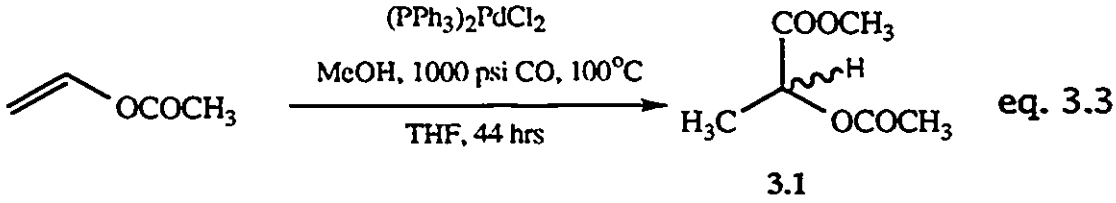
The origin of the work presented in this chapter stems from a European Patent filed in 1983 which describes the non-stereodifferentiating hydroesterification of vinyl acetate using a Pd/PR_3 complex.[74] The purpose of choosing this invention as a starting point is two-fold. Firstly, from a fundamental perspective, this system projects the opportunity to investigate the factors which influence regio- and enantioselectivity. It is possible to envision incorporation of a chiral

phosphine ligand in order to effect some degree of chiral induction. This is particularly convenient in light of the wide variety of readily available chiral phosphine ligands. Secondly, focusing on vinylic esters as the substrate is of paramount interest from an industrial perspective. The product ester is easily hydrolyzed to the corresponding α-hydroxy acid - in this case, lactic acid. If produced as either the R- or S-enantiomer, the product becomes an extremely valuable synthon and commodity chemical. Lactic acid is commercially important in the baking industry, the cheese industry, in dying wool and in making plasticizers for resins.[74] An additional advantage is that vinyl acetate is readily available on an industrial scale and is inexpensive. The classical methods for the production of lactic acid are either by fermentation from molasses or by a non-catalytic synthesis employing acetaldehyde and the highly toxic gas, hydrogen cyanide, which produces, during the acidic work-up, a stoichiometric amount of $(NH_4)_2SO_4$ along with lactic acid.[74] Therefore, the development of a more efficient asymmetric, catalytic system for the generation of optically enriched α-acetoxy esters is of great value, both from an academic and an industrial perspective.

3.2 RESULTS AND DISCUSSION

3.2.1 HYDROESTERIFICATION OF VINYL ACETATE IN THE PRESENCE OF BIS(TRIPHENYLPHOSPHINE) PALLADIUM DICHLORIDE

The $PdCl_2(PPh_3)_2$ catalyzed hydroesterification of vinyl acetate, with CO/MeOH to produce regioselectively the branched ester, methyl-2-acetyloxypropanoate, (3.1), has been reported to proceed in 82% yield.[74](eq. 3.3)

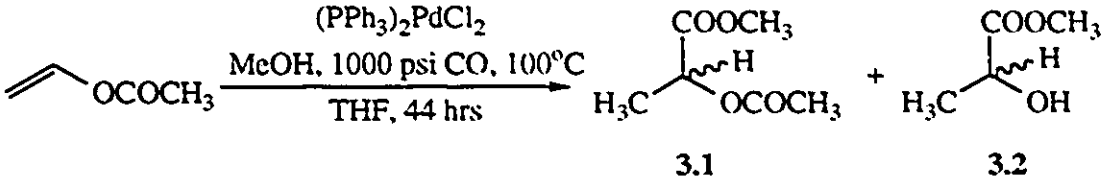


eq. 3.3

3.1

At first sight, this procedure seemed simple and straight forward, but unfortunately was not reproducible in our hands without an essential modification. Under conditions which were identical to those described in the patent, i.e., 100°C, 1000 psi CO, 45±1 hours, THF and $(PPh_3)_2PdCl_2$ (10 mole percent), the best yield of **3.1** obtained was 12% (Table **3.1**). In spite of this disappointingly low yield, we decided to study the possibility of chiral induction through the addition of a chiral ligand. When the reaction was carried under the previously described conditions but in the presence of 10% (R)-(-)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate, the product esters were obtained in a surprisingly

high yield of 43%. Based on the 'H NMR, 84% of this mixture was the desired ester **3.1**, and the remaining 16% was methyl lactate, **3.2**, accounted for by the acid catalyzed hydrolysis of the acetate (eq. 3.4).



3.1 **3.2**

eq. 3.4

Unfortunately no optical induction was incurred (determined by polarimetric analysis). Both the production of the methyl lactate, (**3.2**) and the dramatic increase in yield for the reaction, upon the addition of (R)-(-)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate, point to an important role of acid for the production of the active catalyst in the catalytic cycle. To verify this, the much simpler parent acid, H_3PO_4 was used as an additive. Indeed, addition of 10% H_3PO_4, relative to the substrate, produced esters in 32% yield. Note that the 'H NMR of the crude product mixture showed the presence of the hydrolyzed ester, **3.2** (Figure 3.1).

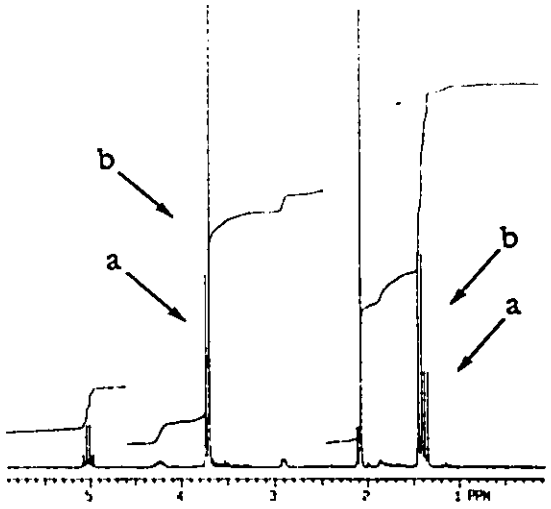


Figure 3.1 ^{1}H NMR of mixture of **3.1** and **3.2** (a) methyl doublet of **3.2**; (b) methyl doublet of **3.1**

To circumvent this, the amount of added H_3PO_4 was reduced, (1% relative to substrate; 10% relative to catalyst) which not only significantly reduced the hydrolysis problem, (Figure 3.2), but resulted in an isolated yield in **3.1** of 70% (Figure 3.2).

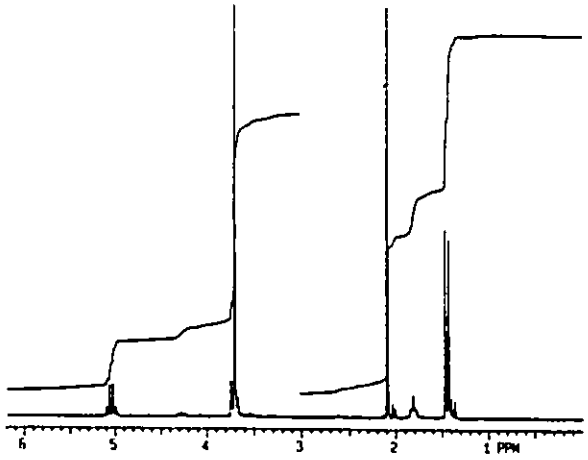
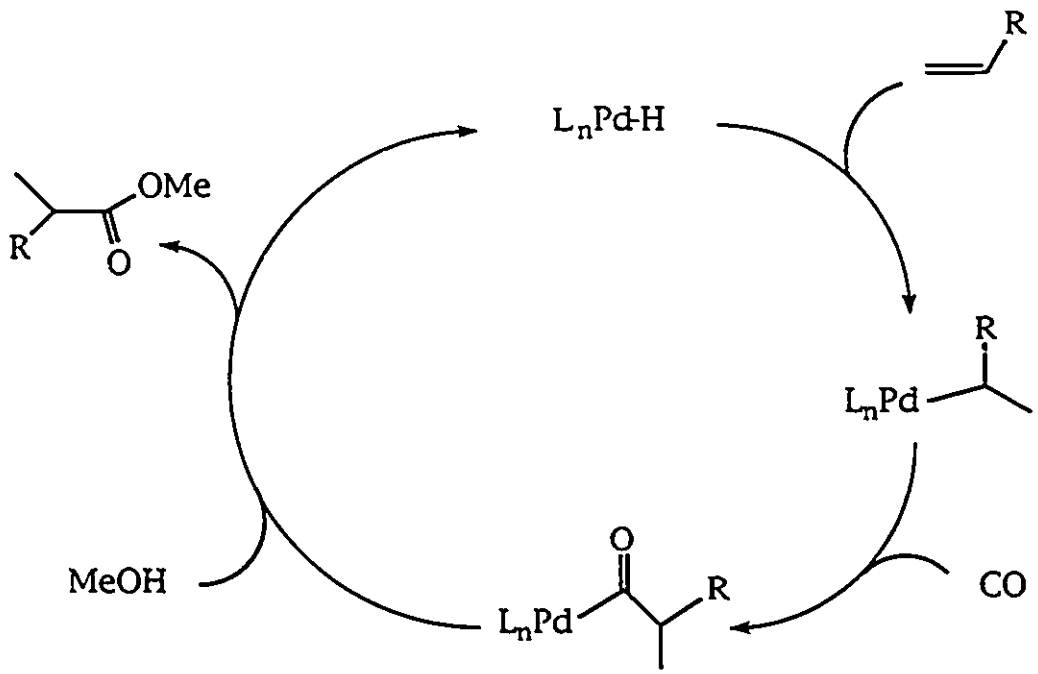


Figure 3.2 ^{1}H NMR of **3.1** (and a trace of **3.2**); reaction carried out in the presence of only 1% H_3PO_4

The role of the acid in this catalytic cycle in not clear. The crucial role of acid in catalysis has however been observed in the past. For example, Pearson et al. made a detailed study of the acid catalyzed cleavage of acyl-metallo species with methanol.[76] More recently, Consiglio et al. observed the necessity of acid in the carbonylation of alkenes to ketones with the idea of an equilibrium existing between two metallic complexes - one being catalytically active and the other not.[76]

We would like to consider an alternate role of the acid in our catalytic system. It is clear that some palladium hydrido species must have been generated during the catalytic process. Presumably, the palladium hydride adds across the carbon-carbon double bond of the substrate to produce the corresponding σ-alkyl complex. The latter then undergoes transformation into its corresponding acyl derivative in the presence of carbon monoxide. Interaction between the acyl complex and methanol results in the desired carbonylated product (scheme 3.1).

It remains unclear as to how the catalytically important species is formed from the added complex, $[(PPh_3)_2PdCl_2]$. The paper by Consiglio *et al.* employs the concept of a palladium hydride intermediate in the catalytic carbonylation. However no explanation was presented regarding possible routes to its generation *in situ* from the palladium (II), non hydrido, complex.[76]

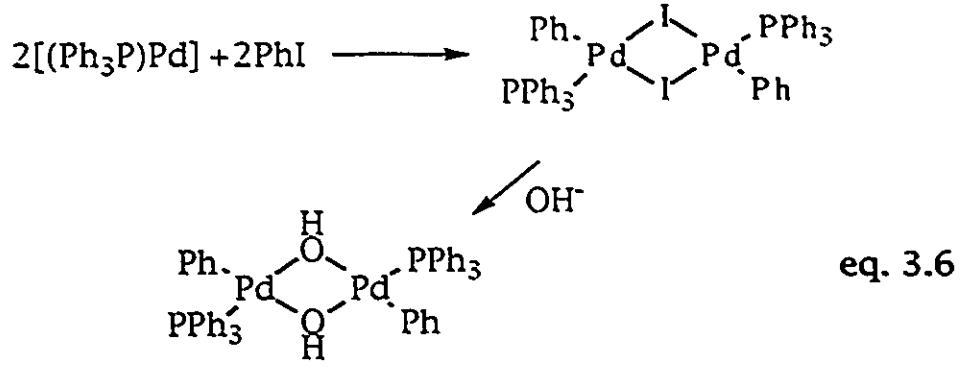


Scheme 3.1

It has been been shown recently that OH^- is capable of promoting the intramolecular reduction/oxidation of palladium (II) tertiary phosphine complexes, $[L_2PdCl_2]$, resulting in the production of triphenylphosphine oxide and the highly reactive, coordinatively unsaturated palladium(0) complex.[77] Although the latter could not be isolated, its generation was supported by the formation of a σ-phenyl palladium(II) dimer after the reaction with iodobenzene (eqs 3.5 and 3.6).

$$[(Ph_3P)_2PdCl_2] + 2\,KOH \longrightarrow [(Ph_3P)Pd] + 2KCl + Ph_3PO + H_2O$$

eq. 3.5

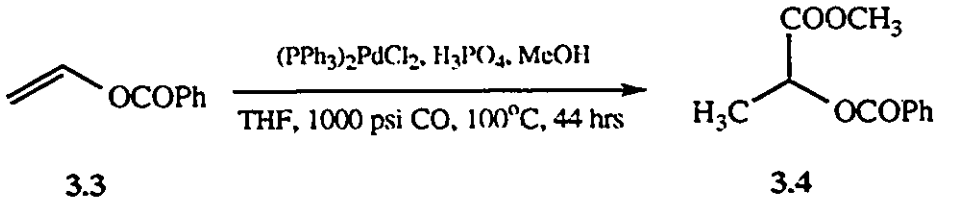


eq. 3.6

Although the reaction was conducted in the presence of concentrated alkali, it was shown that even very low concentrations of OH^- are sufficient to affect this redox process. In fact, we observed the production of triphenylphosphine oxide (^{31}P NMR) after the hydration reaction. It is possible that, the addition of dilute aqueous acid facilitated the generation of [LnPd(0)] followed by its protonation to give $(LnPd\text{-}H]^+$ which might have been responsible for the catalysis. Protonation of low valent transition metal complexes has been well documented in the literature.[78, 79] We assume that both generation of the palladium (0) and subsequent protonation do not require strong bases and acids, respectively. Some low valent transition metal complexes are very basic, for example, $[(Et_3P)_3Pt]$ in aqueous THF has a pH of approximately 14.[81]

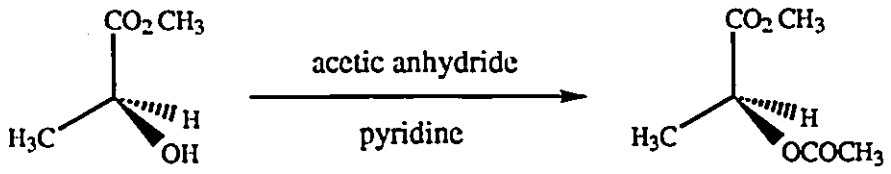
Product **3.1** was isolated from the reaction mixtures by vacuum distillation and analyzed spectroscopically and compared to the literature (see experimental section). Due to difficulties in the isolation of the relatively low boiling ester **3.1**, vinyl benzoate, **3.3** was chosen as a more convenient substrate to investigate some aspects of the catalytic system for asymmetric hydroesterification. The identical

reaction conditions were employed and resulted in the production of ester **3.4**, which was easily isolated in 74% yield (eq. 3.7).



3.3 **3.4** eq. 3.7

Before proceeding to the next logical step of adding chiral ligands to the catalytic system, it was necessary to verify that the reaction conditions were not too severe in allowing for asymmetric induction. That is, if optically enriched esters were indeed generated, it was essential to prevent their subsequent racemization. Therefore, (-)-methyl O-acetyllactate was synthesized from commercially available (S)-(-)-methyl lactate by treatment with acetic anhydride and pyridine.[81] (eq. 3.8)

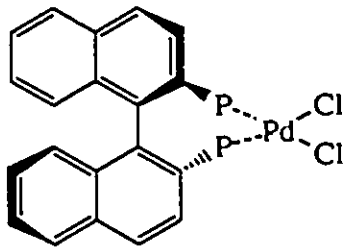


eq. 3.8

After purification and isolation of the desired lactate, the optical rotation was measured using standard polarimetric methods to give $[\alpha]_D^{25}$ -51.4° (c 3.4, acetone). This isomer was then subjected to the identical reaction conditions as those necessary to affect the hydroesterification of vinyl acetate, ($(PPh_3)_2PdCl_2$, MeOH, H_3PO_4, THF, 100°C, 1000 psi of CO - no vinyl acetate). After the required reaction time (2 days), the lactate was isolated and found to have an $[\alpha]_D^{25}$ -50.9° (c 2.9, acetone). Thus, should optically enriched (or pure) product be produced, the reaction conditions, although quite severe, will not result in racemization of the product ester, **3.1**. It was also shown that at a reaction temperature of 50°C, the optically enriched product did not racemize and was recovered with the same optical rotation as originally measured. Unfortunately however, hydroesterification of vinyl acetate was not possible at such a low temperature.

While maintaining a reaction temperature of 100°C, a number of chiral ligands were added *in situ* in an attempt to induce chirality during the catalytic cycle. The chiral ligands included those with phosphorus coordinating atoms, [e.g.(R)-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl and (+)-2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino) butane], nitrogen coordinating atoms [e.g. (R)-(+)-a-methylbenzylamine and poly-L-leucine] and oxygen coordinating atoms in diisopropyl D-tartrate. In all cases, after isolation and purification of the ester, **3.1**, the optical rotation was measured and found to be zero. For situations where chiral ligands are added *in situ*, there is always the possibility that the ligand does not actually coordinate to the metal. To try to circumvent

this, the palladium complex, [(R)-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl]palladium(II) chloride, 3.5, was employed, but no reaction resulted.



3.5

TABLE 3.1 Palladium(II) - Catalyzed Hydroesterification of Vinyl Acetate[a]

Vinyl Acetate	MeOH	$(PPh_3)PdCl_2$	ACID	THF	TIME	ISOLATED YIELD
(mmol)	(mmol)	(mmol)	(mmol)	(mL)	hrs	%
0.48	2.5	0.048	0	5	44	82[b]
0.48	2.5	0.048	0	5	44	12
2.5	12.5	0.25	0.025[d]	25	46	70[c]
5.76	30	0.576	0.576[d]	50	45	32
5.7	30	0.576	0.576[e]	25	44	0
5.76	30	0.576	0.576[f]	50	45	43

[a] Reaction conditions: 100°C, 1000 psi CO; [b] GC yield; result from reference 10; [c] isolated; [d] H_3PO_4; [e] HCl; [f] (R)-(-)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate

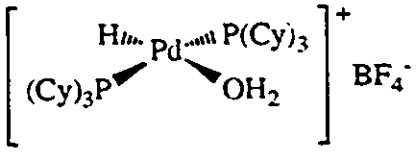
Although it was successfully shown that **3.1**, if formed with some optical activity, will not racemize, it is still likely that the reaction conditions are too severe. It is easy to envision that at the transition state, the two processes (one to produce (S)- and the second to produce (R)-esters) have very similar energies and that with such forcing conditions a racemic mixture can result.

Thus, not only was it necessary to modify the palladium catalyst to include an asymmetric ligand system, but it was also necessary to use a more active catalyst which would facilitate the desired hydroesterification under milder conditions.

3.2.2 HYDROESTERIFICATION OF VINYL BENZOATE IN THE PRESENCE OF A CATIONIC PALLADIUM(II) AQUO HYDRIDE

It is widely accepted in the literature that the Pd(II) catalyzed hydroesterification reactions involve an *in situ* generated palladium hydrido intermediate which is critical in the catalytic cycle. Generally, the complexes used are simply pre-catalysts because of their availability and ease of handling. Ideally, however, the active catalyst would be a complex which is stable and simple to synthesize complex. Obviously, the pre-catalyst should be easily transformable, under the reaction conditions, into a highly reactive intermediate in order to affect the catalysis with maximum efficiency. Recently, a palladium(II) hydrido complex has been synthesized and well characterized.[82] This complex $[(Cy_3P)_2Pd(H)(H_2O)]^+BF_4^-$, **3.5**, is stable and can easily be

handled in air. In addition, many postulated mechanisms involve an intermediate metal hydride.[66-68] For these reasons, complex 3.5 was chosen as a likely candidate for the catalytic hydroesterification of vinyl esters.



3.5

Hydroesterification reactions were carried out in benzene at 50°C and 200 psi of carbon monoxide with molar ratios of substrate / complex 3.5 / achiral bidentate phosphine / acid / MeOH of 1.0 / 0.012 / 0.012 / 0.024 / 5.0.[a] The original reaction temperature was 100°C which may be too severe for reactions in the presence of chiral ligands. When reduced to 50°C, the reaction was too sluggish to produce any ester after two days. However, if a non-polar solvent (e.g. benzene) was used instead of a coordinating solvent, (THF, see section 3.2.1), the reaction was effective at 50°C. Although the conversion of alkene 3.3 was relatively low (10%) after three days, the yield of the branched ester is two times higher than that in the best example of asymmetric hydroesterification known to date.[74] In addition, with the wealth of NMR techniques available, it is still possible to study the degree of asymmetric induction with high accuracy.

[a] It was shown recently that the addition of a bidentate phosphine, usually bis(diphenylphosphino)butane, and an acid were necessary to affect the hydroesterification of various olefins.[83]

The cationic palladium (II) aquo hydride catalyst required one equivalent of a bidentate phosphorous ligand to affect any hydroesterification. Thus, the facility to exchange the achiral ligand DPPB to one which is chiral is a simple but potentially fruitful method to achieve asymmetric induction.

We have studied the hydroesterification of vinyl benzoate in the presence of both optically pure (R)-(+)- and (S)-(-)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP). Under the conditions stated above, using a 1:1 mole ratio of (S)-(-)-BINAP to the metal, the branched ester, **3.4**, was obtained exclusively in 6% yield having an enantiomeric excess of 31%. The enantiomers were resolved by using the chiral NMR shift reagent, $Eu(hfc)_3$ and the ratios compared using the integration from their NMR spectra. The identical experiment was conducted in the presence of the opposite isomer, (R)-(+)-BINAP. The chemical yield was identical but the enantiomeric excess of the opposite product isomer was 21%. (Figures 3.3 and 3.4)

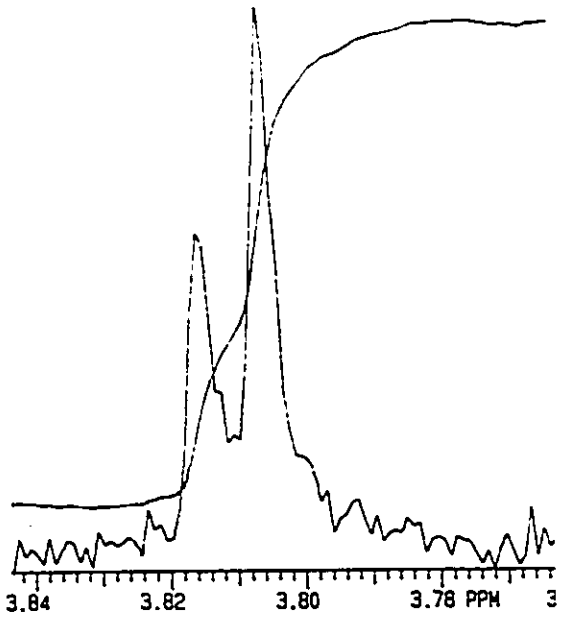


Figure 3.3 ^{1}H NMR of the methoxy ester signal after resolution with Eu(hfc)$_3$ for the hydroesterification of vinyl benzoate in the presence of (S)-(-)-BINAP

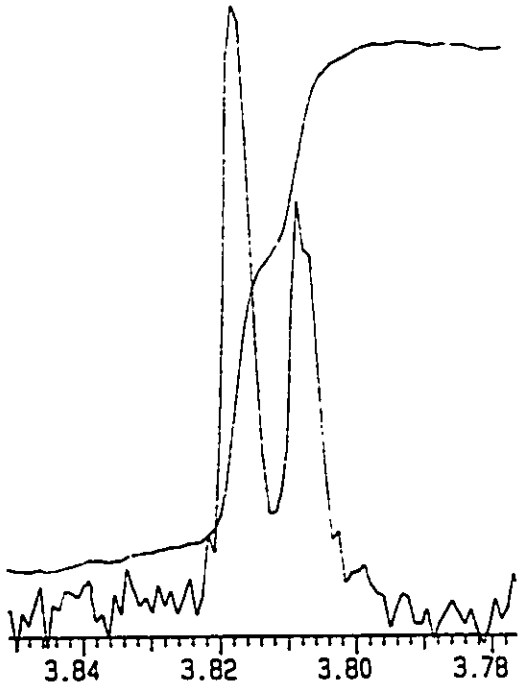


Figure 3.4 ^{1}H NMR of the methoxy ester signal after resolution with Eu(hfc)$_3$ for the hydroesterification of vinyl benzoate in the presence of (R)-(+)-BINAP

In order to increase the reaction rate, the reaction temperature was increased to 85°C and the pressure increased to 500 psi. With a 1:1 mole ratio of (S)-(-)-BINAP to metal, the conversion increased from 10% to 26%. Unfortunately, the mixture of esters consisted of 13% branched and 9% linear. In addition, the enantiomeric excess for the branched ester decreased from 31% to 18%.

In an attempt to increase the chiral induction for this reaction, the relative amount of added (S)-(-)-BINAP was doubled. The result was rather surprising in that not only did the conversion decrease to 12%, but the enantiomeric excess for the branched ester decreased to 12%. To further verify this trend, four equivalents of (S)-(-)-BINAP was added resulting in a conversion of 7% and an enantiomeric excess of 5%. The decrease in conversion can be rationalized by a loss in available coordination sites on the catalyst as the amount of phosphine ligand is increased. It is difficult however to visualize how the respective inductions decreased.

From these experiments, it is clear that the reaction temperature must be reduced to 50°C to achieve the highest obtainable enantiomeric excess of 31%. When the reaction temperature was further reduced to 30°C and the reaction time increased to 6.5 days the chiral induction remained at 31% enantiomeric excess and the branched ester was produced exclusively in 4% yield.

All of the above mentioned hydroesterification reactions were carried out in the presence of p-toluenesulfonic acid. Since the ratio of

acid to catalyst was critical (2:1), it seemed reasonable to explore the effect of varying the nature of the acid in an attempt to improve the conversion of the olefin to branched ester. To verify that p-toluenesulfonic acid was essential as an acid rather than simply supplying an anion, it's sodium salt was used in an analogous reaction. The result was no conversion. Other acids such as trifluoroacetic acid, tetrafluoroboric acid and formic acid were not successful in achieving any hydroesterification. Phosphoric acid however yielded similar results as when p-toluene sulfonic acid was used.

In conclusion, the highest achievable asymmetric induction (enantiomeric excess 21-31%) for the hydroesterification of vinyl esters was obtained using the cationic Pd(II) hydrido complex **3.5** in the presence of optically pure BINAP as the added phosphine ligand.

CHAPTER 4

DESIGN AND ATTEMPTED SYNTHESIS OF NEW CHIRAL RHODIUM COMPLEXES FOR ASYMMETRIC HYDROFORMYLATION

4.1 INTRODUCTION

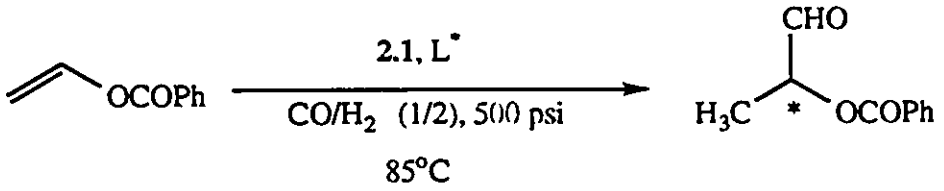
As discussed in Section 2.1, the hydroformylation of α-olefins can yield both branched and linear aldehydes, where the ratio is dependent upon the catalytic species, substrate and reaction conditions (eq. 2.1).[45,47,50] Although cobalt and rhodium based catalysts have shown remarkable reactivity, relative to these species, the rhodium zwitterionic complex, **2.1**, exhibits a high degree of reactivity as well as regioselectivity under surprisingly mild conditions.[53,54] In the formation of branched aldehydes, a new chiral centre is generated. Therefore, systems which favour the branched aldehyde are excellent candidates for exploration of stereoselective differentiation, with the eventual goal of obtaining enantiomeric enrichment.

Considering the efficiency with which (1,5-COD)$Rh^{+}(\eta^{6}$-$C_6H_5)B^{-}(C_6H_5)_3$ is able to produce regioselectively (sometimes regiospecifically) the branched aldehyde under such mild reaction conditions, it is obviously important to examine the potential of this rhodium zwitterionic complex to effect some degree of stereoselectivity during hydroformylation. Literature examples describe very efficient stereoselective hydroformylation reactions, however they are generally poor with respect to yielding branched aldehydes.[37,38,84] To date, there have been no attempts to modify the rhodium zwitterionic catalyst in order to incorporate some elements of asymmetry, thus effecting chiral induction. The work described in this chapter reflects the efforts to achieve catalytic asymmetric hydroformylation using this catalytic

system. Two main strategies have been employed: 1. *in situ* formation of a chiral 'species' through the combination of **2.1** and chiral phosphine ligands, and 2. attempted synthesis of chiral analogs of the symmetric $(1,5COD)Rh^{+}(\eta^{6}\text{-}C_6H_5)B^{-}(C_6H_5)_3$ complex.

4.1.1 HYDROFORMYLATION OF VINYL BENZOATE IN THE PRESENCE OF THE RHODIUM ZWITTERIONIC COMPLEX, $(1,5COD)Rh^{+}(\eta^{6}\text{-}C_6H_5)B^{-}(C_6H_5)_3$ AND OPTICALLY PURE LIGANDS

Amongst the known procedures for affecting asymmetric catalysis (see Chapter 1, Section 1.2) we have chosen to first attempt one of the most direct and facile methods for the *in situ* generation of an optically active catalyst, namely the combination of complex **2.1** and an added chiral ligand. The results for the asymmetric hydroformylation of vinyl benzoate are summarized in Table 4.1. (See eq. 4.1). Asymmetric hydroformylation of vinyl esters is of particular interest because the chiral 2-benzoyloxypropanal can be used as a precursor for the synthesis of the amino acid threonine.



eq. 4.1

Table 4.1 Asymmetric Hydroformylation of Vinylbenzoate Utilizing the Rhodium Zwitterionic Complex, **2.1**, Plus Chiral Ligands Added *In Situ*.

#	Substrate (mmol)	Catalyst (mmol)	Ligand (mmol)	Temp (°C)	Time (hrs)	SM	branched aldehyde	linear aldehyde	% ee[a]
1	2.0	0.02	-	70	22	0	100	0	-
2	1.0	0.01	S-(-)-BINAP 0.02	85	22	>90	<10	0	33
3	1.0	0.01	S-(-)-BINAP 0.01	85	16	trace	>95	trace	0
4	1.0	0.01	(-)-DIOP 0.03	75	22	74	26	0	27
5	1.0	0.01	Polymer[b] 0.005	70	20	0	>95	0	0

[a] resolution of enantiomers using $Eu(hfc)_3$; [b] Poly-L-leucine MW 21700

The first entry, see Table 4.1, is the hydroformylation of vinyl benzoate in the absence of chiral auxiliaries, to produce regiospecifically and in quantitative yield, the branched aldehyde, 2-(benzoyloxy)propanal. Upon addition of the chiral phosphine ligand, (S)-(-)-BINAP, the conversion was reduced to less than 10%. Despite the low yield, the reaction remained regiospecific and had a moderate enantioselectivity of 33% (determined by ^1H NMR, see Experimental Section). This reaction had a catalyst to chiral ligand ratio of 1/2. It is

reasonable to assume that the phosphine ligand itself "consumes" all of the available coordination sites, thus causing the reduced reactivity. When the amount of (S)-(-)-BINAP was reduced to one equivalent relative to the rhodium complex, the result is almost complete conversion with equally high regioselectivity favouring the branched aldehyde, but the stereoselectivity was completely lost. The less sterically rigid bidentate phosphine (-)-DIOP was used instead of (S)-(-)BINAP (entry 4, Table 4.1), resulting in higher conversion (26%) and a similar enantiomeric excess (27%). The nitrogen containing chiral polymer, (poly)L-leucine had no effect on the conversion, relative to no added ligand, and resulted in no chiral induction.

The results obtained by the *in situ* generation of a chiral complex via the combination of the rhodium zwitterionic complex, **2.1** and a chiral ligand are comparable to the best systems found in the literature.[35,84] It is also clear from the results presented in Table 4.1, that the addition of phosphine ligands, although reaching modest enantiomeric excesses, cause a substantial reduction in the conversion to aldehyde. As an alternative to the *in situ* addition of chiral ligands, modification of the rhodium zwitterionic complex itself to incorporate some elements of asymmetry was attempted.

4.1.2 STABILITY OF THE η^6-TETRAPHENYLBORATE MOIETY IN (1,5COD)$Rh^+(\eta^6\text{-}C_6H_5)B^-(C_6H_5)_3$ DURING HYDROFORMYLATION

At the beginning of these investigations, the nature of the catalytically active rhodium species was unclear. It is certain, however,

that the zwitterion, **2.1**, is not a simple precursor to rhodium-carbonyl clusters of the type, $Rh_x(CO)_y$. These complexes, e.g. $Rh_6(CO)_{16}$, are poor hydroformylating catalysts. For example, the reaction catalyzed by $Rh_6(CO)_{16}$, at 55°C and 500 psi of syn gas (1/2 CO/H_2) resulted in only trace amounts of aldehyde from allylphenyl ether. The rhodium zwitterionic complex, however, under identical conditions resulted in 100% conversion of the same substrate to give a 58/42 ratio of branched to linear aldehyde.

Before modifying the zwitterionic rhodium complex, **2.1**, it is essential to verify the coordination environment of the metal centre during catalysis, i. e., the presence of either olefin or borate ligand in the metal coordination sphere. Based on previous results, it has been shown that the olefin dissociates during the initial steps of the catalytic cycle.[85] Analogous zwitterionic complexes of **2.1**, incorporating as their diene, 2,3-dimethoxy-1,3-butadiene and 1,5-hexadiene, gave identical hydroformylation results. This is reasonable if one considers the weak coordination ability of olefins. The focus then was on the tetraphenylborate ligand and whether or not the η^6-bound phenyl substituent remains coordinated to the rhodium.

The ^1H NMR of $(1,5COD)Rh^+(\eta^6\text{-}C_6H_5)B^-(C_6H_5)_3$ shows clearly the proton signals for the arene ring which is coordinated to the rhodium.[52] (see Figure 4.1) It is also known that the chemical shift of these protons strongly depends on the ancillary ligands in the coordination sphere of the metal.[86] When the olefin coordination sites are substituted by carbon monoxide there can be a dramatic downfield shift for the protons of the arene which remain coordinated to the metal. This shift

would result from the stronger back-bonding ability of carbon monoxide versus an olefin, causing the protons of the coordinated phenyl ring of the tetraphenylborate ligand to become deshielded. This is consistent with the ^{1}H NMR spectrum obtained when complex **2.1** is exposed to carbon monoxide.[85] (Figure 4.1)

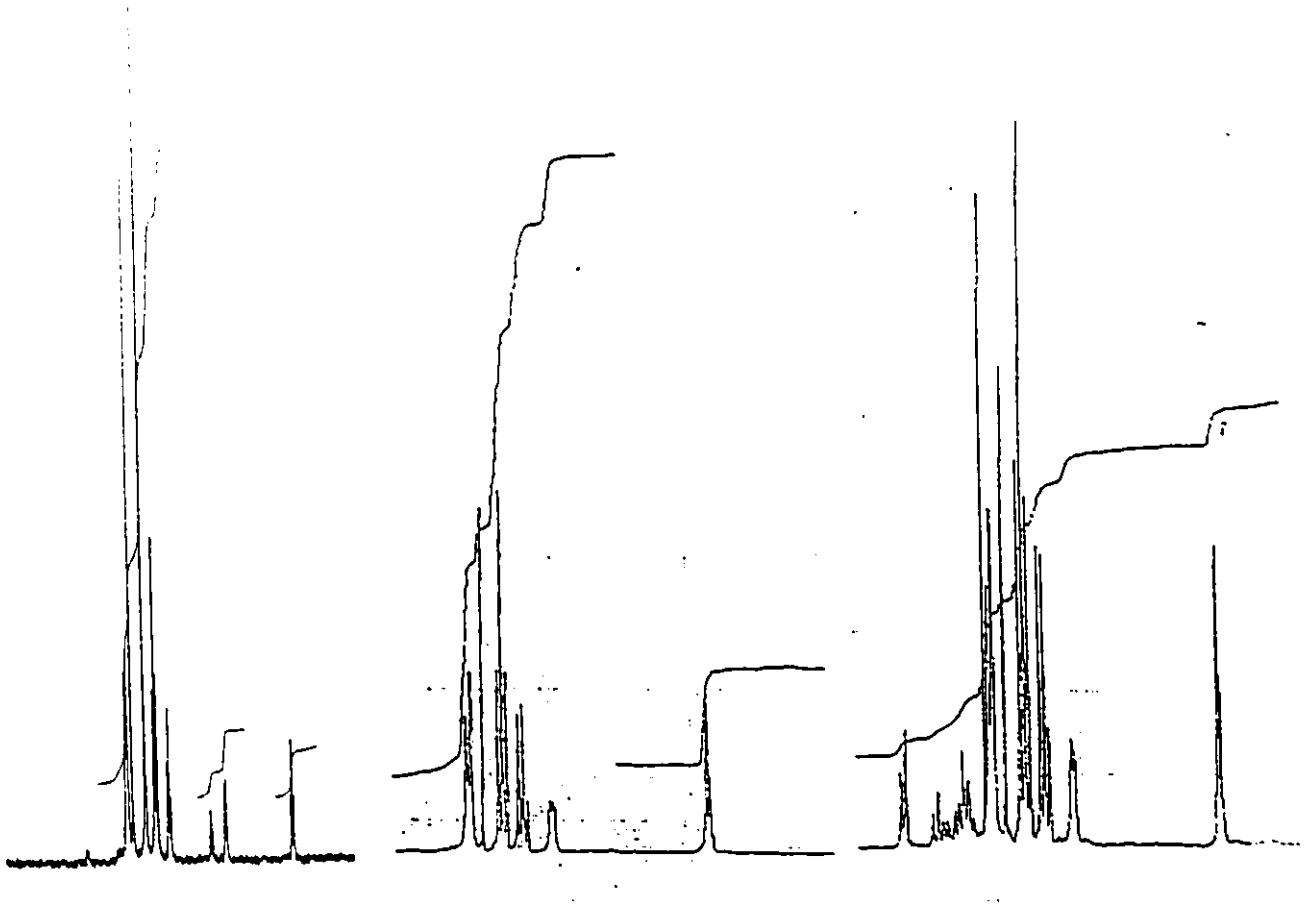
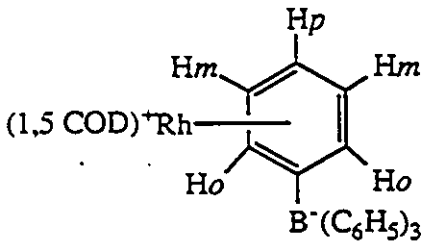
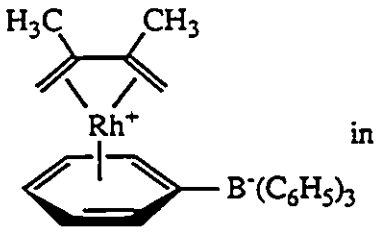


Figure 4.1 ^1H NMR of aromatic region for rhodium coordinated arenes

(a)



(b)



in $CDCl_3$

(I)

(c) (I) in $CDCl_3$ after bubbling of CO

Amer and Alper[85] observed the downfield shift of the protons of the arene ring which is coordinated to the rhodium of **2.1**, in an experiment which was conducted utilizing ten percent catalyst relative to the substrate styrene. As expected, after three hours at 50°C and a CO/H_2 (1/2) pressure of 500 psi, almost all of the styrene was converted to the branched aldehyde. Figure 4.2 shows the ^1H NMR spectrum of the branched plus linear aldehyde along with trace amounts of styrene. The point of relevance however, is the obvious disappearance of the proton resonances for the arene ring which is coordinated to the rhodium (δ 6.0 - 6.7 ppm) and the subsequent appearance of a new set of proton resonances downfield from the bulk of the aromatic signals (δ 7.8 - 7.9 ppm). These signals were attributed to a rhodium - coordinated arene ring of a complex that now contains new ancillary ligands, presumably more electron withdrawing than the diene. These results indicate that the η^6-arene ring remains bound to the rhodium after being subjected to the hydroformylation conditions. What this experiment fails to demonstrate is the critical point of whether or not the borate ligand remains coordinated during the catalytic cycle or whether it dissociates and re-associates.

The addition of excess tetraphenylborate ligand in a catalytic reaction was examined as a method to probe whether or not dissociation of the ligand is a key step. Tetrabutylammonium tetraphenylborate was used due to the complete insolubility of sodium tetraphenylborate in the reaction solvent, $CDCl_3$. The ^1H NMR spectrum of the crude reaction mixture was shown previously in Figure 4.2. The conversion of styrene compares favourably with the identical reaction performed in

the absence of any excess borate ligand. In addition, the protons of the coordinated arene of the borate are visible and well resolved from the resonances of the free arenes of the borate as well as those associated with the product 2-phenyl propanal. The addition of excess tetraphenylborate ligand does not quench the reaction, however the question of dissociation of the tetraphenylborate ligand followed by it's re-association is not answered.

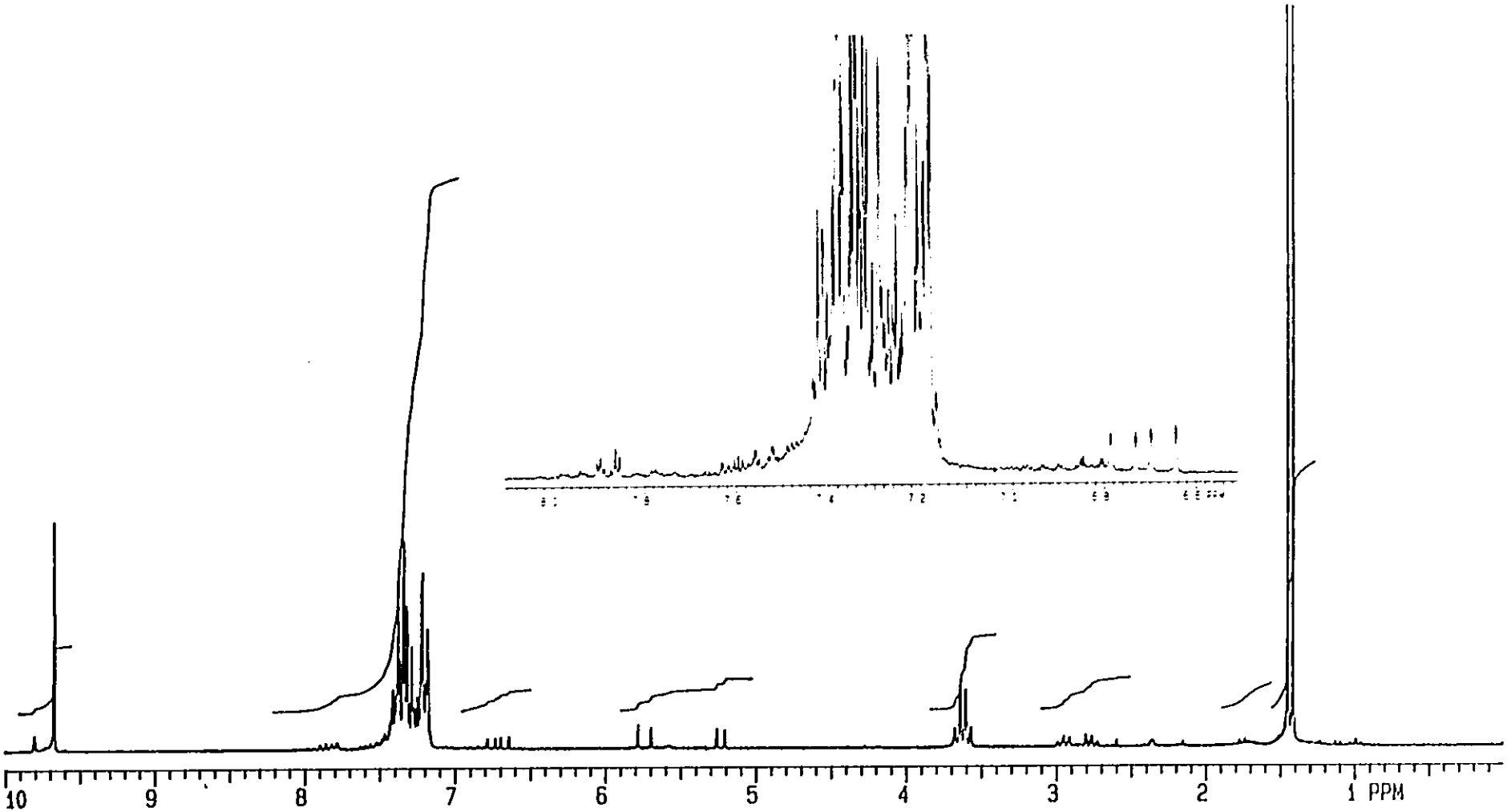
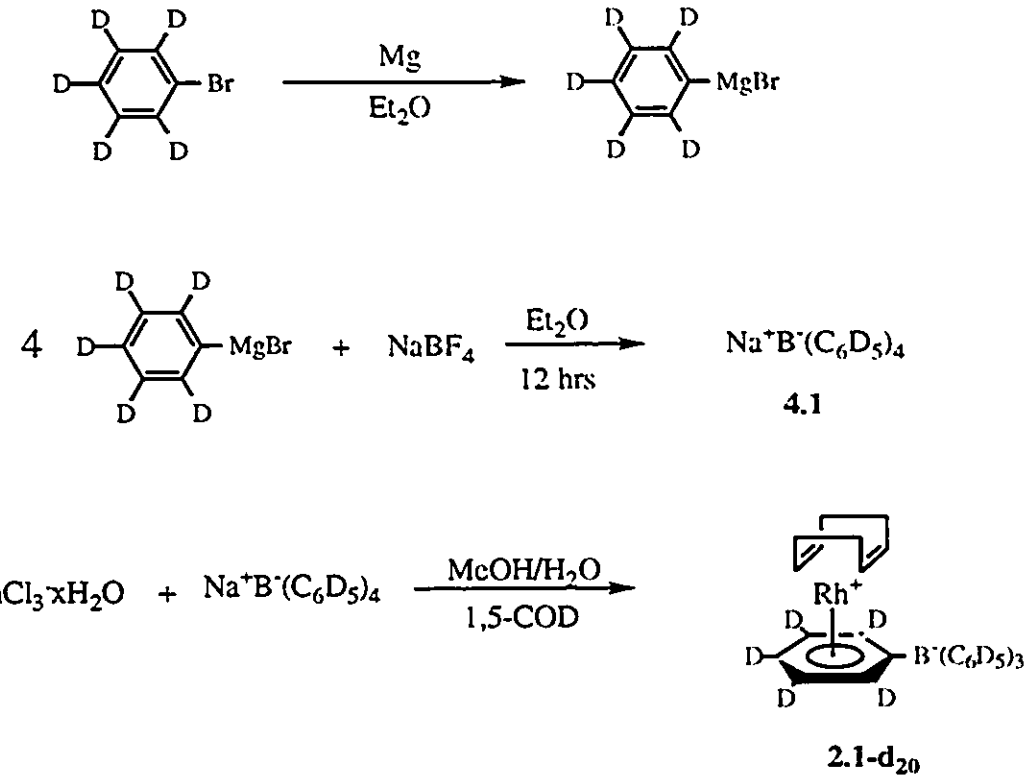


Figure 4.2. ^{1}H NMR of the crude reaction mixture after the hydroformylation of styrene with 10% (1,5-COD)Rh^{+}(η6-C_6H_5)B^{-}(C_6H_5)$_3$.

Although it is difficult to discern the exact nature of the reactive intermediates, in order to probe the possibility of dissociation and re-association of the tetraphenylborate ligand during catalysis, a deuterium labeled cross-over experiment was conducted. Tetraphenylborate-d_{20} was synthesized (see experimental section) and the complex, $(1,5COD)Rh^{+}(\eta^{6}\text{-}C_6D_5)B^{-}(C_6D_5)_3$, was formed according to Scheme 4.1.



Scheme 4.1

The deuterium labeled analog of complex, **2.1**, **2.1-d_{20}**, was used for the hydroformylation of styrene under standard conditions (50°C, 500 psi (CO/H_2 1/2), 3 hours) in the presence of one equivalent of a protio tetraphenylborate. The results were the same with the exception

that no signals in the region corresponding to protons on the aromatic ring which is bound to the metal could be found (see Figure 4.3). This can be interpreted as an indication that the tetraphenylborate does not dissociate during the course of the reaction. Dissociation of the deuteriotetraphenylborate fcllowed by re-association, would present opportunity for coordination of protio tetraphenylborate which in turn would result in the appearance in the ^1H NMR of resonances between 7.7 to 8.9 ppm. Thus, modification of the tetraarylborate ligand to incorporate some elements of asymmetry was investigated.

4.2 SYNTHESIS OF ASYMMETRIC BORATES AS POTENTIAL CHIRAL LIGANDS. ATTEMPTED PREPARATIONS OF NEW CHIRAL ANALOGS OF (1,5COD)$Rh^+B^-(C_6H_5)_4$.

Based on the previous NMR studies[85] and the cross-over experiment just described, modification of the arene-coordinated tetraphenylborate in order to introduce chirality into this ligand was undertaken. This section discusses these efforts. The approaches included introduction of both chiral alkyl and alkoxide moieties to the boron centre.

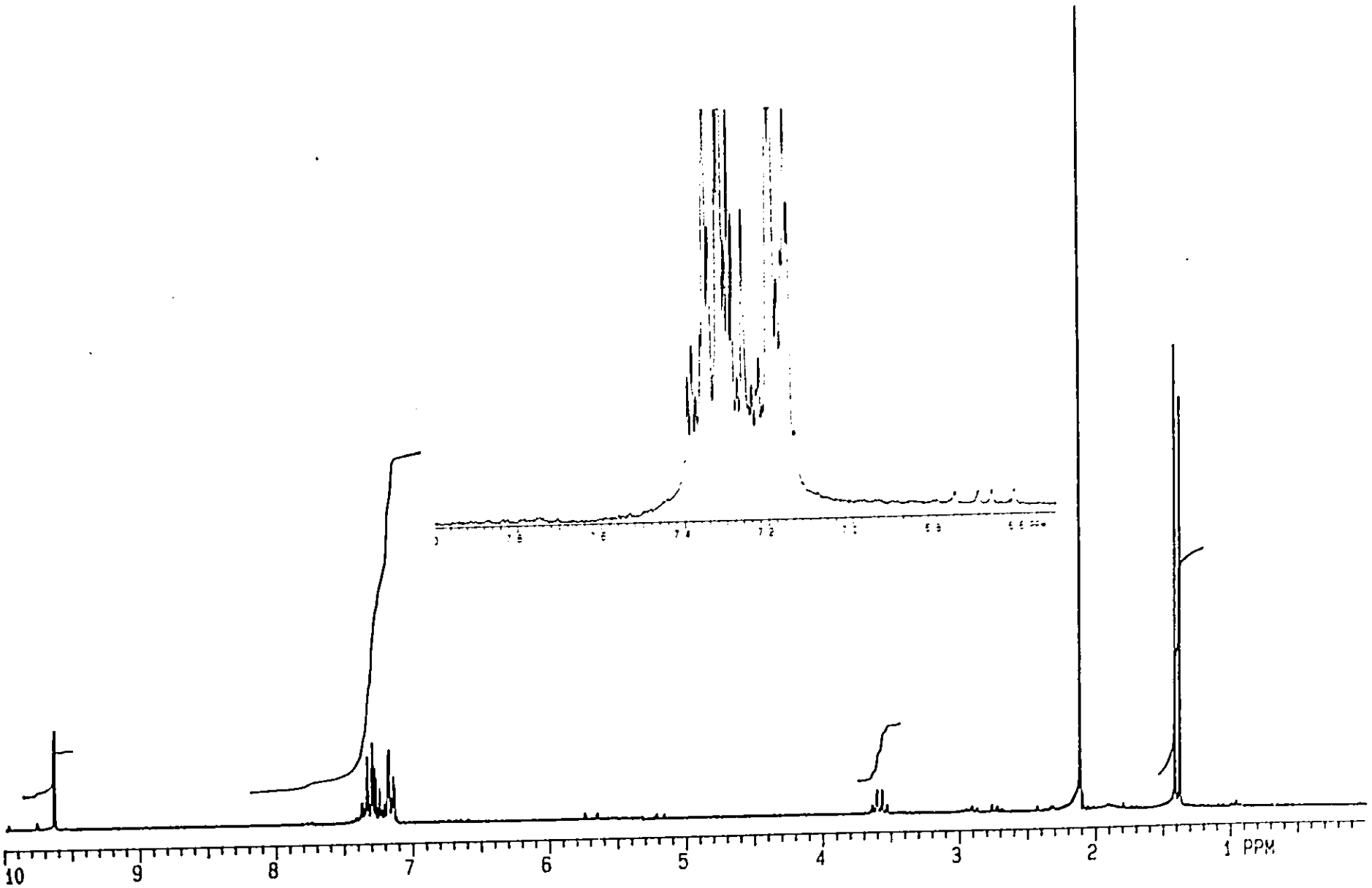
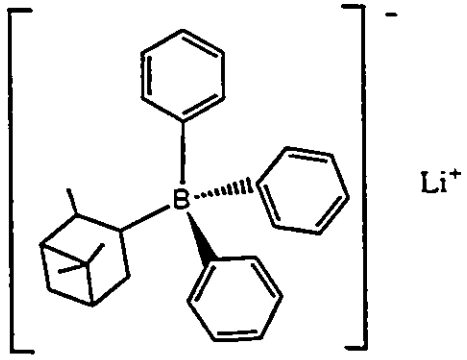


Figure 4.3 ^{1}H NMR of the crude reaction after the hydroformylation of styrene with 10% (1,5-COD)$Rh^{+}(\eta 6\text{-}C_6D_5)B^{-}(C_6D_5)_3$.

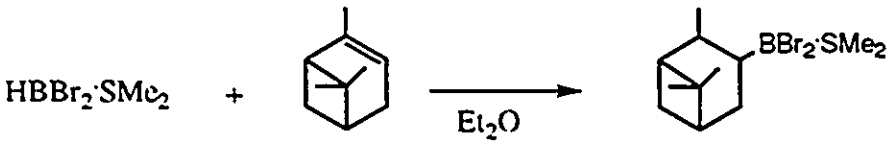
4.2.1 PREPARATION OF β-DIBROMOISOPINOCAMPHEYL-BORANE. REACTIONS WITH PHENYL LITHIUM OR 3,5-DIMETHYLPHENYLMAGNESIUM BROMIDE.

The desired chiral borate, **4.3**, contains three phenyl rings (any of which can easily coordinate to rhodium), and an optically pure and sterically rigid isopinocampheyl group.



4.3

One approach to **4.3** is based on hydroboration of α-pinene beginning with the dimethyl sulfide adduct of dibromoborane, as shown in equation 4.2.[87]



eq. 4.2

4.4

In order to facilitate the subsequent addition of phenyl lithium, ether was chosen as the reaction solvent. The presence of hydroborated

product, **4.4**, was verified by oxidation with hydrogen peroxide in the presence of 3M sodium hydroxide. The formation of isopinocampheol was confirmed by ^1H NMR.

The final step, i.e., the addition of the aryl anions proved to be problematic. Reaction of excess phenyllithium with **4.4** failed to produce the desired salt (based on NMR spectra). In order to eliminate possible interference of the coordinated dimethylsulfide, the next attempt was the addition of a strong Lewis acid, boron tribromide, to the borane, **4.4**. The newly formed adduct, $BBr_3 \cdot SMe_2$, precipitated, producing free B-dibromoisopinocampheylborane (eq. 4.3).

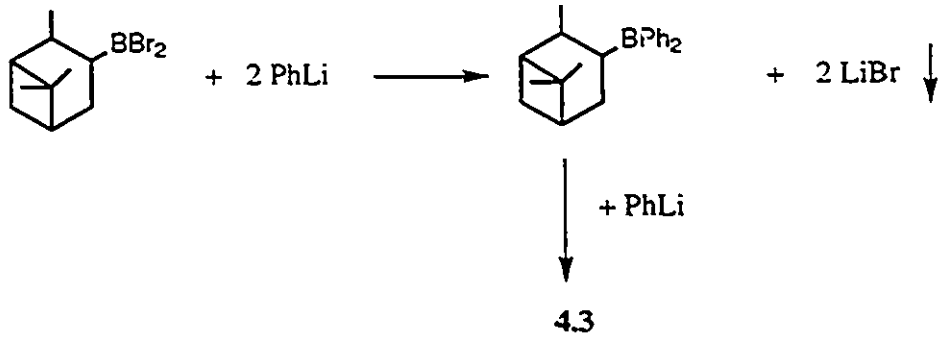
4.4

eq. 4.3

Removal of the $BBr_3 \cdot SMe_2$ by filtration, followed by addition of excess phenyl lithium again failed to yield the desired salt, **4.3**. The amount of added phenyl lithium was reduced to three equivalents, but ^1H NMR spectra did not reveal the presence of the desired product.

In an effort to simplify the purification of the desired salt, **4.3**, two equivalents of phenyl lithium was reacted with base-free, B-dibromoisopinocampheylborane. Removal of the ethereal solvent and replacement with pentane to re-dissolve the borane leaves behind

lithium bromide. The final equivalent of phenyl lithium was added after filtration and replacement of ether for the pentane. (Scheme 4.2)



4.3

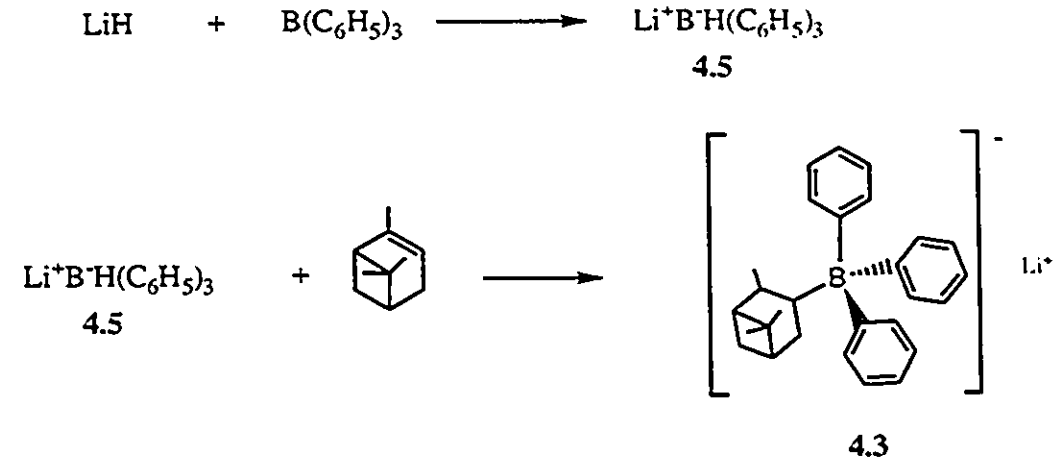
Scheme 4.2

From this procedure, white solid was obtained which exhibited a complex aromatic and aliphatic pattern in the NMR spectrum. Repeated preparations yielded products whose NMR spectra exhibited varying relative amounts of aliphatic/aromatic integrations. A similar approach was tried substituting phenylithium, for the more lipophilic 3,5-dimethylphenylmagnesium bromide. The results were similar to the reactions with phenyl lithium.

4.2.2 HYDROBORATION OF α-PINENE DIRECTLY WITH LITHIUM TRIPHENYL HYDROBORATE

An alternative approach to achieve the same chiral salt, **4.3**, is depicted in Scheme 4.3, and is based on the hydroboration of α-pinene with triphenyl hydroborate. The reaction of lithium hydride with molten triphenyl boron yielded the lithium triphenylhydroborate in high yield, after recrystallization from dioxane.[88] The hydroboration

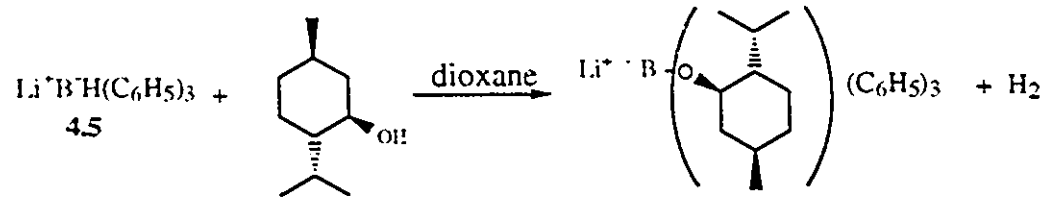
was carried out at room temperature for 14 hours followed by heating at 100°C for an additional four hours. Monitoring the disappearance of α-pinene by GC indicated that no reaction took place. A likely problem with the use of hydroborate salts as the hydroborating reagent is the lack of an available coordination site for the olefin on the boron centre. Transition metal catalysts are known to activate the B-H bond and catalyze insertion of olefins in the B-H bond.[89-91] With this in mind, Wilkinson's catalyst was added and a variety of experimental conditions were explored. Unfortunately GC analysis revealed no consumption of α-pinene.



Scheme 4.3

4.2.3 DEHYDROCONDENSATION OF (1R, 2S, 5R)-(-)-MENTHOL WITH LITHIUM TRIPHENYLBOROHYDRIDE.

Due to the problems encountered in the synthesis of **4.3**, a new approach for the introduction of chirality onto the borate was examined. Namely, the synthesis of **4.6**. Alcoholysis of lithium triphenylhydroborate with a stoichiometric amount of the chiral alcohol, (1R, 2S, 5R)-(-)-menthol (equation 4.4), was performed.

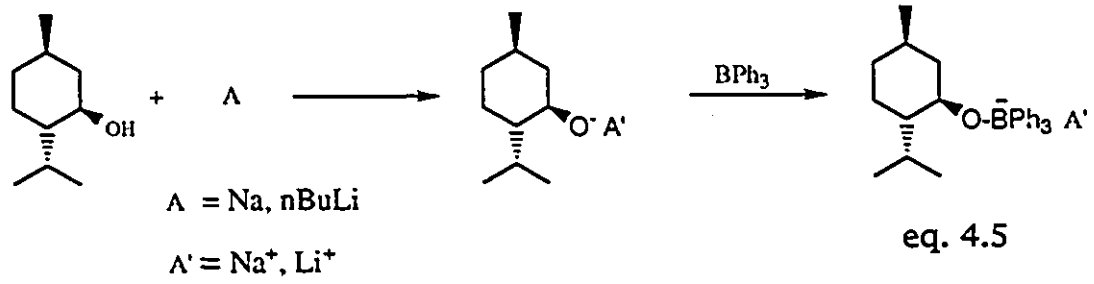


eq. 4.4

Even with prolonged reaction time (2 days) and heating, no hydrogen gas evolution was observed and menthol was continually present in the GC.

4.2.4 REACTION OF ALKALI METAL ALKOXIDES WITH TRIPHENYL BORON FOLLOWED BY FORMATION OF THE RHODIUM COMPLEX

Another route to **4.6** was the direct reaction between a chiral alkoxide salt and triphenylboron (equation 4.5).



eq. 4.5

Alkoxide was prepared in either THF or benzene by the direct reaction between either n-butyllithium or sodium metal. Triphenylboron was then added.

It was necessary to avoid the preparation of the zwitterion from $RhCl_3 \cdot xH_2O$ because in that case, MeOH was necessary as a reducing agent for the rhodium.[52] The presence of methanol would likely

compete with the chiral alkoxide by forming a methoxide anion. As a result, a solution of the rhodium (I) dimer, $[Rh(COD)Cl]_2$, in methylene chloride was directly added to the solutions containing the menthoxytriphenylborate salt. An orange coloured solid, indicative of complex formation, precipitated after ten minutes, but subsequently decomposed to a black oily residue. Subsequent experiments revealed that this reaction was very sensitive to the ratio of "borate" to rhodium dimer. In fact, it was found that a 2 - 4 fold excess of the borate was necessary, however, a larger excess results in decomposition.

Identification of the complex formed in these reactions proved difficult and therefore a model reaction, substituting methanol for menthol, was done. Thus, sodium methoxide was generated in benzene followed by the addition of triphenylboron to prepare a methoxy triphenyl borate. Addition of the rhodium dimer to the reaction mixture resulted in the generation of an air stable, yellow rhodium complex. Unfortunately, the ^1H NMR revealed no aromatic signals for the phenyl rings of the borate. There were, however, signals which are characteristic of rhodium - coordinated 1,5-cyclooctadiene by (1,5-COD). While the chemical shift of the allylic protons for the coordinated 1,5-COD was rather constant, and independent of the nature of the bridging species, the vinylic protons resonate at a frequency which varies, depending on the bridging species. Thus, it is possible to distinguish three compounds in the yellow solid; one species is the starting choride dimer[92] (δ 4.2 ppm, vinylic protons), the second is the methoxy bridged species[93] (δ 3.5 ppm, vinylic protons) and the final is unknown (δ 3.9

ppm, vinylic protons), although it seems likely, based on the chemical shift, to be the mixed bridged dimer, i.e., one methoxy and one chloride.

The results of the model studies (methoxide) suggest that the yellow complex formed in the above reactions is a mixture of dimeric rhodium species - none of which contain a borate ligand. Therefore, it is likely that the secondary chiral alcohol (menthol) reactions yield similar species.

The synthesis of chiral borate ligands and their rhodium complexes is clearly not a trivial task. The above studies revealed many unexpected difficulties, however, in our opinion, despite these complications, the importance of this goal still remains. Although these syntheses are a challenging synthetic problem, overcoming them would likely reveal important features in asymmetric catalysis.

CHAPTER 5

EXPERIMENTAL

5.1 INSTRUMENTATION

Bruker AMX 500, Varian XL 300 and Gemini 200 NMR spectrometers were used for recording ^{1}H, ^{13}C, ^{31}P and ^{11}B spectra. ^{1}H and ^{13}C NMR chemical shifts are reported in ppm and referenced to residual protons in the deuterated solvents (7.24 ppm for $CDCl_3$, 2.04 for acetone-d_6, 7.15 ppm for benzene-d_6, 2.49 ppm for dimethyl-d_6 sulfoxide, 4.78 and 3.30 ppm for methyl alcohol-d_4 and 3.58 and 1.73 ppm for tetrahydrofuran-d_6). ^{31}P and ^{11}B NMR chemical shifts are reported in ppm relative to the external standards 85% H_3PO_4 and $BF_3 \cdot OEt_2$, respectively. Chemical shifts reported upfield of zero are defined as negative.

A Bomem MB100 FTIR spectrometer, interfaced to a NEC 286 computer was used with Bomem version 1.45 Michelson series software for all infrared analyses. The samples were run neat, as nujol mulls, in solution or as KBr pellets.

A VG7070E spectrometer was used for mass spectral determinations. The energy of ionization was 70 eV. For complex mixtures, the mass spectrometer was coupled to a gas chromatograph for GC-MS analysis.

A Fisher-Johns melting point apparatus was used and the uncorrected values are reported.

Varian 3300 and Hewlett Packard chromatographs were used for the GLC analyses. Both instruments were equipped with flame ionization detectors and packed columns containing OV-101 and 1.5 % OV-17 + 1.95% OV-210 on Chromosorb W-HP (100-200 mesh), respectively.

A Perkin-Elmer 241 polarimeter was used for measuring optical rotations.

A standard vacuum line equipped with a two stage Edwards pump was used for handling air and moisture sensitive materials.

Parr stainless steel autoclaves fitted with glass liners were used for all high pressure reactions. For experiments at elevated temperatures a silicone oil bath was used.

5.1.2 CHEMICALS AND SOLVENTS

All starting materials and ligands were purchased from Aldrich, Pfaltz, Fluka, Strem Chemicals or Johnson Matthey and used as received, unless otherwise noted. The solvents were dried, purified and distilled as described in the literature.[94]

5.1.3 ELEMENTAL ANALYSIS

Elemental analysis were carried out by either Guelph Chemical Laboratories, Guelph, Ontario, Canada, or MHW Laboratories, Phoenix, AZ.

5.1.4 CATALYSTS

The complexes [(1,5-COD)$Rh^+BPh_4^-$],[52] [$(PPh_3)_2NiCl(1\text{-}C_{10}H_7)$],[3] [$(PPh_3)_2PdCl_2$],[95] [$(Cy_3P)_2Pd(H)(H_2O)]^+BF_4^-$,[82] [$Rh(COD)Cl]_2$[92] were synthesized as described in the literature.

5.2 EXPERIMENTAL FOR CHAPTER 2

5.2.1 HYDROFORMYLATION OF 2-NAPHTHYL VINYL SULFONE, 2 d

A mixture of 2-naphthyl vinyl sulfone, **2d**, (188 mg, 0.862 mmol), (1,5-COD)$Rh^+BPh_4^-$ (5.6 mg, 0.009 mmol), **2.1**, and DPPB, (7.3 mg, 0.017 mmol) were added to dry CH_2Cl_2 (10mL) in a 46 mL Parr autoclave which was fitted with a glass liner and magnetic stirring bar. The system was purged three times with CO to displace the air and subsequently pressurized to 600 psi with a 1/1 mixture of CO and H_2. The vessel was heated with stirring at 75°C for 19 hours. The reaction mixture was filtered through celite, and the filtrate was concentrated by rotary evaporation. The aldehydic sulfone, **3d**, was isolated by

crystallization from methylene chloride/pentane, followed by successive washings with pentane to remove residual hydrogenated product, **4d**. The NMR yield of **3d** (ferrocene as internal standard) was 83%.

mp 96-98°C; ^{1}H NMR ($CDCl_3$): δ 1.44 (d, 3H, J=7Hz, CH_3), 4.07 (dq,1H, J=7 Hz, 1.6 Hz, CH), 7.5 - 8.5 (m, 7H, $C_{10}H_7$), 9.91 (d, 1H, J=1.6 Hz, CHO); ^{13}C NMR ($CDCl_3$): d 8.7 (CH_3), 70.2 (CH), 122.8, 128.0, 129.2, 129.4, 129.6, 129.8, 131.0, 132.0, 133.5, 135.6 (aromatic carbons C_1-C_{10}), 193.0 (CHO); Anal. calcd. for $C_{13}H_{12}O_3S$; C, 62.90; H, 4.89; S, 12.93. Found: C, 62.87; H, 5.04; S, 13.20.

5.2.2 HYDROFORMYLATION OF 2-PHENYLVINYLSULFONE, 2c

Under the reaction conditions specified in **4.2.1**, phenyl vinyl sulfone was hydroformylated for 18 hours to yield 83% of the aldehydic sulfone, **3c**, (yield determined by NMR with ferrocene as the internal standard). The aldehyde **3c** (contaminated with the hydrogenated product **4c**) was isolated by bulb-to-bulb distillation under vacuum (ca. 1 mm), and subsequently converted to its enamine derivative for purification and characterization. The clear distillate was diluted with approximately 1 mL of methylene chloride and added to one equivalent of α-methylbenzylamine, (242 mg, 2.0 mmol), and stirred over calcinated molecular sieves (4 Å). The physical data for the enamine derivative, $(C_6H_5)S(O)_2C(CH_3)$=CHCHNHCH-$(CH_3)(C_6H_5)$ are as follows:

mp 159-161°C; ^{1}H NMR ($CDCl_3$): δ 1.46 (d, 3H, J=7 Hz, CH_3), 1.61 (s, 3H, CH_3), 4.40 (m, 1H, CH), 4.73 (m, 1H, NH), 7.16-7.48 (m, 10H, aromatic), 7.69 (d,1H, J= 8 Hz, =CH); ^{13}C NMR ($CDCl_3$): δ 9.5 (CH_3); 23.4 (CH_3); 57.1 (CH); 100.5 (-C=); 126.0, 126.9, 127.6, 128.8, 131.8, 142.2,

143.6 (aromatic carbons); 144.0 (=CH); Anal. Calcd. for $C_{17}H_{19}NSO_2$: C, 67.73; H, 6.37; N, 4.65; S, 10.64. Found: C, 67.81; H, 6.08; N, 4.81; S, 10.54.

5.2.3 HYDROFORMYLATION OF ETHYL VINYL SULFONE, 2b

Under the reaction conditions specified in **4.2.1**, ethyl vinyl sulfone, **2b**, was hydroformylated for 26 hours to yield 98% of the aldehydic sulfone, **3b** (yield determined by ^1H NMR with ferrocene as the internal standard). The 2-(ethylsulfonyl)propanal, **3b**, was isolated (90% yield) by bulb-to-bulb distillation under reduced pressure (ca. 1 mm Hg).

^1H NMR ($CDCl_3$): δ 1.37 (t, 3H, J= 7 Hz, CH_3), 1.59 (d, 3H, J= 7 Hz, CH_3), 3.00 (m, 2H, CH_2), 3.83 (dq, 1H, J= 7 Hz, 2 Hz, CH), 9.72 (d, 1H, J= 2 Hz, CHO); ^{13}C NMR ($CDCl_3$): δ 5.8 (CH_3); 7.7 (CH_3); 46.5 (CH_2); 66.3 (CH); 194.2 (CHO). Anal. Calcd. for $C_5H_{10}SO_3$: C, 39.97; H, 6.72; S, 21.35 Found: C, 39.65; H, 6.66; S, 20.99.

5.2.4 HYDROFORMYLATION OF METHYL VINYL SULFONE, 2a

Under the reaction conditions specified in **4.2.1**, ethyl vinyl sulfone, **2a**, was hydroformylated for 26 hours to yield 98% of the aldehydic sulfone, **3a** (yield determined by ^1H NMR with ferrocene as the internal standard). The 2-(methylsulfonyl)propanal, **3a**, was isolated (85% yield) by bulb-to-bulb distillation under reduced pressure (ca. 1 mm Hg).

^{1}H NMR ($CDCl_3$): δ 1.57 (d, 3H, J= 7 Hz, CH_3), 2.87 (s, 3H, CH_3), 3.89 (dq, 1H, J= 7 Hz, 2 Hz, CH), 9.74 (d, 1H, J= 2 Hz, CHO); ^{13}C NMR ($CDCl_3$): δ 8.1 (CH_3); 39.2 (CH_3); 68.4 (CH); 194.1 (CHO). Anal. Calcd. for $C_4H_8SO_3$; C, 35.27; H, 5.93; S, 23.55. Found: C, 35.62; H, 6.11; S, 23.47.

5.2.5 HYDROFORMYLATION OF 2-PHENYLVINYL SULFOXIDE, 5

A mixture of phenyl vinyl sulfoxide, **5**, (304 mg, 2.0 mmol), (1,5-COD)$Rh^+BPh_4^-$ (13 mg, 0.02 mmol), **2.1**, and DPPB (34 mg, 0.08 mmol) were added to dry CH_2Cl_2 (10 mL) in a 46 mL Parr autoclave which was fitted with a glass liner and magnetic stirring bar. The system was purged three times with CO to displace the air and subsequently pressurized to 600 psi with a 1/1 mixture of CO/H_2. The vessel was heated with stirring at 75°C for two hours.

The pressure (after time t) was released and replaced by an atmosphere of nitrogen. For quantitative analyses, ferrocene, (30 mg, 0.16 mmol), was added to the reaction mixture. A small aliquot (0.5 mL) was withdrawn. The remaining mixture was re-pressurized in the autoclave. Nitrogen was passed over the aliquot to remove the solvent. The residue was dissolved in $CDCl_3$ and the ^{1}H NMR was recorded. The maximum yield (by ^{1}H NMR) of 2-(phenylsulfinyl)propanal was 50% (see Chapter 2, Section 2.2.1). The aldehyde was isolated and purified as its enamine derivative, $(C_6H_5)S(O)C(CH_3)=CHNHCH(CH_3)(C_6H_5)$ (see section **4.2.1**). The physical data for the enamine derivative follows:

mp 127-129°C; ^1H NMR ($CDCl_3$): δ 1.43 (d, 3H, J= 1 Hz, CH_3), 1.51 (d, 3H, J= 7 Hz, CH_3), 4.11 (m, 1H, NH), 4.42 (m, 1H, CH), 6.85 (dd, 1H, J= 13 Hz, 1 Hz, =CH), 7.23-7.54 (m, 10 H, aromatic); ^{13}C NMR ($CDCl_3$): δ 6.0 (CH_3); 23.6 (CH); 56.4 (CH_2); 107.5 (-C=); 124.9, 126.1, 127.7, 128.6, 128.8, 128.9, 129.5, 143.5, 144.1 (aromatic carbons); 142.4 (=CH-). Anal. Calcd. for $C_{17}H_{19}NSO$; C, 71.53; H, 6.72; N, 4.91; S, 11.24. Found: C, 71.57; H, 6.38; N, 4.91; S, 11.24.

5.2.6 SYNTHESIS OF NICKEL COMPLEX, σ-NAPHTHYL-$Ni(PPh_3)_2Cl$[65]

The nickel complex was synthesized by zinc reduction of $(PPh_3)_2NiBr_2$ in dimethylformamide, under an atmosphere of nitrogen, followed by addition of α-chloronaphthalene. Zinc powder was substituted in place of the recommended manganese/iron alloy, and served as an adequate reductant. The solution changed from a bright green colour to yellow in a few minutes and then darkened to orange. After approximately three hours, the excess zinc was removed by filtration and the catalyst precipitated from solution using methanol. The yellow/orange Ni complex was isolated by recrystallization from hot benzene (23% yield). A chloride test with $Ag(NO_3)$ was positive. mp 162-167°C (lit. mp 172°C)

5.2.7 SYNTHESIS OF 2-NAPHTHYLVINYL SULFIDE

A solution of 2-naphthalenethiol (3.84 g, 24 mmol) in NaOH (25 mL, 30 %) was gradually added at room temperature to a solution of vinyl bromide (2.57 g, 24 mmol), $C_{10}H_7Ni[P(C_6H_5)_3]_2Cl$ (1.0 g 1.3 mmol),[63b] (see section 5.2.6) hexadecyltri-n-butylphosphonium bromide (507 mg, 1 mmol), and $P(C_6H_5)_3$ (0.35 g 1.3 mmol) in toluene (20 mL). Due to the volatility of vinyl bromide (bp 16°C) it was added into the reaction vessel periodically to compensate for losses due to evaporation. After 24 hours, the organic phase was separated, and the aqueous layer was extracted with ether (3x25mL) and evaporated. The combined organic solution were dried over $MgSO_4$ and evaporated. The residual oil was chromatographed on a column (neutral alumina, pentane) to give 65% of 2-naphthyl vinyl sulfide.[63a] ^1H NMR ($CDCl_3$): δ 5.38 (d, 1H, J= 17 Hz, CH), 5.39 (d, 1H, J= 9 Hz, CH), 6.61 (dd, 1H, 17 Hz, 9 Hz, CH), 7.00-8.00 (m, 7H, aromatic).

5.2.8 OXIDATION OF 2-NAPHTHYL VINYL SULFIDE

2-Naphthyl vinyl sulfide (0.93 g, 5 mmol) was oxidized with t-BuOOH according to the literature,[65] noting that no diisopropyltartrate was used. The mixture was separated by preparative thin layer chromatography (SiO_2), using 30% ethyl acetate in hexane as eluant, to yield 2-naphthyl vinyl sulfone (162 mg).

^{1}H NMR ($CDCl_3$): δ 6.03 (dd, 1H, J = 1 Hz, 10 Hz, CH), 6.48 (dd, 1H, J = 1 Hz, 16 Hz, CH), 6.70 (dd, 1H, J = 10 Hz, 16 Hz, CH), 7.58-8.47 (m, aromatic protons).

5.3 EXPERIMENTAL FOR CHAPTER 3

5.3.1 HYDROESTERIFICATION OF VINYL ACETATE

5.3.1.1 HYDROESTERIFICATION OF VINYL ACETATE IN THE PRESENCE OF H_3PO_4 (1% relative to the substrate)

After termination of the reaction, the autoclave was cooled to room temperature and the pressure released. The product, methyl-2-acetyloxypropanoate, **3.1**, was isolated by initial distillation of the solvent at reduced pressure (50 mm Hg) using a short path distillation set-up which was connected to a water aspirator. The residue (containing the product and catalyst) was then transferred to a small Schlenk flask, containing a magnetic stirring bar, for an additional micro-distillation. The Schlenk flask was fitted with a cold finger, at the end of which was fastened a small collection cup. The cold finger was filled with a dry ice/acetone mixture. The flask was connected to a vacuum line (ca. 1 mm Hg) and evacuated briefly and then closed. The ester distilled and collected in the cup. The yield was 70%. ^{1}H NMR ($CDCl_3$): δ 1.46 (d, 3H, J = 7 Hz, CH_3), 2.11 (s, 3H, $OCOCH_3$), 3.73 (s, 3H,

$COOCH_3$), 5.06 (q, 1H, J = 7 Hz, CH); ^{13}C NMR ($CDCl_3$): δ 17.5 (CH_3); 21.3 ($C(O)CH_3$); 52.9 (CH); 69.1 (OCH_3); 171.0 (CO); 171.9 (CO).

5.3.1.2 HYDROESTERIFICATION OF VINYL ACETATE IN THE ABSENCE OF ACID

The reaction was carried out identical to that in section **5.3.1.1** but no phosphoric acid was used. **3.1** was isolated in 12% yield.

5.3.1.3 HYDROESTERIFICATION OF VINYL ACETATE IN THE PRESENCE OF (R)-(-)-1,1'-BINAPHTHYL-2,2'-DIYL HYDROGEN PHOSPHATE (10% relative to the substrate)

The reaction was performed analogous to **5.3.1.1** but scaled-up. The autoclave was charged with vinyl acetate (495 mg, 5.76 mmol), methanol (960 mg, 30 mmol) $(PPh_3)_2PdCl_2$ (404 mg, 0.576 mmol) and (R)-(-)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate (201 mg, 0.576 mmol). No other acid was added. The total amount of esters isolated was 43%; the ratio of **3.1/3.2** was 84/16 (determined by their respective ^1H NMR integrations). The optical rotation was determined to be zero by polarimetry.

5.3.1.4 HYDROESTERIFICATION OF VINYL ACETATE IN THE PRESENCE OF H_3PO_4 (10% relative to the substrate)

Identical conditions were employed as in **5.3.1.3** except that H_3PO_4 (65 mL, 0.576 mmol) was substituted for the previously used (R)-(-)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate. The total amount of esters isolated was 32%; the ratio of **3.1/3.2** was 70/30 (determined by their respective ^1H NMR integrations).

5.3.1.5 HYDROESTERIFICATION OF VINYL ACETATE IN THE PRESENCE OF HCl (10% relative to the substrate)

A mixture of vinyl acetate (495 mg, 5.76 mmol), $(PPh_3)_2PdCl_2$ (404 mg, 0.576 mmol), methanol (960 mg, 30 mmol), and 37% HCl (57 μL, 0.576 mmol) was added to dry THF (25 mL) in a 125 mL Parr autoclave which was fitted with a glass liner and magnetic stirring bar. The system was purged three times with CO to displace the air and subsequently pressurized to 1000 psi. The vessel was heated with stirring at 100°C for 46 hours. No product ester was isolated.

5.3.2 OPTICALLY PURE (-)-METHYL O-ACETYLLACTATE (or methyl-2-acetyloxypropanoate)

5.3.2.1 SYNTHESIS OF (-)-METHYL O-ACETYLLACTATE

(S)-(-)-Methyl lactate (1.04 g, 10 mmol) was treated with acetic anhydride (50 mL) and pyridine (10 mL) and stirred overnight at room temperature. The reaction mixture was poured into water and extracted with ether. The ether fractions were combined and washed with 10% HCl and saturated sodium bicarbonate solution, dried over anhydrous magnesium sulfate and concentrated. The 'H NMR compared to literature values.[81] ^1H NMR ($CDCl_3$): δ 1.46 (d, 3H, J = 7 Hz, CH_3), 2.11 (s, 3H, $OCOCH_3$), 3.73 (s, 3H, $COOCH_3$), 5.06 (q, 1H, J = 7 Hz, CH). Polarimetry measurements revealed an $[\alpha]_D^{25}$ -51.4° (c 3.4, acetone).

5.3.2.2 TEST FOR THE RACEMIZATION OF 3.2 DURING CATALYSIS

To an autoclave, was added (-)-methyl O-acetyllactate (183 mg, 1.25 mmol), methanol (400 mg, 12.5 mmol) and THF (25 mL). The catalyst, $(PPh_3)PdCl_2$ (175 mg, 0.25 mmol) was then added, followed by H_3PO_4 (2.8 μL, 0.025 mmol). The autoclave was pressurized (following the usual method) to 1000 psi with carbon monoxide. The vessel was then heated to 100°C and stirred for 44 hours. After termination of the reaction, the autoclave was cooled to room temperature and the pressure was released. The product, methyl O-acetyllactate, **3.1**, was re-isolated by initial distillation of the solvent at reduced pressure (50 mm Hg) using a short path distillation set-up which was connected to a water aspirator. The residue (containing the product and catalyst) was filtered through a small (0.5 cm x 5 cm) column of celite and transferred to a Schlenk flask for micro-distillation to separate the product from the remaining palladium catalyst. High vacuum (0.1 mm Hg) was applied prior to the distillation to ensure complete removal of the solvent. The ester, **3.1**, was recovered and its optical activity, $[\alpha]_D^{25}$ -50.9° (c 2.9, acetone), was determined by polarimetry.

5.3.3 ATTEMPTED ASYMMETRIC HYDROESTERIFICATION OF VINYL ACETATE

5.3.3.1 HYDROESTERIFICATION OF VINYL ACETATE AT 100°C IN THE PRESENCE OF CHIRAL LIGANDS, L*

The following is a representative description for the hydroesterification of vinyl acetate in the presence of $(PPh_3)_2PdCl_2$ and

L^* (L^* = (R)-(+)-α-methylbenzylamine, poly(L-leucine), diisopropyl D-tartrate, (+)-2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane and (R)-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl).

A mixture of vinyl acetate (215 mg, 2.5 mmol), $(PPh_3)_2PdCl_2$ (175 mg, 0.25 mmol), diisopropyl D-tartrate (59 mg, 0.25 mmol), methanol (400 mg, 12.5 mmol), and 87% H_3PO_4 (2.8 μL, 0.025 mmol) was added to dry THF (25 mL) in a 125 mL Parr autoclave which was fitted with a glass liner and magnetic stirring bar. The system was purged three times with CO to displace the air and subsequently pressurized to 1000 psi. The vessel was heated with stirring at 100°C for 46 hours.

After termination of the reaction, the autoclave was cooled to room temperature and the pressure released. The product, methyl-2-acetyloxypropanoate, **3.1**, was isolated following the procedure outlined in section **5.3.1.1**. Polarimetry measurements yielded no optical rotation in all cases.

5.3.3.2 HYDROESTERIFICATION OF VINYL ACETATE AT 100°C IN THE PRESENCE OF [(R)-(+)- 2,2'-BIS(DIPHENYL-PHOSPHINO) - 1,1'-BINAPHTHYL] PALLADIUM (II) DICHLORIDE, 3.5, with 0%, 1% and 10% H_3PO_4 (relative to the substrate)

A mixture of vinyl acetate (215 mg, 2.5 mmol), 3.5 (200 mg, 0.25 mmol), methanol (400 mg, 12.5 mmol), and 87% H_3PO_4 (0 mL ; 2.8 μL, 0.025 mmol; or 28 μL , 0.25 mmol) was added to dry THF (25 mL) in a 125 mL Parr autoclave which was fitted with a glass liner and magnetic stirring bar. The system was purged three times with CO to displace the air and subsequently pressurized to 1000 psi. The vessel was heated with stirring at 100°C for 46 hours. All reactions were worked up as described above, but in all cases no reaction resulted.

5.3.4 HYDROESTERIFICATION OF VINYL BENZOATE IN THE PRESENCE OF $(PPh_3)_2PdCl_2$ AND H_3PO_4 (1% relative to the substrate)

To an autoclave was added vinyl benzoate, 3.3, (370 mg, 2.5 mmol), methanol (400 mg, 12.5 mmol) and THF (25 mL). The catalyst, $(PPh_3)_2PdCl_2$ (175 mg, 0.25 mmol) was then added, followed by H_3PO_4 (2.8 μL, 0.025 mmol). The autoclave was subsequently pressurized to 1000 psi with carbon monoxide and then stirred at 100°C for 47 hours. The product ester, methyl 2-benzoyloxypropanoate, 3.4, was purified by bulb-to-bulb distillation (387 mg, 1.86 mmol) and isolated in 74% yield. ^1H NMR ($CDCl_3$): δ 1.61 (d, 3H, J = 7 Hz, CH_3); 3.75 (s, 3H, OCH_3); 5.32 (q, 1H, J = 7 Hz, CH); 7.30-8.20 (m, 5H, aromatic protons).

5.3.5 HYDROESTERIFICATION OF VINYL BENZOATE IN THE PRESENCE OF $[(Cy_3P)_2Pd(H)(H_2O)]^+BF_4^-$, 3.5

5.3.5.1 HYDROESTERIFICATION OF VINYL BENZOATE IN THE PRESENCE OF $[(Cy_3P)_2Pd(H)(H_2O)]^+BF_4^-$, 3.5 and (S)-(-)-BINAP

An autoclave was charged with vinyl benzoate (148 mg, 1.0 mmol), methanol (0.2 mL, 5.0 mmol) and benzene (5 mL) followed by the catalyst, 3.5 (10 mg, 0.012 mmol), p-toluene sulfonic acid (4.6 mg, 0.024 mmol) and the chiral ligand, (S)-(-)-BINAP (7.5 mg, 0.012 mmol). The atmosphere was purged three times with carbon monoxide and subsequently filled to 200 psi. The vessel was then stirred at 52°C for three days. After completion of the experiment, the autoclave was cooled to room temperature and the pressure was released. The solvent was removed and the ^1H NMR of the reaction mixture was measured, revealing mostly starting material (90%) and the branched ester, 3.4 (6%). Slow and consecutive additions of $Eu(hfc)_3$ (ca. 2 mg) to the NMR sample (in $CDCl_3$) caused a downfield shift and eventual resolution of the enantiomers. The methoxy ester singlets were resolved to nearly baseline resolution and the enantiomeric excess was calculated to be 31% based on their relative integrations.

5.3.5.2 HYDROESTERIFICATION OF VINYL BENZOATE IN THE PRESENCE OF $[(Cy_3P)_2Pd(H)(H_2O)]^+BF_4^-$, 3.5 and (R)-(+)-BINAP

An autoclave was charged with vinyl benzoate (148 mg, 1.0 mmol), methanol (0.2 mL, 5.0 mmol) and benzene (5 mL) followed by

the catalyst, 3.5 (10 mg, 0.012 mmol), p-toluene sulfonic acid (4.6 mg, 0.024 mmol) and the chiral ligand, (R)-(+)-BINAP (7.5 mg, 0.012 mmol). The atmosphere was purged three times with carbon monoxide and subsequently filled to 200 psi. The vessel was then stirred at 52°C for three days. After completion of the experiment, the autoclave was cooled to room temperature and the pressure was released. The solvent was removed and the ^1H NMR of the reaction mixture was measured, revealing mostly starting material (88%) and the branched ester, 3.4 (6%). Slow and consecutivie additions of $Eu(hfc)_3$ (ca. 2 mg) to the NMR sample (in $CDCl_3$) caused a downfield shift and eventual resolution of the enantiomers. The methoxy ester singlets were resolved to nearly baseline resolution and the enantiomeric excess was calculated to be 21% based on their relative integrations (the enantiomer which was in excess is opposite to that which was in excess above).

5.3.5.3 HYDROESTERIFICATION OF VINYL BENZOATE IN THE PRESENCE OF 3.5 AND DPPB AT 85°C and 1000 psi CO

An autoclave was charged with vinyl benzoate (148 mg, 1.0 mmol), methanol (0.2 mL, 5.0 mmol) and benzene (5 mL) followed by the catalyst, 3.5 (10 mg, 0.012 mmol), p-toluene sulfonic acid (4.6 mg, 0.024 mmol) and the phosphine ligand, DPPB (5.2 mg, 0.012 mmol). The atmosphere was purged three times with carbon monoxide and subsequently filled to 1000 psi. The vessel was then stirred at 85°C for three days. After completion of the experiment, the autoclave was cooled to room temperature and the pressure was released. The solvent was removed and the ^1H NMR of the reaction mixture was measured,

revealing starting material (55%) and branched (18%) to linear (23%) esters in a ratio of 43/57.

5.3.5.4 HYDROESTERIFICATION OF VINYL BENZOATE IN THE PRESENCE OF 3.5 AND ONE EQUIVALENT OF (S)-(-)-BINAP AT 85°C and 500 psi CO

An autoclave was charged with vinyl benzoate (148 mg, 1.0 mmol), methanol (0.2 mL, 5.0 mmol) and benzene (5 mL) followed by the catalyst, **3.5** (10 mg, 0.012 mmol), p-toluene sulfonic acid (4.6 mg, 0.024 mmol) and the chiral ligand, (S)-(-)-BINAP (7.5 mg, 0.012 mmol). The atmosphere was purged three times with carbon monoxide and subsequently filled to 500 psi. The vessel was then stirred at 85°C for three days. After completion of the experiment, the autoclave was cooled to room temperature and the pressure was released. The solvent was removed and the ^{1}H NMR of the reaction mixture was measured, revealing starting material (74%) and branched (13%) to linear (9%) esters in a ratio of 59/41. The methoxy ester singlets were resolved to nearly baseline resolution and the enantiomeric excess was calculated to be 18% based on their relative integrations

5.3.5.5 HYDROESTERIFICATION OF VINYL BENZOATE IN THE PRESENCE OF 3.5 AND TWO EQUIVALENTS OF (S)-(-)-BINAP AT 85°C and 500 psi CO

An autoclave was charged with vinyl benzoate (148 mg, 1.0 mmol), methanol (0.2 mL, 5.0 mmol) and benzene (5 mL) followed by the catalyst, **3.5** (10 mg, 0.012 mmol), p-toluene sulfonic acid (4.6 mg, 0.024 mmol) and the chiral ligand, (S)-(-)-BINAP (15 mg, 0.024 mmol).

The atmosphere was purged three times with carbon monoxide and subsequently filled to 500 psi. The vessel was then stirred at 85°C for three days. After completion of the experiment, the autoclave was cooled to room temperature and the pressure was released. The solvent was removed and the ^1H NMR of the reaction mixture was measured, revealing starting material (88%) and branched (7%) to linear (4%) esters in a ratio of 63/37. The methoxy ester singlets were resolved to nearly baseline resolution and the enantiomeric excess was calculated to be 12% based on their relative integrations

5.3.5.6 HYDROESTERIFICATION OF VINYL BENZOATE IN THE PRESENCE OF 3.5 AND FOUR EQUIVALENTS OF (S)-(-)-BINAP AT 85°C and 500 psi CO

An autoclave was charged with vinyl benzoate (148 mg, 1.0 mmol), methanol (0.2 mL, 5.0 mmol) and benzene (5 mL) followed by the catalyst, **3.5** (10 mg, 0.012 mmol), p-toluene sulfonic acid (4.6 mg, 0.024 mmol) and the chiral ligand, (S)-(-)-BINAP (30 mg, 0.048 mmol). The atmosphere was purged three times with carbon monoxide and subsequently filled to 500 psi. The vessel was then stirred at 85°C for three days. After completion of the experiment, the autoclave was cooled to room temperature and the pressure was released. The solvent was removed and the ^1H NMR of the reaction mixture was measured, revealing starting material (95%) and the branched (5%) ester. The methoxy ester singlets were resolved to nearly baseline resolution and the enantiomeric excess was calculated to be 5% based on their relative integrations

5.3.5.7 HYDROESTERIFICATION OF VINYL BENZOATE IN THE PRESENCE OF $[(Cy_3P)_2Pd(H)(H_2O)]^+BF_4^-$, 3.5 and (S)-(-)-BINAP AT 30°C for 6.5 DAYS

An autoclave was charged with vinyl benzoate (148 mg, 1.0 mmol), methanol (0.2 mL, 5.0 mmol) and benzene (5 mL) followed by the catalyst, 3.5 (10 mg, 0.012 mmol), p-toluene sulfonic acid (4.6 mg, 0.024 mmol) and the chiral ligand, (S)-(-)-BINAP (7.5 mg, 0.012 mmol). The atmosphere was purged three times with carbon monoxide and subsequently filled to 500 psi. The vessel was then stirred at 85°C for 6.5 days. After completion of the experiment, the autoclave was cooled to room temperature and the pressure was released. The solvent was removed and the ^1H NMR of the reaction mixture was measured, revealing starting material (91%) and the branched (4%) ester plus only a trace amount of linear aldehyde. The methoxy ester singlets were resolved to nearly baseline resolution and the enantiomeric excess was calculated to be 31% based on their relative integrations.

5.3.5.8 HYDROESTERIFICATION OF VINYL BENZOATE IN THE PRESENCE OF $[(Cy_3P)_2Pd(H)(H_2O)]^+BF_4^-$, 3.5: EFFECT OF DIFFERENT ADDITIVES

All hydroesterification reactions were carried out as in section 5.3.5.1 except p-toluene sulfonic acid (0.024 mmol) was substituted for the same amount of trifluoroacetic acid, tetrafluoroboric acid, formic acid or phosphoric acid. Only the latter resulted in similar results to that of p-toluene sulfonic acid whereas the others resulted in no reaction.

5.4 EXPERIMENTAL FOR CHAPTER 4

5.4.1 HYDROFORMYLATION OF VINYL BENZOATE WITH NO ADDED LIGAND

A mixture of vinyl benzoate (148 mg, 1.0 mmol) and (1,5 COD)Rh^{+}-BPh_4 (7 mg, 0.01 mmol) were added to CH_2Cl_2 (5 mL) in a 46 mL Parr autoclave which was fitted with a glass linear and magnetic stirring bar. The system was purged three times with CO to displace the air and subsequently pressurized to 600 psi with a 1/1 mixture of CO and H_2. The vessel was heated with stirring at 70 °C for 22 hours. The reaction mixture was filtered through celite and the filtrate was concentrated by rotary evaporation. 2-(Benzoyloxy)propanal was isolated (192 mg, 1.0 mmol) in quantitative yield. Spectral data agreed well with the literature.

^1H NMR ($CDCl_3$): δ 1.51 (d, 3H, J = 7 Hz, CH_3), 5.28 (dq, 1H, J= 7 Hz, 1 Hz, CH), 7.30 - 8.20 (m, 5H, C_6H_5), 9.64 (d, 1H, J= 1 Hz, CHO); ^{13}C NMR ($CDCl_3$): δ 14.3 (CH_3), 75.1 (CH), 128.5, 129.8, 133.3, 133.5 (aromatic carbons), 166.0 (CO_2), 198.6 (CHO).

5.4.2 HYDROFORMYLATION OF VINYL BENZOATE IN THE PRESENCE OF TWO EQUIVALENTS OF S-(-)-BINAP (rel. to 2.1).

The reaction was carried out as described in **5.4.1**, with the exception that (S)-(-)-BINAP (12 mg, 0.02 mmol) was included in the addition of reagents to the autoclave. The vessel was heated to 85 °C and stirred for 22 hours. The ^1H NMR of the reaction mixture revealed

mostly starting material (99 %) plus the branched aldehyde, 2-(benzoyloxy)propanal (6 %). Addition of tris[3-[(trifluoromethyl)-hydroxymethylene]-d-camphorato]europium, $Eu(hfc)_3$, caused doubling of the methyl doublet, revealing an enantiomeric excess of 33 % (based on the relative integrations).

5.4.3 HYDROFORMYLATION OF VINYL BENZOATE IN THE PRESENCE OF ONE EQUIVALENT OF S-(-)-BINAP (rel. to 2.1)

The reaction was carried out as described in **5.4.1**, with the exception that (S)-(-)-BINAP (6 mg, 0.01 mmol) was included in the addition of reagents to the autoclave. The vessel was heated to 85 °C and stirred for 16 hours. The ^1H NMR of the reaction mixture revealed only a trace of starting material and linear aldehyde with the branched aldehyde, 2-(benzoyloxy)-propanal, produced as the major product in 95 % yield (based on ^1H NMR signal relative to the starting material). Addition of $Eu(hfc)_3$ caused resolution of the enantiomers, revealing no enantiomeric excess.

5.4.4 HYDROFORMYLATION OF VINYL BENZOATE IN THE PRESENCE OF THREE EQUIVALENTS OF (-)-DIOP (rel. to 2.1)

The reaction was carried out as described in **5.4.1**, with the exception that (-)-2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane (15 mg, 0.03 mmol) was included in the addition of reagents to the autoclave. The vessel was heated to 75°C and stirred for 22 hours. The ^1H NMR of the reaction mixture revealed

starting material (74%) plus the branched aldehyde, 2-(benzoyloxy)propanal (26%). Addition of $Eu(hfc)_3$ caused doubling of the methyl doublet, revealing an enantiomeric excess of 27% (based on the relative integration).

5.4.5 HYDROFORMYLATION OF VINYL BENZOATE IN THE PRESENCE OF (POLY)L-LEUCINE

The reaction was carried out as described in **5.4.1**, with the exception that poly(L-leucine) (MW 21700), (100 mg, 0.005 mmol) was included in the addition of reagent to the autoclave. The vessel was heated to 70 °C and stirred for 20 hours. The ^1H NMR of the reaction mixture revealed only 2-(benzoyloxy)propanal (>95 %) with no starting material. Addition of $Eu(hfc)_3$ resulted in resolution of the enantiomers, revealing no enantiomeric excess.

5.4.6 HYDROFORMYLATION OF ALLYL PHENYL ETHER WITH $Rh_6(CO)_{16}$ AS CATALYST

To a 46 mL Parr autoclave, fitted with a glass linear and magnetic stirring bar was added allyl phenyl ether (145 mg, 1.0 mmol), and $Rh_6(CO)_{16}$ (33 mg, 0.031 mmol) in $CHCl_3$ (3 mL). The system was purged three times with carbon monoxide to displace the air and subsequently pressurized to 500 psi with a 2/1 mixture of H_2 and CO. The final solution was dark green with a black precipitate. After filtration through celite and concentration by evaporation, the resulting ^1H NMR of the reaction mixture revealed only a trace of linear aldehyde plus many unidentified by-products.

5.4.7 HYDROFORMYLATION OF ALLYL PHENYL ETHER WITH (1,5-COD)$Rh^+BPh_4^-$ AS CATALYST

To a 46 mL Parr autoclave, fitted with a glass linear and magnetic stirring bar was added allylphenylether (145 mg, 1.0 mmol), and (1,5 COD)$RhBPh_4$ (20 mg, 0.037 mmol) in $CHCl_3$ (3 mL). The system was purged three times with carbon monoxide to displace the air and subsequently pressurized to 500 psi with a 2/1 mixture of H_2 and CO. The vessel was heated with stirring at 55 °C for 22 hours. The dark orange solution was filtered through celite and concentrated by evaporation. The resulting ^1H NMR of the reaction mixture revealed complete conversion of starting material. The ratio of branched to linear aldehyde was measured from the ^1H NMR resonances and found to be 58/42.

5.4.8 HYDROFORMYLATION OF STYRENE IN THE PRESENCE OF (1,5-COD)$Rh^+BPh_4^-$

To a 46 mL autoclave, fitted with a glass liner and magnetic stirring bar was added styrene (137 mg, 1.3 mmol) and (1,5-COD)$Rh^+BPh_4^-$ (20 mg, 0.037 mmol) in $CHCl_3$ (3mL). The system was purged three times with carbon monoxide to displace the air and subsequently pressurized to 500 psi with a 2/1 mixture of H_2 and CO. The vessel was heated with stirring at 55°C for 22 hours. The solution was filtered through celite and concentrated by evaporation. The resulting ^1H NMR of the reaction mixture revealed complete conversion

of the starting material producing only 2-phenylpropanal with a trace amounts of 3-phenylpropanal.

^{1} H NMR of 2-phenylpropanal ($CDCl_3$): δ 1.45 (d, 3H, J= 7 Hz, CH_3), 4.64 (dq, 1H, J= 7 Hz, 2 Hz, CH), 7.0- 7.6 (m, 5H, aromatic protons), 9.65 (d, 1H, J= 2 Hz, CHO).

^{1} H NMR of Rh complex ($CDCl_3$): δ 7.1-7.5 (m, aromatic protons of arene rings not coordinated to Rh), δ 7.5-7.95 (m, aromatic protons of arene rings with coordinated to Rh).

5.4.9 HYDROFORMYLATION OF STYRENE IN THE PRESENCE OF (1,5-COD)$Rh^+BPh_4^-$ AND ONE EQUIVALENT OF TETRABUTYLAMMONIUM TETRAPHENYLBORATE-d_{20}.

To a 46 mL autoclave, fitted with a glass liner and magnetic stirring bar was added styrene (104 mg, 1.0 mmol) and (1,5-COD)$Rh^+BPh_4^-$ (55 mg, 0.10 mmol) and tetrabutylammonium tetraphenylborate-d_{20} (56 mg, 0.10 mmol) in $CHCl_3$ (2 mL). The system was purged three times with carbon monoxide to displace the air and subsequently pressurized to 500 psi with a 2/1 mixture of H_2 and CO. The vessel was heated with stirring at 55°C for 22 hours. The solution was filtered through celite. The resulting ^{1}H NMR of the reaction mixture was identical to that obtained in section 5.4.8.

5.4.10 SYNTHESIS OF C_6D_5MgBr

In a dry, three necked round bottom flask fitted with a reflux condenser, bromobenzene-d_5 (1.79 g, 11.0 mmol) was added to magnesium turnings (265 mg, 11.0 mmol) in dry and distilled ether (6

mL). The Grignard reaction initiated immediately at room temperature and was allowed to stir for an additional 3 hours (in a N_2 atmosphere) until all of magnesium disappeared. The resulting Grignard reagent C_6D_5MgBr (11.0 mmol) was used directly (see section 5.4.11).

5.4.11 SYNTHESIS OF SODIUM TETRAPHENYLBORATE-d_{20}

To the ether solution containing C_6D_5MgBr (11.0 mmol) (see section 5.4.10), sodium tetrafluoroborate (303 mg, 2.76 mmol) was added as a solid under a strong flow of nitrogen. The solution changed from a clear brown to a cloudy yellow solution and a white precipitate formed. The insoluble $NaBF_4$ disappeared forming a new solid (less crystalline). The reaction was allowed to stir overnight. The precipitate was filtered in air. Careful washes with methanol yield quantitatively the desired product, $Na^+B^-(C_6D_5)_4^-$.

^{11}B NMR (DMSO-d_6): δ -6.2 ppm (ref. $BF_3{\cdot}Et_2O$)

5.4.12 SYNTHESIS OF (1,5-COD)$Rh^+(\eta 6\text{-}C_6D_5)B(C_6D_5)_3^-$, 2.1-$d_{20}$

To a solution of $[Rh(COD)Cl]_2$ (200 mg, 0.40 mmol) in CH_2Cl_2 (4 mL) was added a solution of $Na^+B(C_6D_5)_4^-$ (300 mg, 0.83 mmol) in methanol (20 mL). A yellow precipitate formed almost immediately but the reaction was allowed to stir for an additional 2 hours. The yellow (1,5-COD)$Rh^+B(C_6D_5)_4^-$ complex was fittered and washed with methanol and ether.

^{11}B NMR (300 MHz) in $CDCl_3$: δ -7.6 ppm, s. (ref. $BF_3.Et_2O$)

^1H NMR (500 MHz) in $CDCl_3$: δ 1.94 (m, 4H, CH_2), 2.30 (m, 4H, CH_2), 4.20 (m, 4H, vinylic protons).

cf. ^{11}B NMR (300 MHz) in $CDCl_3$ of (1,5-COD)$Rh^+B(C_6D_5)_4^-$: δ -7.5 ppm, s

^1H NMR (500 MHz) in $CDCl_3$: δ 1.94 (m, 4H, CH_2), 2.30 (m, 4H, CH_2), 4.20 (m, 4H, vinylic protons), 6.07 (t, 2H, J= 6 Hz, aromatic meta protons), 6.62 (2H, J= 6 Hz, aromatic ortho protons), 6.73 (t, 1H, J= 6 Hz, aromatic para protons), 7.0-7.6 (m, 15H non-coordinated protons).

5.4.13 CROSS-OVER EXPERIMENT

To a 46 mL autoclave, fitted with a glass liner and magnetic stirring bar was added styrene (104 mg, 1.0 mmol) and (1,5-COD)$Rh^+BPh_4^-$ (55 mg, 0.10 mmol) and $Bu_4N^+B(C_6D_5)_4^-$ (56 mg, 0.1 mmol) in $CDCl_3$ (2 mL). The system was purged three times with carbon monoxide to displace the air and subsequently pressurized to 500 psi with a 2/1 mixture of H_2 and CO. The vessel was heated with stirring at 50°C for 3 hours. The ^1H NMR of the reaction mixture revealed conversion of the starting material to 2-phenylpropanal (Section 5.4.8). No proton signals were observed downfield of the aromatic protons between δ 7.1 and 7.5 ppm.

5.4.14 HYDROBORATION OF α-PINENE FOLLOWED BY OXIDATION TO ISOPINOCAMPHENOL

To a 25 mL round bottom flask, equipped with a reflux condenser and flushed with nitrogen, was added 2.6 mL of freshly distilled ether (Na/benzophenone) and $HBBr_2 \cdot SMe_2$ (640 µl, 5.0 mmol). To this was added α-pinene (797 µl, 5.0 mmol) dropwise by syringe. The flask was

placed in a room temperature water bath and stirring was maintained throughout. The reaction continued at room temperature for 4 hours at which time an aliquot was examined for remaining olefin by quenching the aliquot in water/ice and extraction with ether to isolate the organic products (GC analysis: column-OV101, 100°C/3min.; ramped at 20°C/min.; final temperature 285°C). By comparison with an authentic sample of α-pinene (retention time of 1 min.), complete consumption of α-pinene in the reaction was confirmed.

5.4.15 PRODUCTION OF THE FREE LEWIS ACID, B-DIBROMO-ISOPINOCAMPHENYLBORANE.

The hydroboration of α-pinene was conducted under the identical conditions described in Section 5.4.14, with the exception that dry pentane (2.6 mL) was substituted for ether as the reaction solvent. The reaction was allowed to stir at room temperature overnight. To the reaction mixture was added boron tribromide (474 µl, 5.0 mmol) dropwise via syringe to yield a milky white suspension. The B-dibromoisopinocamphenylborane solution was separated from the insoluble BBr_3•SMe_2 by filtration through a cannula and transfered to an inlet flask. The borane was not isolated but used directly for the reaction with phenyllithium (Section 5.4.16).

5.4.16 REACTION OF B-DIBROMOISOPINO-CAMPHENYLBORANE WITH PHENYLLITHIUM

In the general reaction scheme, isolated B-dibromoisopino camphenylborane solution (Section 5.4.15) was cooled to -78°C with a

dry ice/acetone slush, phenyllithium (1.6M) was added via syringe and the reaction mixture was allowed to warm to room temperature. Reactions with excess PhLi (3.2 to 4 equivalents) yield products, which after removal of the reaction solvent and replacement with acetone-d_6 or $CDCl_3$, have a complex ^1H NMR signal in the aromatic and aliphatic regions which is clearly not the desired product. When the reaction is carried out with 2 equivalents of PhLi followed by filtration to remove LiBr and subsequent addition of one equivalent of PhLi, similar uncharacterized products were obtained.

5.4.17 SYNTHESIS OF TRIPHENYLHYDROBORATE

To a dry Schlenk flask was added $B(C_6H_5)_3$ (3g, 12.4 mmol) and LiH (1.2g, 150 mmol) and a stirring bar. Under an atmosphere of argon the contents of the flask were heated in and oil bath at 180°C until the solids became a flowing melt. After cooling, 25mL of dioxane (freshly distilled from Na/benzophenone) was added. The flask was equipped with a filter and warmed in a 120°C oil bath. Once the filter frit had become warm with the solvent vapours, the system was inverted in order to separate the excess LiH from the hydroborate. Upon cooling, clear colorless crystals separated from the solvent (2.12g, 8.5 mmol).
^{11}B NMR (THF): δ = -7.9ppm, d, J_{B-H} = 79 Hz

5.4.18 REACTION α-PINENE WITH LITHIUM TRIPHENYL HYDROBORATE.

In a dry Schlenk flask under and atmosphere of argon, $LiHBPh_3$ (1.7g, 6.8 mmol) was dissolved in a minimum amount of dioxane. To

this was added α-pinene (1.0 mL, 6.8 mmol). The reaction was allowed to stir at room temperture for 14 hours, followed by 4 hours at 100°C. $RhCl(PPh_3)_3$[90, 91] (126 mg, 0.136 mmol) dissolved in 9 ml of THF was added to the reaction mixture. This mixture was allowed to stir for an addtional 17 hours at room temperature and 4.5 hours at 100°C. At no stage was there a reaction with α-pinene.

5.4.19 REACTION OF (1R, 2S, 5R)-(-)-MENTHOL WITH LITHIUM TRIPHENYLHYDROBORATE.

In a Schlenk flask under an atmosphere of argon, $LiHBPh_3$ (330mg, 1.3 mmol) was dissolved in 10 mL of THF. To this was added (1R, 2S, 5R)-(-)-menthol (206 mg, 1.3 mmol). The reaction was allowed to stir at room temperture overnight. No gas evolution was observed. ^{11}B NMR (dioxane): δ = -7.2 ppm (d, J_{B-H} = 65 Hz)

5.4.20 REACTON OF SODIUM MENTHOXIDE WITH TRIPHENYLBORON. "RHODIUM COMPLEX" FORMATION.

To a Schlenk flask containing 5 mL of menthol was added sodium metal (58 mg, 2.5 mmol). The mixture was stirred until all of the sodium was consumed at which time triphenylboron (605 mg, 2.5 mmol), dissolved in MeOH (1 mL), was added, by syringe, to the reaction mixture. This reaction was allowed to stir overnight. A 1 mL aliquot was removed for analysis. ^1H NMR (DMSO-d_6): δ 2.7 ppm, (s). An aliquot (4 mL, 1mmol) was transfered to a flask containing $[Rh(COD)Cl]_2$ (80 mg, 0.163 mmol) dissolved in CH_2Cl_2. A yellow precipitate formed immediately. After filtration, the complex was dried. ^1H NMR ($CDCl_3$):

δ(ppm) 1.6 (m), 2.4 (m), 3.5 (m), 3.9 (m), 4.2 (m) (see Section 4.2.4 for discussion)

CONCLUSIONS

Rhodium catalyzed hydroformylation of functionally substituted olefins, and in particular, a series of vinyl sulfones and sulfoxides, with CO/H_2 has been explored. These substrates have presented an academic challenge in light of the frequent poisoning of transition metal catalysts by sulfur containing compounds. In addition to the potential synthetic utility of the resulting aldehydic sulfones and sulfoxides, the starting olefin has built-in functionality which can direct both favorable regio- and stereodifferentiation. The zwitterionic rhodium (I) complex, **2.1**, together with DPPB was found to be an active and regiospecific catalytic system for the hydroformylation of aryl and alkyl vinyl sulfones and aryl vinyl sulfoxides. The previously unknown aldehydic sulfones and sulfoxides were generated in good to excellent yields. Exploration of the optical inducing ability of the complex, **2.1**, with the dissymmetric bidentate phosphine ligand BINAP resulted in moderate diastereomeric and enantiomeric excesses for the asymmetric hydroformylation of phenyl vinyl sulfoxide.

Palladium catalyzed asymmetric hydroesterification of vinyl esters was conducted. Experiments revealed the necessity for a small (1 mol % relative the [Pd]) but critical amount of phosphoric acid. A new cationic palladium-hydrido complex, $(Cy_3P)_2Pd(H)(H_2O)^+BF_4^-$, was applied in combination with the optically active ligand, BINAP, resulting in ee's of 30%. Although modest, these results compare favorably to related catalytic asymmetric hydroesterification results known to date.

CLAIMS TO ORIGINAL RESEARCH

1. Highly regiospecific synthesis of previously unknown aldehydic sulfones and sulfoxides via the hydroformylation of aromatic and aliphatic vinyl sulfones and sulfoxides with CO/H_2 catalyzed by the zwitterionic rhodium complex, 1,5-cyclooctadiene rhodium tetraphenylborate, $(1,5\text{-}(COD)Rh^{+}(\eta^{6}\text{-}C_6H_5)B(C_6H_5)_3^{-})$.

2. The hydroformylation of phenyl vinyl sulfoxide in the presence of $1,5\text{-}(COD)Rh^{+}(\eta^{6}\text{-}C_6H_5)B(C_6H_5)_3^{-}$ and the chiral phosphine ligand, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, (BINAP), demonstrated considerable stereodifferentiating ability.

3. The study of hydroesterification of vinyl esters with CO/MeOH/ $(PPh_3)_2PdCl_2$ revealed the critical necessity of acid (e.g. H_3PO_4).

4. The cationic palladium(II) aquo hydrido complex, $[(Cy_3P)_2Pd(H)(H_2O)]^{+}BF_4^{-}$, in the presence of BINAP catalyzes the asymmetric hydroesterification of vinyl esters to yield optically enriched lactic acid derivatives.

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