Synthesis of C2-symmetric P-chiral bis(phosphine borane)s and their application in rhodium(I) catalyzed asymmetric transformation
by Holly Ann Heath

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry
Montana State University

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A new development for the synthesis C2-Synnnetric P-Chiral Bis(phosphine borane) ligands is reported, These ligands are based on the asymmetric induction of prochiral phosphine ligands with organolithium/chiral diamine complexes. These ligands have been evaluated in asymmetric rhodium(I) catalyzed hydrogenation and [4 + 2] cycloisomerization reactions. Enantiomeric excesses as high as 99% were obtained for ene-diene cycloadditions.

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APPROVAL

of a dissertation submitted by

Holly Ann Heath

This dissertation has been read by each member of the dissertation committee and has been found to be satisfactory regarding content, English usage, format, citations, bibliographic style, and consistency, and is ready for submission to the College of Graduate Studies.

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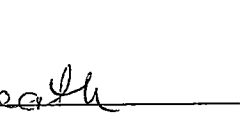
Signature 

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ABSTRACT

A new development for the synthesis C_2-Symmetric *P*-Chiral Bis(phosphine borane) ligands is reported. These ligands are based on the asymmetric induction of prochiral phosphine ligands with organolithium/chiral diamine complexes. These ligands have been evaluated in asymmetric rhodium(I) catalyzed hydrogenation and [4 + 2] cycloisomerization reactions. Enantiomeric excesses as high as 99% were obtained for ene-diene cycloadditions.

CHAPTER 1

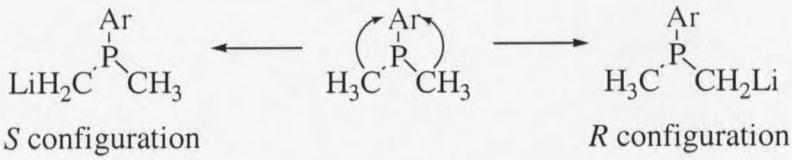
INTRODUCTION

Enantiomerically pure substances are of economic importance in industry. The need for efficient enantioselective syntheses remains a constant challenge. One of the most common methods to obtain stereoisomerically pure compounds involves the use of a stoichiometric quantity of a chiral resolving agent. This method, however, requires the recovery of the resolving agent which can be time consuming and costly. Hence, the development of chiral catalysis is of great interest because of its potential to be more economically feasible and efficient.

Chiral phosphine ligands have been used in transition metal complexes as catalysts for production of enantiomerically pure compounds. There are a variety of reactions where these ligands are not efficient in their reactivity or selectivity and a continued search for well designed chiral ligands remain an important goal. The objective of the research described herein was to design new C_2-symmetric *P*-chiral phosphine ligands for use as enantiocontrollers in asymmetric rhodium(I) catalyzed [4 + 2] cycloisomerizations of olefins. These new ligands were also evaluated to determine their efficacy in asymmetric reduction of C=C linkages.

The synthesis and application of new chiral diphosphine ligands are reported herein. A key feature of these ligands is that the chirality is at the phosphorus atom. In catalytic processes involving phosphine ligands reactivity can be fine-tuned by altering

the environment surrounding the phosphorus atom. These alterations result in a change in the steric and/or electronic environment around the phosphorus. Therefore, the reactivity of phosphorus ligands were studied by preparing a number of chiral phosphine-borane ligands starting with prochiral phosphine-borane (Figure 1).



S configuration *R* configuration

Figure 1. Prochiral Aryldimethylphosphine.

A new method to prepare chiral phosphine-borane ligands was achieved by starting with prochiral phosphine-borane (Figure 1). Asymmetric induction of prochiral phosphine ligands with organolithium/chiral diamine complexes allowed for an efficient method for asymmetric synthesis of new phosphine-borane ligands. The fundamental concepts of organolithium/chiral diamine complexes for asymmetric induction of prochiral phosphine ligands will be discussed. An overview will be given of the use and versatility of these complexes.

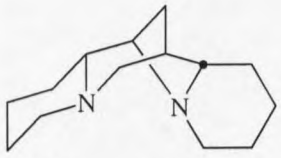
The logic behind the design and development of homochiral phosphine ligands during the course of this research will be discussed as well as the evaluation of these ligands in asymmetric catalytic hydrogenation and rhodium(I) catalyzed [4 + 2] cycloisomerization reactions.

CHAPTER 2

BACKGROUND

Organolithium/Chiral Diamine Complexes

The use of complexes formed between organolithium reagents and enantiopure ligands in asymmetric chemistry offers convenient approaches to syntheses of enantioenriched compounds.

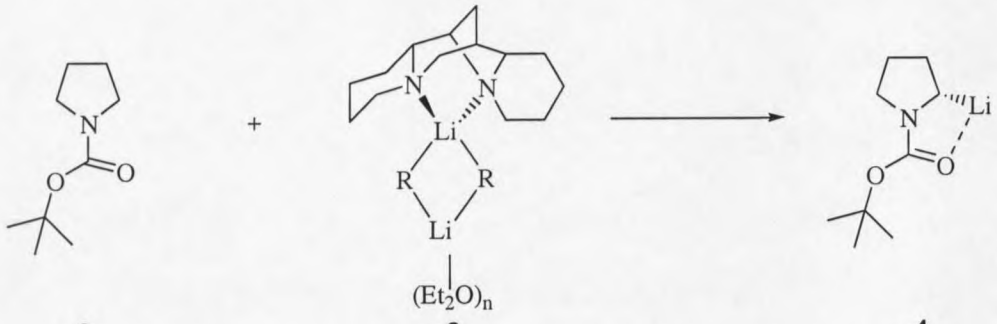


(-)-sparteine
(**1**)

Figure 2. Chiral Diamine (-)-Sparteine (**1**).

Hoppe and co-workers reported that *sec*-BuLi and the C_1 symmetric diamine (-)-sparteine (**1**) (Figure 2) form a complex that can be used to lithiate a nonconjugated oxygen-substituted system.[1,2,3] Beak and co-workers later reported a highly enantioselective deprotonation using **3** for a nonconjugated nitrogen system (Scheme 1).[4] Complex **3** was determined to be configurationally stable at –78 °C and to react with

electrophiles with retention of configuration.[5] NMR spectroscopy established the structure of RLi/(-)-sparteine to be an unsymmetrical dimer in which one of the lithium atoms is complexed by (-)-sparteine and the other lithium atom is complexed by Et_2O. Asymmetric deprotonation of Boc-pyrrolidine (**2**) with **3** resulted in a configurationally stable lithiated species **4** which could be trapped with various electrophiles to give 2-substituted Boc-pyrrolidines in high enantioenrichment (Scheme 1)[4].

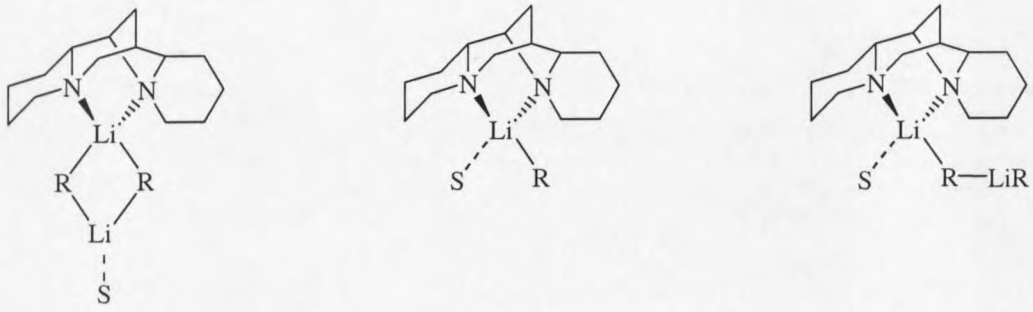


2 **3** **4**

Scheme 1. Asymmetric Deprotonation of Boc-pyrrolidine (**2**).

A kinetic investigation of the reaction strongly suggests that deprotonation is the rate-determining step and that the complexation/decomplexation equilibrium is fast relative to the deprotonation reaction. The predominant species in solution is the prelithiation complex and though the structure is speculative there are three possibilities (Figure 3).[4] Complex **5** is consistent with the kinetic investigation data; however, the distance between the substrate and (-)-sparteine makes it difficult to envision how asymmetric induction occurs. Complex structures **6**[4] and **7**,[6] however, allow the substrate

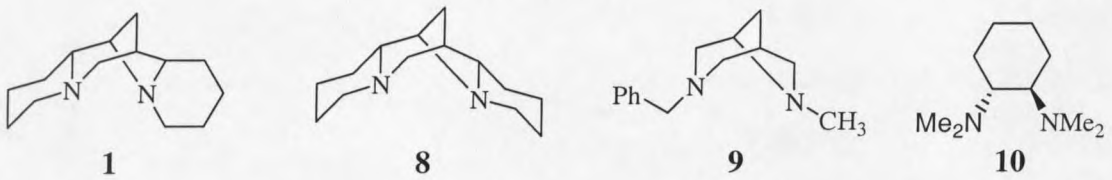
to be in closer proximity to the chirality introduced by the (-)-sparteine. There has been support for both complexes **6** and **7**. While Beak suggests a transition state that would proceed from the monomeric **6**,[4] Collum proposes a linear dimer **7** based on the lithium dialkylamide transition states.[6]



5 **6** **7**

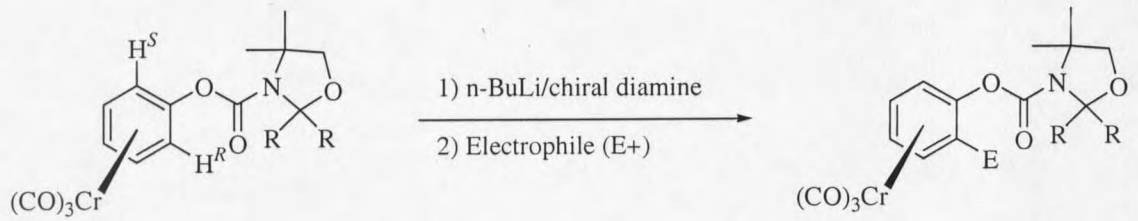
Figure 3. Proposed Prelithiation Complexes of (**1**).

A variety of ligand systems including (-)-sparteine (**1**) were investigated by Beak, of particular interest were, (-)-isosparteine (**8**), 3-benzyl-6-methyl-3,6-diaza-bicyclo[3.2.1]octnane (**9**), and trans-1,2-bis(dimethylamino)cyclohexane (**10**) (Figure 4). Beak found ligands **8** and **9** provided useful enantiomeric excess (ee) with low conversion to product, while **10** gave no enantioselectivity but provided a good conversion to product (~90%).[5]



1 **8** **9** **10**

Figure 4. Chiral Diamines for Enantioselective Lithiations.



R R= -$(CH_2)_5$-

11 **12**

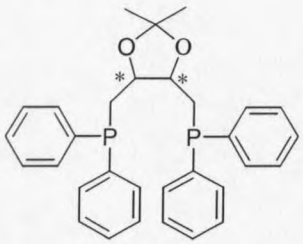
Table 1. Enantioselective *Ortho* Lithiation of Phenylcarbamate Chromium Complexes.

Entry	complex	diamine	solvent	E^+	Yield (%)	% ee (abs. config.)
1	**11**	**10**	Et_2O	DMF	90	41 (1*R*,2*S*)
2	**11**	**10**	toluene	DMF	69	59 (1*R*,2*S*)
3	**11**	**1**	toluene	DMF	62	17 (1*S*,2*R*)

Uemura and co-workers later found that **10** gave good to excellent yields for the enantioselective *ortho* lithiation of phenylcarbamate chromium complex (**11**) with 41 and 59% ee (Table 1, entry 1 and 2). Furthermore, Uemura determined that (-)-sparteine gave the opposite absolute configuration in 62% yield and 17% ee (entry 3). They also found solvent could affect both the yield and enantioselectivity (entry 1 and 2).[7]

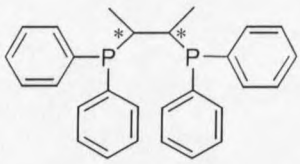
Chiral Phosphine Ligands

Optically active phosphines with the chirality in either the framework of the phosphine (**13 – 15**)[8,9,10,11] or at the phosphorus atom (**16**)[12] have found wide use as ligands for transition metals (Figure 5). Until recently, there have been few examples of *P*-chiral diphosphine ligands in the literature. Their absence is due to the difficulty in the synthesis and purification of the enantioenriched phosphorus stereocenter.



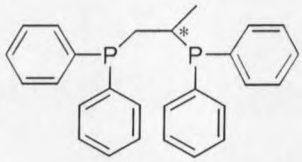
(DIOP)

13



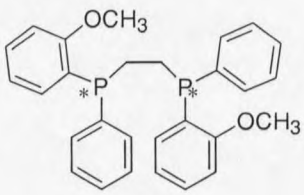
(CHIRAPHOS)

14



(PROPHOS)

15



(DIPAMP)

16

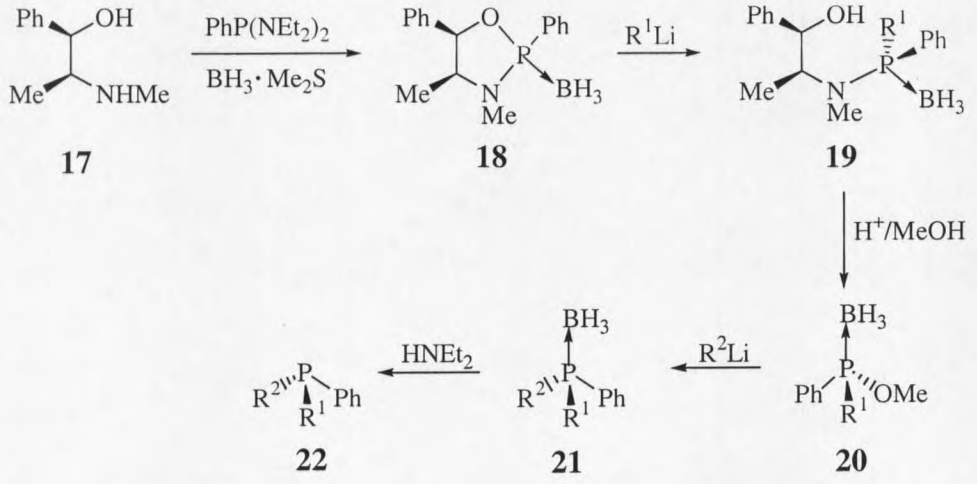
(The asterisks denote the chiral centers.)

Figure 5. Chiral Bisphosphines.

Enantiomerically enriched molecules can either be synthesized in racemic form then resolved, or the synthesis can be performed by asymmetric induction of chirality or kinetic resolution[13]. Resolution of racemates with resolving agents[14] or high-performance chromatographic techniques[15] using chiral stationary phases is a common method of obtaining optically active organophosphorus compounds. Chromatography or crystallization of self-resolving systems that introduce *C*-chiral units[16,17] to the final phosphine structure can also achieve enantioenriched compounds. Kinetic resolution[18]

utilizing chiral auxiliaries and enzymatic[13] techniques are additional methods to achieve optical enhancement.

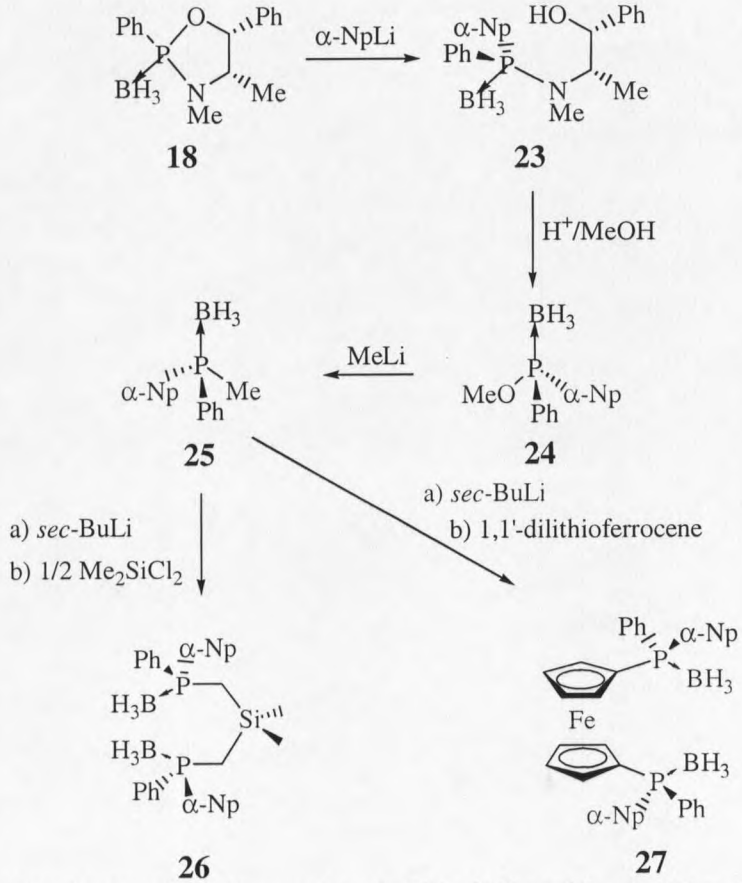
Asymmetric synthesis is an attractive route to chiral phosphorus compounds. Jugé and co-workers[19] have developed a methodology for synthesis of enantiomerically enriched borane-protected *P*-chiral phosphines. They elaborated a general method based on the regio and stereoselectivity of the ring opening of the oxazaphospholidine-borane complex. Diastereomerically pure oxazaphospholidine-borane complex (**18**) was prepared in one step from (-)-ephedrine (**17**), bis(diethylamino)phenylphosphine, and borane-methyl sulfide complex.



Scheme 2. Asymmetric Synthesis of *P*-Chiral Phosphine

Using Oxazaphospholidine Borane.

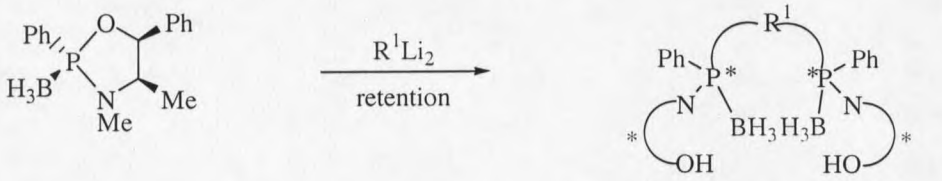
Treatment of oxazaphospholidine borane with an organolithium gives the aminophosphine borane diastereomer (**19**). Acid catalyzed methanolysis provides quantitatively the corresponding phosphinite borane (**20**). Reaction of **20** with an addition of another organolithium reagent gives optically active phosphine boranes (**21**) (Scheme 2). Recrystallization provides the enantioenriched phosphine boranes in >99% ee. Treatment of the phosphine borane with diethylamine quantitatively yields the free phosphine (**22**) with retention of configuration. While this procedure is over a decade old it is still the most frequently used method for preparation of *P*-chiral phosphine boranes.



Scheme 3. Synthesis of C_2-Symmetric *P*-Chiral Phosphinnes **26** and **27**.

Mezzetti and co-workers[20] utilized this method developed by Jugé to make phosphine boranes. Deprotonation of **25** with *sec*-BuLi then separately treated with dichlorodimethylsilane and 1,1'-dilithioferrocene as the electrophiles gave diphosphine boranes **26** and **27** with diastereomeric ratios of 99:1 and 100:0 respectively (Scheme 3).

The oxazaphospholidine borane route was once again applied for the synthesis of C_2-symmetric *P*-chiral bisphosphine ligands. Van Leeuwin and Widhalm[21] employed this method to prepare C_2-symmetric *P*-chiral phosphines. Efforts to introduce a dilithioaryl species at the P-O bond cleavage step led to the formation of either monosubstituted products or mixtures of diastereomers in a 65:35 ratio of (R_P,R_P) and (R_P,S_P) (**29**) (Scheme 4).



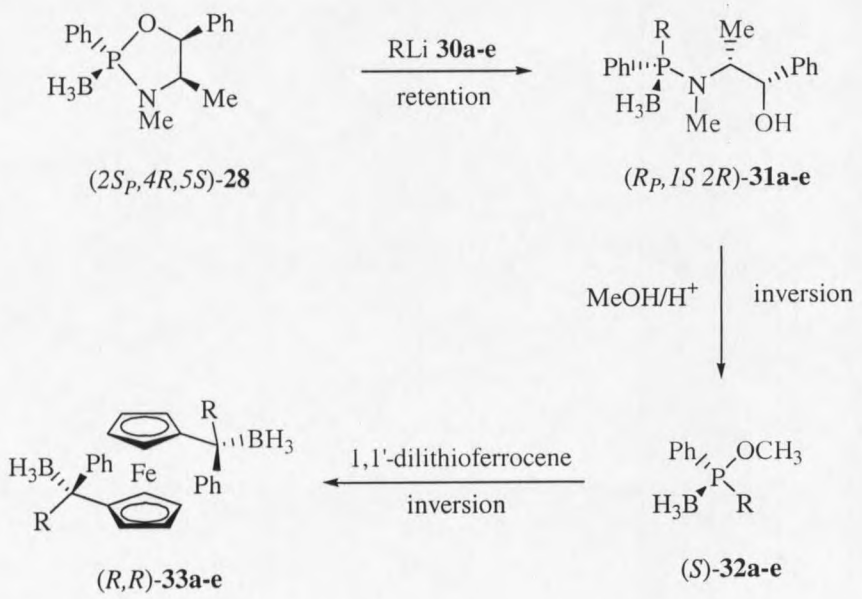
(*2S*$_P$,*4R*,*5S*)-**28**

29 (mixture of diastereomers and monosubstituted product)

Scheme 4. Introduction of Dilithioaryl Species to Cleave P-O Bond of Oxazaphospholidine Derivative **28**.

Steric bulk surrounding the phosphine amide appears to interfere with the nucleophilic attack and/or also promotes stereorearrangement, which would account for

the observed results. These results prompted van Leeuwin to perform acid catalyzed methanolysis. Treatment of **28** with aryllithium reagents **30a-e** afforded aminophosphine boranes **31a-e** in 85 – 94% yield. Acid catalyzed methanolysis affords the phosphinite borane complexes **32a-e** with inversion of configuration in at least 98% ee (Scheme 5).

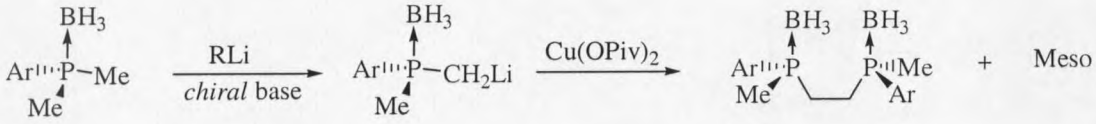


a: R = 1-napthyl
b: R = 2-napthyl
c: R = 2-anisyl
d: R = 2-biphenylyl
e: R = 9-phenanthryl

Scheme 5. Synthetic Pathway Towards Ferrocenyl Tethered *P*-chiral Ligands.

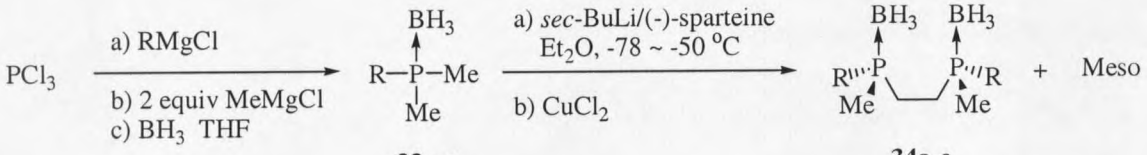
Treatment of the phosphinite borane complexes **32a-e** with 1,1′-dilithioferrocene at –40 °C then warming to room temperature over a period of 15 h provided the desired C_2-symmetric *P*-chiral bisphosphine boranes **33a-e** (Scheme 5). Approximately 10% of

the monosubstituted byproduct was formed. After decomplexation of the borane complexes, the P-chiral bisphosphine ligands were obtained in >98% ee.



Scheme 6. Two Step Process Approach to C_2-Symmetric *P*-Chiral Diphosphines.

Muci and Evans[22] demonstrated the use of prochiral aryldimethylphosphine borane as a precursor for the synthesis of C_2-symmetric *P*-chiral bisphosphine boranes. As in our laboratories, they performed successive asymmetric deprotonation of aryldimethylphosphine boranes and subsequent oxidative coupling to provide the diphosphine products with good enantioselectivity (Scheme 6).



a: R = *t*-Bu
b: R = Et_3C
c: R = 1-adamantyl
d: R = *c*-C_5H_9
e: R = *c*-C_6H_{11}

Scheme 7. Preparation of 1,2-Bis(trialkylphoshino)ethanes

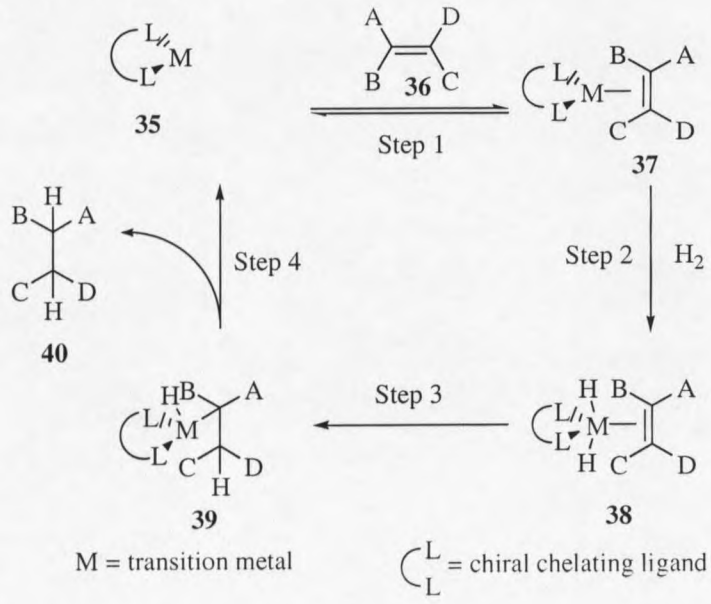
Imamoto[23] also showed the versatility of this method in the preparation of 1,2-bis(trialkylphosphino)ethanes. Treating PCl_3 with two consecutive Grignard reactions, followed by protecting with $BH_3{\cdot}SMe_2$ provided alkyldimethylphosphine boranes **33a-e**. Asymmetric deprotonation using *sec*-BuLi/(-)-sparteine complex and subsequent copper(I)-mediated coupling yielded the desired products **34a-e** with the *meso*-diastereomer (Scheme 7). Purification to separate the enantiomers from the *meso*-compound was accomplished by HPLC and enantioenrichment was improved by recrystallization.

Catalytic Asymmetric Hydrogenation

The discovery of catalysts bearing chiral phosphine ligands has become significant in the development of organotransition-metal chemistry. Most notably is the catalyzed asymmetric hydrogenation of prochiral olefins where optical yields approach 100% ee.

Rhodium complexes with chelating chiral phosphine ligands have been used as catalysts for hydrogenation. Complexes using chelating chiral diphosphine ligands with rhodium, such as DIOP (**13**),[8,9] CHIRAPHOS (**14**),[10] PROPHOS (**15**),[11] and DIPAMP (**16**),[12] are used as catalyst precursors in asymmetric hydrogenation of various dehydroamino acids and their methyl esters. Many groups have actively carried out mechanistic studies of the asymmetric hydrogenation during the last three decades. A discussion of all the efficient systems that are available for asymmetric hydrogenation is beyond the scope of this thesis. Instead, an examination in detail of a well-studied

system will be considered, followed by recent examples of hydrogenation of unsaturated compounds.

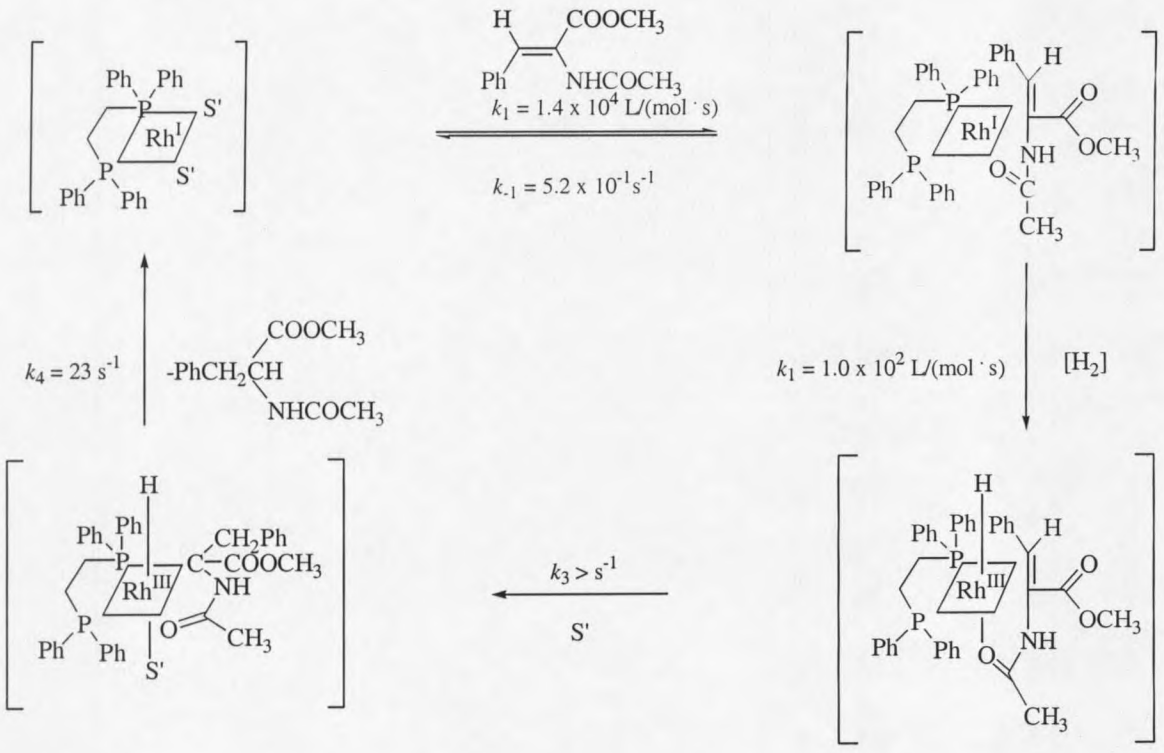


Scheme 8. Mechanistic Scheme for Olefin Hydrogenation.[24]

In this schematic mechanistic interpretation (Scheme 8) the chiral ligand, usually a chelating diphosphine, remains attached to the metal throughout the cycle. The metal complex **35** (which is shown without its coordinating solvent molecules) binds with substrate **36** to form intermediate **37** (step 1). Oxidative addition of dihydrogen to the metal produces **38** (step 2). Transfer of a hydrogen atom to the substrate gives **39** (step 3) followed by the second hydrogen atom transfer and subsequent decomplexation of the

fully reduced product **40** regenerates the catalyst **35** and completes the cycle. As each new chiral center is created, the substrate remains as part of the chiral complex, which provides an efficient asymmetric synthesis. This cyclic representation in Figure 6 is not the only possible mechanism; however, it most generally represents the mechanism of the broad spectrum of most homogeneous asymmetric hydrogenations.

Knowles and colleagues,[25] of the Monsanto Company, developed one of the most studied systems for asymmetric hydrogenation. Their goal was to design phosphine ligands to control selectivity in the hydrogenation of acetamidocinnamic acid to give the precursor of L-dopa (3,4-dihydroxyphenylalanine), a drug used in the treatment of Parkinson's disease. Detailed kinetic experiments were carried out to determine the catalytic cycle for hydrogenation of the dehydroamino acid with a rhodium complex containing DIPHOS. Further experiments were performed using the chiral diphosphine ligand, DIPAMP (**16**). The catalytic cycle giving the chiral product was found to be closely similar to that of Scheme 9.

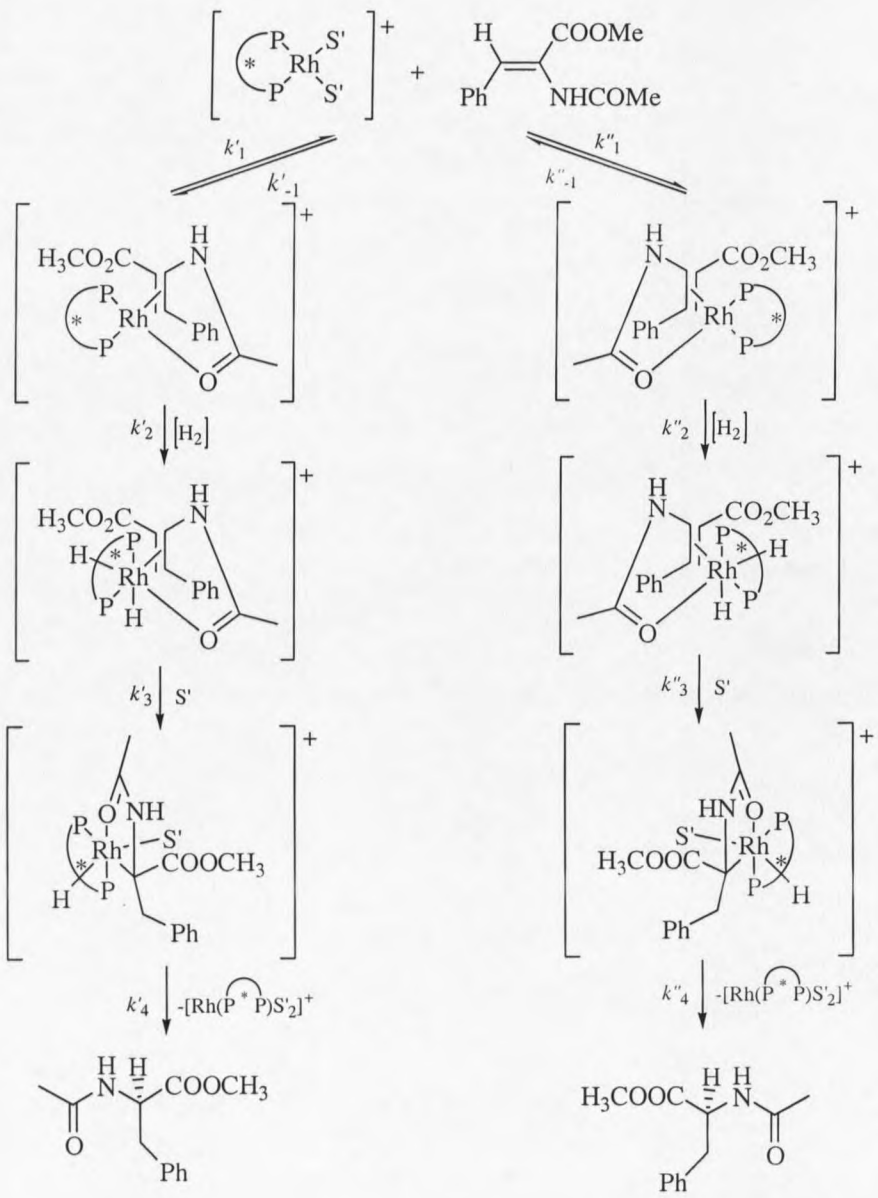


Scheme 9. Asymmetric Catalytic Cycle for Hydrogenation of Olefins.

Two pathways were found for the chiral hydrogenation of the dehydroamino acid, as shown in Scheme 10. The pathway at the left of the illustration gives the preferred mode of initial binding of the reactant to the catalyst, while the pathway shown at the right involves a minor isomer. Accordingly, these pathways provide products with different stereochemistries.

The mechanistic studies showed that, contrary to the first expectation, the chirality of the product was not determined by the preferred mode of initial binding of the

reactant. The complexation of the substrate to the catalyst gives two diastereoisomeric complexes that are in rapid equilibrium. The oxidative addition of the molecular hydrogen was found to be irreversible and rate determining. The stereoselectivity of the overall reaction depended on the relative rates of oxidative addition to the two complexes. The predominant product resulted from the minor isomer pathway by virtue of a much higher reactivity of the reactant-catalyst adduct with hydrogen. It was found that the ratio $k''_2:k'_2$ was 573:1, and the equilibrium ratio of the complexation of the substrate to the catalyst was 1:11. These values taken together provides a product ratio of ~52:1 in favor of the minor isomer. In consequence, the minor catalyst-substrate complex provided the major enantiomer of the product.



Scheme 10. Parallel Reaction Paths for Asymmetric Hydrogentation of Olefins.

Coordination onto the prochiral C=C bond can occur on either face. Oxidative addition of hydrogen takes place on the face of the alkene that is coordinated to the metal.

All the intermediates retain the carbonyl group coordinating to the metal center throughout the reaction (Scheme 10). This structural feature is important in many substrates that provide high enantiomeric excesses. Substrates known as dehydro-α-acylamino acids have been one of the most extensively studied. Selected examples of recent asymmetric hydrogenations of this class of compound are given in Table 2.

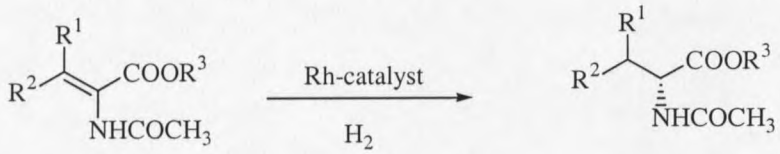


Table 2. Asymmetric Hydrogenation of Dehydro-α-Acylamino Acids.

Entry	R^1	R^2	R^3	H_2 (atm)	Temp (°C)	Ee (%) (*R*)
1[26]	H	Ph	H	1	rt	97
2[27]	H	Ph	Me	1	rt	98
3[27]	H	H	Me	1	rt	>99.9
4[28]	H	Ph	Me	2	rt	99.9
5[1]	Me	Me	Me	6	rt	53.3
6[20]	H	Ph	Me	1	20	91
7[20]	H	Ph	Me	1	35	88
8[20]	H	Ph	Me	20	35	85
9[29]	H	Ph	Me	1	rt	96.8 (*S*)
10[29]	H	H	Me	1	rt	97.5 (*S*)

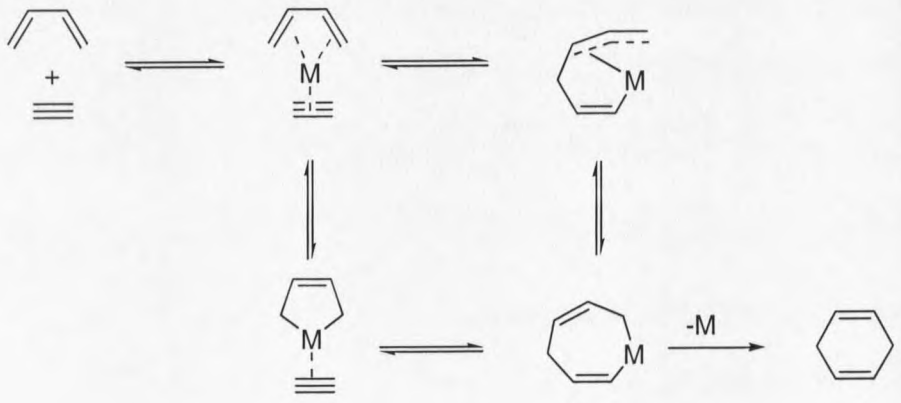
2.4 Transition Metal-Catalyzed [4 + 2] Cycloadditions

Reactions that deal with stereo- and enantiocontrol and are compatible with a variety of functional groups are important tools in applications for organic chemistry. Some of the most important reactions are bond, ring, and stereocenter formations. Among the most powerful reactions for forming multiple bonds and stereogenic centers in a single synthetic operation are the cycloaddition reactions. Heat, light, Lewis acids,[30] high pressure,[31] sonication, special solvent effects,[32] and more recently, metal catalysts,[33] have all been used to promote these reactions.

The most widely used method for preparation of six-membered rings is the Diels-Alder [4 + 2] cycloaddition.[34,35] The versatility of the Diels-Alder reaction has made this one of the most widely studied methods in organic chemistry and is the standard by which other cycloadditions are compared. The Diels-Alder [4 + 2] cycloaddition is very useful in ring formation where chemo- and stereoselectivity are dictated by the diene and dienophile substrates. However, the Diels-Alder reaction is often restricted to the electronic requirements that govern this concerted process: an electron rich diene and an electron deficient dienophile. The reaction of unactivated olefins, dienes and acetylenes is inefficient and strenuous conditions are necessary to obtain good yields of the cycloadducts. The cycloaddition of two unactivated species proved to be difficult since

homodimerization can be a competitive and dominant reaction pathway. Due to these restrictions and the necessity of high temperatures required for the uncatalyzed process, the scope of these [4 +2] cycloadditions are limited. As a result, transition metal-catalyzed [4 + 2] cycloisomerization between electronically similar components offer advantages over traditional Diels-Alder processes.

Metal catalysis allows greater opportunities for highly selective cycloaddition reactions since complexation of the metal to an olefin, diene, or acetylene significantly modifies the reactivity of this moiety. A quintessential feature of this strategy is the ability to establish enantioselective transformations by adding chiral ligands while maintaining the already observed rate enhancement.



Scheme 11. Possible Paths of Metal Catalyzed [4 + 2] Cycloisomerization.

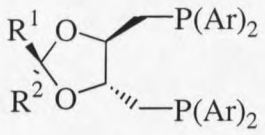
Metal catalysts activate the [4 + 2] cycloisomerization by a combination of proximity and complexation induced polarization effects. Interaction of the π-bonds of

the diene and the dienophile give rise to the formation of the π-complex. There are two ways oxidative coupling could occur: by generating a η^1,η^3-complex[36,41] or the formation of the metallacyclopentene (Scheme 11).[37] Both could be precursors to the formation of the metallacycle that could then give the carbocycle and regenerate the active catalyst by reductive elimination. To date, Rh, Ni, Ti, Fe, and Pd have been reported to catalyze the [4 + 2] cycloaddition.[38]

Mortreux and co-workers[39] have studied the chemo- and enantioselectivity of the Diels-Alder reaction between 1,3-butadiene and methyl sorbate. Using a low-valent nickel complex in the presence of chiral aminophosphine-phosphite and diphosphine ligands, the yield and the chemoselectivity were only moderate, and the enantioselectivity was unfortunately low (5% ee). Previously, Garratt[40] showed that low-valent nickel complex (generated by reduction of $Ni(acac)_2$ with Et_3Al) influenced the selectivity of this reaction. Under thermal conditions methyl sorbate was the "diene" component and the 1,3-butadiene was the "dienophile". However, the low-valent nickel complex reversed the reactivity rendering 1,3-butadiene as the "diene" component and methyl sorbate as the "dienophile" component.

Previous work done in the Livinghouse laboratories has shown that a variety of Rh(I) catalysts can accelerate intramolecular [4 +2] cycloisomerization reactions at low temperatures.[41,42,43] Furthermore, it has been determined that bisphosphines that form 7-member chelates are effective ligands for the intramolecular [4 +2] cycloaddition reaction.[41] A series of bisphosphine ligands **41** and **42** (Figure 6), related to (+)-DIOP,

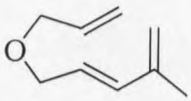
were chosen to evaluate the possibility of asymmetric rhodium(I) catalyzed [4 +2] cycloisomerizations. These ligands provided moderate to good levels of enantioselection.



41: $R^1=R^2=CH_3$, Ar=Ph
42: $R^1=CH_3$, R^2=Ar=Ph

Figure 6. (+)-DIOP Derivatives **41** and **42**.

The results of some of the cyclizations of ene-dienes and diene-ynes are summarized in Table 3. The ^{1}H-NMR resonance for the corresponding diastereomeric Mosher's esters[17] was used to determine the enantiomeric excesses. The experimental results suggest that by slightly altering the 1,3-dioxolane ring the absolute sense of the asymmetric induction is reversed.



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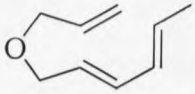

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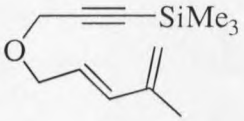

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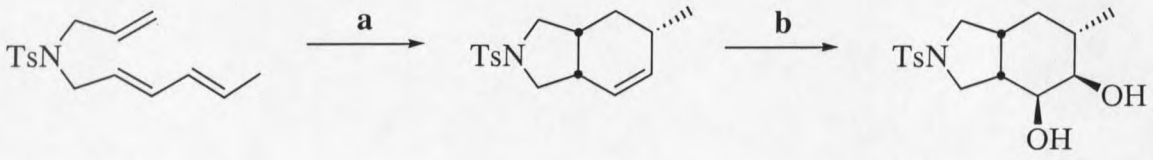
Table 3. Enantioselective Rh(I)-Catalyzed [4 + 2] Cycloisomerization Using (+)-DIOP Related Ligands.

Cycloadduct	Ligand	% de (abs. config.)
43	**41**	7 (R)
44	**41**	73 (R)
45	**41**	52 (R)
43	**42**	20 (S)
44	**42**	47 (S)
45	**42**	87 (S)

Continued advances were made in the Livinghouse laboratory to improve the asymmetric induction and to provide high turn over frequencies. Increasing the reactivity of the catalyst system can be accomplished by changing the nature of the rhodium complex. The use of counterions has shown increased reaction rates.

The counterion effect was examined with the use of an electron-rich ligand, (+)-DIOP, for use in the rhodium catalyzed [4 + 2] cycloaddition of the tosyl-protected azatriene **46** (Table 4).[43] The bromide as the counterion showed similar ee but a decrease in the rate relative to the chloride while the iodide and trichlorostannyl anions demonstrated low activity. The cationic triflate species led to the bicycloadduct with similar reaction rates but reduced enantioselectivity.

When using the weakly ligating counterion, hexafluoroantimonate, milder conditions were utilized (a weakly coordinating solvent dichloroethane [DCE] and lower temperature (40 °C)). It was found that complete isomerization of the bicycloadduct **47** was observed with the more polar solvent (trifluoroethanol [TFE]). The hexafluoroantimonate anions resulted in a lower reaction rate and a slight decrease in enantioselectivity. However, a cationic species generated by hydrogenation of a pre-formed Rh-phosphine complex enhanced the rate and maintained the degree of enantioselection. The catalyst generated from $[(NBD)_2Rh]SbF_6$ is the preferred method for screening chiral phosphine ligands due to the mild conditions, similar reactivity and enantioselectivity.



46 **47** **48**

(**a**) $[(COE)_2RhCl]_2$ (2 mol%), (+)-DIOP (4 mol%), additive (4 mol%), solvent, 55 °C. (**b**) OsO_4 (5 mol%), NMO, EtOAc/H_2O (1/1).

Table 4. Counterion Effect of Enantioselective Cyclization

Anion	Additive	Solvent	Time (hrs.)	Yield (%)	ee (%)
Cl	none	DCE/TFE (1/1)	2	97	76
Br[a]	none	DCE/TFE (1/1)	4	76	77
Br[a]	none	DCE/TFE (1/3)	4	86	79
I	NaI	DCE/TFE (1/1)	4	trace	(-)
$SnCl_3$	$SnCl_2$	DCE/TFE (1/1)	4	trace	(-)
OTf	AgOTf	DCE/TFE (1/1)	2	84	61
SbF_6[b]	$AgSbF_6$	DCE (40 °C)	5	70	66
SbF_6[c]	H_2	DCE (40 °C)	4	96	68

[a] $[(COE)_2RhBr]_2$ (2 mol%); [b] $[(COE)_2RhCl]_2$ (1 mol%);

[c] [((+)-DIOP)Rh(NBD)][SbF_6] (2 mol%)

Recently, Gilbertson[44] reported the use of commercially available chiral bisphosphine ligands to catalyze the [4 + 2] cycloisomerization reaction in which both triene and dieneyne substrates were investigated. Table 5 shows the results of asymmetric induction of triene **49**. Both CHIRAPHOS and DIOP provided cyclization product in good ee. Their enantioselectivity is comparable to our aforementioned catalyst system employing DIOP. Consequently, their most selective ligand was BINAP. Their initial attempts to utilize this system only resulted in the isomerization of the triene unit. This result also is comparable to our system using BINAP; however, they reexamined this catalyst in EtOAc instead of CH_2Cl_2 and obtained cycloisomerization product in 98% ee.

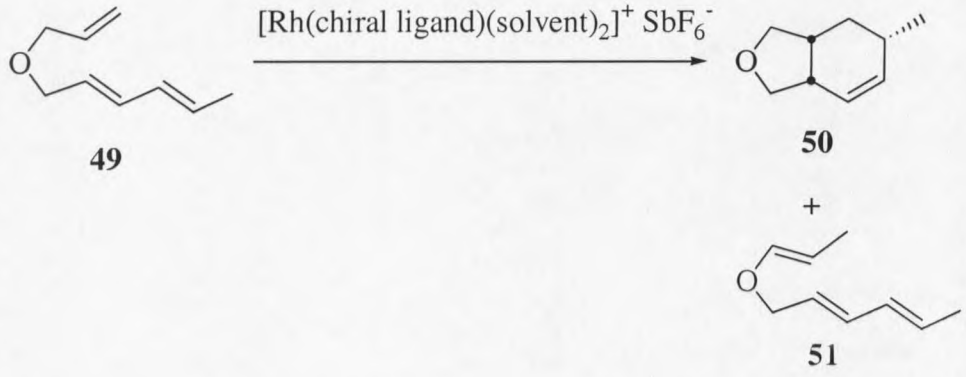
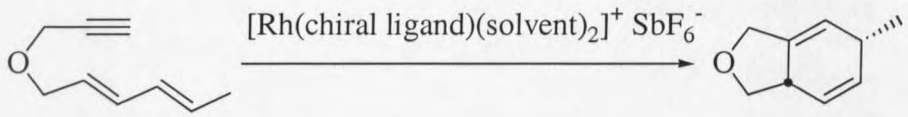


Table 5. Asymmetric Induction of Triene **49**.

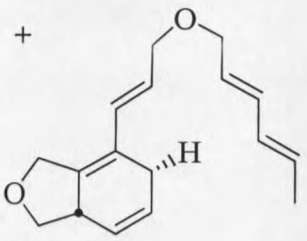
Chiral ligand	Conditions	Yield **50** (%)	ee (%)	Yield **51** (%)
(S,S)-CHIRAPHOS	CH_2Cl_2, 25 °C, 18 h	76	72	0
(S,S)-DIOP	CH_2Cl_2, 55 °C, 24 h	42	77	0
(S,S)-DUPHOS	CH_2Cl_2/EtOAc (6:1), 55 °C, 1 h	0	0	54
(S)-BINAP	CH_2Cl_2, 25 °C, 8 h	0	0	52
(S)-BINAP	EtOAc, 10 mol % cat., 55 °C, 72 h	64	>98	0

[a] Reactions were carried out with 0.07~0.1 mmol substrate and 6 mol % chiral ligand unless otherwise specified. The catalyst was prepared by prehydrogenation of the phosphine rhodium olefin complex before addition of the substrate.

Gilbertson[44] then found that BINAP, CHIRAPHOS, and DIOP did not work well in the catalysis of the cycloisomerization of dieneyne **52**. The reactions using these ligands gave the cyclic product with low selectivity (9 ~ 43% ee). DUPHOS gave a low yield (15%) with good selectivity (81% ee); however, the major product was the dimer **54**. They studied a variety of reaction conditions in an attempt to decrease the reactivity of the catalyst precursor. Under these conditions (3% catalyst with a (6/1) mixture of CH_2Cl_2/EtOAc and excess ligand) the product was obtained in good yield (85%) and high selectivity (95% ee). It seems when EtOAc was added as part of the solvent system that higher enantioselectivities were obtained. To this point, the role of EtOAc in enhancing the enantioenrichment is unclear.



52 **53**



54

Table 6. Asymmetric Induction of Dienyne **52**.

Chiral ligand	Conditions	Yield **53** (%)	ee (%)	Yield **54** (%)
(S)-BINAP	EtOAc, 55 °C, 60 h	79	39	0
(S,S)-CHIRAPHOS	CH_2Cl_2, 25 °C, 24 h	70	9	0
(S,S)-DIOP	CH_2Cl_2, 25 °C, 24 h	70	43	0
(S,S)-DUPHOS	CH_2Cl_2, 25 °C, 2 h	15	81	60
(S,S)-DUPHOS	CH_2Cl_2/EtOAc (6/1), 55 °C, 4 h	85	95	0

[a] Reactions were carried out with 0.07~0.1 mmol substrate and 6 mol % chiral ligand unless otherwise specified. The catalyst was prepared by prehydrogenation of the phosphine rhodium olefin complex before addition of the substrate.

CHAPTER 3

RESULTS AND DISCUSSION

Organolithium/Chiral Diamine Complexes

Asymmetric deprotonation from complexes formed between organolithium reagents and enantioenriched ligands can afford highly enantioenriched products. Hoppe[1,2,3] was the first to report the use of *s*-BuLi/(-)-sparteine to provide α-oxygen substituted dipole stabilized carbanion products with high enantioenrichments in a lithiation-substitution sequence. Beak[45] later established that *s*-BuLi/(-)-sparteine can be used with *N*-Boc-pyrrolidine in an asymmetric deprotonation-electrophilic substitution sequence to provide highly enantioenriched 2-substituted *N*-Boc-pyrrolidines. Asymmetric deprotonation using organolithium/chiral diamine complexes show promise for the synthesis of homochiral phosphine ligands.

One of the objectives for the research herein was to design a beneficial sequence for asymmetric synthesis of *P*-chiral phosphine ligands. Sparteine has been known to be an effective external chiral ligand for asymmetric induction and was perceived as a potential route towards the synthesis of *P*-chiral phosphine ligands. It was also speculated that other chiral diamines might be useful in asymmetric deprotonation reactions to provide *P*-chiral phosphine ligands. Combinations of the following criteria prove to be essential in providing an effective ligand in the asymmetric deprotonation

reaction. It is advantageous for highly enantioselective deprotonation reactions that the chiral ligand bind the organolithium species strongly enough to keep the concentration of reactive racemic species low. The ligand must also have proper steric interactions and provide sufficient flexibility to allow the substrate to adopt the proper diastereomeric transition state in order to introduce enantioselectivity. Furthermore, the ligands should accelerate the lithiation reaction compared to the ligand-free reaction.

Based on the criteria listed above the goals put forth for this part of the research were to determine if the *s*-BuLi/(-)-sparteine complex would be effective in the asymmetric deprotonation of dimethylphenylphosphine-borane and to provide other synthetically useful ligands in both enantiomeric forms. Accordingly, the efficacies of selected ligands for the organolithium/chiral diamine ligand complexes as reagents for asymmetric deprotonation of dimethylphenylphosphine-borane were evaluated. Asymmetric lithiation of dimethylphenylphosphine-borane was investigated using (-)-sparteine and chiral diamine ligand systems of *trans*-cyclohexanediamine derivatives and their antipodes (Figure 7).

In order to determine ligand structure-enantioselectivity relationships, each ligand was assayed for reaction sequence **57** to **58** (Scheme 12). A 1:1 organolithium/chiral diamine ligand complex was formed at –78 °C then dimethylphenylphosphine borane was added and allowed to stir at –78 °C for 4 h before the addition of benzophenone. Once the addition was complete the reaction mixture was warmed to –20 °C and allowed to stir for 17 h. The reaction was quenched with saturated $NH_4^+Cl^-$ then the enantiomeric excess of **58** was determined by chiral HPLC and compared to the racemic product.

Solvent effects using either diethyl ether (Et_2O) or *tert*-butyl methyl ether (^{t}BuOMe) were also evaluated (Table 7).

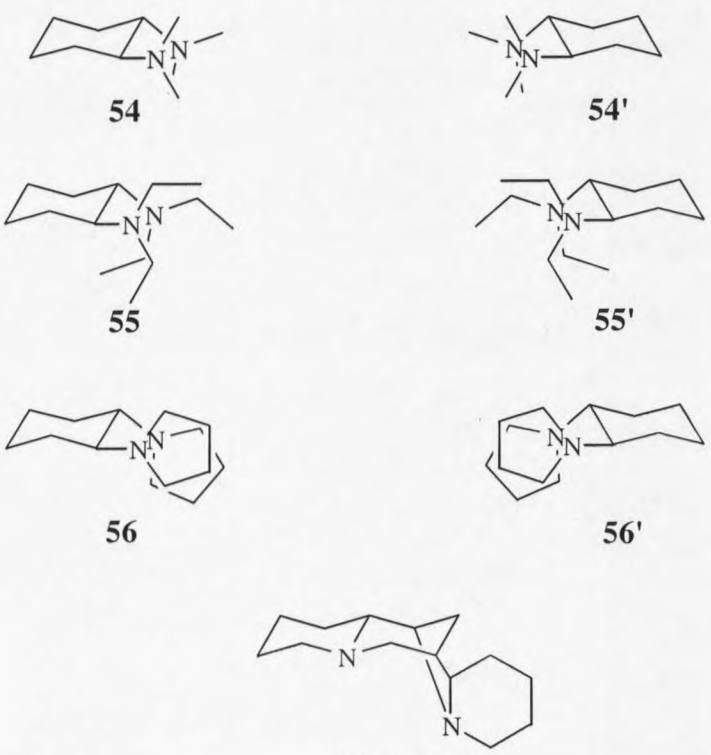
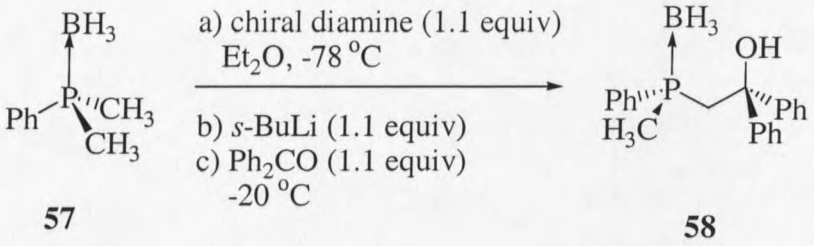


Figure 7. *Trans*-Cyclohexanediamine Derivatives and Their Antipodes.



57 **58**

Scheme 12. Benzophenone Trapped Asymmetrically Lithiated Dimethylphosphine Borane with Chiral Diamines **54** - **56**.

Table 7. Benzophenone Trapped Asymmetrically Lithiated Dimethylphosphine Borane with Chiral Diamines **54** - **56**.

Ligand	Organolithium	Solvent	ee (%)
54	*s*-BuLi	Et_2O	37
55	"	"	1.1
56	"	"	81
(-)-sparteine	"	"	77
56	*n*-BuLi	"	28
(-)-sparteine	"	"	82
"	*t*-BuLi	"	2.5
56	*s*-BuLi	^{t}BuOMe	61
(-)-sparteine	"	"	87
56	*n*-BuLi	"	27
(-)-sparteine	"	"	36

The initial attempt towards the asymmetric deprotonation was using *s*-BuLi/chiral diamine complex in Et_2O. The first ligand examined, (-)-sparteine, provided a 77% ee. Encouraged by this result, the other three ligands were investigated. Chiral ligand **54** gave a 37% ee with good yields. A negligible selectivity was obtained when the reaction was run with ligand **55**. It was initially hoped that as steric interactions increased so would the enantiomeric excess of the product. These interactions are clearly not present in **55**, suggesting that the methyl on the ethyl substituents are situated away from the binding sites and that the methylene group of the ethyl does not have as much steric interactions as the methyl substituent of ligand **54**. However, replacement of the alkyl substituents with a cyclic substituent, **56,** allowed enough steric interactions along with sufficient flexibility to provide the desired product in 81% ee.

Since (-)-sparteine and **56** were the most effective ligands in the initial investigation for the asymmetric deprotonation of dimethylphenylphosphine borane, these ligands were examined under other conditions. The results described in table 7 show that **56** did not continue to provide useful enantiomeric excess under any of the other conditions. The most successful of the ligands assayed was (-)-sparteine, which afforded the highest enantioselectivity (87% ee) when using *s*-BuLi as the organolithium and ^{t}BuOMe as the solvent.

In conclusion, although ligand **56** provided substantial enantioselectivity in the asymmetric lithiation of dimethylphenylphosphine borane, it did not provide enantioselectivities as high as (-)-sparteine. The combination of binding, rigidity, and the

specific steric features of (-)-sparteine contribute to its effectiveness as a chiral ligand. Indeed, the other ligands investigated did possess the binding modes and some of the rigidity of (-)-sparteine but did not provide an adequate steric environment for effective asymmetric deprotonation.

Chiral Diphosphine Ligands

It has long been recognized that changing substituents on phosphorus ligands can cause noticeable changes in the behavior of the free ligands and of their transition metal complexes. In 1970, quantitative measures of electronic and steric effects were proposed based on A_1 carbonyl stretching frequencies (ν) in $Ni(CO)_3L$ complexes, and ligand cone angles (θ) of space-filling CPK molecular models.[46] Since then a large number of papers have appeared which show that both steric and electronic effects are equally as important.

Previous work done in the Livinghouse laboratories have demonstrated that slight alterations in the steric and/or electronics of the phosphorus ligand can change the absolute stereochemistry of the rhodium(I) catalyzed [4 + 2] cycloisomerization product and the reactivity of the rhodium(I) catalyst. Altering the backbone of the bisphosphine ligand (+)-DIOP derivatives with stericly encumbered and/or electronically differentiating substituents markedly changed the reactivity and selectivity of the rhodium(I) catalyst. These ligands gave cycloaddition products with moderate selectivity and in good yields. With the chirality of the (+)-DIOP derivatives existing on the backbone of the ligands and not near the reaction site may account for the moderate to low selectivity.[44]

It was hoped that creating a ligand with chiral phosphorus would increase the asymmetric induction of the rhodium(I) catalyst by allowing the chirality to be in closer proximity to the metal center. The focuses of the studies were to understand the importance of steric and electronic effects that were investigated by studying the

conformational variances within the phosphorus ligand. This study was geared towards the modification of the phosphine; in particular, making the ligand chiral at phosphorus in order to fully define the scope of the asymmetric cycloisomerization reaction and improve the level of asymmetric induction.

Advances towards the synthesis of chiral monophosphines were made in Livinghouse laboratories via the precursor, 2-substituted-3,4-dimethyl-5-phenyloxazaphospholidine. This method provided *P*-chiral diarylmethylphosphine ligands in >99% ee. The process to obtain the desired ligands is laborious due to multiple synthetic steps and the necessity to purify at several key steps by recrystallization to induce high enantioenrichment. The desired *P*-chiral diphosphines were achieved by treatment of these diarylmethylphosphines with an organolithium reagent and subsequent copper-mediated coupling.

While these ligands may independently incorporate the chirality on either the linking carbon chain or the phosphorus centers, comparatively few *P*-chiral ligands have received attention due to the difficulties associated with the synthesis of enantiomerically enriched phosphorus stereocenters. This thesis discloses a convenient method to the synthesis of a variety of C_2-symmetric *P*-chiral bis(phosphine borane)s which can be directly prepared from prochiral aryldimethylphosphine boranes. As discussed in section 3.1, high enantioselective deprotonation of dimethylphenylphosphine borane has been achieved using *s*-BuLi/(-)-sparteine complex. The approach taken herein involves asymmetric deprotonation of aryldimethylphosphineborane with *s*-BuLi/(-)-sparteine complexes followed by oxidative or silyative coupling.

The electronic effect of the aryldimethylphosphine borane depends considerably on the nature of the substituent atoms on the phosphorus. Since the proposed ligands have two methyl and one aryl as substituents it was necessary to create the steric and electronic environment with the aromatic ring. Based on CO stretching frequencies of $Ni(CO)_3L$, Tolman found that more electron withdrawing substituents give higher CO stretching frequencies. The order of electron withdrawal for some substituents of interest was found to be CF_3>>*p*-C_6H_4F>Ph>*o*-Tolyl>2,4,6-$(CH_3)_3C_6H_2$>*t*-Bu.[46]

Both the steric and electronics of the bis(phosphine borane)s are important for transition metal chemistry. The design for the trivalent phosphines incorporates the electron donor and acceptor properties while containing steric interactions. Phosphorus ligands containing the right proportions of these properties might be achieved by placing different electronic substituents on the *ortho* position of the aromatic ring. The investigation of the phosphine ligands begun with the following aryl substituents: 2,6-$(CH_3O)_2C_6H_3$, 2,4,6-$(CH_3)_3C_6H_2$, 2-$(CF_3)C_6H_4$, and 1-Ferrocenyl. The 1-ferrocenyl aryl group is different from the others in the series; however, it is electron donating and possesses large steric interactions, all of which should make an interesting ligand.

Treatment of the corresponding dichlorophosphines with CH_3MgCl (2.51 equiv) followed by complexation with H_3B-$S(CH_3)_2$ afforded the aryldimethylphosphine boranes (**59** – **62**). Asymmetric metalation of the aryldimethylphosphine boranes with the *s*-BuLi/(-)-sparteine complex (1.1 equiv) in Et_2O at –78 °C for 5 h, followed by trapping with benzophenone (1.1 equiv) in THF at –20 °C, afforded the corresponding alcohols (Scheme 13). The enantiomeric ratios of the alcohols were determined by

HPLC using a CHIRALPAK® AD column (Table 8). Corresponding racemic alcohols for HPLC comparisons were prepared by metalation with *s*-BuLi without (-)-sparteine.

Scheme 13. Benzophenone Trapped Lithiated

Phosphine Boranes **59** – **62** with (-)-Sparteine.

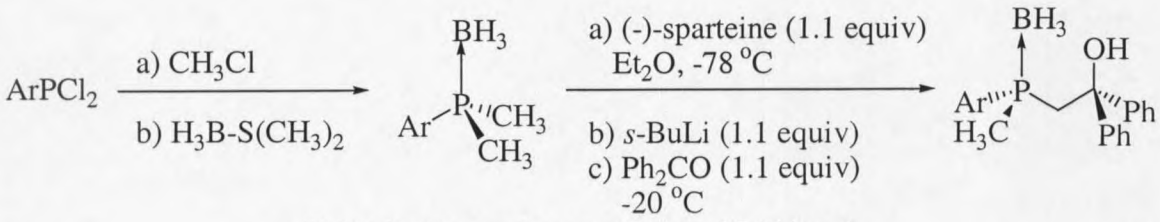


Table 8. Benzophenone Trapped Lithiated

Phosphine Boranes **59** – **62** with (-)-Sparteine.

Phosphine	Ar	Alcohol	ee (%)
59	2-$(CF_3)C_6H_4$	**63**	84
60	2,6-$(CH_3O)_2C_6H_3$	**64**	95
61	2,4,6-$(CH_3)_3C_6H_2$	**65**	65
62	1-Ferrocenyl	**66**	89

The highest enantioselectivity was observed with **60**, which provided **63** in 95% ee. Similarly, good enantioselectivity of 84 and 89% ee were obtained for **59** and **62**

respectively. However, **61** did not provide sufficient enantioenrichment (65% ee). One consideration for the selection for the aryldimethylphosphine boranes for the bis(phosphine borane)s synthesis is the enantioenrichment of the asymmetric deprotonation. Considerable effort was invested in an attempt to improve the enantioselective deprotonation of **61**.

The goal was to prepare C_2-symmetric *P*-chiral diphosphines that provide good selectivities while maintaining sufficient reactivity. For the [4 + 2] cycloisomerization reaction, Livinghouses laboratories found that diphosphines which form 7-member chelates provide very reactive complexes for this transformation with a general trend being 7>6>5>4. Ligands of the general type, **67**, **68** and **69**, could possibly provide the necessary requirements to form effective catalysts (Figure 8).

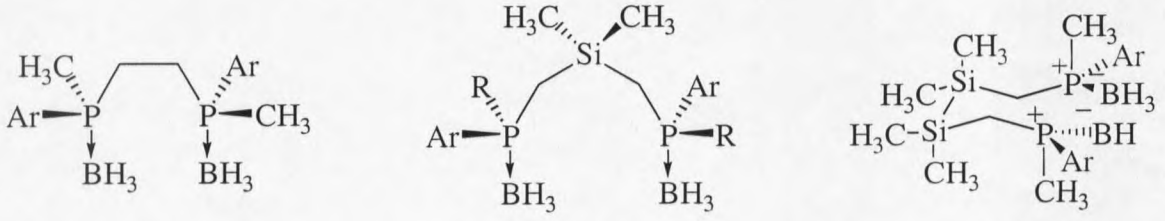
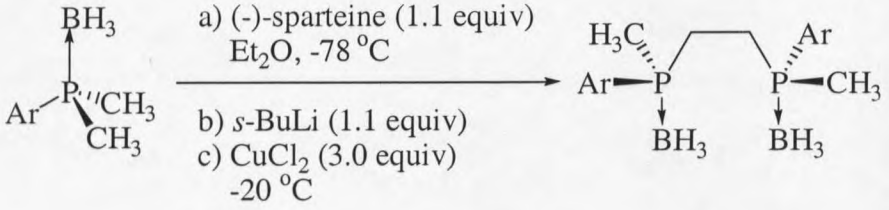


Figure 8. General Type of *P*-Chiral Bisphosphine Ligands **67** - **69**.

Oxidative Coupling. (Scheme 14) Successive enantioselective deprotonation of aryldimethylphosphine boranes with *s*-BuLi/(-)-sparteine complex and subsequent oxidative coupling with $CuCl_2$ provided C_2-symmetric *P*-chiral bis(phosphine borane)s.

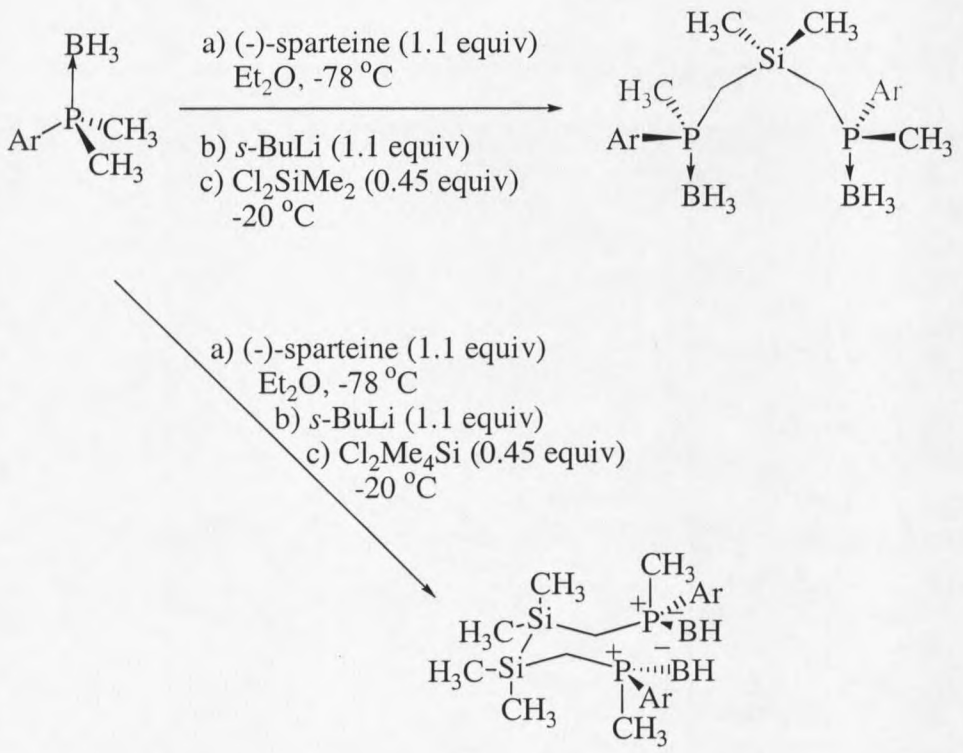
Analysis of the products by chiral HPLC using a CHIRALPAK® AD and OD-H column was not successful at resolving the enantiomers. Nevertheless, the C_2-symmetric bisphosphine boranes were separated from the meso diastereomeric products by selective crystallization.



Scheme 14. Oxidative Coupling to Give

C_2-Symmetric *P*-Chiral Bis(phosphine borane)s.

Silylative Coupling. (Scheme 15) Successive enantioselective deprotonation of aryldimethylphosphine boranes with *s*-BuLi/(-)-sparteine complex and subsequent silylative coupling to Me_2SiCl_2 and Cl_2Me_4Si gives C_2-symmetric *P*-chiral bis(phosphine borane)s. Analysis of the products by chiral HPLC using a CHIRALPAK® AD and OD-H column was not successful at resolving the enantiomers.



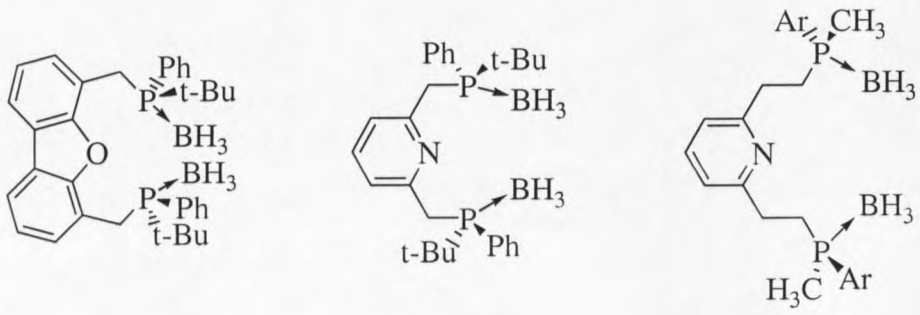
Scheme 15. Silylative Coupling to Give

C_2-Symmetric *P*-Chiral Bis(phosphine borane)s.

Another series of ligands were proposed during the course of this thesis. Osborn[47] and Zhang[48] have described the use of chiral PNP diphosphines in asymmetric synthesis; likewise, Ito[49] and Trost[50] have shown that *trans*-binding diphosphines possess superior qualities as chirality controllers in several asymmetric transformations.

In Livinghouse's laboratories, a related series of *P*-chiral tridentate ligands was proposed. The new ligands described here are constructed around a heteroaromatic core that links two *P*-chiral phosphines. By virtue of this design feature, coplanarity will be rigorously maintained over the five contiguous centers containing the central heteroatomic ligand. Accordingly, the *P*-chiral phosphine moieties of the ligands **70** and **71** should be held in *trans* binding array with respect to the catalytic metal center.

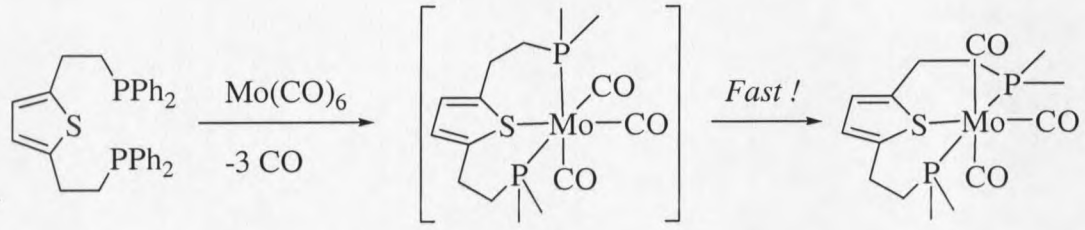
For ligand **72**, *trans* binding of the phosphines should be preferred thermodynamically but ligation at the *fac* positions cannot be ruled out. In addition, the *mer* complexes derived from **72** are expected to possess a greater degree of conformational mobility than complexes from the corresponding **70** and **71** ligands.



70 **71** **72**

Figure 9. General Type of *P*-Chiral Tridentate Ligands **70** - **72**.

Mathieu has shown that reaction of $Mo(CO)_6$ with **73** gives the corresponding *fac*-tricoordinate complex **74** kinetically. Subsequent rearrangement of **74** to the thermodynamic *mer* isomer **75** was found to be rapid at room temperature (Scheme 16).[51]

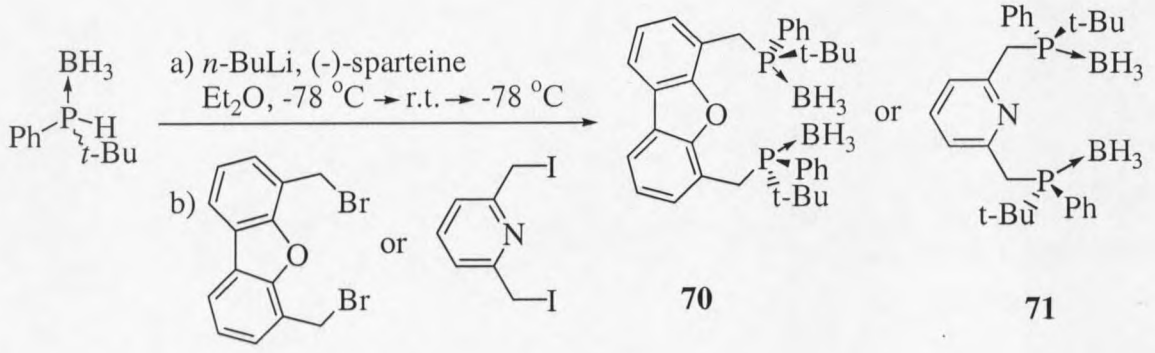


73 **74** **75**

Scheme 16. Bonding Property of Tridentate Ligand **76** with $Mo(CO)_6$.

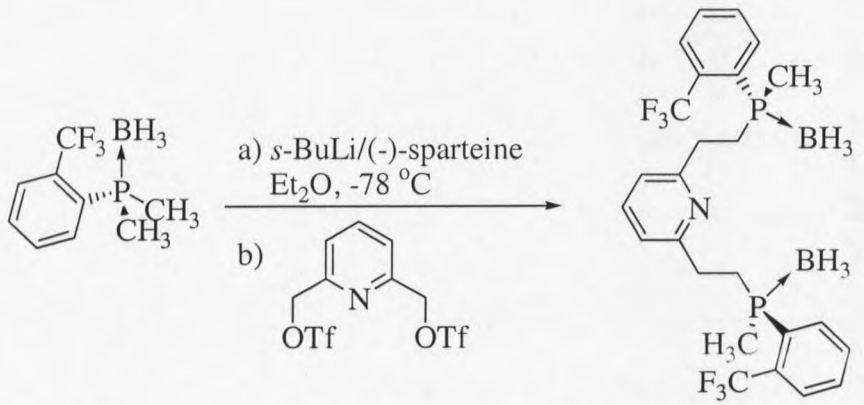
It should be emphasized that the *trans* orientation of the *P*-chiral phosphine centers in complexes derived from the aforementioned ligands is expected to provide a very favorable stereochemical environment for asymmetric catalysis. In addition, the donor ability of the central heteroatom in these ligands is expected to decrease in the order N>S>O. This should provide a means by which the electronic characteristics of the bound, catalytically active metal could be conveniently modified.

Ligands **70** and **71** were synthesized by Wolfe via dynamic resolution of lithiated racemic *t*-butylphenylphosphine borane with (-)-sparteine. The C_2-symmetric bis(phosphine borane) was derived by metallation of the secondary phosphine borane with *n*-BuLi (1.0 equiv) at –78 °C in the presence of (-)-sparteine (1.3 equiv). The solution was warmed to ambient temperature and stirred for 30 min followed by cooling to –78 °C and immediate bis-alkylation with the requisite dihalide (0.5 equiv) delivered **70** and **71** (Scheme 17).[52]



Scheme 17. Bis-Alkylations Invovling Dynamically Resolved *t*-Butylphenylphosphine-Borane.

Asymmetric lithiation of **59** followed by alkylative coupling with 2,6-bis(hydroxymethyl)pyridine ditriflate (0.5 equiv) provided the PNP diphosphine borane **76** in 48% yield after recrystallized purification to remove a small amount of the accompanying *meso* derivative and unreacted prochiral phosphine borane (Scheme 18).



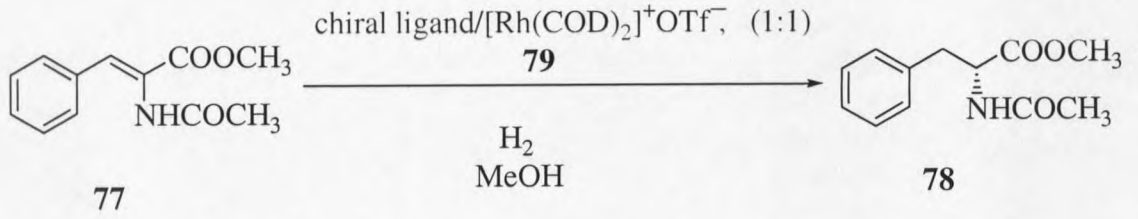
59 **76**

Scheme 18. Bis-Alkylation to Give PNP Ligand **76**.

High enantioselectivity is significant for the synthesis of the bis(phosphine borane)s; likewise, purification of the phosphine products is just as important in the overall scheme. It was necessary to have crystalline material and/or be able to separate the diastereomers by chromatography. Until the chiral phosphine was clean of the diastereomer, it was not useable in the transition metal transformations; therefore, it was imperative to have ligands that could be purified. Unfortunately, there were several ligands synthesized that could not be resolved.

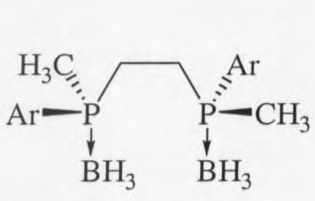
Asymmetric Rhodium(I) Catalyzed Hydrogenation

α-Acylaminoacrylic acid derivatives have proven to be excellent precursors for asymmetric rhoduim(I) catalyzed hydrogenation. Enantiomeric excesses of 95-99% are now possible with these derivatives. Bisphosphine catalysts are not as sensitive to reaction variables as earlier catalysts. And excellent results were obtained at higher temperatures and pressures. The efficacies of chiral bisphosphine ligands are analyzed using α-acylaminoacrylic acid derivatives. To determine the efficiency of the aforementioned C_2-symmetric *P*-chiral phosphine ligands, *Z*-α-acylaminoacrylic acid derivative **77** was used in the asymmetric hydrogenation with complex **79** as catalyst.

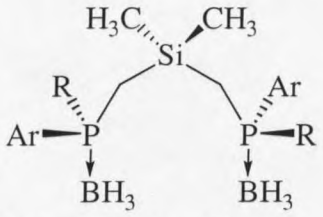


77 **78**

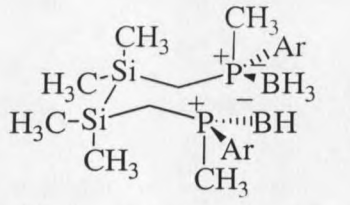
Scheme 19. Asymmetric Hydrogenation of *Z*-α-Acylaminoacrylic Acid Derivative **77** with Catalyst Complex **79**.



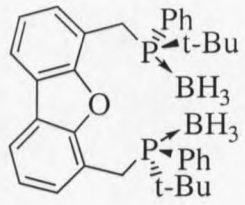
80: Ar= 2-$(CF_3)C_6H_4$
81: Ar= 2,6-$(OCH_3)_2C_6H_3$



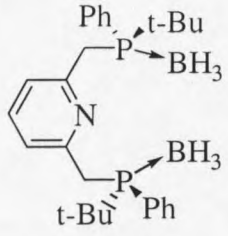
82: R= *t*-Bu, Ar= Ph
83: R= CH_3, Ar= 1-Ferrocenyl
84: R= 2-$(CF_3)C_6H_4$, Ar= Ph
85: R= CH_3. Ar= 2-$(CF_3)C_6H_4$



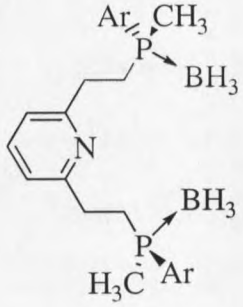
86: Ar= 2,6-$(OCH_3)_2C_6H_3$



70



71



76: Ar= 2-$(CF_3)C_6H_4$

Figure 10. C_2-Symmetric *P*-Chiral Bis(phosphine borane)s.

Ligands **70**, **71**, **76**, **80** - **86** (Figure 10) were tested in the rhodium(I) catalyzed hydrogenation of α-acetamidocinnamic acid derivative **77** (Scheme 19). The results are summarized in Table 9. The catalytic system formed in situ from DIPAMP (**16**) and $[Rh(COD)_2]OTf^-$ hydrogenates methyl (Z)-α-acetamidocinnamate (**77**) to (R)-*N*-acetylphenylalanine methyl ester (**78**) with 99% ee at ambient temperature and 30 psi H_2 (Table 9, entry 1). Likewise, a similar system using CHIRAPHOS (**14**) provides 85% ee under identical reaction conditions (entry 2). By contrast, the in situ formed catalytic

system using chiral ligand **80** gives only 50% ee (entry 12). Despite extensive experimentation in this area, most of the chiral ligands resulted in disappointingly low enantioselectivity (entries 3-11) in the rhodium(I) catalyzed hydrogenation reaction.

Table 9. Asymmetric Hydrogenation of Z-α-Acylaminoacrylic Acid Derivative **77** with Catalyst Complex **79**.

entry	chiral ligand	ee (%)
1	**16**	99
2	**14**	85
3	**70**	0.3
4	**71**	7.0
5	**82**	9.0
6	**83**	16.0
7	**84**	24.0
8	**81**	12.0
9	**86**	31.0
10	**76**	4.0
11	**85**	29.0
12	**80**	50.0

[a] All reactions were carried out in MeOH with mmol substrate and mol % chiral ligand unless otherwise specified. They were carried out at ambient temperature and an initial H_2 pressure of 30 psi. [b] The selectivities were determined by analytical chiral capillary GC using Chrompack Chiral-L-Val column (25 m). In all cases, the ee were determined by comparison with racemic compound.

Contrary to the original concept, placing a stereogenic P atom in the immediate proximity of the metal did not help provide good enantioselectivity in the asymmetric hydrogenation. Various degrees of steric bulk of the substituents placed on the P atom of the ligands prepared in the Livinghouse laboratories provided little selectivity. Efforts towards studying the effects of varying rigidity of the linkages between the stereogenic P atoms did not improve the stereodifferentiating ability of the chiral ligand for the hydrogenation reaction. However, the catalyst system using ligands **80** and **85** (entries 11 and 12) exhibited a trend affording slightly higher enantioselectivity in the hydrogenation. These ligands all have an electron deficient substituent, *o*-trifluoromethylphenyl, on the phosphine. Based on this information the focus of this thesis was directed towards the use of these electron deficient phosphines in the asymmetric rhodium(I) catalyzed [4 + 2] cycloisomerizations.

Asymmetric Rhodium(I) Catalyzed [4 + 2] Cycloaddition

Rhodium catalyzed [4 + 2] cycloisomerization of unactivated ene-dienes and diene-ynes are transformations that can be performed on substrates that do not readily undergo thermal or Lewis acid catalyzed Diels-Alder reactions. The scope of this work was to develop and investigate a series of asymmetric phosphine catalysts that were sufficiently active and general for an asymmetric version of this transformation.

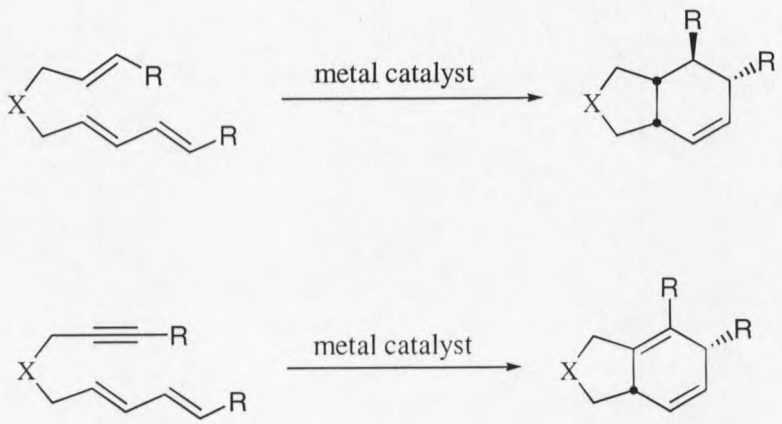


Figure 11. Ene-diene and Diene-yne Substrates for Metal Catalyzed Cycloadditions.

The use of the new chiral bisphosphine ligands, **80**, **85**, **87** – **89**, (Figure 12) to catalyze the cycloisomerization of ene-diene and diene-yne substrates (Figure 11) were investigated. Selectivities as high as 99% ee for ene-diene substrates are reported.