NEW PHOSPHORUS LIGANDS: DEVELOPMENT AND APPLICATIONS IN TRANSITION METAL CATALYSIS

A Thesis in Chemistry

by

Qian Dai

© 2007 Qian Dai

Submitted in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy

May 2007
The thesis of Qian Dai was reviewed and approved* by the following:

Xumu Zhang  
Professor of Chemistry  
Thesis Advisor  
Chair of Committee

Steven M. Weinreb  
Russell and Mildred Marker Professor of Natural Products Chemistry

Blake R. Peterson  
Associate Professor of Chemistry

Qing Wang  
Assistant Professor of Material Science and Engineering

Ayusman Sen  
Professor of Chemistry  
Head of the Department of Chemistry

*Signatures are on file in the Graduate School
ABSTRACT

Transition metal catalyzed reactions are among the most powerful and direct approaches for the synthesis of organic molecules. During the past several decades, phosphorous-containing ligands have been extensively used in transition metal catalyzed C-C and C-H bond forming reactions. Development of new phosphine ligands for palladium catalyzed coupling reactions and rhodium-catalyzed asymmetric hydrogenations are the focus of this dissertation. A variety of triazole-containing monophosphine ligands have been prepared via efficient 1,3-dipolar cycloaddition of readily available azides and acetylenes. Their palladium complexes have been investigated in amination reactions (up to 98% yield) and Suzuki-Miyaura coupling reactions (up to 99% yield) of electronically unactivated aryl chlorides. A CAChe model for one of the Pd-complexes shows that a Pd-arene interaction might be a rationale for its high catalytic reactivity. A new class of $C_1$-symmetric bisphosphine ligands with three hindered quadrant motif has been obtained through facile synthesis from chiral binol derivatives. Their rhodium complexes have exhibited high enantioselectivities (up to 98% ee) in the asymmetric hydrogenation of various unsaturated prochiral olefins, providing an efficient catalytic system for the enantioselective synthesis of chiral amino acids and amines. Utilizing a rhodium complex of an electron-donating bisphosphine ligand (TangPhos), a highly efficient method for the enantioselective synthesis of a new class of N-aryl substituted β-amino acid derivatives has been developed with high conversions and enantioselectivities (up to 96.3% ee). This methodology exhibited the potential application in the synthesis of several biological active molecules. Chiral $C_2$-
symmetric bisphospholane ligand \((S,S,S,S\text{-Me-ketalphos})\) and \((R,S,S,R\text{-Me-ketalphos})\) were prepared from readily available \(\text{D-mannitol}\). Their rhodium complexes were isolated and further investigated as catalysts in the asymmetric hydrogenation of various functionalized olefins such as \(\alpha\)-dehydroamino acids, enamides and itaconic acid derivatives with high enantioselectivities. An improved synthetic route is reported for the synthesis of a series of phosphine-oxazoline ligands from commercially available phenyl glycinol. The catalytic potential of these \(P,N\) ligands has been demonstrated in several highly enantioselective metal catalyzed reactions, including Pd-catalyzed allylic substitution and intermolecular Heck reactions in addition to the previously reported Ir-catalyzed asymmetric hydrogenation of unfunctionalized alkenes and \(\alpha,\beta\)-unsaturated esters.
# TABLE OF CONTENTS

LIST OF FIGURES ..................................................................................................... vii

LIST OF TABLES ....................................................................................................... ix

ACKNOWLEDGEMENTS .............................................................................................. x

Chapter 1  Triazole-Based Monophosphine Ligands for Palladium-Catalyzed Coupling Reactions of Aryl Chlorides................................................................... 1

1.1 Introduction and Background ........................................................................ 1
  1.1.1 Palladium-Catalyzed Amination Reactions............................................. 3
  1.1.2 Palladium-Catalyzed Suzuki-Miyaura Coupling Reactions................. 9
1.2 Results and Discussion ................................................................................... 12
  1.2.1 Ligand Design and Synthesis ............................................................... 12
  1.2.2 Pd-Catalyzed Amination Reactions...................................................... 15
  1.2.3 Pd-Catalyzed Suzuki-Miyaura Coupling Reactions............................. 19
1.3 Conclusion ...................................................................................................... 28

Experimental Section ............................................................................................ 29

References and Notes ........................................................................................... 47

Chapter 2  Development of a New Class of C1-Symmetric Bisphosphine Ligands for Rhodium-Catalyzed Asymmetric Hydrogenation........................................... 53

2.1 Introduction and Background ........................................................................ 53

2.2 Results and Discussion ................................................................................... 61
  2.2.1 Ligand Synthesis .................................................................................. 61
  2.2.2 Rh-Catalyzed Asymmetric Hydrogenation .......................................... 65
    2.2.2.1 Asymmetric Hydrogenation of Dehydroamino Acid Derivatives .......... 65
    2.2.2.2 Asymmetric Hydrogenation of α-Aryl Enamides.............................. 69
2.3 Conclusion ...................................................................................................... 70

Experimental Section ............................................................................................ 71

References and Notes ........................................................................................... 83

Chapter 3  Efficient Rhodium-Catalyzed Asymmetric Hydrogenation for the Synthesis of a New Class of N-Aryl β-Amino Acid Derivatives ................................. 87

3.1 Introduction and Background ........................................................................ 87

3.2 Results and Discussion ................................................................................... 91
  3.2.1 Substrate Preparation ........................................................................... 91
  3.2.2 Asymmetric Hydrogenation of N-Aryl β-Enamino Esters.......... 92
3.3 Conclusion ...................................................................................................... 97
### Chapter 4  Chiral Bisphospholane Ligands (Me-Ketalphos): Synthesis of their Rh(I) Complexes and Applications in Asymmetric Hydrogenation

<table>
<thead>
<tr>
<th>Section</th>
<th>Pages</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.1 Introduction and Background</td>
<td>111</td>
</tr>
<tr>
<td>4.2 Results and Discussion</td>
<td>114</td>
</tr>
<tr>
<td>4.2.1 Synthesis of Chiral Bisphospholane Ligands 1 and 2</td>
<td>114</td>
</tr>
<tr>
<td>4.2.2 Preparation of Rh-Me-KetalPhos Complex</td>
<td>115</td>
</tr>
<tr>
<td>4.2.3 Rh-Catalyzed Asymmetric Hydrogenation</td>
<td>116</td>
</tr>
<tr>
<td>4.3 Conclusion</td>
<td>123</td>
</tr>
</tbody>
</table>

### Chapter 5  Improved Synthesis of a Class of Phosphine-Oxazoline Ligands for Palladium Catalyzed Reactions

<table>
<thead>
<tr>
<th>Section</th>
<th>Pages</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.1 Introduction and Background</td>
<td>130</td>
</tr>
<tr>
<td>5.2 Results and Discussion</td>
<td>132</td>
</tr>
<tr>
<td>5.2.1 Synthesis of P, N Ligands 9</td>
<td>132</td>
</tr>
<tr>
<td>5.2.2 Pd-Catalyzed Asymmetric Allylic Alkylation Reactions</td>
<td>136</td>
</tr>
<tr>
<td>5.2.3 Pd-Catalyzed Asymmetric Intermolecular Heck Reaction</td>
<td>143</td>
</tr>
<tr>
<td>5.3 Conclusion</td>
<td>149</td>
</tr>
</tbody>
</table>

---

Experimental Section .............................................................. 97
References and Notes ................................................................. 108

Experimental Section .............................................................. 123
References and Notes ................................................................. 127
LIST OF FIGURES

Figure 1-1: General Mechanism for Transition Metal Catalyzed Cross-coupling Reactions............................................................................................................................... 2

Figure 1-2: Pd-Catalyzed C-X Coupling Reactions............................................................................................................................... 3

Figure 1-3: Some Representative Ligands for the Pd-Catalyzed Amination Reactions............................................................................................................................... 4

Figure 1-4: Catalytic Cycle for Pd-Catalyzed Amination Reaction ........................................ 5

Figure 1-5: Some Representative Ligands for Pd-Catalyzed Suzuki-Miyaura Reactions............................................................................................................................... 10

Figure 1-6: MM2 Calculations of Pd/16i Complex Based on the CAChe Program.... 28

Figure 2-1: First Generation Ligands (1970 - Present): Diaryl Alkyl Phosphines ...... 54

Figure 2-2: “Unsaturated Pathway” of Rh-Catalyzed Asymmetric Hydrogenation.... 55

Figure 2-3: Second Generation Ligands (1990 - Present): Dialkyl Aryl Phosphines.. 56

Figure 2-4: Third Generation Ligands (1998 - Present): P-Chiral Trialkyl Phosphines ............................................................................................................................... 57

Figure 2-5: “Dihydride Pathway” of Rh-Catalyzed Asymmetric Hydrogenation........ 58

Figure 2-6: TrichickenfootPhos and its Application in Asymmetric Hydrogenation.. 60

Figure 3-1: Chiral Phosphate Ligands used in Rh-Catalyzed Asymmetric Hydrogenation of β-(Acylamino)acrylates................................................................. 88

Figure 3-2: Synthesis of Substrates...................................................................................... 91

Figure 3-3: Ligands Screened in Asymmetric Hydrogenation........................................ 92

Figure 4-1: Examples of Chiral Bisphospholane Ligands ............................................... 112

Figure 4-2: Modified DuPhos Type Ligands: Me-KetalPhos........................................... 113

Figure 4-3: Rationalization of the Origin of Enantioselectivity .................................... 122

Figure 5-1: Some Examples of P, N Ligands ................................................................. 131

Figure 5-2: Catalytic Cycle for Pd-Catalyzed AAA Reactions........................................ 137
Figure 5-3: AAA Reaction via Symmetrically Substituted Allyl Systems.................137

Figure 5-4: a Cache Model of Pd/9a (H atoms have been omitted for clarity) ........141

Figure 5-5: General Mechanism of Pd-Catalyzed Heck Reaction............................144

Figure 5-6: Proposed Origin of Enantioselection in Pd-Catalyzed Heck Reaction.....149
LIST OF TABLES

Table 1-1: Screening of Ligands and Reaction Conditions .......................................... 16
Table 1-2: Pd/ClickPhos Catalyzed Amination of Aryl Chloride with Various Amines ................................................................................................................................. 18
Table 1-3: Screening of Ligands and Reaction Conditions ........................................... 21
Table 1-4: Pd-Catalyzed Suzuki-Miyaura Coupling of Aryl Chlorides ..................... 23
Table 1-5: Screening of Ligands and Reaction Conditions .......................................... 24
Table 1-6: Pd-Catalyzed Suzuki-Miyaura Coupling of Hindered Aryl Chlorides ...... 26
Table 2-1: Different P=O Bond Reduction Conditions ............................................... 62
Table 2-2: Screening of Solvent for Asymmetric Hydrogenation of 13a ...................... 66
Table 2-3: Asymmetric Hydrogenation of Several α-Dehydroamino Acid Derivatives ................................................................................................................................. 67
Table 2-4: Asymmetric Hydrogenation of Several β-Dehydroamino Acid Derivatives ................................................................................................................................. 69
Table 2-5: Asymmetric Hydrogenation of α-Aryl Enamides ...................................... 70
Table 3-1: Asymmetric Hydrogenation of Substrate 1a .............................................. 93
Table 3-2: Asymmetric Hydrogenation of Substrates 1a-1i, 2a-2e ............................. 95
Table 4-1: Rh-Catalyzed Asymmetric Hydrogenation of an Enamide 11a ................. 117
Table 4-2: Asymmetric Hydrogenation of Enamides by 9 and 10 ......................... 118
Table 4-3: Asymmetric Hydrogenation of α-Dehydroamino Acid Derivates by 9 and 10 ......................................................................................................................... 120
Table 4-4: Asymmetric Hydrogenation of Itaconic Acid Derivatives by 9 and 10 .... 121
Table 5-1: Pd-Catalyzed Asymmetric Allylic Alkylation .......................................... 139
Table 5-2: Pd-Catalyzed Asymmetric Intermolecular Heck Reaction ...................... 148
ACKNOWLEDGEMENTS

I sincerely thank Professor Xumu Zhang for his guidance, encouragement, and inspiration throughout my graduate career. I would also like to thank my committee members: Dr. Steven M. Weinreb, Dr. Blake R. Peterson and Dr. Qing Wang for their time and valuable discussions. I want to acknowledge the past and present Zhang group members as well, for providing a pleasant and friendly working environment. In particular, I am very grateful to Dr. Duan Liu, Dr. WenZhong Gao, Dr. Chungjiang Wang, Miss Weiran Yang and Miss Lea M. Kapes for their collaborations in my research. I would also like to thank Dr. Shulin Wu, Dr. Aiwen Lei, Dr. Minsheng He, Dr. Weimin Wang, Dr. Le Zhou, Dr. Yongjun Yan and Xianfeng Sun for their generous help and suggestions. Support and understanding from my parents in the past five years has always been a great encouragement for my life and study at Penn State. Last but not least, I want to give my deepest appreciation to Zachary M. Biddle. My research would not have been completed without his love, help, and inspiration. I dedicate this thesis to all my family and friends.
Chapter 1

Triazole-Based Monophosphine Ligands for Palladium-Catalyzed Coupling
Reactions of Aryl Chlorides

1.1 Introduction and Background

Transition metal catalyzed cross-coupling reactions to form C-C, C-N, C-O and C-S bonds are among the most powerful organometallic transformations in organic chemistry. In the past few decades, there has been remarkable progress in the cross-coupling reaction of organometallic reagents containing B, Mg, Li, Sn, Al, Zn with unsaturated electrophiles containing alkenyl, aryl, allyl and alkynyl groups. The general catalytic cycle involves an oxidative addition of the organic electrophile to a coordinatively unsaturated metal complex, followed by transmetallation from the nucleophile to the intermediate species formed in the first step. Reductive elimination affords the coupling products with regeneration of the catalyst (Figure 1-1)
Palladium is one of the most commonly used transition metal catalysts due to its low toxicity and ease of handling. Pd-catalyzed cross-coupling reactions, Heck reactions, Sonogashira reactions and Buchwald-Hartwig amination reactions have been extensively used in the synthesis of natural products and drug molecules (Figure 1-2). It has been recognized that structural and conformational information imparted through metal-bound ligands has a significant impact on the reactivity and stereochemical outcomes of these processes. Designing ligands that can activate the transition metal, stabilize the intermediates in each elemental step, and also direct selectivity for the desired transformations, is crucial for solving the challenging problems in this area.

Figure 1-1: General Mechanism for Transition Metal Catalyzed Cross-coupling Reactions
1.1.1 Palladium-Catalyzed Amination Reactions

Aromatic amines are of fundamental interest in the fine chemical industry. They are important building blocks for pharmaceuticals, agrochemicals and new materials. Many synthetic methods for the construction of an aryl-nitrogen bond have been reported, but in general these methods have suffered from harsh reaction conditions and were only applicable to a limited range of substrates. Pd-catalyzed amination of aryl halides is a principle method for the synthesis of aniline derivatives. Employing readily available aryl chlorides in this transformation has been a recent focus. Since the initial
findings reported by Kosugi, numerous ligands have been developed for this type of transformation (Figure 1-3).

Initially, \textit{in situ} generated aminostannanes were used in the coupling reaction with aryl bromides catalyzed by Pd/P(o-tolyl)$_3$ (Scheme 1-1). The monophosphine employed in this reaction is usually considered as the first generation ligand for Pd-catalyzed amination reactions. The high reactivity/instability of aminostannanes limited the further application of this method.

Figure 1-3: Some Representative Ligands for the Pd-Catalyzed Amination Reactions

Initially, \textit{in situ} generated aminostannanes were used in the coupling reaction with aryl bromides catalyzed by Pd/P(o-tolyl)$_3$ (Scheme 1-1). The monophosphine employed in this reaction is usually considered as the first generation ligand for Pd-catalyzed amination reactions. The high reactivity/instability of aminostannanes limited the further application of this method.
Scheme 1-1: The First Example of Pd-Catalyzed Amination Reactions

\[
\begin{align*}
\text{Bu}_3\text{Sn}-\text{N} & \quad \text{Br} \\
R_1 & \quad \text{R}_2 \\
+ & \quad + \\
\frac{[\text{L}_2\text{PdCl}_2]}{\text{L} = \text{P(o-tolyl)}_3} & \quad \rightarrow \\
\text{NR}_1\text{R}_2 & \quad + \text{Bu}_3\text{SnBr}
\end{align*}
\]

Starting in the mid 1990’s, Buchwald and Hartwig developed more elegant approaches to Pd-catalyzed amination that allowed the use of simple secondary amines under basic conditions instead of aminostannanes (Scheme 1-2).\(^7\) Utilizing this improved method, secondary amines could be readily coupled with aryl bromides in good to excellent yields. However, when primary amines were applied in this reaction, large amounts of β-hydride elimination side products were formed along with very low yields of the desired products, which limited the applicability of this method.

Scheme 1-2: Initial Tin-Free Amination of Aryl Halides

\[
\begin{align*}
\text{Br} & \quad \text{NR}_1\text{R}_2 \\
\text{R} & \quad + \\
[\text{L}_2\text{PdCl}_2] & \quad \text{base = NaO}^\text{tBu} \text{ or LiN(SiMe}_3)_2
\end{align*}
\]

Figure 1-4: Catalytic Cycle for Pd-Catalyzed Amination Reaction
To circumvent these limitations, the use of chelating bidentate phosphine ligands was exploited (known as the second generation ligands). A general mechanism for Pd-catalyzed amination reactions was proposed (Figure 1-4). The reaction is initiated by the oxidative addition of an aryl halide to the Pd(0) complex that is ligated by phosphine ligands, which is likely the rate-determining step. The resulting arylpalladium halide reacts with amines to form an amino complex by transmetallation. A fast reductive elimination affords the aryl amine as final product. The major side reaction is the competing β-hydride elimination which generates large amount of arene side products. By using bidentate ligands such as BINAP and DPPF instead of the original monophosphine ligand P(ο-tolyl)₃, the yields of the desired products were greatly improved. The effectiveness of the ligands is believed to be due to a combination of steric and electronic properties that promote the oxidative addition, Pd-N bond formation and reductive elimination. Extensive mechanistic studies have been reported by Hartwig and coworkers. In general, increasing the electron density at the metal center by employing chelating alkyl, rather than aryl phosphine ligands may accelerate reaction rates. The reductive elimination also proceeds from a three or four-coordinate intermediate. Increasing the size of the phosphine ligand accelerates this step. By using sterically hindered and electron-rich phosphine ligands, both the oxidative addition and reductive elimination steps can be accelerated.

Among all aryl halides, aryl chlorides are the most attractive ones for synthetic applications on large scales, as they are inexpensive and readily available in large quantities. However, the much lower reactivity of aryl chlorides due to their reluctance to undergo oxidative addition to Pd(0) has prevented their wide utilization. Regarding
catalyst development, P(o-tolyl)$_3$ gave poor results for the reaction of primary amines and aryl halides, yielding large amount of β-hydride elimination products. Bidentate bisphosphine ligands like BINAP$^7$d, 9a DPPF and D'BPF$^{11}$ were introduced as the second ligand generation and their Pd complexes have been shown to be very efficient with primary amines (Scheme 1-3). Nevertheless, these ligands did not give satisfactory results for the coupling reaction with aryl chlorides.

Scheme 1-3: Second Generation Ligands

A class of bulky, electron rich monophosphine ligands was developed by Buchwald in the late 1990’s.$^{12}$ Ligand 3a and 3b were reported to be excellent for C-C,$^{12b,c}$ C-N$^{12b,d}$ and C-O$^{12e}$ bond forming reactions. However, the scope of room-temperature amination reactions was somewhat limited. For unactivated aryl chlorides, the yields were low and reaction times were much longer compared to activated aryl chlorides. Owing to the use of the strong base NaO'Bu, functional group tolerance was also limited. At elevated temperatures, the scope of the amination was considerably broader. In 2003, a steric bulky monophosphine 4 (XPhos) was also reported by Buchwald for the Pd-catalyzed amination of aryl tosylates and the first amidation reaction of aryl sulonates.$^{13}$
More recently, Beller and coworkers reported the use of ligand 5 for the coupling of sterically hindered amines with aryl chlorides.\textsuperscript{14} In 2004, Beller also reported a facile synthesis of a group of \textit{N}-phenylindole-based phosphine ligands 6.\textsuperscript{15} Most of these ligands led to efficient catalysts for the Pd-catalyzed room temperature amination of activated aryl chlorides. Remarkably high yields were obtained (up to 96\%) under mild reaction conditions (rt to 60 °C). On the other hand, excellent catalyst activity were also observed (TON = 8000, TOF = 14000 h\textsuperscript{-1}) by increasing the ligand/metal ratio to 50:1. Later, a series of \textit{N}-aryl-2-(dialkylphosphino)imidazoles ligands 7 was reported by Beller using a similar synthetic method as that used for ligands 6.\textsuperscript{16} All of the prepared ligands have shown good to excellent catalyst performance in both amination and Suzuki coupling reactions. These sterically hindered and electron-rich monophosphines can be termed as the third ligand generation for Pd-catalyzed coupling reactions.

More recently, Hartwig employed Josiphos (8) in the Pd catalyzed amination of heteroaryl chlorides with different functionalized primary amines.\textsuperscript{17} Exceptionally low catalyst loading (as low as 0.005 mol\%) was utilized without diminishing the product yields. Additionally, for certain chloropyridine substrates, the TON can be as high as 86,000. This catalytic efficiency is about two orders of magnitude higher than most commonly reported catalytic systems employed in the amination of chloropyridine. Apart from phosphine ligands, the utilization of \textit{N}-heterocyclic carbene ligand 9 as a catalyst for amination reactions was reported by Nolan.\textsuperscript{18} A remarkable aspect is the tolerance of these reactions to both air and moisture as the experiments could be performed on the benchtop in reagent grade solvent (Scheme 1-4).
Scheme 1-4:

\[
\begin{align*}
&\text{Cl} \quad + \quad \text{RNH}_2 \quad \xrightarrow{0.001-1 \text{ mol}\% \, \text{Pd(OAc)}_2} \quad \xrightarrow{0.001-1 \text{ mol}\% \, \text{8}} \quad \text{NHR} \\
&\quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \text{NaO^tBu/DME} \\
&\quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \text{25-100} \, \text{ oC} \\
&\quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \text{up to 98\%}
\end{align*}
\]

\[
\begin{align*}
&\text{Cl} \quad + \quad \text{HNR}_2 \quad \xrightarrow{[\text{Pd/9}] = 1 \text{ mol}\%} \quad \text{NR}^1\text{R}^2 \\
&\quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \text{KO^tBu, DME, rt} \\
&\quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \text{up to 99\%} \\
&\quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \text{reaction time as short as 20 min}
\end{align*}
\]

1.1.2 Palladium-Catalyzed Suzuki-Miyaura Coupling Reactions

Among palladium-catalyzed cross-coupling reactions, the Suzuki-Miyaura coupling reaction of aryl halides/triflates with aryl boronic acids is one of the most attractive methods for the preparation of biaryl compounds.\textsuperscript{19} Several factors contribute to the popularity of this reaction, such as the wide functional group tolerance, the availability of a large number of commercial available boronic acids as well as their stability and non-toxic nature.\textsuperscript{19} In the early years of development, most reports involved the use of aryl bromides, aryl iodides, heteroaryl chlorides and electron-deficient aryl chlorides (Scheme 1-5).\textsuperscript{20} A very wide range of Pd(0) catalysts or precursors can be used for Suzuki-coupling reactions. Pd(PPh\textsubscript{3})\textsubscript{4} is the most commonly used catalyst. PdCl\textsubscript{2}(PPh\textsubscript{3})\textsubscript{2} and Pd(OAc)\textsubscript{2}/PPh\textsubscript{3} are also efficient as they are readily reduced to active Pd(0) complexes. Prior to 1998, there was no report of an effective catalyst system for palladium-catalyzed Suzuki-Miyaura reactions of electron-neutral or electron-rich aryl chlorides.
Scheme 1-5: Some Examples of Pd-Catalyzed Suzuki Reaction of Activated Aryl Chlorides

Recent progress with this reaction has focused on the use of unactivated aryl chlorides as coupling partners in view of their low cost and availability. A number of reports have shown that Pd complexes derived from sterically hindered and electron-rich phosphines are effective catalysts for this transformation (Figure 1-5).

Figure 1-5: Some Representative Ligands for Pd-Catalyzed Suzuki-Miyaura Reactions
Some notable examples include the use of bulky trialkylphosphines (i.e. P^tBu_3) by Fu,\textsuperscript{22} dialkyl-biphenylphosphines 3 and 11 by Buchwald,\textsuperscript{12a-d, 23} and dialkyl-heteroaromatic phosphines 12 by Beller.\textsuperscript{16, 24} Using sterically hindered N-heterocyclic carbenes (NHCs, i.e. 9) as ligands by Herrmann et al.,\textsuperscript{25} and using palladacycles (i.e. 13, 14 and 9) as the precatalysts by Bedford et al. and Nolan et al.,\textsuperscript{26} also led to efficient catalytic systems for the coupling of aryl chlorides (Scheme 1-6). Recently, microwave irradiation was found to be capable of activating aryl chlorides for Suzuki-Miyaura couplings as well.\textsuperscript{27}

Scheme 1-6: Examples of Suzuki-Miyaura Reactions of Unactivated Aryl Chlorides

\[
\begin{align*}
\text{R}^1 \text{Cl} + (\text{HO})_2\text{B} & \quad \xrightarrow{1.5\% \text{[Pd}_2(\text{dba})_3]} \quad 3.6\% \text{P}^t\text{Bu}_3 \\
\text{R}^1 = 4-\text{COMe, Me, OMe} & \quad \text{R}^2 = 4-\text{CF}_3, \text{H, OMe} \quad \xrightarrow{1.2 \text{ eq. Cs}_2\text{CO}_3 \text{ dioxane, 80-90 } ^\circ\text{C}} \quad \text{82-92}\% \\
\text{R} = 4-\text{COMe, 2-Me, OMe} & \quad \xrightarrow{\text{catalyst 13}} \quad \text{C}_2\text{CO}_3 \text{ dioxane, 100 } ^\circ\text{C} \quad \text{74-100}\% 
\end{align*}
\]

In this chapter, the synthetic background for the development of new monophosphine ligands will be introduced. The application of these ligands in the Pd catalyzed amination and Suzuki coupling reactions will be discussed in detail. Finally, a CaChe model of a Pd/ligand complex based on MM2 calculations will be provided to rationalize the superior catalytic reactivity of this ligand.
1.2 Results and Discussion

1.2.1 Ligand Design and Synthesis

The rapid development of the fine chemical and pharmaceutical industry has encouraged the introduction of economically attractive and powerful ligands for palladium catalyzed coupling reactions. As is well known, there is no universally effective ligand. Most of the high yielding ligands for coupling reactions are highly substrate-dependent. It would be desirable to design ligands with modular structures for various types of substrates. Recently, Sharpless and coworkers have reported elegant methodology for the formation of 1,4 and 1,5-disubstituted triazole compounds, which they termed “click chemistry”. Properties such as modularity, wide reaction scope, mild reaction conditions, high yields and regioselectivity, are the key criteria of click chemistry.

Click chemistry ideas are beautifully represented in hetero-cycloaddition reactions, most notably 1,3-dipolar cycloadditions. Huisgen 1,3-cycloaddition of azides and alkynes is a classic method for the formation of 1,2,3-triazoles. The original synthetic method for the transformation required elevated temperature and usually resulted in a mixture of 1,4-and 1,5-regioisomers. Due to the unique structure and chemical properties of triazole compound, it may have useful application in organic and medicinal chemistry. However, little attention has been paid to applications of this reaction, most likely due to safety concerns associated with use of azides.
A copper(I)-catalyzed regioselective Huisgen cycloaddition was recently reported by Rostovtsev, Sharpless et al. (Scheme 1-7). Using an *in situ* prepared Cu(I) catalyst, the reaction was complete in 8 h at room temperature with a high yield (91%) of 1,4-disubstituted product and complete regioselectivity.

Scheme 1-7:

![Reaction Scheme](image)

On the basis of earlier published results, a new synthesis of 1,5-disubstituted triazoles was reported recently. The scope of this reaction was first investigated by Akimova et al. in the late 1960s but no further use of this one-step reaction was reported, likely due to the poor yields of the triazole products. A bromomagnesium acetylide was generated *in situ* by the reaction of a terminal alkyne with a Grignard reagent. By addition of these bromomagnesium acetylides to azides, a wide array of triazoles was obtained in improved yields. Additionally, the intermediates of this reaction can be quenched with various electrophiles to form 1,4,5-trisubstituted triazoles. A possible mechanism for this reaction has been proposed (Scheme 1-8). Nucleophilic attack of the acetylide on the terminal nitrogen atom of the azide, followed by ring closure, affords the 4-metalotriazole intermediate. After hydrolysis, preferentially 1,5-disubstituted triazoles are obtained.
Following the general procedure reported by Sharpless, a straightforward two-step synthesis of ClickPhos ligands has been developed (Scheme 1-9). 1,5-Disubstituted triazoles $15a$-$15e$ were obtained in good yields from phenyl azide and various aryl acetylenes, which can be easily prepared from Corey-Fuchs reaction of the corresponding aldehydes. Treatment of $15a$-$15e$ with LDA, followed by addition of various chlorophosphines, furnished ligands $16a$-$j$ in good to excellent yields.

Scheme 1-9: Synthesis of ClickPhos $16a$-$j$

$16a$ Ar = R = Ph 90%
$16b$ Ar = Ph, R = Cy 93%
$16c$ Ar = Ph, R = $^t$Bu 91%
$16d$ Ar = 1-Np, R = Cy 81%
$16e$ Ar = 1-Np, R = $^t$Bu 75%
$16f$ Ar = 2-MeO-Ph, R = Cy 64%
$16g$ Ar = 2-MeO-Ph, R = $^t$Bu 76%
$16h$ Ar = 2-NMe$_2$-Ph, R = $^t$Bu 69%
$16i$ Ar = 2,6-dimethoxy-Ph, R = $^t$Bu 79%
$16j$ Ar = 2,6-dimethoxy-Ph, R = Cy 76%
1.2.2 Pd-Catalyzed Amination Reactions

To evaluate the effectiveness of ClickPhos ligands in the Pd-catalyzed amination of unactivated aryl chlorides, we first tested the reaction between 4-chlorotoluene (17a) and aniline (18a) with ligand 16c (Table 1-1, entries 1-6). The reactions were performed with 0.5 to 1 mol% of Pd(OAc)$_2$ or Pd(dba)$_2$. Pd(dba)$_2$ afforded a slightly higher yield than Pd(OAc)$_2$ (Table 1-1, entries 1-3). Different bases have also been tested, and both KO'Bu and NaO'Bu gave similar results. When the reaction temperature was increased from 80 °C to 110 °C, higher yields were obtained. In general, ligands bearing di-tert-butylphosphino substituent are more efficient than those having di-cyclohexylphosphino groups. Catalysts generated from ligands 16b, 16d, 16e, 16h and 16i provided comparable results to 16c, while 16f and 16j gave slightly lower yields (Table 1-1, entries 7-10, 12-14). ClickPhos 16g was found to be the ligand of choice, giving the highest yield of product 19a (95%, Table 1-1, entry 11). These results demonstrated that delicate tuning of the electronic and steric properties of the ligands by varying substituent groups on the triazole ring can enhance the reaction yield.$^{15,17}$
On the basis of the optimized reaction conditions, the coupling reactions between several aryl chlorides and a variety of primary and secondary amines were carried out to explore the substrate scope of the Pd(dba)$_2$/16g catalytic system (Table 1-2). In most cases, the corresponding anilines were obtained in good to excellent yields (>90%) with
a low catalyst loading (0.5 mol% Pd). For electron-rich amine 20b, a higher yield was obtained when a stronger base (KOtBu) was used instead of NaOtBu (Table 1-2, entry 2). In the case of an aliphatic primary amine (Table 1-2, entry 8), a large excess of n-butylamine (5 equivalents) was used to suppress formation of disubstituted products. Ortho-substituents on the aryl chlorides are tolerated as well, leading to the corresponding hindered coupled products in high yields (Table 1-2, entries 9-12). These results demonstrate the broad substrate scope and high catalytic efficiency of the Pd(dba)₂/16g system for the amination reactions of aryl chlorides, which are comparable or better than those reported to date with other catalytic systems.15, 17
Table 1-2: Pd/ClickPhos-Catalyzed Amination of Aryl Chloride with Various Amines

<table>
<thead>
<tr>
<th>entry&lt;sup&gt;a&lt;/sup&gt;</th>
<th>aryl chloride</th>
<th>amine</th>
<th>product</th>
<th>yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me-Cl 17a</td>
<td>18a</td>
<td>19a</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>Me-Cl 17a</td>
<td>18b</td>
<td>19b</td>
<td>93&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>Me-Cl 17a</td>
<td>18c</td>
<td>19c</td>
<td>94</td>
</tr>
<tr>
<td>4</td>
<td>Me-Cl 17a</td>
<td>18d</td>
<td>19d</td>
<td>98</td>
</tr>
<tr>
<td>5</td>
<td>Me-Cl 17a</td>
<td>18e</td>
<td>19e</td>
<td>97</td>
</tr>
<tr>
<td>6</td>
<td>Me-Cl 17a</td>
<td>18f</td>
<td>19f</td>
<td>88</td>
</tr>
<tr>
<td>7</td>
<td>Me-Cl 17a</td>
<td>18g</td>
<td>19g</td>
<td>78</td>
</tr>
<tr>
<td>8</td>
<td>Me-Cl 17a</td>
<td>18h</td>
<td>19h</td>
<td>89&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> 1 mmol of aryl chloride 17, 1.2 mmol of arylamine 18, 1.2 mmol of NaO<sub>t</sub>Bu, 0.5 mol% of Pd(dba)<sub>2</sub>, 1 mol% of ligand 16g, 3 mL of toluene, 20 h, 110 °C. <sup>b</sup> Isolated yield. Purity was confirmed by <sup>1</sup>H NMR. <sup>c</sup> KO<sub>t</sub>Bu was used instead of NaO<sub>t</sub>Bu. <sup>d</sup> 5 equiv. of amine was used.
The high activity of the Pd/ClickPhos catalysts in amination reactions led us to further explore their applications in Suzuki-Miyaura coupling reactions of aryl chlorides. The reaction between 4-chlorotoluene (17a) and phenylboronic acid (20a) was first tested with ligands 16a-h (Table 1-3, entries 1-8). The reactions were performed in the presence of the catalysts derived from 1 mol% of Pd(dba)$_2$ and 2 mol% of ligands. While very low yield (<5%) of the coupling product was observed with diphenyl phosphine ligand 16a, good to excellent yields were achieved with dialkyl phosphine ligands 16b.
and 16c (70% and 94%, respectively). These results are consistent with the general trend of the ligand efficiency observed in coupling reactions with other structurally related ligand sets. In general, sterically hindered and electron-rich ligands are more efficient for coupling reactions. Catalysts generated from ligands 16e and 16g, having a di-tert-butylphosphino substituent, also provided the coupling product in comparable yields to 16c (Table 1-3, entries 5 and 7). Ligand 16d afforded similar results to its analogue 16e, while 16f and 16h gave much lower yields (Table 1-3, entries 4, 6, 8). Using the best ligand 16c, a variety of bases, such as K3PO4, KF and CsF, were examined. K3PO4 was found to be the base of choice for the Pd/16c catalytic system (Table 1-3, entries 3, 9 and 10).
With the optimized reaction conditions, the coupling reactions between a range of aryl chlorides and several aryl boronic acids were carried out to explore the general effectiveness of the Pd/16c catalytic system (Table 1-4). Excellent yields of biaryl products were obtained with 0.1 mol% of the catalyst in the reactions between various electron-deficient aryl chlorides and phenylboronic acid (Table 1-4, entries 5-12). Notably, a heteroaromatic chloride 17k coupled with phenylboronic acid (20a) providing
product 21l in nearly quantitative yield (Table 1-4, entry 13). For more challenging electronically unactivated and deactivated aryl chlorides, the corresponding biaryl products were obtained in good to excellent yields (Table 1-4, entries 1-4). Ortho-substituents on the aryl chlorides can be tolerated as well, leading to the corresponding hindered coupled products in high yields (Table 1-4, entries 2, 3, 10-12). Reactions using aryl boronic acid 20b were also performed and the yields were comparable to those of 20a (Table 1-4, entries 12, 14). Furthermore, when applying very low catalyst loading (0.01 mol% of catalyst), aryl chloride 17d also coupled efficiently with phenylboronic acid (20a), giving the product 21d in 93% yield (Table 1-4, entry 6, 9,300 TON).
While excellent results have been achieved in the coupling of a wide range of aryl chlorides and several boronic acids, coupling between ortho-substituted aryl chlorides and ortho-substituted boronic acids, forming highly hindered biaryls, are considerably
more challenging reactions. This is due to the steric hindrance of these structures, which prevents an effective oxidative addition of aryl chlorides to the palladium center. Recently, Buchwald reported a highly active ligand 11 containing a 2,6-dimethoxybenzene moiety for this type of reaction, which prompted us to modify ClickPhos for Suzuki-Miyaura coupling of more hindered substrates.

Table 1-5: Screening of Ligands and Reaction Conditions

![Chemical structure](image)

<table>
<thead>
<tr>
<th>entry&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ligand</th>
<th>yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>16c Ar = Ph, R = tBu</td>
<td>89</td>
</tr>
<tr>
<td>2</td>
<td>16d Ar = 1-Np, R = Cy</td>
<td>17</td>
</tr>
<tr>
<td>3</td>
<td>16e Ar = 1-Np, R = tBu</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>16f Ar = 2-MeO-Ph, R = Cy</td>
<td>45</td>
</tr>
<tr>
<td>5</td>
<td>16g Ar = 2-MeO-Ph, R = tBu</td>
<td>94</td>
</tr>
<tr>
<td>6</td>
<td>16h Ar = 2-NMe&lt;sub&gt;2&lt;/sub&gt;-Ph, R = tBu</td>
<td>63</td>
</tr>
<tr>
<td>7</td>
<td>16i Ar = 2,6-dimethoxy-Ph, R = tBu</td>
<td>96</td>
</tr>
<tr>
<td>8</td>
<td>16j Ar = 2,6-dimethoxy-Ph, R = Cy</td>
<td>55</td>
</tr>
</tbody>
</table>

<sup>a</sup> 1 mmol of 17c, 1.5 mmol of 20c, 2 mmol of K<sub>3</sub>PO<sub>4</sub>, 0.1 mol% of Pd(dba)<sub>2</sub>, 0.2 mol% of ligand 16, 3 mL of toluene, 12 h, 80 °C. <sup>b</sup> Isolated yield. Purity was confirmed by <sup>1</sup>H NMR.

Reaction between 2-chloro-p-xylene (17c) and 2-methylphenylboronic acid (20c) was first tested with ligands 16c-j (Table 1-5). In most cases, moderate to good yields of the hindered biaryl product were obtained with the exception that ligand 16d only gave
17% yield (Table 1-5, entry 2). A general trend is that ligands bearing a di-tert-butylphosphino group (16c, 16e, 16g, and 16i) give much higher yields than their dicyclohexylphosphino analogues (16d, 16f, 16h, and 16j). Ligand 16i, which has a 2,6-dimethoxybenzene moiety on the triazole ring, provided the best yield of biaryl 21d (96%, Table 1-5, entry 7).

Using ligands 16c, 16i, and 16j, several hindered disubstituted aryl chlorides were employed in the Pd-catalyzed Suzuki-Miyaura reaction with boronic acids (Table 1-6). For 2-chloro-p-xylene (17c), ligand 16c gave results comparable to that achieved with 16i (Table 1-6, entries 1-4). However, for the more hindered substrate 2-chloro-m-xylene (17m), the coupling with 2-methoxyboronic acid (20d) proceeded to give biaryl 21o in only 12% yield even with 1 mol% of the catalyst derived from 16c. In contrast, using the catalyst derived from 16i, the yield was greatly increased to 72% (Table 1-6, entry 6). Ligand 16j was also effective for this reaction, affording a moderate yield of 57% (Table 1-6, entry 7). The electronic properties of boronic acids also play an important role in this type of reaction. When a less electron-rich boronic acid 20c was used, higher yields were generally achieved (Table 1-6, entry 8-10). Ligand 16i was again found to be the most efficient ligand, giving 90% yield of biaryl 21p (Table 1-6, entry 9). Compared to ligand 16j, the higher catalytic efficiency observed with ligand 16i is likely due to the bulky di-tert-butyl groups that can better facilitate the dissociation of the phosphine ligand from the bisphosphine Pd complex in the catalyst activation step.\textsuperscript{31}
Table 1-6: Pd-Catalyzed Suzuki-Miyaura Coupling of Hindered Aryl Chlorides

<table>
<thead>
<tr>
<th>entry</th>
<th>aryl chloride</th>
<th>boronic acid</th>
<th>ligand</th>
<th>product</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeCl</td>
<td>B(OH)₂</td>
<td>16c</td>
<td>21m</td>
<td>89</td>
</tr>
<tr>
<td>2</td>
<td>MeCl</td>
<td>B(OH)₂</td>
<td>16c</td>
<td>21n</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td>MeCl</td>
<td>B(OH)₂</td>
<td>16i</td>
<td></td>
<td>96</td>
</tr>
<tr>
<td>4</td>
<td>MeCl</td>
<td>B(OH)₂</td>
<td>16i</td>
<td></td>
<td>95</td>
</tr>
<tr>
<td>5</td>
<td>MeCl</td>
<td>B(OH)₂</td>
<td>16c&lt;sup&gt;c&lt;/sup&gt;</td>
<td>21o</td>
<td>12&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>MeCl</td>
<td>B(OH)₂</td>
<td>16i&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td>72&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>7</td>
<td>MeCl</td>
<td>B(OH)₂</td>
<td>16&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td>57&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> 1 mmol of 17, 1.5 mmol of 20, 2 mmol of K₃PO₄, 0.1 mol% of Pd(dba)₂, 0.2 mol% of ligand 16, 3 mL of toluene, 12 h, 80 °C.  
<sup>b</sup> Isolated yield. Purity was confirmed by <sup>1</sup>H NMR.  
<sup>c</sup> 1 mol% of Pd(dba)₂ and 2 mol% of ligand were used.  
<sup>d</sup> The reaction was carried out at 120 °C.
In order to further understand the unique activity of ligand 16i, a CACHe model of Pd/16i complex based on MM2 calculations was obtained (Figure 1-6). The key feature of the complex structure is the orientation of the arene group on the 5-position of the triazole ring. The distance between the palladium and the $sp^2$-carbon on the 2,6-dimethoxybenzene moiety (as indicated by the arrow in Figure 1-6) is around 2.245 Å based on MM2 calculations, which is appreciably shorter than the sum of the van der Waals radii for Pd and C, 3.33 Å (Pd = 1.63 Å, C = 1.70 Å). This points to the likelihood of a metal-arene interaction, which might stabilize the palladium complex in the catalytic cycle and therefore enhance the catalyst reactivity. Similar observations have previously been reported by Buchwald,$^{23c}$ and Fink.$^{32}$
1.3 Conclusion

In conclusion, we have developed a new series of monophosphine ligands 16 (ClickPhos) bearing a triazole heterocycle in the backbone. These ligands are readily accessible and can be easily diversified via efficient 1,3-dipolar cycloadditions of various azides and acetylenes. With the Pd complex derived from ligand 16g, up to 98% yield was achieved in the amination reactions of aryl chlorides. Pd/16c complex proved to be a highly active catalyst for Suzuki-Miyaura coupling of aryl chlorides in excellent yields and TONs. Among the ClickPhos series, ligand 16i, which has a 2,6-dimethoxybenzene moiety on the triazole ring, was particularly effective in the Pd-catalyzed Suzuki-Miyaura coupling to form hindered biaryl compounds (up to 96% yield). A CAChE model for the Pd/16i complex shows that the likelihood of a Pd-arene interaction might be a rationale for its high catalytic reactivity.
Experimental Section

**General Methods.** All reactions and manipulations were performed in a nitrogen-filled glove-box or under nitrogen using standard Schlenk techniques, unless otherwise noted. THF and toluene were dried and distilled from sodium-benzophenone ketyl under nitrogen. Column chromatography was performed using Sorbent silica gel 60 Å (230×450 mesh). $^1$H, $^{13}$C, and $^{31}$P NMR spectral data were recorded on Bruker DPX-300, CDPX-300, AMX-360, and DRX-400 MHz spectrometers. Chemical shifts are reported in ppm upfield to tetramethysilane with the solvent resonance as the internal standard. Mass spectra were recorded on a KRATOS MS 9/50 mass spectrometer for LR-ESI and HR-ESI.

**1,5-Diphenyl-1H-[1,2,3]triazole (15a).** To a solution of EtMgBr in THF (1.0 M, 11.9 mL) was added phenylacetylene (1.3 mL, 11.9 mmol) at rt. The reaction mixture was heated at 50 °C for 15 min. After cooling the mixture to rt, a solution of phenylazide (1.41 g, 11.9 mmol) in THF (4 mL) was added. The resulting solution was stirred at rt for 30 min, and then heated at 50 °C for 1 h before quenching with saturated NH$_4$Cl (10 mL). The layers were separated, and the aqueous layer was extracted with CH$_2$Cl$_2$ (10 mL × 3). The combined organic layers were dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane:EtOAc, 80:20) to afford 15a as a white solid (1.98 g, 75%). $^1$H NMR (CDCl$_3$, 300 MHz) δ 7.86 (s, 1H), 7.44-7.30 (m, 8H), 7.23-7.20 (m, 2H); $^{13}$C NMR (CDCl$_3$, 75 MHz) δ 137.6, 136.5, 133.4, 129.3, 129.2, 128.8, 128.5, 126.7, 125.1.
1-Phenyl-5-(1-naphthyl)-1H-[1,2,3]triazole (15b). To a solution of EtMgBr in THF (3.0 M, 2.5 mL) was added 1-naphthlyne (1.12 g, 7.36 mmol) at rt. The reaction mixture was heated at 50 °C for 15 min. After cooling the mixture to rt, a solution of phenylazide (0.88 g, 7.36 mmol) in THF (4 mL) was added. The resulting solution was stirred at rt for 30 min, and then heated at 50 °C for 1 h before quenching with saturated NH₄Cl (10 mL). The layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (10 mL × 3). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane:EtOAc, 80:20) to afford 15b as a white solid (1.16 g, 58%). ¹H NMR (CDCl₃, 360 MHz) δ 7.98 (s, 1H), 7.94 (t, J = 9.2 Hz, 3H), 7.67 (d, J = 8.3 Hz, 1H), 7.56-7.46 (m, 3H), 7.35-7.24 (m, 6H); ¹³C NMR (CDCl₃, 90 MHz) δ 136.6, 135.7, 135.4, 133.6, 131.7, 130.2, 129.2, 129.0, 128.8, 128.6, 127.2, 126.6, 125.1, 124.8, 124.6, 124.1; HRMS (ESI+) calcd. for C₁₈H₁₄N₃ (MH⁺) 272.1188, found 272.1182.

1-Phenyl-5-(2-methoxyphenyl)-1H-[1,2,3]triazole (15c). To a solution of EtMgBr in THF (3.0 M, 2.3 mL) was added 2-methoxyphenylacetylene (0.92 g, 6.96 mmol) at rt. The reaction mixture was heated at 50 °C for 15 min. After cooling the mixture to rt, a solution of phenylazide (0.83 g, 6.96 mmol) in THF (4 mL) was added. The resulting solution was stirred at rt for 30 min, and then heated at 50 °C for 1 h before quenching with saturated NH₄Cl (10 mL). The layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (10 mL × 3). The combined organic layers were dried
over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane:EtOAc, 80:20) to afford 15c as a white solid (1.45 g, 83%). ¹H NMR (CDCl₃, 300 MHz) δ 7.85 (s, 1H), 7.44-7.33 (m, 6H), 7.01 (t, J = 7.5 Hz, 1H), 6.87 (d, J = 8.3 Hz, 1H) 3.44 (s, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ 156.9, 138.1, 135.1, 134.9, 131.7, 129.4, 129.0, 124.2, 121.2, 116.6, 111.8, 55.3; HRMS (ESI+) calcd. for C₁₅H₁₄N₃O (MH⁺) 252.1137, found 252.1127.

1-Phenyl-5-(2-N,N-dimethylphenyl)-1H-[1,2,3]triazole (15d). To a solution of EtMgBr in THF (3.0 M, 2.3 mL) was added 2-N,N-dimethylphenylacetylene (1.01 g, 6.96 mmol) at rt. The reaction mixture was heated at 50 °C for 15 min. After cooling the mixture to rt, a solution of phenylazide (0.83 g, 6.96 mmol) in THF (4 mL) was added. The resulting solution was stirred at rt for 30 min, and then heated at 50 °C for 1 h before quenching with saturated NH₄Cl (10 mL). The layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (10 mL × 3). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane:EtOAc, 80:20) to afford 15d as a yellow solid (1.12 g, 61%). ¹H NMR (300 MHz, CDCl₃) δ 7.87 (s, 1H), 7.25-7.35 (m, 7H), 7.02-7.05 (m, 1H), 6.88 (d, J = 8.2 Hz, 1H), 2.19 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 151.5, 137.8, 137.1, 133.6, 131.4, 130.6, 128.6, 128.2, 122.7, 119.8, 118.8, 41.9; HRMS (ESI+) calcd. for C₁₆H₁₇N₄ (MH⁺) 265.1453, found 265.1444.

1-Phenyl-5-(2,6-dimethoxy-phenyl)-1H-[1,2,3]triazole (15e). To a solution of EtMgBr in THF (3.0 M, 2.3 mL) was added 2,6-dimethoxyphenylacetylene (0.95 g, 6.96
mmol) at rt. The reaction mixture was heated at 50 °C for 15 min. After cooling the mixture to rt, a solution of phenylazide (0.83 g, 6.96 mmol) in THF (4 mL) was added. The resulting solution was stirred at rt for 30 min, and then heated at 50 °C for 1 h before quenching with saturated NH₄Cl (10 mL). The layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (10 mL × 3). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane:EtOAc, 80:20) to afford 15e as a white solid (1.39 g, 78%). ¹H NMR (300 MHz, CDCl₃) δ 7.76 (s, 1H), 7.27-7.33 (m, 6H), 6.49 (d, J = 8.4 Hz, 2H), 3.51 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 158.0, 137.7, 135.5, 131.5, 130.3, 128.6, 128.3, 123.3, 104.6, 103.7, 55.4; HRMS (ESI+) calcd. for C₁₆H₁₅N₃O₂Na (M + Na⁺) 304.1062, found 304.1063.

4-Di-tert-butylphosphanyl-1,5-diphenyl-1H-[1,2,3]triazole (16c). To a solution of 1,5-diphenyl-1H-[1,2,3]triazole (15a) (0.52 g, 2.35 mmol) in THF (20 mL) was added LDA (2.35 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 h followed by addition of P'TBu₂Cl (0.45 mL, 2.35 mmol). The resulting mixture was slowly warmed to rt and stirred overnight. TLC showed the reaction was essentially complete after 16 h. The solvent was removed under vacuum. A degassed mixture of brine/H₂O (1:1) was added, and the resulting mixture was extracted with degassed ether (15 mL × 3). The combined organic layers were dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel under nitrogen (hexanes:ether, 80:20) to afford 16c as a sticky solid (0.78 g, 91%). ¹H NMR (CD₂Cl₂, 360 MHz) δ 7.41-7.23 (m, 10H), 1.27 (d, J = 12.1 Hz, 18H); ¹³C NMR (CDCl₃, 90 MHz)
δ 145.2 (d, J = 39.0 Hz), 142.2 (d, J = 27.9 Hz), 137.2, 131.1 (d, J = 2.5 Hz), 129.4, 129.3, 129.0, 128.6, 128.5, 125.2, 33.1 (d, J = 17.0 Hz), 30.6 (d, J = 14.4 Hz); $^{31}$P NMR (CD$_2$Cl$_2$, 145 MHz) δ 3.51; HRMS (ESI+) calcd. for C$_{22}$H$_{29}$N$_3$P (MH$^+$) 366.2084, found 366.2099.

**4-Diphenylphosphanyl-1,5-diphenyl-1H-[1,2,3]triazole (16a).** To a solution of 1,5-diphenyl-1H-[1,2,3]triazole (15a) (0.26 g, 1.18 mmol) in THF (20 mL) was added LDA (1.18 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 h followed by addition of PPh$_2$Cl (0.24 mL, 1.24 mmol). The resulting mixture was slowly warmed to rt and stirred overnight. TLC showed the reaction was essentially complete after 12 h. The solvent was removed under vacuum. A degassed mixture of brine/H$_2$O (1:1) was added, and the resulting mixture was extracted with degassed ether (15 mL × 3). The combined organic layers were dried over Na$_2$SO$_4$ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel under nitrogen (hexanes:ether, 80:20) to afford 16a as a sticky solid (0.43 g, 90%). $^1$H NMR (CDCl$_3$, 360 MHz) δ 7.73-7.69 (m, 4H), 7.44-7.36 (m, 14H), 7.26 (d, J = 7.3 Hz, 2H); $^{13}$C NMR (CDCl$_3$, 90 MHz) δ 143.3 (d, J = 39.5 Hz), 141.1 (d, J = 14.2 Hz), 136.40, 136.38 (d, J = 15.4 Hz), 133.8, 133.5, 130.1 (d, J = 3.5 Hz), 129.2, 129.0, 128.8, 128.6, 128.35, 128.28, 128.2, 126.5, 124.8; $^{31}$P NMR (CDCl$_3$, 145 MHz) δ −35.85; HRMS (ESI+) calcd. for C$_{26}$H$_{21}$N$_3$P (MH$^+$) 406.1475, found 406.1473.
**4-Dicyclohexylphosphanyl-1,5-diphenyl-1H-[1,2,3]triazole (16b).** To a solution of 1,5-diphenyl-1H-[1,2,3]triazole (15a) (0.50 g, 2.26 mmol) in THF (20 mL) at 0 °C was added LDA (2.26 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 h followed by addition of PCy₂Cl (0.50 mL, 2.26 mmol). The resulting mixture was slowly warmed to rt and stirred for 4 h. TLC showed the reaction was essentially complete. The organic solution was washed with brine (10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel under nitrogen (hexanes:ether, 80:20) to afford 16b as a white solid (0.88 g, 93%). ^1H NMR (CD₂Cl₂, 360 MHz) δ 7.41-7.23 (m, 10H), 2.28-2.21 (m, 2H), 1.87-1.67 (m, 10H), 1.38-1.09 (m, 10H); ^13C NMR (CDCl₃, 90 MHz) δ 144.7 (d, J = 34.8 Hz), 141.2 (d, J = 24.6 Hz), 137.2, 130.9 (d, J = 2.9 Hz), 129.4, 129.3, 129.1, 128.6, 128.0, 125.3, 33.5 (d, J = 8.4 Hz), 30.8 (d, J = 16.3 Hz), 29.8 (d, J = 7.5 Hz), 27.5 (d, J = 18.5 Hz), 27.4 (d, J = 1.6 Hz), 26.8; ^31P NMR (CD₂Cl₂, 145 MHz) δ −27.76; HRMS (ESI+) calcd. for C₂₆H₃₃N₃P (MH⁺) 418.2419, found 418.2412.

**4-Dicyclohexylphosphanyl-1-phenyl-5-(1-naphthyl)-1H-[1,2,3]triazole (16d).**

To a solution of 1-phenyl-5-(1-naphthyl)-1H-[1,2,3]triazole (15b) (0.54 g, 2.0 mmol) in THF (20 mL) was added LDA (2.0 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 h followed by addition of PCy₂Cl (0.44 mL, 2.0 mmol). The resulting mixture was slowly warmed to rt and stirred overnight. TLC showed the reaction was essentially complete after 16 h. The solvent was removed under vacuum. A degassed mixture of brine/H₂O (1:1) was added, and the resulting mixture was extracted with degassed ether
35 mL × 3). The combined organic layers were dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel under nitrogen (hexanes:ether, 80:20) to afford 16d as a white solid (0.76 g, 81%).

\[ ^1H \text{NMR (300 MHz, CD}_2\text{Cl}_2) \delta 7.93 (dd, J = 8.3, 18.7 Hz, 2H), 7.24-7.53 (m, 10H), 2.36 (t, J = 11.3 Hz, 1H), 2.09 (t, J = 11.2 Hz, 1H), 1.52-1.98 (m, 10H), 0.97-1.48 (m, 10H); \]

\[ ^13C \text{NMR (75 MHz, CD}_2\text{Cl}_2) \delta 143.5 (d, J = 27.4 Hz), 143.2, 143.0, 137.2, 133.7, 132.4, 130.3, 129.3, 128.9, 128.8, 127.1, 126.7, 125.9, 125.5, 125.3, 124.2, 33.6 (d, J = 9.2 Hz), 30.9 (d, J = 16.3 Hz), 30.0 (d, J = 8.8 Hz), 27.4 (d, J = 10.3 Hz), 27.2 (d, J = 3.7 Hz), 26.8; \]

\[ ^31P \text{NMR (145 MHz, CD}_2\text{Cl}_2) \delta -28.31; \]

HRMS (ESI+) calcd. for C₃₀H₃₅N₃P (MH⁺) 468.2569, found 468.2571.

4-Di-tert-butylphosphanyl-1-phenyl-5-(1-naphthyl)-1H-[1,2,3]triazole (16e).

To a solution of 1-phenyl-5-(1-naphthyl)-1H-[1,2,3]triazole (15b) (0.54 g, 2.0 mmol) in THF (20 mL) was added LDA (2.0 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 h followed by addition of P'Bu₂Cl (0.38 mL, 2.0 mmol). The resulting mixture was slowly warmed to rt and stirred overnight. TLC showed the reaction was essentially complete after 16 h. The solvent was removed under vacuum. A degassed mixture of brine/H₂O (1:1) was added, and the resulting mixture was extracted with degassed ether (15 mL × 3). The combined organic layers were dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel under nitrogen (hexanes:ether, 80:20) to afford 16e as a white solid (0.67 g, 75%).

\[ ^1H \text{NMR (CD}_2\text{Cl}_2, 300 MHz) \delta 7.98-7.88 (m, 2H), 7.55-7.21 (m, 10H), 1.34-1.24 (m, 18H); \]
$^{13}$C NMR (CDCl$_3$, 75 MHz) δ 144.1 (d, $J = 14.9$ Hz), 143.7 (d, $J = 28.6$ Hz), 137.3, 133.7, 132.4, 130.6, 130.3, 129.3, 129.0, 128.8, 127.0, 126.6, 126.1, 125.6, 125.3, 124.2, 32.9 (dd, $J = 17.0, 21.7$ Hz), 30.8 (dd, $J = 10.3, 14.3$ Hz); $^{31}$P NMR (CD$_2$Cl$_2$, 145 MHz) δ 3.63; HRMS (ESI+) calcd. for C$_{26}$H$_{31}$N$_3$P (MH$^+$) 416.2256, found 416.2252.

4-Dicyclohexylphosphanyl-1-phenyl-5-(2-methoxyphenyl)-1H-[1,2,3]triazole (16f). To a solution of 1-phenyl-5-(2-methoxyphenyl)-1H-[1,2,3]triazole (15c) (0.504 g, 2.0 mmol) in THF (20 mL) was added LDA (2.0 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 h followed by addition of PCy$_2$Cl (0.44 mL, 2.0 mmol). The resulting mixture was slowly warmed to rt and stirred overnight. TLC showed the reaction was essentially complete after 16 h. The solvent was removed under vacuum. A degassed mixture of brine/H$_2$O (1:1) was added, and the resulting mixture was extracted with degassed ether (15 mL × 3). The combined organic layers were dried over Na$_2$SO$_4$ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel under nitrogen (hexanes:ether, 80:20) to afford 16f as a white solid (0.574 g, 64%). $^1$H NMR (360 MHz, CD$_2$Cl$_2$) δ 7.36-7.42 (m, 6H), 7.30 (dd, $J = 1.3, 7.5$ Hz, 1H), 7.05-7.09 (m, 1H), 6.89 (d, $J = 8.4$ Hz, 1H), 3.47 (s, 3H), 2.10-2.33 (m, 2H), 1.61-2.05 (m, 10H), 0.98-1.52 (m, 10H); $^{13}$C NMR (90 MHz, CD$_2$Cl$_2$) δ 157.2, 141.8 (d, $J = 27.4$ Hz), 141.5 (d, $J = 15.3$ Hz), 137.6, 132.4, 131.1, 128.8, 128.4, 123.8, 120.3, 117.1, 111.1, 55.0, 33.0 (d, $J = 42.4$ Hz), 30.3, 29.4 (d, $J = 30.8$ Hz), 27.2 (d, $J = 19.5$ Hz), 27.1, 26.6; $^{31}$P NMR (145 MHz, CD$_2$Cl$_2$) δ -27.99; HRMS (ESI+) calcd. for C$_{27}$H$_{35}$N$_3$OP (MH$^+$) 448.2518, found 448.2510.
4-Di-tert-butylphosphanyl-1-phenyl-5-(2-methoxyphenyl)-1H-[1,2,3]triazole (16g). To a solution of 1-phenyl-5-(2-methoxyphenyl)-1H-[1,2,3]triazole (15c) (0.504 g, 2.0 mmol) in THF (20 mL) was added LDA (2.0 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 h followed by addition of P\text{t}Bu\text{2}Cl (0.38 mL, 2.0 mmol). The resulting mixture was slowly warmed to rt and stirred overnight. TLC showed the reaction was essentially complete after 16 h. The solvent was removed under vacuum. A degassed mixture of brine/H\textsubscript{2}O (1:1) was added, and the resulting mixture was extracted with degassed ether (15 mL × 3). The combined organic layers were dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel under nitrogen (hexanes:ether, 80:20) to afford 16g as a white solid (0.602 g, 76%). \textsuperscript{1}H NMR (CD\textsubscript{2}Cl\textsubscript{2}, 360 MHz) \(\delta\) 7.47-7.32 (m, 7H), 7.09 (t, \(J = 7.2\) Hz, 1H), 6.90 (d, \(J = 8.2\) Hz, 1H), 3.48 (s, 3H), 1.41 (d, \(J = 11.8\) Hz, 9H), 1.24 (d, \(J = 11.8\) Hz, 9H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 90 MHz) \(\delta\) 157.3, 142.5 (d, \(J = 9.3\) Hz), 142.2 (d, \(J = 24.5\) Hz), 137.6, 132.6 (d, \(J = 2.6\) Hz), 131.1, 128.8, 128.5, 123.9, 120.3, 117.4, 111.0, 54.9, 32.5 (dd, \(J = 10.3, 17.0\) Hz), 30.2 (dd, \(J = 14.1, 44.1\) Hz); \textsuperscript{31}P NMR (CD\textsubscript{2}Cl\textsubscript{2}, 145 MHz) \(\delta\) 3.47; HRMS (ESI+) calcd. for C\textsubscript{23}H\textsubscript{31}N\textsubscript{3}OP (MH\textsuperscript{+}) 396.2205, found 396.2202.

4-Di-tert-butylphosphanyl-1-phenyl-5-(2,N,N-dimethylphenyl)-1H-[1,2,3]-triazole (16h). To a solution of 1-phenyl-5-(2,N,N-dimethylphenyl)-1H-[1,2,3]triazole (15d) (0.53 g, 2.0 mmol) in THF (20 mL) was added LDA (2.0 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 h followed by addition of P\text{t}Bu\text{2}Cl (0.38 mL, 2.0 mmol). The resulting mixture was slowly warmed to rt and stirred overnight. TLC
showed the reaction was essentially complete after 16 h. The solvent was removed under vacuum. A degassed mixture of brine/H2O (1:1) was added, and the resulting mixture was extracted with degassed ether (15 mL × 3). The combined organic layers were dried over Na2SO4 and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel under nitrogen (hexanes:ether, 80:20) to afford 16h as a white solid (0.57 g, 69%). 1H NMR (360 MHz, CD2Cl2) δ 7.53 (d, J = 7.6 Hz, 1H), 7.35-7.40 (m, 4H), 7.26-7.29 (m, 2H), 7.05-7.10 (m, 1H), 6.88 (d, J = 8.2 Hz, 1H), 2.16 (s, 6H), 1.38 (d, J = 11.8 Hz, 9H), 1.30 (d, J = 12.1 Hz, 9H); 13C NMR (90 MHz, CD2Cl2) δ 151.8, 143.9 (d, J = 38.2 Hz), 141.5 (d, J = 28.6 Hz), 138.2, 133.5 (d, J = 5.0 Hz), 130.4, 128.6, 128.1, 122.8, 120.7, 120.1, 118.8, 41.8, 33.1 (dd, J = 17.1, 22.3 Hz), 30.6 (dd, J = 8.7, 14.4 Hz); 31P NMR (145 MHz, CD2Cl2) δ 2.72; HRMS (ESI+) calcd. for C24H34N4P (MH+) 409.2521, found 409.2537.

**4-Di-tert-butylphosphanyl-1-phenyl-5-(2,6-dimethoxyphenyl)-1H-[1,2,3]-triazole (16i).** To a solution of 1-phenyl-5-(2,6-dimethoxyphenyl)-1H-[1,2,3]triazole (15e) (0.562 g, 2.0 mmol) in THF (20 mL) was added LDA (2.0 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 h followed by addition of P’Bu2Cl (0.38 mL, 2.0 mmol). The resulting mixture was slowly warmed to rt and stirred overnight. TLC showed the reaction was essentially complete after 16 h. The solvent was removed under vacuum. A degassed mixture of brine/H2O (1:1) was added, and the resulting mixture was extracted with degassed ether (15 mL × 3). The combined organic layers were dried over Na2SO4 and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel under nitrogen (hexanes:ether, 80:20) to afford 16i as a
white solid (0.673 g, 79%). $^1$H NMR (360 MHz, CD$_2$Cl$_2$) $\delta$ 7.37-7.42 (m, 6H), 6.58 (d, $J$ = 8.4 Hz, 2H), 3.63 (s, 6H), 1.28 (d, $J$ = 12.0 Hz, 18 H); $^{13}$C NMR (90 MHz, CD$_2$Cl$_2$) $\delta$ 158.5, 143.0, 139.5, 137.4, 131.5, 128.7, 128.5, 124.1, 105.7, 103.3, 55.2, 32.3 (d, $J$ = 16.2 Hz), 30.2 (d, $J$ = 14.4 Hz); $^{31}$P NMR (145 MHz, CD$_2$Cl$_2$) $\delta$ 4.73; HRMS (ESI+) calcd. for C$_{24}$H$_{33}$N$_3$O$_2$P (MH$^+$) 426.2310, found 426.2307.

4-Dicyclohexylphosphanyl-1-phenyl-5-(2,6-dimethoxyphenyl)-1H-[1,2,3]-triazole (16j). To a solution of 1-phenyl-5-(2,6-dimethoxyphenyl)-1H-[1,2,3]triazole (15e) (0.562 g, 2.0 mmol) in THF (20 mL) was added LDA (2.0 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 h followed by addition of PCy$_2$Cl (0.44 mL, 2.0 mmol). The resulting mixture was slowly warmed to rt and stirred overnight. TLC showed the reaction was essentially complete after 16 h. The solvent was removed under vacuum. A degassed mixture of brine/H$_2$O (1:1) was added, and the resulting mixture was extracted with degassed ether (15 mL × 3). The combined organic layers were dried over Na$_2$SO$_4$ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel under nitrogen (hexanes:ether, 80:20) to afford 16j as a white solid (0.727 g, 76%). $^1$H NMR (360 MHz, CD$_2$Cl$_2$) $\delta$ 7.38-7.42 (m, 6H), 6.59 (d, $J$ = 8.4 Hz, 2H), 3.65 (s, 6H), 2.16-2.22 (m, 2H), 1.69-1.77 (m, 10H), 1.13-1.39 (m, 10H); $^{13}$C NMR (90 MHz, CD$_2$Cl$_2$) $\delta$ 158.9, 142.6 (d, $J$ = 20.4 Hz), 139.0 (d, $J$ = 40.6 Hz), 137.7, 131.9, 129.1, 128.8, 124.2, 105.9, 103.8, 55.7, 33.2 (d, $J$ = 7.8 Hz), 30.5 (d, $J$ = 16.3 Hz), 29.7 (d, $J$ = 7.9 Hz), 27.5 (d, $J$ = 10.5 Hz), 27.4 (d, $J$ = 6.0 Hz), 26.9; $^{31}$P NMR (145 MHz, CD$_2$Cl$_2$) $\delta$ -27.36; HRMS (ESI+) calcd. for C$_{28}$H$_{37}$N$_3$O$_2$P (MH$^+$) 478.2623, found 478.2599.
General procedure for amination of aryl chlorides. To a Schlenk tube, which was flame-dried under vacuum and backfilled with nitrogen, NaOtBu (1.2 mmol), toluene (3 mL), a stock solution of ligand 16 in toluene (0.01 mmol), a stock solution of Pd(dba)$_2$ (0.005 mmol) in toluene, aryl chloride 17 (1.0 mmol) and amine 18 (1.2 mmol) were subsequently added. The flask was sealed and the reaction mixture was heated at 110 °C with vigorous stirring for 20 h. After cooling the mixture to rt, 15 mL of EtOAc was added and the mixture was washed with 5 mL of brine. The organic layer was dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography on basic Al$_2$O$_3$.

Phenyl-$p$-tolylamine (19a). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.32 (t, $J$ = 7.8 Hz, 2H), 7.17 (d, $J$ = 8.1 Hz, 2H), 7.10-7.06 (m, 4H), 6.97 (t, $J$ = 7.2 Hz, 1H), 5.64 (br s, 1H), 2.39 (s, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 143.9, 140.3, 130.9, 129.8, 129.3, 120.3, 118.9, 116.8, 20.7.

4-Methoxyphenyl-$p$-tolylamine (19b). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.05-7.27 (m, 4H), 6.87-6.90 (m, 4H), 5.43 (br s, 1H), 3.83 (s, 3H), 2.32 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 154.8, 142.4, 136.6, 129.8, 129.3, 121.1, 116.5, 114.6, 55.6, 20.5.

Diphenyl-$p$-tolylamine (19c). $^1$H NMR (360 MHz, CDCl$_3$) $\delta$ 7.33-7.38 (m, 4H), 7.16-7.24 (m, 8H), 7.08-7.13 (m, 2H), 2.46 (s, 3H); $^{13}$C NMR (90 MHz, CDCl$_3$) $\delta$ 148.0, 145.2, 132.6, 129.9, 129.1, 124.9, 123.5, 122.2, 20.8.
Methylphenyl-\(p\)-tolylamine (19d). \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 7.33-7.28 (m, 2H), 7.19 (d, \(J = 8.2\) Hz, 2H), 7.10-7.05 (m, 2H), 7.02-6.98 (m, 2H), 6.97-6.92 (m, 1H), 3.36 (s, 3H), 2.40 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 75 MHz) \(\delta\) 149.3, 146.5, 132.0, 129.9, 129.0, 122.5, 119.7, 118.1, 40.3, 20.7.

4-\(p\)-Tolylmorpholine (19e). \(^1\)H NMR (360 MHz, CDCl\(_3\)) \(\delta\) 7.15 (d, \(J = 8.2\) Hz, 2H), 6.89 (d, \(J = 8.2\) Hz, 2H), 3.91 (t, \(J = 4.6\) Hz, 4H), 3.15 (t, \(J = 4.8\) Hz, 4H), 2.35 (s, 3H); \(^{13}\)C NMR (90 MHz, CDCl\(_3\)) \(\delta\) 149.1, 129.5, 129.3, 115.8, 66.8, 49.7, 20.3.

1-Methyl-4-\(p\)-tolylpiperazine (19f). \(^1\)H NMR (360 MHz, CDCl\(_3\)) \(\delta\) 7.09 (d, \(J = 8.2\) Hz, 2H), 6.87 (d, \(J = 8.2\) Hz, 2H), 3.18 (t, \(J = 4.9\) Hz, 4H), 2.59 (t, \(J = 5.0\) Hz, 4H), 2.36 (s, 3H), 2.29 (s, 3H); \(^{13}\)C NMR (90 MHz, CDCl\(_3\)) \(\delta\) 149.3, 129.7, 129.2, 116.4, 55.2, 49.7, 46.2, 20.5.

Dibenzyl-\(p\)-tolylamine (19g). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.41-7.51 (m, 10H), 7.17 (d, \(J = 8.4\) Hz, 2H), 6.86 (d, \(J = 8.6\) Hz, 2H), 4.78 (s, 4H), 2.43 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 147.8, 139.6, 130.5, 129.4, 127.6, 127.5, 126.5, 113.4, 55.1, 21.0.

Butyl-\(p\)-tolylamine (19h). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.07-7.10 (m, 2H), 6.60-6.65 (m, 2H), 3.46 (br s, 1H), 3.18 (t, \(J = 4.0\) Hz, 2H), 2.34 (s, 3H), 1.65-1.71 (m, 2H), 1.48-1.56 (m, 2H), 1.06 (t, \(J = 7.3\) Hz, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 146.2, 129.6, 126.1, 112.8, 44.0, 31.7, 20.3, 20.2, 13.8.
Phenyl-o-tolylamine (19i). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.30-7.23 (m, 4H), 7.18 (t, $J = 7.5$ Hz, 1H), 7.00-6.92 (m, 4H), 5.38 (br s, 1H), 2.28 (s, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 143.9, 141.1, 130.9, 129.2, 128.3, 126.7, 122.0, 120.4, 118.8, 117.3, 17.8.

Diphenyl-o-tolylamine (19j). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.31-7.39 (m, 8H), 7.14-7.18 (m, 4H), 7.05-7.10 (m, 2H), 2.22 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 147.4, 145.3, 136.4, 131.6, 129.5, 129.0, 127.3, 126.0, 121.5, 121.3, 18.6.

(2, 5-Dimethylphenyl)phenylamine (19k). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.44-7.48 (m, 2H), 7.30 (d, $J = 8.4$ Hz, 2H), 7.11-7.15 (m, 3H), 6.99 (d, $J = 7.5$ Hz, 1H), 5.50 (br s, 1H), 2.49 (s, 3H), 2.41 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 144.1, 140.8, 136.3, 130.6, 129.2, 125.3, 122.8, 120.1, 119.6, 117.2, 21.0, 17.3.

(2, 5-Dimethylphenyl)diphenylamine (19l). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.57-7.67 (m, 5H), 7.38-7.48 (m, 6H), 7.33-7.37 (m, 2H), 2.71 (s, 3H), 2.47 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 147.4, 145.0, 136.9, 133.2, 131.4, 130.0, 128.9, 126.9, 121.4, 121.2, 20.8, 18.1.

General procedure for Suzuki coupling of aryl chlorides. A Schlenk tube was charged with boronic acid 20 (1.5 mmol) and K$_3$PO$_4$ (2 mmol). The flask was evacuated and backfilled with nitrogen three times. Toluene (3 mL), a stock solution of ligand 16 in toluene (0.002 mmol), a stock solution of Pd(dba)$_2$ (0.001 mmol) in toluene, and aryl
chloride 17 (1.0 mmol) were subsequently added. The flask was sealed and the reaction mixture was heated at 80 °C with vigorous stirring for 12 h. After cooling the mixture to rt, 15 mL of EtOAc was added and the mixture was washed with 5 mL of 1 N NaOH (aq.) and 5 mL of brine. The organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (hexane: EtOAc, 10:1).

4-Methylbiphenyl (21a). ¹H NMR (CDCl₃, 400 MHz) δ 7.67-7.64 (m, 2H), 7.59-7.55 (m, 2H), 7.51-7.47 (m, 2H), 7.41-7.37 (m, 1H), 7.32 (d, J = 7.9 Hz, 2H), 2.47 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 141.1, 138.3, 137.0, 129.5, 128.7, 127.0, 126.9, 21.1.

2-Methylbiphenyl (21b). ¹H NMR (CDCl₃, 400 MHz) δ 7.54-7.50 (m, 2H), 7.45-7.41 (m, 3H), 7.38-7.34 (m, 4H), 2.39 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 141.95, 141.91, 135.3, 130.3, 129.8, 129.2, 128.0, 127.2, 126.7, 125.7, 20.4.

2,4-Dimethylbiphenyl (21c). ¹H NMR (CDCl₃, 400 MHz) δ 7.50-7.46 (m, 2H), 7.42-7.40 (m, 3H), 7.25 (d, J = 8.2 Hz, 1H), 7.17-7.15 (m, 2H), 2.44 (s, 3H), 2.32 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 142.1, 141.7, 135.1, 132.1, 130.5, 130.2, 129.1, 128.0, 127.9, 126.6, 20.9, 19.9.
4-Methoxybiphenyl (21d). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.61-7.56 (m, 4H), 7.47-7.43 (m, 2H), 7.36-7.32 (m, 1H), 7.01 (dt, $J = 2.2$, 8.8 Hz, 1H), 3.88 (s, 3H); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 159.1, 140.8, 133.7, 128.7, 128.1, 126.7, 126.6, 114.1, 55.3.

4-Acetylbiphenyl (21e). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 8.04 (dd, $J = 1.6$, 7.6 Hz, 2H), 7.69 (dd, $J = 1.6$, 6.9 Hz, 2H), 7.65-7.62 (m, 2H), 7.50-7.41 (m, 3H), 2.64 (s, 3H); $^{13}$C NMR (CDCl$_3$, 90 MHz) $\delta$ 197.4, 145.4, 139.5, 135.6, 128.73, 128.67, 128.0, 127.0, 126.9, 26.4.

4-Nitrobiphenyl (21f). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 8.30 (dt, $J = 2.5$, 9.3 Hz, 2H), 7.74 (dt, $J = 2.0$, 8.9 Hz, 2H), 7.65-7.62 (m, 2H), 7.53-7.45 (m, 3H); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 147.5, 147.0, 138.7, 129.1, 128.9, 127.7, 127.3, 124.0.

4-Carbomethoxybiphenyl (21g). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 8.12 (dt, $J = 1.8$, 8.5 Hz, 2H), 7.69-7.62 (m, 4H), 7.50-7.46 (m, 2H), 7.43-7.39 (m, 1H), 3.95 (s, 3H); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 166.9, 145.5, 139.9, 130.0, 128.9, 128.8, 128.1, 127.2, 127.0, 52.1.

4-Trifluoromethylbiphenyl (21h). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.72 (s, 4H), 7.66-7.60 (m, 2H), 7.54-7.41 (m, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 144.7, 139.8, 129.3 (q, $J = 32.1$ Hz), 129.0, 128.2, 127.4, 127.3, 125.7 (q, $J = 3.7$ Hz), 124.4 (q, $J = 272$ Hz).
2-Acetylbiphenyl (21i). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.58 (dd, $J = 1.2$, 7.6 Hz, 1H), 7.53 (dt, $J = 1.4$, 7.5 Hz, 1H), 7.47-7.35 (m, 7H), 2.03 (s, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 204.7, 140.8, 140.6, 140.4, 130.6, 130.1, 128.8, 128.6, 127.79, 127.77, 127.4, 30.3.

2-Cyanobiphenyl (21j). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.77 (dd, $J = 1.1$, 7.7 Hz, 1H), 7.65 (dt, $J = 1.3$, 7.7 Hz, 1H), 7.59-7.57 (m, 2H), 7.53-7.44 (m, 5H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 145.3, 138.0, 133.6, 132.7, 130.0, 128.63, 128.60, 127.4, 118.6, 111.1.

2-Cyano-4$'$-methylbiphenyl (21k). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.76 (dd, $J = 0.9$, 7.8 Hz, 1H), 7.63 (dt, $J = 1.3$, 7.7 Hz, 1H), 7.51 (d, $J = 7.9$ Hz, 1H), 7.49 (d, $J = 8.1$ Hz, 2H), 7.42 (dt, $J = 1.1$, 7.6 Hz, 1H), 7.32 (d, $J = 8.0$ Hz, 2H), 2.43 (s, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 145.4, 138.5, 135.1, 133.6, 132.7, 129.9, 129.3, 128.5, 127.2, 118.8, 111.0, 21.1.

2-Phenylpyridine (21l). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 8.71 (d, $J = 4.8$ Hz, 1H), 8.01 (d, $J = 7.7$ Hz, 2H), 7.72 (d, $J = 3.3$ Hz, 2H), 7.49 (t, $J = 7.4$ Hz, 2H), 7.42 (t, $J = 7.3$ Hz, 1H), 7.21 (dd, $J = 4.5$, 8.6 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 157.3, 149.5, 139.3, 136.6, 128.8, 128.6, 126.8, 122.0, 120.4.
**2,5,2'-Trimethylbiphenyl (21m).** $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.25-7.18 (m, 3H), 7.13 (d, $J$ = 7.7 Hz, 1H), 7.10-7.04 (m, 2H), 6.92 (s, 1H), 2.32 (s, 3H), 2.05 (s, 3H), 2.00 (s, 3H); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 141.7, 141.4, 135.8, 134.9, 132.6, 129.9, 129.7, 129.6, 129.2, 127.8, 127.0, 125.5, 20.9, 19.8, 19.3.

**2'-Methoxy-2,5-dimethylbiphenyl (21n).** $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.35 (ddd, $J$ = 1.8, 7.5 8.2 Hz, 1H), 7.17 (dd, $J$ = 1.6, 7.4 Hz, 2H), 7.09 (d, $J$ = 7.7 Hz, 1H), 7.04 (d, $J$ = 1.0 Hz, 1H), 7.01 (dd, $J$ = 1.0, 7.4 Hz, 1H), 6.97 (d, $J$ = 8.2 Hz, 1H), 3.77 (s, 3H), 2.36 (s, 3H), 2.13 (s, 3H); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 156.5, 138.4, 134.7, 133.6, 130.93, 130.90, 130.6, 129.4, 128.4, 128.0, 120.4, 110.5, 55.3, 20.9, 19.4.

**2'-Methoxy-2,6-dimethylbiphenyl (21o).** $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.47-7.50 (m, 1H), 7.26-7.33 (m, 3H), 7.12-7.20 (m, 3H), 3.87 (s, 3H), 2.19 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 156.4, 138.1, 136.5, 130.6, 129.4, 128.3, 127.0, 126.9, 120.6, 110.7, 55.3, 20.4.

**2,6,2'-Trimethylbiphenyl (21p).** $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.39-7.45 (m, 3H), 7.26-7.36 (m, 3H), 7.17-7.20 (m, 1H), 2.15 (s, 3H), 2.13 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 141.0, 140.5, 135.7, 135.5, 129.9, 128.8, 127.2, 127.0, 126.9, 126.0, 20.3, 19.4.
References and Notes


Chapter 2

Development of a New Class of $C_1$-Symmetric Bisphosphine Ligands for Rhodium-Catalyzed Asymmetric Hydrogenation

2.1 Introduction and Background

The development of the pharmaceutical and fine chemical industry requires the large scale production of enantiomerically pure organic molecules as chiral building blocks. Among the catalytic asymmetric methods that have been explored, late transition metal (Rh, Ru, Ir) catalyzed asymmetric hydrogenation of prochiral olefins has become one of the most efficient and powerful strategies. The transition metal catalyzed hydrogenation reaction is environmentally friendly and cost effective, hence it is among the most widely investigated areas in modern organometallic chemistry.

Homogeneous asymmetric hydrogenation was initially investigated by Knowles and Horner in the late 1960s, albeit with poor enantioselectivity. Later, two breakthroughs were reported by Kagan and Knowles, respectively, in the 1970s. Kagan reported the synthesis of DIOP, the first example of a chiral bisphosphine ligand, for Rh-catalyzed asymmetric hydrogenation reactions. The success of DIOP greatly influenced ligand design in several ways. The $C_2$-symmetry of DIOP has proven to be an important structural feature in future ligand development. Furthermore, the chelating bidentate phosphine ligands may lead to superior enantioselectivities compared to monophosphine ligands. Knowles’s P-chiral ligand DIPAMP has been employed in the industrial
production of L-DOPA (up to 96% ee), due to its high efficiency in the Rh-catalyzed asymmetric hydrogenation of dehydroamino acids. This success enabled Montsano to be the primary supplier of the main drug used in alleviating the effects of Parkinson’s disease. Ligands developed in this period usually bear two bisarylphosphino groups, which are known as the first generation ligands (Figure 2-1). These ligands have the advantage of relative stability in the air and ease of preparation as diarylphosphines are readily available and air stable. But several general drawbacks in this category of ligands include their low reactivity and limited substrate scope.

When ligand development was in its infancy, the mechanism of Rh-catalyzed asymmetric hydrogenation was actively being investigated. Brown and Halpern have proposed a generally accepted mechanism of asymmetric hydrogenation of enamides when the Rh complexes of tetraaryl-substituted diphosphines are used (such as DIPAMP and ChiraPhos). The so called “unsaturated mechanism” is shown in Figure 2-2.
The mechanism consists of four primary steps: (a) reversible binding of the substrate to the Rh-diphosphine complex to form two possible diastereomers; (b) irreversible insertion of dihydrogen into the Rh-substrate complex; (c) irreversible migratory insertion of the alkene into the Rh-H bond to form a catalyst-product complex; (d) reductive elimination affording the final product and regenerating the catalyst. The minor diastereomer generated in the oxidative addition step is believed to have much higher reactivity than the major isomer for steric reasons, which determines the enantioselectivity of the product.

Figure 2-2: “Unsaturated Pathway” of Rh-Catalyzed Asymmetric Hydrogenation
In the early 1990s, Burk introduced a new series of efficient chiral bisphospholane ligands, Duphos and BPE, in Rh-catalyzed asymmetric hydrogenation reactions.\(^9\) Extremely high reactivities have been observed in the hydrogenation of \(\alpha\)-dehydroamino acids, enamides, itaconic acid derivatives and enol acetates. Encouraged by the success of Duphos and BPE, the second generation ligands designed in this period shared similar structural features as \(C_2\)-symmetric dialkyl aryl bisphosphines (Figure 2-3). For example, RoPhos,\(^{10}\) water-soluble BASPHOS,\(^{11}\) and MalPHOS\(^{12}\) are modified DuPhos-type ligands made by either adding substituent groups on the 3 and 4 position of the phospholane or modifying the ligand backbone. These ligands maintain the high efficiency of DuPhos and BPE in Rh-catalyzed hydrogenation reactions. Recent research by Landis\(^{13}\) and coworkers, based on computer modeling, showed that Rh-DuPhos catalyzed hydrogenation reaction follows similar mechanistic pathways as described in Figure 2-2. Compared with the first generation, the second generation of ligands extensively expanded the substrate scope and decreased the catalyst loading. However, these ligands are relatively air sensitive and usually require handling under an inert atmosphere.

Figure 2-3: Second Generation Ligands (1990 - Present): Dialkyl Aryl Phosphines
Since the first P-chiral ligand DIPAMP was reported by Knowles in the 1970s, the development of this type of ligands has been relatively slow due to the difficulties in ligand synthesis. It was not until BisP* reported by Imamoto in 1998 that P-chiral ligands regained significant attention.14 These ligand systems can be categorized as the third ligand generation (Figure 2-4). BisP*, which bears an electron-rich trialkyl bisphosphino moiety, is highly efficient in the Rh-catalyzed asymmetric hydrogenation of a variety of prochiral olefins. Other representative P-chiral ligands, such as TangPhos15 and BINAPINE16 by Zhang, have shown good enantioselectivities in asymmetric hydrogenation of a wide range of functionalized olefins. More recently, C₁-symmetric bisphospine ligand trichickenfootPhos, which has three hindered quadrants, was reported by Hoge and coworkers from Pfizer.17 It affords extremely high selectivity and reactivity in Rh-catalyzed hydrogenation of α-dehydroamino acids under mild conditions (ee up to 99%). Furthermore, with TON up to 27,000, this system is approximately 10 fold as efficient as comparable systems such as DuPhos.

Mechanistic studies by Gridnev and Imamoto18 suggested a different pathway for Rh-catalyzed asymmetric hydrogenation than the “unsaturated pathway” suggested by Halpern, termed the “dihydride pathway” (Figure 2-5). The first step of the catalytic
cycle is the oxidative addition of the dihydrogen to the solvated Rh-ligand complex which generates two possible diastereomers, followed by the coordination of the substrate to the Rh-hydride intermediate. Subsequent migratory insertion of the olefin and reductive elimination provides the hydrogenation product. In contrast with the “unsaturated pathway”, the coordination of the substrate to the Rh center takes place before the oxidative addition of the dihydrogen.

![Diagram](image)

**Figure 2-5**: “Dihydride Pathway” of Rh-Catalyzed Asymmetric Hydrogenation

It is notable that most of the highly enantioselective chiral phosphorus ligands for asymmetric hydrogenation have inherent backbone chirality. There are few examples of efficient P-chiral phosphorus ligands. The synthetic difficulties in the construction of
stereogenic phosphorus centers have slowed the development of P-chiral ligands for nearly two decades after the first report of DIPAMP by Knowles. Moreover, a major drawback of many P-chiral phosphine synthetic methods developed by Imamoto, Juge, Corey, Evans and Livinghouse is that either only one enantiomer of the ligand is readily accessible due to the nature of the chiral auxiliaries that were used for chiral induction, or a tedious diastereomeric derivatization sequence is needed. On the other hand, the success of $C_2$-symmetry design for potentially high enantioselectivities has also delayed the widespread development of useful $C_1$-symmetric bisphosphine ligands. Recently, Hoge reported the synthesis of a bisphosphine ligand (trichickenfootPhos) with three hindered quadrants. Its rhodium complex has been successfully used in the asymmetric hydrogenation of a pharmaceutical candidate, pregabalin, with extremely high TON (Figure 2-6). However, one major drawback of the synthetic approach for this ligand is the requirement for chiral HPLC separation to obtain both enantiomeric forms of the ligand, which limits its large scale production and application in industry. Our ligand design involves a modification which puts a linkage between the two phosphorus atoms. With this variation, alternative chiral separation methods can be used in the ligand synthesis to circumvent the present limitation of trichickenfootPhos.
In this chapter, the development of a new series of $C_1$-symmetric bisphosphine ligands will be discussed. Their application in Rh-catalyzed asymmetric hydrogenation of various functionalized olefins will be covered as well. The hydrogenation results have shown that the ligand performance is highly substrate dependent and different phosphino substituent groups on the ligands have a great impact on the reactivity and selectivity of the reaction.

Figure 2-6: TrichickenfootPhos and its Application in Asymmetric Hydrogenation
2.2 Results and Discussion

2.2.1 Ligand Synthesis

Scheme 2-1: Initial Synthetic Design Utilizing Optical Resolution

To overcome the synthetic limitation of trichickenfootPhos, we initially designed ligand 1. This design is beneficial for the enantioseparation of this ligand as optical resolution can be used in place of chiral HPLC to isolate the two enantiomers (Scheme 2-1). Cyclic monophosphine oxide 2 can be obtained from readily available bischloromethylbenzene in one step in 70% yield.\(^{20}\) Ortho-lithiation of 2 with LDA and electrophilic attack of \(\text{P}^\text{t}\text{Bu}_2\text{Cl}\), followed by \(\text{H}_2\text{O}_2\) oxidation, generated the diphosphine oxide 3 as a racemic mixture in 65% yield. Optical resolution of racemic 3 with DBTA (DBTA = dibenzoyl tartaric acid) afforded both enantiomeric forms of 3 in good yields. Unfortunately, reduction of 3 to ligand 1 has proven to be very difficult.

Several commonly used P=O reducing reagents were employed in the reduction of 3 (Table 2-1). When HSiCl\(_3\)/TEA and HSiCl\(_3\)/Bu\(_3\)N were used (Table 2-1, entry 1-2),
only the $\text{P=O}$ on the five-membered ring was reduced. Use of LAH/MeOTf gave multiple decomposed side products (Table 2-1, entry 3).\textsuperscript{21a} $\text{Si}_2\text{Cl}_6$ and other reducing agents have also been tested but none afforded the desired product. A possible explanation of the difficulty in the reduction step is the steric hindrance generated by the di-\textit{tert}-butylphosphine oxide moiety. To the best of our knowledge, there is only one example of reducing a simple di-\textit{tert}-butylphosphine oxide which employed neat $\text{Ph}_2\text{SiH}_2$ at 240 °C.\textsuperscript{21b} When this methodology was applied to the reduction of 3, only decomposition products were obtained (Table 2-1, entry 6).

Table 2-1: Different $\text{P=O}$ Bond Reduction Conditions

<table>
<thead>
<tr>
<th>entry</th>
<th>reducing agent</th>
<th>solvent</th>
<th>$T(\degree \text{C})$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$\text{HSiCl}_3$/TEA</td>
<td>toluene</td>
<td>110</td>
</tr>
<tr>
<td>2</td>
<td>$\text{HSiCl}_3$/Bu$_3$N</td>
<td>$\text{o-xylene}$</td>
<td>140</td>
</tr>
<tr>
<td>3</td>
<td>LiAlH$_4$/MeOTf</td>
<td>DME</td>
<td>0 °C-rt</td>
</tr>
<tr>
<td>4</td>
<td>$\text{Si}_2\text{Cl}_6$</td>
<td>toluene</td>
<td>110</td>
</tr>
<tr>
<td>5</td>
<td>$\text{Si}_2\text{Cl}_6$</td>
<td>$\text{o-xylene}$</td>
<td>140</td>
</tr>
<tr>
<td>6</td>
<td>$\text{Ph}_2\text{SiH}_2$</td>
<td></td>
<td>240</td>
</tr>
<tr>
<td>7</td>
<td>$\text{Ti(O}^\text{iPr})_4$/HSi(OEt)$_3$</td>
<td>toluene</td>
<td>110</td>
</tr>
<tr>
<td>8</td>
<td>$\text{BH}_3\text{Me}_2\text{S}$</td>
<td>THF</td>
<td>70</td>
</tr>
</tbody>
</table>
As the reduction step in our initially designed ligand system proved to be quite problematic, a revised ligand design was proposed utilizing chiral backbone induction (Scheme 2-2). Starting from commercially available (S)-BINOL, cyclic monophosphine sulfide 8 could be obtained in three steps in good overall yield.\textsuperscript{16} Subsequent ortho-lithiation by 'BuLi/HMPA/TMEDA at -78 °C, followed by electrophilic attack by various phosphine chlorides, afforded 9a-d as intermediates. When the R group on the phosphine is o-tolyl (9b) or 'Bu (9d), direct purification by flash column chromatography can be performed. Once purified, 9b and 9d can be reduced with hexachlorodisilane to provide the desired product 4b and 4d. On the other hand, when R = Ph (9a) or Cy (9c), the intermediates are quite air sensitive and large amounts of oxidation occurred when subjected to flash column purification. To circumvent this problem, the intermediates were further reduced with Si\textsubscript{2}Cl\textsubscript{6} and protected with BH\textsubscript{3}·THF to generate 10 or directly protected with BH\textsubscript{3}·THF to generate 11. These protected phosphines could be easily purified by flash column chromatography without being subject to rapid oxidation. Removal of BH\textsubscript{3} with DABCO (1,4-diazabicyclo[2,2,2]octane) and reduction of the P=S bond with hexachlorodisilane afforded 4a and 4c in moderate yields.
Scheme 2-2: a Revised Synthetic Design Utilizing Chiral Backbone Induction

1. n-BuLi, TMEDA, Et₂O
2. tBuPCl₂, S, THF,

1) Si₂Cl₆, toluene 39%
2) BH₃·THF

DABCO toluene, 60 °C

TMEDA = N,N,N',N'-tetramethylethylenediamine
HMPA = hexamethylphosphoric triamide
DABCO = 1,4-diazabicyclo[2.2.2]octane
2.2.2 Rh-Catalyzed Asymmetric Hydrogenation

In order to examine the catalytic efficiency of 4a-d, cationic Rh complexes [Rh(cod)BF₄] (cod = 1,5-cyclooctadiene) (12a-d) were prepared following a standard procedure (Cf. Experimental Section). The use of these complexes as precatalysts for the hydrogenation of various prochiral olefins was also investigated.

2.2.2.1 Asymmetric Hydrogenation of Dehydroamino Acid Derivatives

α-Dehydroamino acid derivatives are a typical class of substrates for the evaluation of asymmetric hydrogenation catalysts. Initially, rhodium complex 12c was used in the solvent screening for the hydrogenation of methyl α-(acetamido)acrylate (13a) under very mild conditions (room temperature, 50 psi of H₂ pressure, Table 2-2). After 12 h, quantitative yields and high enantiomeric excess of the products were observed regardless of the solvent polarity. The highest enantioselectivity of 97.5% was achieved when methanol was used (Table 2-2, entry 1).
Using the optimized conditions, we have investigated asymmetric hydrogenation of several α-dehydroamino acid derivatives using rhodium complexes 12a-d as catalysts (Table 2-3). In most cases, complete conversions were observed with the exception of substrate 13c, a tetrasubstituted α-dehydroamino ester (Table 2-3, entries 9 and 10). Complex 12d, while providing moderate enantioselectivity in the hydrogenation of the simple substrate 13a, afforded the highest enantioselectivity in the hydrogenation of 13c (Table 2-3, entries 4 and 11). The relationship between steric hindrance of the ligand 4a-
around the metal center and catalytic efficiency is under investigation. This relationship may provide an explanation for the high substrate-dependent properties of complex 12d.

Table 2-3: Asymmetric Hydrogenation of Several α-Dehydroamino Acid Derivatives

<table>
<thead>
<tr>
<th>entry&lt;sup&gt;a&lt;/sup&gt;</th>
<th>substrate</th>
<th>complex</th>
<th>conv.(%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>ee(%) (config.)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13a R&lt;sup&gt;1&lt;/sup&gt;, R&lt;sup&gt;2&lt;/sup&gt; = H</td>
<td>12a</td>
<td>100</td>
<td>97.0% (R)</td>
</tr>
<tr>
<td>2</td>
<td>13a</td>
<td>12b</td>
<td>100</td>
<td>91.1% (R)</td>
</tr>
<tr>
<td>3</td>
<td>13a</td>
<td>12c</td>
<td>100</td>
<td>97.5% (R)</td>
</tr>
<tr>
<td>4</td>
<td>13a</td>
<td>12d</td>
<td>100</td>
<td>77.5% (S)</td>
</tr>
<tr>
<td>5</td>
<td>13b R&lt;sup&gt;1&lt;/sup&gt; = 4-MeO-Ph, R&lt;sup&gt;2&lt;/sup&gt; = H</td>
<td>12a</td>
<td>100</td>
<td>92.0% (R)</td>
</tr>
<tr>
<td>6</td>
<td>13b</td>
<td>12b</td>
<td>100</td>
<td>47.0% (R)</td>
</tr>
<tr>
<td>7</td>
<td>13b</td>
<td>12c</td>
<td>100</td>
<td>89.7% (R)</td>
</tr>
<tr>
<td>8</td>
<td>13b</td>
<td>12d</td>
<td>72</td>
<td>41.4% (S)</td>
</tr>
<tr>
<td>9</td>
<td>13c R&lt;sup&gt;1&lt;/sup&gt;, R&lt;sup&gt;2&lt;/sup&gt; = C&lt;sub&gt;4&lt;/sub&gt;H&lt;sub&gt;8&lt;/sub&gt;</td>
<td>12a</td>
<td>64</td>
<td>38.7% (R)</td>
</tr>
<tr>
<td>10</td>
<td>13c</td>
<td>12c</td>
<td>55</td>
<td>8.5% (R)</td>
</tr>
<tr>
<td>11</td>
<td>13c</td>
<td>12d</td>
<td>100</td>
<td>49.6% (R)</td>
</tr>
</tbody>
</table>

<sup>a</sup> See Experimental Section for a general procedure. <sup>b</sup> The conversions were based on GC detection. <sup>c</sup> The enantiomeric excess was determined by chiral GC (Chirasil-VAL III FSOT) and HPLC. The absolute configurations were assigned by comparison of optical rotations with reported data.

Asymmetric hydrogenation of β-(acetamido)acrylate derivatives, one of the most efficient and practical ways to obtain unnatural enantiomerically enriched β-amino acids,
remains much less successful compared to the hydrogenation of their \( \alpha \)-analogues.\textsuperscript{22} As shown in Table 2-4, several \( \beta \)-dehydroamino acid derivatives were hydrogenated with Rh complexes 12 as the catalyst precursor using two different solvent systems. For (Z)-ethyl 3-acetamido-2-butenoate (15a), both 12a and 12c gave good enantioselectivities of up to 90\% (Table 2-4, entries 1 and 3) when methanol was used. Changing solvent to THF in the hydrogenation reaction with complexes 12b and 12c gave slightly better enantioselectivities although complete conversions were not obtained (Table 2-4, entries 5-6). For more challenging \( \beta \)-aryl substituted substrates 15b and 15c, high ee values (90\% and 93\%) were also obtained with 12a and 12c, respectively (Table 2-4, entries 7 and 9). While still under investigation, we currently do not have a viable hypothesis regarding the variable enantioselectivities with this series of ligands.
2.2.2.2 Asymmetric Hydrogenation of α-Aryl Enamides

Hydrogenation of α-arylenamides was also investigated with Rh complexes 12 as the catalyst precursor. As shown in Table 2-5, both acyclic enamide 17a and cyclic enamide 17b were employed in the hydrogenation reactions. When 12c was used in the hydrogenation of 17a, the highest enantioselectivity of 80% ee was achieved (Table 2-5, entry 3). In contrast, complex 12c only afforded a poor ee of 32% when cyclic substrate

### Table 2-4: Asymmetric Hydrogenation of Several β-Dehydroamino Acid Derivatives

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>solvent</th>
<th>complex</th>
<th>conv.(%)</th>
<th>ee(%) (config.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15a R= Me</td>
<td>MeOH</td>
<td>12a</td>
<td>100</td>
<td>89.8% (R)</td>
</tr>
<tr>
<td>2</td>
<td>15a</td>
<td>MeOH</td>
<td>12b</td>
<td>100</td>
<td>22.4% (R)</td>
</tr>
<tr>
<td>3</td>
<td>15a</td>
<td>MeOH</td>
<td>12c</td>
<td>100</td>
<td>88.5% (R)</td>
</tr>
<tr>
<td>4</td>
<td>15a</td>
<td>MeOH</td>
<td>12d</td>
<td>100</td>
<td>17.7% (R)</td>
</tr>
<tr>
<td>5</td>
<td>15a</td>
<td>THF</td>
<td>12b</td>
<td>100</td>
<td>34.8% (R)</td>
</tr>
<tr>
<td>6</td>
<td>15a</td>
<td>THF</td>
<td>12c</td>
<td>93</td>
<td>92.6% (R)</td>
</tr>
<tr>
<td>7</td>
<td>15b R= Ph</td>
<td>THF</td>
<td>12a</td>
<td>80</td>
<td>89.6% (S)</td>
</tr>
<tr>
<td>8</td>
<td>15b</td>
<td>THF</td>
<td>12b</td>
<td>100</td>
<td>16.1% (S)</td>
</tr>
<tr>
<td>9</td>
<td>15c R= 4-OMe-Ph</td>
<td>MeOH</td>
<td>12c</td>
<td>100</td>
<td>92.5% (R)</td>
</tr>
</tbody>
</table>

---

*a See Experimental Section for a general procedure. *b The conversions were based on GC detection. *c The enantiomeric excess was determined by chiral GC (Chirasil-VAL III FSOT). The absolute configurations were assigned by comparison of optical rotations with reported data.
17b was used (Table 2-5, entry 7). Complex 12d, which gave the best results in the hydrogenation of tetrasubstituted dehydroamino acid derivatives, again proved to be the complex of choice for the tetrasubstituted enamide (Table 2-5, entry 8).

Table 2-5: Asymmetric Hydrogenation of α-Aryl Enamides

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>complex</th>
<th>conv.(%)</th>
<th>ee(%) (config.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17a Ar=3-Me-Ph</td>
<td>12a</td>
<td>100</td>
<td>53.5% (R)</td>
</tr>
<tr>
<td>2</td>
<td>17a</td>
<td>12b</td>
<td>100</td>
<td>53.7% (S)</td>
</tr>
<tr>
<td>3</td>
<td>17a</td>
<td>12c</td>
<td>100</td>
<td>79.7% (R)</td>
</tr>
<tr>
<td>4</td>
<td>17a</td>
<td>12d</td>
<td>100</td>
<td>71.8% (S)</td>
</tr>
<tr>
<td>5</td>
<td>17b</td>
<td>12a</td>
<td>100</td>
<td>37.1% (S)</td>
</tr>
<tr>
<td>6</td>
<td>17b</td>
<td>12b</td>
<td>60</td>
<td>69.7% (R)</td>
</tr>
<tr>
<td>7</td>
<td>17b</td>
<td>12c</td>
<td>100</td>
<td>31.5% (S)</td>
</tr>
<tr>
<td>8</td>
<td>17b</td>
<td>12d</td>
<td>100</td>
<td>84.5% (R)</td>
</tr>
</tbody>
</table>

a See Experimental Section for a general procedure. b The conversions were based on GC detection. c The enantiomeric excess was determined by chiral GC (Chirasil-VAL III FSOT). The absolute configurations were assigned by comparison of optical rotations with reported data.

2.3 Conclusion

In conclusion, we have developed a series of C1-symmetric bisphosphine ligands 4a-d with three hindered quadrants from enantiomerically pure (S)-BINOL. Several
slightly different synthetic routes were used in the ligand syntheses based on different
chemical properties of the reaction intermediates 9a-d. The hydrogenation of various
functionalized prochiral olefins was performed with the rhodium complexes of these
ligands. In most cases, good to excellent enantioselectivities were achieved with some
substrate-dependence noted.

**Experimental Section**

**General Methods.** All reactions and manipulations were performed in a
nitrogen-filled glovebox or under nitrogen using standard Schlenk techniques. All the
solvents are dried and deoxygened from solvent purification system. Column
chromatography was performed using EM silica gel 60 Å (230~400 mesh). $^1$H, $^{13}$C, and
$^{31}$P NMR spectral data were recorded on Bruker DPX-300, CDPX-300, AMX-360, and
DRX-400 MHz spectrometers. Chemical shifts are reported in ppm upfield to
tetramethylsilane with the solvent resonance as the internal standard. Mass spectra were
recorded on a KRATOS MS 9/50 mass spectrometer for LR-ESI and HR-ESI. GC
analyses were carried out on a Helwett-Packard 6890 gas chromatograph, using chiral
capillary columns. HPLC analyses were carried out on a Waters™ 600 chromatograph.

4-tert-Butyl-3-diphenylphosphanyl-3,5-dihydro-4-phosphacyclohepta[2,1-α; 3,4-α′]dinaphthalene-4-sulfide (9a). At $-78$ °C, to a solution of 8 (0.40 g, 1 mmol),
TMEDA (182 µL, 1.2 mmol) in THF (10 mL) was added dropwise $^t$BuLi (0.88 mL, 1.7
M in pentane, 1.5 mmol). The reaction mixture was stirred at –78 °C for 4 h, followed by slow addition of a solution of PPh2Cl (0.204 mL, 1.1 mmol) in 3 mL of THF at the same temperature. The resulting mixture was allowed to slowly warm to rt and stirred overnight before quenching with NH4Cl (aq). The organic layer was extracted with ether (3 × 10 mL) and washed with brine (10 mL), dried over Na2SO4 and concentrated under reduced pressure. The residue was directly used in the next step without further purification.

4-tert-Butyl-3-(di-o-tolylphosphanyl)-3,5-dihydro-4-phosphacyclohepta[2,1-α; 3,4-α′]dinaphthalene-4-sulfide (9b). At –78 °C, to a solution of 8 (2.00 g, 5 mmol), TMEDA (0.91 mL, 6 mmol) in THF (25 mL) was added dropwise tBuLi (4.4 mL, 1.7 M in pentane, 7.5 mmol). The reaction mixture was stirred at –78 °C for 4 h, followed by slow addition of a solution of P(o-tolyl)2Cl (1.37 g, 5.5 mmol) in 8 mL of THF at the same temperature. The resulting mixture was allowed to slowly warm to rt and stirred overnight before quenching with NH4Cl (aq). The organic layer was extracted with ether (3 × 15 mL) and washed with brine (10 mL), dried over Na2SO4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexenes:EtOAc, 95:5) to afford 9b as a white solid (1.93 g, 63%). 1H NMR (CDCl3, 360 MHz) δ 8.08 (d, J = 8.4 Hz, 1H), 7.97 (d, J = 8.2 Hz, 1H), 7.89 (s, 2H), 7.85 (d, J = 8.1 Hz, 1H), 7.80 (d, J = 7.7 Hz, 1H), 7.77 (dd, J = 1.4, 7.6 Hz, 1H), 7.65-7.67 (m, 1H), 7.37-7.44 (m, 2H), 7.01-7.16 (m, 4H), 6.88-6.98 (m, 2H), 6.80-6.83 (m, 2H), 6.56-6.60 (m, 1H), 6.24 (d, J = 8.5 Hz, 1H), 4.81 (dd, J = 5.4, 9.1 Hz, 1H), 3.62 (dd, J = 10.0, 12.7 Hz, 1H), 2.90-2.96 (m, 1H), 2.43 (s, 3H), 1.19 (d, J = 15.7 Hz, 9H), 1.14 (d, J = 2.1 Hz,
\[ \begin{align*}
\text{\(^{13}\text{C}\ NMR (CDCl}_3, 75 \text{ MHz})} & \quad \delta 144.0, 143.6, 140.5, 140.2, 136.6, 136.3, 135.5, \\
& \quad 135.4, 135.0, 134.1, 133.9, 132.8 (d, J = 2.5 \text{ Hz}), 132.7 (d, J = 5.2 \text{ Hz}), 132.5, 132.4, \\
& \quad 131.0 (d, J = 2.7 \text{ Hz}), 130.2 (d, J = 6.0 \text{ Hz}), 129.7 (d, J = 3.3 \text{ Hz}), 129.6 (d, J = 5.6 \text{ Hz}), \\
& \quad 128.4 (d, J = 2.0 \text{ Hz}), 127.9, 127.8, 127.6, 127.4, 127.3, 127.2, 126.0, 125.9, 125.7, \\
& \quad 125.3, 125.2, 124.2, 44.0 (t, J = 39.7 \text{ Hz}), 36.6 (d, J = 41.4 \text{ Hz}), 34.8 (d, J = 41.5 \text{ Hz}), \\
& \quad 25.8, 22.0 (d, J = 24.1 \text{ Hz}), 20.5 (d, J = 29.0 \text{ Hz}); \quad \text{\(^{31}\text{P}\ NMR (CDCl}_3, 145 \text{ MHz})} \quad \delta 86.85 \\
& \quad (d, J_{P-P} = 69.9 \text{ Hz}), -40.69 (d, J_{P-P} = 69.8 \text{ Hz}); \quad \text{HRMS (ESI\textsuperscript{+}) calcd. for C}_{40}H_{39}P_2S (MH\textsuperscript{+}) \\
& \quad 613.2248, \text{ found } 613.2227. 
\end{align*} \]

\textit{4-\textit{tert}-Butyl-3-dicyclohexylphosphanyl-3,5-dihydro-4-phosphacyclohepta-[2,1-\textit{\alpha}; 3,4-\textit{\alpha}'\textit{]dinaphthalene-4-sulfide (9c).}} At \(-78 ^\circ\text{C, to a solution of } 8 (0.60 \text{ g, 1.5 mmol), TMEDA (0.27 mL, 1.8 mmol) in THF (15 mL) was added dropwise tBuLi (1.32 mL, 1.7 M in pentane, 2.25 mmol). The reaction mixture was stirred at \(-78 ^\circ\text{C for 4 h, followed by slow addition of a solution of PCy}_2\text{Cl (0.364 mL, 1.65 mmol) in 5 mL of THF at the same temperature. The resulting mixture was allowed to slowly warm to rt and stirred overnight before quenching with NH}_4\text{Cl (aq). The organic layer was extracted with ether (3 \times 10 mL) and washed with brine (10 mL), dried over Na}_2\text{SO}_4 and concentrated under reduced pressure. The residue was directly used in the next step without further purification.}

\textit{4-\textit{tert}-Butyl-3-(\textit{di-\textit{tert}-butyl-phosphanyl)-3,5-dihydro-4-phosphacyclohepta-[2,1-\textit{\alpha}; 3,4-\textit{\alpha}'\textit{]dinaphthalene-4-sulfide (9d).}} At \(-78 ^\circ\text{C, to a solution of } 8 (1.20 \text{ g, 3}
mmol), TMEDA (0.55 mL, 3.6 mmol), HMPA (0.62 mL, 3.6 mmol) in THF (35 mL) was added dropwise \( ^{t} \text{BuLi} \) (2.1 mL, 1.7 M in pentane, 3.6 mmol). The reaction mixture was stirred at \(-78^\circ\text{C}\) for 4 h, followed by slow addition of a solution of \( \text{P}^{t} \text{Bu}_2\text{Cl} \) (0.59 mL, 3.1 mmol) in 10 mL of THF at the same temperature in 10 min. The resulting mixture was stirred at \(-78^\circ\text{C}\) for another 30 min then allowed to slowly warm to room temperature and refluxed overnight before quenching with \( \text{NH}_4\text{Cl} \) (aq). The organic layer was extracted with ether (3 \times 15 mL) and washed with brine (10 mL), dried over \( \text{Na}_2\text{SO}_4 \) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexenes:EtOAc, 95:5) to afford \( 9d \) as a white solid (0.75 g, 46%). \(^1\text{H NMR (CDCl}_3, 360 \text{MHz}) \ \delta \ 7.86 \ (q, \ J = 4.3 \text{ Hz}, \ 3H), \ 7.81 \ (s, \ 1H), \ 7.57 \ (t, \ J = 8.8 \text{ Hz}, \ 2H), \ 7.36-7.43 \ (m, \ 3H), \ 7.18 \ (ddd, \ J = 1.3, \ 7.9, \ 9.6 \text{ Hz}, \ 1H), \ 7.09-7.13 \ (m, \ 2H), \ 4.16 \ (dd, \ J = 3.6, \ 18.7 \text{ Hz}, \ 1H), \ 2.68-2.82 \ (m, \ 2H), \ 1.21 \ (d, \ J = 15.0 \text{ Hz}, \ 9H), \ 1.12 \ (d, \ J = 11.1 \text{ Hz}, \ 9H), \ 1.00 \ (d, \ J = 15.0 \text{ Hz}, \ 9H); \ ^{13}\text{C NMR (CDCl}_3, 90 \text{ MHz}) \ \delta \ 136.6, \ 136.0 \ (d, \ J = 5.4 \text{ Hz}), \ 134.7, \ 133.8, \ 133.7, \ 133.6, \ 133.2, \ 133.1, \ 133.0, \ 132.9, \ 132.6, \ 129.7, \ 129.3, \ 127.8, \ 127.7, \ 127.6, \ 127.5, \ 125.8, \ 125.7, \ 125.0, \ 42.3, \ 41.9, \ 41.5, \ 32.9 \ (d, \ J = 7.4 \text{ Hz}), \ 32.6 \ (d, \ J = 7.1 \text{ Hz}), \ 29.7(d, \ J = 24.6 \text{ Hz}), \ 29.3, \ 28.7(d, \ J = 10.3 \text{ Hz}); \ ^{31}\text{P NMR (CDCl}_3, \ 145 \text{ MHz}) \ \delta \ 93.52 \ (d, \ J_{p-p} = 69.4 \text{ Hz}), \ 37.63 \ (d, \ J_{p-p} = 69.2 \text{ Hz}); \ \text{HRMS (ESI+)} \ \text{calcd. for C}_{34}\text{H}_{43}\text{P}_2\text{S} (\text{MH}^+) \ 545.2561, \ \text{found} \ 545.2526.

4-\text{tert}-\text{Butyl-3-diphenylphosphanyl-3,5-dihydro-4-phospha-cyclohepta[2,1-\alpha; 3,4-\alpha']dinaphthalene bisborane complex (10).} \ \text{To the solution of crude product 9a in 12 mL of toluene was slowly added Si}_2\text{Cl}_6 \ (1.72 mL, \ 10 \text{ mmol). The reaction mixture}
was heated to reflux and stirred for 20 h before quenched with 15 mL of NaOH solution (30% w/w). The resulting mixture was heated at 60 °C for 1 h until both layers became clear. The organic layer was extracted with ether (3 × 5 mL), washed with brine (5 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was redissolved in 10 mL of THF and cooled to 0 °C followed by addition of 6 mL of BH₃·THF (1M). The resulting mixture was allowed to warm to rt and stirred overnight. Methanol was added to quench excess of BH₃·THF. After removal of solvents, the residue was purified by flash column chromatography on silica gel (hexenes:EtOAc, 97:3) to afford 10 as a white solid (0.23 g, 39%). ¹H NMR (CDCl₃, 360 MHz) δ 7.82-7.89 (m, 3H), 7.59-7.71 (m, 5H), 7.22-7.44 (m, 8H), 7.06-7.11 (m, 1H), 6.94-7.09 (m, 2H), 6.80-6.85 (m, 2H), 6.69 (d, J = 8.5 Hz 1H), 4.35 (dd, J = 12.9, 18.5 Hz, 1H), 3.21 (dd, J = 12.9, 16.8 Hz, 1H), 2.84 (d, J = 12.8 Hz, 1H), 1.26-1.42 (m, 3H), 1.12 (d, J = 13.2 Hz, 9H), 0.83-0.97 (m, 3H); ¹³C NMR (CDCl₃, 90 MHz) δ 135.6 (d, J = 4.7 Hz), 135.0 (d, J = 10.3 Hz), 134.0, 133.6, 133.1 (d, J = 5.2 Hz), 133.0 (dd, J = 5.4, 12.4 Hz), 132.8 (d, J = 12.1 Hz), 132.5 (d, J = 2.6 Hz), 131.6, 130.8 (d, J = 11.2 Hz), 129.6, 129.5, 129.4, 129.0, 128.5, 128.4, 128.0 (d, J = 9.9 Hz), 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3, 125.8, 125.1, 122.5, 121.9, 41.5 (d, J = 15.3 Hz), 33.1 (dd, J = 3.5, 23.2 Hz), 28.3 (d, J = 29.8 Hz), 26.3; ³¹P NMR (CDCl₃, 145 MHz) δ 67.12 (br s), 31.20 (br s); MS (ESI+) m/z 603.2 (MNa⁺).

4-tert-Butyl-3-dicyclohexylphosphanyl-3,5-dihydro-4-phosphacyclohepta-
[2,1-α; 3,4-α']dinaphthalene-4-sulfide monoborane complex (11). To the solution of
crude product 9c in 15 mL of THF was added 9 mL of BH$_3$·THF (1M) dropwise at 0 °C. The resulting mixture was allowed to warm to rt and stirred overnight. Methanol was added to quench excess of BH$_3$·THF. After removal of solvents, the residue was purified by flash column chromatography on silica gel (hexenes:EtOAc, 97:3) to afford 11 as a white solid (0.55 g, 61%). $^1$H NMR (CDCl$_3$, 360 MHz) $\delta$ 8.01 (d, $J = 8.4$ Hz, 1H), 7.86-7.93 (m, 3H), 7.68 (dd, $J = 1.3$, 8.4 Hz, 1H), 7.41-7.51 (m, 3H), 7.10-7.27 (m, 3H), 6.93 (d, $J = 8.5$ Hz, 1H), 4.22 (t, $J = 16.2$ Hz, 1H), 3.75 (dd, $J = 10.4$, 13.0 Hz, 1H), 3.03 (dd, $J = 10.3$, 13.1 Hz, 1H), 2.89 (d, $J = 13.5$ Hz, 1H), 2.47 (d, $J = 12.3$ Hz, 1H), 2.04 (d, $J = 8.5$ Hz, 1H), 1.85 (d, $J = 11.2$ Hz, 1H), 1.16-1.71 (m, 7H), 0.98 (d, $J = 6.6$ Hz, 9H), 0.96-1.16 (m, 5H), 0.83-0.91 (m, 4H), 0.38-0.65 (m, 5H); $^{13}$C NMR (CDCl$_3$, 90 MHz) $\delta$ 135.1, 134.5, 134.2 (d, $J = 4.1$ Hz), 133.8 (d, $J = 2.4$ Hz), 133.7, 133.6, 133.3 (d, $J = 2.0$ Hz), 133.0, 132.7, 129.4, 128.9, 128.8 (d, $J = 9.6$ Hz), 128.3, 128.1, 128.0, 127.7, 127.4, 126.6, 126.2 (d, $J = 13.0$ Hz), 126.0, 42.5 (d, $J = 34.0$ Hz), 39.4 (d, $J = 40.6$ Hz), 36.6 (d, $J = 44.3$ Hz), 33.0 (d, $J = 25.9$ Hz), 31.7 (d, $J = 21.0$ Hz), 29.6 (d, $J = 26.8$ Hz), 28.5 (d, $J = 6.0$ Hz), 27.5, 26.6 (dd, $J = 17.7$, 28.0 Hz), 26.1, 26.0, 25.7 (d, $J = 45.4$ Hz); $^{31}$P NMR (CDCl$_3$, 145 MHz) $\delta$ 89.15 (d, $J_{P,P} = 22.2$ Hz), 55.76 (br s); HRMS (ESI+) calcd. for C$_{38}$H$_{49}$BP$_2$SNa (MNa$^+$) 633.3021, found 633.2997.

4-tert-Butyl-3-diphenylphosphanyl-3,5-dihydro-4-phosphacyclohepta[2,1-$\alpha$; 3,4-$\alpha'$]dinaphthalene (4a). To a solution of 10 (150 mg, 0.26 mmol) in 10 mL of toluene was added DABCO (0.234 g, 2.08 mmol) in one portion. The reaction mixture was stirred at 50 °C for 4 h. After removal of the solvent, the residue was purified by
flash column chromatography on silica gel under nitrogen (hexanes:ether, 50:50) to afford 4a as a white solid (128 mg, 90%). $^1$H NMR (CD$_2$Cl$_2$, 360 MHz) δ 8.04 (d, $J = 8.4$ Hz, 1H), 7.99 (d, $J = 8.1$ Hz, 1H), 7.84 (d, $J = 8.1$ Hz, 1H), 7.77 (d, $J = 8.4$ Hz, 1H), 7.69 (d, $J = 8.4$ Hz, 1H), 7.42-7.52 (m, 4H), 7.36-7.40 (m, 1H), 7.07-7.27 (m, 11H), 6.72 (d, $J = 8.5$ Hz, 1H), 4.00 (s, 1H), 2.74-2.90 (m, 2H), 0.94 (d, $J = 11.4$ Hz, 9H); 31P NMR (CD$_2$Cl$_2$, 145 MHz) δ 29.86 (d, $J_{p-p} = 161.7$ Hz), -9.55 (d, $J_{p-p} = 161.2$ Hz); HRMS (ESI+) calcd. for C$_{38}$H$_{35}$P$_2$ (MH$^+$) 553.2214, found 553.2250.

4-tert-Butyl-3-(di-o-tolylphosphanyl)-3,5-dihydro-4-phosphacyclohepta[2,1-α;3,4-α’]dinaphthalene (4b). To the solution of 9b (1.72 g, 2.8 mmol) in 20 mL of toluene was added Si$_2$Cl$_6$ (2.89 mL, 16.8 mmol) slowly. The reaction mixture was heated to reflux and stirred for 24 h before being quenched with 20 mL of NaOH solution (30% w/w). The resulting mixture was heated at 60 °C for 1 h until both layers became clear. The organic layer was extracted with ethyl ether (3 × 15 mL), washed with brine (15 mL), dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel under nitrogen (hexanes:ether, 50:50) to afford 4b as a white solid (1.35 g, 83%). $^1$H NMR (CD$_2$Cl$_2$, 360 MHz) δ 8.01 (d, $J = 8.4$ Hz, 1H), 7.96 (d, $J = 8.2$ Hz, 1H), 7.85-7.92 (m, 3H), 7.78 (d, $J = 8.5$ Hz, 1H), 7.68 (dd, $J = 1.0$, 8.4 Hz, 1H), 7.35-7.40 (m, 3H), 7.21-7.23 (m, 1H), 7.07-7.16 (m, 3H), 6.94-7.05 (m, 4H), 6.75-6.78 (m, 1H), 6.62 (d, $J = 8.5$ Hz, 1H), 3.98 (d, $J = 1.5$ Hz, 1H), 2.71-2.84 (m, 2H), 2.21 (s, 3H), 1.29 (d, $J = 2.6$ Hz, 3H), 0.87 (d, $J = 11.6$ Hz, 9H); 13C NMR (CD$_2$Cl$_2$, 100 MHz) δ 145.7 (d, $J = 31.3$ Hz), 143.2 (d, $J = 29.9$ Hz), 137.8 (d, $J =
17.3 Hz), 137.5, 137.0 (d, \(J = 7.6\) Hz), 136.8, 136.6, 134.6, 134.5, 134.4, 134.1, 133.0 (d, \(J = 6.7\) Hz), 132.5, 132.4, 131.9, 130.1 (d, \(J = 4.2\) Hz), 129.6 (d, \(J = 5.8\) Hz), 129.4, 129.0 (d, \(J = 5.9\) Hz), 128.6, 128.3, 128.2, 128.1, 127.7, 127.3, 127.0, 126.1, 126.0, 125.8, 25.5, 125.2, 124.9, 41.4 (dd, \(J = 24.3, 36.1\) Hz), 30.8 (dd, \(J = 11.3, 25.4\) Hz), 28.3 (d, \(J = 23.9\) Hz), 28.0 (d, \(J = 14.1\) Hz), 22.5 (dd, \(J = 7.1, 24.5\) Hz), 20.3 (d, \(J = 27.1\) Hz); \(^{31}\)P NMR (CD\(_2\)Cl\(_2\), 145 MHz) \(\delta\) 28.41 (d, \(J_{P-P} = 157.1\) Hz), -40.76 (d, \(J_{P-P} = 157.1\) Hz); HRMS (ESI+) calcd. for C\(_{40}\)H\(_{39}\)P\(_2\) (MH\(^+\)) 581.2527, found 581.2470.

**4-tert-Butyl-3-dicyclohexylphosphanyl-3,5-dihydro-4-phosphacyclohepta-[2,1-\(\alpha\); 3,4-\(\alpha\)']dinaphthalene (4c).** To the solution of 11 (0.495 g, 0.83 mmol) in 15 mL of toluene was added Si\(_2\)Cl\(_6\) (1.14 mL, 6.64 mmol) slowly. The reaction mixture was heated at reflux and stirred for 24 h before being quenched with 15 mL of NaOH solution (30% w/w). The resulting mixture was heated at 60 °C for 1 h until both layers became clear. The organic layer was extracted with ether (3 × 5 mL), washed with brine (5 mL), dried over Na\(_2\)SO\(_4\) and concentrated under reduced pressure. The crude compound was redissolved in 10 mL of toluene and DABCO (0.372 g, 3.32 mmol) was added in one portion. The resulting mixture was stirred at 50 °C for 4 h. After the reaction was completed, solvent was removed under vacuum. The residue was purified by flash column chromatography on silica gel under nitrogen (hexanes:ether, 50:50) to afford 4c as a white solid (0.225 g, 48%). \(^1\)H NMR (CD\(_2\)Cl\(_2\), 360 MHz) \(\delta\) 7.84-7.93 (m, 4H), 7.60 (d, \(J = 8.3\) Hz, 1H), 7.33-7.47 (m, 3H), 7.13-7.25 (m, 3H), 7.02 (d, \(J = 8.5\) Hz, 1H), 3.52 (s, 1H), 2.87 (d, \(J = 11.5\) Hz, 1H), 2.74 (dd, \(J = 11.9, 15.6\) Hz, 1H), 1.63-1.82 (m, 6H), 1.29-1.57 (m, 6H), 1.15-1.23 (m, 4H), 1.05 (d, \(J = 11.1\) Hz, 9H), 0.67-0.88 (m, 5H), 0.52
(s, 1H); $^{13}$C NMR (CD$_2$Cl$_2$, 75 MHz) $\delta$ 138.3 (d, $J = 4.2$ Hz), 134.7 (d, $J = 3.3$ Hz), 134.0, 133.8, 133.6, 133.1, 132.8, 132.5, 131.6, 128.8, 128.5, 128.3, 127.8 (d, $J = 2.0$ Hz), 127.7, 127.3, 127.0, 125.9, 125.6, 125.3, 124.7, 36.0 (d, $J = 3.2$ Hz), 35.8 (d, $J = 13.1$ Hz), 35.5, 35.1, 34.8 (d, $J = 4.5$ Hz), 34.4 (d, $J = 4.3$ Hz), 33.1 (dd, $J = 7.6$, 13.5 Hz), 31.9 (dd, $J = 3.6$, 13.0 Hz), 31.8, 31.6, 31.4, 31.3, 29.2, 28.5 (d, $J = 13.3$ Hz), 28.2 (dd, $J = 2.2$, 16.8 Hz), 28.1 (d, $J = 13.8$ Hz), 27.0, 26.7; $^{31}$P NMR (CD$_2$Cl$_2$, 145 MHz) $\delta$ 34.70 (d, $J_{P-P} = 133.8$ Hz), 10.38 (d, $J_{P-P} = 133.6$ Hz).

4-tert-Butyl-3-(di-tert-butylphosphanyl)-3,5-dihydro-4-phosphacyclohepta-[2,1-α; 3,4-α′]dinaphthalene (4d). To the solution of 9d (0.40 g, 0.73 mmol) in 10 mL of toluene was added Si$_2$Cl$_6$ (1.22 mL, 7.1 mmol) slowly. The reaction mixture was heated at reflux and stirred for 24 h before being quenched with 12 mL of NaOH solution (30% w/w). The resulting mixture was heated at 60 °C for 1 h until both layers became clear. The organic layer was extracted with ethyl ether (3 × 15 mL), washed with brine (15 mL), dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel under nitrogen (hexanes:ether, 50:50) to afford 4d as a white solid (0.31 g, 82%). $^1$H NMR (CD$_2$Cl$_2$, 360 MHz) $\delta$ 7.83-7.92 (m, 4H), 7.59 (d, $J = 8.2$ Hz, 1H), 7.34-7.47 (m, 3H), 7.11-7.22 (m, 3H), 7.00 (d, $J = 8.5$ Hz, 1H), 3.34 (s, 1H), 2.69-2.86 (m, 2H), 1.23 (d, $J = 15.0$ Hz, 9H), 1.12 (d, $J = 11.1$ Hz, 9H), 1.02 (d, $J = 15.0$ Hz, 9H); $^{31}$P NMR (CD$_2$Cl$_2$, 145 MHz) $\delta$ 56.61 (d, $J_{P-P} = 32.9$ Hz), 35.23 (d, $J_{P-P} = 32.3$ Hz); HRMS (ESI+) calcd. for C$_{34}$H$_{43}$P$_2$ (MH$^+$) 513.2840, found 513.2812.
General procedure for preparation of Rh complexes 12. A solution of ligand 4 (0.25 mmol) in 5 mL of THF was added dropwise to a solution of [Rh(cod)2]BF4 (0.25 mmol) in 8 mL of methanol at rt while stirring. After addition, the reaction mixture was stirred for 1 h and solvents were removed in vacuo to provide an orange solid.

[Rh(cod)4a]BF4 (12a). 1H NMR (CD2Cl2, 360 MHz) 8.12 (d, J = 8.2 Hz, 1H), 7.82-8.04 (m, 3H), 7.78 (d, J = 8.1 Hz, 1H), 7.42-7.59 (m, 8H), 7.23 (t, J = 7.1 Hz, 1H), 7.06-7.10 (m, 1H), 6.82-6.86 (m, 2H), 6.62-6.67 (m, 3H), 6.48-6.54 (m, 2H), 5.98 (m, 2H), 5.78 (br s, 1H), 5.54 (s, 2H), 5.14 (br s, 1H), 4.96 (br s, 1H), 3.42 (d, J = 12.9 Hz, 1H), 3.24 (t, J = 14.9 Hz, 1H), 2.83-2.92 (m, 1H), 2.51-2.54 (m, 3H), 2.24-2.31 (m, 2H), 1.24 (d, J = 15.0 Hz, 9H); 31P NMR (CD2Cl2, 145 MHz) 22.92 (dd, J = 72.1, 127.1 Hz), -23.11 (dd, J = 72.1, 134.2 Hz); HRMS (ESI+) calcd. for C46H46P2Rh (cation) 763.2130, found 763.2094; HRMS (ESI−) calcd. for BF4 (anion) 87.0029, found 87.0023.

[Rh(cod)4b]BF4 (12b). 1H NMR (CD2Cl2, 360 MHz) 8.18-8.23 (m, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.96 (d, J = 8.5 Hz, 1H), 7.86 (d, J = 8.1 Hz, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.76 (d, J = 8.1 Hz, 1H), 7.70 (d, J = 8.4 Hz, 1H), 7.62 (t, J = 7.6 Hz, 1H), 7.37-7.42 (m, 2H), 7.24 (t, J = 7.7 Hz, 1H), 6.99-7.11 (m, 3H), 6.66-6.69 (m, 2H), 6.50 (t, J = 7.5 Hz, 1H), 6.35 (dd, J = 3.3, 7.3 Hz, 1H), 6.09-6.20 (m, 3H), 6.02 (d, J = 8.6 Hz, 1H), 5.53 (s, 2H), 5.40 (br s, 1H), 5.10 (br s, 1H), 3.22-3.29 (m, 2H), 2.85 (d, J = 3.8 Hz, 2H), 2.27 (s, 3H), 2.14-2.25 (m, 5H), 1.30 (d, J = 14.8 Hz, 9H), 1.10 (s, 3H); 31P NMR (CD2Cl2, 145 MHz) 26.52 (dd, J = 62.3, 131.3 Hz), -17.52 (dd, J = 63.5, 131.2 Hz); HRMS
(ESI+) calcd. for C\textsubscript{48}H\textsubscript{50}P\textsubscript{2}Rh (cation) 791.2413, found 791.2443; HRMS (ESI−) calcd. for BF\textsubscript{4} (anion) 87.0029, found 87.0021.

\[
[Rh(cod)\textsubscript{4}c]BF\textsubscript{4} (12c). \quad \textsuperscript{1}H NMR (CD\textsubscript{2}Cl\textsubscript{2}, 360 MHz) \ \delta \ 8.18 \ (d, J = 8.3 \ Hz, 1H),
\]
7.95-8.05 (m, 4H), 7.52 (t, J = 7.2 Hz, 2H), 7.41 (d, J = 8.4 Hz, 1H), 7.21-7.29 (m, 2H), 7.14 (d, J = 8.5 Hz, 1H), 7.00 (d, J = 8.5 Hz, 1H), 5.71 (s, 1H), 5.39 (s, 1H), 5.32 (s, 1H), 5.08-5.15 (m, 2H), 3.66-3.69 (m, 3H), 3.40-3.43 (m, 1H), 3.22-3.30 (m, 1H), 2.61 (q, J = 7.1 Hz, 2H), 2.31-2.34 (m, 5H), 2.14-2.20 (m, 4H), 1.74-2.03 (m, 9H), 1.32-1.51 (m, 4H), 1.14 (d, J = 14.7 Hz, 9H), 1.02-1.06 (m, 3H); \textsuperscript{13}C NMR (CD\textsubscript{2}Cl\textsubscript{2}, 100 MHz) \ \delta \ 134.9, 134.1, 133.7, 133.6, 133.4, 131.9, 131.8, 130.6, 130.1, 129.4, 129.3, 129.0, 128.6, 128.5, 128.1, 127.9, 127.8, 127.1, 127.0, 126.5, 103.7 (t, J = 8.0 Hz), 97.4 (t, J = 8.0 Hz), 96.3 (t, J = 7.7 Hz), 91.2, 68.1, 52.2 (t, J = 17.0 Hz), 38.8 (d, J = 9.6 Hz), 36.5, 35.5, 33.2, 32.8, 31.6, 31.4, 29.7, 28.8, 28.5 (d, J = 9.0 Hz), 28.3 (d, J = 4.6 Hz), 28.2 (d, J = 6.0 Hz), 28.0 (d, J = 8.5 Hz), 27.5 (d, J = 8.7 Hz), 27.2 (d, J = 3.9 Hz), 26.3, 26.0, 25.9 (d, J = 15.1 Hz), 25.2, 25.1; \textsuperscript{31}P NMR (CD\textsubscript{2}Cl\textsubscript{2}, 145 MHz) \ \delta \ 21.72 (dd, J = 59.8, 129.5 Hz), -6.09 (dd, J = 59.9, 125.4 Hz); HRMS (ESI+) calcd. for C\textsubscript{46}H\textsubscript{58}P\textsubscript{2}Rh (cation) 775.3069, found 775.3003; HRMS (ESI−) calcd. for BF\textsubscript{4} (anion) 87.0029, found 87.0023.

\[
[Rh(cod)\textsubscript{4}d]BF\textsubscript{4} (12d). \quad \textsuperscript{1}H NMR (CD\textsubscript{2}Cl\textsubscript{2}, 360 MHz) \ \delta \ 8.10 \ (d, J = 8.4 \ Hz, 1H),
\]
7.91-7.99 (m, 3H), 7.70 (d, J = 8.4 Hz, 1H), 7.43-7.50 (m, 3H), 7.14 (p, J = 7.5 Hz, 2H), 7.02 (d, J = 8.7 Hz, 1H), 6.71 (d, J = 8.7 Hz, 1H), 5.92 (t, J = 8.1 Hz, 2H), 5.47 (t, J = 14.7 Hz, 1H), 5.43 (s, 1H), 5.04 (s, 1H), 3.29-3.40 (m, 2H), 2.43-2.52 (m, 4H), 2.11-2.27
(m, 4H), 1.56 (d, J = 13.3 Hz, 9H), 1.19 (d, J = 14.2 Hz, 9H), 0.46 (s, 9H); $^{13}$C NMR (CD$_2$Cl$_2$, 75 MHz) $\delta$ 135.9, 135.8, 134.4 (d, J = 2.0 Hz), 134.3, 134.2, 133.3, 131.4, 130.6, 130.5, 130.4, 130.3, 128.9, 128.5, 128.4, 128.2 (d, J = 3.6 Hz), 127.9, 127.3, 127.0, 126.6, 126.5, 104.0 (t, J = 7.0 Hz), 98.9 (dd, J = 6.5, 10.1 Hz), 96.5 (t, J = 7.4 Hz), 91.7 (dd, J = 6.8, 11.0 Hz), 56.8 (d, J = 13.9 Hz), 41.7 (d, J = 4.1 Hz), 39.3, 37.9, 32.6, 32.1, 31.9 (d, J = 4.3 Hz), 30.9, 28.7 (d, J = 3.9 Hz), 28.4, 28.0; $^{31}$P NMR (CD$_2$Cl$_2$, 145 MHz) $\delta$ 36.26 (dd, J = 36.5, 127.3 Hz), 26.32 (dd, J = 36.3, 133.4 Hz); HRMS (ESI+) calcd. for C$_{42}$H$_{54}$P$_2$Rh (cation) 723.2697, found 723.2756; HRMS (ESI−) calcd. for BF$_4$ (anion) 87.0029, found 87.0019.
References and Notes


Chapter 3

Efficient Rhodium-Catalyzed Asymmetric Hydrogenation for the Synthesis of a New Class of N-Aryl β-Amino Acid Derivatives

3.1 Introduction and Background

Enantiomerically pure β-amino acids and their derivatives are very important chiral building blocks for the synthesis of β-peptides, β-lactams and many important biologically active compounds. Several examples of diastereoselective syntheses of β-amino acids have been reported in which chiral auxiliaries were utilized to achieve stereoselectivities. Some of these examples include: Michael addition of amines or lithium amides to α, β-unsaturated esters and Ti(IV) mediated addition to imines. Among the stoichiometric and catalytic methods for β-amino acid synthesis, asymmetric hydrogenation is one of the most atom economic and efficient approaches. Many rhodium and ruthenium complexes with chiral bidentate phosphorus ligands such as BINAP, Duphos, BICP, Bu-BisP, and TangPhos have been successfully used in the asymmetric hydrogenation of β-(acylamino)acrylate derivatives. Recently, monophosphoramidites ligands such as MonoPhos, SIPHOS were also employed to give excellent enantioselectivities in this type of reaction (Figure 3-1).

Rhodium-catalyzed hydrogenation of functionalized olefins is generally considered to proceed by way of a metal chelate complex in which the C-C double bond and a functional group heteroatom are simultaneously coordinated to the metallic center.
Presently, most of the current approaches to Rh-catalyzed asymmetric hydrogenation of unsaturated β-amino acids require an acyl protecting group on the nitrogen of the substrate as a chelating group to achieve high reactivities and enantioselectivities. One major drawback to these approaches is the difficulty of introducing and removing this protecting group. There are few reports of direct acylation of an enamine. In addition, removal of the acyl group requires heating under strong acidic or basic conditions, which might be incompatible with other functional groups in the molecule. All these factors limit the application of this method.

\[
\text{(S)-BINAP: } R = \text{Ph} \quad \text{(S,S)-DuPhos} \quad \text{(R,R)-BICP}
\]

\[
\text{\((S,S)^{-}\text{Bu-BisP}^*: } R = \text{tBu} \quad \text{(S,S,R,R)-TangPhos} \quad \text{(S)-MonoPhos} \quad \text{(S)-SIPHOS}
\]

Figure 3-1: Chiral Phosphine Ligands used in Rh-Catalyzed Asymmetric Hydrogenation of β-(Acylamino)acrylates

\[\text{\(N\)-Aryl \(\beta\)-amino acid derivatives are key structural elements of many natural products and drug intermediates. The most direct and elegant way to prepare such compounds is to perform asymmetric hydrogenation of } N\text{-aryl } \beta\text{-enamino esters (Scheme 3-1). For example, the most efficient way to synthesize drug candidate CGP-68730A}^{10a}\]
is the enantioselective hydrogenation of the analogous \(N\)-aryl \(\beta\)-enamine (Scheme 3-1, route a). It is very difficult to efficiently couple the corresponding aryl moiety with the appropriate chiral amine block (Scheme 3-1, route b). In another example, drug candidate LG-121104\(^{10b}\) can be synthesized through palladium catalyzed amination reaction (Scheme 3-1, route d). However, a more direct and cost effective synthesis of this molecule would be through asymmetric hydrogenation of an \(N\)-aryl \(\beta\)-enamine (Scheme 3-1, route c).

Scheme 3-1: Examples of Drug Candidates and Potential Substrates for Hydrogenation

To the best of our knowledge, only the Merck process group has reported the synthesis of \(\beta\)-amino acids via asymmetric hydrogenation of unprotected enamines with Rh complexes prepared from ferrocenyl-based JosiPhos type ligands.\(^{11}\) Mechanistic
studies show that the reaction possibly proceeds through the corresponding imine tautomer (Scheme 3-2). However, direct formation of unprotected amino esters has the potential to limit the reaction performance (TON: up to 300). The basicity and nucleophilicity of the amine product causes its strong coordination to the rhodium metal center which inhibits the catalytic cycle. There have been no reports on the asymmetric hydrogenation of N-aryl β-enamines. Herein, we report a highly enantioselective hydrogenation of N-aryl β-enamino esters using rhodium complexes with the electron-donating bisphosphines developed in our lab (e.g. TangPhos, DuanPhos, Binapine).

Scheme 3-2: Enamines and Imine Tautomers

\[
\begin{align*}
\text{R} & \quad \text{O} \\
\text{NH}_2 & \quad \text{OR}' \\
\hline
\text{R} & \quad \text{O} \\
\text{NH} & \quad \text{OR}'
\end{align*}
\]

In this chapter, the development of the Rh-TangPhos catalyst system for the asymmetric hydrogenation of N-aryl β-enamino esters will be discussed. The generation of enantioselectivity of this catalytic system based on a dihydride pathway mechanism will also be described.
3.2 Results and Discussion

3.2.1 Substrate Preparation

A family of enamines has been prepared from the corresponding β-keto esters and aniline derivatives (Figure 3-2). For most β-alkyl enaminoo esters 1, the condensation reaction could be performed without solvent in an ultrasound bath. For β-aryl enaminoo esters 2, the condensation reactions were conducted in ethanol with catalytic amount of PTSA (p-toluenesulfonic acid). These compounds are obtained exclusively as the (Z)-isomers according to literature procedures.14
3.2.2 Asymmetric Hydrogenation of N-Aryl β-Enamino Esters

To investigate the asymmetric hydrogenation of N-aryl β-enamino esters, substrate 1a was first employed in the screening of reaction conditions with several ligand systems (Figure 3-3). Surprisingly, poor enantioselectivity (31.9% ee) was obtained for a JosiPhos ligand-derived catalyst (Table 3-1, entry 1), which was previously reported highly effective for hydrogenation of unprotected β-enamines. While chiral biaryl bisphosphine (S)-C₃-TunePhos¹⁵ offered moderate conversion and enantioselectivity (Table 3-1, entry 2), higher conversion was achieved with a more electron-donating trialkyl-bisphosphine TangPhos¹⁶a (Table 3-1, entry 4). (R,R)-Et-DuPhos was also tested, which gave only 47.9% ee and 52% conversion (Table 1, entry 3). Several solvents were also test with the Rh-TangPhos catalytic system (Table 3-1, entries 4-6). TFE (2,2,2-trifluoroethanol) was found to be the optimal solvent for achieving both high conversion and enantioselectivity (Table 3-1, entry 6). Interestingly, we also found that there is a strong pressure effect for this reaction (Table 3-1, entries 7-
Increasing the reaction pressure led to a decrease in the enantioselectivities. Under the optimized reaction conditions, lower conversions and enantioselectivities were obtained with DuanPhos \(^{16b}\) (Table 3-1, entry 10) and Binapine \(^{2f}\) (Table 3-1, entry 11) compared to TangPhos (Table 3-1, entry 6).

Table 3-1: Asymmetric Hydrogenation of Substrate 1a.

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst (^a)</th>
<th>solvent</th>
<th>T(°C)</th>
<th>P (H(_2)) [atm]</th>
<th>conv. (%) (^b)</th>
<th>ee(%) (^c)</th>
<th>config. (^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>TFE</td>
<td>50</td>
<td>6</td>
<td>100</td>
<td>31.9</td>
<td>(-)</td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>MeOH</td>
<td>50</td>
<td>6</td>
<td>67</td>
<td>76.7</td>
<td>(+)</td>
</tr>
<tr>
<td>3</td>
<td>3c</td>
<td>MeOH</td>
<td>50</td>
<td>6</td>
<td>52</td>
<td>47.9</td>
<td>(-)</td>
</tr>
<tr>
<td>4</td>
<td>3d</td>
<td>MeOH</td>
<td>50</td>
<td>6</td>
<td>95</td>
<td>76.1</td>
<td>(-)</td>
</tr>
<tr>
<td>5</td>
<td>3d</td>
<td>CH(_2)Cl(_2)</td>
<td>50</td>
<td>6</td>
<td>77</td>
<td>94.6</td>
<td>(-)</td>
</tr>
<tr>
<td>6</td>
<td>3d</td>
<td>TFE</td>
<td>50</td>
<td>6</td>
<td>100</td>
<td>90.9</td>
<td>(-)</td>
</tr>
<tr>
<td>7</td>
<td>3d</td>
<td>TFE</td>
<td>rt</td>
<td>6</td>
<td>67</td>
<td>92.9</td>
<td>(-)</td>
</tr>
<tr>
<td>8</td>
<td>3d</td>
<td>TFE</td>
<td>rt</td>
<td>30</td>
<td>83</td>
<td>77.7</td>
<td>(-)</td>
</tr>
<tr>
<td>9</td>
<td>3d</td>
<td>TFE</td>
<td>rt</td>
<td>95</td>
<td>75</td>
<td>72.9</td>
<td>(-)</td>
</tr>
<tr>
<td>10</td>
<td>3e</td>
<td>TFE</td>
<td>50</td>
<td>6</td>
<td>78</td>
<td>69.6</td>
<td>(-)</td>
</tr>
<tr>
<td>11</td>
<td>3f</td>
<td>TFE</td>
<td>50</td>
<td>6</td>
<td>58</td>
<td>50.1</td>
<td>(+)</td>
</tr>
</tbody>
</table>

\(^a\) Catalyst 3a: (R)-(S)-JosiPhos/[Rh(cod)Cl]\(_2\); 3b: [Rh(S)-C\(_3\)-TunePhos(cod)]BF\(_4\); 3c: [Rh(R,R)-Et-DuPhos(cod)]BF\(_4\); 3d: [Rh(S,S,R,R)-TangPhos(nbd)]SbF\(_6\); 3e: [Rh(S,R,C)DuanPhos(nbd)]SbF\(_6\); 3f: [Rh(S)-Binapine(cod)]BF\(_4\).  
\(^b\) Assayed by NMR.  
\(^c\) Assayed by chiral HPLC.  
\(^d\) Absolute configuration were not determined.  

Using the optimized reaction conditions for the hydrogenation of 1a (Table 3-1, entry 6), we examined a variety of \(N\)-aryl β-alkyl enamino esters (Table 3-2, entries 2-9). High enantioselectivities were obtained for most of these substrates. Increasing the steric
bulk of the $R^1$ group resulted in a decrease in the ee value (Table 3-2, entry 4). Low conversion and enantioselectivity were observed for substrate $1e$ which has an electron-withdrawing trifluoromethyl group (Table 3-2, entry 5). In order to explore the full potential of this catalytic system, the hydrogenation of $N$-aryl $\beta$-aryl enamine $2b$ was tested under the optimized reaction conditions for the hydrogenation of $N$-aryl $\beta$-alkyl enamines. However, low conversion was observed under these conditions. To address the reactivity issue, the temperature was increased from 50 °C to 80 °C. This modification afforded complete conversion and 91.1% ee (Table 3-2, entry 11). For hydrogenation of $N$-aryl $\beta$-aryl enamines $2$ (Table 3-2, entries 10-14), it was noted that introduction of an electron-withdrawing group on the $\beta$-aryl group resulted in higher enantioselectivity (Table 3-2, entry 12). Furthermore, substrates with ortho-substituted electron-donating $\beta$-aryl groups led to much lower enantioselectivities and reactivities (Table 3-2, entries 13-14).
The origin of enantioselection in the asymmetric hydrogenation of \( N \)-aryl \( \beta \)-enamines with the Rh-TangPhos system is believed to be similar to the hydrogenation with the Rh\( \cdot \)Bu-BisP* system proposed by Gridnev and Imamoto (Scheme 3-3). Two possible intermediates \( A \) and \( B \) in quadrant diagrams were proposed based on a modified quadrant rule. In the favored transition intermediate \( A \), the substrate interacts with the methylene group in the lower left quadrant. On the other hand, the substrate interacts

Table 3-2: Asymmetric Hydrogenation of Substrates 1a-1i, 2a-2e

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>conv.(^{c})</th>
<th>ee(^{d})</th>
<th>config.(^{e})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>100</td>
<td>90.9</td>
<td>(-)</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>100</td>
<td>94.8</td>
<td>(-)</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>100</td>
<td>94.9</td>
<td>(+)</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>100</td>
<td>89.7</td>
<td>(+)</td>
</tr>
<tr>
<td>5</td>
<td>1e</td>
<td>48</td>
<td>78.9</td>
<td>(+)</td>
</tr>
<tr>
<td>6</td>
<td>1f</td>
<td>100</td>
<td>96.3</td>
<td>(-)</td>
</tr>
<tr>
<td>7</td>
<td>1g</td>
<td>83</td>
<td>96.1</td>
<td>(-)</td>
</tr>
<tr>
<td>8</td>
<td>1h</td>
<td>78</td>
<td>93.8</td>
<td>( R )(^{f})</td>
</tr>
<tr>
<td>9</td>
<td>1i</td>
<td>88</td>
<td>95.7</td>
<td>(-)</td>
</tr>
<tr>
<td>10</td>
<td>2a</td>
<td>100</td>
<td>92.3</td>
<td>(-)</td>
</tr>
<tr>
<td>11</td>
<td>2b</td>
<td>100</td>
<td>91.1</td>
<td>(-)</td>
</tr>
<tr>
<td>12</td>
<td>2c</td>
<td>100</td>
<td>95.3</td>
<td>(+)</td>
</tr>
<tr>
<td>13</td>
<td>2d</td>
<td>100</td>
<td>89.7</td>
<td>(-)</td>
</tr>
<tr>
<td>14</td>
<td>2e</td>
<td>67</td>
<td>79.3</td>
<td>(+)</td>
</tr>
</tbody>
</table>

\(^{a}\) Reaction conditions: 1 mol% catalyst, 50\(^{\circ}\)C, 6 atm of \( H_2 \), 18 h.

\(^{b}\) Reaction conditions: 1 mol% catalyst, 80\(^{\circ}\)C, 6 atm of \( H_2 \), 24 h.

\(^{c}\) Assayed by NMR. \(^{d}\) Assayed by chiral HPLC. \(^{e}\) Absolute configurations were not determined. \(^{f}\) Absolute configuration was determined by comparison of the sign of the optical rotation with the reported data.
with a much more hindered \textit{t}Bu group in the lower right quadrant in the disfavored transition intermediate \textbf{B}. Thus, \textbf{A} is substantially more stable than \textbf{B}, eventually leading to the product with \textit{R} configuration. The modified quadrant rule predicts that: (a) ligands with bulky substituents on the phosphorus atoms in the top-left and bottom-right quadrants give \textit{R}-hydrogenation products; ligands with the opposite orientation give \textit{S}-hydrogenation products; (b) if the substituents are the same or comparable in size, more steric hindrance is given by \textit{quasi}-axial substituents.$^{17a}$

Scheme 3-3: Interpretation of Enantioselection in the Asymmetric Hydrogenation of \textit{N}-Aryl \textit{\beta}-Enamines
3.3 Conclusion

In conclusion, we have developed a highly efficient method for the synthesis of a new class of N-aryl substituted β-amino acid derivatives. The reaction has proven to be highly substrate-dependent. Use of the highly electron-donating trialkyl phosphine ligand TangPhos, is critical for achieving high conversion and enantioselectivity. This method is potentially useful for the preparation of a number of chiral drug intermediates.

Experimental Section

General Methods. All reactions and manipulations were performed under nitrogen unless otherwise stated. Column chromatography was performed using EM silica gel 60 (230~400 mesh). $^1$H, $^{13}$C, and $^{31}$P were recorded on Bruker DPX-300, AMX-360, and CDPX-300 spectrometers. Chemical shifts are reported in ppm downfield from tetramethylsilane with the solvent resonance as the internal standard. Mass spectra were recorded on a KRATOS mass spectrometer MS 9/50 for LR-ESI and HR-ESI. GC analysis was carried out on a Helwett-Packard 6890 gas chromatograph using chiral capillary columns. HPLC analysis was carried out on a Waters™ 600 chromatograph.

General procedure for preparation of 1a-1d, 1f-1i: 3-phenylaminobut-2-enoic acid methyl ester (1a). A mixture of methyl acetoacetate (1.16 g, 10 mmol), aniline (0.93 g, 10 mmol) and acetic acid (60.1 mg, 1 mmol) was placed in a ultrasound bath
Branson 1210 for 3 h. At the end of the reaction, 5 mL of ethanol was added. The solution was dried with Na₂SO₄ and concentrated under reduced pressure. The residue was purified by passing through a silica gel column (hexane:EtOAc, 10:1) to give the pure product as a white solid (1.35 g, 70%). ¹H NMR (300 MHz, CDCl₃) δ 10.38 (br s, 1H), 7.27-7.36 (m, 2H), 7.08-7.19 (m, 3H), 4.71 (s, 1H), 3.69 (s, 3H), 2.00 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 170.7, 159.1, 139.2, 129.0, 125.0, 124.4, 85.5, 50.2, 20.3.

3-Phenylaminobut-2-enoic acid ethyl ester (1b). This compound was obtained from ethyl acetoacetate by the same method used for 1a as a yellow oil (60%). ¹H NMR (300 MHz, CDCl₃) δ 10.44 (br s, 1H), 7.30-7.35 (m, 2H), 7.08-7.18 (m, 3H), 4.72 (s, 1H), 4.17 (q, J = 7.1 Hz, 2H), 2.00 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 170.2, 158.7, 139.2, 128.9, 124.7, 124.1, 85.9, 58.5, 20.1, 14.4.

3-Phenylaminopent-2-enoic acid ethyl ester (1c). This compound was obtained from 3-oxopentanoic acid ethyl ester by the same method used for 1a as a yellow oil (58%). ¹HNMR (400 MHz, CDCl₃) δ 10.42 (br s, 1H), 7.30-7.34 (m, 2H), 7.09-7.18 (m, 3H), 4.75 (s, 1H), 4.16 (q, J = 7.1 Hz, 2H), 2.33 (q, J = 7.5 Hz, 2H), 1.30 (t, J = 7.2 Hz, 3H), 1.04 (t, J = 7.5 Hz, 3H); ¹³CNMR (75 MHz, CDCl₃) δ 171.2, 165.1, 139.7, 129.5, 125.6, 125.5, 84.5, 59.2, 25.9, 15.0, 12.8; MS (ESI) m/z 220 (MH⁺); HRMS calcd. for C₁₃H₁₈NO₂ 220.1338, found 220.1336.

6-Methyl-3-phenylaminohept-2-enoic acid ethyl ester (1d). This compound was obtained from 6-methyl 3-oxoheptanoic acid ethyl ester by the same method used for
1a as a yellow oil (55%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$10.34 (br s, 1H), 7.31-7.36 (m, 2H), 7.09-7.20 (m, 3H), 4.74 (s, 1H), 4.16 (q, $J = 7.1$ Hz, 2H), 2.28-2.33 (m, 2H), 1.48 (sept, $J = 6.6$ Hz, 1H), 1.28-1.37 (m, 5H), 0.77 (d, $J = 6.5$ Hz, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 170.6, 163.8, 139.1, 129.0, 125.1, 125.0, 84.8, 58.6, 37.1, 30.1, 27.6, 22.1, 14.5; MS (ESI) $m/z$ 262 (MH$^+$); HRMS calcd. for C$_{16}$H$_{24}$NO$_2$ 262.1799, found 262.1807.

3-(4-Fluorophenylamino)-but-2-enoic acid ethyl ester (1f). This compound was obtained from ethyl acetoacetate and 4-fluoroaniline by the same method used for 1a as a yellow oil (68%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 10.24 (br s, 1H), 6.97-7.07 (m, 4H), 4.68 (s, 1H) 4.14 (q, $J = 7.1$ Hz, 2H), 1.91 (s, 3H), 1.27 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 170.4, 160.2 (d, $J = 244.9$ Hz), 159.0, 135.2 (d, $J = 2.9$ Hz), 126.6 (d, $J = 8.2$ Hz), 115.7 (d, $J = 22.5$ Hz), 85.8, 58.7, 20.0, 14.5.

3-(3-Bromophenylamino)-but-2-enoic acid ethyl ester (1g). This compound was obtained from ethyl acetoacetate and 3-bromoaniline by the same method used for 1a as a colorless oil (59%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 10.38 (br s, 1H), 7.21-7.24 (m, 2H), 7.14 (t, $J = 7.9$ Hz, 1H), 6.98 (d, $J = 8.3$ Hz, 1H), 4.71 (s, 1H), 4.12 (q, $J = 7.1$ Hz, 2H), 1.99 (s, 3H), 1.26 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 170.0, 157.7, 140.7, 130.1, 127.3, 126.5, 122.4, 122.2, 87.4, 58.7, 20.1, 14.4; MS (ESI) $m/z$ 284 (MH$^+$); HRMS calcd. for C$_{12}$H$_{15}$NO$_2$Br 284.0286, found 284.0286.

3-(4-Methoxyphenylamino)-but-2-enoic acid ethyl ester (1h). This compound was obtained from ethyl acetoacetate and $p$-anisidine by the same method used for 1a as
a yellow solid (70%). $^1$H NMR (300 MHz, CDCl$_3$) δ 10.16 (br s, 1H), 7.01-7.04 (d, $J = 8.5$ Hz, 2H), 6.84-6.86 (d, $J = 8.6$ Hz, 2H), 4.65 (s, 1H), 4.14 (q, $J = 7.1$ Hz, 2H), 3.79 (s, 3H), 1.88 (s, 3H), 1.28 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 170.4, 159.9, 157.4, 132.0, 126.7, 114.1, 84.6, 58.5, 55.3, 20.0, 14.5.

3-(3-Methoxyphenylamino)-but-2-enoic acid ethyl ester (1i). This compound was obtained from ethyl acetoacetate and $m$-anisidine by the same method used for 1a as a yellow oil (63%). $^1$H NMR (300 MHz, CDCl$_3$) δ 10.41 (br s, 1H), 7.20 (t, $J = 8.1$ Hz, 1H), 6.61-6.70 (m, 3H), 4.69 (s, 1H), 4.14 (q, $J = 7.1$ Hz, 2H), 3.77 (s, 3H), 2.01 (s, 3H), 1.28 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 170.2, 160.0, 158.6, 140.4, 129.5, 116.3, 110.1, 109.7, 86.1, 58.6, 55.0, 20.2, 14.4.

General procedure for preparation of 1e and 2a-2e: 3-phenyl-3-phenylaminoacrylic acid ethyl ester (2a). A mixture of ethyl benzoylacetae (1.92 g, 10 mmol), aniline (0.93 g, 10 mmol) and $p$-toluenesulfonic acid monohydrate (0.19 g, 1 mmol) was dissolved in 10 mL of ethanol and refluxed overnight. After the reaction mixture was cooled to rt, the solution was dried with Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by passing through a silica gel column (hexane:EtOAc, 10:1) to give the final product as a pale yellow oil (1.36 g, 51%). $^1$H NMR (300 MHz, CDCl$_3$) δ 10.65 (br s, 1H), 7.60-7.70 (m, 5H), 7.42 (t, $J = 7.4$ Hz, 2H), 7.16-7.30 (m, 1H), 7.00 (d, $J = 7.5$ Hz, 2H), 5.34 (s, 1H), 4.55 (q, $J = 7.1$ Hz, 2H), 1.66 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 170.1, 159.0, 140.3, 135.9, 129.4, 128.6, 128.4, 128.2, 122.9, 122.2, 91.1, 59.3, 14.5.
4,4,4-Trifluoro-3-phenylaminobut-2-enoic acid ethyl ester (1e). This
compound was obtained from ethyl 4,4,4-trifluoroacetooacetate and aniline by the same
method used for 2a as a colorless oil (45%). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 9.90 (br s, 1H), 7.32-7.37 (m, 2H), 7.20-7.27 (m, 3H), 5.38 (s, 1H), 4.22 (q, \(J = 7.1\) Hz, 2H), 1.31 (t, \(J = 7.1\) Hz, 3H); \(^1^3\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 169.6, 147.0 (q, \(J = 31.5\) Hz), 138.3, 129.2, 128.9, 126.6, 126.0, 88.4 (d, \(J = 5.3\) Hz), 60.0, 14.2.

3-Phenylamino-3-\(p\)-tolylacrylic acid methyl ester (2b). This compound was
obtained from methyl 4-methyl-benzoylacetate and aniline by the same method used for
2a as a pale yellow solid (60%). \(^1\)H NMR (360 MHz, CDCl\(_3\)) \(\delta\) 10.33 (br s, 1H), 7.27-7.29 (m, 2H), 7.11-7.15 (m, 4H), 6.93-6.98 (m, 1H), 6.72-6.75 (m, 2H), 5.05 (s, 1H), 3.78 (s, 3H), 2.37 (s, 3H); \(^1^3\)C NMR (90 MHz, CDCl\(_3\)) \(\delta\) 170.4, 159.3, 140.5, 139.6, 132.9, 129.1, 128.6, 128.1, 122.9, 122.2, 90.3, 50.6, 21.3; MS (ESI) \(m/z\) 268 (MH\(^+\)); HRMS calcd. for C\(_{17}\)H\(_{18}\)NO\(_2\) 268.1338, found 268.1340.

3-(4-Fluorophenyl)-3-phenylaminoacrylic acid methyl ester (2c). This
compound was obtained from methyl 4-fluorobenzoylacetate and aniline by the same
method used for 2a as a white solid (58%). \(^1\)H NMR (360 MHz, CDCl\(_3\)) \(\delta\) 10.30 (br s, 1H), 7.33-7.36 (m, 2H), 7.09-7.13 (m, 2H), 6.94- 7.00 (m, 3H), 6.68-6.70 (m, 2H), 5.01 (s, 1H), 3.76 (s, 3H); \(^1^3\)C NMR (90 MHz, CDCl\(_3\)) \(\delta\) 170.2, 163.2 (d, \(J = 249.5\) Hz), 157.9, 140.1, 131.8 (d, \(J = 3.1\) Hz), 130.0 (d, \(J = 8.4\) Hz), 128.6, 123.1, 122.2 (d, \(J = 6.6\) Hz), 115.4 (d, \(J = 21.4\) Hz), 90.7, 50.6; MS (ESI) \(m/z\) 272 (MH\(^+\)); HRMS calcd. for C\(_{16}\)H\(_{15}\)NO\(_2\)F 272.1087, found 272.1073.
3-(2-Methoxyphenyl)-3-phenylaminoacrylic acid methyl ester (2d). This compound was obtained from methyl 2-methoxybenzoylacetaate and aniline by the same method used for 2a as a white solid (67%). $^1$H NMR (300 MHz, CDCl$_3$) δ 10.52 (br s, 1H), 7.33-7.37 (m, 2H), 6.91-7.08 (m, 4H), 6.66-6.73 (m, 3H), 4.86 (s, 1H), 3.74 (s, 3H), 3.40 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 170.5, 157.6, 155.9, 140.3, 130.8, 130.0, 128.1, 124.9, 123.1, 121.3, 120.7, 110.9, 88.4, 55.0, 50.4; MS (ESI) m/z 284 (MH$^+$); HRMS calcd. for C$_{17}$H$_{18}$NO$_3$ 284.1287, found 284.1283.

3-Phenylamino-3-o-tolylacrylic acid methyl ester (2e). This compound was obtained from methyl 2-methylbenzoylacetaate and aniline by the same method used for 2a as a white solid (62%). $^1$H NMR (360 MHz, CDCl$_3$) δ 10.59 (br s, 1H), 7.12-7.31 (m, 3H), 6.95-7.03 (m, 3H), 6.77-6.86 (m, 1H), 6.52-6.55 (m, 2H), 4.73 (s, 1H), 3.68 (s, 3H), 2.07 (s, 3H); $^{13}$C NMR (90 MHz, CDCl$_3$) δ 170.5, 159.4, 139.7, 135.7, 135.4, 130.3, 129.1, 128.7, 128.6, 125.9, 123.0, 120.6, 88.9, 50.5, 19.3; MS (ESI) m/z 268 (MH$^+$); HRMS calcd. for C$_{17}$H$_{18}$NO$_2$ 268.1338, found 268.1341.

General asymmetric hydrogenation procedure. In a glovebox, 0.002 mmol of catalyst and 0.2 mmol of substrates were dissolved in 1 mL of TFE (2,2,2-trifluoroethanol). This solution was then transferred to an autoclave. The hydrogenation was performed at 50 °C (for 1) and 80°C (for 2) under 6 atm of H$_2$ for 18 to 24 h. After carefully releasing the hydrogen, the reaction mixture was directly passed through a short silica gel plug. The enantiomeric excess was determined by chiral HPLC and the conversion was determined from the crude NMR spectrum.
3-Phenylamino-butyric acid methyl ester (4a). $^1$H NMR (360 MHz, CDCl$_3$) $\delta$ 7.17-7.27 (m, 2H), 6.72 (t, $J$ = 7.3 Hz, 1H), 6.64 (d, $J$ = 7.7 Hz, 2H), 3.95-3.99 (m, 2H), 3.69 (s, 3H), 2.66 (dd, $J$ = 5.2, 15.0 Hz, 1H), 2.44 (dd, $J$ = 6.9, 15.1 Hz, 1H), 1.29 (d, $J$ = 6.4 Hz, 3H); $^{13}$C NMR (90 MHz, CDCl$_3$) $\delta$ 172.2, 146.7, 129.4, 117.7, 113.6, 51.6, 46.0, 40.7, 20.6; $[\alpha]_{20}^{20}$D = -5.5 (c = 1, CHCl$_3$) for 90.9 % ee; Chiralpak OD-H, hex:ipa = 99:1, 1 mL/min, $t_1$ = 21.5 min, $t_2$ = 27.0 min.

3-Phenylamino-butyric acid ethyl ester (4b). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.18-7.23 (m, 2H), 6.64-6.76 (m, 3H), 4.16 (q, $J$ = 7.1 Hz, 2H), 3.94-4.01 (m, 1H), 3.81 (br s, 1H), 2.65 (dd, $J$ = 5.3, 15.0 Hz, 1H), 2.43 (dd, $J$ = 6.9, 15.0 Hz, 1H), 1.26-1.34 (m, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 172.3, 147.3, 129.8, 118.1, 114.0, 60.9, 46.4, 41.5, 21.1, 14.7; $[\alpha]_{20}^{20}$D = -2.2 (c = 1, CHCl$_3$) for 94.8 % ee; Chiralpak OD-H, hex:ipa = 99:1, 1 mL/min, $t_1$ = 15.3 min, $t_2$ = 18.1 min.

3-Phenylaminopentanoic acid ethyl ester (4c). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.15-7.20 (m, 2H), 6.62-6.72 (m, 3H), 4.12 (q, $J$ = 7.2 Hz, 2H), 3.74-3.78 (m, 1H), 2.56 (dd, $J$ = 5.8, 15.0 Hz, 1H), 2.48 (dd, $J$ = 6.2, 15.0 Hz, 1H), 1.60-1.66 (m, 2H), 1.24 (t, $J$ = 7.1Hz, 3H), 0.99 (t, $J$ = 7.4 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 172.1, 147.3, 129.4, 117.5, 113.5, 60.5, 51.8, 39.0, 27.8, 14.2, 10.5; MS (ESI) $m/z$ 222 (MH$^+$); HRMS calcd. for C$_{13}$H$_{20}$NO$_2$ 222.1494, found 222.1498; $[\alpha]_{20}^{20}$D = 7.9 (c = 1, CHCl$_3$) for 94.9 % ee; Chiralpak OD-H, hex:ipa = 99:1, 1 mL/min, $t_1$ = 12.8 min, $t_2$ = 14.4 min.
**6-Methyl-3-phenylaminoheptanoic acid ethyl ester (4d).** $^1$H NMR (300 MHz, CDCl$_3$) δ 7.16-7.27 (m, 2H), 6.63-6.73 (m, 3H), 4.13 (q, $J = 7.1$ Hz, 2H), 3.77 (m, 2H), 2.51-2.62 (m, 2H), 1.54-1.61 (m, 3H), 1.23-1.37 (m, 5H), 0.88-0.91 (m, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 172.0, 147.2, 129.3, 117.3, 113.3, 60.4, 50.6, 39.3, 35.2, 32.8, 28.0, 22.6, 22.5, 14.2; MS (ESI) m/z 264 (MH$^+$); HRMS calcd. for C$_{16}$H$_{26}$NO$_2$ 264.1964, found 264.1957; $[\alpha]^{20}_D = 2.7$ (c = 1, CHCl$_3$) for 89.7 % ee; Chiralpak OD-H, hex:ipa = 99:1, 1 mL/min, $t_1 = 10.5$ min, $t_2 = 12.5$ min.

**4,4,4-Trifluoro-3-phenylaminobutyric acid ethyl ester (4e).** $^1$H NMR (300 MHz, CDCl$_3$) δ 7.25 (t, $J = 7.9$ Hz, 2H), 6.85 (t, $J = 7.0$ Hz, 1H), 6.77 (d, $J = 8.2$ Hz, 2H), 4.46-4.64 (m, 1H), 4.17 (q, $J = 7.1$ Hz, 2H), 3.95-4.00 (m, 1H), 2.87 (dd, $J = 4.5$, 15.6 Hz, 1H), 2.66 (dd, $J = 8.8$, 15.6 Hz, 1H), 1.24 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 169.9, 146.2, 129.8, 119.8, 114.4, 61.8, 53.8 (q, $J = 30.4$ Hz), 35.5 (d, $J = 1.7$ Hz), 14.4; $[\alpha]^{20}_D = 1.4$ (c = 1, CHCl$_3$) for 78.9 % ee; Chiralpak OJ-H, hex:ipa = 99:1, 1 mL/min, $t_1 = 31.2$ min, $t_2 = 40.7$ min.

**3-(4-Fluorophenylamino)-butyric acid ethyl ester (4f).** $^1$H NMR (300 MHz, CDCl$_3$) δ 6.86-6.93 (m, 2H), 6.55-6.61 (m, 2H), 4.17 (q, $J = 7.2$ Hz, 2H), 3.84-3.92 (m, 1H), 3.69 (br s, 1H), 2.59 (dd, $J = 5.4$, 15.0 Hz, 1H), 2.42 (dd, $J = 6.6$, 15.0 Hz, 1H), 1.24-1.34 (m, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 171.8, 155.9 (d, $J = 235.3$ Hz), 143.1, 115.7 (d, $J = 22.2$ Hz), 114.7 (d, $J = 7.4$ Hz), 60.5, 46.8, 40.8, 20.5, 14.2; MS (ESI) m/z 226 (MH$^+$); HRMS calcd. for C$_{12}$H$_{17}$NO$_2$F 226.1243, found 226.1248; $[\alpha]^{20}_D = -2.3$ (c =
1, CHCl₃) for 96.3 % ee; Chiralpak OJ-H, hex:ipa = 99:1, 1 mL/min, \( t_1 = 30.1 \text{ min}, \quad t_2 = 36.1 \text{ min}.

3-(3-Bromophenylamino)-butyric acid ethyl ester (4g). \(^1\)H NMR (300 MHz, CDCl₃) \( \delta \) 7.02 (t, \( J = 8.0 \text{ Hz}, 1\)H), 6.76-6.82 (m, 2H), 6.52-6.55 (m, 1H), 4.15 (q, \( J = 7.1 \text{ Hz}, 2\)H), 3.88-3.94 (m, 2H), 2.59 (dd, \( J = 5.3, 15.1 \text{ Hz}, 1\)H), 2.45 (dd, \( J = 6.4, 15.1 \text{ Hz}, 1\)H), 1.24-1.33 (m, 6H); \(^{13}\)C NMR (75 MHz, CDCl₃) \( \delta \) 171.5, 148.1, 130.6, 123.3, 120.2, 115.9, 112.1, 60.6, 45.8, 40.8, 20.4, 14.2; MS (ESI) \( m/z \) 286 (MH\(^+\)); HRMS calcd. for C₁₂H₁₇NO₂ 286.0443, found 286.0424; \([\alpha]^{20}_D = -1.6 \) (c = 0.9, CHCl₃) for 96.1 % ee; Chiralpak OJ-H, hex:ipa = 99:1, 1 mL/min, \( t_1 = 33.4 \text{ min}, \quad t_2 = 44.9 \text{ min}.

3-(4-Methoxyphenylamino)-butyric acid ethyl ester (4h). \(^1\)H NMR (300 MHz, CDCl₃) \( \delta \) 6.76-6.81 (m, 2H), 6.59-6.64 (m, 2H), 4.14 (q, \( J = 7.1 \text{ Hz}, 2\)H), 3.79-3.90 (m, 1H), 3.74 (s, 3H), 3.41 (br s, 1H), 2.60 (dd, \( J = 5.3, 15.0 \text{ Hz}, 1\)H), 2.39 (dd, \( J = 6.8, 14.9 \text{ Hz}, 1\)H), 1.23-1.28 (m, 6H); \(^{13}\)C NMR (75 MHz, CDCl₃) \( \delta \) 171.9, 152.3, 140.9, 115.3, 114.8, 60.3, 55.6, 47.1, 40.9, 20.5, 14.1; \([\alpha]^{20}_D = -4.0 \) (c = 0.5, MeOH) for 93.8 % ee, and the absolute configuration was determined to be R by comparison with the reported data;\(^{18}\) Chiralpak OJ-H, hex:ipa = 99:1, 1 mL/min, \( t_1 = 80.0 \text{ min}, \quad t_2 = 89.9 \text{ min}.

3-(3-Methoxyphenylamino)-butyric acid ethyl ester (4i). \(^1\)H NMR (300 MHz, CDCl₃) \( \delta \) 7.09 (t, \( J = 8.1 \text{ Hz}, 1\)H), 6.19-6.30 (m, 3H), 4.15 (q, \( J = 7.1 \text{ Hz}, 2\)H), 3.79-3.94 (m, 2H), 3.78 (s, 3H), 2.64 (dd, \( J = 5.1, 15.0 \text{ Hz}, 1\)H), 2.43 (dd, \( J = 6.9, 15.0 \text{ Hz}, 1\)H), 1.24-1.29 (m, 6H); \(^{13}\)C NMR (75 MHz, CDCl₃) \( \delta \) 171.7, 160.8, 148.2, 130.0, 106.5,
102.7, 99.4, 60.4, 55.0, 45.9, 40.9, 20.5, 14.2; MS (ESI) m/z 238 (M+); HRMS calcd. for C_{13}H_{20}NO_{3} 238.1443, found 238.1428; \([\alpha]^{20}_{D} = -3.1\) (c = 1, CHCl_{3}) for 95.7 % ee; Chiralpak OJ-H, hex:ipa = 99:1, 1 mL/min, \(t_1 = 28.9\) min, \(t_2 = 35.1\) min.

3-Phenyl-3-phenylaminopropionic acid ethyl ester (5a). \(^1\)H NMR (300 MHz, CDCl_{3}) \(\delta\) 7.29-7.44 (m, 5H), 7.11-7.17 (m, 2H), 6.59-6.71 (m, 3H), 4.87 (t, \(J = 6.6\) Hz, 1H), 4.62 (br s, 1H), 4.15 (q, \(J = 7.1\) Hz, 2H), 2.83-2.90 (m, 2H), 1.23 (t, \(J = 7.1\) Hz, 3H); \(^{13}\)C NMR (75 MHz, CDCl_{3}) \(\delta\) 171.6, 147.2, 142.6, 129.6, 129.2, 127.9, 126.7, 118.2, 114.1, 61.3, 55.4, 43.4, 14.6; \([\alpha]^{20}_{D} = -1.3\) (c = 1, CHCl_{3}) for 92.3 % ee; Chiralpak OJ-H, hex:ipa = 90:10, 1 mL/min, \(t_1 = 42.0\) min, \(t_2 = 47.5\) min.

3-Phenylamino-3-\(p\)-tolylpropionic acid methyl ester (5b). \(^1\)H NMR (360 MHz, CDCl_{3}) \(\delta\) 7.28-7.31 (m, 2H), 7.12-7.18 (m, 4H), 6.60-6.73 (m, 3H), 4.85 (t, \(J = 6.7\) Hz, 1H), 4.57 (br s, 1H), 3.68 (s, 3H), 2.84 (d, \(J = 6.5\) Hz, 2H), 2.35 (s, 3H); \(^{13}\)C NMR (90 MHz, CDCl_{3}) \(\delta\) 171.6, 146.7, 139.1, 137.0, 129.4, 129.1, 126.1, 117.7, 113.6, 54.6, 51.8, 42.6, 21.0; MS (ESI) m/z 270 (M+); HRMS calcd. for C_{17}H_{20}NO_{2} 270.1494, found 270.1493; \([\alpha]^{20}_{D} = -16.9\) (c = 0.5, CHCl_{3}) for 91.1 % ee; Chiralpak OD-H, hex:ipa = 95:5, 1 mL/min, \(t_1 = 10.3\) min, \(t_2 = 13.3\) min.

3-(4-Fluoro-phenyl)-3-phenylaminopropionic acid methyl ester (5c). \(^1\)H NMR (300 MHz, CDCl_{3}) \(\delta\) 7.34-7.38 (m, 2H), 6.99-7.15 (m, 4H), 6.67-6.73 (m, 1H), 6.54-6.57 (m, 2H), 4.83 (t, \(J = 6.6\) Hz, 2H), 4.57 (br s, 1H), 3.67 (s, 3H), 2.81 (d, \(J = 6.6\) Hz, 2H); \(^{13}\)C NMR (75 MHz, CDCl_{3}) \(\delta\) 171.4, 146.5, 137.8, 129.2, 127.7 (d, \(J = 8.1\) Hz), 118.0,
115.6 (d, \( J = 21.2 \) Hz), 113.7, 54.2, 51.9, 42.6; MS (ESI) \( m/z \) 274 (MH\(^+\)); HRMS calcd. for C\(_{16}\)H\(_{17}\)NO\(_2\)F 274.1243, found 274.1240; \([\alpha]\)^{20}D = 12.2 (c = 0.5, CHCl\(_3\)) for 95.3 % ee; Chiralpak OD-H, hex:ipa = 95:5, 1 mL/min, \( t_1 = 11.6 \) min, \( t_2 = 18.4 \) min.

3-(2-Methoxyphenyl)-3-phenylamino-propionic acid methyl ester (5d). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.28-7.33 (m, 2H), 7.09-7.15 (m, 2H), 6.89-6.92 (m, 2H), 6.58-6.67 (m, 3H), 5.13-5.18 (m, 1H), 4.74 (br s, 1H), 3.93 (s, 3H), 3.65 (s, 3H), 2.94 (dd, \( J = 5.1, 14.9 \) Hz, 1H), 2.83 (dd, \( J = 7.9, 14.9 \) Hz, 1H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 172.1, 156.8, 146.9, 129.2, 129.1, 128.4, 127.6, 120.7, 117.5, 113.7, 110.5, 55.3, 51.7, 50.6, 40.2; MS (ESI) \( m/z \) 286 (MH\(^+\)); HRMS calcd. for C\(_{17}\)H\(_{20}\)NO\(_3\) 286.1443, found 286.1444; \([\alpha]\)^{20}D = -1.7 (c = 0.5, CHCl\(_3\)) for 89.7 % ee; Chiralpak AS, hex:ipa = 99:1, 1 mL/min, \( t_1 = 14.8 \) min, \( t_2 = 20.4 \) min.

3-Phenylamino-3-o-tolylpropionic acid methyl ester (5e). \(^1\)H NMR (360 MHz, CDCl\(_3\)) \( \delta \) 7.39-7.42 (m, 1H), 7.09-7.19 (m, 5H), 6.68 (t, \( J = 7.3 \) Hz, 1H), 6.52 (d, \( J = 7.7 \) Hz, 2H), 5.02-5.06 (m, 1H), 4.50 (br s, 1H), 3.67 (s, 3H), 2.74-2.83 (m, 2H), 2.48 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 172.2, 147.1, 140.2, 135.4, 131.3, 129.6, 127.8, 127.1, 125.5, 118.2, 113.9, 52.4, 51.9, 41.4, 19.5; MS (ESI) \( m/z \) 270 (MH\(^+\)); HRMS calcd. for C\(_{17}\)H\(_{20}\)NO\(_2\) 270.1449, found 270.1444; \([\alpha]\)^{20}D = 2.7 (c = 0.5, CHCl\(_3\)) for 79.3 % ee; Chiralpak OD-H, hex:ipa = 95:5, 1 mL/min, \( t_1 = 11.1 \) min, \( t_2 = 15.6 \) min.
References and Notes


Chapter 4

Chiral Bisphospholane Ligands (Me-Ketalphos): Synthesis of their Rh(I) Complexes and Applications in Asymmetric Hydrogenation

4.1 Introduction and Background

Development of new chiral phosphine ligands has played a significant role in transition metal-catalyzed asymmetric reactions during the last several decades.\(^1\) As the structure of the chiral ligands has a significant impact on the stereochemical outcomes of these processes, design of new and effective chiral ligands based on structural variations of known ligands remains an important pathway for new ligand development. Subtle changes in the geometric, steric and electronic properties of chiral ligands can lead to dramatic variations in catalyst reactivity and enantioselectivity. The chiral \(C_2\)-symmetric bisphospholane ligands DuPhos and BPE reported by Burk and coworkers have attracted much attention due to their effectiveness for asymmetric hydrogenation of functionalized olefins and ketones.\(^2\) Many bisphospholane ligands systems have been developed based on structural modification of DuPhos and BPE (Figure 4-1).
For example, RoPhos reported by Börner, which bears ether substituents on the 3 and 4 positions of the phospholane ring, maintains the high efficiency of DuPhos and BPE in Rh-catalyzed asymmetric hydrogenations. A four-hydroxyl water-soluble ligand, BASPhos, developed by Holz and Börner, enables the hydrogenation reactions to be conducted in aqueous solution with high enantioselectivities. MalPhos, which bears a maleic anhydride backbone, has provided high enantioselectivities in the hydrogenation of (β-acylamino)acrylates. Another water soluble ligand, HydroPhos, which has four hydroxyl groups on the 3 and 4 positions of the phospholanes, has recently been reported independently by the RajanBabu and Zhang groups. Zhang has reported a 1,1’-bis(phospholanyl)ferrocene ligand (Me-f-KetalPhos) with ketal substituents at positions 3
This ligand has shown excellent enantioselectivities in hydrogenation of \( \alpha \)-dehydroamino acid derivatives. The ketal groups of the ligand are important for achieving high enantioselectivities, as the corresponding ligand without these groups only provides moderate ee values.\(^{8b}\) A major advantage of these ligands is their ease of preparation from readily available \( \text{D-mannitol} \).

Carbohydrates have recently attracted extensive attention as ligand precursors since they are readily available enantiomerically pure and have broad functional group diversity. Based on the reported ligand systems that have been successfully used in the Rh-catalyzed asymmetric hydrogenation, we have designed a series of modified DuPhos-type ligands with ketal groups on the 3 and 4 positions of the phospholanes termed Me-ketalPhos (Figure 4-2). Since preparation of the enantiomer of \( 1 \) requires the expensive \( \text{L-mannitol} \), it is more practical to use its diastereomer \( 2 \) as the ligand candidate to achieve the opposite enantioselectivities in asymmetric hydrogenation. In this chapter, the synthesis of \((2S, 3S, 4S, 5S)-\text{Me-ketalPhos} (1)\) and its diastereomer \( 2 \) will be described as well as their application in the Rh-catalyzed asymmetric hydrogenation of functionalized olefins.

![Figure 4-2: Modified DuPhos Type Ligands: Me-KetalPhos](image-url)
4.2 Results and Discussion

4.2.1 Synthesis of Chiral Bisphospholane Ligands 1 and 2

Scheme 4-1: Ligand Synthesis

Reagents and Conditions: a. i) acetone, H$_2$SO$_4$ (cat.), rt, 2 d; ii) HOAc (70%, aq), 2 h; b. i) TsCl, pyridine, CH$_2$Cl$_2$, 0 °C 4 h; ii) LAH, THF, rt 1 h, then refluxing for 2 h; c. i) BzCl, Pyridine, CH$_2$Cl$_2$, -78 °C - 0 °C; ii) TsCl, Et$_3$N, DMAP, CH$_2$Cl$_2$, 0 °C - rt; iii) K$_2$CO$_3$ (5eq), MeOH, CH$_2$Cl$_2$, rt; d. LiHB(Et)$_3$, THF, 0 °C - rt; e. i) SOCl$_2$, Et$_3$N, CH$_2$Cl$_2$, 0 °C, 1 h; ii) NaI0$_4$, RuCl$_3$·xH$_2$O, CH$_3$CN, CCl$_4$, H$_2$O; f. (i) 1,2-H$_2$PC$_6$H$_4$PH$_2$, n-BuLi, THF, (ii) n-BuLi, THF, rt overnight.

The synthetic routes for ligand 1 and 2 are illustrated in Scheme 4-1. D-Mannitol was first converted to 4-O-isopropylidene-D-mannitol (3). Subsequent reduction with
LiAlH₄ furnished the 1, 4-diol 4. Cyclic sulfate 5 was obtained by esterification of 4 with thionyl chloride followed by oxidation with RuCl₃/NaIO₄. Nucleophilic attack on 5 with 1, 2-diphosphinobenzene in the presence of n-BuLi afforded 1 as a white crystalline solid which was purified by recrystallization from ether/methanol. Dibenzoylation and ditosylation of 3, followed by an intramolecular S_N2 reaction, gave diepoxide 6 with inversion of configuration of the two stereogenic centers.⁹ Reduction of diepoxide 6 afforded the desired chiral diol 7 which can be further converted to the final product 2 using the same procedure as for the preparation of 1.

### 4.2.2 Preparation of Rh-Me-KetalPhos Complex

In certain cases, the use of in situ formed metal-ligand complexes leads to slightly lower ee values in comparison to using the corresponding isolated complexes.²d, ¹⁰ A possible explanation is that the formation of the achiral rhodium catalyst species competes with the chiral active catalyst. In our previous attempts to prepare the complexes in situ, we found that the catalysts were inactive in asymmetric hydrogenation, possibly due to the short incubation time of the metal precursor and the ligands. Based on a more recent report,⁶c we were able to obtain an active species by extending the incubation time. However, the asymmetric hydrogenation results via the in situ method of mixing metal precursors with ligands 1 and 2 led to lower enantioselectivities compared to the isolated complexes. In addition, the results for the in situ method were not reproducible. The advantages of using isolated complexes include consistent reproducibility, high enantioselectivity and ease of handling. Since Rh-nbd (nbd =
norbornadiene) complex precursor is more reactive than the Rh-cod (cod = 1,5-cyclooctadiene) complex in the catalyst initiation step,\textsuperscript{11} we selected [Rh(nbd)₂]BF₄ as the complex precursor in our catalyst precursor preparation (Scheme 4-2). Typically, metal complexes were prepared by addition of 1 equivalent of the complex precursor to a solution of ligand in methanol. After removal of the solvent, the appropriate ketalPhos complexes were formed with high purity.

Scheme 4-2: Synthesis of Rhodium Bisphospholane Complex 9 and 10

\[
\begin{align*}
[Rh(nbd)_2]BF_4 + \text{ligand} \quad &\xrightarrow{\text{CH}_3\text{OH, rt, 15 min}} [Rh(nbd)(\text{ligand})]BF_4 \\
9: \text{ligand} = &1 \\
10: \text{ligand} = &2
\end{align*}
\]

4.2.3 Rh-Catalyzed Asymmetric Hydrogenation

Enamides are a typical class of substrates for the evaluation of asymmetric hydrogenation catalysts. Using enamide 11a as the substrate, we have optimized the reaction solvent under typical hydrogenation conditions (10 atm of hydrogen pressure at rt for 24 h). As illustrated in Table 4-1, solvent variation had little to no effect on enantioselectivity with the exception of ethanol (Table 4-1, entry 3, 87% ee). In the screening of reaction solvents, methanol was found to provide inconsistent results while both methylene chloride and isopropanol gave good reproducibility and high enantioselectivity (Table 4-1, entries 1 and 4).\textsuperscript{12}
Table 4-1: Rh-Catalyzed Asymmetric Hydrogenation of an Enamide 11a

- The reactions were carried out at rt under 10 atm of H₂ pressure for 24 h with 100% conversions.
- Enantiomeric excesses were determined by chiral GC using a Supelco Chiral Select 1000 (0.25 mm x 30 m) column.

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>ee(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₂Cl₂</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>CH₃OH</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td>C₂H₅OH</td>
<td>87</td>
</tr>
<tr>
<td>4</td>
<td>i-PrOH</td>
<td>97</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>94</td>
</tr>
<tr>
<td>6</td>
<td>toluene</td>
<td>92</td>
</tr>
</tbody>
</table>

Under the optimized reaction conditions, we investigated asymmetric hydrogenation of a series of enamides utilizing rhodium complexes 9 and 10 as catalysts (Table 4-2). Complete conversions and very high enantioselectivities were observed with complex 9 (92-98% ee’s). Furthermore, trisubstituted enamides gave slightly higher enantioselectivities than did disubstituted substrates (Table 4-2, entries 4-6 vs. entries 2-3). A more detailed study of substrate 11d showed that the TON can be as high as 1000 without any deterioration of the enantioselectivity. The reaction time was not optimized to ensure complete conversion, hence TOF (turnover frequency) was only 70
Catalyst 10 also exhibits similar catalytic performance, providing slightly lower enantioselectivities.

Table 4-2: Asymmetric Hydrogenation of Enamides by 9 and 10

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>complex</th>
<th>ee (%)</th>
<th>config.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ar=Ph, R=isopropyl 11a</td>
<td>9</td>
<td>96</td>
<td>S</td>
</tr>
<tr>
<td>2</td>
<td>Ar=Ph, R=H 11b</td>
<td>9</td>
<td>92</td>
<td>S</td>
</tr>
<tr>
<td>3</td>
<td>Ar=p-CF3-Ph, R=H 11c</td>
<td>9</td>
<td>96</td>
<td>S</td>
</tr>
<tr>
<td>4</td>
<td>Ar=p-OMe-Ph, R=CH3 11d</td>
<td>9</td>
<td>97</td>
<td>S</td>
</tr>
<tr>
<td>5</td>
<td>Ar=p-CF3-Ph, R=CH3 11e</td>
<td>9</td>
<td>97</td>
<td>S</td>
</tr>
<tr>
<td>6</td>
<td>Ar=Ph, R=CH3 11f</td>
<td>9</td>
<td>98</td>
<td>S</td>
</tr>
<tr>
<td>7</td>
<td>11a</td>
<td>10</td>
<td>93</td>
<td>R</td>
</tr>
<tr>
<td>8</td>
<td>11b</td>
<td>10</td>
<td>94</td>
<td>R</td>
</tr>
<tr>
<td>9</td>
<td>11c</td>
<td>10</td>
<td>93</td>
<td>R</td>
</tr>
<tr>
<td>10</td>
<td>11d</td>
<td>10</td>
<td>94</td>
<td>R</td>
</tr>
<tr>
<td>11</td>
<td>11e</td>
<td>10</td>
<td>95</td>
<td>R</td>
</tr>
<tr>
<td>12</td>
<td>11f</td>
<td>10</td>
<td>93</td>
<td>R</td>
</tr>
</tbody>
</table>

*The reactions were carried out at rt under 10 atm of H2 pressure for 24 h with 100% conversions. Enantiomeric excesses were determined by chiral GC using a Supelco Chiral Select 1000 (0.25 mm x 30 m) column. The absolute configurations were assigned by comparision of the sign of optical rotation with reported data.*

To further explore the potential of this ligand system, we also performed asymmetric hydrogenation of a variety of α-dehydroamino acid derivatives under very mild conditions (dichloromethane as solvent, room temperature, 3 atm of H2, Table 4-3).
Complex 10 was found to be an excellent catalyst for this type of substrate. High enantioselectivities were achieved (Table 4-3, entries 1-7), showing the general effectiveness of the catalytic system. In Rh-catalyzed asymmetric hydrogenations, tetra-substituted olefins usually are more challenging substrates in both reactivity and selectivity compared with trisubstituted ones. With this system, 92% ee and 100% conversion were achieved for tetrasubstituted substrate 13h under mild reaction conditions (Table 4-3, entry 8), which is comparable to the best results that have been previously reported.8a, 15 However, the complex 9 of diastereomeric phospholane 1 only gave hydrogenation products of opposite configurations with much lower enantioselectivities. The detailed reason for the different catalytic behavior of complex 9 and 10 in the hydrogenation of α-dehydroamino acid derivatives is not clear as ligand 1 and 2 are diastereomers rather than enantiomers.
We have also explored hydrogenation of itaconic acid derivatives with catalysts 9 and 10. Excellent results (up to >98% ee) were achieved with an itaconic ester 10a and

Table 4-3: Asymmetric Hydrogenation of α-Dehydroamino acid Derivates by 9 and 10

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>complex</th>
<th>ee&lt;sup&gt;b&lt;/sup&gt;(%)</th>
<th>config.</th>
<th>&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R&lt;sup&gt;1&lt;/sup&gt;=H, R&lt;sup&gt;2&lt;/sup&gt;=H 13a</td>
<td>10</td>
<td>99</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>R&lt;sup&gt;1&lt;/sup&gt;=Ph, R&lt;sup&gt;2&lt;/sup&gt;=H 13b</td>
<td>10</td>
<td>99</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>R&lt;sup&gt;1&lt;/sup&gt;=o-Cl-Ph, R&lt;sup&gt;2&lt;/sup&gt;=H 13c</td>
<td>10</td>
<td>98</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>R&lt;sup&gt;1&lt;/sup&gt;=p-F-Ph, R&lt;sup&gt;2&lt;/sup&gt;=H 13d</td>
<td>10</td>
<td>99</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>R&lt;sup&gt;1&lt;/sup&gt;=m-Br-Ph, R&lt;sup&gt;2&lt;/sup&gt;=H 13e</td>
<td>10</td>
<td>99</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>R&lt;sup&gt;1&lt;/sup&gt;=2-thienyl, R&lt;sup&gt;2&lt;/sup&gt;=H 13f</td>
<td>10</td>
<td>99</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>R&lt;sup&gt;1&lt;/sup&gt;=2-naphthyl, R&lt;sup&gt;2&lt;/sup&gt;=H 13g</td>
<td>10</td>
<td>99</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>R&lt;sup&gt;1&lt;/sup&gt;=CH&lt;sub&gt;3&lt;/sub&gt;, R&lt;sup&gt;2&lt;/sup&gt;=CH&lt;sub&gt;3&lt;/sub&gt; 13h</td>
<td>10</td>
<td>92</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>13a</td>
<td>9</td>
<td>74</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>13b</td>
<td>9</td>
<td>59</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>13c</td>
<td>9</td>
<td>89</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>13d</td>
<td>9</td>
<td>76</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>13e</td>
<td>9</td>
<td>81</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>13f</td>
<td>9</td>
<td>96</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>13h</td>
<td>9</td>
<td>69</td>
<td>S</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> The reactions were carried out at rt under 3 atm of H₂ pressure for 12 h.  
<sup>b</sup> Enantiomeric excesses were determined by chiral GC using a Chirasil-Val III column.  
<sup>c</sup> The absolute configurations were assigned by comparing the sign of optical rotation with reported data.
an β-substituted itaconic acid 10b (Table 4-4), which is comparable to hydrogenation results using rhodium complexes derived from TangPhos,\textsuperscript{16a} or Et-DuPhos.\textsuperscript{16b}

**Table 4-4: Asymmetric Hydrogenation of Itaconic Acid Derivatives by 9 and 10**

<table>
<thead>
<tr>
<th>entry(^a)</th>
<th>substrate</th>
<th>complex</th>
<th>ee(^b) (%)</th>
<th>config.(^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R(^1) = H, R(^2) = CH(_3) 15a</td>
<td>9</td>
<td>98</td>
<td>R</td>
</tr>
<tr>
<td>2</td>
<td>R(^1) = i-Pr, R(^2) = H 15b</td>
<td>9</td>
<td>99(^c)</td>
<td>R</td>
</tr>
<tr>
<td>3</td>
<td>15a</td>
<td>10</td>
<td>99</td>
<td>S</td>
</tr>
<tr>
<td>4</td>
<td>15b</td>
<td>10</td>
<td>98(^c)</td>
<td>S</td>
</tr>
</tbody>
</table>

\(^a\) The reactions were carried out at rt under 10 atm of H\(_2\) pressure for 24 h with 100\% conversions. \(^b\) Enantiomeric excesses were determined by chiral GC using a Gamma-DEX 225 column. \(^c\) % ee was determined on the corresponding methyl esters. \(^d\) The absolute configurations were assigned by comparing the sign of optical rotation with reported data.

To investigate the mechanistic origin of the enantioselectivity of this ligand system, we chose a simple substrate α-(acylamino)acrylate 13b to study the possible transition states with complex 10 (Figure 4-3). Two possible intermediates A and B in quadrant diagrams were considered on the basis of the modified quadrant rule proposed by Gridnev and Imamoto.\textsuperscript{17} In the favored transition intermediate A, the substrate interacts with the methyl group in the lower left quadrant. On the other hand, the substrate interacts with the ketal group in the lower right quadrant in the disfavored
transition intermediate $B$. Thus, $A$ is substantially more stable than $B$, eventually leading to the product with the $R$ configuration. The modified quadrant rule predicts that: (a) ligands with bulky substituents on the phosphorus atoms in the top-left and bottom-right quadrants give $R$ hydrogenation products; ligands with opposite orientation give $S$ hydrogenation products; (b) if the substituents are the same or comparable in size, more steric hindrance is given by quasi-axial substituents.$^{17}$ The observed enantioselection is consistent with this hypothesis.

![Figure 4-3: Rationalization of the Origin of Enantioselectivity](image-url)
4.3 Conclusion

In summary, the modified DuPhos type ligand (2S, 3S, 4S, 5S)-Me-ketalPhos (1) and its diastereomer (2R, 3S, 4S, 5R)-Me-ketalPhos (2) were prepared from readily available D-mannitol. Their rhodium complexes 9 and 10 were isolated and characterized. The investigation of 9 and 10 as catalysts for the asymmetric hydrogenation of several different types of functionalized olefins shows the high reactivity and enantioselectivity of this catalytic system. Quadrant diagrams were also proposed to explain the high enantioselectivity of this catalyst system.

Experimental Section

General Methods. All reactions and manipulations were performed in a nitrogen-filled glovebox or using standard Schlenk techniques. $^1$H, $^{13}$C, and $^{31}$P were recorded on Bruker DPX-300, AMX-360, and CDPX-300 spectrometers. Chemical shifts are reported in ppm downfield from tetramethylsilane with the solvent resonance as the internal standard. Mass spectra were recorded on a KRATOS mass spectrometer MS 9/50 for LR-ESI and HR-ESI. GC analysis was carried out on a Helwett-Packard 6890 gas chromatograph using chiral capillary columns: Chirasil-Val III FOST (dimensions: 30 m $\times$ 0.25 mm) for dehydroamino acid derivatives; Chiral Select 1000 column (dimensions: 15m x 0.25mm) for enamides; $\gamma$ -225 (dimensions: 30 m $\times$ 0.25 mm) for itaconic acid derivatives.
**Ligand 1.** To a stirred solution of 1,2-bis(phosphino)-benzene (1.24 g, 8.72 mmol) in THF (200 mL) was added dropwise n-BuLi (1.6 M n-hexane solution, 10.9 mL, 17.4 mmol) via a syringe at -78 °C. Then the resulting yellow solution was stirred for 2 h at room temperature. After the mixture was cooled to -78 °C, cyclic sulfate 5 (4.39 g, 17.4 mmol) in THF (50 mL) was added over 10 min. The solution was then warmed to room temperature and stirred for 4 h. The mixture was cooled to -78 °C, and n-BuLi (1.6 M solution in n-hexane, 11.0 mL, 17.5 mmol) was added. After the mixture was stirred at room temperature for another 20 h, the solvent was removed under reduced pressure. The residue was dissolved in 50 mL of ethyl ether and washed with 50 mL of brine. The aqueous layer was then extracted with ethyl ether (3 × 40 mL). The combined organic layer was dried over Na₂SO₄ and concentrated to afford a colorless crystalline solid. Recrystallization from Et₂O/MeOH gave the pure product (3.42 g, 87% yield) as a white solid. ³¹H NMR (360 MHz, CDCl₃) δ 7.38-7.33 (m, 4H), 4.46-4.36 (m, 4H), 2.89-2.82 (m, 2H), 2.56-2.51 (m, 2H), 1.47 (s, 6H), 1.42 (s, 6H), 1.33-1.28 (m, 6H), 0.73-0.69 (m, 6H); ¹³C NMR (90 MHz, CDCl₃) δ 140.5, 130.6, 129.0, 117.4, 81.4, 80.5 (t, J = 6.5 Hz), 27.3, 27.3, 25.1 (t, J =10.3 Hz), 24.2, 13.7 (t, J = 19.6 Hz), 12.2; ³¹P NMR (145 MHz, CDCl₃) δ 45.1 (s); HRMS calcd. for C₂₄H₃₇O₄P₂ (MH⁺) 451.2167, found 451.2164.

**Ligand 2.** Prepared from cyclic sulfate 8 using the same procedure for the synthesis of 1. Recrystallization from Et₂O/MeOH gave the pure product as white crystals in 65% yield. ¹H NMR (CDCl₃): δ 7.71 (m, 2 H), 7.44 (m 2 H), 3.83 (m, 4 H), 2.71 (m, 2H), 2.44 (m, 2H), 1.51 (s, 6 H), 1.50 (s, 6 H), 1.35 (m, 6 H), 0.87 (m, 6 H); ¹³C NMR
(CDCl₃): δ 140.3, 132.7, 129.4, 118.4, 89.1, 86.7 (t, J = 7.0 Hz), 29.4 (t, J = 11.0 Hz), 29.0, 27.6, 27.5, 17.1 (t, J = 17.0 Hz), 15.2; ³¹P NMR (CDCl₃): δ 33.7 (s); HRMS calcd. for C₂₄H₃₇O₄P₂ (MH⁺) 451.2167, found 451.2162.

**General procedure for the synthesis of 9 and 10.** To a solution of Me-ketalphos 1 (135 mg, 0.3 mmol) in 20 mL of methanol was added [Rh(nbd)₂]BF₄ (112.2 mg, 0.3 mmol)[nbd = norbornadiene], and the resulting bright orange solution was stirred at rt for 15 min. Solvent was removed under reduced pressure.

[Rh(nbd)(1)]BF₄ 9: ¹H NMR (360 MHz, CD₃OD) δ 7.91-7.96 (m, 2H), 7.78-7.82 (m, 2H), 6.13 (s, 2H), 5.91 (s, 2H), 4.72 (dd, J = 8.04, 10.49 Hz, 2H), 4.29 (dd, J = 7.41, 10.31 Hz, 4H), 3.26-3.32 (m, 2H), 2.77-2.86 (m, 2H), 1.93 (s, 2H), 1.55 (s, 6H), 1.54 (s, 6H), 1.30-1.37 (m, 6H), 0.73-0.79 (m, 6H); ³¹P NMR (CD₃OD) δ 100.1 (d, J_Rh-P = 153.5 Hz); HRMS (cation) m/z calcd. for C₃₁H₄₄O₄P₂Rh 645.1770, found 645.1737; HRMS (anion) m/z calcd. for BF₄ 87.0029, found 87.0024.

[Rh(nbd)(2)]BF₄ 10: ¹H NMR (360 MHz, CD₃OD) δ 8.04-8.28 (m, 2H), 7.86-7.88 (m, 2H), 6.14 (s, 2H), 4.40 (s, 2H), 4.28 (dd, J = 10.1, 18.9 Hz, 2H), 3.76 (dd, J = 8.9, 11.4 Hz, 4H), 2.81-2.92 (m, 2H), 2.62-2.79 (m, 2H), 2.06 (s, 2H), 1.64 (s, 6H), 1.62 (s, 6H), 1.30-1.60 (m, 6H), 0.87-0.93 (m, 6H); ³¹P NMR (CD₃OD) δ 100.8 (d, J_Rh-P = 158.0 Hz); HRMS (cation) m/z calcd. for C₃₁H₄₄O₄P₂Rh 645.1770, found 645.1752; HRMS (anion) m/z calcd. for BF₄ 87.0029, found 87.0021.
General asymmetric hydrogenation procedure using 9 or 10. In a glove box, a solution of 0.005 mmol of catalyst in 1 mL of CH$_2$Cl$_2$ was added 0.5 mmol of substrate. The resulting mixture was transferred to an autoclave. The hydrogenation was performed at rt under 3 to 10 atm of hydrogen for 12 to 24 h. The hydrogen was carefully released and the reaction mixture was passed through a short silica gel plug to remove the catalyst. The enantiomeric excesses were measured by GC with a chiral column directly without any further purification. The absolute configurations of the products were determined by comparing the sign of optical rotation with the reported values.

All the physical characterization data for compounds 3-8 can be found in references $^6$ and $^7$. All the substrates for asymmetric hydrogenation and the hydrogenated products can be found in reference $^{18}$ and the references therein.
References and Notes


128


12. Phosphorus NMR showed that the complex decomposed after a certain period of time (overnight) with detection of a small peak at 83 ppm.

13. The hydrogenation reaction was performed with 0.1 mol % loading of complex 4 under standard reaction conditions for enamides for 16 h with 100% conversion.

14. The hydrogenation reaction was performed with 0.1 mol % loading of complex 4 under standard reaction conditions for enamides for 2 h with 14% conversion.


Chapter 5

Improved Synthesis of a Class of Phosphine-Oxazoline Ligands for Palladium Catalyzed Reactions

5.1 Introduction and Background

C$_2$-Symmetry in ligand design was first proposed by Kagan with the introduction of DIOP.$^1$ Since then, numerous C$_2$-symmetric ligands have been reported and successfully utilized in asymmetric catalysis. C$_2$-Symmetry reduces the number of possible catalyst-substrate coordinations, and as a result, analysis of the possible reaction pathways and the transition states is also simplified. In general, C$_2$-symmetry design is advantageous in studying the mechanism of enantioselection.$^2$ Compared to the popularity of C$_2$-symmetric ligands, unsymmetrical ligands are far less developed. Inspired by the structural features of Crabtree’s catalyst 1,$^3$ Pfaltz reported the synthesis of a number of phosphine oxazoline ligands (termed as PHOX, 2).$^4$ As unsymmetrical ligands, they have been successfully applied in Ir-catalyzed asymmetric hydrogenations, Pd-catalyzed allylic alkylations, Heck reactions and conjugate additions to enones.$^4$ The $\pi$-acceptor character of the phosphorus can stabilize a metal center in a low oxidation state, while the nitrogen $\sigma$-donor ability can facilitate oxidative addition to the metal. This combination can help to stabilize intermediate oxidation states or geometries which form during the catalytic cycle.$^5$ The excellent performance of PHOX has driven Pfaltz and coworkers to develop a further series of efficient P, N ligands, such as phosphite-
oxazoline $^3$, PyrPHOX $^4$, phosphine-imidazoline (PHIM) $^5$, and phosphinite-oxazoline $^6$. Burgess has also reported JM-Phos $^7$ and imidazolylidine-oxazolines $^8$ for Ir-catalyzed asymmetric hydrogenation of unfunctionalized olefins. The Zhang group has recently developed a phospholane-oxazoline ligand $^9$, which has given excellent results in the hydrogenation of unfunctionalized alkenes and unsaturated esters (Figure 5-1).

![Figure 5-1: Some Examples of P, N Ligands](image)

Although JM-Phos exhibits good enantioselectivities in the asymmetric hydrogenation of several unfunctionalized alkenes, we hypothesized that changing the
conformationally flexible ethylene group to a more rigid linker could enhance the enantioselectivities since bidentate ligands bearing more rigid linkers can reduce the number of possible conformations of the metal-substrate complexes in the stereo-determining step, which consequently enhances the enantioselection.\textsuperscript{13} During our effort to design a new class of P, N ligands \textbf{9a-e}, a 1,2-phenyl linker was introduced instead of the ethylene linker. Since ligands \textbf{9a-e} have a structural resemblance to PHOX ligands, we believe that these ligands should have similar catalytic behavior compared with that of PHOX.

In this chapter, the development of a new class of phosphine-oxazoline ligands \textbf{9} will be discussed. An improved synthetic route has been established to circumvent the synthetic issues in the original routes.\textsuperscript{14} Finally, their applications in Pd-catalyzed asymmetric allylic alkylations and Heck reactions will be described.

### 5.2 Results and Discussion

#### 5.2.1 Synthesis of P, N Ligands \textbf{9}

Inexpensive enantiopure phenyl glycinol has been widely used as a building block for the preparation of chiral ligands and chiral auxiliaries.\textsuperscript{15} We believe that the most direct and efficient way to prepare P, N ligands \textbf{9} would involve the \textit{ortho}-substitution of phenyl glycinol. On the basis of a procedure reported by Polniaszek et al.,\textsuperscript{16} we have successfully carried out the \textit{ortho}-lithiation of a silyl-protected phenyl glycinol. Subsequent electrophilic substitution with I\textsubscript{2} or various phosphine chlorides generates
intermediates that are highly modular chiral synthons for the further transformation into an array of P, N ligands.

Based on this method, two different synthetic routes were explored (Scheme 5-1). In route A, (R)-phenyl glycino (10) was protected with TBSCl to give intermediate 11, which was directly subjected to ortho-lithiation with 3 equiv of n-BuLi. Subsequent iodination, followed by aqueous workup, afforded aryl iodide 12. Oxazoline formation by literature methods gave the key intermediate 13. Lithium-halogen exchange of 13 with tBuLi, followed by reaction with PPh₂Cl, afforded the desired ligand 9a. Variation of the phosphine chloride in the last step could allow for facile tuning of the phosphines.

Scheme 5-1: Two divergent Synthetic Routes for Ligands 9

**Route A:**

10 → n-BuLi, THF; TBSCl → 11 → n-BuLi, ether; I₂ → 12

1. tBuCO₂H, EDC, HOBT; 2N HCl → 13 → tBuLi; Ph₂PCl → 9a

TBSCI: tert-butyldimethylsilyl chloride;
EDC: 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride;
HOBT: 1-hydroxy-benzotriazole hydrate;
TEA: triethylamine; DIPEA: diisopropylethylamine
In route B, a phosphine chloride, in place of I₂, was used as the electrophile after the ortho-lithiation. In situ protection of the phosphine with elemental sulfur followed by aqueous workup generated a phosphine sulfide \( \text{14} \), which could be further converted into a series of oxazolines \( \text{15} \) with various \( R^2 \) substituents at the 2-position by reaction with different carboxylic acids. Reduction of sulfide \( \text{15} \) with Raney Ni\(^{17} \) afforded phosphine ligands \( \text{9b-e} \) in excellent yields. The combination of route A and B enable easy modification of both the phosphine and oxazoline moieties.

To circumvent complications with the large scale synthesis of this ligand system, an improved synthetic route was explored which avoided the use of the expensive coupling reagents EDC and HOBT, and also avoided the requirement for column
chromatographic purification of the intermediate 12 and 14 before transformation to 13 and 15 (Scheme 5-2).

Scheme 5-2: Route C (Improved Synthesis of Ligands 9)

Route C:

\[ \text{Raney Ni, MeCN} \]

10

\[ \text{HCl (Conc.), MeOH} \]

56%

16

In route C, following installation of the phosphino group and subsequent sulfur protection, the intermediate was directly treated with concentrated HCl aqueous solution to afford the ammonium salt of the amino alcohol 16. Followed by a standard extraction procedure, the ammonium salt was converted back to amino alcohol 16 under basic conditions providing the compound in over 90% purity and 56% yield. In addition, this intermediate can be directly used in the following transformations without further purification. Inexpensive acid chlorides can be applied in the formation of the amide intermediate to avoid the use of the relatively expensive EDC and HOBT reagents.
Comparable yields of the intermediate oxazolines 15b-e were obtained with this new method. Further reduction of P=S functionality with Raney Ni afforded the final product 9b-e in nearly quantitative yield. This improved route has been successfully utilized in the multigram synthesis of ligand 9a.

5.2.2 Pd-Catalyzed Asymmetric Allylic Alkylation Reactions

Pd-catalyzed asymmetric allylic alkylation reactions (Pd-AAA reactions) have been demonstrated to be a very powerful and efficient approach for asymmetric transformations. While other more widely utilized asymmetric reactions such as hydrogenation and epoxidation can only construct one type of bond, Pd-AAA reactions can be employed to form a variety of C-C, C-O, C-S, C-N and C-H bonds. In most metal catalyzed asymmetric reactions, ligands induce the asymmetry through enantio-differentiation, while application of phosphine-oxazoline ligands in Pd-AAA reactions relies on electronic differentiation by generating electronic asymmetry on the metal center through the presence of different donor atoms. The general catalytic cycle involves olefin complexation, subsequent ionization of a leaving group, followed by nucleophilic addition and decomplexation (Figure 5-2).
To further explore the enantioselection of Pd-catalyzed AAA reactions, we use a symmetrically substituted allyl system as a simple model. In this case, the enantioselectivity is determined by the regioselectivity of the nucleophilic attack. One of the most extensively studied substrates in this system is 1,3-diphenylallyl acetate (17), which generates a meso π-allyl intermediate after ionization (Figure 5-3).

Figure 5-2: Catalytic Cycle for Pd-Catalyzed AAA Reactions

Figure 5-3: AAA Reaction via Symmetrically Substituted Allyl Systems
In Pd-catalyzed AAA reactions, dimethyl malonate is the most commonly used nucleophile in conjunction with allylic acetics or carbonates as substrates. Other nucleophiles, such as amines, nitro compounds, and alcohols were also investigated. In low polarity solvents such as dichloromethane, neutral nucleophiles in combination with N,O-bis(trimethylsilyl)acetamide (BSA) and a catalytic amount of sodium acetate (BSA method) were used to increase substrate solubility.

In order to test the potential of our ligand system, 1,3-diphenylpropenyl acetate (17), in conjunction with the *in situ* formed dimethyl metallomalonate as a nucleophile, was first explored with ligands 9a-d. Under standard reaction conditions with [Pd(η^3-C_3H_5)Cl]_2 as the catalyst precursor, BSA as a base, and KOAc as an additive in CH_2Cl_2 at room temperature, all the catalysts derived from 9a-d provided product 18 in very good yields (86-97%) with high enantiomeric excesses (93-97%, Table 5-1, entries 1-4). Surprisingly, the catalyst derived from ligand 9b showed essentially no enantioselectivity in this reaction. Lowering the reaction temperature is often effective in improving the enantioselectivities in some allylic substitutions. Thus, we carried out the same reaction with ligand 9a at 0 °C. Surprisingly, not only did the yield of the product diminish, but the enantioselectivity dropped from 93% to 88% (Table 5-1, entry 1 vs. entry 5). On the other hand, increasing the reaction temperature from room temperature to 40 °C led to the product with a higher ee (98%, Table 5-1, entry 6). While for ligand 9d, little difference was observed regarding both yield and enantioselectivities of 18 at elevated temperature (Table 5-1, entry 7).
Since a higher temperature, in general, increases the reactivity of a catalyst, this relatively uncommon property of ligand 9a (higher enantioselectivity at higher temperature) prompted us to test the catalytic efficiency of the Pd/9a system at elevated temperatures. As shown in Table 5-1 entry 8, when the reaction was carried out with only 0.2 mol% of Pd catalyst at 40 °C for 12 h, product 18 was obtained in 73% yield without diminishing the enantioselectivity (98% ee). Such a low catalyst loading (substrate-catalyst ratio, S/C = 500) has rarely been reported for Pd-catalyzed allylic

---

Table 5-1: Pd-Catalyzed Asymmetric Allylic Alkylation

<table>
<thead>
<tr>
<th>Entry&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Ligand</th>
<th>Temp</th>
<th>Time</th>
<th>Yield (%)</th>
<th>Ee (%)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9a</td>
<td>rt</td>
<td>12 h</td>
<td>97</td>
<td>93(S)</td>
</tr>
<tr>
<td>2</td>
<td>9b</td>
<td>rt</td>
<td>12 h</td>
<td>93</td>
<td>2(S)</td>
</tr>
<tr>
<td>3</td>
<td>9c</td>
<td>rt</td>
<td>12 h</td>
<td>86</td>
<td>93(S)</td>
</tr>
<tr>
<td>4</td>
<td>9d</td>
<td>rt</td>
<td>12 h</td>
<td>91</td>
<td>97(S)</td>
</tr>
<tr>
<td>5</td>
<td>9a</td>
<td>0 °C</td>
<td>12 h</td>
<td>85</td>
<td>88(S)</td>
</tr>
<tr>
<td>6</td>
<td>9a</td>
<td>40 °C</td>
<td>4 h</td>
<td>97</td>
<td>98(S)</td>
</tr>
<tr>
<td>7</td>
<td>9d</td>
<td>40 °C</td>
<td>4 h</td>
<td>90</td>
<td>97(S)</td>
</tr>
<tr>
<td>8&lt;sup&gt;b&lt;/sup&gt;</td>
<td>9a</td>
<td>40 °C</td>
<td>12 h</td>
<td>73</td>
<td>98(S)</td>
</tr>
</tbody>
</table>

<sup>a</sup> See Experimental Section for a general procedure. <sup>b</sup> 0.1 mol% of [Pd(C<sub>3</sub>H<sub>5</sub>)Cl]<sub>2</sub> and 0.2 mol% of 9a were used. <sup>c</sup> The enantiomeric excess was determined by chiral HPLC (Chiralpak AD column) and the absolute configuration was assigned by comparison of the sign of the optical rotation with reported data.
substitution reactions with P, N-ligands (S/C typically range from 10 to 100), which indicates the high reactivity of the catalyst derived from ligand 9a.

To test the substrate scope and limitations of our new catalysts in allylation reaction of dimethyl malonate, more challenging substrates 19 and 20 were tested with ligand 9a. Under the standard reaction conditions, products 21 and 22 were obtained in good yields but with low enantioselectivities (Scheme 5-3). For the reaction of cyclic substrate 19,20c, 25 product (S)-21 was formed with only 36% ee. For the reaction of unsymmetrical substrate 20,26 a mixture of two regioisomers 22a and 22b was obtained in a 4:1 ratio with 20% ee for the major isomer 2-(1-methyl-3-phenylallyl)malonic acid dimethyl ester (22a). These results indicate that the enantioselectivity of Pd/9a-catalyzed allylic substitution is highly substrate dependent.

**Scheme 5-3: Additional Examples of Pd-Catalyzed Asymmetric Allylic Alkylation**

```
\[ \begin{align*}
\text{OAc} & \quad \text{MeO}_2\text{C} - \text{CO}_2\text{Me} \\
\text{19} & \quad \left[\text{Pd}(\text{C}_3\text{H}_5)\text{Cl}\right]_2 (2.5 \text{ mol%}); \\
& \quad 9a (5 \text{ mol%}) \\
& \quad \text{CH}_2(\text{CO}_2\text{Me})_2 \\
& \quad \text{BSA, KOAc, CH}_2\text{Cl}_2 \\
& \quad \text{rt, 12 h} \\
\text{Ph} & \quad \text{MeO}_2\text{C} - \text{CO}_2\text{Me} & \quad \text{MeO}_2\text{C} - \text{CO}_2\text{Me} \\
\text{20} & \quad (S)\text{-21} & \quad 75\% \text{ yield} \\
& \quad 36\%\text{ ee} \\
& \quad 20\% \text{ ee} & \quad 22a \\
& \quad 91\% \text{ (22a:22b = 4:1)} & \quad 22b
\end{align*} \]
```
To further investigate the origin of the enantioselectivity of Pd-catalyzed AAA reactions, we chose 1,3-diphenyl acetate (17) as a model to study the possible intermediates involved in the enantioselection with Pd/9a as the catalyst. First, a Cache model of Pd/9a was obtained by MM2 calculations (Figure 5-4).

According to extensive mechanistic studies reported by other groups, substrate 17 coordinates to the Pd complex in two possible ways and forms two diastereometric π-allyl intermediates A (exo isomers) and B (endo isomer), which are in rapid equilibration favoring the exo isomer (Scheme 5-4). The possible explanation is that the dominant steric interaction between the ligand and allylic moiety originates from the equatorial phenyl ring of the ligand, which is severer for the endo isomer than for the exo isomer. The preferred product can be obtained by reaction at the allylic carbon trans to the P of the exo isomer or cis to the endo isomer. Mechanistic studies based on 2D NMR suggest that the nucleophile preferentially attacks the carbon trans to the phosphorus atom of the exo isomer. In addition, low-temperature 1H NMR studies of the initially formed product, the alkene-Pd complex, suggest that it arose from a least motion rotation.
following nucleophilic addition.\textsuperscript{27b, 28} Therefore, in order to form the alkene-Pd complex C from the intermediate A, a clockwise rotation of the allylic moiety of approximately 30° must occur. The corresponding activation energy of this reaction pathway would be high as the rotation puts the phenyl group in front of the \( t \)Bu group, given that a late transition state mechanism has been postulated. On the other hand, the formation of complex D from the minor intermediate B via a counter-clockwise rotation of the allylic moiety is favored in energy by releasing the steric congestion between the phenyl and \( t \)Bu groups. Thus, complex D is preferentially formed in a faster reaction rate, leading to the major substitution product with \( S \) configuration. A similar stereochemical interpretation has also been described recently by Wilson et al. for a P, N ligand.\textsuperscript{24a}
**5.2.3 Pd-Catalyzed Asymmetric Intermolecular Heck Reaction**

The Pd-catalyzed vinylation of aryl halides was first reported independently over 30 years ago by Mizoroki and Heck.²⁹ Pd(0)-mediated coupling of an aryl or vinyl halide or triflate with an alkene is now generally defined as the Heck reaction.³⁰ During the past
decade, the catalytic asymmetric version of the Heck reaction has emerged as a reliable method for enantioselective carbon-carbon bond formation.\textsuperscript{31} For instance, intramolecular Heck reaction can generate tertiary stereocenters in natural product synthesis.\textsuperscript{31b} The mechanism of the Heck reaction with bidentate phosphine ligands is generally considered to follow a four step catalytic cycle (shown in Figure 5-5): (a) initial oxidative addition to Pd(0) to form an $\alpha$-arylpalladium(II) complex; (b) subsequent coordination and $\text{syn}$ addition of an alkene to form an $\alpha$-alkylpalladium(II) complex; (c) $\beta$-hydride elimination to release the alkene Heck product; (d) reductive elimination of the hydridopalladium(II) complex to regenerate the active Pd(0) species in presence of a base.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure5-5.png}
\caption{General Mechanism of Pd-Catalyzed Heck Reaction}
\end{figure}
The first example of asymmetric intermolecular Heck reaction was reported by Hayashi in 1991.\textsuperscript{32} It involved the asymmetric arylation of 2,3-hydrofuran (23) using aryl triflates with Pd(OAc)\textsubscript{2}/BINAP catalyst system (Scheme 5-5). The major product was the 2-aryl-2,3-hydrofuran (25) with small amount of 2,5-dihydrofuran (26) isomer.

**Scheme 5-5: First Example of Asymmetric Intermolecular Heck Reaction**

\[
\text{Ph}^+ + \text{Pd(OAc)}_2 \text{(3 mol\%)} \text{ (R)-BINAP (6 mol\%)} \text{i-Pr}_2\text{NEt (3 equiv.)}
\xrightarrow{\text{benzene, 40 oC}}
\begin{align*}
\text{23} & \text{24} & \text{25} & \text{26} \\
& & 71\% (93\%\text{ee}) & 7\% (67\% \text{ee}) \\
\end{align*}
\]

The rationale for the outcome of the result is illustrated in Scheme 5-6 by Hayashi.\textsuperscript{33} Pd(II) complex can coordinate to the alkene on either face of the substrate, affording (R)-27 and (S)-27, which are readily converted to (R) and (S)-28 by \textit{syn} addition. In the case of (S)-28, unfavorable steric factors cause a fast \(\beta\)-hydride elimination to form (S)-29 and release the final product (S)-26. On the other hand, (R)-28 can undergo a re-insertion into the Pd-H bond followed by a second \(\beta\)-hydride elimination, giving the final product (R)-26. The proposed mechanism was further reinforced by the studies of Brown using NMR and mass spectrometry.\textsuperscript{34}
A number of reported asymmetric Heck reactions have utilized BINAP as the ligand, which is very effective in many cases. The most dramatic development has been the introduction by Pfaltz and coworkers of oxazoline-based P, N ligands such as 2 with improved enantioselectivities in several previously reported asymmetric Heck reactions.³⁵ In contrast to the Pd catalysts derived from BINAP, no C-C double bond migration is observed with the Pd/PHOX system. Hence, in cases in which migrated products are undesired, phosphine-oxazolines are the ligands of choice. Recently, several new types of P, N ligands have been synthesized by Kündig,³⁶ Hashimoto,³⁷ Hou,³⁸ and Gilberson.³⁹
These ligands give good enantioselectivities in the Hayashi-type intermolecular Heck reactions.

To further probe the utility of ligand 9, a Pd-catalyzed asymmetric intermolecular Heck reaction of 2,3-dihydrofuran (23) and phenyl triflate (24) was investigated (Table 5-2). Under typical Heck reaction conditions, with Pd$_2$(dba)$_3$ as the catalyst precursor and N,N-diisopropylethylamine as base in benzene at 70 °C, both ligands 9a and 9d provided product 32 in good yield and with high enantioselectivity (Table 5-2, entry 1 and 4). Poor yields and ee values for 32 were observed with 9b and 9c (Table 5-2, entry 2 and 3), implying that a bulky substituent R$^2$ on the oxazoline ring of the ligand is beneficial for both high reactivity and enantioselectivity in this reaction. Regioisomer 33 was not observed under these conditions. Changing the catalyst precursor from Pd$_2$(dba)$_3$ to Pd$_2$(dba)$_3$·CHCl$_3$ resulted in a mixture of 32 and 33 (93:7), although the overall yield and the ee value of the major product 32 were not significantly affected (Table 5-2, entry 1 vs. 5). Using THF in place of benzene as reaction solvent improved both the yield and enantioselectivity of 32 (Table 5-2, entry 1 vs. 6 and entry 5 vs. 7). Therefore, 32 was obtained in almost quantitative yield and 94% ee (Table 5-2, entry 6), which is comparable to the best results obtained with other P, N ligands. Surprisingly, proton sponge, another commonly used base in this transformation, did not promote this reaction (Table 5-2, entry 8).
Table 5-2: Pd-Catalyzed Asymmetric Intermolecular Heck Reaction

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>Pd complex</th>
<th>base</th>
<th>solvent</th>
<th>yield(%) (32:33)</th>
<th>ee(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9a</td>
<td>Pd$_2$(dba)$_3$ dba</td>
<td>iPr$_2$EtN</td>
<td>Benzene</td>
<td>87(&gt;99:1)</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>9b</td>
<td>Pd$_2$(dba)$_3$ dba</td>
<td>iPr$_2$EtN</td>
<td>Benzene</td>
<td>32(&gt;99:1)</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>9c</td>
<td>Pd$_2$(dba)$_3$ dba</td>
<td>iPr$_2$EtN</td>
<td>Benzene</td>
<td>45(&gt;99:1)</td>
<td>78</td>
</tr>
<tr>
<td>4</td>
<td>9d</td>
<td>Pd$_2$(dba)$_3$ dba</td>
<td>iPr$_2$EtN</td>
<td>Benzene</td>
<td>91(&gt;99:1)</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>9a</td>
<td>Pd$_2$(dba)$_3$ CHCl$_3$</td>
<td>iPr$_2$EtN</td>
<td>Benzene</td>
<td>90(93:7)</td>
<td>90(86)</td>
</tr>
<tr>
<td>6</td>
<td>9a</td>
<td>Pd$_2$(dba)$_3$ dba</td>
<td>iPr$_2$EtN</td>
<td>THF</td>
<td>99(&gt;99:1)</td>
<td>94</td>
</tr>
<tr>
<td>7</td>
<td>9a</td>
<td>Pd$_2$(dba)$_3$ CHCl$_3$</td>
<td>iPr$_2$EtN</td>
<td>THF</td>
<td>93(93:7)</td>
<td>93(91)</td>
</tr>
<tr>
<td>8</td>
<td>9a</td>
<td>Pd$_2$(dba)$_3$ dba</td>
<td>proton sponge</td>
<td>Benzene</td>
<td>no rxn</td>
<td>n/a</td>
</tr>
</tbody>
</table>

$^a$ See Experimental Section for a general procedure. $^b$ The total isolated yield of 32 and 33. The ratio of 32:33 was determined by GC. $^c$ The enantiomeric excess of the major isomer 32. The data in parentheses was the enantiomeric excess of the minor isomer 33, if detectable. They were all determined by chiral GC (β-DEX 120 column). The absolutive configuration of 32 was assigned by comparison of the sign of the optical rotation with reported data.

A proposed stereochemical interpretation for the observed enantioselection with ligand 9a is depicted in Figure 5-6. Complex A and B are the two diastereomeric intermediates in the asymmetric Heck reaction of 2,3-dihydrofuran (23) and phenyl triflate (24). Since the chelation of the P, N ligand to the Pd center produces a square planar geometry (as indicated by Cache modeling, Figure 5-4), with the tBu group of the oxazoline ring extending toward lower right corner of the coordination plane, the 2,3-
dihydrofuran substrate suffers severe steric interaction with the \textsuperscript{1}Bu group in complex A relative to complex B. Thus, the reaction preferentially proceeds through the sterically favored intermediate B, leading to \((R)-32\), which is consistent with our experimental observation.

![Proposed Origin of Enantioselection in Pd-Catalyzed Heck Reaction](image)

**Figure 5-6:** Proposed Origin of Enantioselection in Pd-Catalyzed Heck Reaction

### 5.3 Conclusion

In summary, we have developed a novel and efficient method for the syntheses of a new class of conformationally rigid phosphino-oxazoline ligands \(9\) via divergent synthetic routes from inexpensive phenyl glycino. A procedure suitable for large scale ligand preparation is also described. The catalytic potential of these ligands has been demonstrated in highly enantioselective Pd-catalyzed allylic alkylations and
intermolecular Heck reactions. Rationales for the origin of the enantioselection were also proposed based on study of the mechanistically relevant diastereomeric intermediates.

**Experimental Section**

**General Methods.** All reactions and manipulations were performed in a nitrogen-filled glovebox or using standard Schlenk techniques, unless otherwise noted. THF and ether and benzene were dried and distilled from sodium-benzophenone ketyl under nitrogen. Methylene chloride was dried over CaH$_2$ under nitrogen. Column chromatography was performed using Sorbent silica gel 60 Å (230×450 mesh). $^1$H, $^{13}$C, and $^{31}$P were recorded on Bruker DPX-300, CDPX-300, AMX-360, or DRX-400 MHz spectrometers. Chemical shifts are reported in ppm upfield to tetramethylsilane with the solvent resonance as the internal standard. Mass spectra were recorded on a KRATOS MS 9/50 mass spectrometer for LR-ESI and HR-ESI or LR-APCI and HR-APCI. GC analysis was carried out on a Helwett-Packard 6890 gas chromatograph using chiral capillary columns. HPLC analysis was carried out on a Waters$^{\text{TM}}$ 600 chromatograph.

**2-(tert-Butyldimethylsilyloxy)-(1R)-(2-iodophenyl)-ethylamine (12).** To a suspension of ($R$)-$\alpha$-methylbenzylamine 10 (1.37 g, 10.0 mmol) in 40 mL of THF at -78 °C was added $^n$BuLi (2.5 M solution in hexane, 8 mL) dropwise. The resulting purple solution was stirred at -78 °C for 30 min before a solution of TBSCl (tert-butyldimethylsilyl chloride) (3.17 g, 21.0 mmol) in 20 mL of THF was added at the same
temperature. The reaction mixture was allowed to warm to rt naturally and was stirred overnight. After removing the THF solvent under reduced pressure, the residue was redissolved in 50 mL of ether. To this solution at -78 °C was added n-BuLi (2.5 M solution in hexane, 12 mL) dropwise. The reaction mixture was allowed to slowly warm to rt over a period of 3 h and stirred at rt for 1 h. I₂ (5.08 g, 20.0 mmol) was added at -78 °C and the reaction mixture was allowed to warm to rt and stirred for 1 h. 10% Na₂S₂O₃ solution (20 mL) was added and the resulting mixture was stirred vigorously for 10 min. After the usual work up, product 12 was purified by flash column chromatography on silica gel (hexane:EtOAc, 80:20) as a brown oil (2.27 g, 60%). [α]D²⁰ = -49.4 (c = 0.82, CHCl₃); ¹H NMR (CDCl₃, 360 MHz) δ 7.79 (dd, J = 1.1 Hz, J = 7.9 Hz, 1H), 7.57 (dd, J = 1.6 Hz, J = 7.8 Hz, 1H), 7.32 (dt, J = 1.0 Hz, J = 7.8 Hz, 1H), 6.93 (dt, J = 1.7 Hz, J = 7.7 Hz, 1H), 4.33 (dd, J = 3.6 Hz, J = 7.9 Hz, 1H), 3.80 (dd, J = 3.6 Hz, J = 9.9 Hz, 1H), 3.42 (dd, J = 7.9 Hz, J = 9.9 Hz, 1H), 1.82 (s, 2H), 0.91 (s, 9H), 0.07 (s, 3H), 0.03 (s, 3H); ¹³C NMR (CDCl₃, 90 MHz) δ 144.5, 139.5, 129.1, 128.3, 99.9, 67.6, 60.9, 26.1, 18.4, -5.1, -5.2; HRMS (MH⁺) m/z calcd. for C₁₄H₂₅NOSiI 378.0745, found 378.0764.

2-(tert-Butyldimethylsilanyloxy)-(1R)-(2-(diphenylphosphinothioyl)-phenyl)-ethyamine (14a). To a suspension of (R)-α-methylbenzylamine 10 (1.37 g, 10.0 mmol, 1 equiv) in 40 mL of THF at -78 °C was added dropwise n-BuLi (2.5 M solution in hexane, 8 mL). The resulting purple solution was stirred at -78 °C for 30 min before a solution of TBSCI (3.17 g, 21.0 mmol) in 20 mL of THF was added at the same temperature. The reaction mixture was allowed to warm to rt and stirred overnight. After
removing the THF solvent under reduced pressure, the residue was redissolved in 50 mL ether. To this solution at -78 °C was added "BuLi (2.5 M solution in hexane, 12 mL) dropwise. The reaction mixture was allowed to slowly warm to rt during 3 h and stirred at rt for 1 h. Diphenylchlorophosphine (4.42 g, 20.0 mmol) was slowly added at -78 °C and the resulting solution was allowed to warm to rt and stirred overnight. Sulfur (0.960 g, 30.0 mmol) was added at rt and the mixture was stirred for 1 h before water was added. After the usual work up, product 14a was isolated by flash column chromatography (hexane:EtOAc, 90:10) as a white solid (3.03 g, 65%). \( [\alpha]_D^{20} = -66.6 \) (c = 1.6, CHCl\(_3\)); \(^1\)H NMR (360 MHz, CDCl\(_3\)) \( \delta \) 7.85-7.74 (m, 5H), 7.56-7.46 (m, 7H), 7.14 (m, 1H), 6.87 (dd, \( J = 7.8 \) Hz, \( J = 14.7 \) Hz, 1H), 4.80 (dd, \( J = 3.6 \) Hz, \( J = 8.0 \) Hz, 1H), 3.60-3.47 (m, 2H), 1.73 (s, 2H), 0.83 (s, 9H), -0.04 (s, 3H), -0.07 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 147.2 (d, \( J = 9.0 \) Hz), 133.5-131.6 (m), 130.2 (d, \( J = 10.2 \) Hz), 128.6 (d, \( J = 1.2 \) Hz), 128.4 (d, \( J = 1.6 \) Hz), 126.8 (d, \( J = 12.7 \) Hz), 66.9, 53.6 (d, \( J = 7.0 \) Hz), 25.8, 18.2, -5.3, -5.5; \(^{31}\)P NMR (145 MHz, CDCl\(_3\)) \( \delta \) 42.11; HRMS (MH\(^+\)) \textit{m/z} calcd. for C\(_{26}\)H\(_{35}\)NOSiPS 468.1941, found 468.1909.

\textbf{2-(tert-Butyldimethylsilyloxy)-(1R)-[2-(dicyclohexylphosphinothioyl)-phenyl]-ethylamine (14b).} To a suspension of (R)-\( \alpha \)-methylbenzylamine 10 (0.343 g, 2.50 mmol, 1 equiv) in 10 mL THF at -78 °C was added dropwise "BuLi (2.5 M solution in hexane, 2 mL). The resulting purple solution was stirred at -78 °C for 30 min before a solution of TBSCl (0.791 g, 5.25 mmol) in 5 mL THF was added at the same temperature. The reaction mixture was allowed to warm to rt naturally and was stirred
overnight. After removing the THF solvent under reduced pressure, the residue was redissolved in 15 mL ether. To this solution at -78 °C was added "BuLi (2.5 M solution in hexane, 3 mL) dropwise. The reaction mixture was allowed to slowly warm to rt during 3 h and was stirred at rt for 1 h. Dicyclohexylchlorophosphine (0.873 g, 3.75 mmol) was slowly added at -78 °C and the resulting solution was allowed to warm to rt and was stirred overnight. Sulfur (0.240 g, 7.50 mmol) was added at rt and the mixture was stirred for 1 h before water was added. After the usual work up, product 14b was isolated by flash column chromatography (hexane:EtOAc, 90:10) as a yellow oil (0.660 g, 55%).

\[ \alpha \] D

-48.6 (c = 1.1, CHCl 3); \(^1\)H NMR (CDCl 3, 360 MHz) \( \delta \) 8.00 (br s, 1H), 7.72-7.69 (m, 1H), 7.52-7.47 (m, 1H), 7.38-7.34 (m, 1H), 5.18 (br s, 1H), 3.82-3.70 (m, 2H), 2.41-2.35 (m, 2H), 2.11-2.08 (m, 2H), 1.87-1.19 (m, 20H), 0.95 (s, 9H), 0.11 (s, 6H); \(^13\)C NMR (CDCl 3, 90 MHz) \( \delta \) 147.1, 133.5 (m), 130.9, 128.5 (m), 127.0, 126.6, 126.5, 126.3, 68.2, 53.1, 39.8 (d, \( J = 44.6 \) Hz), 39.3 (d, \( J = 48.9 \) Hz), 27.0, 26.8, 26.4-26.1 (m), 25.7, 25.5, 18.0, -5.4, -5.5; \(^31\)P NMR (CDCl 3, 145 MHz) \( \delta \) 61.43 (br s); HRMS (MH\(^+\)) m/z calcd. for C\(_{26}\)H\(_{46}\)NOSiPS 480.2880, found 480.2854.

**General procedure for preparation of oxazolines 13 and 15b-e:** 2-adamantan-1-yl-(4R)-[2-(diphenylphosphinothioyl)-phenyl]-4,5-dihydrooxazole (15d). A mixture of 14a (437 mg, 0.934 mmol), EDC·HCl (1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride) (357 mg, 1.87 mmol), HOBT·H\(_2\)O (1-hydroxy-benzotriazole hydrate) (126 mg, 0.934 mmol), 1-adamantanecarboxylic acid (168 mg, 0.934 mmol), and TEA (triethylamine) (0.53 mL, 3.7 mmol) in 10 mL of DMF was
stirred at 70 °C overnight. To the cooled reaction mixture was added 10 mL of 2N HCl solution followed by 20 mL of EtOAc. The resulting mixture was stirred at rt for 30 min and then the layers were separated. The aqueous layer was extracted with EtOAc (10 mL × 2). The combined organic layers were washed with water and brine, dried over Na2SO4, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane:EtOAc:CH2Cl2, 70:20:10) to give the condensation product as a white solid (336 mg). To a mixture of the above condensation product (316 mg, 0.613 mmol), DIPEA (N,N-diisopropylethylamine) (0.73 mL, 2.5 mmol) and TEA (0.51 mL, 6.1 mmol) in 10 mL of CH2Cl2, was added methanesulfonyl chloride (95 μL, 1.2 mmol) at 0 °C. The resulting mixture was allowed to warm to rt and stirred overnight. After removal of the solvent and the excess DIPEA and TEA under reduced pressure, 15d was isolated by flash column chromatography on silica gel (hexane:EtOAc, 85:15) as a white solid (235 mg, 54% for two steps). \([\alpha]^0_{D} +9.35 \ (c = 0.77, \ CHCl_3); \]  
\[^1\text{H} \text{NMR} \ (\text{CDCl}_3, \ 360 \text{ MHz}) \delta \]  
7.83-7.66 (m, 4H), 7.52-7.40 (m, 7H), 7.32 (dd, \(J = 4.8 \text{ Hz}, J = 6.8 \text{ Hz}, 1\text{H})\), 7.12 (m, 1H), 6.85 (ddd, \(J = 0.7 \text{ Hz}, J = 7.8 \text{ Hz}, J = 14.8 \text{ Hz}, 1\text{H})\), 5.74 (t, \(J = 9.0 \text{ Hz}, 1\text{H})\), 4.49 (dd, \(J = 9.0 \text{ Hz}, J = 9.9 \text{ Hz}, 1\text{H})\), 3.78 (t, \(J = 8.4 \text{ Hz}, 1\text{H})\), 1.98 (s, 3H), 1.91 (s, 6H), 1.69 (s, 6H); \[^{13}\text{C} \text{NMR} \ (\text{CDCl}_3, \ 75 \text{ MHz}) \delta 175.5, 147.4 \ (d, J = 8.5 \text{ Hz}), 133.0 \ (d, J = 5.5 \text{ Hz}), \]  
132.7-132.3 (m), 131.9-131.7 (m), 131.6 (d, \(J = 2.9 \text{ Hz})\), 130.5 (d, \(J = 83.4 \text{ Hz})\), 128.8-128.4 (m), 126.7 (d, \(J = 12.5 \text{ Hz})\), 75.3, 66.6 (d, \(J = 7.0 \text{ Hz})\), 39.6, 36.5, 35.3, 27.8; \[^{31}\text{P} \text{NMR} \ (\text{CDCl}_3, \ 145 \text{ MHz}) \delta 42.30; \]  
HRMS (MH\(^+\)) \text{m/z} \text{ calcd. for } C_{33}H_{33}NOPS \text{ 498.2015, found 498.1990.}
2-tert-Butyl-(4R)-(2-iodophenyl)-4,5-dihydrooxazole (13). This compound was produced from 12 and dimethyl acetic acid following the general procedure as a colorless oil (60%). \([\alpha]_D^{20} = -87.5\) (c = 1.3, CHCl3); \(^1\)H NMR (CDCl3, 360 MHz) \(\delta 7.79\) (dd, \(J = 1.2\) Hz, \(J = 7.9\) Hz, 1H), 7.32 (dt, \(J = 1.2\) Hz, \(J = 7.7\) Hz, 1H), 7.20 (dd, \(J = 1.7\) Hz, \(J = 7.8\) Hz, 1H), 6.94 (dt, \(J = 1.8\) Hz, \(J = 7.6\) Hz, 1H), 5.37 (dd, \(J = 7.8\), \(J = 10.3\) Hz, 1H), 4.76 (dd, \(J = 8.5\) Hz, \(J = 10.3\) Hz, 1H), 3.85 (t, \(J = 8.1\) Hz, 1H), 1.32 (s, 9H); \(^{13}\)C NMR (CDCl3, 90 MHz) \(\delta 176.3, 146.0, 139.2, 129.1\) (d, \(J = 22.0\) Hz), 128.6, 127.4, 98.3, 74.3, 72.8, 33.6, 28.1; HRMS (MH\(^+\)) m/z calcd. for C\(_{13}\)H\(_{17}\)NOI 330.0349, found 330.0363.

2-Benzhydryl-(4R)-(2-(diphenylphosphinothioyl)-phenyl)-4,5-dihydrooxazole (15b). This compound was produced from 14a and diphenyl acetic acid following the general procedure as a white solid (52%). \([\alpha]_D^{20} = +35.4\) (c = 0.65, CHCl3); \(^1\)H NMR (CDCl3, 360 MHz) \(\delta 7.83-7.71\) (m, 4H), 7.56-7.45 (m, 7H), 7.41-7.24 (m, 11H), 7.16 (m, 1H), 6.87 (dd, \(J = 7.7\) Hz, \(J = 14.8\) Hz, 1H), 5.91 (t, \(J = 9.1\) Hz, 1H), 5.26 (s, 1H), 4.72 (t, \(J = 9.6\) Hz, 1H), 3.96 (t, \(J = 8.5\) Hz, 1H); \(^{13}\)C NMR (CDCl3, 75 MHz) \(\delta 169.4, 146.8\) (d, \(J = 8.5\) Hz), 139.2 (d, \(J = 8.7\) Hz), 133.1-130.1 (m), 129.0-128.5 (m), 127.2 (d, \(J = 4.2\) Hz), 127.0 (d, \(J = 12.5\) Hz), 76.3, 66.8 (d, \(J = 7.2\) Hz), 51.2; \(^{31}\)P NMR (CDCl3, 145 MHz) \(\delta 42.38\); HRMS (MH\(^+\)) m/z calcd. for C\(_{34}\)H\(_{29}\)NOPS 530.1702, found 530.1735.

2-(3,5-Di-tert-butylphenyl)-(4R)-[2-(diphenylphosphinothioyl)-phenyl]-4,5-dihydrooxazole (15c). This compound was produced from 14a and 3,5-di-tert-butylbenzoic acid following the general procedure as a white solid (50%). \([\alpha]_D^{20} = +34.0\) (c
$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.54-7.49 (m, 2H), 7.37-7.31 (m, 2H), 6.53 (m, 1H), 4.94 (t, $J$ = 9.5 Hz, 1H), 3.92 (t, $J$ = 8.0 Hz, 1H), 2.54 (m, 1H), 2.31 (m, 1H), 2.09 (m, 1H), 1.91-1.13 (m, 19H), 1.34 (s, 9H); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 175.7, 149.2, 131.7 (d, $J$ = 2.6 Hz), 131.3, 128.6 (d, $J$ = 9.0 Hz), 126.3 (d, $J$ = 10.5 Hz), 125.0 (d, $J$ = 63.8 Hz), 76.2, 66.5 (d, $J$ = 3.7 Hz), 41.2 (d, $J$ = 48.2 Hz), 36.5 (d, $J$ = 51.2 Hz), 33.3, 27.9, 26.6-25.2 (m); $^{31}$P NMR (CDCl$_3$, 145 MHz) $\delta$ 57.27 (br); HRMS (MH$^+$) $m/z$ calcd. for C$_{25}$H$_{39}$NOPS 432.2484, found 432.2462.

2-tert-Butyl-(4R)-[2-(dicyclohexylphosphinothioyl)-phenyl]-4,5-dihydro-oxazole (15e). This compound was produced from 14b and dimethyl acetic acid following the general procedure as a colorless oil (52%). [$\alpha$$_D$$^{20}$ -78.0 ($c$ = 0.50, CHCl$_3$); $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.54-7.49 (m, 2H), 7.37-7.31 (m, 2H), 6.53 (m, 1H), 4.94 (t, $J$ = 9.5 Hz, 1H), 3.92 (t, $J$ = 8.0 Hz, 1H), 2.54 (m, 1H), 2.31 (m, 1H), 2.09 (m, 1H), 1.91-1.13 (m, 19H), 1.34 (s, 9H); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 175.7, 149.2, 131.7 (d, $J$ = 2.6 Hz), 131.3, 128.6 (d, $J$ = 9.0 Hz), 126.3 (d, $J$ = 10.5 Hz), 125.0 (d, $J$ = 63.8 Hz), 76.2, 66.5 (d, $J$ = 3.7 Hz), 41.2 (d, $J$ = 48.2 Hz), 36.5 (d, $J$ = 51.2 Hz), 33.3, 27.9, 26.6-25.2 (m); $^{31}$P NMR (CDCl$_3$, 145 MHz) $\delta$ 57.27 (br); HRMS (MH$^+$) $m/z$ calcd. for C$_{35}$H$_{39}$NOPS 552.2484, found 552.2470.

2-tert-Butyl-(4R)-(2-diphenylphosphanylphenyl)-4,5-dihydrooxazole (9a). To a solution of 13 (94 mg, 0.286 mmol) in 4 mL of ether was added tBuLi (1.7 M solution, 0.34 mL) at -78 °C. The reaction mixture was stirred at -78 °C for 30 min before diphenylchlorophosphine (2.43 g, 11.0 mmol) was added slowly. The solution was
allowed to warm to rt and stirred overnight. Water was added and the aqueous layer was separated and extracted with CH$_2$Cl$_2$. The combined organic layers were dried over Na$_2$SO$_4$ and concentrated. The residue was purified by flash column chromatography to give 9a as a white solid (44 mg, 40%). [α]$^D_{30}$ –50.9 (c = 2.0, CHCl$_3$); $^1$H NMR (CD$_2$Cl$_2$, 360 MHz) δ 7.40-7.26 (m, 12H), 7.19 (dt, $J = 1.5$ Hz, $J = 7.5$ Hz, 1H), 6.93-6.89 (m, 1H), 5.82-5.75 (m, 1H), 4.24 (dd, $J = 8.4$ Hz, $J = 10.2$ Hz, 1H), 3.64 (dt, $J = 0.5$ Hz, $J = 8.4$ Hz, 1H), 1.28 (s, 9H); $^{13}$C NMR (CD$_2$Cl$_2$, 90 MHz) δ 175.8, 148.4 (d, $J = 24.0$ Hz), 136.9 (d, $J = 10.2$ Hz), 135.4-134.2 (m), 130.0-129.3 (m), 127.9 (br s), 126.8 (br s), 75.4 (d, $J = 4.4$ Hz), 67.5 (m), 33.9, 28.3; $^{31}$P NMR (CD$_2$Cl$_2$, 145 MHz) δ -14.97; HRMS (MH$^+$) m/z calcd. for C$_{25}$H$_{27}$NOP 388.1825, found 388.1793.

**General procedure for preparation of ligands 9b-e: 2-adamantan-1-yl-(4R)-(2-diphenylphosphanylphenyl)-4,5-dihydrooxazole (9d).** To a N$_2$-flushed Schlenk flask was loaded 1 g of Raney Ni 2800 slurry. The Raney Ni was washed sequentially with methanol (3 mL × 3), ether (3 mL × 3), and dried and degassed CH$_3$CN (3 mL × 3). To this flask was then transferred a solution of 15d (190 mg, 0.382 mmol) in 6 mL of CH$_3$CN. The resulting mixture was stirred under N$_2$ at rt for 1 d. The mixture was filtered under N$_2$. The Raney Ni solid was washed with CH$_3$CN (3 mL × 3). The combined filtrates were concentrated under reduced pressure and the residue was passed through a short silica gel plug under N$_2$ to give product 9d as a white solid (162 mg, 91%). [α]$^D_{30}$ = 66.1 (c = 0.75, CHCl$_3$); $^1$H NMR (CDCl$_3$, 300 MHz) δ 7.31-7.05 (m, 12H), 6.79 (ddd, $J = 0.9$ Hz, $J = 4.4$ Hz, $J = 7.8$ Hz, 1H), 5.74 (ddd, $J = 5.1$ Hz, $J = 8.3$ Hz, $J = 13.4$ Hz, 1H),
2-Benzhydryl-(4R)-(2-diphenylphosphanylphenyl)-4,5-dihydrooxazole (9b). This compound was produced from 15b following the general procedure as a white solid (94%). [α]$^0_{D}$ –67.9 (c = 0.66, CHCl$_3$); $^1$H NMR (CD$_2$Cl$_2$, 360 MHz) δ 7.44-7.21 (m, 23H), 6.98-6.95 (m, 1H), 5.97 (dt, $J = 5.6$ Hz, $J = 9.4$ Hz, 1H), 5.24 (s, 1H), 4.38 (dd, $J = 8.6$ Hz, $J = 10.3$ Hz), 3.74 (t, $J = 8.6$ Hz); $^{13}$C NMR (CD$_2$Cl$_2$, 90 MHz) δ 169.3, 147.9 (d, $J = 24.4$ Hz), 140.4 (d, $J = 3.6$ Hz), 136.7 (d, $J = 10.3$ Hz), 135.5-134.0 (m), 130.1-126.9 (m), 75.6 (d, $J = 5.3$ Hz), 68.0, 51.7; $^{31}$P NMR (CD$_2$Cl$_2$, 145 MHz) δ -15.10; HRMS (MH$^+$) m/z calcd. for C$_{31}$H$_{33}$NOP 466.2294, found 466.2262.

2-(3,5-Di-tert-butylphenyl)-(4R)-(2-diphenylphosphanylphenyl)-4,5-dihydrooxazole (9c). This compound was produced from 15c following the general procedure as a white solid (95%). [α]$^0_{D}$ –48.3 (c = 0.87, CHCl$_3$); $^1$H NMR (CD$_2$Cl$_2$, 360 MHz) δ 7.95 (d, $J = 1.8$ Hz, 2H), 7.67 (t, $J = 1.8$ Hz, 1H), 7.50-7.47 (m, 1H), 7.43-7.34 (m, 1H), 7.24 (dt, $J = 1.3$ Hz, $J = 7.5$ Hz, 1H), 7.01 (ddd, $J = 1.1$ Hz, $J = 4.4$ Hz, $J = 7.6$ Hz, 1H), 6.11 (ddd, $J = 5.9$ Hz, $J = 8.7$ Hz, $J = 14.5$ Hz, 1H), 4.48 (dd, $J = 8.4$ Hz, $J =$
10.2 Hz, 1H), 3.90 (t, J = 8.5 Hz, 1H), 1.42 (s, 18H); \(^{13}\)C NMR (CD\(_2\)Cl\(_2\), 90 MHz) \(\delta\) 166.1, 151.7, 148.2 (d, J = 23.9 Hz), 137.0 (m), 135.6-133.9 (m), 130.2-126.3 (m), 123.3, 75.4 (d, J = 4.2 Hz), 68.6, 35.5, 31.9; \(^3\)P NMR (CD\(_2\)Cl\(_2\), 145 MHz) \(\delta\) -14.83. HRMS (MH\(^+\)) m/z calcd. for C\(_{35}\)H\(_{39}\)NOP 520.2764, found 520.2750.

**2-tert-Butyl-(4R)-(2-dicyclohexylphosphanylphenyl)-4,5-dihydrooxazole (9e).**

This compound was produced from 15e following the general procedure as a colorless oil (90%). \(\left[\alpha\right]_D^{20} -70.9\) (c = 0.53, CHCl\(_3\)); \(^1\)H NMR (CD\(_2\)Cl\(_2\), 360 MHz) \(\delta\) 7.49-7.47 (m, 1H), 7.37-7.24 (m, 3H), 6.02 (ddd, J = 5.7 Hz, J = 8.4 Hz, J = 14.1 Hz, 1H), 4.76 (dd, J = 8.3 Hz, J = 10.3 Hz, 1H), 3.79 (t, J = 8.3 Hz, 1H), 2.00-0.85 (m, 31H); \(^{13}\)C NMR (CD\(_2\)Cl\(_2\), 75 MHz) \(\delta\) 175.2, 151.0 (d, J = 25.3 Hz), 133.2 (d, J = 20.8 Hz), 133.1 (d, J = 3.4 Hz), 129.5, 126.7, 126.2 (d, J = 6.3 Hz), 75.9 (d, J = 7.2 Hz), 67.9 (d, J = 25.9 Hz), 35.2 (d, J = 12.9 Hz), 34.0 (d, J = 11.7 Hz), 33.7, 31.3-30.9 (m), 30.0 (d, J = 10.2 Hz), 29.2 (d, J = 6.2 Hz), 28.1, 27.7-27.3 (m), 26.8 (d, J = 3.9 Hz); \(^3\)P NMR (CD\(_2\)Cl\(_2\), 145 MHz) \(\delta\) -14.46; HRMS (MH\(^+\)) m/z calcd. for C\(_{25}\)H\(_{39}\)NOP 400.2764, found 400.2726.

**Multigram synthesis of ligand 9a via route C. 2-Hydroxyl-(1R)-(2-(diphenylphosphinothioyl)-phenyl)-ethylamine (16).**

To a suspension of (R)-\(\alpha\)-methylbenzylamine (10) (5.46 g, 0.04 mol) in 150 mL of THF at -78 °C was added \(^9\)BuLi (2.5 M solution in hexane, 32 mL) dropwise. The resulting purple solution was stirred at -78 °C for 30 min before a solution of TBSCl (12.7 g, 0.084 mol) in 80 mL of THF was added at the same temperature. The reaction mixture was allowed to warm to rt and
stirred overnight. After removing the THF solvent under reduced pressure, the residue was redissolved in 200 mL of ether. To this solution at −78 °C was added nBuLi (2.5 M solution in hexane, 48 mL) dropwise. The reaction mixture was allowed to slowly warm to rt during 3 h and stirred at rt for 1 h. Diphenylchlorophosphine (17.7 g, 0.08 mol) was slowly added at −78 °C and the resulting solution was allowed to warm to rt and was stirred overnight. Sulfur (3.84 g, 0.12 mol) was added at rt and the mixture was stirred for 1 h. The solvent was removed and the residue was dissolved in 100 mL of methanol followed by addition of 20 mL of conc. HCl. The mixture was heated at 50 °C for 4 h. After removal of methanol the yellow solid residue was redissolved in 150 mL of water and washed with ether (80 mL × 3). The aqueous layer was then basified by adding 60 mL of 4N NaOH solution. The precipitate formed from the previous step was dissolved in CH2Cl2 and extracted from the aqueous layer. After removal of the solvent, the crude product 16 was obtained as an off-white solid (7.88 g, 56%, about 90% purity by NMR).

\[
\begin{align*}
^{1}H \text{ NMR (360 MHz, CDCl}_3) & \delta 7.68-7.72 (m, 4H), 7.41-7.49 (m, 8H), 7.10 (m, 1H), 6.81 (m, 1H), 4.69 (dd, J = 1.3 Hz, J = 6.6 Hz, 1H), 3.48 (d, J = 6.9 Hz, 2H), 1.88 (s, 2H); \\
^{13}C \text{ NMR (75 MHz, CDCl}_3) & \delta 132.3-132.9 (m), 129.0-129.3 (m), 127.4 (d, J = 13.1 Hz), 67.1, 53.9; \\
^{31}P \text{ NMR (145 MHz, CDCl}_3) & \delta 42.4.
\end{align*}
\]

**2-tert-Butyl-(4R)-[2-(diphenylphosphinothioyl)-phenyl]-4,5-dihydrooxazole (15a).** A mixture of 16 (7.88 g, 22.3 mmol), trimethylacetyl chloride (3.0 mL, 24.5 mmol), and TEA (13.0 mL, 89.2 mmol) in 200 mL of CH2Cl2 was stirred at 0 °C for 2 h. 10 equiv of TEA (32.5 mL, 0.223 mol), 4 equiv of DIPEA (15.6 mL, 89.2 mmol), and 2
equiv of methanesulfonyl chloride (3.45 mL, 44.6 mmol) was added sequentially at the same temperature. The resulting mixture was allowed to warm to rt over a period of 2 h and stirred for another 24 h. TLC showed the completion of the reaction. After removal of the solvent under reduced pressure, 15a was purified by flash column chromatography on silica gel (hexane:EtOAc, 85:15) as a white solid (4.4 g, 47% yield).

2-tert-Butyl-(4R)-(2-diphenylphosphanylphenyl)-4,5-dihydrooxazole (9a). To a N2-flushed Schlenk flask was added about 20 g of Raney Ni 2800 slurry. The Raney Ni was washed sequentially with methanol (30 mL × 3), ether (30 mL × 3), and anhydrous CH₃CN (30 mL × 3). To this flask was then transferred a solution of 15a (4.4 g, 10.5 mmol) in CH₃CN (100 mL). The resulting mixture was stirred under N₂ at rt for 1 d. The reaction mixture was filtered under N₂ and washed with CH₃CN (50 mL × 3). The combined filtrate was concentrated under reduced pressure and the residue was passed through a short silica gel plug under N₂ to give 9a as a white solid (3.66 g, 90% yield).

General procedure for asymmetric allylic substitutions: 2-(1,3-diphenylallyl)malonic acid dimethyl ester (18). In a Schlenk tube, allylpalladium chloride dimer (4.57 mg, 0.0125 mmol), ligand 9a (9.68 mg, 0.025 mmol), and solid potassium acetate (4.9 mg, 0.05 mmol) were dissolved in 2 mL of CH₂Cl₂. The solution was stirred at rt for 15 min. Dimethyl malonate (17) (0.172 mL, 1.5 mmol), N,O-bis(trimethylsilyl)acetamide (0.37 mL, 1.5 mmol), and a solution of rac-(E)-1-acetoxy-1,3-diphenyl-2-propene (16) (126 mg, 0.5 mmol) in 1 mL of CH₂Cl₂ were subsequently added. The reaction mixture was stirred at rt for 12 h. The solvent was removed under reduced pressure and the
residue was purified by flash column chromatography on silica gel (hexanes:EtOAc, 9:1) to give product 18 (157 mg, 97%). \(^1\)H NMR (360 MHz, CDCl\(_3\)) \(\delta\) 7.15-7.29 (m, 10H), 6.45 (d, \(J = 15.8\) Hz, 1H), 6.31 (dd, \(J = 15.7, 8.5\) Hz, 1H), 4.24 (dd, \(J = 10.3, 8.8\) Hz, 1H), 3.93 (d, \(J = 10.9\) Hz, 1H), 3.70 (s, 3H), 3.65 (s, 3H). The enantiomeric excess of 93% was determined by chiral HPLC using a Chiralpak AD column (hexanes:iPrOH, 90:10).

2-Cyclohex-2-enylmalonic acid dimethyl ester (21). \(^1\)H NMR (360 MHz) \(\delta\) 5.68-5.71 (m, 1H), 5.43-5.46 (m, 1H), 3.66 (s, 6H), 3.21 (d, \(J = 9.5\) Hz, 1H), 2.82-2.84 (m, 3H), 1.27-1.92 (m, 6H). The enantiomeric excess was determined by chiral GC using a Chiral Select 1000 column (120 °C).

2-(1-Methyl-3-phenylallyl)malonic acid dimethyl ester (22a). \(^1\)H NMR (360 MHz, CDCl\(_3\)) \(\delta\) 7.11-7.21 (m, 5H), 6.31 (d, \(J = 15.8\) Hz, 1H), 5.98 (dd, \(J = 15.8, 8.5\) Hz, 1H), 3.60 (s, 3H), 3.53 (s, 3H), 3.25 (d, \(J = 8.9\) Hz, 1H), 2.97-3.00 (m, 1H), 1.05 (d, \(J = 6.8\) Hz, 3H). \(^1\)H NMR for the minor isomer 2-(1-phenyl-but-2-enyl)malonic acid dimethyl ester (22b) can be found in literature.\(^{21d}\) The enantiomeric excess of 22a was determined by chiral HPLC using a Chiralcel OJ-H column (hexanes:iPrOH, 95:5).

General procedure for asymmetric Heck reactions: 2-phenyl-2,5-dihydrofuran (32). In a Schlenk tube, [Pd\(_2\)(dba)\(_3\):dba] (8.61 mg, 0.015 mmol) and ligand 9a (11.61 mg, 0.03 mmol) were dissolved in 3 mL of THF. The solution was stirred at 70 °C for 15 min. Phenyl triflate (24) (80.7 μL, 0.5 mmol), 2,3-dihydrofuran
(23) (0.19 mL, 2.5 mmol), and N,N-diisopropylethylamine (0.26 mL, 1.5 mmol) were subsequently added. The reaction mixture was stirred at 70 °C for 3 d. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (hexanes:EtOAc, 9:1) to afford 32 (72 mg, 99%). \[^1\text{H} \text{NMR}\] (360 MHz, CDCl\textsubscript{3}) \(\delta\) 7.20-7.25 (m, 5H), 5.92 (m, 1H), 5.79 (m, 1H), 5.70 (m, 1H), 4.76 (m, 1H), 4.69 (m, 1H). The enantiomeric excess of 94% was determined by chiral GC using a \(\beta\)-DEX 120 column (125 °C).
References and Notes


VITA

Qian Dai

EDUCATION

The Pennsylvania State University, University Park, PA  
2002 – 2007  
(anticipated)

Doctor of Philosophy, Organic and Organometallic Chemistry  
Thesis Title: “New phosphorus ligands: development and applications in transition metal catalysis”

University of Science and Technology of China, Hefei, P.R.China  
1998 – 2002

Bachelor of Science, Chemistry

PUBLICATIONS AND SCIENTIFIC PRESENTATIONS


