The Pennsylvania State University

The Graduate School

Department of Chemistry

NEW PHOSPHORUS LIGANDS: DEVELOPMENT AND APPLICATIONS IN TRANSITION METAL CATALYSIS

A Thesis in

Chemistry

by

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*-Me-ketalphos) and (*R,S,S,R*-Me-ketalphos) were prepared from readily available $_D$-mannitol. Their rhodium complexes were isolated and further investigated as catalysts in the asymmetric hydrogenation of various functionalized olefins such as α-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 α,β-unsaturated esters.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

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.[1] 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)

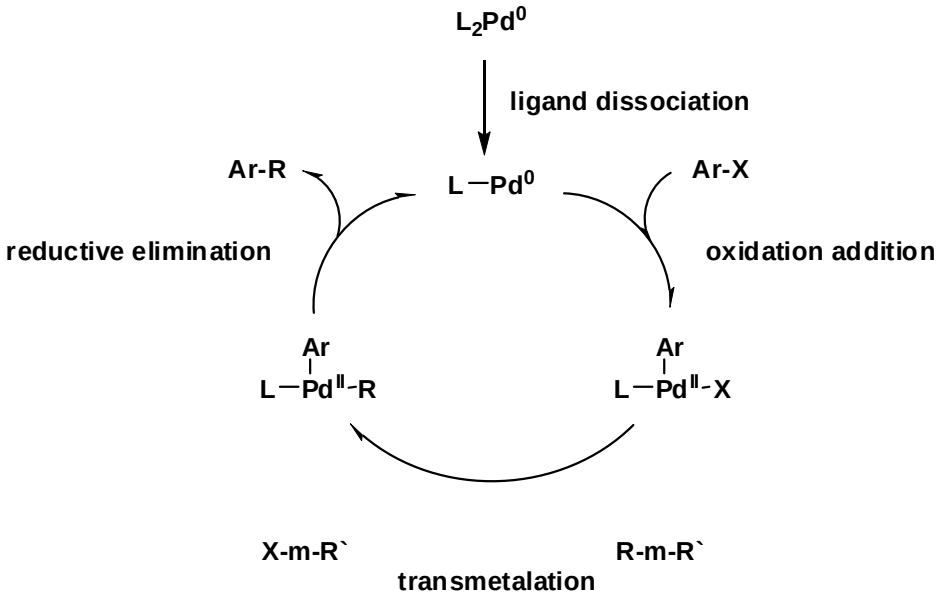


Figure **1-1**: General Mechanism for Transition Metal Catalyzed Cross-coupling Reactions

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.[2] 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.

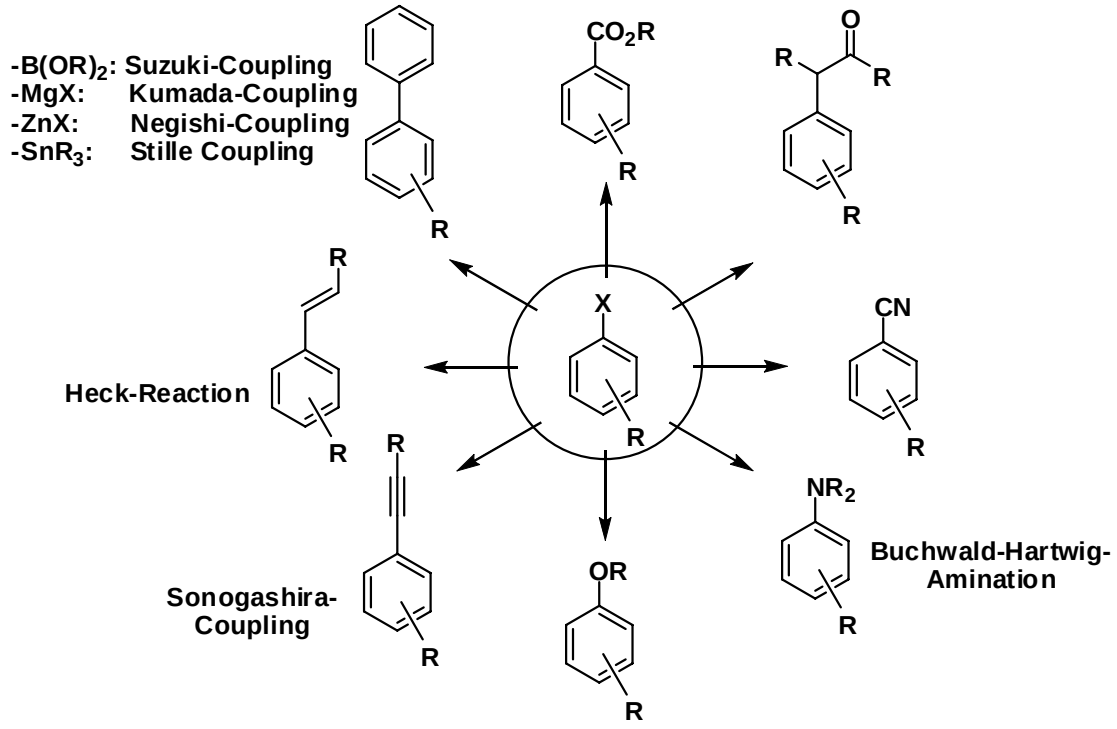


Figure **1-2**: Pd-Catalyzed C-X Coupling Reactions

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.[3] 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.[4] 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,[5] numerous ligands have been developed for this type of transformation (Figure 1-3).

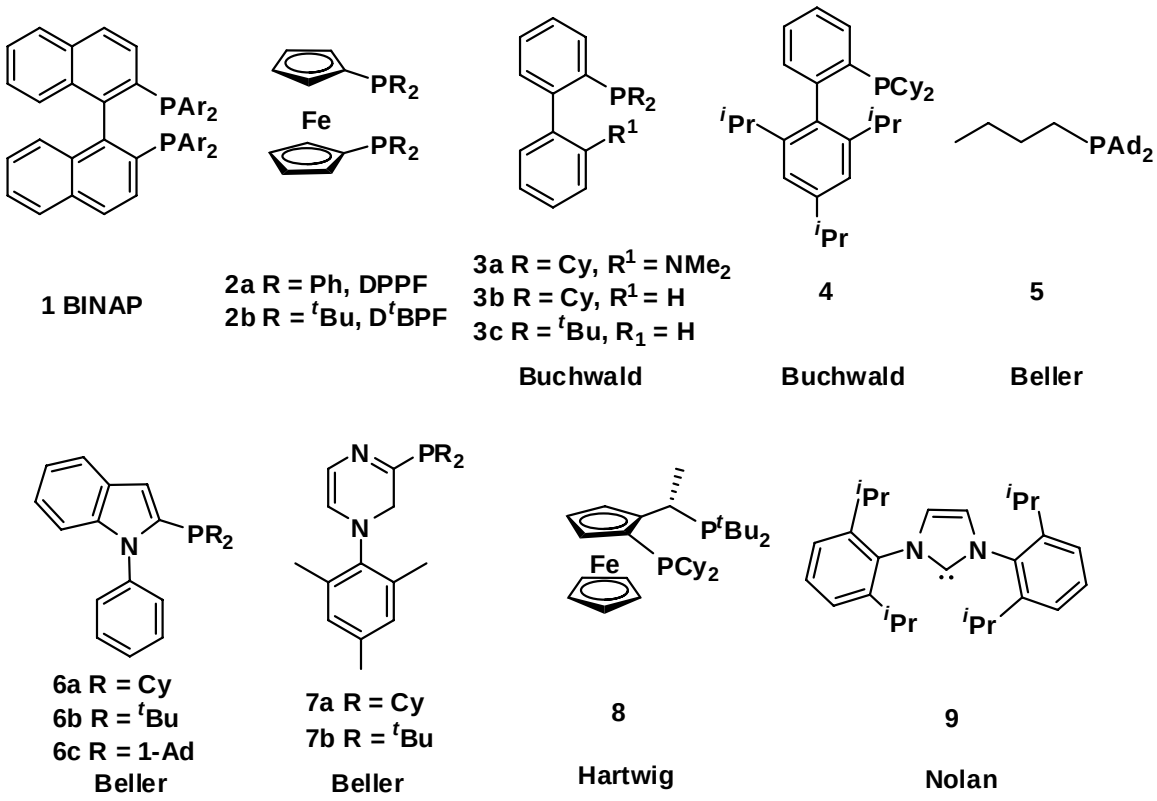
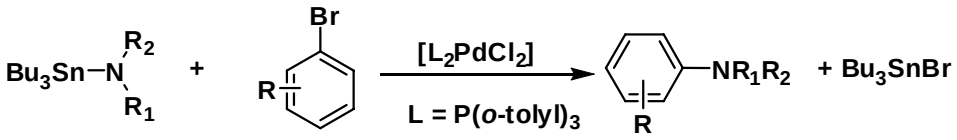


Figure **1-3**: Some Representative Ligands for the Pd-Catalyzed Amination Reactions

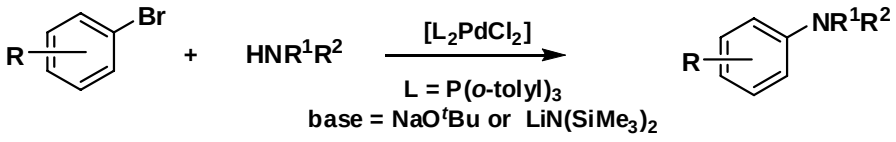
Initially, *in situ* generated aminostannanes were used in the coupling reaction with aryl bromides catalyzed by Pd/P(*o*-tolyl)$_3$ (Scheme 1-1).[5] The monophosphine employed in this reaction is usually considered as the first generation ligand for Pd-catalyzed amination reactions. The high reactivity/instability of aminostannanes limited the further application of this method.[6]

Scheme **1-1**: The First Example of Pd-Catalyzed Amination Reactions



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



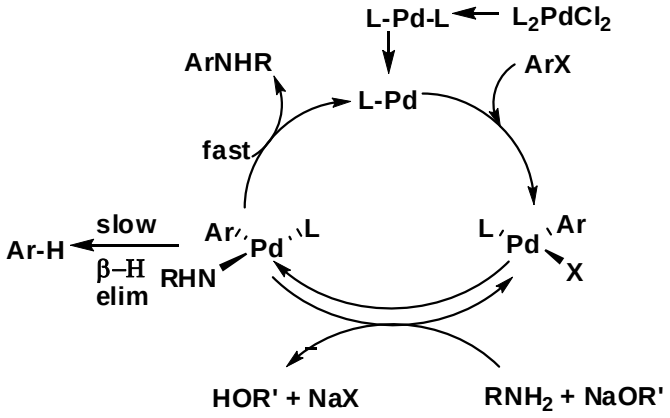


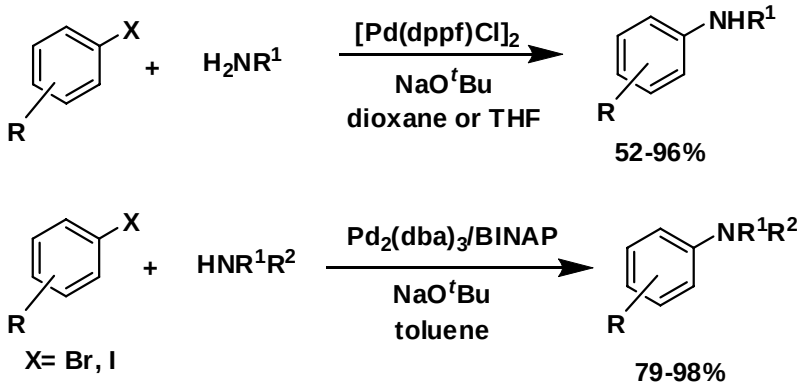
Figure **1-4**: Catalytic Cycle for Pd-Catalyzed Amination Reaction

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).[8] 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.[6c] 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(*o*-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.[9] 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.[10] 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,[7d, 9a] DPPF and D^{t}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

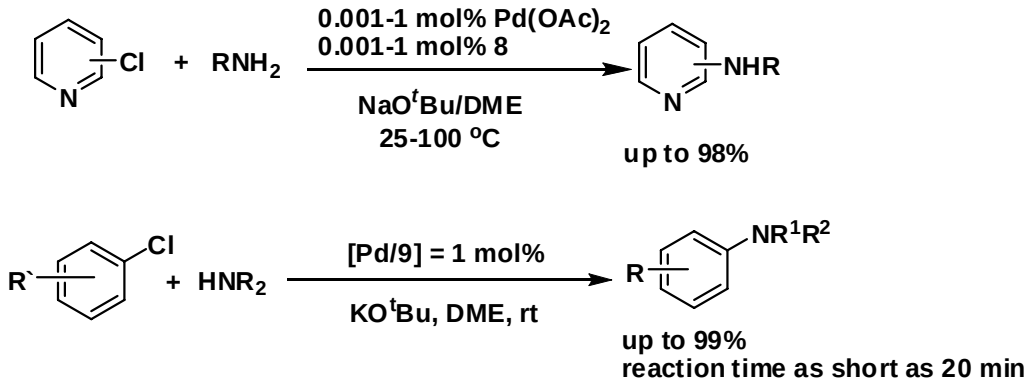


A class of bulky, electron rich monophosphine ligands was developed by Buchwald in the late 1990's.[12] Ligand **3a** and **3b** were reported to be excellent for C-C,[12b,c] C-N[12b,d] and C-O[12e] bond forming reactions. However, the scope of room-temperature amination reactions was somewhat limited. 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^{t}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 sufonates.[13]

More recently, Beller and coworkers reported the use of ligand **5** for the coupling of sterically hindered amines with aryl chlorides.[14] In 2004, Beller also reported a facile synthesis of a group of *N*-phenylindole-based phosphine ligands **6**.[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 ^{o}C). On the other hand, excellent catalyst activity were also observed (TON = 8000, TOF = 14000 h^{-1}) by increasing the ligand/metal ratio to 50:1. Later, a series of *N*-aryl-2-(dialkylphosphino)imidazoles ligands **7** was reported by Beller using a similar synthetic method as that used for ligands **6**.[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.[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 *N*-heterocyclic carbene ligand **9** as a catalyst for amination reactions was reported by Nolan.[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).

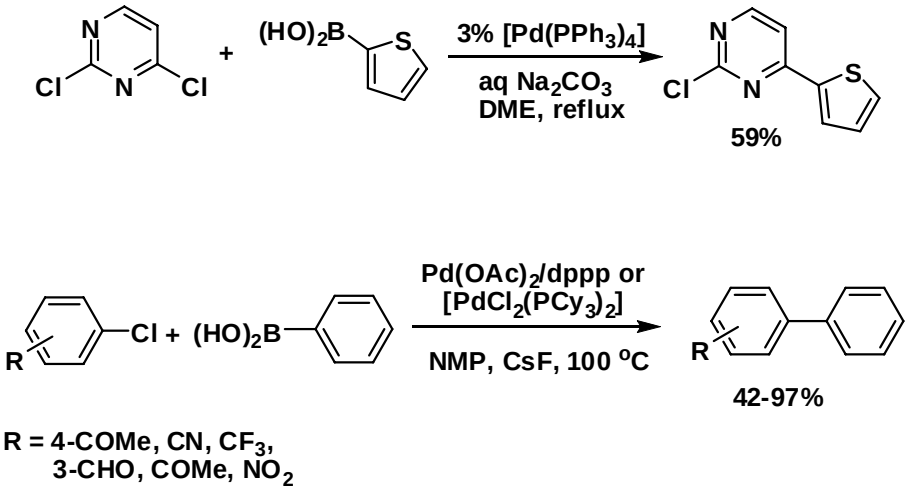
Scheme **1-4**:



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.[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.[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).[20] A very wide range of Pd(0) catalysts or precursors can be used for Suzuki-coupling reactions. $Pd(PPh_3)_4$ is the most commonly used catalyst. $PdCl_2(PPh_3)_2$ and $Pd(OAc)_2/PPh_3$ 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.[21] 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).

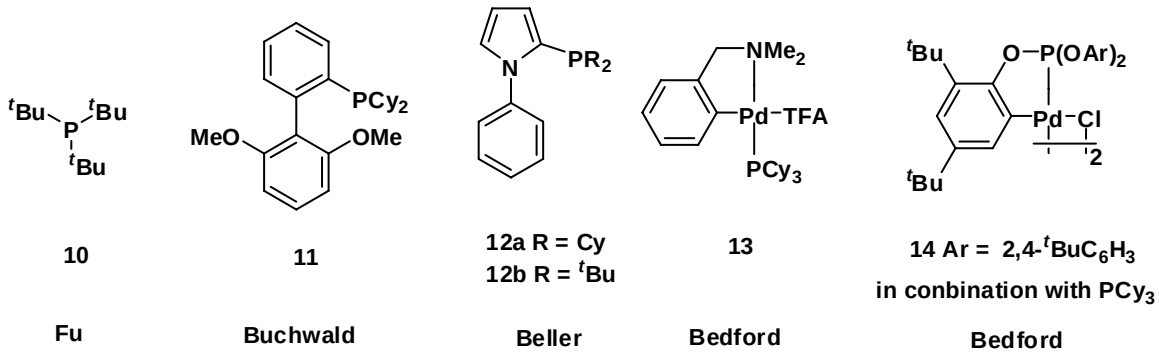
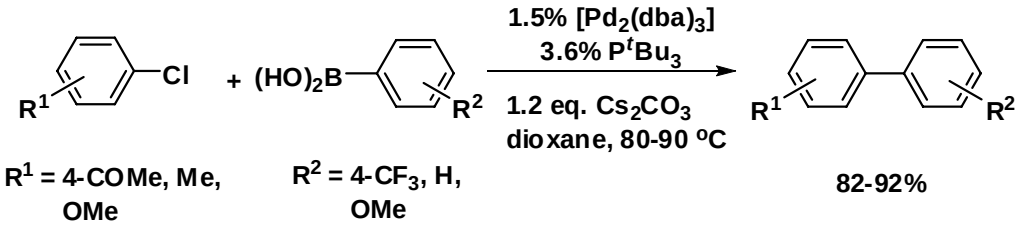
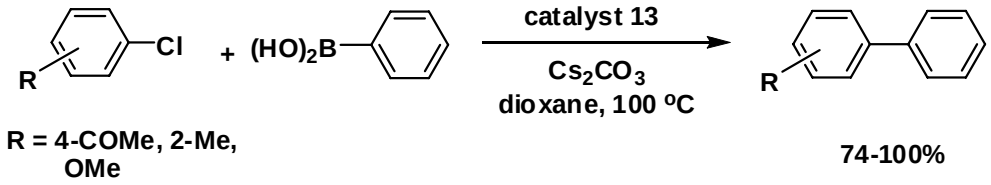


Figure **1-5**: Some Representative Ligands for Pd-Catalyzed Suzuki-Miyaura Reactions

Some notable examples include the use of bulky trialkylphosphines (i.e. P^tBu_3) by Fu,[22] dialkyl-biphenylphosphines **3** and **11** by Buchwald,[12a-d, 23] and dialkyl-heteroaromatic phosphines **12** by Beller.[16, 24] Using sterically hindered *N*-heterocyclic carbenes (NHCs, i.e. **9**) as ligands by Herrmann et al.,[25] and using palladacycles (i.e. **13, 14** and **9**) as the precatalysts by Bedford et al. and Nolan et al.,[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.[27]

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





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

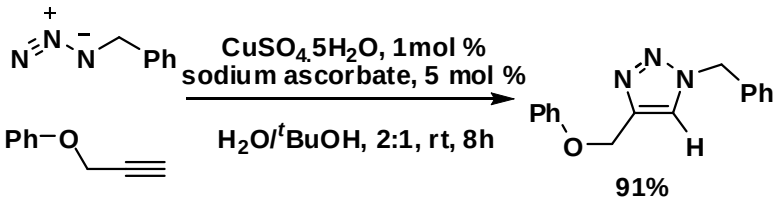
1.2.1 Ligand Design and Synthesis

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".[28] Properties such as modularity, wide reaction scope, mild reaction conditions, high yields and regioselectivity, are the key criteria of click chemistry.[28]

Click chemistry ideas are beautifully represented in hetero-cycloaddition reactions, most notably 1,3-dipolar cycloadditions.[29] Huisgen 1,3-cycloaddition of azides and alkynes is a classic method for the formation of 1,2,3-triazoles.[29] 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.

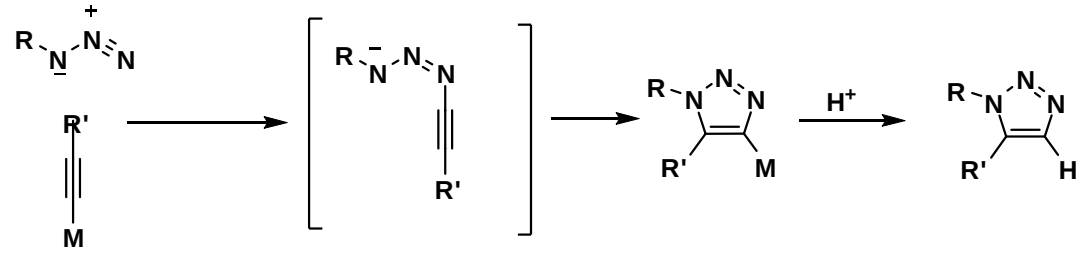
A copper(I)-catalyzed regioselective Huisgen cycloaddition was recently reported by Rostovtsev, Sharpless et al. (Scheme 1-7).[28b] Using an *in situ* prepared Cu(I) catalyst, the reaction was complete in 8 h at room temperature with a high yield (91%) of 1,4-disubstituted product and complete regioselectivity.

Scheme **1-7**:



On the basis of earlier published results, a new synthesis of 1,5-disubstituted triazoles was reported recently.[28c] 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-trisubstitued triazoles. A possible mechanism for this reaction has been proposed (Scheme 1-8).[28c] 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.

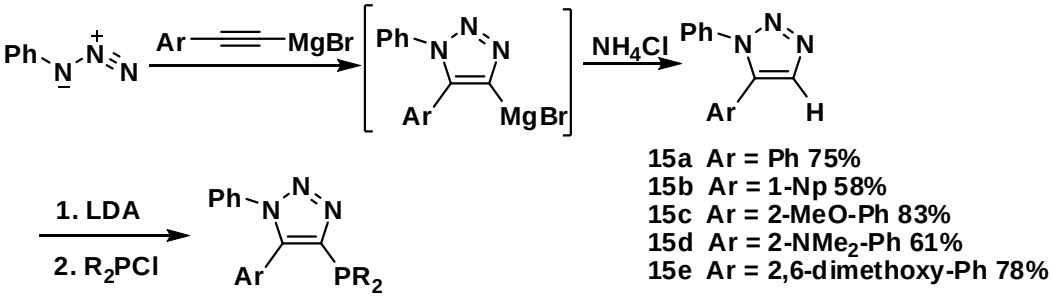
Scheme **1-8**:



M = MgBr, Li

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.[30] 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**



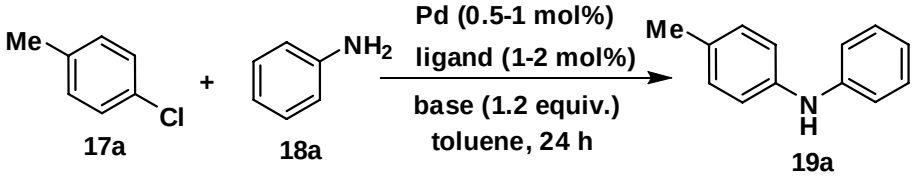
15a Ar = Ph 75%
15b Ar = 1-Np 58%
15c Ar = 2-MeO-Ph 83%
15d Ar = 2-NMe_2-Ph 61%
15e Ar = 2,6-dimethoxy-Ph 78%

16a Ar = R = Ph 90%
16bAr = Ph, R = Cy 93%
16cAr = Ph, R = ^{t}Bu 91%
16d Ar = 1-Np, R = Cy 81%
16eAr = 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^tBu and NaO^tBu gave similar results. When the reaction temperature was increased from 80 ^oC to 110 ^oC, 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 varing substituent groups on the triazole ring can enhance the reaction yield.[15, 17]

Table **1-1**: Screening of Ligands and Reaction Conditions



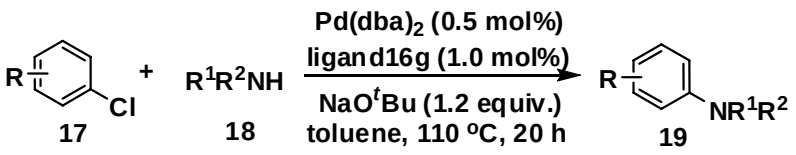
entry[a]	Pd (mol%)	ligand (mol %)	base	temp (^{o}C)	yield (%)[b]
1	1% $Pd(OAc)_2$	**16c**(2%)	KO^{t}Bu	80	87
2	1% $Pd(dba)_2$	**16c**(2%)	KO^{t}Bu	80	92
3	1% $Pd(dba)_2$	**16c**(2%)	KO^{t}Bu	110	94
4	1% $Pd(dba)_2$	**16c**(2%)	NaO^{t}Bu	110	94
5	0.5% $Pd(dba)_2$	**16c**(1%)	NaO^{t}Bu	80	88
6	0.5% $Pd(dba)_2$	**16c**(1%)	NaO^{t}Bu	110	92
7	0.5% $Pd(dba)_2$	**16b**(1%)	NaO^{t}Bu	110	91
8	0.5% $Pd(dba)_2$	**16d**(1%)	NaO^{t}Bu	110	90
9	0.5% $Pd(dba)_2$	**16e**(1%)	NaO^{t}Bu	110	91
10	0.5% $Pd(dba)_2$	**16f**(1%)	NaO^{t}Bu	110	85
11	0.5% $Pd(dba)_2$	**16g**(1%)	NaO^{t}Bu	110	95
12	0.5% $Pd(dba)_2$	**16h**(1%)	NaO^{t}Bu	110	93
13	0.5% $Pd(dba)_2$	**16i** (1%)	NaO^{t}Bu	110	90
14	0.5% $Pd(dba)_2$	**16j** (1%)	NaO^{t}Bu	110	88

[a] 1 mmol of aryl chloride **17**, 1.2 mmol of aryl amine **18**, 1.2 mmol of base, 0.5-1 mol% of Pd, 1-2 mol% of ligand **16**, 3 mL of toluene, 24 h. [b] Isolated yield. Purity was confirmed by ^{1}H NMR.

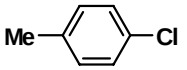
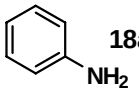
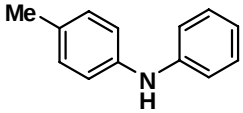
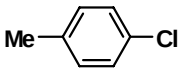
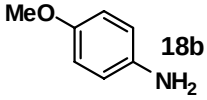
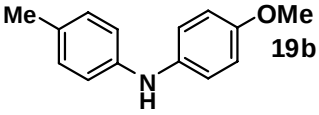
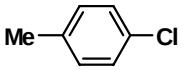
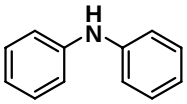
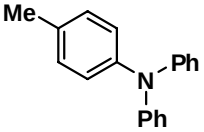
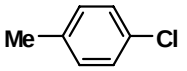
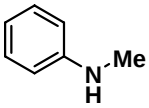
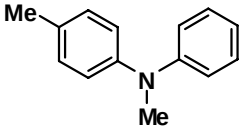
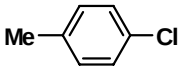
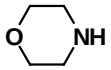
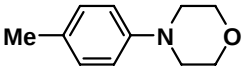
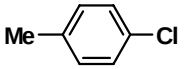
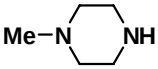
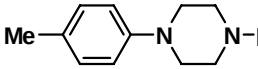
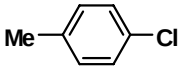
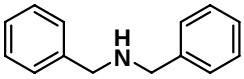
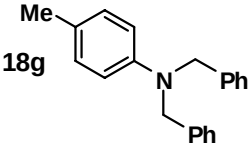
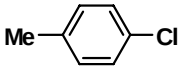
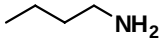
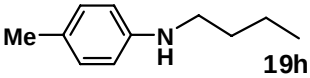
On the basis of the optimized reaction conditions, the coupling reactions between several aryl chlorides and a variety of primary and secondary amines were carried out to explore the substrate scope of the $Pd(dba)_2$/**16g** catalytic system (Table 1-2). In most cases, the corresponding anilines were 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 (KO^{t}Bu) was used instead of NaO^{t}Bu (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 withVarious Amines

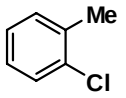
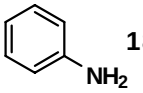
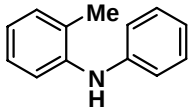
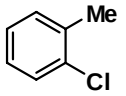
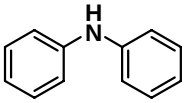
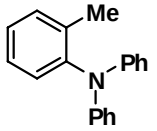
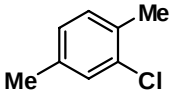
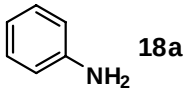
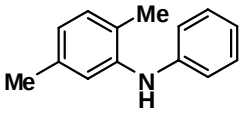
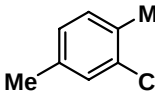
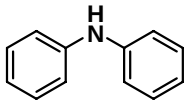
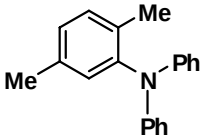


17 18 19

entry[a]	aryl chloride	amine	product	yield (%) [b]
1	 **17a**	 **18a**	 **19a**	95
2		 **18b**	 **19b**	93 [c]
3		 **18c**	 **19c**	94
4		 **18d**	 **19d**	98
5		 **18e**	 **19e**	97
6		 **18f**	 **19f**	88
7		 **18g**	 **19g**	78
8		 **18h**	 **19h**	89 [d]

[a] 1 mmol of aryl chloride **17,** 1.2 mmol of arylamine **18**, 1.2 mmol of NaO^{t}Bu, 0.5 mol% of Pd(dba)$_2$, 1 mol% of ligand **16g**, 3 mL of toluene, 20 h, 110 ^{o}C. [b] Isolated yield. Purity was confirmed by ^{1}H NMR. [c] KO^{t}Bu was used instead of NaO^{t}Bu. [d] 5 equiv. of amine was used.

Table **1-2**: Continued

entry[a]	aryl chloride	amine	product	yield (%) [b]
9	 **17b**	 **18a**	 **19i**	94
10	 **17b**	 **18c**	 **19j**	96
11	 **17c**	 **18a**	 **19k**	95
12	 **17c**	 **18c**	 **19l**	94

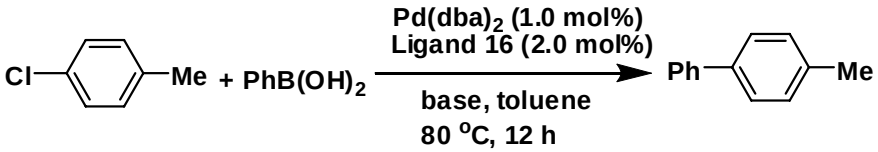
[a] 1 mmol of aryl chloride **17,** 1.2 mmol of arylamine **18**, 1.2 mmol of NaO^{t}Bu, 0.5 mol% of Pd(dba)$_2$, 1 mol% of ligand **16g**, 3 mL of toluene, 20 h, 110 ^{o}C. [b] Isolated yield. Purity was confirmed by ^{1}H NMR. [c] KO^{t}Bu was used instead of NaO^{t}Bu. [d] 5 equiv. of amine was used.

1.2.3 Pd-Catalyzed Suzuki-Miyaura Coupling Reactions

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.[23] 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 K_3PO_4, KF and CsF, were examined. K_3PO_4 was found to be the base of choice for the Pd/**16c** catalytic system (Table 1-3, entries 3, 9 and 10).

Table **1-3**: Screening of Ligands and Reaction Conditions



17a **20a** **21a**

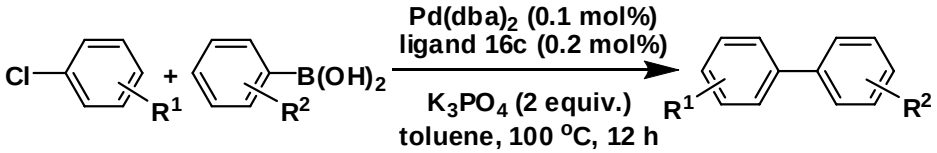
entry[a]	ligand	base	yield (%)[b]
1	**16a**	K_3PO_4	<5
2	**16b**	K_3PO_4	70
3	**16c**	K_3PO_4	94
4	**16d**	K_3PO_4	88
5	**16e**	K_3PO_4	91
6	**16f**	K_3PO_4	20
7	**16g**	K_3PO_4	91
8	**16h**	K_3PO_4	79
9	**16c**	KF	86
10	**16c**	CsF	57

[a] 1 mmol of 4-chlorotoluene (**17a**), 1.5 mmol of phenylboronic acid (**20a**), 2 mmol of base, 1 mol% of $Pd(dba)_2$, 2 mol% of ligand **16**, 3 mL of toluene, 12 h, 80 °C. [b] Isolated yield. Purity was confirmed by ^1H NMR.

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).

Table **1-4**: Pd-Catalyzed Suzuki-Miyaura Coupling of Aryl Chlorides



17 **20** **21**

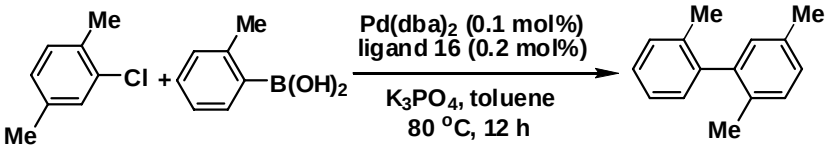
entry[a]	aryl chloride	boronic acid	yield (%)[b]
1	R^1 = *p*-Me **17a**	R^2 = H **20a**	89 (**21a**)
2	R^1 = *o*-Me **17b**	R^2 = H **20a**	92 (**21b**)
3	R^1 = 2,5-di-Me **17c**	R^2 = H **20a**	98 (**21c**)
4	R^1 = *p*-OMe **17d**	R^2 = H **20a**	86 (**21d**)
5	R^1 = *p*-COMe **17e**	R^2 = H **20a**	99 (**21e**)
6[c]	R^1 = *p*-COMe **17e**	R^2 = H **20a**	93 (**21e**)
7	R^1 = *p*-NO_2 **17f**	R^2 = H **20a**	96 (**21f**)
8	R^1 = *p*-CO_2Me **17g**	R^2 = H **20a**	94 (**21g**)
9	R^1 = *p*-CF_3 **17h**	R^2 = H **20a**	91 (**21h**)
10	R^1 = *o*-COMe **17i**	R^2 = H **20a**	89 (**21i**)
11	R^1 = *o*-CN **17j**	R^2 = H **20a**	90 (**21j**)
12	R^1 = *o*-CN **17j**	R^2 = *p*-Me **20b**	92 (**21k**)
13	R^1 = 2-pyridinyl**17k**	R^2 = H **20a**	99 (**21l**)
14	R^1 = H **17l**	R^2 = *p*-Me **20b**	99 (**21a**)

[a] 1 mmol of aryl chloride **17**, 1.5 mmol of aryl boronic acid **20**, 2 mmol of K_3PO_4, 0.1 mol% of $Pd(dba)_2$, 0.2 mol% of ligand **16c**, 3 mL of toluene, 12 h, 100 °C. [b] Isolated yield. Purity was confirmed by ^{1}H NMR. [c] 0.01 mol% of $Pd(dba)_2$ and 0.02 mol% of ligand **16c** were used.

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,[23a] which prompted us to modify ClickPhos for Suzuki-Miyaura coupling of more hindered substrates.

Table **1-5**: Screening of Ligands and Reaction Conditions



entry[a]	ligand	yield (%)[b]
1	**16c** Ar = Ph, R = ^{t}Bu	89
2	**16d** Ar = 1-Np, R = Cy	17
3	**16e** Ar = 1-Np, R = ^{t}Bu	70
4	**16f** Ar = 2-MeO-Ph, R = Cy	45
5	**16g** Ar = 2-MeO-Ph, R = ^{t}Bu	94
6	**16h** Ar = 2-NMe_2-Ph, R = ^{t}Bu	63
7	**16i** Ar = 2,6-dimethoxy-Ph, R = ^{t}Bu	96
8	**16j** Ar = 2,6-dimethoxy-Ph, R = Cy	55

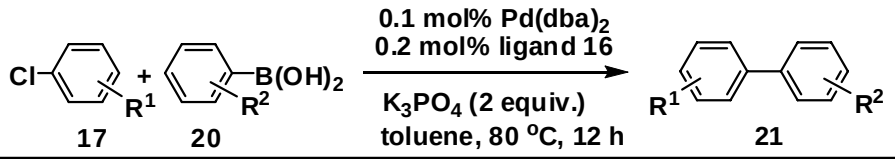
[a] 1 mmol of **17c**, 1.5 mmol of **20c**, 2 mmol of K_3PO_4, 0.1 mol% of $Pd(dba)_2$, 0.2 mol% of ligand **16**, 3 mL of toluene, 12 h, 80 °C. [b] Isolated yield. Purity was confirmed by ^{1}H NMR.

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

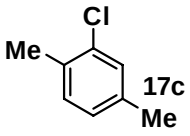
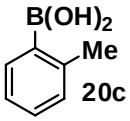
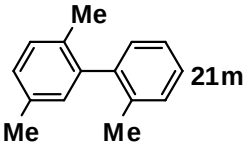
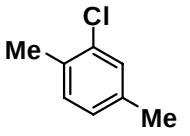
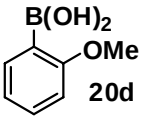
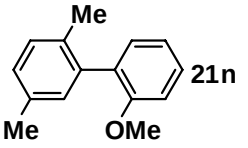
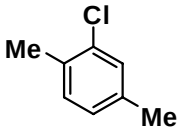
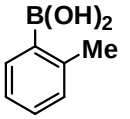
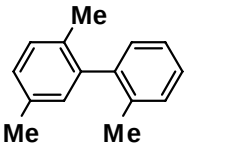
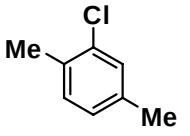
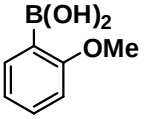
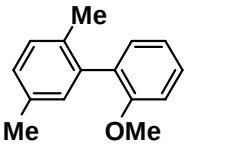
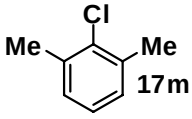
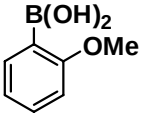
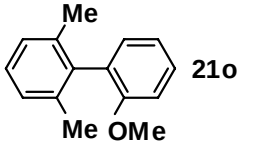
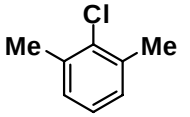
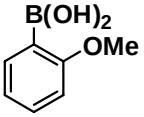
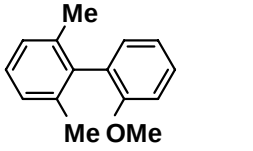
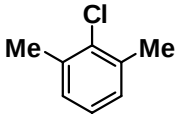
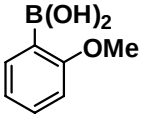
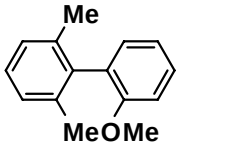
17% yield (Table 1-5, entry 2). A general trend is that ligands bearing a di-*tert*-butylphosphino group (**16c**, **16e**, **16g**, and **16i**) give much higher yields than their dicyclohexylphospino analogues (**16d**, **16f**, **16h**, and **16j**). Ligand **16i**, which has a 2,6-dimethoxybenzene 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 constrast, 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.[31]

Table **1-6**: Pd-Catalyzed Suzuki-Miyaura Coupling of Hindered Aryl Chlorides

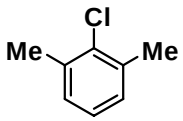
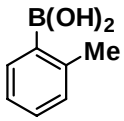
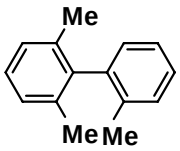
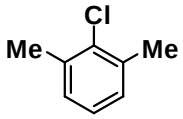
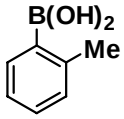
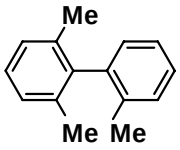
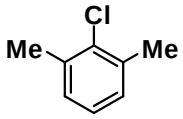
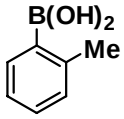
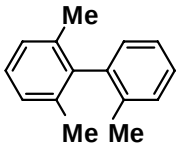


17 20 21

entry[a]	aryl chloride	boronic acid	ligand	product	yield (%)[b]
1	 **17c**	 **20c**	**16c**	 **21m**	89
2		 **20d**	**16c**	 **21n**	85
3			**16i**		96
4			**16i**		95
5	 **17m**		**16c**[c]	 **21o**	12[d]
6			**16i**[c]		72[d]
7			**16j**[c]		57[d]

[a] 1 mmol of **17**, 1.5 mmol of **20**, 2 mmol of K_3PO_4, 0.1 mol% of $Pd(dba)_2$, 0.2 mol% of ligand **16**, 3 mL of toluene, 12 h, 80 °C. [b] Isolated yield. Purity was confirmed by ^1H NMR. [c] 1 mol% of $Pd(dba)_2$ and 2 mol% of ligand were used. [d] The reaction was carried out at 120 °C.

Table **1-7**: Continued

entry[a]	aryl chloride	boronic acid	ligand	product	yield (%)[b]
8			**16c**[c]	 **21p**	32[d]
9			**16i**[c]		90[d]
10			**16j**[c]		60[d]

[a] 1 mmol of **17**, 1.5 mmol of **20**, 2 mmol of K_3PO_4, 0.1 mol% of $Pd(dba)_2$, 0.2 mol% of ligand **16**, 3 mL of toluene, 12 h, 80 °C. [b] Isolated yield. Purity was confirmed by ^1H NMR. [c] 1 mol% of $Pd(dba)_2$ and 2 mol% of ligand were used. [d] 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]

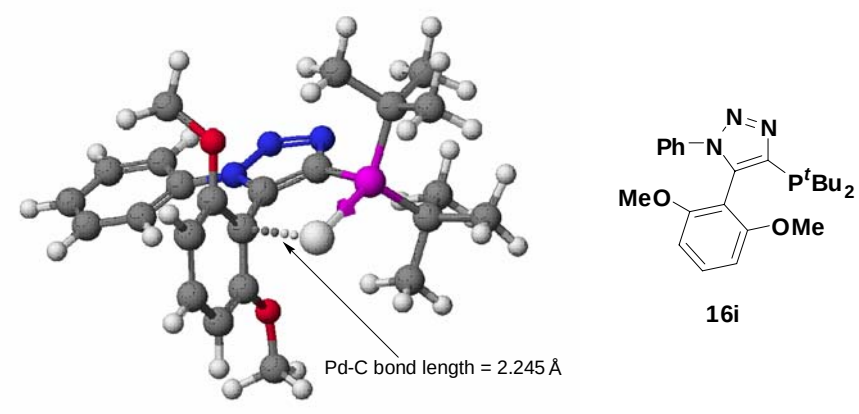


Figure **1-6**: MM2 Calculations of Pd/**16i** Complex Based on the CAChe Program

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 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.

1,5-Diphenyl-1*H*-[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 ^{o}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 ^{o}C for 1 h before quenching with saturated NH_4Cl (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (10 mL × 3). The combined organic layers were dried over Na_2SO_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)-1*H*-[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 ^{o}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 ^{o}C for 1 h before quenching with saturated NH_4Cl (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (10 mL × 3). The combined organic layers were dried over Na_2SO_4 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%). ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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 $C_{18}H_{14}N_3$ (MH^+) 272.1188, found 272.1182.

1-Phenyl-5-(2-methoxyphenyl)-1*H*-[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 ^{o}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 ^{o}C for 1 h before quenching with saturated NH_4Cl (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (10 mL × 3). The combined organic layers were dried

over Na_2SO_4 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%). ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.9, 138.1, 135.1, 134.9, 131.7, 131.4, 129.4, 129.0, 124.2, 121.2, 116.6, 111.8, 55.3; HRMS (ESI+) calcd. for $C_{15}H_{14}N_3O$ (MH^+) 252.1137, found 252.1127.

1-Phenyl-5-(2-*N,N*-dimethylphenyl)-1*H*-[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 ^{o}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 ^{o}C for 1 h before quenching with saturated NH_4Cl (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (10 mL × 3). The combined organic layers were dried over Na_2SO_4 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%). ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{16}H_{17}N_4$ (MH^+) 265.1453, found 265.1444.

1-Phenyl-5-(2,6-dimethoxy-phenyl)-1*H*-[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 ^{o}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 ^{o}C for 1 h before quenching with saturated NH_4Cl (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (10 mL × 3). The combined organic layers were dried over Na_2SO_4 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%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.27-7.33 (m, 6H), 6.49 (d, J = 8.4 Hz, 2H), 3.51 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{16}H_{15}N_3O_2Na$ (M + Na^+) 304.1062, found 304.1063.

4-Di-*tert*-butylphosphanyl-1,5-diphenyl-1*H*-[1,2,3]triazole (16c). To a solution of 1,5-diphenyl-1*H*-[1,2,3]triazole (**15a**) (0.52 g, 2.35 mmol) in THF (20 mL) was added LDA (2.35 mmol) at 0 ^{o}C. The reaction mixture was stirred at 0 ^{o}C for 1.5 h followed by addition of P^{t}Bu$_2$Cl (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/H_2O (1:1) was added, and the resulting mixture was extracted with degassed ether (15 mL × 3). The combined organic layers were dried over Na_2SO_4 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%). ^{1}H NMR (CD_2Cl_2, 360 MHz) δ 7.41-7.23 (m, 10H), 1.27 (d, J = 12.1 Hz, 18H); ^{13}C NMR ($CDCl_3$, 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_2Cl_2, 145 MHz) δ 3.51; HRMS (ESI+) calcd. for $C_{22}H_{29}N_3P$ (MH^+) 366.2084, found 366.2099.

4-Diphenylphosphanyl-1,5-diphenyl-1*H*-[1,2,3]triazole (16a). To a solution of 1,5-diphenyl-1*H*-[1,2,3]triazole (**15a**) (0.26 g, 1.18 mmol) in THF (20 mL) was added LDA (1.18 mmol) at 0 ^{o}C. The reaction mixture was stirred at 0 ^{o}C for 1.5 h followed by addition of PPh_2Cl (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_2O (1:1) was added, and the resulting mixture was extracted with degassed ether (15 mL × 3). The combined organic layers were dried over Na_2SO_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 $C_{26}H_{21}N_3P$ (MH^+) 406.1475, found 406.1473.

4-Dicyclohexylphosphanyl-1,5-diphenyl-1*H*-[1,2,3]triazole(16b). To a solution of 1,5-diphenyl-1*H*-[1,2,3]triazole (**15a**) (0.50g, 2.26 mmol) in THF (20 mL) at 0 ^{o}C was added LDA (2.26 mmol) at 0 ^{o}C. The reaction mixture was stirred at 0 ^{o}C for 1.5 h followed by addition of PCy_2Cl (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 Na_2SO_4 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%). ^{1}H NMR (CD_2Cl_2, 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); ^{13}C NMR ($CDCl_3$, 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; ^{31}P NMR (CD_2Cl_2, 145 MHz) δ –27.76; HRMS (ESI+) calcd. for $C_{26}H_{33}N_3P$ (MH^+) 418.2419, found 418.2412.

4-Dicyclohexylphosphanyl-1-phenyl-5-(1-naphthyl)-1*H*-[1,2,3]triazole (16d). To a solution of 1-phenyl-5-(1-naphthyl)-1*H*-[1,2,3]triazole (**15b**) (0.54 g, 2.0 mmol) in THF (20 mL) was added LDA (2.0 mmol) at 0 ^{o}C. The reaction mixture was stirred at 0 ^{o}C for 1.5 h followed by addition of PCy_2Cl (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_2O (1:1) was added, and the resulting mixture was extracted with degassed ether

(15 mL × 3). The combined organic layers were dried over Na_2SO_4 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 off-white solid (0.76 g, 81%). ^{1}H NMR (300 MHz, CD_2Cl_2) δ 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); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 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; ^{31}P NMR (145 MHz, CD_2Cl_2) δ -28.31; HRMS (ESI+) calcd. for $C_{30}H_{35}N_3P$ (MH^+) 468.2569, found 468.2571.

4-Di-*tert*-butylphosphanyl-1-phenyl-5-(1-naphthyl)-1*H*-[1,2,3]triazole (16e). To a solution of 1-phenyl-5-(1-naphthyl)-1*H*-[1,2,3]triazole (**15b**) (0.54 g, 2.0 mmol) in THF (20 mL) was added LDA (2.0 mmol) at 0 ^{o}C. The reaction mixture was stirred at 0 ^{o}C for 1.5 h followed by addition of P^{t}Bu$_2$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_2O (1:1) was added, and the resulting mixture was extracted with degassed ether (15 mL × 3). The combined organic layers were dried over Na_2SO_4 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%). ^{1}H NMR (CD_2Cl_2, 300 MHz) δ 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_2Cl_2, 145 MHz) δ 3.63; HRMS (ESI+) calcd. for $C_{26}H_{31}N_3P$ (MH^+) 416.2256, found 416.2252.

4-Dicyclohexylphosphanyl-1-phenyl-5-(2-methoxyphenyl)-1*H*-[1,2,3]triazole (16f). To a solution of 1-phenyl-5-(2-methoxyphenyl)-1*H*-[1,2,3]triazole (**15c**) (0.504 g, 2.0 mmol) in THF (20 mL) was added LDA (2.0 mmol) at 0 ^{o}C. The reaction mixture was stirred at 0 ^{o}C for 1.5 h followed by addition of PCy_2Cl (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_2O (1:1) was added, and the resulting mixture was extracted with degassed ether (15 mL × 3). The combined organic layers were dried over Na_2SO_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_2Cl_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_2Cl_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_2Cl_2) δ -27.99; HRMS (ESI+) calcd. for $C_{27}H_{35}N_3OP$ (MH^+) 448.2518, found 448.2510.

4-Di-*tert*-butylphosphanyl-1-phenyl-5-(2-methoxyphenyl)-1*H*-[1,2,3]triazole (16g). To a solution of 1-phenyl-5-(2-methoxyphenyl)-1*H*-[1,2,3]triazole (**15c**) (0.504 g, 2.0 mmol) in THF (20 mL) was added LDA (2.0 mmol) at 0 ^{o}C. The reaction mixture was stirred at 0 ^{o}C for 1.5 h followed by addition of P^{t}Bu$_2$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_2O (1:1) was added, and the resulting mixture was extracted with degassed ether (15 mL × 3). The combined organic layers were dried over Na_2SO_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%). ^{1}H NMR (CD_2Cl_2, 360 MHz) δ 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); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 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); ^{31}P NMR (CD_2Cl_2, 145 MHz) δ 3.47; HRMS (ESI+) calcd. for $C_{23}H_{31}N_3OP$ (MH^+) 396.2205, found 396.2202.

4-Di-*tert*-butylphosphanyl-1-phenyl-5-(2-*N*,*N*-dimethylphenyl)-1*H*-[1,2,3]-triazole(16h). To a solution of 1-phenyl-5-(2-*N,N*-dimethylphenyl)-1*H*-[1,2,3]triazole (**15d**) (0.53 g, 2.0 mmol) in THF (20 mL) was added LDA (2.0 mmol) at 0 ^{o}C. The reaction mixture was stirred at 0 ^{o}C for 1.5 h followed by addition of P^{t}Bu$_2$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_2O (1:1) was added, and the resulting mixture was extracted with degassed ether (15 mL × 3). The combined organic layers were dried over Na_2SO_4 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%). ^{1}H NMR (360 MHz, CD_2Cl_2) 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); ^{13}C NMR (90 MHz, CD_2Cl_2) 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); ^{31}P NMR (145 MHz, CD_2Cl_2) δ 2.72; HRMS (ESI+) calcd. for $C_{24}H_{34}N_4P$ (MH^+) 409.2521, found 409.2537.

4-Di-*tert*-butylphosphanyl-1-phenyl-5-(2,6-dimethoxyphenyl)-1*H*-[1,2,3]-triazole (16i). To a solution of 1-phenyl-5-(2,6-dimethoxyphenyl)-1*H*-[1,2,3]triazole (**15e**) (0.562 g, 2.0 mmol) in THF (20 mL) was added LDA (2.0 mmol) at 0 ^{o}C. The reaction mixture was stirred at 0 ^{o}C for 1.5 h followed by addition of P^{t}Bu$_2$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_2O (1:1) was added, and the resulting mixture was extracted with degassed ether (15 mL × 3). The combined organic layers were dried over Na_2SO_4 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_2Cl_2) δ 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_2Cl_2) δ 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_2Cl_2) δ 4.73; HRMS (ESI+) calcd. for $C_{24}H_{33}N_3O_2P$ (MH^+) 426.2310, found 426.2307.

4-Dicyclohexylphosphanyl-1-phenyl-5-(2,6-dimethoxyphenyl)-1*H*-[1,2,3]-triazole (16j). To a solution of 1-phenyl-5-(2,6-dimethoxyphenyl)-1*H*-[1,2,3]triazole (**15e**) (0.562 g, 2.0 mmol) in THF (20 mL) was added LDA (2.0 mmol) at 0 ^{o}C. The reaction mixture was stirred at 0 ^{o}C for 1.5 h followed by addition of PCy_2Cl (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_2O (1:1) was added, and the resulting mixture was extracted with degassed ether (15 mL × 3). The combined organic layers were dried over Na_2SO_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_2Cl_2) δ 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_2Cl_2) δ 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_2Cl_2) δ -27.36; HRMS (ESI+) calcd. for $C_{28}H_{37}N_3O_2P$ (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, NaO^{t}Bu (1.2 mmol), toluene (3 mL), a stock solution of ligand 1**6** 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 ^oC 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_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography on basic Al_2O_3.

Phenyl-*p*-tolylamine (19a). ^1H NMR ($CDCl_3$, 400 MHz) δ 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) δ 143.9, 140.3, 130.9, 129.8, 129.3, 120.3, 118.9, 116.8, 20.7.

4-Methoxyphenyl-*p*-tolylamine (19b). ^1H NMR (300 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 154.8, 142.4, 136.6, 129.8, 129.3, 121.1, 116.5, 114.6, 55.6, 20.5.

Diphenyl-*p*-tolylamine (19c). ^1H NMR (360 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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) δ 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) δ 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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) δ 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) δ 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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_3PO_4 (2 mmol). The flask was evacuated and backfilled with nitrogen three times. Toluene (3 mL), a stock solution of ligand 1**6** 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 ^{o}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 Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (hexane: EtOAc, 10:1).

4-Methylbiphenyl (21a). ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 141.1, 138.3, 137.0, 129.5, 128.7, 127.0, 126.9, 21.1.

2-Methylbiphenyl (21b). ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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). ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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) δ 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) δ 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) δ 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) δ 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) δ 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) δ 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) δ 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) δ 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) δ 7.72 (s, 4H), 7.66-7.60 (m, 2H), 7.54-7.41 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 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) δ 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) δ 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) δ 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) δ 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) δ 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) δ 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) δ 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) δ 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) δ 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) δ 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) δ 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) δ 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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

1. (a) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: New York, 1985. (b) Collman, J. P., Hegedus, L. S., Norton, J. R., Finke, R. G., Eds.; *Principles and Applications of Organotransition Metal Chemistry*; University Science: Mill Valley, CA, 1987. (c) Diederich, F., Stang, P. J., Eds.; *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: Weinheim, 1998. (d) Diederich, F., Meijere, A. D, Eds.; *Metal-Catalyzed Cross-Coupling Reactions*; 2nd edition, Wiley-VCH: Weinheim, 2004.
2. (a) Christmann, U.; Vilar, R. *Angew. Chem., Int. Ed. Engl.* **2005**, *44*, 366 and references cited therein. (b) Miura, M. *Angew. Chem., Int. Ed. Engl.* **2004**, *43*, 2201.
3. March, J. *Advanced Organic Chemistry*, 4th edition; Wiley-VCH: New York, 1992.
4. For recent reports on nucleophilic aromatic substitution reactions of *N*-nucleophiles with activated aromatic substrates, see: (a) Hattori, T.; Sakamoto, J. Hayashizaka, M.; Miyano, S. *Synthesis* **1994,** 199. (b) Semmelhack, M. R.; Rhee, H. *Tetrahedron Lett.* **1993**, *4*, 1395.
5. Kosugi, M.; Kameyama, M.; Migita, T. *Chem. Lett.* **1983**, 927.
6. (a) Guram, A. S.;Buchwald, S. L. *J. Am. Chem. Soc*. **1994**, *116,* 7901. (b) Paul, F.; Patt, J.; Hartwig, J. F. *J. Am. Chem. Soc*. **1994,** *116*, 5969. (c) Paul, F.; Hartwig, J. F. *J. Am. Chem. Soc*. **1995,** 117, 5373. (d) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc*. **1995**, *117*, 4708.

7. (a) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem.,Int. Ed. Engl.* **1995**, *34*, 1348. (b) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 1133. (c) Louie, J.; Hartwig, J. F. *Tetrahedron. Lett.* **1995**, *36*, 3609. (d) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215. (e) Mann, G.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118,* 13109. (f) Marcoux, J.; Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1997,** *62*, 1568.

8. Hartwig, J. F.; Richards, S.; Barañano, D.; Paul, F. *J. Am. Chem. Soc.* **1996**, *118*, 3626.

9. (a) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998,** *120*, 7369. (b) Alcazar-Roman, L. M.; Hartwig, J. F.; Rheingold, A. L.; Liable-Sands, L. M.; Buzei, I. A. *J. Am. Chem. Soc.* **2000**, *122*, 4618.

10. Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047.

11. (a) Mann, G.; Hartwig, J. F.; Driver, M. S.; Fernándex-Rivas, C. *J. Am. Chem. Soc.* **1998**, *120*, 7369. (b) Driver, M. S.; Hartwig, J. F. *J. Am .Chem. Soc.* **1996**, *118,* 7215.

12. (a) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722. (b)Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2413. (c) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550. (d) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158. (e) Aranyos, A.; Old, D. W.; Kiyomori, A.; Wolfe, J. P.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4369.

13. Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6654.

14. Ehrentraut, A.; Zarf, A.; Beller, M. *J. Mol. Catal.* **2002**, *182*, 515.

15. Rataboul, F.; Zapf, A.; Jackstell, R.; Harkal, S.; Riermeier, T.; Monsees, A.; Beller, M. *Chem. Eur. J.* **2004**, *10*, 2983.

16. Harkal, S.; Rataboul, F.; Zapf, A.; Fuhrmann, C.; Riermeier, T.; Monsees, A.; Beller, M. *Adv. Synth. Catal.* **2004**, *346*, 1742.

17. Shen, Q.; Shekhar, S.; Stambuli, J. P.; Hartwig, J. F. *Angew. Chem., Int. Ed. Engl.* **2005**, *44*, 1371.

18. (a) Marion, N.; Navarro, O.; Mei, J.; Stevens, E. D.; Scott, N. M.; Nolan, S. P. *J. Am. Chem. Soc.* **2006**, *128*, 4101. (b) Viciu, M. S.; Kissling, R. M.; Stevens, E. D.; Nolan, S. P. *Org. Lett.* **2004**, *4*, 2229.

19. (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Suzuki, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998; Chapter 2. (c) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147. (d) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 4544. (e) Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 11. (f) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359. (g) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633. (h) Suzuki, A. In *Modern Arene Chemistry*; Astruc, D., Ed.; Wiley-VCH: Weinheim, 2002; pp 53-106. (i) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, 2419.

20. Gronowitz, S.; Hornfeldt,A. B; Kristjansson,V.; Musil, T. *Chem. Scr.* **1986**, *26*, 305. For more recent examples of this selectivity, see:(a) Cocuzza, A. J.; Hobbs, F. W.; Arnold, C. R.; Chidester, D. R.; Yarem, J. A.; Culp, S.; Fitzgerald, L.; Gilligan, P. J.; *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1057. (b) Jiang, B.; Yang, C.-G *Heterocycles*

2000, *53*, 1489. (c) Schomaker, J. M.; Delia, T. J. *J. Org. Chem.* **2001**, *66*, 7125. (d) Gong, Y.; Pauls, H. W. *Synlett* **2000**, 829.

21. For a review on Pd-catalyzed couplings of aryl chlorides: Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 4176.

22. (a) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed. Engl.***1998**, *37*, 3387. (b) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020. (c) Netherton, M. R.; Dai, C.; Neuschütz, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 10099. (d) Kirchhoff, J. H.; Netherton, M. R.; Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 13662. (e) Kirshhoff, J. H.; Dai, C.; Fu, G. C. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 1945. (f) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 1340.

23. (a) Yin, J.; Rainka, M. P.; Zhang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1162. (b) Barder, T. E.; Buchwald, S. L. *Org. Lett.* **2004**, *6*, 2649. (c) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **2004**, *43*, 1871. (d) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685

24. Zapf, A.; Jackstell, R.; Rataboul, F.; Reirmeier, T.; Monsees, A.; Fuhrmann, C.; Shaikh, N.; Dingerdissen, U.; Beller, M. *Chem. Commun.* **2004**, 38.

25. (a) Gstöttmayr, C. W. K.; Böhm, V. P. W.; Herdtweck, E.; Grosche, M.; Herrmann, W. A. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 1363. (b) Grasa, G. A.; Viciu, M. S.; Huang, J.; Zhang, C.; Trudell, M. L.; Nolan, S. P. *Organometallics* **2002**, *21*, 2866. (c) Viciu, M. S.; Germaneau, R. F.; Navarro-Fernandez, O.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2002**, *21*, 5470. (d) Navarro, O.; Kelly, R. A., III; Nolan, S. P. *J. Am. Chem. Soc*. **2003**, *125*, 16194. (e) Navarro, O.; Kaur, H.; Mahjoor, P.; Nolan,

S. P. *J. Org. Chem*. **2004**, *69*, 3173. (f) Lebel, H.; Janes, M. K.; Charette, A. B.; Nolan, S. P. *J. Am. Chem. Soc*. **2004**, *126*, 5046.

26. (a) Bedford, R. B.; Cazin, C. S. J.; Hazelwood, S. L. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 4120. (b) Bedford, R. B.; Hazelwood, S. L.; Limmert, M. E. *Chem. Commun.* **2002**, 2610. (c) Bedford, R. B.; Hazelwood, S. L.; Limmert, M. E.; Albisson, D. A.; Draper, S. M.; Scully, P. N.; Coles, S. J.; Hursthouse, M. B. *Chem. Eur. J*. **2003**, *9*, 3216. (d) Bedford, R. B.; Blake, M. E.; Butts, C. P.; Holder, D. *Chem. Commun*. **2003**, 466. (e) Bedford, R. B.; Hazelwood, S. L.; Limmert, M. E. *Organometallics* **2003**, *22*, 1364.

27. (a) Leadbeater, N. E.; Marco, M. *Org. Lett.* **2002**, 4, 2973. (b) Bedford, R. B.; Butts, C. P.; Hurst, T. E.; Lidstrom, P. *Adv. Synth. Catal.* **2004**, *346*, 1627. (c) Miao, G.; Ye, P.; Yu, L.; Baldino, C. M. *J. Org. Chem*. **2005**, *70*, 2332. (d) Arvela, R. K.; Leadbeater, N. E. *Org. Lett.* **2005**, *7*, 2101.

28. (a) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew .Chem., Int. Ed. Engl.* **2001**, *40*, 2004. (b) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 2596. (c) Krasinski, A.; Fokin, V. V.; Sharpless, K. B. *Org. Lett*. **2004**, *6*, 1237. (d) Feldman, A. K.; Colasson, B.; Fokin, V. V. *Org. Lett.* **2004**, *6*, 3897. (e) Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. *J. Am. Chem. Soc*. **2005**, *127*, 210.

29. (a) Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa A., Ed.; Wiley: New York, 1984; pp 1 – 176. (b) Padwa, A. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 4, pp 1069 – 1109. (b) Huisgen, R. *Pure*

Appl. Chem. **1989**, *61,* 613. (c) Huisgen, R.;Szeimies, G.; Moebius, L. *Chem. Ber*. **1967**, *100*, 2494.

30. (a) Zhu, W.; Ma, D. *Chem. Commun.* **2004**, *7*, 888. (b) Gilbert, A. M.; Miller, R.; Wulff, W. D. *Tetrahedron* **1999**, *55*, 1607.

31. Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 13978.

32. Reid, S. M.; Boyle, R. C.; Mague, J. T.; Fink, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 7816.

Chapter 2

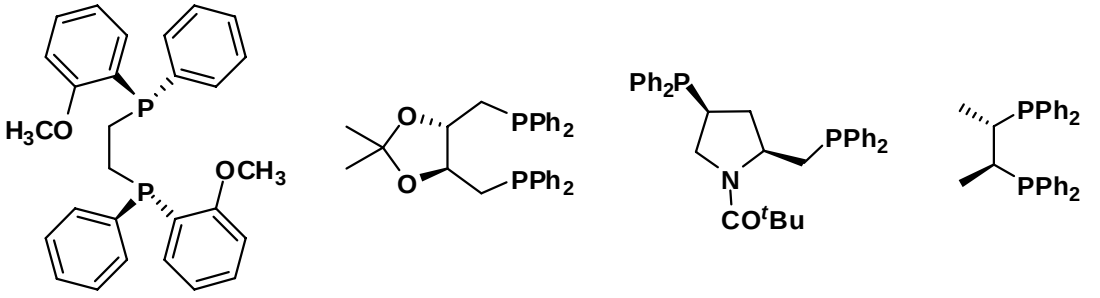
Development of a New Class of C_1-Symmetric Bisphosphine Ligands for Rhodium-Catalyzed Asymmetric Hydrogenation

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.[1] 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.[2] 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.[2]

Homogeneous asymmetric hydrogenation was initially investigated by Knowles and Horner in the late 1960s, albeit with poor enantioselectivity.[3] 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.[4] 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.[5] This success enabled Montsano to be the primary supplier of the main drug used in alleviating the effects of Parkinson's disease.[6] 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.

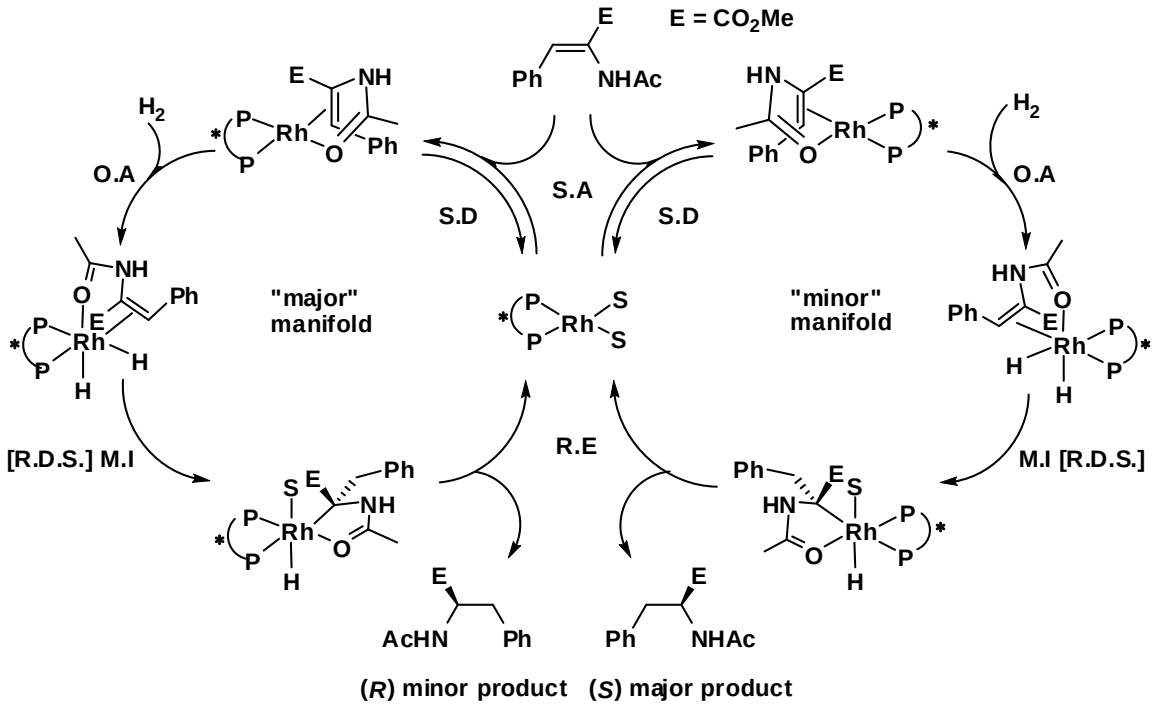


DIPAMP **DIOP** **BPPM** **CHIRAPHOS**

Knowles **Kagan** **Alchiwa** **Bosnich**

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

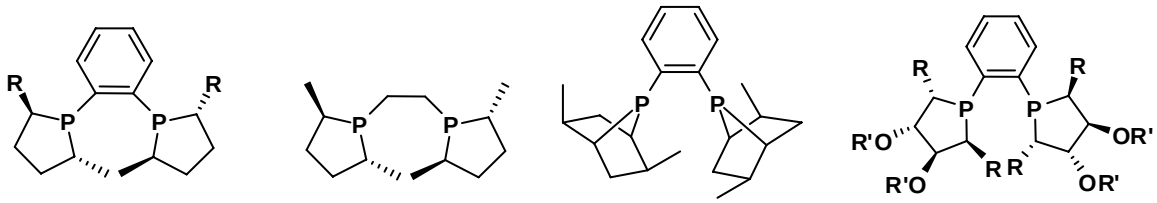
When ligand development was in its infancy, the mechanism of Rh-catalyzed asymmetric hydrogenation was actively being investigated. Brown[7] and Halpern[8] have proposed a generally accepted mechanism of asymmetric hydrogenation of enamides when the Rh complexes of tetraaryl-substituted diphosphines are used (such as DIPAMP and ChiraPhos). The so called "unsaturated mechanism" is shown in Figure 2-2.



S.A. = Substrate Association; S.D. = Substrate Dissociation; O.A. = Oxidative Addition; M.I. = Migratory Insertion; R.E. = Reductive Elimination; R.D.S. = Rate Determining Step

Figure **2-2**: "Unsaturated Pathway" of Rh-Catalyzed Asymmetric Hydrogenation

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.

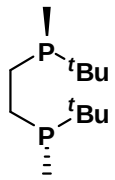


Me-DuPhos **Me-BPE** **Me-PennPhos** **RoPhos**

Burk **Zhang** **Börner**

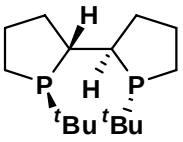
Figure **2-3**: Second Generation Ligands (1990 - Present): Dialkyl Aryl Phosphines

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 α-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.



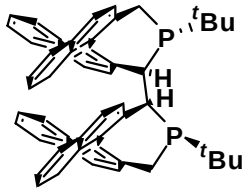
BisP*

Imamoto



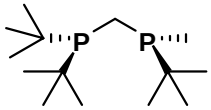
TangPhos

Zhang



BINAPINE

Zhang



Trichickenfootphos

Hoge

Figure **2-4**: Third Generation Ligands (1998 - Present): P-Chiral Trialkyl 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 TangPhos[15] and BINAPINE[16] by Zhang, have shown good enantioselectivities in asymmetric hydrogenation of a wide range of functionalized olefins. More recently, C_1-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 Imamoto[18] 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.

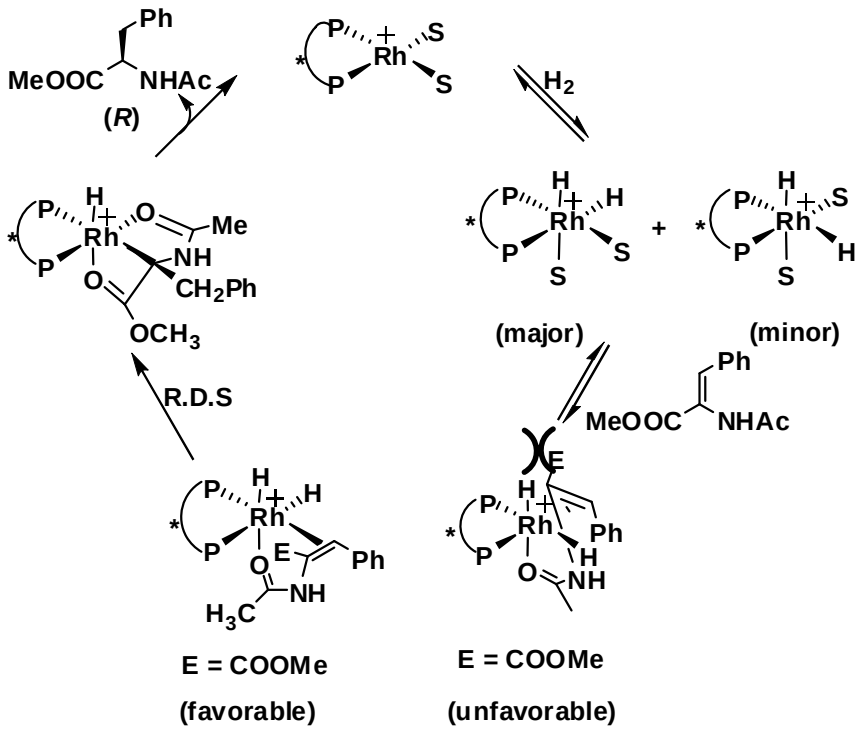


Figure **2-5**: "Dihydride Pathway" of Rh-Catalyzed Asymmetric Hydrogenation

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.[19] Moreover, a major drawback of many P-chiral phosphine synthetic methods developed by Imamoto,[19a] Juge,[19b] Corey,[19c] Evans[19e] and Livinghouse[19g] 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 bisphospine ligands. Recently, Hoge reported the synthesis of a bisphosphine ligand (trichickenfootPhos) with three hindered quadrants.[17] 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.

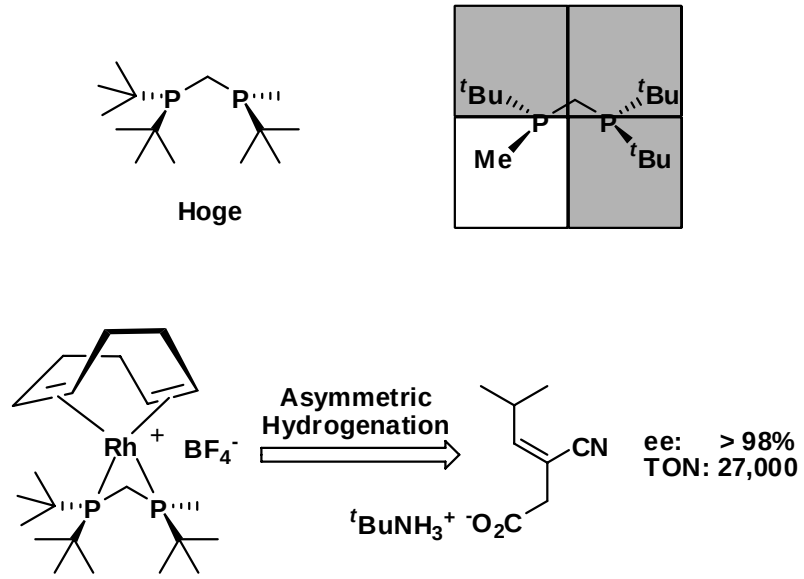


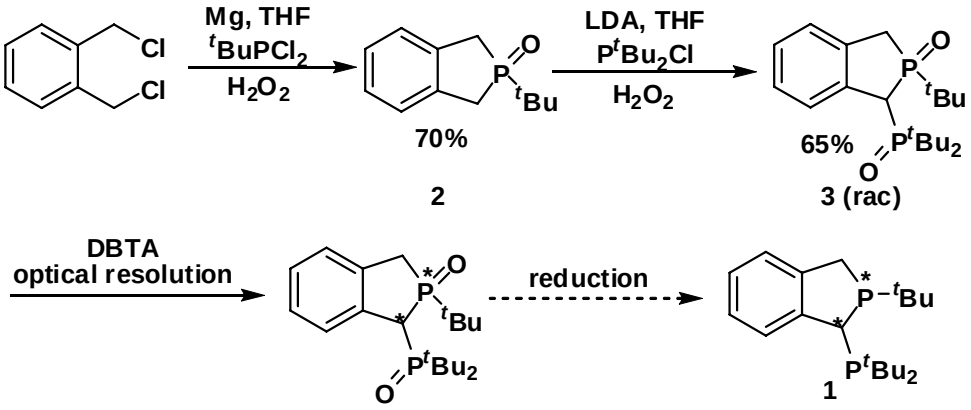
Figure **2-6**: TrichickenfootPhos and its Application in Asymmetric Hydrogenation

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.

2.2 Results and Discussion

2.2.1 Ligand Synthesis

Scheme **2-1**: Initial Synthetic Design Utilizing Optical Resolution

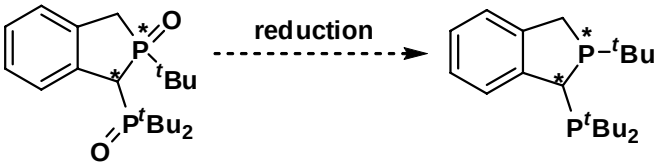


To overcome the synthetic limitation of trichickenfootPhos, we initially designed ligand **1**. This design is beneficial for the enantioseparation of this ligand as optical resolution can be used in place of chiral HPLC to isolate the two enantiomers (Scheme 2-1). Cyclic monophosphine oxide **2** can be obtained from readily available bischloromethylbenzene in one step in 70% yield.[20] *Ortho*-lithiation of **2** with LDA and electrophilic attack of P^tBu_2Cl, followed by H_2O_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_3N were used (Table 2-1, entry 1-2),

only the P=O on the five-membered ring was reduced. Use of LAH/MeOTf gave multiple decomposed side products (Table 2-1, entry 3).[21a] Si_2Cl_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-*tert*-butylphosphine oxide moiety. To the best of our knowledge, there is only one example of reducing a simple di-*tert*-butylphosphine oxide which employed neat Ph_2SiH_2 at 240 ^oC. [21b] When this methodology was applied to the reduction of **3**, only decomposition products were obtained (Table 2-1, entry 6).

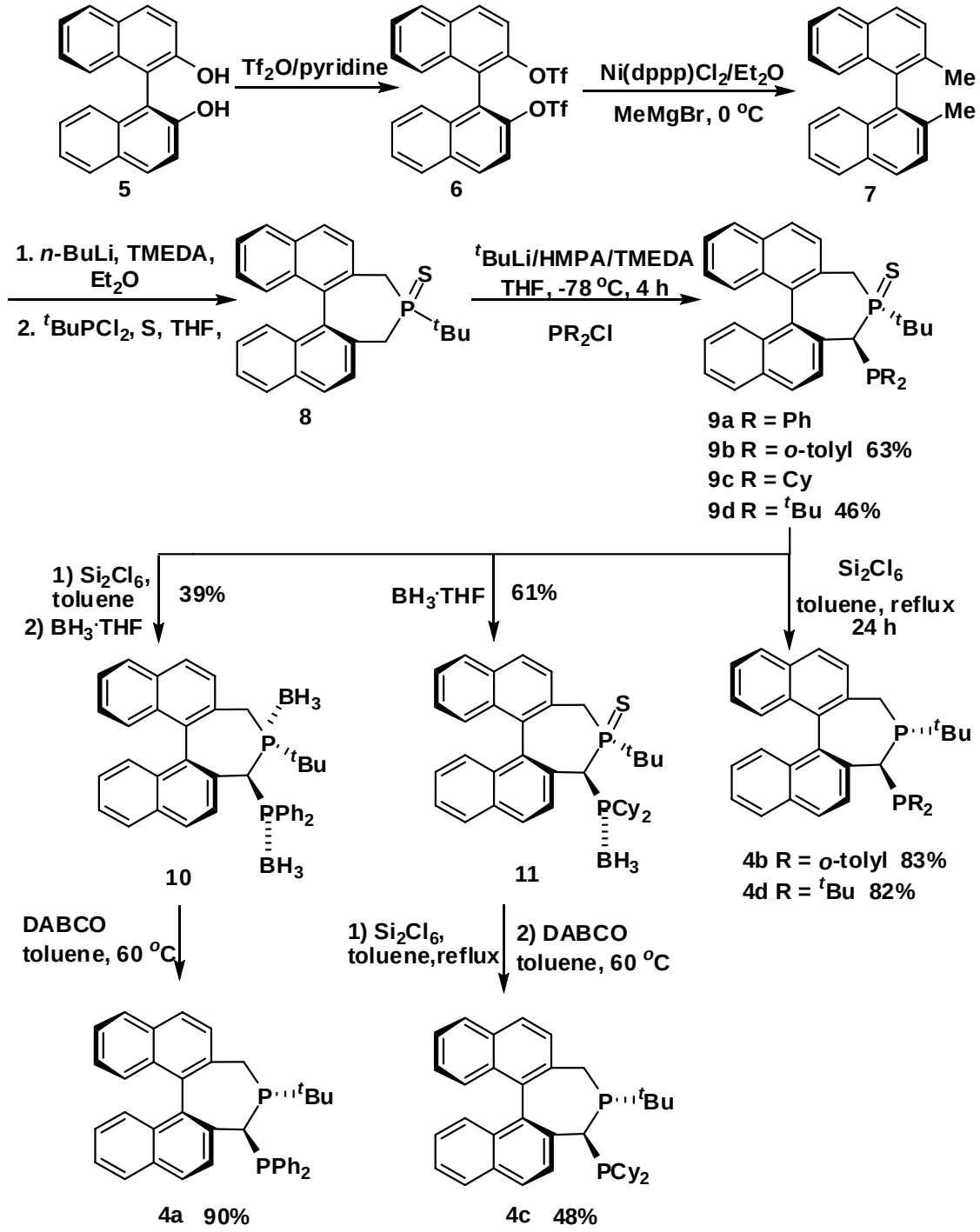
Table **2-1**: Different P=O Bond Reduction Conditions



entry	reducing agent	solvent	T(^{o}C)
1	$HSiCl_3$/TEA	toluene	110
2	$HSiCl_3$/Bu_3N	*o*-xylene	140
3	$LiAlH_4$/MeOTf	DME	0 ^{o}C-rt
4	Si_2Cl_6	toluene	110
5	Si_2Cl_6	*o*-xylene	140
6	Ph_2SiH_2		240
7	$Ti(O^iPr)_4$/$HSi(OEt)_3$	toluene	110
8	BH_3·Me_2S	THF	70

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.[16] Subsequent *ortho*-lithiation by ^{t}BuLi/HMPA/TMEDA at -78 ^{o}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 ^{t}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_2Cl_6 and protected with BH_3·THF to generate **10** or directly protected with BH_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_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



TMEDA = *N*,*N*,*N'*,*N'*-tetramethylethylenediamine
HMPA = hexamethylphosphoric triamide
DABCO = 1,4-diazabicyclo[2.2.2]octane

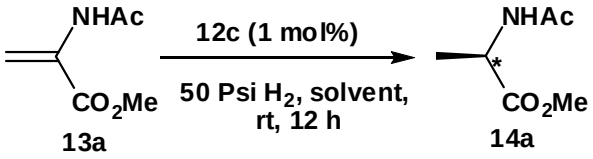
2.2.2 Rh-Catalyzed Asymmetric Hydrogenation

In order to examine the catalytic efficiency of **4a-d**, cationic Rh complexes [Rh(cod)**4**]BF_4 (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 H_2 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).

Table **2-2**: Screening of Solvents for Asymmetric Hydrogenation of **13a**



13a **14a**

100% conversion

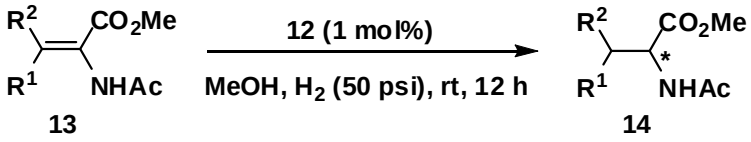
entry[a]	solvent	ee (%)[b](config.)
1	**MeOH**	**97.5 (*R*)**
2	EtOH	95.0 (*R*)
3	^{i}PrOH	95.5 (*R*)
4	THF	96.0 (*R*)
5	DCM	94.7 (*R*)
6	EtOAc	96.8 (*R*)
7	acetone	95.1 (*R*)
8	toluene	97.1 (*R*)

[a] See Experimental Section for a general procedure.
[b] The enantiomeric excess was determined by chiral GC (Chirasil-VAL III FSOT). The *R* absolute configuration was assigned by comparison of optical rotations with reported data.

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-**

d 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



13 **14**

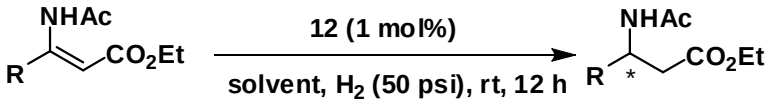
entry[a]	substrate	complex	conv.(%)[b]	ee(%) (config.)[c]
1	**13a** R^1, R^2 = H	**12a**	100	97.0% (*R*)
2	**13a**	**12b**	100	91.1% (*R*)
3	**13a**	**12c**	100	97.5% (*R*)
4	**13a**	**12d**	100	77.5% (*S*)
5	**13b** R^1 = 4-MeO-Ph, R^2 = H	**12a**	100	92.0% (*R*)
6	**13b**	**12b**	100	47.0% (*R*)
7	**13b**	**12c**	100	89.7% (*R*)
8	**13b**	**12d**	72	41.4% (*S*)
9	**13c** R^1, R^2 = C_4H_8	**12a**	64	38.7% (*R*)
10	**13c**	**12c**	55	8.5% (*R*)
11	**13c**	**12d**	100	49.6% (*R*)

[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) 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 α-analogues.[22] As shown in Table 2-4, several β-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 β-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.

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



15 **16**

entry[a]	substrate	solvent	complex	conv.(%)[b]	ee(%) (config.)[c]
1	**15a** R= Me	MeOH	**12a**	100	89.8% (*R*)
2	**15a**	MeOH	**12b**	100	22.4% (*R*)
3	**15a**	MeOH	**12c**	100	88.5% (*R*)
4	**15a**	MeOH	**12d**	100	17.7% (*R*)
5	**15a**	THF	**12b**	100	34.8% (*R*)
6	**15a**	THF	**12c**	93	92.6% (*R*)
7	**15b** R = Ph	THF	**12a**	80	89.6% (*S*)
8	**15b**	THF	**12b**	100	16.1% (*S*)
9	**15c** R = 4-OMe-Ph	MeOH	**12c**	100	92.5% (*R*)

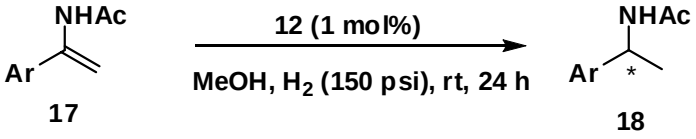
[a] See Experimental Section for a general procedure. [b] The conversions were based on GC detection. [c] The enantiomeric excess was determined by chiral GC (Chirasil-VAL III FSOT). The absolute configurations were assigned by comparison of optical rotations with reported data.

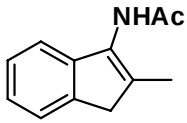
2.2.2.2 Asymmetric Hydrogenation of α-Aryl Enamides

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

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



entry[a]	substrate	complex	conv.(%)[b]	ee(%) (config.)[c]
1	**17a** Ar=3-Me-Ph	**12a**	100	53.5% (*R*)
2	**17a**	**12b**	100	53.7% (*S*)
3	**17a**	**12c**	100	79.7% (*R*)
4	**17a**	**12d**	100	71.8% (*S*)
5	**17b** 	**12a**	100	37.1% (*S*)
6	**17b**	**12b**	60	69.7% (*R*)
7	**17b**	**12c**	100	31.5% (*S*)
8	**17b**	**12d**	100	84.5% (*R*)

[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 C_1-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^{TM} 600 chromatograph.

4-*tert*-Butyl-3-diphenylphosphanyl-3,5-dihydro-4-phosphacyclohepta[2,1-α; 3,4–α′]dinaphthalene-4-sulfide (9a). At –78 ^{o}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 PPh_2Cl (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 NH_4Cl (aq). The organic layer was extracted with ether (3 × 10 mL) and washed with brine (10 mL), dried over Na_2SO_4 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 ^{t}BuLi (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)$_2$Cl (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 NH_4Cl (aq). The organic layer was extracted with ether (3 × 15 mL) and washed with brine (10 mL), dried over Na_2SO_4 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%). ^{1}H NMR ($CDCl_3$, 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,

3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.0, 143.6, 140.5, 140.2, 136.6, 136.3, 135.5, 135.4, 135.0, 134.1, 133.9, 132.8 (d, *J* = 2.5 Hz), 132.7 (d, *J* = 5.2 Hz), 132.5, 132.4, 131.0 (d, *J* = 2.7 Hz), 130.2 (d, *J* = 6.0 Hz), 129.7 (d, *J* = 3.3 Hz), 129.6 (d, *J* = 5.6 Hz), 128.4 (d, *J* = 2.0 Hz), 127.9, 127.8, 127.6, 127.4, 127.3, 127.2, 126.0, 125.9, 125.7, 125.3, 125.2, 124.2, 44.0 (t, *J* = 39.7 Hz), 36.6 (d, *J* = 41.4 Hz), 34.8 (d, *J* = 41.5 Hz), 25.8, 22.0 (d, *J* = 24.1 Hz), 20.5 (d, *J* = 29.0 Hz); ^{31}P NMR ($CDCl_3$, 145 MHz) δ 86.85 (d, $J_{P\text{-}P}$ = 69.9 Hz), -40.69 (d, $J_{P\text{-}P}$ = 69.8 Hz); HRMS (ESI+) calcd. for $C_{40}H_{39}P_2S$ (MH^+) 613.2248, found 613.2227.

4-*tert*-Butyl-3-dicyclohexylphosphanyl-3,5-dihydro-4-phosphacyclohepta-[2,1-α; 3,4–α′]dinaphthalene-4-sulfide (9c). At –78 °C, to a solution of **8** (0.60 g, 1.5 mmol), TMEDA (0.27 mL, 1.8 mmol) in THF (15 mL) was added dropwise ^{t}BuLi (1.32 mL, 1.7 M in pentane, 2.25 mmol). The reaction mixture was stirred at –78 °C for 4 h, followed by slow addition of a solution of PCy_2Cl (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_4Cl (aq). The organic layer was extracted with ether (3 × 10 mL) and washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was directly used in the next step without further purification.

4-*tert*-Butyl-3-(di-*tert*-butyl-phosphanyl)-3,5-dihydro-4-phosphacyclohepta-[2,1-α; 3,4–α′]dinaphthalene-4-sulfide (9d). At –78 °C, to a solution of **8** (1.20 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}BuLi (2.1 mL, 1.7 M in pentane, 3.6 mmol). The reaction mixture was stirred at –78 ^{o}C for 4 h, followed by slow addition of a solution of P^{t}Bu$_2$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 ^{o}C for another 30 min then allowed to slowly warm to room temperature and refluxed overnight before quenching with NH_4Cl (aq). The organic layer was extracted with ether (3 × 15 mL) and washed with brine (10 mL), dried over Na_2SO_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}H NMR ($CDCl_3$, 360 MHz) δ 7.86 (q, *J* = 4.3 Hz, 3H), 7.81 (s, 1H), 7.57 (t, *J* = 8.8 Hz, 2H), 7.36-7.43 (m, 3H), 7.18 (ddd, *J* = 1.3, 7.9, 9.6 Hz, 1H), 7.09-7.13 (m, 2H), 4.16 (dd, *J* = 3.6, 18.7 Hz, 1H), 2.68-2.82 (m, 2H), 1.21 (d, *J* = 15.0 Hz, 9H), 1.12 (d, *J* = 11.1 Hz, 9H), 1.00 (d, *J* = 15.0 Hz, 9H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 136.6, 136.0 (d, *J* = 5.4 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 Hz), 32.6 (d, *J* = 7.1 Hz), 29.7(d, *J* = 24.6 Hz), 29.3, 28.7(d, *J* = 10.3 Hz); ^{31}P NMR ($CDCl_3$, 145 MHz) δ 93.52 (d, $J_{P\text{-}P}$ = 69.4 Hz), 37.63 (d, $J_{P\text{-}P}$ = 69.2 Hz); HRMS (ESI+) calcd. for $C_{34}H_{43}P_2S$ (MH^+) 545.2561, found 545.2526.

4-*tert*-Butyl-3-diphenylphosphanyl-3,5-dihydro-4-phospha-cyclohepta[2,1-α; 3,4–α′]dinaphthalene bisborane complex (10). To the solution of crude product **9a** in 12 mL of toluene was slowly added Si_2Cl_6 (1.72 mL, 10 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 ^{o}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_2SO_4 and concentrated under reduced pressure. The crude product was redissolved in 10 mL of THF and cooled to 0 ^{o}C followed by addition of 6 mL of BH_3·THF (1M). 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 **10** as a white solid (0.23 g, 39%). ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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; ^{31}P NMR ($CDCl_3$, 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 ^oC. 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%). ^1H NMR ($CDCl_3$, 360 MHz) δ 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) δ 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) δ 89.15 (d, $J_{P\text{-}P}$ = 22.2 Hz), 55.76 (br s); HRMS (ESI+) calcd. for $C_{38}H_{49}BP_2SNa$ (MNa^+) 633.3021, found 633.2997.

4-*tert*-Butyl-3-diphenylphosphanyl-3,5-dihydro-4-phosphacyclohepta[2,1-α; 3,4–α′]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 ^oC 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_2Cl_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); ^{31}P NMR (CD_2Cl_2, 145 MHz) δ 29.86 (d, $J_{P\text{-}P}$ = 161.7 Hz), -9.55 (d, $J_{P\text{-}P}$ = 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_2Cl_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 ^{o}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_2SO_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_2Cl_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); ^{13}C NMR (CD_2Cl_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_2Cl_2, 145 MHz) δ 28.41 (d, $J_{P\text{-}P}$ = 157.1 Hz), -40.76 (d, $J_{P\text{-}P}$ = 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-α; 3,4–α′]dinaphthalene (4c). To the solution of **11** (0.495 g, 0.83 mmol) in 15 mL of toluene was added Si_2Cl_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 ^oC 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_2SO_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 ^oC 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_2Cl_2, 360 MHz) δ 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_2Cl_2, 75 MHz) δ 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_2Cl_2, 145 MHz) δ 34.70 (d, $J_{P\text{-}P}$ = 133.8 Hz), 10.38 (d, $J_{P\text{-}P}$ = 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_2Cl_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 ^{o}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_2SO_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_2Cl_2, 360 MHz) δ 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_2Cl_2, 145 MHz) δ 56.61 (d, $J_{P\text{-}P}$ = 32.9 Hz), 35.23 (d, $J_{P\text{-}P}$ = 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 $[Rh(cod)_2]BF_4$ (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**]BF_4 (**12a**). ^{1}H NMR (CD_2Cl_2, 360 MHz) δ 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); ^{31}P NMR (CD_2Cl_2, 145 MHz) δ 22.92 (dd, *J* = 72.1, 127.1 Hz), -23.11 (dd, *J* = 72.1, 134.2 Hz); HRMS (ESI+) calcd. for $C_{46}H_{46}P_2Rh$ (cation) 763.2130, found 763.2094; HRMS (ESI−) calcd. for BF_4 (anion) 87.0029, found 87.0023.

[Rh(cod)**4b**]BF_4 (**12b**). ^{1}H NMR (CD_2Cl_2, 360 MHz) δ 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); ^{31}P NMR (CD_2Cl_2, 145 MHz) δ 26.52 (dd, *J* = 62.3, 131.3 Hz), -17.52 (dd, *J* = 63.5, 131.2 Hz); HRMS

(ESI+) calcd. for $C_{48}H_{50}P_2Rh$ (cation) 791.2413, found 791.2443; HRMS (ESI−) calcd. for BF_4 (anion) 87.0029, found 87.0021.

[Rh(cod)**4c**]BF_4 (**12c**). ^{1}H NMR (CD_2Cl_2, 360 MHz) δ 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); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 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; ^{31}P NMR (CD_2Cl_2, 145 MHz) δ 21.72 (dd, *J* = 59.8, 129.5 Hz), -6.09 (dd, *J* = 59.9, 125.4 Hz); HRMS (ESI+) calcd. for $C_{46}H_{58}P_2Rh$ (cation) 775.3069, found 775.3003; HRMS (ESI−) calcd. for BF_4 (anion) 87.0029, found 87.0023.

[Rh(cod)**4d**]BF_4 (**12d**). ^{1}H NMR (CD_2Cl_2, 360 MHz) δ 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_2Cl_2, 75 MHz) δ 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_2Cl_2, 145 MHz) δ 36.26 (dd, J = 36.5, 127.3 Hz), 26.32 (dd, J = 36.3, 133.4 Hz); HRMS (ESI+) calcd. for $C_{42}H_{54}P_2Rh$ (cation) 723.2697, found 723.2756; HRMS (ESI−) calcd. for BF_4 (anion) 87.0029, found 87.0019.

References and Notes

1. (a) Izumi, Y.; Tai, A. *Stereo-Differentiating Reactions: The Nature of Asymmetric Reactions*; Academic Press: New York, 1977. (b) Bosnich, B., Ed.; *Asymmetric Catalysis*; Martinus Nijhoff: New York, 1986. (c) Ojima, I., Ed.; *Catalytic Asymmetric Synthesis*; VCH: New York, 1993. (d) Brunner, H.; Zettlmeier, W. *Handbook of Enantioselective Catalysis*; VCH: Weinheim, 1993. (e) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994. (f) Jannes, G., Dubois, V., Eds.; *Chiral Reactions in Heterogeneous Catalysis*; Plenum: New York, 1995. (g) Cornils, B., Herrmann, W. A., Eds.; *Applied Homogeneous Catalysis with Organometallic Compounds*; VCH: Weinheim, 1996; Vol. 1, 2. (h) Beller, M., Bolm, C. Eds.; *Transition Metals for Organic Synthesis*: *Building Blocks and Fine Chemicals*; Wiley-VCH: Weinheim, 1998; Vol. 1, 2. (i) Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; *Comprehensive Asymmetric Catalysis*; Springer: Berlin, 1999; Vol. 1-3. (j) Ojima, I., Ed.; *Catalytic Asymmetric Synthesis*; Wiley-VCH: New York, 2000.

2. (a) Noyori, R.; Kitamura, M. In *Modern Synthetic Methods*, Scheffold, R., Ed.; Springer: Berlin, 1989; Vol. 5, p 115. (b) Takaya, H.; Ohta, T.; Noyori, R. In *Catalytic Asymmetric Synthesis*, Ojima, I., Ed.; VCH: New York, 1993; p 1. (c) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994; Chapter 2. (d) Ohkuma, T.; Noyori, R. In *Transition Metals for Organic Synthesis*: *Building Blocks and Fine Chemicals*, Beller, M., Bolm, C. Eds.; Wiley-VCH: Weinheim, 1998; Vol. 2, p 25.

3. (a) Knowles, W. S.; Sabacky, M. J. *J. Chem. Soc., Chem. Commun.* **1968**, 1445. (b) Horner, L.; Siegel, H.; Büthe, H. *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 941.

4. (a) Kagan, H. B.; Dang, T. P. *J. Chem. Soc., Chem. Commun.* **1971**, 481. (b) Kagan, H. B.; Dang, T. P. *J. Am. Chem. Soc.* **1972**, *94*, 6429. (c) Kagan, H. B.; Langlois, N.; Dang, T. P. *J. Organomet. Chem.* **1975**, *90*, 353.

5. (a) Vineyard, B. D.; Knowles, W. S.; Sabacky, M. J.; Bachman, G. L.; Weinkauff, O. J. *J. Am. Chem. Soc.* **1977**, *99*, 5946. (b) Knowles, W. S. *Acc. Chem. Res.* **1983**, 16, 106.

6. Genet, J. P. *Acc. Chem. Res.* **2003**, *36*, 908.

7. (a) Brown, J. M.; Chaloner, P. A. *J. Chem. Soc., Chem. Commun.* **1978**, 321. (b) Brown, J. M.; Chaloner, P. A. *Tetrahedron Lett.* **1978**, *19*, 1877. (c) Brown, J. M.; Chaloner, P. A. *J. Chem. Soc., Chem. Commun.* **1979**, 613. (d) Brown, J. M.; Chaloner, P. A. *J. Chem. Soc., Chem. Commun.* **1980**, 344. (e) Brown, J. M.; Chaloner, P. A.; Glaser, R.; Geresh, S. *Tetrahedron* **1980**, *36*, 815. (f) Alcock, N. W.; Brown, J. M.; Derome, A.; Lucy, A. R. *J. Chem. Soc., Chem. Commun.* **1985**, 575. (g) Brown, J. M.; Chaloner, P. A.; Morris, G. A. *J. Chem. Soc., Perkin Trans. 2*, **1987**, 1583. (h) Brown, J. M. *Chem. Soc. Rev.* **1993**, *22*, 25.

8. (a) Halpern, J.; Riley, D. P.; Chan, A. S. C.; Pluth, J. J. *J. Am. Chem. Soc*. **1977**, *99*, 8055. (b) Chan, A. S. C.; Halpern, J. *J. Am. Chem. Soc.* **1980**, *102*, 838. (c) Chan, A. S. C.; Pluth, J. J.; Halpern, J. *J. Am. Chem. Soc.* **1980**, *102*, 5952. (d) Halpern, J. *Science* **1982**, *217*, 401. (e) Landis, C. R.; Halpern, J. *J. Am. Chem. Soc.* **1987**, *109*, 1746. (f) Ashby, M. T.; Halpern, J. *J. Am. Chem. Soc.* **1991**, *113*, 589.

9. (a) Burk, M. J.; Feaster, J. E.; Harlow, R. L. *Organometallics* **1990**, *9*, 2653. (b) Nugent, W. A.; RajanBabu, T. V.; Burk, M. J. *Science* **1993**, *259*, 479. (c) Burk, M. J. *Acc. Chem. Res.* **2000**, *33*, 363.

10. (a) Holz, J.; Quirmbach, M.; Schmidt, U.; Heller, D.; Stürmer, R.; Börner, A. *J. Org. Chem.* **1998**, *63*, 8031. (b) Holz, J.; Stürmer, R.; Schmidt, U.; Drexler, H.-J.; Heller, D.; Krimmer, H.-P.; Börner, A. *Eur. J. Org. Chem.* **2000**, 4615.

11. (a) Holz, J.; Heller, D.; Stürmer, R.; Börner, A. *Tetrahedron Lett.* **1999**, *40*, 7059. (b) Holz, J.; Stürmer, R.; Schmidt, U.; Drexler, H.-J.; Heller, D.; Krimmer, H.-P.; Börner, A. *Eur. J. Org. Chem.* **2000**, 4615.

12. Holz, J.; Monsees, A.; Jiao, H.; You, J.; Komarov, I. V.; Fischer, C.; Drauz, K.; Börner, A. *J. Org. Chem.* **2003**, *68*, 1701.

13. (a) Landis, C. R.; Hilfenhaus, P.; Feldgus, S. *J. Am. Chem. Soc.* **1999**, *121*, 8741. (b) Feldgus, S.; Landis, C. R. *J. Am. Chem. Soc.* **2000**, *122*, 12714.

14. (a) Imamoto, T.; Watanabe, J.; Wada, Y.; Masuda, H.; Yamada, H.; Tsuruta, H.; Matsukawa, S.; Yamaguchi, K. *J. Am. Chem. Soc.* **1998**, *120*, 1635. (b) Gridnev, I, D.; Yamanoi, Y.; Higashi, N.; Tsuruta, H.; Yasutake, M.; Imamoto, T. *Adv. Synth. Catal.* **2001**, *343*, 118.

15. (a) Tang, W.; Zhang, X. *Angew. Chem., Int. Ed. Engl.* ***2002, 41,*** 1612. (b) Tang, W.; Zhang, X. *Org. Lett.* **2002**, *4*, 4159. (c) Tang, W.; Liu, D.; Zhang, X. *Org. Lett.* **2003**, *5*, 205.

16. Tang, W., Wang, W., Chi, Y. and Zhang, X. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 3509.

17. Hoge, G.; Wu, H.-P.; Kissel, W. S.; Pflum, D. A.; Greene, D. J.; Bao, J. *J. Am. Chem. Soc.* **2004**, *126*, 5966.

18.(a) Gridnev, I. D.; Higashi, N.; Asakura, K.; Imamoto, T. *J. Am. Chem. Soc.* **2000**, *122*, 7183. (b) Gridnev, I. D.; Higashi, N.; Imamoto, T. *J. Am. Chem. Soc.* **2000**, *122*, 10486. (c) Gridnev, I. D.; Imamoto, T. *Organometallics* **2001**, *20*, 545.

19. (a) Imamoto, T.; Oshiki, T.; Onozawa, T.; Kusumoto, T.; Kazuhiko, S. *J. Am. Chem. Soc.* **1990**, *112*, 5244. (b) Juge, S.; Stephan, M.; Laffitte, J. A.; Genet, J. P. *Tetrahedron Lett.* **1990**, *31*, 6357. (c) Corey, E. J.; Chen, Z.; Tanoury, G. J. *J. Am. Chem. Soc.* **1993**, *115*, 11000. (d) Pietrusiewicz, K. M.; Zablocka, M. *Chem. Rev.* **1994**, *94*, 1375. (e) Muci, A. R.; Campos, K. R.; Evans, D. A. *J. Am. Chem. Soc.* **1995**, *117*, 9075. (f) Ohff, M.; Holz, J.; Quirmbach, M.; Borner, A. *Synthesis* **1998**, 1391. (g) Wolfe, B.; Livinghouse, T. *J. Am. Chem. Soc.* **1998**, *120*, 5116. (h) Al-Masum, M.; Kumaraswamy, G.; Livinghouse, T. *J. Org. Chem.* **2000**, *65*, 4776. (i) Moncarz, J. R.; Laritcheva, N. F.; Glueck, D. S. *J. Am. Chem. Soc.* **2002**, *124*, 13356. (j) Leung, P.-H. *Acc. Chem. Res.* **2004**, *37*, 169.

20. Liu, Duan Ph. D dissertation, The Pennsylvania State University, University Park, Pennsylvania, 2005, Chapter 1, p 15.

21. (a) Imamoto, T.; Kikuchi S.; Miura, T.; Wada, Y. *Org. Lett*. **2001**, *3*, 87. (b) Dahl, O.; Jensen, F. K. *Acta Chem. Scand. Ser. B*. **1975**, *29*, 863

22. Drexler, H.-J.; You, J.; Zhang, S.; Fischer, C.; Baumann, W.; Spannenberg, A.; Heller, D. *Org. Proc. Res. Dev.* **2003**, *7*, 355 and references cited therein.

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.[1] Several examples of diastereoselective syntheses of β-amino acids have been reported in which chiral auxiliaries were utilized to achieve stereoselectivities.[1b] 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.[2] Many rhodium and ruthenium complexes with chiral bidentate phosphorus ligands such as BINAP,[3] Duphos,[4a] BICP,[4b] *t*Bu-BisP*,[4c] and TangPhos[4d] have been successfully used in the asymmetric hydrogenation of β-(acylamino)acrylate derivatives. Recently, monophosphoramidites ligands such as MonoPhos,[5a] SIPHOS[5b] 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.[6]

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.[3, 7] 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.[8] 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.

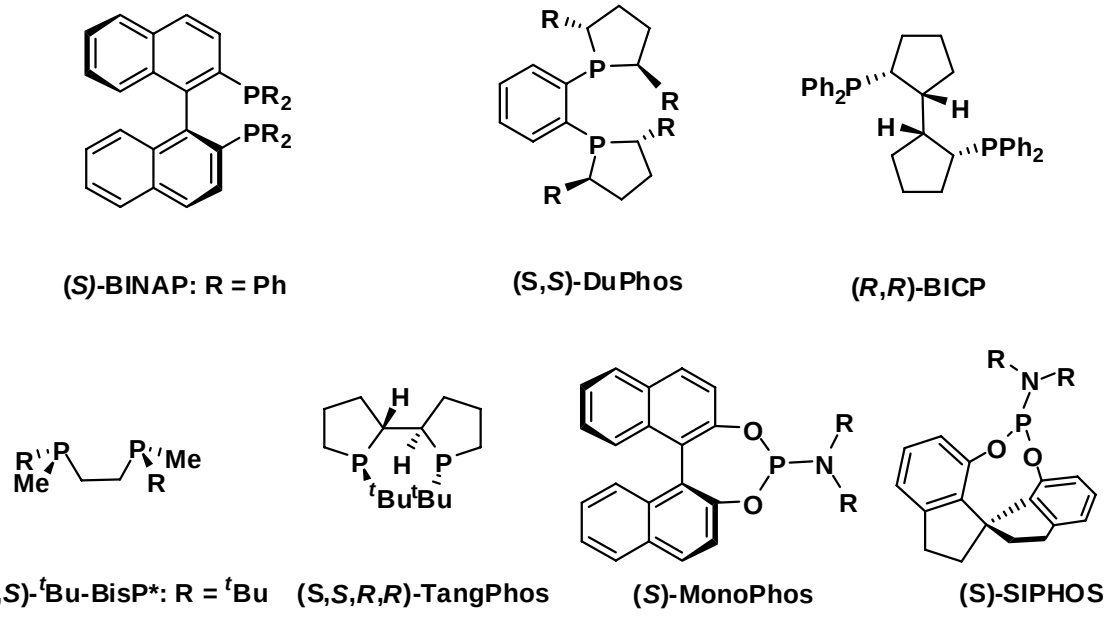
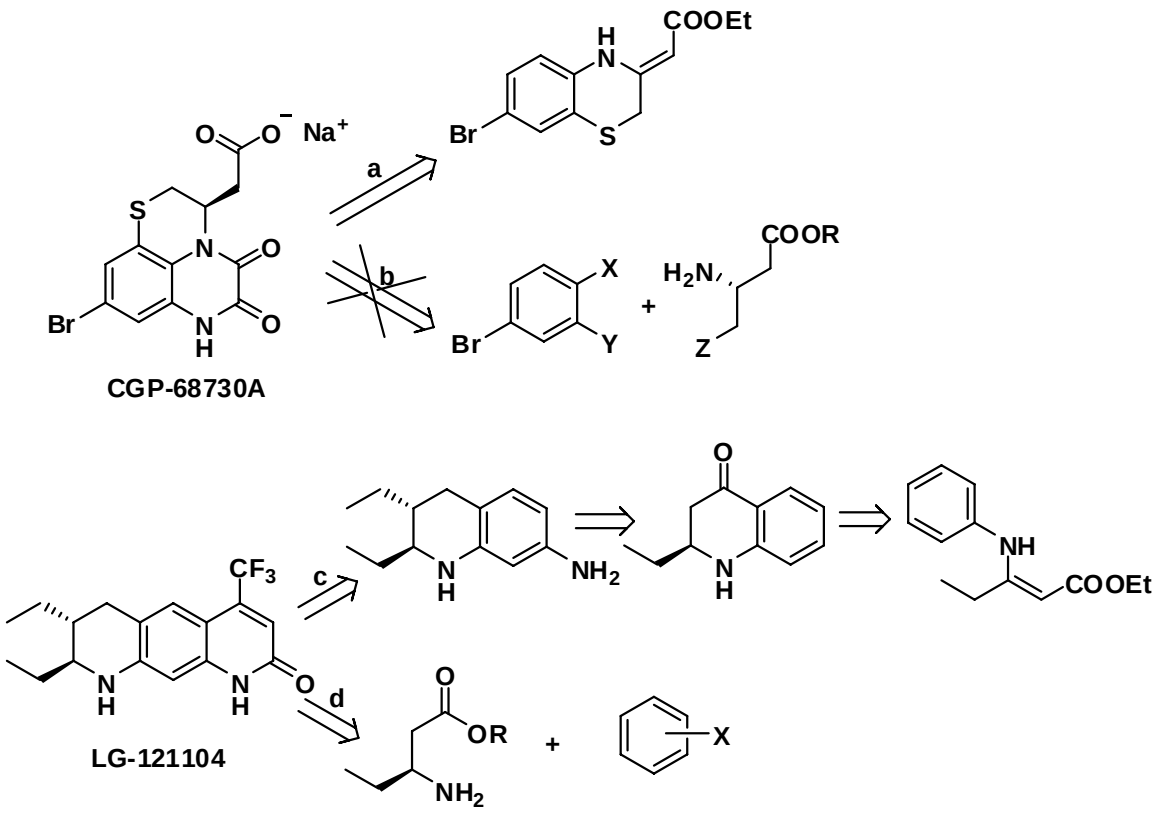


Figure **3-1**: Chiral Phosphine Ligands used in Rh-Catalyzed Asymmetric Hydrogenation of β-(Acylamino)acrylates

N-Aryl β-amino acid derivatives are key structural elements of many natural products and drug intermediates.[9] The most direct and elegant way to prepare such compounds is to perform asymmetric hydrogenation of *N*-aryl β-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 β-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 β-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 β-amino acids via asymmetric hydrogenation of unprotected enamines with Rh complexes prepared from ferrocenyl-based JosiPhos type ligands.[11] Mechanistic

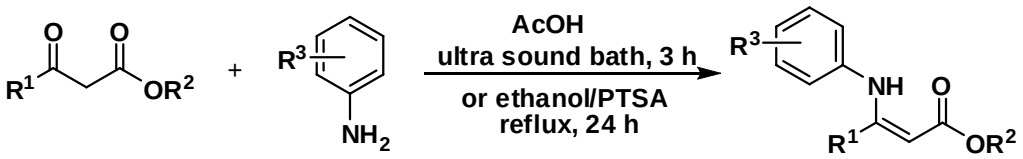
studies show that the reaction possibly proceeds through the corresponding imine tautomer (Scheme 3-2). However, direct formation of unprotected amino esters has the potential to limit the reaction performance (TON: up to 300).[12] The basicity and nucleophilicity of the amine product causes its strong 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).

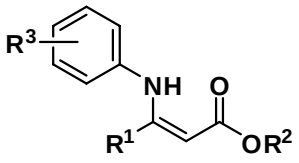
Scheme **3-2**: Enamines and Imine Tautomers

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

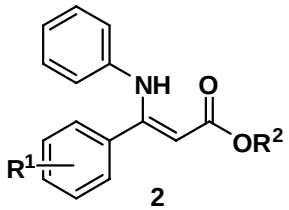
3.2.1 Substrate Preparation





1

1a: R^1 = Me, R^2 = Me, R^3 = H;
1b: R^1 = Me, R^2 = Et, R^3 = H;
1c: R^1 = Et, R^2 = Et, R^3 = H;
1d: R^1 = isopentyl, R^2 = Et, R^3 = H;
1e: R^1 = CF_3, R^2 = Et, R^3 = H;
1f: R^1 = Me, R^2 = Et, R^3 = *p*-F;
1g: R^1 = Me, R^2 = Et, R^3 = *m*-Br;
1h: R^1 = Me, R^2 = Et, R^3 = *p*-OMe;
1i: R^1 = Me, R^2 = Et, R^3 = *m*-OMe



2

2a: R^1 = H, R^2 = Et;
2b: R^1 = *p*-Me, R^2 = Me;
2c: R^1 = *p*-F, R^2 = Me;
2d: R^1 = *o*-OMe, R^2 = Me;
2e: R^1 = *o*-Me, R^2 = Me

Figure **3-2**: Synthesis of Substrates

A family of enamines has been prepared from the corresponding β-keto esters and aniline derivatives (Figure 3-2).[13] For most β-alkyl enamino esters **1**, the condensation reaction could be performed without solvent in an ultrasound bath. For β-aryl enamino 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

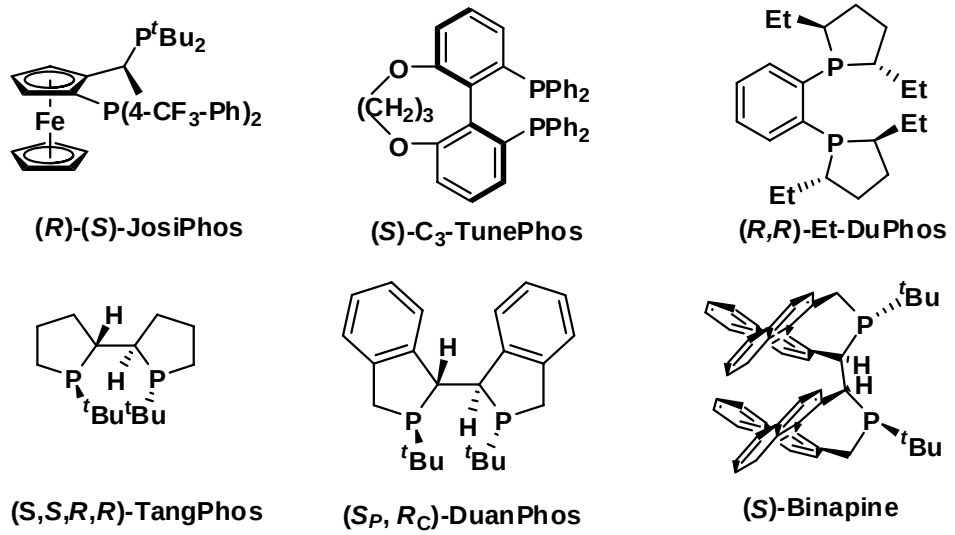
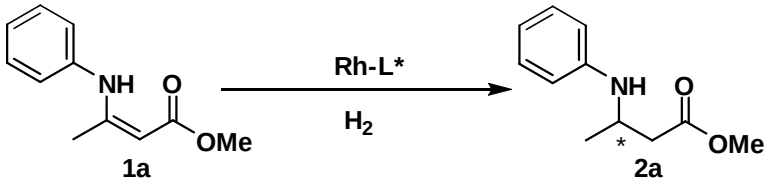


Figure **3-3**: Ligands Screened in Asymmetric Hydrogenation

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.[11] While chiral biaryl bisphosphine (*S*)-C_3-TunePhos[15] offered moderate conversion and enantioselectivity (Table 3-1, entry 2), higher conversion was achieved with a more electron-donating trialkyl-bisphosphine TangPhos[16a] (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-

9). 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**.



1a **2a**

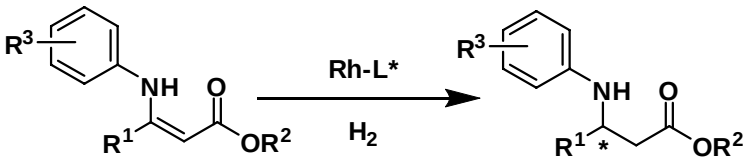
entry	catalyst[a]	solvent	T(°C)	P (H_2)[atm]	conv.(%)[b]	ee(%)[c]	config.[d]
1	**3a**	TFE	50	6	100	31.9	(−)
2	**3b**	MeOH	50	6	67	76.7	(+)
3	**3c**	MeOH	50	6	52	47.9	(−)
4	**3d**	MeOH	50	6	95	76.1	(−)
5	**3d**	CH_2Cl_2	50	6	77	94.6	(−)
6	**3d**	TFE	50	6	100	90.9	(−)
7	**3d**	TFE	rt	6	67	92.9	(−)
8	**3d**	TFE	rt	30	83	77.7	(−)
9	**3d**	TFE	rt	95	75	72.9	(−)
10	**3e**	TFE	50	6	78	69.6	(−)
11	**3f**	TFE	50	6	58	50.1	(+)

[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_P,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 β-aryl enamine **2b** was tested under the optimized reaction conditions for the hydrogenation of *N*-aryl β-alkyl enamines. However, low conversion was observed under these conditions. To address the reactivity issue, the temperature was increased from 50 ^{o}C to 80 ^{o}C. This modification afforded complete conversion and 91.1% ee (Table 3-2, entry 11). For hydrogenation of *N*-aryl β-aryl enamines **2** (Table 3-2, entries 10-14), it was noted that introduction of an electron-withdrawing group on the β-aryl group resulted in higher enantioselectivity (Table 3-2, entry 12). Furthermore, substrates with *ortho*-substituted electron-donating β-aryl groups led to much lower enantioselectivities and reactivities (Table 3-2, entries 13-14).

Table **3-2**: Asymmetric Hydrogenation of Substrates **1a-1i**[a], **2a-2e**[b]



1 or 2 **4 or 5**

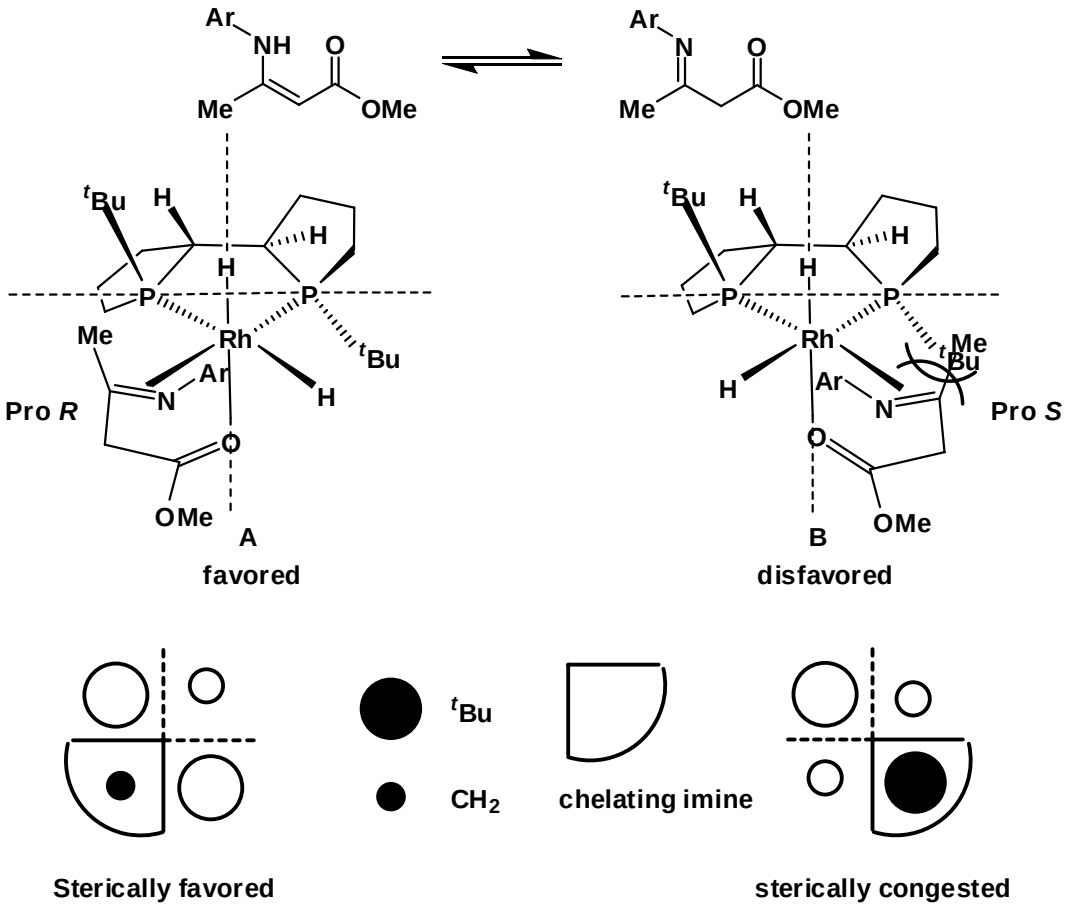
entry	substrate	conv.(%)[c]	ee(%)[d]	config.[e]
1	**1a**	100	90.9	(−)
2	**1b**	100	94.8	(−)
3	**1c**	100	94.9	(+)
4	**1d**	100	89.7	(+)
5	**1e**	48	78.9	(+)
6	**1f**	100	96.3	(−)
7	**1g**	83	96.1	(−)
8	**1h**	78	93.8	*R* [f]
9	**1i**	88	95.7	(−)
10	**2a**	100	92.3	(−)
11	**2b**	100	91.1	(−)
12	**2c**	100	95.3	(+)
13	**2d**	100	89.7	(−)
14	**2e**	67	79.3	(+)

[a] Reaction conditions: 1 mol% catalyst, 50°C, 6 atm of H_2, 18 h. [b] Reaction conditions: 1 mol% catalyst, 80°C, 6 atm of H_2, 24h. [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.[18]

The origin of enantioselection in the asymmetric hydrogenation of *N*-aryl β-enamines with the Rh-TangPhos system is believed to be similar to the hydrogenation with the Rh-^{t}Bu-BisP* system proposed by Gridnev and Imamoto (Scheme 3-3).[17] 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

with a much more hindered ^{t}Bu 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 *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 the 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.[17a]

Scheme **3-3**: Interpretation of Enantioselection in the Asymmetric Hydrogenation of *N*-Aryl β-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^{TM} 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 Na_2SO_4 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 %). ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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%). ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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%). ^{1}HNMR (400 MHz, $CDCl_3$) 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); ^{13}CNMR (75 MHz, $CDCl_3$) 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 $C_{13}H_{18}NO_2$ 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, $CDCl_3$) δ10.34 (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, $CDCl_3$) δ 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{12}H_{15}NO_2Br$ 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 benzoylacetate (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_2SO_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 = 7.5Hz, 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-trifluoroacetoacetate and aniline by the same method used for **2a** as a colorless oil (45%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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); ^{13}C NMR (90 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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); ^{13}C NMR (90 MHz, $CDCl_3$) δ 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 $C_{16}H_{15}NO_2F$ 272.1087, found 272.1073.

3-(2-Methoxyphenyl)-3-phenylaminoacrylic acid methyl ester (2d). This compound was obtained from methyl 2-methoxybenzoylacetate 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-methylbenzoylacetate 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 ^{o}C (for **1**) and 80^{o}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, $CDCl_3$) δ 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, $CDCl_3$) δ 172.2, 146.7, 129.4, 117.7, 113.6, 51.6, 46.0, 40.7, 20.6; $[\alpha]^{20}_{D}$ = -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, $CDCl_3$) δ 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, $CDCl_3$) δ 172.3, 147.3, 129.8, 118.1, 114.0, 60.9, 46.4, 41.5, 21.1, 14.7; $[\alpha]^{20}_{D}$ = -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, $CDCl_3$) δ 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, $CDCl_3$) δ 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; $[\alpha]^{20}_{D}$ = 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}CNMR (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 $C_{12}H_{17}NO_2F$ 226.1243, found 226.1248; $[\alpha]^{20}_D$ = -2.3 (*c* =

1, $CHCl_3$) for 96.3 % ee; Chiralpak OJ-H, hex:ipa = 99:1, 1 mL/min, t_1 = 30.1min, t_2 = 36.1 min.

3-(3-Bromophenylamino)-butyric acid ethyl ester (4g). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.02 (t, J = 8.0 Hz, 1H), 6.76-6.82 (m, 2H), 6.52-6.55 (m, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.88-3.94 (m, 2H), 2.59 (dd, *J* = 5.3, 15.1 Hz, 1H), 2.45 (dd, *J* = 6.4, 15.1 Hz, 1H), 1.24-1.33 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 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 $C_{12}H_{17}NO_2$ 286.0443, found 286.0424; $[\alpha]^{20}_D$ = -1.6 (*c* = 0.9, $CHCl_3$) for 96.1 % ee; Chiralpak OJ-H, hex:ipa = 99:1, 1 mL/min, t_1 = 33.4 min, t_2 = 44.9 min.

3-(4-Methoxyphenylamino)-butyric acid ethyl ester (4h). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.76-6.81 (m, 2H), 6.59-6.64 (m, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.79-3.90 (m, 1H), 3.74 (s, 3H), 3.41 (br s, 1H), 2.60 (dd, *J* = 5.3, 15.0 Hz, 1H), 2.39 (dd, *J* = 6.8, 14.9 Hz, 1H), 1.23-1.28 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 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 min, t_2 = 89.9 min.

3-(3-Methoxyphenylamino)-butyric acid ethyl ester (4i). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 (t, *J* = 8.1 Hz, 1H), 6.19-6.30 (m, 3H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.79-3.94 (m, 2H), 3.78 (s, 3H), 2.64 (dd, *J* = 5.1, 15.0 Hz, 1H), 2.43 (dd, *J* = 6.9, 15.0 Hz, 1H), 1.24-1.29 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 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 (MH^+); 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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 (MH^+); 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{16}H_{17}NO_2F$ 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{17}H_{20}NO_2$ 270.1494, found 270.1494; $[\alpha]^{20}_D$ = 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

1. (a) Hoekstra, W. J., Ed. The Chemistry and Biology of β-Amino Acids. *Curr. Med. Chem.* **1999**, *6*, 905. (b) *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, **1997**. (c) Ma, J. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 4290.
2. (a) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029. (b) Dumas, F.; Mezrhab, B.; d'Angelo, J.; Riche, C.; Chiaroni, A. *J. Org. Chem.* **1996**, *61*, 2293. (c) Kobayashi, S.; Ishitani, H.; Ueno, M. *J. Am. Chem. Soc*. **1998**, *120,* 431. (d) Tang, T. P.; Ellman, J. A. *J. Org. Chem*. **1999**, *64,* 12. (e) Zhou, Y.; Tang, W.; Wang, W.; Li, W.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124.* (f) Tang, W.; Wang, W.; Chi, Y.; Zhang, X. *Angew. Chem., Int. Ed. Engl.* **2003**, *42,* 3509. (g) Tang, W.; Wu, S.; Zhang, X. *J. Am. Chem. Soc.* **2003**, *125*, 9570. (h) You, J.; Drexler, H.; Zhang, S.; Fischer, C.; Heller, D. *Angew. Chem., Int. Ed. Engl.* **2003**, *42,* 913.
3. Lubell, W. D.; Kitamura, M.; Noyori, R. *Tetrahedron: Asymmetry* **1991**, *2*, 543.
4. (a) Heller, D.; Holz, J.; Drexler, H. J.; Lang, J.; Drauz, K.; Krimmer, H.-P.; Börner, A. *J. Org. Chem*. **2001**, *66*, 6816. (b) Zhu, G.; Chen, Z.; Zhang, X. *J. Org. Chem.* **1999**, *64*, 6907. (c) Yasutake, M.; Gridnev, I. D.; Higashi, N.; Imamoto, T. *Org. Lett.* **2001**, *3*, 1701. (d) Tang, W.; Zhang, X. *Org. Lett.* **2002**, *4*, 4159.
5. (a) Peña, D.; Minnaard, A. J.; de Vries, J. G.; Feringa, B. L. *J. Am. Chem. Soc.* **2002**, *124*, 14552. (b) Fu, Y,; Guo, X.; Zhu, S.; Hu, A.; Xie, J.; Zhou, Q. *J. Org. Chem.* **2004**, *69*, 4648.

6. Halpern, J. In *Asymmetrc Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol.5, Chapter 2.

7. Halpern, J. *Science* **1982**, *217*, 401.

8. Burk, M. J.; Casy, G.; Johnson, N. B. *J. Org. Chem.* **1998**, *63*, 6084.

9. For previous examples of asymmetric hydrogenation of electron-rich *N*-alkyl and *N*, *N*-dialkyl enamines, see: (a) Lee, N. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 5985. (b) Tararov, V. I.; Kadyrov, R.; Riermeier, T. H.; Holz, J.; Börner, A. *Tetrahedron Lett.* **2000**, *41*, 2351.

10. (a) Pozza, M. F.; Zimmermann, K.; Bischoff, S.; Lingenhohl, K. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* **2000,** *24***,** 647. **(**b) Zhi, L.; Tegley, C. M.; Marschke, K. B.; Jones, T. K. *Bioorg. Med. Chem. Lett*. **1999,** 1009.

11. Hsiao, Y.; Rivera, N. R.; Rosner, T.; Krska, S. W.; Njolito, E.; Wang, F.; Sun, Y.; Armstrong, J. D. III.; Grabowski, E. J. J.; Tillyer, R. D.; Spindler, F.; Malan, C. *J. Am. Chem. Soc.* **2004**, *126*, 9918.

12. Hansen, K. B.; Rosner, T.; Kubryk, M.; Dormer, P.G.; Armstrong, J. D., III *Org. Lett*. **2005**, *7*, 4935.

13. Brandt, C. A.; Silva, A. C.; Pancote, C. G.; Brito, C. L.; Solveira, M. *Synthesis* **2004**, *10*, 1557.

14. Xie, W.; Fang, J.; Li, J.; Wang, P. G. *Tetrahedron* **1999**, *55*, 12929.

15. (a) Zhang, Z.; Qian, H.; Longmire, J.; Zhang, X. *J. Org. Chem*. **2000**, *65*, 6223. (b) Lei, A.; He, M.; Wu, S.; Zhang, X. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 3457.

16. (a) Tang, W.; Zhang, X. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 1612. (b) Liu, D.; Zhang, X. *Eur. J. Org. Chem.* **2005**, 646.

17. (a) Gridnev, I. D.; Higashi, N.; Asakura, K.; Imamoto, T. *J. Am. Chem. Soc.* **2000**, *122*, 7183. (b) Yasutake, M.; Gridnev, I. D.; Higashi, N.; Imamoto, T. *Org. Lett.* **2001**, *3*, 1701.

18. Park, S.; Lee, S. *J. Chem. Res. Synop.* **2001**, *11*, 498.

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).

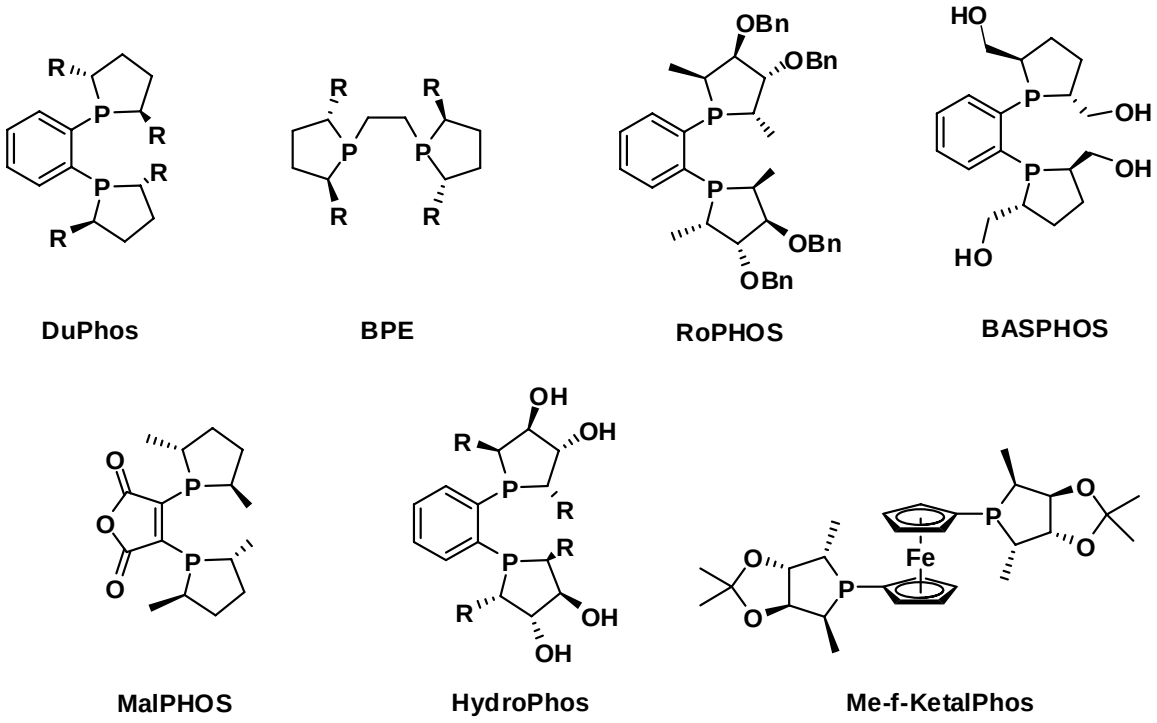
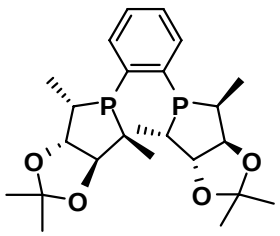


Figure **4-1**: Examples of Chiral Bisphospholane Ligands

For example, RoPhos reported by Börner,[3] 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.[4] MalPhos, which bears a maleic anhydride backbone, has provided high enantioselectivities in the hydrogenation of (β-acylamino)acrylates.[5] 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[6] and Zhang groups[7]. Zhang has reported a 1,1′-bis(phospholanyl)ferrocene ligand (Me-f-KetalPhos) with ketal substituents at positions 3

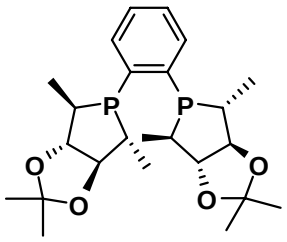
and 4.[8a] This ligand has shown excellent enantioselectivities in hydrogenation of α-dehydroamino acid derivatives. The ketal groups of the ligand are important for achieving high enantioselectivities, as the corresponding ligand without these groups only provides moderate ee values.[8b] A major advantage of these ligands is their ease of preparation from readily available $_{D}$-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 $_{L}$-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 (2*S*, 3*S*, 4*S*, 5*S*)-Me-ketalPhos (**1**) and its diastereomer **2** will be described as well as their application in the Rh-catalyzed asymmetric hydrogenation of functionalized olefins.



1

(2*S*, 3*S*, 4*S*, 5*S*)-Me-KetalPhos



2

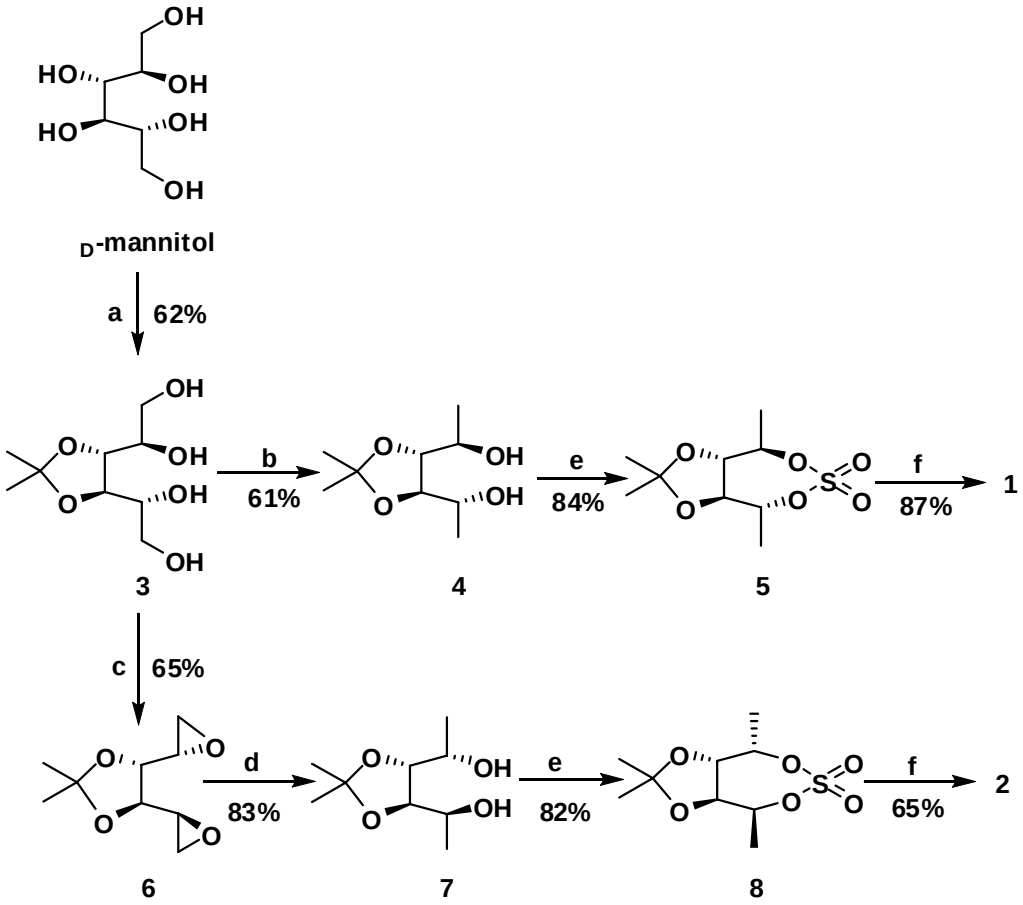
(2*R*, 3*S*, 4*S*, 5*R*)-Me-KetalPhos

Figure **4-2**: Modified DuPhos Type Ligands: Me-KetalPhos

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_2SO_4 (cat.), rt, 2 d; ii) HOAc (70%, aq), 2 h; b. i) TsCl, pyridine, CH_2Cl_2, 0 ^oC 4 h; ii) LAH, THF, rt 1 h, then refluxing for 2 h; c. i) BzCl, Pyridine, CH_2Cl_2, -78 ^oC - 0 ^oC; ii) TsCl, Et_3N, DMAP, CH_2Cl_2, 0 ^oC - rt; iii) K_2CO_3 (5eq), MeOH, CH_2Cl_2, rt; d. $LiHB(Et)_3$, THF, 0 ^oC - rt; e. i) $SOCl_2$, Et_3N, CH_2Cl_2, 0 ^oC, 1 h; ii) $NaIO_4$, $RuCl_3.xH_2O$, CH_3CN, CCl_4, H_2O; f. (i) 1,2-$H_2PC_6H_4PH_2$, *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

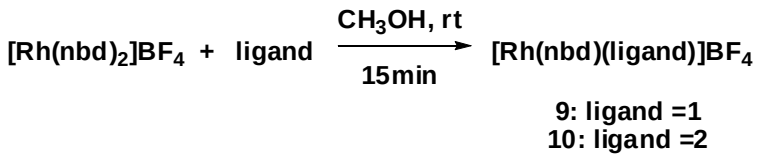
$LiAlH_4$ furnished the 1, 4-diol **4**. Cyclic sulfate **5** was obtained by esterification of **4** with thionyl chloride followed by oxidation with $RuCl_3/NaIO_4$. Nucleophilic attack on **5** with 1, 2-diphosphinobenzene in the presence of *n*-BuLi afforded **1** as a white crystalline solid which 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 consistant 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,[11] we selected $[Rh(nbd)_2]BF_4$ 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.

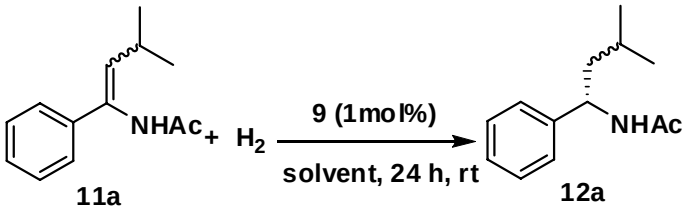
Scheme **4-2**: Synthesis of Rhodium Bisphospholane Complex **9** and **10**



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).[12]

Table **4-1**: Rh-Catalyzed Asymmetric Hydrogenation of an Enamide **11a**



11a **12a**

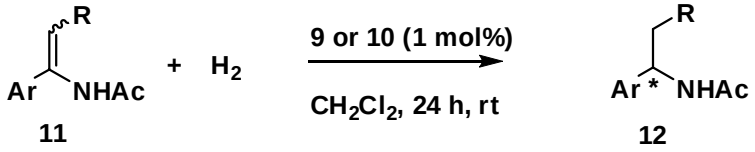
entry[a]	solvent	ee[b](%)
1	CH_2Cl_2	97
2	CH_3OH	92
3	C_2H_5OH	87
4	*i*-PrOH	97
5	THF	94
6	toluene	92

[a] The reactions were carried out at rt under 10 atm of H_2 pressure for 24 h wih 100% conversions. [b] Enantiomeric excesses were determined by chiral GC using a Supelco Chiral Select 1000 (0.25 mm x 30 m) column.

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.[13] The reaction time was not optimized to ensure complete conversion, hence TOF (turnover frequency) was only 70

h^{-1}.[14] Catalyst **10** also exhibits similar catalytic performance, providing slightly lower enantioselectivities.

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



11 **12**

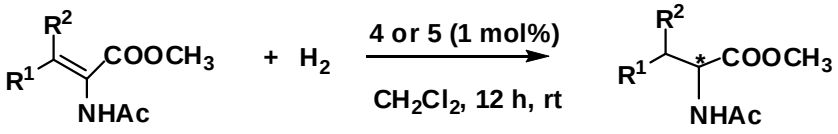
entry[a]	substrate	complex	ee [b](%)	config.[c]
1	Ar= Ph, R=isopropyl **11a**	**9**	96	*S*
2	Ar=Ph, R=H **11b**	**9**	92	*S*
3	Ar=p-CF_3-Ph, R=H **11c**	**9**	96	*S*
4	Ar=p-OMe-Ph, R=CH_3 **11d**	**9**	97	*S*
5	Ar=p-CF_3-Ph, R=CH_3 **11e**	**9**	97	*S*
6	Ar=Ph, R=CH_3 **11f**	**9**	98	*S*
7	**11a**	**10**	93	*R*
8	**11b**	**10**	94	*R*
9	**11c**	**10**	93	*R*
10	**11d**	**10**	94	*R*
11	**11e**	**10**	95	*R*
12	**11f**	**10**	93	*R*

[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 Supelco Chiral Select 1000 (0.25 mm x 30 m) column. [c] 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 H_2, 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.

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



13 **14**

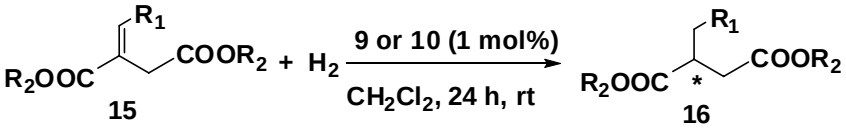
entry[a]	substrate	complex	ee[b](%)	config.[c]
1	R^1=H, R^2=H **13a**	**10**	99	*R*
2	R^1=Ph, R^2=H **13b**	**10**	99	*R*
3	R^1=o-Cl-Ph, R^2=H **13c**	**10**	98	*R*
4	R^1=p-F-Ph, R^2=H **13d**	**10**	99	*R*
5	R^1=m-Br-Ph, R^2=H **13e**	**10**	99	*R*
6	R^1=2-thienyl, R^2=H **13f**	**10**	99	*R*
7	R^1=2-naphthyl, R^2=H **13g**	**10**	99	*R*
8	R^1=CH_3, R^2=CH_3 **13h**	**10**	92	*R*
9	**13a**	**9**	74	*S*
10	**13b**	**9**	59	*S*
11	**13c**	**9**	89	*S*
12	**13d**	**9**	76	*S*
13	**13e**	**9**	81	*S*
14	**13f**	**9**	96	*S*
15	**13h**	**9**	69	*S*

[a] The reactions were carried out at rt under 3 atm of H_2 pressure for 12 h. [b] Enantiomeric excesses were determined by chiral GC using a Chirasil-Val III column. [c] The absolute configurations were assigned by comparing the sign of optical rotation with reported data.

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

an β-substituted itaconic acid **10b** (Table 4-4), which is comparable to hydrogenation results using rhodium complexes derived from TangPhos,[16a] or Et-DuPhos.[16b]

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



entry[a]	substrate	complex	ee[b] (%)	config.[d]
1	R^1= H, R^2= CH_3 **15a**	**9**	98	*R*
2	R^1= i-Pr, R^2= H **15b**	**9**	99[c]	*R*
3	**15a**	**10**	99	*S*
4	**15b**	**10**	98[c]	*S*

[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.[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.

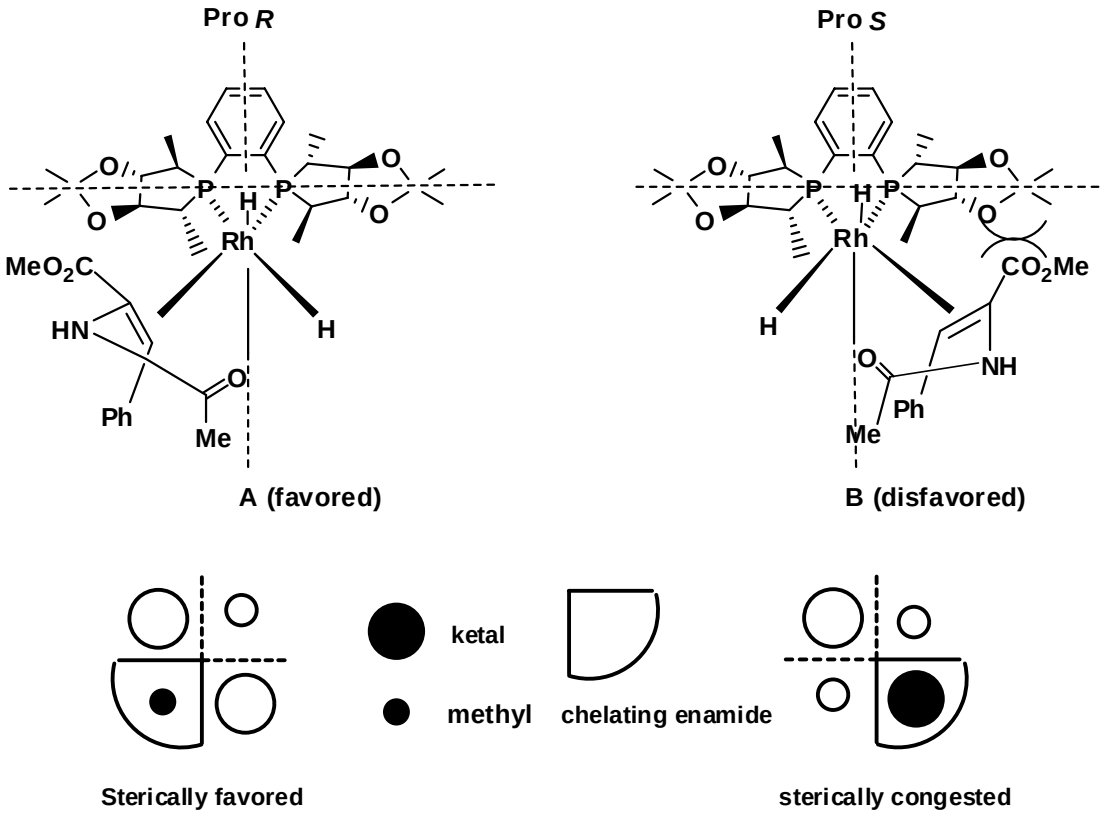


Figure **4-3**: Rationalization of the Origin of Enantioselectivity

4.3 Conclusion

In summary, the modified DuPhos type ligand (2*S,* 3*S,* 4*S,* 5*S*)-Me-ketalPhos (**1**) and its diastereomer (2*R,* 3*S*, 4*S,* 5*R*)-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 × 0.25 mm) for dehydroamino acid derivatives; Chiral Select 1000 column (dimensions: 15m x 0.25mm) for enamides; ɣ-225 (dimensions: 30 m × 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 Na_2SO_4 and concentrated to afford a colorless crystalline solid. Recrystallization from Et_2O/MeOH gave the pure product (3.42 g, 87% yield) as a white solid. ^{1}H NMR (360 MHz, $CDCl_3$) 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); ^{13}C 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; ^{31}P NMR (145 MHz, $CDCl_3$) δ 45.1 (s); HRMS calcd. for $C_{24}H_{37}O_4P_2$ (MH^+) 451.2167, found 451.2164.

Ligand 2. Prepared from cyclic sulfate **8** using the same procedure for the synthesis of **1**. Recrystalization from Et_2O/MeOH gave the pure product as white crystals in 65% yield. ^{1}H NMR ($CDCl_3$): 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); ^{13}C NMR

($CDCl_3$): 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; ^{31}P NMR ($CDCl_3$): δ 33.7 (s); HRMS calcd. for $C_{24}H_{37}O_4P_2$ (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 $[Rh(nbd)_2]BF_4$ (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.

$[Rh(nbd)(\mathbf{1})]BF_4$ **9**: ^{1}H NMR (360 MHz, CD_3OD) 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); ^{31}P NMR (CD_3OD) δ 100.1 (d, $J_{Rh\text{-}P}$ = 153.5 Hz); HRMS (cation) *m/z* calcd. for $C_{31}H_{44}O_4P_2Rh$ 645.1770, found 645.1737; HRMS (anion*) m/z* calcd. for BF_4 87.0029, found 87.0024.

$[Rh(nbd)(\mathbf{2})]BF_4$ **10**: ^{1}H NMR (360 MHz, CD_3OD) 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); ^{31}P NMR (CD_3OD) δ 100.8 (d, $J_{Rh\text{-}P}$ = 158.0 Hz); HRMS (cation) *m/z* calcd. for $C_{31}H_{44}O_4P_2Rh$ 645.1770, found 645.1752; HRMS (anion) *m/z* calcd. for BF_4 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_2Cl_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

1. Brunner, H.; Zettlmeier, W. *Handbook of Enantioselective Catalysis with Transition Metal Compounds*; VCH Verlagsgesellschaft: Weinheim, 1993; Vol. 2, ligands references, p 359.
2. (a) Burk, M. J.; Feaster, J. E.; Harlow, R. L. *Organometallics* **1990**, *9*, 2653. (b) Burk, M. J.; Harlow, R. L. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1462. (c) Burk, M. J. *J. Am. Chem. Soc.* **1991**, *113*, 8518. (d) Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc*. **1993**, *115*, 10125. (e) Burk, M. J.; Lee, J. R.; Martine, J. P. *J. Am. Chem. Soc.* **1994**, *116*, 10847. (f) Burk, M. J.; Wang, Y. M.; Lee, J. R. *J. Am. Chem. Soc*. **1996**, *118*, 5142.
3. Holz, J.; Quirmbach, M.; Schmidt, U.; Heller, D.; Stürmer, R.; Börner, A. *J. Org. Chem*. **1998**, *63*, 8031.
4. (a) Holz, J.; Stürmer, R.; Schmidt, U.; Drexler, H.-J.; Heller, D.; Krimmer, H.-P.; Börner, A. *Eur. J. Org. Chem*. **2000**, *65*, 4615. (b) Holz, J.; Heller, D.; Stürmer, R.; Börner, A. *Tetrahedron Lett*. **1999**, *40*, 7059.
5. Holz, J.; Monsees, A.; Jiao, H.; You, J.; Komarov, I. V.; Fischer, C.; Drauz, K.; Borner, A. *J. Org. Chem.* **2003**, *68*, 1701.
6. (a) Shin, S.; RajanBabu, T. V. *Org. Lett*. **1999**, *1,* 1229. (b) Yan, Y.; RajanBabu, T. V. *J. Org. Chem*. **2000,** *65*, 900. (c) RajanBabu, T. V.; Yan, Y.; Shin, S. *J. Am. Chem. Soc*. **2001**, *123*, 10207.

7. (a) Li, W .; Zhang, Z.; Xiao, D.; Zhang, X. *Tetrahedron Lett*. **1999**, *40*, 6701. (b) Li, W.; Zhang, Z.; Xiao, D.; Zhang, X. *J. Org. Chem*. **2000,** *65*, 3489.

8. (a) Liu, D.; Li, W.; Zhang, X. *Org. Lett*. **2002**, *4*, 4471. (b) Burk, M. J.; Gross, M. F. *Tetrahedron Lett.* **1994**, *35*, 9363.

9. Le Merrer, Y; Duréault, A.; Greck, C.; Micas-Languin, D.; Gravier, C.; Depezay, J.-C. *Heterocycles* **1987**, *25*, 541.

10. Brunner, H. In *Applied Homogeneous Catalysis with Organometallic compounds*; Cornils, B., Herrmann, W. A. Eds.; 2nd Edition, Wiley-VCH: Weinheim, 2001; p 209.

11 Cobley, C. J.; Lennon,I. C.; McCague, R; Ramsden, J. A.; Zannotti- Gerosa, A. *Tetrahedron Lett.* **2001**, *42*, 7481.

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.

15. (a) Evans, D. A.; Michael, F. E.; Tedrow, J. S.; Campos, K. R. *J. Am. Chem. Soc.* **2003**, *125*, 3534. (b) Ohashi, A.; Imamoto, T. *Org. Lett.* **2001**, *3*, 373. (c) Imamoto, T.; Watanabe, J.; Wada, Y.; Masuda, H.; Yamada, H.; Tsuruta, H.; Matsukawa, S.; Yamaguchi, K. *J. Am. Chem. Soc.* **1998**, *120*, 1635. (d) Burk, M. J.; Gross, M. F.; Martinez, J. P. *J. Am. Chem. Soc*. **1995**, *117*, 9375. (e) Sawamura, M.; Kuwano, R.; Ito, Y. *J. Am. Chem. Soc.* **1995**, *117*, 9602.

16. (a) Tang, W.; Liu, D.; Zhang, X. *Org. Lett.* **2002**, *4*, 4159. (b) Burk, M. J.; Bienewald, F.; Harris, M.; Zanotti-Ferosa, A. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1931.

17. Gridnev, I. D.; Higashi, N.; Asakura, K.; Imamoto, T. *J. Am. Chem. Soc.* **2000**, *122*, 7183.

18. (a) Zhu, G.; Zhang, X. *J. Org. Chem.* **1998**, *63*, 3133. (b) Li, W.; Zhang, X. *J. Org. Chem.* **2002**, *65*, 5871. (c) Wu, S.; Wang, W.; Tang, W.; Lin, M.; Zhang, X. *Org. Lett.* **2002**, *4*, 4495.

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 π-acceptor character of the phosphorus can stabilize a metal center in a low oxidation state, while the nitrogen σ-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**,[6] PyrPHOX **4**,[7] phosphine-imidazoline (PHIM) **5**,[8] and phosphinite-oxazoline **6**.[9] Burgess has also reported JM-Phos **7**[10] and imidazolylidine-oxazolines[11] for Ir-catalyzed asymmetric hydrogenation of unfunctionalized olefins. The Zhang group has recently developed a phospholane-oxazoline ligand **8**,[12] which has given excellent results in the hydrogenation of unfunctionalized alkenes and unsaturated esters (Figure 5-1).

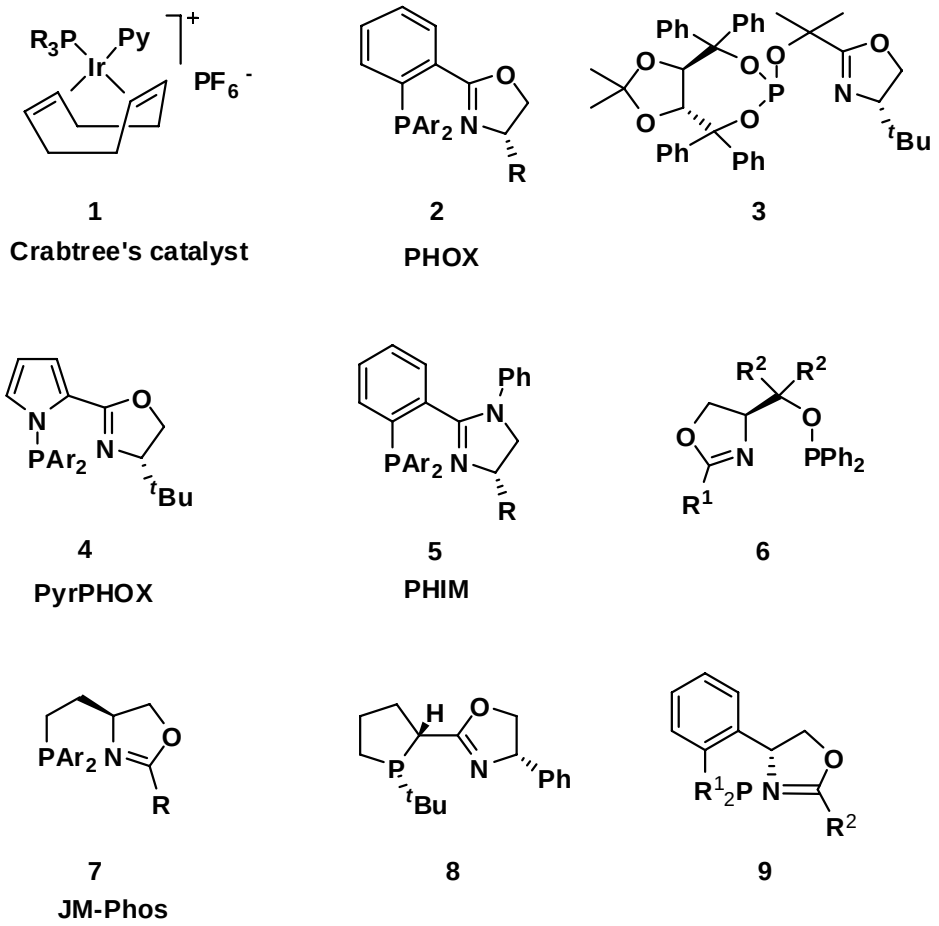


Figure **5-1**: Some Examples of P, N Ligands

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.[13] During our effort to design a new class of P, N ligands **9a-e**, a 1,2-phenyl linker was introduced instead of the ethylene linker. Since ligands **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 **9** will be discussed. An improved synthetic route has been established to circumvent the synthetic issues in the original routes.[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 9

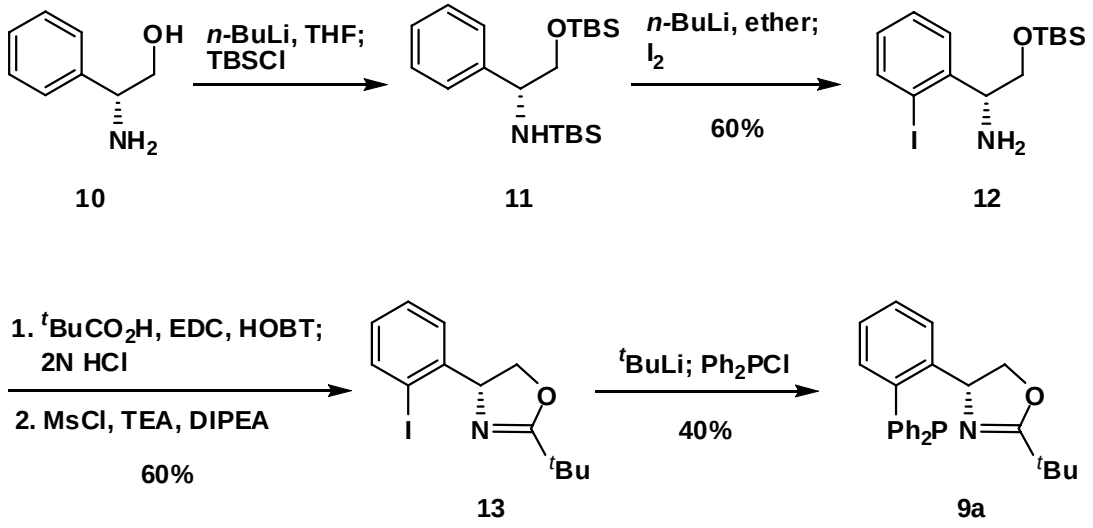
Inexpensive enantiopure phenyl glycinol has been widely used as a building block for the preparation of chiral ligands and chiral auxilaries.[15] We believe that the most direct and efficient way to prepare P, N ligands **9** would involve the *ortho*-substitution of phenyl glycinol. On the basis of a procedure reported by Polniaszek et al.,[16] we have successfully carried out the *ortho*-lithiation of a silyl-protected phenyl glycinol. Subsequent electrophilic substitution with I_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 glycinol (**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[4a-c] gave the key intermediate **13**. Lithium-halogen exchange of **13** with ^{t}BuLi, followed by reaction with PPh_2Cl, afforded the desired ligand **9a**. Variation of the phosphine chloride in the last step could allow for facile tuning of the phosphines.

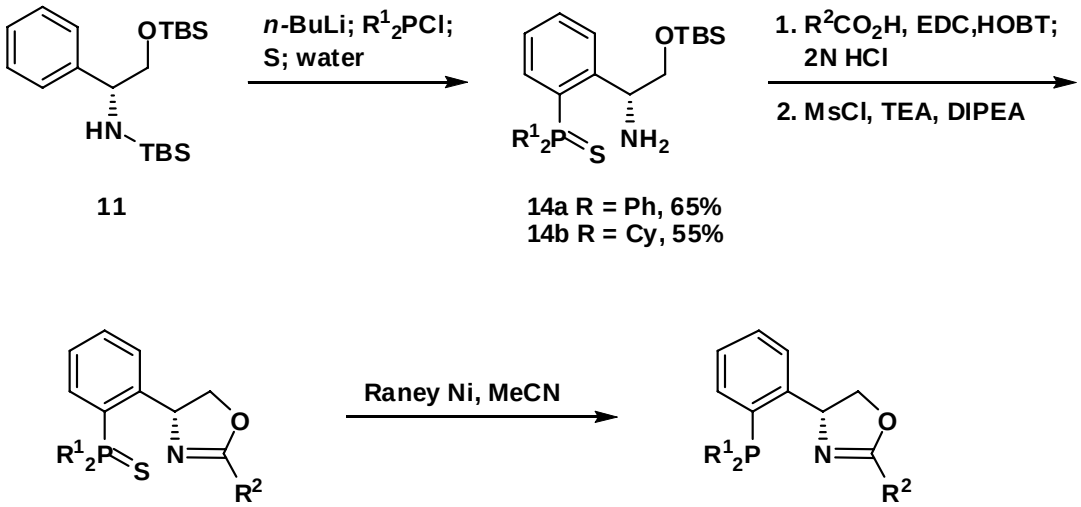
Scheme **5-1**: Two divergent Synthetic Routes for Ligands **9**

Route A:



TBSCl: *tert*-butyldimethylsilyl chloride;
EDC: 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride;
HOBT: 1-hydroxy-benzotriazole hydrate;
TEA: triethylamine; DIPEA: diisopropylethylamine

Route B:



11

14a R = Ph, 65%
14b R = Cy, 55%

15b R^1 = Ph, R^2 = $CHPh_2$, 52%
15c R^1 = Ph, R^2 = 3,5-di-*tert*-butylphenyl, 50%
15d R^1 = Ph, R^2 = adamantyl, 54%
15e R^1 = Cy, R^2 = *tert*-butyl, 52%

9b R^1 = Ph, R^2 = $CHPh_2$, 94%
9c R^1 = Ph, R^2 = 3,5-di-*tert*-butylphenyl, 95%
9d R^1 = Ph, R^2 = adamantyl, 91%
9e R^1 = Cy, R^2 = *tert*-butyl, 90%

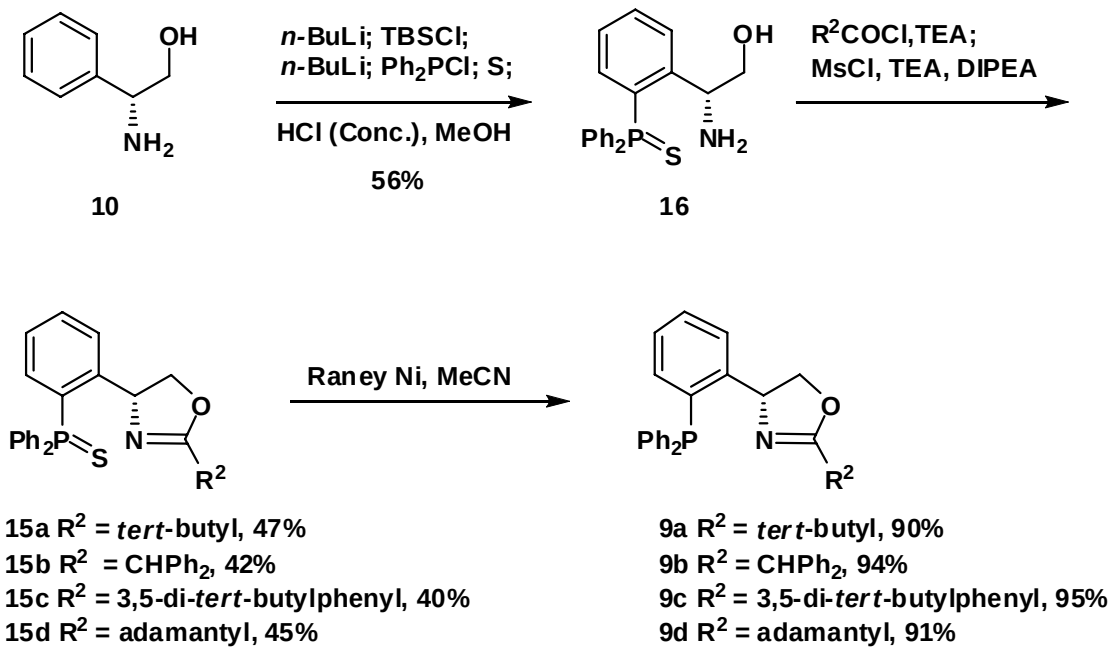
In route B, a phosphine chloride, in place of I_2, was used as the electrophile after the *ortho*-lithiation. *In situ* protection of the phosphine with elemental sulfur followed by aqueous workup generated a phosphine sulfide **14**, which could be further converted into a series of oxazolines **15** with various R^2 substituents at the 2-position by reaction with different carboxylic acids. Reduction of sulfide **15** with Raney Ni[17] afforded phosphine ligands **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:



15a R^2 = *tert*-butyl, 47%
15b R^2 = $CHPh_2$, 42%
15c R^2 = 3,5-di-*tert*-butylphenyl, 40%
15d R^2 = adamantyl, 45%

9a R^2 = *tert*-butyl, 90%
9b R^2 = $CHPh_2$, 94%
9c R^2 = 3,5-di-*tert*-butylphenyl, 95%
9d R^2 = adamantyl, 91%

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 stardard 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.[18] 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).[19]

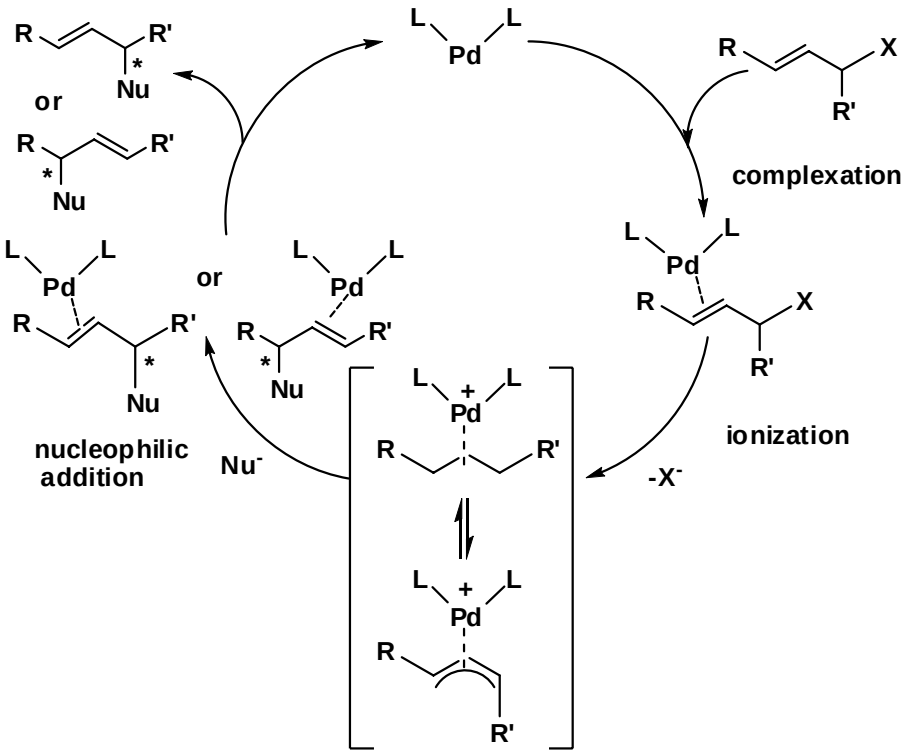


Figure **5-2**: Catalytic Cycle for Pd-Catalyzed AAA Reactions

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).

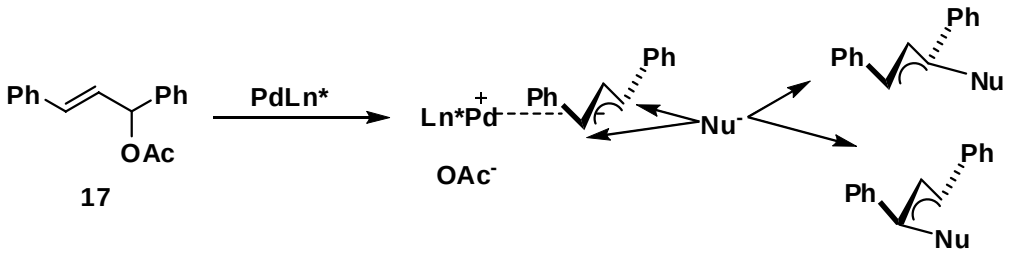
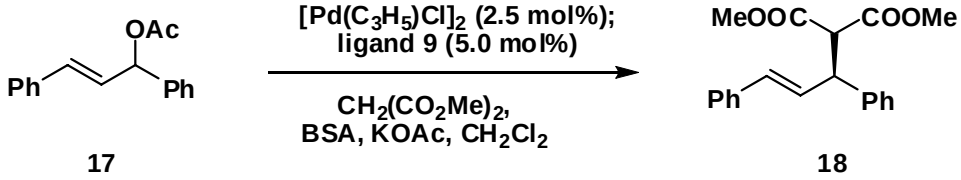


Figure **5-3**: AAA Reaction via Symmetrically Substituted Allyl Systems

In Pd-catalyzed AAA reactions, dimethyl malonate is the most commonly used nucleophile in conjunction with allylic acetates or carbonates as substrates.[20] Other nucleophiles, such as amines,[21] nitro compounds,[22] and alcohols[23] 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 $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ 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.[24] Thus, we carried out the same reaction with ligand **9a** at 0 ^{o}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 ^{o}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).

Table **5-1**: Pd-Catalyzed Asymmetric Allylic Alkylation



17 **18**

entry[a]	ligand	temp	time	yield (%)	*ee* (%)[c]
1	**9a**	rt	12 h	97	93(*S*)
2	**9b**	rt	12 h	93	2(*S*)
3	**9c**	rt	12 h	86	93(*S*)
4	**9d**	rt	12 h	91	97(*S*)
5	**9a**	0 °C	12 h	85	88(*S*)
6	**9a**	40 °C	4 h	97	98(*S*)
7	**9d**	40 °C	4 h	90	97(*S*)
8[b]	**9a**	40 °C	12 h	73	98(*S*)

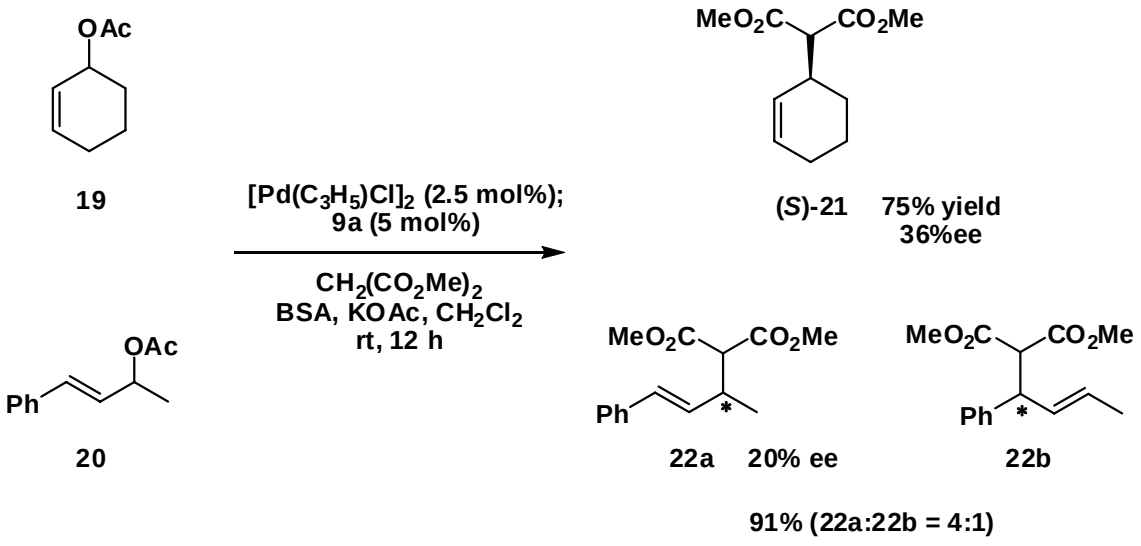
[a] See Experimental Section for a general procedure. [b] 0.1 mol% of $[Pd(C_3H_5)Cl]_2$ and 0.2 mol% of **9a** were used. [c] The enantiomeric excess was determined by chiral HPLC (Chiralpak AD column) and the absolute configuration was assigned by comparison of the sign of the optical rotation with reported data.

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

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



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)

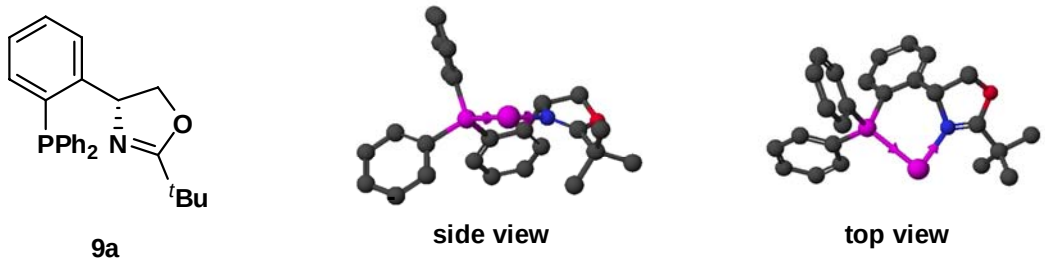
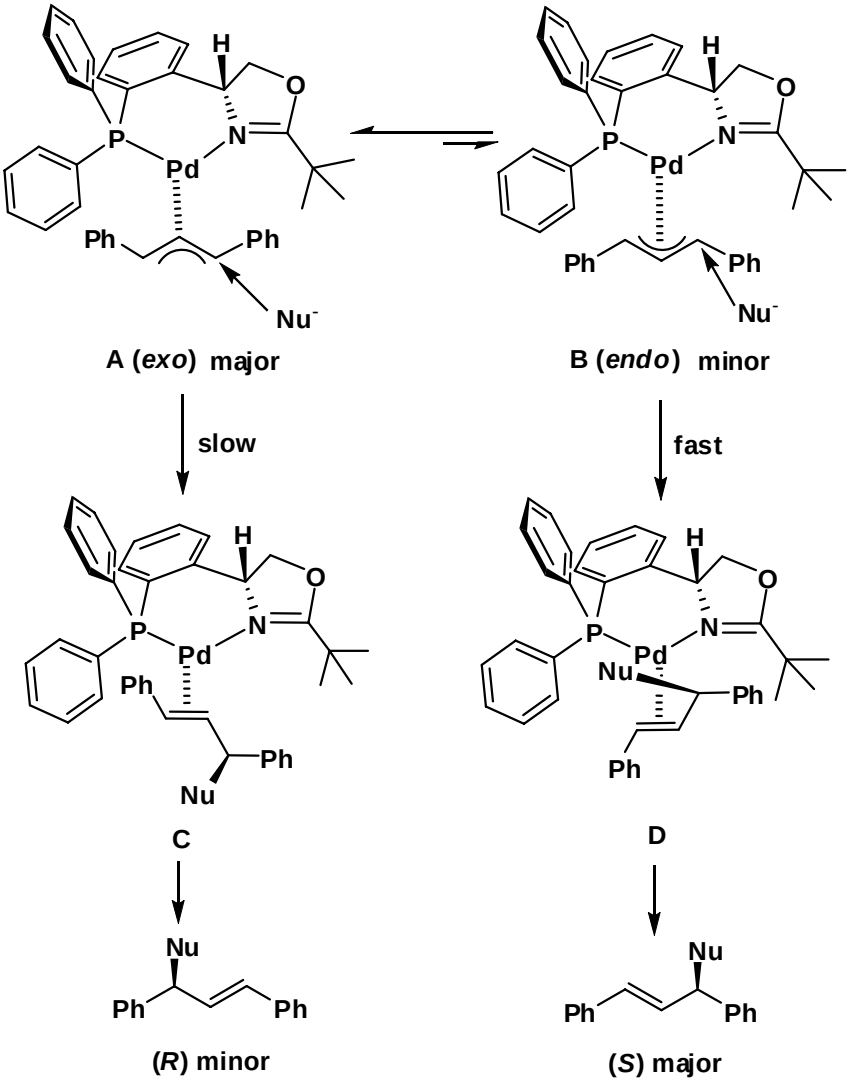


Figure **5-4**: a Cache Model of Pd/**9a** (H atoms have been omitted for clarity)

According to extensive mechanistic studies reported by other groups,[2, 19] 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.[27] In addition, low-temperature ^{1}H NMR studies of the initially formed product, the alkene-Pd complex, suggest that it arose from a least motion rotation

following nucleophilic addition.[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.[24a]

Scheme **5-4**: Interpretation of Enantioselectivity



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.[31] For instance, intramolecular Heck reaction can generate tertiary stereocenters in natural product synthesis.[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 α-arylpalladium(II) complex; (b) subsequent coordination and *syn* addition of an alkene to form an α-alkylpalladium(II) complex; (c) β-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.

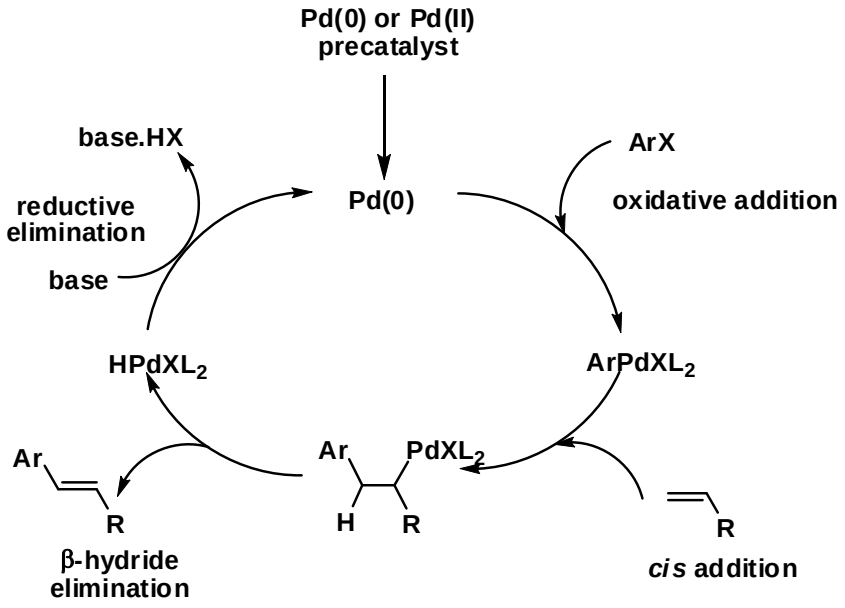
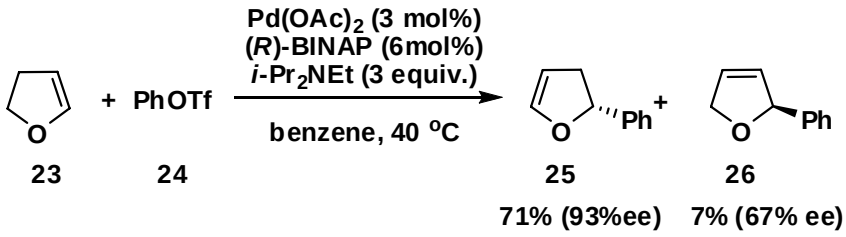


Figure **5-5**: General Mechanism of Pd-Catalyzed Heck Reaction

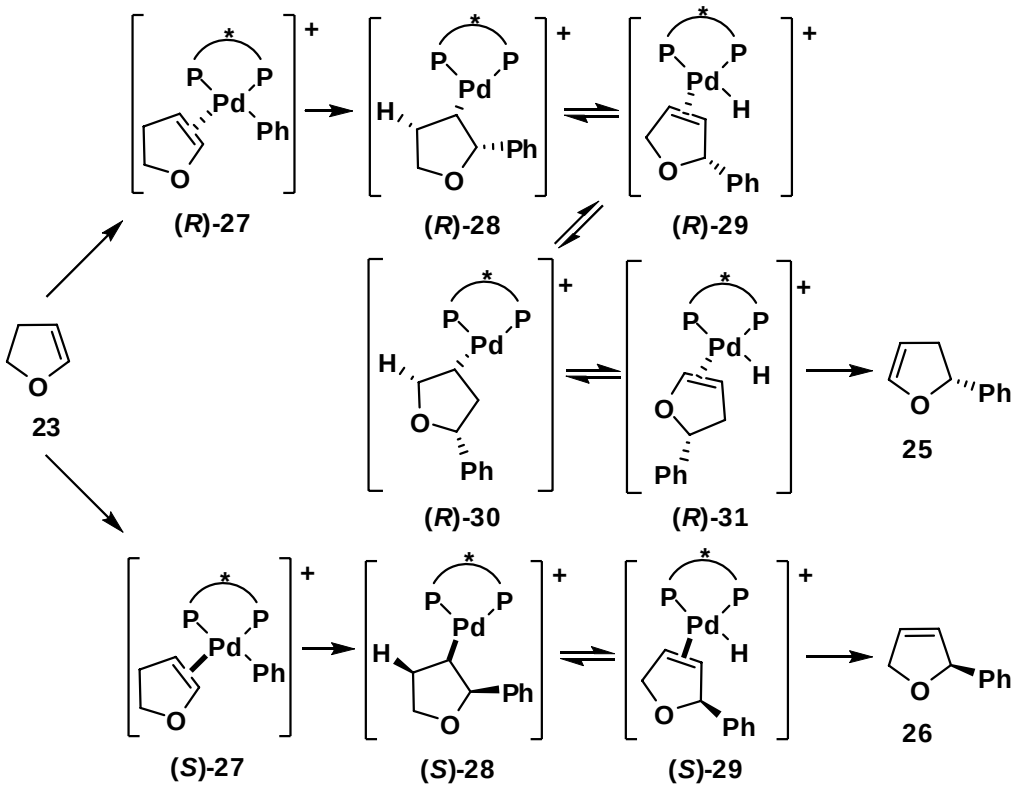
The first example of asymmetric intermolecular Heck reaction was reported by Hayashi in 1991.[32] It involved the asymmetric arylation of 2,3-hydrofuran (**23**) using aryl triflates with $Pd(OAc)_2$/BINAP catalyst system (Scheme 5-5). The major product was the 2-aryl-2,3-hydrofuran (**25**) with small amount of 2,5-dihydrofuran (**26**) isomer.

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



The rationale for the outcome of the result is illustrated in Scheme 5-6 by Hayashi.[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 *syn* addition. In the case of (*S*)-**28**, unfavorable steric factors cause a fast β-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 β-hydride elimination, giving the final product (*R*)-**26**. The proposed mechanism was further reinforced by the studies of Brown using NMR and mass spectrometry.[34]

Scheme **5-6**: Mechanism for Asymmetric Heck Reaction of **23**

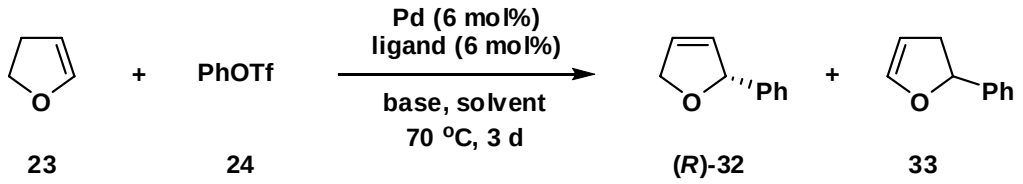


A number of reported asymmetric Heck reactions have utilized BINAP as the ligand, which is very effective in many cases. The most dramatic development has been the introduction by Pfaltz and coworkers of oxazoline-based P, N ligands such as **2** with improved enantioselectivities in several previously 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 $Pd_2(dba)_3$·dba as the catalyst precursor and *N*,*N*-diisopropylethylamine as base in benzene at 70 ^oC, 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 $Pd_2(dba)_3$·dba 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.[35] 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



23 **24** **(*R*)-32** **33**

entry[a]	ligand	Pd complex	base	solvent	yield(%)(32:33)[b]	ee(%)[c]
1	**9a**	$Pd_2(dba)_3.dba$	$^iPr_2EtN$	Benzene	87(>99:1)	91
2	**9b**	$Pd_2(dba)_3.dba$	$^iPr_2EtN$	Benzene	32(>99:1)	88
3	**9c**	$Pd_2(dba)_3.dba$	$^iPr_2EtN$	Benzene	45(>99:1)	78
4	**9d**	$Pd_2(dba)_3.dba$	$^iPr_2EtN$	Benzene	91(>99:1)	90
5	**9a**	$Pd_2(dba)_3.CHCl_3$	$^iPr_2EtN$	Benzene	90(93:7)	90(86)
6	**9a**	$Pd_2(dba)_3.dba$	$^iPr_2EtN$	THF	99(>99:1)	94
7	**9a**	$Pd_2(dba)_3.CHCl_3$	$^iPr_2EtN$	THF	93(93:7)	93(91)
8	**9a**	$Pd_2(dba)_3.dba$	proton sponge	Benzene	no rxn	n/a

[a] See Experimental Section for a general precedure. [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 absolution 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 ^{t}Bu 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 ^{t}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.

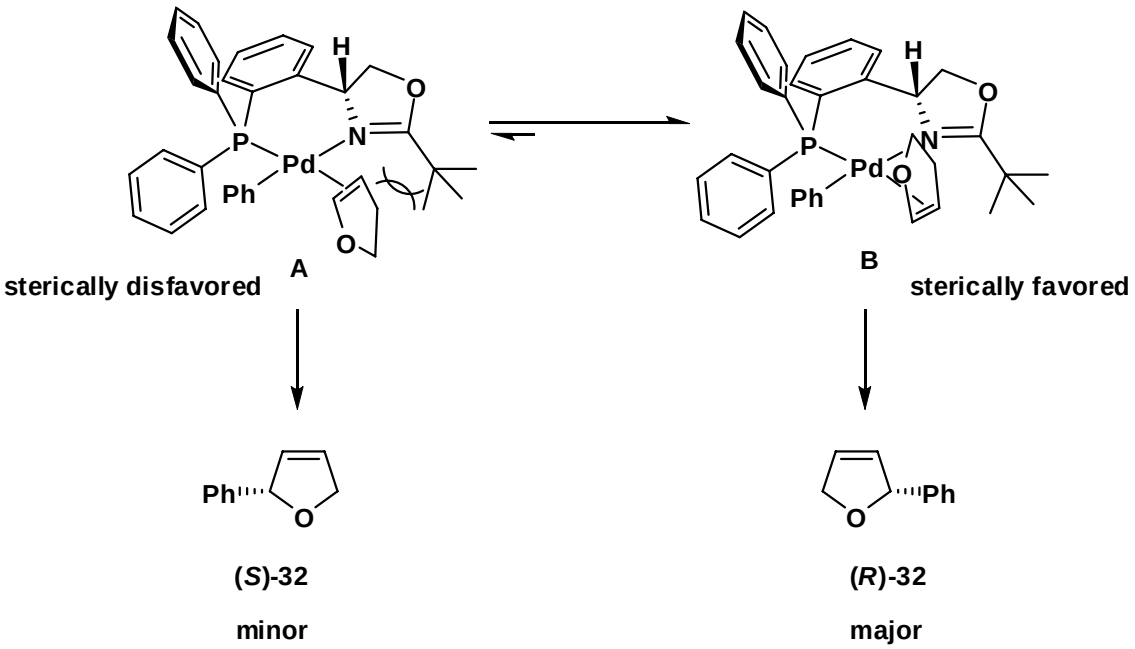


Figure **5-6**: Proposed Origin of Enantioselection in Pd-Catalyzed Heck Reaction

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 glycinol. 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^{TM} 600 chromatograph.

2-(*tert*-Butyldimethylsilanyloxy)-(1*R*)-(2-iodophenyl)-ethylamine (12). To a suspention of (*R*)-α-methylbenzylamine **10** (1.37 g, 10.0 mmol) in 40 mL of THF at -78 ^{o}C was added ^{n}BuLi (2.5 M solution in hexane, 8 mL) dropwise. The resulting purple solution was stirred at -78 ^{o}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 ^{o}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. I_2 (5.08 g, 20.0 mmol) was added at -78 ^{o}C and the reaction mixture was allowed to warm to rt and stirred for 1 h. 10% $Na_2S_2O_3$ 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%). $[\alpha]_D^{20}$ –49.4 (*c* = 0.82, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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 $C_{14}H_{25}NOSiI$ 378.0745, found 378.0764.

2-(*tert*-Butyldimethylsilanyloxy)-(1*R*)-[2-(diphenylphosphinothioyl)-phenyl]-ethylamine (14a). To a suspension of (*R*)-α-methylbenzylamine **10** (1.37 g, 10.0 mmol, 1 equiv) in 40 mL of THF at -78 ^{o}C was added dropwise ^{n}BuLi (2.5 M solution in hexane, 8 mL). The resulting purple solution was stirred at -78 ^{o}C for 30 min before a solution of TBSCl (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 ^{o}C was added ^{n}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 ^{o}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 ususal 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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, $CDCl_3$) δ 42.11; HRMS (MH^+) *m/z* calcd. for $C_{26}H_{35}NOSiPS$ 468.1941, found 468.1909.

2-(*tert*-Butyldimethylsilanyloxy)-(1*R*)-[2-(dicyclohexylphosphinothioyl)-phenyl]-ethylamine (14b). To a suspention of (*R*)-α-methylbenzylamine **10** (0.343 g, 2.50 mmol, 1 equiv) in 10 mL THF at -78 ^{o}C was added dropwise ^{n}BuLi (2.5 M solution in hexane, 2 mL). The resulting purple solution was stirred at -78 ^{o}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 ^{o}C was added ^{n}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 ^{o}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 ususal work up, product **14b** was isolated by flash column chromatography (hexane:EtOAc, 90:10) as a yellow oil (0.660 g, 55%). $[\alpha]_D^{20}$ –48.6 (*c* = 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 360 MHz) δ 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) δ 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) δ 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-(4*R*)-[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_2O (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 ^{o}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 Na_2SO_4, and concenctrated. The residue was purified by flash column chromatography on silica gel (hexane:EtOAc:CH_2Cl_2, 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 CH_2Cl_2, was added methanesulfonyl chloride (95 μL, 1.2 mmol) at 0 ^{o}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). $[\alpha]_D^{20}$ +9.35 (*c* = 0.77, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.83-7.66 (m, 4H), 7.52-7.40 (m, 7H), 7.32 (dd, *J* = 4.8 Hz, *J* = 6.8 Hz, 1H), 7.12 (m, 1H), 6.85 (ddd, *J* = 0.7 Hz, *J* = 7.8 Hz, *J* = 14.8 Hz, 1H), 5.74 (t, *J* = 9.0 Hz, 1H), 4.49 (dd, *J* = 9.0 Hz, *J* = 9.9 Hz, 1H), 3.78 (t, *J* = 8.4 Hz, 1H), 1.98 (s, 3H), 1.91 (s, 6H), 1.69 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.5, 147.4 (d, *J* = 8.5 Hz), 133.0 (d, *J* = 5.5 Hz), 132.7-132.3 (m), 131.9-131.7 (m), 131.6 (d, *J* = 2.9 Hz), 130.5 (d, *J* = 83.4 Hz), 128.8-128.4 (m), 126.7 (d, *J* = 12.5 Hz), 75.3, 66.6 (d, *J* = 7.0 Hz), 39.6, 36.5, 35.3, 27.8; ^{31}P NMR ($CDCl_3$, 145 MHz) δ 42.30; HRMS (MH^+) *m/z* calcd. for $C_{31}H_{33}NOPS$ 498.2015, found 498.1990.

2-*tert*-Butyl-(4*R*)-(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, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 360 MHz) δ 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 ($CDCl_3$, 90 MHz) δ 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-(4*R*)-[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, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 360 MHz) δ 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 ($CDCl_3$, 75 MHz) δ 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 ($CDCl_3$, 145 MHz) δ 42.38; HRMS (MH^+) *m/z* calcd. for $C_{34}H_{29}NOPS$ 530.1702, found 530.1735.

2-(3,5-Di-*tert*-butylphenyl)-(4*R*)-[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*

= 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 360 MHz) δ 7.92-7.76 (m, 6H), 7.57-7.49 (m, 9H), 7.19 (t, *J* = 7.4 Hz, 1H), 6.95 (dd, *J* = 7.7 Hz, *J* = 14.8 Hz, 1H), 6.03 (t, *J* = 8.9 Hz, 1H), 4.72 (t, *J* = 9.7 Hz, 1H), 4.07 (t, *J* = 8.5 Hz, 1H), 1.35 (s, 18H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 166.6, 151.1, 147.5 (d, *J* = 8.5 Hz), 133.4-131.6 (m), 130.7, 129.6-129.0 (m), 127.1, 125.9, 123.0, 75.9, 68.0, 35.2, 31.6; ^{31}P NMR ($CDCl_3$, 145 MHz) δ 42.30; HRMS (MH^+) *m/z* calcd. for $C_{35}H_{39}NOPS$ 552.2484, found 552.2470.

2-*tert*-Butyl-(4*R*)-[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, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 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) δ 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) δ 57.27 (br); HRMS (MH^+) *m/z* calcd. for $C_{25}H_{39}NOPS$ 432.2484, found 432.2462.

2-*tert*-Butyl-(4*R*)-(2-diphenylphosphanylphenyl)-4,5-dihydrooxazole (9a). To a solution of **13** (94 mg, 0.286 mmol) in 4 mL of ether was added ^{t}BuLi (1.7 M solution, 0.34 mL) at -78 ^oC. The reaction mixture was stirred at -78 ^oC 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_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography to give **9a** as a white solid (44 mg, 40%). $[\alpha]_D^{20}$ –50.9 (*c* = 2.0, $CHCl_3$); ^{1}H NMR (CD_2Cl_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_2Cl_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_2Cl_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-(4*R*)-(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_3CN (3 mL × 3). To this flask was then transferred a solution of **15d** (190 mg, 0.382 mmol) in 6 mL of CH_3CN. 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_3CN (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%). $[\alpha]_D^{20}$ –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),

4.15 (dd, J = 8.5 Hz, J = 10.3 Hz, 1H), 3.53 (t, J = 8.3 Hz, 1H), 1.96 (s, 3H), 1.90 (s, 6H), 1.66 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.2, 147.8 (d, J = 24.3 Hz), 136.4-136.1 (m), 134.7, 134.4, 134.0, 133.7, 133.5, 129.7, 129.2, 128.9, 128.8, 128.7, 127.6, 126.1 (d, J = 5.7 Hz), 74.6 (d, J = 5.0 Hz), 66.8 (d, J = 24.2 Hz), 39.9, 36.8, 35.6, 28.2; ^{31}P NMR ($CDCl_3$, 145 MHz) δ -15.14; HRMS (MH^+) *m/z* calcd. for $C_{31}H_{33}NOP$ 466.2294, found 466.2262.

2-Benzhydryl-(4*R*)-(2-diphenylphosphanylphenyl)-4,5-dihydrooxazole (9b). This compound was produced from **15b** following the general procedure as a white solid (94%). $[\alpha]_D^{20}$ –67.9 (*c* = 0.66, $CHCl_3$); ^{1}H NMR (CD_2Cl_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_2Cl_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_2Cl_2, 145 MHz) δ -15.10; HRMS (MH^+) *m/z* calcd. for $C_{34}H_{29}NOP$ 498.1981, found 498.1977.

2-(3,5-Di-*tert*-butylphenyl)-(4*R*)-(2-diphenylphosphanylphenyl)-4,5-dihydrooxazole (9c). This compound was produced from **15c** following the general procedure as a white solid (95%). $[\alpha]_D^{20}$ –48.3 (*c* = 0.87, $CHCl_3$); ^{1}H NMR (CD_2Cl_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_2Cl_2, 90 MHz) δ 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; ^{31}P NMR (CD_2Cl_2, 145 MHz) δ -14.83. HRMS (MH^+) *m/z* calcd. for $C_{35}H_{39}NOP$ 520.2764, found 520.2750.

2-*tert*-Butyl-(4*R*)-(2-dicyclohexylphosphanylphenyl)-4,5-dihydrooxazole (9e). This compound was produced from **15e** following the general procedure as a colorless oil (90%). $[\alpha]_D^{20}$ –70.9 (*c* = 0.53, $CHCl_3$); ^{1}H NMR (CD_2Cl_2, 360 MHz) δ 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_2Cl_2, 75 MHz) δ 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); ^{31}P NMR (CD_2Cl_2, 145 MHz) δ -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-(1*R*)-[2-(diphenylphosphinothioyl)-phenyl]-ethylamine (16). To a suspension of (*R*)-α-methylbenzylamine (**10**) (5.46 g, 0.04 mol) in 150 mL of THF at -78 ^{o}C was added ^{n}BuLi (2.5 M solution in hexane, 32 mL) dropwise. The resulting purple solution was stirred at -78 ^{o}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 ^{o}C was added ^{n}BuLi (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 ^{o}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 ^{o}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 CH_2Cl_2 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). ^{1}H NMR (360 MHz, $CDCl_3$) δ 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 NMR (75 MHz, $CDCl_3$) δ 132.3-132.9 (m), 129.0-129.3 (m), 127.4 (d, J = 13.1 Hz), 67.1, 53.9; ^{31}P NMR (145 MHz, $CDCl_3$) δ 42.4.

2-*tert*-Butyl-(4*R*)-[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 CH_2Cl_2 was stirred at 0 ^{o}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-(4*R*)-(2-diphenylphosphanylphenyl)-4,5-dihydrooxazole (9a). To a N_2-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 CH_3CN (30 mL × 3). To this flask was then transferred a solution of **15a** (4.4 g, 10.5 mmol) in CH_3CN (100 mL). The resulting mixture was stirred under N_2 at rt for 1 d. The reaction mixture was filtered under N_2 and washed with CH_3CN (50 mL × 3). The combined filtrate was concentrated under reduced pressure and the residue was passed through a short silica gel plug under N_2 to give **9a** as a white solid (3.66 g, 90% yield).

General procedure for asymmetric allylic substitutions: 2-(1,3-diphenyl-allyl)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 CH_2Cl_2. 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 CH_2Cl_2 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, $CDCl_3$) δ 7.15-7.29 (m, 10H), 6.45 (d, *J* = 15.8Hz, 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:^{i}PrOH, 90:10).

2-Cyclohex-2-enylmalonic acid dimethyl ester (21). ^{1}H NMR (360 MHz) δ 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 ^{o}C).

2-(1-Methyl-3-phenylallyl)malonic acid dimethyl ester (22a). ^{1}H NMR (360 MHz, $CDCl_3$) δ 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:^{i}PrOH, 95:5).

General procedure for asymmetric Heck reactions: 2-phenyl-2,5-dihydrofuran (32). In a Schlenk tube, $[Pd_2(dba)_3 \cdot dba]$ (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 ^{o}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 ^{o}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}H NMR (360 MHz, $CDCl_3$) δ 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 β-DEX 120 column (125 ^{o}C).

References and Notes

1. (a) Kagan, H. B.; Dang, T. P. *J. Chem. Soc., Chem. Commun.* **1971**, 481. (b) Kagan, H. B.; Dang, T. P. *J. Am. Chem. Soc.* **1972**, *94*, 6429. (c) Kagan, H. B.; Langlois, N.; Dang, T. P. *J. Organomet. Chem.* **1975**, *90*, 353.

2. (a) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336. (b) Guiry, P. J.; Saunders, C. P. *Adv. Synth. Catal.* **2004**, *346*, 497.

3. Crabtree, R. H. *Acc. Chem. Res.* **1979**, *12*, 331.

4. (a) von Matt, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 566. (b) Dawson, G. J.; Frost, C. G.; Williams, J. M. J.; Coote, S. J. *Tetrahedron Lett.* **1993**, *34*, 3149. (c) Sprinz, J.; Helmchen, G. *Tetrahedron Lett.* **1993**, *34*, 1769. (d) Helmchen, G.; Kudis, S.; Sennhenn, P.; Steinhagen, H. *Pure Appl. Chem.* **1997**, *69*, 513. (e) Pfaltz, A. *Acta Chem. Scand. B*. **1996**, *50*, 189. (f) Williams, J. M. J. *Synlett* **1996**, 705.

5. Akerrnarj, B.; Krakenberger, S.; Hannsson, S.; Vitagliano, A. *Organometallics* **1987**, *6*, 620.

6. Hilgraf, R.; Pfaltz, A. *Synlett* **1999**, 1814.

7. Cozzi, P. G.; Zimmermann, N.; Hilgraf, R.; Schaffner, S.; Pfaltz, A. *Adv. Synth. Catal.* **2001**, *343*, 450.

8. Menges, F.; Neuburger, M.; Pfaltz, A. *Org. Lett.* **2002**, *4*, 4713.

9. Blankenstein, J.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 4445.

10. Hou, D.-R.; Reibenspies, J.; Colacot, T. J.; Burgess, K. *Chem. Eur. J.* **2001**, *7*, 5391.

11. Powell, M. T.; Hou, D.-R.; Perry, M. C.; Cui, X.; Burgess, K. *J. Am. Chem. Soc.* **2001**, *343*, 450.

12. Tang, W.; Wang, W.; Zhang, X. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 943.

13. Brown, J. M.; Chaloner, P. A. *Homogeneous Catalysis with Metal Phosphine Complexes*; Pignolet, L. H., Ed.; Plenum: New York, 1983; p 137.

14. (a) Liu, D.; Tang, W.; Zhang, X. *Org. Lett*. **2004**, *6*, 513. (b) Liu, D.; Dai, Q.; Zhang, X. *Tetrahedron* **2005**, *61*, 6460. (c) Liu, Duan Ph. D dissertation, The Pennsylvania State University, University Park, Pennsylvania, 2005, Chapter 2.

15. (a) Jiang, Y.; Jiang, Q.; Zhang, X. *J. Am. Chem. Soc.* **1998**, *120*, 3817. (b) Davies, I. W.; Gerena, L.; Cai, D.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1997**, *38*, 1145. (c) Evans, D. A.; Lectka, T.; Miller, S. J. *Tetrahedron Lett.* **1993**, *34*, 7027.

16. (a) Polniaszek, R. P.; Lichti, C. F. *Synth. Commun.* **1992**, *22*, 171. (b) Polniaszek, R. P.; Kaufman, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 4859.

17. Gilbertson, S. R.; Fu, Z. *Org. Lett.* **2001**, *3*, 161.

18. (a) Trost, B. M.; Machacek, M. R.; Aponick, A. *Acc. Chem. Res.* **2006**, *39*, 747. (b) Trost, B. M.; Crawley, M. L.*Chem. Rev.* **2003**, *103*, 2921. and earlier citations therein.

19. (a) Trost, B. M.; Van Vranken, D. *Chem. Rev*. **1996**, *96*, 395. (b) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis*; Springer: Heidelberg, 1999; Vol. 2, Chapter 24.

20. (a) Trost, B. M.; Van Vranken, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 444. (b) Bergner, E. J.; Helmchen, G. *Eur. J. Org. Chem.* **2000**, 419. (c) Trost, B. M.; Bunt, R. C. *J.*

Am. Chem. Soc. **1994**, *116*, 4089. (d) Kudis, S.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3047. (e) Evans, D. A.; Campoo, K. R.; Tedrow, J. S.; Michael, F. E.; Gagne, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 7905. (f) Ernst, M.; Helmchen, G. *Synthesis* **2002**, *14*, 1953.

21. (a) Trost, B. M.; Krische, M. J.; Radinov, R.; Zanoni, G. *J. Am. Chem. Soc.* **1996**, *118*, 6297. (b) Hayashi, T.; Kishi, K.; Yamamoto, A.; Ito, Y. *Tetrahedron Lett.* **1990**, *31*, 1743. (c) You, S.-L.; Zhu, X.-Z.; Luo, Y.-M.; Hou, X.-L.; Dai, L.-X. *J. Am. Chem. Soc.* **2001**, *123*, 7471. (d) Constantine, R. N.; Kim, N.; Bunt, R. C. *Org. Lett.* **2003**, *5*, 2279. (e) Muchow, G.; Brunel, J. M.; Maffei, M.; Pardigon, O.; Buono, G. *Tetrahedron* **1998**, *54*, 10435. (f) Trost, B. M.; Calkins, T. L.; Oertelt, C.; Zambrano, J. *Tetrahedron Lett.* **1998**, *39*, 1713.

22. (a) Trost, B. M.; Chupak, L. S.; Luebbers, T. *J. Am. Chem. Soc.* **1998**, *120*, 1732. (b) Trost, B. M.; Dirat, O.; Dudash, J., Jr.; Hembre, E. J. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 3658. (c) Trost, B. M.; Dudash, J., Jr.; Dirat, O. *Chem. Eur. J.* **2002**, *8*, 259. (d) Trost, B. M.; Kallander, L. S. *J. Org. Chem.* **1999**, *64*, 5427. (e) Trost, B. M.; Surivet, J. P. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 3122

23. (a) Trost, B. M.; Tang, W.; Schulte, J. L. *Org. Lett.* **2000**, *2*, 4013. (b) Trost, B. M.; Tang, W. *Org. Lett.* **2001**, *3*, 3409.

24. (a) Lyle, M. P.; Narine, A. A.; Wilson, P. D. *J. Org. Chem.* **2004**, *69*, 5060. (b) Jones, G.; Richards, C. J. *Tetrahedron Lett.* **2001**, *42*, 5553.

25. Vyskocil, S.; Smrcina, M.; Hanus, V.; Polasek, M.; Kocovsky, P. *J. Org. Chem.* **1998**, *63*, 7738.

26. (a) Pena-Cabrera, E.; Norrby, P.-O.; Sjogren, M.; Vitagliano, A.; De Felice, V.; Oslob, J.; Ishii, S.; O'Neill, D.; Akermark, B.; Helquist, P. *J. Am. Chem. Soc.* **1996**, *118*, 4299. (b) Togni, A. *Tetrahedron: Asymmetry* **1991**, *2*, 683. (c) Hayashi, T.; Yamamoto, A.; Hagihara, T. *J. Org. Chem.* **1986**, *51,* 723.

27. (a) Breutel, C.; Pregosin, P. S.; Salzmann, R.; Togni, A. *J. Am. Chem. Soc.* **1994**, *116*, 4067. (b) Steinhagen, H.; Reggelin, M.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2108. (c) Togni, A.; Bruckhardt, U.; Gramlich, V.; Pregosin, P. S.; Salzmann, R. *J. Am. Chem. Soc*. **1996**, *118*, 1031. (d) von Matt, P.; Lloyd-Jones, G. C.; Pfaltz, A.; Macko, L.; Neuburger, M.; Zehnder, M.; Ruegger, H.; Pregosin, P. S. *Helv. Chim. Acta* **1995**, *78*, 265. (e) Sprinz, J.; Kiefer, M.; Helmchen, G.; Huttner, G.; Walter, O.; Zsolnai, L.; Reggelin, M. *Tetrahedron Lett*. **1994**, *35*, 1523.

28. Junker, J.; Reif, B.; Junker, B.; Felli, I. C.; Reggelin, M.; Griesinger, C. *Chem. Eur. J.* **2000**, *6*, 3281.

29. (a) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn*. **1971**, *44*, 581. (b) Heck, R. F.; Nolley, J. P., Jr. *J. Org. Chem.* **1972**, *37*, 2320.

30. Selected reviews, see: a) de Meijere, A.; Meyer, F. E. A*ngew. Chem. Int. Ed. Engl.* **1994**, *33,* 2379. (b) Bräse, S.; de Meijere, A. In *Metal-Catalyzed Cross Coupling Reactions*; Stang, P. J., Diederich, F., Eds; Wiley-VCH: Weinheim, 1998; Chapter 3. (c) Link, J. T.; Overman, L. E. In *Metal-Catalyzed Cross CouplingReactions*; Stang, P. J., Diederich, F., Eds; Wiley-VCH: Weinheim, 1998; Chapter 6. (d) Link, J. T. *Organic Reactions*; Wiley: Hoboken, NJ, 2002; Vol. 60, Chapter 2.

31. For recent reviews of the asymmetric Heck reaction, see: (a) Shibasaki, M.; Vogl, E. M. *J. Organomet. Chem*. **1999**, 1. (b) Donde, Y.; Overman, L. E. In *Catalytic*

Asymmetric Synthesis; Ojima, I., Ed.; Wiley-VCH: New York, 2000; Chapter 8. (c) Shibasaki, M.; Vogl, E, M.; Ohshima, T. *Adv. Syn. Catal.* **2004**, *346* 1533. (d) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945.

32. Ozawa, F.; Kubo, A.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113,* 1417.

33. (a) Hayashi, T.; Kubo, A.; Ozawa, F. *Pure Appl. Chem*. **1992**, *64*, 421. (b) Ozawa, F.; Kubo, A.; Hayashi, T. *Tetrahedron Lett.* **1992**, *33*, 1485. (c) Ozawa, F.; Kobatake, T.; Hayashi, T. *Tetrahedron Lett.* **1993**, *34*, 2505.

34. Hii, K. K.; Claridge, T. D. W.; Brown, J. M.; Smith, A.; Deeth, R. J. *Helv. Chim. Acta* **2001**, *84*, 3043.

35. Loiseleur, O; Meier, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 200.

36. Kündig, E. P.; Meier, P. *Helv. Chim. Acta* **1999**, *82*, 1360.

37. Hashimoto, Y.; Horie, Y.; Hayashi, M.; Saigo,K. *Tetrahedron: Asymmetry* **2000**, *11*, 2205.

38. (a) Deng, W.-P.; Hou, X.-L.; Dai, L.-X.; Dong, X.-W. *Chem. Commun.* **2000**, 1483. (b) Tu, T.; Deng, W.-P.; Hou, X.-L.; Dai, L.-X.; Dong, X.-W. *Chem. Eur. J.* **2003**, *9*, 3073. (c) Dai, L.-X.; Tu, T.; You, S.-L.; Deng, W.-P.; Hou, X.-L. *Acc. Chem. Res.* **2003**, *36*, 659. (d) Tu, T.; Hou, X.-L.; Dai, L.-X. *Org. Lett*. **2003**, *5*, 3651.

39. (a) Gilbertson, S. R.; Genov, D. G.; Rheingold, A. L. *Org. Lett*. **2000**, *2*, 2885. (b) Gilbertson, S. R.; Fu, Z. *Org. Lett*. **2001**, *3*, 161. (c) Gilbertson, S. R.; Fu, Z.; Xie, D. *Tetrahedron Lett.* **2001**, *42*, 365. (d) Gilbertson, S. R.; Xie, D.; Fu, Z. *J. Org. Chem.* **2001**, *66*, 7240.

VITA

Qian Dai

EDUCATION

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

Doctor of Philosophy, Organic and Organometallic Chemsitry
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

1. **Dai Q.**; Gao, W.; Liu, D.; Kapes, L. M.; Zhang, X. "Triazole-based monophosphine ligands for palladium catalyzed cross-coupling reactions of aryl chlorides" *J. Org. Chem.* **2006**, *71*, 3928 – 3934.

2. **Dai, Q.;** Wang, C.; Zhang, X. "Chiral bisphospholane ligands (Me-Ketalphos): Synthesis of their Rh(I) complexes and applications in asymmetric hydrogenation" *Tetrahedron* **2006**, *62*, 868 – 871.

3. **Dai Q.**; Yang, W.; Zhang, X. "Efficient rhodium catalyzed asymmetric hydrogenation for the synthesis of a new class of *N*-aryl β-amino acid derivatives" *Org. Lett.* **2005**, *7*, 5343 – 5345.

4. Liu, D.; Gao, W.; **Dai, Q.**; Zhang, X. "Triazole-based monophosphines for Suzuki-Miyaura coupling and amination reactions of aryl chlorides" *Org. Lett.* **2005**, *7*, 4907 – 4910.

5. Liu, D.; **Dai, Q.**; Zhang, X. "A new class of readily available and conformationally rigid phosphino-oxazoline ligands for asymmetric catalysis" *Tetrahedron* **2005,** *61*, 6460 – 6471.

6. **Dai, Q.**; Yang, W.; Zhang, X. "Efficient synthesis of protected β-amino acid derivatives via asymmetric hydrogenation" The 230th ACS National Meeting, Washington, D.C., Fall 2005.

7. **Dai, Q.**; Liu, D.; Zhang, X. "Synthesis and application of new phosphine-oxazoline ligands" The 228th ACS National Meeting, Philadelphia, PA, Fall 2004.