Asymmetric C-P bond formation via hydrophosphination activated by palladacycles : synthesis of chiral tertiary phosphines

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**ASYMMETRIC C-P BOND FORMATION VIA
HYDROPHOSPHINATION ACTIVATED BY
PALLADACYCLES: SYNTHESIS OF CHIRAL
TERTIARY PHOSPHINES**

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SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

2012

Asymmetric C–P Bond Formation *via*
Hydrophosphination Activated by Palladacycles:
Synthesis of Chiral Tertiary Phosphines

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Abbreviations and Symbols

Ad	adamantyl
An	anisoyl
Ar	aryl
Bn	benzyl
Bu	butyl
<i>ca.</i>	about (Latin <i>circa</i>)
calcd	calculated
conc.	concentrated
Cp	cyclopentadienyl
CSA	10-camphorsulfonic acid
Cy	cyclohexyl
d	doublet, day(s)
DBT	dibenzoyltartaric acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
dd	doublet of a doublet
ddd	doublet of a doublet of a doublet
de	diastereomeric excess
dec	decomposed
deg	degree(s)

dm	decimeter
DMPP	3,4-dimethyl-1-phenylphosphole
dr	diastereomeric ratio
ee	enantiomeric excess
eq	equatorial
Et	ethyl
<i>et. al.</i>	and others (Latin <i>alii</i>)
g	gram(s)
h	hour(s)
Hex	hexyl
Hz	hertz
<i>i.e.</i>	that is (Latin <i>id est</i>)
<i>i</i>	iso
<i>J</i>	coupling constant
m	multiplet
<i>m</i>	<i>meta</i>
Me	methyl
Men	menthyl
min	minute(s)
mp	melting point
MS(ESI)	Mass Spectrometry (Electrospray Ionization)
MS(FAB)	Mass Spectrometry (Fast Atom Bombardment)

<i>n</i>	straight chain
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect
<i>o</i>	<i>ortho</i>
<i>p</i>	<i>para</i>
Pr	propyl
Ph	phenyl
ppm	parts per million
q	quartet
qn	quintet
<i>R</i>	<i>rectus</i> (Latin: right absolute configuration)
ROESY	2D rotating frame Nuclear Overhauser Enhancement
<i>S</i>	<i>sinister</i> (Latin: left absolute configuration)
s	singlet
<i>s</i>	secondary
t	triplet
<i>t</i>	tertiary
THF	tetrahydrofuran
tol	tolyl
Å	angstrom(s)
δ	NMR chemical shift in ppm
[α] _D	specific rotation measured at sodium D line (589 nm)

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Summary

This thesis, consisting of three chapters, describes the development of asymmetric C–P bond formation (including C*–P, C*–P*, and double C*–P) *via* hydrophosphination reactions activated by palladacycles. This methodology provides the access to a series of tertiary C-stereogenic monophosphines, C- and P-stereogenic monophosphines, and C-stereogenic PCP diphosphines (chiral PCP pincer ligands) in high yields with excellent stereoselectivities.

Firstly, in chapter I, a brief introduction of chiral phosphines and their synthetic strategies, the development of palladacycles and their applications in the preparation of chiral phosphines including related research development in our laboratory, and the objectives of this project were presented.

In addition, chapter II investigated a chiral palladacycle containing *ortho*-metalated (*R*)-(1-(dimethylamino)ethyl)naphthalene as the auxiliary promoted asymmetric hydrophosphination of conjugate allenes with Ph₂PH in high regio- and stereoselectivities. The hydrophosphination reactions involves double C–P bonds formation (C–P and C*–P bonds formation), generating 1,2-diphosphines with one stereogenic center at the carbon backbone as bidentate chelates on the palladacycle. The chiral auxiliary subsequently was removed chemoselectively to give the corresponding dichloro complexes followed by ligand displacement with aqueous cyanide to obtain optically pure 1,2-diphosphines.

Lastly, in chapter III, palladacycle-catalyzed asymmetric hydrophosphination reactions were developed which were further divided into four sub-sections (3.1-3.4): 3.1) several chiral palladacycles were designed and synthesized as potential catalysts for asymmetric hydrophosphination reactions; 3.2) palladacycle-catalyzed asymmetric C*-P bond formation *via* hydrophosphination of enones with Ph₂PH was developed, yielding a series of enantiomerically pure C-stereogenic monophosphines in high yields with excellent stereoselectivities. A putative catalytic cycle was proposed for the reaction; 3.3) palladacycle-catalyzed asymmetric C*-P* bond formation *via* hydrophosphination of enones with (±) R(R')PH was expanded, obtaining a series of C- and P-stereogenic monophosphines in high yields with good stereoselectivities. A putative catalytic cycle was also proposed for the reaction; 3.4) palladacycle-catalyzed asymmetric double C*-P bond formation *via* hydrophosphination of bis(enones) was built up, generating a series of C-stereogenic PCP diphosphines (chiral PCP pincer ligands) in high yields with excellent stereoselectivities. A putative catalytic cycle was also proposed for the reaction. As an illustration, the directly synthesized diphosphine reacted with selected metals (Pd, Pt) to prepare chiral PCP pincer complexes in high yields.

CHAPTER I

General Introduction

1-1 Chiral Phosphines

1-1.1 Significance of Chiral Phosphines

Molecular chirality plays a very important role in life, science and technology. It is well known that the biological activities of pharmaceuticals, agrochemicals and other fine chemicals are often associated with their absolute configuration. The increasing demand in enantiomerically pure pharmaceuticals, agrochemicals and other fine chemicals has driven the development of asymmetric technologies.¹ Chiral phosphines, as highly valuable ligands for transition metal catalysis and efficient organocatalysts, have greatly contributed to the development of asymmetric technologies in organic and organometallic chemistry.^{1,2} Progress in the development of transition-metal catalysts for enantioselective reactions, especially hydrogenation processes, heavily depends on the availability of suitable chiral phosphine ligands.³ The development of efficient chiral phosphine ligands, to some extent, may represent the development of asymmetric technologies.¹

The first optically active phosphine $[R^1(R^2)(R^3)P]$ was prepared in 1961 by Horner *et al.*⁴ In 1968, Horner *et al.* and Knowles *et al.* simultaneously used chiral phosphines as ligands for the first time in homogeneous asymmetric hydrogenation.⁵ Since then, optically active phosphines have attracted great attention and thousands of them have been developed which stimulated asymmetric technologies both for research and industrial applications. During

the development of chiral phosphines for asymmetric transformation reactions in decades, there are several remarkable significant chiral phosphine ligands such as DIOP (Kagan, 1971),⁶ DIPAMP (Knowles, 1977),⁷ BINAP (Noyori, 1980)⁸ and DuPhos (Burk, 1993).⁹ The significance is fully confirmed by the award of the 2001 Nobel Prize in chemistry to Knowles and Noyori.

Encouraged by the excellent results of such chiral ligands, many research groups have devoted their efforts to discovering new efficient chiral phosphine ligands for asymmetric transformation reactions. Structural variation on the basis of known phosphine ligands motif may often create new efficient chiral ligands. It may also help to understand the influence of structural, electronic, and steric properties of ligands to asymmetric transformations.¹ It is an art for chemists to control the properties of catalysts such as reactivity and selectivity for the targeted transformation reactions *via* tuning ligand system. The great diversities of chiral phosphines in structural, electronic and steric properties leave a huge space for chemists to explore in the relative fields.

1-1.2 Types of Chiral Phosphines

The term 'phosphine' is defined as compounds in which the phosphorus

atom is connected to carbon or hydrogen atoms only. Phosphorus-nitrogen, phosphorus-sulfur and other hetero-polydentate ligands are excluded in this chapter. Optically active phosphines can involve one or several sources of chirality. Besides phosphines having stereogenic phosphorus center, chirality can also originate from the chiral unit that is external to phosphorus (usually with center, axis or plane of chirality). Chiral phosphines having both stereogenic phosphorus center and side-chain chirality are also known, but less common. Although chiral phosphine ligands have been developed with great structural diversities, most of these ligands can be divided into several different categories. Considering from the phosphorous numbers, chiral phosphines can be divided into monophosphines, diphosphines and polyphosphines. Considering from the source of chirality, chiral phosphines can be divided into the following categories:

(1) Chiral Phosphines with P-Chiral Center(s)

(*R*)-CAMP

1

2

3

4

(*S,S*)-*t*Bu-BisP*: R = *t*Bu
(*S,S*)-Cy-BisP*: R = Cy

(*S,S*)-*t*Bu-MiniPhos: R = *t*Bu
(*S,S*)-Cy-MiniPhos: R = Cy
(*S,S*)-*i*Pr-MiniPhos: R = *i*Pr

5

(2) Chiral Phosphines with Chiral Center(s) in the Side-Chain

(3) Chiral Phosphines with Chirality both at Phosphorous and in the Side-Chain

(4) Chiral Phosphines with Axial Chirality in the Side-Chain

In 1980, Noyori firstly reported the atropisomeric C_2 -symmetrical bisphosphine BINAP and found that BINAP-Ru complexes are efficient catalysts for asymmetric hydrogenations of a variety of olefins and ketones with high enantioselectivity, as well as many other asymmetric reactions.⁸ Inspired by the success of BINAP, many other atropisomeric axial chiral bisphosphines have been developed based on modification of the electronic and steric properties of BINAP. Several selected examples are shown below:

(S)-BINAP

(S)-H₈-BINAP

(S)-SEGPHOS

XPhos

SPhos

(S)-BisbenzodioxanPhos

(5) Chiral Phosphines with Planar Chirality in the Side-Chain

Another important class of chiral phosphines is the one with planar chirality in the side-chain. Most of these chiral phosphines based on the backbone of ferrocene or (arene)tricarbonylchromium(0) complexes, with many of them having both center and planar chiralities. Some selected examples of this kind of chiral phosphines are given below:

(R,S)-PPF-OMe

(R,S)-JosiPhos

(R,S)-Cy₂PF-PCy₂

TaniaPhos

(S,S)-FerroPhos

BoPhos

1-1.3 Applications of Chiral Phosphines

Chiral phosphines as highly valuable ligands for transition metal catalysis have been widely used for asymmetric transformation reactions in organic and organometallic chemistry.² The asymmetric transformation reactions involving chiral phosphine ligands include carbon–hydrogen bond, carbon–carbon bond and carbon–heteroatom bond formation and so on. Due to the vast amount of literature available for the applications of chiral phosphines, only selected examples will be mentioned for illustration.

(1) Asymmetric Hydrogenation Reaction: C–H Bond Formation

1) Hydrogenation of C=C Double Bonds

Scheme 1.1

(*S,S*)-CHIRAPHOS,¹⁰ (*R,R*)-DIPAMP,¹¹ (*S,S*)-DuPHOS,¹² (*1S,1S'*)-TANGPHOS,¹³ (*S,S*)-FERROPHOS¹⁴ *etc.*, were reported as efficient chiral ligands for hydrogenation of C=C double bonds.

2) Hydrogenation of C=O Double Bonds

Scheme 1.2

(R)-BINAP,¹⁵ *(S)*-MeO-BIPHEP,¹⁶ *(R,R)*-BPE,¹⁷ *(S)*-SEGPPOS,¹⁸ *(R)*-SYNPHOS¹⁹ *etc.*, were reported as efficient chiral ligands for this kind of hydrogenation of C=O double bonds.

3) Hydrogenation of C=N Bonds

Scheme 1.3

Compared with great accomplishments that have been achieved in the highly enantioselective hydrogenation of prochiral alkenes and ketones, relatively limited progress has been made in the asymmetric hydrogenation of prochiral imines.¹ The recent development of some Ir complexes provides a few efficient chiral catalyst systems for the hydrogenation of imines.²⁰

(2) Asymmetric Conjugate 1,4-Addition: C–C Bond Formation

Besides the asymmetric hydrogenation, chiral phosphines have also been widely used as ligands in transition metal catalyzed asymmetric C–C bond formation reactions. The conjugate addition of a nucleophile to olefins is one of the most important methods for C–C bond formation reactions. Organometallic

reagents including organozinc, organolithium, organomagnesium (Grignard reagents) are the efficient nucleophiles for conjugate 1,4-addition reactions which provide β -substituted functionalized products.²¹

Scheme 1.4

(*R,S*)-JOSIPHOS²² and (*S*)-TolBINAP²³ were reported as efficient chiral phosphine ligands for the Cu-catalyzed enantioselective conjugate addition of Grignard reagents to α,β -unsaturated enones, esters and thioesters.

(3) Other Reactions: C–X Bond Formation

Apart from C–H and C–C bond formation reactions, chiral phosphines have also proven to be efficient ligands in C–X (X = hetero atoms) bond formation reactions. An example of asymmetric formation of C–P bond is given below:²⁴

Scheme 1.5

For most cases, chiral phosphines are utilized as ligands for transition-metal catalysis. Over the past decades, their use as efficient chiral organocatalysts has been realized.²⁵ An example of chiral phosphine catalyzed

asymmetric [3+2] cycloaddition is given below:^{25a}

Scheme 1.6

1-2 Synthetic Strategies for Preparation of Chiral Phosphines

Enantiomers have identical chemical and physical properties in the absence of an external chiral influence. Therefore, synthesis of one optically active phosphine must involve a chiral source. Generally, the preparation of chiral phosphines can be divided into three methods: (1) chiral resolution; (2) transformation from chiral substrates; (3) asymmetric synthesis. Due to the vast amount of literature available for the synthesis of chiral phosphines, only selected examples will be mentioned to illustrate the various strategies and methods used.

1-2.1 Chiral Resolution

Chiral resolution in stereochemistry is a process for the separation of racemic compounds into their enantiomers.²⁶ Racemic compounds can be converted into diastereomers by reaction with an optically pure reagent. Unlike enantiomers, diastereomers have different physical properties and thus can be

separated by means of fractional crystallization or column chromatography, followed by removing the resolving reagent to liberate each enantiomer. It is an important tool in the production of optically active compounds. Other terms with the same meaning are optical resolution and mechanical resolution. Until the early 1970s, the conventional resolution of racemates was the primary method used to obtain optically active compounds.

Optically pure organic acids such as (*R,R*)-dibenzoyltartaric acid ((-)-DBT) and (*S*)-(+)-10-camphorsulfonic acid ((+)-CSA) are a class of important resolving reagents. The well known chiral NORPHOS was synthesized from Diels-Alder reaction between cyclopentadiene and dienophile followed by resolution using ((-)-DBT) as the resolving reagent and reduction to give enantiomerically pure (*R,R*)- and (*S,S*)-NORPHOS (Scheme 1.7).²⁷

Scheme 1.7

Enantiomerically pure (*R,R*)- and (*S,S*)-CHIRAPHOS were also resolved by the similar resolution process (Scheme 1.8).²⁸

Scheme 1.8

Similarly, P-chiral diphosphines (*S,S*)-**10** can also be synthesized by means of resolution (Scheme 1.9).²⁹

Scheme 1.9

Optical resolution is also an important method for the preparation of atropisomeric chiral diphosphines. A typical example is the synthesis of BINAP resolved by (+)-CSA reported by Noyori (Scheme 1.11).^{8b}

Scheme 1.11

However, one disadvantage of chiral resolution of racemates compared to direct asymmetric synthesis of the targeted enantiomer is that only 50% (at most) of a desired enantiomer could be obtained.

1-2.2 Transformation from Chiral Substrates

Transformation from chiral substrates involves the conversion of readily available chiral substrates to the desired chiral compounds. It is the most obvious way to obtain a chiral compound since it modifies an appropriate chiral precursor from an available source in several chemical steps to form the final product. Normally, the chiral center(s) of product is preserved or inverted from the starting materials, no new chiral center forming in the process. Optically pure DIOP,³⁰ (*R*)-PRPPHOS and (*S,S*)-CHIRAPHOS,³¹ for example, are prepared by this method (Scheme 1.12 and 1.13).

Scheme 1.12

Scheme 1.13

1-2.3 Asymmetric Synthesis

There are several ways for asymmetric synthesis of chiral phosphines from prochiral/racemic substrates among which the synthesis *via* asymmetric C–P bond formation is the dominated one. The asymmetric C–P bond formation may be classified into two types of reactions:³² (1) phosphination (substitution, or cross-coupling reaction), the substitution at sp^3 (alkyl halides, allylic acetates, Scheme 1.14)³³ or sp^2 carbon (aryl halides, Scheme 1.15)³⁴ with secondary phosphines, P–H bond removed often by a base; (2) hydrophosphination, the addition of P–H bond(s) to unsaturated C–X (X = C, N, O) bonds (Scheme

1.16).³⁵

Scheme 1.14

Scheme 1.15

Scheme 1.16

Apart from these examples of metal complexes catalyzed asymmetric synthesis of chiral phosphines *via* C–P bond formation, there are some examples of metal complexes promoted synthesis of chiral phosphines *via* C–P bond formation (Scheme 1.25 to Scheme 1.29). In these examples, stoichiometric amount of metal complex is needed.

Besides the asymmetric formation of C–P bond, asymmetric transformation of prochiral phosphines to chiral phosphines is also a good method for the synthesis of chiral phosphines. For example, our group reported chiral metal complexes promoted cycloaddition of DMPP (3,4-dimethyl-1-phenylphosphole) with olefins to give chiral phosphines (Scheme 1.24). In addition, our group reported the transformation of prochiral $R^1P(\text{alkyne})_2$ to $R^1P^*(R^2)(\text{alkyne})$ *via* addition promoted by chiral metal complexes with stereogenic center at phosphorus (Scheme 1.25).

The development of chiral phosphines has made undoubtedly significant impact on the asymmetric transformations. Catalytic asymmetric synthesis which relies on control of the stereochemistry of C–P bond formation is a valuable method to prepare chiral phosphines. However, compared with the wide application of chiral phosphines, catalytic asymmetric synthesis of chiral phosphines is surprisingly rare. Therefore, more efforts in developing new methodologies and catalysts for catalytic asymmetric synthesis of chiral phosphines are needed and the advance in the field should be of great importance in asymmetric catalysis.

1-3 Development of Chiral Palladacycles and Their Applications in Preparation of Chiral Phosphines

1-3.1 Development of Chiral Palladacycles

Cyclic organo-transition metal complexes containing a covalent

metal-carbon σ -bond (M–C) and a metal-donor atom bond (M–E) have been a topic of continuing interest since the discovery in the 1960s.³⁶ Complexes of this type were initially termed “intramolecular coordination compounds”, but are now more commonly called “cyclometallated complexes”, or in the case of compounds containing aryl carbon-metal σ -bonds, “*ortho*-metallated complexes”. Cyclometallation that represents a facile method for the C–H bond activation and construction of cyclometallated complexes have attracted much attention in the past decades. In this reaction, a ligand bearing an electronic donating atom (E = N, P, As, S, *etc.*) coordinated to a metal undergoes intramolecular metallation to form a chelating ring containing M–C bond which is stabilized by M–E bond (Scheme 1.17)

Scheme 1.17

Cyclic palladium complexes containing at least one carbon-palladium bond intramolecularly stabilized by at least one donor atom are called palladacycles which are one of the most popular classes of organopalladium derivatives. Cyclopalladation of nitrogen-donor ligands has been extensively studied and has acquired great interest due to their wide applications in organometallic and organic chemistry.³⁷

Most of the cyclopalladated systems contain N, P, As or S-heteroatoms and the following discussion will mainly focus on the nitrogen-donor palladacycles due to their special interest and wide applications in preparation of chiral phosphines.

In 1968, Cope and co-workers firstly reported *N,N*-dimethylbenzylamine could react efficiently with a palladium salt to form a benzylamine palladacycle complex **11** in 95% yield (Scheme 1.17).³⁸

Scheme 1.17

In 1971, Otsuka and co-workers reported the first chiral benzylamine palladium(II) complex (*S*)-**12** which was prepared from the chiral benzylamine and sodium tetrachloropalladate(II) (Scheme 1.18).³⁹ This chiral palladium complex (*S*)-**12** was applied in the kinetic resolution of a variety of tertiary phosphines by the bridge-splitting reactions.

Scheme 1.18

In 1977, Tani and co-workers reported the chiral palladacycle complex (*S*)-**13** by treatment of a chiral naphthylamine with sodium tetrachloropalladate in presence of triethylamine (Scheme 1.19).⁴⁰

Scheme 1.19

In 1982, Wild and co-workers reported the synthesis of the chiral palladium complex (*R*)-**14** using lithium tetrachloropalladate(II) and the chiral naphthylamine (Scheme 1.20).⁴¹

Scheme 1.20

In 1992, Leung and co-workers reported the chiral bisacetonitrile complex (*R*)-**15** prepared by treatment of (*R*)-**14** with AgClO_4 in presence of acetonitrile (Scheme 1.21).⁴² (*R*)-**15** has two active sites readily available for coordination.

Scheme 1.21

Over the past decades, many other chiral palladacycles derived from complexes **12-15** have been developed and applied in organic and organometallic chemistry.⁴³

1-3.2 Applications in Preparation of Chiral Phosphines

Palladacycles have been extensively studied and have attracted great interest due to the range of applications of them in many areas, for example, organic synthesis, homogeneous catalysis, the design of new drugs, asymmetric synthesis and resolution of racemic ligands.³⁷ Among the chiral palladacycles, complexes **12**, **14** and **15** are those of the mostly used ones. The major applications of these chiral palladacycles in preparation of chiral phosphines are described as below:

(1) Chiral Resolution

The chiral palladacycle (*S*)/(*R*)-**12** containing (*S*)/(*R*)-(1-(dimethylamino)ethyl)benzene as the chiral auxiliary is an efficient resolving reagent which is able to provide coordination sites around palladium atom. The well known *C*₂-symmetrical atropisomeric diphosphine BINAP was firstly prepared by

Noyori in its enantiomerically pure form by means of resolution using (*S*)-**12** as the resolving reagent.^{8a}

Scheme 1.22

A series of chiral tertiary phosphines and arsines were attained by Wild using the same approach.^{41, 44} An example is shown below (Scheme 1.23):

Scheme 1.23

(2) Asymmetric Cycloaddition Reactions

Over the last two decades, Leung and co-workers have successfully

employed the chiral palladacycle (*R*)/(*S*)-**15** as an efficient promoter in preparing a series of chiral phosphines *via* cycloaddition reactions (Scheme 1.24).⁴⁵ The five-membered heterocycle 3,4-dimethyl-1-phenylphosphole (DMPP) itself is not a reactive cyclic diene for the cycloaddition, but becomes reactive when it is coordinated onto a transition metal. This feature provides the chiral palladacycle complex the opportunity for activating DMPP as well as controlling the stereochemistry for the cycloaddition reactions between DMPP and dienophiles.

Scheme 1.24

(3) Asymmetric Hydroamination, Hydrophosphination, and Hydroarsination Reactions

Leung and co-workers have also successfully employed the same chiral palladacycle as an efficient promoter for the hydroamination⁴⁶ (Scheme 1.25), the hydrophosphination⁴⁷ (Scheme 1.26 and Scheme 1.27), and the

hydroarsination⁴⁸ (Scheme 1.28) reactions to give the corresponding chiral palladium complexes. The major complexes generated can be isolated and treated with HCl to remove the auxiliary, followed by the treatment with KCN to liberate the tertiary chiral phosphine ligands (Scheme 1.29).

Scheme 1.25

Scheme 1.26

Scheme 1.27

Scheme 1.28

Scheme 1.29

1-4 Objectives of the Present Project

Over the past decades, Leung and co-workers have made many efforts in developing chiral palladacycles and their applications as efficient promoters in

(2) Palladacycle-Catalyzed Asymmetric C*-P Bond Formation *via*

Hydrophosphination of Enones with Ph₂PH

(3) Palladacycle-Catalyzed Asymmetric C*-P* Bond Formation *via*

Hydrophosphination of Enones with (±) R(R')PH

(4) Palladacycle-Catalyzed Asymmetric Double C*-P Bond Formation *via*

Hydrophosphination of Bis(enones)

CHAPTER II

Palladacycle-Promoted Asymmetric C–P Bond Formation via Hydrophosphination of Conjugate Allenes

2-1 Introduction

Chiral tertiary diphosphines are well known as highly valuable ligands for metal catalyzed enantioselective transformations in organic and organometallic chemistry.^{1,2} Among the chiral diphosphines, 1,2-diphosphines bearing chirality on the carbon backbone, such as CHIRAPHOS, PROPHOS, and NORPHOS, have special interest due to their strong bonding ability with metal and stereocontrol for asymmetric transformation reactions.⁴⁹ However, their preparation usually involving resolution process or chiral starting materials (Scheme 1.7, Scheme 1.8, Scheme 1.13)^{27,28,31}. Development of efficient methodology allowing the conversion of inexpensive substrates into the desired chiral 1,2-diphosphines in good yields is of importance.

(S)-PROPHOS

(S,S)-CHIRAPHOS

(S,S)-NORPHOS

Hydrophosphination, the formal addition of a P-H bond to C-C multiple bonds, is a highly desirable and atom-economical process for the preparation of phosphine derivatives, particularly chiral phosphine derivatives, which are widely used in organic and organometallic chemistry.¹ It is known that with free phosphines, addition onto unsaturated C-C bonds has been achieved under basic,⁵⁰ acidic,⁵¹ radical,⁵² or thermal⁵³ activation. However, severe reaction conditions are typically required, which most of the functional groups do not

tolerate without protection. Transition metal-,⁵⁴ lanthanide complex-⁵⁵, and organocatalyst⁵⁶-catalyzed addition of a P–H bond to multiple C–C bonds has been reported in recent years. The use of these kinds of catalysts for such addition reactions often offers improvement in functional group tolerance, rate, and selectivity. In terms of asymmetric addition of a P–H moiety to unsaturated C–C bonds, it is still relatively limited. Transition-metal-mediated asymmetric hydrophosphination reaction is attractive due to the ability of transition-metal complexes to control the regioselectivity and stereoselectivity of a reaction through construction of the chiral phosphine ligand architecture. Development of an easy and rather general process allowing the efficient preparation of desired chiral phosphines in good yields with high selectivity still represents a challenging and highly desirable asymmetric transformation.

Allenes are a class of unique compounds with two π -orbitals perpendicular to each other. For a long period of time, allenes were considered as unstable compounds which retarded the development of the chemistry of allenes. Actually, they are stable enough to be synthesized in a laboratory. They also exist in many natural products with interesting biological activities.⁵⁷ During the past decade, allenes have demonstrated interesting reactivities as well as selectivities, which can usually be tuned by the electronic or steric effects and the nature of the catalysts involved.⁵⁸ However, reports on hydrophosphination of allenes are quite limited due to the poor chemoselectivity and the lack of efficient methodologies and catalysts.

Asymmetric hydrophosphination of allenes, to the best of our knowledge, has never been reported before.

In preceding contributions, our group has reported the asymmetric hydrophosphination of coordinated vinylic phosphines and functionalized alkynes (Scheme 1.26, Scheme 1.27) promoted by organopalladium complexes to prepare chiral phosphines.⁴⁷ To extend this protocol to the hydrophosphination of cumulated unsaturated bond systems in the synthesis of functionalized chiral diphosphine ligands, the asymmetric hydrophosphination of conjugate allenes promoted by an palladacycle to synthesize functionalized 1,2-diphosphines is described in this chapter. Observations on factors affecting the scope and the regio- and stereoselectivity of these transformations are discussed.

2-2 Results and Discussion

In the absence of a metal ion, diphenylphosphine shows no reactivity with either allenic ester **18a** or allenic ketone **18b** (Scheme 2.1) under ambient temperature. However, in the presence of the organopalladium complex (*R_c*)-**15**, the asymmetric hydrophosphination reaction proceeded smoothly at $-78\text{ }^{\circ}\text{C}$ to form four corresponding hydrophosphination products. The ester or ketone functional group of allenes is crucial for this kind of reaction. The nonconjugated allenes we tried, such as 3-methyl-1,2-butadiene, 1-methyl-1-(trimethylsilyl) allene, and methoxyallene, did not undergo this kind

of hydrophosphination reaction under the same conditions.

2-2.1 Complex (*R*)-**15** Promoted Asymmetric Hydrophosphination of Conjugate Allenes

Treatment of ethyl 2,3-butadienoate **18a** (1 equiv) with diphenylphosphine (2 equiv) at $-78\text{ }^{\circ}\text{C}$ in the presence of the chiral complex (*R_c*)-**15** (1 equiv) and triethylamine (0.4 equiv) gave the corresponding hydrophosphination products (Scheme 2.1). Prior to purification, the $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum (CDCl_3) of the crude reaction products exhibited four pairs of doublets which are consistent with the formation of four isomeric products being generated during the hydrophosphination reaction. The four pairs of doublets were recorded at δ (30.4, 64.1, $J_{\text{PP}} = 33.6\text{ Hz}$), (38.7, 74.5, $J_{\text{PP}} = 24.4\text{ Hz}$), (45.2, 51.0, $J_{\text{PP}} = 33.9\text{ Hz}$), and (46.0, 50.2, $J_{\text{PP}} = 31.0\text{ Hz}$), with the relative intensities of 2.2:1.0:10.6:2.0, respectively. The amount of triethylamine added had an impact on the selectivity and 0.4 equiv of triethylamine was found to be the appropriate amount, with more or less amine decreasing the regio- and stereoselectivity. Subsequently, the major isomer was separated by fractional crystallization as pale yellow prisms from dichloromethane-diethyl ether. The single-crystal X-ray diffraction analysis revealed that it was (*R, S*)-**19a** (Figure 2.1).

Similarly, treatment of 3,4-Pentadien-2-one **18b** (1 equiv) with diphenylphosphine (2 equiv) under the same conditions gave four

corresponding hydrophosphination products recorded at δ (31.4, 65.9, $J_{\text{PP}} = 32.8$ Hz), (38.8, 74.5, $J_{\text{PP}} = 24.1$ Hz), (45.7, 51.8, $J_{\text{PP}} = 33.8$ Hz), and (46.0, 50.8, $J_{\text{PP}} = 30.7$ Hz) with the intensities of 1.4:1.0:5.9:1.6. The major isomer was separated by the same way as described for (*R,S*)-**19a**. The single-crystal X-ray diffraction analysis revealed that it was (*R,S*)-**19b** (Figure 2.2).

The molecular structure of (*R,S*)-**19a** and (*R,S*)-**19b** are quite similar. The newly formed stereogenic center at carbon adopts the *S* absolute configuration and the five-membered diphosphine chelate adopts the δ ring configuration in both (*R,S*)-**19a** and (*R,S*)-**19b**. The coordination geometry around the palladium atom in both complexes is square planar with slight tetrahedral distortion evident (4.6° for (*R,S*)-**19a** and 3.0° for (*R,S*)-**19b**). The phosphorus atom adjacent to the ester or ketone substituent coordinates *trans* to the naphthalene carbon. Selected bond lengths and angles are given in Table 2.1 and Table 2.2.

Scheme 2.1

Figure 2.1 Molecular structure and absolute stereochemistry of complex (*R,S*)-**19a** with 50% probability thermal ellipsoids shown. Hydrogen atoms except those on the chiral center are omitted for clarity.

Table 2.1 Selected Bond Lengths (Å) and Angles (deg) of (*R,S*)-**19a**

Pd1–C1	2.064(4)	Pd1–N1	2.140(4)
Pd1–P1	2.347(1)	Pd1–P2	2.250(1)
C27–P1	1.864(4)	C27–C32	1.540(7)
C32–P2	1.827(5)	C27–C28	1.520(7)
C28–C29	1.489(8)	C29–O2	1.215(6)
C29–O1	1.329(6)	C30–O1	1.441(7)
C1–Pd1–N1	80.9(2)	C1–Pd1–P2	96.4(1)
N1–Pd1–P2	175.3(1)	C1–Pd1–P1	177.7(1)
N1–Pd1–P1	98.3(1)	P2–Pd1–P1	84.6(1)
C32–C27–P1	104.6(3)	C27–C32–P2	108.1(3)
C27–P1–Pd1	105.8(2)	C32–P2–Pd1	108.1(2)
C28–C27–P1	117.1(3)	C28–C27–C32	113.5(4)

Figure 2.2 Molecular structure and absolute stereochemistry of complex (*R,S*)-**19b** with 50% probability thermal ellipsoids shown. Hydrogen atoms except those on the chiral center are omitted for clarity.

Table 2.2 Selected Bond Lengths (Å) and Angles (deg) of (*R,S*)-**19b**

Pd1–C9	2.064(3)	Pd1–N1	2.140(3)
Pd1–P1	2.355(1)	Pd1–P2	2.248(1)
C40–P1	1.855(3)	C40–C39	1.527(5)
C39–P2	1.836(3)	C40–C41	1.530(5)
C41–C42	1.507(5)	C42–O1	1.215(5)
C9–Pd1–N1	80.3(1)	C9–Pd1–P2	94.5(1)
N1–Pd1–P2	174.3(1)	C9–Pd1–P1	178.2(1)
N1–Pd1–P1	100.0(1)	P2–Pd1–P1	85.1(1)
C39–C40–P1	106.6(2)	C40–C39–P2	110.5(2)
C40–P1–Pd1	105.6(1)	C31–P2–Pd1	108.8(1)
C41–C40–P1	115.2(3)	C39–C40–C41	112.6(2)

2-2.2 Removing the Auxiliary of the Phosphine Complexes

A solution of (*R,S*)-**19a** in dichloromethane was subsequently treated with concentrated hydrochloric acid to remove the naphthylamine auxiliary chemoselectively to obtain the neutral dichloro complex (*S*)-**23a** (Scheme 2.2). Complex (*S*)-**23a** can be crystallized from chloroform-diethyl ester as pale yellow prisms. The $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum of the isolated complex in CD_2Cl_2 showed a pair of doublets at δ (52.1, 70.7, $J_{\text{PP}} = 7.1$ Hz). The single-crystal X-ray diffraction analysis revealed that the five-membered diphosphine chelate with the δ ring configuration and the stereogenic center at carbon with *S* configuration were intact. There are two crystallographically independent molecules in the asymmetric unit with slightly different bond lengths and angles. Figure 2.3 shows the molecular structure and absolute stereochemistry of (*S*)-**23a**. Selected bond lengths and angles are given in Table 2.3. Similarly, the dichloro complex (*S*)-**23b** was obtained from (*R,S*)-**19b** and the $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum (CD_2Cl_2) of it showed a pair of doublets at δ (53.6, 71.6, $J_{\text{PP}} = 7.1$ Hz).

Scheme 2.2

Figure 2.3 Molecular structure and absolute stereochemistry of complex (*S*)-**23a** with 50% probability thermal ellipsoids shown. Hydrogen atoms except those on the chiral center are omitted for clarity.

Table 2.3 Selected Bond Lengths (Å) and Angles (deg) of (*S*)-**23a**

Pd1–P1	2.237(2)	Pd1–P2	2.226(2)
C13–P1	1.852(7)	C13–C18	1.520(10)
C13–C14	1.550(10)	C14–C15	1.497(11)
P2–Pd1–P1	86.5(1)	Cl2–Pd1–Cl1	93.8(1)
P1–Pd1–Cl2	177.7(1)	P2–Pd1–Cl1	173.2(1)
P1–Pd1–Cl1	88.4(1)	P2–Pd1–Cl2	91.3(1)
C18–C13–P1	106.2(5)	C13–C18–P2	108.1(5)

2-2.3 Liberation of Optically Pure Phosphines

Treatment of (*S*)-**23a** with aqueous potassium cyanide at room

temperature for 20 min gave the optically pure ligand (*S*)-**24a** as white solid after removing solvent. The $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum (CDCl_3) showed a pair of doublet resonances at δ (−0.6, −22.2, $J_{\text{PP}} = 29.7$ Hz). Similarly, the optically pure ligand (*S*)-**24b** was obtained from (*S*)-**23b** and the $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum (CDCl_3) showed a pair of doublet resonances at δ (−0.6, −21.7, $J_{\text{PP}} = 34.1$ Hz) (Scheme 2.3).

Scheme 2.3

2-2.4 Re-coordination of Optically Pure Phosphines

In order to confirm the optical purity of the free diphosphines and to establish the identity of the minor isomers that were generated in the original hydrophosphination reaction, the liberated optically pure (*S*)-**24a** was re-coordinated to (*R*)-**15** as illustrated in Scheme 2.4. The $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum of the crude product exhibited only two pairs of doublets at δ (30.4, 64.1, $J_{\text{PP}} = 33.6$ Hz), (45.2, 51.0, $J_{\text{PP}} = 33.9$ Hz). The resonance signals at δ (45.2, 51.0, $J_{\text{PP}} = 33.9$ Hz) were identical to those observed for the major product (*R,S*)-**19a** in the original hydrophosphination reaction. The signals at δ (30.4, 64.1, $J_{\text{PP}} = 33.6$ Hz) matched signals detected in the original reaction mixture and were assigned to the regioisomeric product of (*R,S*)-**19a**, that is,

(*R,S*)-20a.

Similarly, the $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum (CDCl_3) of the crude re-complexation mixture from (*S*)-**24b** and (*R*)-**15** exhibited two pairs of doublets at δ (51.8, 45.7, $J_{\text{PP}} = 33.3$ Hz) and (65.9, 31.6, $J_{\text{PP}} = 31.8$ Hz). These signals were identical to those originally recorded from complexes (*R,S*)-**19b** and (*R,S*)-**20b**.

As a further confirmation of the optical purity of (*S*)-**24a**, the re-complexation reaction with the equally accessible enantiomerically pure complex (*S*)-**15** gave only two distinct doublets at δ (38.7, 74.5, $J_{\text{PP}} = 24.4\text{Hz}$), (46.0, 50.2, $J_{\text{PP}} = 31.0\text{Hz}$). These signals are consistent with (*R,R*)-**21a**, (*R,R*)-**22a**, which are enantiomeric forms of (*S,S*)-**25a**, (*S,S*)-**26a** respectively. In the absence of any chiral deuterated solvent, the two enantiomers should exhibit identical NMR signals. Similarly, re-coordination of (*S*)-**24b** to (*S*)-**15** gave two distinct doublets at δ (50.6, 46.4, $J_{\text{PP}} = 30.9$ Hz) and (74.6, 38.9, $J_{\text{PP}} = 24.0$ Hz). These signals are consistent with (*R,R*)-**21b**, (*R,R*)-**22b**, which are enantiomeric forms of (*S,S*)-**25b**, (*S,S*)-**26b**, respectively. The re-coordination reaction therefore confirmed that the liberated diphosphine ligands (*S*)-**24a** and (*S*)-**24b** were enantiomerically pure.

Scheme 2.4

2-3 Mechanistic Considerations

Metal mediated/catalyzed hydrophosphination of alkenes usually involves the following steps:^{54f, 59} (a) oxidative addition of the P–H bond to the metal to form M–H and M–P bonds, or protonolysis of P–H bond to give M–P phosphido complex; (b) insertion of alkene into the M–H or M–P bonds, or alternatively the nucleophilic phosphido complex undergoes addition to alkene; (c) reductive elimination or protonolysis to give the product. It has been reported that upon coordination of secondary phosphines to palladium or platinum, the P–H proton is relatively acidified and can be deprotonated easily.⁶⁰

Scheme 2.5

In order to better understand the mechanism of the current hydrophosphination of conjugate allenes (addition of 2 equivalent of Ph₂PH) promoted by the palladacycle (*R*)-**15**, we wonder that whether the addition can be accomplished step by step and whether the monohydrophosphination intermediate can be obtained. Therefore, we carried out the hydrophosphination with 1 equivalent of Ph₂PH under the same reaction condition with the purpose to get the monohydrophosphination product (*R*)-**28**. The Ph₂PH quickly coordinated to palladacycle (*R*)-**15** to form (*R*)-**27** (³¹P{¹H} NMR: δ 12.5) which was expected to react with the allene **18a** to give the monophosphine adduct complex (*R*)-**28** (Scheme 2.5). However, to our surprise, the monohydrophosphination did not move under the same conditions while the double hydrophosphination proceeded smoothly as described in Scheme 2.1. Based on the results and studies, we proposed the mechanism path way for the palladacycle promoted hydrophosphination of conjugate allenes as follows:

Scheme 2.6

The palladacycle (R)-15 reacted with 2 equivalent of Ph₂PH quickly to give the bisphosphine complex (R)-29. The ³¹P{¹H} NMR spectrum of it showed a pair of doublets recorded at δ (11.5, -9.8, *J*_{PP} = 38.3 Hz). However, in the bisphosphine complex (R)-29, the coordinated diphenylphosphines, especially the one *trans* to carbon are labilized and can undergo dissociation easily which gives chance for allene to coordinate with palladium. Meanwhile, the coordinated diphenylphosphine is acidified and can be deprotonated immediately when Et₃N was added with characteristic color change to form the phosphido intermediate (R)-30 which underwent 1,4-addition to give the vinylphosphine intermediate. The phosphorus was exclusively attached to the middle carbon of the allene system. The first C-P bond formation *via*

hydrophosphination is accomplished with high regioselectivity. The free diphenylphosphine can coordinated back to palladium and be deprotonated, and the vinylphosphosphine can be delocalized by palladium to form the intermediate (*R*)-**31**. The bisphosphine intermediate (*R*)-**31** can under exchange to form (*R*)-**32** due to the labilization which was observed in similar cases.⁶¹ The phosphido intermediates (*R*)-**31** and (*R*)-**32** are very active and can underwent the second 1,4-addition even at $-78\text{ }^{\circ}\text{C}$ to give the mixture of complexes **19-22**, and thus the second C-P bond formation was achieved. Due to the chirality of the auxiliary of the palladacycle, good stereoselectivity was achieved in this step. (*R,S*)-**19** and (*R,S*)-**20** are a pair of regioisomers which can undergo equilibrium under thermal conditions. So do the other pair of regioisomers (*R,R*)-**21** and (*R,R*)-**22**.

2-4 Conclusion

In summary, the chiral palladacycle promoted asymmetric hydrophosphination of conjugate allenes with diphenylphosphine involving the formation of two C-P bonds has been successfully developed. The reaction proceeded smoothly under mild conditions with good regio- and stereoselectivities. The major hydrophosphination products coordinated with the palladacycle were isolated, and treated with hydrochloride and followed by KCN to give optical pure functionalized 1,2-diphosphines. The optical purity of the diphosphine products was confirmed by the re-coordination process. The

single-crystal X-ray diffraction analysis revealed the absolute configuration of the intermediate complexes involved. The possible mechanistic path way for the hydrophosphination reaction was proposed.

2-5 Experimental Section

All air-sensitive manipulations were performed under a positive pressure of argon using standard Schlenk line. Solvents were dried and degassed prior to use when necessary. NMR spectra were recorded at 25 °C on Brüker ACF 300, 400 and 500 spectrometers. Chemical shifts are reported in δ ppm referenced to an internal SiMe₄ standard (δ = 0 ppm) for ¹H NMR, chloroform-d (δ = 77.23 ppm) for ¹³C NMR and to an external 85% H₃PO₄ standard for ³¹P{¹H} NMR. Optical rotations were measured on the specified solution in a 0.1 dm cell at 20 °C with a Perkin-Elmer 341 polarimeter. Melting points were measured using the SRS Optimelt Automated Melting Point System, SRS MPA100.

The chiral palladium templates (*R*)-**15** and (*S*)-**15** were prepared as previously reported.⁴² Ethyl 2,3-butadienoate was bought from Sigama-Aldrich company. 3,4-Pentadien-2-one was prepared according to literature.⁶²

Caution! *Perchlorate salts of metal complexes are potentially explosive compounds and should be handled with care.*

[(*R*)-1-[1-(Dimethylamino)ethyl]-2-naphthalenyl-C,N][ethyl (*S*)-3,4-bis(diphenylphosphino)butanoate]palladium(II) Perchlorate, (*R,S*)-19a**.** A solution of the complex (*R*)-**15** (0.24 g, 0.50 mmol) and diphenylphosphine (0.19 g, 1.0 mmol) in dichloromethane (5 mL) was cooled to -78°C with stirring. Ethyl 2,3-butadienoate (0.06 g, 0.50 mmol) in dichloromethane (0.5 mL) was added subsequently, followed by adding triethylamine (0.20 g, 0.20 mmol) in dichloromethane (0.5 mL). The reaction mixture was allowed to stir for 2 h at -78°C , and then warm to room temperature gradually, and continue to stirring for 5 h. The solvent was removed under reduced pressure to give a mixture of hydrophosphination products. Upon fractional crystallization in dichloromethane-diethyl ether, product (*R,S*)-**19a** was isolated as white prisms (0.25 g, 56 %): $[\alpha]_{\text{D}} = -112.6$ (c 1.0, CH_2Cl_2). Mp: $190-192^{\circ}\text{C}$. Anal. Calcd for C, 59.5; H, 5.2; N, 1.6. Found: C, 59.6; H, 5.6, N, 1.7. $^{31}\text{P}\{^1\text{H}\}$ NMR (CD_2Cl_2 , 121MHz): δ 45.2 (d, $J_{\text{PP}} = 33.9$ Hz), 51.0 (d, $J_{\text{PP}} = 33.9$ Hz). ^1H NMR (CD_2Cl_2 , 400 MHz): δ 1.09 (t, 3H, $J_{\text{HH}} = 7.2$ Hz, CH_2CH_3), 1.88-1.98 (m, 1H, $\text{CH}'\text{HCO}_2\text{Et}$), 1.93 (d, 3H, $J_{\text{HH}} = 6.2$ Hz, CHMe), 2.10-2.17 (m, 1H, $\text{CH}'\text{HCO}_2\text{Et}$), 2.42 (s, 3H, NMe), 2.60 (s, 3H, NMe), 2.61-2.73 (m, 2H, P^2CH_2), 3.11 (dtd, 1H, $J_{\text{PH}} = 54.8$ Hz, $J_{\text{HH}} = 14.0$ Hz, $J_{\text{PH}} = 3.8$ Hz, P^1CHCH_2), 3.94 (qn, 2H, $J_{\text{HH}} = 7.2$ Hz, CH_2CH_3), 4.52 (m, 1H, CHCH_3), 6.96-8.30 (m, 26H, Ar). ^{13}C NMR (CD_2Cl_2 , 100 MHz): δ 14.3 (s, 1C, CH_2CH_3), 25.5 (s, 1C, CHCH_3), 34.7 (dd, 1C, $J_{\text{PC}} = 17.6$ Hz, $J_{\text{PC}} = 5.6$ Hz, $\text{CH}_2\text{CO}_2\text{Et}$), 35.4 (dd, 1C, $J_{\text{PC}} = 24.9$ Hz, $J_{\text{PC}} = 11.8$ Hz, P^1CH), 36.1 (dd, 1C, $J_{\text{PC}} = 36.5$ Hz, $J_{\text{PC}} = 20.9$ Hz, P^2CH_2), 50.7

(s, 1C, NMeMe), 52.3 (s, 1C, NMeMe), 61.9 (s, 1C, CH₂CH₃), 76.0 (s, 1C, CHCH₃), 122.3-158.1 (m, 34C, Ar), 170.9 (d, 1C, J_{PC} = 9.8 Hz, COMe).

[(*R*)-1-[1-(Dimethylamino)ethyl]-2-naphthalenyl-C,N][(S)-4,5-bis(diphenylphosphino)pentan-2-one]palladium(II) Perchlorate, (*R,S*)-19b**.** The same

procedure was adopted for hydrophosphination reaction of 3,4-Pentadien-2-one (0.04g, 0.50 mmol), product (*R,S*)-**19b** was isolated as white prisms by fractional crystallization in dichloromethane-diethyl ether (0.22 g, 51%): $[\alpha]_D = -92.3^\circ$ (c 1.3, CH₂Cl₂). Mp: 225–227 °C. Anal. Calcd for C₄₃H₄₄ClNO₅P₂Pd: C, 60.2; H, 5.2; N, 1.6. Found: C, 60.1; H, 5.3; N, 1.8. ³¹P{¹H} NMR (CDCl₃, 121 MHz): δ 51.8 (d, J_{PP} = 33.3 Hz), 45.7 (d, J_{PP} = 33.3 Hz). ¹H NMR (CDCl₃, 400 MHz): δ 1.85 (m, 1H, CH'HCOMe), 1.93 (d, 3H, J_{HH} = 6.1 Hz, CHMe), 2.03 (s, 3H, COMe), 2.44 (s, 3H, NMe), 2.47 (m, 1H, CH'HCOMe), 2.61 (s, 3H, NMe), 2.68 (m, 2H, PCH₂), 3.05 (dtd, 1H, J_{PH} = 55.6, J_{HH} = 14.2 Hz, J_{PH} = 3.7 Hz, PCHCH₂), 4.54 (m, 1H, CHCH₃), 6.94-8.28 (m, 26H, Ar). ¹³C NMR (CDCl₃, 100 MHz): δ 25.2 (s, 1C, CHCH₃), 30.1 (s, 1C, COCH₃), 33.8 (dd, 1C, J_{PC} = 26.0 Hz, J_{PC} = 11.5 Hz, P¹CH), 35.2 (dd, 1C, J_{PC} = 36.5 Hz, J_{PC} = 20.8 Hz, P²CH₂), 42.6 (dd, 1C, J_{PC} = 16.8 Hz, J_{PC} = 5.6 Hz, CH₂COMe), 50.4 (s, 1C, NMeMe), 51.8 (s, 1C, NMeMe), 75.4 (s, 1C, CHCH₃), 122.4-157.6(m, 34C, Ar), 206.1 (d, 1C, J_{PC} = 7.6 Hz, COMe).

Dichloro[ethyl (*S*)-3,4-bis(diphenylphosphino)butanoate]palladium(II), (*S*)-

23a. A solution of (*R,S*)-**19a** (0.44 g, 0.50 mmol) in dichloromethane (10 mL)

was treated with concentrated hydrochloric acid (4 mL) for 5 h at room

temperature. The mixture was then washed with water (3 x 20 mL), dried over MgSO_4 , and subsequently crystallized from chloroform-diethyl ether to give the dichloro complex as pale yellow prisms (0.31 g, 94%): $[\alpha]_D = +47.2$ (c 1.0, CH_2Cl_2). Mp: 232–235°C. Anal. Calcd for $\text{C}_{30}\text{H}_{30}\text{Cl}_2\text{O}_2\text{P}_2\text{Pd}$: C, 54.4; H, 4.6. Found: C, 54.0; H, 4.5. $^{31}\text{P}\{^1\text{H}\}$ NMR (CD_2Cl_2 , 121 MHz): δ 52.1 (d, $J_{\text{PP}} = 7.1$ Hz), 70.7 (d, $J_{\text{PP}} = 7.1$ Hz). ^1H (400 MHz, CD_2Cl_2): δ 1.12 (t, 3H, $J_{\text{HH}} = 7.1$ Hz, CH_2CH_3), 2.06–2.20 (m, 2H, CHHCO_2Et , P^2CHH), 2.58 (dd, 1H, $J_{\text{HH}} = 17.0$ Hz, $J_{\text{PH}} = 0.6$ Hz, CHHCO_2Et), 2.96 (dtd, 1H, $J_{\text{PH}} = 21.1$ Hz, $J_{\text{HH}} = 12.0$ Hz, $J_{\text{HH}} = 4.8$ Hz, P^2CHH), 3.21–3.27 (m, 1H, P^1CHCH_2), 4.01 (qn, 2H, $J_{\text{HH}} = 7.1$ Hz, CH_2CH_3), 7.51–8.08 (m, 20H, Ar). ^{13}C NMR (CD_2Cl_2 , 100 MHz): δ 14.4 (s, 1C, $\text{CO}_2\text{CH}_2\text{CH}_3$), 33.3 (dd, 1C, $J_{\text{PC}} = 35.2$ Hz, $J_{\text{PC}} = 16.8$ Hz, $\text{P}^2\text{CH}_2\text{CHP}^1$), 34.8 (d, 1C, $J_{\text{PC}} = 18.5$ Hz, $\text{CH}_2\text{CO}_2\text{Et}$), 36.6 (dd, 1C, $J_{\text{PC}} = 31.9$ Hz, $J_{\text{PC}} = 16.1$ Hz, P^1CHCH_2), 62.0 (s, 1C, $\text{CO}_2\text{CH}_2\text{CH}_3$), 124.9–136.7 (m, 24C, Ar), 170.9 (d, 1C, $J_{\text{PC}} = 12.9$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$).

Dichloro[(*S*)-4,5-bis(diphenylphosphino) pentan-2-one]palladium(II), (*S*)-

23b. The same procedure was used to prepare dichloro complex (*S*)-**23b** (0.28 g, 89%) from (*R,S*)-**19b** (0.43 g, 0.50 mmol): $[\alpha]_D = +65.0^\circ$ (c 1.0, CH_2Cl_2). Mp: 329–331 °C. Anal. Calcd for $\text{C}_{29}\text{H}_{28}\text{Cl}_2\text{OP}_2\text{Pd}$: C, 55.13; H, 4.47. Found: C, 54.93; H, 4.45. $^{31}\text{P}\{^1\text{H}\}$ NMR (CD_2Cl_2 , 121 MHz): δ 71.6 (d, $J_{\text{PP}} = 7.1$ Hz), 53.6 (d, $J_{\text{PP}} = 7.1$ Hz). ^1H NMR (CD_2Cl_2 , 300 MHz): δ 1.87 (s, 3H, COMe), 2.04 (m, 1H, $\text{PCH}'\text{H}$), 2.28 (m, 1H, $\text{CH}'\text{HCOMe}$), 2.60 (m, 1H, $\text{PCH}'\text{H}$), 2.89 (m, 1H, $\text{CH}'\text{HCOMe}$), 3.33 (m, 1H, PCHCH_2), 7.49–8.05 (m, 20H, Ar). ^{13}C

NMR (CD₂Cl₂, 75 MHz): δ 29.4 (s, 1C, COMe), 32.3 (dd, J_{PC} = 35.1 Hz, J_{PC} = 16.3 Hz, P²CH₂), 34.5 (dd, J_{PC} = 32.7 Hz, J_{PC} = 15.5 Hz, P¹CH), 42.5 (d, 1C, J_{PC} = 16.4 Hz, CH₂COMe), 124.9-135.7 (m, 24C, Ar), 204.3 (d, 1C, J_{PC} = 9.9 Hz, COMe).

Ethyl 3,4-bis(diphenylphosphino)butanoate, (S)-24a. A solution of complex (S_c)-**23a** (0.20 g, 0.30 mmol) in dichloromethane (10 mL) was stirred vigorously with aqueous KCN (0.5 g, 7.68 mmol) for 10 min. The organic layer was separated, washed with water (3 x 12 mL), and dried over MgSO₄. The diphosphine ligand (S)-**24a** was obtained as a white solid upon removal of solvent under reduced pressure (0.13 g, 90%): $[\alpha]_D = -37.3$ (*c* 2.4, CH₂Cl₂). ³¹P{¹H} NMR (CDCl₃, 121 MHz): δ -0.6 (d, J_{PP} = 29.7 Hz), -21.9 (d, J_{PP} = 29.7 Hz). ¹H NMR (CDCl₃, 300 MHz): δ 1.11 (t, 3H, J_{HH} = 7.1 Hz, CH₂CH₃), 1.88-2.00 (m, 1H, CHH'CO₂Et), 2.13-2.23 (m, 1H, CHH'CO₂Et), 2.43-2.66 (m, 2H, P²CH₂CH), 2.74-2.82 (m, 1H, P¹CHCH₂), 3.82-3.93 (m, 2H, CH₂CH₃), 7.16-7.25 (m, 20H, Ar).

4,5-Bis(diphenylphosphino)pentan-2-one, (S)-24b. The same procedure was used to prepare (S)-**24b** (0.13 g, 92%) from (S)-**23b** (0.19 g, 0.30 mmol): $[\alpha]_D = -56.4^\circ$ (*c* 1.5, CH₂Cl₂). ³¹P{¹H} NMR (CDCl₃, 121 MHz): δ -0.6 (d, J_{PP} = 34.1 Hz), -21.7 (d, J_{PP} = 34.1 Hz). ¹H NMR (CDCl₃, 300 MHz): δ 1.90 (s, 3H, COMe), 1.96 (m, 1H, CH'HCOMe), 2.29 (m, 1H, CH'HCOMe), 2.59 (m, 1H, PCH'H), 2.77 (m, 1H, P¹CH'H), 3.06 (m, 1H, P²CHCH₂), 7.22-7.39 (m, 20H, Ar).

Crystal Structure Determinations of Complexes (R,S)-19a, (R,S)-19b, and (S)-23a. X-ray crystallographic data for all three complexes are given in the Appendices. Crystal data were collected on a Brüker X8 CCD diffractometer with Mo K α radiation (graphite monochromator). SADABS absorption corrections were applied. All non-hydrogen atoms were refined anisotropically, while the hydrogen atoms were introduced at calculated positions and refined with a riding model. The absolute configurations of all chiral complexes were determined unambiguously by using the Flack parameter. We thank Dr Li Yongxin for undertaking the X-ray analysis.

CHAPTER III

Palladacycle-Catalyzed Asymmetric C–P Bond Formation via Hydrophosphination of Enones and Bis(enones)

The past half century has witnessed enormous growth in chiral tertiary phosphines both as highly valuable ligands for transition metal catalysis as well as efficient organocatalysts for enantioselective transformations in organic and organometallic chemistry.^{1,2} Compared with their wide applications in research and in industry, their preparation is much less developed, though some methods for synthesis of chiral phosphines have been developed over the past decades including chiral resolution, transformation from chiral substrates, asymmetric synthesis, and so on (as described in Chapter 1).

From the point of view of “green chemistry” and the “atom efficiency” principle, one of the cleanest routes toward chiral phosphines is the asymmetric hydrophosphination (addition of a P–H bond to unsaturated bonds). Therefore, catalytic asymmetric hydrophosphination for synthesis of chiral phosphines is one of the most attractive methods. However, efficient catalytic asymmetric synthesis of chiral phosphines remains a challenge and is of great significance.

Based on the preliminary results and mechanistic insights achieved in Chapter 2, we explored palladacycle catalyzed asymmetric hydrophosphination for synthesis of chiral phosphines and the results are presented in this chapter. Firstly, several palladacycles were synthesized as potential useful catalysts. Importantly, asymmetric C–P bond formation (including C*–P bond, C*–P* bond, and double C*–P bonds) *via* hydrophosphination catalyzed by palladacycles was developed which is an efficient method for preparation of various kinds of chiral tertiary phosphines.

3-1 Design and Synthesis of Novel Chiral Palladacycle Catalysts

3-1.1 Introduction

The palladacycles containing a covalent metal–carbon σ -bond and a metal-donor atom bond were initially isolated and characterized from the cyclopalladation of azobenzene derivatives in the middle 1960s.⁶³ Since then, numerous publications have been dedicated to their synthesis, structural aspects, and applications in organic and organometallic synthesis, catalysis, and new molecular materials.⁶⁴ Recently, chiral palladacycles with stereogenic center(s) on the auxiliary attracted special interest because they can be used as: (1) efficient resolving reagents for the optical resolution of chiral phosphines, amines, arsines *etc.*;⁶⁵ (2) highly sensitive diamagnetic shift reagents for the determination of enantiomeric purities by NMR spectroscopy;⁶⁶ (3) clear and reliable stereochemical references for the NMR assignments of absolute configurations of new compounds in solution;⁶⁷ (4) highly versatile catalysts and templates for asymmetric transformation reactions.^{45-48,68,69}

Among the chiral palladacycles, complexes **12** and **14**, as well as their derivatives **33** and **15**, are the most commonly used. It has been proven that **14** is superior to **12** in many applications attributed to the conformationally rigid *ortho*-palladated naphthylamine ring.^{43a,b} In complex (*R*)-**14**, the steric interaction between H(8) and the methyl group at the stereogenic carbon center

confines the methyl group in the axial position and hence locks the five-membered ring into stable δ conformation in both solid state and solution. Due to this unique ring conformation, the chirality of the naphthylamine ring is transmitted efficiently *via* its prochiral NMe₂ group onto the neighboring coordination site. However, in complex **12** and its derivative **33**, the five-membered organometallic ring is not locked due to lack of internal steric repulsion. The puckered benzylamine ring undergoes transformation between δ and λ conformations in solution. Upon isolation in the solid state, both the δ and λ conformations were found as diastereomeric mixtures in metal complexes derived from complexes **12** and **33**.

Our group has employed (*S*)- and (*R*)-**14** and their derivatives (*S*)- and (*R*)-**15** as promoters in Diels-Alder,⁴⁵ hydroamination,⁴⁶ hydrophosphination⁴⁷ and hydroarsination reactions⁴⁸ (Scheme 1.24-1.29), as well as catalysts for Claisen rearrangement reaction.⁶⁹ However, in some cases, the reactivity and stereoselectivity has yet to be improved. Therefore, our group has been making efforts to design and synthesize novel chiral palladacycles, with the purpose to tune electronic and steric properties of metal center. As a result, a series of chiral complexes including complexes **34-41** were developed by our group over the past decade.⁴³

Most of these complexes were designed by the modification of aryl group with more steric substituents to improve stereoselectivity for asymmetric reactions. In pursuit of our interest in this scenario, we continue to design and synthesize new chiral palladacycles with new features. Based on the insights from previous studies, we want to retain the naphthyl group which can lock the five member ring and transmit the chiral effect efficiently to the active site around the metal center.

In this section, chiral dimeric palladacycles and their derivatives (Complexes **42** to **47**) with a more sterically demanding substituent on the chiral carbon center or on the nitrogen were designed. In addition, the phosphapallacycle complex **48** derived from the dimeric palladacycle **40** was also prepared with the purpose to tune electronic property on the metal center, as well as steric property. The dimeric complexes are easy to undergo the bridge-cleavage and release a vacant site. And their derivatives have two active sites (occupied by solvents such as NCMe and H₂O). These complexes are

successfully synthesized as potential catalysts for asymmetric transformation reactions.

3-1.2 Results and Discussion

(1) Synthesis of Chiral Complexes (R)-43 and (R)-45

The steric effect is one of the essential factors in the chiral discriminatory ability in complex design. With the aim to improve chiral discriminatory ability, dimeric complexes **42** and **44** with a more steric substituent on the chiral carbon were designed. They were synthesized as racemates, followed by resolution using (*S*)-proline as the resolving reagent. Finally, the resolved dimeric complexes were treated with AgClO_4 to give the optical pure bisacetonitrile complexes **43** and **45**.

1) Synthesis of Racemic Dimeric Complexes ($\pm$) **42** and ($\pm$) **44**

The preparation of *ortho*-palladated racemic complexes is illustrated in Scheme 3.1.1. On the basis of the reported procedure with slight modification,

the corresponding imines **49** and **50** were prepared in high yields by treatment of 1-bromonaphthalene with BuLi and nitriles (^tBuCN and AdCN). Subsequently, the obtained imines **49** and **50** were reduced to the racemic substituted amines (±) **51** and (±) **52** using AlLiH₄ as the reducing agent.⁷⁰ The obtained racemic substituted amines (±) **51** and (±) **52** underwent methylation to form racemic substituted tertiary amines (±) **53** and (±) **54** followed by palladation in presence of NaOAc as a base to give the racemic dimeric *ortho*-palladated complexes (±) **42** and (±) **44**.

Scheme 3.1.1

2) Optical Resolution of Racemic Complexes (±) **42** and (±) **44**

The optical resolution of racemic dimeric complexes (±) **42** and (±) **44** were achieved through the formation and separation of a pair of diastereomeric (*S*)-prolinate derivatives **55**, **56** (Scheme 3.1.2). By treatment of the racemic dimeric complexes (±) **42** and (±) **44** with two molar equivalents of sodium (*S*)-prolinate, the expected diastereomeric adducts [(*R,S*)-**55** vs (*S,S*)-**55**, (*R,S*)-**56** vs (*S,S*)-**56**, respectively] were formed with equal ratio according to ¹H NMR spectroscopy. Successful optical resolution was achieved by fractional crystallization. The less-soluble diastereomers (*R,S*)-**55** and (*R,S*)-**56** were

crystallized in chloroform/diethyl ether, and the other diastereomers (*S,S*)-**55** and (*S,S*)-**56** were crystallized from dichloromethane/diethyl ether. Their absolute configurations were confirmed by X-ray crystal diffractive analysis (Figure 3.1.1 and 3.1.2). Selected bond lengths and angles are given in Table 3.1.1 and Table 3.1.2. The X-ray crystallographic study reveals the substituted group R occupies the expected axial position. The δ conformation for the five-membered ring (*C,N*-ligand metallated with palladium) was found in (*R,S*)-**55** and (*R,S*)-**56**, and λ for (*S,S*)-**55** and (*S,S*)-**56**.

Scheme 3.1.2

Figure 3.1.1 Molecular structure and absolute stereochemistry of complex (*R,S*)-**55** with 50% probability thermal ellipsoids shown. Hydrogen atoms except those on the chiral center are omitted for clarity.

Table 3.1.1 Selected Bond Lengths (Å) and Angles (deg) of (*R,S*)-**55**

Pd1–C1	1.975(6)	Pd1–N1	2.086(5)
Pd1–N2	2.037(5)	Pd1–O1	2.124(4)
C1–C10	1.385(8)	C10–C11	1.514(7)
C11–C12	1.570(8)	C11–N1	1.520(7)
C18–O1	1.278(7)	C18–O2	1.229(7)
C18–C19	1.541(8)	C19–N2	1.501(8)
C19–C20	1.530(8)	C20–C21	1.530(10)
C21–C22	1.484(9)	C12–C13	1.546(8)
C12–C14	1.543(8)	C12–C15	1.533(8)
C1–Pd1–N1	80.8(2)	C1–Pd1–N2	98.1(2)
N2–Pd1–N1	176.5(2)	C1–Pd1–O1	179.2(2)
N2–Pd1–O1	81.2(2)	N1–Pd1–O1	99.9(2)
Pd1–N2–H(N2)	124(5)	C10–C11–N1	103.6(4)
C10–C11–C12	115.9(4)	C10–C11–H11	107.8
N1–C11–H11	107.8	C12–C11–H11	107.8
C12–C13–H13A	109.5	C12–C13–H13B	109.5
C12–C13–H13C	109.5	C11–N1–Pd1	107.1

Figure 3.1.2 Molecular structure and absolute stereochemistry of complex (*R,S*)-**56** with 50% probability thermal ellipsoids shown. Hydrogen atoms except those on the chiral center are omitted for clarity.

Table 3.1.2 Selected Bond Lengths (Å) and Angles (deg) of (*R,S*)-**56**

Pd1–C1	1.967(3)	Pd1–N1	2.066(3)
Pd1–N2	2.043(3)	Pd1–O1	2.112(2)
C1–C10	1.392(4)	C10–C11	1.524(4)
C11–C12	1.581(5)	C11–N1	1.531(4)
C22–N1	1.494(4)	C23–N1	1.482(4)
C24–O1	1.276(4)	C24–O2	1.238(4)
C24–C25	1.533(4)	C25–N2	1.481(4)
C25–C26	1.523(4)	C25–H25	1.000
C26–C27	1.535(6)	C27–C28	1.546(8)
C28–N2	1.477(4)	N2–H2A	0.824(19)
C1–Pd1–N1	81.1(1)	C1–Pd1–N2	100.0(1)
N2–Pd1–N1	177.7(1)	C1–Pd1–O1	179.0(1)
N2–Pd1–O1	80.5(1)	N1–Pd1–O1	98.6(9)
C24–O1–Pd1	113.9(2)	C10–C11–N1	102.5(2)
C10–C11–C12	112.9(3)	C10–C11–H11	108.0
N1–C11–H11	108.0	C12–C11–H11	108.0
C12–C13–H13A	109.5	C12–C13–H13B	109.5
O2–C24–O1	124.1(3)	O2–C24–C25	118.9(3)

In order to further investigate the interaction between the substituent R group and its neighboring groups in solution, 2D ^1H - ^1H ROESY NMR study of compound (*R,S*)-**55** was performed (Figure 3.1.3).

Figure 3.1.3 2D ^1H - ^1H ROESY NMR spectrum of (*R,S*)-**55** in CDCl_3 . Selected ROESY Interactions: (A) H8 - ^tBu ; (B) ^tBu - NMe(eq); (C) H9 - ^tBu .

As shown in the 2D ^1H - ^1H ROESY NMR spectrum of (*R,S*)-**55**, we can

see the strong interaction (**A**) between the ^tBu group and the naphthylene proton (H8). In addition, the ^tBu group also exhibits a strong interaction with the NMe(eq) group (**B**) while no interaction with the NMe(ax) group. Other strong interaction (**C**) between the ^tBu group and H9 was also observed. These interactions confirm that the five-membered ring is locked and the chirality of the naphthylamine ring can be transmitted *via* its NMe₂ group onto the palladium coordination site.

The resolved complexes (*R,S*)-**55**, (*S,S*)-**55**, (*R,S*)-**56** and (*S,S*)-**56** were treated with dilute HCl (1 M) to remove the (*S*)-proline forming the chiral dimeric complexes (*R*)-**42**, (*S*)-**42**, (*R*)-**44** and (*S*)-**44**, respectively. Their absolute configurations were confirmed by X-ray crystal diffractive analysis (Figure 3.1.4 and 3.1.5).

Figure 3.1.4 Molecular structure and absolute stereochemistry of complex (*R,S*)-**42** with 50% probability thermal ellipsoids shown. Hydrogen atoms except those on the chiral center are omitted for clarity.

Table 3.1.3 Selected Bond Lengths (Å) and Angles (deg) of (*R,S*)-**42**

Pd1–C1	1.970(6)	Pd1–N1	2.090(5)
Pd1–Cl1	2.467(2)	Pd1–Cl2	2.344(2)
Pd2–C18	1.976(6)	Pd2–N2	2.087(5)
Pd2–Cl1	2.339(2)	Pd2–Cl2	2.488(2)
C1–C10	1.391(8)	C1–C2	1.423(9)
C10–C11	1.517(8)	C11–N1	1.516(7)
C11–C12	1.570(8)	C27–C28	1.516(8)
C28–C29	1.577(8)	C28–N2	1.527(7)
C1–Pd1–N1	80.6(2)	C1–Pd1–Cl2	96.8(2)
N1–Pd1–Cl2	177.3(2)	C1–Pd1–Cl1	177.0(2)
N1–Pd1–Cl1	96.9(2)	Cl2–Pd1–Cl1	85.6(1)
C18–Pd2–N2	80.0(2)	C18–Pd2–Cl2	178.3(2)
C18–Pd2–Cl1	95.1(2)	N2–Pd2–Cl1	175.0(2)
N2–Pd2–Cl2	99.7(2)	Cl1–Pd2–Cl2	85.3(5)
N1–C11–C10	104.0(4)	N1–C11–C12	117.2(4)
C10–C11–C12	113.3(4)	N1–C11–H11	107.3
C18–C27–C28	116.0(5)	C27–C28–N2	103.5(4)
C26–C27–C28	123.6(5)	N2–C28–C29	116.4(4)

Figure 3.1.5 Molecular structure and absolute stereochemistry of complex (*R,S*)-**44** with 50% probability thermal ellipsoids shown. Hydrogen atoms except those on the chiral center are omitted for clarity.

Table 3.1.4 Selected Bond Lengths (Å) and Angles (deg) of (*R,S*)-**44**

Pd1–C1	1.972(4)	Pd1–N1	2.082(3)
Pd1–Cl1	2.337(1)	Pd1–Cl1A	2.476(1)
C1–C10	1.390(5)	C1–C2	1.417(5)
C10–C11	1.530(5)	C11–N1	1.533(5)
C11–C12	1.575(6)	C11–H11	1.000
C12–C17	1.536(6)	C12–C13	1.561(5)
C12–C21	1.563(5)	C13–C14	1.531(5)
C22–N1	1.482(6)	C23–N1	1.499(6)
C1–Pd1–N1	80.5(2)	C1–Pd1–Cl1	95.8(1)
N1–Pd1–Cl1	176.3(1)	C1–Pd1–Cl1A	177.4(1)
N1–Pd1–Cl1A	97.8(1)	Cl1–Pd1–Cl1A	85.9(3)
C10–C11–Pd1	115.1(3)	C2–C1–Pd1	124.1(3)
C10–C11–N1	103.0(3)	C10–C11–Cl2	113.7(3)
N1–C11–Cl2	116.7(3)	C10–C11–H11	107.7
N1–C11–H11	107.7	C12–C11–H11	107.7
C17–C12–C13	107.5(3)	C17–C12–C21	109.7(3)
N1–C22–H(22A)	109.5	N1–C22–H22B	109.5
N1–C22–H(23A)	109.5	N1–C22–H(23B)	109.5

3) Formation of Bisacetonitrile Complexes (*R*)-43 and (*R*)-45 **Scheme 3.1.3**

The resolved chiral dimeric complexes (*R*)-**42** and (*R*)-**44** were transformed to the bisacetonitrile complexes (*R*)-**43** and (*R*)-**45** by treatment with AgClO₄ in presence of acetonitrile. (*R*)-**43** was successfully crystallized in chloroform/diethyl ether while (*R*)-**45** was failed to crystallize in several solvents we tried. The absolute configuration of (*R*)-**43** was confirmed by X-ray crystal diffractive analysis (Figure 3.6). Selected bond lengths and angles are

given in Table 3.5. Similarly, (*S*)-**42** and (*S*)-**44** can be transformed into (*S*)-**43** and (*S*)-**45**, respectively.

Figure 3.1.6 Molecular structure and absolute stereochemistry of complex (*R*)-**43** with 50% probability thermal ellipsoids shown. Hydrogen atoms except those on the chiral center are omitted for clarity.

Table 3.1.5. Selected Bond Lengths (Å) and Angles (deg) of (*R*)-**43**

Pd1–C1	1.975(2)	Pd1–N1	2.064(1)
Pd1–N2	2.112(2)	Pd1–N3	2.005(2)
C1–C10	1.384(2)	C1–C2	1.416(2)
C10–C11	1.519(2)	C11–N1	1.528(2)
C16–N1	1.489(2)	C17–N1	1.498(2)
C18–N2	1.137(2)	C20–N3	1.143(2)
C18–C19	1.455(2)	C20–C21	1.445(3)
C1–Pd1–N1	81.0(1)	C1–Pd1–N3	93.5(1)
N3–Pd1–N1	173.5(1)	C1–Pd1–N2	178.0(6)
N3–Pd1–N2	88.0(1)	N1–Pd1–N2	97.4(2)
C10–C1–Pd1	114.2(1)	C2–C1–Pd1	125.1(1)
C10–C11–N1	103.5(1)	C10–C11–C12	114.7(1)
N1–C11–C12	115.6(1)	N1–C11–H11	107.5
C16–N1–Pd1	115.7(1)	C17–N1–Pd1	106.6(1)
C11–N1–Pd1	107.2(8)	C18–N2–Pd1	172.0(2)
C20–N3–Pd1	174.5(2)	C16–N1–C17	105.2(1)

(2) Synthesis of Chiral Complex (R_C, S_N)-47

The preparation of *ortho*-Palladated complex (R_C, S_N)-47 was illustrated in Scheme 3.1.4. The chiral naphthylamine (R)-57 which is commercially available condensed with acetone, and reduced by NaBH_4 in one pot to give the secondary amine (R)-58.⁷¹ The secondary amine (R)-58 underwent N-methylation and *ortho*-palladation to form the dimeric complex (R_C, S_N)-46. There are two chiral centers in this complex. One is at the carbon, and the other is at the nitrogen. After the completion of *ortho*-palladation, the product was isolated and its structure was confirmed by X-ray crystal diffractive analysis (Figure 3.1.7). Selected bond lengths and angles are given in Table 3.1.6. (R_C, S_N)-46 was treated with AgClO_4 to form complex (R_C, S_N)-47. The absolute configuration was also confirmed by X-ray crystal diffractive analysis (Figure 3.1.8). Selected bonds and angles were shown in Table 3.1.7.

Scheme 3.1.4

Figure 3.1.7 Molecular structure and absolute stereochemistry of complex (*R,S*)-**46** with 50% probability thermal ellipsoids shown. Hydrogen atoms except those on the chiral center are omitted for clarity.

Table 3.1.6 Selected Bond Lengths (Å) and Angles (deg) of (*R,S*)-**46**

Pd1–C1	1.971(2)	Pd1–N1	2.090(2)
Pd1–Cl1	2.450(1)	Pd1–Cl2	2.352(1)
Pd2–C17	1.966(2)	Pd2–N2	2.104(2)
Pd2–Cl1	2.337(1)	Pd2–Cl2	2.495(1)
C10–C11	1.504(3)	C11–N1	1.509(3)
C11–C12	1.526(3)	C13–N1	1.492(3)
C14–N1	1.533(3)	C14–H14	1.000
C14–C15	1.519(3)	C14–C16	1.525(3)
C1–Pd1–N1	81.2(7)	C1–Pd1–Cl2	96.8(6)
N1–Pd1–Cl2	175.3(1)	C1–Pd1–Cl1	173.0(1)
N1–Pd1–Cl1	97.5(1)	Cl2–Pd1–Cl1	85.0(2)
C17–Pd2–N2	81.6(1)	C17–Pd2–Cl1	94.7(1)
N2–Pd2–Cl2	100.2(1)	Cl1–Pd2–Cl2	84.3(2)
C10–C1–Pd1	113.4(2)	C2–C1–Pd1	127.3(2)

Figure 3.1.8 Molecular structure and absolute stereochemistry of complex (*R,S*)-**47** with 50% probability thermal ellipsoids shown. Hydrogen atoms except those on the chiral center are omitted for clarity.

Table 3.1.7 Selected Bond Lengths (Å) and Angles (deg) of (*R,S*)-**47**

Pd1–C1	1.959(2)	Pd1–N1	2.068(2)
Pd1–N2	2.016(2)	Pd1–O1	2.191(2)
C1–C10	1.390(3)	C10–C11	1.506(3)
C11–N1	1.522(2)	C11–C12	1.524(3)
C13–N1	1.492(2)	C14–N1	1.522(3)
C14–C15	1.527(3)	C14–C16	1.528(3)
C17–N2	1.131(3)	C17–C18	1.464(3)
O1–H1O	0.73(2)	O1–H2O	0.71(2)
C1–Pd1–N1	82.5(1)	C1–Pd1–N2	94.7(1)
N2–Pd1–N1	176.0(1)	C1–Pd1–O1	175.3(1)
N2–Pd1–O1	93.6(1)	C10–C1–C2	119.6(2)
C10–C1–Pd1	113.7(2)	C2–C1–Pd1	126.7(2)
N1–C14–C15	113.1(2)	N1–C14–C16	111.4(2)
C13–N1–C11	110.6(2)	C13–N1–C14	110.4(2)

(3) Synthesis of Chiral Complex (R)-48

Leung *at al.* previously reported the synthesis of the dimeric phosphapalladacycle (R)-40.^{43c} It was expected that its derivative (R)-48 with two active sites on the palladium may be more interesting and a good candidate catalyst for asymmetric transformation reactions. With this aim, we synthesized it by treatment of (R)-40 with AgClO₄ in the presence of acetonitrile (Scheme 3.1.5). The absolute configuration of (R)-48 was confirmed by X-ray crystal diffractive analysis (Figure 3.1.9). Selected bond lengths and angles are given in Table 3.1.8. Similarly, the equally available complex (S)-48 can be obtained from (S)-40 by the same method.

Scheme 3.1.5

Figure 3.1.9 Molecular structure and absolute stereochemistry of complex (*R*)-**48** with 50% probability thermal ellipsoids shown. Hydrogen atoms except those on the chiral center and anion are omitted for clarity.

Table 3.1.8 Selected Bond Lengths (Å) and Angles (deg) of (*R*)-**48**

Pd1–C1	2.009(2)	Pd1–N1	2.107(2)
Pd1–P1	2.218(1)	Pd1–N2	2.125(2)
C1–C10	1.394(3)	C10–C11	1.517(3)
C11–C12	1.529(3)	C11–P1	1.838(2)
P1–C13	1.811(2)	P1–C19	1.813(2)
C25–N1	1.133(3)	C25–C26	1.460(4)
C27–N2	1.132(3)	C27–C28	1.464(4)
C1–Pd1–N1	177.2(1)	C1–Pd1–N2	94.7(1)
N1–Pd1–N2	87.5(1)	C1–Pd1–P1	78.5(1)
N1–Pd1–P1	99.3(1)	N2–Pd1–P1	172.9(1)
C13–C14–P1	122.6(2)	C18–C13–P1	118.7(2)
C25–N1–Pd1	175.1(2)	C27–N2–Pd1	177.3(2)
C13–P1–C19	104.8(1)	C13–P1–C11	110.9(1)
C19–P1–C11	107.0(1)	C13–P1–Pd1	116.3(1)
C19–P1–Pd1	115.7(1)	C11–P1–Pd1	102.0(1)

3-1.3 Conclusion

We designed several novel chiral palladacycle complexes based on the previous studies. The racemic dimeric complexes **42** and **44** were synthesized from 1-bromonaphthalene and relative nitriles in 4 steps in high yields: condensation, reduction, methylation and palladation. Subsequently, the racemic dimeric complexes **42** and **44** were efficiently resolved using (*S*)-proline as the resolving reagent to give the enantiomerically pure dimeric complexes **42** and **44**. The dimeric complexes **42** and **44** can be derived to complexes **43** and **45** by treating with AgClO₄. Chiral complex (*R,S*)-**47**, with two chiral centers at carbon and nitrogen respectively, was synthesized from the commercially available chiral amine (*R*)-**57** without resolution. In addition, an chiral phosphapalladacycle **48** was also prepared from the reported dimeric complex (*R*)-**40**. These chiral palladacycle complexes with two active sites around the metal are potential catalysts for asymmetric transformation reactions.

3-1.4 Experimental Section

All air-sensitive manipulations were performed under a positive pressure of argon using standard Schlenk line. Solvents were dried and degassed prior to use when necessary. NMR spectra were recorded at 25 °C on Brüker ACF 300, 400 and 500 spectrometers. Chemical shifts are reported in δ ppm referenced to an internal SiMe₄ standard (δ = 0 ppm) for ¹H NMR, chloroform-d (δ = 77.23

ppm) for ^{13}C NMR and to an external 85% H_3PO_4 standard for $^{31}\text{P}\{^1\text{H}\}$ NMR.

Optical rotations were measured on the specified solution in a 0.1 dm cell at 20 °C with a Perkin-Elmer 341 polarimeter. Melting points were measured using the SRS Optimelt Automated Melting Point System, SRS MPA100.

Compounds ($\pm$) **51**, ($\pm$) **52** were prepared according to literature with slight modification.⁷⁰ Chiral amine (*R*)-**58** was prepared according to literature with slight modification.⁷¹

Caution! *Perchlorate salts of metal complexes are potentially explosive compounds and should be handled with care.*

Synthesis of racemic amine ($\pm$) **53**

($\pm$) **53**

The compound ($\pm$) **53** (9.6 g, 45.8 mmol) was dissolved in formic acid (20 mL) and then treated with formaldehyde (35%, 40 mL). The reaction mixture was heated to 107 °C for 10 h. The mixture was cooled to room temperature and treated with concentrated HCl (2 mL). The excess formic acid and formaldehyde were removed under vacuum. The residue was dissolved in dichloromethane, treated with dilute sodium hydroxide (5 M, 15 mL), washed by water, and dried over MgSO_4 . The solvent was removed under reduced pressure to give the product as colorless oil, 10.1 g (93 %). HRMS (ESI): calcd for $\text{C}_{17}\text{H}_{24}\text{N}$ $[\text{M}+\text{H}]^+$ 242.1909; found 242.1913. ^1H NMR (CDCl_3 , 300 MHz): δ 1.12 (s, 9H, CMe_3), 2.33 (s, 6H, NMe_2), 4.32 (s, 1H, CHNMe_2), 7.44-8.30 (m, 7H, Ar). ^{13}C NMR (CDCl_3 , 75 MHz): δ 29.4 (s, 3C, CMe_3), 36.8 (s, 1C,

CHCMe₃), 45.6 (s, 2C, NMe₂), 70.0 (s, 1C, CMe₃), 124.0-136.1 (m, 10C, Ar).

Synthesis of racemic amine (±) **54**

(±) **54** The same procedure as the above was used to prepare the title compound (±) **54** (8.5g, 91%) from (±) **52** (8.5 g, 29.2 mmol). Mp: 89–92 °C. HRMS (ESI): calcd for C₂₃H₃₀N [M+H]⁺ 320.2378; found 320.2380. ¹H NMR (CDCl₃, 400 MHz): δ 1.63 (m, 12H, Ad, broad), 1.96 (m, 3H, Ad, broad), 2.30 (s, 6H, NMe₂), 7.44-8.26 (m, 7H, Ar). ¹³C NMR (CDCl₃, 100 MHz): δ 29.0 (s, 4C, Ad), 37.3(s, 3C, Ad), 40.9 (s, 3C, Ad), 45.4 (s, 2C, NMe₂), 71.1 (s, 1C, CMe₃), 124.1-134.7 (m, 10C, Ar).

Synthesis of racemic dimeric complex (±) **42**

(±) **42** A mixture of palladium(II) chloride (3.7 g, 20.7 mmol) and lithium chloride (3.5 g, 82.8 mmol) in methanol (50 mL) was stirred at room temperature for 3 h. Sodium acetate trihydrate (3.4 g, 24.8 mmol) was then dissolved into the solution followed by addition of the racemic amine (±) **53** (5.0 g, 20.7 mmol). The resulting mixture was stirred at room temperature for 10 h and then filtered. The residue was dissolved dichloromethane, and filtered through Celite. The filtrate was dried over MgSO₄ and evaporated under vacuum to give the crude product (±) **42**. The crude product was purified by chromatography (silica gel; dichloromethane/hexane = 1:1) to afford (±) **42** (7.4

(*S,S*)-**55**

The previously described mother liquor of (*R,S*)-**55** was evaporated to dryness, and the residue was dissolved in dichloromethane. The addition of Et₂O to the solution resulted in the precipitation of the other diastereomer (*S,S*)-**55**, in the form of pale-yellow prisms: 1.8 g (78%, based on half of the mixture used). [α]_D = +205.1 (*c* 1.2, CH₂Cl₂). Mp: 187–189°C. Anal. Calcd for C₂₂H₃₀N₂O₂Pd: C, 57.3; H, 6.6; N, 6.1. Found: C, 57.6; H, 6.8; N, 6.0. ¹H NMR (CDCl₃, 300 MHz): δ 1.31 (s, 9H, *t*Bu), 1.78 (m, 1H, CH₂), 1.97 (m, 1H, CH₂), 2.27 (m, 1H, CH₂), 2.36 (m, 1H, CH₂), 2.63 (s, 3H, NMeMe), 2.96 (s, 3H, NMeMe), 3.31 (m, 1H, CH₂), 3.47 (m, 1H, CH₂), 4.13 (m, 2H, NH, CHCMe₃, overlap), 5.25 (m, 1H, CHCO₂), 7.29–7.70 (m, 6H, Ar). ¹³C NMR (CDCl₃, 75 MHz): δ 25.8 (s, 1C, CH₂), 30.6 (s, 3C, CMe₃), 30.8 (s, 1C, CH₂), 36.2 (s, 1C, CMe₃), 50.6 (s, 1C, NMeMe), 53.7 (s, 1C, CH₂), 55.7 (s, 1C, NMeMe), 65.1 (s, 1C, CHCO₂), 85.2 (s, 1C, CHNMe₂), 123.7–147.9 (m, 10C, Ar), 182.0 (s, 1C, CO₂).

Synthesis of *ortho*-palladated (*R,S*)-**56**

(*R,S*)-**56**

A solution of sodium proline (1.2 g, 10.5 mmol) in methanol (10 mL) was added to the racemic dimer ($\pm$) **44** (4.8 g, 5.2 mmol), which was suspended in the same solvent (20 mL). The mixture was stirred at room temperature for 5 h, and the solvent was removed under reduced pressure.

The residue was dissolved in dichloromethane (100 mL), washed with water (15 mL x 2), and dried over MgSO₄, and then the solvent was removed to give the diastereomeric mixture in the form of pale-yellow powder (5.3 g, 95%). The addition of Et₂O to the solution of this diastereomeric mixture in chloroform slowly precipitated the less-soluble diastereomer (*R,S*)-**56** in the form of pale-yellow flakes: 2.2 g (83%, based on half of the mixture used). [α]_D = +21.3 (*c* 1.2, CH₂Cl₂). Mp: 204–206 °C. Anal. Calcd for C₂₈H₃₆N₂O₂Pd: C, 62.4; H, 6.7; N, 5.2. Found: C, 62.6; H, 6.4; N, 5.0. ¹H NMR (CDCl₃, 400 MHz): δ 1.55 (m, 6H, Ad, overlap), 1.79 (m, 7H, CH₂, Ad, overlap), 2.04 (m, 1H, CH₂), 2.33 (m, 5H, CH₂, Ad, overlap), 2.60 (s, 3H, NMeMe), 3.03 (s, 3H, NMeMe), 3.32 (m, 1H, CH₂), 3.45 (m, 1H, CH₂), 3.94 (s, 1H, CHCMe₃), 4.13 (m, 1H, CHCO₂), 4.71 (m, 1H, NH), 7.20–7.73 (m, 6H, Ar). ¹³C NMR (CDCl₃, 100 MHz): δ 25.9 (s, 1C, CH₂), 28.9, 30.9, 36.7, 38.4, 41.2 (Ad), 51.5 (s, 1C, NMeMe), 53.9 (s, 1C, CH₂), 56.1 (s, 1C, NMeMe), 65.2 (s, 1C, CHCO₂), 86.1 (d, 1C, CHNMe₂), 123.5–147.9 (m, 10C, Ar), 181.7 (s, 1C, CO₂).

Synthesis of *ortho*-palladated (*R*)-**43**

(*R*)-**43**

The dimeric complex (*R*)-**42** (1.50 g, 1.96 mmol) was dissolved in dichloromethane (80 mL) and acetonitrile (5 mL) at room temperature. A solution of AgClO₄ (0.61 g, 2.34 mmol, 1.5 equiv) in H₂O (2 mL) was added. The mixture was stirred vigorously in dark for 1 h and then filtered through Celite, washed with H₂O, dried over MgSO₄, and subsequently crystallized from CH₂Cl₂(or CHCl₃)-Et₂O to give the product (*R*)-**43** as pale

yellow prisms (1.88 g, 91% yield). $[\alpha]_D = -108.8$ (c 1.0, CH_2Cl_2). Mp: 167–169 °C (dec). Anal. Calcd for $\text{C}_{21}\text{H}_{28}\text{ClN}_3\text{O}_4\text{Pd}$: C, 47.7; H, 5.3; N, 8.0. Found: C, 47.9; H, 5.5; N, 8.3. ^1H NMR (CDCl_3 , 400 M): δ 1.36 (s, 9H, ^tBu), 2.41 (s, 3H, NCMe), 2.56 (s, 3H, NCMe), 2.80 (s, 3H, NMe), 2.94 (s, 3H, NMe), 4.21 (s, 1H, CH^tBu), 7.11–7.76 (m, 6H, Ar); ^{13}C NMR (CDCl_3 , 100 M): δ 30.5 (s, 3C, ^tBu), 36.3 (s, 1C, C^tBu), 52.0 (s, 1C, NMe), 56.8 (s, 1C, NMe), 87.2 (s, 1C, CHNMe_2), 120.2–145.2 (m, 10C, Ar).

Synthesis of *ortho*-palladated (*R*)-43

(*R*)-45

The same procedure as the above was used to prepare the racemic amine (*R*)-45 (80%) from (*R*)-44. $[\alpha]_D = -91.5$ (c 1.0, CH_2Cl_2). Mp: 174–177 °C (dec). Anal. Calcd for $\text{C}_{27}\text{H}_{34}\text{ClN}_3\text{O}_4\text{Pd}$: C, 53.5; H, 5.7; N, 6.9. Found: C, 53.9; H, 5.5; N, 6.7. ^1H NMR (CDCl_3 , 400 M): δ 1.47, 1.63, 1.66, 1.84, 2.26, 2.29, 2.32, 2.45, 2.58, 2.89 (Ad, NMe_2 , NCMe , overlap), 3.96 (s, CHAd), 7.06–7.66 (m, 6H, Ar). ^{13}C NMR (CDCl_3 , 100 M): δ 28.1, 30.5, 35.9, 37.7, 40.1, 52.4, 53.5, 56.4, (Ad, NMe_2), 87.2 (s, 1C, CHNMe_2), 119.8–143.8 (m, 10C, Ar).

Synthesis of chiral amine (*R*)-59

(*R*)-59

The compound (*R*)-58 (6.4 g, 30.0 mmol) was dissolved in formic acid (3.5 g, 75 mmol) and then treated with formaldehyde (6.4 g, 35 %, 75 mmol). The reaction mixture was heated to 107 °C for 10 h. The mixture was cooled to room temperature and treated with concentrated hydrochloric acid (2 ml). The excess formic acid and formaldehyde were removed under vacuum. The residue was dissolved in dichloromethane, treated with dilute sodium

hydroxide (5 M, 15 mL), washed by water, and dried over MgSO₄. The solvent was removed under reduced pressure to give the product as colorless oil, 6.3 g (92 %): $[\alpha]_D = +49.3$ (*c* 1.5, CH₂Cl₂). Anal. Calcd for C₁₆H₂₁N: C, 84.5; H, 9.3; N, 6.2. Found: C, 84.6; H, 9.4; N, 6.0. ¹H NMR (CDCl₃, 400 MHz): δ 0.93 (d, 3H, *J* = 6.5 Hz, CH(CH₃)CH₃), 1.00 (d, 3H, *J* = 6.6 Hz, CH(CH₃)CH₃), 1.44 (d, 3H, *J* = 6.6 Hz, CHCH₃), 2.20 (s, 3H, NCH₃), 3.01 (m, 1H, CH(CH₃)CH₃), 4.33 (m, 1H, CHCH₃), 7.39-8.52 (m, 7H, Ar). ¹³C NMR (CDCl₃, 100 MHz): δ 16.4 (s, 1C, CHCH₃), 19.3 (s, 1C, CH(CH₃)CH₃), 20.7 (s, 1C, CH(CH₃)CH₃), 31.8 (s, 1C, NCH₃), 49.2 (s, 1C, CH(CH₃)CH₃), 59.5 (s, 1C, CHCH₃), 124.4-142.3 (m, 10C, Ar).

Synthesis of chiral dimeric complex (*R,S*)-**46**

A mixture of palladium(II) chloride (5.3 g, 29.5 mmol) and lithium chloride (5.0 g, 118.0 mmol) in methanol (50 mL) was stirred at room temperature for 3 h. Sodium acetate trihydrate (4.5 g, 32.5 mmol) was then dissolved into the solution followed by addition of the chiral amine (*R*)-**59** (6.7 g, 29.5 mmol). The resulting mixture was stirred at room temperature for 10 h and then filtered. The residue was dissolved dichloromethane, and filtered through Celite. The filtrate was dried over MgSO₄ and evaporated under vacuum to give the crude product (*R,S*)-**46**. The crude product was purified by chromatography (silica gel; dichloromethane/hexane = 1:2), and crystallized from dichloromethane-diethyl ether to afford (*R,S*)-**46** as pale yellow prisms

(9.8 g, 90%). The dimeric (*R,S*)-**46** is the mixture of *cis* and *trans* isomers. $[\alpha]_D = -132.2$ (*c* 1.2, CH₂Cl₂). Mp: 189–192 °C. Anal. Calcd for C₃₂H₄₀Cl₂N₂Pd₂: C, 52.2; H, 5.5; N, 3.8. Found: C, 51.9; H, 5.8; N, 3.7. ¹H NMR (CDCl₃, 300 MHz): δ 1.06 (m, 3H, CHCH₃), 2.02 (m, 6H, CH(CH₃)CH₃), 2.60 (d, 3H, NCH₃), 3.34 (m, 1H, CH(CH₃)CH₃), 4.63 (m, 1H, CHCH₃), 7.30-7.78 (m, 6H, Ar). ¹³C NMR (CDCl₃, 75 MHz): δ 15.2 (s, 1C, CHCH₃), 22.8 (s, 1C, CH(CH₃)CH₃), 24.7 (d, 1C, CH(CH₃)CH₃), 39.0 (d, 1C, NCH₃), 60.4 (s, 1C, CH(CH₃)CH₃), 68.2 (d, 1C, CHCH₃), 122.9-147.8 (m, 10C, Ar).

Synthesis of chiral dimeric complex (*R,S*)-**47**

(*R,S*)-**47**

The dimeric complex (*R*)-**46** (1.5 g, 2.0 mmol) was dissolved in dichloromethane (80 mL) and acetonitrile (5 mL) at room temperature. A solution of AgClO₄ (0.42 g, 3.0 mmol, 1.5 equiv) in H₂O (2 mL) was added. The mixture was stirred vigorously in dark for 1 h and then filtered through Celite, washed with H₂O, dried over MgSO₄, and subsequently crystallized from CHCl₃-Et₂O to give the product (*R,S*)-**47** as pale yellow prisms (1.9 g, 91% yield). $[\alpha]_D = -89.8$ (*c* 1.1, CH₂Cl₂). Mp: 160–163 °C. Anal. Calcd for C₁₈H₂₅ClN₂O₅Pd: C, 44.0; H, 5.1; N, 5.7. Found: C, 44.3; H, 4.9; N, 5.8. ¹H NMR (CDCl₃, 300 MHz): δ 1.06 (m, 3H, CHCH₃), 2.02 (m, 6H, CH(CH₃)CH₃), 2.60 (d, 3H, NCH₃), 3.34 (m, 1H, CH(CH₃)CH₃), 4.63 (m, 1H, CHCH₃), 7.30-7.78 (m, 6H, Ar). ¹³C NMR (CDCl₃, 75 MHz): δ 15.2 (s, 1C, CHCH₃), 22.8 (s, 1C, CH(CH₃)CH₃), 24.7 (d, 1C, CH(CH₃)CH₃), 39.0 (d, 1C, NCH₃),

60.4 (s, 1C, CH(CH₃)CH₃), 68.2 (d, 1C, CHCH₃), 122.9-147.8 (m, 10C, Ar).

Synthesis of chiral complex (*R*)-48

The dimeric complex (*R*)-40 (1.50 g, 1.56 mmol) was dissolved in dichloromethane (80 mL) and acetonitrile (5 mL) at room temperature. A solution of AgClO₄ (0.48 g, 2.34 mmol, 1.5 equiv) in H₂O (2 mL) was added. The mixture was stirred vigorously in dark for 1 h and then filtered through Celite, washed with H₂O, dried over MgSO₄, and subsequently crystallized from CH₂Cl₂(or CHCl₃)-Et₂O to give the product (*R*)-27 as pale yellow prisms (1.78 g, 91% yield). [α]_D = −495.1 (*c* 1.0, CHCl₃). Mp: 205–207 °C (dec). Anal. Calcd for C₂₈H₂₆ClN₂O₄PPd: C, 53.6; H, 4.2; N, 4.5. Found: C, 53.3; H, 4.3; N, 4.7. ³¹P NMR(CDCl₃, 121 M): δ 63.4; ¹H NMR (CDCl₃, 300 M): δ 1.49 (dd, 3H, *J* = 19.3 Hz, 7.1 Hz, CHCH₃), 2.37–3.00 (6H, NMe), 4.57 (m, 1H, CHCH₃), 7.32–7.58 (m, 16H, Ar); ¹³C NMR (CDCl₃, 75 M): δ 20.4 (d, 1C, ²*J*_{PC} = 2.8 Hz, CHCH₃), 44.2 (d, 1C, ¹*J*_{PC} = 39.4 Hz, CHCH₃), 124.4–147.1 (m, 22C, Ar).

3-2 Palladacycle-Catalyzed Asymmetric C*-P Bond Formation *via* Hydrophosphination of Enones with Ph₂PH

3-2.1 Introduction

While more and more efficient chiral diphosphines both as valuable ligands for metal catalysis and as organocatalysts have been discovered and applied in organic and organometallic chemistry,^{1,2} the development of chiral monophosphine for asymmetric reactions is slow.⁷² However, this does not mean that monophosphines cannot be as effective as diphosphines for asymmetric reactions. It has been found that some chiral monophosphines with stereogenic center(s) at phosphorus or side chain can be efficiently applied in asymmetric catalysis. For example, the chiral monophosphine (*S*)-**53** can efficiently catalyze the [3+2] cycloaddition reaction between allenes (or alkynes) and olefins with up to 98% yield and 99% ee (Scheme 3.2.1).^{2c,g}

Scheme 3.2.1

Despite their importance, to date, chiral phosphines are prepared dominantly either by tedious resolution or by the use of stoichiometric

amounts of chiral auxiliaries or enantiomerically pure substrates.^{73,74} Though a few methods of catalytic asymmetric synthesis of chiral phosphines have been reported *via* asymmetric C–P bond formation which includes phosphination of alkylhalogens, arylhalogens, and allylic acetates with secondary phosphines (alkylation and arylation of secondary phosphines),^{33,34} and hydrophosphination (addition of secondary phosphines to unsaturated bonds).³² Among the catalytic methods, asymmetric hydrophosphination, the stereocontrolled addition of a P–H bond to unsaturated C–C bonds, is one of the most efficient and desired protocols which provides direct, atom-economic and “green” access to the desired chiral phosphines. During the past decades, a few strategies of catalytic asymmetric hydrophosphination for synthesis of chiral tertiary phosphines including C-stereogenic or P-stereogenic phosphines have been developed. Glueck and co-workers reported Pt^0 -(Me-Duphos)- and Pt^0 -(diphos) complex-catalyzed hydrophosphination of vinyl esters and vinyl nitriles (Scheme 3.2.2):⁷⁵

Scheme 3.2.2

Togni and co-workers reported Ni^{II} complex catalyzed hydrophosphination of methacrylonitrile (Scheme 3.2.3):⁷⁶

Scheme 3.2.3

Cordova and Melchiorre reported organocatalyst-catalyzed hydrophosphination of nitroalkenes and α,β -unsaturated aldehydes (Scheme 3.2.4 and 3.2.5):⁷⁷

Scheme 3.2.4

Scheme 3.2.5

However, most of the reported methods suffered, more or less, from some drawbacks such as low stereoselectivity, low reactivity (excess hydrophosphinating reagents were required), and narrow substrate scope. Above all, phosphine-oxides, phosphine-sulphides or phosphine-boranes were obtained instead of tertiary phosphines in most cases due to their air sensitivity which makes them difficult to handle and purify. In terms of the use for transition metal catalysis or organocatalysts, enantiomerically pure tertiary phosphines are preferred rather than these oxides, sulphides or boranes. Conversion of these phosphine adducts to tertiary phosphines frequently involves strong reaction conditions and low yields. Therefore, it is our judgment that it is desirable to generate tertiary phosphines directly from a catalytic process. To the best of our knowledge, no catalytic method existed for straightforward access to enantiomerically pure tertiary phosphines.

Based on previous work in the area of asymmetric hydrophosphination promoted by palladacycles, in this section, we explored palladacycle-catalyzed asymmetric hydrophosphination of enones. Chiral monophosphines with stereogenic center at carbon were prepared in high yields with excellent enantioselectivities when Ph_2PH was employed as a hydrophosphinating reagent ($\text{C}^*\text{-P}$ bond formation) (eq 1). These chiral monophosphine products were purified to be enantiomerically pure *via* a single re-crystallization or just washing by a solvent.

When we were preparing the manuscript of the asymmetric hydrophosphination of enones with Ph_2PH for publication, Duan *et al.* reported a similar hydrophosphination reaction catalyzed by a pincer complex (Scheme 3.2.6):⁷⁸

Scheme 3.2.6

Very recently, Gong and Song *et al.* reported a modified pincer complex and its application in the same reaction (Scheme 3.2.6):⁷⁹

Scheme 3.2.7

3-2.2 Results and Discussion

The asymmetric hydrophosphination of allenes was successfully promoted by a chiral palladium complex to prepare 1,2-diphosphines (Chapter 2), however, stoichiometric amounts of palladium complex was used. We

planned to explore whether the palladium complex can be used as a catalyst for asymmetric hydrophosphination reactions. Based on the preliminary studies, we found that 1,2-diphosphines form stable chelating complexes with palladium which makes it difficult to release free phosphine products. Therefore the palladium complex was needed in stoichiometric quantity. To avoid this problem, we hence aimed at the synthesis of monophosphines (eq 1) because they will not chelate with metals which makes the catalytic cycle possible.

(1) Screening of Reaction Conditions

Initially, we employed the palladium complex (*R*)-**15** as the catalyst and chose cinnamaldehyde ($R^1 = \text{Ph}$, $R^2 = \text{H}$) as the substrate for the hydrophosphination reaction, but it showed no reactivity under the conditions described in Table 3.2.1. Then we tried methyl cinnamate ($R^1 = \text{Ph}$, $R^2 = -\text{OMe}$) and 4-phenyl-3-buten-2-one ($R^1 = \text{Ph}$, $R^2 = \text{Me}$), but failed again. Finally we tried *trans*-chalcone ($R^1 = R^2 = \text{Ph}$). To our delight, it showed good reactivity and selectivity under the same conditions. The reaction was conveniently monitored by $^{31}\text{P}\{^1\text{H}\}$ NMR spectroscopy. The enantiomeric excess (ee) value was determined from $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum of the diastereomers which resulted from treatment of the phosphine products with an enantiomerically pure chiral palladium complex (*R*)-**14** containing an chiral naphthyl amine auxiliary.⁷⁶ X-ray crystal diffraction analysis of the corresponding diastereomers revealed that the absolute configurations of the major and minor

products on the chiral carbon centre were *S* and *R*, respectively (For more details, see experimental section).

Encouraged by the result, we then screened the conditions including solvent, temperature, base and catalyst effects for the hydrophosphination reaction and the results are given in Table 3.2.1. In presence of 5 mol% of complex (*R*)-**15** as the catalyst, the results of solvent screening (Table 3.2.1, entries 1-6) showed that THF is the best one for the hydrophosphination reaction. Good selectivity was also achieved in acetone, toluene and dichloromethane. We further surveyed the temperature effect. As temperature was raised from $-80\text{ }^{\circ}\text{C}$ to $-40\text{ }^{\circ}\text{C}$ and $20\text{ }^{\circ}\text{C}$, ee value dropped from 77% to 74% and 51%, respectively (entries 4, 7, 8). Base also plays an important role in the reaction. In the absence of base, there is no reaction at all at $-80\text{ }^{\circ}\text{C}$, and only half conversion was observed at room temperature after 8 days. The results of screening of bases showed that Et_3N is the appropriate choice. It can be removed under vacuum which contributed to obtaining clean products. Higher temperature is necessary if DBU is used as a base with associated low ee (22% ee). If $t\text{BuOK}$ (solution in THF) is used as a base, the reaction is completed very fast, but the selectivity is quite low (16% ee). The amount of catalyst loading, as well as the amount of base, has little effect on selectivity, but impacts the rate of the reaction. Longer time is required to complete the reaction decreasing catalyst loading.

Table 3.2.1 Catalyst, solvent, base, and temperature effects on the reaction of Ph₂PH and *trans*-chalcone^a

Entry	Cat	Solvent	Temp (°C)	Base	ee ^b (%)
1	(<i>R</i>)- 15	DCM	−80	Et ₃ N	62
2	(<i>R</i>)- 15	Acetone	−80	Et ₃ N	68
3	(<i>R</i>)- 15	Toluene	−80	Et ₃ N	68
4	(<i>R</i>)- 15	THF	−80	Et ₃ N	77
5	(<i>R</i>)- 15	CHCl ₃	−40	Et ₃ N	49
6	(<i>R</i>)- 15	NCMe	−40	Et ₃ N	31
7	(<i>R</i>)- 15	THF	−40	Et ₃ N	74
8	(<i>R</i>)- 15	THF	20	Et ₃ N	51
9	(<i>R</i>)- 15	THF	20	none	49 ^c
10	(<i>R</i>)- 15	THF	−80 to 20	DBU	27
11	(<i>R</i>)- 15	THF	−80	^t BuOK	16
12	(<i>R</i>)- 60	THF	20	Et ₃ N	−25
13	(<i>R</i>)- 33	THF	−80	Et ₃ N	—
14	(<i>R</i>)- 39	THF	−80 to 20	Et ₃ N	31
15	(<i>R</i>)- 38	THF	−80 to 20	Et ₃ N	13
16	(<i>R</i>)- 36	THF	−80 to 20	Et ₃ N	5
17	(<i>R</i>)- 43	THF	−80 to 20	Et ₃ N	−38
18	(<i>R</i>)- 45	THF	−80 to 20	Et ₃ N	—
19	(<i>R</i>)- 47	THF	−80 to 20	Et ₃ N	15
20	(<i>R</i>)- 48	THF	−80	Et ₃ N	99

^a Conditions: 0.35 mmol Ph₂PH, 5 mol % of Cat, 1.0 equiv of *trans*-chalcone, 0.5 equiv of base were reacted at the given temperature. The reaction was stopped till full conversion of Ph₂PH, unless otherwise noted. ^b ee was determined from ³¹P{¹H} NMR integration of the signals.

With the optimized condition of solvent, base, and temperature established, we then screened a serial of catalysts (entries 12-20). It was found that the *C,N*-complexes with mild to bad selectivities are not the ideal catalysts for the hydrophination reaction. Especially those bearing more bulky substitution showed lower reactivity. In cases where the reactivity is not satisfactory, we raised the temperature gradually to room temperature. However, the back ground reaction occurred leading to low selectivity. Finally, when the phosphapalladacycle complex (R)-48 was employed as the catalyst, to our delight, excellent selectivity (99% ee) and reactivity (full conversion) at –80 °C were achieved (entry 20).

(2) Substrate Scope

With the optimal conditions established, a range of aromatic enones were screened for the asymmetric hydrophosphination reaction catalyzed by (R)-48. The results are presented in Table 3.2.2.

Table 3.2.2. Substrate scope of the (*R*)-**48**-catalyzed enantioselective hydrophosphination of enones with Ph₂PH^a

Entry	R ¹	R ²	Time (h)	62	Yield ^b (%)	ee ^c (%)
1	Ph	Ph	2	62a	99 (90)	98 (>99)
2	4-NO ₂ C ₆ H ₄	Ph	2	62b	99 (89)	98 (>99)
3	3-NO ₂ C ₆ H ₄	Ph	8	62c	99 (85)	96 (>99)
4	4-BrC ₆ H ₄	Ph	5	62d	99 (89)	98 (>99)
5	4-ClC ₆ H ₄	Ph	4	62e	99 (90)	98 (>99)
6	4-FC ₆ H ₄	Ph	5	62f	99 (91)	99 (>99)
7	4-CF ₃ C ₆ H ₄	Ph	2	62g	99 (91)	96 (>99)
8	4-MeC ₆ H ₄	Ph	12	62h	99 (90)	99 (>99)
9	4-MeOC ₆ H ₄	Ph	30	62i	99 (92)	99 (>99)
10		Ph	30	62j	99 (90)	98 (>99)
11	2-Naph	Ph	7	62k	99 (91)	99 (>99)
12	2-Naph	4-FC ₆ H ₄	7	62l	99 (89)	97 (>99)
13	Ph	2-Naph	24	62m	98 (90)	98 (>99)
14	Ph	4-BrC ₆ H ₄	6	62n	99 (88)	96 (>99)
15	Ph	4-ClC ₆ H ₄	4	62o	99 (89)	97 (>99)
16	Ph	4-FC ₆ H ₄	6	62p	99 (90)	97 (>99)
17	Ph	2-Pyridinyl	20	62q	99 (71)	92 (>99)
18 ^d	Ph	4-MeOC ₆ H ₄	40	62r	98 (88)	98 (>99)
19	4-FC ₆ H ₄	4-ClC ₆ H ₄	5	62s	99 (90)	97 (>99)
20	4-ClC ₆ H ₄	4-FC ₆ H ₄	4	62t	99 (90)	98 (>99)

^a Conditions: 0.30 mmol Ph₂PH, 5 mol % of Cat, 5 ml THF, 1.0 equiv. of enone, 0.5 equiv. of Et₃N were reacted at –80 °C, unless otherwise noted. ^b Yield was calculated from ³¹P{¹H} NMR. In parentheses are the yields of isolated products after a single recrystallization. ^c ee was determined from ³¹P{¹H} NMR integration of the signals. In parentheses are the ee's after a single recrystallization. ^d 1.1equiv of enone was used.

The results given in Table 3.2.2 showed that the reaction proceeded to full conversion of Ph₂PH under the given conditions, allowing the transformation of a wide range of aromatic enone substrates to the chiral phosphine products. The process tolerates a broad range of functional groups such as nitro, halogens (F, Cl, Br), trifluoromethyl, alkyl, methoxy, pyridinyl and naphthyl *etc.* Both electron withdrawing and electron donating group substituted aromatic enones are suitable substrates and provide nearly quantitative yields and excellent enantioselectivities. Those bearing electron withdrawing groups (entries 2 to 7) are more reactive than those bearing electron donating groups (entries 8 to 10). As far as substituents on R¹ (R¹ = NO₂, for example) are concerned, *p*-substituted enones showed best reactivity and selectivity (entry 2, 98% ee) followed by the *m*-substituted (entry 3, 96% ee), and the *o*-substituted is the worst (91% ee).⁸⁰ Those with substituent on R¹ showed a little better reactivity and selectivity (entry 4, for example) compared with those with the same substituent on R² (entry 14, for example). It is worth to highlight that enantiomerically pure phosphine products can thus be obtained by a single re-crystallization or just washing with cold acetone using a Schlenk line under nitrogen protection though these tertiary phosphine products are quite air sensitive.

(3) Proposed Mechanism

Based on the primary studies and experimental results, a mechanism was proposed for the palladacycle complex catalyzed asymmetric hydrophosphination of enones with Ph₂PH (Figure 3.2.1).

Figure 3.2.1

The auxiliary (*C, P*-ligand) is a bidentate ligand with chiral projection *via* a conformational rigid chelation on palladium. Free Ph₂PH has high affinity to palladium leading to the replacement of the coordinated solvent (NCMe) on (*R*)-48 to form the bisphosphine complex. However, the coordinated phosphines, especially the one *trans* to carbon, are labilized and could

dissociate easily which provides the chance for the enone substrate to come in and coordinate to palladium. Thus the coordinated enone is somewhat activated. Meanwhile, the coordinated phosphine is acidified by the palladium and can be easily deprotonated by Et_3N to form the phosphido species. The phosphido intermediate is so active that it can undergo 1,4-addition with the coordinated enone at $-80\text{ }^\circ\text{C}$ to form the coordinated phosphine product. Free phosphine will easily release the product on the palladium by replacement and the catalytic cycle is completed. Therefore the palladium serves as a Lewis acid both for Ph_2PH and enones, and makes the 1,4-addition proceed smoothly in an intramolecular manner.

3-2.3 Conclusion

We have successfully developed a general method for asymmetric $\text{C}^*\text{-P}$ bond formation *via* hydrophosphination catalyzed by a palladacycle complex (*R*)-**48**. A series of tertiary monophosphines with chiral centre at carbon were prepared in high yields with excellent enantioselectivities when Ph_2PH were employed as the hydrophosphinating reagent. After a single re-crystallization, these tertiary monophosphines can be purified to be enantiomerically pure. The catalytic cycle was proposed for the palladacycle complex catalyzed hydrophosphination reactions.

3-2.4 Experimental Section

All air-sensitive manipulations were performed under a positive pressure of nitrogen or argon using standard Schlenk line. Solvents were degassed prior to use when necessary. THF was purchased from TEDIA COMPANY (AR, stabilized with 0.02-0.03% BHT) and distilled before use. Low Temp PAIRSTIRRER PSL-1800 machine was used for controlling low temperatures for reactions. Column chromatography was conducted on Silica gel 60 (Merck). NMR spectra were recorded on Brüker ACF 300, 400 and 500 spectrometers. Chemical shifts are reported in δ ppm referenced to an internal SiMe₄ standard ($\delta = 0$ ppm) for ¹H NMR, chloroform-d ($\delta = 77.23$ ppm) for ¹³C NMR and to an external 85% H₃PO₄ standard for ³¹P{¹H} NMR. Optical rotations were measured on the specified solution in a 0.1 dm cell at 20 °C with a Perkin-Elmer 341 polarimeter. The phosphine products were measured as soon as possible without inert gas protection. Melting points were measured using the SRS Optimelt Automated Melting Point System, SRS MPA100.

The enones were prepared according to literatures.⁸¹

Caution! *Perchlorate salts of metal complexes are potentially explosive compounds and should be handled with care.*

(1) General Procedure

To a solution of Ph_2PH **17** (55.9 mg, 0.30 mmol, 1.0 equiv) in THF (5 mL) is added (*R*)-**48** (9.4 mg, 0.015 mmol, 5 mol%) and the solution was cooled to $-80\text{ }^\circ\text{C}$. Subsequently, aromatic enones **61** (0.30 mmol, 1.0 equiv) was added. Et_3N (15.2 mg, 0.15 mmol, 0.5 equiv) in THF (0.5 mL) was added dropwise. The solution was subsequently stirred at $-80\text{ }^\circ\text{C}$. The reaction was monitored by $^{31}\text{P}\{^1\text{H}\}$ NMR. After the reaction is completed, the mixture was warmed to room temperature and the solution was evaporated by vacuum pump to give crude the monophosphine product (air sensitive) as solids. The crude product was dissolved in 10 ml DCM, and filtered through a short silica gel column using a pipette fixed on a two-neck Schlenk flask protected by nitrogen or argon. The solvent was removed by vacuum pump to give the product as solids. A single re-crystallization from acetone or just washing by cold acetone gave enantiomerically pure monophosphine products.

(2) Determination of ee

The obtained crude products (filtered through a short silica gel column using a pipette fixed on a two-neck Schlenk flask protected by nitrogen or argon as described above) was added 0.51 eq of the dimeric complex (*R*)-**14** (a little in excess) in dichloromethane to form a pair diastereomers (*R,S*)-**63** ($^{31}\text{P}\{^1\text{H}\}$ NMR: $\delta \sim 50$) and (*R,R*)-**63** ($^{31}\text{P}\{^1\text{H}\}$ NMR: $\delta \sim 45$).

Scheme 4.7

The ee value was calculated according the ratio of the diastereomers (R,S)-63 (major product) and (R,R)-63 (minor product):

$$ee = \frac{(S)\text{-62} - (R)\text{-62}}{(S)\text{-62} + (R)\text{-62}} = \frac{(R,S)\text{-63} - (R,R)\text{-63}}{(R,S)\text{-63} + (R,R)\text{-63}}$$

The diastereomers (R,S)-63 and (R,R)-63 (can be prepared using (S)-48 as the catalyst) can be separated by silica gel column (EA/Hexane = 1/4) and crystallized from benzene/pentane system. Absolute configurations of (R,S)-63a (Figure 3.2.3) and (R,R)-63a (Figure 3.2.4) were confirmed by X-ray crystal diffraction analysis.

$[\alpha]_D = -129.3$ (c 1.0, CH_2Cl_2). Mp: 180 – 182 °C. Anal.

Calcd for $\text{C}_{41}\text{H}_{39}\text{ClINO}\text{PPd}$: C, 67.0; H, 5.4; N, 1.9. Found: C, 67.3; H, 5.3; N,

1.7. $^{31}\text{P}\{^1\text{H}\}$ NMR(CDCl_3 , 161 MHz): δ 49.1 Hz; ^1H NMR (CDCl_3 , 400 MHz):

δ 1.98 (d, 3H, $^3J_{\text{HH}} = 6.2$ Hz, CHMe), 2.66 (s, 3H, NMeMe), 3.05 (d, 3H, $^4J_{\text{PH}} =$

2.1 Hz, NMeMe), 3.83 – 3.90 (m, 1H, CHHCOPh), 4.26 – 4.29 (m, 1H, CHMe),

4.54 – 4.61 (m, 1H, CHHCOPh), 4.76 – 4.81 (m, 1H, PCHCH₂), 6.38 – 8.39 (m,

26H, Ar); ^{13}C NMR (CDCl_3 , 100 MHz): δ 23.0 (s, 1C, CHMe), 43.5 (d, 1C, $^2J_{\text{PC}}$ = 6.7 Hz, CH_2COPh), 43.8 (d, 1C, $^1J_{\text{PC}}$ = 28.5 Hz, PCH), 48.0 (s, 1C, NMeMe), 50.6 (s, 1C, NMeMe), 72.9 (d, 1C, $^3J_{\text{PC}}$ = 2.6 Hz, CHCH_3), 123.0 – 151.2 (m, 34C, Ar), 197.7 (d, 1C, $^3J_{\text{PC}}$ = 13.5 Hz, CPh).

Figure 3.2.2 Molecular structure and absolute stereochemistry of complex (*R,S*)-**63a** with 50% probability thermal ellipsoids shown. Hydrogen atoms except those on the chiral center are omitted for clarity.

Table 3.2.3 Selected Bond Lengths (Å) and Angles (deg) of (*R,S*)-**63a**

Pd1–C1	2.008(2)	Pd1–N1	2.137(2)
Pd1–P1	2.265(1)	Pd1–Cl1	2.381(1)
C1–C10	1.383(3)	C1–C2	1.419(4)
C11–N1	1.505(3)	C11–C12	1.515(6)
C13–N1	1.485(4)	C14–N1	1.484(3)
C15–P1	1.876(3)	C15–C16	1.543(4)
C15–C24	1.520(4)	C15–C16	1.543(4)
C16–C17	1.515(4)	C17–O1	1.220(3)
C1–Pd1–N1	79.8(1)	C1–Pd1–P1	96.6(1)
N1–Pd1–P1	175.1(1)	C1–Pd1–Cl1	170.4(1)
N1–Pd1–Cl1	93.1(1)	P1–Pd1–Cl1	90.8(1)
C36–P1–C30	105.8(1)	C36–P1–C15	105.1(1)
C30–P1–C15	97.3(1)	C36–P1–Pd1	109.9(1)
C30–P1–Pd1	117.6(1)	C15–P1–Pd1	119.5(1)

$[\alpha]_D = +181.6$ (c 1.0, CH_2Cl_2). Mp: 188 – 190 °C (dec). Anal.

Calcd for $\text{C}_{41}\text{H}_{39}\text{ClINO}\text{PPd}$: C, 67.0; H, 5.4; N, 1.9. Found: C, 66.9; H, 5.0; N, 1.8. $^{31}\text{P}\{^1\text{H}\}$ NMR(CDCl_3 , 161 MHz): δ 44.9; ^1H NMR (CDCl_3 , 400 MHz): δ 1.88 (d, 3H, $^3J_{\text{HH}} = 6.3$ Hz, CHMe), 2.60 (s, 3H, NMeMe), 3.00 (d, 3H, $^4J_{\text{PH}} = 2.9$ Hz, NMeMe), 3.54 – 3.60 (m, 1H, CHHCOPh), 3.88 – 3.95 (m, 1H, CHHCOPh), 4.20 – 4.26 (m, 1H, CHMe), 5.60 – 5.65 (m, 1H, PCHCH_2), 6.02 – 7.91 (m, 26H, Ar); ^{13}C NMR (CDCl_3 , 100 MHz): δ 23.1 (s, 1C, CHMe), 38.0 (d, 1C, $^1J_{\text{PC}} = 24.6$ Hz, PCH), 41.0 (s, 1C, CH_2COPh), 48.4 (s, 1C, NMeMe), 51.0 (s, 1C, NMeMe), 73.1 (d, 1C, $^3J_{\text{PC}} = 2.9$ Hz, CHCH_3), 123.1 – 151.5 (m, 34C, Ar), 197.2 (d, 1C, $^3J_{\text{PC}} = 11.4$ Hz, COPh).

Figure 3.2.3 Molecular structure and absolute stereochemistry of complex (R,R)-63a with 50% probability thermal ellipsoids shown. Hydrogen atoms except those on the chiral centre are omitted for clarity.

Table 3.2.4 Selected Bond Lengths (Å) and Angles (deg) of (*R,R*)-**63a**

Pd1–C1	2.016(3)	Pd1–N1	2.134(3)
Pd1–P1	2.265(1)	Pd1–Cl1	2.417(1)
C1–C10	1.380(4)	C1–C2	1.426(4)
C11–N1	1.493(4)	C11–C12	1.531(5)
C13–N1	1.486(4)	C14–N1	1.491(4)
C15–P1	1.828(3)	C15–C16	1.404(4)
C21–P1	1.829(3)	C21–P1	1.829(3)
C27–C28	1.518(4)	C27–C34	1.542(4)
C34–C35	1.522(4)	C35–O1	1.220(4)
C1–Pd1–N1	79.3(1)	C1–Pd1–P1	95.9(1)
N1–Pd1–P1	174.2(1)	C1–Pd1–Cl1	169.8(1)
N1–Pd1–Cl1	92.9(1)	P1–Pd1–Cl1	92.3(3)
C15–P1–C21	99.5(2)	C15–P1–C27	106.8(1)
C21–P1–C27	106.7(1)	C15–P1–Pd1	115.0(1)
C21–P1–Pd1	116.0(1)	C27–P1–Pd1	111.6(1)

(3) Synthesis of Chiral Monophosphines (Table 3.2.2) **(*S*)-Ph₂PCH(Ph)CH₂COPh, (*S*)-62a (Entry 1)**

Crude (*S*)-**62a** was synthesized according to general procedure (99% yield, 98% ee). Pure (*S*)-**62a** was obtained after purification as solids (90% yield, >99% ee) (airsensitive): $[\alpha]_D^{20} = -152.5$ (c 1.2, CH₂Cl₂). ³¹P NMR(CDCl₃, 121 MHz): δ 0.1; ¹H NMR (CDCl₃, 300 MHz): δ 3.07 (ddd, 1H, $J = 17.3$ Hz, 8.3 Hz, 2.8 Hz, CHHCOPh), 3.58 – 3.69 (m, 1H, CHHCOPh), 4.23 – 4.29 (m, 1H, PCHCH₂), 6.98 – 7.68 (m, 20H, Ar); ¹³C NMR (CDCl₃, 75 MHz): δ 40.0 (d, 1C, ¹ $J_{PC} = 11.4$ Hz, PCH), 42.6 (d, 1C, ² $J_{PC} = 22.1$ Hz, CH₂COPh), 126.5 – 141.0 (m, 24C, Ar), 198.1 (d, 1C, ³ $J_{PC} = 12.8$ Hz, COPh).

After purification (90% yield, >99% ee).

(*S*)-**Ph₂PCH(4-NO₂C₆H₄)CH₂COPh**, (*S*)-**62b** (Entry 2)

Crude (*S*)-**62b** was synthesized according to general procedure (99% yield, 98% ee). Pure (*S*)-**62b** was obtained after purification as solids (89% yield, >99% ee)

(airsensitive): $[\alpha]_D^{20} = -248.0$ (c 1.3, CH_2Cl_2). ^{31}P NMR(CDCl_3 , 121 MHz): δ 1.5; ^1H NMR (CDCl_3 , 300 MHz): δ 3.19 (ddd, 1H, $J = 17.8$ Hz, 7.7 Hz, 2.8 Hz, CHHCOPh), 3.60 – 3.71 (m, 1H, CHHCOPh), 4.34 – 4.40 (m, 1H, PCHCH_2), 7.07 – 7.91 (m, 19H, Ar); ^{13}C NMR (CDCl_3 , 75 MHz): δ 39.4 (d, 1C, $^1J_{\text{PC}} = 11.8$ Hz, PCH), 42.4 (d, 1C, $^2J_{\text{PC}} = 22.0$ Hz, CH_2COPh), 123.6 – 149.4 (m, 24C, Ar), 197.3 (d, 1C, $^3J_{\text{PC}} = 12.6$ Hz, COPh).

(S)-62c

(S)-**Ph₂PCH(3-NO₂C₆H₄)CH₂COPh**, (S)-**62c** (Entry 3)

Crude (S)-**62c** was synthesized according to general procedure (99% yield, 96% ee). Pure (S)-**62c** was obtained after purification as solids (85% yield, >99% ee) (airsensitive): $[\alpha]_D^{20} = -230.3$ (c 1.0, CH_2Cl_2). ^{31}P NMR(CDCl_3 , 161 MHz): δ 0.3; ^1H NMR (CDCl_3 , 400 MHz): δ 3.20 (ddd, 1H, $J = 17.8$ Hz, 7.8 Hz, 2.7 Hz, CHHCOPh), 3.63 – 3.71 (m, 1H, CHHCOPh), 4.35 – 4.39 (m, 1H, PCHCH_2), 7.07 – 7.97 (m, 19H, Ar); ^{13}C NMR (CDCl_3 , 125 MHz): δ 39.8 (d, 1C, $^1J_{\text{PC}} = 13.0$ Hz, PCH), 41.9 (d, 1C, $^2J_{\text{PC}} = 21.8$ Hz, CH_2COPh), 121.6 – 148.2 (m, 24C, Ar), 197.3 (d, 1C, $^3J_{\text{PC}} = 12.6$ Hz, COPh).

(S)-62d

(S)-**Ph₂PCH(4-BrC₆H₄)CH₂COPh**, (S)-**62d** (Entry 4)

Crude (S)-**62d** was synthesized according to general procedure (99% yield, 98% ee). Pure (S)-**62d** was obtained after purification as solids (89% yield, >99% ee)

(airsensitive): $[\alpha]_D^{20} = -164.2$ (c 1.7, CH_2Cl_2). ^{31}P NMR(CDCl_3 , 161 MHz): δ - 0.7; ^1H NMR (CDCl_3 , 400 MHz): δ 3.07 (ddd, 1H, $J = 17.2$ Hz, 7.6 Hz, 2.4 Hz, CHHCOPh), 3.53 - 3.61 (m, 1H, CHHCOPh), 4.20 - 4.25 (m, 1H, PCHCH_2), 7.00 - 7.68 (m, 19H, Ar); ^{13}C NMR (CDCl_3 , 100 MHz): δ 39.4 (d, 1C, $^1J_{\text{PC}} = 11.8$ Hz, PCH), 42.3 (d, 1C, $^2J_{\text{PC}} = 21.2$ Hz, CH_2COPh), 120.3 - 140.2 (m, 24C, Ar), 197.8 (d, 1C, $^3J_{\text{PC}} = 12.6$ Hz, COPh).

(S)-**62e**

(S)-**Ph₂PCH(4-ClC₆H₄)CH₂COPh**, (S)- **62e** (Entry 5)

Crude (S)-**62e** was synthesized according to general procedure (99% yield, 98% ee). Pure (S)-**62e** was obtained after purification as solids (90% yield, >99% ee) (airsensitive): $[\alpha]_D^{20} = -208.7$ (c 1.2, CH_2Cl_2). ^{31}P NMR(CDCl_3 , 121 MHz): δ 0.0; ^1H NMR (CDCl_3 , 300 MHz): δ 3.07 (ddd, 1H, $J = 17.4$ Hz, 7.9 Hz, 2.8 Hz, CHHCOPh), 3.52 - 3.63 (m, 1H, CHHCOPh), 4.20 - 4.27 (m, 1H, PCHCH_2), 7.02 - 7.68 (m, 19H, Ar); ^{13}C NMR (CDCl_3 , 75 MHz): δ 39.4 (d, 1C, $^1J_{\text{PC}} = 11.8$ Hz, PCH), 42.4 (d, 1C, $^2J_{\text{PC}} = 22.0$ Hz, CH_2COPh), 128.1 - 139.6 (m, 24C, Ar), 197.8 (d, 1C, $^3J_{\text{PC}} = 12.6$ Hz, COPh).

(S)-**62f**

(S)-**Ph₂PCH(4-FC₆H₄)CH₂COPh**, (S)-**62f** (Entry 6)

Crude (S)-**62f** was synthesized according to general procedure (99% yield, 99% ee). Pure (S)-**62f** was obtained after purification as solids (91% yield, >99% ee)

(airsensitive): $[\alpha]_D^{20} = -145.0$ (c 1.0, CH_2Cl_2). ^{31}P NMR(CDCl_3 , 162 MHz): δ - 0.9; ^1H NMR (CDCl_3 , 400 MHz): δ 3.06 (ddd, 1H, $J = 17.6$ Hz, 8.0 Hz, 2.8 Hz, CHHCOPh), 3.54 - 3.62 (m, 1H, CHHCOPh), 4.21 - 4.26 (m, 1H, PCHCH_2), 6.71 - 7.68 (m, 19H, Ar); ^{13}C NMR (CDCl_3 , 100 MHz): δ 39.3 (d, 1C, $^1J_{\text{PC}} = 11.4$ Hz, PCH), 42.5 (d, 1C, $^2J_{\text{PC}} = 22.3$ Hz, CH_2COPh), 115.2 - 162.7 (m, 24C, Ar), 198.0 (d, 1C, $^3J_{\text{PC}} = 13.0$ Hz, COPh). ^{19}F NMR (CDCl_3 , 376.5 MHz): δ - 116.4

(S)-62g

(S)-Ph₂PCH(4-CF₃C₆H₄)CH₂COPh, (S)-62g (Entry 7)

Crude (S)-62g was synthesized according to general procedure (99% yield, 96% ee). Pure (S)-62g was obtained after purification as solids (91% yield, >99% ee) (airsensitive): $[\alpha]_D^{20} = -156.4$ (c 1.1, CH_2Cl_2). ^{31}P NMR(CDCl_3 , 162 MHz): δ 0.2; ^1H NMR (CDCl_3 , 400 MHz): δ 3.14 (ddd, 1H, $J = 17.6$ Hz, 8.0 Hz, 2.8 Hz, CHHCOPh), 3.60 - 3.69 (m, 1H, CHHCOPh), 4.30 - 4.35 (m, 1H, PCHCH_2), 7.05 - 7.70 (m, 19H, Ar); ^{13}C NMR (CDCl_3 , 100 MHz): δ 40.0 (d, 1C, $^1J_{\text{PC}} = 12.7$ Hz, PCH), 42.2 (d, 1C, $^2J_{\text{PC}} = 21.4$ Hz, CH_2COPh), 123.0 - 145.5 (m, 25C, Ar), 197.6 (d, 1C, $^3J_{\text{PC}} = 12.3$ Hz, COPh). ^{19}F NMR (CDCl_3 , 376.5 MHz): δ - 62.4

(S)-62h

(S)-Ph₂PCH(4-MeC₆H₄)CH₂COPh, (S)-62h (Entry 8)

Crude (*S*)-**62h** was synthesized according to general procedure (99% yield, 99% ee). Pure (*S*)-**62h** was obtained after purification as solids (90% yield, >99% ee) (airsensitive): $[\alpha]_D^{20} = -169.3$ (*c* 1.1, CH₂Cl₂). ³¹P NMR(CDCl₃, 121 MHz): δ - 0.3; ¹H NMR (CDCl₃, 300 MHz): δ 2.13 (s, 3H, CH₃O), 3.03 (ddd, 1H, *J* = 17.4 Hz, 8.4 Hz, 3.0 Hz, CHHCOPh), 3.52 – 3.63 (m, 1H, CHHCOPh), 4.20 – 4.26 (m, 1H, PCHCH₂), 6.85 – 7.67 (m, 19H, Ar); ¹³C NMR (CDCl₃, 75 MHz): δ 21.2 (s, 1C, CH₃O), 39.5 (d, 1C, ¹*J*_{PC} = 11.3 Hz, PCH), 42.5 (d, 1C, ²*J*_{PC} = 22.1 Hz, CH₂COPh), 128.1 – 137.8 (m, 24C, Ar), 198.2 (d, 1C, ³*J*_{PC} = 12.7 Hz, COPh).

(*S*)-**62i**

(*S*)-Ph₂PCH(4-MeOC₆H₄)CH₂COPh, (*S*)-**62i** (Entry 9)

Crude (*S*)-**62i** was synthesized according to general procedure (99% yield, 99% ee). Pure (*S*)-**62i** was obtained after purification as solids (92% yield, >99% ee) (airsensitive): $[\alpha]_D^{20} = -178.5$ (*c* 1.3, CH₂Cl₂). ³¹P NMR(CDCl₃, 161 MHz): δ - 1.4; ¹H NMR (CDCl₃, 400 MHz): δ 3.03 (ddd, 1H, *J* = 17.1 Hz, 7.9 Hz, 2.6 Hz, CHHCOPh), 3.53 – 3.62 (m, 1H, CHHCOPh), 3.63 (s, 3H, CH₃O), 4.18 – 4.23 (m, 1H, PCHCH₂), 6.60 – 7.68 (m, 19H, Ar); ¹³C NMR (CDCl₃, 100 MHz): δ 39.1 (d, 1C, ¹*J*_{PC} = 11.0 Hz, PCH), 42.7 (d, 1C, ²*J*_{PC} = 22.4 Hz, CH₂COPh), 55.3 (s, 1C, CH₃O), 113.9 – 158.2 (m, 24C, Ar), 198.3 (d, 1C, ³*J*_{PC} = 13.0 Hz, COPh).

(S)-62j

(S)-Ph₂PCH(3,4-methylenedioxy)CH₂COPh, (S)-62j

(Entry 10) Crude (S)-62j was synthesized according to general procedure (99% yield, 98% ee). Pure (S)-62j was obtained after purification as solids (90% yield, >99% ee) (airsensitive): $[\alpha]_D^{20} = -195.6$ (c 0.9, CH₂Cl₂). ³¹P NMR(CDCl₃, 121 MHz): δ -0.7; ¹H NMR (CDCl₃, 300 MHz): δ 3.00 (ddd, 1H, $J = 17.1$ Hz, 7.8 Hz, 2.7 Hz, CHHCOPh), 3.48 - 3.59 (m, 1H, CHHCOPh), 4.15 - 4.21 (m, 1H, PCHCH₂), 5.74 (dd, 2H, $J = 5.4$ Hz, 1.5 Hz, CH₂O₂), 6.45 - 7.68 (m, 18H, Ar); ¹³C NMR (CDCl₃, 75 MHz): δ 39.8 (d, 1C, ¹J_{PC} = 11.2 Hz, PCH), 42.8 (d, 1C, ²J_{PC} = 22.7 Hz, CH₂COPh), 100.9 (s, 1C, CH₂O₂), 108.3 - 147.6 (m, 24C, Ar), 198.1 (d, 1C, ³J_{PC} = 12.8 Hz, COPh).

(S)-62k

(S)-Ph₂PCH(2-Naph)CH₂COPh, (S)-62k (Entry 11)

Crude (S)-62k was synthesized according to general procedure (99% yield, 99% ee). Pure (S)-62k was obtained after purification as solids (91% yield, >99% ee) (airsensitive): $[\alpha]_D^{20} = -229.0$ (c 1.1, CH₂Cl₂). ³¹P NMR(CDCl₃, 161 MHz): δ -0.7; ¹H NMR (CDCl₃, 400 MHz): δ 3.15 (ddd, 1H, $J = 17.4$ Hz, 8.2 Hz, 2.7 Hz, CHHCOPh), 3.70 - 3.78 (m, 1H, CHHCOPh), 4.42 - 4.47 (m, 1H, PCHCH₂), 6.99 - 7.68 (m, 22H, Ar); ¹³C NMR (CDCl₃, 75 MHz): δ 40.0 (d, 1C, ¹J_{PC} = 11.7 Hz, PCH), 42.6 (d, 1C, ²J_{PC} = 22.4 Hz, CH₂COPh), 125.5 - 138.7 (m, 28C, Ar), 197.9 (d, 1C, ³J_{PC} = 12.3 Hz, COPh).

(S)-Ph₂PCH(2-Naph)CH₂CO(4'-FC₆H₄), (S)-62l (Entry 12)

Crude (S)-62l was synthesized according to general procedure (99% yield, 97% ee). Pure (S)-62l was obtained after purification as solids (89% yield, >99% ee) (airsensitive): $[\alpha]_D^{20} = -153.3$ (*c* 0.8, CH₂Cl₂). ³¹P NMR(CDCl₃, 162 MHz): δ - 0.8; ¹H NMR (CDCl₃, 400 MHz): δ 3.11 (ddd, 1H, *J* = 17.2 Hz, 8.0 Hz, 2.8 Hz, CHHCOPh), 3.64 – 3.72 (m, 1H, CHHCOPh), 4.39 – 4.43 (m, 1H, PCHCH₂), 6.90 – 7.70 (m, 21H, Ar); ¹³C NMR (CDCl₃, 100 MHz): δ 41.2 (d, 1C, ¹*J*_{PC} = 12.8 Hz, PCH), 46.5 (d, 1C, ²*J*_{PC} = 21.7 Hz, CH₂COPh), 115.6 – 138.6 (m, 28C, Ar), 196.5 (d, 1C, ³*J*_{PC} = 12.4 Hz, COPh). ¹⁹F NMR (CDCl₃, 376.5 MHz): δ - 105.2

(S)-Ph₂PCHPhCH₂CO(2'-Naph), (S)-62m (Entry 13)

Crude (S)-62m was synthesized according to general procedure (98% yield, 98% ee). Pure (S)-62m was obtained after purification as solids (90% yield, >99% ee) (airsensitive): $[\alpha]_D^{20} = -145.8$ (*c* 1.1, CH₂Cl₂). ³¹P NMR(CDCl₃, 121 MHz): δ 0.1; ¹H NMR (CDCl₃, 300 MHz): δ 3.21 (ddd, 1H, *J* = 16.9 Hz, 8.2 Hz, 2.8 Hz, CHHCOPh), 3.70 – 3.81 (m, 1H, CHHCOPh), 4.27 – 4.33 (m, 1H, PCHCH₂), 6.97 – 8.15 (m, 22H, Ar); ¹³C NMR (CDCl₃, 75 MHz): δ 40.3 (d, 1C, ¹*J*_{PC} = 11.4 Hz, PCH), 42.7 (d, 1C, ²*J*_{PC} = 22.2 Hz, CH₂COPh), 124.0 – 140.8 (m, 28C, Ar), 198.1 (d, 1C, ³*J*_{PC} = 13.2 Hz, COPh).

(S)-Ph₂PCHPhCH₂CO(4'-BrC₆H₄), (S)-62n (Entry 14)

Crude (S)-62n was synthesized according to general procedure (99% yield, 96% ee). Pure (S)-62n was obtained after purification as solids (88% yield, >99% ee) (airsensitive): $[\alpha]_D^{20} = -120.6$ (*c* 1.0, CH₂Cl₂). ³¹P NMR(CDCl₃, 121 MHz): δ 0.1; ¹H NMR (CDCl₃, 300 MHz): δ 3.02 (ddd, 1H, *J* = 17.1 Hz, 8.4 Hz, 3.0 Hz, CHHCOPh), 3.49 – 3.60 (m, 1H, CHHCOPh), 4.18 – 4.25 (m, 1H, PCHCH₂), 6.98 – 7.63 (m, 19H, Ar); ¹³C NMR (CDCl₃, 75 MHz): δ 40.2 (d, 1C, ¹*J*_{PC} = 11.6 Hz, PCH), 42.6 (d, 1C, ²*J*_{PC} = 22.2 Hz, CH₂COPh), 126.6 – 140.8 (m, 24C, Ar), 197.2 (d, 1C, ³*J*_{PC} = 12.8 Hz, COPh).

(S)-Ph₂PCHPhCH₂CO(4'-ClC₆H₄), (S)-62o (Entry 15)

Crude (S)-62o was synthesized according to general procedure (99% yield, 97% ee). Pure (S)-62o was obtained after purification as solids (89% yield, >99% ee) (airsensitive): $[\alpha]_D^{20} = -144.0$ (*c* 1.0, CH₂Cl₂). ³¹P NMR(CDCl₃, 121 MHz): δ 0.0; ¹H NMR (CDCl₃, 300 MHz): δ 3.02 (ddd, 1H, *J* = 17.1 Hz, 8.6 Hz, 2.9 Hz, CHHCOPh), 3.50 – 3.61 (m, 1H, CHHCOPh), 4.18 – 4.25 (m, 1H, PCHCH₂), 6.97 – 7.60 (m, 19H, Ar); ¹³C NMR (CDCl₃, 75 MHz): δ 40.1 (d, 1C, ¹*J*_{PC} = 11.7 Hz, PCH), 42.4 (d, 1C, ²*J*_{PC} = 22.3 Hz, CH₂COPh), 126.6 – 140.8 (m, 24C, Ar), 196.9 (d, 1C, ³*J*_{PC} = 12.7 Hz, COPh).

(S)-Ph₂PCHPhCH₂CO(4'-FC₆H₄), (S)-62p (Entry 16)

Crude (S)-62p was synthesized according to general procedure (99% yield, 97% ee). Pure (S)-62p was obtained after purification as solids (90% yield, >99% ee) (airsensitive): $[\alpha]_D^{20} = -138.9$ (*c* 0.9, CH₂Cl₂). ³¹P NMR(CDCl₃, 121 MHz): δ 0.1; ¹H NMR (CDCl₃, 300 MHz): δ 3.02 (ddd, 1H, *J* = 17.1 Hz, 8.1 Hz, 3.0 Hz, CHHCOPh), 3.52 – 3.63 (m, 1H, CHHCOPh), 4.20 – 4.26 (m, 1H, PCHCH₂), 6.89 – 7.70 (m, 19H, Ar); ¹³C NMR (CDCl₃, 75 MHz): δ 40.1 (d, 1C, ¹*J*_{PC} = 11.6 Hz, PCH), 42.5 (d, 1C, ²*J*_{PC} = 22.3 Hz, CH₂COPh), 115.6 – 167.5 (m, 24C, Ar), 196.5 (d, 1C, ³*J*_{PC} = 12.9 Hz, COPh). ¹⁹F NMR (CDCl₃, 282.4 MHz): δ -105.3

(S)-Ph₂PCH(Ph)CH₂CO(2'-Pyridine), (S)-62q (Entry 17)

Crude (S)-62q was synthesized according to general procedure (99% yield, 92% ee). Pure (S)-62q was obtained after purification as solids (71% yield, 99% ee) (airsensitive): $[\alpha]_D^{20} = -133.0$ (*c* 1.0, CH₂Cl₂). ³¹P NMR(CDCl₃, 162 MHz): δ 0.6; ¹H NMR (CDCl₃, 400 MHz): δ 3.30 (ddd, 1H, *J* = 17.6 Hz, 7.7 Hz, 3.2 Hz, CHHCOPh), 3.98 – 4.06 (m, 1H, CHHCOPh), 4.27 – 4.32 (m, 1H, PCHCH₂), 6.96 – 8.55 (m, 19H, Ar); ¹³C NMR (CDCl₃, 100 MHz): δ 40.1 (d, 1C, ¹*J*_{PC} = 17.6 Hz, PCH), 41.6 (d, 1C, ²*J*_{PC} = 22.0 Hz, CH₂COPh), 122.0 – 153.4 (m, 24C, Ar), 199.9 (d, 1C, ³*J*_{PC} = 12.7 Hz, COPh).

(S)-Ph₂PCHPhCH₂CO(4'-FC₆H₄), (S)-**62r** (Entry 18)

Crude (S)-**62r** was synthesized according to general procedure (99% yield, 92% ee). Pure (S)-**62r** was obtained after purification as solids (71% yield, 99% ee) (airsensitive): $[\alpha]_D^{20} = -150.6$ (*c* 0.9, CH₂Cl₂). ³¹P NMR(CDCl₃, 161 MHz): δ - 0.5; ¹H NMR (CDCl₃, 400 MHz): δ 3.01 (ddd, 1H, *J* = 17.2 Hz, 8.4 Hz, 2.8 Hz, CHHCOPh), 3.55 - 3.63 (m, 1H, CHHCOPh), 3.73 (s, 3H, CH₃O), 4.23 - 4.28 (m, 1H, PCHCH₂), 6.73 - 7.68 (m, 19H, Ar); ¹³C NMR (CDCl₃, 100 MHz): δ 40.1 (d, 1C, ¹*J*_{PC} = 11.4 Hz, PCH), 42.5 (d, 1C, ²*J*_{PC} = 22.0 Hz, CH₂COPh), 55.6 (s, 1C, CH₃O), 113.8 - 163.6 (m, 24C, Ar), 196.6 (d, 1C, ³*J*_{PC} = 12.8 Hz, COPh).

(S)-Ph₂PCH(4-FC₆H₄)CH₂CO(4'-ClC₆H₄), (S)-**62s** (Entry 19)

Crude (S)-**62s** was synthesized according to general procedure (99% yield, 97% ee). Pure (S)-**62s** was obtained after purification as solids (90% yield, 99% ee) (airsensitive): $[\alpha]_D^{20} = -133.9$ (*c* 0.6, CH₂Cl₂). ³¹P NMR(CDCl₃, 121 MHz): δ - 0.2; ¹H NMR (CDCl₃, 400 MHz): δ 3.03 (ddd, 1H, *J* = 17.2 Hz, 8.0 Hz, 2.8 Hz, CHHCOPh), 3.47 - 3.55 (m, 1H, CHHCOPh), 4.18 - 4.22 (m, 1H, PCHCH₂), 6.72 - 7.60 (m, 18H, Ar); ¹³C NMR (CDCl₃, 100 MHz): δ 39.4 (d, 1C, ¹*J*_{PC} = 11.7 Hz, PCH), 42.5 (d, 1C, ²*J*_{PC} = 22.6 Hz, CH₂COPh), 115.2 - 162.8 (m, 24C, Ar), 196.9 (d, 1C, ³*J*_{PC} = 12.8 Hz, COPh). ¹⁹F NMR

(CDCl₃, 282.4 MHz): δ - 116.3.

(*S*)-Ph₂PCH(4-ClC₆H₄)CH₂CO(4'-FC₆H₄), (*S*)-**62t** (Entry 20)

Crude (*S*)-**62t** was synthesized according to general procedure (99% yield, 98% ee). Pure (*S*)-**62t** was obtained after purification as solids (90% yield, 99% ee) (airsensitive): $[\alpha]_D^{20} = -172.7$ (*c* 0.9, CH₂Cl₂). ³¹P NMR(CDCl₃, 121 MHz): δ 0.0; ¹H NMR (CDCl₃, 300 MHz): δ 3.04 (ddd, 1H, *J* = 17.4 Hz, 7.8 Hz, 2.7 Hz, CHHCOPh), 3.47 – 3.58 (m, 1H, CHHCOPh), 4.18 – 4.24 (m, 1H, PCHCH₂), 6.92 – 7.72 (m, 18H, Ar); ¹³C NMR (CDCl₃, 75 MHz): δ 39.5 (d, 1C, ¹*J*_{PC} = 12.0 Hz, PCH), 42.4 (d, 1C, ²*J*_{PC} = 22.1 Hz, CH₂COPh), 115.7 – 167.6 (m, 24C, Ar), 196.3 (d, 1C, ³*J*_{PC} = 12.7 Hz, COPh). ¹⁹F NMR (CDCl₃, 282.4 MHz): δ - 104.9.

3-3 Palladacycle-Catalyzed Asymmetric C*-P* Bond Formation *via* Hydrophosphination of Enones with (±) R(R')PH

3-3.1 Introduction

P-stereogenic tertiary phosphines are configurationally stable at room temperature. This stability can be accounted for on the basis that rehybridisation must take place for inversion to occur.^{82,83} The energy required to invert tertiary trialkyl phosphines is in the range of 30–38 kcal mol⁻¹ (eq 1).⁸⁴ Temperature dependence studies indicate that tertiary phosphines are configurationally stable for up to 3 h at 130 °C.^{85,86}

Pyramidal inversion in tertiary phosphines (PR¹(R²)(R³)) undergoes slowly,^{84d} however, the inversion in metal phosphido complexes [M-P(R¹)R²] is very fast, often occurring on the NMR time scale.⁸⁷ Therefore, phosphido complexes containing a chiral ligand [(L*)MP(R¹)R²] (R¹ ≠ R²) are mixtures of rapidly interconverting diastereomers.⁸⁸ These properties make it possible to asymmetric synthesize enantiomerically pure/enriched P-stereogenic compounds from racemic unsymmetrical secondary phosphines (±) R¹(R²)PH *via* transition

metal complexes mediated or catalyzed reactions through the metal phosphido intermediates.⁸⁹

Scheme 3.3.1

As shown in Scheme 3.3.1, the key intermediates, the phosphido complexes **65**, would be formed from a catalyst precursor and the racemic secondary phosphine. If the inversion which interconverts diastereomers **65R** and **65S** is much faster than their P*-C formation reactions leading to tertiary phosphines **66**, then P-stereogenic phosphines could be formed enantioselectively, and the product ratio (ee) would be depend on the equilibrium constant ($K_{\text{eq}} = [\mathbf{65R}]/[\mathbf{65S}]$) and the rate constants for P*-C bond formation involving these diastereomers (k_S and k_R , Scheme 3.3.1).^{83,90} The reported P*-C bond formation reactions in this process are almost limited to phosphination reactions (alkylation and arylation of racemic unsymmetrical secondary phosphines).³³

In recent years, P-stereogenic phosphines have been used as important ligands with transition metal for asymmetric catalytic transformations. These ligands allow for control over reactivity and selectivity with efficiencies similar to those obtained with their non P-stereogenic counterparts, in some cases superior.⁸² For example, Buchwald *et al.* used a P-stereogenic analogue (**67**) of KenPhos for the palladium catalyzed arylation of oxindoles (Scheme 3.3.2) leading to a significant improvement of the enantiomeric excess (from 74% to 97% ee).⁹¹

Scheme 3.3.2

P-stereogenic phosphines have also begun to show great potential to advance organocatalysis. Vedejs *et al.* reported a P-stereogenic phosphine catalyzed Steglich rearrangement of enol carbonates to azlactones containing an asymmetric quaternary carbon (Scheme 3.3.3).⁹²

Scheme 3.3.3

The value of P-stereogenic phosphines both as ligands for metal catalysis and as organocatalysts has generated a demand for new routes for their preparation. Most strategies make use of a resolution process or a chiral auxiliary. The synthesis of P-stereogenic phosphines *via* catalytic asymmetric methods are attractive but to date remains limited.⁸² Among the few reported catalytic examples, most of them are achieved through phosphination of alkylhalogens, arylhalogens, and allylic acetates with secondary phosphines (alkylation and arylation of secondary phosphines),^{33,34}. As far as we know, the only example of synthesis of P-stereogenic phosphines by the more atom-economic method – hydrophosphination has been reported by Glueck *et al.* (Scheme 3.2.2), but the results were not synthetically useful because enantioselectivities are too low.^{73c} Synthesis of chiral tertiary phosphines *via* catalytic asymmetric transformations in which the carbon–phosphorus bond and stereogenic centers both at carbon and phosphorous are simultaneously formed (C*–P* bond formation) is unprecedented.

Based on the preliminary studies, we think that the palladacycle catalyzed asymmetric hydrophosphination of enones also involves the phosphido intermediates as described in the catalytic cycle in Figure 3.2.1. If this is true,

P-stereogenic phosphines could be formed enantioselectively *via* hydrophosphination if racemic secondary phosphines ($\pm$) $R(R')PH$ ($R \neq R'$) used as the hydrophosphinating reagents instead of Ph_2PH (addition of racemic unsymmetrical secondary phosphines to unsaturated bonds) (eq 2).

3-3.2 Results and Discussion

Encouraged by the excellent yields and selectivities achieved in the hydrophosphination reaction between Ph_2PH and enones (Table 3.2.2) and the insights of the mechanism (Figure 3.2.1), we explored the asymmetric hydrophosphination of enones with racemic unsymmetrical secondary phosphines ($\pm$) $R(R')PH$ ($R \neq R'$) to synthesize chiral phosphines with stereogenic centers both at phosphorus and carbon (P^*-C^* bond formation).

(1) Screen of Reaction Conditions

Several racemic unsymmetrical secondary phosphines and temperature conditions were screened for the reaction (Table 3.3.1). THF was chosen as the solvent based on the preliminary studies. The reaction was conveniently monitored by $^{31}P\{^1H\}$ NMR spectroscopy. The diastereoselectivity (dr) was determined from $^{31}P\{^1H\}$ NMR spectrum of the crude products. The ee values were determined from $^{31}P\{^1H\}$ NMR spectrum of the diastereomers which

resulted from the treatment of the phosphine products with an enantiopure chiral palladium complex (*R*)-**14** containing an chiral naphthyl amine auxiliary (same method as described previously).⁷⁶ X-ray crystal diffraction analysis of the corresponding diastereomer revealed that the absolute configurations of the major product on the chiral carbon centers at phosphorous and carbon were both *S* (For more details, see experimental section).

Table 3.3.1 Screening of conditions for (*R*)-**48**-catalyzed asymmetric hydrophosphination^a

Entry	R ³	R ⁴	Time (h)	Temp (°C)	Yield ^b (%)	d:r ^c	ee ^d (%)
1	Ph	Me	14	−80	99	87:13	71
2	Ph	Me	12	−40	99	85:15	68
3	Ph	Me	5	−10	99	79:21	63
4	Ph	Me	5	0	97	77:23	62
5	Ph	Me	4	20	95	70:30	52
6	Ph	^t Bu	24	20	trace	—	—
7	Ph	Mes ^e	60	20	95	59:41	79

^a Conditions: 0.36 mmol (±) Ph(Me)PH, 10 mol % of cat, 5 ml THF, 1.2 equiv. of *trans*-chalcone, 1.0 equiv. of Et₃N were reacted at the given temperature, unless otherwise noted. ^b Yield was calculated from ³¹P{¹H} NMR. ^c dr was determined from ³¹P{¹H} NMR of the crude products. ^d ee was determined from ³¹P{¹H} NMR integration of the signals. ^e Mes = (2,4,6)-trimethylphenyl.

The racemic ($\pm$) Ph(Me)PH showed less reactivity compared with Ph₂PH. However, in presence of 10 mol % of the catalyst (*R*)-**48**, it can react with *trans*-chalcone in full conversion after 14 h at $-80\text{ }^{\circ}\text{C}$ with 87:13 dr and 71% ee. The results showed that the dr drops significantly as temperature is raised, while the ee decreases a little. These results support that the inversion in metal phosphido complexes [(L*)Pd-P(Me)Ph] can take place at $-80\text{ }^{\circ}\text{C}$, and it is much faster than the P*-C* bond formation (hydrophosphination reaction).

It has been reported that the energy required for inversion has a strong dependence on the nature of the substituents on the phosphorus atom.⁹³ Increasing the steric bulk of the substituent on phosphorus (from Me to ^tBu, for example) lowers the barrier of inversion.⁹⁴ Substituents which allow for delocalization of the lone pair into neighbouring π -systems also decrease the inversion barrier. In contrast, heteroatom substituents increase the barrier to inversion.⁹⁵ Based on these reported knowledge, we screened ($\pm$) Ph(^tBu)PH which is expected with lower inversion barrier than ($\pm$) Ph(Me)PH. However, it showed very low reactivity even at $20\text{ }^{\circ}\text{C}$ (entry 6). This may be due to that the P-C bond formation is more difficult compared with ($\pm$) Ph(Me)PH though its inversion barrier is lower. Then we screened ($\pm$) Ph(Mes)PH with expectation of better selectivity because Mes is more bulky than Me group and it has an aromatic ring which can delocalize the lone pair on phosphorus which contributes to the decrease of the barrier to inversion. As a matter of fact, it showed no reactivity at $-80\text{ }^{\circ}\text{C}$, but it can react with *trans*-chalcone at $20\text{ }^{\circ}\text{C}$

gradually (entry 7). Therefore, ($\pm$) Ph(Me)PH is selected for screening of substrates for the hydrophosphination reaction.

Based on the results and studies, we can conclude that the substituents of aromatic rings on the phosphorus atom can facilitate the palladacycle catalyzed hydrophosphination reaction (for example, Ph₂PH is more reactive than Ph(Me)PH). Electron donating substituents at the aromatic ring may decrease the reactivity (for example, Ph₂PH is more reactive than Ph(Mes)PH).

(2) Substrate Scope

With the optimal conditions established, a range of aromatic enones were screened for the asymmetric hydrophosphination reaction catalyzed by (*R*)-**48**. The results are presented in Table 3.3.2 which showed that the reaction proceeded smoothly under the given conditions, allowing the transformation of a wide range of aromatic enone substrates to the tertiary phosphine products with chiral centres both at phosphorus and carbon. The process tolerates a broad range of functional groups such as nitro, halogens (F, Cl, Br), trifluoromethyl, alkyl, methoxy, pyridinyl and naphthyl *etc.* Both electron withdrawing and electron donating group substituted aromatic enones are suitable substrates and provide high yields and mild to good stereoselectivities. Those bearing electron withdrawing groups (entries 2 to 6) are more reactive but less stereoselective compared with those bearing electron donating groups (entries 7 to 8, 13, 15) which are less reactive but more stereoselective.

Table 3.3.2 (*R*)-**48**-catalyzed asymmetric hydrophosphination of various aromatic enones with ($\pm$) Ph(Me)PH^a

Entry	R ¹	R ²	Time h	Yield (%)	d:r ^c	ee ^d (%)
1	Ph	Ph	14 h	99	87:13	71
2	4-NO ₂ C ₆ H ₄	Ph	5 h	99	82:18	42
3	4-BrC ₆ H ₄	Ph	12 h	97	87:13	62
4	4-ClC ₆ H ₄	Ph	6 h	98	87:13	63
5	4-FC ₆ H ₄	Ph	14 h	98	88:12	66
6	4-CF ₃ C ₆ H ₄	Ph	5 h	98	85:15	39
7	4-MeOC ₆ H ₄	Ph	6 d	99	91:9	82
8		Ph	5 d	95	91:9	75
9	2-Naph	Ph	30 h	93	87:13	73
10	2-Naph	4-FC ₆ H ₄	7 h	95	87:13	72
11	Ph	2-Naph	30 h	96	85:15	72
12	Ph	4-BrC ₆ H ₄	14 h	97	78:22	61
13	Ph	4-ClC ₆ H ₄	8 h	95	76:24	61
14	Ph	4-FC ₆ H ₄	17 h	96	87:13	72
15	4-FC ₆ H ₄	4-ClC ₆ H ₄	7 h	95	83:17	57

^a Conditions: 0.36 mmol ($\pm$) Ph(Me)PH, 10 mol % of cat, 5 ml THF, 1.2 equiv. of enones, 1.0 equiv. of Et₃N were reacted at –80 °C, unless otherwise noted. ^b Yield was calculated from ³¹P{¹H} NMR. ^c dr was determined from ³¹P{¹H} NMR of the crude products. ^d ee was determined from ³¹P{¹H} NMR integration of the signals.

(3) Proposed Mechanism

Based on the preliminary studies and the results, a mechanism is proposed for the palladacycle-catalyzed asymmetric hydrophosphination of enones with racemic unsymmetrical secondary phosphines ($\pm$) $R(R')PH$ ($R \neq R'$).

Figure 3.3.1

The mechanism is similar to that shown in Figure 3.2.1. The secondary phosphine can easily replace the solvent (NCMe) which was coordinated on the two active sites of the palladium catalyst (*R*)-**48** to form the bisphosphine complex. However, the phosphine *trans* to carbon is labilized and could dissociate easily due to the *trans* effect which give the chance to the enone substrate to come in and coordinate with palladium. Thus the coordinated enone is activated. Meanwhile, the coordinated phosphine is acidified by the palladium and can easily be deprotonated by Et₃N to form the phosphido species. The inversion occurs on the phosphorus center leading to the formation of equilibrating metal–phosphido complexes, a process facilitated by the delocalization of the phosphorus lone pair into the metal d-orbitals (*via* decrease of the inversion barrier). This allows for rapid interconversion of the two diastereomers. Because the phosphine R³(R⁴)PH is not symmetrical, one diastereomer reacting significantly faster than the other resulted from the chiral auxiliary. A central aspect in the process is that the selectivity on phosphorus results from this inversion. The phosphido intermediates are so active that it can undergo 1,4-addition with the coordinated enones at –80 °C to form the coordinated phosphine products. The secondary free phosphines will easily release the products on the palladium by replacement and the catalytic cycle is completed. The interplay of P inversion and P–C bond formation as shown in Figure 3.3.1 was suggested to be responsible for diastereo- and enantioselection.

3-3.3 Conclusion

We have successfully developed the asymmetric C*-P* bond formation *via* palladacycle-catalyzed hydrophosphination using unsymmetrical secondary phosphines ($\pm$) R(R')PH ($R \neq R'$) as the hydrophosphinating reagents. A series of tertiary monophosphines with chiral centres both at phosphorus and carbon were prepared in high yields with good enantioselectivities. A catalytic cycle involving metal phosphido intermediates was proposed for the palladacycle-catalyzed hydrophosphination reaction.

3-3.4 Experimental Section

All air-sensitive manipulations were performed under a positive pressure of nitrogen or argon using standard Schlenk line. Solvents were degassed prior to use when necessary. THF was purchased from TEDIA COMPANY (AR, stabilized with 0.02-0.03% BHT) and distilled before use. Low Temp PAIRSTIRRER PSL-1800 machine was used for controlling low temperatures for reactions. Column chromatography was conducted on Silica gel 60 (Merck). NMR spectra were recorded on Brüker ACF 300, 400 and 500 spectrometers. Chemical shifts are reported in δ ppm referenced to an internal SiMe₄ standard ($\delta = 0$ ppm) for ¹H NMR, chloroform-d ($\delta = 77.23$ ppm) for ¹³C NMR and to an external 85% H₃PO₄ standard for ³¹P{¹H} NMR. Optical rotations were measured on the specified solution in a 0.1 dm cell at 20 °C with a Perkin-Elmer 341 polarimeter. The phosphine products were measured as soon

as possible without inert gas protection. Melting points were measured using the SRS Optimelt Automated Melting Point System, SRS MPA100.

The enones⁸¹ and racemic secondary phosphines⁹⁶ were prepared according to literatures.

Caution! Perchlorate salts of metal complexes are potentially explosive compounds and should be handled with care.

(1) General Procedure

To a solution of ($\pm$) Ph(Me)PH **64** (44.7 mg, 0.36 mmol, 1.0 equiv) in THF (5 mL) is added (*R*)-**48** (22.6 mg, 0.036 mmol, 10 mol%) and the solution was cooled to -80°C . Subsequently, aromatic enones **61** (0.43 mmol, 1.2 equiv) was added. Et₃N (36.4 mg, 0.36 mmol, 1.0 equiv) in THF (0.5 mL) was added dropwise. The solution was subsequently stirred at -80°C . The reaction was monitored by $^{31}\text{P}\{^1\text{H}\}$ NMR. After the reaction is completed, the mixture was warmed to room temperature and the solution was evaporated by vacuum pump to give crude the monophosphine products (air sensitive). The crude products were dissolved in 10 ml DCM, and filtered through a short silica gel column using a pipette fixed on a two-neck Schlenk flask protected by nitrogen or argon. The solvent was removed by vacuum pump to give the products.

These kinds of monophosphine products can not be purified by the same method as previously described.

(2) Determination of dr and ee

The diastereoselectivity (dr) was determined from the integration of $^{31}\text{P}\{^1\text{H}\}$ NMR signals of the crude products (before filtration through silica gel column). The crude products are a mixture of two pairs of diastereomers: (*S_C*,*S_P*)-**68**, (*S_C*,*R_P*)-**68**, (*R_C*,*R_P*)-**68**, and (*R_C*,*S_P*)-**68**. (*S_C*,*S_P*)-**68** and (*R_C*,*R_P*)-**68** are a pair of enantiomers (major) with same $^{31}\text{P}\{^1\text{H}\}$ NMR (around δ -19) chemical shifts. (*S_C*,*R_P*)-**68** and (*R_C*,*S_P*)-**68** are the other pair of enantiomers (minor) with same $^{31}\text{P}\{^1\text{H}\}$ NMR (around δ : -18) chemical shifts. Therefore, dr can be calculated as follows:

$$\text{dr} = \frac{(\text{S}_{\text{C}},\text{S}_{\text{P}})\text{-68} + (\text{R}_{\text{C}},\text{R}_{\text{P}})\text{-68}}{(\text{S}_{\text{C}},\text{R}_{\text{P}})\text{-68} + (\text{R}_{\text{C}},\text{S}_{\text{P}})\text{-68}}$$

The enantioselectivity ee was determined by the similar way as previously described. The obtained crude products (filtered through a short silica gel column using a pipette fixed on a two-neck Schlenk flask protected by nitrogen or argon as described above) was added 0.51 eq of the dimeric complex (*R*)-**14** (a little in excess) in dichloromethane to form two pairs of diastereomers: (*R_C*,*S_C*,*R_P*)-**69**, (*R_C*,*S_C*,*S_P*)-**69**, (*R_C*,*R_C*,*S_P*)-**69**, and (*R_C*,*R_C*,*R_P*)-**69** (Scheme 3.3.4). They were recorded ($^{31}\text{P}\{^1\text{H}\}$ NMR: CDCl_3) at δ ~32, ~32, ~29, ~28.

Scheme 3.3.4

The major product $(R_C, S_C, R_P)\text{-69a}$ ($R_1 = \text{Ph}$, $R_2 = \text{Ph}$) ($^{31}\text{P}\{^1\text{H}\}$ NMR: δ 28.0) was isolated by silica gel column (EA/Hexane = 1/4) and crystallized from benzene/pentane system. Its absolute configuration was confirmed by X-ray crystal diffraction analysis (Figure 4.5). Therefore the major free tertiary phosphine products can be deduced to be $(S_C, S_P)\text{-68}$. In order to identify the minor enantiomer $(R_C, R_P)\text{-68a}$ which is other enantiomer of $(S_C, S_P)\text{-68a}$, the $(S)\text{-48}$ was employed as the catalyst instead of $(R)\text{-48}$ to catalyze the same reaction. After coordination with $(R)\text{-14}$, the same two pairs of diastereomers were obtained with reversed ratios. Based on the results and comparison, $(R_C, R_P)\text{-68a}$ which recorded at δ 31.8 ($^{31}\text{P}\{^1\text{H}\}$ NMR) can be identified. Therefore, the dr and ee value of the major isomers can be calculated:

$$ee = \frac{(S_C, S_P)\text{-68} - (R_C, R_P)\text{-68}}{(S_C, S_P)\text{-68} + (R_C, R_P)\text{-68}} = \frac{(R_C, S_C, R_P)\text{-69} - (R_C, R_C, S_P)\text{-69}}{(R_C, S_C, R_P)\text{-69} + (R_C, R_C, S_P)\text{-69}}$$

Due to the dr and ee both are not ideal enough, it is difficult to isolate enantiopure P-stereogenic phosphine products using the similar method as described in section 3-2. We measured dr and ee using the method presented above and did not collect the data of the free P-stereogenic phosphine products.

Figure 3.3.2 Molecular structure and absolute stereochemistry of complex (*R_C*, *S_C*, *R_P*)-**69a** with 50% probability thermal ellipsoids shown. Hydrogen atoms except those on the chiral center are omitted for clarity.

Table 3.3.3 Selected Bond Lengths (Å) and Angles (deg) of (*R_C*,*S_C*,*R_P*)-**69a**

Pd1–C1	2.019(3)	Pd1–N1	2.142(2)
Pd1–P1	2.274(1)	Pd1–Cl1	2.371(1)
C1–C10	1.384(4)	C1–C2	1.422(4)
C11–N1	1.494(4)	C11–C12	1.541(4)
C13–N1	1.489(4)	C14–N1	1.489(4)
C15–P1	1.835(3)	C16–C25	1.515(4)
C16–C17	1.531(3)	C16–P1	1.869(3)
C18–O1	1.209(3)	C18–C19	1.505(4)
C31–P1	1.816(3)		
C1–Pd1–N1	81.3(1)	C1–Pd1–P1	97.8(1)
N1–Pd1–P1	178.6(1)	C1–Pd1–Cl1	170.6(1)
N1–Pd1–Cl1	89.6(1)	P1–Pd1–Cl1	91.2(1)
C25–C16–P1	115.8(2)	C17–C16–P1	106.1(2)
C15–P1–C16	101.7(2)	C10–C1–Pd1	112.6(2)
C31–P1–Pd1	110.7(1)	C2–C1–Pd1	129.3(2)
C15–P1–Pd1	121.8(1)	C16–P1–Pd1	109.4(1)

3-4 Palladacycle-Catalyzed Asymmetric Double C*-P Bond Formation *via* Hydrophosphination of Bis(enones)

3-4.1 Introduction

In 1968, Horner and Knowles simultaneously used chiral phosphines as ligands for the first time in homogeneous asymmetric hydrogenation which opened up new horizons in organic and organometallic chemistry.⁵ Since then, chiral phosphines have received an extraordinary level of attention in asymmetric catalysis as ligands for transition metals and as organocatalysts.^{1,2} Numerous chiral phosphines including monophosphines, diphosphines and polyphosphines with stereogenic center(s) at phosphorus or in the side-chain have been prepared. As described in Chapter 1, some diphosphines such as DIOP,⁶ DIPAMP,⁷ BINAP,⁸ and DuPhos⁹ have remarkable significance in enantioselective transformations which earned Knowles and Noyori the award of the 2001 Nobel Prize in chemistry.

In the early 1970s, a new kind of diphosphine called PCP pincer ligands was firstly reported.⁹⁷ Since then, PCP ligands have received great attention and have quickly proven to be very important ligands providing rigid chelating with transition metal (Ni, Pd, Pt, Ir, Fe, Ru, Rh, *etc.*) to form pincer complexes (Scheme 3.4.1) which are widely used in organic and organometallic chemistry, and touching other fields as well.⁹⁸ However, the development of chiral PCP diphosphines is comparatively slow.⁹⁹ The PCP pincer complexes have a

unique balance of stability and reactivity which are the two aspects of fundamental interest in catalyst design. The modifications at the backbone (R^1 , R^2) and donor groups (R^3) allow the fine tuning of both electronic and steric properties, providing an enhancement in the reactivity, stability, and selectivity of a given complex.¹⁰⁰

Scheme 3.4.1

Despite their importance, to date, chiral phosphines are prepared dominantly either by resolution process or by the use of stoichiometric amounts of chiral auxiliaries or enantiomerically pure substrates,^{73,74} though some reports on catalytic synthesis of chiral monophosphines have occurred during the past decades.^{33-34,75-78} Catalytic asymmetric synthesis of chiral diphosphines is surprisingly rare, presumably due to the fact that they may form chelating complexes with metal which may disrupt the catalytic cycle.

However, some efforts have been made towards catalytic synthesis of chiral diphosphines. Toste *et al.* reported a Ru-catalyzed enantioselective synthesis of P-stereogenic phosphines *via* alkylation which included one example of a PCP diphosphine with chiral center at phosphorus.^{33b,c}

Scheme 3.4.2

Duan *et al.* reported pincer palladium complex catalyzed enantioselective addition of diarylphosphines to enones included a PCP palladium pincer complex synthesized in one-pot.⁷⁸

Scheme 3.4.3

Glueck *et al.* reported Pt-catalyzed asymmetric alkylation of the bis(secondary phosphines) with aryl halides.¹⁰¹ However, the diastereo- and enantioselectivities were quite low.

Scheme 3.4.4

Considering the importance of chiral diphosphines and their scarcity of catalytic synthetic methods,³ development of efficient catalysts and methodologies for direct and stereoselective preparation of them is of significance.

In preceding contributions, our group has reported the asymmetric synthesis of chiral diphosphines promoted by palladacycles.⁴⁷ However, stoichiometric amounts of palladium is needed. In this section, we describe a highly reactive asymmetric hydrophosphination reaction between bis(enones) and Ph₂PH catalyzed by a palladacycle (*R*)-**48** involving successive formation of two C*-P bonds (eq 1), for the straightforward preparation of chiral tertiary PCP diphosphines. Broad functional group tolerance is exhibited, and a wide range of substrates can be efficiently converted into the desired products in high yields with excellent stereoselectivities.

3-4.2 Results and Discussion

Inspired by the good results achieved by the palladacycle catalyzed asymmetric hydrophosphination of enones for preparation of chiral monophosphines with stereogenic center at carbon or both at carbon and phosphorus, we wonder whether we can expand this protocol to catalytic asymmetric synthesis of diphosphines. In order to avoid 1,2-diphosphines which are more likely to form stable chelation with metals, we designed catalytic synthesis of chiral PCP type diphosphines (eq 1).

(1) Screening of Reaction Conditions

Based on the studies of the palladacycle catalyzed asymmetric hydrophosphination of enones, we employed the same catalyst (*R*)-**48** for asymmetric hydrophosphination of a bis(enone) (**70a**). To our delight, (*R*)-**48** showed high reactivity and excellent stereoselectivity in THF as the solvent at $-80\text{ }^{\circ}\text{C}$. The reaction was conveniently monitored by $^{31}\text{P}\{^1\text{H}\}$ NMR spectroscopy. The diastereoselectivity ($\text{dr} = \text{rac}/\text{meso}$) was determined from $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum of the crude product and the enantiomeric excess (ee) was determined from $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum of the derivatives which resulted from the treatment of the phosphine product with an enantiopure chiral Pd complex (for more details see experimental section). X-ray crystal diffraction analysis of the corresponding derivative revealed that the absolute configurations of the major product at the two chiral carbon centers both were *S* (Figure 3.4.1).

Various reaction conditions including solvent, temperature and base effect were subsequently screened and the results are given in Table 3.4.1. The results showed that toluene is the best solvent for the reaction with 99:1 dr and $> 99\%$ ee (entry 4). Good selectivity was also achieved in THF, acetone, and benzene. We further surveyed the temperature effect. It was found that the ee value decreased to 98% at $-40\text{ }^{\circ}\text{C}$ and 93% at $20\text{ }^{\circ}\text{C}$ (entries 6 to 7), respectively. Yield also decreased as the temperature raised due to some unknown byproducts occurred. Base also plays an important role in the reaction.

In the absence of base, only trace conversion was observed at $-80\text{ }^{\circ}\text{C}$ after 24 hours. The results of base screening showed that Et_3N is the best one for the reaction due to its appropriate basicity level and its easy removal under vacuum which contributes to obtaining clean products. As expected, when the equally accessible (*S*)-**48** is employed as the catalyst, the same enantioselectivity was

Table 3.4.1 Screening of reaction conditions^a

entry	solvent	temp ($^{\circ}\text{C}$)	base	yield ^b (%)	dr ^c	ee ^d (%)
1	CH_2Cl_2	-80	Et_3N	43	81:19	99
2	Acetone	-80	Et_3N	99	87:13	99
3	THF	-80	Et_3N	99	94:6	99
4	Toluene	-80	Et_3N	99	99:1	>99
5 ^e	Toluene	-80	Et_3N	99	99:1	>99
6	Toluene	-40	Et_3N	99	98:2	98
7	Toluene	20	Et_3N	90	96:4	93
8	Benzene	20	Et_3N	90	96:4	99
9	Toluene	-80	None	trace	—	—
10	Toluene	-80	DBU	14	—	—
11	Toluene	-80	$t\text{BuOK}^f$	trace	—	—

^a Conditions: 0.30 mmol Ph_2PH , 5 mol % of cat, 0.5 mmol of dienone, 2.0 equiv. of base, 5 ml solvent were reacted at the given temperature for 24 h, unless otherwise noted. ^b Yield was calculated from $^{31}\text{P}\{^1\text{H}\}$ NMR of the crude product. ^c dr was calculated from $^{31}\text{P}\{^1\text{H}\}$ NMR. Errors may occur due to overlap. ^d ee was determined from $^{31}\text{P}\{^1\text{H}\}$ NMR integration of the signals. ^e (*S*)-**48** was employed as the catalyst. ^f Solid $t\text{BuOK}$ was used.

achieved with reversal in configuration at the chiral centre (entry 5). The amount of catalyst loading has little effect on the selectivity, but affects the rate of the reaction. Longer time is required to complete the reaction with decreasing catalyst loading.

(2) Substrate Scope

With the optimal conditions established, a range of aromatic dienones were screened for the asymmetric hydrophosphination reaction catalyzed by (*R*)-**48**. The results are presented in Table 3.4.2. The results revealed that the reaction proceeded to almost full conversion of Ph₂PH under the given conditions, allowing the transformation of a wide range of aromatic bis(enone) substrates to the chiral diphosphine products. Since the solubility of some bis(enone) substrates was poor in toluene, THF was used as the solvent for such cases. The process tolerates a broad range of functional groups such as halogens (F, Cl, Br), trifluoromethyl, alkyl, heterocyclic-ring (pyridinyl, thienyl, furyl), naphthyl *etc.* Both electron withdrawing and electron donating group substituted aromatic bis(enones) are suitable substrates for hydrophosphination with excellent enantereoselectivities. However, those bearing electron withdrawing groups (entries 2 to 7, 10) are more reactive than those bearing electron donating groups (entries 8 to 9, 15). The substituent on the backbone (*R*¹) also provides a possibility to fine-tune electronic and steric properties for the design of novel PCP pincer complexes.

Table 3.4.2 Substrate scope of the (*R*)-**48**-catalyzed asymmetric hydrophosphination of bis(enones)^a

entry	R ¹	R ²	time (h)	71	yield ^b (%)	dr ^c	ee ^d (%)
1 ^e	H	Ph	8	71a	99	99:1	>99
2 ^e	H	4-FC ₆ H ₄	45	71b	99	99:1	>99
3 ^e	H	3-FC ₆ H ₄	45	71c	99	94:6	>99
4	H	4-ClC ₆ H ₄	6	71d	99	98:2	>99
5	H	3-ClC ₆ H ₄	6	71e	99	98:2	>99
6	H	4-BrC ₆ H ₄	6	71f	94	95:5	>99
7	H	3-BrC ₆ H ₄	6	71g	98	98:2	>99
8 ^e	H	4-MeC ₆ H ₄	72	71h	99	99:1	>99
9 ^e	H	3-MeC ₆ H ₄	72	71i	99	98:2	>99
10	H	4-CF ₃ C ₆ H ₄	6	71j	94	92:8	>99
11	H	2-Naph	44	71k	99	97:3	>99
12	H	2-Pyridinyl	10	71l	95	93:7	>99
13	H	2-Thienyl	48	71m	98	99:1	>99
14	H	2-Furyl	36	71n	98	97:3	>99
15	Me	Ph	48	71o	88	97:3	>99
16	Br	Ph	7	71p	98	95:5	>99

^a Conditions: 0.40 mmol Ph₂PH, 5 mol % of cat, 8 ml THF, 0.5 equiv. of bis(enone), 2.0 equiv. of Et₃N were reacted at –80 °C, unless otherwise noted. ^b

Yield was calculated from ³¹P{¹H} NMR of the crude product. ^c dr was calculated from ³¹P{¹H} NMR. Errors may occur due to overlap. ^d ee was

determined from ³¹P{¹H} NMR integration of the signals. ^e Toluene was used as the solvent.

(3) Proposed Mechanism

Based on the preliminary studies and experimental results, a mechanism was proposed for (*R*)-**48**-catalyzed asymmetric hydrophosphination of bis(enones) involving formation of two C*–P bonds (Figure 3.4.1). Free Ph₂PH having high affinity to palladium gives the bisphosphine complex by displacement of the coordinated solvent (NCMe) on (*R*)-**48**. However, the coordinated Ph₂PH moieties, especially the one *trans* to carbon, are labilized and could dissociate easily, allowing bis(enone) to coordinate to palladium. Meanwhile, the Ph₂PH coordinated on palladium is acidified and can be easily deprotonated by Et₃N to form the phosphido intermediate which is very active and can undergo 1,4-addition with the coordinated bis(enone) even at –80 °C to form the phosphine product (monophosphine **I** which was observed by ³¹P NMR during the reaction). The monophosphine **I** can be released by incoming free Ph₂PH on palladium and undergoes the second addition to generate the diphosphine product. In order to further investigate the mechanism, we carried out the reaction with equal amount (mol) of bis(enone) and Ph₂PH. Both monophosphine **I** and diphosphine products were observed which supports the proposed addition.

Bifunctional symmetrical substrates with two equivalent reactive sites present special opportunities or problems in asymmetric catalysis.¹⁰⁰ After the first addition of P–H bond to bis(enone), the selectivity of the second addition of P–H bond may be the same (*rac* product) or different (*meso* product)

depending on the nature of the catalyst and substrates involved. In this reaction, high *rac* selectivity was achieved. In the catalyst system, the palladium serves as a Lewis acid both for Ph_2PH and bis(enones), and make the 1,4-addition proceed smoothly in an intramolecular manner. The stably *ortho*-palladated chiral *C,P*-auxiliary toward displacement by free phosphines in conjunction with the fact that the phosphine species involved are inherently labile on the palladium center is a crucial factor which aids the catalytic cycle (Figure 3.4.1).

Figure 3.4.1

3-4.3 Synthesis of Chiral PCP Pincer Complexes

It should be noted that the chiral PCP diphosphines are versatile ligands forming pincer complexes with broad range of metals. As an illustration, we used the directly synthesized chiral PCP ligand and selected metals (Pd and Pt) for synthesis of chiral PCP pincer complexes in high yields (Scheme 3.4.3). Such kinds of pincer complexes have been reported as efficient catalysts for asymmetric transformations.^{99,78}

Scheme 3.4.3

The PCP ligand (**71a**) reacted with $Pd(NCMe)_2Cl_2$ in dichloromethane smoothly. After 20 h, the palladium pincer complex **72a** (^{31}P NMR: δ 44.8) was successfully formed and isolated in 85% yield. However, the formation of the platinum pincer complex **73a** is much difficult. The PCP ligand (**71a**) reacted with $Pt(NCMe)_2Cl_2$ in toluene refluxing for 2 h to give **73a** (^{31}P NMR: δ 46.7, $J_{Pt-P} = 2947.4$ Hz) in 78% yield.

3-4.4 Conclusion

In summary, we have developed a novel method for straightforward preparation of chiral tertiary diphosphines by hydrophosphination of bis(enoens) catalyzed by a phosphopalladacycle. Broad functional-group tolerance is exhibited and a wide range of substrates can be efficiently converted into the desired products in high yields with excellent diastereo- and enantioselectivities. A putative mechanism was proposed for the asymmetric hydrophosphination involving formation of double C*-P bonds. As an illustration, chiral PCP palladium and platinum pincer complexes were prepared using the directly synthesized chiral PCP ligand (**71a**). One area that will receive increasing interest in the future is the application of chiral PCP pincer complexes. Our protocol is expected to stimulate the chemistry of this area.

3-4.5 Experimental Section

All air-sensitive manipulations were performed under a positive pressure of nitrogen or argon using standard Schlenk line. Solvents were degassed prior to use when necessary. Toluene, THF and acetone were purchased from TEDIA COMPANY (AR) and used without being dried. Low Temp PAIRSTIRRER PSL-1800 machine was used for controlling low temperatures for reactions. Column chromatography was conducted on Silica gel 60 (Merck). NMR spectra were recorded on Brüker ACF 300, 400 and 500 spectrometers. Chemical shifts are reported in δ ppm referenced to an internal SiMe₄ standard ($\delta = 0$ ppm) for

^1H NMR, chloroform- d (δ = 77.23 ppm) for ^{13}C NMR to an external 85% H_3PO_4 standard for $^{31}\text{P}\{^1\text{H}\}$ NMR. Optical rotations of the diphosphine products were measured as soon as possible without inert gas protection on the specified solution in a 0.1 dm cell at 20 °C with a Perkin-Elmer 341 polarimeter. Elemental analyses were performed by the Elemental Analysis Laboratory of the Division of Chemistry and Biological Chemistry at Nanyang Technological University. Melting points were measured using the SRS Optimelt Automated Melting Point System, SRS MPA100.

The bis(enones) were prepared according to literatures.¹⁰²

Caution! Perchlorate salts of metal complexes are potentially explosive compounds and should be handled with care.

(1) General Procedure

To a solution of Ph_2PH **17** (78.2 mg, 0.42 mmol, 1.0 equiv) in toluene or THF (8 mL) is added (*R*)-**48** (7.9 mg, 0.0126 mmol, 3 mol%). The solution was stirred at room temperature for 10 minutes, and then was cooled to -80 °C. Subsequently, aromatic bis(enone) **70** (0.21 mmol, 0.5 equiv) was added. Et_3N (21.2 mg, 0.21 mmol, 0.5 equiv) in toluene or THF (0.5 mL) was added dropwise. The solution was subsequently stirred at -80 °C. The reaction was

monitored by $^{31}\text{P}\{^1\text{H}\}$ NMR. After the reaction is completed, the mixture was warmed to room temperature. Diastereoselectivity (dr) was measured by $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum of the crude products. If THF was used as the solvent for the reaction, then the solution was evaporated by vacuum pump to give crude the diphosphine product **71** (air sensitive). The crude product was dissolved in 10 ml DCM, and filtered through a short silica gel column using a pipette fixed on a two-neck Schlenk flask protected by nitrogen or argon (in order to remove the catalyst and phosphine oxides, if any). If toluene was used as the solvent, the solution was filtered directly through a short silica gel. The solvent was removed by vacuum pump to give the diphosphine product **71**.

(2) Determination of dr and ee

The obtained diphosphine product **71** was allowed to react with 1.01 equiv of enantiopure dimeric complex (*R*)-**14** (a little excess) in dichloromethane to form derivatives (Scheme 3.4.4). Theoretically, there are four possible derivatives (*R,S,S,R*)-**73**, (*R,S,R,R*)-**73**, (*R,R,R,R*)-**73** and (*R,R,S,R*)-**73**. The major isomer (*R,S,S,R*)-**73a** ($\text{R}^1=\text{H}$, $\text{R}^2=\text{Ph}$) was isolated and crystallized from benzene-pentane as gray prisms. Its structure was confirmed by fractional X-ray analysis (Figure 3.4.2).

Diastereomeric ratio (dr) and enantiomeric excess (ee %) were measured by $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum of the corresponding compounds.

$$\text{dr} = \frac{\text{rac-71}}{\text{meso-71}} = \frac{(\text{S,S})\text{-71} + (\text{R,R})\text{-71}}{(\text{S,R})\text{-71} + (\text{R,S})\text{-71}}$$

$$ee = \frac{(S,S)\text{-71} - (R,R)\text{-71}}{(S,S)\text{-71} + (R,R)\text{-71}} = \frac{(R,S,S,R)\text{-73} - (R,R,R,R)\text{-73}}{(R,S,S,R)\text{-73} + (R,R,R,R)\text{-73}}$$

Scheme 3.4.4

Figure 3.4.2 Molecular structure and absolute stereochemistry of (*R,S,S,R*)-**73a** with 50% probability thermal ellipsoids shown. Hydrogen atoms except those on the chiral center and solvent are omitted for clarity.

Table 3.4.3 Selected Bond Lengths (Å) and Angles (deg) of (*R,S,S,R*)-**73a**

Pd1–C1	2.033(7)	Pd1–N1	2.142(6)
Pd1–P1	2.274(2)	Pd1–Cl1	2.405(2)
Pd2–C63	2.026(6)	Pd2–N2	2.137(5)
Pd2–P2	2.267(2)	Pd2–Cl2	2.408(2)
C15–P1	1.846(7)	C21–P1	1.823(7)
C27–P1	1.886(7)	C42–P2	1.878(6)
C51–P2	1.848(6)	C57–P2	1.814(7)
C1–Pd1–N1	79.7(2)	C1–Pd1–P1	97.4(2)
N1–Pd1–P1	175.8(2)	C1–Pd1–Cl1	167.9(2)
N1–Pd1–Cl1	91.8(2)	P1–Pd1–Cl1	91.6(6)
C63–Pd2–N2	79.9(2)	C63–Pd2–P2	95.2(2)
N2–Pd2–P2	175.0(2)	C63–Pd2–Cl2	169.1(2)
N2–Pd2–Cl2	91.2(2)	P2–Pd2–Cl2	93.8(7)
C10–C1–Pd1	113.2(5)	C2–C1–Pd1	127.4(5)
C20–C15–P1	122.7(5)	C16–C15–P1	116.9(5)
C43–C42–P2	112.6(4)	C40–C42–P2	110.5(4)
C56–C51–P2	118.6(5)	C52–C51–P2	123.2(5)

Identification of monophosphine product, *rac*-71 and *meso*-71:

(1) Synthesis of monophosphine

Bis(enone) **70a** (1eq) and Ph_2PH **17** (1eq) were reacted under the same conditions with the expectation to obtain the monophosphine product, however, the mixture of monophosphine product and diphosphine **71a** was obtained. The ^{31}P NMR spectrum of the crude mixture was shown as below:

(2) The mixture of *rac*-71a and *meso*-71a

The mixture of *rac*-**71a** and *meso*-**71a** isomers is shown in the ^{31}P NMR spectrum.

Identification of (*S,S*)-**71** and (*R,R*)-**71** and their derivatives (*R,S,S,R*)-**73**, (*R,R,R,R*)-**73**

Asymmetric addition of Ph_2PH **17** to a bis(enone), **70a** for example, catalyzed by catalyst (*R*)-**48** to form the major product (*S,S*)-**71a** followed by treatment with (*R*)-**14** leading to (*R,S,S,R*)-**73a** (spectrum A, page 144) which was confirmed by fractional X-ray analysis. There are two ways to identify the $^{31}\text{P}\{^1\text{H}\}$ NMR chemical shift of the other enantiomer of (*S,S*)-**71a**, that is (*R,R*)-**71a**: (1) Treatment of (*S,S*)-**71a** with (*S*)-**14** leads to (*S,S,S,S*)-**73a** (spectrum B, page 144) which is an enantiomer of (*R,R,R,R*)-**73a**. Therefore, (*S,S,S,S*)-**73a** and (*R,R,R,R*)-**73a** have the identical $^{31}\text{P}\{^1\text{H}\}$ NMR chemical shift. (2) Prepare (*R,R*)-**71** using catalyst (*S*)-**48** instead of (*R*)-**48** under the same conditions followed by treatment of (*R*)-**14** leading to (*R,R,R,R*)-**73a** (spectrum C, page 144). Indeed, (*S,S,S,S*)-**73a** and (*R,R,R,R*)-**73a** have the identical $^{31}\text{P}\{^1\text{H}\}$ NMR chemical shift as shown in the spectrum. Therefore, ee can be measured from the integration of the corresponding compounds:

$$\text{ee} = \frac{(\text{S,S})\text{-71} - (\text{R,R})\text{-71}}{(\text{S,S})\text{-71} + (\text{R,R})\text{-71}} = \frac{(\text{R,S,S,R})\text{-73} - (\text{R,R,R,R})\text{-73}}{(\text{R,S,S,R})\text{-73} + (\text{R,R,R,R})\text{-73}} = \frac{(\text{R,S,S,R})\text{-73} - (\text{S,S,S,S})\text{-73}}{(\text{R,S,S,R})\text{-73} + (\text{S,S,S,S})\text{-73}}$$

(3) Synthesis of Chiral Diphosphines

(*S,S*)-**71a**

(Table 3.4.2, Entry 1)

(*S,S*)-**71a** was synthesized according to general procedure (99% yield, >99% ee)

(airsensitive): $[\alpha]_D^{20} = -251.2$ (c 1.7, toluene). ^{31}P NMR(CDCl_3 , 162 M):

δ -1.8; ^1H NMR (CDCl_3 , 400 M): δ 2.93 (ddd, 2H, $J = 17.1$ Hz, 8.6 Hz, 2.8 Hz,

CHHCOPh), 3.53 – 3.61 (m, 2H, CHHCOPh), 4.18 – 4.23 (m, 2H, PCHCH_2),

6.78 – 7.58 (m, 34H, Ar); ^{13}C NMR (CDCl_3 , 100 M): δ 40.0 (d, 2C, $^1J_{\text{PC}} = 10.9$

Hz, PCH), 42.9 (d, 2C, $^2J_{\text{PC}} = 22.2$ Hz, CH_2COPh), 128.0 – 141.2 (m, 42C, Ar),

198.0 (d, 2C, $^3J_{\text{PC}} = 12.8$ Hz, COPh).

Checking dr: ^{31}P $\{^1\text{H}\}$ NMR

(*S,S*)-**71b**

(Table 3.4.2, Entry 2)

(*S,S*)-**71b** was synthesized according to general procedure (99% yield, >99% ee).

(airsensitive): $[\alpha]_D^{20} = -233.3$ (*c* 1.8, toluene). ^{31}P NMR(CDCl_3 , 162 M):

δ - 1.8; ^1H NMR (CDCl_3 , 400 M): δ 2.87 (ddd, 2H, $J = 16.8$ Hz, 8.2 Hz, 2.4 Hz, CHHCOPh), 3.49 – 3.57 (m, 2H, CHHCOPh), 4.15 – 4.20 (m, 2H, PCHCH_2), 6.77 – 7.60 (m, 32H, Ar); ^{13}C NMR (CDCl_3 , 100 M): δ 40.2 (d, 2C, $^1J_{\text{PC}} = 11.1$ Hz, PCH), 42.8 (d, 2C, $^2J_{\text{PC}} = 22.5$ Hz, CH_2COPh), 115.5 – 167.0 (m, 42C, Ar), 196.6 (d, 2C, $^3J_{\text{PC}} = 12.9$ Hz, COPh).

(*S,S*)-**71c**

(Table 3.4.2, Entry 3)

(*S,S*)-**71c** was synthesized according to general procedure (99% yield, >99% ee).

(airsensitive): $[\alpha]_D^{20} = -170.7$ (*c* 1.2, CH_2Cl_2). ^{31}P NMR(CDCl_3 , 162 M):

δ - 1.9; ^{19}F NMR(CDCl_3 , 376.5 M): δ - 111.9; ^1H NMR (CDCl_3 , 400 M): δ 2.87 (ddd, 2H, $J = 17.2$ Hz, 8.4 Hz, 2.8 Hz, CHHCOPh), 3.48 – 3.56 (m, 2H, CHHCOPh), 4.15 – 4.20 (m, 2H, PCHCH_2), 6.79 – 7.58 (m, 32H, Ar); ^{13}C NMR (CDCl_3 , 100 M): δ 40.0 (d, 2C, $^1J_{\text{PC}} = 11.2$ Hz, PCH), 43.0 (d, 2C, $^2J_{\text{PC}} = 22.3$ Hz, CH_2COPh), 114.7 – 164.0 (m, 42C, Ar), 196.8 (d, 2C, $^3J_{\text{PC}} = 12.5$ Hz, COPh).

(*S,S*)-**71d**

(Table 3.4.2, Entry 4)

(*S,S*)-**71d** was synthesized according to general procedure (99% yield, >99% ee). (airsensitive): $[\alpha]_{\text{D}}^{20} = -156.1$ (*c* 1.0, CH₂Cl₂). ³¹P NMR(CDCl₃, 162 M): δ -1.9; ¹H NMR (CDCl₃, 400 M): δ 2.85 (ddd, 2H, *J* = 16.9 Hz, 8.2 Hz, 2.8 Hz, CHHCOPh), 3.47 – 3.55 (m, 2H, CHHCOPh), 4.14 – 4.19 (m, 2H, PCHCH₂), 6.76 – 7.30 (m, 32H, Ar); ¹³C NMR (CDCl₃, 100 M): δ 40.2 (d, 2C, ¹*J*_{PC} = 11.2 Hz, PCH), 42.8 (d, 2C, ²*J*_{PC} = 22.7 Hz, CH₂COPh), 128.0 – 141.2 (m, 42C, Ar), 197.0 (d, 2C, ³*J*_{PC} = 12.9 Hz, COPh).

(*S,S*)-**71e**

(Table 3.4.2, Entry 5)

(*S,S*)-**71e** was synthesized according to general procedure (99% yield, >99% ee). (airsensitive): $[\alpha]_{\text{D}}^{20} = -181.0$ (*c* 1.0, CH₂Cl₂). ³¹P NMR(CDCl₃, 162 M): δ -1.8; ¹H NMR (CDCl₃, 400 M): δ 2.90 (ddd, 2H, *J* = 17.2 Hz, 8.2 Hz, 2.8 Hz, CHHCOPh), 3.47–3.55 (m, 2H, CHHCOPh), 4.11–4.20 (m, 2H, PCHCH₂), 6.79–7.34 (m, 32H, Ar); ¹³C NMR (CDCl₃, 100 M): δ 40.0 (d, 2C, ¹*J*_{PC} = 11.3 Hz, PCH), 42.8 (d, 2C, ²*J*_{PC} = 22.9 Hz, CH₂COPh), 126.3–141.1 (m, 42C, Ar), 196.8 (d, 2C, ³*J*_{PC} = 12.9 Hz, COPh).

(Table 3.4.2, Entry 6)

(*S,S*)-**71f** was synthesized according to general procedure (94% yield, >99% ee).

(airsensitive): $[\alpha]_{\text{D}}^{20} = -100.6$ (*c* 1.0, CH₂Cl₂). ³¹P NMR(CDCl₃, 162 M): δ -1.9;

¹H NMR (CDCl₃, 400 M): δ 2.84 (ddd, 2H, *J* = 16.8 Hz, 8.1 Hz, 2.4 Hz,

CHHCOPh), 3.46–3.54 (m, 2H, *CHHCOPh*), 4.13–4.18 (m, 2H, *PCHCH*₂),

6.77–7.59 (m, 32H, Ar); ¹³C NMR (CDCl₃, 100 M): δ 40.2 (d, 2C, ¹*J*_{PC} = 11.3

Hz, *PCH*), 42.8 (d, 2C, ²*J*_{PC} = 22.6 Hz, CH₂COPh), 127.9–141.2 (m, 42C, Ar),

197.2 (d, 2C, ³*J*_{PC} = 12.9 Hz, COPh).

(Table 3.4.2, Entry 7)

(*S,S*)-**71g** was synthesized according to general procedure (98% yield, >99%

ee). (airsensitive): $[\alpha]_{\text{D}}^{20} = -154.3$ (*c* 1.1, CH₂Cl₂). ³¹P NMR(CDCl₃, 162 M):

δ -1.8; ¹H NMR (CDCl₃, 400 M): δ 2.89 (ddd, 2H, *J* = 17.1 Hz, 8.2 Hz, 2.9 Hz,

CHHCOPh), 3.46–3.54 (m, 2H, *CHHCOPh*), 4.14–4.19 (m, 2H, *PCHCH*₂),

6.79–7.56 (m, 32H, Ar); ¹³C NMR (CDCl₃, 100 M): δ 40.0 (d, 2C, ¹*J*_{PC} = 11.3

Hz, *PCH*), 43.0 (d, 2C, ²*J*_{PC} = 22.7 Hz, CH₂COPh), 123.0–141.1 (m, 42C, Ar),

196.7 (d, 2C, ³*J*_{PC} = 12.8 Hz, COPh).

(*S,S*)-**71h**

(Table 3.4.2, Entry 8)

(*S,S*)-**71h** was synthesized according to general procedure (99% yield, >99% ee). (airsensitive): $[\alpha]_{\text{D}}^{20} = -240.4$ (*c* 1.9, toluene). ^{31}P NMR(CDCl_3 , 162 M): δ -1.7; ^1H NMR (CDCl_3 , 400 M): δ 2.21 (s, 6H, CH_3), 2.89 (ddd, 2H, $J = 17.0$ Hz, 8.6 Hz, 2.7 Hz, CHHCOPh), 3.51–3.59 (m, 2H, CHHCOPh), 4.17–4.22 (m, 2H, PCHCH_2), 6.73–7.47 (m, 32H, Ar); ^{13}C NMR (CDCl_3 , 100 M): δ 21.7 (s, 2C, CH_3), 40.1 (d, 2C, $^1J_{\text{PC}} = 10.9$ Hz, PCH), 42.7 (d, 2C, $^2J_{\text{PC}} = 22.4$ Hz, CH_2COPh), 127.9–143.7 (m, 42C, Ar), 197.7 (d, 2C, $^3J_{\text{PC}} = 12.8$ Hz, COPh).

(*S,S*)-**71i**

(Table 3.4.2, Entry 9)

(*S,S*)-**71i** was synthesized according to general procedure (99% yield, >99% ee). (airsensitive): $[\alpha]_{\text{D}}^{20} = -199.3.4$ (*c* 1.5, CH_2Cl_2). ^{31}P NMR(CDCl_3 , 162 M): δ -1.6; ^1H NMR (CDCl_3 , 400 M): δ 2.22 (s, 6H, CH_3), 2.93 (ddd, 2H, $J = 17.2$ Hz, 8.6 Hz, 2.8 Hz, CHHCOPh), 3.53–3.61 (m, 2H, CHHCOPh), 4.18–4.23 (m, 2H, PCHCH_2), 6.75–7.57 (m, 32H, Ar); ^{13}C NMR (CDCl_3 , 100 M): δ 21.5 (s, 2C, CH_3), 40.0 (d, 2C, $^1J_{\text{PC}} = 10.9$ Hz, PCH), 42.9 (d, 2C, $^2J_{\text{PC}} = 22.7$ Hz, CH_2COPh), 125.4–141.3 (m, 42C, Ar), 198.2 (d, 2C, $^3J_{\text{PC}} = 12.7$ Hz, COPh).

(Table 3.4.2, Entry 10)

(S,S)-**71j** was synthesized according to general procedure (94% yield, >99% ee). (airsensitive): $[\alpha]_D^{20} = -114.3$ (*c* 1.0, CH₂Cl₂). ³¹P NMR(CDCl₃, 162 M): δ-1.9; ¹⁹F NMR(CDCl₃, 376.5 M): δ-63.1; ¹H NMR (CDCl₃, 400 M): δ2.90 (ddd, 2H, *J* = 17.0 Hz, 8.0 Hz, 2.7 Hz, CHHCOPh), 3.51–3.59 (m, 2H, CHHCOPh), 4.15–4.20 (m, 2H, PCHCH₂), 6.81–7.60 (m, 32H, Ar); ¹³C NMR (CDCl₃, 100 M): δ 40.2 (d, 2C, ¹*J*_{PC} = 11.5 Hz, PCH), 43.2 (d, 2C, ²*J*_{PC} = 22.5 Hz, CH₂COPh), 122.3–141.1 (m, 42C, Ar), 197.4 (d, 2C, ³*J*_{PC} = 13.1 Hz, COPh).

(Table 3.4.2, Entry 11)

(S,S)-**71k** was synthesized according to general procedure (99% yield, >99% ee). (airsensitive): $[\alpha]_D^{20} = -183.0$ (*c* 1.1, CH₂Cl₂). ³¹P NMR(CDCl₃, 162 M): δ-1.8; ¹H NMR (CDCl₃, 400 M): δ3.04 (ddd, 2H, *J* = 17.1 Hz, 8.8 Hz, 2.6 Hz, CHHCOPh), 3.65–3.73 (m, 2H, CHHCOPh), 4.23–4.28 (m, 2H, PCHCH₂), 6.82–8.06 (m, 38H, Ar); ¹³C NMR (CDCl₃, 100 M): δ 40.2 (d, 2C, ¹*J*_{PC} = 10.9 Hz, PCH), 43.0 (d, 2C, ²*J*_{PC} = 22.6 Hz, CH₂COPh), 123.9–141.3 (m, 50C, Ar), 197.9 (d, 2C, ³*J*_{PC} = 12.7 Hz, COPh).

(*S,S*)-**71l**

(Table 3.4.2, Entry 12)

(*S,S*)-**71l** was synthesized according to general procedure (95% yield, >99% ee) (airsensitive): $[\alpha]_D^{20} = -186.6$ (*c* 1.5, CH₂Cl₂). ³¹P NMR(CDCl₃, 162 M): δ -0.4; ¹H NMR (CDCl₃, 400 M): δ 3.22 (ddd, 2H, *J* = 17.5 Hz, 8.0 Hz, 3.4 Hz, CHHCOPh), 3.86–3.94 (m, 2H, CHHCOPh), 4.18–4.23 (m, 2H, PCHCH₂), 6.71–8.55 (m, 32H, Ar); ¹³C NMR (CDCl₃, 100 M): δ 40.0 (d, 2C, ¹*J*_{PC} = 12.2 Hz, PCH), 41.8 (d, 2C, ²*J*_{PC} = 22.4 Hz, CH₂COPh), 121.8–153.4 (m, 40C, Ar), 199.6 (d, 2C, ³*J*_{PC} = 12.2 Hz, COPh).

(*S,S*)-**71m**

(Table 3.4.2, Entry 13)

(*S,S*)-**71m** was synthesized according to general procedure (98% yield, >99% ee) (airsensitive): $[\alpha]_D^{20} = -170.6$ (*c* 1.1, CH₂Cl₂). ³¹P NMR(CDCl₃, 162 M): δ -1.8; ¹H NMR (CDCl₃, 400 M): δ 2.87 (ddd, 2H, *J* = 16.3 Hz, 8.2 Hz, 2.8 Hz, CHHCOPh), 3.46–3.54 (m, 2H, CHHCOPh), 4.14–4.19 (m, 2H, PCHCH₂), 6.71–7.61 (m, 30H, Ar); ¹³C NMR (CDCl₃, 100 M): δ 40.5 (d, 2C, ¹*J*_{PC} = 11.3 Hz, PCH), 43.5 (d, 2C, ²*J*_{PC} = 22.3 Hz, CH₂COPh), 128.0–144.5 (m, 38C, Ar), 191.0 (d, 2C, ³*J*_{PC} = 13.4 Hz, COPh).

(*S,S*)-**71n**

(Table 3.4.2, Entry 14)

(*S,S*)-**71n** was synthesized according to general procedure (98% yield, >99% ee)

(airsensitive): $[\alpha]_D^{20} = -274.5$ (*c* 1.5, CH₂Cl₂). ³¹P NMR(CDCl₃, 162 M): δ -1.5;

¹H NMR (CDCl₃, 400 M): δ 2.78 (ddd, 2H, *J* = 16.4 Hz, 8.0 Hz, 3.0 Hz,

CHHCOPh), 3.39–3.47 (m, 2H, CHHCOPh), 4.13–4.18 (m, 2H, PCHCH₂),

6.22–7.62 (m, 30H, Ar); ¹³C NMR (CDCl₃, 100 M): δ 40.1 (d, 2C, ¹*J*_{PC} = 11.6

Hz, PCH), 43.5 (d, 2C, ²*J*_{PC} = 22.2 Hz, CH₂COPh), 117.6–152.8 (m, 38C, Ar),

187.1 (d, 2C, ³*J*_{PC} = 13.1 Hz, COPh).

(*S,S*)-**71o**

(Table 3.4.2, Entry 15)

(*S,S*)-**71o** was synthesized according to general procedure (88% yield, >99% ee)

(airsensitive): $[\alpha]_D^{20} = -163.8$ (*c* 1.0, CH₂Cl₂). ³¹P NMR(CDCl₃, 121 M): δ -0.8;

¹H NMR (CDCl₃, 300 M): δ 1.88 (s, 3H, CH₃), 2.92 (ddd, 2H, *J* = 17.0 Hz, 8.7

Hz, 2.8 Hz, CHHCOPh), 3.49–3.59 (m, 2H, CHHCOPh), 4.12–4.19 (m, 2H,

PCHCH₂), 6.56–7.59 (m, 33H, Ar); ¹³C NMR (CDCl₃, 75 M): δ 21.3 (s, 1C,

CH₃), 39.9 (d, 2C, ¹*J*_{PC} = 11.0 Hz, PCH), 42.8 (d, 2C, ²*J*_{PC} = 22.4 Hz,

CH₂COPh), 126.5–141.0 (m, 42C, Ar), 198.1 (d, 2C, ³*J*_{PC} = 12.6 Hz, COPh).

(Table 3.4.2, Entry 16)

(*S,S*)-**71p** was synthesized according to general procedure (98% yield, >99% ee)

(airsensitive): $[\alpha]_{\text{D}}^{20} = -179.8$ (*c* 1.1, CH₂Cl₂). ³¹P NMR(CDCl₃, 162 M):

δ - 1.2; ¹H NMR (CDCl₃, 400 M): δ 3.05 (ddd, 2H, *J* = 17.4 Hz, 8.6 Hz, 2.8 Hz,

CHHCOPh), 3.58 - 3.66 (m, 2H, CHHCOPh), 4.21 - 4.29 (m, 2H, PCHCH₂),

6.99 - 7.69 (m, 33H, Ar); ¹³C NMR (CDCl₃, 100 M): δ 39.5 (d, 2C, ¹*J*_{PC} = 12.1

Hz, PCH), 42.5 (d, 2C, ²*J*_{PC} = 22.1 Hz, CH₂COPh), 122.1 - 143.4 (m, 42C, Ar),

197.5 (d, 2C, ³*J*_{PC} = 12.3 Hz, COPh).

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2-Nitrochalcone 1.1 eq., reacted at $-80\text{ }^{\circ}\text{C}$ for 2 days, then at $-10\text{ }^{\circ}\text{C}$ for another 2 days. The product cannot be purified by recrystallization.

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Publications

1. **Yinhua Huang**, Sumod A. Pullarkat, Mingjun Yuan, Yi Ding, Yongxin Li, and Pak-Hing Leung*, Palladium Template Promoted Asymmetric Synthesis of 1,2-Diphosphines by Hydrophosphination of Functionalized Allenes. *Organometallics* **2010**, 29, 536-542.
2. **Yinhua Huang**, Sumod A. Pullarkat, Yongxin Li, and Pak-Hing Leung*, Palladium (II)-catalyzed asymmetric hydrophosphination of enones: efficient access to chiral tertiary phosphines, *Chem. Commun.* **2010**, 46, 6950-6952. (**Highlighted in SYNFACTS and ChemInform**).
3. **Yinhua Huang**, Renta Jonathan Chew, Yongxin Li, Sumod A. Pullarkat* and Pak-Hing Leung*, Direct Synthesis of Chiral Tertiary Diphosphines *via* Pd(II)-Catalyzed Asymmetric Hydrophosphination of Dienones. *Org. Lett.* **2011**, 13, 5862-5865.
4. **Yinhua Huang**, Sumod A. Pullarkat, Yongxin Li and Pak-Hing Leung*, Palladacycle-Catalyzed Asymmetric Hydrophosphination of Enones for Synthesis of C*- and P*-Chiral Tertiary Phosphines. *Inorg. Chem.* **2012**, 51, 2533-2540.
5. **Yinhua Huang**, Sumod A. Pullarkat, Siewping Teong, Renta Jonathan Chew, Yongxin Li and Pak-Hing Leung*, Asymmetric Intermolecular Construction of Chiral Tertiary *P*-Heterocycles by Pd (II)-Catalyzed Stepwise Addition of H-P-H Bonds to Bis(enones). Manuscript, submitted for publication.

6. **Yinhua Huang**, Selvi, Sumod A. Pullarkat, Yongxin Li and Pak-Hing Leung*, Design, Synthesis and Resolution of Novel Chiral Palladacycles. Manuscript in preparation.
7. Yuan, M.; Pullarkat, S. A.; Ma, M.; Zhang, Y.; **Huang, Y.**; Li, Y.; Goel, A.; Leung, P.-H., Asymmetric Synthesis of Functionalized 1,2-Diphosphine via the Chemoselective Hydrophosphination of Coordinated Allylic Phosphines. *Organometallics* **2009**, 28, 780-786

Conference Publications

1. **Yinhua Huang**, Yongxin Li, Sumod A. Pullarkat, Pak-Hing Leung, Palladium(II) catalysed enantioselective addition of diphenylphosphine to enones: efficient access to chiral tertiary phosphines, 241st American Chemical Society (ACS) National Meeting and Exposition, 27-31 March 2011, Anaheim, California, USA.
2. **Yinhua Huang**, Sumod A. Pullarkat, Yongxin Li and Pak-Hing Leung, Direct Synthesis of Chiral Tertiary Diphosphines *via* Pd(II)-Catalyzed Asymmetric Hydrophosphination of Dienones, 3rd A*STAR Chemistry Symposium, 10 November 2011, Singapore.
3. **Yinhua Huang**, Sumod A. Pullarkat, Yongxin Li and Pak-Hing Leung, Palladium(II) catalysed Asymmetric Hydrophosphination of enones: efficient access to chiral tertiary phosphines, 6th Asian-European Symposium, 7-9 June 2010, Singapore.

Appendices

X-ray Crystallographic Data

The X-ray structural analyses were kindly performed by Dr Yongxin Li at Division of Chemistry & Biological Chemistry, Nanyang Technological University. Complete tables of crystal data, data collection, solution and refinement, final positional parameters, bond distances and angles, thermal parameters of non-hydrogen atoms and calculated hydrogen parameters are available from Professor Leung Pak Hing upon request.

$$R1 = \sum ||F_o| - |F_c|| / \sum |F_o|;$$
$$wR2 = \sqrt{\{\sum [w(F_o^2 - F_c^2)^2] / \sum [w(F_o^2)^2]\}}, w^{-1} = \sigma^2(F_o)^2 + (aP)^2 + bP.$$

Table A-1.1. Crystal Data and Structure Refinement for (R,S)-19a

Empirical formula	C ₄₄ H ₄₆ Cl N O ₆ P ₂ Pd	
Formula weight	888.61	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 8.6173(2) Å	α = 90°.
	b = 21.5832(6) Å	β = 90°.
	c = 21.7076(6) Å	γ = 90°.
Volume	4037.37(18) Å ³	
Z	4	
Density (calculated)	1.462 Mg/m ³	
Absorption coefficient	0.655 mm ⁻¹	
F(000)	1832	
Crystal size	0.34 x 0.14 x 0.08 mm ³	
Theta range for data collection	1.88 to 26.46°.	
Index ranges	-10 ≤ h ≤ 10, -27 ≤ k ≤ 27, -27 ≤ l ≤ 27	
Reflections collected	33851	
Independent reflections	8311 [R(int) = 0.0481]	
Completeness to theta = 26.46°	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9495 and 0.8081	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	8311 / 73 / 546	
Goodness-of-fit on F ²	1.150	
Final R indices [I > 2σ(I)]	R1 = 0.0366, wR2 = 0.0901	
R indices (all data)	R1 = 0.0501, wR2 = 0.1151	
Absolute structure parameter	-0.05(3)	
Largest diff. peak and hole	0.821 and -0.842 e.Å ⁻³	

Table A-1.2. Crystal Data and Structure Refinement for (R,S)-19b

Empirical formula	C43 H44 Cl N O5 P2 Pd	
Formula weight	858.58	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 11.9241(2) Å	$\alpha = 90^\circ$.
	b = 15.8526(3) Å	$\beta = 90^\circ$.
	c = 21.0733(4) Å	$\gamma = 90^\circ$.
Volume	3983.44(13) Å ³	
Z	4	
Density (calculated)	1.432 Mg/m ³	
Absorption coefficient	0.659 mm ⁻¹	
F(000)	1768	
Crystal size	0.20 x 0.16 x 0.14 mm ³	
Theta range for data collection	1.61 to 26.66°.	
Index ranges	-14 ≤ h ≤ 14, -19 ≤ k ≤ 19, -26 ≤ l ≤ 26	
Reflections collected	36321	
Independent reflections	8295 [R(int) = 0.0328]	
Completeness to theta = 26.66°	99.1 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9134 and 0.8795	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	8295 / 30 / 482	
Goodness-of-fit on F ²	1.146	
Final R indices [I > 2σ(I)]	R1 = 0.0306, wR2 = 0.0900	
R indices (all data)	R1 = 0.0378, wR2 = 0.1112	
Absolute structure parameter	0.00(3)	
Largest diff. peak and hole	1.361 and -0.979 e.Å ⁻³	

Table A-1.3. Crystal Data and Structure Refinement for (S)-23a

Empirical formula	C _{30.50} H _{30.50} Cl _{3.50} O ₂ P ₂ Pd	
Formula weight	721.46	
Temperature	103(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 10.9534(8) Å	α = 90°.
	b = 13.6798(10) Å	β = 90°.
	c = 41.156(3) Å	γ = 90°.
Volume	6166.8(8) Å ³	
Z	8	
Density (calculated)	1.554 Mg/m ³	
Absorption coefficient	1.036 mm ⁻¹	
F(000)	2920	
Crystal size	0.40 x 0.30 x 0.08 mm ³	
Theta range for data collection	1.79 to 40.00°.	
Index ranges	-11 ≤ h ≤ 19, -24 ≤ k ≤ 24, -69 ≤ l ≤ 74	
Reflections collected	156260	
Independent reflections	38198 [R(int) = 0.0376]	
Completeness to theta = 40.00°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9217 and 0.6820	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	38198 / 247 / 760	
Goodness-of-fit on F ²	1.236	
Final R indices [I > 2σ(I)]	R1 = 0.0748, wR2 = 0.1671	
R indices (all data)	R1 = 0.0856, wR2 = 0.1768	
Absolute structure parameter	0.04(2)	
Largest diff. peak and hole	1.777 and -2.855 e.Å ⁻³	

Table A-2.1.1 Crystal Data and Structure Refinement for (*R,S*)-55

Empirical formula	C ₂₂ H ₃₀ N ₂ O ₂ Pd
Formula weight	460.88
Temperature	103(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	P2(1)2(1)2(1)
Unit cell dimensions	$a = 10.0810(6) \text{ Å}$ $\alpha = 90^\circ$. $b = 16.6942(12) \text{ Å}$ $\beta = 90^\circ$. $c = 23.9570(17) \text{ Å}$ $\gamma = 90^\circ$.
Volume	4031.8(5) Å ³
Z	8
Density (calculated)	1.519 Mg/m ³
Absorption coefficient	0.940 mm ⁻¹
F(000)	1904
Crystal size	0.14 x 0.10 x 0.08 mm ³
Theta range for data collection	2.09 to 30.88°.
Index ranges	0 ≤ h ≤ 14, 0 ≤ k ≤ 24, 0 ≤ l ≤ 34
Reflections collected	7976
Independent reflections	7976 [R(int) = 0.0000]
Completeness to theta = 30.88°	99.5 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9286 and 0.8797
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	7976 / 2 / 504
Goodness-of-fit on F ²	1.096
Final R indices [I > 2σ(I)]	R1 = 0.0439, wR2 = 0.0920
R indices (all data)	R1 = 0.0598, wR2 = 0.1128
Absolute structure parameter	0.46(4)
Largest diff. peak and hole	0.800 and -1.155 e.Å ⁻³

Table A-2.1.2 Crystal Data and Structure Refinement for (R,S)-56

Empirical formula	C ₃₀ H ₃₈ Cl ₆ N ₂ O ₂ Pd	
Formula weight	777.72	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 10.2707(3) Å	α = 90°.
	b = 16.4956(5) Å	β = 90°.
	c = 19.5964(7) Å	γ = 90°.
Volume	3320.05(18) Å ³	
Z	4	
Density (calculated)	1.556 Mg/m ³	
Absorption coefficient	1.072 mm ⁻¹	
F(000)	1584	
Crystal size	0.40 x 0.20 x 0.12 mm ³	
Theta range for data collection	1.61 to 30.56°.	
Index ranges	-14 ≤ h ≤ 14, -23 ≤ k ≤ 23, -28 ≤ l ≤ 27	
Reflections collected	43263	
Independent reflections	10172 [R(int) = 0.0431]	
Completeness to theta = 30.56°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.8821 and 0.6736	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	10172 / 1 / 375	
Goodness-of-fit on F ²	1.076	
Final R indices [I > 2σ(I)]	R1 = 0.0376, wR2 = 0.0989	
R indices (all data)	R1 = 0.0449, wR2 = 0.1097	
Absolute structure parameter	0.01(2)	
Largest diff. peak and hole	1.615 and -1.131 e.Å ⁻³	

Table A-2.1.3 Crystal Data and Structure Refinement for (*R,S*)-42

Empirical formula	C35 H45 Cl5 N2 Pd2
Formula weight	883.78
Temperature	103(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P1
Unit cell dimensions	$a = 9.7725(4)$ Å $\alpha = 81.602(2)^\circ$. $b = 11.8479(4)$ Å $\beta = 81.779(2)^\circ$. $c = 15.9094(6)$ Å $\gamma = 89.998(2)^\circ$.
Volume	1803.16(12) Å ³
Z	2
Density (calculated)	1.628 Mg/m ³
Absorption coefficient	1.395 mm ⁻¹
F(000)	892
Crystal size	0.40 x 0.38 x 0.14 mm ³
Theta range for data collection	1.31 to 33.00°.
Index ranges	-14 ≤ h ≤ 14, -18 ≤ k ≤ 18, -24 ≤ l ≤ 24
Reflections collected	36623
Independent reflections	24019 [R(int) = 0.0301]
Completeness to theta = 33.00°	97.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.8286 and 0.6053
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	24019 / 18 / 801
Goodness-of-fit on F ²	1.087
Final R indices [I > 2σ(I)]	R1 = 0.0582, wR2 = 0.1411
R indices (all data)	R1 = 0.0680, wR2 = 0.1489
Absolute structure parameter	-0.01(3)
Largest diff. peak and hole	5.588 and -2.892 e.Å ⁻³

Table A-2.1.4 Crystal Data and Structure Refinement for (R,S)-44

Empirical formula	C ₄₈ H ₅₉ Cl ₇ N ₂ Pd ₂	
Formula weight	1124.92	
Temperature	103(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	C222(1)	
Unit cell dimensions	a = 14.7142(7) Å	α = 90°.
	b = 17.0743(7) Å	β = 90°.
	c = 39.0046(17) Å	γ = 90°.
Volume	9799.3(7) Å ³	
Z	8	
Density (calculated)	1.525 Mg/m ³	
Absorption coefficient	1.151 mm ⁻¹	
F(000)	4576	
Crystal size	0.30 x 0.26 x 0.20 mm ³	
Theta range for data collection	1.83 to 31.05°.	
Index ranges	-21 ≤ h ≤ 21, -24 ≤ k ≤ 24, -56 ≤ l ≤ 56	
Reflections collected	122249	
Independent reflections	15678 [R(int) = 0.0337]	
Completeness to theta = 31.05°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.8025 and 0.7241	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	15678 / 126 / 691	
Goodness-of-fit on F ²	1.118	
Final R indices [I > 2σ(I)]	R1 = 0.0452, wR2 = 0.1293	
R indices (all data)	R1 = 0.0540, wR2 = 0.1435	
Absolute structure parameter	-0.01(3)	
Largest diff. peak and hole	2.568 and -1.772 e.Å ⁻³	

Table A-2.1.5 Crystal Data and Structure Refinement for (R)-43

Empirical formula	C ₂₁ H ₂₈ Cl N ₃ O ₄ Pd
Formula weight	528.31
Temperature	103(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)
Unit cell dimensions	a = 12.1127(2) Å α = 90°. b = 7.52470(10) Å β = 110.0910(10)°. c = 13.4714(2) Å γ = 90°.
Volume	1153.13(3) Å ³
Z	2
Density (calculated)	1.522 Mg/m ³
Absorption coefficient	0.951 mm ⁻¹
F(000)	540
Crystal size	0.40 x 0.30 x 0.24 mm ³
Theta range for data collection	3.22 to 37.19°.
Index ranges	-20 ≤ h ≤ 20, -12 ≤ k ≤ 8, -22 ≤ l ≤ 22
Reflections collected	25592
Independent reflections	10464 [R(int) = 0.0256]
Completeness to theta = 37.19°	99.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.8038 and 0.7021
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	10464 / 192 / 324
Goodness-of-fit on F ²	1.048
Final R indices [I > 2σ(I)]	R1 = 0.0247, wR2 = 0.0568
R indices (all data)	R1 = 0.0280, wR2 = 0.0584
Absolute structure parameter	-0.019(14)
Largest diff. peak and hole	0.526 and -0.858 e.Å ⁻³

Table A-2.1.6 Crystal Data and Structure Refinement for (*R,S*)-46

Empirical formula	C ₃₂ H ₄₀ Cl ₂ N ₂ Pd ₂
Formula weight	736.36
Temperature	103(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)
Unit cell dimensions	a = 13.7792(5) Å α = 90°. b = 7.4897(2) Å β = 107.240(2)°. c = 15.1824(5) Å γ = 90°.
Volume	1496.46(8) Å ³
Z	2
Density (calculated)	1.634 Mg/m ³
Absorption coefficient	1.404 mm ⁻¹
F(000)	744
Crystal size	0.30 x 0.20 x 0.14 mm ³
Theta range for data collection	1.55 to 38.20°.
Index ranges	-21 ≤ h ≤ 23, -11 ≤ k ≤ 13, -25 ≤ l ≤ 26
Reflections collected	36286
Independent reflections	13779 [R(int) = 0.0300]
Completeness to theta = 38.20°	99.3 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.8276 and 0.6780
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	13779 / 1 / 351
Goodness-of-fit on F ²	1.062
Final R indices [I > 2σ(I)]	R ₁ = 0.0280, wR ₂ = 0.0537
R indices (all data)	R ₁ = 0.0313, wR ₂ = 0.0618
Absolute structure parameter	-0.007(14)
Largest diff. peak and hole	0.716 and -0.868 e.Å ⁻³

Table A-2.1.7 Crystal Data and Structure Refinement for (R,S)-47

Empirical formula	C ₁₈ H ₂₅ Cl N ₂ O ₅ Pd	
Formula weight	491.25	
Temperature	103(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 10.7404(3) Å	a = 90°.
	b = 7.4773(2) Å	b = 110.9310(10)°.
	c = 13.9114(3) Å	g = 90°.
Volume	1043.49(5) Å ³	
Z	2	
Density (calculated)	1.563 Mg/m ³	
Absorption coefficient	1.047 mm ⁻¹	
F(000)	500	
Crystal size	0.40 x 0.08 x 0.03 mm ³	
Theta range for data collection	2.98 to 31.13°.	
Index ranges	-15 ≤ h ≤ 15, -10 ≤ k ≤ 6, -20 ≤ l ≤ 20	
Reflections collected	13959	
Independent reflections	5623 [R(int) = 0.0258]	
Completeness to theta = 31.13°	98.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9693 and 0.6795	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	5623 / 2 / 255	
Goodness-of-fit on F ²	1.038	
Final R indices [I > 2σ(I)]	R ₁ = 0.0215, wR ₂ = 0.0492	
R indices (all data)	R ₁ = 0.0231, wR ₂ = 0.0500	
Absolute structure parameter	-0.021(16)	
Largest diff. peak and hole	0.608 and -0.671 e.Å ⁻³	

Table A-2.1.8 Crystal Data and Structure Refinement for (R)-48

Empirical formula	C ₂₉ H ₂₇ Cl ₄ N ₂ O ₄ P Pd
Formula weight	746.70
Temperature	103(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)
Unit cell dimensions	a = 8.9778(6) Å α = 90°. b = 14.5290(11) Å β = 100.458(3)°. c = 12.2226(9) Å γ = 90°.
Volume	1567.8(2) Å ³
Z	2
Density (calculated)	1.582 Mg/m ³
Absorption coefficient	1.021 mm ⁻¹
F(000)	752
Crystal size	0.40 x 0.40 x 0.06 mm ³
Theta range for data collection	1.69 to 31.13°.
Index ranges	-13 ≤ h ≤ 13, -21 ≤ k ≤ 21, -17 ≤ l ≤ 17
Reflections collected	27074
Independent reflections	9721 [R(int) = 0.0343]
Completeness to theta = 31.13°	99.1 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9413 and 0.6856
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	9721 / 16 / 410
Goodness-of-fit on F ²	1.101
Final R indices [I > 2σ(I)]	R1 = 0.0264, wR2 = 0.0625
R indices (all data)	R1 = 0.0300, wR2 = 0.0751
Absolute structure parameter	0.009(16)
Largest diff. peak and hole	0.529 and -0.609 e.Å ⁻³

Table A-2.2.1 Crystal Data and Structure Refinement for (*R,S*)-63a

Empirical formula	C ₄₇ H ₄₅ Cl N O P Pd
Formula weight	812.66
Temperature	103(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)
Unit cell dimensions	a = 11.9358(3) Å α = 90°. b = 10.0903(3) Å β = 105.1340(10)°. c = 17.0594(4) Å γ = 90°.
Volume	1983.31(9) Å ³
Z	2
Density (calculated)	1.361 Mg/m ³
Absorption coefficient	0.612 mm ⁻¹
F(000)	840
Crystal size	0.40 x 0.08 x 0.02 mm ³
Theta range for data collection	1.77 to 33.07°.
Index ranges	-17 ≤ h ≤ 17, -8 ≤ k ≤ 15, -25 ≤ l ≤ 25
Reflections collected	34075
Independent reflections	12613 [R(int) = 0.0393]
Completeness to theta = 33.07°	98.1 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9879 and 0.7919
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	12613 / 1 / 472
Goodness-of-fit on F ²	1.083
Final R indices [I > 2σ(I)]	R1 = 0.0331, wR2 = 0.0722
R indices (all data)	R1 = 0.0446, wR2 = 0.0882
Absolute structure parameter	-0.023(16)
Largest diff. peak and hole	0.796 and -1.073 e.Å ⁻³

Table A-2.2.2 Crystal Data and Structure Refinement for (*R,R*)-63a

Empirical formula	C ₄₁ H ₃₉ Cl N O P Pd	
Formula weight	734.55	
Temperature	103(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 15.6428(8) Å	α = 90°.
	b = 17.0104(11) Å	β = 90°.
	c = 25.5760(16) Å	γ = 90°.
Volume	6805.5(7) Å ³	
Z	8	
Density (calculated)	1.434 Mg/m ³	
Absorption coefficient	0.705 mm ⁻¹	
F(000)	3024	
Crystal size	0.34 x 0.14 x 0.02 mm ³	
Theta range for data collection	1.59 to 31.05°.	
Index ranges	-18 ≤ h ≤ 22, -22 ≤ k ≤ 24, -37 ≤ l ≤ 33	
Reflections collected	63762	
Independent reflections	21013 [R(int) = 0.0455]	
Completeness to theta = 31.05°	98.3 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9860 and 0.7956	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	21013 / 0 / 835	
Goodness-of-fit on F ²	1.093	
Final R indices [I > 2σ(I)]	R1 = 0.0362, wR2 = 0.0781	
R indices (all data)	R1 = 0.0522, wR2 = 0.0962	
Absolute structure parameter	-0.008(14)	
Largest diff. peak and hole	1.839 and -0.844 e.Å ⁻³	

Table A-2.3.1 Crystal Data and Structure Refinement for (R,S,R)-63a

Empirical formula	C ₃₆ H ₃₇ Cl N O P Pd
Formula weight	672.49
Temperature	103(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)
Unit cell dimensions	a = 17.7791(5) Å α = 90°. b = 9.7695(3) Å β = 110.341(2)°. c = 19.4755(6) Å γ = 90°.
Volume	3171.81(16) Å ³
Z	4
Density (calculated)	1.408 Mg/m ³
Absorption coefficient	0.749 mm ⁻¹
F(000)	1384
Crystal size	0.40 x 0.40 x 0.06 mm ³
Theta range for data collection	1.92 to 33.39°.
Index ranges	-27 ≤ h ≤ 27, -15 ≤ k ≤ 12, -26 ≤ l ≤ 30
Reflections collected	54694
Independent reflections	21891 [R(int) = 0.0380]
Completeness to theta = 33.39°	99.4 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9565 and 0.7538
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	21891 / 1 / 747
Goodness-of-fit on F ²	1.058
Final R indices [I > 2σ(I)]	R1 = 0.0388, wR2 = 0.0888
R indices (all data)	R1 = 0.0514, wR2 = 0.1013
Absolute structure parameter	-0.016(14)
Largest diff. peak and hole	2.482 and -1.003 e.Å ⁻³

Table A-2.4.1 Crystal Data and Structure Refinement for (R,S,S,R)-73a

Empirical formula	[C ₇₆ H ₇₂ Cl ₂ N ₂ O ₂ P ₂ Pd ₂ .(16/3)C ₆ H ₆]	
Formula weight	1807.57	
Temperature	103(2) K	
Wavelength	0.71073 Å	
Crystal system	Tetragonal	
Space group	I422	
Unit cell dimensions	a = 39.8657(12) Å	α = 90°.
	b = 39.8657(12) Å	β = 90°.
	c = 38.2114(13) Å	γ = 90°.
Volume	60728(3) Å ³	
Z	24	
Density (calculated)	1.186 Mg/m ³	
Absorption coefficient	0.486 mm ⁻¹	
F(000)	22512	
Crystal size	0.40 x 0.40 x 0.36 mm ³	
Theta range for data collection	1.44 to 25.03°.	
Index ranges	-44 ≤ h ≤ 47, -45 ≤ k ≤ 47, -45 ≤ l ≤ 42	
Reflections collected	246984	
Independent reflections	26847 [R(int) = 0.1200]	
Completeness to theta = 25.03°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.8444 and 0.8292	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	26847 / 463 / 1371	
Goodness-of-fit on F ²	1.027	
Final R indices [I > 2σ(I)]	R1 = 0.0665, wR2 = 0.1648	
R indices (all data)	R1 = 0.0891, wR2 = 0.1752	
Absolute structure parameter	0.01(2)	
Largest diff. peak and hole	1.670 and -0.868 e.Å ⁻³	