Palladacycle catalyzed asymmetric hydrophosphination : pushing the boundaries in C*-P bond formation

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**NANYANG
TECHNOLOGICAL
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**PALLADACYCLE CATALYZED ASYMMETRIC
HYDROPHOSPHINATION:
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C*-P BOND FORMATION**

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SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

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List of Symbols and Abbreviations

δ	chemical shift (ppm)	g	gram(s)
$^{\circ}\text{C}$	degree centigrade	hr(s)	hour(s)
AHP	asymmetric hydrophosphination	Hz	Hertz
An	anisoyl	IC ₅₀	Concentration at which cell forming ability is reduced by 50%
m	multiplet	i.e.	that is (Latin: <i>id est</i>)
aq.	aqueous	J	coupling constant
Ar	aryl	m	meta
Bn	benzyl	Me	methyl
Bu	butyl	min(s)	minute(s)
Bz	benzoyl	MS	mass spectroscopy
<i>ca.</i>	about (Latin: <i>circa.</i>)	n	linear chain
cat.	catalyst/catalytic	Nap	naphthyl
<i>conc.</i>	concentrated	NMR	Nuclear Magnetic Resonance
DCM	dichloromethane	o	ortho
d	doublet	p	para
dd	doublet of a doublet	Ph	phenyl
<i>ee</i>	enantiomeric excess	ppm	parts of million
equiv.	equivalent(s)	Pr	propyl
<i>er</i>	enantiomeric ratio		
ESI	electron spray ionization		
Et	ethyl		
<i>et al.</i>	and others (Latin: <i>alii</i>)		

R right absolute configuration
(Latin: *rectus*)

S left absolute configuration
(Latin: *sinister*)

s singlet

t triplet

t tertiary

THF tetrahydrofuran

tol tolyl

$[\alpha]_{\text{D}}$ specific rotation measured
at sodium D line (589 nm)

Abstract

The significance of chiral phosphines is well-known in the field of Chemistry; yet conventional approaches for their preparation are wasteful, expensive and cumbersome. This thesis reports on the direct preparation of chiral phosphines using a palladacycle catalyst via the addition of secondary phosphines to novel and challenging prochiral substrates, thereby generating a library of highly enantioenriched functionalised phosphines in typically high yields. Throughout the studies, novel compounds which have never been known to be Michael acceptors have been uncovered, as well as the never before observed enantiodivergence in P-H addition systems. The undertaken studies and the results obtained further our collective understanding of various reaction mechanisms and methodologies, representing a salient contribution to Chemistry in general.

Chapter 1

General Introduction

1-1 Significance of Chiral Phosphines

Many molecules in nature exhibit chirality, a property more easily understood by laymen as handedness. These isomers, accurately known as enantiomers or optical-/stereo-isomers are known to rotate the plane of polarized light in the opposite directions. The manifestation of chirality in nature is evident: *D*-glucose, *L*-amino acids and the right-handed DNA helix are representative examples that are inherent in all known life-forms on Earth. Today, chirality is a critical characteristic in numerous aspects of the modern society. It is of paramount importance in fine chemical syntheses such as in the pharmaceutical, and agrochemical industries;^[1] since the effectiveness/toxicity of compounds produced can be directly dependent on their stereochemistries. Thalidomide for example was initially meant to relieve pregnant women of nausea and morning sickness. Sadly, it was discovered that the *S* stereoisomer was a teratogen only after numerous infants were born with phocomelia. Realizing the significance and impact of chirality, the requirement to produce enantiopure compounds has expedited the development of asymmetric technologies over the past centuries.

Extending to the field of Chemistry, the use of chiral phosphines to achieve chemo- and stereo-control in metal-mediated transformations is well-established today.^[2] In addition to their conventional roles as ligands, phosphines also function as efficient organocatalysts in various organic reactions.^[3] Unlike most amines which readily interconvert between the pyramidal ground state (C_{3v}) and its planar transition state (D_{3h}) even at room temperatures, phosphines however possess comparatively higher barriers to pyramidal inversions (*ca.* 30-40 kcal/mol),^[4] rendering them capable of unambiguous transmission of chiral information

to the reacting species during a reaction.^[5] Pioneering the first homogenous asymmetric transformation, Knowles and Sabacky reported the enantioselective hydrogenation of olefins using rhodium and both P-stereogenic (PMe(Ph)(*i*-Pr)) as well as C-stereogenic (PhP(CH₂-CHMeEt)₂) phosphines.^[6] Following this success, chiral phosphines have to a large extent spurred the development of asymmetric technologies critical in industry and in research.

The significance of chiral phosphines and their versatile applications in a multitude of chemical reactions was further highlighted when Noyori, Knowles and Sharpless were awarded the Nobel Prize in Chemistry in 2001, with the former two working on asymmetric hydrogenations using independently developed phosphines (Noyori: BINAP^[7]; Knowles: DiPAMP^[8]). BINAP, together with other developed classes of ligands (*eg.* DuPhos, DIOP) make up a portion of the privileged ligands as they exhibit generality for many reactions, and show high degree of tolerance in variation of substrates (Figure 1).^[9]

Figure 1: Phosphorus containing privileged class ligands and the types of reactions they participate in.

1-2 General Classification of Chiral Phosphine Ligands

Through the years, a wide variety of chiral phosphines have been developed at a steady rate, owing to the demand for alternatives that possess dissimilar stereoelectronic properties so as to be able to achieve the desired reaction outcomes. Despite the extensive

number of chiral phosphine ligands known to date, they can generally be categorized into a few distinct classes: 1) C-stereogenic center(s) on the side chain, 2) P-stereogenic center(s), 3) a combination of both C- and P-stereogenic center(s), 4) axial chirality on the side chain, 5) planar chirality on the side chain. In addition, each class can be further sub-divided into mono-, di-, or poly-phosphines. It should be noted that the phosphines described in this section only include compounds bearing phosphorus-carbon/hydrogen single bonds and excludes those with phosphorus-heteroatom (N, O, S, Cl, *etc.*) bonds.

1-2.1 Ligands bearing C-, P-, C,P-Stereogenic Centers

The majority of ligands exhibit either P-stereogenicity or C-stereogenic centers on its side chains (Figure 2). Ligands exhibiting both C,P-stereogenicity are less common (Figure 3).

Figure 2: Selected phosphine ligands exhibiting C- or P-stereogenic centers.

Figure 3: Phosphine ligands with C,P-stereogenic centers.

1-2.2 Phosphine Ligands exhibiting Axial Chirality

Compounds exhibiting atropisomerism owing to hindered axial rotations arising from intramolecular steric repulsions are said to exhibit axial chirality. Initially synthesized by Noyori and co-workers, BINAP and its derivatives have since been employed as a versatile class of ligand for asymmetric hydrogenations,^[7b-d] isomerisation (synthesis of menthol),^[10] allylations^[11] and many more. Following the successful applications of BINAP, similar atropisomers with variation in steric and electronic properties have been developed over the years. A select handful of these phosphines are presented in Figure 4.

Figure 4: Selected phosphine ligands exhibiting axial chirality.

1-2.3 Phosphine Ligands exhibiting Planar Chirality

One of the earliest classes of chelating diphosphine ligands with planar chirality on its side chain is the Josiphos class of ligands. Bearing a ferrocenyl scaffold, they can be furnished with various appendages/functional groups on both ferrocene and on phosphorus in order

to achieve the desired stereoelectronic requirements for catalysis. The first Josiphos class ligand was originally developed in the 1990s. Following studies on their applications, they were found to be able to effect a wide range of asymmetric transformations including the Aldol reaction,^[12] hydroformylation^[13] and reductive aminations.^[14] Building on Josiphos's design, various phosphines were subsequently developed through the years. A select few are shown in Figure 5.

Figure 5: Selected phosphine ligands exhibiting planar chirality.

1-3 Applications of Chiral Phosphines as Ligands and Organocatalysts

The range of enantioselective transformations that chiral phosphines directly (organocatalysis) or indirectly (metal-mediated catalysis) participate in is widespread. Some of the common classes include C-H, C-C, C-X (X=N, O, P, Si, *etc.*) bond construction; encompassing reductions, alkylations, allylations, cycloadditions and oxidation reactions. Owing to the extensive number of reports available, only representative examples are described in this section.

1-3.1 C-H Bond Formation: Synthesis of (*L*)-DOPA via Asymmetric Hydrogenation

(*L*)-DOPA is an amino acid synthesized by both humans and animals for subsequent biotransformation to various neurotransmitters such as dopamine and adrenaline. Sufferers of Parkinson's disease experience degeneration in their motor capabilities, owing to inadequate production of dopamine by the brain. Following G. Cotzias discovery in 1968 that administration of large quantities of (*L*)-DOPA was useful for the management of the disease,^[15] it indirectly hastened the advent of the first large-scale industrial preparation of (*L*)-DOPA (*Monsanto Process*) via the Rh-DiPAMP catalyzed asymmetric hydrogenation of an enamide (Scheme 1).^[8b]

Scheme 1: Synthesis of (*L*)-DOPA using Ru-(*R,R*)-DiPAMP as the catalytic complex.

1-3.2 C-C Bond Formation: Asymmetric Arylation of Imines

As significant attention was paid to metal mediated transformations made possible by chiral diphosphine ligands in the earlier days, there was comparatively less interest on the applications of chiral monodentate phosphine (cMOP) ligands as they were believed to form less robust metal-ligand complexes as compared to with diphosphine analogs. Following extensive development in ligand design, newer generation of cMOPs are now able to achieve chemo- and regioselectivities that could only be previously obtained with

diphosphines. In addition, it was found that cMOPs can be employed in tandem to improve reaction outcomes,^[16] a feature that cannot be achieved with diphosphine ligands.

One example of the diverse applications of cMOPs is in the asymmetric arylations of imines with organostannanes in the presence of a Rh(II) catalyst. In the hands of Hayashi and co-workers, excellent yields and enantioselectivities were achieved in 12 hrs with a 3 mol% catalyst loading (Scheme 2).^[17]

Scheme 2: Asymmetric arylation of sulfonamides with organostannanes using Rh-MOP* catalytic complexes.

1-3.3 C-Si Bond Formation: Asymmetric Hydrosilylation of Prochiral Ketones

Many phosphine supported metal mediated transformation typically involve precious metals such as Pd, Rh, Pt, *etc.* Recent work reported by Chan *et al.* involve the asymmetric hydrosilylation of prochiral aryl alkyl ketones using (S) -Xyl-P-Phos and copper (II) fluoride, giving highly versatile chiral alcohols after acid hydrolysis (Scheme 3).^[18]

Scheme 3: Cu(II) catalyzed highly enantioselective hydrosilylation of ketones.

1-3.4 Synthesis of Piperidine Derivatives *via* Organocatalytic Asymmetric [4+2] Cyclizations

Despite the previous lack of interest in asymmetric organic molecule catalysis, the study in the applicability of chiral phosphines as organocatalysts has gained momentum in recent years. In addition, organocatalysis has generally been accepted as a valuable alternative to metal-mediated transformations considering that certain organometallic systems that are either costly, poisonous and air/water sensitive.^[19] To date, extensive literature describing successful chiral phosphine organocatalyzed reactions such as cycloadditions, allylic substitutions, Morita-Baylis-Hillman as well as conjugate additions have since been reported.^[3a, b] One example is the cyclization of imines and allenes to give chiral piperidines using chiral phosphine. More importantly, only a catalyst loading of 5 mol% was required, giving excellent *cis:trans* ratios and enantioselectivities (Scheme 4).^[20]

Scheme 4: Chiral phosphine organocatalyzed [4+2] cyclization of allenes and imines.

1-4 Traditional Synthetic Methods for the Preparation of Chiral Phosphines

Despite the importance of chiral phosphines, established synthetic methodologies have traditionally been cumbersome and wasteful. There are 3 primary approaches for their syntheses: one, *via* resolution of racemic products; two, the use of chiral starting materials; and three: chiral auxiliary promoted asymmetric reactions. While each of these approaches has its advantages, it is generally accepted that cost, multi-step procedures, reduced yields, *etc.* are common drawbacks.

1-4.1 *Via* Resolution of Racemates

As enantiomers have identical chemical and physical properties with their optical activities being the only exception, separation without a chiral medium is of considerable challenge. As such, one of the earliest solutions to obtain chiral targets is *via* the resolution of racemic products after complexation with a chiral derivatizing agent. To date, a variety of resolving agents have been reported. Some of the common entities include (*R*)-camphorsulfonic acid [(*-*)-CSA], (*S,S*)-dibenzoyltartaric acid [(*+*)-DBTA], (*R,R*)-TADDOLs and (*-*)-menthol [(*-*)-MenOH]. While this approach is generally reliable, the greatest drawback is that only 50%

of the desired stereoisomer can be obtained. A handful of chiral phosphines have been synthesized *via* this approach; for example, Tang and co-workers synthesized both BIBOP^[21] and POP^[22] ligands using (+)-menthyl chloroformate as the derivatizing agent for the racemic starting material (Scheme 5). Employment of BIPOP and POP as ligands in Ru/Rh catalyzed asymmetric hydrogenation of olefins yielded products in excellent enantioselectivities of up to >99%.^[21-22]

Scheme 5: Synthesis of BIBOP and POP ligands using (+)-menthyl chloroformate as the chiral derivatizing agent.

Another example is the preparation of a chiral tertiary unsymmetrical monophosphine *via* the resolution of racemic phosphorus compounds. Employing paraformaldehyde and (+)-camphorsulfonic acid (CSA), diastereomic α -hydroxymethylphosphonium salts formed were separated by crystallization and chromatography (Al_2O_3). Treatment of the resolved phosphonium salt with triethylamine then gave the enantiopure tertiary phosphine as the product (Scheme 6).^[23]

Scheme 6: Preparation of a chiral tertiary phosphine using (+)-camphorsulfonic acid as the resolving agent.

1-4.2 Chiral Pool Synthesis

As many chiral molecules in nature are produced only in a particular hand form, this manifestation can be leveraged for the preparation of chiral compounds. Compared to the wasteful approach *via* resolution of racemic products, this approach is advantageous as chiral starting materials obtained from natural sources can be cheap and readily available. However, its drawbacks include the absence of unnatural stereoisomers (*eg.* *D*-lactic acid, *D*-tartaric acid, (+)-menthol), limited number of compounds available, and that certain chiral substrates are costly and difficult to prepare. It should be noted that inversion of configuration occurs in methodologies involving nucleophilic substitutions at the stereogenic center(s) (Walden inversion). An example is the preparation of one of the privileged ligands, CHIRAPHOS, achieved using natural occurring (*L*)-tartaric acid as the starting material (Scheme 7).^[24]

Scheme 7: Fryzuk's synthesis of (*S,S*)-CHIRAPHOS from natural occurring (*L*)-tartaric acid.

In the following year, Fryzuk and Bosnich reported the preparation of (*R*)-ProPhos, a monodentate phosphine ligand using natural occurring lactic acid as the starting material

(Scheme 8). (*R*)-ProPhos aided in the catalytic asymmetric hydrogenation of olefins to give a series of enantioenriched amino acids.^[25]

Scheme 8: Preparation of (*R*)-ProPhos from (*S*)-lactic acid.

1-4.3 Chiral Auxiliary Promoted Preparation

The concept of transient incorporation of a chiral auxiliary into a compound so as to influence the stereochemical outcomes of derivatives was initially pioneered by E. J. Corey in 1975.^[26] Today, a series of auxiliaries have been developed to aid in the preparation of chiral targets. Some of the well-known auxiliaries include oxazolidones (Evans),^[27] SAMP/RAMP (Enders & Corey)^[28] and ephedrine derivatives. To date, they have contributed to the establishment of many successful asymmetric methodologies including alkylations, Diels-Alder and the aldol reaction. Utilizing this approach, chiral phosphines have also been prepared utilizing the established pool of chiral auxiliaries and natural occurring compounds (*eg.* menthol). Imamoto and co-workers in 1990 reported the one-pot preparation of (*S,S*)-DiPAMP using (-)-menthol as the chiral auxiliary. Chiral monophosphine-borane adducts produced were subjected to oxidative coupling with copper (II) chloride to give DiPAMP after removal of borane with diethylamine (Scheme 9).^[29]

Scheme 9: Asymmetric synthesis of (S,S)-DiPAMP with (-)-menthol as the chiral auxiliary.

Adopting a similar approach, Hoge synthesized P-stereogenic bisphospholaneethane ligands using halophosphines as the starting material. (-)-menthol was also employed as the chiral auxiliary to achieve asymmetric alkylation, a critical step towards the synthesis of the target product (Scheme 10).^[30] In the presence of a Rh catalyst, the bisphospholaneethane ligand aided the asymmetric hydrogenation of acetamidoacrylic acid derivatives, giving pregabalin which is an analgesic used for the treatment of central neuropathic pain^[31] and anxiety disorders.^[32]

Scheme 10: Synthesis of chelating bisphospholaneethane ligands using (-)-menthol as the chiral auxiliary.

On top of using (-)-menthol as the chiral auxiliary, Juge *et al.* employed (-)-ephedrine in the preparation of PAMP ligands (Scheme 11).^[33] These PAMP monophosphine ligands can further be oxidatively coupled to give chelating DiPAMP analogs. Separation

Scheme 11: (-)-ephedrine as chiral auxiliary for asymmetric synthesis of PAMP ligands.

1-5 Brief Development and Applications of Palladacycles

Cyclometallated complexes containing at least one metal-carbon bond and another electron donating atom (eg. N, P, S, O, As, *etc.*) bound to palladium in a cyclic fashion are collectively known as (C-Y type) palladacycles (Figure 6).

Figure 6: General structure of C-Y class palladacycles

In 1965, Cope and Siekman reported an ‘unusual reaction’ whereby a unexpected *ortho* metal-carbon covalent bond was formed after treatment of azobenzene and its analogs with potassium tetrachloroplatinate(II) or palladium chloride (II), affording dimeric chloro-bridged complexes (Scheme 12).^[34] In the subsequent years, they also found that the cyclometallation reaction was also feasible when *N,N*-dimethylbenzylamine was employed as the substrate.^[35]

Scheme 12: First platina-/palladacycles synthesized by Cope and Siekman.

However, the prominence of such complexes as catalysts were not discovered until Herrmann and co-workers employed a phosphapalladacycle in the Heck olefination of bromo- and chloroarenes (Scheme 13).^[36] Certain noteworthy features arising from the employment of palladacycle catalyst in the Heck reaction versus conventional catalytic systems (*i.e.* $\text{Pd}(\text{OAc})_2$ +phosphine ligands) include high TONs of up to 200,000; no requirement of additional phosphine ligands were needed (usually 3 equivalents to catalyst loading); and that the absence of elemental palladium deposits which are typically found at the end of the reaction strongly demonstrated palladacycles' long-term stability.

Scheme 13: Palladacycle catalyzed Heck olefination of bromo and chloroarenes.

Realizing the potential of palladacycles as efficient and versatile catalysts, a wide variety of palladacycles has been synthesized with modification in donor atoms/groups and ring size (Figure 7). Also presented in Figure 7 are pincer-class palladacycles, but their

developments and applications are excluded from this dissertation. Established synthetic methodologies incorporating C-H activations, oxidative additions or transmetalations are now frequently employed techniques today to access target palladacycles.^[37]

As palladacycles were found to be highly versatile catalysts for a multitude of reactions, growing interest in asymmetric technologies have led to swift methodological development for the preparation of chiral palladacycles. One of the first chiral palladacycles synthesized was achieved by Otsuka and co-workers in 1971 via the treatment of enantiopure *N,N*-dimethylbenzylamine with lithium tetrachloropalladate(II). In the same study, Otsuka attempted the resolution of racemic tertiary phosphines using his newly prepared chiral Pd complex. Treatment of the separated Pd-P* diastereomic adducts with dppe liberated the

C-Y class palladacycles

Pincer class palladacycles

Figure 7: Selected palladacycles exhibiting variation in donor atoms/groups and ring size.

resolved free tertiary phosphines (Scheme 14).^[38]

Scheme 14: First synthesis of a chiral palladacycle and its application as a resolving agent.

In the following years, Tani^[39] and Wild^[40] independently developed chiral naphthylamine palladacycles (Figure 8), the latter's complex (*R*)-**1** was found to a superior resolving agent as compared to the benzylamine predecessor developed by Otsuka. To date, Wild has successfully employed **1** as a resolving agent from monodentate to quadridentate phosphines and arsines.^[41] Through crystallographic and NMR studies, Leung and co-workers uncovered the underlying principles for **1**'s superior performance.^[42] A locking mechanism arising from intramolecular steric repulsion between the methyl group on the chiral atom and H₈ of the naphthalene ring leads to the cyclometallated ring being fixed in a puckered conformation (δ for *R* isomer, λ for *S* isomer), allowing chiral information to be effectively transmitted to the coordinating site(s). However, such a locking mechanism is absent in benzylamine palladacycles which explains its inferior performance in chiral resolutions

Figure 8: Chiral naphthylamine containing palladacycles by Tani and Wild.

.In addition to its conventional role as a resolving agent, extensive studies by Leung and co-workers found **1** to be an excellent promoter for asymmetric transformations, such as the Diels-Alder reaction as well as in hydrofunctionalizations. Furthermore, they developed an alternate class of palladacycles bearing a phosphorus atom with bulkier phenyl groups (**2**). These chloro-bridged dimeric complexes were subsequently treated with silver perchlorate in acetonitrile to remove the kinetically inert chloride to give bisacetonitrile complexes (**3**^[43], **4**^[44]) (Scheme 15). They were subsequently applied in both asymmetric syntheses and catalysis which will be reviewed in the subsequent sections.

Scheme 15: Treatment of chloro-bridged dimers with AgClO₄ to remove the kinetically inert chloride.

1-6 Applications of Palladacycles in Chiral Phosphine Preparation

A review of the literature on palladacycle mediated transformations revealed the wide-ranging reactions that these cyclometallated complexes could accomplish. However, since there were no known reports on straightforward chiral phosphine preparation, Leung conceived the idea of employing these versatile palladacycles to directly access chiral phosphines. This effectively overcame conventional phosphine synthesis methodologies which are generally wasteful and require tedious manipulations. This section focuses on the representative studies that Leung has undertaken, aiming to provide a clearer

understanding of developments over the past two decades. The brief summary will in turn put into perspective the significance and novelty of my undertaken work as described in the following chapters.

1-6.1 As Resolving Agents and Reaction Promoters

The establishment of palladacycle **1** as an excellent resolving agent for both phosphines and arsines^[41] have influenced Leung to focus his earlier studies on the resolution of functionalized chiral phosphines. One of the more significant endeavours was the resolution of [(methylsulfinyl)methyl/ethyl]diphenylphosphines (($\pm$)-**5**), a P,O-chelating ligand with a stereogenic center on sulphur. The work bears significance in that the sulfinyl group which is susceptible to both oxidizing and reducing agents, remained unchanged throughout the resolution process. As it was not possible for ($\pm$)-**5** to bind as a chelate to **1** owing to the presence of the inert chloride, (*S*)-**3** was instead employed as the acetonitrile molecules are readily displaced. Treatment of the separated diastereomeric adducts with dppe liberated enantiopure phosphines (**5**) as products (Scheme 16).^[45]

Scheme 16: Resolution of *S*-stereogenic sulfinyl phosphines using (*S*)-**3** as the chiral derivatizing agent.

Following extensive exploratory research, Leung succeeded in the employment of **1** as a promoter in a series of asymmetric synthetic reactions. Among them is the Diels-Alder (DA) reaction, a highly valued transformation for the preparation of 6-membered rings. In the absence of any transition metal catalyst, no cycloadditions were observed between 3,4-dimethyl-1-phenylphosphole (DMPP) and olefin dienophiles. However in the presence of (*R*)-**1**, facile cycloadditions between the bound DMPP and a series of functionalized olefins ensued after chloride abstraction by silver perchlorate, affording coordinated P-stereogenic phosphanorbonenes **6** in a stereospecific manner. Treatment of these *exo*-DA complexes (**6**) with dppe or aqueous potassium cyanide (KCN) liberates the bound phosphines (**7**) without loss of optical purities (Scheme 17).^[46]

Entry	E	Yield (%)
6a	-C(O)NMe ₂	85
6b	-C(O)Et	73
6c	-C(O)OMe	48
6d	-C(S)OMe	15

Scheme 17: Syntheses of P-stereogenic phosphanorbonenes *via* template promoted asymmetric Diels-Alder reaction.

In the following years, Leung succeeded in the template promoted asymmetric

hydrophosphination of unsaturated compounds. One of the most notable works was the preparation of (*R/S*)-PROPHOS, previously synthesized by Fryzuk from (*S*)-lactic acid *via* a multi-step methodology. Applying (*S*)-**1** as a promoter, P-C* bonds were constructed between (*Z*)-diphenyl-1-propenylphosphine and diphenylphosphine (Ph₂PH). It should be noted that Ph₂PH added regiospecifically to the olefin but due to ligand redistribution after the reaction, four diastereomeric complexes (**8,9**) were formed with **8a,b** and **9a,b** being regioisomers. Treatment of the major complexes (**8**) with concentrated HCl followed by aqueous KCN gives (*S*)-PROPHOS as the product (Scheme 18).^[47] (*R*)-PROPHOS could be obtained using the *trans* isomer of the olefin starting material.

Scheme 18: Syntheses of (*S*)-PROPHOS *via* template promoted asymmetric AHP reaction.

Despite the success, Leung and co-workers continued to expand the class of substrates and types of reactions these palladacycles could promote. Using a similar approach, Leung reported on the asymmetric di-hydrophosphination of alkynes,^[48] hydroamination^[49] as

well as less reported hydroarsination reaction^[50] (Scheme 19), affording bidentate P-E ligands (E=P, N, As) that may possess potential applications in catalysis. (*R,R*)-**10** was further functionalized with gold(I), affording diphosphine-digold complexes that have demonstrated tremendous potential as a chemotherapeutic drug.^[51]

Double asymmetric hydrophosphination

Asymmetric hydroamination

Asymmetric hydroarsination

Scheme 19: Azapalladacycle template promoted hydrofunctionalizations (P, N, As).

1-6.2 As Catalysts in Asymmetric Hydrophosphinations (AHP)

While the transformations reviewed in the preceding section were interesting and that the methodologies remain effective towards the preparation of chelating ligands, this approach to obtain chiral phosphines is indirect and periodically require the use of highly toxic chemicals (KCN) to liberate the bound phosphines. Catalysis is an essential green technology in the 21st century especially when mankind is constantly faced with issues of dwindling natural resources and environmental degradation. Keeping in tandem with the demands of modern science, Leung and his associates embarked on the palladacycle

catalyzed asymmetric hydrophosphination reaction.

One of the first catalytic hydrophosphination studies was reported by Leung in 2010. Employing azapalladacycle (*R*)-**3** as the catalyst, the AHP of *trans*-chalcone were attempted. Following optimization of reaction conditions, a series of enones were screened to afford chiral monophosphine adducts in 92-99% yield and *ees* of 33-86%. A single recrystallization was able to improve the optical activity of the enantioenriched products to up to 99% *ee* (Scheme 20).^[52] Supported by experimental evidence, a plausible mechanistic cycle has also been proposed. The mechanism will be described in detail in Chapter 2 as a similar catalyst (**4**) has been employed in my work.

Scheme 20: The first azapalladacycle catalyzed asymmetric hydrophosphination reaction.

A new class of phosphapalladacycle (**4**) was developed and its effectiveness and versatility proven in several instances. α,β -unsaturated ketones^[44, 53], imines^[54] and esters^[55] were found to be suitable substrates, affording aliphatic and cyclic C- and/or P-stereogenic phosphines with tremendous improvements in reactivities, yields and stereoselectivities in comparison to when the azapalladacycle **3** was employed as the catalyst (Figure 9).

Figure 9: Chiral phosphines synthesized from various substrate classes.

1-7 Scope and Summary of this Thesis

The listed examples shown in the previous sections have demonstrated the versatility of chiral phosphines as ligands in metal-mediated catalysis and organocatalysts. However, conventional synthetic methodologies remain cumbersome and costly until Leung and Duan^[56] pioneered the catalytic asymmetric hydrophosphination of prochiral substrates. Yet, Duan and co-workers routinely protect the phosphine products via oxidation, sulphurization or boration for ease of purification and characterization. Ironically, this defeats the purpose of developing new methodologies to access tertiary phosphines as the lone electron pair on phosphorus is critical for their supposed functions. In addition, reductions and/or borane removal to regenerate these free phosphines generally require harsh conditions and frequently suffer from complications such as reduced yields and optical inversions.^[57]

While Leung have made certain advancements in the field of AHP, the substrates reported however are typical Michael acceptors (α,β -unsaturated ketone, imines, diesters) with good electrophilicities. Realizing that there remain areas to be improved, my research revolves around the AHP of novel and challenging substrates, as well as the application of the phosphine products in biological studies. My studies have also helped prove the previously

proposed catalytic cycle; and simultaneously leveraged on the unique characteristic of the catalyst in achieving enantiodivergent catalysis. The contents of the following chapters are summarized in the following graphical abstracts.

Chapter II: Pd-Catalyzed Asymmetric Hydrophosphination of (*E*)-3-methy-4-nitro-5-alkenylisoxazoles

Chapter III: Palladacycle Catalyzed Asymmetric C-P Addition of β,γ -Unsaturated α -Ketoesters and Amides

Chapter IV: Palladium Mediated phospho-Michael Addition of *N*-Enoyl Phthalimides and Benzotriazoles: Efficient Access to Functionalized Phosphines

Part 1: *N*-Enoyl Phthalimides

Part 2: *N*-Enoyl Benzotriazoles

Chapter V: Solvent Induced Enantiodivergent Syntheses of Chiral
Phosphinocarboxamides

Chapter II

*Pd-Catalyzed Asymmetric
Hydrophosphination of (E)-3-methyl-4-nitro-
5-alkenylisoxazoles*

2-1 Introduction

Functionalized isoxazoles and their analogs have demonstrated their value as potential chemotherapeutic drugs and in biomedical research in recent years: they were found to exhibit anti-cancer,^[58] anti-inflammatory,^[59] anti-mycobacterial resistance,^[60] as well as inhibitory effects including towards multidrug resistance protein transporters.^[61] While significant interest has been paid to the applications of isoxazoles and their derivatives, studies focusing on their synthetic methodologies via the addition of nucleophiles to olefinic side chains of isoxazoles are however sparse. Literature review revealed that while only a handful of reports have employed alkenylisoxazoles as reactants such as in cyclopropanation^[62] and hydro-sulfenylation^[63] reactions, they provide sufficient indication that alkenyl functionalized isoxazoles can potentially function as excellent Michael acceptors depending on the presence and position of effective electron withdrawing moieties in the electrophile. In line with our goals of chiral tertiary phosphine syntheses via hydrophosphination of novel substrates, we investigated the enantioselective hydrophosphination of (*E*)-3-methy-4-nitro-5-alkenylisoxazoles. Adducts obtained can be further functionalized with gold, affording gold(I)-phosphines which possess the potential in becoming a highly efficient anti-tumour drug.

2-2 Results and Discussions

Following extensive deliberation on substrate design, our investigations began with the use of (*E*)-3-methy-4-nitro-5-styrylisoxazole (**11a**) as the prototypical substrate. The presence of a 4-positioned nitro group on the heterocyclic ring serves as an excellent electron sink, effectively activating the vinyl moiety for conjugate additions. As reviewed in the previous

chapter, the highly versatile chiral phosphapalladacycle **4** was employed as the catalyst in this study. Preliminary studies revealed that the P-H addition was complete within an hour using an acceptable catalyst loading of 5 mol%. Yet, it afforded an unsatisfactory enantiomeric excess (*ee*) value despite conducting the reaction at a low temperature of -45 °C (Table 1, entry 1). Efforts to reduce the amounts of catalyst employed led to

Table 1: Optimization of reaction conditions for the asymmetric hydrophosphination of (*E*)-3-methy-4-nitro-5-styrylisoxazole (**11a**) with diphenylphosphine (Ph₂PH)^[a]

Entry	Solvent	Temp [°C]	Cat. loading [mol %]	Base [eq.]	Time [hr]	Yield ^[b] [%]	<i>ee</i> ^[c] [%]
1	THF	-45	5	1	1	99	28
2	THF	-45	3	1	1	99	30
3	THF	-45	1.5	1	1	99	39
4	THF	-45	1	1	1	99	19
5	THF	-45	1.5	0.5	1	96	34
6	THF	-45	1.5	0.2	1	82	2
7	acetone	-45	1.5	1	1	99	63
8	toluene	-45	1.5	1	13	68	26
9	CHCl ₃	-45	1.5	1	1	99	93
10	DCM	-45	1.5	1	1	99	89
11	DCM	-60	1.5	1	1	99	92
12	DCM	-80	1.5	1	1	99	92

^[a] Reaction conditions: 0.2 mmol Ph₂PH and **11a** in 5 mL of degassed solvent.

^[b] Yield is determined from the ³¹P{¹H}NMR of the crude product. ^[c] *ee* is calculated from the ratio of diastereomers (**13**) formed from treatment of **12a** with (*S*) or (*R*)-**1**.

unexpected outcomes, with a decrease in catalyst loadings generally leading to improved enantioselectivities (Table 1, entries 2-3); the optimum loading was established to be at 1.5 mol%. A handful of solvents were subsequently screened, with chloroform emerging to be the solvent of choice (Table 1, entries 7-10). In a bid to enhance enantioselectivities, lower temperatures were employed using DCM as the solvent. However, the lowered temperatures only resulted in a slightly improved *ee* of 92% (Table 1, entries 11-12), which is comparable to when chloroform was previously employed at -45 °C.

The enantiomeric excesses of the products of the reactions were established via coordination studies with optically pure chiral derivatizing agent(s). As (*S*)-**1**'s effectiveness as a resolving agent have been well-proven, coordination of the isoxazole-phosphine product (**12**) to (*S*)-**1** affords diastereomers **13**. Subsequent $^{31}\text{P}\{^1\text{H}\}$ NMR analyses of the diastereomeric mixture allows the establishment of obtained enantiomeric excesses (Scheme 21). Isolation of the major diastereomer [(*S,R*)-**13b**, Ar=4-ClC₆H₄] by silica column chromatography, followed by X-ray analyses of single crystals revealed that the absolute configuration of the newly formed chiral center is *R* (See experimental section).

Scheme 21: Coordination studies for *ee* determination.

With the optimal conditions established, a series of nitro-substituted alkenyl isoxazoles were screened and the findings presented in Table 2. It was found that the protocol was able to accommodate modification in functionalities on the phenyl ring, ranging from electron withdrawing (Table 2, entries 3-9), neutral (Table 2, entries 1, 10) to electron donating moieties (Table 2, entry 11). In addition, O and N-containing heterocycles were

Table 2: Substrate scope for the (*S*)-**4** catalyzed asymmetric hydrophosphination of alkenylisoxazoles (**11**)^[a]

Entry	11	Ar	Time [hr]	12	Yield ^[b] [%]	ee ^[c] [%]
1	11a	Ph	1	12a	>99	92
2	11b	4-ClC ₆ H ₄	1	12b	99	89
3	11c	3-ClC ₆ H ₄	1	12c	99	89
4	11d	2-ClC ₆ H ₄	1.5	12d	98	58
5	11e	4-FC ₆ H ₄	1	12e	99	80
6	11f	4-CF ₃ C ₆ H ₄	1	12f	99	91
7	11g	4-BrC ₆ H ₄	1	12g	>99	79
8	11h	4-MeO ₂ CC ₆ H ₄	1	12h	>99	91
9	11i	4-NCC ₆ H ₄	1	12i	98	89
10	11j	4-MeC ₆ H ₄	1	12j	>99	72
11	11k	4-MeOC ₆ H ₄	1	12k	99	73
12	11l	2-furanyl	1	12l	98	67
13	11m	2-pyrrolyl	25	12m	93	64
14	11n	3-pyridyl	1	12n	99	90
15	11o	4-pyridyl	1	12o	99	91

^[a] Reaction conditions: 0.2 mmol Ph₂PH and **11** in 5 mL of degassed solvent at -45 °C. ^[b] Yield is determined from the ³¹P{¹H}NMR of the crude product.

^[c] ee is calculated from the ratio of diastereomers (**13**) formed from treatment of **12** with (*S*) or (*R*)-**1**.

also well tolerated (Table 2, entries 12-15). In general, the substrates produced excellent results with yields and *ees* of up to >99% and 92% respectively being achieved. While *meta* and *para* substituents produced excellent enantioselectivities, *ortho*-positioned substrates however gave poorer outcomes which can be attributed to unfavourable steric interactions.

2-3 Proposed Catalytic Cycle

Based on the proposed mechanism for the (*R*)-**3** catalyzed asymmetric hydrophosphination of *trans*-chalcones,^[52] a similar mechanism is herein proposed for the AHP of alkenyl isoxazoles (Scheme 22). As phosphines generally possess high affinities towards metals, diphenylphosphine readily displaces the weakly bound acetonitrile molecules in (*S*)-**4**. By virtue of the naphthyl ring exerting a significant *trans*-effect, the *trans* positioned diphenylphosphine is labilized, allowing the substrate (**11**) to bind to palladium via the oxygen atom of the heterocyclic ring. The pronounced oxophilicity of this coordination site has been demonstrated in a previous report whereby a ambidentate phosphine-sulphoxide ligand prefers the formation of a 6-membered P,O-chelate instead of a 5-membered P,S-chelate.^[45a] The observation was surprising as Pd was believed to be “soft” and would thus prefer to bind preferentially with a “softer” S than the “harder” O. The remaining diphenylphosphine which is now acidified, arising from coordination to Pd is readily deprotonated with triethylamine (Et₃N) to give a highly reactive phosphido species. Nucleophilic attack on the electrophilic alkenyl carbon ensue (with the phosphorus nucleophile attacking from slightly above the square planar to the *Re* face of the electrophilic carbon), followed by proton transfer to give the coordinated product.

Displacement of the chiral phosphine product by Ph_2PH regenerates the catalytically active species. In retrospect, it was interesting to find that there are in fact several electron-donating atoms borne by the substrate (heterocyclic oxygen and nitrogen as well as the nitro's oxygens) that can coordinate to the catalyst, potentially leading to the generation of

Scheme 22: Proposed catalytic cycle and the possible intermediates (A-C) due to multiple donor atoms on the substrate

undesired stereoisomers. In-depth analyses revealed that only the heterocyclic oxygen coordinated exclusively to Pd for the desired AHP transformation (Scheme 22-A). From a purely electronic point of view, the nitro oxygens which are electronically richer should bind favourably to Pd in the presence of a *trans* electron-withdrawing naphthyl ring (Scheme 22-B). However, an unfavourable 8-membered transition state will be required for the subsequent nucleophilic attack which is significantly less favourable than a 6-membered moiety with **A** where it is the heterocyclic oxygen that binds. In addition, while it is possible that the heterocyclic nitrogen bind to Pd (Scheme 22-C), the electrophilic carbon is now positioned far away from the phosphido nucleophile. The reaction of only the most suitable intermediate for nucleophilic attack is thus critical for obtaining excellent optical purities.

2-4 Conclusions

In summary, the first asymmetric hydrophosphination of functionalized alkenyl isoxazoles have been achieved, affording highly enantioenriched tertiary phosphines as products. The protocol is able to tolerate variation in the substrate, albeit *ortho* functionalised substituents producing poorer stereoselectivities and lowered reactivities. A feasible mechanistic cycle has been proposed, with in-depth analyses of the plausible intermediates formed over the course of the reaction.

The contents of this chapter have been published in *Advanced Synthesis and Catalysis* **2013**, 355, 1403-1408.

2-5 Experimental Section

All air sensitive manipulations were performed under a positive pressure of nitrogen using Schlenk techniques. Solvents were degassed prior to use when necessary. Chloroform (AR) and dichloromethane (AR) were purchased from Merck Millipore; tetrahydrofuran (AR) and acetonitrile (AR) from TEDIA Company and toluene from Fischer Scientific. Solvents were used directly without further purification. Low Temp PAIRSTIRRER PSL-1800 machine was used for controlling low temperatures for reactions. Silica plug filtration was conducted on SiliCycle silica gel F60 (0.040-0.063mm). Diphenylphosphine and the alkenyl isoxazoles were prepared according to literature methods (*J. Org. Chem.* **1958**, 23, 1063; and *Heterocycles* **2007**, 71, 1173 respectively).

NMR spectra were recorded on Bruker ACF 300, 400 and 500 spectrometers. ^1H NMR spectra chemical shifts were reported in δ ppm relative to tetramethylsilane ($\delta = 0.00$ ppm). Reported yields are calculated from the $^{31}\text{P}\{^1\text{H}\}$ NMR spectra of the products. Multiplicities were given as: s (singlet), d(doublet), t (triplet), q (quartet) and m (multiplet). The number of protons (n) for a given resonance was indicated by nH while coupling constants were reported as *J* value in Hertz (Hz). ^{13}C NMR spectra chemical shifts were recorded relative to solvent resonance (CDCl_3 : $\delta = 77.23$ ppm). $^{31}\text{P}\{^1\text{H}\}$ NMR spectra chemical shifts are referenced to an external standard of 85% H_3PO_4 . Optical rotations of monophosphine products were measured as soon as possible without inert gas protection in the specified solution using a 0.1 dm cell at 20 °C with either a Perkin-Elmer 341 or Jasco P-1030 polarimeter. Chiral palladacycles **1** and **4** and substituted vinyl isoxazoles **11**^[64] were prepared according to literature methods.

2-5.1 General procedure for the (*S*)-**4** catalyzed asymmetric hydrophosphination of alkenylisoxazoles (**11**)

To a solution of Ph_2PH (37.2 mg, 0.2 mmol, 1 equiv.) in degassed chloroform (CHCl_3 , 4 mL) was added (*S*)-**4** (1.9 mg, 0.003 mmol, 1.5 mol%) and stirred at room temperature until complete dissolution before cooling to $-45\text{ }^\circ\text{C}$. Subsequently, substituted vinyl isoxazole **11** (0.2 mmol, 1 equiv.) was added, followed by dropwise addition of Et_3N (20.2 mg, 0.2 mmol, 1 equiv.) in CHCl_3 (1 mL) over a period of 20 minutes. The solution was stirred at $-45\text{ }^\circ\text{C}$ and the reaction monitored by $^{31}\text{P}\{^1\text{H}\}$ NMR. Upon completion, the reaction vessel was allowed to warm to room temperature and the reaction mixture was filtered through a silica plug using a Pasteur pipette fixed on a nitrogen filled 2-neck Schenk flask to remove (*S*)-**4** and phosphine oxides (if any). Solvents were removed from the eluent under reduced pressure to afford chiral tertiary phosphine **12** as the pure product. Enantiomeric excess (*ee*) is determined from the integration of signals of diastereomers **13** arising from the treatment of **12** with (*R*)/(*S*)-**1**.

2-5.2 Coordination studies for *ee* determination

$$ee = \frac{(S,R)\text{-13} - (S,S)\text{-13}}{(S,R)\text{-13} + (S,S)\text{-13}} = \frac{(R,R)\text{-13} - (R,S)\text{-13}}{(R,R)\text{-13} + (R,S)\text{-13}}$$

Monophosphine products (**12**) were allowed to react with enantiopure dimeric complex **(S)-1** and/or **(R)-1** (0.51 equiv) in dichloromethane to form derivatives **13**. Enantiomeric excess (*ee* %) was then determined from the $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum of the integral ratios of the respective diastereomers.

2-5.3 X-ray analyses of Pd-P adduct

Isolation of one of the major diastereomers (**(S,R)-13b**, Ar=4-ClC₆H₄) by silica column chromatography, followed by crystallization from chloroform and diethyl ether afforded clear yellow prisms. X-ray analyses revealed that the absolute configuration at the newly formed chiral centre is *R* (Figure 10).

Figure 10: Molecular structure and absolute stereochemistry of (*S,R*)-**13b** with 50% thermal ellipsoids shown. Hydrogen atoms except those on the stereogenic centres are omitted for clarity. CCDC 915696 contains the supplementary crystallographic data for (*S,R*)-**13b**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

2-5.4 Product characterization

(*R*)-**12a** was prepared according to general procedure stated in **2-5.1** (>99% yield, 92% *ee*): $[\alpha]_{\text{D}}^{20} = +109.2$ [*c* 0.7, CH₂Cl₂]. ³¹P{¹H} (CDCl₃, 162 MHz): δ 0.88; ¹H (CDCl₃, 500 MHz): δ 2.26 (s, 3H), 3.36-3.41 (m, 1H), 3.64-3.71 (m, 1H), 4.04-4.08 (m, 1H), 7.02-7.67 (m, 15H); ¹³C (CDCl₃, 126 MHz): δ 11.7 (s, 1C), 32.0 (d, 1C, ²*J*_{CP} = 26.5 Hz), 42.7 (d, 1C, ¹*J*_{CP} = 16.4 Hz), 127.3-138.7 (m, 19C), 155.4 (s, 1C), 173.2 (d, 1C, ³*J*_{CP} = 12.6 Hz).

(S)-**12a** was prepared according to general procedure stated in **2-5.1** (>99% yield, 88% *ee*) with the exception of using (*R*)-**4** as the catalyst: $[\alpha]_D^{20} = -101.6$ [*c* 0.6, CH₂Cl₂]. ³¹P{¹H} (CDCl₃, 162 MHz): δ 0.89; ¹H (CDCl₃, 400 MHz): δ 2.27 (s, 3H), 3.36-3.42 (m, 1H), 3.64-3.72 (m, 1H), 4.03-4.09 (m, 1H), 7.01-7.67 (m, 15H); ¹³C (CDCl₃, 101 MHz): δ 11.7 (s, 1C), 32.0 (d, 1C, ²*J*_{CP} = 27.3 Hz), 42.7 (d, 1C, ¹*J*_{CP} = 15.2 Hz), 127.3-138.7 (m, 19C), 155.4 (s, 1C), 173.3 (d, 1C, ³*J*_{CP} = 13.1 Hz).

(R)-**12b** was prepared according to general procedure stated in **2-5.1** (99% yield, 89% *ee*): $[\alpha]_D^{20} = +111.5$ [*c* 0.6, CH₂Cl₂]. ³¹P{¹H} (CDCl₃, 162 MHz): δ 1.36; ¹H (CDCl₃, 400 MHz): δ 2.28 (s, 3H), 3.34-3.40 (m, 1H), 3.60-3.68 (m, 1H), 4.02-4.07 (m, 1H), 6.95-7.66 (m, 14H); ¹³C (CDCl₃, 100 MHz): δ 11.7 (s, 1C), 31.8 (d, 1C, ²*J*_{CP} = 27.0 Hz), 42.1 (d, 1C, ¹*J*_{CP} = 16.0 Hz), 128.3-137.3 (m, 19C), 155.5 (s, 1C), 172.9 (d, 1C, ³*J*_{CP} = 12.0 Hz).

(R)-**12c** was prepared according to general procedure in stated in **2-5.1** (99% yield, 89% *ee*): $[\alpha]_D^{20} = +105.7$ [*c* 0.6, CH₂Cl₂]. ³¹P{¹H} (CDCl₃, 162 MHz): δ 1.62; ¹H (CDCl₃, 400 MHz): δ 2.29 (s, 3H), 3.38-3.43 (m, 1H), 3.59-3.67 (m, 1H), 4.00-4.05 (m, 1H), 6.93-7.66 (m, 14H); ¹³C (CDCl₃, 100 MHz): δ 11.7 (s, 1C), 31.7 (d, 1C, ²*J*_{CP} = 27.0 Hz), 42.5 (d, 1C, ¹*J*_{CP} = 16.0 Hz), 126.9-141.0 (m, 19C), 155.5 (s, 1C), 172.8 (d, 1C, ³*J*_{CP} = 12.0 Hz).

12.0 Hz)

(*R*)-**12d**

(*R*)-**12d** was prepared according to general procedure in stated in **2-5.1** (98% yield, 58% *ee*): $[\alpha]_D^{20} = +23.3$ [*c* 0.6, CH₂Cl₂]. ³¹P{¹H} (CDCl₃, 202 MHz): δ 2.92; ¹H (CDCl₃, 400 MHz): δ 2.29 (s, 3H), 3.40-3.51 (m, 2H), 4.79-4.84 (m, 1H), 6.94-7.71 (m, 14H); ¹³C (CDCl₃, 100 MHz): δ 11.7 (s, 1C), 31.9 (d, 1C, ²J_{CP} = 26.0 Hz), 37.6 (d, 1C, ¹J_{CP} = 8.0 Hz), 127.4-136.8 (m, 19C), 155.4 (s, 1C), 172.7 (d, 1C, ³J_{CP} = 12.0 Hz).

(*R*)-**12e**

(*R*)-**12e** was prepared according to general procedure in stated in **2-5.1** (99% yield, 80% *ee*): $[\alpha]_D^{20} = +86.4$ [*c* 0.5, CH₂Cl₂]. ³¹P{¹H} (CDCl₃, 162 MHz): δ 1.06; ¹H (CDCl₃, 400 MHz): δ 2.28 (s, 3H), 3.34-3.40 (m, 1H), 3.60-3.68 (m, 1H), 4.02-4.07 (m, 1H), 6.72-7.68 (m, 14H); ¹⁹F (CDCl₃, 282 MHz): δ -114.9 (d, 1F, J_{FP} = 5.6 Hz); ¹³C (CDCl₃, 101 MHz): δ 11.7 (s, 1C), 32.0 (d, 1C, ²J_{CP} = 27.3 Hz), 42.0 (d, 1C, ¹J_{CP} = 16.2 Hz), 115.5-135.6 (m, 19C), 155.5 (s, 1C), 173.0 (d, 1C, ³J_{CP} = 13.1 Hz).

(*R*)-**12f**

(*R*)-**12f** was prepared according to general procedure stated in **2-5.1** (99% yield, 91% *ee*): $[\alpha]_D^{20} = +110.4$ [*c* 0.6, CH₂Cl₂]. ³¹P{¹H} (CDCl₃, 162 MHz): δ 2.35; ¹H (CDCl₃, 400 MHz): δ 2.28 (s, 3H), 3.41-3.47 (m, 1H), 3.68-3.74 (m, 1H), 4.11-4.15 (m, 1H), 7.04-7.67 (m, 14H); ¹⁹F (CDCl₃, 377 MHz): δ -62.7 (d, 1F, J_{FP} = 150.8 Hz); ¹³C

(CDCl₃, 100 MHz): δ 11.7 (s, 1C), 31.6 (d, 1C, $^2J_{CP}$ = 26.0 Hz), 42.6 (d, 1C, $^1J_{CP}$ = 17.0 Hz), 125.6-143.1 (m, 19C), 155.6 (s, 1C), 172.7 (d, 1C, $^3J_{CP}$ = 12.0 Hz).

(R)-12g was prepared according to general procedure stated in **2-5.1** (>99% yield, 79% *ee*): $[\alpha]_D^{20}$ = +64.0 [*c* 0.4, CH₂Cl₂]. $^{31}\text{P}\{^1\text{H}\}$ (CDCl₃, 162 MHz): δ 1.40; ^1H (CDCl₃, 500 MHz): δ 2.30 (s, 3H), 3.35-3.40 (m, 1H), 3.63-3.68 (m, 1H), 4.02-4.06 (m, 1H), 6.90-7.66 (m, 14H); ^{13}C (CDCl₃, 100 MHz): δ 11.7 (s, 1C), 31.7 (d, 1C, $^2J_{CP}$ = 17.0 Hz), 42.2 (d, 1C, $^1J_{CP}$ = 16.0 Hz), 121.1-137.9 (m, 19C), 155.6 (s, 1C), 172.9 (d, 1C, $^3J_{CP}$ = 13.0 Hz).

(R)-12h was prepared according to general procedure stated in **2-5.1** (99% yield, 91% *ee*): $[\alpha]_D^{20}$ = +92.1 [*c* 0.6, CH₂Cl₂]. $^{31}\text{P}\{^1\text{H}\}$ (CDCl₃, 162 MHz): δ 2.00; ^1H (CDCl₃, 400 MHz): δ 2.27 (s, 3H), 3.39-3.45 (m, 1H), 3.66-3.74 (m, 1H), 3.77 (s, 3H), 4.11-4.16 (m, 1H), 7.03-7.76 (m, 14H); ^{13}C (CDCl₃, 100 MHz): δ 11.7 (s, 1C), 31.6 (d, 1C, $^2J_{CP}$ = 26.0 Hz), 42.9 (d, 1C, $^1J_{CP}$ = 17.0 Hz), 52.2 (s, 1C), 128.3-155.5 (m, 20C), 166.9 (s, 1C), 172.8 (d, 1C, $^3J_{CP}$ = 13.0 Hz).

(R)-12i was prepared according to general procedure stated in **2-5.1** (98% yield, 89% *ee*): $[\alpha]_D^{20}$ = +122.2 [*c* 0.5, CH₂Cl₂]. $^{31}\text{P}\{^1\text{H}\}$ (CDCl₃, 162 MHz): δ 2.91; ^1H (CDCl₃, 400 MHz): δ 2.30 (s, 3H), 3.42-3.49 (m, 1H), 3.65-3.74 (m, 1H), 4.10-4.15 (m,

1H), 7.03-7.68 (m, 14H); ^{13}C (CDCl_3 , 100 MHz): δ 11.7 (s, 1C), 31.3 (d, 1C, $^2J_{\text{CP}} = 26.0$ Hz), 43.0 (d, 1C, $^1J_{\text{CP}} = 18.0$ Hz), 111.1 (s, 1C), 118.7 (s, 1C), 128.5-144.6 (m, 18C), 155.6 (s, 1C), 172.4 (d, 1C, $^3J_{\text{CP}} = 13.0$ Hz).

(*R*)-**12j**

(*R*)-**12j** was prepared according to general procedure stated in **2-5.1** (>99% yield, 72% *ee*): $[\alpha]_{\text{D}}^{20} = +79.8$ [*c* 0.6, CH_2Cl_2]. $^{31}\text{P}\{^1\text{H}\}$ (CDCl_3 , 162 MHz): δ 0.36; ^1H (CDCl_3 , 400 MHz): δ 2.13 (s, 3H), 2.26 (s, 3H), 3.31-3.37 (m, 1H), 3.61-3.67 (m, 1H), 4.01-4.06 (m, 1H), 6.84-7.66 (m, 14H); ^{13}C (CDCl_3 , 100 MHz): δ 11.7 (s, 1C), 21.2 (s, 1C), 32.2 (d, 1C, $^2J_{\text{CP}} = 26.0$ Hz), 42.2 (d, 1C, $^1J_{\text{CP}} = 15.0$ Hz), 128.2-136.8 (m, 19C), 155.4 (s, 1C), 173.4 (d, 1C, $^3J_{\text{CP}} = 12.0$ Hz).

(*R*)-**12k**

(*R*)-**12k** was prepared according to general procedure stated in **2-5.1** (99% yield, 73% *ee*): $[\alpha]_{\text{D}}^{20} = +58.8$ [*c* 0.7, CH_2Cl_2]. $^{31}\text{P}\{^1\text{H}\}$ (CDCl_3 , 162 MHz): δ 0.27; ^1H (CDCl_3 , 400 MHz): δ 2.27 (s, 3H), 3.30-3.36 (m, 1H), 3.59-3.67 (m, 1H), 3.61 (s, 3H), 3.99-4.04 (m, 1H), 6.58-7.67 (m, 14H); ^{13}C (CDCl_3 , 100 MHz): δ 11.7 (s, 1C), 32.2 (d, 1C, $^2J_{\text{CP}} = 28.0$ Hz), 41.8 (d, 1C, $^1J_{\text{CP}} = 15.0$ Hz), 55.3 (s, 1C), 114.1 (s, 2C), 128.2-136.1 (m, 16C), 155.4 (s, 1C), 158.7 (d, 1C, $^5J_{\text{CP}} = 2.0$ Hz), 173.4 (d, 1C, $^3J_{\text{CP}} = 13.0$ Hz).

(*R*)-**12l**

(*R*)-**12l** was prepared according to general procedure stated in **2-5.1** (98%

yield, 67% *ee*): $[\alpha]_D^{20} = +45.9$ [*c* 0.6, CH₂Cl₂]. $^{31}\text{P}\{^1\text{H}\}$ (CDCl₃, 162 MHz): δ -2.04; ^1H (CDCl₃, 400 MHz): δ 2.33 (s, 3H), 3.32-3.38 (m, 1H), 3.58-3.64 (m, 1H), 4.17-4.22 (m, 1H), 5.84 (d, 1H, $^1J_{\text{HH}} = 3.2$ Hz), 6.06 (dd, 1H, $^1J_{\text{HH}} = 2.8$ Hz, 2.0 Hz), 7.12-7.61 (m, 11H); ^{13}C (CDCl₃, 100 MHz): δ 11.7 (s, 1C), 30.5 (d, 1C, $^2J_{\text{CP}} = 27.0$ Hz), 36.3 (d, 1C, $^1J_{\text{CP}} = 17.0$ Hz), 108.1-151.9 (m, 17C), 155.5 (s, 1C), 172.9 (d, 1C, $^3J_{\text{CP}} = 12.0$ Hz).

(R)-**12m** was prepared according to general procedure stated in **2-5.1** (93% yield, 64% *ee*): $[\alpha]_D^{20} = +46.0$ [*c* 0.5, CH₂Cl₂]. $^{31}\text{P}\{^1\text{H}\}$ (CDCl₃, 162 MHz): δ -2.42; ^1H (CDCl₃, 400 MHz): δ 2.33 (s, 3H), 3.25-3.31 (m, 1H), 3.56-3.65 (m, 1H), 4.11-4.16 (m, 1H), 5.80 (m, 1H), 5.90-5.92 (m, 1H), 6.46 (m, 1H), 7.00-7.60 (m, 10H), 7.85 (br. s, 1H); ^{13}C (CDCl₃, 100 MHz): δ 11.8 (s, 1C), 31.6 (d, 1C, $^2J_{\text{CP}} = 27.0$ Hz), 36.1 (d, 1C, $^1J_{\text{CP}} = 16.0$ Hz), 107.9 (d, 1C, $^2J_{\text{CP}} = 5.0$ Hz), 108.9 (s, 1C), 117.8 (s, 1C), 128.1-136.3 (m, 14C), 155.6 (s, 1C), 173.2 (d, 1C, $^3J_{\text{CP}} = 12.0$ Hz).

(R)-**12n** was prepared according to general procedure stated in **2-5.1** (99% yield, 90% *ee*): $[\alpha]_D^{20} = +81.5$ [*c* 0.6, CH₂Cl₂]. $^{31}\text{P}\{^1\text{H}\}$ (CDCl₃, 162 MHz): δ 1.90; ^1H (CDCl₃, 400 MHz): δ 2.29 (s, 3H), 3.43-3.49 (m, 1H), 3.63-3.72 (m, 1H), 4.06-4.11 (m, 1H), 7.03-7.69 (m, 12H), 8.10 (br. s, 1H), 8.27 (d, 1H, $^4J_{\text{HP}} = 4.8$ Hz); ^{13}C (CDCl₃, 100 MHz): δ 11.5 (s, 1C), 31.3 (d, 1C, $^2J_{\text{CP}} = 27.0$ Hz), 39.9 (d, 1C, $^1J_{\text{CP}} = 17.0$ Hz), 123.3 (s, 1C), 128.3-135.8 (m, 15C), 148.6 (d, 1C, $^3J_{\text{CP}} = 2.0$ Hz), 150.2 (d, 1C, $^2J_{\text{CP}} = 6.0$ Hz), 155.4 (s, 1C), 172.4 (d, 1C, $^3J_{\text{CP}} = 13.0$ Hz).

(*R*)-**12o**

(*R*)-**12o** was prepared according to general procedure stated in **2-5.1** (99% yield, 91% *ee*): $[\alpha]_D^{20} = +119.7$ [*c* 0.6, CH₂Cl₂]. ³¹P{¹H}(CDCl₃, 162 MHz): δ 2.70; ¹H (CDCl₃, 400 MHz): δ 2.29 (s, 3H), 3.40-3.46 (m, 1H), 3.67-3.75 (m, 1H), 4.04-4.09 (m, 1H), 6.92 (d, 1H, ³*J*_{HH} = 4.8 Hz), 7.07-7.66 (m, 10H), 8.27 (d, 1H, ²*J*_{HH} = 6.0 Hz); ¹³C (CDCl₃, 100 MHz): δ 11.6 (s, 1C), 30.9 (d, 1C, ²*J*_{CP} = 26.0 Hz), 42.2 (d, 1C, ¹*J*_{CP} = 18.0 Hz), 123.8 (d, 2C, ³*J*_{CP} = 9.0 Hz), 128.4-134.6 (m, 12C), 148.0 (d, 2C, ²*J*_{CP} = 9.0 Hz), 150.0 (s, 2C), 155.6 (s, 1C), 172.3 (d, 1C, ³*J*_{CP} = 12.0 Hz).

2-5.5 Representative NMR spectra

$^{31}\text{P}\{^1\text{H}\}$

Chapter III

*Palladacycle Catalyzed Asymmetric C-P
Addition of β,γ -Unsaturated α -Ketoesters and
Amides*

3-1 Introduction

The constant demand for novel chiral phosphine compounds as ligands in metal-mediated transformations have led to recent advancements in synthetic methodologies for their preparation. As the asymmetric conjugate addition is one of the most powerful methods in accessing chiral compounds, typical prochiral substrates such as *trans*-chalcones, α,β -unsaturated aldehydes, imines, esters were established to be suitable Michael acceptors for the asymmetric hydrophosphination (AHP) reaction. Determined to expand the established substrate classes and to demonstrate the versatility of our palladacycle catalyst (**4**), novel electrophiles were studied in hope of achieving the asymmetric *phospha*-Michael addition. Literature review revealed that β,γ -unsaturated α -ketoesters have served as excellent electrophiles for typical C-C conjugate additions,^[65] including less common *oxy*-,^[66] *aza*-^[67] and *sulfa*-additions.^[68] In addition to their conventional roles as Michael acceptors, they also participate in the Friedel-Crafts,^[69] Stetter^[70] and Diels-Alder^[71] reactions. Their superior reactivity owing to additional activation by the ester functionality have led to β,γ -unsaturated α -ketoesters being significantly better electrophiles than typical α,β -unsaturated carbonyls. However to the best of our knowledge, there have been no known reports on the addition of phosphorus nucleophiles to β,γ -unsaturated α -ketoesters up till the inception of this study. More importantly, the resultant adducts can potentially be further functionalized to give amino-acid ester phosphines, a potential versatile heterobidentate P,N ligand via the reductive amination of the phosphine adducts.^[72]

3-2 Results and Discussions

Studies began with the employment of (*E*)-2-methyl-2-oxo-4-phenylbut-3-enoate (**14a**) as

the prototypical substrate. While it was expected of **14** to exhibit superior reactivities, it was intriguing to note that the P-H addition occurred without the requirement of any catalyst at room temperature (Table 3, entry 1). As it was uncommon for uncatalyzed hydrophosphinations to occur under mild conditions, the revelation made the desired asymmetric transformation considerably more challenging. In order to overcome the possibility of obtaining racemic products or a poorly enantioenriched mixture even in the presence of a chiral catalyst, a highly reduced temperature of -80 °C was employed which fortuitously suppressed the uncatalyzed pathway (Table 3, entry 2). In the presence of catalyst (*R*)-**4**, commendable results could be obtained with the appropriate combination of promoters and conditions. A reduction in base loading from 0.5 to 0.2 equivalents produced improved enantioselectivities (Table 3, entries 3-4), and that subsequent screening of solvents revealed that a mixed chloroform-dichloromethane (10%) solvent system gave the best outcomes (Table 3, entries 5-9,11). A separate reaction employing (*S*)-**4** as the catalyst gave very similar results albeit producing the enantiomeric product. The employment of a weaker base or a azapalladacycle catalyst (*R*)-**3** however led to significantly poorer enantiomeric excess obtained (Table 3, entries 12-13).

Enantiomeric excesses were determined from coordination studies followed by $^{31}\text{P}\{^1\text{H}\}$ NMR analyses. X-ray diffraction studies of an isolated phosphine-palladium adduct revealed that the newly formed stereogenic centre exhibits the *S* configuration (See **3-4 Experimental Section** for details).

It was observed from the $^{31}\text{P}\{^1\text{H}\}$ and ^1H NMR spectra (Refer to **3-4.5 Product**

Table 3: Optimization of reaction conditions for the asymmetric hydrophosphination of (*E*)-2-methyl-2-oxo-4-phenylbut-3-enoate (**14a**) with diphenylphosphine (Ph₂PH)^[a]

Entry	Catalyst / Loading [mol%]	Solvent	Temperature [°C]	Base [equiv.]	Time [hr]	Yield ^[b] [%]	ee ^[c] [%]
1	- / 0%	CHCl ₃	21 (rt)	Et ₃ N (1.0 eq.)	>2	99	0
2	- / 0%	DCM	-80	Et ₃ N (0.2 eq.)	>15	16	0
3	(<i>R</i>)- 4 / 5%	DCM	-80	Et ₃ N (0.5 eq.)	2	99	70
4	(<i>R</i>)- 4 / 5%	DCM	-80	Et ₃ N (0.2 eq.)	>1.5	99	80
5	(<i>R</i>)- 4 / 5%	acetone	-80	Et ₃ N (0.2 eq.)	<2.5	99	70
6	(<i>R</i>)- 4 / 5%	THF	-80	Et ₃ N (0.2 eq.)	2	99	71
7	(<i>R</i>)- 4 / 5%	CHCl ₃	-50	Et ₃ N (0.2 eq.)	2	99	70
8	(<i>R</i>)- 4 / 5%	CHCl ₃ /DCM (5%)	-80	Et ₃ N (0.2 eq.)	4	98	76
9	(<i>R</i>)- 4 / 5%	CHCl ₃ /DCM (10%)	-80	Et ₃ N (0.2 eq.)	2.5	98	81
10	(<i>S</i>)- 4 / 5%	CHCl ₃ /DCM (10%)	-80	Et ₃ N (0.2 eq.)	2.5	98	77
11	(<i>R</i>)- 4 / 5%	DCE/DCM (25%)	-80	Et ₃ N (0.2 eq.)	>3	99	68
12	(<i>R</i>)- 4 / 5%	CHCl ₃ /DCM (10%)	-80	piperidine (0.2 eq.)	2.5	55	52
13	(<i>R</i>)- 5 / 5%	CHCl ₃ /DCM (10%)	-80	Et ₃ N (0.2 eq.)	31	20	29

^[a] Reaction conditions: 0.1-0.15 mmol Ph₂PH, **14a** (1 equiv.) in 4 mL of degassed solvent(s). ^[b] Yield is determined from the ³¹P{¹H}NMR of the crude product. ^[c] ee is calculated from the ratio of diastereomers (**17** and **18**) formed from treatment of **15a** and **16a** with (*R*)-**1**.

Characterization and **3-4.6 Representative NMR spectra** for details) that the phosphine adduct tended to exhibit a small degree of tautomerization since the enol tautomer (**16**) could be stabilized by intramolecular hydrogen bonding. As the keto functionality in ketoesters is in fact as reactive as an aldehyde, there have been reports where the undesirable 1,2-addition occurs.^[65b] Fortunately in this study, the phosphorus nucleophile added chemospecifically to the electrophilic alkenyl carbon via a 1,4-attack, sparing the keto's carbonyl carbon.

With the optimal conditions established, a series of β,γ -unsaturated α -ketoesters (**14**) were screened and the results presented in Table 4. The established protocol was able to tolerate substrates bearing various functionalities including alkoxy, alkyl, nitro, halo as well as heterocycles; alkyl substituents regrettably gave no reaction. All substrates gave excellent yields in the range of 98 to >99% under relatively short reaction times. A slight improvement in enantioselectivities was observed when the methyl ester is substituted with a bulkier isopropyl ester group (Table 4, entry 2). For heterocyclic substituents, *ortho*-positioned substrates performed poorer than *meta*-positioned analogs (Table 4, entries 11-12) probably owing to unfavourable steric/electronic interactions.

In addition to diphenylphosphine as the phosphinating agent, a di-substituted secondary phosphine ((*p*-Tol)₂PH) was also examined. It was found that reactivities were reduced and that only moderate enantiomeric excesses were obtained (Table 4, entries 13-16). A plausible explanation for the poorer stereoselectivities is that the slower deprotonation step with (*p*-Tol)₂PH versus diphenylphosphine allowed for the uncatalyzed pathway to be

marginally predominant, leading to *ee* values being lower than when Ph₂PH is employed.

Table 4: Substrate scope for the asymmetric *phospha*-Michael addition of diarylphosphines to β,γ -unsaturated α -ketoesters and amides.^[a]

Entry	Substrate	R	R'	Ar	Time [hr]	Yield ^[b,c] [%]	<i>ee</i> ^[d] [%]
1	14a	Ph	OMe	Ph	2.5	98 (93)	81
2	14b	Ph	O ⁱ Pr	Ph	4	98 (94)	83
3	14c	<i>p</i> -FC ₆ H ₄	OMe	Ph	2.5	98 (93)	83
4	14d	<i>p</i> -ClC ₆ H ₄	OMe	Ph	2.5	98 (94)	85
5	14e	<i>m</i> -ClC ₆ H ₄	OMe	Ph	2.5	98 (90)	85
6	14f	<i>p</i> -BrC ₆ H ₄	OMe	Ph	2.5	99 (95)	87
7	14g	<i>p</i> -CF ₃ C ₆ H ₄	OMe	Ph	2.5	98 (90)	90
8	14h	<i>p</i> -NO ₂ C ₆ H ₄	OMe	Ph	4	98 (94)	89
9	14i	<i>p</i> -MeC ₆ H ₄	OMe	Ph	5	98 (91)	71
10	14j	<i>p</i> -MeOC ₆ H ₄	OMe	Ph	5	93 (95)	78
11	14k	<i>m</i> -pyridyl	OMe	Ph	2	90 (93)	84
12	14l	2-thienyl	OMe	Ph	4	94 (95)	65
13	14a	Ph	OMe	<i>p</i> -tolyl	3.5	98 (96)	66
14	14d	<i>p</i> -ClC ₆ H ₄	OMe	<i>p</i> -tolyl	3.5	>99 (96)	71
15	14i	<i>p</i> -MeC ₆ H ₄	OMe	<i>p</i> -tolyl	6	98 (94)	70
16	14k	<i>m</i> -pyridyl	OMe	<i>p</i> -tolyl	3.5	>99 (90)	75
17	14aa	Ph	NEt ₂	Ph	23	95 (>99)	70

^[a] Reaction conditions: 0.1 mmol Ar₂PH, **14a** (1 equiv.) in 3.6 mL of chloroform and 0.4 mL of dichloromethane. Solvents were degassed prior to use. ^[b] Yield is determined from the ³¹P{¹H}NMR of the crude product. ^[c] Values in parentheses indicates the abundance of the keto tautomer (**15**) as determined from ³¹P{¹H}NMR of the crude product. ^[d] *ee* is calculated from the ratio of diastereomers (**17** and **18**) formed from treatment of **15** and **16** with (*R*)-**1**.

Furthermore, the protocol was also applicable to β,γ -unsaturated α -ketoamides **14aa**. Owing to electronic donation by nitrogen into the conjugated system, the reactivity of **14aa** is lowered which lead to significantly longer reaction times and poorer enantioselectivities (Table 4, entry 17).

3-3 Conclusion

In summary, the protocol for the highly efficient *phospha*-Michael addition of diarylphosphines to β,γ -unsaturated α -ketoesters and amides is established. The employment of a highly reduced temperature is critical in suppressing the uncatalyzed P-H addition pathway. Excellent yields (of up to >99%) and commendable enantiomeric excesses (of up to 90%) can be achieved even with variation in functional group borne on the substrate. Phosphine adducts can potentially be further functionalized, affording chiral P,N-heterobidentate ligands.

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3-4 Experimental Section

All air sensitive manipulations were performed under a positive pressure of nitrogen using Schlenk techniques. Solvents were degassed prior to use when necessary. Chloroform (AR) and dichloromethane (AR) were purchased from Merck Mililipore and Fischer Scientific; tetrahydrofuran (AR) and toluene from TEDIA Company, acetone from QREC (Asia) and 1,2-dichloroethane (DCE) from Alfa Aesar. Solvents were used directly without further

purification. Low Temp PAIRSTIRRER PSL-1800 machine was used for controlling low temperatures for reactions. Silica plug filtration was conducted on Merck silica gel 60 (0.040-0.063mm). β,γ -unsaturated α -ketoesters were synthesized in accordance to literature methods (*Journal of Organic Chemistry* **2010**, 75, 6027-6030).

NMR spectra were recorded on Bruker ACF 400 spectrometers. ^1H NMR spectra chemical shifts were reported in δ ppm relative to tetramethylsilane ($\delta = 0.00$ ppm) or chloroform ($\delta = 7.26$ ppm). Multiplicities were given as: s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). The number of protons (n) for a given resonance was indicated by nH while coupling constants were reported as J value in Hertz (Hz). ^{13}C NMR spectra chemical shifts were recorded relative to solvent resonance (CDCl_3 : $\delta = 77.23$ ppm). $^{31}\text{P}\{^1\text{H}\}$ NMR spectra chemical shifts are referenced to an external standard of 85% H_3PO_4 . Optical rotations of monophosphine products were measured as soon as possible without inert gas protection in the specified solution using a 0.1 dm cell at 23 $^\circ\text{C}$ with a Atago AP-300 polarimeter.

3-4.1 General Procedure for the enantioselective *phospha*-Michael addition of diarylphosphines to β,γ -unsaturated α -ketoesters and amides

To a degassed 2-neck round bottom flask at room temperature was charged with

diarylphosphine (0.1 mmol, 1 equiv.), degassed chloroform (2.8 mL) and dichloromethane (0.4 mL). The solution was slightly agitated before introduction of (*R*)-**4** (0.005 mmol, 5 mol%) with stirring to achieve complete dissolution. The reaction vessel was brought to -80 °C followed by addition of **14** (0.1 mmol, 1 equiv.) and dropwise addition of triethylamine (0.02 mmol, 0.2 equiv.) in chloroform (0.8 mL) over a period of 15 minutes. The reaction was stirred at -80 °C and its progress monitored by $^{31}\text{P}\{^1\text{H}\}$ NMR. Upon completion, the reaction flask is brought to room temperature and the solvents removed via a vacuum pump. Degassed chloroform (10 mL) was then added to dissolve the solids which have precipitated, before passing it through a silica plug in a Pasteur pipette into a separate degassed 2-neck flask in order to remove (*R*)-**4** as well as phosphine oxides (if any). The filtrate was then subjected to solvent removal under reduced pressure to afford the desired product. Enantiomeric excess (*ee*) is determined from the $^{31}\text{P}\{^1\text{H}\}$ NMR integration signals of diastereomers **17** and **18** arising from the treatment of **15** and **16** with (*R*)-**1** and/or (*S*)-**1**.

3-4.2 Determination of enantiomeric excesses via coordination studies

Enantioenriched products **15** and **16** were treated with ≥ 0.51 equivalents of (*R*)-**1** to give diastereoisomeric adducts **17** and **18**. Enantiomeric excesses were calculated from the $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum of the integral ratios of the obtained diastereoisomers.

$$ee = \left| \frac{[(R,S)\text{-17} + (R,S)\text{-18}] - [(R,R)\text{-17} + (R,R)\text{-18}]}{[(R,S)\text{-17} + (R,S)\text{-18}] + [(R,R)\text{-17} + (R,R)\text{-18}]} \right|$$

3-4.3 Establishment of absolute configuration of the chiral product

A diastereomeric mixture of **17a** and **18a** were purified using flash chromatography on silica gel, eluting 2 compounds. The major fraction was recrystallized from ethyl acetate and pentane to give yellow prisms. X-ray diffraction analyses of the purified product however showed that instead of the expected **17a** or **18a**, a phosphine-enolate chelate (*R,S*)-**19a** (Figure 11) was obtained via elimination of a molecule of hydrogen chloride. NMR analyses showed that (*R,S*)-**19a** corresponds to a new signal at 63.82 ppm (Figure 12)

Figure 11: Molecular structure and absolute stereochemistry of (*R,S*)-**19a** with 50% thermal ellipsoids shown. Hydrogen atoms except those on the stereogenic centres are omitted for clarity. CCDC 988281 contains the supplementary crystallographic data for (*R,S*)-**19a**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

After treatment of adducts 15 and 16 with (*R*)-1

Figure 12: $^{31}\text{P}\{^1\text{H}\}$ NMR analyses of adducts before and after silica gel purification.

3-4.4 Identification of corresponding signals in $^{31}\text{P}\{^1\text{H}\}$ NMR spectra

To establish conclusively the chemical shifts of (*R,S*)-**17a** and (*R,S*)-**18a** on the $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum, (*R,S*)-**19a** ($\delta = 63.82$ ppm) was treated with aqueous KCN (in degassed water) and stirred vigorously at room temperature for 2.5 hours to give (*S*)-**15** and **16**. The solution is extracted trice with DCM before re-coordination with (*R*)-**1**. Subsequent $^{31}\text{P}\{^1\text{H}\}$ NMR of the mixture confirms that the chemical shifts of (*R,S*)-**17a** and (*R,S*)-**18a**

mixture of **17a** & **18a**
 (observed 49.23, 45.77, 44.04 ppm)

silica gel
 -HCl

(R,S)-19a
 (observed 63.82 ppm)

1) KCN
 2) (*R*)-**1**

(R,S)-17a,18a
 (observed 49.23, 45.77 ppm)

Figure 13: $^{31}\text{P}\{^1\text{H}\}$ NMR spectra showing the identified chemical shifts of **17** and **18** following re-coordination studies.

3-4.5 Product characterization

(S)-15a was prepared according to general procedure stated in **3-4.1** (98% yield [7% as **(S)-16a**], 81% *ee*): $[\alpha]_{\text{D}}^{23} = -155.6^\circ$ [c 0.5, CHCl_3]. $^{31}\text{P}\{^1\text{H}\}$ (CDCl_3 , 162 MHz): δ 0.12 [**(S)-15a**], 3.66 [**(S)-16a**]; ^1H (CDCl_3 , 400 MHz): δ 2.92-2.99 (m, 1H), 3.42-3.51 (m, 1H), 3.64 (s, 3H), 4.05-4.10 (m, 1H), 7.03-7.59 (m, 15H); ^{13}C (CDCl_3 , 101 MHz): δ 39.7 (d, 1C, $^2J_{\text{CP}} = 14$ Hz), 43.4 (d, 1C, $^1J_{\text{CP}} = 22$ Hz), 53.1 (s, 1C), 126.9-139.9 (m, 18C), 161.1 (d, 1C, $^4J_{\text{CP}} = 3$ Hz), 192.2 (d, 1C, $^3J_{\text{CP}} = 12$ Hz).

(S)-15b was prepared according to general procedure stated in **3-4.1** (98% yield [6% as **(S)-16b**], 83% *ee*): $[\alpha]_{\text{D}}^{23} = -137.9^\circ$ [c 0.4, CHCl_3]. $^{31}\text{P}\{^1\text{H}\}$ (CDCl_3 , 162 MHz): δ 0.29 [**(S)-15b**], 3.98 [**(S)-16b**]; ^1H (CDCl_3 , 400 MHz): δ 1.14 (d, 3H, $^3J_{\text{HH}} = 4$ Hz), 1.15 (d, 3H, $^3J_{\text{HH}} = 4$ Hz), 2.91-2.96 (m, 1H), 3.41-3.48 (m, 1H), 4.05-4.09 (m, 1H), 4.86-4.93 (m, 1H), 7.03-7.58 (m, 15H); ^{13}C (CDCl_3 , 101 MHz): δ 21.7 (s, 2C), 39.8 (d, 1C, $^2J_{\text{CP}} = 10$ Hz), 43.2 (d, 1C, $^1J_{\text{CP}} = 18$ Hz), 70.9 (s, 1C), 126.9-139.9 (m, 18C), 160.4 (d, 1C, $^4J_{\text{CP}} = 2$ Hz), 193.1 (d, 1C, $^3J_{\text{CP}} = 10$ Hz).

(S)-15c was prepared according to general

procedure stated in **3-4.1** (98% yield [7% as **(S)-16c**], 83% *ee*): $[\alpha]_{\text{D}}^{23} = -140.4^{\circ}$ [c 0.4, CHCl₃]. ³¹P{¹H} (CDCl₃, 162 MHz): δ -0.17 [(**S**)-**15c**], 3.66 [(**S**)-**16c**]; ¹H (CDCl₃, 400 MHz): δ 2.91-2.98 (m, 1H), 3.39-3.47 (m, 1H), 3.65 (s, 3H), 4.04-4.07 (m, 1H), 6.75-7.58 (m, 14H); ¹⁹F (CDCl₃, 377 MHz): δ -115.82 (d, 1F, ⁶J_{FP} = 4 Hz) [(**S**)-**15c**], -116.3 (d, 1F, ⁶J_{FP} = 4 Hz) [(**S**)-**16c**]; ¹³C (CDCl₃, 101 MHz): δ 38.9 (d, 1C, ²J_{CP} = 13 Hz), 43.4 (d, 1C, ¹J_{CP} = 23 Hz), 53.1 (s, 1C), 115.3-135.9 (m, 18C), 161.0 (d, 1C, ⁴J_{CP} = 3 Hz), 192.1 (d, 1C, ³J_{CP} = 13 Hz).

(S)-15d was prepared according to

general procedure stated in **3-4.1** (98% yield [6% as **(S)-16d**], 94% *ee*): $[\alpha]_{\text{D}}^{23} = -211.6^{\circ}$ [c 0.5, CHCl₃]. ³¹P{¹H} (CDCl₃, 162 MHz): δ 0.00 [(**S**)-**15d**], 3.83 [(**S**)-**16d**]; ¹H (CDCl₃, 400 MHz): δ 2.91-2.99 (m, 1H), 3.38-3.47 (m, 1H), 3.66 (s, 3H), 4.02-4.07 (m, 1H), 7.00-7.56 (m, 14H); ¹³C (CDCl₃, 101 MHz): δ 39.1 (d, 1C, ²J_{CP} = 13 Hz), 43.3 (d, 1C, ¹J_{CP} = 22 Hz), 53.2 (s, 1C), 128.3-138.6 (m, 18C), 161.0 (d, 1C, ⁴J_{CP} = 3 Hz), 192.0 (d, 1C, ³J_{CP} = 13 Hz).

(S)-15e was prepared according to

general procedure stated in **3-4.1** (98% yield [10% as (*S*)-**16e**], 85% *ee*): $[\alpha]_{\text{D}}^{23} = -258.8^{\circ}$ [c 0.4, CHCl₃]. ³¹P{¹H} (CDCl₃, 162 MHz): δ 0.45 [(*S*)-**15e**], 4.38 [(*S*)-**16e**]; ¹H (CDCl₃, 400 MHz): δ 2.94-3.00 (m, 1H), 3.39-3.48 (m, 1H), 4.02 (s, 3H), 4.01-4.05 (m, 1H), 6.96-7.57 (m, 14H); ¹³C (CDCl₃, 101 MHz): δ 39.4 (d, 1C, ²J_{CP} = 14 Hz), 43.2 (d, 1C, ¹J_{CP} = 23 Hz), 53.2 (s, 1C), 127.1-142.2 (m, 18C), 161.0 (d, 1C, ⁴J_{CP} = 2 Hz), 191.9 (d, 1C, ³J_{CP} = 12 Hz).

(*S*)-**15f** was prepared according to

general procedure stated in **3-4.1** (99% yield [5% as (*S*)-**16f**], 87% *ee*): $[\alpha]_{\text{D}}^{23} = -160.3^{\circ}$ [c 0.4, CHCl₃]. ³¹P{¹H} (CDCl₃, 162 MHz): δ 0.05 [(*S*)-**15f**], 3.82 [(*S*)-**16f**]; ¹H (CDCl₃, 400 MHz): δ 2.91-2.98 (m, 1H), 3.38-3.46 (m, 1H), 3.66 (s, 3H), 4.01-4.06 (m, 1H), 6.95-7.56 (m, 14H); ¹³C (CDCl₃, 101 MHz): δ 39.2 (d, 1C, ²J_{CP} = 14 Hz), 43.2 (d, 1C, ¹J_{CP} = 23 Hz), 53.2 (s, 1C), 120.7-139.2 (m, 18C), 161.1 (d, 1C, ⁴J_{CP} = 2 Hz), 192.0 (d, 1C, ³J_{CP} = 13 Hz).

(*S*)-**15g** was prepared according to

general procedure stated in **3-4.1** (98% yield [10% as (*S*)-**16g**], 90% *ee*): $[\alpha]_{\text{D}}^{23} = -92.7^{\circ}$ [c 0.4, CHCl₃]. ³¹P{¹H} (CDCl₃, 162 MHz): δ 0.78 [(*S*)-**15g**], 4.33 [(*S*)-**16g**]; ¹H (CDCl₃, 400 MHz): δ 2.97-3.04 (m, 1H), 3.45-3.54 (m, 1H), 3.67 (s, 3H), 4.11-4.16 (m, 1H), 7.05-7.56 (m, 14H); ¹⁹F (CDCl₃, 377 MHz): δ -62.49 [(*S*)-**15c**], -62.76 [(*S*)-**16c**]; ¹³C (CDCl₃, 101 MHz): δ 39.5 (d, 1C, ²J_{CP} = 15 Hz), 43.1 (d, 1C, ¹J_{CP} = 21 Hz), 53.2 (s, 1C), 125.5-135.4 (m, 19C), 161.0 (d, 1C, ⁴J_{CP} = 3 Hz), 191.8 (d, 1C, ³J_{CP} = 12 Hz).

(S)-**15h** was prepared according to general procedure stated in **3-4.1** (98% yield [6% as (S)-**16h**], 89% *ee*): $[\alpha]_{\text{D}}^{23} = -133.9^{\circ}$ [c 0.4, CHCl₃]. ³¹P{¹H} (CDCl₃, 162 MHz): δ 1.64 [(S)-**15h**], 6.07 [(S)-**16h**]; ¹H (CDCl₃, 400 MHz): δ 3.02-3.10 (m, 1H), 3.47-3.56 (m, 1H), 3.68 (s, 3H), 4.16-4.21 (m, 1H), 7.07-7.94 (m, 14H); ¹³C (CDCl₃, 101 MHz): δ 39.8 (d, 1C, ²*J*_{CP} = 16 Hz), 42.9 (d, 1C, ¹*J*_{CP} = 21 Hz), 53.3 (s, 1C), 123.7-148.2 (m, 18C), 160.9 (d, 1C, ⁴*J*_{CP} = 2 Hz), 191.6 (d, 1C, ³*J*_{CP} = 13 Hz).

(S)-**15i** was prepared according to general procedure stated in **3-4.1** (98% yield [9% as (S)-**16i**], 71% *ee*): $[\alpha]_{\text{D}}^{23} = -135.4^{\circ}$ [c 0.4, CHCl₃]. ³¹P{¹H} (CDCl₃, 162 MHz): δ -0.42 [(S)-**15i**], 2.65 [(S)-**16i**]; ¹H (CDCl₃, 400 MHz): δ 2.16 (s, 3H), 2.89-2.96 (m, 1H), 3.37-3.46 (m, 1H), 3.63 (s, 3H), 4.02-4.07 (m, 1H), 6.88-7.57 (m, 14H); ¹³C (CDCl₃, 101 MHz): δ 21.2 (s, 1C), 39.2 (d, 1C, ²*J*_{CP} = 13 Hz), 43.6 (d, 1C, ¹*J*_{CP} = 22 Hz), 53.0 (s, 1C), 128.2-136.7 (m, 18C), 161.1 (d, 1C, ⁴*J*_{CP} = 3 Hz), 192.3 (d, 1C, ³*J*_{CP} = 13 Hz).

(S)-**15j** was prepared according to general procedure stated in **3-4.1** (93% yield [5% as (S)-**16j**], 78% *ee*): $[\alpha]_{\text{D}}^{23} = -158.2^{\circ}$ [c

0.4, CHCl₃]. ³¹P{¹H} (CDCl₃, 162 MHz): δ -0.67 [(*S*)-**15j**], 2.56 [(*S*)-**16j**]; ¹H (CDCl₃, 400 MHz): δ 2.88-2.95 (m, 1H), 3.36-3.45 (m, 1H), 3.64 (s, 3H), 3.65 (s, 3H), 4.00-4.05 (m, 1H), 6.62-7.57 (m, 14H); ¹³C (CDCl₃, 101 MHz): δ 38.8 (d, 1C, ²J_{CP} = 13 Hz), 43.6 (d, 1C, ¹J_{CP} = 23 Hz), 53.1 (s, 1C), 55.4 (s, 1C), 114.0-158.5 (m, 18C), 161.1 (d, 1C, ⁴J_{CP} = 3 Hz), 192.4 (d, 1C, ³J_{CP} = 13 Hz).

(*S*)-**15k** was prepared according to general procedure stated in **3-4.1** (90% yield [7% as (*S*)-**16k**], 84% *ee*): [α]_D²³ = -157.7° [c 0.4, CHCl₃]. ³¹P{¹H} (CDCl₃, 162 MHz): δ 0.36 [(*S*)-**15k**], 4.45 [(*S*)-**16k**]; ¹H (CDCl₃, 400 MHz): δ 3.00-3.08 (m, 1H), 3.44-3.53 (m, 1H), 3.69 (s, 3H), 4.06-4.11 (m, 1H), 7.02-8.28 (m, 14H); ¹³C (CDCl₃, 101 MHz): δ 36.9 (d, 1C, ²J_{CP} = 15 Hz), 42.9 (d, 1C, ¹J_{CP} = 23 Hz), 53.3 (s, 1C), 123.43-136.5 (m, 17C), 160.9 (d, 1C, ⁴J_{CP} = 3 Hz), 191.7 (d, 1C, ³J_{CP} = 13 Hz).

(*S*)-**15l** was prepared according to general procedure stated in **3-4.1** (94% yield [5% as (*S*)-**16l**], 65% *ee*): [α]_D²³ = -67.9° [c 0.4, CHCl₃]. ³¹P{¹H} (CDCl₃, 162 MHz): δ 0.71 [(*S*)-**15l**], 4.32 [(*S*)-**16l**]; ¹H (CDCl₃, 400 MHz): δ 2.93-3.00 (m, 1H), 3.37-3.45 (m, 1H), 3.68 (s, 3H), 4.41-4.43 (m, 1H), 6.66-7.55 (m, 13H); ¹³C (CDCl₃, 101 MHz): δ 34.8 (d, 1C, ²J_{CP} = 14 Hz), 44.7 (d, 1C, ¹J_{CP} = 23 Hz), 53.2 (s, 1C), 124.4-143.4 (m, 16C), 161.0 (d, 1C, ⁴J_{CP} = 3 Hz), 191.8 (d, 1C, ³J_{CP} = 12 Hz).

(S)-15a' was prepared according to general procedure stated in **3-4.1** (98% yield [4% as (S)-16a'], 66% *ee*): $[\alpha]_{\text{D}}^{23} = -194.6^{\circ}$ [c 0.5, CHCl₃]. ³¹P{¹H} (CDCl₃, 162 MHz): δ -0.44 [(S)-15a'], 2.20 [(S)-16a']; ¹H (CDCl₃, 400 MHz): δ 2.16 (s, 3H), 2.29 (s, 3H), 2.89-2.96 (m, 1H), 3.39-3.47 (m, 1H), 3.63 (s, 3H), 4.01-4.06 (m, 1H), 6.85-7.46 (m, 13H); ¹³C (CDCl₃, 101 MHz): δ 21.4 (s, 1C), 21.6 (s, 1C), 39.8 (d, 1C, ²*J*_{CP} = 13 Hz), 43.5 (d, 1C, ¹*J*_{CP} = 23 Hz), 53.0 (s, 1C), 126.8-140.2 (m, 18C), 161.1 (d, 1C, ⁴*J*_{CP} = 2 Hz), 192.4 (d, 1C, ³*J*_{CP} = 12 Hz).

(S)-15d' was prepared according to general procedure stated in **3-4.1** (>99% yield [4% as (S)-16d'], 71% *ee*): $[\alpha]_{\text{D}}^{23} = -150.0^{\circ}$ [c 0.5, CHCl₃]. ³¹P{¹H} (CDCl₃, 162 MHz): δ -1.53 [(S)-15d'], 2.39 [(S)-16d']; ¹H (CDCl₃, 400 MHz): δ 2.17 (s, 3H), 2.29 (s, 3H), 2.89-2.95 (m, 1H), 3.34-3.43 (m, 1H), 3.65 (s, 3H), 3.98-4.03 (m, 1H), 6.89-7.45 (m, 12H); ¹³C (CDCl₃, 101 MHz): δ 21.4 (s, 1C), 21.6 (s, 1C), 39.2 (d, 1C, ²*J*_{CP} = 14 Hz), 43.3 (d, 1C, ¹*J*_{CP} = 22 Hz), 53.1 (s, 1C), 128.7-140.2 (m, 18C), 161.0 (d, 1C, ⁴*J*_{CP} = 3 Hz), 192.2 (d, 1C, ³*J*_{CP} = 13 Hz).

(S)-15i' was prepared according to general procedure stated in **3-4.1** (98% yield [6% as (S)-16i'], 70% *ee*): $[\alpha]_{\text{D}}^{23} = -107.1^{\circ}$ [c 0.5, CHCl₃]. ³¹P{¹H} (CDCl₃, 162 MHz): δ -2.00 [(S)-15i'], 1.11 [(S)-16i']; ¹H (CDCl₃, 400 MHz): δ 2.16 (s, 6H), 2.29 (s, 3H), 2.87-2.93 (m, 1H), 3.33-3.41 (m, 1H), 3.63 (s, 3H), 3.99-4.04 (m, 1H), 6.87-7.45 (m, 12H); ¹³C (CDCl₃, 101 MHz): δ 21.2 (s, 1C), 21.4 (s, 1C), 21.6 (s, 1C), 39.3 (d, 1C, ²J_{CP} = 13 Hz), 43.7 (d, 1C, ¹J_{CP} = 22 Hz), 53.0 (s, 1C), 129.0-140.0 (m, 18C), 161.1 (d, 1C, ⁴J_{CP} = 2 Hz), 192.5 (d, 1C, ³J_{CP} = 12 Hz).

(S)-15k' was prepared according to general procedure stated in **3-4.1** (>99% yield [10% as (S)-16k'], 75% *ee*): $[\alpha]_{\text{D}}^{23} = -84.4^{\circ}$ [c 0.5, CHCl₃]. ³¹P{¹H} (CDCl₃, 162 MHz): δ -1.07 [(S)-15k'], 3.09 [(S)-16k']; ¹H (CDCl₃, 400 MHz): δ 2.17 (s, 3H), 2.30 (s, 3H), 2.97-3.05 (m, 1H), 3.40-3.49 (m, 1H), 3.67 (s, 3H), 4.01-4.06 (m, 1H), 6.89-8.27 (m, 12H); ¹³C (CDCl₃, 101 MHz): δ 21.4 (s, 1C), 21.6 (s, 1C), 37.0 (d, 1C, ²J_{CP} = 15 Hz), 43.0 (d, 1C, ¹J_{CP} = 22 Hz), 53.2 (s, 1C), 129.3-150.7 (m, 17C), 161.0 (d, 1C, ⁴J_{CP} = 3 Hz), 191.9 (d, 1C, ³J_{CP} = 12 Hz).

(S)-15aa was prepared according to general procedure stated in **3-4.1** (95% yield [$<1\%$ as **(S)-16aa**], 70% *ee*): $[\alpha]_D^{23} = -200.0^\circ$ [c 0.5, CHCl_3]. $^{31}\text{P}\{^1\text{H}\}(\text{CDCl}_3, 162 \text{ MHz})$: δ -5.45 [**(S)-15aa**], 1.14 [**(S)-16aa**]; ^1H ($\text{CDCl}_3, 400 \text{ MHz}$): δ 0.77 (t, 3H, $^3J_{\text{HH}} = 7\text{Hz}$), 0.98 (t, 3H, $^3J_{\text{HH}} = 7\text{Hz}$), 2.39-2.46 (m, 2H), 3.09-3.25 (m, 4H), 3.64 (s, 3H), 4.07-4.11 (m, 1), 7.00-7.62 (m, 15H); ^{13}C ($\text{CDCl}_3, 101 \text{ MHz}$): δ 12.6 (s, 1C), 14.1 (s, 1C), 39.6 (d, 1C, $^2J_{\text{CP}} = 14 \text{ Hz}$), 39.6 (s, 1C), 41.5 (s, 1C), 43.8 (d, 1C, $^1J_{\text{CP}} = 22 \text{ Hz}$), 126.9-139.9 (m, 18C), 166.2 (d, 1C, $^4J_{\text{CP}} = 1 \text{ Hz}$), 199.8 (d, 1C, $^3J_{\text{CP}} = 13 \text{ Hz}$).

3-4.6 Representative NMR spectra

Chapter IV

*Palladium Mediated phospho-Michael
Addition of N-Enoyl Phthalimides and
Benzotriazoles: Efficient Access to
Functionalized Chiral Phosphines*

4-1 Introduction (*N*-Enoyl Phthalimides)

Chiral phosphines bearing variation in attached functional group(s) are of tremendous significance in metal-mediated catalysis. Among the many categories of functionalized phosphines, chiral phosphino carboxamides have emerged to be a highly versatile class of heteroatom (bidentate) ligand for numerous reactions.^[73] In addition, they also function as efficient organocatalysts^[74] and are of value in biomedicine.^[75] One well-known example of chiral phosphino carboxamides is the Trost ligand, a diamidodiphosphine previously introduced in the 1990's.^[76] Following modifications to the original structural backbone, its analogs were able to aid in a range of metal catalyzed transformations including nucleophilic substitutions, hydrovinylation, cycloisomerizations, *etc.*

Simple chiral phosphino carboxamides were also developed in tandem with preparation of new Trost ligands, their synthetic routes occur either via condensation reactions between chiral phosphino carboxylic acids and secondary phosphines,^[77] or the diastereoselective lithiation/phosphination of chiral α,β -amides.^[78] While these approaches have proven to be feasible, they however require chiral starting materials which may be costly and that multistep transformations are needed to achieve them. A solution would be the direct addition of phosphorus nucleophiles to α,β -amides in an enantioselective fashion. However, to our knowledge, there have been no reports as it is well-understood that the tendency for the amide nitrogen to donate electrons into the carbonyl system renders α,β -amides significantly less prone to nucleophilic attack. To overcome such an impediment, activating-protecting groups can be introduced to the amide functionality. Yet depending on the activating groups incorporated, the degree of activation may not suffice which

necessitates for less desirable reaction conditions, such as higher catalyst loadings and/or temperatures.

Literature review revealed that phthalimides not only play a role in primary amine preparation (Gabriel synthesis)^[79] but also are a powerful tool in the protection of amino functional groups.^[80] We envisaged that by directing the electrons borne on the amide nitrogen, it would render these protected amides more susceptible to nucleophilic attack under mild conditions and low catalyst loadings. Following extensive studies, the asymmetric phospho-Michael addition of *N*-enoyl phthalimides was successfully achieved.

4-2 Results and Discussions (*N*-Enoyl Phthalimides)

Studies began with the examination of increasing potent electron withdrawing activating-protecting groups incorporated in cinnamide **20** which increasingly delocalizes the electrons from the conjugated enone system. While **20** was expected to be relatively inert, compounds **21-23** too showed no visible conversions in the presence of diphenylphosphine and a palladacycle catalyst (*R*)-**4** (Figure 14). Determined to achieve our desired objective, a dual-carbonyl activating phthalimido functionality was introduced which resulted in a breakthrough.

Figure 14: Introduction of increasingly potent activators to cinnamide (**20**).

Using 2-cinnamoylisobenzofuran-1,3-dione (**24a**) as the prototypical substrate, conditions for the asymmetric hydrophosphination reaction were optimized. While it was expected that

24a would be more activated than the other protected compounds, it was astonishing that the *phospha*-Michael addition was able to proceed in the absence of any catalyst at room temperature (Table 5, entry 1). Fortunately, the application of a reduced temperature (-40 °C) was effective in suppressing the uncatalyzed pathway (Table 5, entry 2), thus allowing for stereocontrol over the course of the reaction. An attempt to improve the stereoselectivity by further reducing the applied temperature (-60 °C) however gave the same *ee* as at -40 °C (Table 5, entry 5). Lowering of the catalyst loadings from 5 to 1 mol% revealed that a 3 mol% catalyst loading was ideal as it produced the same *ee* as when 5 mol% was applied (Table 5, entry 6); a further lowered loading of 1 mol% however led to an undesirable drop in enantioselectivity (Table 5, entry 7). Subsequent screening of solvent systems to improve enantioselectivities was futile as chloroform remained the ideal choice (Table 5, entries 8-13). Lastly, a weaker base (diethylamine) was employed but unfortunately produced a comparable but slightly lowered *ee* of 93%.

Enantiomeric excesses were routinely determined in coordination studies where the enantiomerically enriched mixture (**26**) were bound to enantiopure (*S*)- or (*R*)-**1**, producing diastereomers **27** whose ratios determined by $^{31}\text{P}\{^1\text{H}\}$ NMR would reflect the *ee* values of **26**. Isolation of the major diastereomeric complex **27aw** via flash chromatography on silica gel instead gave an electronically neutral phosphine-carboxylate chelate **28aw** formed via the hydrolysis of phthalimide during purification. X-ray analyses revealed that the configuration of the newly formed stereogenic centre is *S*. (See **4-4 Experimental Section**).

Table 5: Optimization of reaction conditions for the asymmetric hydrophosphination of 2-cinnamoylisindoline-1,3-dione (**24a**)^[a]

Entry	Catalyst / Loading [mol%]	Solvent	Base [equiv.]	Temp [°C]	Time [h]	Yield ^[b] [%]	<i>ee</i> ^[c] [%]
1	-	CHCl ₃	Et ₃ N [1.0 eq.]	rt (21)	3	29	0
2	-	CHCl ₃	Et ₃ N [1.0 eq.]	-40	3	2	0
3	5%	CHCl ₃	Et ₃ N [1.0 eq.]	rt (21)	3	81	54
4	5%	CHCl ₃	Et ₃ N [1.0 eq.]	-40	3	96	94
5	5%	CHCl ₃	Et ₃ N [1.0 eq.]	-60	3	99	94
6	3%	CHCl ₃	Et ₃ N [1.0 eq.]	-40	2.5	95	94
7	1%	CHCl ₃	Et ₃ N [1.0 eq.]	-40	7	84	89
8	3%	CHCl ₃	Et ₃ N [0.5 eq.]	-40	4.5	88	93
9	3%	CH ₂ Cl ₂	Et ₃ N [1.0 eq.]	-40	2.5	99	91
10	3%	THF	Et ₃ N [1.0 eq.]	-40	6	72	90
11	3%	acetone	Et ₃ N [1.0 eq.]	-40	2.5	94	92
12	3%	EA	Et ₃ N [1.0 eq.]	-40	2.5	88	93
13	3%	Et ₂ O/CHCl ₃	Et ₃ N [1.0 eq.]	-40	2.5	90	91
14	3%	CHCl ₃	Et ₂ NH [1.0 eq.]	-40	2.5	99	93

^[a] Reaction conditions: 0.1-0.15 mmol Ph₂PH, **24a** (1 equiv.) in 4 mL of degassed solvent(s).^[b] Yield is determined from the ³¹P{¹H}NMR of the crude product. ^[c] *ee* is calculated from the ratio of diastereomers **27aw** formed from treatment of **26aw** with (*S*)-**1**.

With the establishment of the optimal conditions, the substrate scope for the asymmetric hydrophosphination of *N*-enoyl phthalimides was explored and the results presented in Table 6. The protocol was able to tolerate variation in functional groups borne on the aromatic ring of the phthalimido substrate (**24**), ranging from electron withdrawing chloro, to electronically neutral methyl as well as electron donating methoxy functionalities (Table 6, entries 1-10). In addition, a separate reaction employing (*S*)-**4** as the catalyst afforded

Table 6: Substrate scope for the (*R*)-**4** catalyzed enantioselective *phospha*-Michael addition of *N*-enoyl phthalimides **24** with diarylphosphines **25**.^[a]

Entry	Substrate	Ar	Ar'	Time [hr]	Yield ^[b] [%]	<i>ee</i> ^[c] [%]
1	24a	Ph	Ph	2.5	95	94
2	24a	Ph	Ph	2.5	93	-94 ^[d]
3	24b	<i>p</i> -FC ₆ H ₄	Ph	2	90	95
4	24c	<i>p</i> -ClC ₆ H ₄	Ph	2.5	89	96
5	24d	<i>m</i> -ClC ₆ H ₄	Ph	2.5	89	92
6	24e	<i>p</i> -BrC ₆ H ₄	Ph	2.5	86	94
7	24f	<i>p</i> -MeO ₂ CC ₆ H ₄	Ph	2.5	83	92
8	24g	<i>p</i> -NCC ₆ H ₄	Ph	2.5	64	89
9	24h	<i>p</i> -MeC ₆ H ₄	Ph	3.5	89	94
10	24i	<i>p</i> -MeOC ₆ H ₄	Ph	4	88	95
11	24a	Ph	<i>p</i> -tolyl	4.25	93	93
12	24c	<i>p</i> -ClC ₆ H ₄	<i>p</i> -tolyl	3.25	90	96
13	24h	<i>p</i> -MeC ₆ H ₄	<i>p</i> -tolyl	6.75	93	89
14	24i	<i>p</i> -MeOC ₆ H ₄	<i>p</i> -tolyl	9	92	96
15	24a	Ph	<i>m</i> -tolyl	1	>99	97
16	24c	<i>p</i> -ClC ₆ H ₄	<i>m</i> -tolyl	1	88	96
17	24h	<i>p</i> -MeC ₆ H ₄	<i>m</i> -tolyl	3.25	97	98
18	24i	<i>p</i> -MeOC ₆ H ₄	<i>m</i> -tolyl	3	93	97
19	24a	Ph	<i>o</i> -tolyl	5	0	-

^[a] Reaction conditions: 0.1-0.15 mmol Ph₂PH, **24a** (1 equiv.) in 4 mL of degassed solvent(s).^[b] Yield is determined from the ³¹P{¹H}NMR of the crude product. ^[c] *ee* is calculated from the ratio of diastereomers **27aw** formed from treatment of **26aw** with (*R*)/(*S*)-**1**. ^[d] Catalyst (*S*)-**4** employed.

almost identical outcomes albeit the product being the opposite enantiomer (*R*)-**26aw** (Table 6, entry 2).

On top of the routine variation of the substrate simply by changing the functional groups on the aromatic ring, effects arising from the presence and position of substituents on the phosphinating agent were investigated (Figure 15). It was surprising to find that di(*m*-tolyl)phosphine (**25y**) required the least reaction times (Table 6, entries 15-18) while di(*p*-tolyl)phosphine (**25x**) required the longest (Table 6, entries 11-14) even when the exact same conditions were applied. While the slower reaction with di(*p*-tolyl)phosphine (**25x**) is due to typical electron donating *para*-methyl group, it was extraordinary that di(*m*-tolyl)phosphine (**25y**) which similarly bears electron donating methyls albeit on the *meta* position resulted in the fastest reaction. Density functional theory (DFT) calculations for the deprotonation of the diarylphosphines (**25w-y**) shows that their ΔG° and *pK_a* values of **25w** and **25y** are only marginally different (See **4-4 Experimental Section**). This revelation furnishes sufficient evidence to exclude electronic contributions in the observed reactivities. Seeking an plausible explanation from the stereochemical viewpoint, Drieding models of the 3 diarylphosphines (**25w-y**) were constructed which revealed that di(*m*-tolyl)phosphine (**25y**) possessed the largest cone angle. Rudimentary models and their corresponding bond angles were further substantiated by literature which reported the solid cone angles of tri-substituted arylphosphines (Table 7).^[81] While both diphenylphosphine (**25w**) and di(*m*-tolyl)phosphine (**25y**) could approach the palladium catalyst during the reaction, the formation of a more sterically hinder tertiary phosphine adduct with **25y** led

Figure 15: Series of substituted diarylphosphines screened

Table 7: Reported cone angles of triarylphosphines.^[81]

Ar ₃ P	Ar=Ph	Ar= <i>p</i> -Tol	Ar= <i>m</i> -Tol	Ar= <i>o</i> -Tol
Solid cone angle (°)	129	135	140	142

to more facile product elimination than with **25w**, hence accounting for the accelerated rate of reaction. The isomeric di(*o*-tolyl)phosphine (**25z**) is however too sterically bulky which hinders the approach of the electrophile (**24**), accounting for the absence of any conversions even when subjected to prolonged reaction times (Table 6, entry 19).

Keeping in mind the primary objectives of the study, free enantioenriched tertiary phosphine **26aw** was treated with aqueous hydrazine for deprotection of the phthalimidoyl group. It was fortuitous that quantitative yields were obtained with practically no loss in enantioselectivities (Scheme 23). While the deprotection may seem trivial and routine, the transformation is significant as the direct asymmetric phosphination of unactivated α,β -amides under mild conditions is of tremendous challenge. Additionally, application of reduction protocols from phosphine oxide and sulphides to access free chiral phosphino-carboxamides may lead to undesired issues such as racemisation and functional group intolerances.

Scheme 23: Transformation of **26** via deprotection of phthalimidoyl group to afford **29**.

4-3 Conclusions (*N*-Enoyl Phthalimides)

In conclusion, the first catalytic enantioselective *phospha*-Michael addition of *N*-enoyl phthalimides has been developed. Furthermore, *N*-enoyl phthalimides have never been reported as feasible Michael acceptors. Excellent enantioselectivities can be obtained by conducting the reaction under reduced temperatures which effectively suppresses the uncatalyzed pathway. The structure-reactivity relationship between position of substituents on the phosphinating agents are elucidated via modelling studies. Lastly, the product can be deprotected to give free chiral tertiary phosphino-carboxamides which are currently inaccessible via the phosphination of conventional α,β -amides.

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4-4 Experimental Section (*N*-Enoyl Phthalimides)

All air sensitive manipulations were performed under a positive pressure of nitrogen using Schlenk techniques. Solvents were degassed prior to use when necessary. Chloroform (AR) and was purchased from Fischer Scientific; dichloromethane (AR), ethyl acetate (AR), ethanol (AR) and diethylether (AR) from Merck Mililipore; tetrahydrofuran (AR) from TEDIA Company and acetone (AR) from QREC (Asia). Solvents were used directly without further purification. Low Temp PAIRSTIRRER PSL-1800 machine was used for controlling low temperatures for reactions. Silica plug filtration was conducted on Merck silica gel 60 (0.040-0.063mm).

NMR spectra were recorded on Bruker ACF 400 and 500 spectrometers. ^1H NMR spectra chemical shifts were reported in δ ppm relative to tetramethylsilane ($\delta = 0.00$ ppm) or chloroform ($\delta = 7.26$ ppm). Multiplicities were given as: s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). The number of protons (n) for a given resonance was indicated by nH while coupling constants were reported as J value in Hertz (Hz). ^{13}C NMR spectra chemical shifts were recorded relative to solvent resonance (CDCl_3 : $\delta = 77.23$ ppm). $^{31}\text{P}\{^1\text{H}\}$ NMR spectra chemical shifts are referenced to an external standard of 85% H_3PO_4 . Optical rotations of monophosphine products were measured as soon as possible without inert gas protection in the specified solution using a 0.1 dm cell with a Atago AP-300 polarimeter. Chiral HPLC data was obtained using Agilent Technologies 1200 Series HPLC coupled with a Daicel CHIRALPAK® IC column. Chiral palladacycles and N-enoyl phthalimides **24**^[82] were prepared according to literature methods.

4-4.1 General Procedure for the palladacycle catalyzed *phospha*-Michael addition of N-enoyl phthalimides (**24**) with diarylphosphines (**25**)

A nitrogen flushed 2-neck flask was charged with diarylphosphine (**25**) (0.1 mmol, 1 equiv.) and degassed chloroform (3 mL) at room temperature. The solution was agitated before addition of $(R)\text{-4}$ (2.02 mg, 0.003 mmol, 3 mol%) with vigorous stirring to achieve complete dissolution. The reaction vessel was brought to $-40\text{ }^\circ\text{C}$ followed by addition of **24** (0.1 mmol, 1 equiv.) and subsequent washing the walls of the vessel with chloroform (0.5 mL). Triethylamine (0.1 mmol, 1 equiv.) in chloroform (0.5 mL) was then added dropwise

over a period of 5 minutes. The reaction was stirred at -40 °C and its progress monitored by $^{31}\text{P}\{^1\text{H}\}$ NMR. Upon completion, the reaction flask is warmed to room temperature and the solvents removed under reduced pressure followed by gentle heating to entirely remove volatilities. Degassed chloroform (10 mL) was then added to dissolve the solids which have precipitated, before passing it through a silica plug in a Pasteur pipette into a separate degassed 2-neck flask for the removal of (*R*)-**4** as well as phosphine oxides (if any). The filtrate was then subject to solvent strip under reduced pressure to afford the desired product (**26**).

4-4.2 Procedure for the preparation of β -phosphinoamides (**29,30**) via deprotection of **26**

Reaction setup from the General Procedure (Section 4-4.1) was brought to room temperature and the solvents removed under reduced pressure followed by gentle heating to entirely remove volatilities. Degassed ethanol (3 mL) and chloroform (1 mL) was added, followed by hydrazine monohydrate (21 mg, 20 μL , 6 equiv.) before refluxing under inert atmosphere for 2 hours to give **29cy** in quantitative yield as observed from $^{31}\text{P}\{^1\text{H}\}$ NMR. As coordination of **29cy** to (*R*)/(*S*)-**1** afforded messy signals, it was necessary to protect and isolate **29cy** for characterization and *ee* determination. The reaction vessel was allowed to cool to room temperature before charging with excess elemental sulphur and stirring for 10 minutes. Crude product is then subject to purification by flash

chromatography on silica gel (Eluent = Hexane : ethyl acetate; 1:2) to afford **30cy** as a white powder.

4-4.3 Coordination studies for enantiomeric excess (*ee*) determination

Obtained adducts **26** were reacted with optically pure (*R*)/(*S*)-**1** (≥ 0.51 equiv.) in degassed chloroform to give diastereomers **27**. Enantiomeric excess of **26** is then determined from ratios derived from the $^{31}\text{P}\{^1\text{H}\}$ NMR spectra of **27**.

$$ee = \left| \frac{(\textcolor{red}{S},R)\text{-}\mathbf{27} - (\textcolor{red}{S},S)\text{-}\mathbf{27}}{(\textcolor{red}{S},R)\text{-}\mathbf{27} + (\textcolor{red}{S},S)\text{-}\mathbf{27}} \right|$$

4-4.4 Establishment of absolute configuration of the chiral product

To determine the stereochemistry of the newly formed chiral centre, diastereomeric mixture (**27a**) was purified by flash chromatography on silica gel. However, it was observed that the chemical shifts of the major diastereomer shifted from 49.7 ppm before purification to 49.4 ppm after purification (See NMR below). Single crystal X-ray diffraction studies of the resultant compound revealed that a phosphine-carboxylate chelate (*R,S*)-**28aw** is formed via metal activated hydrolysis with concomitant removal of

phthalimide. The absolute configuration of the new chiral centre is found to be *S* (Figure 16). CCDC 915696 contains the supplementary crystallographic data for (*R,S*)-**28aw**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Figure 16: Molecular structure and absolute stereochemistry of (*R,S*)-**28aw** with 50% thermal ellipsoids shown. Hydrogen atoms except those on the stereogenic centres are omitted for clarity.

4-4.5 DFT calculations

pK_a values (gaseous phase) of selected secondary phosphines were calculated based on density functional theory [B3LYP/6-311G(d,P)]

Reaction	ΔG° in Gas Phase	pK_a at 298.15 K
$\text{Ph}_2\text{PH} \rightarrow \text{Ph}_2\text{P}^- + \text{H}^+$	351.97 kCal/mol	61.67
$(m\text{-Tol})_2\text{PH} \rightarrow (m\text{-Tol})_2\text{P}^- + \text{H}^+$	351.66 kCal/mol	61.60
$(p\text{-Tol})_2\text{PH} \rightarrow (p\text{-Tol})_2\text{P}^- + \text{H}^+$	354.98 kCal/mol	62.18

As observed in the table above, the difference of both ΔG° and pK_a between Ph_2PH (**25w**) and di(*m*-tolyl)phosphine (**25y**) is only marginal. As such, it provides experimental evidence to exclude electronic factors in the difference in chemical reactivities.

4-4.6 Product characterization

(S)-**26aw** was prepared according to general procedure

stated in **4-4.1** (95% yield, 94% *ee*): $[\alpha]_D^{26} = -150.4^\circ$ [c 0.3, CHCl₃]. ³¹P{¹H} (CDCl₃, 162 MHz): δ -0.29; ¹H (CDCl₃, 500 MHz): δ 3.08-3.14 (m, 1H), 3.75-3.82 (m, 1H), 4.14-4.18 (m, 1H), 6.95-7.90 (m, 19H); ¹³C (CDCl₃, 126 MHz): δ 40.4 (d, 1C, ²J_{CP} = 14 Hz), 42.7 (d, 1C, ¹J_{CP} = 25 Hz), 124.5-148.0 (m, 24C), 165.2 (s, 2C), 170.5 (d, 1C, ³J_{CP} = 16 Hz).

(R)-**26aw** was prepared according to general procedure stated in **4-4.1** (90% yield, 95% *ee*): $[\alpha]_D^{26} = -59.2^\circ$ [c 0.3, CHCl₃]. ³¹P{¹H} (CDCl₃, 162 MHz): δ -0.60; ¹H (CDCl₃, 400 MHz): δ 3.08-3.14 (m, 1H), 3.71-3.80 (m, 1H), 4.13-4.17 (m, 1H), 6.71-7.80 (m, 18H); ¹³C (CDCl₃, 101 MHz): δ 39.6 (d, 1C, ²J_{CP} = 12 Hz), 42.7 (d, 1C, ¹J_{CP} = 24 Hz), 115.2-146.6 (m, 24C), 165.3 (s, 2C), 170.3 (d, 1C, ³J_{CP} = 20 Hz).

(S)-**26bw** was prepared according to general procedure stated in **4-4.1**

(90% yield, 95% *ee*): $[\alpha]_D^{26} = -59.2^\circ$ [c 0.3, CHCl₃]. ³¹P{¹H} (CDCl₃, 162 MHz): δ -0.60; ¹H (CDCl₃, 400 MHz): δ 3.08-3.14 (m, 1H), 3.71-3.80 (m, 1H), 4.13-4.17 (m, 1H), 6.71-7.80 (m, 18H); ¹³C (CDCl₃, 101 MHz): δ 39.6 (d, 1C, ²J_{CP} = 12 Hz), 42.7 (d, 1C, ¹J_{CP} = 24 Hz), 115.2-146.6 (m, 24C), 165.3 (s, 2C), 170.3 (d, 1C, ³J_{CP} = 20 Hz).

(S)-**26cw** was prepared according to general procedure stated in **4-4.1**

(89% yield, 96% *ee*): $[\alpha]_D^{25} = -114.3^\circ$ [c 0.3, CHCl₃]. $^{31}\text{P}\{^1\text{H}\}$ (CDCl₃, 162 MHz): δ -0.46; ^1H (CDCl₃, 400 MHz): δ 3.07-3.13 (m, 1H), 3.71-3.79 (m, 1H), 4.13-4.16 (m, 1H), 6.99-7.80 (m, 18H); ^{13}C (CDCl₃, 101 MHz): δ 39.8 (d, 1C, $^2J_{\text{CP}} = 13$ Hz), 42.5 (d, 1C, $^1J_{\text{CP}} = 24$ Hz), 120.3-146.4 (m, 24C), 165.3 (s, 2C), 170.3 (d, 1C, $^3J_{\text{CP}} = 16$ Hz).

(S)-**26dw** was prepared according to general procedure stated in **4-4.1**

(89% yield, 92% *ee*): $[\alpha]_D^{26} = -120.2^\circ$ [c 0.3, CHCl₃]. $^{31}\text{P}\{^1\text{H}\}$ (CDCl₃, 162 MHz): δ 0.13; ^1H (CDCl₃, 400 MHz): δ 3.10-3.16 (m, 1H), 3.73-3.78 (m, 1H), 4.12-4.15 (m, 1H), 6.94-7.90 (m, 18H); ^{13}C (CDCl₃, 101 MHz): δ 40.1 (d, 1C, $^2J_{\text{CP}} = 14$ Hz), 42.4 (d, 1C, $^1J_{\text{CP}} = 23$ Hz), 121.1-146.1 (m, 24C), 165.3 (s, 2C), 170.2 (d, 1C, $^3J_{\text{CP}} = 16$ Hz).

(S)-**26ew** was prepared according to general procedure stated in **4-4.1**

(86% yield, 94% *ee*): $[\alpha]_D^{25} = -90.1^\circ$ [c 0.3, CHCl₃]. $^{31}\text{P}\{^1\text{H}\}$ (CDCl₃, 162 MHz): δ -0.45; ^1H (CDCl₃, 400 MHz): δ 3.06-3.12 (m, 1H), 3.71-3.79 (m, 1H), 4.11-4.16 (m, 1H), 7.02-7.90 (m, 18H); ^{13}C (CDCl₃, 101 MHz): δ 39.9 (d, 1C, $^2J_{\text{CP}} = 14$ Hz), 42.5 (d, 1C, $^1J_{\text{CP}} = 24$ Hz), 120.4-146.5 (m, 24C), 165.3 (s, 2C), 170.2 (d, 1C, $^3J_{\text{CP}} = 16$ Hz).

(S)-**26fw** was prepared according to general procedure stated in **4-4.1** (83% yield, 92% *ee*): $[\alpha]_{\text{D}}^{25} = -148.1^{\circ}$ [c 0.3, CHCl₃]. ³¹P{¹H} (CDCl₃, 162 MHz): δ 0.47; ¹H (CDCl₃, 400 MHz): δ 3.12-3.19 (m, 1H), 3.75 (s, 3H), 3.77-3.85 (m, 1H), 4.21-4.25 (m, 1H), 7.05-7.80 (m, 18H); ¹³C (CDCl₃, 101 MHz): δ 40.5 (d, 1C, ²J_{CP} = 14 Hz), 42.4 (d, 1C, ¹J_{CP} = 23 Hz), 52.1 (s, 1C), 123.8-146.0 (m, 24C), 165.2 (s, 2C), 167.1 (s, 1C), 170.1 (d, 1C, ³J_{CP} = 16 Hz).

(S)-**26gw** was prepared according to general procedure stated in **4-4.1** (64% yield, 89% *ee*): $[\alpha]_{\text{D}}^{25} = -120.9^{\circ}$ [c 0.3, CHCl₃]. ³¹P{¹H} (CDCl₃, 162 MHz): δ 0.77; ¹H (CDCl₃, 400 MHz): δ 3.15-3.22 (m, 1H), 3.77-3.86 (m, 1H), 4.21-4.25 (m, 1H), 6.94-7.94 (m, 18H); ¹³C (CDCl₃, 101 MHz): δ 40.6 (d, 1C, ²J_{CP} = 15 Hz), 42.1 (d, 1C, ¹J_{CP} = 24 Hz), 110.4 (s, 1C), 119.0 (s, 1C), 110.4-146.4 (m, 23C), 165.2 (s, 2C), 170.0 (d, 1C, ³J_{CP} = 17 Hz).

(S)-**26hw** was prepared according to general procedure stated in **4-4.1** (89% yield, 94% *ee*): $[\alpha]_{\text{D}}^{24} = -90.6^{\circ}$ [c 0.3, CHCl₃]. ³¹P{¹H} (CDCl₃, 162 MHz): δ -0.85; ¹H (CDCl₃, 400 MHz): δ 2.06 (s, 3H), 3.02-3.09 (m, 1H), 3.70-3.78 (m, 1H), 4.09-4.14 (m, 1H), 6.82-7.78 (m, 18H); ¹³C (CDCl₃, 101 MHz): δ 21.1 (s, 1C), 40.1 (d, 1C, ²J_{CP} = 13 Hz), 42.8 (d, 1C, ¹J_{CP} = 24 Hz), 124.5-137.0 (m, 24C), 165.2 (s, 2C), 170.6 (d, 1C, ³J_{CP} = 16

Hz).

(S)-**26iw** was prepared according to general procedure stated in **4-4.1** (88% yield, 95% *ee*): $[\alpha]_D^{24} = -89.0^\circ$ [c 0.3, CHCl₃]. ³¹P{¹H} (CDCl₃, 162 MHz): δ -1.14; ¹H (CDCl₃, 400 MHz): δ 3.03-3.09 (m, 1H), 3.57 (s, 3H), 3.67-3.76 (m, 1H), 4.08-4.12 (m, 1H), 6.56-7.89 (m, 18 H); ¹³C (CDCl₃, 101 MHz): δ 39.7 (d, 1C, ²J_{CP} = 13 Hz), 42.8 (d, 1C, ¹J_{CP} = 25 Hz), 55.3 (s, 1C), 113.9-158.4 (m, 24C), 165.3 (s, 2C), 170.6 (d, 1C, ³J_{CP} = 16 Hz).

(S)-**26ax** was prepared according to general procedure stated in **4-4.1** (93% yield, 93% *ee*): $[\alpha]_D^{25} = -59.1^\circ$ [c 0.3, CHCl₃]. ³¹P{¹H} (CDCl₃, 162 MHz): δ -1.79; ¹H (CDCl₃, 400 MHz): δ 2.15 (s, 3H), 2.25 (s, 3H), 3.06-3.13 (m, 1H), 3.69-3.78 (m, 1H), 4.09-4.14 (m, 1H), 6.85-7.92 (m, 17H); ¹³C (CDCl₃, 101 MHz): δ 21.4 (s, 1C), 21.5 (s, 1C), 40.6 (d, 1C, ²J_{CP} = 13 Hz), 42.8 (d, 1C, ¹J_{CP} = 24 Hz), 124.5-148.0 (m, 24C), 165.2 (s, 2C), 170.6 (d, 1C, ³J_{CP} = 16 Hz).

(S)-**26cx** was prepared according to general procedure stated in **4-4.1** (90% yield, 96% *ee*): $[\alpha]_D^{25} = -121.0^\circ$ [c 0.3, CHCl₃]. ³¹P{¹H} (CDCl₃, 162 MHz): δ -1.96; ¹H (CDCl₃, 400 MHz): δ 2.16 (s, 3H), 2.25 (s, 3H), 3.06-3.11 (m, 1H), 3.67-3.74 (m, 1H),

4.09-4.12 (m, 1H), 6.88-7.92 (m, 16H); ^{13}C (CDCl_3 , 101 MHz): δ 21.4 (s, 1C), 21.5 (s, 1C), 39.9 (d, 1C, $^2J_{\text{CP}} = 13$ Hz), 42.6 (d, 1C, $^1J_{\text{CP}} = 24$ Hz), 124.5-146.4 (m, 24C), 165.2 (s, 2C), 170.4 (d, 1C, $^3J_{\text{CP}} = 15$ Hz).

(S)-**26hx** was prepared according to general procedure stated in **4-4.1**

(93% yield, 89% *ee*): $[\alpha]_{\text{D}}^{24} = -60.4^\circ$ [c 0.3, CHCl_3]. $^{31}\text{P}\{^1\text{H}\}$ (CDCl_3 , 162 MHz): δ -2.42; ^1H (CDCl_3 , 400 MHz): δ 2.06 (s, 3H), 2.15 (s, 3H), 2.24 (s, 3H), 3.01-3.07 (m, 1H), 3.65-3.73 (m, 1H), 4.05-4.10 (m, 1H), 6.82-7.77 (m, 16H); ^{13}C (CDCl_3 , 101 MHz): δ 21.1 (s, 1C), 21.4 (s, 1C), 21.5 (s, 1C), 40.2 (d, 1C, $^2J_{\text{CP}} = 13$ Hz), 42.9 (d, 1C, $^1J_{\text{CP}} = 24$ Hz), 118.7-148.2 (m, 24C), 165.2 (s, 2C), 170.7 (d, 1C, $^3J_{\text{CP}} = 15$ Hz).

(S)-**26ix** was prepared according to general procedure stated in **4-4.1**

(92% yield, 96% *ee*): $[\alpha]_{\text{D}}^{25} = -119.1^\circ$ [c 0.3, CHCl_3]. $^{31}\text{P}\{^1\text{H}\}$ (CDCl_3 , 162 MHz): δ -2.66; ^1H (CDCl_3 , 400 MHz): δ 2.15 (s, 3H), 2.25 (s, 3H), 3.01-3.07 (m, 1H), 3.57 (s, 3H), 3.64-3.72 (m, 1H), 4.04-4.08 (m, 1H), 6.56-7.91 (m, 16H); ^{13}C (CDCl_3 , 101 MHz): δ 21.4 (s, 1C), 21.5 (s, 1C), 39.8 (d, 1C, $^2J_{\text{CP}} = 12$ Hz), 42.9 (d, 1C, $^1J_{\text{CP}} = 24$ Hz), 55.3 (s, 1C), 113.9-158.3 (m, 24C), 165.2 (s, 2C), 170.7 (d, 1C, $^3J_{\text{CP}} = 16$ Hz).

(S)-**26ay** was prepared according to general procedure stated in **4-4.1**

(>99% yield, 97% *ee*): $[\alpha]_D^{24} = -89.9^\circ$ [c 0.3, CHCl₃]. $^{31}\text{P}\{^1\text{H}\}$ (CDCl₃, 162 MHz): δ 0.21; ^1H (CDCl₃, 400 MHz): δ 2.06 (s, 3H), 2.28 (s, 3H), 3.06-3.13 (m, 1H), 3.72-3.80 (m, 1H), 4.11-4.15 (m, 1H), 6.78-7.78 (m, 17H); ^{13}C (CDCl₃, 101 MHz): δ 21.4 (s, 1C), 21.7 (s, 1C), 40.5 (d, 1C, $^2J_{\text{CP}} = 13$ Hz), 42.7 (d, 1C, $^1J_{\text{CP}} = 24$ Hz), 119.8-140.4 (m, 24C), 165.2 (s, 2C), 170.6 (d, 1C, $^3J_{\text{CP}} = 16$ Hz).

(S)-26cy was prepared according to general procedure stated in **4-4.1**

(88% yield, 96% *ee*): $[\alpha]_D^{25} = -90.5^\circ$ [c 0.3, CHCl₃]. $^{31}\text{P}\{^1\text{H}\}$ (CDCl₃, 162 MHz): δ 0.15; ^1H (CDCl₃, 400 MHz): δ 2.10 (s, 3H), 2.28 (s, 3H), 3.06-3.13 (m, 1H), 3.69-3.76 (m, 1H), 4.10-4.13 (m, 1H), 6.84-7.81 (m, 16H); ^{13}C (CDCl₃, 101 MHz): δ 21.5 (s, 1C), 21.7 (s, 1C), 39.9 (d, 1C, $^2J_{\text{CP}} = 14$ Hz), 42.5 (d, 1C, $^1J_{\text{CP}} = 24$ Hz), 123.8-146.4 (m, 24C), 165.2 (s, 2C), 170.4 (d, 1C, $^3J_{\text{CP}} = 16$ Hz).

(S)-26hy was prepared according to general procedure stated in **4-4.1**

(97% yield, 98% *ee*): $[\alpha]_D^{25} = -90.1^\circ$ [c 0.3, CHCl₃]. $^{31}\text{P}\{^1\text{H}\}$ (CDCl₃, 162 MHz): δ -0.31; ^1H (CDCl₃, 400 MHz): δ 2.07 (s, 6H), 2.27 (s, 3H), 3.02-3.08 (m, 1H), 3.68-3.76 (m, 1H), 4.06-4.11 (m, 1H), 6.81-7.78 (m, 16H); ^{13}C (CDCl₃, 101 MHz): δ 21.1 (s, 1C), 21.5 (s, 1C), 21.6 (s, 1C), 40.2 (d, 1C, $^2J_{\text{CP}} = 13$ Hz), 42.7 (d, 1C, $^1J_{\text{CP}} = 24$ Hz), 124.4-138.5 (m, 24C), 165.2 (s, 2C), 170.7 (d, 1C, $^3J_{\text{CP}} = 16$ Hz).

(S)-**26iy** was prepared according to general procedure stated in **4-4.1**

(93% isolated yield, 97% *ee*): $[\alpha]_D^{25} = -90.7^\circ$ [c 0.3, CHCl₃]. *Ee* was determined with ³¹P{¹H} (CDCl₃, 162 MHz): δ -0.66; ¹H (CDCl₃, 400 MHz): δ 2.08 (s, 3H), 2.28 (s, 3H), 3.01-3.08 (m, 1H), 3.58 (s, 3H), 3.66-3.80 (m, 1H), 4.05-4.10 (m, 1H), 6.56-7.78 (m, 16H); ¹³C (CDCl₃, 101 MHz): δ 21.5 (s, 1C), 21.7 (s, 1C), 39.7 (d, 1C, ²*J*_{CP} = 13 Hz), 42.8 (d, 1C, ¹*J*_{CP} = 25 Hz), 55.3 (s, 1C), 113.9-158.3 (m, 24C), 165.2 (s, 2C), 170.7 (d, 1C, ³*J*_{CP} = 17 Hz).

(S)-**30cy** was prepared according to procedure stated in **4-4.2** (21.4 mg,

50% isolated yield, 97% *ee*): $[\alpha]_D^{23} = -304.9^\circ$ [c 0.3, CHCl₃]. *Ee* was determined using a Agilent Technologies 1200 Series HPLC coupled with a Daicel CHIRALPAK® IC column using hexane/2-propanol = 70/30 as eluent. Retention times: 4.81 min (*S* enantiomer) and 7.00 min (*R* enantiomer) [See pg 85 for HPLC spectra]. ³¹P{¹H} (CDCl₃, 162 MHz): δ 50.63; ¹H (CDCl₃, 400 MHz): δ 2.02 (s, 3H), 2.43 (s, 3H), 2.71-2.78 (m, 1H), 2.94-3.03 (m, 1H), 4.50-4.56 (m, 1H), 5.26 (s, 1H), 5.39 (s, 1H), 7.09-7.99 (m, 12H); ¹³C (CDCl₃, 101 MHz): δ 21.5 (s, 1C), 21.8 (s, 1C), 36.9 (d, 1C, ²*J*_{CP} = 3 Hz), 42.2 (d, 1C, ¹*J*_{CP} = 53 Hz), 128.0-133.1 (m, 18C), 172.0 (d, 1C, ³*J*_{CP} = 17 Hz). LCMS (ESI): Calcd for C₂₃H₂₃ClNOPS: 427.09, found 428.06.

HPLC analyses for enantioenriched (S)-30cy

4-5 Introduction (N-Enoyl Benzotriazoles)

The catalytic asymmetric hydrophosphination has been regarded as one of the cleanest reaction today: free chiral phosphines are obtained with 100% atom economy, and without the need for protection-deprotection protocols which can lead to implications including racemizations, yields and unintended reductions of certain functionalities. Literature review revealed that significant progress in the field of asymmetric hydrophosphination have been made in recent years, with challenging and novel substrates such as alkenyl isoxazoles and *N*-enoyl phthalimides being reported; the latter functioning as a proxy to α,β -unsaturated amides which conventionally not prone to nucleophilic attacks under mild conditions. While the product can readily be functionalized to give chiral phosphino carboxamides, subsequent transformation of the amide group to other functionalities such

as carboxylic acids or esters is challenging and cumbersome.

Phosphino carboxylic acids are critical ligands in the economically important Shell Higher Olefin Process (SHOP),^[83] while phosphino carboxylic acid esters (PHEST) are versatile ligands in catalysis.^[84] Despite their utility, there are however very limited examples of their direct syntheses presumably due to poor activation at the electrophilic carbon in α,β -unsaturated mono esters. Reported examples were only limited to di-substituted alkenyl ester^[55] or that the mono-ester had to possess a highly electron withdrawing alcohol.^[85] In view of the constraints and limitations, we envisaged the development of a substrate which bears a sufficiently activating analog to facilitate the initial asymmetric hydrophosphination reaction, but simultaneously is an excellent leaving group to be displaced by a variety of nucleophiles to give functionalized (carboxylic acid, ester, thio-, seleno-esters) chiral phosphines (Scheme 24).

Scheme 24: Envisioned protocol to efficient access of free chiral functionalized phosphines.

4-6 Results and Discussions (*N*-Enoyl Benzotriazoles)

Following extensive deliberations, *N*-enoyl benzotriazoles (Bt) were selected as the ideal substrate due to their low cost, ease of synthesis and more importantly, a suitable candidate that for acyl nucleophilic substitution reaction.^[86] Studies commenced with the optimization of reaction conditions for the initial asymmetric hydrophosphination of *N*-enoyl benzotriazoles. Similar to highly activated substrates reported in the previous

chapters, it was also found that the P-H addition reaction could proceed at room temperature without the requirement of any catalyst (Table 8, entry 1). As such, the employment of a low temperature is paramount in achieving good enantioselectivities. The preliminary reaction proceeded favourably, affording commendable yields and enantiomeric excess (Table 8, entry 2). Attempts to lower the catalyst loading (to 3 mol%) proved to be counterproductive as it led to a decline in stereoselectivity (Table 8, entry 3). A series of solvents, as well as types and amounts of bases were subsequently screened and it was established that a chloroform-acetone (10%) mixture coupled with two equivalents triethylamine at -80 °C afforded the best outcomes (Table 8, entry 14).

Enantiomeric excesses were conveniently determined by coordination studies, where the phosphine products (**32**) were treated with optically pure (*R*)/(*S*)-**1** to give diastereomeric adducts (**33**). $^{31}\text{P}\{^1\text{H}\}$ NMR analyses of **33** would then allow the derivation of the enantiomeric excess of **32**. Results from chiral HPLC analyses also support the feasibility and reliability of such coordination studies for *ee* determination (See **4-8 Experimental Section**). In order to establish the structure and stereochemistry of the product, the diastereomeric mixture (**33a**) was purified by flash chromatography on silica gel in an attempt to isolate the major isomer. However, the complex surprisingly hydrolysed during purification to give a phosphino-carboxylate (P,O) chelate (**28aw**), the same complex generated in Chapter IV (See **4-8 Experimental Section**).

With the optimal conditions established, a range of N-enoyl benzotriazoles (**31**) and diarylphosphines (**25w-y**) were screened and the results shown in Table 9. The established

Table 8: Optimization of reaction conditions for the asymmetric hydrophosphination of **31a** with diphenylphosphine **25w**^[a]

Entry	Catalyst loading [mol%]	Solvent	Base [equiv.]	Temp. [°C]	<i>t</i> [hr]	Yield ^[b] [%]	<i>ee</i> ^[c] [%]
1	0	CHCl ₃	Et ₃ N (1 eq.)	rt (21)	4	11	0
2	5	CHCl ₃	Et ₃ N (1 eq.)	-40	6	96	96
3	3	CHCl ₃	Et ₃ N (1 eq.)	-40	6	95	93
4	5	DCM	Et ₃ N (1 eq.)	-40	6	98	91
5	5	EA	Et ₃ N (1 eq.)	-40	6	82	94
6	5	acetone	Et ₃ N (1 eq.)	-40	6	88	97
7	5	toluene	Et ₃ N (1 eq.)	-40	6	71	92
8	5	CHCl ₃ /MeOH (10%)	Et ₃ N (1 eq.)	-40	6	88	91
9	5	CHCl ₃ /acetone (10%)	Et ₃ N (1 eq.)	-40	6	97	95
10	5	CHCl ₃ /acetone (10%)	Et ₂ NH (1 eq.)	-40	6	91	89
11	5	CHCl ₃ /acetone (10%)	Et ₃ N (2 eq.)	-40	4	94	96
12	5	CHCl ₃ /acetone (10%)	Et ₃ N (3 eq.)	-40	4	94	95
13	5 ^[d]	CHCl ₃ /acetone (10%)	Et ₃ N (2 eq.)	-40	6	40	81
14	5	CHCl ₃ /acetone (10%)	Et ₃ N (2 eq.)	-80	8	93	97

^[a] Reaction conditions: Equimolar of Ph₂PH (**25w**) and **31a** (0.06 mmol) in 3.6 mL of degassed solvent(s). ^[b] Yield is determined from the ³¹P{¹H}NMR of the crude product. ^[c] *ee* is calculated from the ratio of diastereomers **33a** formed from treatment of **32a** with (*R*)/(*S*)-**1**. ^[d] Catalyst (*S*)-**3** employed.

Table 9: Substrate scope for the enantioselective hydrophosphination of N-enoyl benzotriazoles **31** with diarylphosphines **25** ^[a]

Entry	Substrate	R	Ar	Yield ^[b] [%]	<i>ee</i> ^[c] [%]
1	31a	Ph	Ph	93, 95 ^[d]	97, -98 ^[d]
2	31b	2-Nap	Ph	95	98
3	31c	4-FC ₆ H ₄	Ph	95	99
4	31d	4-F ₃ CC ₆ H ₄	Ph	96	98
5	31e	4-ClC ₆ H ₄	Ph	99	99
6	31f	3-ClC ₆ H ₄	Ph	94	99
7	31g	4-BrC ₆ H ₄	Ph	95	99
8	31h	4-NCC ₆ H ₄	Ph	91	99
9	31i	4-MeO ₂ CC ₆ H ₄	Ph	91	99
10	31j	4-MeC ₆ H ₄	Ph	96	99
11	31k	4- ^t BuC ₆ H ₄	Ph	96	98
12	31l	4-MeOC ₆ H ₄	Ph	98	98
13	31m		Ph	86	98
14	31n	2-furyl	Ph	91	88
15	31o	2-thienyl	Ph	93	97
16	31a	Ph	<i>p</i> -tolyl	95	99
17	31a	Ph	<i>m</i> -tolyl	95	99
18 ^[e]	31p	CO ₂ Me	Ph	92	73

^[a] General reaction conditions: Equimolar of Ar_2PH (**25**) and **31a** (0.06 mmol) in 3.6 mL of degassed solvents. ^[b] Yield is determined from the $^{31}\text{P}\{^1\text{H}\}$ NMR of the product. ^[c] *ee* is calculated from the ratio of diastereomers **33** formed from treatment of **32** with (*R*)/(*S*)-**1**. ^[d] Catalyst (*R*)-**4** employed. ^[e] Experiment conducted at -65°C .

protocol was able to tolerate an assortment of electronically variable substituents on the aromatic ring including fluoro, ester, *tert*-butyl, alkoxy as well as heterocycles; giving predominantly commendable yields and enantiomeric excesses. The protocol also worked

favourably when the aromatic ring was substituted with a methyl ester functionality (**31p**), albeit a moderate *ee* of 73% owing to **31p** being highly activated and thus allowing the uncatalyzed pathway to be slightly more dominant (Table 9, entry 18). Employment of catalyst (*R*)-**4** produced almost identical outcomes albeit the opposite enantiomeric product being formed (Table 8, entry 1). Ditolylphosphines **25x,y** were screened, which likewise produced excellent outcomes (Table 9, entries 16-17).

To demonstrate the feasibility of the concept where chiral products (**32**) can be transformed via nucleophilic substitution reaction(s) to give functionalized phosphines, **32aw** was treated with sodium methoxide in methanol and chloroform in a one-pot fashion (after the initial hydrophosphination reaction) to give chiral phosphino carboxylic mono ester **34aw** (Scheme 25). While the role of chloroform was seemingly insignificant, it was necessary as **32aw** was poorly soluble in pure methanol. Treatment of **34aw** with elemental sulphur gave **35aw** for ease of isolation and characterization. More importantly, an overall yield of 80% coupled with practically no loss in optical purity proves the viability and practicality in functionalized chiral phosphine preparation. Nevertheless, when **32aw** was subjected to other heteroatom nucleophiles such as thiols and amines with lithium diisopropylamide, the reaction produced significant amount of unidentified side products. Our group remains dedicated in optimizing the reaction conditions to minimize side-product formation, as well as to expand the range and complexity of nucleophilic agents.

Scheme 25: Transformation of chiral phosphine product to phosphino carboxylic esters **34** & **35**.

While significant development in chiral phosphine syntheses have been achieved to date, the products are routinely dedicated to their conventional roles as ligands and organocatalysts. Significantly lesser attention has been paid to their potentials as chemotherapeutic drugs which could lead to a breakthrough in the effectiveness of the existing arsenal of commercially available drugs. Today, the bulk of medicines employed in cancer treatments typically are harmful towards all cells, leading to unwanted side effects.^[87] Gold complexes have been investigated for their tumour suppression activities since the 20th century. While cisplatin remain as the first chemotherapeutic drug towards metastatic cancers, it is however ineffective towards ovarian, breast and prostate cancers.^[88] Gold complexes were thus deemed potential alternatives to conventional platinum based drugs due to their differing mode of action/mechanisms.^[89]

Leung and co-workers have in recent years found that gold(I)-phosphine adducts exhibit anti-cancer activities with improved dose tolerance compared to cisplatin.^[51, 90] Adopting the established protocol for functionalized chiral phosphine syntheses, gold(I) coordinated phosphine complexes **36** were prepared (Figure 17) and their efficiencies screened against human breast cancer cell line MDA-MB-231, one of the cancers resistant to cisplatin. (Note: Biological screening was conducted by a collaborator, Li Bin-Bin. The details of the biological studies can be found in her dissertation: Synthesis and anti-cancer evaluation of optically pure gold(I) phosphine complexes, 2015. Results presented in this dissertation is

Figure 17: Screening of chiral gold(I)-complexes towards human breast cancer cells.

in a highly summarized form.) X-ray analyses demonstrated no racemization occurred during the adopted coordination procedure (See **4-8 Experimental Section**)

Preliminary results showed that the screened complexes were generally effective in tumour suppression, with obtained IC₅₀ values of 0.41-0.58 μ M (Table 10) being significantly lower than that of other gold complexes of 4-90 μ M.^[91] Studies conducted by other groups employing the same breast cancer cell line (MDA-MB-231) afforded IC₅₀ values of 0.20 μ M onwards,^[92] to being ineffective.^[93] Objectively, albeit being not the most effective compounds available, the prepared gold-phosphine complexes **36** exhibited consistent cancer suppression activities. Additional studies are currently being conducted to achieve improved results, contributing to the continuous search for improved life-saving drugs.

Table 10: IC₅₀ values of gold(I)-phosphine complexes against human breast cancer cell line MDA-MB-231.

Compound	36a	36b	36c	36d
IC ₅₀ (μ M)	0.51	0.41	0.58	0.5

4-7 Conclusions (*N*-Enoyl Benzotriazoles)

In summary, the highly efficient asymmetric hydrophosphination of *N*-enoyl benzotriazoles has been achieved. The established protocol is able to tolerate a range of functionalities and substituents, affording products with commendable results. The phosphine adducts can be further transformed to give functionalized phosphines without loss in optical purity, their direct syntheses from unactivated Michael acceptors having proved to be challenging. Gold(I)-phosphine adducts demonstrated good cytotoxicities towards human breast cancer

cells, one of the handful type of cancers resistant to cisplatin treatment.

The contents of this sub-chapter have been published in *Advanced Synthesis and Catalysis* **2015**, 357, 3297-3302; *Synfacts* **2016**, 12, 117.

4-8 Experimental Section (N-Enoyl Benzotriazoles)

All air sensitive manipulations were performed under a positive pressure of nitrogen using Schlenk techniques. Solvents were degassed prior to use when necessary. Methanol (AR), toluene (AR) and hexane (AR) were purchased from Avantor Performance Materials. Chloroform (AR) was purchased from Fischer Scientific, dichloromethane (AR) from Alfa Aesar and ethyl acetate (AR) from Merck. Acetone (AR) was purchased from QReC. Solvents were used directly without further purification. Low Temp PAIRSTIRRER PSL-1800 machine was used for controlling low temperatures for reactions. Silica plug filtration was conducted on Merck silica gel Geduran Si 60 (0.040-0.063mm).

NMR spectra were recorded on Bruker ACF 400 spectrometer. ^1H NMR spectra chemical shifts were reported in δ ppm relative to tetramethylsilane ($\delta = 0.00$ ppm). Multiplicities were given as: s (singlet), d(doublet), t (triplet), q (quartet) and m (multiplet). The number of protons (n) for a given resonance was indicated by nH while coupling constants were reported as J value in Hertz (Hz). ^{13}C NMR spectra chemical shifts were recorded relative to solvent resonance (CDCl_3 : $\delta = 77.16$ ppm). $^{31}\text{P}\{^1\text{H}\}$ NMR spectra chemical shifts are referenced to an external standard of 85% H_3PO_4 . Optical rotations of monophosphine products were measured as soon as possible without inert gas protection in the specified

solution using a 0.1 dm cell with an Atago AP-300 automatic polarimeter. Chiral HPLC was performed on a Agilent Technologies 1200 Series machine incorporating a Diacel CHIRAPAK IC column. Chiral palladacycles and substituted *N*-enoylbenzotriazoles **31**^[94] were prepared according to literature methods.

4-8.1 General procedure for the enantioselective hydrophosphination of *N*-enoyl benzotriazoles **31**

To a solution of Ar₂PH (ca. 0.060 mmol, 1 equiv.) in degassed chloroform (3.2 mL) and acetone (0.4 mL) was added (*S*)-**4** (0.8 mg, 0.003 mmol, 5 mol%) and stirred at room temperature under nitrogen environment until complete dissolution before cooling to -80 °C. Subsequently, *N*-enoylbenzotriazole and its derivatives **31** (1 equiv.) was added and the walls of the reaction flask washed with chloroform (0.5 mL). Triethylamine (6.1 mg, 0.060 mmol, 2 equiv.) in CHCl₃ (0.5 mL) was then added dropwise over a period of 5 minutes. The solution was stirred at -80 °C and the reaction monitored by ³¹P{¹H} NMR. Upon completion, the reaction vessel was moved to ambient temperature and the reaction mixture subjected to vacuum with heating to remove any volatiles. The dried mixture was re-dissolved in chloroform (8 mL) and filtered through a silica plug using a Pasteur pipette fixed on a separate nitrogen filled 2-neck Schenk flask to remove (*S*)-**4** and phosphine oxides (if any). Solvent was removed from the eluent under reduced pressure to afford chiral tertiary phosphine **32** as the pure product.

4-8.2 Procedure for the substitution reaction to give chiral phosphino carboxylic esters **34** & **35**

32aw was obtained in accordance with general procedure in **4-8.2**, except then the reaction mixture was not passed through a silica plug. The vacuum-dried reaction mixture was re-dissolved in CHCl_3 (1.7 mL) and MeOH (4.2 mL), followed by addition of NaOMe (3.20 mg, 0.060 mmol, 1 equiv.) and stirred at room temperature for 1 hour to afford **34aw**. Solution was subsequently treated with elemental sulphur (1.90 mg, 0.060 mmol, 1 equiv.) and stirred for 0.5 hours. Crude product was purified by flash chromatography on silica gel (Hex:EA = 6:1) to afford **35aw** as the pure product.

4-8.3 Procedure for the preparation of gold(I)-phosphine complexes **36**

Compounds **32** and **34** were obtained in accordance to procedures stated in **4-8.1** & **8.2** respectively. Dichloromethane (10 mL) was added to the reaction mixture, followed by $\text{AuCl} \cdot \text{SMe}_2$ (17.67 mg, 0.060 mmol, 1 equiv.) and stirred at room temperature for 1 hour in the dark. Crude mixtures were subsequently purified by flash-chromatography on silica gel to afford the desired product.

4-8.4 Coordination studies for *ee* determination

The obtained monophosphines **32** were allowed to react with enantiopure dimeric complex (*R*)/(*S*)-**1** (≥ 0.5 equiv.) in chloroform to form derivatives **33**. Enantiomeric excess (*ee* %) was then determined from the $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum of the integral ratios of respective diastereomers.

4-8.5 Determination of absolute configuration of the chiral products **28** & **36**

While **33** are stable and can be detected by NMR, purification of **33aw** on silica gel led to hydrolysis with concomitant elimination of the benzotriazole group. $^{31}\text{P}\{^1\text{H}\}$ NMR analyses of the compounds before and after purification is present in the spectra below. Binding of carboxylate to Pd forms a *P,O*-chelate **28aw**. Single crystal X-ray of **28aw** revealed that the absolute configuration of the newly formed chiral centre is *R* (Figure 18,19). CCDC 1060157 and 1060706 contains the supplementary crystallographic data for (*S,R*)-**28aw** and (*R*)-**36b** respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Figure 18. Molecular structure and absolute stereochemistry of the derivative complex **(S,R)-28aw** with 50% thermal ellipsoids shown. Hydrogen atoms except those on the chiral centre are omitted for clarity.

Figure 19. Molecular structure and absolute stereochemistry of the derivative complex (*R*)-**36b** with 50% thermal ellipsoids shown. Hydrogen atoms except those on the chiral centre are omitted for clarity.

4-8.6 Experimental details for biological (anti-cancer) studies

(**Note:** Biological screening was conducted by a collaborator/group mate, Li Bin-Bin. The details of the biological studies can be found in her dissertation: Synthesis and anti-cancer evaluation of optically pure gold(I) phosphine complexes, 2015)

MDA-MB-231 (human breast adenocarcinoma) were maintained in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% heat-inactivated fetal bovine serum (FBS). All the drug treatment experiments were performed in serum-free DMEM medium. The cytotoxicity of complexes **36** against the breast cancer cell line was analyzed by propidium iodide (PI) staining coupled with flow cytometry analysis (BD Accuri C6).

4-8.7 Product characterization

(R)-32aw was prepared according to general procedure stated in 4-8.1 (93% yield, 97% *ee*): $[\alpha]_D^{24} = +129.8^\circ$ [*c* 0.3, CHCl₃]. ³¹P{¹H} (CDCl₃, 162 MHz): δ 0.61; ¹H (CDCl₃, 400 MHz): δ 3.65-3.71 (m, 1H), 4.15-4.23 (m, 1H), 4.42-4.46 (m, 1H), 7.12-8.15 (m, 19H); ¹³C (CDCl₃, 101 MHz): δ 39.67 (d, 1C, ²*J*_{CP} = 24 Hz), 40.80 (d, 1C, ¹*J*_{CP} = 13 Hz), 114.55-146.22 (m, 24C), 170.70 (d, 1C, ³*J*_{CP} = 15 Hz).

(S)-32aw was prepared according to general procedure stated in 4-8.1, except that catalyst (R)-4 was employed (95% yield, 98% *ee*): $[\alpha]_D^{26} = -149.2^\circ$ [*c* 0.7, CHCl₃]. ³¹P{¹H} (CDCl₃, 162 MHz): δ 0.61; ¹H (CDCl₃, 400 MHz): δ 3.53-3.59 (m, 1H), 4.03-4.11 (m, 1H), 4.30-4.34 (m, 1H), 7.00-8.03 (m, 19H); ¹³C (CDCl₃, 101 MHz): δ 39.66 (d, 1C, ²*J*_{CP} = 25 Hz), 40.78 (d, 1C, ¹*J*_{CP} = 14 Hz), 114.54-146.20 (m, 24C), 170.69 (d, 1C, ³*J*_{CP} = 15 Hz).

(R)-32bw was prepared according to general procedure stated in 4-8.1 (95% yield, 98% *ee*): $[\alpha]_D^{25} = +167.9^\circ$ [*c* 0.7, CHCl₃]. ³¹P{¹H} (CDCl₃, 162 MHz): δ 0.50; ¹H (CDCl₃, 400 MHz): δ 3.60-3.67 (m, 1H), 4.14-4.23 (m, 1H), 4.48-4.53 (m, 1H), 7.00-7.98 (m, 21H); ¹³C (CDCl₃, 101 MHz): δ 39.66 (d, 1C, ²*J*_{CP} = 24 Hz), 40.84 (d, 1C, ¹*J*_{CP} = 15 Hz), 114.52-146.19 (m, 28C), 170.65 (d, 1C, ³*J*_{CP} = 14 Hz).

(*R*)-**32cw** was prepared according to general procedure stated in **4-8.1** (95% yield, 99% *ee*): $[\alpha]_D^{26} = +152.4^\circ$ [*c* 0.7, CHCl₃]. ³¹P{¹H} (CDCl₃, 162 MHz): δ 0.47; ¹H (CDCl₃, 400 MHz): δ 3.51-3.58 (m, 1H), 3.99-4.07 (m, 1H), 4.28-4.32 (m, 1H) 6.73-8.03 (m, 18H); ¹³C (CDCl₃, 101 MHz): δ 39.68 (d, 1C, ²*J*_{CP} = 25 Hz), 40.11 (d, 1C, ¹*J*_{CP} = 14 Hz), 114.49-146.22 (m, 24C), 170.59 (d, 1C, ³*J*_{CP} = 15 Hz).

(*R*)-**32dw** was prepared according to general procedure stated in **4-8.1** (96% yield, 98% *ee*): $[\alpha]_D^{24} = +131.3^\circ$ [*c* 0.7, CHCl₃]. ³¹P{¹H} (CDCl₃, 162 MHz): δ 1.54; ¹H (CDCl₃, 400 MHz): δ 3.58-3.64 (m, 1H), 4.08-4.12 (m, 1H), 4.37-4.40 (m, 1H), 7.09-8.03 (m, 18H); ¹³C (CDCl₃, 101 MHz): δ 39.26 (d, 1C, ²*J*_{CP} = 24 Hz), 40.67 (d, 1C, ¹*J*_{CP} = 15 Hz), 114.47-144.06 (m, 25C), 170.36 (d, 1C, ³*J*_{CP} = 15 Hz).

(*R*)-**32ew** was prepared according to general procedure stated in **4-8.1** (99% yield, 99% *ee*): $[\alpha]_D^{26} = +134.7^\circ$ [*c* 0.7, CHCl₃]. ³¹P{¹H} (CDCl₃, 162 MHz): δ 0.71; ¹H (CDCl₃, 400 MHz): δ 3.52-3.58 (m, 1H), 4.01-4.27 (m, 1H), 4.29-4.32 (m, 1H), 7.02-8.03 (m, 18H); ¹³C (CDCl₃, 101 MHz): δ 39.47 (d, 1C, ²*J*_{CP} = 24 Hz), 40.25 (d, 1C, ¹*J*_{CP} = 15 Hz), 114.50-146.24 (m, 24C), 170.50 (d, 1C, ³*J*_{CP} = 15 Hz).

(R)-**32fw** was prepared according to general procedure stated in **4-8.1** (94% yield, 99% *ee*): $[\alpha]_D^{27} = +147.3^\circ$ [*c* 0.7, CHCl₃]. ³¹P{¹H} (CDCl₃, 162 MHz): δ 1.09; ¹H (CDCl₃, 400 MHz): δ 3.55-3.61 (m, 1H), 4.02-4.076(m, 1H), 4.27-4.30 (m, 1H), 6.98-8.04 (m, 18H); ¹³C (CDCl₃, 101 MHz): δ 39.35 (d, 1C, ²*J*_{CP} = 24 Hz), 40.48 (d, 1C, ¹*J*_{CP} = 16 Hz), 114.51-146.24 (m, 24C), 170.39 (d, 1C, ³*J*_{CP} = 15 Hz).

(R)-**32gw** was prepared according to general procedure stated in **4-8.1** (95% yield, 99% *ee*): $[\alpha]_D^{26} = +135.2^\circ$ [*c* 0.7, CHCl₃]. ³¹P{¹H} (CDCl₃, 162 MHz): δ -1.82; ¹H (CDCl₃, 400 MHz): δ 3.51-3.58 (m, 1H), 3.98-4.07 (m, 1H), 4.27-4.31 (m, 1H), 7.02-8.03 (m, 18H); ¹³C (CDCl₃, 101 MHz): δ 39.40 (d, 1C, ²*J*_{CP} = 24 Hz), 40.29 (d, 1C, ¹*J*_{CP} = 14 Hz), 114.50-146.23 (m, 24C), 170.46 (d, 1C, ³*J*_{CP} = 16 Hz).

(R)-**32hw** was prepared according to general procedure stated in **4-8.1** (91% yield, 99% *ee*): $[\alpha]_D^{26} = +197.0^\circ$ [*c* 0.7, CHCl₃]. ³¹P{¹H} (CDCl₃, 162 MHz): δ 2.05; ¹H (CDCl₃, 400 MHz): δ 3.58-3.65 (m, 1H), 4.04-4.13 (m, 1H), 4.34-4.39 (m, 1H), 7.10-8.02 (m, 18H); ¹³C (CDCl₃, 101 MHz): δ 39.02 (d, 1C, ²*J*_{CP} = 24 Hz), 41.17 (d, 1C, ¹*J*_{CP} = 16 Hz), 110.63-146.25 (m, 25C), 170.19 (d, 1C, ³*J*_{CP} = 14 Hz).

(R)-**32iw** was prepared according to general procedure stated in **4-8.1**

(91% yield, 99% *ee*): $[\alpha]_{\text{D}}^{24} = +58.6^{\circ}$ [*c* 0.7, CHCl₃]. $^{31}\text{P}\{^1\text{H}\}$ (CDCl₃, 162 MHz): δ 1.53; ^1H (CDCl₃, 400 MHz): δ 3.58-3.64 (m, 1H), 3.76 (s, 3H), 4.05-4.13 (m, 1H), 4.36-4.40 (m, 1H), 7.08-8.02 (m, 18H); ^{13}C (CDCl₃, 101 MHz): δ 39.30 (d, 1C, $^2J_{\text{CP}} = 24$ Hz), 41.02 (d, 1C, $^1J_{\text{CP}} = 15$ Hz), 52.11 (s, 1C), 114.48-146.22 (m, 24C), 166.97 (s, 1C), 170.38 (d, 1C, $^3J_{\text{CP}} = 14$ Hz).

(R)-32jw was prepared according to general procedure stated in **4-8.1** (96% yield, 99% *ee*): $[\alpha]_{\text{D}}^{25} = +60.3^{\circ}$ [*c* 0.7, CHCl₃]. $^{31}\text{P}\{^1\text{H}\}$ (CDCl₃, 162 MHz): δ 0.09; ^1H (CDCl₃, 400 MHz): δ 2.13 (s, 3H), 3.50-3.56 (m, 1H), 4.00-4.07 (m, 1H), 4.29-4.32 (m, 1H), 6.86-8.03 (m, 18H); ^{13}C (CDCl₃, 101 MHz): δ 21.16 (s, 1C), 39.76 (d, 1C, $^2J_{\text{CP}} = 24$ Hz), 40.27 (d, 1C, $^1J_{\text{CP}} = 13$ Hz), 114.58-146.20 (m, 24C), 170.77 (d, 1C, $^3J_{\text{CP}} = 15$ Hz).

(R)-32kw was prepared according to general procedure stated in **4-8.1** (96% yield, 98% *ee*): $[\alpha]_{\text{D}}^{26} = +89.7^{\circ}$ [*c* 0.3, CHCl₃]. $^{31}\text{P}\{^1\text{H}\}$ (CDCl₃, 162 MHz): δ 0.46; ^1H (CDCl₃, 400 MHz): δ 1.13 (s, 9H), 3.50-3.57 (m, 1H), 4.02-4.11 (m, 1H), 4.27-4.32 (m, 1H), 7.04-8.04 (m, 18H); ^{13}C (CDCl₃, 101 MHz): δ 31.41 (s, 3C), 34.48 (s, 1C), 39.64 (d, 1C, $^2J_{\text{CP}} = 25$ Hz), 40.14 (d, 1C, $^1J_{\text{CP}} = 13$ Hz), 114.56-149.75 (m, 24C), 170.84 (d, 1C, $^3J_{\text{CP}} = 15$ Hz).

(R)-32lw was prepared according to general procedure stated in **4-8.1**

(98% yield, 98% *ee*): $[\alpha]_D^{25} = +121.2^\circ$ [*c* 0.7, CHCl₃]. $^{31}\text{P}\{^1\text{H}\}$ (CDCl₃, 162 MHz): δ -0.13; ^1H (CDCl₃, 400 MHz): δ 3.48-3.55 (m, 1H), 3.61 (s, 3H), 3.98-4.06 (m, 1H), 4.26-4.30 (m, 1H), 6.60-8.04 (m, 18H); ^{13}C (CDCl₃, 101 MHz): δ 39.83 (d, 1C, $^2J_{\text{CP}} = 25$ Hz), 39.97 (d, 1C, $^1J_{\text{CP}} = 13$ Hz), 55.25 (s, 1H), 113.96-158.44 (m, 24C), 170.81 (d, 1C, $^3J_{\text{CP}} = 15$ Hz).

(*R*)-**32mw**

(*R*)-**32mw** was prepared according to general procedure stated in **4-8.1**

(86% yield, 98% *ee*): $[\alpha]_D^{26} = +148.5^\circ$ [*c* 0.7, CHCl₃]. $^{31}\text{P}\{^1\text{H}\}$ (CDCl₃, 162 MHz): δ -0.30; ^1H (CDCl₃, 400 MHz): δ 3.46-3.52 (m, 1H), 3.93-4.02 (m, 1H), 4.23-4.28 (m, 1H), 5.76 (s, 1H), 5.77 (s, 1H), 6.48-8.05 (m, 17H); ^{13}C (CDCl₃, 101 MHz): δ 39.98 (d, 1C, $^2J_{\text{CP}} = 25$ Hz), 40.55 (d, 1C, $^1J_{\text{CP}} = 14$ Hz), 101.01 (s, 1C), 108.30-147.73 (m, 24C), 170.66 (d, 1C, $^3J_{\text{CP}} = 16$ Hz).

(*R*)-**32nw**

(*R*)-**32nw** was prepared according to general procedure stated in **4-8.1** (91%

yield, 88% *ee*): $[\alpha]_D^{26} = +73.6^\circ$ [*c* 0.7, CHCl₃]. $^{31}\text{P}\{^1\text{H}\}$ (CDCl₃, 162 MHz): δ -1.54; ^1H (CDCl₃, 400 MHz): δ 3.51-3.58 (m, 1H), 3.97-4.06 (m, 1H), 4.46-4.51 (m, 1H), 5.87 (d, 1H, $^3J_{\text{HH}} = 3.2$ Hz), 6.07-6.08 (m, 1H), 7.13-8.11 (m, 15H); ^{13}C (CDCl₃, 101 MHz): δ 34.16 (d, 1C, $^2J_{\text{CP}} = 16$ Hz), 37.79 (d, 1C, $^1J_{\text{CP}} = 24$ Hz), 107.50-152.90 (m, 22C), 170.55 (d, 1C, $^3J_{\text{CP}} = 14$ Hz).

(*R*)-**32ow**

(*R*)-**32ow** was prepared according to general procedure stated in **4-8.1** (93%

yield, 97% *ee*): $[\alpha]_D^{26} = +103.7^\circ$ [*c* 0.7, CHCl₃]. $^{31}\text{P}\{^1\text{H}\}$ (CDCl₃, 162 MHz): δ -0.63; ^1H (CDCl₃, 400 MHz): δ 3.54-3.61 (m, 1H), 3.96-4.05 (m, 1H), 4.64-4.68 (m, 1H), 6.68-8.08 (m, 17H); ^{13}C (CDCl₃, 101 MHz): δ 35.90 (d, 1C, $^2J_{\text{CP}} = 14$ Hz), 41.07 (d, 1C, $^1J_{\text{CP}} = 26$ Hz), 114.56-146.24 (m, 22C), 170.35 (d, 1C, $^3J_{\text{CP}} = 14$ Hz).

(R)-**32ax** was prepared according to general procedure stated in **4-8.1** (95% yield, 99% *ee*): $[\alpha]_D^{26} = +88.6^\circ$ [*c* 0.7, CHCl₃]. $^{31}\text{P}\{^1\text{H}\}$ (CDCl₃, 162 MHz): δ -0.88; ^1H (CDCl₃, 400 MHz): δ 2.17 (s, 3H), 2.18 (s, 1H), 3.54-3.61 (m, 1H), 3.95-4.03 (m, 1H), 4.27-4.32 (m, 1H), 6.88-8.09 (m, 17H); ^{13}C (CDCl₃, 101 MHz): δ 21.36 (s, 1C), 21.40 (s, 1C), 39.78 (d, 1C, $^2J_{\text{CP}} = 24$ Hz), 40.84 (d, 1C, $^1J_{\text{CP}} = 14$ Hz), 114.56-148.95 (m, 24C), 170.81 (d, 1C, $^3J_{\text{CP}} = 14$ Hz).

(R)-**32ay** was prepared according to general procedure stated in **4-8.1** (95% yield, 99% *ee*): $[\alpha]_D^{26} = +120.5^\circ$ [*c* 0.7, CHCl₃]. $^{31}\text{P}\{^1\text{H}\}$ (CDCl₃, 162 MHz): δ 1.13; ^1H (CDCl₃, 400 MHz): δ 2.08 (s, 3H), 2.25 (s, 3H), 3.56-3.61 (m, 1H), 4.00-4.05 (m, 1H), 4.29-4.32 (m, 1H), 6.82-8.02 (m, 17H); ^{13}C (CDCl₃, 101 MHz): δ 21.41 (s, 1C), 21.56 (s, 1C), 39.72 (d, 1C, $^2J_{\text{CP}} = 24$ Hz), 40.83 (d, 1C, $^1J_{\text{CP}} = 14$ Hz), 114.56-146.21 (m, 24C), 170.77 (d, 1C, $^3J_{\text{CP}} = 15$ Hz).

(R)-**32pw** was prepared according to general procedure stated in **4-8.1** (92% yield, 73% *ee*): $[\alpha]_D^{26} = +73.5^\circ$ [*c* 0.7, CHCl₃]. $^{31}\text{P}\{^1\text{H}\}$ (CDCl₃, 162 MHz): δ -0.08; ^1H

(CDCl₃, 400 MHz): δ 3.36 (s, 3H), 3.54-3.61 (m, 1H), 3.99-4.09 (m, 2H), 7.18-8.15 (m, 14H); ¹³C (CDCl₃, 101 MHz): δ 36.35 (d, 1C, ¹J_{CP} = 23 Hz), 39.72 (d, 1C, ³J_{CP} = 25 Hz), 52.22 (s, 1C), 114.56-146.37 (m, 18C), 170.94 (d, 1C, ¹J_{CP} = 15 Hz), 172.31 (d, 1C, ³J_{CP} = 4 Hz),

(*R*)-**35aw**

(*R*)-**35aw** was prepared according to procedure stated in **4-8.2** (22.4 mg, 80% yield, 96% *ee*): $[\alpha]_D^{26} = +114.3^\circ$ [*c* 0.6, CHCl₃]. ³¹P{¹H} (CDCl₃, 162 MHz): δ 50.36; ¹H (CDCl₃, 400 MHz): δ 2.81-2.89 (m, 1H), 3.19-3.27 (m, 1H), 3.47 (s, 3H), 4.44-4.49 (m, 1H), 7.12-8.18 (m, 15H); ¹³C (CDCl₃, 101 MHz): δ 35.49 (d, 1C, ²J_{CP} = 4 Hz), 43.28 (d, 1C, ¹J_{CP} = 53 Hz), 52.09 (s, 1C), 127.76-134.43 (m, 18C), 171.88 (d, 1C, ³J_{CP} = 19 Hz). LCMS (ESI): Calcd for :380.10, found 381.08.

(*R*)-**36a**

(*R*)-**36a** was prepared according to general procedure stated in **4-8.3** (16.0mg, 40% yield): $[\alpha]_D^{25} = +76.9^\circ$ [*c* 0.6, CHCl₃]. ³¹P{¹H} (CDCl₃, 162 MHz): δ 45.08; ¹H (CDCl₃, 400 MHz): δ 3.75-3.82 (m, 1H), 4.42-4.51 (m, 1H), 4.77-4.85 (m, 1H), 7.17-8.09 (m, 19H); ¹³C (CDCl₃, 101 MHz): δ 38.33 (d, 1C, ²J_{CP} = 13 Hz), 40.79 (d, 1C, ¹J_{CP} = 36 Hz), 114.34-146.28 (m, 24C), 168.65 (d, 1C, ³J_{CP} = 20 Hz).

(*R*)-**36b**

(*R*)-**36b** was prepared according to general procedure stated in **4-8.3** (14.9 mg, 43% yield): $[\alpha]_D^{25} = +60.6^\circ$ [*c* 0.7, CHCl₃]. ³¹P{¹H} (CDCl₃, 162 MHz): δ 44.55; ¹H

(CDCl₃, 400 MHz): δ 2.80-2.88 (m, 1H), 3.17-3.26 (m, 1H), 3.50 (s, 3H), 4.37-4.44 (m, 1H), 7.19-8.00 (m, 15H); ¹³C (CDCl₃, 101 MHz): δ 37.08 (d, 1C, ²J_{CP} = 11 Hz), 41.09 (d, 1C, ¹J_{CP} = 36 Hz), 52.24 (s, 1C), 127.02-134.73 (m, 18C), 170.66 (d, 1C, ³J_{CP} = 21 Hz).

(*R*)-**36c**

(*R*)-**36c** was prepared according to general procedure stated in **4-8.3** (12.8 mg, 36% yield): $[\alpha]_D^{25} = +125.0^\circ$ [*c* 1.3, CHCl₃]. ³¹P{¹H} (CDCl₃, 162 MHz): δ 44.64; ¹H (CDCl₃, 400 MHz): δ 1.05 (t, 3H, ³J_{HH} = 7 Hz) 2.79-2.86 (m, 1H), 3.16-3.25 (m, 1H), 3.93 (q, 2H, ³J_{HH} = 7 Hz), 4.36-4.43 (m, 1H), 7.18-8.00 (m, 15H); ¹³C (CDCl₃, 101 MHz): δ 14.05 (s, 1C), 37.31 (d, 1C, ²J_{CP} = 12 Hz), 41.16 (d, 1C, ¹J_{CP} = 36 Hz), 61.24 (s, 1C), 127.05-134.74 (m, 18C), 170.18 (d, 1C, ³J_{CP} = 20 Hz).

(*R*)-**36d**

(*R*)-**36d** was prepared according to general procedure stated in **4-8.3** (18.8 mg, 49% yield): $[\alpha]_D^{25} = +131.6^\circ$ [*c* 0.8, CHCl₃]. ³¹P{¹H} (CDCl₃, 162 MHz): δ 44.79; ¹H (CDCl₃, 400 MHz): δ 2.82-2.90 (m, 1H), 3.18-3.27 (m, 1H), 3.50 (s, 3H), 3.88 (s, 3H), 4.43-4.51 (m, 1H), 7.24-7.98 (m, 14H); ¹³C (CDCl₃, 101 MHz): δ 36.87 (d, 1C, ²J_{CP} = 11 Hz), 41.23 (d, 1C, ¹J_{CP} = 35 Hz), 52.34 (s, 1C), 52.36 (s, 1C), 126.61-140.17 (m, 18C), 166.60 (s, 1C), 170.39 (d, 1C, ³J_{CP} = 20 Hz).

Chapter V

Solvent Induced Enantiodivergent Syntheses of Chiral Phosphinocarboxamides

5-1 Introduction

The significance of chiral phosphines in catalysis has been repeatedly demonstrated in literature; in particular, their synthetic methodologies highlighted in this dissertation. To date, there have been a substantial number of reports involving the addition of phosphorus nucleophiles to various substrates. A quick review of the classes of reactants suitable for the asymmetric hydrophosphination reaction reveal a similar trend: they are usually excellent (highly activated) Michael acceptors which may contain more than one identical activating groups to successfully effect the desired AHP reaction. An example is dimethyl 2-benzylidenemalonate, an analog of methyl cinnamate with the introduction of an additional methyl-ester group. Of which, the latter which is inert to *phospha* nucleophilic attacks in the presence of palladacycle catalysts.^[55] In addition, these applied substrates are specifically designed to generate only a single electrophilic carbon so as to circumvent complications arising from regioselective nucleophilic attacks.

In view of the narrow substrate scope that undeniably restricts the design and application of substrates in the field of AHP, a novel substrate bearing two electronically unique activating groups is envisioned. The presence of dissimilar activators with unique electron-withdrawing tendencies could potentially lead to unsatisfactory regioselectivities; coupled with the requirement to achieve high enantioselectivities contributes to the challenges posed by such substrates.

Following deliberation in substrate design, (*E*)-4-oxo-enamides **37** were determined to be the representative class of substrate for this study as they possess distinct

activating/coordinating sites that can bind to the palladium catalyst. Albeit anticipating poor regioselectivities, our studies however revealed that phosphorus nucleophiles added to **37** in a regiospecific manner, and that enantiodivergent catalysis can be achieved with variation in the applied solvent systems. The underlying mechanisms leading to the observed enantiodivergence was elucidated, simultaneously substantiating our proposed general catalytic cycle (Scheme 22) on palladacycle catalyzed hydrofunctionalizations.

5-2 Results and Discussions

Preliminary studies began with the chiral palladacycle **4** catalyzed hydrophosphination of (*E*)-4-*oxo*-enamides **37a**, 3-benzoylacrylic acid and the methyl ester analog of **37a**, methyl 3-benzoylacrylate (Figure 20). While 3-benzoylacrylic acid was found to be inert to nucleophilic attacks, methyl 3-benzoylacrylate gave regiospecific adducts within relatively short reaction times but were regrettably racemic. In subsequent studies with (*E*)-4-*oxo*-enamide (**37a**), moderate yield and enantioselectivity were achieved under a set of predetermined conditions. Encouraged by the positive results, a thorough investigation was undertaken to improve the obtained values, and the results presented in Table 11. Similar to highly activated Michael acceptors, **37a** was capable of reacting with diphenylphosphine in the absence of any catalysts at room temperature (Table 11, entry 1).

Figure 20. Analogs of **37** screened for the catalytic asymmetric hydrophosphination reaction

Table 11: Optimization of reaction conditions for the enantioselective hydrophosphination of (*E*)-4-oxo-enamide **37a**.^[a]

Entry	Catalyst loading [mol%]	Solvent	Base [equiv.]	Temp. [°C]	<i>t</i> [h]	Yield ^[b] [%]	<i>ee</i> ^[c] [%]
1	-	CHCl ₃	Et ₃ N (1 eq.)	RT (21)	3.25	21	-
2	-	CHCl ₃	Et ₃ N (1 eq.)	-40	3.25	3	-
3	5	CHCl ₃	Et ₃ N (1 eq.)	-40	2.25	98	72 (<i>S</i>)
4	3	CHCl ₃	Et ₃ N (1 eq.)	-40	3	99	67 (<i>S</i>)
5	1.5	CHCl ₃	Et ₃ N (1 eq.)	-40	3.25	99	61 (<i>S</i>)
6	5	DCM	Et ₃ N (1 eq.)	-40	2	99	49 (<i>S</i>)
7	5	acetone	Et ₃ N (1 eq.)	-40	2	97	11 (<i>S</i>)
8	5	butanone	Et ₃ N (1 eq.)	-40	2.5	88	8 (<i>R</i>)
9	5	THF	Et ₃ N (1 eq.)	-40	2	76	39 (<i>R</i>)
10	5	EA	Et ₃ N (1 eq.)	-40	2	99	52 (<i>R</i>)
11	5	toluene	Et ₃ N (1 eq.)	-40	15	98	92 (<i>R</i>)
12	5	toluene	Et ₂ NH (1 eq.)	-40	>15	96	69 (<i>R</i>)
13	5	toluene	Et ₃ N (0.5 eq.)	-40	>15	93	89 (<i>R</i>)
14	5 ^[d]	toluene	Et ₃ N (1 eq.)	-40	21	93	36 (<i>R</i>)
15	5	toluene/CHCl ₃ (4:6)	Et ₃ N (1 eq.)	-40	2	74	33 (<i>R</i>)
16	5	CHCl ₃ /MeOH (9:1)	Et ₃ N (1 eq.)	-40	2	95	93 (<i>S</i>)

^[a] General reaction conditions: Equimolar of Ph₂PH and **37a** (0.08 mmol) in 4.5 mL of degassed solvents, (*R*)-**4** catalyst is employed unless stated otherwise. ^[b] Yield is derived from the ³¹P{¹H}NMR of the crude product. ^[c] Enantiomeric excess (*ee*) is calculated from the ratio of diastereomers **39** formed from treatment of **37** with (*R*)/(*S*)-**1**. ^[d] Catalyst (*R*)-**3** employed.

Fortuitously, conducting the reaction at a reduced temperature of -40 °C proved to be effective in curtailing the uncatalyzed pathway (Table 11, entry 2). Albeit obtaining

excellent yields regardless of the amounts of catalysts employed, attempts to lower the catalyst loading proved to be deleterious as enantiomeric excesses were proportionately lowered from 72 to 61%, (Table 11, entries 3-5). A weaker base (diethylamine) as well as a lowering of the amount of base employed unfortunately produced poorer outcomes (Table 11, entries 12-13). The employment of (*R*)-**3** as the catalyst expectedly led to significantly longer reaction times and unsatisfactory enantioselectivities (Table 11, entry 14). To verify that a variation in solvent employed indeed does lead to a reversal of obtained stereochemistry, a mixture of pure solvents (i.e. toluene and chloroform) which gave the best opposing *ees* was applied. A drastic reduction of the *ee* obtained substantiated the initial observations (Table 1, entry 15). In summary, the most critical outcomes that were obtained from the optimization studies were: 1) the AHP additions were entirely regiospecific (following ^1H , ^{13}C , ^{31}P and X-ray crystallographic analyses) regardless of variation in conditions applied and, 2) changes in solvent systems employed led to a never before observed reversal of stereoselectivity in reported AHP reactions.

Enantiomeric excesses were determined from coordination studies between **38** and enantiopure (*R*)/(*S*)-**1**, followed by $^{31}\text{P}\{^1\text{H}\}$ NMR analyses. X-ray diffraction studies of isolated phosphine-palladium adducts revealed that the newly formed stereogenic centre exhibits the *R* configuration when toluene was employed as the solvent, while the use of chloroform/methanol as the solvent gave *S* adducts. (See **5-5 Experimental Section** for details). Regardless of the stereochemical configuration of the chiral center, X-ray analyses validates that the nucleophilic attack occurs regiospecifically at the β -carbon with respect to the keto functionality.

With the optimal conditions established, a series of (*E*)-4-*oxo*-enamides (**37**) were studied and the outcomes presented in Table 12. The established protocols (Conditions A and B) were able to tolerate variation in electron properties in the substrates: electron donating, neutral, withdrawing and heterocyclic rings, as well as differing position of substituents on the aromatic ring (Table 2, entries 5-15). Moreover, the protocols also worked well with differences in complexity in the amide group (Table 2, entries 2-4). A separate reaction using (*S*)-**4** as the catalyst afforded identical outcomes as when (*R*)-**4** was employed, albeit the opposite enantiomer obtained (Table 2, entry 1, Condition A).

5-3 Mechanistic Considerations

To establish the underlying factors accounting for the observed enantiodivergence, a detailed investigation of the possible mechanisms was conducted. A thorough inspection of our previous work revealed that *R* catalysts consistently gave *S* products and *vice versa* regardless of the solvents employed. As such, it was logical to exclude the possibility that differences in solvents employed can lead to a reversal of the catalyst's stereinduction capabilities. With no plausible explanation for the obtained results, a compilation of the obtained results as well as a review of the proposed mechanistic cycle (Scheme 22) led to a hypothesis that variation in the binding modes between the substrate (**37**) and the catalyst (via the keto or amide oxygen) could give rise to the observed enantiodivergence. Literature review on typical solvent induced-enantiodivergent reactions revealed that the solvents' relative permittivity/polarity (ϵ_r) was the root cause of the inversion. However, when we compared the results in this study with the relative permittivity of the solvent employed, it showed no correlation between ϵ_r and *ee* (Table 13).

Table 12: Substrate scope for the solvent-induced enantiodivergent hydrophosphination of (*E*)-4-oxo-enamides with diphenylphosphine.^[a]

Entry	Substrate	Ar	R	Condition A ^[b]		Condition B ^[c]	
				Yield ^[d] [%]	<i>ee</i> ^[e] [%]	Yield ^[d] [%]	<i>ee</i> ^[e] [%]
1	37a	Ph	Et	98	92, -92 ^[f]	95	93
2	37b	Ph	<i>i</i> -Pr	96	87	97	88
3	37c	Ph	pyrrolidyl	98	59	95	86
4	37d	Ph	morpholino	83	79	-	-
5	37e	2-Naphthyl	Et	96	84	95	96
6	37f	<i>p</i> -PhC ₆ H ₄	Et	98	88	95	95
7	37g	<i>p</i> -FC ₆ H ₄	Et	97	85	96	95
8	37h	<i>p</i> -ClC ₆ H ₄	Et	99	84	97	96
9	37i	<i>m</i> -ClC ₆ H ₄	Et	99	77	96	95
10	37j	<i>o</i> -ClC ₆ H ₄	Et	98	46	90	90
11	37k	<i>p</i> -BrC ₆ H ₄	Et	97	81	95	95
12	37l	<i>p</i> -MeC ₆ H ₄	Et	96	86	98	94
13	37m	<i>m</i> -MeC ₆ H ₄	Et	98	89	96	94
14	37n	<i>p</i> -MeOC ₆ H ₄	Et	97	80	97	95
15	37o	2-Thienyl	Et	98	86	95	95

^[a] General reaction conditions: **37** (0.08 mmol), Ph_2PH (0.08 mmol) in 4.5 mL of degassed solvent(s). ^[b] Toluene as solvent, reaction time = $\geq 15\text{ h}$. ^[c] Chloroform/methanol(10%) as solvent, reaction time = 2 h. ^[d] Yield is derived from the $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum of the product. ^[e] Enantiomeric excess (*ee*) is determined from the $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum integration of signals of diastereomers **39** arising from the treatment of **38** with enantiopure (*R*)/(*S*)-**1**. ^[f] Catalyst (*S*)-**4** employed.

Table 13: Solvents' ϵ_r versus the *ee* of the major enantiomer.

Solvent (ϵ_r)	Product hand-form (<i>ee</i>)	Solvent (ϵ_r)	Product hand-form (<i>ee</i>)
toluene (2.38)	<i>R</i> (-92)	DCM (8.93)	<i>S</i> (+49)
CHCl ₃ (4.89)	<i>S</i> (+72)	butanone (9.20)	<i>R</i> (-8)
EA (6.02)	<i>R</i> (-52)	acetone (20.56)	<i>S</i> (+18)
THF (7.58)	<i>R</i> (-39)		

As it was clear that the solvent's relative permittivity was not the key factor in influencing enantiodivergence, an in-depth literature search on the solvents' properties was performed, leading us to find an article which reported on the effect of the charge stabilization factor (Q_{stab}) of solvents on influencing reaction rates.^[95] It should be noted that Q_{stab} refers to the aggregate of the cation and anion solvating tendencies as defined by Swain.^[95] Although the reaction studied in the literature is distinctly different from this study, it was remarkable that when the obtained *ee* values were plotted against the Q_{stab} of the corresponding solvents, a unique relationship between the two variables can be established (Figure 21; +*ee* represents *S* products, linear regression $R^2=0.97$): Solvents with high Q_{stab} values ($Q_{stab}>1$) affords *S* products while those with lowered Q_{stab} values ($Q_{stab}<1$) gave *R* adducts.

With this critical discovery, it is now possible to propose a plausible mechanism for the solvent-induced enantiodivergence. As amides possess the tendency to preferentially exhibit resonance structures under different conditions, there are in fact up to 4 possible coordination modes that the substrate (**37**) can bind to the Pd catalyst (Scheme 26): when **37** exists in the amide form and binds to Pd via the keto or amide oxygen (Intermediate **A**

Figure 21: Scatter plot of obtained ee values against the solvents' corresponding charge stabilization tendency (Q_{stab}).

and **B**, respectively); or when **37** exists as the imide form and also coordinates to Pd via the keto or amide oxygen (Intermediates **C** and **D**, respectively). It is well established that the (*R*)-palladated ring in **4** adopts an absolute δ configuration, with the methyl group fixed in an axial conformation and the prochiral phenyls (Ph_{eq}, Ph_{ax}) on phosphorus pointing in opposing directions from the square plane. On the basis that the phosphorus nucleophile consistently attacks from the top face, Dreiding models of the intermediates **A-D** were constructed to observe any undesirable steric interactions between the bound substrate and the functionalities of the catalyst. It should be noted that Bürgi-Dunitz trajectories for nucleophilic attack on a sp^2 carbon was taken into account during the construction of the models, which predicts the appropriate orientation and conformation of the substrates, in turn influencing the final stereochemistry of the product (Figure 22).

Figure 22: Stereochemical perspectives of Intermediates **A-D**.

In solvents of low Q_{stab} ($Q_{\text{stab}} < 1$), the substrate prefers to exist in the predominantly amide resonance species (Intermediates **A** and **B**) as any charge separation is poorly stabilized by the solvent. When the substrate coordinates to Pd via the keto oxygen (Intermediate **A**), the aryl group experiences a greater repulsion with Ph_{eq} , as compared to the R groups on nitrogen when it is the amide oxygen that binds (Intermediate **B**). The latter intermediate is favourable considering that the (O)C-N bond is rotatable, thus able to point the R groups on nitrogen away from Ph_{eq} to minimise unfavourable steric repulsions. This produces products (major enantiomer) bearing a *R* configuration.

On the other hand with solvents of high Q_{stab} ($Q_{\text{stab}} > 1$), the substrate exists predominantly in the imide form (Intermediate **C** and **D**) as the solvent can readily stabilize the separated charges. When the substrate coordinates to Pd via the imide oxygen (Intermediate **D**),

restricted rotation of the (O)C=N bond creates unfavourable steric repulsion between the R groups on nitrogen and Ph_{eq}. On the contrary, when the substrate binds to Pd via the keto oxygen, the steric repulsion experienced by Intermediate **C** is significantly lesser as compared to than in Intermediate **D**. As a result, the phosphine adducts (major enantiomer) possess an absolute *S* configuration.

5-4 Conclusion

In conclusion, the regiospecific and highly enantioselective hydrophosphination of 4-oxo-enamides have been achieved, allowing the direct access to chiral phosphino carboxamides. Unexpected solvent-induced enantiodivergence was observed and the underlying distinct mechanisms elucidated, which was found to arise due depending on the employed solvent's charge stabilization tendencies.

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5-5 Experimental Section

All air sensitive manipulations were performed under a positive pressure of nitrogen using standard Schlenk techniques. Solvents were degassed prior to use when necessary. Chloroform (AR) and was purchased from Fischer Scientific; dichloromethane (AR), ethyl acetate (AR), from Merck Millipore; butanone (ACS grade) from Alfa Aesar, tetrahydrofuran (AR) and methanol (AR) from Anhui Fulltime Specialized Solvents & Reagents, acetone (AR) from QREC (Asia), and toluene from J. T. Baker. Solvents were

used directly without further purification. Low Temp PAIRSTIRRER PSL-1800 machine was used for controlling low temperatures for reactions. Silica plug filtration was conducted on Merck silica gel 60 (0.040-0.063mm). Substrates 37 were prepared in accordance to literature methods (*Org. Lett.* **2014**, *16*, 1802).

NMR spectra were recorded on Bruker ACF 400 spectrometers. ^1H NMR spectra chemical shifts were reported in δ ppm relative to tetramethylsilane ($\delta = 0.00$ ppm) or chloroform ($\delta = 7.26$ ppm). Multiplicities were given as: s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). The number of protons (n) for a given resonance was indicated by nH while coupling constants were reported as J value in Hertz (Hz). ^{13}C NMR spectra chemical shifts were recorded relative to solvent resonance (CDCl_3 : $\delta = 77.23$ ppm). $^{31}\text{P}\{^1\text{H}\}$ s NMR spectra chemical shifts are referenced to an external standard of 85% H_3PO_4 . Optical rotations of phosphine products were measured as soon as possible without inert gas protection in the specified solution using a 0.1 dm cell with a Atago AP-300 polarimeter. Chiral HPLC data was obtained using Agilent Technologies 1200 Series HPLC coupled with a Daicel CHIRALPAK® IC column.

5-5.1 General procedure for the palladacycle catalyzed regiospecific and enantiodivergent asymmetric *phospha*-Michael addition of diphenylphosphine to 4-oxo-enamides (37**)**

-Condition A: Toluene as solvent, time = $\geq 15\text{h}$, gives (R)-**38** as product

-Condition B: Chloroform/methanol (10%) as solvent, time = 2h, gives (S)-**38** as product

To a nitrogen (N_2) flushed two-neck flask at RT was charged with diphenylphosphine (0.08 mmol, 1 equiv.) and solvent(s) (3 mL). (R)-**4** is subsequently introduced followed by vigorous agitation to ensure complete dissolution. The reaction flask is cooled to the designated temperature before consecutive addition of a solution of **37** (0.08 mmol, 1 equiv., 1 mL solvent) and triethylamine (0.08 mmol, 1 equiv. 0.5 mL solvent) dropwise over a period of 5 minutes. The progress of the reaction was monitored by $^{31}\text{P}\{^1\text{H}\}$ NMR analyses and the reaction apparatus moved to RT upon completion. Solvents were removed under reduced pressure with gentle heating to completely eliminate volatiles. Subsequently, degassed chloroform (10 mL) is added before passing the solution through a silica plug in a N_2 flushed Pasteur pipette (to remove (R)-**4** and phosphine oxides, if any). The filtrate is collected in a separate degassed 2-neck flask before subjecting it to reduced pressure again to afford the desired product **38**.

5-5.2 Determination of enantiomeric excess (*ee*) via coordination studies

Product (**38**) obtained was treated with optically pure (*R*)/(*S*)-**1** (0.51 equiv.) in degassed chloroform to give diastereomers **39**. Enantiomeric excess of **38** is then determined from the $^{31}\text{P}\{^1\text{H}\}$ NMR spectra of **39**.

5-5.3 Determination of absolute configuration of the chiral products under conditions

A and B

To determine the stereochemistry of the newly formed chiral centres, attempts to purify the mixture of air-stable diastereomers (**39a**) on silica gel were futile as **39a** was surprisingly prone to decomposition. As such, 0.49 equiv. of **1** was employed in the coordination reaction and the resultant solution concentrated and directly recrystallized via solvent diffusion (chloroform/pentane) to give single crystals. X-ray diffraction studies of the resultant compounds revealed that toluene (Condition A) generated the *R* product [Figure 23, (*R,R*)-**39**], while chloroform/methanol mixture (Condition B) generated the enantiomeric *S* product [Figure 24, (*S,S*)-**39** as corresponding adducts] using the same *R*

hand-form catalyst (*R*)-**4**).

Figure 23. Molecular structure and absolute stereochemistry of the derivative complex (*R,R*)-**39a** with 50% thermal ellipsoids shown. Hydrogen atoms except those on the chiral centre are omitted for clarity. CCDC-1028552 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Figure 24. Molecular structure and absolute stereochemistry of the derivative complex (*R,R*)-**39a** with 50% thermal ellipsoids shown. Hydrogen atoms except those on the chiral centre are omitted for clarity. CCDC-1028554 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

5-5.4 Product characterization

(R)-38a was prepared according to **General Procedure, Condition A** (98% yield, 92% *ee*): $[\alpha]_D^{27} = +120.6^\circ$ [c 0.3, CHCl₃]. $^{31}\text{P}\{^1\text{H}\}$ (CDCl₃, 162 MHz): δ -0.62; ^1H (CDCl₃, 400 MHz): δ 0.90 (t, 3H, $J=7$), 1.03 (t, 3H, $J=7$), 2.77-2.84 (m, 1H), 2.87-2.96 (m, 1H), 3.00-3.08 (m, 1H), 3.21-3.36 (m, 2H), 3.91-3.99 (m, 1H), 4.13-4.17 (m, 1H), 7.18-7.80 (m, 15H); ^{13}C (CDCl₃, 101 MHz): δ 13.1 (s, 1C), 13.8 (s, 1C), 36.0 (d, 1C, $^1J_{\text{CP}} = 19$ Hz), 40.0 (d, 1C, $^2J_{\text{CP}} = 16$ Hz), 40.8 (s, 1C), 42.4 (s, 1C), 128.4-136.8 (m, 18C), 171.1 (d, 1C, $^2J_{\text{CP}} = 7$ Hz), 199.1 (d, 1C, $^3J_{\text{CP}} = 11$ Hz).

(S)-38a was prepared according to a) **General Procedure, Condition A** except that (S)-4 is employed as the catalyst (98% yield, 92% *ee*): $[\alpha]_D^{27} = -119.2^\circ$ [c 0.3, CHCl₃] and; b) **General Procedure, Condition B** (95% yield, 93% *ee* (91% *ee* by HPLC)): $[\alpha]_D^{26} = -120.0^\circ$ [c 0.5, CHCl₃]. $^{31}\text{P}\{^1\text{H}\}$ (CDCl₃, 162 MHz): δ -0.61; ^1H (CDCl₃, 400 MHz): δ 0.90 (t, 3H, $J=7$), 1.03 (t, 3H, $J=7$), 2.77-2.84 (m, 1H), 2.87-2.97 (m, 1H), 3.00-3.09 (m, 1H), 3.21-3.36 (m, 2H), 3.91-3.99 (m, 1H), 4.13-4.17 (m, 1H), 7.18-7.80 (m, 15H); ^{13}C (CDCl₃, 101 MHz): δ 13.1 (s, 1C), 13.8 (s, 1C), 36.0 (d, 1C, $^1J_{\text{CP}} = 20$ Hz), 40.0 (d, 1C, $^2J_{\text{CP}} = 16$ Hz), 40.8 (s, 1C), 42.4 (s, 1C), 128.4-136.8 (m, 18C), 171.1 (d, 1C, $^2J_{\text{CP}} = 7$ Hz), 199.1 (d, 1C, $^3J_{\text{CP}} = 11$ Hz).

(*R*)-**38b** was prepared according to **General Procedure, Condition A**

(96% yield, 87% *ee*): $[\alpha]_{\text{D}}^{26} = -77.8^{\circ}$ [c 0.5, CHCl₃] and; (*S*)-**38b** was prepared according to **General Procedure, Condition B** (97% yield, 88% *ee*): $[\alpha]_{\text{D}}^{25} = -79.3^{\circ}$ [c 0.5, CHCl₃].

³¹P{¹H} (CDCl₃, 162 MHz): δ -1.59; ¹H (CDCl₃, 400 MHz): δ 0.65 (d, 3H, *J* = 7 Hz), 1.15-1.21 (m, 9H), 2.72-2.79 (m, 1H), 3.14-3.21 (m, 1H), 3.87-3.95 (m, 1H), 4.09-4.15 (m, 1H), 4.17-4.21 (m, 1H), 7.18-7.79 (m, 15H); ¹³C (CDCl₃, 101 MHz): δ 20.4 (s, 1C), 20.69 (s, 1C), 20.73 (s, 1C), 21.0 (s, 1C), 37.1 (d, 1C, ¹*J*_{CP} = 19 Hz), 39.8 (d, 1C, ²*J*_{CP} = 14 Hz), 46.4 (s, 1C), 49.9 (s, 1C), 128.4-137.1 (m, 18C), 170.4 (d, 1C, ²*J*_{CP} = 8 Hz), 199.4 (d, 1C, ³*J*_{CP} = 10 Hz).

(*R*)-**38c** was prepared according to **General Procedure, Condition A**

(98% yield, 59% *ee*): $[\alpha]_{\text{D}}^{25} = +30.4^{\circ}$ [c 0.3, CHCl₃] and; (*S*)-**38c** was prepared according to **General Procedure, Condition B** (95% yield, 86% *ee*): $[\alpha]_{\text{D}}^{26} = -59.5^{\circ}$ [c 0.5, CHCl₃].

³¹P{¹H} (CDCl₃, 162 MHz): δ -2.23; ¹H (CDCl₃, 400 MHz): δ 2.89-2.96 (m, 1H), 2.98-3.03 (m, 1H), 3.16-3.22 (m, 1H), 3.25-3.31 (m, 1H), 3.42-3.54 (m, 4H), 3.63-3.67 (m, 1H), 3.98-4.06 (m, 1H), 4.19-4.24 (m, 1H), 7.18-7.82 (m, 15H); ¹³C (CDCl₃, 101 MHz): δ 35.8 (d, 1C, ¹*J*_{CP} = 17 Hz), 40.4 (d, 1C, ²*J*_{CP} = 20 Hz), 42.4 (s, 1C), 46.7 (s, 1C), 66.4 (s, 1C), 66.7 (s, 1C), 128.3-136.4 (m, 18C), 171.1 (d, 1C, ²*J*_{CP} = 6 Hz), 198.6 (d, 1C, ³*J*_{CP} = 13 Hz).

(R)-38d was prepared according to **General Procedure, Condition A**

(83% yield, 79% *ee*): $[\alpha]_{\text{D}}^{25} = +58.2^{\circ}$ [c 0.3, CHCl₃]. ³¹P{¹H} (CDCl₃, 162 MHz): δ -2.46; ¹H (CDCl₃, 400 MHz): δ 1.27-1.41 (m, 2H), 1.57-1.70 (m, 2H), 2.57-2.63 (m, 1H), 2.83-2.90 (m, 1H), 3.05-3.11 (m, 1H), 3.26-3.32 (m, 1H), 3.58-3.64 (m, 1H), 4.01-4.09 (m, 2H), 7.18-7.81 (m, 15H); ¹³C (CDCl₃, 101 MHz): δ 24.3 (s, 1C), 25.9 (s, 1C), 38.8 (d, 1C, ¹J_{CP} = 17 Hz), 40.2 (d, 1C, ²J_{CP} = 20 Hz), 45.9 (s, 1C), 46.7 (s, 1C), 128.2-136.5 (m, 18C), 170.2 (d, 1C, ²J_{CP} = 6 Hz), 198.8 (d, 1C, ³J_{CP} = 13 Hz).

(R)-38e was prepared according to **General Procedure, Condition A**

(96% yield, 84% *ee*): $[\alpha]_{\text{D}}^{26} = +100.8^{\circ}$ [c 0.5, CHCl₃] and; **(S)-38e** was prepared according to **General Procedure, Condition B** (95% yield, 96% *ee*): $[\alpha]_{\text{D}}^{26} = -120.0^{\circ}$ [c 0.5, CHCl₃]. ³¹P{¹H} (CDCl₃, 162 MHz): δ -0.48; ¹H (CDCl₃, 400 MHz): δ 0.89 (t, 3H, *J* = 7 Hz), 1.02 (t, 3H, *J* = 7 Hz), 2.86-2.96 (m, 2H), 2.99-3.08 (m, 1H), 3.20-3.35 (m, 2H), 4.08-4.15 (m, 1H), 4.19-4.23 (m, 1H), 7.17-7.82 (m, 17H); ¹³C (CDCl₃, 101 MHz): δ 13.1 (s, 1C), 13.8 (s, 1C), 36.2 (d, 1C, ¹J_{CP} = 19 Hz), 40.1 (d, 1C, ²J_{CP} = 17 Hz), 40.8 (s, 1C), 42.35 (s, 1C), 124.0-136.3 (m, 22C), 171.1 (d, 1C, ²J_{CP} = 8 Hz), 199.0 (d, 1C, ³J_{CP} = 12 Hz).

(R)-38f was prepared according to **General Procedure, Condition A**

(98% yield, 88% *ee*): $[\alpha]_{\text{D}}^{26} = +57.6^{\circ}$ [c 0.5, CHCl₃] and; **(S)-38f** was prepared according

to **General Procedure, Condition B** (95% yield, 95% *ee*): $[\alpha]_D^{26} = -99.3^\circ$ [c 0.5, CHCl₃]. ³¹P{¹H} (CDCl₃, 162 MHz): δ -0.57; ¹H (CDCl₃, 400 MHz): δ 0.91 (t, 3H, *J* = 7 Hz), 1.03 (t, 3H, *J* = 7 Hz), 2.79-2.86 (m, 1H), 2.88-2.97 (m, 1H), 3.00-3.09 (m, 1H), 3.21-3.35 (m, 2H), 3.94-4.02 (m, 1H), 4.15-4.19 (m, 1H), 7.17-7.87 (m, 19H); ¹³C (CDCl₃, 101 MHz): δ 13.1 (s, 1C), 13.8 (s, 1C), 36.1 (d, 1C, ¹*J*_{CP} = 19 Hz), 40.0 (d, 1C, ²*J*_{CP} = 16 Hz), 40.8 (s, 1C), 42.4 (s, 1C), 127.3-146.0 (m, 24C), 171.1 (d, 1C, ²*J*_{CP} = 7 Hz), 198.7 (d, 1C, ³*J*_{CP} = 11 Hz).

(*R*)-**38g** was prepared according to **General Procedure, Condition A** (97% yield, 85% *ee*): $[\alpha]_D^{25} = +80.0^\circ$ [c 0.5, CHCl₃] and; (*S*)-**38g** was prepared according to **General Procedure, Condition B** (96% yield, 95% *ee*): $[\alpha]_D^{26} = -139.2^\circ$ [c 0.5, CHCl₃]. ³¹P{¹H} (CDCl₃, 162 MHz): δ -0.64; ¹⁹F{¹H} (CDCl₃, 377 MHz): δ -105.2; ¹H (CDCl₃, 400 MHz): δ 0.90 (t, 3H, *J* = 7 Hz), 1.03 (t, 3H, *J* = 7 Hz), 2.72-2.78 (m, 1H), 2.86-2.94 (m, 1H), 3.00-3.07 (m, 1H), 3.22-3.35 (m, 2H), 3.86-3.94 (m, 1H), 4.11-4.15 (m, 1H), 6.95-7.52 (m, 14H); ¹³C (CDCl₃, 101 MHz): δ 13.1 (s, 1C), 13.8 (s, 1C), 36.1 (d, 1C, ¹*J*_{CP} = 20 Hz), 39.8 (d, 1C, ²*J*_{CP} = 16 Hz), 40.8 (s, 1C), 42.4 (s, 1C), 115.6-136.1 (m, 16C), 164.7 (s, 1C), 167.3 (s, 1C), 171.0 (d, 1C, ²*J*_{CP} = 7 Hz), 197.6 (d, 1C, ³*J*_{CP} = 10 Hz).

(*R*)-**38h** was prepared according to **General Procedure, Condition A** (99% yield, 84% *ee*): $[\alpha]_D^{25} = +60.8^\circ$ [c 0.5, CHCl₃] and; (*S*)-**38h** was prepared according to **General Procedure, Condition B** (97% yield, 96% *ee*): $[\alpha]_D^{27} = -99.3^\circ$ [c 0.5, CHCl₃].

$^{31}\text{P}\{^1\text{H}\}$ (CDCl_3 , 162 MHz): δ -0.67; ^1H (CDCl_3 , 400 MHz): δ 0.90 (t, 3H, $J = 7$ Hz), 1.03 (t, 3H, $J = 7$ Hz), 2.71-2.78 (m, 1H), 2.85-2.91 (m, 1H), 3.00-3.05 (m, 1H), 3.22-3.35 (m, 2H), 3.85-3.93 (m, 1H), 4.10-4.14 (m, 1H), 7.18-7.74 (m, 14H); ^{13}C (CDCl_3 , 101 MHz): δ 13.1 (s, 1C), 13.8 (s, 1C), 36.1 (d, 1C, $^1J_{\text{CP}} = 20$ Hz), 39.8 (d, 1C, $^2J_{\text{CP}} = 16$ Hz), 40.8 (s, 1C), 42.4 (s, 1C), 128.6-139.8 (m, 18C), 170.9 (d, 1C, $^2J_{\text{CP}} = 7$ Hz), 198.1 (d, 1C, $^3J_{\text{CP}} = 10$ Hz).

(*R*)-**38i** was prepared according to **General Procedure, Condition A** (99% yield, 77% *ee*): $[\alpha]_{\text{D}}^{26} = +99.4^\circ$ [c 0.5, CHCl_3] and; (*S*)-**38i** was prepared according to **General Procedure, Condition B** (96% yield, 95% *ee*): $[\alpha]_{\text{D}}^{26} = 118.3^\circ$ [c 0.5, CHCl_3]. $^{31}\text{P}\{^1\text{H}\}$ (CDCl_3 , 162 MHz): δ -0.74; ^1H (CDCl_3 , 400 MHz): δ 0.91 (t, 3H, $J = 7$ Hz), 1.04 (t, 3H, $J = 7$ Hz), 2.72-2.79 (m, 1H), 2.82-2.92 (m, 1H), 2.99-3.08 (m, 1H), 3.21-3.36 (m, 2H), 3.86-3.94 (m, 1H), 4.10-4.14 (m, 1H), 7.18-7.76 (m, 14H); ^{13}C (CDCl_3 , 101 MHz): δ 13.1 (s, 1C), 13.8 (s, 1C), 36.0 (d, 1C, $^1J_{\text{CP}} = 20$ Hz), 40.0 (d, 1C, $^2J_{\text{CP}} = 16$ Hz), 40.8 (s, 1C), 42.3 (s, 1C), 126.5-138.3 (m, 18C), 170.8 (d, 1C, $^2J_{\text{CP}} = 7$ Hz), 198.0 (d, 1C, $^3J_{\text{CP}} = 11$ Hz).

(*R*)-**38j** was prepared according to **General Procedure, Condition A** (98% yield, 46% *ee*): $[\alpha]_{\text{D}}^{26} = +39.2^\circ$ [c 0.5, CHCl_3] and; (*S*)-**38j** was prepared according to **General Procedure, Condition B** (90% yield, 90% *ee*): $[\alpha]_{\text{D}}^{26} = -60.8^\circ$ [c 0.5, CHCl_3].

$^{31}\text{P}\{^1\text{H}\}$ (CDCl_3 , 162 MHz): δ -0.95; ^1H (CDCl_3 , 400 MHz): δ 0.95 (t, 3H, $J = 7$ Hz), 1.07 (t, 3H, $J = 7$ Hz), 2.76-2.83 (m, 1H), 2.91-2.96 (m, 1H), 3.05-3.10 (m, 1H), 3.29-3.41 (m, 2H), 3.70-3.78 (m, 1H), 4.10-4.13 (m, 1H), 7.14-7.51 (m, 14H); ^{13}C (CDCl_3 , 101 MHz): δ 13.1 (s, 1C), 13.9 (s, 1C), 36.3 (d, 1C, $^1J_{\text{CP}} = 22$ Hz), 41.0 (s, 1C), 42.5 (s, 1C), 43.6 (d, 1C, $^2J_{\text{CP}} = 13$ Hz), 127.0-139.1 (m, 18C), 170.8 (d, 1C, $^2J_{\text{CP}} = 8$ Hz), 202.1 (d, 1C, $^3J_{\text{CP}} = 10$ Hz).

(*R*)-**38k** was prepared according to **General Procedure, Condition A**

(97% yield, 81% *ee*): $[\alpha]_{\text{D}}^{26} = +60.0^\circ$ [c 0.5, CHCl_3] and; (*S*)-**38k** was prepared according to **General Procedure, Condition B** (95% yield, 95% *ee*): $[\alpha]_{\text{D}}^{27} = -79.1^\circ$ [c 0.5, CHCl_3].

$^{31}\text{P}\{^1\text{H}\}$ (CDCl_3 , 162 MHz): δ -0.65; ^1H (CDCl_3 , 400 MHz): δ 0.90 (t, 3H, $J = 7$ Hz), 1.03 (t, 3H, $J = 7$ Hz), 2.70-2.77 (m, 1H), 2.83-2.92 (m, 1H), 2.98-3.07 (m, 1H), 3.20-3.36 (m, 2H), 3.84-3.92 (m, 1H), 4.09-4.13 (m, 1H), 7.18-7.50 (m, 14H); ^{13}C (CDCl_3 , 101 MHz): δ 13.1 (s, 1C), 13.8 (s, 1C), 36.0 (d, 1C, $^1J_{\text{CP}} = 21$ Hz), 39.8 (d, 1C, $^2J_{\text{CP}} = 15$ Hz), 40.8 (s, 1C), 42.4 (s, 1C), 128.5-136.0 (m, 18C), 170.9 (d, 1C, $^2J_{\text{CP}} = 7$ Hz), 198.3 (d, 1C, $^3J_{\text{CP}} = 11$ Hz).

(*R*)-**38l** was prepared according to **General Procedure, Condition A**

(96% yield, 86% *ee*): $[\alpha]_{\text{D}}^{26} = +60.4^\circ$ [c 0.5, CHCl_3] and; (*S*)-**38l** was prepared according to **General Procedure, Condition B** (98% yield, 94% *ee*): $[\alpha]_{\text{D}}^{26} = -79.1^\circ$ [c 0.5, CHCl_3].

$^{31}\text{P}\{^1\text{H}\}$ (CDCl_3 , 162 MHz): δ -0.53; ^1H (CDCl_3 , 400 MHz): δ 0.89 (t, 3H, $J = 7$ Hz), 1.01 (t, 3H, $J = 7$ Hz), 2.28 (s, 3H), 2.75-2.82 (m, 1H), 2.88-3.00 (m, 1H), 3.00-3.08 (m, 1H), 3.21-3.33 (m, 2H), 3.88-3.96 (m, 1H), 4.12-4.16 (m, 1H), 7.08-7.50 (m, 14H); ^{13}C (CDCl_3 , 101 MHz): δ 13.1 (s, 1C), 13.8 (s, 1C), 21.8 (s, 1C), 36.0 (d, 1C, $^1J_{\text{CP}} = 19$ Hz), 39.9 (d, 1C, $^2J_{\text{CP}} = 16$ Hz), 40.8 (s, 1C), 42.4 (s, 1C), 128.5-144.1 (m, 18C), 171.1 (d, 1C, $^2J_{\text{CP}} = 7$ Hz), 198.7 (d, 1C, $^3J_{\text{CP}} = 11$ Hz).

38m

(*R*)-**38m** was prepared according to **General Procedure, Condition A** (98% yield, 89% *ee*): $[\alpha]_{\text{D}}^{25} = +77.1^\circ$ [c 0.5, CHCl_3] and; (*S*)-**38m** was prepared according to **General Procedure, Condition B** (96% yield, 94% *ee*): $[\alpha]_{\text{D}}^{27} = -117.2^\circ$ [c 0.5, CHCl_3]. $^{31}\text{P}\{^1\text{H}\}$ (CDCl_3 , 162 MHz): δ -0.62; ^1H (CDCl_3 , 400 MHz): δ 0.90 (t, 3H, $J = 7$ Hz), 1.01 (t, 3H, $J = 7$ Hz), 2.27 (s, 3H), 2.76-2.83 (m, 1H), 2.86-2.95 (m, 1H), 3.00-3.08 (m, 1H), 3.19-3.34 (m, 2H), 3.92-4.00 (m, 1H), 4.13-4.17 (m, 1H), 7.17-7.61 (m, 14H); ^{13}C (CDCl_3 , 101 MHz): δ 13.1 (s, 1C), 13.8 (s, 1C), 21.5 (s, 1C), 36.0 (d, 1C, $^1J_{\text{CP}} = 19$ Hz), 40.1 (d, 1C, $^2J_{\text{CP}} = 17$ Hz), 40.8 (s, 1C), 42.4 (s, 1C), 125.6-138.4 (m, 18C), 171.1 (d, 1C, $^2J_{\text{CP}} = 7$ Hz), 199.3 (d, 1C, $^3J_{\text{CP}} = 11$ Hz).

38n

(*R*)-**38n** was prepared according to **General Procedure, Condition A** (97% yield, 80% *ee*): $[\alpha]_{\text{D}}^{26} = +40.3^\circ$ [c 0.5, CHCl_3] and; (*S*)-**38n** was prepared according to **General Procedure, Condition B** (97% yield, 95% *ee*): $[\alpha]_{\text{D}}^{26} = -98.3^\circ$ [c 0.5, CHCl_3].

$^{31}\text{P}\{^1\text{H}\}$ (CDCl_3 , 162 MHz): δ -0.53; ^1H (CDCl_3 , 400 MHz): δ 0.89 (t, 3H, $J = 7$ Hz), 1.00 (t, 3H, $J = 7$ Hz), 2.72-2.79 (m, 1H), 2.88-3.07 (m, 2H), 3.20-3.33 (m, 2H), 3.74 (s, 3H), 3.86-3.94 (m, 1H), 4.12-4.16 (m, 1H), 6.76-7.77 (m, 14H); ^{13}C (CDCl_3 , 101 MHz): δ 13.1 (s, 1C), 13.8 (s, 1C), 36.1 (d, 1C, $^1J_{\text{CP}} = 19$ Hz), 39.6 (d, 1C, $^2J_{\text{CP}} = 15$ Hz), 40.8 (s, 1C), 42.4 (s, 1C), 55.6 (s, 1C), 113.8-163.7 (m, 18C), 171.2 (d, 1C, $^2J_{\text{CP}} = 8$ Hz), 197.5 (d, 1C, $^3J_{\text{CP}} = 10$ Hz).

(*R*)-**38o** was prepared according to **General Procedure, Condition A** (98% yield, 86% *ee*): $[\alpha]_{\text{D}}^{26} = +78.1^\circ$ [c 0.5, CHCl_3] and; (*S*)-**38o** was prepared according to **General Procedure, Condition B** (95% yield, 95% *ee*): $[\alpha]_{\text{D}}^{28} = -79.1^\circ$ [c 0.5, CHCl_3].

$^{31}\text{P}\{^1\text{H}\}$ (CDCl_3 , 162 MHz): δ -0.67; ^1H (CDCl_3 , 400 MHz): δ 0.88 (t, 3H, $J = 7$ Hz), 1.00 (t, 3H, $J = 7$ Hz), 2.74-2.81 (m, 1H), 2.84-2.93 (m, 1H), 2.98-3.07 (m, 1H), 3.15-3.34 (m, 1H), 3.81-3.89 (m, 1H), 4.09-4.13 (m, 1H), 6.96-7.55 (m, 13H); ^{13}C (CDCl_3 , 101 MHz): δ 13.0 (s, 1C), 13.8 (s, 2C), 36.1 (d, 1C, $^1J_{\text{CP}} = 20$ Hz), 40.4 (d, 1C, $^2J_{\text{CP}} = 16$ Hz), 40.8 (s, 1C), 42.3 (s, 1C), 128.3-143.9 (m, 16C), 170.9 (d, 1C, $^2J_{\text{CP}} = 8$ Hz), 191.9 (d, 1C, $^3J_{\text{CP}} = 11$ Hz).

Future Work

It is clear from this thesis that considerable advancements to the field of catalytic asymmetric hydrophosphination have been made. Nevertheless, significantly more work have to be done especially towards the preparation of highly enantioenriched hybrid phosphines as they are known to be efficient alternatives to conventional bisphosphine ligands. In addition, modifications towards the existing palladacycle catalyst to render it more stable thermally may be considered as being able to survive elevated temperatures aids in advancement in the catalytic hydrophosphination of unactivated olefins.

As our group has previously established the potential of various chiral phosphine-gold adducts in anti-cancer studies in in-vitro systems, more extensive studies on the classes of adducts as well as in-depth in-vivo studies could be conducted to further contribute towards the continuous fight against cancer.

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List of Publications

- 1) **Our Odyssey with Functionalized Chiral Phosphines: From Optical Resolution to Asymmetric Synthesis, to Catalysis** (*Account, By invitation*)

R. J. Chew and P.-H. Leung, *Chem. Rec.* **2016**, 16, 141-158.

- 2) **Investigation of Functional Group Effects on Palladium Catalyzed Asymmetric P-H Addition** (*Special Issue*)

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