Development of C-P and N-P bond formation reactions

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Development of C-P and N-P Bond Formation Reactions

Balázs László Bertalan

SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

2020

Development of C-P and N-P Bond Formation Reactions

Balázs László Bertalan

SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

A thesis submitted to the Nanyang Technological
University in partial fulfilment of the requirement for the
degree of Doctor of Philosophy

2020

Statement of Originality

I hereby certify that the work embodied in this thesis is the result of original research done by me except where otherwise stated in this thesis. The thesis work has not been submitted for a degree or professional qualification to any other university or institution. I declare that this thesis is written by myself and is free of plagiarism and of sufficient grammatical clarity to be examined. I confirm that the investigations were conducted in accord with the ethics policies and integrity standards of Nanyang Technological University and that the research data are presented honestly and without prejudice.

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I have reviewed the content and presentation style of this thesis and declare it of sufficient grammatical clarity to be examined. To the best of my knowledge, the thesis is free of plagiarism and the research and writing are those of the candidate's except as acknowledged in the Author Attribution Statement. I confirm that the investigations were conducted in accord with the ethics policies and integrity standards of Nanyang Technological University and that the research data are presented honestly and without prejudice.

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Leung Pak-Hing

Authorship Attribution Statement

This thesis contains materials from 3 papers published in the following peer-reviewed journals in which I am listed as an author.

In **Chapter II**, the following subchapters: 2.1, 2.2, 2.4 and 2.5 are published as L.B. Balázs, W.S. Tay, Y.X. Li, S.A. Pullarkat and P.-H. Leung. Synthesis of Stereoprojecting, Chiral N-C(sp³)-E Type Pincer Complexes. *Organometallics* **37**, 2272-2285 (2018). DOI: 10.1021/acs.organomet.8b00262.

The contributions of the co-authors are as follows:

- Prof Leung P.-H., Dr Pullarkat S.A. and Ms Tay W.S. provided the initial project direction and gave me suggestions during the project.
- Dr Li Y.X. performed the X-ray analyses (including data collection and interpretation).
- I performed all the laboratory work (starting material syntheses, optimization of the reaction conditions, product syntheses and isolation, characterizations and coordination studies).
- I prepared the drafts of the manuscript and the Supporting Information (SI). The manuscript and the SI were revised by Prof Leung P.-H. and Dr Pullarkat S.A.

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In **Chapter III**, the following subchapters: 3.1, 3.2, 3.4 and 3.5 are published as L.B. Balázs, J.B. Khalikuzzaman, Y.X. Li, D. Csókás, S.A. Pullarkat and P.-H. Leung. Tandem double hydrophosphination of $\alpha,\beta,\gamma,\delta$ -unsaturated-1,3-indandiones: diphosphine synthesis, mechanistic investigations and coordination chemistry. *Chem. Commun.* **55**, 10936-10939 (2019). DOI: 10.1039/c9cc05384k.

The contributions of the co-authors are as follows:

- Prof Leung P.-H., Dr Pullarkat S.A. and I co-designed the initial project direction.
- Dr Li Y.X. performed the X-ray analyses (including data collection and interpretation).
- Dr Csókás D. performed theoretical studies (the details of the calculations are not presented in this thesis).
- Ms Khalikuzzaman J.B. performed the following synthetic work under my guidance: synthesis, purification and characterization of **36b**, **36f** (starting materials); **38ba**, **38ca** and **38da** (diphosphine products); optimization of control experiment 4 for mechanistic study (table 16), we optimized together the reaction conditions for **38aa** synthesis (table 14) and scaled-up the synthesis of **51a** and **51b** for application studies.
- All the remaining synthetic work which was not mentioned above (at the section of Ms Khalikuzzaman J.B.) was conducted by me (starting material syntheses, product syntheses and isolation, characterizations and spectroscopic studies for mechanistic investigations).
- I prepared the drafts of the manuscript and the Electronic Supplementary Information (ESI). The manuscript and the ESI were revised by Prof Leung P.-H. and Dr Pullarkat S.A.

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In **Chapter IV**, subchapter 4.4 and the figures and schemes of subchapters 4.1 and 4.2 are published as L.B. Balázs, Y.H. Huang, J.B. Khalikuzzaman, Y.X. Li, S.A. Pullarkat and P.-H. Leung. Catalytic Asymmetric Diarylphosphine Addition to α -Diazoesters for the Synthesis of P-Stereogenic Phosphinates via P*-N Bond Formation. *J. Org. Chem.* (2020) (in press). DOI: 10.1021/acs.joc.0c00181.

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- Prof Leung P.-H., Dr Pullarkat S.A., Dr Huang Y.H. and I co-designed the initial project direction.
- Dr Li Y.X. performed the X-ray analyses (including data collection and interpretation).
- Ms Khalikuzzaman J.B. performed the following synthetic work under my guidance: synthesis of some of the starting materials and support in product isolation.
- I performed the following laboratory work: starting material syntheses, optimization of the reaction conditions, extension of the substrate scope, product syntheses and isolation, characterizations, experimental mechanistic studies and derivatization reactions).
- I prepared the drafts of the manuscript and the Supporting Information (SI). The manuscript and the SI were revised by Prof Leung P.-H. and Dr Pullarkat S.A.

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23/4/2020

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Balázs László Bertalan

Abstract

Chiral phosphine ligands are well-established as exceptional synthetic tools for various asymmetric transformations, since their discoveries at the beginning of the 1960's. These important compounds can be synthesized via various catalytic and non-catalytic synthesis scenarios. Palladacycles are traditionally used as chiral resolving agents and chiral templates in asymmetric template promoted protocols for the generation of chiral phosphines. In recent years, palladacycles were found to be extraordinary catalysts in asymmetric hydrophosphination for C- and P-chiral phosphine syntheses. The P-H addition protocol to unsaturated double bond is a highly demanding strategy for C*-P bond formation, due to its atom economical nature and the variations of this reaction (C*-P* and O-P* bond formation protocols) can lead to the formation of numerous new chiral phosphine products. However, according to the investigations performed by our group, there are substrates which are significantly more challenging due to the relatively weaker double bond activation or chelating properties to the palladacycle catalyst. In this thesis, synthesis strategies are disclosed for novel C*-P, double C-P and N-P* bond formation for C- and P-stereogenic phosphine syntheses using P-H addition strategies. The generated chiral phosphines were applied in cyclometalation to obtain optically pure N-C(sp³)-E (E=S,O) type pincer complexes; coordination studies for chiral bimetallic palladium complex synthesis; and derivatization resulted in the formation of enantioenriched P-chiral diarylphosphinates. Mechanistic studies supported by NMR investigations revealed important aspects in the reaction mechanism of the new synthetic methods.

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Abbreviations and symbols

$[\alpha]_D$	specific rotation measured at sodium D line (589 nm)
δ	NMR chemical shift in ppm
μ	Greek letter for bridging ligand
Ac	acetyl
Ar	aryl group
<i>p</i> -ABSA	4-acetamidobenzenesulfonyl azide
BDPP	2,4-bis(diphenylphosphino)pentane
Bn	benzyl group
Bp	boiling point
calc.	calculated
conc.	concentrated
conv.	Conversion
Cp	cyclopentadienyl
Cy	cyclohexyl
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
dec.	decomposed
DIPEA	<i>N,N</i> -diisopropylethylamine
DKR	dynamic kinetic resolution
DMA	<i>N,N</i> -dimethylaniline
DMPU	<i>N,N</i> -dimethylpropylene urea
DMPP	3,4-dimethyl-1-phenylphosphole
dppe	1,2-bis(diphenylphosphanyl)ethane

dr	diastereomeric ratio
DTBP	2,6-ditert-butyl piridine
DYKAT	dynamic kinetic asymmetric transformation
EDG	electron-donating group
<i>ee</i>	enantiomeric excess
equiv	equivalent
ESI-MS	electrospray ionization mass spectrometry
EWG	electron-withdrawing group
KR	kinetic resolution
L	neutral ligand
M	metal
Mp	melting point
NBS	<i>N</i> -bromosuccinimide
NHC	<i>N</i> -heterocyclic carbene
PTC	phase transfer catalyst
pybim	1,3-bis(imidazolin-2-yl)pyridine
pybox	pyridinebisoxazoline
rt	room temperature
TBD	1,5,7-triazabicyclo[4.4.0]dec-5-ene
THF	tetrahydrofuran
TMG	1,1,3,3-tetramethylguanidine
TMS	tetramethylsilane
Ts	toluenesulfonyl (=tosyl) group
OTf	trifluoromethanesulfonate (=triflate) group
OTs	tosylate group
X	anionic ligand

Summary

The research work presented in this thesis is mainly focused on phosphine ligand syntheses via C-P and N-P bond formation.

In Chapter 1, a brief introduction of chiral phosphine chemistry is presented, including various synthesis strategies via asymmetric catalysis. This chapter also presents a general overview of palladacycles and applications established by our group.

In Chapter 2, the generation of chiral N-C(sp³)-E (E=S,O) type pincer complexes by using asymmetric hydrophosphination synthetic strategy is discussed. Coordination studies revealed the N-chelating properties of the starting material enones to palladium. Since the substrate chelation suppressed the catalytic activity of the applied C(sp²)-P type palladacycle, another catalyst, a P-C(sp²)-P type pincer complex was used during the asymmetric hydrophosphination, to avoid any unwanted substrate chelation. Based on the optimization and coordination studies, the intermolecular catalytic cycle was preferred over the intramolecular mechanistic pathway in the tridentate ligand synthesis. Cyclometalation of the synthesized chiral ligands provided the formation of several new N-C(sp³)-E type chiral pincer compounds.

In Chapter 3, a novel double hydrophosphination protocol was established in a transition metal-free transformation. Experimental mechanistic studies revealed the order of the double addition process and the retro-phospha-Michael addition at the 1,4-position was established. The coordination properties of the generated diphosphine ligand was investigated and an unexpected P,O-bidentate and P-monodentate coordination mode was detected, instead of the traditional P,P-bidentate chelation. Upon separation of the generated diastereomers, optically pure bimetallic palladium complexes were obtained.

In Chapter 4, the catalytic asymmetric phosphination of electrophilic diazo compounds was established. In the transformation, enantioenriched P-stereogenic phosphinic hydrazones were generated. Acidic methanolysis of the generated N-P* bond provided the formation of enantioenriched P-stereogenic phosphinates, without the loss of enantioselectivity. Experimental coordination studies were conducted, and a plausible mechanistic pathway was proposed based on the findings. The synthetic route demonstrated a novel strategy, in which P-stereogenic phosphine compounds can be generated via an asymmetric catalytic N-P* bond formation.

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CHAPTER I

General Introduction

1.1 Significance of chirality in chemistry

Chemical chirality plays a crucial role in our daily life. Many compounds in nutrients, cosmetics, perfumes, pesticides and pharmaceutical drugs contain one or more stereocenter(s) in their chemical structure.¹ Most of the physical properties of the opposite enantiomers, such as melting point, boiling point, solubility, polarity etc., are identical, except the optical rotation, the direction in which they rotate the plane polarized light. The different enantiomers often have different taste, odor and biological activities.¹ In biological systems, all the receptors are chiral and within a chiral surrounding, the two enantiomers often behave entirely differently. This is the reason, why we need to consider the opposite enantiomers as different compounds when they are screened for pharmaceutical activity. A few examples of opposite enantiomers with different biological behavior are shown in Figure 1.²

Figure 1. Different behavior of opposite enantiomers.

The increasing demand of chiral chemicals leads to the continuous development of this area for scientific and for industrial purpose.³ Optically active compounds can be synthesized via various methods. Some of the most important strategies are: a) synthesis from nature's chiral pool; b) resolution: formation of diastereomers by using external chiral auxiliaries, separation of the diastereomers and elimination of the chiral auxiliary; c) asymmetric catalysis. For the synthesis of enantiopure chiral compounds, we must consider several factors in order to choose the best strategy, such as the cost of the starting material, the number of synthesis steps and the purpose of the obtained product. For instance, sometimes it may be desirable to obtain both enantiomers in the synthesis for biological evaluation, in this case, resolution is a reasonable strategy to choose. In contrast, resolution can cause a huge amount of waste, if the purpose is to

synthesize and utilize only one of the enantiomers in industrial production. In this case, asymmetric catalysis seems to be a much better strategy to choose, if possible.

In general, asymmetric catalysis is an exceptional tool to obtain optically active enantiomers using only a catalytic amount of chiral source.⁴ These sources can be either metal complexes (in which a chiral ligand is coordinated to a main group element⁵ or transition metal⁶) or organocatalysts.⁷ Among the commonly used ligands, chiral phosphines are one of the most impactful compounds, which have been widely applied in asymmetric chemistry since their discoveries, up to these days.

1.2 General overview of chiral phosphine ligands

In the past 50 years, tertiary phosphines have gained an increasing interest in synthetic chemistry.⁸ One of the unique features of these compounds is the available lone pair on the phosphorus atom which can easily interact with various transition metals, creating a stable coordination bond. Tertiary phosphines have both σ -donating and π -accepting properties and this double interaction can stabilize the metals in different oxidation states. The generated metal complexes can be widely applied in catalytic synthesis scenarios.

The first examples of chiral phosphines [$\text{PR}^1\text{R}^2\text{R}^3$ ($\text{R}^1, \text{R}^2, \text{R}^3 = \text{alkyl, aryl}$)] were reported by Horner and co-workers in 1961 (Figure 2).⁹ The stereogenic center in these compounds was located on the phosphorus atom. Few years later, in 1968, Knowles and Horner reported independently the first application of optically active phosphine ligands in asymmetric catalysis.¹⁰

Figure 2. The first examples of chiral phosphine derivatives and their application.

In these reports, the enantioenriched phosphine ligands were successfully applied in rhodium-catalyzed asymmetric hydrogenation. After the establishment of the above-mentioned monophosphines ligands, Kagan reported in 1971 the first chiral bidentate phosphine, the DIOP (Figure 2).¹¹ This diphosphine ligand performed even better in the rhodium-catalyzed asymmetric hydrogenation when compared to the monophosphines synthesized by Horner and Knowles. The *N*-acetyl amino acid derivatives, the products of the hydrogenation reaction, were obtained in good enantiomeric excess. Further structural modifications resulted in the development of the P-chiral DIPAMP (by Knowles),¹² the C-chiral CHIRAPHOS (by Bosnich)¹³ and the axially chiral BINAP (by Noyori),¹⁴ just to name a few pioneering examples. Since that time, the structural development of chiral phosphine ligands has been continuous, even in recent years, various new ligand structures appear in the literature and they are widely applied in asymmetric transformations, such as hydrogenation of C=C, C=N and C=O bond; C-C and C-heteroatom bond formation; hydroformylation reactions; conjugate additions and polymerization reactions, just to name a few examples.^{8a, 8b, 8d,}

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The optically active phosphine ligands can be differentiated by the nature of their chirality: a) central chirality on carbon or phosphorus atom (C- or P-chirality); b) axial chirality; c) planar chirality; d) helical chirality (Figure 3).

Figure 3. Phosphines bearing different type of chirality.

In general, phosphines with C-stereogenic center, axial- or planar-chirality are more commonly used in catalysis, compared to the P-chiral and helical phosphines, due to the relatively more challenging synthesis of the P-chiral and helical derivatives.

To obtain enantiomerically pure phosphine ligands, it is inevitable to use an external chiral source at some point of the synthesis. The more common strategies to generate chiral phosphines are: a) usage of chiral starting material; b) resolution; c) asymmetric template promoted techniques; d) asymmetric catalysis. The generation of

chiral phosphines have been excessively studied over the last few decades, thus countless amount of literature examples are available for synthesis protocols. In order to demonstrate the most significant strategies, only a few selected examples are presented herein:

a) Usage of chiral starting material:

A typical strategy to generate chiral phosphines is to start the synthesis from chiral starting materials. The chiral starting materials are traditionally obtained from the nature; however, in more recent studies, the chiral materials are commonly synthesized by asymmetric catalysis.

In the first report of the (*S,S*)-CHIRAPHOS, presented by Bosnich in 1977, the chiral diphosphine was synthesized using a chiral starting material, (*2R,3R*)-butanediol (Scheme 1).¹³ The (*2R,3R*)-butanediol, can be obtained from various biological sources, such as sugarcane molasses, sugar-beet molasses, grain mash substrates etc. by fermentation techniques using various bacteria strains.¹⁶

Scheme 1. Synthesis of (*S,S*)-CHIRAPHOS from natural chiral pool.

In the chiral pool strategy, new stereogenic centers are usually not formed during the synthesis; however, inversion of the chirality is plausible. Other classical examples for this method are the synthesis of (*R,R*)-DIOP (from *L*-tartaric acid)^{11a} and (*R*)-PROPHOS (from (*S*)-lactic acid).¹⁷

A more recent example for this strategy was reported by Stoltz et al. in 2007 (Scheme 2).¹⁸ In this study, the chiral aryl bromide starting materials were synthesized from chiral amino alcohols, which can be generated from chiral amino acids via reduction.¹⁹ The coupling reactions between the aryl halides and the secondary phosphines were catalyzed by CuI/ *N,N'*-dimethylethylenediamine catalyst system in the presence of cesium carbonate. The reaction provided direct access to chiral phosphinooxazoline (PHOX) ligands.

Scheme 2. Synthesis of PHOX type ligands by Stoltz, 2007.

b) Resolution:

For the separation of the racemic phosphines via resolution, the usage of a chiral derivatizing agent is necessary to generate diastereomers in the first step. Since the diastereomeric pairs have different physical properties (unlike enantiomer pairs), the separation of them via crystallization or chromatography is possible. After separation, the elimination of the resolving agent makes the resolution completed. Typical resolving agents are (*R*)-camphorsulfonic acid, *L*-dibenzoyltartaric acid, (*R,R*)-TADDOL and *L*-menthol, just to name a few. In 1979, Brunner and Pieronczyk reported a resolution procedure to obtain optically pure (*R,R*)- and (*S,S*)-NORPHOS, by resolving the racemate ($\pm$)-NORPHOSO using *L*-dibenzoyltartaric acid ((-)-DBT) (Scheme 3).²⁰

Scheme 3. Synthesis of (*R,R*)- and (*S,S*)-NORPHOS by resolution.

Resolution method was also applied in optically pure *P*-stereogenic phosphine synthesis,²¹ CHIRAPHOS synthesis (by resolving ($\pm$)-CHIRAPHOSO))²² and BINAP synthesis (by resolving ($\pm$)-BINAPO).²³

c) Asymmetric template promoted techniques:

Our group has been excessively studied the synthesis of chiral phosphine ligands via asymmetric template promoted methods using aza-palladacycle

complexes.²⁴ Among these strategies, the cycloaddition reactions were found to be excellent synthetic protocols to obtain optically pure chiral phosphines (Scheme 4).

Scheme 4. Chiral metal template promoted cycloaddition reactions.

The next milestone in this area was the discovery of asymmetric metal promoted hydrophosphination protocols. Our group established various methods in this P-H addition strategy, in which the aza-palladacycle was bearing the chiral information and the hydrophosphination reactions proceeded in an intramolecular fashion upon coordination of the reactants to the metal center. Numerous different types of substrates were used in this transformation, and among the reaction partners, one was usually the diphenylphosphine, bearing the P-H moiety for the addition reaction to occur. The other substrate typically contained unsaturated double- or triple bond, which was functioning as the acceptor in the addition. One of the earliest example of these reactions was the template promoted hydrophosphination of vinylphosphines, which protocol resulted in the formation of enantiopure (*R*)- or (*S*)-PROPHOS (Scheme 5).²⁵

Scheme 5. Chiral metal template promoted P-H addition to vinylphosphines.

In this transformation, the bischloro-azapalladacycle (**1**) was used as a chiral template. In this compound, the two bridging-chlorides develop one σ - and one coordination-bond to the palladium centers. In other words, one of the chlorides is an ‘X-type’ and the other one is an ‘L-type’ ligand. This is an important feature of this complex, because these chlorides allow only a mono-dentate ligand coordination, by the replacement of the ‘L-type’ chloride. In order to liberate the other coordination site, the strong metal-halogen bond must be broken (usually by inorganic silver salt), in order to make the second coordination site available. This replacement can be done *in situ* or in advance. If complex **1** is treated with a silver salt (e.g. silver perchlorate) in a coordinating solvent (e.g. acetonitrile), then both chlorides are converted to silver chloride precipitation which can be simply filtered out of the mixture and the product can be crystallized. In this case, the bisacetonitrile aza-palladium complex **2** is generated (Scheme 6). This complex can be directly used in metal template promoted transformations. For instance, the hydrophosphination of terminal alkynes was investigated by our group using the bisacetonitrile (*R*)-**2** complex (Scheme 7).²⁶

Scheme 6. Transformation of the chloride-dimer aza-palladacycle to bisacetonitrile complex.

Scheme 7. Chiral metal template promoted P-H addition to terminal alkynes.

Other applicable substrates for the template promoted hydrophosphination, demonstrated by us, are internal alkynes,²⁷ terminal alkynols,²⁸ activated olefins,²⁹ allylic phosphines³⁰ and functionalized allenes³¹ just to name a few selected examples. For more details on these strategies, see chapter 1.6.3.

d) Asymmetric catalysis:

Nowadays catalytic asymmetric synthesis is considered as one of the most active areas in chemical research.^{1a, 1c, 4a} In these reactions, at least one new chiral center is generated in the product with a usage of a chiral catalyst. The three main strategies are the enzyme-catalyzed reactions,³² metal-catalyzed reactions³³ and asymmetric organocatalytic transformations.³⁴ Asymmetric catalytic strategies for the generation of chiral phosphines have been widely studied over the last few decades.³⁵ In chapters 1.3, 1.4 and 1.5 selected examples are presented for asymmetric catalytic phosphine formation, focusing mostly on recent examples.

1.3 Catalytic asymmetric synthesis for C-chiral phosphine formation

In 2008, Togni reported a palladium-catalyzed enantioselective allylic phosphination of 1,3-diphenylallyl acetate (Scheme 8).³⁶ In this transformation, the racemic starting material was converted into the synthetically valuable, enantioenriched phosphine product via C*-P bond formation using Josiphos type chiral ligand. The observed enantiomeric excess was up to 96% and the isolated yield up to 92%.

Scheme 8. Chiral metal template promoted P-H addition to terminal alkynes.

In the same year, Ricci established the synthesis of chiral α -amino phosphonic acid derivatives from α -amido sulfones in an asymmetric hydrophosphonylation, in the presence of chiral cinchonindinium phase-transfer catalyst (PTC) (Scheme 9).³⁷ Acidic hydrolysis of the ester moiety and the removal of the protecting group did not cause

Scheme 9. Asymmetric hydrophosphonylation by cinchonindinium-catalyzed transformation.

any loss of the enantioselectivity. Upon hydrolysis, the hydrochloride salt of the α -amino phosphinic acid was obtained.

Shibata et al. reported in 2011 a direct enantioselective three-component Kabachnik-Fields reaction for chiral α -amino phosphinic acid synthesis (Scheme 10).³⁸ The applied catalyst system was a chiral zinc(II) complex with 1,3-bis(imidazolin-2-ly)pyridine (=pybim) type ligand scaffold. The method was applied on a broad substrate scope (over 17 examples) and the observed enantiomeric excess was good (up to $ee=93\%$). The selective removal of the *para*-methoxyphenyl group was demonstrated using equivalent amount of *N*-bromosuccinimide (NBS), followed by the acidic hydrolysis of the phosphinic ester moiety. The deprotection and the hydrolysis took place without the loss of the enantioselectivity.

Scheme 10. Asymmetric Kabachnik-Fields reaction for α -amino phosphinic acid synthesis.

In 2011, Jørgensen established an asymmetric organocatalytic protocol for electrophilic phosphination (Scheme 11).³⁹ The electrophilic activation of the phosphine chloride moiety was induced by the cinchona-type, $(DHQD)_2PYP$ organocatalyst.

Scheme 11. Asymmetric organocatalytic electrophilic phosphination.

Recently, in 2018, Dong et al. reported an enantioselective coupling protocol between dienes and phosphine oxides in a Pd-catalyzed asymmetric transformation, using Josiphos type chiral ligand, (Scheme 12).⁴⁰ The effectiveness of the synthetic method was proved by the wide substrate scope (over 25 examples presented in the study) and the high enantioselectivity (up to *ee*=96%).

Scheme 12. Enantioselective hydrophosphinylation of dienes.

In the previous examples (Scheme 8 - 12), the formation of the carbon stereogenic center took place during C*-P bond formation, when the phosphine moiety was introduced to the acceptor molecule. Another approach to obtain C-chiral phosphine ligands is the generation of the carbon stereogenic center in the asymmetric catalytic reaction, without new C-P bond formation. In this strategy, the phosphine fragment is already a part of the starting material and the substrate has a reactive unit (typically an unsaturated bond), where the formation of the new stereogenic center can occur. In this discussion, only one type of these methods is presented by selected examples, the hydrogenation strategy (Scheme 13). In 2001, Genet reported the asymmetric hydrogenation of α -aryl substituted ethenylphosphonic acids and diesters using a Ru(II)-BINAP catalyst system.⁴¹ The generated 1-arylethylphosphonates were obtained with moderate enantioselectivity (up to *ee*=74%). Zheng reported in 2009 the synthesis of a new class of ferrocene-based chiral ligands, containing imidazole ring in the structure.⁴² The generated (*R,S*)-ImiFerroPhos ligands were successfully applied in a Rh-catalyzed hydrogenation protocol to obtain 3-phosphono-2-arylmethylpropanoic acid derivatives with good enantioselectivity (up to *ee*=98%). Ding established in 2014 a Rh-catalyzed strategy to generate chiral α -aryl and α -alkyl ethylphosphonic acids with excellent enantioselectivity (*ee*>99%) in the presence of triethylamine base⁴³ and a few years later, Zhang reported a base-free method through noncovalent ion-pair interaction between the substrate and the catalyst.⁴⁴

Scheme 13. Asymmetric hydrogenation strategy to generate C-chiral phosphines.

Besides these synthetic methods presented above, various other asymmetric catalytic protocols have been established for C-chiral phosphine synthesis. The asymmetric P-H addition of diaryl phosphites, dialkyl phosphites and secondary phosphine oxides to unsaturated C=C and C=N bonds, are one of the most significant approaches. In most of the cases, the double bond is activated by an electron-withdrawing group (=EWG) and the chiral information is induced by a chiral organocatalyst or complex. The reaction occurs via a C*-P bond formation process. Selected examples of this synthesis strategy are presented herein.

In 2007, Wang reported an asymmetric catalytic P-H addition of diphenyl phosphites to nitroalkenes, catalyzed by cinchona alkaloid (Scheme 14).⁴⁵ In this transformation, the β -nitrophosphate products were obtained with good to high enantiomeric excesses ($ee=45\%$ to $ee=88\%$). Hydrolysis of the ester function and reduction of the nitro-moiety resulted in the formation of β -aminophosphonic acid

derivatives. In the same year, Terada reported the syntheses of axially chiral guanidine organocatalysts, which were applied in the same P-H addition reaction, reported by Wang.⁴⁶ The observed enantioselectivity improved significantly with the new catalyst system (*ee*=80% to *ee*=97%).

Reported by	Year	EWG	R ^a	R' ^a	best <i>ee</i> ^b	best yield	catalyst
Wang	2007		aryl (12) alkyl (4)	OPh	88%	88%	
Terada	2007		aryl (8) alkyl (3)	OPh	97%	98%	
Tan	2007		aryl (9)	aryl (6)	96% (>99%)	99%	
Namboothiri	2008		aryl (6)	OEt OMe OPh	>99%	74%	
Wang	2009		aryl (14) alkyl (6)	OAlkyl (4) OPh	88%	88%	Et ₂ Zn +
Wang	2010		aryl (14) alkyl (4)	Alkyl (4)	99%	99%	Me ₂ Zn +
Ishihara	2013	 	aryl (6) Cy aryl (9)	aryl (3) OMe OEt	96% 86% (>99%)	93% 96%	Bu ₂ Mg +

^aThe numbers in parentheses represent the number of examples presented in the original article. ^bThe values in parentheses represent the obtained *ee* after a single recrystallization.

Scheme 14. Selected P-H addition strategies to C=C bond using phosphites and phosphine oxides.

In 2007, Tan reported the P-H addition of diaryl phosphine oxides to nitroalkenes, catalyzed by a guanidine-based organocatalyst.⁴⁷ The generated chiral β -nitrophosphine oxides were converted to β -aminophosphine oxides by reduction, which could be further transformed to β -aminophosphines. Further improvement on these types of reactions was achieved by Namboothiri, in 2008, who extended the substrate scope by using dialkyl phosphites in the P-H addition to nitroalkenes.⁴⁸ In this study, an axially chiral heterobimetallic Al-Li complex was used as a catalyst. The above-mentioned synthetic protocols were one of the first approaches in enantioselective catalytic P-H addition strategies. Other extension of this methodology includes the modification of the alkene substrate. Wang investigated the P-H addition to *N*-acylpyrroles using phosphites⁴⁹ and dialkyl phosphine oxides,⁵⁰ catalyzed by a dinuclear zinc catalyst. Ishihara applied esters and ketones as substrates in the P-H addition with diaryl phosphine oxides and dialkyl phosphites, respectively.⁵¹ The transformation was catalysed by a chiral magnesium(II) binaphtholate aqua complex.

The P-H addition of phosphites and phosphine oxides was established not only to C=C unsaturated bonds, but also to C=N fragments. Jacobsen reported in 2004 an asymmetric hydrophosphonylation of *N*-benzyl imines using diphenyl- and dialkyl phosphites (Scheme 15).⁵² The chiral thiourea catalyst applied in the reaction provided excellent enantioselectivity (up to *ee*=99%). Hydrolysis of the phosphinic ester moiety and reduction of the imine fragment resulted in the formation of enantioenriched α -amino phosphonic acids. In the next year, 2005, Akiyama used a cyclic phosphoric acid derivative as a catalyst, synthesized from (*R*)-BINOL, in the P-H addition of dialkyl phosphites to *N*-substituted imines.⁵³ The aldimine type substrates derived from cinnamaldehyde analogues provided high enantioselectivity in the transformation (up to *ee*=90%). In 2009, chiral guanidinium salt was employed as a chiral catalyst by Tan in the reaction between diaryl phosphine oxides and *N*-tosylated imines.⁵⁴ The observed enantioselectivity was high (up to *ee*=92%). In this report, the P-H addition of *H*-phosphinates, HP(O)(OBn)(Alk) (=alkyl benzylphosphinates), to imines was also investigated. The reaction proceeded with good diastereoselectivity (up to *dr*=16:1) and good enantioselectivity of the major isomer (up to *ee*=94%). In the same year, 2009, Wang applied a dinuclear zinc catalyst, in the addition reaction of diethyl phosphite to *N*-acylimines.⁵⁰ The obtained enantioselectivity was excellent (up to *ee*>99%) and they

successfully demonstrated that the generated products can be easily converted to enantiopure α -amino phosphinic acid derivatives.

Reported by	Year	Substrates: ^a	R ^a	best ee	best yield	catalyst
Jacobsen	2004	 R'=aryl (13), alkyl (4)	OPh OAlkyl (6)	99%	93%	
Akiyama	2005	 R'=aryl (8)	OEt OPr	90%	97%	
Tan	2009	 R'=aryl (5), alkyl (2)	aryl (3)	92%	98%	
Wang	2009	 R'=aryl (10), Cy	OEt	>99%	91%	Et ₂ Zn +

^aThe numbers in parentheses represent the number of examples presented in the original article.

Scheme 15. Selected P-H addition strategies to C=N bond using phosphites and phosphine oxides.

To sum it up, various techniques were developed for C-chiral phosphine ligand synthesis by asymmetric catalysis over the past decades. The importance of the chiral phosphines keeps this research area active and the demand for developing new strategies is always present. Nowadays an efficient and elegant method for C-chiral phosphine synthesis is the asymmetric P-H addition of secondary phosphines (HPR₂) to unsaturated double bonds in metal-catalyzed pathways. This technique is discussed in more details in chapter 1.6.3.

1.4 Catalytic asymmetric synthesis for P-chiral phosphine formation

In general, chiral phosphines bearing central, planar or axial chirality are more commonly employed in synthetic chemistry, compared to the P-stereogenic counterparts, despite the effectiveness of the latter in asymmetric syntheses. The reason is the relatively few effective synthetic strategies for the generation of P-chiral phosphines; although, several promising methodologies were established in recent years, in which the P-chiral phosphines were generated in asymmetric catalytic protocol. Herein, selected examples are presented among these methodologies.

One of the most significant transformations in this field are the asymmetric catalytic cross-coupling reactions. In 2002, Glueck reported the first asymmetric cross-coupling between a racemic secondary phosphine (HP(Me)(Is), Is= 2,4,6-ⁱPr)₃C₆H₂) and aryl halides (PhI, PhBr) and triflate (PhOTf), catalyzed by a Pd-((*R,R*)-Me-Duphos)(Ph)(I) system (Scheme 16).⁵⁵ The highest enantiomeric excess they achieved in this study was 78%. A few years later, the same group reported a broadened substrate scope, mechanistic and kinetic investigations of the transformation.⁵⁶ They achieved up to 88% enantiomeric excess and 91% diastereomeric excess (with HP(Me)(Menthyl) substrate).

Scheme 16. Asymmetric cross-coupling by Glueck.

In 2004, Helmchen developed an asymmetric C-P coupling between *ortho*-substituted aryl iodides and racemic secondary diarylphosphines (Scheme 17).⁵⁷ In this study, the Pd-(*R,R*)-Et-FerroTANE catalyst system was used, which was generated *in situ* from Pd₂(dba)₃, LiBr and the ferrocene based (*R,R*)-Et-FerroTANE phosphine ligand. Various substrates were investigated in the transformation and the best enantiomeric excess (*ee*=93%) was achieved in the cross-coupling between HP(Ph)(2-CF₃C₆H₄) and 2-CO₂^tBuC₄H₄I.

Scheme 17. Asymmetric cross-coupling by Helmchen.

In 2007, Toste reported an asymmetric arylation procedure of racemic silylphosphines in a Pd-catalyzed cross-coupling reaction with iodoarenes (Scheme 18).⁵⁸ Wide substrate scope was established with excellent enantiomer excess (up to *ee*=98%). For the transformation, (*R,R*)-Et-FerroTANE ligand was applied in the presence of *N,N'*-dimethylpropylene urea (=DMPU).

Scheme 18. Asymmetric cross-coupling by Toste.

Toste and his group also established (in 2006 and further investigated in 2009) a three-component, Ru(II)-catalyzed phosphine alkylation procedure, using racemic secondary phosphines as starting materials (Scheme 19).⁵⁹

Scheme 19. Asymmetric alkylation by Toste.

In this comprehensive study, various ligands were selected after the optimization procedure for different type of substrates. This study includes not only the generation of P-stereogenic monodentate phosphine boranes, but also the formation of bidentate diphosphine boranes.

In 2006, Glueck presented a Pt-catalyzed asymmetric alkylation of racemic secondary phosphines using benzyl halides (Scheme 20).⁶⁰ The (*R,R*)-Me-Duphos diphosphine was applied as the ligand in the synthesis and sodium trimethylsilanolate (=NaOSiMe₃) was used as base. Both mono- and bidentate phosphines were generated.

Scheme 20. Asymmetric alkylation by Glueck.

In recent years, C-H activation became one of the most powerful strategies in synthetic chemistry.⁶¹ This useful synthetic tool was also applied for P-stereogenic phosphine formation via desymmetrization protocol. In 2015, Duan described an intramolecular C-H arylation catalyzed by palladium (Scheme 21).⁶² The P-stereogenic cyclic phosphinic amides were obtained in good (up to *ee*=93%) enantioselectivity. The applied chiral ligand was a TADDOL-based *N*-Et phosphoramidite ligand in the desymmetrization.

Scheme 21. P-stereogenic phosphinic amide synthesis via C-H activation by Duan.

In the same year, Han established an intermolecular C-H activation using arylboronic acid pinacol esters for P-stereogenic phosphinic amide formation catalyzed by palladium (Scheme 22).⁶³ In this transformation, N-protected chiral amino acid

derivative was used as ligand, Ag_2CO_3 as oxidant, benzoquinone (=BQ) as additive and Li_2CO_3 as base. The desymmetrization procedure provided the P-chiral phosphinic amides with excellent enantioselectivity.

Scheme 22. P-stereogenic phosphinic amide synthesis via C-H activation by Han.

Cramer disclosed recently, in 2017, a highly enantioselective desymmetric C-H bond activation process for cyclic phosphinic amide generation (Scheme 23).⁶⁴ The reaction was catalyzed by a Rh(III) catalyst system bearing axially chiral cyclopentadienyl ligand, Ag_2CO_3 was used as oxidant, K_2CO_3 as base and catalytic amount of dibenzoylperoxide ($=(\text{PhCO}_2)_2$) was also applied.

Scheme 23. P-stereogenic cyclic phosphinic amide synthesis via C-H activation by Cramer.

In 2016, Chi et al. reported a N-heterocyclic carbene(=NHC)-catalyzed asymmetric desymmetrization protocol of bisphenols for the formation of P-stereogenic diaryl phosphinates, phosphine amides and triarylphosphine oxides (Scheme 24).⁶⁵ During the organocatalytic reaction, the formation of a new carboxylic ester occurred on one of the aromatic rings in the transformation between an aldehyde and a phenol hydroxyl group. The P-chiral compounds were obtained with excellent enantioselectivity (up to $ee=98\%$). The reaction was also examined in bigger scale (15 mmol), with lower catalyst loading (1 mol%) and the desired phosphinate was observed still with good enantiomeric excess ($ee=88\%$, after single recrystallization: $ee=94\%$) and high yield (95%, after single recrystallization: 80%). Derivatization of

the monophosphinate resulted in the formation of a chiral bidentate Lewis base, which was successfully applied as a catalyst in asymmetric reactions of enones and aldehydes.

Scheme 24. NHC-catalyzed desymmetrization of bisphenols by Chi.

A few years later, in 2019, Cheng disclosed a desymmetrization strategy via asymmetric allylic alkylation (=AAA) of bisphenols, catalyzed by a cinchona-type organocatalyst, (DHQ)₂PHAL (Scheme 25).⁶⁶ The AAA took place on one of the bisphenol rings and the phosphine oxide products were observed with high enantiomeric excesses (up to *ee*=97%). Large scale reaction (1 mmol scale), theoretical studies to determine the transition states of the desymmetrization, derivatization to bidentate Lewis base and catalytic application of the generated product were disclosed in this study.

Scheme 25. Cinchona-catalyzed desymmetrization of bisphenols by Cheng.

All the above-mentioned desymmetrization techniques are considered as exceptional synthetic strategies for P-stereogenic phosphine formation via asymmetric catalysis. The next milestone in this area was achieved by Trost, who reported a novel desymmetrization method of phosphinic acid analogues in 2019 (Scheme 26). While the previous desymmetrizations occurred by selective functionalization of one of the two identical carbon sidechains, Trost achieved to selectively alkylate one of the two enantiotopic oxygen atoms of the carboxylate moiety. The importance of this change is, that this strategy allows to install two different carbon sidechains onto the starting

materials, thus the structural diversity of the generated phosphinates is even broader. Large scale reaction, derivatization and broad substrate scope was reported with high enantiomeric excesses in this publication (up to $ee=99\%$).

Scheme 26. Desymmetrization of phosphinic acids by Trost.

A unique approach to generate P-stereogenic compounds by molybdenum-catalyzed asymmetric ring-closing metathesis was reported by Hoveyda and Gouverneur in 2009 (Scheme 27).⁶⁷ The asymmetric olefin metathesis of phosphine oxides and phosphinates resulted in the generation of enantioenriched five-, six- and seven-membered phosphorus-heterocycles (over 10 examples) with good to excellent enantiomeric excesses (up to $ee=98\%$). The choice of the applied molybdenum catalyst was crucial, for different substrates, usually different catalysts demonstrated better performance.

Scheme 27. Asymmetric ring-closing metathesis by Hoveyda and Gouverneur.

In 2016, Gaunt disclosed the asymmetric arylation of racemic secondary phosphine oxides using diaryliodonium salts in a Cu-catalyzed transformation (Scheme 28).⁶⁸ The chiral induction was controlled by a pyridinebisoxazoline (=pybox) type ligand, which provided excellent enantioselectivity (up to $ee=98\%$). Exceptionally broad substrate scope (over 36 examples) was presented in this study.

Scheme 28. Asymmetric arylation of secondary phosphine oxides by Gaunt.

Recently, in 2019, Zhang reported the first example of a Ni-catalyzed asymmetric allylation of secondary phosphines (Scheme 29).⁶⁹ Various substrates were tested in the transformation and high enantiomeric excess was achieved (up to *ee*=95%). The (2*S*,4*S*)-2,4-bis(diphenylphosphino)pentane (=(*S,S*)-BDPP), a CHIRAPHOS analogue, was used as the chiral ligand. Kinetic studies revealed the role of the base in the transformation. When K₃PO₄ was applied in the reaction, kinetic resolution (=KR) was observed; however, in case of KOAc, dynamic kinetic asymmetric transformation (=DYKAT) took place. The kinetic study was conducted by recording the conversion values, the *ee*'s of the remaining starting materials and that of the produced products after every hour during the whole transformation (overall 14 hours). The observed enantiomeric excess of the generated product was approximately constant in case of KOAc during the whole transformation (*ee*>90%). In contrast, if K₃PO₄ was applied, high *ee* values (*ee*>80%) could be recorded only in the beginning of the reaction (first three hours), which was continuously decreasing during the whole transformation until *ee*<20% by 14 hours reaction time.

Scheme 29. Asymmetric allylation of secondary phosphine oxides by Zhang.

1.5 Catalytic asymmetric synthesis for axial phosphine ligand formation

While recently various asymmetric catalytic strategies have been reported in C- and P-chiral phosphine ligand syntheses, the formation of axially chiral phosphine

analogues by catalysis seems exceptionally challenging and scarce in the literature. Among the few successful methodologies, the first example of enantioselective QUINAP formation via a Pd-catalyzed kinetic- and dynamic kinetic resolution was reported by Stoltz and Virgil, in 2013 (Scheme 30).⁷⁰ In their study, they performed the syntheses starting from the racemic mixture of 1-(2-bromonaphthalen-1-yl) isoquinoline, which reacted with secondary diarylphosphines. In the kinetic resolution (=KR), the applied ligand was a ferrocene-based diphosphine, (*S,S*)-Me-Ferrocene; *N,N*-Diisopropylethylamine (=DIPEA) was used as base and tetra-*n*-butylammonium bisulfate (=tBu₄NHSO₄) as additive.

Kinetic resolution (KR):

Cross-coupling of enantioenriched aryl bromide:

Dynamic kinetic resolution (DKR):

ligand:

Scheme 30. QUINAP synthesis via dynamic kinetic resolution by Stoltz and Virgil.

During the KR, the (*S*)-enantiomer of the racemic aryl bromide mixture reacted with higher reaction rate, thus the (*S*)-QUINAP analogues were obtained in enantioenriched form (up to *ee*=95%). At the same time, the unreacted (*R*)-aryl bromide was recovered with high enantioselectivity (up to *ee*=96%). Despite it could be performed even in gram scale, the drawback of the KR was the maximum 50% theoretical yield. In order to enhance the effectivity of this strategy, the recovered (*R*)-aryl bromide was used in Pd-catalyzed cross-coupling in the generation of enantioenriched (*R*)-QUINAP. Interestingly, when the achiral 1,1'-Bis(dicyclohexylphosphino)ferrocene (=dcypf) ligand, or the racemic BINAP was applied in the cross-coupling, the enantiomeric excess dropped drastically (*ee*=32% and *ee*=80% respectively). To achieve higher selectivity, the chiral (*S,S*)-Me-Ferrocene ligand was required to use for the transformation. In order to further improve the effectivity of this synthetic strategy, careful investigation of a possible dynamic kinetic resolution (DKR) was performed. The aim was to find a condition, which caused the racemization of the aryl bromide (or any intermediates), but did not racemize the produced QUINAP. After screening of various catalysts and conditions, it was found that using aryl triflate for the reaction in the presence of (*R,S*)-JOSIPHOS ligand and with the slow addition of the secondary phosphine (over 4 hours), the DKR was possible. The enantioselectivity observed in DKR was good (*ee*=90%) and the yield was 86%. While the substrate scope was still limited in this study, it was the first example of the synthesis of axially chiral phosphine ligands in an asymmetric catalytic synthesis scenario.

Just a few years later, in 2016, Gómez-Bengoa and Lassaletta published a procedure, in which QUINAP analogues were synthesized in a dynamic kinetic C-P cross-coupling reaction catalyzed by a Pd/ Josiphos system (Scheme 31).⁷¹ In this strategy, a broader substrate scope (over 16 examples) was established including QUINAP, PINAP, PyPHOS and QUINAZOLINAP type phosphine products with good to excellent enantioselectivity (up to *ee*=95%). Theoretical calculations supported the dynamic kinetic asymmetric transformation (DYKAT) pathway.

Scheme 31. QUINAP synthesis via dynamic kinetic resolution by Stoltz and Virgil.

The research field of generating axially chiral phosphine ligands via asymmetric catalysis is still unexplored and there is a demand to develop further synthetic strategies to obtain these valuable phosphine ligands.

1.6 Palladacycles

Palladacycle complexes with bidentate or tridentate ligand scaffolds were found to be one of the most effective promoters in phosphine ligand synthesis over the past decades.⁷² Our group has been established various strategies of chiral phosphine ligand syntheses using aza- and phospha-palladacycles, bearing C(sp²)-N and C(sp²)-P type bidentate ligands, and pincer complexes, incorporating E-C(sp²)-E and E-C(sp³)-E type tridentate scaffolds. Bidentate C(sp²)-E type palladacycles contain a C(sp²)-Pd-E core structure in the molecule, in which an anionic carbon and a donor atom (E=N, P, As, S, O etc.) is coordinated to the metal center (Figure 4). In the E-C-E type palladium pincer complexes, the central carbon of the tridentate ligand (the ‘anchor’ of the pincer structure) can be either an aromatic sp²- or an aliphatic sp³-hybridized carbon.

Figure 4. General structures of C(sp²)-E and E-C-E palladacycles.

The two ‘arm’ sites of the tridentate framework are connected to the metal via coordination of E type donor atoms. If the two arms are identical, the pincer complex

is symmetrical, in contrast, unsymmetrical pincer complexes have different type of arms attached to the metal center. In this chapter, a brief introduction of these complexes is presented, including the historical development and catalytic application in chiral phosphine synthesis.

1.6.1 Bidentate C(sp²)-E type palladacycles

Since their discoveries in the middle of the 1960's, C(sp²)-E type palladacycles became one of the most influential organometallic species for various synthetic applications.⁷³ They were recognized as crucial intermediates in organic syntheses,⁷⁴ and shortly, the catalytic application of bidentate palladacycles were established in C-C cross-coupling reactions.^{73c, 75} The asymmetric catalytic properties of the C(sp²)-E palladacycles were widely investigated in asymmetric sigmatropic rearrangements⁷⁶ (including our work in this area).⁷⁷ Our group also made a significant contribution in utilizing palladacycles as chiral templates in stoichiometric Diels-Alder reactions for chiral phosphine generation^{24a, 78} and the chiral template-promoted asymmetric hydrophosphination was also thoroughly investigated by us.^{24b, 25-28, 79} Moreover, since 2010, our group has been investigating the palladacycle-catalyzed asymmetric hydrophosphination for chiral phosphine ligand generation.⁸⁰ For more details of our work, see chapter 1.6.3. In addition to the synthetic applications, photoluminescence⁸¹ and anti-cancer properties⁸² of the bidentate palladacycles were also established. All these selected examples demonstrate the significance of C(sp²)-E type palladacycle compounds and encourage us to continue the investigation on these useful organometallic complexes.

Palladacycles compounds are generally synthesized by cyclometalation of the bidentate C(sp²)-E type ligand. Over the decades, various studies were performed to establish the mechanism of the metalation reaction and among these reports, the direct C-H activation approach is the most commonly discussed topic.^{73b} The simplified metalation process can be demonstrated as it starts with the coordination of the metal center to the donor atom, followed by the intramolecular C-H activation (Figure 5).^{72a, 72b} Over the years, various different pathways were proposed for the C-H cleavage;^{72b} in this discussion, the currently two most accepted approaches are presented.

Figure 5. Proposed mechanisms of cyclometalation via C-H activation.

In one pathway, the metalation process is considered similar to the typical electrophilic aromatic substitution. In the first step, the metal coordinates to the donor atom of the ligand structure, followed by the generation of a π -complex. Upon rearrangement, the arenium complex (or σ -complex) is formed. The last step of the mechanism is the proton abstraction, which leads to the final metallacycle. Another possible pathway starts with the coordination of the donor atom to the palladium, followed by the formation of a six-membered ring, via the interaction between the hydrogen of the aromatic carbon and the palladium. The next step is the development of an agostic interaction between the palladium and the C-H bond. The X-ligand dissociates from the palladium, then proton abstraction results in the formation of the metallacycle. The agostic mechanism was proposed based on theoretical calculations conducted by Davies and Macgregor in 2005.⁸³ Although, in this study only one cyclometalation process was investigated using one ligand (dimethylbenzylamine) and one palladium salt ($\text{Pd}(\text{OAc})_2$) in the calculation, the possible extension of this theory was predicted by the authors. A few years later, in 2011, Babić and co-workers found similar results in their theoretic investigations in the cyclometalation of azobenzene and PdCl_2 in dimethylformamide solvent.⁸⁴ In this case, the same agostic pathway was found to be the most favorable one compared to other possible directions. Other proposed mechanistic pathways including oxidative addition-reductive elimination, multicentered mechanism, σ -bond metathesis and intermolecular C-H activation were also proposed in the past, but the detailed presentation of these approaches are excluded from this discussion.^{72b, 73b}

Historically, the palladacycles were established in the 1960's via multiple events. The first important step was the discovery of the first metalation reaction by Dubeck and Kleinman in 1963, who reported a reaction between azobenzene and NiCp₂.⁸⁵ At this stage, the proposed structure of the obtained product contained an η^2 -type coordination mode of the N=N fragment to the nickel (Figure 6). In 1965, Cope and co-workers reported the cyclometalation between azobenzene and PdCl₂, and in this study, they proposed the C(sp²)-E type metallacycle structure (**3**) for the first time.⁸⁶ Three years later, in 1968, the same research group reported the cyclometalation of *N,N*-dimethylbenzylamine using Li₂PdCl₄.⁸⁷ The products of the metalation reactions (**3** and **4**) reported by Cope were fully characterized, including UV-VIS, IR and NMR spectroscopic measurements. The first chiral analogue of the palladacycles was reported by Otuska in 1971.⁸⁸ In this study, the generated chiral palladacycle (*S*)-**5** was applied in partial resolution of racemic tertiary phosphines for the first time. Upon coordination of the racemic monophosphine to the (*S*)-**5** dimeric palladacycle, the formation of two diastereomers, (*S,S*)-**6a** and (*S,R*)-**6b** were observed. Upon separation of the diastereomers on Florisil column chromatography, the observed diastereomeric ratio was 5.7 to 4.3, detected by ¹H NMR measurement. After treatment of the isolated complexes (**6**) with 1,2-bis(diphenylphosphino)ethane (=dppe), enantioenriched tertiary phosphines were observed. Although the separation of the produced diastereomers **6a** and **6b** was only partially selective, this study was the first example of applying a chiral palladacycle for an asymmetric synthetic protocol (resolution). The next milestone in this research area was achieved by Wild and co-workers in 1982, who reported a new palladacycle analogue, having a naphthyl ring in the ligand structure (**1**), instead of the phenyl ring in the previously reported derivatives (**3** to **5**).⁸⁹ By testing the possible application of this new complex, it was found that its performance in kinetic resolution is significantly better, compared to its predecessor. The naphthyl ring of this ligand scaffold turned out to be a crucial part of the complex and detailed investigations, conducted by our group, revealed the reason behind the improved performance. It was established by Leung and Mok, that an intramolecular steric repulsion is developed between the H₈ proton of the naphthyl ring and the methyl group located on the chiral carbon.⁹⁰ Because of this sterical interaction, the five-membered palladacycle fragment is locked into a fix conformation. Due to this stereogenic lock, the prochiral stereoprojecting groups on the donor atom (on nitrogen in complex **1** and **2**; and on the phosphorus in complex **7**) occupy fix positions in space.

Figure 6. General structures of C(sp²)-E and E-C-E palladacycles.

This is the reason, why the performance of these complexes (**1**, **2** and **7**) in asymmetric transformations are highly improved compared to the palladacycles incorporating a phenyl ring. In case of the phenyl ring-based palladacycles (**5**), the conformation of the five-membered ring can change in liquid state, thus the projecting groups (methyl moieties in complex **5**) are able to move around, causing a weaker performance in asymmetric transformations (including resolution, chiral template promoted syntheses or asymmetric catalysis). Our group investigated various types of applications of compound **1**, including asymmetric template promoted hydrophosphination,^{29, 80b, 91} hydroarsination⁹² and hydroamination.⁹³ In compound **1**, the two bridging chlorides develop different type of coordination modes to the metal center. One of the chlorides develop a strong metal-chloride σ -bond (as an X-type ligand) and the other chloride coordinates via a significantly weaker lone pair coordination (L-type ligand). In many reactions, especially hydrophosphination and hydroarsination, the coordinating trivalent phosphine or arsine is strong enough to replace the weaker L-type chloride, but the X-type chloride stays intact. Due to this nature, in compound **1** only one coordination site is available for the reactants to coordinate to the metal center (important feature in resolution and template-promoted P-H additions). The next significant structural modification of this class of palladacycles was the replacement of

the bridging chlorides to coordinating acetonitrile molecules, by the treatment of **1** with silver perchlorate in acetonitrile, to obtain the bisacetonitrile complex **2** (see Scheme 6). By this ligand exchange, two reactive coordination sites became available, due to the labile coordinating nature of the acetonitriles. This modification opened new synthetic strategies by taking advantage of the two available coordination sites in the asymmetric transformations. Our group has applied complex **2** successfully in the resolution of P,O-chelating sulfinyl phosphine⁹⁴ and sulfinyl arsine derivatives,⁹⁵ template promoted double-hydrophosphination of activated internal alkynes,²⁷ and also in asymmetric catalytic hydrophosphination of α,β -unsaturated ketones (see chapter 1.6.3 for more details).^{80a} In 2011, our group reported the synthesis of complex **7**, a new phosphapalladacycle, bearing two acetonitriles coordinated to the metal center. By comparing this structure to complex **2**, the stereochemical projecting groups on the donor atom (two phenyl rings located on the phosphorus) are much bigger than that of in **2** (two methyl groups on the nitrogen). Furthermore, changing the nitrogen donor atom to phosphorus provided different electronic characters for the complex. The enhanced steric effect and the electronic properties caused a significant improvement in the catalytic performance of **7** in asymmetric hydrophosphination reactions.^{80b, 96} Over the years, our group developed various new aza- and phosphapalladacycles and investigated their performance in chiral phosphine and arsine ligand syntheses (selected examples: Figure 7).⁹⁷

Figure 7. Palladacycles developed by our group.

1.6.2 Tridentate E-C-E type palladacycles

Pincer palladacycles complexes have been widely investigated over the last decades, since their discovery in the late 1970's.^{72c, 98} The main structural difference between pincer complexes and the C(sp²)-E compounds is the ligand backbone, the

former incorporates a tridentate ligand and the latter is generated from a bidentate ligand. Due to the robust structure, arising from the strong interaction between the metal and the tridentate ligand scaffold, pincer complexes have exceptional thermal stability. The ability to fine-tuning the metal center by simple modification of the ligand backbone makes these compounds extremely useful in synthetic chemical aspects. Over the decades, various synthetic application modes were investigated,⁹⁸⁻⁹⁹ such catalytic activity in transfer hydrogenation,¹⁰⁰ alkane dehydrogenation,¹⁰¹ coupling reactions,¹⁰² hydroamination¹⁰⁴ etc., just to name a few examples. In addition, the luminescence activity of several pincer derivatives was also established.¹⁰⁵

Pincer complexes are typically synthesized via C-H activation of the central carbon atom, which can be either sp^2 - or sp^3 -hybridized (Figure 8). Other known synthetic strategies are the step-wise lithiation-transmetalation, oxidative addition and transcyclometalation.^{72c, 98}

Figure 8. Synthetic methods of E-C-E pincer complexes.

Among these strategies, the direct C-H activation is one of the most common synthetic methods for pincer complex synthesis, as in case of the C(sp²)-E type palladacycles, and the mechanistic aspects of the C-H activation were intensely studied over the years.⁹⁹ The most commonly discussed pathways for the C-H activation process are the electrophilic substitution and the agostic interaction, similar to what was demonstrated with the C(sp²)-E complexes.⁹⁹ However, in the chemistry of pincer complexes, even more experimental evidences are available which support the agostic interaction over the electrophilic substitution. Although these complexes are extremely rare in the literature, a couple of pincer compounds containing agostic interaction were synthesized, isolated and fully characterized.¹⁰⁶ Considering all the proposed mechanisms for the C-H activation process for both of the C(sp²)-E bidentate and the E-C-E tridentate pincer compounds, it is not trivial to decide which is the exact pathway (especially in view of the difficulties in the isolation of the reactive intermediates). It may be also possible that different substrates prefer different reaction pathways; also, we need to consider if the metalation process occurs simultaneously via multiple pathways at the same time. At this stage we can only state that the two “most-likely” processes are the electrophilic substitution and the agostic interaction.

The first pincer complexes were reported by Shaw in 1976, who successfully coordinated the tridentate P-C(sp²)-P type diphosphine ligand to various transition metals, such as Ni, Pd, Pt, Rh and Ir (Figure 9).¹⁰⁷ Two years later, in 1978, van Koten reported the first N-C(sp²)-N type palladium- and platinum-pincer complexes¹⁰⁸ and one year later, in 1979, McDonald and Shaw established the first P-C(sp³)-P type aliphatic pincer complex.¹⁰⁹ The same group reported in 1980 an S-C(sp²)-S type palladium complex.¹¹⁰ After the discovery of the first examples of these organometallic species, countless number of new ligand structures were designed over the decades.^{72c,}
¹¹¹ The typical way to refer to a certain pincer complex family is to indicate what kind of donor atoms and central atom are connected to the metal center. Over the years, numerous different pincer structures were established, such as the symmetrical P-C(sp²)-P,¹⁰⁷ N-C(sp²)-N,¹⁰⁸ S-C(sp²)-S,¹¹⁰ P-O-C(sp²)-O-P,¹¹² P-N-C(sp²)-N-P,¹¹³ N-N-N,¹¹⁴ and unsymmetrical N-N-N,¹¹⁵ N-C(sp²)-P,¹¹⁶ N-N-P,¹¹⁷ P-O-C(sp²)-N,¹¹⁸ and carbene complexes,¹¹⁹ just to name a few examples (for more examples, see selected reviews^{98-99, 120} and books^{72c, 111}). The aliphatic pincer complexes are also well known in the literature;^{72c, 121} however, the synthesis of the E-C(sp³)-E type metal

complexes is significantly more difficult compared to the E-C(sp²)-E counterparts, due to several reasons.¹²¹⁻¹²² One important aspect is, the significantly more challenging C-H activation during the cyclometalation process. While the proposed electrophilic substitution mechanistic route for C-H activation includes the pre-coordination of the aromatic π -system to the metal center, such interaction cannot occur in the case of the C(sp³)-H bond activation.^{73b} Another aspect is that although the C(sp²)-H bond is relatively stronger than the C(sp³)-H bond (which implies easier C(sp³)-H bond activation), the generated C(sp²)-M bond is much more stable compared to the C(sp³)-M bond.¹²³ In recent years, our group became interested in the development of optically active E-C(sp²)-E aromatic and E-C(sp³)-E aliphatic pincer complexes and their possible application in metal-catalyzed asymmetric transformations. For selected pincer compounds, established by us, see Figure 9.

First examples of pincer complexes:

Pincer complexes developed by our group:

Figure 9. First pincer complexes in the history and recent compounds developed by our group.

1.6.3 Application of C(sp²)-E and E-C-E palladacycles in chiral phosphine syntheses.

Our group has been excessively studying the application of chiral C(sp²)-E and E-C-E palladacycles in asymmetric synthesis scenarios for chiral phosphine ligand generation. The most studied procedures investigated by us include resolution (a), chiral template promoted cycloadditions (b), template promoted hydrophosphination of unsaturated double and triple bonds (c) and asymmetric catalysis (d).

a) Resolution:

The C(sp²)-E type palladacycles are generally known to be excellent resolving agents for optically active phosphine and arsine ligand generation.¹²⁴ The resolution starts by the coordination of the racemic phosphine to the chiral metal template which leads to the formation of diastereomers. Since the physical properties of the diastereomers are different, they can be separated from each other by column chromatography or crystallization. After separation, the optically active phosphine ligand can be obtained by the removal of the ligand from the metal template (by using a better coordinating agent, such as dppe, or by chemical reactions, such as treatment with hydrochloric acid, followed by the reaction with potassium cyanide). For the general scheme of the resolution process with metal templates, see Figure 6, Otsuka's work. In 1999, our group reported the resolution of a heterocyclic diphospholene by using (*S*)-**1** as a chiral template (Figure 10).¹²⁵ Upon coordination of the racemic diphosphine to the template and separation of the diastereomers, the liberation of the optically active P-stereogenic diphosphine took place via two steps. Firstly, the compound was treated with hydrochloric acid to generate a dichloro-palladium phosphine complex by removal of the chiral naphthyl ethylamine auxiliary. In the next step, the Cl₂Pd fragment was removed by potassium cyanide to obtain the optically pure P-stereogenic diphosphine. Other selected synthetic examples developed by us include the resolution of methylsulfinyl phosphines⁹⁴⁻⁹⁵ and naphthyl ethyl phosphine.¹²⁶

b) Chiral template promoted cycloadditions:

The asymmetric Diels-Alder addition promoted by a chiral metal template is one of the most elegant synthetic methods to generate optically active mono- and diphosphines bearing a chiral six-membered ring.

Figure 10. Resolution of a heterocyclic diphospholene by our group.

In our procedures, one of the most commonly applied starting materials was the 3,4-dimethyl-1-phenylphosphole (DMPP), a cyclic diene, which cannot go under any addition reaction itself, without coordination to a transition metal ion. Upon activation of DMPP to the chiral metal template, it could react with numerous substrates^{78c, 127} in the cycloaddition reaction. In the first step of the cycloaddition, the DMPP coordinated to the palladium at the *trans* position to the N-donor atom and the perchlorate anion was connected to the metal center *cis* to the nitrogen (Figure 11). The reason behind this fixed arrangement is because the aromatic carbon has a strong π -accepting character, thus a significant backdonation takes place from the d orbitals of the metal. Due to this interaction, the coordination site *trans* to the aromatic carbon (or in other words, *cis* to the nitrogen) is less favorable for the coordinating monodentate ligands, because the d orbitals are less available for another backdonation. Thus, in the complex, the coordinating perchlorate anion develops a highly labile coordination bond to the metal center. This substituent can be easily replaced by the reaction partner dienophiles, bearing an electron-rich functionality. Upon coordination of the dienophile, an intramolecular reaction takes place to generate the chelating E,P-complex.

Figure 11. Chiral template promoted asymmetric cycloadditions developed by our group.

The removal of the chiral template can be done by adding dppe to the reaction mixture, which results in the stereoselective formation of the chiral *exo* product. Interestingly, if the starting complex contains a chloride ligand *trans* to the aromatic carbon, the reaction outcome is entirely different. In this case, the coordinating abilities of the reaction partner dienophiles are generally not strong enough to replace the chloride ligand, due to the stable M-Cl bond. In this case, an intermolecular reaction takes place, which leads to the formation of two stereoisomeric *endo*-adducts, coordinated to the metal center in a monodentate fashion. Unfortunately, the diastereoselectivity of the intermolecular cycloaddition is not as good compared to the intramolecular version. The reason is the rotatable Pd-P bond, the only connection between the chiral template and the DMPP. However, the generated diastereomers can be easily separated from each other by column chromatography or crystallization. The intermolecular addition provides the formation of the *endo* phosphine products exclusively.

c) Template promoted hydrophosphination of unsaturated double and triple bonds:

In terms of atom economy and synthetic value, the P-H addition to unsaturated bonds has an immense significance in chiral phosphine synthesis. Our group has successfully developed numerous synthetic protocols to generate chiral phosphine ligands via asymmetric template promoted hydrophosphination. In these reactions, the metal-template was utilized in stoichiometric amount (just as we have seen it in the

asymmetric cycloaddition reactions). In the first step of the transformation, the unsaturated substrate and the diphenylphosphine coordinated to the two available coordination sites of the palladium center, then the template promoted hydrophosphination occurred. Due to the newly formed chiral center on the chelating E,E'-type ligand, regioisomers were generated in the reaction mixture, which could be separated from each other by column chromatography or crystallization. Upon separation, the chiral C(sp²)-E auxiliary was removed by treatment of the optically pure complex with hydrochloride acid. In the last step, potassium cyanide was utilized to liberate the enantiopure chiral phosphine ligand. The methodology was successfully extended for terminal and internal triple-bonds (Scheme 32),²⁶⁻²⁷ allenes (Scheme 33)³¹ and double-bonds (Scheme 34).^{28-30, 79a, 91a, 128}

Scheme 32. Chiral template promoted asymmetric P-H addition to triple bonds.

Scheme 33. Chiral template promoted asymmetric P-H addition to allenes.

Scheme 34. Chiral template promoted asymmetric P-H addition to double bonds.

d) Asymmetric catalysis:

In spite of the success of the above-mentioned procedures, there is still a demand to further improve our chiral phosphine ligand synthesis strategies. Due to the highly atom economic nature of the P-H addition to unsaturated bonds, it was essential to examine any possible improvement of this transformation. One of the most influential discoveries in this research field was the first asymmetric catalytic hydrophosphination of activated double-bonds. This method was a huge improvement over the previously established template promoted methodologies, because the amount of metal source used in the transformation could be reduced from stoichiometric to catalytic amount. The palladium-catalyzed asymmetric hydrophosphination of α,β -unsaturated ketones (the first asymmetric catalytic pathway) was established in 2010, by Leung^{80a} and Duan,¹²⁹ independently (Scheme 35). In our study, the asymmetric P-H addition was catalyzed by the C(sp²)-N type bidentate palladacycle **2** and Duan utilized a P-C(sp²)-P type pincer complex. After the first report, several attempts were made by our group to improve the enantioselectivity and the reaction rate in the transformation. Two years later, it turned out that phospho-palladacycle **7** is a significantly more effective catalyst in this reaction, compared to the C(sp²)-N ancestor (**2**).

Scheme 35. Asymmetric hydrophosphination of enones.

The maximum enantiomeric excess achieved with compound **2** was 86% and the reaction time was between 23 hours and 7 days to obtain full conversion. In contrast, by using complex **7**, the observed *ee*'s were between 92% and 99% in 20 examples and full conversion was achieved between 2 and 40 hours in every case. One of the reasons behind the better selectivity achieved with the phosphapalladacycle (**7**) is probably the sterically more demanding projecting groups connected to the phosphorus donor atom in the C(sp²)-P ligand structure. The higher reaction rate can be explained by analyzing the mechanism of the transformation. In the proposed catalytic cycle, the first step is the coordination of the diphenylphosphine and the ketone substrate to the metal center. Upon deprotonation of the secondary phosphine, a phosphido intermediate is formed, which can attack the activated carbon at the 1,4-position on the ketone substrate. After the intramolecular attack, intermediate **A** or **B** is generated (depending on the applied catalyst). By examination of these structures, it can be seen that the P,O-chelation in intermediate **A** is much more stronger compared to that of in **B**, due to the different donor atoms (nitrogen vs. phosphorus) in the chiral complex. In compound **B**, the

P-Pd-P interaction is much weaker, compared to the N-Pd-P interaction in **A**. The reason is the strong backdonation from the palladium to the phosphorus atom of the C(sp²)-P bidentate ligand, which makes the palladium's d orbitals less available for a second backdonation towards to the phosphorus of the P,O-ligand structure. Due to the lack of this π -backdonation to the coordinating phosphorus, the product elimination is much faster in case of intermediate **B** compared to **A**.

In 2011, our group reported an asymmetric catalytic protocol to generate enantiopure tridentate phosphine ligands and the cyclometalation process established a novel and effective way to generate P-C(sp²)-P type pincer complexes.^{96a} A few years later, in 2015, the extension of the substrate scope in the metalation process was investigated by our group and the generation of complex **18** was established.¹³⁰ The catalytic performance of **18** was tested in the hydrophosphination of α,β -unsaturated diester substrates and a possible intermolecular mechanism was proposed for the hydrophosphination process (Scheme 36). Although the obtained selectivity was low, these results implied for us to do more investigations on the pincer-catalyzed hydrophosphination reactions.

Scheme 36. Asymmetric hydrophosphination of diester substrates catalyzed by **(R,R)-7**.

Further investigations in the asymmetric hydrophosphination of $\alpha,\beta,\gamma,\delta$ -unsaturated dimalonates revealed that the two different palladacycle catalysts, the bidentate **(R)-7**

and (*R,R*)-**18** pincer complex, induce the formation of two different products, the 1,4-adduct (**23**) and the 1,6-adduct (**24**) respectively (Scheme 37).^{130b} The reason behind the different regioselectivity must be based on the difference of the mechanistic pathways of the catalysts. According to our investigations, the intramolecular attack (in case of (*R*)-**7**) prefers the 1,4-addition during the catalysis and the intermolecular attack (in case of (*R,R*)-**18**) results in the formation of the 1,6 adduct.

Scheme 37. Asymmetric hydrophosphination of $\alpha,\beta,\gamma,\delta$ -unsaturated dimalonate.

Utilizing the C(sp²)-E and pincer catalysts, numerous substrates were tested by us in the asymmetric hydrophosphination protocol (Scheme 38).^{96a, 130b, 131}

Scheme 38. Extension of the asymmetric hydrophosphination developed by us.

In 2016, our group developed a synthetic procedure to generate unsymmetrical N-C(sp³)-E type pincer complexes (**17**) via asymmetric hydrophosphination followed by cyclometalation (Scheme 39).¹³² The newly synthesized compounds had two chiral centers, one is located on the sp³ hybridized aliphatic carbon, connected directly to the metal center, and the other one is just beside it.

Scheme 39. Synthesis of N-C(sp³)-E pincer complexes.

With this compound, our group started to investigate the chemistry of the E-C(sp³)-E aliphatic pincer complexes. The aliphatic carbon connected to the palladium provides entirely different electronic characteristics to the metal center. In contrast to the sp² hybridized aromatic pincers, the aliphatic derivatives are in the lack of π -accepting properties, due to the sp³ hybridized state. Because of this, the electronic density around the metal center is relatively much higher, compared to the aromatic analogues. Another important characteristic is the stereogenic center which is connected directly to the palladium. For certain applications, especially for asymmetric syntheses, it may be beneficial that the chiral center is located in close proximity to the metal center. In the same report, not only the synthesis but also the application of the new aliphatic complexes was disclosed. Compounds **17a** and **17b** were found to be efficient catalysts in the asymmetric hydrophosphination of enone **25**, the same starting material, which was also used for the complex generation. The maximum selectivity achieved using **17a** complex as catalyst was *ee*=96%.

Later, other N-C(sp³)-E derivatives were also established by our group, including bimetallic species **19**, **20** and **21** (see Figure 9).¹³³ The bimetallic N-C(sp³)-E complexes were tested as chiral catalysts in the hydrophosphination of enone **22** (see Scheme 37). Although enantioselectivity was not achieved in this case, the catalysts

provided excellent regioselectivity (up to $dr=0 : 100$ for the generation of the 1,6-adduct (**24**)).

Recently, in 2014, a new type of P-H addition was established in our group, in which racemic diarylphosphines reacted with substituted benzoquinones to generate enantioenriched P-chiral phosphine products incorporating P*-O bond formation (Scheme 40).¹³⁴ The enantioenriched products could be easily derivatized into various P-chiral phosphorus compounds without the loss of the enantioselectivity.

Scheme 40. Asymmetric P-H addition to substituted benzoquinones.

1.7 Objectives of the present projects

Chiral phosphine ligands have enormous importance in modern synthetic technologies and over the past decades, numerous strategies have been developed for the synthesis of chiral organophosphorus compounds. Our group pioneered number of innovative strategies for chiral phosphine generation, starting from resolution of racemic mixtures, through the template promoted cycloadditions and hydrophosphinations, all the way to asymmetric catalysis. Palladacycle complexes are standing in the center of these strategies. In the present projects, the extension of the synthetic methods was in the focus.

Chapter II: Synthesis of stereoprojecting N-C(sp³)-E type Pincer Complexes.

In the second chapter, the structural extension of the N-C(sp³)-E type aliphatic pincer complexes was the main goal. New ligand scaffolds were designed to increase the stereoprojecting properties of the final complex by introducing sterically more demanding groups at the “N-arm site” of the complex. The new tridentate ligands were synthesized in Pd-catalyzed asymmetric hydrophosphination, incorporating C*-P bond formation.

Chapter III: Tandem Double Hydrophosphination of $\alpha,\beta,\gamma,\delta$ -Unsaturated Indandiones.

The aim of this research project was to investigate a novel double C-P bond formation procedure, the double hydrophosphination of $\alpha,\beta,\gamma,\delta$ -unsaturated indandiones. The selective 1,4- and selective 1,6-addition to such highly conjugated systems have been already established in the literature; however, to the best of our knowledge, there was no report on double C-P bond formation using P-H addition protocol before this study. The generated diphosphines were coordinated to chiral palladacycles, resulting in a P,O-bidentate and a P-monodentate chelation instead of the P,P-ligand coordination, which is generally expected for diphosphine motifs. Upon separation of the generated diastereomers, optically pure bimetallic complexes were synthesized, which were further derivatized. Detailed mechanistic investigations revealed the plausible mechanistic pathway of the double addition process.

Chapter IV: Palladium-Catalyzed Asymmetric P-H Addition to Electrophilic α -Diazoesters.

The objective of this project was the detailed investigation of a new asymmetric Pd-catalyzed P-H addition protocol to electrophilic α -diazoesters, which includes a N-P* bond formation. The α -diazo compounds are very well known as excellent metal carbene precursors, which includes nitrogen gas elimination from the substrate via the reactive metal carbene formation. In contrast to this well-established process, the terminal nitrogen of the diazo fragment can also act as an electrophile and it can participate in new bond formation reactions. However, the electrophilic character of the terminal nitrogen in the diazo fragment is much less explored. As we know, there is only one report in the literature, in which the electrophilic α -diazoesters were successfully applied in asymmetric catalysis in a N-C* bond formation reaction.¹³⁵ The first asymmetric Pd-catalyzed N-P* bond formation using α -diazoesters and racemic secondary diarylphosphines is disclosed in this study. The generated enantioenriched phosphinic hydrazones can be further derivatized to P-stereogenic diarylphosphinates. The mechanistic considerations of this novel transformation are also presented in this chapter.

CHAPTER II

Synthesis of Stereoprojecting N-C(sp³)-E type Pincer Complexes

2.1 Introduction

The development of palladacyclic compounds, bearing either a bidentate or a tridentate pincer ligand scaffold, has attracted interest in the last few decades, due to the extensive application of these useful organometallic complexes.^{72c, 73a, 73b, 98-99, 111, 120a, 136} Among these materials, the chiral derivatives have attracted interest since their first discovery in asymmetric synthesis scenarios. Their application in the chiral template-promoted cycloadditions and hydrofunctionalization reactions has been extensively explored over the past decade.^{27, 78c, 91b, 127d, 137} In this methodology, the metal complex is required in stoichiometric amount for the reaction. However, it allows the generation of synthetically challenging P,P- and P,N-bidentate ligands, which can develop five- or six-membered-ring chelation with the metal center, circumventing the hurdle of catalyst poisoning.^{79b, 91a, 138} Optically pure C(sp²)-E (E = electron donor atom) type palladacycle complexes can be also successfully applied in catalytic amounts for asymmetric Michael-type addition reactions,¹³⁹ including P-H addition,^{80a, 96, 131a, 131b, 131f, 131h} Hayashi-Miyaura arylboronic acid addition,¹⁴⁰ [3,3]-sigmatropic aza-Claisen rearrangement,^{76a, 76b, 76d, 77, 141} and ring-opening reactions¹⁴² just to name a few.

One of the most important features of the palladacyclic complexes is the extensive synthetic opportunities to modify the ligand backbone. This in turn allows enormous possibilities for the fine tuning of the electronic properties of the metal center as well as control of the stereochemistry around the coordination sites. Both of these factors can have a direct effect on reactivity as well as stereoselectivity when these complexes are employed in asymmetric synthesis. In the aforementioned examples, it has already been proven that each individual complex has its own structural and electronic features that lead to a unique performance in catalysis. Thus, some derivatives may be more efficient in one particular catalytic reaction, while analogues work better in another reaction. While the importance of ligand modifications is evident, in most of the cases it is quite difficult, since each alteration requires an individual, multistep ligand synthesis procedure. For instance, one of the most commonly used chiral C(sp²)-N palladacycles, the bis(μ -chloro) (1-naphthyl)dimethylamine palladacycle **1**, is relatively easy to synthesize; however, its structural modifications, reported by our group, require multistep syntheses, including the need for kinetic resolution (Figure 12).^{89, 97c, 97f, 126, 143} On the basis of these considerations, the

development of a more direct and efficient ligand synthesis for extended structural modifications is unquestionably needed for all kinds of complex families.

Figure 12. Structural modifications of C(sp²)-N type palladacycles.

The generation of achiral N-C(sp²)-E pincer palladacycles has already been established, and their catalytic activity was tested in Suzuki-Miyaura cross-coupling reactions.¹⁴⁴ The aliphatic derivatives of those pincer complexes were also reported previously with the N-C(sp³)-O pincer backbone.¹⁴⁵ However, in these early studies the catalytic activity was not explored. Our group recently reported the synthesis of chiral N-C(sp³)-E (E = O, S) type complexes, including bimetallic derivatives, and the catalytic performance was evaluated in asymmetric hydrophosphination reactions.¹³²⁻¹³³ The new compounds provided the desired chiral phosphine products with high enantioselectivities and regioselectivities. However, the structural modifications of the catalyst have not yet been investigated and the steric control around the catalytic site still can be improved by building up projecting groups at the N site of the complex (Figure 13). Our group is interested in exploring further the chemistry of the relatively less explored chiral N-C(sp³)-E pincer complexes and therefore embarked upon developing an effective and robust synthetic strategy, which also allows easy and convenient structural modifications on the ligand backbone.

Figure 13. Structural modifications of N-C(sp³)-E complexes.

In addition, varying the groups connected to the chiral carbon adjacent to the phosphorus atom may also have some influence on the catalytic performance via alteration of the conformation of the five-membered palladacyclic ring (ring A in Figure 13). It needs to be reiterated that such sterically enhanced, optically pure N-C(sp³)-E complexes have not yet been reported in the literature, nor has a relatively concise and universal synthetic strategy been found that provides easy structural modifications on this new class of complexes. Herein we report an effective and simple method for structural modification, in which the first C(sp³) stereocenter is generated in asymmetric hydrophosphination, followed by cyclometalation which creates the second stereocenter in a highly diastereoselective manner. This method allows us to generate a wide range of new, optically pure N-C(sp³)-E complexes bearing enhanced stereoprojecting units without the need for a time-consuming and often inefficient kinetic resolution step.

2.2 Results and Discussion

In order to build up the steric projection at the N-site of the N-C(sp³)-E complexes, our first attempt was to change the pyridyl group to a quinolyl ring. For this purpose, the synthesis route was initiated with an asymmetric P-H addition step onto an α,β -unsaturated enone (**28a**) bearing a quinolyl ring adjacent to the carbonyl functionality (Scheme 41). In this step, the first stereocenter is generated via an asymmetric hydrophosphination reaction, catalyzed by complex **7**. On the basis of our previous studies, complex **7** is still one of the most powerful and well-established catalysts in asymmetric hydrophosphination reactions.^{80a, 80c, 96, 131a, 131b, 131f, 131h, 146} In the following step, a diastereoselective cyclometalation leads us to the desired, optically active final product (**30aa** for E=S, and **30ab** for E=O). The cyclometalation of the synthesized ligand is also a crucial part of our strategy, since the synthesis of these compounds is known to be exceptionally challenging.

One of the most important components of this aliphatic pincer ligand scaffold is the C(sp³) unit, which is connected directly to the metal center and imparts entirely different features to the complexes in comparison to the C(sp²) counterpart.

Scheme 41. Synthetic plan to generate the quinolyyl-based N-C(sp³)-E complex (30).

These include, but are not limited to, higher electron density around the metal center and a stereogenic carbon donor which is directly coordinated to the metal, thus allowing a more efficient transmission of chiral information. These structural features may have a strong influence on the stereochemistry when the complex is applied in a particular catalytic transformation.

It is generally accepted that intramolecular cyclometalation via C-H activation is preferentially favored in the case of the aromatic ligands in comparison to the aliphatic ligands.^{121-122, 147} One explanation is that, although the alkylic C(sp³)-H bond is generally weaker than the aromatic C(sp²)-H bond, the strength of the generated M-C(sp²) bond is significantly higher than that of the M-C(sp³) bond.¹²³ Another important factor in the C(sp²)-H bond activation is the possible coordination of the π aromatic system to the metal, before the C-H bond cleavage takes place. In the case of aliphatic C(sp³)-H bond activation, such precoordination does not occur.^{73a, 73b, 98} In addition, the enhanced flexibility of the aliphatic backbone complicates the selective generation of the well-defined compounds. There are indeed only a few reports in the literature in which the M-C(sp³) bond formation was promoted over the M-C(sp²) formation.¹⁴⁸

Therefore, while initiating our ligand synthesis, we took all the possible difficulties in the P-H addition into consideration.

It has been demonstrated previously that the P,N-chelating phosphine ligands, which are generated in asymmetric hydrophosphination, can alter the catalytic performance of complex 7 by acting as a catalyst poison.^{128d, 149} However, in our P-H addition reactions the source of the problem was not the generated ligands but the N-chelating enone starting materials (28) themselves. Since the synthesis of N-C(sp³)-E pincer complexes requires the use of these types of N-chelating substrates during the ligand synthesis, the effect of N-chelation also plays a crucial role in the development of our synthetic strategy and provides fundamental insights into this aspect of coordination in this class of compounds.

With the N-chelating enones (**28**), the source of the difficulty is the lone pair of the N-moiety that takes part in the final coordination in the N-C(sp³)-E complexes (**30**), as well as in the chelation to the palladium before the P-H addition. To explore the coordination behavior of the selected N-chelating substrates, compound **28a** was treated with 1 equiv of complex **4** and stirred at room temperature in CDCl₃ for 15 min (coordination experiment 1 = coord. exp. 1; Scheme 42, top left).

Scheme 42. Coordination properties of N-chelating enones.

Within this time, a dynamic equilibrium was set up between the starting materials and the product (**31**). Compound **31** was generated by N chelation via the nitrogen of the quinolyl ring to the metal center. The ratio between complex **31** and the starting materials was found to be 0.30 : 1 as determined by ¹H NMR. The coordination product can be isolated via crystallization from the solvent, and it was found to be stable in the solid state. However, when the isolated product was redissolved in CDCl₃, the same equilibrium was reestablished.

Another proof for the existence of the equilibrium was the presence of the same amount of complex **32** in the mixture even after more than 10 days, without any changes in the ratio. This experiment excludes the possibility of a one-way coordination reaction. The single-crystal X-ray diffraction analysis of complex **32** confirmed its structure (Figure 14).

Figure 14. ORTEP structure of complex **31**. All hydrogen atoms were omitted for clarity.

In the bis(chloro)-C(sp²)-N dimer **4**, which was used for the coordination test, the bridging chlorides make a stronger X-type and a weaker L-type coordination to the palladium centers. On the basis of the findings, the quinolyl enone (**28a**) is strong enough to replace the L-type chloride, but the X-type chloride stays intact. According to the NMR measurements, significant coordination via the carbonyl oxygen was not recognized under the mentioned reaction conditions (for NMR spectra, see chapter 2.4).

Complex **32** was generated from complex **4** by mixing it with 1 equiv of AgClO₄ in acetonitrile. After the chloride atoms were removed, the two acetonitrile molecules provided a more hemilabile coordination to the metal center. Introducing a stoichiometric amount of enone **28a** to compound **32** leads to the formation of complex **33** (coordination experiment 2 = coord. exp. 2; Scheme 42, top right). After isolation of the coordination product (**33**), the ORTEP structure revealed that the quinolyl substrate **28a** can indeed replace one acetonitrile in a position *trans* to the nitrogen of the C(sp²)-N ligand while the other acetonitrile remains coordinated to the palladium (Figure 15). Coordination complex **33** exists in equilibrium in CDCl₃, giving a 1 : 0.30 ratio with the starting materials.

Figure 15. ORTEP structures of complex **33**. All hydrogen atoms were omitted for clarity.

In a subsequent experiment, the coordination ability of the pyridyl ring was tested by treatment of complex **32** with enone **28b** (coordination experiment 3 = coord. exp. 3; Scheme 42, bottom right). The equilibrium was also observed in this case, giving a 1 : 0.20 ratio between the coordination product (**34**) and the starting materials in the same solvent system at the same temperature. According to an X-ray analysis, in this case both coordinated acetonitrile molecules were replaced by the substrate (**28b**), leading to N,O-chelation to the palladium center (Figure 16). Single coordination by the nitrogen or the oxygen was not observed under the experimental conditions.

Figure 16. ORTEP structure of complex **34**. All hydrogen atoms were omitted for clarity.

Treatment of the *trans*-chalcone (**35**) with the CN bis(acetonitrile) complex **32** did not show any coordination at ambient temperature on the basis of ^1H NMR measurements in CDCl_3 . This means that, without a stronger electron donor atom in the aromatic ring of the enone substrate, coordination does not take place between the substrate and the metal.

To sum up, on the basis of these experimental studies, the nitrogen atom in the heterocyclic ring has a crucial role in coordination to the palladium center. Coordination via the oxygen atom was observed only upon mixing enone **28b** and complex **32**, thus generating an N,O-type chelation. The different coordination properties of the pyridyl- and quinolyl-based substrates were thus established in these experiments, and on the basis of these findings, their different performances in the palladacycle-catalyzed asymmetric hydrophosphination were surmised.

In order to synthesize the tridentate pincer ligands (**29**) for the N-C(sp³)-E type complexes (**30**), the first P-H addition step was carried out in an asymmetric fashion using chiral catalysts (Table 1).

Table 1. Optimization of P-H addition onto enone **28a**.^a

Entry	Catalyst	Solvent	T[°C]	t	Yield ^b [%]	ee ^c [%]
1 ^d	(R)-7	THF	-40	20 h	99	6.3
2 ^d	(R)-7	THF	-80	20 h	99	52.3
3 ^d	(R)-7	MeCN	-40	20h	99	12.3
4 ^d	(R)-7	toluene	-40	21 h	99	0.5
5 ^d	(R)-7	toluene	-80	20 h	99	0
6 ^d	(R)-7	CHCl ₃	-40	14 h	99	25.6
7 ^d	(R)-7	DCM	-40	22 h	99	14.0
8 ^d	(R)-7	DCM	-80	20 h	99	41.8
9 ^d	(R)-7	DCM/MeOH (10:1)	-80	20 h	99	3.2
10 ^{d,e}	(R)-7	acetone	-40	1 h	99	27.1
11	(R,R)-18	acetone	rt	1.5 h	99	48.9
12	(R,R)-18	acetone	0	1.5 h	99	51.0
13 ^d	(R,R)-18	acetone	0	1.5 h	99	52.6
14 ^e	(R,R)-18	acetone	0	1 h	99	67.8
15 ^f	(R,R)-18	acetone	0	0.5 h	99	22.6
16 ^e	(R,R)-18	acetone	-20	1 h	99	81.1
17 ^e	(R,R)-18	acetone	-40	1 h	99 (76)	96.6 (>99)
18 ^e	(R,R)-18	acetone	-60	2 h	99	84.6
19	(R,R)-18	CHCl ₃	0	20 h	99	28.9
20	(R,R)-18	toluene	0	20 h	99	-40.6

^aReaction conditions: enone **28a** (85 μmol, 1.0 eq.), HPPH₂ (93.5 μmol, 1.1 eq.), catalyst (4.25 μmol, 5 mol%), solvent (2.6 mL). ^bThe yield was calculated from ³¹P{¹H} NMR. In parentheses are the isolated yields after a single recrystallization. ^cThe ee was determined by chiral HPLC. In parentheses are the ee's after a single recrystallization. ^dTriethylamine (85 μmol, 1.0 eq.) was added to the reaction. ^eIn the reaction, 10 mol% of catalyst was used. ^fIn the reaction 15 mol% of catalyst was used.

As previously reported by us, a wide range of α,β-unsaturated ketones can be effectively transformed into the corresponding chiral phosphine ligands, catalyzed by the C(sp²)-P type palladacycle **7**. This transformation included the pyridyl enone derivative **28b**, which successfully went through the P–H addition with 92%

enantiomeric excess and provided the desired product in quantitative yield.^{96b} In accordance with this study, we started our synthesis plan with the addition reaction under the same conditions using the quinolyl-based enone derivative **28a**. In the addition reaction the phosphine product **29aa** was produced in quantitative yield; however, the enantioselectivity dropped drastically (*ee* = 52.3%) (Table 1, entry 2).

By changes in the reaction conditions, several attempts were made to improve the stereoselectivity in the reaction, but no increase in enantioselectivity was achieved (Table 1, entries 1-10). The optimization study was continued by using the P-C(sp²)-P type pincer complex **18**, which was also reported by our group previously.¹³⁰

For complex **7**, the addition of a base was necessary for the reaction to be completed; however, complex **18** does not require the use of triethylamine in the transformation (Table 1, entries 12 and 13). The reason is the presence of acetate ion, coordinated to the palladium, which can take the role of the internal base.

The amount of the catalyst was also optimized, and according to the results, the best conditions require 10 mol% catalyst loading (Table 1, entries 12, 14, and 15). A higher catalyst loading of 15 mol % significantly accelerated the reaction (2 times faster than that of with 5 mol % loading); however, the faster transformation slightly decreased the enantioselectivity.

Modification of the temperature revealed that the highest enantiomeric excess can be achieved at -40 °C (Table 1, entries 11, 14, and 16–18). In general, the choice of the lower temperature is more advantageous in asymmetric hydrophosphination reactions, however in this case -60 °C was found to be too low for the transformation in terms of selectivity. After trying out different conditions, eventually the usage of complex **18** with 10 mol % catalyst loading at -40 °C in acetone gave the best overall result (Table 1, entry 17).

The desired phosphine ligand (**29aa**) was generated after 1 h reaction time in quantitative yield with excellent (*ee*=96.6%) enantioselectivity. After a single recrystallization from the DCM/ Et₂O solvent system, the enantiomerically pure (*ee*>99%) compound was observed in 76% isolated yield.

The optimization showed that substrate **28a**, bearing the quinolyl ring instead of the pyridyl moiety, acts in an entirely different way from substrate **28b** during the catalysis. We have reported the reaction mechanism of similar hydrophosphination

reactions using (*R,R*)-**18** as the catalyst for other pyridyl-substituted substrates.^{130b} The aforementioned coordination studies with the C(sp²)-N palladacycles demonstrated the different chelating properties of these two enone derivatives, which may be one of the reasons for the unusual performance in the addition reaction catalyzed by complex **7**. However, this finding still does not provide an explanation for the different behavior in the hydrophosphination reactions catalyzed by complexes **7** and **18**.

In order to examine this aspect, substrate **28a** and complex **7** were mixed in CDCl₃ in equivalent amounts and stirred for 15 min (coordination experiment 5 = coord. exp. 5; Scheme 43, top). The same experiment was carried out with 1 equiv of complex **18** as well (coordination experiment 6 = coord. exp. 6; Scheme 43, bottom). According to ³¹P{¹H} and ¹H NMR measurements, complex **7** and substrate **28a** develop a dynamic connection, a continuous coordination, and decoordination between the reactants, providing different possible coordination products.

Scheme 43. Coordination behavior of enone **28a** with (*R*)-**7** and (*R,R*)-**18**.

While coordination between compound **28a** and the C(sp²)-N type complex **32** developed a well-defined equilibrium (see above), in the case of the C(sp²)-P palladacycle (**7**), the coordination is far more flexible and the chelation is fairly hemilabile (for NMR spectra, chapter 2.4).

However, mixing enone **28a** and complex **18** did not show any coordination at all, which can be explained by the steric repulsion between the phenyl groups in the P-C(sp²)-P pincer complex and enone **28a** (see Figure 17). The metal center in compound **18** is evidently much less accessible than that in **7**.

Figure 17. Steric repulsion between enone **28a** and P-C(sp²)-P complex **18**. The structure of **18** is simplified for clarity.

We have reported previously that catalysts (*R,R*)-**18** and (*R*)-**7** operate via different reaction mechanisms.^{80c, 146, 149}

Catalyst **7** involves an intramolecular mechanism in which the reacting phosphine and the substrate coordinate simultaneously on the palladium catalyst (Scheme 35). On the other hand, catalyst (*R,R*)-**18** adopts an intermolecular mechanism in which only the phosphine coordinates to the palladium during the course of the addition reaction (Scheme 36). The substrate chelation to complex **7** might be one explanation for the suppressed catalytic performance in the P–H addition reaction. Since we did not experience such chelation with complex **18**, the transfer of the chiral information is much more effective.

On application of the optimized conditions, a series of tridentate N-C(sp³)-E type ligands were synthesized bearing an extended group at the N-site (Scheme 44). To make a comparison between the new ligand synthesis route and the previously reported systems, at first, pyridyl enone **28b** was used in the addition reaction. The generated ligand **29ba** was observed with 97.4% enantiomeric excess in quantitative isolated yield after 5 h reaction time. This result is slightly better than those in earlier studies on this substrate.^{96b, 145c} In order to enhance the projection in the N-C(sp³)-E complexes, not only the quinolyl derivatives but also the 6-Me- and 6-anisyl-substituted pyridyl enones (**28c** and **28d**) were applied in the hydrophosphination reaction.

The former enone **28c** provided the corresponding ligand **29ca** in quantitative yield with high enantiomeric excess (*ee*=96.6%), and the latter enone **28d** was transformed into the desired product **29da** in an enantiomerically pure transformation. In the next step, the effect of different substituents on the R² aryl ring was tested. These modifications may also alter the catalytic performance of the final complexes, by changing the ring conformation in the N-C(sp³)-E pincer palladacycles.

Scheme 44. Extension of N-C(sp³)-E pincer ligand synthesis.

Among the modified structures (**28e-i**), the 4-methoxysubstituted compound (**28f**) turned out to be the most challenging in this series. The reaction proceeded with high 95.1% yield with a longer 30 h reaction time and the enantiomeric excess was slightly lower at 82.1%. If the substituent was changed to another electron-donating group, such as 4-bromo (**28g**), the reaction provided high ee and yield in 6 h.

The presence of an electron-withdrawing group, such as a *p*-trifluoromethyl substituent on the aryl ring (**28h**), also did not change the efficiency of the synthesis. A sterically more hindered group (2-naphthyl) in the R² position was also tested in the addition reaction onto enone **28i**, and the transformation was complete, giving similar results. Altering the position of the N donor atom on the aryl ring also did not cause any drawbacks to the reaction; the corresponding phosphine **29ja** was observed with excellent selectivity and yield within a short reaction time.

On the basis of our findings, the new synthesis system has a very high tolerance toward substrate modifications. Overall, almost all of the tridentate ligands were produced in a short reaction (less than 6 h) in quantitative or nearly quantitative yield (97–99%), with good to excellent enantiomeric excesses ($ee=82.1\%$ to $ee>99\%$). It is worth mentioning that, after a single recrystallization, the enantiomerically pure ($ee>99\%$) ligands **29aa**, **29ca**, **29ga**, **29ha** and **29ia** were observed in good (up to 82%) yield.

Asymmetric hydrophosphination is an extraordinary tool to generate the chiral phosphine ligands in a single step with high atom economy. This transformation makes our synthetic plan certainly powerful. After the first stereocenter is generated in this addition step, the second step is the cyclometalation of the tridentate ligand.

During the optimization process of the metalation step, various solvents and palladium sources were tried out (Table 2).

Table 2. Optimization of cyclometalation of (*S*)-**29aa**.^a

Entry	Palladium source	Solvent	t	Yield [%]
1	Li ₂ PdCl ₄	DCM	40 h	23
2	Li ₂ PdCl ₄	MeOH	40 h	26
3	Li ₂ PdCl ₄	Acetone	40 h	21
4	Li ₂ PdCl ₄	MeOH/CHCl ₃ (2:1)	40 h	40
5	K ₂ PdCl ₄	MeOH/CHCl ₃ (2:1)	40 h	25
6 ^b	PdCl ₂ (MeCN) ₂	DCM	40 h	33
7 ^c	Pd(MeCN) ₄ (ClO ₄) ₂	MeCN	2 h	45
8	Li ₂ PdCl ₄	MeOH/CHCl ₃ (2:1)	5 days	44
9 ^d	Li ₂ PdCl ₄	MeOH/CHCl ₃ (2:1)	5 days	72

^aReaction conditions: ligand (*S*)-**29aa** (42 μ mol, 1.0 eq.), reagent (42 μ mol, 1.0 eq.), solvent (20 mL), RT. ^bNaOAc (42 μ mol, 1.0 eq.) was added to the reaction. ^cAfter completion of the metalation, LiCl (42 μ mol, 1.0 eq.) was added to the reaction. ^dTriethylamine (42 μ mol, 1.0 eq.) was added to the reaction.

The best palladium source was found to be Li₂PdCl₄ in a methanol/ chloroform (2/ 1) solvent mixture, which gave a moderate 40% isolated yield after 40 h at ambient temperature. Under the same conditions, a longer reaction time did not improve the

conversion significantly (Table 2, entries 4 and 8). However, if 1 equiv of triethylamine was introduced to the system, the yield increased to 72% after a reaction time of 5 days (Table 2, entry 9). Applying $\text{Pd}(\text{MeCN})_4(\text{ClO}_4)_2$ as a metal source accelerated the reaction, and after 2 h the isolated yield was 45%. However, this result could not be further improved by extending the reaction time or by adding an additional amount of base (Table 2, entry 7).

The structure and the absolute stereochemistry of (*R,R*)-**30aa** in the solid state was confirmed by single-crystal X-ray crystallographic analysis (Figure 18). The obtained structure revealed that the C1-C12-P1-S1 chelate adopted the λ conformation with the C-Ph group occupying the sterically less favorable axial position. One of the explanations for this aspect may be the possible steric repulsion between the C-Ph and the P-Ph(eq) units. It needs to be noted that, while the first stereocenter is generated via the asymmetric hydrophosphination, during cyclometalation a second chiral center is created in a diastereoselective manner.

Figure 18. ORTEP structure of (*R,R*)-**30aa**. The hydrogen atoms were omitted from the structure for clarity (except on chiral carbons).

On application of the optimal conditions, several new N-C(sp³)-E complexes were synthesized with enhanced steric projection at the N site (Scheme 45).

To test the extent of the synthetic route, the N-C(sp³)-O derivative of the quinolyl ligand **29ab** was also successfully utilized in the cyclometalation reaction, giving 70% yield in the reaction. The N-C(sp³)-S type ligand bearing the 6-methylpyridyl ring **29ca** provided the final complex with a slightly lower isolated yield (63%); however, the generation of the 6-anisylpyridyl complex **30da** was found to be even more difficult. In the test reactions, different modifications on the aryl group, connected to the carbon next to phosphorus, were also performed by introducing 4-CF₃-phenyl and naphthyl groups in the ligands **29ha** and **29ia**.

Scheme 45. Synthesis of stereo-projecting N-C(sp³)-E complexes.

These reactions were carried out in a shorter time and generated the desired complexes (**30ha** and **30ia**) in moderate to good yields. In all syntheses, the applied pincer ligands were used in their enantiomerically pure form (*ee* > 99%) and the transformation provided only one of the possible diastereomers without loss of enantiopurity.

On the basis of the experimental results, if the generated N-C(sp³)-E type ligands are enantiomerically pure, the diastereoselective metalation step provides the optically pure complexes without the loss of chiral purity. The diastereoselectivity can be explained by steric effects during the metalation process (Figure 19). The chiral phosphine ligands in solution may exist as different conformers (A and B).

Figure 19. Explanation of diastereoselectivity in cyclometalation.

Due to the steric repulsion between the phenyl group on C1 and the oxygen of the carbonyl group, the bond between C1 and C2 may undergo rotation to develop the sterically more favourable conformer B. In the cyclometalation step, as a result of the Pd–C σ -bond formation and the rotation between C3 and the quinolyl ring, two five-membered palladacycle rings are generated. Since the stereochemistry of the ligand is fixed, after metalation, one stereocenter out of two is always fixed, corresponding to the chirality on C1. In other words, when the synthesis is started with the (*S*)-ligand, the possible diastereomers have the (*R,X*) general chirality (*R* defines the stereochemistry on C1 and X belongs to C2, which can be either *R* or *S*). Considering the structure of the two possible diastereomers (*R,R*) or (*R,S*), complex **30** with the same configuration on C1 and C2 chiral centers has a much more favorable orientation, in comparison to that having alternate stereochemistry. On the basis of experimental results, the (*R,S*)-diastereomer is not generated during the syntheses.

If the metalation step was carried out by using the phosphine sulfide ligand (*R*)-**29** with the opposite chirality, the obtained N-C(sp³)-E complex acquired the reverse (*S,S*) stereochemistry. The transformation of (*R*)-**29ab** to (*S,S*)-**30ab** established the simple switch between the different enantiomers. The X-ray structure of (*S,S*)-**30ab** confirmed the structure and the chirality (Figure 20). In this case, the C11-C12-P1-O1 chelate developed the δ conformation, once again with the C-Ph moiety located in the unexpected axial position.

Figure 20. ORTEP structure of (*S,S*)-**30ab**. The hydrogens were omitted from the structure for clarity (except on chiral carbons).

The result of the cyclometalation is the generation of two slightly distorted square planar palladacycle rings. The metalation of ligand **29ja**, bearing a 3-quinolyl ring instead of the 2-quinolyl moiety, could provide the formation of a six-membered

palladacycle ring, on the basis of the structural features. However, even after trying different palladium sources, such a transformation was not observed.

The tridentate pincer backbone provides extraordinary stability to the generated N-C(sp³)-E complexes. Complex **30aa** was dissolved and heated to reflux temperature in toluene for more than 10 hours without any observed thermal decomposition.

If we consider the stereochemical stability, it is known in the literature that aliphatic C(sp³)-type pincer complexes can undergo α -hydrogen abstraction, which results in the formation of palladium carbene complexes,¹⁵⁰ as well as α - or β -H elimination.^{111, 136b, 136c} These transformations could result in racemization in our case (since the two chiral centers in the final complexes are located exactly in the positions α and β to the palladium center), if a reversible elimination/ insertion or abstraction/ C-H bond activation would occur. In order to examine this possibility, the optical rotation of the final complexes was monitored over a 2 week period, and no such process was observed. As a result of a reversible α - or β -H elimination, the possible generation of the other diastereomer, with the alternate chirality, could take place. In a test of the stability of pure (*R,R*)-**30aa** in this regard, the ³¹P{¹H} NMR was monitored over a period of 1 month with once again no formation of the other (*R,S*) diastereomer.

2.3 Coordination studies

In our previous studies on the asymmetric hydrophosphination of α,β -unsaturated ketones, it was found that some of the hydrophosphination products tend to develop a five-member ring chelation to the phospho-palladacycle complex **7**, if there is an available electron donor (e.g. nitrogen or oxygen) in the right position (Figure 21).¹⁴⁹ If 2-pyridyl or 2-furyl ring was connected to the chiral carbon in the phosphination product, respectively, a five-member P,N- or P,O-chelation was established by the suppressed catalytic activity of **7** within the hydrophosphination reaction. In this project the chelation was developed not by the generated chelating-products, but the N-chelating starting materials.

Chelation behaviour of a hydrophosphination **product**, described in previous work:

Leung et al., Dalton Trans. **2016**, 45, 13449.

Chelation behaviour of the **starting materials**, described in this work:

Figure 21. Product-chelation and starting-material chelation to palladacycles.

In the aforementioned coordination studies (Scheme 42), mixing the starting materials (**28a** and **28b**) with stoichiometric amount of palladacycle complexes (**4** or **32**), a dynamic equilibrium was developed between the enones and the coordination products (**31**, **33** and **34**). The chelating properties of the substrates were established by X-ray crystallography in solid state and by NMR studies in solution. Herein, the details of the NMR studies are disclosed.

a) Coordination experiment 1 (Scheme 46):

Scheme 46. Coordination experiment 1.

In the ^1H NMR spectrum of the coordination study (coord. exp. 1), we were able to assign the peaks of the coordination product (**31**) and the remaining (/ uncoordinated) starting materials (**28a** and **4**). In Figures 22 and 23, the details of the interpretation is presented and the colorful integration numbers belong to the following compounds: blue – complex **31**, red – **28a**, green – complex **4**. Based on the integration data, the proton signals were assigned to each material in the mixture (complex **31**, and the uncoordinated **28a** and **4**). The identification of the ^1H NMR signals was done by comparing the arising new peaks, with the peaks of the starting materials (Figure 24).

As a further investigation, the ^{13}C NMR spectrum of coordination experiment 1 was also compared to the starting materials' ^{13}C NMR spectra (Figure 25). In case of the other coordination studies (coord. exp. 2 and 3), the same NMR interpretation strategy was applied.

Characterization data of Complex **31**:

Crystal appearance: yellow block-like specimen. ^1H NMR (400 MHz, CDCl_3) δ 9.83 (d, $J = 8.6$ Hz, 1H, ArH), 9.12 (d, $J = 15.6$ Hz, 1H, C(O)CH=CH), 8.48 (d, $J = 8.4$ Hz, 1H, ArH), 7.97 – 7.92 (m, 2H, ArH), 7.95 (d, 1H, $J = 15.8$ Hz, 1H, C(O)CH=CH) 7.86 – 7.75 (m, 3H, ArH), 7.73 (t, 1H, ArH), 7.49 – 7.38 (m, 3H, ArH), 6.91 – 6.82 (m, 2H, ArH), 6.57 – 6.49 (m, 1H, ArH), 5.29 (d, $J = 7.7$ Hz, 1H, ArH), 3.87 (d, $J = 14.0$ Hz, 1H, ArCH₂N), 3.63 (d, $J = 14.0$ Hz, 1H, ArCH₂N), 2.95 (s, 3H, N(CH₃)₂), 2.61 (s, 3H, N(CH₃)₂). ^{13}C NMR (101 MHz, CDCl_3) δ 190.28 (s, 1C, C=O), 159.98 – 121.53 (23C, Ar), 74.23 (s, 1C, ArCH₂N), 53.34 (s, 1C, N(CH₃)₂), 52.37 (s, 1C, N(CH₃)₂). The identity of the compound was determined by X-ray analysis and the purity was established from the multinuclear NMR data.

Figure 22. Assignment of ^1H NMR spectrum (400 MHz, CDCl_3) of coord. exp. 1.

Figure 23. Assignment of ^1H NMR spectrum (400 MHz, CDCl_3) of coord. exp. 1.

Figure 24. Comparison of ^1H NMR spectra (400 MHz, CDCl_3) of coord. exp. 1, 28a and 4.

Figure 25. Comparison of ^{13}C NMR spectra (101 MHz, CDCl_3) of coord. exp. 1, **28a** and **4**.

b) Coordination experiment 2 (Scheme 47):

Scheme 47. Coordination experiment 2.

In coord. exp. 1 and 2, the N-chelating enone (**28a**) was strong enough to replace the coordinating ligand *trans* to the nitrogen of the $\text{C}(\text{sp}^2)\text{-N}$ auxiliary, but the other coordination site (*cis* to the nitrogen) stayed intact in both cases. For ^1H and ^{13}C NMR spectra, see Figures 26 to 28. In Figure 26, the colorful integration numbers belong to the following compounds: blue – complex **33**, red – **28a**, green – complex **32**.

Characterization data of Complex **33**:

Crystal appearance: yellow needle-like specimen. ^1H NMR (400 MHz, CDCl_3) δ 9.57 (d, $J = 8.5$ Hz, 1H, ArH), 8.61 (d, $J = 8.4$ Hz, 1H, ArH), 8.18 (d, $J = 15.8$ Hz, 1H, C(O)CH=CH), 8.09 – 8.00 (m, 2H, ArH), 7.97 (d, $J = 15.7$ Hz, 1H, C(O)CH=CH), 7.89 (d, $J = 8.4$ Hz, 1H, ArH), 7.85 – 7.74 (m, 1H, ArH), 7.54 (d, $J = 7.3$ Hz, 2H, ArH), 7.49 – 7.40 (m, 1H, ArH), 7.40 – 7.31 (m, 2H, ArH), 6.97 (t, $J = 7.3$ Hz, 1H, ArH), 6.88 (d, $J = 7.2$ Hz, 1H, ArH), 6.60 (t, $J = 7.6$ Hz, 1H, ArH), 5.58 (d, $J = 7.7$ Hz, 1H, ArH), 3.73 (s, 2H, ArCH₂N), 2.81 (s, 6H, N(CH₃)₂), 1.73 (s, 3H, NCCH₃). ^{13}C NMR (101 MHz, CDCl_3) δ 190.37 (s, 1C, C=O), 159.88 – 120.24 (24C, Ar + NCCH₃), 72.81 (s, 1C, ArCH₂N), 52.36 (s, 2C, N(CH₃)₂), 2.68 (s, 1C, NCCH₃). The identity of the compound was determined by X-ray analysis and the purity was established from the multinuclear NMR data.

Figure 26. Assignment of ^1H NMR spectrum (400 MHz, CDCl_3) of coord. exp. 2.

Figure 27. Comparison of ^1H NMR spectra (400 MHz, CDCl_3) of coord. exp. 2, **28a** and **32**.

Figure 28. Comparison of ^{13}C NMR spectra (101 MHz, CDCl_3) of coord. exp. 2, **28a** and **32**.

c) Coordination experiment 3 (Scheme 48):

Scheme 48. Coordination experiment 3.

In coordination exp. 3, the pyridyl-based **28b** substrate was tested. In this experiment, an N,O-bidentate chelation to the palladium center was observed, the chelating substrate (**28b**) replaced both acetonitriles of complex **32**. For ^1H and ^{13}C NMR spectra, see Figures 29 to 31. In Figure 29, the integration numbers shown in color belong to the following compounds: blue – complex **34**, red – **28b**, green – complex **32**. The coordination of the carbonyl function to the palladium in solid state was confirmed by the X-ray analysis and in solution, the ^{13}C NMR spectrum supported the Pd-O interaction (Figure 31). The ^{13}C NMR chemical shift of the carbonyl carbon of the uncoordinated enone (**28b**) was located at δ 189.18 ppm, CDCl_3 , 101 MHz and upon coordination, the carbonyl peak of **34** appeared at δ 193.93 ppm, CDCl_3 , 101 MHz. Due to the Pd-O interaction, the chemical peak of the carbonyl carbon significantly shifted towards the low field region (with 4.75 ppm difference), which indicates that it became significantly more electron-deficient. To compare this difference, in coord. exp. 1, the carbonyl peak of **31** was located at a similar chemical shift (δ 190.28 ppm, CDCl_3 , 101 MHz) as that of **28a** (δ 189.77 ppm, CDCl_3 , 101 MHz) in the ^{13}C NMR. In coord. exp. 2, the carbonyl peak of **33** was obtained at δ 190.37 ppm, CDCl_3 , 101 MHz, which is also a relatively similar chemical shift to that of the carbonyl moiety of **28a**. The comparison of the carbonyl chemical shifts of the uncoordinated- and the coordinated enone(s), presented in Table 3.

Table 3. Comparison of the carbonyl carbon's chemical shifts in the chelation.

Coord. exp.	Chemical shift of the carbonyl carbon for the free (uncoordinated) enone	Chemical shift of the carbonyl carbon for the coordinated enone
1	δ 189.77 (enone 28a)	δ 190.28 (complex 31)
2	δ 189.77 (enone 28a)	δ 190.37 (complex 33)
3	δ 189.18 (enone 28b)	δ 193.93 (complex 34)

In this comparison, it can be clearly seen that the biggest difference in the chemical shifts was observed between enone **28b** and complex **34**. The Pd-O interaction was observed only in this experiment

Characterization data of complex **34**:

Crystal appearance: yellow block-like specimen. ^1H NMR (300 MHz, CDCl_3) δ 9.02 (d, $J = 7.5$ Hz, 1H, ArH), 8.84 (d, $J = 4.9$ Hz, 1H, ArH), 8.50 (t, $J = 7.8$ Hz, 1H, ArH), 8.31 (d, $J = 15.2$ Hz, 1H, $\text{C}(\text{O})\text{CH}=\text{CH}$), 8.08 (d, $J = 15.4$ Hz, 1H, $\text{C}(\text{O})\text{CH}=\text{CH}$), 8.01 – 7.90 (m, 2H, ArH), 7.90 – 7.80 (m, 1H, ArH), 7.48 – 7.37 (m, 3H, ArH), 7.19 – 7.11 (m, 2H, ArH), 7.10 – 7.04 (m, 1H, ArH), 7.02 – 6.95 (m, 1H, ArH), 4.13 (s, 2H, ArCH_2N), 3.05 (s, 6H, $\text{N}(\text{CH}_3)_2$). ^{13}C NMR (101 MHz, CDCl_3) δ 193.93 (s, 1C, $\text{C}=\text{O}$), 155.08 – 116.93 (19C, Ar + $\text{C}=\text{C}$), 73.17 (d, $J = 31.3$ Hz, 1C, ArCH_2N), 52.91 (s, 1C, $\text{N}(\text{CH}_3)_2$), 52.31 (s, 1C, $\text{N}(\text{CH}_3)_2$). The identity of the compound was determined by X-ray analysis and the purity was established from the multinuclear NMR data.

Figure 29. Assignment of ^1H NMR spectrum (400 MHz, CDCl_3) of coord. exp. 3.

Figure 30. Comparison of ^1H NMR spectra (400 MHz, CDCl_3) of coord. exp. 3, 28b and 32.

Figure 31. Comparison of ^{13}C NMR spectra (101 MHz, CDCl_3) of coord. exp. 3, 28b and 32.

d) Coordination experiment 4 (Scheme 49):

Scheme 49. Coordination experiment 4.

In case of coord. exp. 4, interaction between the *trans*-chalcone (**35**) and complex **32** was not observed (for NMR spectra see Figure 32). The role of this experiment was to demonstrate, that in the absence of a donating atom, the carbonyl oxygen cannot replace even the labile acetonitrile molecules of **32**. This control experiment also demonstrates, that the usage of N-chelating starting materials is relatively more challenging in the hydrophosphination reaction, compared to the non-chelating chalcone derivatives. Due to the chelation properties, these substrates (**28**) may act as a catalyst poison and suppress the catalytic activity in the Pd-catalyzed P-H addition reactions.

Figure 32. Comparison of ^1H NMR spectra (400 MHz, CDCl_3) of coord. exp. 4, **35** and **32**.

e) Coordination experiment 5 (Scheme 50):

Scheme 50. Coordination experiment 5.

In the next experiment, the possible interaction between enone **28a** and palladacycle **7** was tested. The observed ^1H and $^{31}\text{P}\{^1\text{H}\}$ NMR spectra shows broadened resonance signals, which indicates a dynamic relation between the enone (**28a**) and the $\text{C}(\text{sp}^2)\text{-P}$ complex (**7**) (Figures 33 and 34).

Figure 33. Comparison of ^1H NMR spectra (500 MHz, CDCl_3) of coord. exp. 5, **7** and **28a**.

Figure 34. $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum (162 MHz, CDCl_3) of coord. exp. 5.

Changing the operating frequency of the ^1H measurement (300 MHz, 400 MHz and 500 MHz) did not make any changes in the observed spectrum. Herein we report the ^1H NMR spectrum, measured at 500 MHz. The $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum of complex **7** presents a sharp peak at δ 62.73 ppm. However, in case of coord. exp. 5, a broad resonance signal was developed at δ 63.28 ppm. This observation also implies fast coordination, decoordination process occurring between the compounds. This experiment was the evidence, that there is indeed an interaction between **28a** and **7**, but in this case, we were unable to fully assign one exact structure. Also, any attempts to crystallize one compound from the reaction mixture failed. However, the developing interaction may be one of the reasons, why complex **7** showed a relatively suppressed catalytic activity in the asymmetric hydrophosphination of **28a**.

f) Coordination experiment 6 (Scheme 51):

Scheme 51. Coordination experiment 6.

In the last coordination experiment, equivalent amount of **28a** and **18** was mixed. In the ^1H NMR spectrum of coord. exp. 6, the chemical peaks show simply the 1 to 1 mixture of the starting materials (**28a** and **18**) and the $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum of coord. exp. 6 presents a sharp peak at δ 48.26 ppm, which belongs to the peak of the uncoordinated complex **18** (Figures 35 and 36). Based on these results, the interaction between **28a** and **18** can be excluded. Based on the above-mentioned coordination experiments, it is a reasonable explanation for the suppressed catalytic performance of **7**, that significant N-chelation occurred during the catalysis, which significantly pulled back the catalytic activity. It is noteworthy to mention, that this was highly unexpected, based on the successful catalytic application of **7** for numerous α,β -unsaturated ketones in our previous reports.^{96b} However, the N-chelating starting materials did not show any type of coordination to **18**, which would cause lower catalytic performance.

Figure 35. Comparison of ^1H NMR spectra (400 MHz, CDCl_3) of coord. exp. 6, **18** and **28a**.

Figure 36. $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum (162 MHz, CDCl_3) of coord. exp. 6.

The chelation properties of the starting material enones and the different catalytic behaviour of (*R*)-**7** and (*R,R*)-**18** were experimentally established by the aforementioned coordination experiments (coord. exp. 1-6). Due to the N-chelation of the enones to the (*R*)-**7** bidentate palladacycle, the catalytic performance of this palladium source was weaker, compared to that of (*R,R*)-**18**. The pincer type palladium complex did not show any interaction with the enone substrate under the experimental conditions; thus, the catalytic performance was not weakened by any unwanted compound chelation. Based on our findings, the intermolecular catalytic cycle (using (*R,R*)-**18** as a catalyst) was preferred in this synthesis scenario compared to the intramolecular interaction (which was observed by using (*R*)-**7** as a catalyst). The catalytic cycles of the asymmetric hydrophosphination using (*R*)-**7** and (*R,R*)-**18** as catalysts are presented in Figures 37 and 38. In case of the intramolecular catalytic cycle (Figure 37), the first step is the coordination of the diphenylphosphine molecules to the metal center (**A**), followed by the substrate coordination and deprotonation (**B**). The next step is the intramolecular attack of the phosphido species to the substrate (**C**) and the last step is the product elimination (**D**). The intermolecular catalytic cycle (Figure 38) starts with the secondary phosphine coordination to the palladium center (**A'**) and in the next step, the acetate anion deprotonates the coordinated

diphenylphosphine (**B'**). The cycle continues with the intermolecular attack of the phosphido compound to the enone starting material (**C'**) and the product elimination provides the generation of the chiral phosphine product (**D'**).

Figure 37. Intramolecular catalytic cycle using **(R)-7** as catalyst.

Figure 38. Intermolecular catalytic cycle using **(R,R)-18** as catalyst.

2.4 Conclusion

In conclusion, an effective and extensive synthetic methodology was demonstrated to produce new, stereoprojecting N-C(sp³)-E complexes. The first step of our strategy, the catalytic asymmetric hydrophosphination reaction, was carried out on the more challenging, N-chelating substrates, giving the desired chiral phosphine ligands in quantitative yield with up to *ee*>99%. The N-chelating effect was examined by coordination studies on C(sp²)-N, C(sp²)-P, and P-C(sp²)-P palladacycles. The different chelation properties between the **28b** pyridyl and **28a** quinolyl enones were established, as well as the different performances in catalytic asymmetric hydrophosphination, leading to the reported **29ba** and the new **29aa** chiral ligands. The complexation of the new N-C(sp³)-E type tridentate ligands was also discussed, and all of the generated complexes bear a sterically enhanced group at the N site of the compound. This enhanced stereo-projection may alter the catalytic performance of the N-C(sp³)-E compounds, and studies on this aspect are currently in progress. Overall, the newly developed synthetic pathway allows us to perform easy structural modifications on the enantiomerically pure chiral complexes, within a relatively fast, selective transformation, without the need for time-consuming and wasteful resolution.

2.5 Experimental section

2.5.1 General considerations

All air sensitive manipulations were carried out under positive pressure of nitrogen using Schlenk techniques. Solvents were degassed prior to use. Chloroform (AR), acetonitrile (AR), methanol (AR), dichloromethane (HPLC), acetone(AR), ethyl acetate (AR) and *n*-hexane (HPLC) was purchased from VWR; 2-propanol (HPLC), *n*-hexane (AR) and toluene (AR) from Avantor; diethyl ether (AR) from Fischer Scientific; THF from TEDIA Company. THF was distilled from sodium/benzophenone before usage. NMR spectra were recorded on Bruker AV 300, AV 400, AV 500 and BBFO 400 spectrometers. Chemical shifts were reported in ppm and referenced to an internal SiMe₄ standard (0 ppm) for ¹H NMR, chloroform-*d* (77.22 ppm) for ¹³C NMR and an external 85% H₃PO₄ for ³¹P{¹H} NMR. Low Temp Pairstirrer PSL-1800 was used for low temperature reactions. Column chromatography was performed with Silica gel 60 (purchased from Merck). Melting points were measured using SRS Optimelt

Automated Point System SRS MPA100. In order to determine the purity of the synthesized compounds, elemental analysis (EA) was performed on the EuroVector Euro EA elemental analyzer. In case if EA measurement was not performed, the purity was determined by other measurements stated below. HRMS using electrospray ionization (ESI) method was performed on the Waters Q-ToF Premier spectrometer. Optical rotations were examined with JASCO P-1030 Polarimeter in DCM in a 0.1 dm cell at specified temperatures. The enantioselectivities of the asymmetric hydrophosphination reactions were determined with Agilent 1200 Series HPLC machine fitted with specified Daicel Chiralpak columns eluted with a mixture of *n*-hexane/2-propanol at 23 °C.

(*R*)-C(sp²)-P complex **7**^{96a, 126}, C(sp²)-N achiral palladacycles **4**⁸⁷ and **32**¹⁵¹, (*R,R*)-P-C(sp²)-P pincer complex **18**¹³⁰ were prepared according to literature methods. All other reactants and reagents were used as supplied without further purification unless stated otherwise.

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

2.5.2 Synthesis of the α,β -unsaturated ketones

General procedure A for the synthesis of **28b** (Scheme 52):

Enone **28b** was generated via modified literature procedure.¹⁵²

Scheme 52. Synthesis of **28b**.

The 2-acetylpyridine (1.33g, 11 mmol, 1.1 equiv) and benzaldehyde (1.06 g, 10 mmol, 1 equiv) were added to 100 mL of distilled water under N₂ atmosphere, cooled down to 4 °C and shaken thoroughly forming a fine emulsion. Then 10 mL of 10% of NaOH

aqueous solution was introduced to the mixture and shaken again for 30 seconds. Then the reaction was let to warm up from 4 °C to room temperature and stirred for 24 h. Then the solid product was filtered, dried and pushed through a silica gel column for crude purification eluted with n-hexane/EtOAc 98:2 to 80:20. Then the product was re-crystallized from DCM/*n*-hexane solvent mixture. After crystallization, the isolated compound was stored in tightly-closed bottle under N₂ in the dark. The observed heterocyclic chalcone derivative is acid- and photosensitive.¹⁵³

Enone **28b** was produced according to general procedure A in 85% yield. Appearance: white solid. Mp. was correlated to literature value: Mp. (lit.)¹⁵⁴ 68 – 70 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.69 (d, *J* = 4.5 Hz, 1H, ArH), 8.31 (d, *J* = 16.1 Hz, 1H, COCH=CH), 8.15 (d, *J* = 7.8 Hz, 1H, ArH), 7.93 (d, *J* = 16.1 Hz, 1H, COCH=CH), 7.78 (td, *J* = 7.6, 1.1 Hz, 1H, ArH), 7.72 – 7.62 (m, 2H, ArH), 7.48 – 7.27 (m, 4H, ArH). ¹³C NMR (101 MHz, CDCl₃) δ 189.18 (s, 1C, C=O), 154.04-120.82 (13C, Ar + C=C). Anal. calcd for C₁₄H₁₁NO, C: 80.36, H: 5.30, N: 6.69; found, C: 80.15, H: 5.10, N: 6.52. HRMS (+ESI) *m/z*: (M + H)⁺ calcd for C₁₄H₁₂NO, 210.0919; found, 210.0918.

General procedure B for the synthesis of heterocyclic chalcones catalyzed by CuI (Scheme 53):

The synthesis of enone **28a**, **28c-28j** were carried out via modified literature method.¹⁵⁵

Scheme 53. Synthesis of enone **28** analogues.

The aldehyde (3.18 mmol, 1 equiv), piperidine (270.67 mg, 3.18 mmol, 1 equiv), and alkyne (3.18 mmol, 1 equiv) were added to a reactor tube containing CuI (6 mg, 31.8 μmol, 1 mol%) in the absence of solvent, under N₂ atmosphere. The reaction mixture was warmed to 70 °C and stirred for 20 hours. After cooling down, the mixture was first pushed through a silica gel column for crude purification eluted with n-hexane/EtOAc 98:2 to 80:20. Then single re-crystallization was performed for further purification using DCM/*n*-hexane solvent system. After crystallization, the isolated chalcones were

stored in tightly-closed bottles under N₂ in the dark. The observed heterocyclic chalcone analogues are acid- and photo-sensitive.¹⁵³

Characterization data:

Enone **28a** was produced according to general procedure B in 45% yield. Appearance: yellow solid. Mp. was correlated to literature value: Mp. (lit.)⁹ 132.5 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.53 (d, *J* = 16.1 Hz, 1H; COCH=CH), 8.27 (d, *J* = 6.5 Hz, 3H, ArH), 7.99 (d, *J* = 16.1 Hz, 1H; COCH=CH), 7.85 (dd, *J* = 8.2, 0.8 Hz, 1H, ArH), 7.81 – 7.73 (m, 3H, ArH), 7.62 (ddd, *J* = 8.1, 6.9, 1.1 Hz, 1H, ArH), 7.47 – 7.38 (m, 3H, ArH). ¹³C NMR (101 MHz, CDCl₃) δ 189.77 (s, 1C, C=O), 154.04–119.23 (17C, Ar + C=C). Anal. calcd for C₁₈H₁₃NO, C: 83.37, H: 5.05, N: 5.40; found, C: 83.45, H: 5.21, N: 5.43. HRMS (+ESI) *m/z*: (M + H)⁺ calcd for C₁₈H₁₄NO, 260.1075; found, 260.1076.

Enone **28c** was produced according to general procedure B in 42% yield. Appearance: brown solid. Mp. was correlated to literature value: Mp. (lit.)¹⁵⁵ 54.1 – 55.1 °C (EtOH). ¹H NMR (400 MHz, CDCl₃) δ 8.32 (d, *J* = 16.1 Hz, 1H, COCH=CH), 7.96 (d, *J* = 7.7 Hz, 1H, ArH), 7.91 (d, *J* = 16.1 Hz, 1H, COCH=CH), 7.70 – 7.67 (m, 3H, ArH), 7.38 – 7.36 (m, 3H, ArH), 7.27 (d, *J* = 7.6 Hz, 1H, ArH), 2.63 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 189.66 (s, 1C, C=O), 157.89 – 119.97 (13C, Ar, C=C), 24.50 (s, 1C, ArCH₃). Anal. calcd for C₁₅H₁₃NO, C: 80.69, H: 5.87, N: 6.27; found, C: 80.93, H: 6.14, N: 6.65. HRMS (+ESI) *m/z*: (M + H)⁺ calcd for C₁₅H₁₄NO, 224.1075; found, 224.1080.

Enone **28d** was produced according to general procedure B in 52% yield. Appearance: yellow solid. Mp. 148 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.44 (d, *J* = 16.1 Hz, 1H, COCH=CH), 8.12 – 8.02 (m, 3H, ArH), 7.97 (d, *J* = 16.1 Hz, 1H, COCH=CH), 7.89 – 7.81 (m, 2H, ArH), 7.73 (dd, *J* = 7.4, 1.9 Hz, 2H), 7.47 – 7.38 (m, 3H, ArH), 7.05 (dt, *J* = 9.2, 2.8 Hz, 2H, ArH), 3.88 (s, 3H, OCH₃). ¹³C NMR (101 MHz, CDCl₃) δ 189.91 (s, 1C, C=O), 161.02 – 114.46 (19C, Ar + C=C), 55.57 (s, 1C, ArOC). Anal. calcd for C₂₁H₁₇NO₂, C: 79.98, H: 5.43, N: 4.44; found, C: 80.02, H: 5.61, N: 4.53. HRMS (+ESI) *m/z*: (M + H)⁺ calcd for C₂₁H₁₈NO₂, 316.1338; found, 316.1339.

Enone **28e** was produced according to general procedure B in 44% yield. Appearance: yellow solid. Mp. was correlated to literature value: Mp. (lit.)¹⁵⁶ 108 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.50 (d, *J* = 16.1 Hz, 1H, COCH=CH), 8.34 – 8.23 (m, 3H, ArH), 7.98 (d, *J* = 16.1 Hz, 1H, COCH=CH), 7.88 (d, *J* = 8.1 Hz, 1H, ArH), 7.84 – 7.74 (m, 1H, ArH), 7.69 – 7.63 (m, 3H, ArH), 7.25 (d, *J* = 7.8 Hz, 2H, ArH), 2.40 (s, 3H, ArCH₃). ¹³C NMR (101 MHz, CDCl₃) δ 189.90 (s, 1C, C=O), 154.26 – 119.32 (17C, Ar + C=C), 21.78 (s, 1C, ArC). Anal. calcd for C₁₉H₁₅NO, C: 83.49, H: 5.53, N: 5.12; found, C: 83.23, H: 5.37, N: 4.88. HRMS (+ESI) *m/z*: (M + H)⁺ calcd for C₁₉H₁₆NO, 274.1232; found, 274,1237.

Enone **28f** was produced according to general procedure B in 38% yield. Appearance: yellow solid. Mp. was correlated to literature value: Mp. (lit.)¹⁵⁷ 138 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.42 (d, *J* = 16.0 Hz, 1H, COCH=CH), 8.34 – 8.25 (m, 3H, ArH), 7.98 (d, *J* = 16.0 Hz, 1H, COCH=CH), 7.89 (d, *J* = 8.1 Hz, 1H, ArH), 7.84 – 7.77 (m, 1H, ArH), 7.75 (d, *J* = 8.7 Hz, 2H), 7.69 – 7.61 (m, 1H, ArH), 6.97 (d, *J* = 8.7 Hz, 2H, ArH), 3.87 (s, 3H, OCH₃). ¹³C NMR (101 MHz, CDCl₃) δ 189.83 (s, 1C, C=O), 161.96 – 114.59 (17C, Ar + C=C), 55.63 (s, 1C, ArOC). Anal. calcd for C₁₉H₁₅NO₂, C: 78.87, H: 5.23, N: 4.84; found, C: 78.99, H: 5.34, N: 5.01. HRMS (+ESI) *m/z*: (M + H)⁺ calcd for C₁₉H₁₆NO₂, 290.1181; found, 290.1187.

Enone **28g** was produced according to general procedure B in 54% yield. Appearance: yellow solid. Mp. was correlated to literature value: Mp. (lit.)¹⁵⁵ 123.2 – 124.6 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.49 (d, *J* = 16.1 Hz, 1H, COCH=CH), 8.29 – 8.18 (m, 3H, ArH), 7.87 (d, *J* = 15.6 Hz, 1H, COCH=CH), 7.84 (d, *J* = 6.8 Hz, 1H, ArH), 7.81 – 7.72 (m, 1H, ArH), 7.66 – 7.49 (m, 5H, ArH). ¹³C NMR (101 MHz, CDCl₃) δ 189.48 (s, 1C, C=O), 153.79 – 119.17 (17C, Ar + C=C). Anal. calcd for C₁₈H₁₂NOBr, C: 63.93, H: 3.58, N: 4.14; found, C: 64.12, H: 3.76, N: 4.33. HRMS was correlated to literature value: HRMS (lit.)¹⁵⁵ (+ESI) *m/z*: (M + H)⁺ calcd for C₁₈H₁₂NOBr, 338.0181; found, 338.0176.

Enone **28h** was produced according to general procedure B in 57% yield. Appearance: yellow solid. Mp. 170.9 – 171.1 °C. ^1H NMR (300 MHz, CDCl_3) δ 8.61 (d, J = 16.1 Hz, 1H, COCH=CH), 8.37 – 8.20 (m, 3H, ArH), 7.97 (d, J = 16.1 Hz, 1H, COCH=CH), 7.92 – 7.75 (m, 4H, ArH), 7.75 – 7.60 (m, 3H, ArH). ^{13}C NMR (101 MHz, CDCl_3) δ 189.54 (s, 1C, C=O), 153.71 – 119.24 (18C, Ar + C=C + ArCF_3). Anal. calcd for $\text{C}_{19}\text{H}_{12}\text{NOF}_3$, C: 69.72, H: 3.70, N: 4.28; found, C: 70.05, H: 3.96, N: 4.41. HRMS (+ESI) m/z : ($\text{M} + \text{H}$) $^+$ calcd for $\text{C}_{19}\text{H}_{13}\text{NOF}_3$, 328.0949; found, 328.0952.

Enone **28i** was produced according to general procedure B in 58% yield. Appearance: yellow solid. Mp. 141.6 – 142 °C. ^1H NMR (300 MHz, CDCl_3) δ 8.60 (d, J = 16.0 Hz, 1H, COCH=CH), 8.33 – 8.17 (m, 3H, ArH), 8.12 (d, J = 16.1 Hz, 1H, COCH=CH), 8.05 (s, 1H, ArH), 7.91 (dd, J = 8.6, 1.2 Hz, 1H, ArH), 7.87 – 7.69 (m, 5H, ArH), 7.65 – 7.54 (m, 1H, ArH), 7.54 – 7.40 (m, 2H, ArH). ^{13}C NMR (75 MHz, CDCl_3) δ 189.63 (s, 1C, C=O), 154.04 – 119.20 (21C, Ar + C=C). Anal. calcd for $\text{C}_{22}\text{H}_{15}\text{NO}$, C: 85.41, H: 4.89, N: 4.53; found, C: 85.34, H: 4.76, N: 4.33. HRMS (+ESI) m/z : ($\text{M} + \text{H}$) $^+$ calcd for $\text{C}_{22}\text{H}_{16}\text{NO}$, 310.1232; found, 310.1231.

Enone **28j** was produced according to general procedure B in 44% yield. Appearance: yellow solid. Mp. was correlated to literature value: Mp. (lit.)¹⁵⁸ 138 °C. ^1H NMR (400 MHz, CDCl_3) δ 9.47 (d, J = 2.1 Hz, 1H, ArH), 8.71 (d, J = 1.9 Hz, 1H, ArH), 8.14 (d, J = 8.5 Hz, 1H, ArH), 7.90 (d, J = 8.0 Hz, 1H, ArH), 7.86 (d, J = 15.6 Hz, 1H, COCH=CH), 7.80 – 7.76 (m, 1H), 7.64 – 7.58 (m, 3H, ArH), 7.58 (d, J = 15.6 Hz, 1H, COCH=CH), 7.40 – 7.39 (m, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 188.69 (s, 1C, C=O), 149.53 – 121.30 (17C, Ar + C=C). Anal. calcd for $\text{C}_{18}\text{H}_{13}\text{NO}$, C: 83.37, H: 5.05, N: 5.40; found, C: 83.21, H: 4.83, N: 5.12. HRMS (+ESI) m/z : ($\text{M} + \text{H}$) $^+$ calcd for $\text{C}_{18}\text{H}_{14}\text{NO}$, 260.1075; found, 260.1073.

2.5.3 Synthesis of chiral pincer ligands

General procedure C (Scheme 54):

A nitrogen flushed 2-neck flask was charged with diphenylphosphine (17.4 mg, 93.5 μmol , 1.1 equiv.) and degassed solvent (2 mL) at room temperature, followed by the addition of (*R*)-**7** (2.7 mg, 4.25 μmol , 5 mol%) or (*R,R*)-**18** catalyst (7.6 mg, 8.5 μmol , 10 mol%). The setup was brought to -40 °C and stirred for 10 mins, before introducing enone **28** (85 μmol , 1.0 equiv.). In case of the (*R*)-**7** catalyzed reactions, triethylamine (8.6 mg, 85 μmol , 1.0 equiv.), dissolved in 0.5 ml degassed solvent, was added dropwise to the mixture. The reaction mixture was stirred at low temperature and monitored by $^{31}\text{P}\{^1\text{H}\}$ NMR. Upon completion, H_2O_2 (31% w/w, 0.1 ml) or S_8 (10.9 mg, 42.5 μmol , 0.5 equiv) was added into the flask and the reaction was warmed up to room temperature and stirred for 30 mins. Evaporation of the solvent under reduced pressure generated the crude mixture, which was purified by silica gel column chromatography, eluted with *n*-hexane/EtOAc (97:3 to 70:30) solvent system. The enantiopurity was determined by chiral HPLC as described below.

Scheme 54. Asymmetric hydrophosphinaion of enone **28** analogues.

Characterization data:

Ligand (*S*)-**29aa** was produced according to general procedure C in 99% yield and *ee*=96.6%. HPLC conditions: Daicel Chiralpak IC column, *n*-hexane/2-propanol (90:10), 1 ml/min flowrate, 23 °C column temperature, major peak (*S*): 13.3 min, minor peak (*R*): 16.1 min. Appearance: white solid. $[\alpha]_{\text{D}}^{20}$ -230 (c 0.5, CH_2Cl_2) for *ee*>99%. Mp. 203.5 – 204.0 °C. $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, CDCl_3) δ 51.52 (s, 1P). ^1H NMR (400 MHz, CDCl_3) δ 8.32 – 8.22 (m, 3H, ArH), 8.16 (d, *J* = 8.5 Hz, 1H, ArH), 7.91 (d, *J* = 8.5 Hz, 1H, ArH), 7.83 – 7.78 (m, 2H, ArH), 7.64 (t, *J* = 7.3 Hz, 1H, ArH), 7.58 – 7.49 (m, 4H, ArH), 7.36 – 7.20 (m, 6H, ArH), 7.08 (s, 3H, ArH), 4.94 (td, *J* = 10.7, 2.0 Hz, 1H, *PCHCH*₂), 4.73 – 4.59 (m, 1H, *C(O)CH*₂), 3.66 (ddd, *J* = 17.6, 11.1, 2.2 Hz, 1H, *C(O)CH*₂). ^{13}C NMR (101 MHz, CDCl_3) δ 199.38 (d, *J* = 15.5 Hz, 1C, C=O), 152.59 – 118.32 (27C, Ar),

42.56 (d, $^1J_{\text{PC}} = 52.4$ Hz, 1C, PCH), 38.83 (d, $^2J_{\text{PC}} = 3.5$ Hz, 1C, C(O)CH₂). Anal. calcd for C₃₀H₂₄NOPS, C: 75.45, H: 5.07, N: 2.93; found, C: 75.31, H: 4.93, N: 2.81. HRMS (+ESI) *m/z*: (M + H)⁺ calcd for C₃₀H₂₅NOPS, 478.1394; found, 478.1389.

Ligand (*S*)-**29ab** was produced according to general procedure C in 99% yield and *ee*=96.6%. Appearance: white solid. $[\alpha]_{\text{D}}^{20}$ -121 (c 0.5, CH₂Cl₂) for *ee*>99%. Mp. 172.0 – 173.0 °C (dec). $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, CDCl₃) δ 34.04 (s, 1P). ^1H NMR (400 MHz, CDCl₃) δ 8.21 (d, *J* = 8.4 Hz, 1H, ArH), 8.16 (d, *J* = 8.5 Hz, 1H, ArH), 8.09 – 8.01 (m, 2H, ArH), 7.92 (d, *J* = 8.5 Hz, 1H, ArH), 7.83 – 7.75 (m, 2H, ArH), 7.63 (t, *J* = 7.4 Hz, 1H, ArH), 7.56 – 7.44 (m, 5H, ArH), 7.39 – 7.32 (m, 3H, ArH), 7.29 – 7.22 (m, 2H, ArH), 7.16 – 7.04 (m, 3H, ArH), 4.69 – 4.57 (m, 1H, PCHCH₂), 4.54 – 4.48 (m, 1H, C(O)CH₂), 3.71 (ddd, *J* = 17.9, 10.7, 2.4 Hz, 1H, C(O)CH₂). ^{13}C NMR (101 MHz, CDCl₃) δ 199.33 (d, *J* = 13.7 Hz, 1C, C=O), 151.82 – 118.22 (27C, Ar), 41.49 (d, $^1J_{\text{PC}} = 77.3$ Hz, 1C, PCH), 38.26 (s, 1C, C(O)CH₂). Anal. calcd for C₃₀H₂₄NO₂P, C: 78.08, H: 5.24, N: 3.04; found, C: 78.27, H: 5.35, N: 3.24. HRMS (+ESI) *m/z*: (M + H)⁺ calcd for C₃₀H₂₅NO₂P, 462.1623; found, 462.1625.

Ligand (*S*)-**29ba** was produced according to general procedure C in 99% yield and *ee*=97.4%. HPLC conditions: Daicel Chiralpak IC column, *n*-hexane/2-propanol (90:10), 1 ml/min flowrate, 23 °C column temperature, major peak (*S*): 14.2 min, minor peak (*R*): 18.2 min. Appearance: white solid. The obtained characterization data were consistent with literature report¹³³: $[\alpha]_{\text{D}}^{20}$ -241 (c 0.1, CH₂Cl₂) for *ee*>99%. Mp. 94.0 – 96.0 °C. $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl₃, 162 MHz) δ 51.5 (s, 1P). ^1H NMR (CDCl₃, 400 MHz) δ 8.63–8.61 (m, 1H, ArH), 8.23–8.18 (m, 2H, ArH), 7.80 (d, 1H, *J* = 7.8 Hz, ArH), 7.68 (td, 1H, *J* = 7.7 Hz, *J* = 1.7 Hz, ArH), 7.54–7.49 (m, 5H, ArH), 7.39–7.35 (m, 1H, ArH), 7.33–7.25 (m, 3H, ArH), 7.23–7.19 (m, 2H, ArH), 7.08–7.05 (m, 3H, ArH), 4.87 (td, 1H, *J* = 10.6 Hz, *J* = 2.6 Hz, PCHCH₂), 4.51 (ddd, 1H, *J* = 18.2 Hz, *J* = 10.9 Hz, *J* = 6.2 Hz, C(O)CH₂), 3.51 (ddd, 1H, *J* = 18.4 Hz, *J* = 11.6 Hz, *J* = 2.7 Hz, C(O)CH₂). ^{13}C NMR (CDCl₃, 100 MHz): δ 198.8 (d, *J* = 15.1 Hz, 1C, C=O), 152.9 – 121.8 (23C, Ar), 42.1 (d, $^1J_{\text{PC}} = 52.9$ Hz, 1C, PCH), 38.6 (s, 1C, C(O)CH₂). Anal. calcd for C₂₆H₂₂NOPS, C: 73.05, H: 5.19, N:

3.28; found, C: 72.87, H: 5.02, N: 3.60. HRMS (+ESI) m/z : $(M + H)^+$ calcd for $C_{26}H_{23}NO$, 428.1238; found, 428.1235.

Ligand (*S*)-**29ca** was produced according to general procedure C in 99% yield and $ee=96.6\%$. HPLC conditions: Daicel Chiralpak IC column, *n*-hexane/2-propanol (90:10), 1 ml/min flowrate, 23 °C column temperature, major peak (*S*): 9.0 min, minor peak (*R*): 11.0 min. Appearance: white solid. $[\alpha]_D^{20}$ -245 (c 1.0, CH_2Cl_2) for $ee>99\%$. Mp. 144.0 – 146.0 °C. $^{31}P\{^1H\}$ NMR ($CDCl_3$, 162 MHz) δ 51.59 (s, 1P). 1H NMR (400 MHz, $CDCl_3$) δ 8.27 – 8.18 (m, 2H, ArH), 7.60 (d, $J = 7.6$ Hz, 1H, ArH), 7.57 – 7.45 (m, 6H, ArH), 7.33 – 7.24 (m, 3H, ArH), 7.24 – 7.14 (m, 3H, ArH), 7.10 – 7.01 (m, 3H, ArH), 4.91 (td, $J = 10.7$ Hz, $J = 2.3$ Hz, 1H, $PCHCH_2$), 4.46 (ddd, $J = 17.5$, 11.0, 6.1 Hz, 1H, $C(O)CH_2$), 3.50 (ddd, $J = 17.7$, 11.4, 2.1 Hz, 1H, $C(O)CH_2$), 2.58 (s, 3H, $ArCH_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.00 (d, $J = 15.5$ Hz, 1C, C=O), 158.09 – 119.01 (23C, Ar), 42.17 (d, $^1J_{PC} = 52.5$ Hz, 1C, PCH), 38.84 (d, $^2J_{PC} = 3.4$ Hz, 1C, $C(O)CH_2$), 24.44 (s, 1C, $ArCH_3$). Anal. calcd for $C_{27}H_{24}NO$, C: 73.45, H: 5.48, N: 3.17; found, C: 73.76, H: 5.84, N: 3.30. HRMS (+ESI) m/z : $(M + H)^+$ calcd for $C_{27}H_{25}NO$, 442.1394; found, 442.1390.

Ligand (*S*)-**29da** was produced according to general procedure C in 98% yield and $ee>99\%$. HPLC conditions: Daicel Chiralpak IC column, *n*-hexane/2-propanol (90:10), 1 ml/min flowrate, 23 °C column temperature, major peak (*S*): 14.2 min, minor peak (*R*): 18.2 min. Appearance: white solid. $[\alpha]_D^{20}$ -259 (c 0.5, CH_2Cl_2) for $ee>99\%$. Mp. 210.8 – 211.2 °C. $^{31}P\{^1H\}$ NMR ($CDCl_3$, 162 MHz) δ 51.38 (s, 1P). 1H NMR (400 MHz, $CDCl_3$) δ 8.18 (ddd, $J = 12.0$, 7.5, 1.9 Hz, 2H, ArH), 8.04 (d, $J = 8.8$ Hz, 2H, ArH), 7.79 (dd, $J = 7.7$, 1.2 Hz, 1H, ArH), 7.76 – 7.65 (m, 2H, ArH), 7.58 – 7.43 (m, 5H, ArH), 7.37 – 7.27 (m, 3H, ArH), 7.27 – 7.19 (m, 2H, ArH), 7.13 – 7.02 (m, 5H, ArH), 4.89 (td, $J = 10.5$, 2.8 Hz, 1H, $PCHCH_2$), 4.64 (ddd, $J = 17.6$, 10.8, 6.5 Hz, 1H, $C(O)CH_2$), 3.90 (s, 3H, OCH_3), 3.58 (ddd, $J = 18.2$, 11.6, 2.8 Hz, 1H, $C(O)CH_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.46 (d, $J = 14.9$ Hz, 1C, C=O), 161.14 – 114.53 (29C, Ar), 55.64 (s, 1C, OCH_3), 42.43 (d, $^1J_{PC} = 52.5$ Hz, 1C, PCH), 38.70 (d, $^2J_{PC} = 3.6$ Hz, 1C, $C(O)CH_2$). Anal. calcd for $C_{33}H_{28}NO_2$, C: 74.28, H: 5.29, N: 2.62; found, C:

74.06, H: 5.11, N: 2.40. HRMS (+ESI) m/z : $(M + H)^+$ calcd for $C_{33}H_{29}NO_2PS$, 534.1657; found, 534.1652.

Ligand (*S*)-**29ea** was produced according to general procedure C in 98% yield and $ee=86.7\%$. HPLC conditions: Daicel Chiralpak IC column, *n*-hexane/2-propanol (90:10), 1 ml/min flowrate, 23 °C column temperature, major peak (*S*): 10.2 min, minor peak (*R*): 12.4 min. Appearance: white solid. $[\alpha]_D^{20}$ -273 (c 1.0, CH_2Cl_2) for $ee=86.7\%$. Mp. 167.6 – 168.0 °C. $^{31}P\{^1H\}$ NMR ($CDCl_3$, 162 MHz) δ 51.37 (s, 1P). 1H NMR (400 MHz, $CDCl_3$) δ 8.31 – 8.20 (m, 3H, ArH), 8.15 (d, $J = 8.5$ Hz, 1H, ArH), 7.90 (d, $J = 8.5$ Hz, 1H, ArH), 7.84 – 7.76 (m, 2H, ArH), 7.66 – 7.60 (m, 1H, ArH), 7.60 – 7.50 (m, 5H, ArH), 7.34 (td, $J = 7.2$, 1.6 Hz, 1H, ArH), 7.29 – 7.20 (m, 2H, ArH), 7.16 (dd, $J = 8.2$, 2.1 Hz, 2H, ArH), 6.87 (d, $J = 8.0$ Hz, 2H, ArH), 4.92 (td, $J = 10.8$, 2.7 Hz, 1H, $PCHCH_2$), 4.62 (ddd, $J = 17.6$, 11.1, 6.3 Hz, 1H, $C(O)CH_2$), 3.64 (ddd, $J = 17.9$, 11.1, 2.7 Hz, 1H, $C(O)CH_2$), 2.18 (d, $J = 1.8$ Hz, 3H, $ArCH_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.43 (d, $J = 16.2$ Hz, 1C, $C=O$), 152.60 – 118.33 (27C, Ar), 42.16 (d, $^1J_{PC} = 52.5$ Hz, 1C, PCH), 38.78 (d, $^2J_{PC} = 4.0$ Hz, 1C, $C(O)CH_2$), 21.22 (s, 1C, $ArCH_3$). Anal. calcd for $C_{31}H_{26}NO_2PS$, C: 75.74, H: 5.33, N: 2.85; found, C: 75.93, H: 5.64, N: 3.02. HRMS (+ESI) m/z : $(M + H)^+$ calcd for $C_{31}H_{27}NO_2PS$, 492.1551; found, 492.1554.

Ligand (*S*)-**29fa** was produced according to general procedure C in 95.1% yield and $ee=86.7\%$. HPLC conditions: Daicel Chiralpak IC column, *n*-hexane/2-propanol (90:10), 1 ml/min flowrate, 23 °C column temperature, major peak (*S*): 21.8 min, minor peak (*R*): 28.9 min. Appearance: white solid. $[\alpha]_D^{20}$ -225 (c 0.5, CH_2Cl_2) for $ee=82.1\%$. Mp. 137.6 – 138.0 °C. $^{31}P\{^1H\}$ NMR ($CDCl_3$, 162 MHz) δ 51.27 (s, 1P). 1H NMR (400 MHz, $CDCl_3$) δ 8.32 – 8.22 (m, 3H, ArH), 8.16 (d, $J = 8.5$ Hz, 1H, ArH), 7.91 (d, $J = 8.5$ Hz, 1H, ArH), 7.85 – 7.76 (m, 2H, ArH), 7.64 (t, $J = 7.5$ Hz, 1H, ArH), 7.59 – 7.50 (m, 5H, ArH), 7.34 (td, $J = 7.0$, 1.2 Hz, 1H, ArH), 7.29 – 7.26 (m, 1H, ArH), 7.25 – 7.22 (m, 1H, ArH), 7.19 (dd, $J = 8.8$, 2.2 Hz, 2H, ArH), 6.61 (d, $J = 8.6$ Hz, 2H, ArH), 4.90 (td, $J = 11.1$, 2.6 Hz, 1H, $PCHCH_2$), 4.60 (ddd, $J = 17.6$, 11.2, 6.3 Hz, 1H, $C(O)CH_2$), 3.67 (s, 3H, OCH_3), 3.61 (ddd, $J = 17.7$, 10.7, 2.7 Hz, 1H, $C(O)CH_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.52 (d, $J = 15.8$ Hz, 1C, $C=O$), 159.03 – 113.40 (27C, Ar).

Ar), 55.26 (s, 1C, OCH₃), 41.81 (d, ¹J_{PC} = 53.0 Hz, 1C, PCH), 38.83 (d, ²J_{PC} = 4.1 Hz, 1C, C(O)CH₂). Anal. calcd for C₃₁H₂₆NO₂PS, C: 73.35, H: 5.16, N: 2.76; found, C: 73.27, H: 5.09, N: 2.62. HRMS (+ESI) m/z: (M + H)⁺ calcd for C₃₁H₂₇NO₂PS, 508.1500; found, 508.1495.

Ligand (S)-**29ga** was produced according to general procedure C in 98% yield and ee=95.6%. HPLC conditions: Daicel Chiralpak IC column, *n*-hexane/2-propanol (95:05), 1 ml/min flowrate, 23 °C column temperature, major peak (*S*): 14.7 min, minor peak (*R*): 17.1 min. Appearance: white solid. [α]_D²⁰ -291 (c 1.0, CH₂Cl₂) for ee>99%. Mp. 203.5 – 204.0 °C. ³¹P{¹H} NMR (CDCl₃, 162 MHz) δ 50.93 (s, 1P). ¹H NMR (400 MHz, CDCl₃) δ 8.31 – 8.20 (m, 3H, ArH), 8.17 (d, *J* = 8.5 Hz, 1H, ArH), 7.91 (d, *J* = 8.5 Hz, 1H, ArH), 7.84 – 7.75 (m, 2H, ArH), 7.68 – 7.61 (m, 1H, ArH), 7.61 – 7.50 (m, 5H, ArH), 7.41 – 7.33 (m, 1H, ArH), 7.33 – 7.23 (m, 2H, ArH), 7.23 – 7.12 (m, 4H, ArH), 4.90 (td, *J* = 11.0, 2.6 Hz, 1H, PCHCH₂), 4.62 (ddd, *J* = 17.6, 11.2, 6.1 Hz, 1H, C(O)CH₂), 3.61 (ddd, *J* = 17.9, 10.7, 2.7 Hz, 1H, C(O)CH₂). ¹³C NMR (101 MHz, CDCl₃) δ 199.20 (d, *J* = 15.4 Hz, 1C, C=O), 152.39 – 118.25 (27C, Ar), 42.10 (d, ¹J_{PC} = 52.4 Hz, 1C, PCH), 38.61 (d, ²J_{PC} = 3.4 Hz, 1C, C(O)CH₂). Anal. calcd for C₃₀H₂₃NOPSBr, C: 64.75, H: 4.17, N: 2.52; found, C: 64.90, H: 4.39, N: 2.77. HRMS (+ESI) m/z: (M + H)⁺ calcd for C₃₀H₂₄NOPSBr, 556.0500; found, 556.0493.

Ligand (S)-**29ha** was produced according to general procedure C in 97% yield and ee=94.6%. HPLC conditions: Daicel Chiralpak IC column, *n*-hexane/2-propanol (97:03), 1 ml/min flowrate, 23 °C column temperature, major peak (*S*): 11.1 min, minor peak (*R*): 13.7 min. Appearance: white solid. [α]_D²⁰ -226 (c 1.0, CH₂Cl₂) for ee>99%. Mp. 121.9 – 122.6 °C. ³¹P{¹H} NMR (CDCl₃, 162 MHz) δ 51.27 (s, 1P). ¹H NMR (400 MHz, CDCl₃) δ 8.32 – 8.21 (m, 3H, ArH), 8.17 (d, *J* = 8.5 Hz, 1H, ArH), 7.91 (d, *J* = 8.5 Hz, 1H, ArH), 7.88 – 7.74 (m, 2H, ArH), 7.64 (t, *J* = 7.5 Hz, 1H, ArH), 7.61 – 7.48 (m, 5H, ArH), 7.45 – 7.30 (m, 5H, ArH), 7.30 – 7.19 (m, 2H, ArH), 4.99 (td, *J* = 10.9, 2.4 Hz, 1H, PCHCH₂), 4.70 (ddd, *J* = 17.6, 11.2, 6.0 Hz, 1H, C(O)CH₂), 3.65 (ddd, *J* = 18.1, 11.0, 2.5 Hz, 1H, C(O)CH₂). ¹³C NMR (101 MHz, CDCl₃) δ 199.08 (d, *J* = 15.2 Hz,

1C, C=O), 152.31 – 118.22 (28C, Ar + CF₃), 42.51 (d, ¹J_{PC} = 51.9 Hz, 1C, PCH), 38.62 (d, ²J_{PC} = 3.1 Hz, 1H, C(O)CH₂). Anal. calcd for C₃₁H₂₃NOPSF₃, C: 68.25, H: 4.25, N: 2.57; found, C: 68.12, H: 4.19, N: 2.44. HRMS (+ESI) m/z: (M + H)⁺ calcd for C₃₁H₂₄NOPSF₃, 546.1268; found, 546.1267.

Ligand (*S*)-**29ia** was produced according to general procedure

C in 98% yield and ee=94.3%. HPLC conditions: Daicel Chiralpak IC column, *n*-hexane/2-propanol (90:10), 1 ml/min flowrate, 23 °C column temperature, major peak (*S*): 16.2 min, minor peak (*R*): 21.7 min. Appearance: white solid. [α]_D²⁰ -294 (c 1.0, CH₂Cl₂) for ee>99%. Mp. 208.0 – 210.0 °C (dec). ³¹P{¹H} NMR (CDCl₃, 162 MHz) δ 51.24 (s, 1P). ¹H NMR (400 MHz, CDCl₃) δ 8.35 – 8.24 (m, 3H, ArH), 8.12 (d, *J* = 8.5 Hz, 1H, ArH), 7.86 (d, *J* = 8.5 Hz, 1H, ArH), 7.83 – 7.77 (m, 2H, ArH), 7.74 (s, 1H, ArH), 7.69 – 7.59 (m, 3H, ArH), 7.58 – 7.49 (m, 6H, ArH), 7.41 (d, *J* = 8.5 Hz, 1H, ArH), 7.38 – 7.32 (m, 2H, ArH), 7.32 – 7.26 (m, 1H, ArH), 7.17 (td, *J* = 7.6, 3.1 Hz, 2H, ArH), 5.11 (td, *J* = 10.8, 2.7 Hz, 1H, PCHCH₂), 4.79 (ddd, *J* = 17.6, 11.1, 6.2 Hz, 1H, C(O)CH₂), 3.74 (ddd, *J* = 18.0, 11.0, 2.7 Hz, 1H, C(O)CH₂). ¹³C NMR (101 MHz, CDCl₃) δ 199.33 (d, *J* = 15.5 Hz, 1C, C=O), 152.52 – 118.28 (31C, Ar), 42.77 (d, ¹J_{PC} = 52.3 Hz, 1C, PCH), 38.88 (d, ²J_{PC} = 3.5 Hz, 1C, C(O)CH₂). Anal. calcd for C₃₄H₂₆NOPS, C: 77.40, H: 4.97, N: 2.65; found, C: 77.45, H: 5.13, N: 2.76. HRMS (+ESI) m/z: (M + H)⁺ calcd for C₃₄H₂₇NOPS, 528.1551; found, 528.1552.

Ligand (*S*)-**29ja** was produced according to general procedure C

in 99% yield and ee=95.2%. HPLC conditions: Daicel Chiralpak IG column, *n*-hexane/2-propanol (85:15), 1 ml/min flowrate, 23 °C column temperature, major peak (*S*): 55.6 min, minor peak (*R*): 43.6 min. Appearance: white solid. [α]_D²⁰ -268 (c 1.0, CH₂Cl₂) for ee=95.2%. Mp. 194.6 – 195.0 °C. ³¹P{¹H} NMR (CDCl₃, 121 MHz) δ 51.67 (s, 1P). ¹H NMR (300 MHz, CDCl₃) δ 9.28 (d, *J* = 2.2 Hz, 1H, ArH), 8.63 (d, *J* = 2.0 Hz, 1H, ArH), 8.25 – 8.14 (m, 2H, ArH), 8.10 (d, *J* = 8.5 Hz, 1H, ArH), 7.90 (d, *J* = 8.2 Hz, 1H, ArH), 7.86 – 7.75 (m, 1H, ArH), 7.65 – 7.57 (m, 1H, ArH), 7.57 – 7.46 (m, 5H, ArH), 7.40 – 7.30 (m, 3H, ArH), 7.29 – 7.19 (m, 2H, ArH), 7.16 – 7.06 (m, 3H, ArH), 4.90 (td, *J* = 10.0, 2.8 Hz, 1H, PCHCH₂), 4.20 (ddd, *J* = 17.9, 10.1, 6.2 Hz, 1H, C(O)CH₂), 3.49 (ddd, *J* = 18.0, 12.1,

2.8 Hz, 1H, C(O)CH₂). ¹³C NMR (75 MHz, CDCl₃) δ 196.05 (d, *J* = 14.6 Hz, 1C, C=O), 150.00 – 126.77 (27C, Ar), 41.69 (d, ¹*J*_{PC} = 52.9 Hz, 1C, PCH), 40.03 (d, ²*J*_{PC} = 3.9 Hz, 1C, C(O)CH₂). Anal. calcd for C₃₀H₂₄NOPS, C: 75.45, H: 5.07, N: 2.93; found, C: 75.22, H: 4.93, N: 2.88. HRMS (+ESI) *m/z*: (*M* + *H*)⁺ calcd for C₃₀H₂₅NOPS, 478.1394; found, 478.1393.

2.5.4 synthesis of chiral N-C(sp³)-E pincer complexes:

General procedure D (Scheme 55):

A mixture of PdCl₂ (7.4 mg, 42 μmol, 1.0 eq.) and LiCl (7.1 mg, 168 μmol, 4.0 eq.) in 20 mL solvent was stirred for 30 mins. Then, the ligand (*S*)-**29** (42 μmol, 1.0 eq.) was added to the mixture and it was stirred at room temperature for 2 to 5 days. The reaction was monitored by thin-layer chromatography (ethyl acetate/*n*-hexanes 2:1) and confirmed by ³¹P{¹H} NMR. After completion the solvent was removed under reduced pressure and the crude material was purified via column chromatography by using *n*-hexane/ethyl acetate (from 80:20 to 20:80) eluent system.

Scheme 55. Cyclometalation of ligand **29** analogues.

Complex (*R,R*)-**30aa** was produced according to general procedure D in 72% yield. Appearance: yellow solid. [α]_D²⁰ -90 (c 1.0, CH₂Cl₂). Mp. 214.2 – 215.5 °C (dec). ³¹P{¹H} NMR (CDCl₃, 162 MHz) δ

67.23 (s, 1P). ¹H NMR (400 MHz, CDCl₃) δ 9.47 (d, *J* = 8.8 Hz, 1H, ArH), 8.37 (d, *J* = 8.3 Hz, 1H, ArH), 7.97 – 7.88 (m, 3H, ArH), 7.85 (d, *J* = 7.8 Hz, 1H, ArH), 7.76 (d, *J* = 8.3 Hz, 1H, ArH), 7.71 – 7.62 (m, 4H, ArH), 7.62 – 7.51 (m, 3H, ArH), 7.42 (td, *J* = 7.8, 3.3 Hz, 2H, ArH), 7.25 – 7.19 (m, 1H, ArH), 7.15 (t, *J* = 7.6 Hz, 2H, ArH), 7.02 (d, *J* = 7.4 Hz, 2H, ArH), 5.34 (dd, *J* = 14.8, 8.8 Hz, 1H, PCH), 4.96 (dd, *J* = 8.7, 6.1 Hz, 1H, PdCH). ¹³C NMR (101 MHz, CDCl₃) δ 189.15 (d, *J* = 14.6 Hz, 1C, C=O), 158.23 – 118.33 (27C, Ar), 57.53 (d, ²*J*_{PC} = 5.9 Hz, 1C, PdCH), 53.37 (d, ¹*J*_{PC} = 58.8 Hz, 1C, PCH). Anal. calcd for C₃₀H₂₃NOPPdSCl, C: 58.27, H: 3.75, N: 2.26; found, C:

58.04, H: 3.65, N: 2.41. HRMS (+ESI) m/z : $(M + H)^+$ calcd for $C_{30}H_{24}NOP^{108}PdSCl$, 620.0044; found, 620.0032.

Complex (*R,R*)-**30ab** was produced according to general procedure D in 70% yield. Appearance: yellow solid. $[\alpha]_D^{20}$ -117 (c 1.0, CH_2Cl_2). Mp. 179.0 – 180.0 °C (dec). $^{31}P\{^1H\}$ NMR ($CDCl_3$, 162 MHz) δ 73.24 (s, 1P). 1H NMR (400 MHz, $CDCl_3$) δ 9.44 (d, J = 8.8 Hz, 1H, ArH), 8.36 (d, J = 8.3 Hz, 1H, ArH), 8.01 (dd, J = 11.2, 7.9 Hz, 2H, ArH), 7.91 (t, J = 7.7 Hz, 1H, ArH), 7.81 (d, J = 8.0 Hz, 1H, ArH), 7.72 – 7.48 (m, 8H, ArH), 7.44 – 7.33 (m, 2H, ArH), 7.21 – 7.06 (m, 5H, ArH), 5.27 (dd, J = 7.4, 5.4 Hz, 1H, PdCH), 4.96 (dd, J = 14.1, 7.7 Hz, 1H, PCH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.58 (d, J = 10.1 Hz, 1C, C=O), 159.52 – 118.20 (27C, Ar), 59.70 (s, 1C, PdCH), 48.06 (d, J = 71.7 Hz, 1C, PCH). Anal. calcd for $C_{30}H_{23}NO_2PPdCl$, C: 59.82, H: 3.85, N: 2.33; found, C: 59.99, H: 4.05, N: 2.58. HRMS (+ESI) m/z : $(M + H)^+$ calcd for $C_{30}H_{24}NO_2P^{106}PdCl$, 602.0268; found, 602.0281.

Complex (*R,R*)-**30ca** was produced according to general procedure D in 63% yield. Appearance: yellow solid. $[\alpha]_D^{20}$ -77 (c 1.0, CH_2Cl_2). Mp. 210.5 – 212.0 °C (dec). $^{31}P\{^1H\}$ NMR ($CDCl_3$, 162 MHz) δ 67.30 (s, 1P). 1H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.85 (m, 2H, ArH), 7.75 (t, J = 7.7 Hz, 1H, ArH), 7.69 – 7.50 (m, 7H, ArH), 7.42 (td, J = 7.9, 3.3 Hz, 2H, ArH), 7.29 (d, J = 7.8 Hz, 1H, ArH), 7.24 – 7.17 (m, 1H, ArH), 7.14 (t, J = 7.6 Hz, 2H, ArH), 7.02 – 6.97 (m, 2H, ArH), 5.28 (dd, J = 14.9, 8.8 Hz, 1H, PCH), 4.79 (dd, J = 8.7, 6.1 Hz, 1H, PdCH), 3.09 (s, 3H, ArCH₃). ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.04 (d, J = 14.7 Hz, 1C, C=O), 162.46 – 119.61 (23C, Ar), 56.37 (d, $^2J_{PC}$ = 6.0 Hz, 1C, PdCH), 53.59 (d, $^1J_{PC}$ = 59.0 Hz, 1C, PCH), 26.04 (s, 1C, ArCH₃). Anal. calcd for $C_{27}H_{23}NOPPdSCl$, C: 55.68, H: 3.98, N: 2.41; found, C: 55.51, H: 3.86, N: 2.69. HRMS (+ESI) m/z : $(M + H)^+$ calcd for $C_{27}H_{24}NOPPdSCl$, 582.0040; found, 582.0022.

Complex (R,R)-**30da** was produced according to general procedure D in 31% yield. Appearance: yellow solid. $[\alpha]_D^{20}$ -94 (c 1.0, CH₂Cl₂). Mp. 200.0 – 201.5 °C (dec). ³¹P{¹H} NMR (CDCl₃, 162 MHz) δ 67.35 (s, 1P). ¹H NMR (400 MHz, CDCl₃) δ 8.04 (d, J = 8.8 Hz, 2H, ArH), 7.93 – 7.84 (m, 3H, ArH), 7.83 – 7.74 (m, 2H, ArH), 7.69 – 7.57 (m, 4H, ArH), 7.57 – 7.44 (m, 4H, ArH), 7.25 – 7.15 (m, 3H, ArH), 7.12 (d, J = 8.8 Hz, 2H, ArH), 7.10 – 7.04 (m, 2H, ArH), 5.29 (dd, J = 14.9, 8.7 Hz, 1H, PCH), 4.93 (dd, J = 8.7, 6.4 Hz, 1H, PdCH), 3.93 (s, 3H, OCH₃). ¹³C NMR (75 MHz, CDCl₃) δ 187.81 (d, J = 14.7 Hz, 1C, C=O), 161.72 – 114.28 (29C, Ar), 56.27 (d, $^2J_{PC}$ = 5.6 Hz, 1C, PdCH), 55.57 (s, 1C, OCH₃), 53.51 (d, $^1J_{PC}$ = 59.3 Hz, 1C, PCH). Anal. calcd for C₃₃H₂₇NO₂PPdSCl, C: 58.77, H: 4.04, N: 2.08; found, C: 58.76, H: 3.96, N: 2.09. HRMS (+ESI) m/z: (M + H)⁺ calcd for C₃₃H₂₈NO₂P¹⁰⁸PdSCl, 676.0306; found, 676.0338.

Complex (R,R)-**30ha** was produced according to general procedure D in 58% yield. Appearance: yellow solid. $[\alpha]_D^{20}$ -82 (c 1.0, CH₂Cl₂). Mp. 203.0 – 204.0 °C (dec). ³¹P{¹H} NMR (CDCl₃, 162 MHz) δ 67.63 (s, 1P). ¹H NMR (300 MHz, CDCl₃) δ 9.47 (d, J = 8.7 Hz, 1H, ArH), 8.39 (d, J = 8.4 Hz, 1H, ArH), 8.01 – 7.89 (m, 3H, ArH), 7.86 (d, J = 8.1 Hz, 1H, ArH), 7.76 (d, J = 8.3 Hz, 1H, ArH), 7.74 – 7.54 (m, 7H, ArH), 7.51 – 7.38 (m, 4H, ArH), 7.15 (d, J = 7.4 Hz, 2H, ArH), 5.38 (dd, J = 15.1, 8.7 Hz, 1H, PCH), 4.91 (dd, J = 8.6, 6.3 Hz, 1H, PdCH). ¹³C NMR (101 MHz, CDCl₃) δ 189.37 (d, J = 14.1 Hz, 1C, C=O), 157.96 – 118.33 (28C, Ar + CF₃), 56.86 (d, $^2J_{PC}$ = 5.7 Hz, 1C, PdCH), 53.03 (d, $^1J_{PC}$ = 58.9 Hz, 1C, PCH). Anal. calcd for C₃₁H₂₂NOPPdSF₃Cl, C: 54.24, H: 3.23, N: 2.04; found, C: 54.56, H: 3.49, N: 2.30. HRMS (+ESI) m/z: (M + H)⁺ calcd for C₃₁H₂₃NOP¹⁰⁸PdSF₃Cl, 687.9918; found, 687.9921.

Complex (R,R)-**30ia** was produced according to general procedure D in 42% yield. Appearance: yellow solid. $[\alpha]_D^{20}$ -81 (c 1.0, CH₂Cl₂). Mp. 200.5 – 202.0 °C (dec). ³¹P{¹H} NMR (CDCl₃, 162 MHz) δ 68.07 (s, 1P). ¹H NMR (500 MHz, CDCl₃) δ 9.49 (d, J = 8.8 Hz, 1H, ArH), 8.36 (d, J = 8.3 Hz, 1H, ArH), 7.96 – 7.88 (m, 3H, ArH), 7.85 (d, J = 8.1 Hz, 1H, ArH), 7.78 – 7.72 (m, 4H, ArH), 7.69 (t, J = 7.6 Hz, 1H, ArH), 7.66

– 7.62 (m, 2H, ArH), 7.61 – 7.51 (m, 4H, ArH), 7.47 – 7.37 (m, 4H, ArH), 7.34 (s, 1H, ArH), 7.15 (d, $J = 8.5$ Hz, 1H, ArH), 5.51 (dd, $J = 15.3, 9.3$ Hz, 1H, PCH), 5.06 (dd, $J = 9.3, 5.4$ Hz, 1H, PdCH). ^{13}C NMR (126 MHz, CDCl_3) δ 189.11 (d, $J = 15.5$ Hz, 1C, C=O), 158.22 – 118.38 (31C, Ar), 57.97 (d, $^2J_{\text{PC}} = 6.3$ Hz, 1C, PdCH), 54.04 (d, $^1J_{\text{PC}} = 59.0$ Hz, PCH). Anal. calcd for $\text{C}_{34}\text{H}_{25}\text{NOPdSCl}$, C: 61.09, H: 3.77, N: 2.10; found, C: 61.36, H: 3.90, N: 2.24. HRMS (+ESI) m/z : ($\text{M} + \text{H}$) $^+$ calcd for $\text{C}_{34}\text{H}_{26}\text{NOP}^{106}\text{PdSCl}$, 668.0196; found, 668.0215.

2.5.5 X-ray measurement data

Crystallographic data: complex **31**.

Table 4. Sample and crystal data for complex **31**.

Identification code	CCDC 1835823	
Chemical formula	$\text{C}_{28}\text{H}_{27}\text{Cl}_3\text{N}_2\text{OPd}$	
Formula weight	620.26 g/mol	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal size	0.040 x 0.120 x 0.220 mm	
Crystal habit	yellow block	
Crystal system	triclinic	
Space group	$P\bar{1}$	
Unit cell dimensions	$a = 9.0823(4)$ Å	$\alpha = 104.763(3)^\circ$
	$b = 13.0319(8)$ Å	$\beta = 103.838(3)^\circ$
	$c = 13.7962(9)$ Å	$\gamma = 108.746(3)^\circ$
Volume	$1400.32(14)$ Å 3	
Z	2	
Density (calculated)	1.471 g/cm 3	
Absorption coefficient	0.972 mm $^{-1}$	

Crystallographic data: complex **33**.

Table 5. Sample and crystal data for complex **33**.

Identification code	CCDC 1835825	
Chemical formula	$C_{29}H_{28}ClN_3O_5Pd$	
Formula weight	640.39 g/mol	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal size	0.100 x 0.120 x 0.320 mm	
Crystal habit	yellow needle	
Crystal system	monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	$a = 15.0520(4)$ Å	$\alpha = 90^\circ$
	$b = 14.2265(4)$ Å	$\beta = 93.2390(10)^\circ$
	$c = 12.8452(3)$ Å	$\gamma = 90^\circ$
Volume	$2746.24(12)$ Å ³	
Z	4	
Density (calculated)	1.549 g/cm ³	
Absorption coefficient	0.817 mm ⁻¹	

Crystallographic data: complex **34**.

Table 6. Sample and crystal data for complex **34**.

Identification code	CCDC 1835824	
Chemical formula	$C_{24}H_{24}Cl_4N_2O_5Pd$	
Formula weight	668.65 g/mol	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal size	0.160 x 0.220 x 0.240 mm	
Crystal habit	yellow block	
Crystal system	monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	$a = 13.8557(10)$ Å	$\alpha = 90^\circ$
	$b = 13.5836(10)$ Å	$\beta = 111.047(3)^\circ$
	$c = 15.6071(12)$ Å	$\gamma = 90^\circ$
Volume	$2741.5(4)$ Å ³	
Z	4	
Density (calculated)	1.620 g/cm ³	
Absorption coefficient	1.104 mm ⁻¹	

Crystallographic data: ligand (*S*)-**29aa**.

Table 7. Sample and crystal data for complex (*S*)-**29aa**.

Identification code	CCDC 1836590	
Chemical formula	C ₃₀ H ₂₄ NOPS	
Formula weight	477.53 g/mol	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal size	0.080 x 0.120 x 0.320 mm	
Crystal habit	colorless needle	
Crystal system	orthorhombic	
Space group	<i>P</i> 2 ₁ 2 ₁ 2 ₁	
Unit cell dimensions	<i>a</i> = 6.77440(10) Å <i>b</i> = 15.4029(4) Å <i>c</i> = 22.8583(5) Å	$\alpha = 90^\circ$ $\beta = 90^\circ$ $\gamma = 90^\circ$
Volume	2385.16(9) Å ³	
<i>Z</i>	4	
Density (calculated)	1.330 g/cm ³	
Absorption coefficient	0.227 mm ⁻¹	
Absolute structure parameter	-0.05(3)	

Crystallographic data: ligand (*S*)-**29ca**. **Table 8.** Sample and crystal data for complex (*S*)-**29ca**.

Identification code	CCDC 1836617
Chemical formula	C ₂₇ H ₂₄ NOPS
Formula weight	441.50 g/mol
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal size	0.140 x 0.220 x 0.280 mm
Crystal habit	colorless block
Crystal system	monoclinic

Space group	$P2_1$	
Unit cell dimensions	$a = 16.0322(6) \text{ \AA}$	$\alpha = 90^\circ$
	$b = 19.5446(6) \text{ \AA}$	$\beta = 107.158(2)^\circ$
	$c = 23.0739(11) \text{ \AA}$	$\gamma = 90^\circ$
Volume	$6908.3(5) \text{ \AA}^3$	
Z	12	
Density (calculated)	1.273 g/cm^3	
Absorption coefficient	0.229 mm^{-1}	
Absolute structure parameter	$0.02(6)$	

Crystallographic data: ligand (*S*)-**29ga**.

Table 9. Sample and crystal data for complex (*S*)-**29ga**.

Identification code	CCDC 1835826	
Chemical formula	$\text{C}_{30}\text{H}_{23}\text{BrNOPS}$	
Formula weight	556.43 g/mol	
Temperature	$100(2) \text{ K}$	
Wavelength	$0.71073 \text{ \AA}$	
Crystal size	$0.040 \times 0.100 \times 0.260 \text{ mm}$	
Crystal habit	colorless needle	
Crystal system	triclinic	
Space group	$P1$	
Unit cell dimensions	$a = 6.6051(2) \text{ \AA}$	$\alpha = 63.8970(13)^\circ$
	$b = 10.3822(4) \text{ \AA}$	$\beta = 83.4065(12)^\circ$
	$c = 10.7392(4) \text{ \AA}$	$\gamma = 72.1063(12)^\circ$
Volume	$629.16(4) \text{ \AA}^3$	
Z	1	
Density (calculated)	1.469 g/cm^3	
Absorption coefficient	1.805 mm^{-1}	
Absolute structure parameter	$0.011(5)$	

Crystallographic data: ligand (*S*)-**29ja**.

Table 10. Sample and crystal data for complex (*S*)-**29ja**.

Identification code	CCDC 1835827	
Chemical formula	$C_{30}H_{24}NOPS$	
Formula weight	477.53 g/mol	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal size	0.140 x 0.200 x 0.220 mm	
Crystal habit	colorless block	
Crystal system	monoclinic	
Space group	$P2_1$	
Unit cell dimensions	$a = 12.6248(6)$ Å	$\alpha = 90^\circ$
	$b = 16.7612(7)$ Å	$\beta = 114.8752(12)^\circ$
	$c = 13.0147(5)$ Å	$\gamma = 90^\circ$
Volume	$2498.50(19)$ Å ³	
Z	4	
Density (calculated)	1.269 g/cm ³	
Absorption coefficient	0.217 mm ⁻¹	
Absolute structure parameter	0.03(5)	

Crystallographic data: N-C(sp³)-S complex (*R,R*)-**30aa**.

Table 11. Sample and crystal data for complex (*R,R*)-**30aa**.

Identification code	CCDC 1835818	
Chemical formula	C _{30.50} H ₂₄ Cl ₂ NOPPdS	
Formula weight	660.84 g/mol	
Temperature	103(2) K	
Wavelength	1.54178 Å	
Crystal size	0.020 x 0.120 x 0.200 mm	
Crystal habit	yellow plate	
Crystal system	orthorhombic	
Space group	<i>P</i> 2 ₁ 2 ₁ 2	
Unit cell dimensions	a = 15.7681(2) Å	$\alpha = 90^\circ$
	b = 26.1382(4) Å	$\beta = 90^\circ$
	c = 12.9579(2) Å	$\gamma = 90^\circ$
Volume	5340.60(13) Å ³	
Z	8	
Density (calculated)	1.644 g/cm ³	
Absorption coefficient	8.953 mm ⁻¹	
Absolute structure parameter	0.002(4)	

Crystallographic data: N-C(sp³)-O complex (*S,S*)-**30ab**.

Table 12. Sample and crystal data for complex (*S,S*)-**30ab**.

Identification code	CCDC 1835822	
Chemical formula	C _{30.50} H ₂₄ Cl ₂ NO ₂ PPd	
Formula weight	644.78 g/mol	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal size	0.140 x 0.200 x 0.240 mm	
Crystal habit	orange block	
Crystal system	monoclinic	
Space group	<i>P</i> 2 ₁	
Unit cell dimensions	a = 9.9992(7) Å	$\alpha = 90^\circ$
	b = 26.528(2) Å	$\beta = 100.829(3)^\circ$
	c = 10.2093(7) Å	$\gamma = 90^\circ$
Volume	2659.9(3) Å ³	

Z	4
Density (calculated)	1.610 g/cm ³
Absorption coefficient	0.989 mm ⁻¹
Absolute structure parameter	0.12(5)

Crystallographic data: N-C(sp³)-S complex (*R,R*)-**30ca**.

Table 13. Sample and crystal data for complex (*R,R*)-**30ca**.

Identification code	CCDC 1835819	
Chemical formula	C ₂₇ H ₂₃ ClNOPPdS	
Formula weight	582.34 g/mol	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal size	0.040 x 0.220 x 0.320 mm	
Crystal habit	yellow plate	
Crystal system	orthorhombic	
Space group	<i>P</i> 2 ₁ 2 ₁ 2 ₁	
Unit cell dimensions	<i>a</i> = 8.6314(3) Å	<i>α</i> = 90°
	<i>b</i> = 11.9658(4) Å	<i>β</i> = 90°
	<i>c</i> = 23.0878(7) Å	<i>γ</i> = 90°
Volume	2384.55(14) Å ³	
Z	4	
Density (calculated)	1.622 g/cm ³	
Absorption coefficient	1.066 mm ⁻¹	
Absolute structure parameter	-0.033(16)	

CHAPTER III

Tandem Double Hydrophosphination of $\alpha,\beta,\gamma,\delta$ -Unsaturated Indandiones

3.1 Introduction

Nucleophilic conjugate addition is one of the most powerful strategies to generate a C-C or C-heteroatom bond in synthetic chemistry.¹⁵⁹ Among these transformations, the transition metal-catalysed^{33, 160} and organocatalytic^{34a, 161} 1,4-addition to α,β -unsaturated compounds have developed rapidly in the past decade. In contrast, the addition to extended π -systems, such as $\alpha,\beta,\gamma,\delta$ -unsaturated compounds, has been relatively limited because of the challenge in controlling the regioselectivity (*e.g.*, 1,2-, 1,4- or 1,6-addition).¹⁶² Moreover, double nucleophilic additions to such substrates are even rarer. Although some examples of double addition to $\alpha,\beta,\gamma,\delta$ -unsaturated compounds have already been reported in C-C¹⁶³, C-S¹⁶⁴ and C-N¹⁶⁵ bond formation, to the best of our knowledge no such reports involving C-P bond formation have appeared in literature to date in spite of the importance of diphosphine motifs in several fields.¹⁶⁶

The P-H addition to unsaturated compounds is one of the most favourable approaches in C-P bond formation, due to its inherent atom economic nature.^{80c, 167} Although metal-free hydrophosphination has been gaining increasing attention in recent years,¹⁶⁸ the metal-catalysed protocol is still more common in the literature.^{146, 169} Internal or terminal alkynes are known to undergo double P-H addition catalysed by transition metals (such as Pd²⁶, Fe¹⁷⁰, Rh¹⁷¹, Zr¹⁷², Cu¹⁷³) or bases (KO^tBu¹⁷⁴, KHMDS¹⁷⁵) (Scheme 56a). The double 1,4-addition to dienones generating wide bite angle PCP-type chiral ligands has also been reported (Scheme 56b).^{96a} To date, the reported P-H addition to extended conjugated systems, *e.g.* $\alpha,\beta,\gamma,\delta$ -unsaturated compounds, has resulted in the formation of either 1,4- or 1,6-addition monophosphine products in palladium-catalysed asymmetric hydrophosphination (Scheme 56c).^{130b, 132, 176} It is pertinent to note that the double addition product was not observed in any of these studies. Herein we report the first example of a double P-H addition to $\alpha,\beta,\gamma,\delta$ -unsaturated systems employing a transition metal-free transformation with excellent diastereoselectivity (Scheme 56d). The coordination properties of the generated compounds were subsequently investigated on a Pd(II) center and an unexpected P,O-bidentate and P-monodentate coordination mode was observed to be preferred over the traditional P,P-coordination in these diphosphines. Separation of the generated metal complexes resulted in the isolation of optically pure bimetallic derivatives.

Scheme 56. Double P-H addition to double- and triple-bonds.

3.2 Results and Discussion

During the preliminary screening of P-H addition to $\alpha,\beta,\gamma,\delta$ -unsaturated-1,3-indandiones (**36**), the formation of either 1,4- or 1,6-adducts was expected in view of previous reports on hydrophosphination of activated conjugated substrates. Surprisingly, the generation of a double addition product was seen in the $^{31}P\{^1H\}$ NMR spectrum of the crude reaction mixture. The generated phosphines were always treated with sulphur and the isolation was performed on the air-stable phosphine sulphides. The double addition under base-free conditions provided the diphosphine product in the diketo form (**37**); however, during purification on silica gel, the compound underwent tautomerization and the product was isolated as the corresponding enol phosphine sulphide (**38aa**). In the presence of base, a salt was generated first, followed by protonation and tautomerization on silica gel (Table 14). The $^{31}P\{^1H\}$ NMR spectrum of the crude reaction product clearly indicated the presence of two distinct isomers. Single crystal X-ray crystallography confirmed that the major product is the racemic isomer with the (R^*,R^*) relative configuration and the minor product is the (R^*,S^*) -diastereomer.¹⁷⁷

Table 14. Reaction condition optimization of **38aa** diphosphine synthesis.^a

Entry	Base (equiv)	Solvent	t	Conv. ^{b,c} [%]	d_r^b [XX/XY]
1	-	acetone	1.5 h	99	5.9 : 1
2	Et_3N (1)	acetone	15 mins	99	11.5 : 1
3	Et_3N (2)	acetone	10 mins	99 (95)	>20 : 1
4	Et_3N (5)	acetone	<5 mins	99	16.7 : 1
5	NaOAc (1)	acetone	1.5 h	99	9.1 : 1
6	K_2CO_3 (1)	acetone	2.75 h	99	8.8 : 1
7	NaOMe (1)	acetone	2.75 h	99	6 : 1
8	DABCO^d (1)	acetone	15 mins	99	>20 : 1
9	DABCO^d (0.5)	acetone	20 mins	99	14 : 2
10	DTBP^e (1)	acetone	4 h	99	5.3 : 1
11	Pyridine (1)	acetone	3 h	99	8 : 1
12	DMA^f (1)	acetone	3.5 h	99	8 : 1
13	TMG (1)	acetone	16 h	99	>20 : 1
14	-	DCM	12 h	99	3.4 : 1
15	Et_3N (1)	DCM	30 mins	99	13.2 : 1
16	Et_3N (2)	DCM	10 mins	99	>20 : 1
17	TMG^g (1)	DCM	16 h	99	>20 : 1
18	Et_3N (1)	MeOH	10 h	99	5.3 : 1
19	Et_3N (1)	Toluene	4 h	99	4.8 : 1
20	Et_3N (1)	CHCl_3	4.5 h	99	4.2 : 1
21	Et_3N (1)	MeCN	20 mins	99	15.9 : 1
22	Et_3N (1)	hexanes	24 h	0	-

^aReaction conditions: **36a** (75.7 mmol, 1.0 eq.), HPPH_2 (158.9 mmol, 2.1 eq.), base (75.7

mmol, 1.0 eq.), solvent (2.5 mL). ^bThe conversion and the d_r value were determined by

$^{31}\text{P}\{^1\text{H}\}$ NMR of the crude material. ^cIsolated yield is presented in parenthesis.

^d DABCO : 1,4-diazabicyclo[2.2.2]octane; ^e DTBP : 2,6-ditert-butyl piridine; ^f DMA :

N,N-dimethylaniline, ^g TMG : 1,1,3,3,-tetramethylguanidine

During the optimization process, the impact of various bases and solvents on the reaction rate and diastereoselectivity was examined. Interestingly, even in the absence of any base, the double addition was completed within 1.5 hours in acetone; although

with low diastereoselectivity (Table 14, entry 1). The presence of an additional base improved the selectivity and altered the reaction rate. Certain bases, such as triethylamine or 1,4-diazabicyclo[2.2.2]octane (DABCO) accelerated the reaction, while others (*e.g.* pyridine and K₂CO₃) slowed it down. The condition selected for the screening of substrates was 2 equivalents of triethylamine as the base and acetone as the solvent.

The protocol showed high tolerance to modification of the substituents on the aromatic ring (**36a-h**) in terms of reactivity and selectivity (Table 15).

Table 15. Substrate scope.^a

Entry	R	R'	t	Yield ^b (%)	<i>dr</i> ^c
1	Ph (36a)	Ph	10 mins	95 (38aa)	>20 : 1
2	Ph (36a)	<i>p</i> -tolyl (40)	10 mins	95 (38ab)	>20 : 1
3	Ph (36a)	<i>m</i> -tolyl (41)	10 mins	94 (38ac)	>20 : 1
4	4-MeOC ₆ H ₄ (36b)	Ph	45 mins	95 (38ba)	>20 : 1
5	4-MeOC ₆ H ₄ (36b)	<i>p</i> -tolyl (40)	45 mins	94 (38bb)	>20 : 1
6	4-MeOC ₆ H ₄ (36b)	<i>m</i> -tolyl (41)	45 mins	93 (38bc)	>20 : 1
7	4-NO ₂ C ₆ H ₄ (36c)	Ph	5 mins	75 (38ca)	4.8 : 1
8	4-NO ₂ C ₆ H ₄ (36c)	<i>p</i> -tolyl (40)	5 mins	74 (38cb)	5.5 : 1
9	4-NO ₂ C ₆ H ₄ (36c)	<i>m</i> -tolyl (41)	5 mins	76 (38cc)	8.8 : 1
10	4-NEt ₂ C ₆ H ₄ (36d)	Ph	85 mins	94 (38da)	>20 : 1
11	4-FC ₆ H ₄ (36e)	Ph	10 mins	93 (38ea)	>20 : 1
12	4-ClC ₆ H ₄ (36f)	Ph	10 mins	93 (38fa)	>20 : 1
13	2-MeOC ₆ H ₄ (36g)	Ph	30 mins	94 (38ga)	>20 : 1
14	2-MeOC ₆ H ₄ (36g)	<i>p</i> -tolyl (40)	30 mins	81 (38gb)	10 : 1
15	2-MeOC ₆ H ₄ (36g)	<i>m</i> -tolyl (41)	30 mins	92 (38gc)	>20 : 1
16	2-NO ₂ C ₆ H ₄ (36h)	Ph	40 mins	82 ^d (38ha)	5.9 : 1

^aReaction conditions: **36** (75.7 μmol, 1.0 eq.), HPR'₂ (158.9 μmol, 2.1 eq.), base (151.4 μmol, 2.0 eq.), solvent (2.5 mL). ^bIsolated yield. ^cThe *dr* value was determined by ³¹P{¹H} NMR of the crude material. ^dMixture of two diastereomers in 1 : 0.17 ratio.

The presence of the electron-donating group (EDG) at the *para*- and *ortho*-positions on the aromatic ring slowed down the reaction slightly; however, the dr values were excellent in most cases (Table 15, entries 4-6 and 10-15). The isolated yields of these derivatives were also appreciable (between 81% and 95%). Changing the phenyl moiety of the phosphine nucleophile to *para*- and *meta*-tolyl groups (**40** and **41**) neither affected the reactivity nor the diastereoselectivity in most cases. Electron-withdrawing groups (EWG) located on the aromatic ring at the *para* position enhanced the reactivity but caused lower diastereoselectivity in the reactions (Table 15, entries 7-9). The EWG at the *ortho* position lowered the reaction rate and the dr value (Table 15, entry 16).

To gain more insights into the nature of the double addition protocol, we further performed control experiments in order to elucidate the reaction mechanism (Scheme 57). Firstly, the reaction of **1a** and **2a** was set up in a 1 : 1 ratio (Scheme 57a). In this transformation, diphenylphosphine was presented as a limiting reagent. Although the formation of the diphosphine product could not be avoided, even in the absence of any base, an intermediate monophosphine was detected in the crude mixture after sulfurization. Based on a short optimization, the best solvent for the monophosphine formation was found to be toluene (details in chapter 3.3). Upon purification, the 1,6-adduct (**42**) was obtained in 11% yield.

Scheme 57. Control experiments and plausible mechanism.

This experiment established the consecutive manner of the reaction (1,6- followed by 1,4-addition). The position of the double bond in this intermediate is crucial and it provides insights into why the second P-H addition could take place in our case (unlike in previous reports on 1,6-addition to $\alpha,\beta,\gamma,\delta$ -unsaturated systems^{130b, 132, 176}). If the double bond was located between the β - and γ -positions, like in compound **49** and **44**, an sp^3 carbon would be present at the α -position and this case, the β -carbon is not sufficiently activated by the indandione moiety anymore due to loss of conjugation and therefore the second nucleophilic addition cannot occur. However, in **42** and **48**, the double bond is located between the α - and the β -positions, hence the β -carbon is still activated and primed for the second conjugate addition of the phosphine nucleophile. In order to elucidate the reason behind the preferred formation of **48** over **49**, theoretical calculations were performed to compare the relative stability of the two possible structures. According to our investigations, the relative Gibbs free energy indicates that **48** is significantly more stable compared to **49** ($\Delta G=5.8$ kcal/mol). The reason for this can be attributed to the stability imparted by the extended conjugation in **48** between the double bond and the planar indandione scaffold.¹⁷⁸

Based on preliminary mechanistic experiments performed in deuterated solvents, the 1,4-retro-Michael addition involving compound **47** was also observed by us (for details, see chapter 3.3). To confirm the possible retro-addition process from **39aa**, we performed another control experiment (Scheme 57b). Firstly, compound **39aa** was synthesized using the aforementioned optimized procedure. After this step was completed, the mixture was treated with another primary phosphine, 3 equivalents of **40**, and the reaction was monitored by $^{31}\text{P}\{^1\text{H}\}$ NMR spectroscopy. The study revealed the generation of a new diphosphine product (**45**) and the regeneration of the diphenylphosphine. After 23 hours, the reaction was treated with sulphur and upon purification, a mixed phosphine, compound **46**, was isolated in 64% yield. It was found that during the reaction, the PPh_2 moiety at the 1,4-position was eliminated from **39aa** and subsequently another addition occurred between a 1,6-monophosphine intermediate and **40**. The newly generated mixed diphosphine (**46**) bears different PR_2 units at the 1,4- and 1,6-positions. This experiment was a clear evidence of the labile nature of the C-P bond at the 1,4-position. Based on the control reactions, we propose that the double addition process, both in the presence and the absence of base, starts with a nucleophilic attack at the 1,6-position, generating a monophosphine intermediate

(**48**) followed by a second nucleophilic attack on the β -carbon, which leads to the formation of the diphosphine product in the diketo form (**37**) under base-free conditions, or to the diphosphine salt (**39aa**) in the presence of triethylamine. After sulfurization and purification on silica gel, both reactions provide the major isomers of the enol diphosphine sulphide (**38aa**). The higher stability of the enol form over the diketo form was confirmed by theoretical studies which are presented in the corresponding publication.¹⁷⁸ The reason behind the higher enol stability must be the formation of a hydrogen-bond between the enol hydrogen and the sulphur of the phosphine unit. This secondary interaction was also confirmed by single crystal X-ray diffraction data of compounds **46** and **38aa**.

The coordination properties of the generated diphosphine were also investigated *via* the coordination of **39aa** to a chiral CN-palladacycle (**5**) which provides two possible coordination sites (Scheme 58).

Scheme 58. Coordination properties of the generated diphosphines.

Although it is well known in the literature that small bite angle diphosphine ligands prefer to develop P,P-bidentate coordination to palladium,^{33, 160, 166} in our case, an unexpected anionic P,O-bidentate- and a neutral P-monodentate-coordination was

established. During the formation of the bidentate chelate, the X-type chloride ligand of **5** was replaced by the anionic oxygen of the diphosphine and the remaining coordination site was taken up by the phosphorus atom as an L-type ligand. The replacement of the chloride indicates the high stability of the P,O-chelation. Upon separation of the produced diastereomers on silica gel, optically pure bimetallic species (**51a** and **51b**) were isolated. Furthermore, compound **51a** can be converted to its monometallic derivative (**52** and **53**), by selectively removing only one of the coordinated metals with KCN. Using this strategy, we were able to liberate the phosphine unit at the 1,6-position, but at the same time, the other palladium remained coordinated at the 1,4-position. This palladium coordination stops the retro-Michael addition; thus the lability of the C-P bond is retarded and consequently the chirality of the α -carbon becomes fixed. The catalytic performance of these complexes is currently under investigation.

3.3 Mechanistic investigations

Based on our investigations regarding to this transformation, we have proposed a plausible mechanism for the double hydrophosphination process (Scheme 57). This proposal has been made based on several NMR investigations. The control experiments and selected spectra are disclosed in this chapter. For further details, see the electronic supplementary information of the corresponding publication.¹⁷⁸

a) Control experiments 1 to 3:

Firstly, we started our investigations by identifying the diphosphine intermediates in the reaction, before sulfurization (Scheme 59 to 61).

Scheme 59. Confirmation of the diketo diphosphine formation.

Scheme 60. Confirmation of diphosphine salt formation.

Scheme 61. Transformation of diketo diphosphine to diphosphine salt.

All these control experiments (from 1 to 3) were set up in deuterated solvent (acetone-d₆), which allowed us to record multi nuclei ¹H, ¹³C and ³¹P{¹H} NMR spectra of the intermediates. In control experiment 1, the reaction was performed in the absence of base and the generated diphosphine was detected in its diketo form (**37**). In control experiment 2, the presence of base resulted in the formation of a phosphine salt intermediate (**39aa**). After sulfurization and isolation on silica gel column chromatography, both reactions provided the same product, the enol diphosphine **38aa**. For the structural confirmation of the diketo diphosphine (**37**) and the diphosphine salt (**39aa**), the ¹³C NMR data provided strong evidences. The main difference between the diketo form (**37**) and the phosphine salt (**39aa**) is the presence (or absence) of the highly acidic proton in the α-position in the diketo phosphine (**37**) (Scheme 61). In case of **39aa**, this proton was removed from the α-carbon by the triethylamine base. In the ¹³C NMR spectrum of the diketo phosphine (**37**), the carbonyl peaks were located in the low field region at 199.92 and 199.87 ppm (acetone-d₆), which belongs to the indandione moiety. In contrast, if the reaction was set up in the presence of triethylamine and the α-carbon was deprotonated (control experiment 2), thus these peaks were not found in the spectrum. To obtain a further evidence for our proposed structures, we made an attempt to transform **37** into **39aa**, by deprotonating the generated diketo compound (**37**). In this two-steps control experiment (Scheme 61), **37** was generated firstly in a base-free transformation, followed by the addition of excess amount (3 equivalents) of triethylamine into the reaction mixture (control experiment

3). By comparing the ^1H , ^{13}C and $^{31}\text{P}\{^1\text{H}\}$ NMR spectra of the control experiments, we can clearly see the identical chemical peaks obtained for experiment 3 and **39aa** (control experiment 2). This was a strong evidence, that the deprotonation of **37** results in the formation of **39aa** indeed. For NMR spectra, see Figures 39 to 41.

Figure 39. Comparison of the ^1H NMR spectra of control experiments 1 to 3, measured in acetone- d_6 .

Figure 40. Comparison of the ^{13}C NMR spectra of control experiments 1 to 3, measured in acetone- d_6 .

Figure 41. Comparison of the $^{31}\text{P}\{^1\text{H}\}$ NMR spectra of control experiments 1 to 3, measured in acetone- d_6 .

Characterization data of **37**:

^1H NMR (400 MHz, Acetone- d_6 , mixture) δ 8.01 – 6.95 (m, 29H, ArH), 3.85 – 3.75 (m, 1H, C(O)CHC $\underline{\text{H}}$ Ph), 3.69 (dd, $J_{\text{HH}} = 2.1$, $J_{\text{PH}} = 19.2$ Hz, 1H, C(O)C $\underline{\text{H}}$ CHPh), 3.31 – 3.20 (m, 1H, PC $\underline{\text{H}}$ Ph), 2.56 – 2.40 (m, 1H, CH $_2$), 2.03 – 1.88 (m, 1H, CH $_2$). ^{13}C NMR (101 MHz, Acetone- d_6 , mixture) δ 199.89 (d, $J = 5.0$ Hz, 1C, C(O)), 199.06 (s, 1C, C(O)), 145.09 – 121.05 (36C, Ar), 53.36 (d, $^2J_{\text{PC}} = 14.0$ Hz, (C(O)) $_2$ C $\underline{\text{H}}$), 42.85 (dd, $J = 13.9$, 10.6 Hz, 1C), 33.85 (dd, $J = 24.1$, 21.2 Hz, 1C), 33.14 (dd, $J = 16.2$, 10.8 Hz, 1C). $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, Acetone- d_6 , mixture) δ -0.03 (s, 1P), -7.90 (s, 1P).

Characterization data of **39aa**:

^1H NMR (400 MHz, Acetone- d_6 , mixture) δ 7.59 – 7.53 (m, 2H, ArH), 7.45 – 7.37 (m, 2H, 2H, ArH), 7.35 – 7.15 (m, 12H, 2H, ArH), 7.15 – 7.02 (m, 9H, 2H, ArH), 7.01 – 6.95 (m, 2H, 2H, ArH), 6.95 – 6.90 (m, 2H, 2H, ArH), 3.76 (dd, $J_{\text{HH}} = 10.9$ Hz, $J_{\text{PH}} = 7.0$ Hz, 1H, CH), 3.65 (dd, $J_{\text{HH}} = 10.9$ Hz, $J_{\text{PH}} = 8.0$ Hz, 1H, CH), 2.64 (q, $J = 10.9$ Hz, 1H, CH $_2$), 1.79 (q, $J = 10.9$ Hz, 1H, CH $_2$). ^{13}C NMR (101 MHz, Acetone- d_6 , mixture) δ 143.32 – 101.93 (39C, Ar), 46.82 (s, 3C, NCH $_2$ CH $_3$), 43.49 (t, $J = 11.6$ Hz, 1C), 34.84 (dd, $J = 27.3$, 22.3 Hz, 1C), 30.99 – 28.57 (m, 1C, overlapping peak), 10.17 (s, 3C,

NCH₂CH₃). ¹³C NMR (101 MHz, CD₂Cl₂, mixture) δ 142.85 – 103.11 (39C, Ar), 47.05 (s, 3C, NCH₂CH₃), 43.39 (t, *J* = 11.5 Hz, 1C), 34.80 (dd, *J* = 27.1, 22.9 Hz, 1C), 30.73 – 29.96 (m, 1C), 11.02 (s, 3C, NCH₂CH₃). ³¹P{¹H} NMR (162 MHz, Acetone-d₆, mixture) δ -3.07 (s, 1P), -10.94 (s, 1P).

b) Control experiment 4:

In control experiment (4), the consecutive manner of the double hydrophosphination was established (Scheme 62). The test reaction was set up in the 1 : 1 ratio of the starting materials (**36a** and diphenylphosphine), thus the HPPH₂ became the limiting reagent in the transformation. Since the amount of HPPH₂ was theoretically not enough to complete the two P-H addition to form diphosphine products, we expected the generation of a mono-adduct only. By isolation and characterization of this monophosphine, we intended to determine if 1,4- or 1,6-addition takes place first in the hydrophosphination. Unfortunately, the reaction was too fast to fully exclude the diphosphine formation; in fact, all the starting materials were converted to **39aa** in the presence of triethylamine. In order to slow down the transformation, the reaction was also performed in the absence of any external base. In this case, the formation of the monophosphine adduct was clearly seen in the ³¹P{¹H} NMR spectrum of the crude mixture. Unfortunately, even under base-free conditions, significant amount of diphosphines (both isomers) were formed.

Scheme 62. Consecutive manner of the reaction.

To maximize the monophosphine formation for easier characterization, a short reaction optimization was performed (Table 16).

Table 16. Optimization of the monophosphine formation.

Entry	Base	Solvent	T [°C]	t	Major isomers [ratio] ^a	Minor isomers [ratio] ^a	Mono-phosphine [ratio] ^a	Unreacted HPPH ₂ [ratio] ^a
1	Et ₃ N (5)	acetone	RT	5 mins	1	0.05	0	-
2	-	acetone	-40	7 h	1	0.33	0	1.36
3	-	acetone	RT	1 h	1	0.14	0.23	-
4	-	toluene	RT	24 h	1	0.2	0.74	-
5	-	CHCl ₃	RT	4.5 h	1	0.31	0.51	-
6	-	DCM	RT	4.5 h	1	0.31	-	0.52
7	-	Hexanes	RT	24 h	-	-	-	-
8	-	MeOH	RT	4 h	1	0.27	0.55	-

^aThe ratios of the corresponding compounds produced in the reaction were determined by the ³¹P{¹H} NMR spectrum of the crude mixture.

Based on the condition optimization, the best solvent for the monophosphine formation was toluene with 24 hours reaction time. After the first step of the reaction (hydrophosphination) was completed, sulphur was introduced to the reaction mixture, which was stirred for an additional 15 minutes. Then the solvent was removed, CDCl₃ was introduced and the ratios of the generated compounds were determined by ³¹P{¹H} NMR measurement (for NMR spectrum, see Figure 42).

Remark: during the transfer into CDCl₃, the diketo diphosphine products (37) underwent tautomerization and 38aa (major and minor isomers) were detected in the crude mixture.

Figure 42. Crude ³¹P{¹H} NMR spectrum of the optimized monophosphine formation.

Based on the crude $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum, the formation of the monophosphine adduct was confirmed. After isolation on column chromatography and characterization, the structure of **42** was confirmed. Unfortunately, to the relatively small conversion ratio and the significant overlapping on column chromatography, the generated monophosphine was isolated in only 11% yield. In the structural confirmation, the ^1H NMR data played a huge role. In Figure 43, all the possible monophosphine product structures are presented. The structures of compounds **A**, **B** and **C** represent the 1,6-addition products and compounds **D** and **E** represent the possible 1,4-adducts. The three aliphatic protons which appeared in the aliphatic region of the ^1H NMR spectrum (Figure 44) imply, that the isolated monophosphine has structure **A**.

Figure 43. Possible monophosphine structures.

Figure 44. The ^1H NMR spectrum (400 MHz, CDCl_3) of the isolated monophosphine (**42**).

Moreover, structures **C** and **E** can be excluded due to the missing tautomeric proton peak at the low field region (for comparison, the enol diphosphine **38aa** has a tautomeric proton on the indandione moiety and the chemical peak appeared at δ 11.06 ppm in the ^1H NMR). Regarding to the vinyl proton in structure **A**, we proposed that due to the highly electron-withdrawing nature of the indandione moiety, the vinylic proton has a relatively higher chemical shift, thus it overlaps with the aromatic protons in the ^1H NMR spectrum. Structures **B** and **D** can be excluded due to the different number of the aliphatic protons.

Characterization data:

2-(3-(diphenylphosphorothioyl)-3-phenylpropylidene)-1H-indene-1,3(2H)-dione (**42**). Appearance: white solid, Yield=11%.

^1H NMR (400 MHz, CDCl_3) δ 8.27 – 8.14 (m, 2H, ArH), 8.00 – 7.85 (m, 2H, ArH), 7.82 – 7.72 (m, 2H, ArH), 7.65 – 7.54 (m, 2H, ArH), 7.52 – 7.43 (m, 2H, ArH), 7.37 – 7.30 (m, 2H, ArH), 7.26 – 6.97 (m, 8H, ArH and $\text{C}=\text{CH}$), 4.18 (td, $J = 10.6, 4.3$ Hz, 1H, CH_2CHPh), 3.88 – 3.59 (m, 2H, CH_2). ^{13}C NMR (101 MHz, CDCl_3) δ 190.07 (s, 1C, $\text{C}(\text{O})$), 188.58 (s, 1C, $\text{C}(\text{O})$), 152.41 – 122.63 (26C, Ar and $\text{C}=\text{C}$), 47.07 (d, $^1J_{\text{PC}} = 49.4$ Hz, 1C, CH_2CHPh), 28.78 (d, $^2J_{\text{PC}} = 3.0$ Hz, 1C, CH_2). $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, CDCl_3) δ 50.72 (s, 1P). HRMS (+ESI) m/z calcd for $\text{C}_{30}\text{H}_{24}\text{O}_2\text{PS}$ ($\text{M} + \text{H}$) $^+$: 479.1235; found: 479.1230.

c) Control experiment 5:

In control experiment 5, the reaction between 1 equivalent of **36a** and 2 equivalents of HPPH_2 was set up in the absence of base using deuterated solvent (Scheme 63). The reaction was monitored by continuous, repetitive ^1H and $^{31}\text{P}\{^1\text{H}\}$ NMR measurements, to track any intermediates during the double addition.

Scheme 63. Control experiment 5.

For NMR spectra, see Figures 45 to 48 (“0 mins” refers to the clean spectrum of **36a**).

Figure 45. The ^1H NMR spectra of base-free double hydrophosphination (acetone-d_6).

Figure 46. The ^1H NMR spectra of base-free double hydrophosphination (acetone-d_6).

Figure 47. The ^1H NMR spectra of base-free double hydrophosphination (acetone- d_6).

Figure 48. The $^{31}\text{P}\{^1\text{H}\}$ NMR spectra of base-free double hydrophosphination (acetone- d_6).

By analysing the ^1H and $^{31}\text{P}\{^1\text{H}\}$ NMR spectra, it was clear that a monophosphine intermediate can be detected in the first 30 minutes of the addition. Later, as the starting materials were gradually converted to the diphosphine products, the amount of the new monophosphine intermediate was also decreasing (this can be clearly seen in the $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum, and in the ^1H NMR spectrum by following

the aliphatic and the vinyl protons of the monophosphine). This indicated to us, that a plausible equilibrium may set up between the new monophosphine and the starting materials (**36a** and HPPH₂).

The ¹H NMR spectrum provided insight the plausible structure of the intermediate monophosphine. To determine it, we used the same strategy as we did in control experiment 4, we compared the measured ¹H NMR spectrum with all the possible monophosphine structures (Figure 49).

Figure 49. Possible monophosphine structures.

In the ¹H NMR spectra, it was clear that this monophosphine intermediate is not identical to which we obtained in control experiment 4 (not compound **42**). In this case, a different chemical peak pattern was observed in the spectrum, which showed that this compound bears 2 aliphatic and 2 vinylic protons. Among the proposed structures, two compounds (**B** and **D**) contain the same amount of aliphatic and vinylic protons, which we observed. In order to determine if we had a 1,6-adduct (**B**) or a 1,4-adduct (**D**), the coupling pattern of the corresponding protons were examined and compared to other 1,6- and 1,4-adducts from the literature. Based on this comparison and the observations from the spectroscopic measurements, we assigned the corresponding monophosphine as a 1,4-addition product (compound **D** = **47**):

Characterization data of compound **47**:

NMR data of other 1,6- and 1,4-adducts from the literature:

^1H NMR (400 MHz, CDCl_3 , lit.¹⁷⁹): δ 8.14 (d, $J_{\text{HH}} = 6.3$ Hz, 1H), 7.94–7.89 (m, 2H), 7.79–7.74 (m, 2H), 7.53–7.41 (m, 7H), 7.33–7.29 (m, 1H), 7.24–7.13 (m, 6H), **6.30** (dd, $J = 4.3, 15.9$ Hz, 1H), **6.08** (ddd, $J_{\text{HH}} = 14.9$ and 9.1 Hz, $J_{\text{HP}} = 5.7$ Hz, 1H), **4.20–4.12** (m, 1H, PCHCH_2), **3.76** (ddd, $J_{\text{HH}} = 17.7$ and 10.0 Hz, $J_{\text{HP}} = 8.0$ Hz, 1H, PCHCHH), **3.61** (ddd, $J_{\text{HH}} = 17.5$ and 4.0 Hz, $J_{\text{HP}} = 9.8$ Hz, 1H, PCHCHH).

^1H NMR (CDCl_3 , 400 MHz, lit.¹³²): δ 8.66 (d, 1H, $^3J = 4.2$ Hz, Ar), 8.13–8.07 (m, 2H, Ar), 7.93–7.89 (m, 3H, Ar), 7.78–7.74 (m, 1H, Ar), 7.50–7.38 (m, 7H, Ar), 7.21–7.12 (m, 5H, Ar), **6.29** (dd, 1H, $^3J = 15.9$ Hz, $^4J_{\text{HP}} = 4.6$ Hz, PhCH=CH), **6.16** (ddd, 1H, $^3J = 15.8$ Hz, $^3J_{\text{HP}} = 8.7$ Hz, $^3J = 6.5$ Hz, PhCH=CH), **4.50–4.42** (m, 1H, PCHCH_2), **4.11** (ddd, 1H, $^2J = 17.7$ Hz, $^3J_{\text{PH}} = 10.5$ Hz, $^3J = 5.6$ Hz, O=CCH_2), **3.35** (ddd, 1H, $^2J = 17.6$ Hz, $^3J_{\text{PH}} = 12.5$ Hz, $^3J = 2.3$ Hz, O=CCH_2);

^1H NMR (CDCl_3 , lit.¹⁸⁰): δ 7.91 (t, $J_{\text{HH}} = 8.8$ Hz, 2H), 7.79 (dd, $J = 10.0$ and 8.0 Hz, 2H), 7.57–7.16 (m, 13H), **6.45** (dd, $J = 15.6$ and 3.6 Hz, 1H), **6.25** (s, 2H), **6.13** (ddd, $J = 15.6, 8.8$ and 2.4 Hz, 1H), **4.06** (q, $J = 8.8$ Hz, 1H), **3.41** (ddd, $J_{\text{HH}} = 17.2$ and 10.0 Hz, $J_{\text{HP}} = 4.4$ Hz, 1H), **3.21** (ddd, $J_{\text{HH}} = 16.8$ and 2.0 Hz, $J_{\text{HP}} = 10.8$ Hz, 1H).

^1H NMR (CDCl_3 , 300 MHz, lit.¹⁸¹): δ 7.95–7.88 (m, 4H, Ar), 7.85–7.78 (m, 2H, Ar), 7.55–7.38 (m, 9H, Ar), 7.23–7.12 (m, 5H, Ar), **6.41** (dd, 1H, $^4J_{\text{HP}} = 4.2$ Hz, $^3J_{\text{HH}} = 15.9$ Hz, PhCH=CH), **6.12** (ddd, 1H, $^3J_{\text{HH}} = 15.9$ Hz, $^3J_{\text{HP}} = 9.1$ Hz, $^3J_{\text{HH}} = 6.4$ Hz, PhCH=CH), **4.22–4.11** (m, 1H, PCH), **3.67** (ddd, 1H, $^2J_{\text{HH}} = 17.7$ Hz, $^3J_{\text{HP}} = 10.2$ Hz, $^3J_{\text{HH}} = 4.5$ Hz, PCHCHH), **3.29** (ddd, 1H, $^2J_{\text{HH}} = 17.7$ Hz, $^3J_{\text{HP}} = 11.4$ Hz, $^3J_{\text{HH}} = 2.4$ Hz, PCHCHH).

^1H NMR (400 MHz, CDCl_3 , lit.¹⁸²): δ = 7.90–7.80 (m, 2 H), 7.55–7.16 (m, 9 H), 7.14 (d, J_{HH} = 6.8 Hz, 2 H), 7.06 (d, J_{HH} = 6.4 Hz, 2 H), **6.11** (ddd, J = 14.8, 9.2, 6.8 Hz, 1 H), **5.73** (ddd, J = 14.8, 8.0, 2.8 Hz, 1 H), 4.44 (dd, J = 15.2, 8.8 Hz, 1 H), 3.77 (d, J = 8.4 Hz, 1 H), 1.37 (s, 9 H), 1.36 (s, 9 H), 0.88 (br, 3 H).

^1H NMR (CDCl_3 , 400 MHz, lit.^{130b}): δ 7.86–7.81 (m, 2H, Ar), 7.53–7.47 (m, 5H, Ar), 7.37–7.35 (m, 2H, Ar), 7.30–7.24 (m, 3H, Ar), 7.20–7.17 (m, 3H, Ar), **6.14** (ddd, 1H, 3J = 15.3 Hz, 9.28 Hz, 6.64 Hz, PhCHPC $\underline{H}$ =CH), **5.72** (ddd, 1H, 3J = 15.4 Hz, 9.04 Hz, 3.80 Hz, PhCHPC $\underline{H}$ =CH), 4.29–4.24 (m, 1H, PhC $\underline{H}$ P), 4.10 (q, 2H, 3J = 7.08 Hz, CO $_2$ C $\underline{H}_2$ CH $_3$), 4.03–3.99 (m, 2H, CO $_2$ C $\underline{H}_2$ CH $_3$), 3.93 (d, 1H, 3J = 9.08 Hz, (CO $_2$) $_2$ C $\underline{H}$), 1.19–1.14 (m, 6H, CO $_2$ CH $_2$ C $\underline{H}_3$);

This comparison strongly supports our proposed structure, the 1,4-addition product, due to the same coupling pattern (dd and ddd) of the vinylic protons, to that of reported for other 1,4-adducts from the literature. Since this monophosphine (**47**) can be detected only in the beginning of the transformation, we were considering what happens to this intermediate during the transformation. This monophosphine is not able to accept another phosphine nucleophile attack at the 1,6-position, due to the loss of the conjugation (Figure 50).

Figure 50. Structural considerations of **47**.

Because of this structural feature, the second P-H addition in the double phosphination process cannot take place on this compound, thus compound **47** cannot be converted to **37** diphosphine. Since the amount of this compound was slowly decreasing in the reaction mixture as the reaction was ongoing, it implied to us that a possible retro-Michael addition may occur. In order to prove this hypothesis, another control experiment was set up.

d) Control experiment 6:

In control experiment 6, the usual double hydrophosphination process was carried out in the presence of 2 equivalents amount of triethylamine. After **39aa** was generated, another secondary phosphine, 3 equivalents of di-*para*-tolylphosphine (**40**) was introduced to the mixture (Scheme 64). Based on our hypothesis, if the retro-Michael addition can occur at the 1,4-position, then by introducing a different phosphine reactant, the generation of a mixed diphosphine can be expected. After addition of **40** to the mixture, the reaction was monitored by $^{31}\text{P}\{^1\text{H}\}$ NMR. For NMR spectra, see Figures 51 and 52.

Scheme 64. Control experiment 6.

Figure 51. The $^{31}\text{P}\{^1\text{H}\}$ NMR spectra of the generation of mixed phosphine **45**, measured in acetone.

Figure 52. The $^{31}\text{P}\{^1\text{H}\}$ NMR spectra of the generation of mixed phosphine **45**, measured in acetone.

After 20 minutes reaction time from the addition of **40**, the formation of a new diphosphine (**45**) was already seen in the $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum. As the reaction was ongoing, the amount of the mixed phosphine (containing di-*para*-tolylphosphine moiety in the 1,4-position and diphenylphosphine fragment in the 1,6-position) was gradually increasing. At the same time, more and more diphenylphosphine was detected in the mixture again (due to the elimination of the PPh_2 fragment from **39aa** via the retro-addition process). After 23 hours, the phosphines were sulfurized and then **38aa** and **46** were isolated on silica gel in 20% and 64% isolated yields respectively. Upon isolation, compound **46** was fully characterized (for X-ray structure, see Figure 53).

Figure 53. ORTEP structure of mixed phosphine **46**.

Characterization data of **46**:

2-(1-(di-*p*-tolylphosphaneyl)-3-(diphenylphosphaneyl)-3-phenylpropyl)-3-hydroxy-1*H*-inden-1-one (**9**). Appearance: yellow solid, Yield=64%, Mp.= 177.9-180. ^1H NMR (500

MHz, CDCl_3) δ 11.16 (s, 1H, OH), 7.86 (dd, $J = 11.9, 7.3$ Hz, 2H, ArH), 7.57 (dd, $J = 12.6, 8.2$ Hz, 2H, ArH), 7.44 – 7.36 (m, 5H, ArH), 7.36 – 7.31 (m, 1H, ArH), 7.29 – 7.26 (m, 1H, ArH), 7.25 – 7.22 (m, 1H, ArH), 7.22 – 7.14 (m, 5H, ArH), 7.11 – 7.02 (m, 8H, ArH), 7.02 – 6.97 (m, 2H, ArH), 3.97 – 3.87 (m, 1H, CH_2CHPh), 3.65 (td, $J = 10.4, 2.6$ Hz, 1H, $\text{C}(\text{O})\text{CCHCH}_2$), 2.38 (s, 3H), 2.38 – 2.33 (m, 2H, CH_2), 2.21 (s, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 194.30 (d, $^3J_{\text{PC}} = 6.8$ Hz, 1C, $\text{C}(\text{O})$), 175.87 (d, $^3J_{\text{PC}} = 5.1$ Hz, 1C, $\text{C}=\text{C}-\text{OH}$), 143.21 – 103.38 (37C, Ar and $\text{C}=\text{C}-\text{OH}$), 45.15 (dd, $^1J_{\text{PC}} = 51.4$, $^3J_{\text{PC}} = 13.7$ Hz, 1C, CH_2CHPh), 33.89 (dd, $^1J_{\text{PC}} = 56.3$, $^3J_{\text{PC}} = 15.1$ Hz, 1C, CCHCH_2), 30.34 (t, $^2J_{\text{PC}} = 4.3$ Hz, 1C, CH_2), 21.68 (s, 1C, CH_3), 21.57 (s, 1C, CH_3). $^{31}\text{P}\{^1\text{H}\}$ NMR (202 MHz, CDCl_3) δ 49.38 (d, $^4J_{\text{PP}} = 5.7$ Hz, 1P), 46.71 (d, $^4J_{\text{PP}} = 5.3$ Hz, 1P). HRMS (+ESI) m/z calcd for $\text{C}_{44}\text{H}_{39}\text{O}_2\text{P}_2\text{S}_2$ ($\text{M} + \text{H}$) $^+$: 725.1867; found: 725.1892.

e) Control experiment 7:

In the previous experiments, it became clear that 1,4-retro-Michael addition takes place in case of the diphosphine salt **39aa** and the 1,4-monoposphine adduct **47**. In control experiment 7, the plausible retro-addition was investigated in the diketeto diphosphine **37**, using similar strategy to control experiment 6 (Scheme 65).

Scheme 65. Control experiment 7.

In the first step, the double hydrophosphination was set up under base-free conditions to generate **37**. In the next step, compound **40** was introduced to the reaction mixture and the reaction was monitored by $^{31}\text{P}\{^1\text{H}\}$ NMR (for NMR spectrum, see Figure 54). After addition of **40**, the formation of the mixed diketo diphosphine (**54**) was detected and after 40 minutes, the following ratios were developed between the intermediates: **54** (major isomers)/ **54** (minor isomers)/ **37** (major isomers)/ **37** (minor isomers) = 3.48 : 0.62 : 1 : 0.14. The reason of the relatively higher amount of the minor isomers presented in the mixture is the base-free reaction condition. The absence of external base caused a significant drop in the diastereoselectivity between the major and minor isomers. Interestingly, after the addition of the external base (triethylamine) to the diketo diphosphines (**37** and **54**), the diastereoselectivity of the reaction was highly improved during the generation of the diphosphine salts **45** and **39aa**. (This phenomenon was also observed in coordination experiment 3, in which the diketo diphosphine **37** was generated with low diastereoselectivity first, but upon addition of triethylamine, the generated phosphine salt **39aa** was obtained in excellent dr>20:1 value.) After the mixture (control experiment 7) was stirred at room temperature for an additional 19 hours after triethylamine addition, it was sulfurized and the enol diphosphines **46** and **38aa** were isolated in 61% and 23% yield, respectively. This experiment proved that the 1,4-retro-Michael addition takes place not only in case of **47** and **39aa**, but also with the diketo diphosphine (**37**).

Figure 54. The $^{31}\text{P}\{^1\text{H}\}$ NMR spectra of control experiment 7, measured in acetone.

To sum it up, based on the performed NMR studies, the first step of the double hydrophosphination is a 1,6-addition both in the presence or the absence of base. In the generated 1,6-adduct the double bond is located between the α and β carbons, which arrangement is favored for the second P-H addition to occur. In this species, the β carbon is still activated by the carbonyl moieties of the indandione structure. After the second addition occurs at the 1,4 position, the diphosphine is generated in the diketo form (base-free reaction) or as a diphosphine salt (in the presence of base). After sulfurization and isolation on silica gel, the enol product (**38aa**) is observed independently from the reaction pathway. According to our mechanistic studies, the generated C-P bond at the 1,4 position is highly labile and retro-phospha Michael addition takes place at this position in **47**, **37** and **39aa** (Scheme 57).

3.4 Conclusion

In summary, we have developed a transition metal-free double P-H addition to highly conjugated $\alpha,\beta,\gamma,\delta$ -unsaturated systems in good to excellent diastereoselectivity. The mechanistic investigations established the consecutive manner of the reaction, as well as the retro-phospha-Michael addition at the 1,4-position. Upon coordination of the synthesized diphosphine to palladium, an unexpected P,O-bidentate- and a P-mono-coordination mode was observed over the traditional P,P-coordination seen in diphosphines. After separation, chiral bimetallic species were observed and isolated.

3.5 Experimental section

3.5.1 General considerations

All air sensitive manipulations were carried out under positive pressure of nitrogen using Schlenk techniques. Chloroform (AR), acetonitrile (AR), methanol (AR), dichloromethane (HPLC), acetone (AR) and ethyl acetate (AR) was purchased from VWR; *n*-hexanes (AR) and toluene (AR) from Avantor. Solvents were degassed prior to use. All other reactants and reagents were used as supplied without further purification unless stated otherwise. NMR spectra were recorded on Bruker AV 300, AV 400, AV 500 and BBFO 400 spectrometers. Chemical shifts were reported in ppm and referenced to an internal SiMe₄ standard (0 ppm) in CDCl₃, acetone-*d* (2.09 ppm) in (CD₃)₂CO, dichloromethane-*d* (5.33 ppm) in CD₂Cl₂ for ¹H NMR; chloroform-*d*

(77.22 ppm) in CDCl_3 , acetone-*d* (205.87 ppm) in $(\text{CD}_3)_2\text{CO}$, dichloromethane-*d* (54.24 ppm) in CD_2Cl_2 for ^{13}C NMR and an external 85% H_3PO_4 for $^{31}\text{P}\{^1\text{H}\}$ NMR. Low Temp Pairstirrer PSL-1800 was used for low temperature reactions. Column chromatography was performed with Silica gel 60 (purchased from Merck). Melting points were measured using SRS Optimelt Automated Point System SRS MPA100. HRMS using electrospray ionization (ESI) method was performed on the Waters Q-ToF Premier spectrometer. Optical rotations were examined with JASCO P-1030 Polarimeter in DCM in a 0.1 dm cell at specified temperatures.

Compounds **40**¹⁸³, **41**¹⁸³ and **5**¹⁸⁴ were prepared following reported procedures.

3.5.2 Synthesis of $\alpha,\beta,\gamma,\delta$ -unsaturated-1,3-indandiones

Compounds **36a**, **36b**, **36c**, **36f** and **36h** were synthesized according to reported procedure (the physical data of these compounds correlated to the literature values).^{163d}

Characterization data:

(*E*)-2-(3-phenylallylidene)-1*H*-indene-1,3(2*H*)-dione (**36a**).

Appearance: yellow solid, Mp. (lit.)^{163d} = 160.4-162.0 °C. ^1H NMR (400 MHz, CDCl_3) δ 8.46 (dd, J = 15.5, 11.9 Hz, 1H), 8.03 – 7.95 (m, 2H), 7.83 – 7.75 (m, 2H), 7.69 (d, J = 2.6 Hz, 2H), 7.66 (d, J = 11.9 Hz, 1H), 7.47 – 7.40 (m, 3H), 7.35 (d, J = 15.5 Hz, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 190.61, 190.17, 151.25, 144.75, 142.32, 141.01, 135.70, 135.27, 135.15, 131.06, 129.19, 128.84, 128.31, 128.28, 128.10, 123.80, 123.27, 123.11. ^1H NMR (400 MHz, Acetone- d_6) δ 8.50 (dd, J = 15.6, 11.8 Hz, 1H), 8.07 – 7.90 (m, 4H), 7.79 (dd, J = 7.6, 1.6 Hz, 2H), 7.67 (dd, J = 13.7, 5.0 Hz, 2H), 7.59 – 7.47 (m, 3H). ^{13}C NMR (101 MHz, Acetone- d_6) δ 190.53, 189.61, 151.49, 144.15, 142.74, 141.47, 136.48, 136.03, 135.96, 131.47, 129.81, 129.07, 128.76, 123.83, 123.37, 123.26. ^1H NMR (400 MHz, CD_2Cl_2) δ 8.45 (dd, J = 15.6, 11.9 Hz, 1H), 8.00 – 7.89 (m, 2H), 7.84 – 7.76 (m, 2H), 7.72 – 7.66 (m, 2H), 7.62 (d, J = 11.9 Hz, 1H), 7.50 – 7.41 (m, 3H), 7.38 (d, J = 15.6 Hz, 1H). ^{13}C NMR (101 MHz, CD_2Cl_2) δ 191.08, 190.52, 151.61, 144.87, 142.99, 141.68, 136.45, 135.94, 135.82, 131.64, 129.83, 129.39, 128.91, 124.33, 123.69, 123.58. HRMS (+ESI) m/z calcd for $\text{C}_{18}\text{H}_{13}\text{O}_2$ ($\text{M} + \text{H}$)⁺: 261.0916; found: 261.0912.

(*E*)-2-(3-(4-methoxyphenyl)allylidene)-1*H*-indene-1,3(2*H*)-dione (**36b**). Appearance: yellow solid, Mp. (lit)^{163d} = 220.8-222.5 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.33 (dd, *J* = 15.4, 12.0 Hz, 1H), 8.00 – 7.90 (m, 2H), 7.82 – 7.72 (m, 2H), 7.69 – 7.59 (m, 3H), 7.31 (d, *J* = 15.4 Hz, 1H), 6.95 (d, *J* = 8.8 Hz, 2H), 3.87 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 190.98, 190.54, 162.40, 151.67, 145.62, 142.33, 141.02, 135.12, 134.98, 130.90, 128.73, 126.92, 123.18, 122.99, 121.93, 114.82, 55.68. HRMS (+ESI) *m/z* calcd for C₁₉H₁₅O₃ (M + H)⁺: 291.1021; found: 291.1013.

(*E*)-2-(3-(4-nitrophenyl)allylidene)-1*H*-indene-1,3(2*H*)-dione (**36c**). Appearance: yellow solid, Mp. (lit.)^{163d} = 248.8-250 °C. ¹H NMR (500 MHz, CDCl₃) δ 8.57 (dd, *J* = 15.6, 11.8 Hz, 1H), 8.29 (d, *J* = 8.7 Hz, 2H), 8.05 – 7.95 (m, 2H), 7.89 – 7.75 (m, 4H), 7.63 (d, *J* = 11.8 Hz, 1H), 7.34 (d, *J* = 15.6 Hz, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 190.39, 189.69, 148.71, 146.70, 142.63, 142.50, 141.73, 141.26, 135.78, 135.71, 130.36, 129.13, 127.49, 124.51, 123.65, 123.50. HRMS (+ESI) *m/z* calcd for C₁₈H₁₂NO₄ (M + H)⁺: 306.0766; found: 306.0770.

(*E*)-2-(3-(4-chlorophenyl)allylidene)-1*H*-indene-1,3(2*H*)-dione (**36f**). Appearance: yellow solid, Mp. (lit)^{163d} = 188.8-190.1 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.39 (dd, *J* = 15.5, 11.9 Hz, 1H), 8.00 – 7.91 (m, 2H), 7.84 – 7.73 (m, 2H), 7.63 – 7.54 (m, 3H), 7.38 (d, *J* = 8.5 Hz, 2H), 7.25 (d, *J* = 15.5 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 190.62, 190.08, 149.35, 144.20, 142.36, 141.07, 136.99, 135.40, 135.29, 134.22, 129.90, 129.53, 128.52, 124.25, 123.37, 123.21. HRMS (+ESI) *m/z* calcd for C₁₈H₁₂ClO₂ (M + H)⁺: 295.0526; found: 295.0521.

(*E*)-2-(3-(2-nitrophenyl)allylidene)-1*H*-indene-1,3(2*H*)-dione (**1h**). Appearance: yellow solid, Mp. (lit)^{163d} = 229.7-231.0 °C. ¹H NMR (500 MHz, CDCl₃) δ 8.42 (dd, *J* = 15.4, 11.8 Hz, 1H), 8.05 (dd, *J* = 8.2, 1.0 Hz, 1H), 8.03 – 7.96 (m, 2H), 7.93 (d, *J* = 7.5 Hz, 1H), 7.88 – 7.79 (m, 3H), 7.75 – 7.63 (m, 2H), 7.60 – 7.52 (m, 1H). ¹³C NMR (126 MHz, CDCl₃) δ

190.30, 189.46, 148.37, 144.02, 143.02, 142.25, 141.04, 135.46, 133.49, 131.08, 130.49, 129.91, 129.20, 127.69, 125.11, 123.45, 123.23. HRMS (+ESI) m/z calcd for $C_{18}H_{12}NO_4 (M + H)^+$: 306.0766; found: 306.0762.

General procedure A: Compounds **36d**, **36e** and **36g** were synthesized according to the following procedure (Scheme 66):

Scheme 66. General procedure A.

To a solution of 1,3-Indandione (3.42 mmol, 1 equiv) and cinnamaldehyde (3.42 mmol, 1 equiv) in ethanol (12 mL), 1 drop of piperidine was added under N₂ atmosphere. The reaction mixture was brought to reflux temperature and was stirred until all starting materials were consumed (the reaction was monitored by TLC). After completion of the reaction, the mixture was cooled down to room temperature, followed by the removal of the solvent under vacuum. Then the crude mixture was first pushed through a silica gel column eluted with *n*-hexanes/ethyl acetate 98:2 to 80:20. Then single recrystallization was performed using DCM/*n*-hexanes solvent system to obtain the pure product. The chemical yields of the obtained compounds are listed below.

Characterization data:

(*E*)-2- (3- (4- (diethylamino) phenyl) allylidene) -1*H*- indene-1,3(2*H*)-dione (**36d**). Appearance: yellow solid, Yield=45%, Mp. (lit)¹⁸⁵ = 184-186 °C. ¹H NMR (300 MHz, CDCl₃) δ 8.35 – 7.99 (m, 1H), 7.98 – 7.77 (m, 2H), 7.77 – 7.39 (m, 5H), 7.38 – 7.11 (m, 1H), 6.75 – 6.47 (m, 2H), 3.55 – 3.24 (m, 4H), 1.30 – 0.96 (m, 6H). ¹³C NMR (75 MHz, CDCl₃) δ 191.26, 190.91, 153.96, 150.54, 146.73, 142.15, 140.83, 134.46, 134.29, 131.90, 124.07, 123.19, 122.61, 122.38, 118.99, 111.61, 44.78, 12.78. HRMS (+ESI) m/z calcd for $C_{22}H_{22}NO_2 (M + H)^+$: 332.1651; found: 332.1652.

(*E*)-2-(3-(4-fluorophenyl)allylidene)-1*H*-indene-1,3(2*H*)-dione (**36e**). Appearance: yellow solid, Yield=56%, Mp. (dec.) = 188.5-190 °C. ¹H NMR (300 MHz, CDCl₃) δ 8.34 (dd, *J* = 15.3, 12.0 Hz, 1H), 8.02 – 7.88 (m, 2H), 7.84 – 7.72 (m, 2H), 7.71 – 7.50 (m, 3H), 7.34 – 7.19 (m, 1H), 7.10 (t, *J* = 8.4 Hz, 2H). ¹³C NMR (75 MHz, CDCl₃) δ 190.63, 190.11, 166.08, 162.72, 149.63, 144.49, 142.31, 141.01, 135.30, 135.19, 132.07, 132.03, 130.82, 130.70, 128.14, 123.55, 123.52, 123.30, 123.13, 116.59, 116.29. HRMS (+ESI) *m/z* calcd for C₁₈H₁₂FO₂ (*M* + *H*)⁺: 279.0821; found: 279.0822.

(*E*)-2-(3-(2-methoxyphenyl)allylidene)-1*H*-indene-1,3(2*H*)-dione (**36g**). Appearance: yellow solid, Yield=48%, Mp. (dec.) = 183.2-185 °C. ¹H NMR (500 MHz, CDCl₃) δ 8.45 (dd, *J* = 15.6, 12.1 Hz, 1H), 7.99 – 7.87 (m, 2H), 7.81 – 7.69 (m, 4H), 7.65 (d, *J* = 12.1 Hz, 1H), 7.36 (t, *J* = 7.7 Hz, 1H), 6.99 (t, *J* = 7.7 Hz, 1H), 6.90 (d, *J* = 8.3 Hz, 1H), 3.92 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 190.74, 190.37, 158.63, 146.65, 146.03, 142.28, 140.95, 135.08, 134.94, 132.58, 128.84, 127.30, 124.70, 124.08, 123.11, 122.94, 121.09, 111.35, 55.76. HRMS (+ESI) *m/z* calcd for C₁₉H₁₅O₃ (*M* + *H*)⁺: 291.1021; found: 291.1018.

3.5.3 Optimization of diphosphine synthesis via double hydrophosphination

General procedure for the synthesis and reaction condition optimization of compound **38aa** (Scheme 67):

Scheme 67. Optimization of the double hydrophosphination process.

A nitrogen flushed 2-neck flask was charged with **36a** (19.7 mg, 75.7 μmol , 1 equiv) and base (for the corresponding amount, see Table 14) in de-gassed acetone (2.5 mL) at room temperature, followed by the addition of HPPH_2 (29.6 mg, 159 μmol , 2.1 equiv). The setup was stirred and monitored by TLC. The conversion and the dr was determined by $^{31}\text{P}\{^1\text{H}\}$ NMR measurement of the crude mixture. Upon completion, sulphur (37.9 μmol , 0.5 equiv of S_8) was added into the flask and the mixture was stirred for another 5 mins. Evaporation of the solvent under reduced pressure provided the crude mixture, which was purified by silica gel column chromatography, eluted with *n*-hexane/ EtOAc (97:3 to 70:30) eluent system.

Based on optimization, the selected reaction condition for the generation of **38aa** and for the substrate scope includes the usage of 2 equivalents amount of triethylamine and acetone as a solvent. The product (*R*,R**)-**38aa** was obtained as yellow solid material in 95% isolated yield.

Characterization data:

2- (1,3-bis (diphenylphosphorothioyl) -3- phenylpropyl) -3-hydroxy-1*H*-inden-1-one (**38aa**). Appearance: yellow solid, Yield=95%, Mp. (dec.) = 197.8-199 °C. ^1H NMR (400 MHz, CDCl_3) δ 11.06 (s, 1H, OH), 7.86 (dd, J = 11.7, 7.8 Hz, 2H, ArH), 7.70 (dd, J = 12.6, 7.4 Hz, 2H, ArH), 7.52 (dd, J = 12.7, 7.7 Hz, 2H, ArH), 7.48 – 7.37 (m, 4H, ArH), 7.37 – 7.26 (m, 7H, ArH), 7.24 – 7.14 (m, 6H, ArH), 7.13 – 7.03 (m, 4H, ArH), 7.03 – 6.96 (m, 2H, ArH), 3.98 (t, J = 10.8 Hz, 1H, CH_2CHPh), 3.66 (t, J = 10.5 Hz, 1 H, C(O)CCCHCH_2), 2.48 – 2.29 (m, 2H, CH_2). ^{13}C NMR (101 MHz, CDCl_3) δ 194.18 (d, $^3J_{\text{PC}}$ = 6.7 Hz, 1C, C(O)), 175.90 (d, $^3J_{\text{PC}}$ = 5.1 Hz, 1C, $\text{C}=\text{C}-\text{OH}$), 141.25 – 101.50 (37C, Ar and $\text{C}=\text{C}-\text{OH}$), 45.14 (dd, $^1J_{\text{PC}}$ = 51.4, $^3J_{\text{PC}}$ = 13.7 Hz, 1C, CH_2CHPh), 33.74 (dd, $^1J_{\text{PC}}$ = 56.3, $^3J_{\text{PC}}$ = 15.1 Hz, 1C, CCHCH_2), 30.38 (t, $^2J_{\text{PC}}$ = 4.4 Hz, 1C, CH_2). $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, CDCl_3) δ 49.22 (d, $^4J_{\text{PP}}$ = 5.4 Hz, 1P), 47.10 (d, $^4J_{\text{PP}}$ = 5.8 Hz, 1P). HRMS (+ESI) m/z calcd for $\text{C}_{42}\text{H}_{35}\text{O}_2\text{P}_2\text{S}_2$ ($\text{M} + \text{H}$) $^+$: 697.1554; found: 697.1544.

3.5.4 Determination of diastereomeric ratio (dr) in the double hydrophosphination

In the double hydrophosphination reaction, 4 possible non-superimposable isomers can be produced theoretically with the (R^*,R^*) and (R^*,S^*) relative configurations. According to our investigations (X-ray analysis of isolated major isomers, **38aa**), it turned out that the major product is the racemic (R^*,R^*) isomer. The amount of their diastereomeric (R^*,S^*) isomers produced in the reaction can be decreased by addition of appropriate bases. The dr values were determined by the $^{31}\text{P}\{^1\text{H}\}$ NMR analysis of the crude mixture before sulfurization (Figures 55 and 56). The $^{31}\text{P}\{^1\text{H}\}$ NMR peaks belong to the isomers of compound **37** (produced in the base-free reaction) and **39aa** (in the presence of triethylamine).

Figure 55. Crude $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum of the non-optimized double hydrophosphination.

Figure 56. Crude $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum of the optimized double hydrophosphination.

3.5.5 General procedure of diphosphine synthesis via double hydrophosphination

General Procedure B: Compounds **38ab-38ha** were synthesized according to the following procedure (Scheme 68):

Scheme 68. General procedure B.

A nitrogen flushed 2-neck flask was charged with $\alpha,\beta,\gamma,\delta$ -unsaturated-1,3-indandione (**36**) (75.7 μmol , 1 equiv) and triethylamine (15.3 mg, 151.4 μmol , 2 equiv) in de-gassed acetone (2.5 mL) at room temperature, followed by the addition of diarylphosphine (159 μmol , 2.1 equiv). The setup was stirred and monitored by TLC. Upon completion, sulphur (37.9 μmol , 0.5 equiv of S_8) was added into the flask and the mixture was stirred for another 5 mins. Evaporation of the solvent under reduced pressure provided the crude mixture, which was purified by silica gel column chromatography, eluted with *n*-hexane/EtOAc (97:3 to 70:30) eluent system. The chemical yields of the corresponding diphosphine syntheses are listed below.

Characterization data:

*2-(1,3-bis(di-*p*-tolylphosphorothioyl)-3-phenylpropyl)-3-hydroxy-1*H*-inden-1-one* (**38ab**). Appearance: yellow solid, Yield=95%, Mp. (dec.) = 196.1-198 °C. ^1H NMR (300 MHz, CDCl_3) δ 11.13 (s, 1H, OH), 7.71 (dd, $J = 11.8$, 8.1 Hz, 2H, ArH), 7.56 (dd, $J = 12.6$, 8.2 Hz, 2H, ArH), 7.47 – 7.29 (m, 5H, ArH), 7.20 – 7.10 (m, 4H, ArH), 7.10 – 6.99 (m, 8H, ArH), 6.97 – 6.82 (m, 4H, ArH), 4.02 – 3.81 (m, 1H, CH_2CHPh), 3.68 – 3.52 (m, 1H, C(O)CCHCH_2), 2.36 (s, 3H, CH_3), 2.35 – 2.31 (m, 2H, CH_2), 2.30 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 2.18 (s, 3H, CH_3). ^{13}C NMR (75 MHz, CDCl_3) δ 194.33 (d, $^3J_{\text{PC}} = 6.8$ Hz, 1C, C(O)), 175.85 (d, $^3J_{\text{PC}} = 5.1$ Hz, 1C, C=C-OH), 143.12 – 103.39 (37C, Ar and C=C-OH), 45.37 (dd, $^1J_{\text{PC}} = 51.7$, $^3J_{\text{PC}} = 13.6$ Hz, 1C, CH_2CHPh), 33.88 (dd, $^1J_{\text{PC}} = 56.3$, $^3J_{\text{PC}} = 15.1$ Hz, 1C, CCHCH_2), 30.66 (t, $^2J_{\text{PC}} =$

4.4 Hz, 1C, CH₂), 21.65 (t, *J* = 1.4 Hz, 2C, CH₃), 21.54 (d, *J* = 1.3 Hz, 1C, CH₃), 21.44 (d, *J* = 1.3 Hz, 1C, CH₃). ³¹P{¹H} NMR (202 MHz, CDCl₃) δ 48.75 (d, ⁴*J*_{PP} = 5.6 Hz, 1P), 46.60 (d, ⁴*J*_{PP} = 5.5 Hz, 1P). HRMS (+ESI) *m/z* calcd for C₄₆H₄₃O₂P₂S₂ (M + H)⁺: 753.2180; found: 753.2181.

2-(1,3-bis(di-*m*-tolylphosphorothioyl)-3-phenylpropyl)-3-hydroxy-1*H*-inden-1-one (**38ac**). Appearance: yellow solid, Yield=94%, Mp. (dec.) = 168.7-169 °C. ¹H NMR (400 MHz, CDCl₃) δ 11.09 (s, 1H, OH), 7.75 (d, *J* = 13.0 Hz, 1H, ArH), 7.60 – 7.51 (m, 2H, ArH), 7.47 – 7.27 (m, 7H, ArH), 7.24 – 7.08 (m, 7H, ArH), 7.08 – 6.93 (m, 7H, ArH), 6.90 (d, *J* = 7.7 Hz, 2H, ArH), 3.91 (t, *J* = 10.3 Hz, 1H, CH₂CHPh), 3.61 (t, *J* = 10.3 Hz, 1H, C(O)CCHCH₂), 2.46 – 2.38 (m, 2H, CH₂), 2.30 (s, 3H, CH₃), 2.25 (s, 3H, CH₃), 2.21 (s, 3H, CH₃), 2.07 (s, 3H, CH₃). ¹³C NMR (101 MHz, CDCl₃) δ 194.04 (d, ³*J*_{PC} = 6.4 Hz, 1C, C(O)), 175.70 (d, ³*J*_{PC} = 5.3 Hz, 1C, C=C-OH), 140.21 – 103.60 (37C, Ar and C=C-OH), 45.19 (dd, ¹*J*_{PC} = 50.9, ³*J*_{PC} = 13.7 Hz, 1C, CH₂CHPh), 33.77 (dd, ¹*J*_{PC} = 55.7, ³*J*_{PC} = 15.2 Hz, 1C, CCHCH₂), 29.95 (t, ²*J*_{PC} = 3.9 Hz, 1C, CH₂), 21.73 (s, 1C, CH₃), 21.62 (s, 1C, CH₃), 21.49 (s, 1C, CH₃), 21.37 (s, 1C, CH₃). ³¹P{¹H} NMR (162 MHz, CDCl₃) δ 50.50 (d, ⁴*J*_{PP} = 5.1 Hz, 1P), 48.30 (d, ⁴*J*_{PP} = 5.2 Hz, 1P). HRMS (+ESI) *m/z* calcd for C₄₆H₄₃O₂P₂S₂ (M + H)⁺: 753.2180; found: 753.2178.

2-(1,3-bis (diphenylphosphorothioyl) -3- (4-methoxyphenyl) propyl) -3- hydroxy- 1*H* -inden-1-one (**38ba**). Appearance: yellow solid, Yield=95%, Mp. (dec.) = 201.8-203 °C. ¹H NMR (400 MHz, CDCl₃) δ 11.05 (s, 1H, OH), 7.89 – 7.79 (m, 2H, ArH), 7.77 – 7.66 (m, 2H, ArH), 7.60 – 7.50 (m, 2H, ArH), 7.50 – 7.35 (m, 4H, ArH), 7.35 – 7.26 (m, 7H, ArH), 7.25 – 7.14 (m, 5H, ArH), 7.10 (td, *J* = 7.6, 3.1 Hz, 2H, ArH), 6.91 (dd, *J* = 8.7, 1.8 Hz, 2H, ArH), 6.60 (d, *J* = 8.6 Hz, 2H, ArH), 3.99 (t, *J* = 10.7 Hz, 1H, CH₂CHAr), 3.78 (s, 3H, OCH₃), 3.61 (t, *J* = 10.3 Hz, 1H, C(O)CCHCH₂), 2.45 – 2.20 (m, 2H, CH₂). ¹³C NMR (101 MHz, CDCl₃) δ 194.22 (d, ³*J*_{PC} = 6.7 Hz, 1C, C(O)), 175.86 (d, ³*J*_{PC} = 5.2 Hz, 1C, C=C-OH), 160.39 – 102.45 (37C, Ar and C=C-OH), 55.34 (s, 1C, OCH₃), 44.29 (dd, ¹*J*_{PC} = 52.0, ³*J*_{PC} = 13.7 Hz, 1C, CH₂CHAr), 33.67 (dd, ¹*J*_{PC} = 56.3, ³*J*_{PC} = 15.1 Hz, 1C, CCHCH₂), 30.45 (t, ²*J*_{PC} =

4.8 Hz, 1C, CH₂). ³¹P{¹H} NMR (162 MHz, CDCl₃) δ 49.13 (d, ⁴J_{PP} = 5.5 Hz, 1P), 47.31 (d, ⁴J_{PP} = 5.6 Hz, 1P). HRMS (+ESI) m/z calcd for C₄₃H₃₇O₃P₂S₂ (M + H)⁺: 727.1659; found: 727.1667.

2-(1,3-bis (di-*p*-tolylphosphorothioyl) -3- (4- methoxy phenyl) propyl) -3- hydroxy -1H -inden-1-one (**38bb**).

Appearance: yellow solid, Yield=94%, Mp. (dec.) =

179.0-181 °C. ¹H NMR (400 MHz, CDCl₃) δ 11.12 (s,

1H, OH), 7.69 (dd, *J* = 11.8, 8.1 Hz, 2H, ArH), 7.57 (dd, *J* = 12.5, 8.1 Hz, 2H, ArH), 7.45 – 7.30 (m, 5H, ArH), 7.21 – 7.12 (m, 3H, ArH), 7.07 (d, *J* = 7.9 Hz, 4H, ArH), 6.99 (dd, *J* = 8.7, 1.8 Hz, 2H, ArH), 6.91 (d, *J* = 7.8 Hz, 4H, ArH), 6.60 (d, *J* = 8.6 Hz, 2H, ArH), 3.92 (t, *J* = 11.1 Hz, 1H, CH₂CHAr), 3.80 (s, 3H OCH₃), 3.55 (t, *J* = 10.6 Hz, 1H, C(O)CCHCH₂), 2.37 (s, 3H, CH₃), 2.30 (s, 3H, CH₃), 2.29 – 2.22 (m, 2H, CH₂), 2.21 (s, 3H, CH₃), 2.20 (s, 3H, CH₃). ¹³C NMR (126 MHz, CDCl₃) δ 194.41 (d, ³J_{PC} = 6.9 Hz, 1C, C(O)), 175.85 (d, ³J_{PC} = 5.1 Hz, 1C, C=C-OH), 143.56 – 102.84 (37C, Ar and C=C-OH), 55.32 (s, 1C, OCH₃), 44.51 (dd, ¹J_{PC} = 52.5, ³J_{PC} = 13.6 Hz, 1C, CH₂CHAr), 33.82 (dd, ¹J_{PC} = 56.4, ³J_{PC} = 15.0 Hz, 1C, CCHCH₂), 30.77 (t, ²J_{PC} = 4.7 Hz, 1C, CH₂), 21.67 (s, 2C, CH₃), 21.55 (d, *J* = 1.2 Hz, 1C, CH₃), 21.46 (d, *J* = 0.9 Hz, 1C, CH₃). ³¹P{¹H} NMR (162 MHz, CDCl₃) δ 48.56 (d, ⁴J_{PP} = 6.0 Hz, 1P), 46.57 (d, ⁴J_{PP} = 5.7 Hz, 1P). HRMS (+ESI) m/z calcd for C₄₇H₄₅O₃P₂S₂ (M + H)⁺: 783.2285; found: 783.2278.

2- (1,3-bis (di-*m*-tolylphosphorothioyl) -3- (4-methoxy phenyl) propyl) -3- hydroxy -1H- inden -1- one (**38bc**).

Appearance: yellow solid, Yield=93%, Mp. (dec.) =

165.4-167 °C. ¹H NMR (500 MHz, CDCl₃) δ 11.09 (s, 1H,

OH), 7.74 (d, *J* = 12.9 Hz, 1H, ArH), 7.60 – 7.49 (m, 2H, ArH), 7.47 – 7.27 (m, 7H, ArH), 7.25 – 7.18 (m, 3H, ArH), 7.17 – 7.09 (m, 2H, ArH), 7.05 – 6.96 (m, 5H, ArH), 6.82 (dd, *J* = 8.6, 1.8 Hz, 2H, ArH), 6.59 (d, *J* = 8.6 Hz, 2H, ArH), 3.93 (t, *J* = 10.9 Hz, 1H, CH₂CHAr), 3.78 (s, 3H, OCH₃), 3.58 (t, *J* = 10.5 Hz, 1H, C(O)CCHCH₂), 2.44 – 2.32 (m, 2H, CH₂), 2.30 (s, 3H, CH₃), 2.23 (s, 3H, CH₃), 2.20 (s, 3H, CH₃), 2.09 (s, 3H, CH₃). ¹³C NMR (126 MHz, CDCl₃) δ 194.10 (d, *J* = 6.6 Hz, 1C, C(O)), 175.67 (d, *J* = 5.2 Hz, C=C-OH), 159.60 – 103.42 (37C, Ar and C=C-OH), 55.30 (s, 1C, OCH₃), 44.31

(dd, $^1J_{\text{PC}} = 51.4$, $^3J_{\text{PC}} = 13.7$ Hz, 1C, CH_2CHAr), 33.69 (dd, $^1J_{\text{PC}} = 56.0$, $^3J_{\text{PC}} = 15.1$ Hz, 1C, CCHCH_2), 30.01 (t, $^2J_{\text{PC}} = 4.5$ Hz, 1C, CH_2), 21.64 (s, 1C, CH_3), 21.58 (s, 1C, CH_3), 21.47 (s, 1C, CH_3), 21.39 (s, 1C, CH_3). $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, CDCl_3) δ 49.69 (d, $^4J_{\text{PP}} = 5.6$ Hz, 1P), 47.61 (d, $^4J_{\text{PP}} = 5.7$ Hz, 1P). HRMS (+ESI) m/z calcd for $\text{C}_{47}\text{H}_{45}\text{O}_3\text{P}_2\text{S}_2$ ($\text{M} + \text{H}$) $^+$: 783.2285; found: 783.2283.

2-(1,3-bis(diphenylphosphorothioyl)-3-(4-nitrophenyl)propyl)-3-hydroxy-1H-inden-1-one (**38ca**). Appearance: yellow solid, Yield=75%, Mp. (dec.) = 190.0-192 °C. ^1H NMR (300 MHz, CDCl_3) δ 11.04 (s, 1H, OH), 7.86 – 7.69 (m, 4H, ArH), 7.63 (dd, $J = 12.7$, 7.7 Hz, 2H, ArH), 7.55 – 7.42 (m, 3H, ArH), 7.41 – 7.28 (m, 5H, ArH), 7.26 – 7.15 (m, 8H, ArH), 7.15 – 6.94 (m, 6H, ArH), 3.80 – 3.63 (m, 2H, CH_2CHAr and C(O)CCHCH_2), 2.46 – 2.16 (m, 2H, CH_2). ^{13}C NMR (75 MHz, CDCl_3) δ 194.55 (d, $^3J_{\text{PC}} = 6.9$ Hz, 1C, C(O)), 176.04 (d, $^3J_{\text{PC}} = 5.1$ Hz, 1C, $\text{C}=\text{C}-\text{OH}$), 148.47 – 102.10 (37C, Ar and $\text{C}=\text{C}-\text{OH}$), 45.21 (dd, $^1J_{\text{PC}} = 49.9$, $^3J_{\text{PC}} = 13.4$ Hz, 1C, CH_2CHAr), 34.21 (dd, $^1J_{\text{PC}} = 56.1$, $^3J_{\text{PC}} = 14.5$ Hz, 1C, CCHCH_2), 30.59 (dd, $^2J_{\text{PC}} = 5.2$, $^2J_{\text{PC}} = 3.1$ Hz, 1C, CH_2). $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, CDCl_3) δ 49.23 (d, $^4J_{\text{PP}} = 4.9$ Hz, 1P), 46.94 (d, $^4J_{\text{PP}} = 4.9$ Hz, 1P). HRMS (+ESI) m/z calcd for $\text{C}_{42}\text{H}_{34}\text{NO}_4\text{P}_2\text{S}_2$ ($\text{M} + \text{H}$) $^+$: 742.1405; found: 742.1414.

2-(1,3-bis(di-*p*-tolylphosphorothioyl)-3-(4-nitrophenyl)propyl)-3-hydroxy-1H-inden-1-one (**38cb**). Appearance: yellow solid, Yield=74%, Mp. (dec.) = 182.2-184 °C. ^1H NMR (400 MHz, CDCl_3) δ 11.18 (s, 1H, OH), 7.83 (d, $J = 8.5$ Hz, 2H, ArH), 7.69 (dd, $J = 12.0$, 8.0 Hz, 2H, ArH), 7.56 (dd, $J = 12.5$, 8.1 Hz, 2H, ArH), 7.50 – 7.32 (m, 5H, ArH), 7.25 – 7.15 (m, 5H, ArH), 7.13 – 7.02 (m, 4H, ArH), 6.99 – 6.89 (m, 4H, ArH), 3.83 – 3.64 (m, 2H, CH_2CHAr and C(O)CCHCH_2), 2.40 (s, 3H, CH_3), 2.37 – 2.30 (m, 2H, CH_2), 2.29 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 2.21 (s, 3H, CH_3). ^{13}C NMR (75 MHz, CDCl_3) δ 194.78 (d, $^3J_{\text{PC}} = 7.1$ Hz, 1C, C(O)), 176.01 (d, $^3J_{\text{PC}} = 5.1$ Hz, 1C, $\text{C}=\text{C}-\text{OH}$), 148.46 – 102.78 (37C, Ar and $\text{C}=\text{C}-\text{OH}$), 45.43 (dd, $^1J_{\text{PC}} = 50.3$, $^3J_{\text{PC}} = 13.2$ Hz, 1C, CH_2CHAr), 34.32 (dd, $^1J_{\text{PC}} = 56.2$, $^3J_{\text{PC}} = 14.3$ Hz, 1C, CCHCH_2), 31.11 (dd, $^2J_{\text{PC}} = 4.8$, $^2J_{\text{PC}} = 3.1$ Hz, 1C, CH_2), 21.66 (d, $J = 1.1$ Hz, 1C, CH_3), 21.58 (d, $J = 1.1$ Hz, 2C, CH_3), 21.48 (d, $J = 1.2$ Hz, 1C, CH_3). $^{31}\text{P}\{^1\text{H}\}$ NMR

(162 MHz, CDCl₃) δ 48.52 (d, $^4J_{PP}$ = 5.1 Hz, 1P), 46.15 (d, $^4J_{PP}$ = 5.4 Hz, 1P). HRMS (+ESI) m/z calcd for C₄₆H₄₂NO₄P₂S₂ (M + H)⁺: 798.2031; found: 798.2033.

2- (1,3-bis (di-*m*-tolylphosphorothioyl) -3- (4-nitrophenyl) propyl)-3-hydroxy-1*H*-inden-1-one (**38cc**). Appearance: yellow solid, Yield=76%, Mp. (dec.) = 201.6-203 °C. ¹H

NMR (400 MHz, CDCl₃) δ 11.16 (s, 1H, OH), 7.83 (d, J = 8.6 Hz, 2H, ArH), 7.72 (d, J = 13.2 Hz, 1H, ArH), 7.59 – 7.48 (m, 2H, ArH), 7.45 – 7.32 (m, 6H, ArH), 7.27 – 7.13 (m, 6H, ArH), 7.11 – 7.00 (m, 5H, ArH), 7.00 – 6.93 (m, 2H, ArH), 3.84 – 3.62 (m, 2H, CH₂CHAr and C(O)CCHCH₂), 2.53 – 2.34 (m, 2H, CH₂), 2.31 (s, 3H, CH₃), 2.25 (s, 3H, CH₃), 2.23 (s, 3H, CH₃), 2.10 (s, 3H, CH₃). ¹³C NMR (101 MHz, CDCl₃) δ 194.43 (d, $^3J_{PC}$ = 6.8 Hz, 1C, C(O)), 175.86 (d, $^3J_{PC}$ = 5.2 Hz, 1C, C=C-OH), 148.56 – 102.55 (37C, Ar and C=C-OH), 45.21 (dd, $^1J_{PC}$ = 49.2, $^3J_{PC}$ = 13.3 Hz, 1C, CH₂CHAr), 34.21 (dd, $^1J_{PC}$ = 55.8, $^3J_{PC}$ = 14.5 Hz, 1C, CCHCH₂), 30.30 – 30.09 (m, 1C, CH₂), 21.61 (s, 2C, CH₃), 21.52 (s, 1C, CH₃), 21.43 (s, 1C, CH₃). ³¹P{¹H} NMR (162 MHz, CDCl₃) δ 49.75 (d, $^4J_{PP}$ = 4.7 Hz, 1P), 47.33 (d, $^4J_{PP}$ = 4.5 Hz, 1P). HRMS (+ESI) m/z calcd for C₄₆H₄₂NO₄P₂S₂ (M + H)⁺: 798.2031; found: 798.2012.

2- (3- (4- (diethylamino) phenyl) -1,3- bis(diphenylphosphorothioyl) propyl) -3- hydroxy -1*H*- inden-1-one (**38da**). Appearance: red solid, Yield=94%, Mp. (dec.) = 185.2-187 °C.

¹H NMR (400 MHz, CDCl₃) δ 11.01 (s, 1H, OH), 7.83 (dd, J = 11.8, 7.4 Hz, 2H, ArH), 7.76 – 7.66 (m, 2H, ArH), 7.56 (dd, J = 12.8, 7.4 Hz, 2H, ArH), 7.48 – 7.26 (m, 11H, ArH), 7.25 – 7.03 (m, 7H, ArH), 6.87 (dd, J = 8.6, 1.6 Hz, 2H, ArH), 6.40 (d, J = 8.7 Hz, 2H, ArH), 4.15 – 4.06 (m, 1H, CH₂CHAr), 3.53 (td, J = 10.3, 1.9 Hz, 1H, C(O)CCHCH₂), 3.43 – 3.22 (m, 4H, N(CH₂CH₃)₂), 2.42 – 2.20 (m, 2H, CHCH₂CH), 1.16 (t, J = 7.0 Hz, 6H, N(CH₂CH₃)₂). ¹³C NMR (101 MHz, CDCl₃) δ 194.16 (d, $^3J_{PC}$ = 6.7 Hz, 1C, C(O)), 175.78 (d, $^3J_{PC}$ = 5.1 Hz, 1C, C=C-OH), 148.39 – 101.87 (37C, Ar and C=C-OH), 44.50 (s, 2C, N(CH₂CH₃)₂), 44.33 (dd, $^1J_{PC}$ = 52.3, $^3J_{PC}$ = 14.0 Hz, 1C, CH₂CHAr), 33.53 (dd, $^1J_{PC}$ = 56.3, $^3J_{PC}$ = 15.3 Hz, 1C, CCHCH₂), 30.46 (t, $^2J_{PC}$ = 5.1 Hz, 1C, CHCH₂CH), 12.78 (s, 2C, N(CH₂CH₃)₂). ³¹P{¹H} NMR (162

MHz, CDCl₃) δ 48.86 (d, $^4J_{PP}$ = 6.4 Hz, 1P), 47.14 (d, $^4J_{PP}$ = 6.3 Hz, 1P). HRMS (+ESI) m/z calcd for C₄₆H₄₄NO₂P₂S₂ (M + H)⁺: 768.2289; found: 768.2278.

2-(1,3-bis(diphenylphosphorothioyl)-3-(4-fluorophenyl)propyl)-

3-hydroxy-1H-inden-1-one (**38ea**). Appearance: yellow solid,

Yield=93%, Mp. (dec.) = 176.1-178 °C. ¹H NMR (500 MHz,

CDCl₃) δ 11.08 (s, 1H, OH), 7.87 – 7.81 (m, 2H, ArH), 7.75 –

7.68 (m, 2H, ArH), 7.59 – 7.54 (m, 2H, ArH), 7.52 – 7.47 (m, 1H, ArH), 7.46 – 7.27 (m, 11H, ArH), 7.25 – 7.22 (m, 2H, ArH), 7.18 (td, J = 7.9, 3.0 Hz, 2H, ArH), 7.12 (td, J = 7.9, 3.1 Hz, 2H, ArH), 6.98 – 6.91 (m, 2H, ArH), 6.73 (t, J = 8.6 Hz, 2H, ArH), 3.92 (t, J = 11.0 Hz, 1H, CH₂CHAr), 3.64 (t, J = 10.5 Hz, 1H, C(O)CCHCH₂), 2.44 – 2.32 (m, 1H, CH₂), 2.32 – 2.21 (m, 1H, CH₂). ¹³C NMR (126 MHz, CDCl₃) δ 194.41 (d, $^3J_{PC}$ = 6.7 Hz, 1C, C(O)), 175.99 (d, $^3J_{PC}$ = 5.2 Hz, 1C, C=C-OH), 164.08 – 102.48 (37C, Ar and C=C-OH), 44.31 (dd, $^1J_{PC}$ = 51.8, $^3J_{PC}$ = 13.7 Hz, 1C, CH₂CHAr), 33.83 (dd, $^1J_{PC}$ = 56.3, $^3J_{PC}$ = 14.9 Hz, 1C, CCHCH₂), 30.58 (t, $^2J_{PC}$ = 4.5 Hz, 1C, CH₂). ³¹P{¹H} NMR (202 MHz, CDCl₃) δ 49.23 (d, $^4J_{PC}$ = 4.5 Hz, 1P), 47.04 (d, $^4J_{PC}$ = 5.2 Hz, 1P). HRMS (+ESI) m/z calcd for C₄₂H₃₄FO₂P₂S₂ (M + H)⁺: 715.1460; found: 715.1462.

2-(3-(4-chlorophenyl)-1,3-bis(diphenylphosphorothioyl)propyl)

-3-hydroxy-1H-inden-1-one (**38fa**). Appearance: yellow solid,

Yield=93%, Mp. (dec.) = 179.7-181 °C. ¹H NMR (500 MHz,

CDCl₃) δ 11.08 (s, 1H, OH), 7.87 – 7.79 (m, 2H, ArH), 7.76 –

7.67 (m, 2H, ArH), 7.58 – 7.51 (m, 2H, ArH), 7.51 – 7.47 (m, 1H, ArH), 7.45 – 7.28 (m, 11H, ArH), 7.25 – 7.22 (m, 1H, ArH), 7.20 (d, J = 7.0 Hz, 1H, ArH), 7.19 – 7.10 (m, 4H, ArH), 7.02 – 6.97 (m, 2H, ArH), 6.97 – 6.92 (m, 2H, ArH), 3.90 (t, J = 11.1 Hz, 1H, CH₂CHAr), 3.64 (t, J = 10.6 Hz, 1H, C(O)CCHCH₂), 2.40 – 2.30 (m, 1H, CH₂), 2.30 – 2.19 (m, 1H, CH₂). ¹³C NMR (126 MHz, CDCl₃) δ 194.46 (d, $^3J_{PC}$ = 6.8 Hz, 1C, C(O)), 175.99 (d, $^3J_{PC}$ = 5.0 Hz, 1C, C=C-OH), 141.24 – 102.84 (37C, Ar and C=C-OH), 44.49 (dd, $^1J_{PC}$ = 51.5, $^3J_{PC}$ = 13.6 Hz, 1C, CH₂CHAr), 33.83 (dd, $^1J_{PC}$ = 56.2, $^3J_{PC}$ = 14.8 Hz, 1C, CCHCH₂), 30.74 (t, $^2J_{PC}$ = 4.6 Hz, 1C, CH₂). ³¹P{¹H} NMR (202 MHz, CDCl₃) δ 48.90 (d, $^4J_{PP}$ = 5.3 Hz, 1P), 46.86 (d, $^4J_{PP}$ = 5.5 Hz, 1P). HRMS (+ESI) m/z calcd for C₄₂H₃₄ClO₂P₂S₂ (M + H)⁺: 731.1164; found: 731.1159.

2- (1,3-bis (diphenylphosphorothioyl) -3- (2-methoxyphenyl) propyl) -3- hydroxy-1H-inden-1-one (**38ga**). Appearance: yellow solid, Yield=94%, Mp. (dec.) = 202.4-205 °C. ¹H NMR (500 MHz, CDCl₃) δ 10.78 (s, 1H, OH), 7.98 (dd, *J* = 11.8, 7.3 Hz, 2H, ArH), 7.79 – 7.70 (m, 4H, ArH), 7.58 – 7.50 (m, 2H, ArH), 7.48 – 7.43 (m, 4H, ArH), 7.42 – 7.36 (m, 1H, ArH), 7.32 – 7.27 (m, 4H, ArH), 7.25 – 7.08 (m, 7H, ArH), 6.98 (td, *J* = 7.9, 3.0 Hz, 2H, ArH), 6.82 (t, *J* = 7.5 Hz, 1H, ArH), 6.44 (d, *J* = 8.2 Hz, 1H, ArH), 4.67 (t, *J* = 10.8 Hz, 1H, CH₂CHAr), 3.88 (td, *J* = 11.6, 2.3 Hz, 1H, C(O)CCHCH₂), 3.08 (s, 3H, OCH₃), 2.66 – 2.48 (m, 1H, CH₂), 2.45 – 2.32 (m, 1H, CH₂). ¹³C NMR (126 MHz, CDCl₃) δ 192.31 (d, ³*J*_{PC} = 6.1 Hz, 1C, C(O)), 174.82 (d, ³*J*_{PC} = 5.4 Hz, 1C, C=C-OH), 158.08 – 102.82 (37C, Ar and C=C-OH), 54.28 (s, 1C, OCH₃), 34.20 (dd, ¹*J*_{PC} = 51.5, ³*J*_{PC} = 13.3 Hz, 1C, CH₂CHAr), 33.80 (dd, ¹*J*_{PC} = 55.8, ³*J*_{PC} = 15.7 Hz, 1C, CCHCH₂), 27.79 (t, ²*J*_{PC} = 5.2 Hz, 1C, CH₂). ³¹P{¹H} NMR (202 MHz, CDCl₃) δ 50.83 (s, 1P), 48.45 (s, 1P). HRMS (+ESI) *m/z* calcd for C₄₃H₃₇O₃P₂S₂ (M + H)⁺: 727.1659; found: 727.1656.

2- (1,3- bis (di-*p*-tolylphosphorothioyl)-3-(2-methoxy phenyl) propyl) -3- hydroxy -1H- inden -1- one (**38gb**). Appearance: yellow solid, Yield=81%, Mp. (dec.) = 210.9-212 °C. ¹H NMR (400 MHz, CDCl₃) δ 10.85 (s, 1H, OH), 7.83 (dd, *J* = 11.7, 8.0 Hz, 2H, ArH), 7.67 – 7.53 (m, 4H, ArH), 7.45 – 7.34 (m, 1H, ArH), 7.31 – 7.26 (m, 3H, ArH), 7.25 – 7.12 (m, 6H, ArH), 7.10 – 6.98 (m, 4H, ArH), 6.85 – 6.74 (m, 3H, ArH), 6.45 (d, *J* = 8.2 Hz, 1H, ArH), 4.61 (t, *J* = 10.8 Hz, 1H, CH₂CHAr), 3.83 (t, *J* = 10.4 Hz, 1H, C(O)CCHCH₂), 3.09 (s, 3H, OCH₃), 2.64 – 2.49 (m, 1H, CH₂), 2.43 (s, 3H, CH₃), 2.42 (s, 3H, CH₃), 2.39 – 2.29 (m, 1H, CH₂), 2.20 (s, 3H, CH₃), 2.15 (s, 3H, CH₃). ¹³C NMR (101 MHz, CDCl₃) δ 192.40 (d, ³*J*_{PC} = 6.2 Hz, 1C, C(O)), 174.80 (d, ³*J*_{PC} = 5.3 Hz, 1C, C=C-OH), 158.79 – 102.49 (37C, Ar and C=C-OH), 54.28 (s, 1C, OCH₃), 34.37 (dd, ¹*J*_{PC} = 52.3, ³*J*_{PC} = 13.4 Hz, 1C, CH₂CHAr), 33.90 (dd, ¹*J*_{PC} = 56.2, ³*J*_{PC} = 15.3 Hz, 1C, CCHCH₂), 27.91 (t, ²*J*_{PC} = 4.9 Hz, 1C, CH₂), 21.75 (s, 2C, CH₃), 21.55 (s, 1C, CH₃), 21.39 (s, 1C, CH₃). ³¹P{¹H} NMR (162 MHz, CDCl₃) δ 50.49 (s, 1P), 48.18 (s, 1P). HRMS (+ESI) *m/z* calcd for C₄₇H₄₅O₃P₂S₂ (M + H)⁺: 783.2285; found: 783.2281.

2- (1,3-bis (di-*m*-tolylphosphorothioyl) -3- (2-methoxy phenyl) propyl) -3- hydroxy -1*H*- inden -1- one (**38gc**).

Appearance: yellow solid, Yield=92%, Mp. (dec.) =

183.9-185 °C. ¹H NMR (500 MHz, CDCl₃) δ 10.85 (s,

1H, OH), 7.82 (d, *J* = 12.4 Hz, 1H, ArH), 7.74 – 7.68 (m, 1H, ArH), 7.59 (dd, *J* = 13.4, 7.6 Hz, 2H, ArH), 7.55 – 7.44 (m, 2H, ArH), 7.41 – 7.27 (m, 8H, ArH), 7.19 (t, *J* = 7.8 Hz, 1H, ArH), 7.14 – 7.08 (m, 3H, ArH), 6.96 – 6.81 (m, 5H, ArH), 6.46 (d, *J* = 8.3 Hz, 1H, ArH), 4.64 (t, *J* = 10.7 Hz, 1H, CH₂CHAr), 3.86 (t, *J* = 10.5 Hz, 1H, C(O)CCHCH₂), 3.07 (s, 3H, OCH₃), 2.69 – 2.54 (m, 1H, CH₂), 2.42 (s, 3H, CH₃), 2.41 (s, 3H, CH₃), 2.40 – 2.34 (m, 1H, CH₂), 2.19 (s, 3H, CH₃), 2.03 (s, 3H, CH₃). ¹³C NMR (126 MHz, CDCl₃) δ 192.34 (d, ³*J*_{PC} = 6.1 Hz, 1C, C(O)), 174.70 (d, ³*J*_{PC} = 5.4 Hz, 1C, C=C-OH), 158.12 – 102.49 (37C, Ar and C=C-OH), 54.30 (s, 1C, OCH₃), 34.06 (dd, ¹*J*_{PC} = 51.4, ³*J*_{PC} = 13.4 Hz, 1C, CH₂CHAr), 33.72 (dd, ¹*J*_{PC} = 55.7, ³*J*_{PC} = 15.3 Hz, 1C, CCHCH₂), 27.69 (t, ²*J*_{PC} = 5.1 Hz, 1C, CH₂), 21.81 (s, 1C, CH₃), 21.74 (s, 1C, CH₃), 21.47 (s, 1C, CH₃), 21.27 (s, 1C, CH₃). ³¹P{¹H} NMR (202 MHz, CDCl₃) δ 51.08 (s, 1P), 48.62 (s, 1P). HRMS (+ESI) *m/z* calcd for C₄₇H₄₅O₃P₂S₂ (M + H)⁺: 783.2285; found: 783.2288.

2- (1,3-bis (diphenylphosphorothioyl) -3-(2-nitrophenyl)propyl)-

3-hydroxy-1*H*-inden-1-one (**38ha**). Appearance: yellow solid,

Yield=82% (mixture of diastereomers in 1 : 0.17 ratio, based on

³¹P{¹H} NMR spectrum. The two isomers were not separable.),

Mp. (dec.) = 185.9-188 °C. NMR characterization data of the major diastereomer: ¹H NMR (500 MHz, CDCl₃, mixture) δ 10.73 (s, 1H, OH), 8.09 – 8.01 (m, 2H, ArH), 7.89 – 7.84 (m, 1H, ArH), 7.78 – 7.71 (m, 4H, ArH), 7.64 – 7.57 (m, 2H, ArH), 7.51 – 7.43 (m, 4H, ArH), 7.42 – 7.38 (m, 3H, ArH), 7.36 – 7.30 (m, 3H, ArH), 7.30 – 7.26 (m, 3H, ArH), 7.25 – 7.23 (m, 1H, ArH), 7.19 – 7.15 (m, 1H, ArH), 7.02 – 6.94 (m, 4H, ArH), 5.62 – 5.53 (m, 1H, CH₂CHAr), 3.82 – 3.68 (m, 1H, C(O)CCHCH₂), 2.52 – 2.43 (m, 2H, CH₂). ¹³C NMR (126 MHz, CDCl₃, mixture) δ 193.61 (d, ³*J*_{PC} = 6.3 Hz, 1C, C(O)), 175.34 (d, ³*J*_{PC} = 5.3 Hz, 1C, C=C-OH), 150.22 – 101.82 (37C, Ar and C=C-OH), 37.41 (dd, ¹*J*_{PC} = 48.2, ³*J*_{PC} = 13.4 Hz, 1C, CH₂CHAr), 34.19 (dd, ¹*J*_{PC} = 56.2, ³*J*_{PC} = 14.8 Hz, 1C, CCHCH₂), 28.89 (dd, ²*J*_{PC} = 5.3, ²*J*_{PC} = 4.1 Hz, 1C, CH₂). ³¹P{¹H} NMR (202 MHz, CDCl₃, mixture) δ 52.68 (s, 1P), 47.75 (s, 1P). HRMS (+ESI) *m/z* calcd for C₄₂H₃₄NO₄P₂S₂ (M + H)⁺: 742.1405; found: 742.1409.

3.5.6 Synthesis of optically pure bimetallic complexes:

General Procedure C: Compounds **51** were synthesized according to the following procedure (Scheme 69):

Scheme 69. General procedure C.

A nitrogen flushed 2-neck flask was charged with **36a** (19.7 mg, 75.7 μmol , 1 equiv) and triethylamine (15.3 mg, 151.4 μmol , 2 equiv) in de-gassed acetone (2.5 mL) at room temperature, followed by the addition of HPPH_2 (29.6 mg, 159 μmol , 2.1 equiv). The setup was stirred for 10 mins, then the solvent was removed with vacuum distillation. The generated phosphine salt was dissolved in 2 mL de-gassed DCM, then complex **5** (46.1 mg, 79.5 μmol , 1.05 equiv) was added to the solution. The mixture was stirred at room temperature for another 30 mins. Upon completion of coordination, the generated diastereomers were separated via multiple silica gel column chromatography, using DCM/ ethyl acetate (100:0 to 50:50) eluent system. The chemical yields of the isolated bimetallic complexes are listed below.

Characterization data:

Bimetallic Complex (S,R,R,S)-51a.

Appearance: yellow solid, Yield=45% (after separation of the diastereomers), Mp. (dec.) = 194-196 $^{\circ}\text{C}$, $[\alpha]_{\text{D}}^{20} = -17.4$ (c 0.5, CH_2Cl_2) ^1H NMR (400 MHz, CDCl_3) δ 7.91 – 7.80 (m, 2H, ArH), 7.78 – 7.68 (m, 2H, ArH), 7.35 – 7.19 (m, 10H, ArH), 7.15 – 7.07 (m, 3H, ArH), 7.04 – 6.98 (m, 3H, ArH), 6.97 – 6.87 (m, 3H, ArH), 6.85 – 6.73 (m, 6H,

ArH), 6.72 – 6.61 (m, 3H, ArH), 6.58 – 6.47 (m, 2H, ArH), 6.46 – 6.39 (m, 1H, ArH), 6.06 (t, $J = 7.1$ Hz, 1H, ArH), 5.84 (t, $J = 7.0$ Hz, 1H, ArH), 4.58 (q, $J = 6.3$ Hz, 1H, CH), 3.71 – 3.55 (m, 1H, CH), 3.50 – 3.37 (m, 1H, CH), 2.93 – 2.80 (m, 1H, CH), 2.76 – 2.70 (m, 1H, CH₂), 2.68 (d, $J = 2.8$ Hz, 3H, NCH₃), 2.58 (d, $J = 1.5$ Hz, 3H, NCH₃), 2.53 (d, $J = 2.8$ Hz, 3H, NCH₃), 2.52 – 2.48 (m, 1H, CH₂), 2.46 (d, $J = 1.6$ Hz, 3H, NCH₃), 1.48 (d, $J = 6.5$ Hz, 3H, NCHCH₃), 1.37 (d, $J = 6.7$ Hz, 3H, NCHCH₃). ¹³C NMR (101 MHz, CDCl₃) δ 192.48 (d, $^3J_{PC} = 7.3$ Hz, 1C, C(O)), 186.42 (d, $^3J_{PC} = 5.0$ Hz, 1C, COPd), 155.82 – 101.53 (49C, Ar and C=C-OPd), 75.98 (d, $^3J_{PC} = 2.6$ Hz, 1C, CNMe₂), 71.26 (d, $^3J_{PC} = 2.7$ Hz, 1C, CNMe₂), 50.09 (s, 1C, NCH₃), 46.64 (s, 2C, NCH₃), 46.16 – 45.20 (m, 1C, CCHCH₂), 41.30 (s, 1C, NCH₃), 35.80 (d, $^1J_{PC} = 15.8$ Hz, 1C, CH₂CHPh), 28.18 (dd, $^2J_{PC} = 29.6$, $^2J_{P'C} = 11.8$ Hz, 1C, CH₂), 22.01 (s, 1C, NCHCH₃), 11.80 (s, 1C, NCHCH₃). ³¹P{¹H} NMR (162 MHz, CDCl₃) δ 52.06 (s, 1P), 45.06 (s, 1P). HRMS (+ESI) m/z calcd for C₆₂H₆₂ClN₂O₂P₂¹⁰⁶Pd¹⁰⁸Pd (M + H)⁺: 1177.2049; found: 1177.2041.

Bimetallic Complex (S,S,S,S)-**51b**.

Appearance: yellow solid, Yield=41% (after separation of the diastereomers), Mp. (dec.) = 185-186 °C, $[\alpha]_D^{20} = +53.1$ (c 0.5, CH₂Cl₂) ¹H NMR (400 MHz, CDCl₃) δ 7.80 – 7.70 (m, 2H, ArH), 7.50 – 7.38 (m, 2H, ArH), 7.34 – 7.19 (m, 9H, ArH), 7.18 – 7.09 (m, 5H, ArH), 7.08 – 6.90 (m, 9H, ArH), 6.88 – 6.73 (m, 4H, ArH), 6.64 – 6.48 (m, 3H, ArH), 6.41 (td, $J = 7.5$, 1.2 Hz, 1H, ArH), 6.10 (t, $J = 6.9$ Hz, 1H, ArH), 5.86 (t, $J = 7.0$ Hz, 1H, ArH), 4.34 – 4.19 (m, 1H, CH), 3.63 – 3.49 (m, 2H, 2XCH), 2.95 – 2.83 (m, 1H, CH), 2.69 (s, 3H, NCH₃), 2.59 (s, 3H, NCH₃), 2.51 (d, $J = 2.6$ Hz, 3H, NCH₃), 2.48 – 2.43 (m, 1H, CH₂), 2.39 (d, $J = 3.2$ Hz, 3H, NCH₃), 2.22 – 2.09 (m, 1H, CH₂), 1.74 (d, $J = 6.4$ Hz, 3H, CHCH₃), 1.36 (d, $J = 6.5$ Hz, 3H, CHCH₃). ¹³C NMR (101 MHz, CDCl₃) δ 192.62 (d, $^3J_{PC} = 6.7$ Hz, 1C, C(O)), 186.04 (d, $^3J_{PC} = 4.8$ Hz, 1C, COPd), 157.82 – 101.82 (49C, Ar and C=C-OPd), 74.87 (s, 1C, CNMe₂), 65.77 (s, 1C, CNMe₂), 50.58 (s, 1C, NCH₃), 49.68 (s, 1C, NCH₃), 45.16 (s, 1C, NCH₃), 44.98 (s, 1C, NCH₃), 42.69

– 42.13 (m, 1C, CCHCH₂), 33.41 (d, ¹J_{PC} = 19.5 Hz, 1C, CH₂CHAr), 27.59 (dd, ²J_{PC} = 29.9, ²J_{P'C} = 10.5 Hz, 1C, CH₂), 25.32 (s, 1C, NCHCH₃), 18.96 (s, 1C, NCHCH₃). ³¹P{¹H} NMR (162 MHz, CDCl₃) δ 52.41 (s, 1P), 46.26 (s, 1P). HRMS (+ESI) m/z calcd for C₆₂H₆₂N₂O₂P₂¹⁰⁴Pd¹¹⁰Pd(M + H - Cl)⁺: 1142.2379; found: 1142.2384.

3.5.7 Synthesis of monometallic complex:

General Procedure D: Compound **53** was synthesized according to the following procedure (Scheme 70):

Scheme 70. General procedure C.

A nitrogen flushed 2-neck flask was charged with bimetallic complex (*S,R,R,S*)-**51a** (20 mg, 17 μmol, 1 equiv) in de-gassed DCM (2 mL) at room temperature, followed by the addition of KCN solution (50 mg dissolved in 1 mL de-gassed H₂O). The solution was stirred vigorously for 20 mins. The organic layer was separated and washed with de-gassed water until all the excess amount of KCN was removed. Then 0.1 mL hydrogen peroxide solution (30% H₂O₂ solution in water) was introduced into the flask and the mixture was stirred for 5 mins at room temperature. After completion of the reaction, the organic phase was separated, and the solvent was removed under reduced pressure. The crude mixture was purified on silica gel column chromatography using DCM/ ethyl acetate (80:20 to 20:80) eluent system. The monometallic complex was obtained as yellow solid in 78% yield.

Characterization data:

Monometallic Complex (*S,R,R*)-53. Appearance: yellow solid, Yield=78%, Mp. (dec.) = 173-175 °C, [α]_D²⁰ = -18.4 (c 1.0, CH₂Cl₂) ¹H NMR (400 MHz, CDCl₃) δ 7.87 – 7.74 (m, 2H, ArH), 7.72 – 7.62 (m, 2H, ArH), 7.43 – 7.26 (m, 11H, ArH), 7.26 – 6.98 (m, 14H, ArH), 6.97 – 6.87 (m, 2H, ArH), 6.63 – 6.47 (m, 2H, ArH), 4.51 (q,

$J = 7.0$ Hz, 1H, CH), 3.52 (dd, $J = 10.7$, 6.9 Hz, 1H, CH), 3.22 (dd, $J = 17.1$, 11.1 Hz, 1H, CH), 2.68 (d, $J = 2.9$ Hz, 3H, NCH₃), 2.51 (s, 3H, NCH₃), 2.33 (dd, $J = 22.8$, 10.9 Hz, 1H, CH₂), 2.22 – 2.11 (m, 1H, CH₂), 1.48 (d, $J = 6.6$ Hz, 3H, CHCH₃). ¹³C NMR (101 MHz, CDCl₃) δ 193.25 (d, $J = 7.3$ Hz, 1C, C(O)), 186.92 (d, $J = 4.9$ Hz, 1C, COPd), 153.93 – 102.54 (43C, Ar and C=C-OPd), 71.59 (d, $^3J_{PC} = 2.8$ Hz, 1C, CNMe₂), 46.44 (d, $^3J_{PC} = 2.3$ Hz, 1C, NCH₃), 44.56 (dd, $^1J_{PC} = 68.0$, $^3J_{PC} = 13.9$ Hz, 1C, CCHCH₂), 41.40 (d, $^3J_{PC} = 2.6$ Hz, 1C, NCH₃), 32.68 (d, $^1J_{PC} = 15.4$ Hz, 1C, CH₂CHAr), 28.53 (dd, $^2J_{PC} = 29.3$, $^2J_{P'C} = 14.9$ Hz, 1C, CH₂), 11.68 (s, 1C, NCHCH₃). ³¹P{¹H} NMR (162 MHz, CDCl₃) δ 52.96 (s), 34.17 (s). HRMS (+ESI) m/z calcd for C₅₂H₄₈NO₃P₂Pd (M + H)⁺: 902.2144; found: 902.2132.

3.5.8 X-ray measurement data

Crystallographic data: ligand (*R**,*R**)-**38aa**.

Table 17. Sample and crystal data for (*R**,*R**)-**38aa**.

Identification code	CCDC 1938165
Chemical formula	C ₄₂ H ₃₄ O ₂ P ₂ S ₂
Formula weight	696.75 g/mol
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal size	0.040 x 0.200 x 0.220 mm

Crystal habit	yellow plate	
Crystal system	monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	$a = 8.7505(4) \text{ \AA}$	$\alpha = 90^\circ$
	$b = 20.8649(11) \text{ \AA}$	$\beta = 92.892(2)^\circ$
	$c = 19.0714(9) \text{ \AA}$	$\gamma = 90^\circ$
Volume	$3477.6(3) \text{ \AA}^3$	
Z	4	
Density (calculated)	1.331 g/cm^3	
Absorption coefficient	0.282 mm^{-1}	

Crystallographic data: ligand (R^*,R^*)-**46**.

Table 18. Sample and crystal data for (R^*,R^*)-**46**.

Identification code	CCDC 1938166
Chemical formula	$C_{44}H_{38}O_2P_2S_2$
Formula weight	724.80 g/mol
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal size	0.020 x 0.120 x 0.140 mm
Crystal habit	yellow plate

Crystal system	monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	$a = 23.0930(5) \text{ \AA}$	$\alpha = 90^\circ$
	$b = 8.8734(2) \text{ \AA}$	$\beta = 107.3313(9)^\circ$
	$c = 18.7652(4) \text{ \AA}$	$\gamma = 90^\circ$
Volume	$3670.66(14) \text{ \AA}^3$	
Z	4	
Density (calculated)	1.312 g/cm^3	
Absorption coefficient	0.270 mm^{-1}	

Crystallographic data: complex *(S,R,R,S)*-**51a**.

Remark: hydrogens were omitted from the ORTEP structure for clarity. For chirality, see the additional structure (blue atoms: hydrogens).

Table 19. Sample and crystal data for *(S,R,R,S)*-**51a**.

Identification code CCDC 1938163

Chemical formula	$C_{62}H_{61}ClN_2O_2P_2Pd_2$	
Formula weight	1176.31 g/mol	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal size	0.020 x 0.100 x 0.280 mm	
Crystal habit	orange plate	
Crystal system	orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	$a = 11.4070(9)$ Å	$\alpha = 90^\circ$
	$b = 14.9513(11)$ Å	$\beta = 90^\circ$
	$c = 31.156(3)$ Å	$\gamma = 90^\circ$
Volume	$5313.6(7)$ Å ³	
Z	4	
Density (calculated)	1.470 g/cm ³	
Absorption coefficient	0.834 mm ⁻¹	
Absolute structure parameter	0.028(19)	

Crystallographic data: complex (S,R,R)-**53**.

Remark: hydrogens were omitted from the ORTEP structure for clarity. For chirality, see the additional structure (blue atoms: hydrogens).

Table 20. Sample and crystal data for (*S,R,R*)-**53**.

Identification code	CCDC 1938164	
Chemical formula	C ₅₂ H ₄₉ NO ₄ P ₂ Pd	
Formula weight	920.26 g/mol	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal size	0.080 x 0.140 x 0.200 mm	
Crystal habit	orange block	
Crystal system	orthorhombic	
Space group	<i>P</i> 2 ₁ 2 ₁ 2 ₁	
Unit cell dimensions	a = 9.8394(11) Å	$\alpha = 90^\circ$
	b = 20.038(3) Å	$\beta = 90^\circ$
	c = 22.336(2) Å	$\gamma = 90^\circ$
Volume	4403.8(8) Å ³	
Z	4	
Density (calculated)	1.388 g/cm ³	
Absorption coefficient	0.541 mm ⁻¹	
Absolute structure parameter	-0.025(13)	

CHAPTER IV

Palladium-Catalyzed Asymmetric P-H Addition to Electrophilic α -Diazoesters

4.1 Introduction

Over the past 50 years, chiral phosphine ligands were widely employed in transition metal-catalyzed asymmetric protocols.¹⁸⁶ Generally, phosphine ligands having axial, planar or carbon-centered chirality are more commonly used in these catalytic transformations, compared to phosphorus compounds bearing P-stereogenic center. This observation can be elucidated by the relatively more difficult synthesis of these species.¹⁸⁷ Traditionally, P-chiral phosphines were synthesized with the use of chiral auxiliaries¹⁸⁷⁻¹⁸⁸ (commonly by L-menthol^{12, 189}), and also with chiral metal template-promoted strategies.^{24, 80b, 124} Nowadays, the focus has shifted more onto the development of various asymmetric catalytic synthesis methods in this area (Scheme 71). These protocols include Pd-catalyzed asymmetric cross-coupling,^{55-56, 58} enantioselective C-H activation,⁶²⁻⁶⁴ ring closing metathesis,⁶⁷ alkylation of phosphines with alkyl halides,⁵⁹⁻⁶⁰ asymmetric deprotonation,¹⁹⁰ Cu-catalyzed arylation of phosphine oxides,⁶⁸ asymmetric allylation⁶⁹ and desymmetrization,^{65-66, 191} just to name a few examples (for more details, see chapter 1.4).

Scheme 71. Recent developments of asymmetric catalytic P-chiral phosphine synthesis.

Although there has been significant development in this field recently, the formation of P-chiral phosphorus compounds in an effective, catalytic manner is still a demand in synthetic chemistry.

Asymmetric Pd-catalyzed P-H addition has proved to be an excellent tool for generating C-chiral phosphine species in an atom economical transformation with excellent enantioselectivity and broad substrate scope.^{80c, 146} Asymmetric catalytic P-H addition for P-chiral phosphine generation via C-P* bond formation was first established by Glueck in 2000 (Scheme 72a).¹⁹² In their study, they reported Pt-catalyzed hydrophosphination between racemic secondary phosphines and activated alkenes. A few years later, in 2006, Gaumont investigated a Pd-catalyzed asymmetric P-H addition onto non-activated alkynes, generating C-P* bond.¹⁹³ As the next milestone in this area, our group recently reported a novel method to generate enantioenriched P-stereogenic compounds via O-P* bond formation (Scheme 72b).¹³⁴ The generated compounds could be easily derivatized to obtain various P-chiral species. However, the generation of P-stereogenic phosphorus compounds via N-P* bond formation in an asymmetric catalytic P-H addition scenario has never been reported to date, to the best of our knowledge.

Over the last decade, diazo compounds have been applied in various synthetic protocols.¹⁹⁴ They were commonly used as C-nucleophiles, 1,3-dipoles and metal carbene precursors. The nucleophilic character of the terminal nitrogen and the α -carbon of the diazo moiety was thoroughly investigated; however, the electrophilic nature of the terminal nitrogen remains relatively unexplored.¹⁹⁵ Feng established the first asymmetric catalytic synthesis method to utilize α -diazoesters in Sc-catalyzed N-C* bond formation in 2011 (Scheme 72c).¹³⁵ Two years later, in 2013, Zhu discovered an organocatalytic methodology in which the nucleophile phosphine/ phosphine oxide moiety was attached to the electrophilic nitrogen of α -diazoesters in an achiral transformation.^{195b} Herein, we disclose a novel, Pd-catalyzed asymmetric P-H addition protocol of racemic secondary diarylphosphines to electrophilic α -diazoacetates in N-P* bond formation (Scheme 72d). Subsequent acidic methanolysis of the generated phosphinic hydrazones resulted in the formation of enantioenriched P-stereogenic diarylphosphinates.

a) Asymmetric catalytic P-H addition in **C-P*** bond formation

b) Asymmetric catalytic P-H addition in **O-P*** bond formation

c) Asymmetric catalytic **N-C*** bond formation by electrophilic diazoesters

d) Asymmetric catalytic P-H addition in **N-P*** bond formation (this work)

Scheme 72. Development of asymmetric P-H addition reactions in P-stereogenic compound formation.

4.2 Results and discussions

We started the reaction optimization by using ethyl 2-diazo-2-phenylacetate (**55a**) and racemic (3,5-dimethylphenyl)(phenyl)phosphane (**56a**) as model substrates in the P-H addition. After the phosphination was completed, the generated phosphine was sulfurized and isolated on column chromatography to obtain the phosphinic hydrazone **57aa** (Table 21). In the first step of the optimization protocol, the effect of various palladium catalysts was tested (Table 21, entries 1-17). As control reactions, catalyst- and base-free transformations were also investigated (Table 21, entries 1 and 2). It can be clearly seen from our results that the presence of both palladium and an external base is necessary for the reaction to proceed (Table 21, entries 1-5). The PCP-type pincer complex (**18**) and the Pd salt/ BINAP systems were ineffective in this transformation (Table 21, entries 10-15). The MOP catalysts provided slightly better results, but the results were still not satisfactory (Table 21, entries 16 and 17). By using these catalyst systems, the conversion was low even after prolonged reaction time. Furthermore, significant amount of by-products were formed and the desired product was obtained only in low enantioselectivity. In contrast, the (*R*)-**7** catalyst was found to be more effective in this transformation even in the first trial (Table 21, entry 6). Although the conversion was only 69% after 65 hours reaction time and the

enantioselectivity was found to be 35%, by-product formation was not observed in this case. In order to enhance the reaction rate, as well as the selectivity, higher catalyst loadings were tested in the next step (Table 21, entries 6-9).

Table 21. Optimization of the reaction conditions.

Entry	Catalyst [mol%]	Solvent	Base (1 equiv)	T [°C]	t	Conversion ^a [%]	ee ^b [%]
1	-	CHCl ₃	-	-40	16 h	-	-
2	-	CHCl ₃	Et ₃ N	-40	16 h	-	-
3	5% Pd(OAc) ₂	CHCl ₃	-	-40	16 h	-	-
4	5% Pd(OAc) ₂	acetone	-	rt	22 h	19 ^c	-
5	5% Pd(MeCN) ₂ Cl ₂	CHCl ₃	DBU	rt	24 h	26 ^c	-
6	5% (R)- 7	CHCl ₃	Et ₃ N	-40	65 h	69	35
7	10% (R)- 7	CHCl ₃	Et ₃ N	-40	65 h	79	39
8	15% (R)- 7	CHCl ₃	Et ₃ N	-40	65 h	93	38
9	20% (R)- 7	CHCl ₃	Et ₃ N	-40	65 h	90	38
10	10% (R,R)- 18	CHCl ₃	-	-40	72 h	3 ^c	N.D.
11	10% (R,R)- 18	CHCl ₃	-	rt	48 h	8 ^c	16
12	5% (R,R)-PCP-Cl / 10% AgClO ₄	CHCl ₃ /acetone (8:1)	DBU	-80	15 h	29 ^c	8
13	2.5% Pd ₂ dba ₃ / 6% (R)-BINAP	CHCl ₃ /acetone (8:1)	DBU	-80	15 h	16 ^c	3
14	5% Pd(OAc) ₂ / 6% (R)-BINAP	CHCl ₃	DBU	-40	65 h	no reaction	N.D.
15	5% [(R)-BINAP]-PdCl ₂ / 10% AgClO ₄	CHCl ₃	DBU	-40	65 h	no reaction	N.D.
16	5% (R)-MOP	CHCl ₃ /acetone (8:1)	DBU	-80	40 h	30 ^c	0
17	5% (S)-MOP OAc	CHCl ₃ /acetone (8:1)	DBU	-80	24 h	54 ^c	-15
18	5% (R)- 7	CHCl ₃	DMA ^d	-40	24 h	no reaction	N.D.
19	5% (R)- 7	CHCl ₃	DMA ^d	rt	15 h	61	4
20	5% (R)- 7	CHCl ₃	DBU	-40	24 h	99	36
21	5% (R)- 7	CHCl ₃	TBD ^{e,h}	-40	3 h	99	34
22	5% (R)- 7	CHCl ₃	TMG ^{f,h}	-40	3 h	99	38
23	5% (R)- 7	CHCl ₃	DABCO	-40	65 h	30	39
24	5% (R)- 7	MeCN	Et ₃ N	-40	65 h	99	29
25	5% (R)- 7	toluene	Et ₃ N	-40	65 h	57	17
26	5% (R)- 7	DCM	Et ₃ N	-40	72 h	95	31
27	5% (R)- 7	DCM	Et ₃ N	-80	72 h	60	40

28	5% (<i>R</i>)- 7	acetone	Et ₃ N	-40	72 h	99	28
29	5% (<i>R</i>)- 7	Et ₂ O	Et ₃ N	-40	65 h	32	25
30	5% (<i>R</i>)- 7	THF	Et ₃ N	-40	65 h	7	35
31	5% (<i>R</i>)- 7	neat	Et ₃ N	-40	24 h	47	10
32	5% (<i>R</i>)- 7	MeOH ^h	Et ₃ N	-40	40 h	99	36
33	5% (<i>R</i>)- 7	EtOH	Et ₃ N	-40	40 h	75	29
34	5% (<i>R</i>)- 7	ⁱ PrOH	Et ₃ N	-40	40 h	79	23
35	5% (<i>R</i>)- 7	DCE	Et ₃ N	-40	40 h	28	38
36	5% (<i>R</i>)- 7	CHBr ₃ /DCM (1:1)	Et ₃ N	-40	40 h	no reaction	N.D.
37	5% (<i>R</i>)- 7	CHCl ₃ /acetone (5:1)	Et ₃ N	-80	17 h	78	49
38	10% (<i>R</i>)- 7	CHCl ₃ /acetone (8:1)	Et ₃ N	-80	96 h	60	53
39	10% (<i>R</i>)- 7	CHCl ₃ /acetone (8:1)	DBU	-80	24 h	94 (78%) ^g	55
40	10% (<i>R</i>)- 7	CHCl ₃ /THF (8:1)	DBU	-80	24 h	90	55
41	10% (<i>R</i>)- 7	CHCl ₃ /acetone (8:1)	TMG	-80	12 h	99	49
42	10% (<i>R</i>)- 7	MeOH	TMG	-80	12 h	56	37

^aConversion was determined by ³¹P{¹H} NMR measurement of the crude mixture. ^bEnantiomeric excess was determined by chiral HPLC. ^cSignificant number of unidentified by-products were formed. ^dDMA: dimethylaniline. ^eTBD: 1,5,7-triazabicyclo[4.4.0]dec-5-ene. ^fTMG: 1,1,3,3-tetramethylguanidine. ^gIsolated yield in parentheses. ^hRemark: Methanol as solvent, TBD and TMG as external bases were reasonable choices based on these results; however, at -80 °C the obtained selectivity was lower compared to that of with DBU.

The higher catalyst loading (10%-20%) accelerated the reaction, but the enantioselectivity still remained in the same range (*ee* between 35% and 39%). The best selectivity (*ee*=39%) was observed with 10% catalyst loading and the conversion was 79% after 65 hours in this instance (Table 21, entry 7). In the next step of the optimization attempts, several external bases were evaluated for the addition reaction (Table 21, entries 18-23). From these results, it can be clearly seen that the base has a significant effect on the reaction rate; however, the enantioselectivity values were still similar to what we observed in case of triethylamine (observed *ee*'s in the base-screening reactions were between 34% to 39%). The addition reaction with *N,N*-dimethylaniline (=DMA) did not proceed at low temperature (-40 °C). At ambient temperature, the desired product was formed in 61% conversion within 15 hours, but the observed selectivity was the lowest among these trials (*ee*=4%). The reaction was completed in case of 1,8-diazabicyclo[5.4.0]undec-7-ene (=DBU) within 24 hours and the *ee* was 36%. Stronger bases, such as 1,1,3,3-tetramethylguanidine (=TMG) and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (=TBD) provided the phosphinic hydrazones within 3 hours with full NMR conversion (99%) and the observed enantioselectivity was 34% and 38% respectively. The highest *ee* (39%) was achieved with 1,4-diazabicyclo[2.2.2]octane (=DABCO); although, the reaction was slow (30% conversion after 65 hours). It is noteworthy to mention here, that although TMG seemed

a reasonable choice of base under these conditions (fast reaction and second highest *ee* among the bases), its performance was weaker at -80 °C temperature compared to that of observed with DBU (Table 21, entries 39 and 41). The optimization procedure was followed by solvent-screening (Table 21, entries 24-38). Among these trials, it is noteworthy to mention acetonitrile, acetone and methanol, which provided the desired product in full conversion, without the formation of any byproducts. The enantioselectivity in the case of acetone and acetonitrile were almost the same (*ee*=28% and *ee*=29%, respectively); however, methanol performed slightly better (*ee*=36%) (Table 21, entries 24, 28 and 32). For comparison, under the same reaction conditions (5 mol% (*R*)-**7**, Et₃N, -40 °C), the reaction proceeded in chloroform with 35% enantiomeric excess (Table 21, entry 6). Based on these results, methanol and chloroform were considered as the best choices for the applied solvent; however, further attempts at -80 °C provided better performance with chloroform (Table 21, entries 39 and 42). After consideration of all the optimization attempts, our selected condition was 10 mol% (*R*)-**7** catalyst, DBU as base, -80 °C temperature and chloroform/ acetone (8:1) mixture (in order to prevent solvent freezing below the chloroform's melting point). Under this condition, the phosphinic hydrazone product was formed in 94% conversion within an acceptable (24 hours) reaction time with 55% enantioselectivity (Table 21, entry 39). The isolated yield was 78% in this case. The reason behind the slight drop in the isolated yield compared to the conversion value was due to the acid-sensitivity of the product. The absolute stereochemistry of the generated phosphinic hydrazone was determined by X-ray analysis (Figure 57) and found to be (*R*).

Figure 57. ORTEP structure of phosphinic hydrazone **57aa**.

Unfortunately, the obtained results after optimization (78% yield and 55% enantiomeric excess) remained under our expectations, but we observed these results

as the first demonstration of this challenging transformation in an asymmetric catalytic protocol, which has never been explored before.

To find out if the obtained selectivity could be further improved, we decided to modify the structure of the reaction partners to find a better combination which could provide higher enantioselectivity in this transformation. It must be noted, that several diazo compounds and secondary phosphines were tested in this transformation, but unfortunately not all of them were successful. The unsuccessful diazo substrates and phosphines chosen for the P-H addition are presented in Figures 58 and 59. When these reactants were applied, the reaction did not proceed under the optimized conditions at all, even after 72 hours. By investigation of these failures, a few statements could be made about the transformation. Firstly, in case of compounds **58**, **59** and **60**, the two carbonyl oxygens can develop a six-member ring O,O-bidentate chelation to the palladium center, while **61** can develop a six-membered N,O-chelation. In these cases, the substrates themselves may act as catalyst poison in the reaction. By modifying the aromatic ring of the secondary phosphines, it was observed that the *ortho*-substituted phosphine compounds did not undergo the P-H addition reaction in any cases. The reason for this observation must be the increased stereochemical hindrance around the phosphorus atom, which decreased the coordination abilities of the diazo compounds to the catalyst. By investigating the performance of different diazoesters and secondary phosphines in the transformation, we were looking for a better combination of the reactants which could increase the enantioselectivity within acceptable time and yield.

Figure 58. Unsuccessful diazo compounds in the P-H addition.

Figure 59. Unsuccessful secondary phosphines in the P-H addition.

Despite these failures, other phosphine and diazoester analogues were successfully employed in this transformation (Scheme 73).

Scheme 73. Substrate scope of the phosphinic hydrazone formation.

During the extension of the substrate scope, the generated phosphines were oxidized by hydrogen peroxide and the phosphine oxides were isolated and characterized. Firstly, we increased the steric hindrance of the ester group to see if there is any effect of this structural unit on the selectivity (**57aa'** to **57ca'**). In these trials, the enantiomeric excess increased slightly (*ee*=58% for **57ca'**), but the reaction became slower (48 hours reaction time was necessary). In the next attempts, the size of the *meta*-substituents of the aromatic ring was enhanced on the phosphine compounds (**57cb'** to **57cc'**). This modification improved the selectivity significantly (*ee*=78% for **57cb'** and *ee*=81% for **57cc'**). Introduction of a sterically demanding *tert*-butyl group in the *para*-position did not improve the stereoselectivity unfortunately, the enantioselectivity was consequently low (*ee*=33%) for **57cd'**. Lastly, one of the aromatic rings of the phosphine was changed to the ethyl group and in this case both the reactivity and the selectivity were low in the addition reaction (yield=19% after 80 hours reaction time and *ee*=41%). To sum it up, best results were achieved in case of compounds **57cb'** and **57cc'**, when the *meta*-positions of the phosphine's aromatic ring were occupied with sterically more demanding groups, ethyl and *tert*-butyl moieties respectively. The explanation behind the lower enantioselectivity in case of the *para*-substituted phosphine must be the ineffective chiral induction from the catalyst to the substrate, due to the higher distance between the palladacycle's projecting groups and the *para-tert*-butyl group on the phosphine.

To understand the mechanistic cycle of this transformation, several control experiments were conducted and multi nuclei NMR spectra were recorded. For the clearer spectroscopic results, the achiral diphenylphosphine and triphenyl phosphines were used in these experiments instead of the racemic secondary phosphines. By these changes, any possible formation of diastereomers or byproducts were reduced. At first, we started to investigate the role of the palladium catalyst and the external base in the reaction (Scheme 74).

Scheme 74. Role of the palladium and the base of the P-H addition.

In the base- and catalyst-free reaction, the air-sensitive phosphine product (**62**) was detected in 8% conversion based on the $^{31}\text{P}\{^1\text{H}\}$ NMR measurements after 15 hours. By the addition of equivalent amount of triethylamine, the product conversion increased slightly to 13%. These results indicated that the P-H addition can occur even in the absence of any palladium or base; however, the reactivity is extremely low. However, when 5 mol% $\text{Pd}(\text{OAc})_2$ and 1 equivalent base were applied together, the reactivity significantly increased. Within 1.5 hours, the observed conversion was 87% and the isolated yield for compound **57ai'** was 80%. These experiments clearly showed the important role of both the palladium and the external base for the transformation.

According to our previous investigations on the palladacycle-catalyzed asymmetric hydrophosphination of unsaturated double bonds, the P-H addition can

occur via two mechanisms: intra- or intermolecular pathway (for more details, see Schemes 35 and 36 in chapter 1.6.6).^{96b, 130b} To find out the most possible mechanistic way for the N-P* bond formation, we intended to examine if there is any interaction between the diazo compounds (**55**) and the (*R*)-**7** catalyst (coordination experiments (=coord. exp.) 1 to 3). In the literature, various coordination modes of the diazo functionality to transition metals are reported.¹⁹⁶ According to these studies, the diazo compounds tend to develop either mono- or bidentate chelation to metal centers (Scheme 75a). To investigate any possible substrate coordination to the (*R*)-**7** catalyst system, equivalent amount of palladacycle (**7**) and substrate (**55a**) were mixed in CDCl₃ and multi nuclei NMR spectra were recorded after 15 minutes (Scheme 75b).

a) Reported coordination modes of diazo compounds to transition metals.

b) coordination experiment 1.

c) coordination experiment 2.

d) coordination experiment 3.

Scheme 75. Coordination experiments for mechanistic investigations.

The interaction between the palladacycle and the diazoester were clearly seen in the ¹H, ¹³C and ³¹P{¹H} NMR spectra (Figures 60 to 62). Based on these measurements, unfortunately we were not able to assign one exact structure, but the new resonance signals implied formation of new coordination products based on the NMR spectra.

Figure 60. ^1H NMR spectra of $(R)\text{-7}$, **55a** diazoacetate and coordination experiment 1.

Figure 61. ^{13}C NMR spectra of $(R)\text{-7}$, **55a** diazoacetate and coordination experiment 1.

Figure 62. $^{31}\text{P}\{^1\text{H}\}$ NMR spectra of *(R)*-7, **55a** diazoacetate and coordination experiment 1.

In general, the diazo compounds are widely used as carbene precursors in synthetic transformations. The first step of the metal carbene formation is the coordination of the α -carbon of the diazo functionality to the transition metal. This coordination mode is very well established in the literature and upon coordination, the α -carbon becomes highly electron-deficient. In our coordination experiment 1, we also observed a new carbon resonance signal at the low field region (at 186.4 ppm) in the ^{13}C NMR spectrum. This new signal indicates the formation of a highly electron-deficient carbon. The presence of this peak strongly supports the plausible coordination of the α -carbon to the palladium.

However, it is important to mention that other coordination modes may also occur in our case and the equilibrium of these different structures may arise. In the next coordination experiment, the role of the carbonyl group's oxygen was investigated in the coordination. Stoichiometric amount of palladacycle (**7**) and ethyl phenylacetate (**55a**) was mixed in CDCl_3 and multi nuclei NMR spectra were recorded after 15 minutes. In this case, only the starting material's chemical shifts were observed in the NMR spectra, without the formation of any new chemical peak. Based on this experiment, the coordination mode via the oxygen atom of the carbonyl moiety can be excluded. In coordination experiment 3, the possible interaction between the palladacycle and the diazoester was studied in the presence of a monodentate phosphine

ligand (triphenylphosphine). The role of the triphenylphosphine was to represent the secondary phosphines (**56**), which were used in the catalytic reaction. In the first step of this experiment, the $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum was recorded after the triphenylphosphine addition and it revealed the formation of new two isomers, which was represented by two pairs of doublets in the spectrum (Figure 63). Among these doublets, the higher coupling constant (d, $J_{\text{PP}(\text{trans})}$ =361.5 Hz, at δ 57.25 and 25.72 ppm) represents the *trans* P-Pd-P fragment in compound **64** and significantly smaller coupling constant (d, $J_{\text{PP}(\text{cis})}$ =29 Hz, at δ 62.83 and 17.42 ppm) belongs to the *cis* P-Pd-P moiety in case of compound **65**. The ratio arose between **64** and **65** was 1: 0.3 based on the integration values.

Figure 63. $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum (CDCl_3) of coordination experiment 3.

This ratio implies that the coordination of the phosphine ligand *trans* to the phosphorus atom of the palladacycle is more favorable, compared to the *cis* position (Figure 64).

Figure 64. Coordination sites on the CP-palladacycle (**7**).

This special character of the CP palladacycle (**7**) has already been established by our group previously with coordination experiments and theoretical studies.¹⁹⁷ Due to the relatively stronger *trans* influence of the aromatic carbon, the **A** coordination site is less favorable compared to the **B** site for the coordinating phosphine ligand. The reason behind this character is the relatively stronger backdonation from the palladium to the aromatic carbon than that of to the palladacycle's phosphorus. Because of this stronger backdonation to the aromatic carbon, when a monophosphine ligand coordinates to coordination site **A**, the metal has less available electrons on its overlapping d-orbitals, thus a weaker backdonation is experienced by the coordinating phosphine *trans* to the aromatic carbon. Because of this effect, the ligand coordination at this site is significantly more labile compared to the coordination site **B**.

In the second step of coordination experiment 3, 1 equivalent diazoester (**55a**) was added to compounds **64** and **65**, and after stirring the mixture at room temperature for 15 minutes, multi nuclei NMR spectra were recorded. By comparing the ¹H, ¹³C and ³¹P{¹H} NMR spectra of the a) diazoester substrate (**55a**), b) coordination experiment 3, STEP 1 and c) coordination experiment 3, STEP 2, the formation of new resonance signal was detected again, which is a further evidence of the diazoester-palladacycle interaction, also in the presence of coordinating monophosphines (Figures 65 to 67).

Figure 65. ^1H NMR spectra of a) diazoester **55a**, b) coord. exp. 3, STEP 1 and c) coord. exp. STEP 2 (CDCl_3).

Figure 66. ^{13}C NMR spectra of a) diazoester **55a**, b) coord. exp. 3, STEP 1 and c) coord. exp. 3, STEP 2 (CDCl_3).

Figure 67. $^{31}\text{P}\{^1\text{H}\}$ NMR spectra of coord. exp. 3, STEP 2 (CDCl_3).

In this experiment (coord. exp. 3, STEP 2), the new resonance signals in the ^1H , ^{13}C and $^{31}\text{P}\{^1\text{H}\}$ NMR spectra support the interaction between the metallacycle and the diazoester. Even by careful investigation and comparing the observed records to literature data we were unable to assign one structure, to determine the exact nature of the interaction. However, the resonance signal at the low field region of the ^{13}C spectrum was detected again at the same chemical shift where we obtained it during the coordination experiment 2, at 186.4 ppm. This signal must belong to an electron-deficient carbon, which might be the α -carbon, coordinating to the palladium center, as the first step of the catalytic cycle. In the presence of phosphine ligand, we predict the coordination of the diazoester to the palladium to occur only at the *trans* position to the palladacycle's aromatic carbon (coordination site **A** in Figure 64), due to the labile nature of this coordination site.

Based on the above-mentioned control experiments, we proposed a possible catalytic cycle, which includes intramolecular nucleophilic attack of the phosphine moiety to the electrophilic diazoester (Figure 68).

Figure 68. Proposed catalytic cycle.

In the first step of the proposed catalytic cycle, the racemic secondary diarylphosphines replaced the coordinated acetonitrile molecules at the coordination sites on Pd (**A**). In the next step, the diazoester coordinates to the palladium center via the α -carbon at the *trans* position to the aromatic carbon (**B**), followed by the deprotonation of the phosphine and the formation of a phosphido intermediate (**C**). The intramolecular attack takes place and subsequently the enantioenriched phosphinic hydrazone product dissociates from the coordination site and a new set of diarylphosphine ligands coordinates to the metal (**D**, **E** and **A**).

Our last mechanistic consideration was to find out why we did not observe any nitrogen elimination upon interaction between the palladium source and the diazoester? The nitrogen elimination was highly expected, because it was widely established in the literature that diazo compounds can be used as carbene precursors in various palladium-catalyzed transformations.^{194-195, 195c} Once the nitrogen elimination occurs, the Fisher type metal carbene species develop sigma donation from the carbenic carbon to the metal and backdonation from the metal center to the α -carbon.^{194-195, 195c} In contrast, the diazo functionality was stabilized by the palladium catalyst in our case and the diazo decomposition to generate metal carbene species was prevented. A plausible reason of

this phenomenon is the special stereoelectronic nature of the applied palladacycle,¹⁹⁷ which was discussed previously (Figure 64). Due to the strong backdonation by the palladium center to the aromatic carbon of the palladacycle, the metal's d-orbitals are much less available for further backdonation to the coordinating ligands at coordination site **A**. Because of that, the formation of the metal carbene species did not occur, due to the lack of the backdonation from the metal to the α -carbon of the diazo functionality. To fully establish this statement, further theoretical calculations may be necessary.

Eventually, the possible derivatization of the enantioenriched phosphinic hydrazones were explored (Scheme 76). It was reported in several studies, that a N-P* moiety can be easily transformed to the corresponding MeO-P* unit by acidic methanolysis.¹⁹⁸ This simple synthetic strategy provided direct access to P-stereogenic diarylphosphinates (**66**). The reaction takes place via inversion of the stereochemistry, as it was established before,¹⁹⁸ and the diarylphosphinates (**66**) were obtained with the same enantiomeric excess what we observed with the phosphinic hydrazones (**57**) (the 1% difference in enantioselectivity being within experimental error).

Scheme 76. Derivatization of the enantioenriched phosphinic hydrazones.

4.3 Conclusion

In conclusion a novel synthetic protocol which employs electrophilic α -diazoesters in asymmetric Pd-catalyzed N-P* bond formation was established for the first time. The dynamic kinetic resolution provided direct access to enantioenriched P-stereogenic diarylphosphinates by acidic methanolysis of the generated phosphinic hydrazones. The methanolysis occurred via inversion of the stereochemistry, without the loss of the enantiomeric excess. This novel synthetic approach may open new research directions in P-stereogenic phosphine formation, and it may also broaden the

research area of electrophilic diazoesters utilized in asymmetric catalytic synthesis scenarios.

4.4 Experimental Section

4.4.1 General considerations

All air sensitive manipulations were carried out under positive pressure of nitrogen using Schlenk techniques. Chloroform (AR), acetonitrile (AR), methanol (AR), dichloromethane (HPLC), acetone (AR) and ethyl acetate (AR) was purchased from VWR; *n*-hexanes (AR) and toluene (AR) from Avantor. Solvents were degassed prior to use. All other reactants and reagents were used as supplied without further purification unless stated otherwise. NMR spectra were recorded on Bruker AV 300, AV 400, AV 500 and BBFO 400 spectrometers. Chemical shifts were reported in ppm and referenced to an internal SiMe₄ standard (0 ppm) in CDCl₃ for ¹H NMR; chloroform-*d* (77.00 ppm) in CDCl₃ for ¹³C NMR and an external 85% H₃PO₄ for ³¹P{¹H} NMR. Low Temp Pairstirrer PSL-1800 was used for low temperature reactions. Column chromatography was performed with Silica gel 60 (purchased from Merck). Melting points were measured using SRS Optimelt Automated Point System SRS MPA100. HRMS using electrospray ionization (ESI) method was performed on the Waters Q-ToF Premier spectrometer. Optical rotations were examined with JASCO P-1030 Polarimeter in DCM in a 0.1 dm cell at specified temperatures.

Catalysts (*R*)-**7**^{96a, 126} and (*R,R*)-**18**¹³⁰ were prepared by reported procedures.

4.4.2 Preparation of racemic secondary phosphines

The synthesis of ethyl(phenyl)phosphane (**56e**) was carried out by reported procedure¹⁹⁹.

Characterization data:

Ethyl(phenyl)phosphane (**56e**). Appearance: colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.53 – 7.44 (m, 2H), 7.40 – 7.27 (m, 3H), 4.10 (d, *J* = 209.9 Hz, 1H), 1.86 – 1.74 (m, 2H), 1.11 (dt, *J* = 13.5, 7.5 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 135.46 (d, *J* = 10.9 Hz), 133.60 (d, *J* = 15.2 Hz), 128.32 (d, *J* = 5.8 Hz),

128.02, 16.43 (d, $J = 9.4$ Hz), 12.71 (d, $J = 7.7$ Hz). $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, CDCl_3) δ -44.27. HRMS (+ESI) m/z calcd for $\text{C}_8\text{H}_{12}\text{P}$ ($\text{M} + \text{H}$) $^+$: 139.0677; found: 139.0679.

Compounds **2a-2d** were synthesized by modified literature procedure (Scheme 77).¹³⁴

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Scheme 77. Synthesis of racemic secondary diarylphosphines.

To a solution of PhPCl_2 (4.49 g, 25.1 mmol) in THF (50 mL), ArMgBr (25.1 mmol in 50 mL of THF, prepared from ArBr (25.1 mmol) and Mg (0.72 g, 30.1 mmol)) was added slowly in 50 mL of THF at -80 °C under N_2 atmosphere. The mixture was stirred at -80 °C for 2 hours before it was warmed to room temperature and stirred for overnight. The mixture was cooled to 0 °C and LiAlH_4 (1.14 g, 30.1 mmol) was added in small portions. The mixture was kept stirring at room temperature for 2 hours. Degassed water (10 mL) was added dropwise at 0 °C and the mixture was extracted with diethyl ether (3x). The organic layers were combined and dried over MgSO_4 . The solvent was removed by distillation and the residue was subjected to high vacuum microdistillation to give the corresponding secondary phosphines.

Characterization data:

(3,5-dimethylphenyl)(phenyl)phosphane (**56a**). Appearance: colorless oil, Yield=38%. ^1H NMR (400 MHz, CDCl_3) δ 7.57 – 7.41 (m, 2H), 7.30 (d, $J = 3.5$ Hz, 3H), 7.10 (d, $J = 7.7$ Hz, 2H), 6.94 (s, 1H), 5.18 (d, $J = 218.9$ Hz, 1H), 2.27 (s, 6H). ^{13}C NMR (101 MHz, CDCl_3) δ 138.10, 138.04, 135.08, 134.98, 134.11, 134.03, 133.90, 133.73, 131.86, 131.69, 130.31, 128.52, 128.46, 128.30, 1.20. $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, CDCl_3) δ -40.12. HRMS (+ESI) m/z calcd for $\text{C}_{14}\text{H}_{16}\text{P}$ ($\text{M} + \text{H}$) $^+$: 215.0990; found: 215.0988.

(3,5-diethylphenyl)(phenyl)phosphane (**56b**). Appearance: colorless oil, Yield=36%. ^1H NMR (400 MHz, CDCl_3) δ 7.53 – 7.44 (m, 2H), 7.30 (d, J = 3.6 Hz, 3H), 7.14 (d, J = 7.9 Hz, 2H), 6.99 (s, 1H), 5.22 (d, J = 210.2 Hz, 1H), 2.59 (dd, J = 15.2, 7.6 Hz, 4H), 1.20 (t, J = 7.6 Hz, 6H). ^{13}C NMR (101 MHz, CDCl_3) δ 144.54, 144.48, 135.11, 135.02, 134.05, 133.97, 133.87, 133.70, 131.06, 130.89, 128.50, 128.43, 128.26, 127.92, 28.72, 15.51. $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, CDCl_3) δ -40.15. HRMS (+ESI) m/z calcd for $\text{C}_{16}\text{H}_{20}\text{P}$ ($\text{M} + \text{H}$) $^+$: 243.1303; found: 243.1301.

(3,5-di-*tert*-butylphenyl)(phenyl)phosphane (**56c**). Appearance: colorless oil, Yield=29%. ^1H NMR (400 MHz, CDCl_3) δ 7.44 – 7.37 (m, 2H), 7.32 – 7.28 (m, 1H), 7.27 (d, J = 1.8 Hz, 1H), 7.26 – 7.22 (m, 3H), 7.19 (s, 1H), 1.22 (s, 18H). The PhArPH proton is missing from the spectrum. ^{13}C NMR (75 MHz, CDCl_3) δ 150.93, 150.85, 135.18, 135.05, 133.88, 133.66, 133.01, 132.91, 128.48, 128.45, 128.40, 128.22, 122.75, 34.89, 31.38. $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, CDCl_3) δ -39.41. HRMS (+ESI) m/z calcd for $\text{C}_{20}\text{H}_{28}\text{P}$ ($\text{M} + \text{H}$) $^+$: 299.1929; found: 299.1927.

(4-(*tert*-butyl)phenyl)(phenyl)phosphane (**56d**). Appearance: colorless oil, Yield=42%. ^1H NMR (400 MHz, CDCl_3) δ 7.43 – 7.37 (m, 2H), 7.37 – 7.30 (m, 2H), 7.30 – 7.20 (m, 5H), 5.10 (s, 1H), 1.23 (s, 9H). ^{13}C NMR (101 MHz, CDCl_3) δ 151.71, 135.05 (d, J = 9.6 Hz), 134.01, 133.93, 133.84, 133.76, 130.80 (d, J = 8.6 Hz), 128.51 (d, J = 6.2 Hz), 128.30, 125.62 (d, J = 6.6 Hz), 34.62, 31.22. $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, CDCl_3) δ -42.06. HRMS (+ESI) m/z calcd for $\text{C}_{16}\text{H}_{20}\text{P}$ ($\text{M} + \text{H}$) $^+$: 243.1303; found: 243.1299.

4.4.3 Preparation of α -diaoesters

Ethyl phenylacetate was purchased from SIGMA Aldrich and used directly in the diazo transfer reaction for starting material synthesis.

All the α -diaoesters were prepared by the following general procedure (Scheme 78):

Scheme 78. Synthesis of α -diazoacetates.

STEP A – Esterification:

Synthesis of benzhydryl 2-phenylacetate:

The compound was synthesized by modified literature procedure (Scheme 79):²⁰¹

Scheme 79. Synthesis of benzhydryl 2-phenylacetate.

Phenyl acetic acid (1.36 g, 10 mmol) was introduced to a round-bottom flask, followed by the addition of 4-dimethyliminopyridine (=DMAP, 183 mg, 1.5 mmol) and dicyclohexylcarbodiimide (=DCC, 2.06 g, 10 mmol) in 25 ml DCM. The mixture was stirred at room temperature for 15 minutes, then benzhydrol (921 mg, 5 mmol) was added to the reaction in small portions. The mixture was stirred for 24 hours at room temperature and then filtered. Saturated NaHCO_3 solution was added to the filtrate and the compound was extracted into DCM (3x) and washed with brine (1x). The organic layers were combined, dried over MgSO_4 and filtered. The solvent was removed by reduced pressure. The final product was isolated on silica gel:

Benzhydryl 2-phenylacetate. Appearance: colorless oil, Yield=69%. ^1H NMR (400 MHz, CDCl_3) δ 7.35 – 7.20 (m, 15H), 6.87 (d, J = 3.5 Hz, 1H), 3.71 (d, J = 2.3 Hz, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 170.36, 140.06, 133.77, 129.32, 128.50, 128.40, 127.81, 127.07, 126.96, 77.17, 41.58. HRMS (+ESI) m/z calcd for $\text{C}_{21}\text{H}_{19}\text{O}_2$ ($\text{M} + \text{H}$) $^+$: 303.1385; found: 303.1390.

Synthesis of *tert*-butyl 2-phenylacetate:

The compound was synthesized by following literature procedure (Scheme 80):²⁰²

Scheme 80. Synthesis of *tert*-butyl 2-phenylacetate.

A round-bottom flask was charged with 5 g of MgSO_4 and H_2SO_4 in 40 ml of DCM . At room temperature phenylacetic acid (2 g, 14.7 mmol) and *tert*-butanol (5.45 g, 73.5 mmol) was added to the flask and the solution was stirred for 8h. After completion of the reaction, the reaction mixture was quenched with saturated NaHCO_3 . The product was extracted into DCM (3x), washed with brine, dried over MgSO_4 and filtered. The volatiles were evaporated, and the final product was isolated on silica gel:

Tert-butyl 2-phenylacetate. Appearance: colorless oil, Yield=76%. ^1H NMR (400 MHz, CDCl_3) δ 7.25 – 7.11 (m, 5H), 3.42 (s, 2H), 1.34 (s, 9H). ^{13}C NMR (101 MHz, CDCl_3) δ 170.92, 134.68, 129.15, 128.40, 126.78, 80.76, 42.63, 28.00. HRMS (+ESI) m/z calcd for $\text{C}_{12}\text{H}_{17}\text{O}_2$ ($\text{M} + \text{H}$) $^+$: 193.1229; found: 193.1231.

STEP B – Diazo transfer:

Synthesis of 2-diazo-2-phenylacetates:

The compounds were synthesized by following literature procedure (Scheme 81):²⁰³

Scheme 81. Synthesis of 2-diazo-2-phenylacetates.

The corresponding ester (5 mmol) was introduced to a stirred solution of 4-acetamidobenzenesulfonyl azide (= *p*-ABSA, 1.44 g, 6 mmol) in 8 ml of acetonitrile. The mixture was cooled to 0 °C, then 1,8-diazabicyclo[5.4.0]undec-7-ene (=DBU, 0.9 mL, 6 mmol) was added dropwise. The reaction mixture was stirred at room

temperature for 24 h, followed by the addition of saturated aq. NH_4Cl (30 mL). The mixture was extracted with Et_2O (3x), organic layers were combined, dried over MgSO_4 , filtered and the solvent was evaporated under reduced pressure. Purification by flash chromatography afforded the corresponding α -diazoesters:

Ethyl 2-diazo-2-phenylacetate (55a). Appearance: orange oil, Yield=75%. ^1H NMR (500 MHz, CDCl_3) δ 7.52 – 7.45 (m, 2H), 7.42 – 7.35 (m, 2H), 7.18 (t, J = 7.4 Hz, 1H), 4.34 (q, J = 7.1 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 165.24, 128.91, 125.75, 125.65, 123.99, 60.98, 14.49. HRMS (+ESI) m/z calcd for $\text{C}_{10}\text{H}_{11}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$: 191.0821; found: 191.0822.

Benzhydryl 2-diazo-2-phenylacetate (55b). Appearance: orange oil, Yield=68%. ^1H NMR (400 MHz, CDCl_3) δ 7.51 – 7.45 (m, 2H), 7.39 – 7.30 (m, 10H), 7.30 – 7.24 (m, 2H), 7.18 – 7.12 (m, 1H), 7.07 (s, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 164.13, 140.02, 128.89, 128.56, 128.00, 127.01, 125.89, 125.22, 123.99, 77.27. HRMS (+ESI) m/z calcd for $\text{C}_{21}\text{H}_{17}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$: 329.1290; found: 329.1288

Tert-butyl 2-diazo-2-phenylacetate (55c). Appearance: orange oil, Yield=95%. ^1H NMR (400 MHz, CDCl_3) δ 7.39 (d, J = 8.5 Hz, 2H), 7.29 (t, J = 7.8 Hz, 2H), 7.08 (t, J = 7.4 Hz, 1H), 1.48 (d, J = 1.2 Hz, 9H). ^{13}C NMR (101 MHz, CDCl_3) δ 164.51, 128.80, 126.11, 125.50, 123.96, 81.98, 28.37. HRMS (+ESI) m/z calcd for $\text{C}_{12}\text{H}_{15}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$: 219.1134; found: 219.1132.

4.4.4 Phosphination of α -diazoesters

Phosphination of ethyl 2-diazo-2-phenylacetate:

After optimization of the reaction conditions, the phosphine addition to ethyl 2-diazo-2-phenylacetate (**55a**) was carried out by the following process (Scheme 82):

Scheme 82. Phosphination of the α -diazoacetates.

A nitrogen flushed 2-neck flask was charged with (*R*)-**7** catalyst (4.1 mg, 10 mol%), ethyl 2-diazo-2-phenylacetate (**55a**) (12.5 mg, 65.5 μ mol) and (3,5-dimethylphenyl)(phenyl)phosphane (**56a**) (16.8 mg, 78.6 μ mol) in the mixture of degassed chloroform (2 mL) and acetone (0.3 mL) at room temperature. Then the mixture was cooled to -80 °C, followed by the dropwise addition of 1,8-Diazabicyclo(5.4.0)undec-7-ene (=DBU, 10 mg, 65.5 μ mol) dissolved in 0.4 mL chloroform. The setup was stirred at -80 °C and monitored by TLC. After 24 hours, sulfur (=S₈, 33.6 mg, 131 μ mol) was added to the flask and the mixture was warmed to room temperature, followed by stirring for an additional 15 minutes. Then the solvents were removed by reduced pressure and the product was isolated by column chromatography:

Ethyl (R,E)-2-((3,5-dimethylphenyl)(phenyl)phosphorothioyl)hydrazineylidene-2-phenylacetate (57aa). Appearance: yellow solid, Yield=78%, *ee*=55%, Mp.: 127 – 129 °C, [α]_D²¹ -1.3 (c 0.5, CH₂Cl₂) for *ee*=55%. HPLC conditions: Daicel Chiralpak IE column, *n*-hexane/2-propanol (90:10), 1 ml/min flowrate, 23 °C column

temperature, major peak (*R*): 13.2 min, minor peak (*S*): 12.1 min. ¹H NMR (400 MHz, CDCl₃) δ 7.98 – 7.88 (m, 2H), 7.58 – 7.42 (m, 8H), 7.32 – 7.26 (m, 2H), 7.17 (s, 1H), 7.10 (d, *J* = 24.4 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 2.35 (s, 6H), 1.27 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 163.76, 141.49 (d, *J* = 13.6 Hz), 137.99 (d, *J* = 14.2 Hz), 133.91 (d, *J* = 3.2 Hz), 133.41, 132.59, 132.40, 132.12, 132.01, 131.92 (d, *J* = 3.0 Hz), 131.59, 130.10, 129.78, 129.67, 129.50, 128.54, 128.45, 128.32, 128.19, 61.36, 21.37, 14.15. ³¹P{¹H} NMR (162 MHz, CDCl₃) δ 59.39. HRMS (+ESI) *m/z* calcd for C₂₄H₂₆N₂O₂PS (*M* + H)⁺: 437.1453; found: 437.1453.

Optimization of the reaction conditions:

For optimization of the reaction conditions, the above-mentioned procedure (*Phosphination of ethyl 2-diazo-2-phenylacetate*) was followed. The applied catalyst, base and solvent was varied. The reactions were followed by TLC and after the consumption of the starting materials, the reaction was stopped by adding sulphur to the mixture. The conversion was determined by $^{31}\text{P}\{^1\text{H}\}$ NMR measurement of the crude material. The enantiomeric excess was determined by chiral HPLC.

General phosphination procedure for the substrate scope:

Based on the optimization of the reaction conditions, the phosphine addition reactions to the α -diazoesters were carried out by the following process:

A nitrogen flushed 2-neck flask was charged with (*R*)-**7** catalyst (4.1 mg, 10 mol%), α -diazoester (**55**) (65.5 μmol) and racemic secondary phosphine (**56**) (78.6 μmol) in the mixture of de-gassed chloroform (2 mL) and acetone (0.3 mL) at room temperature. Then the mixture was cooled to $-80\text{ }^{\circ}\text{C}$, followed by the dropwise addition of 1,8-Diazabicyclo(5.4.0)undec-7-ene (=DBU, 10 mg, 65.5 μmol) dissolved in 0.4 mL chloroform. The setup was stirred at $-80\text{ }^{\circ}\text{C}$ and monitored by TLC. After the α -diazoester was consumed in the reaction based on TLC, 0.1 mL (30% sol.) hydrogen peroxide was added to the flask and the mixture was warmed to room temperature, followed by stirring for an additional 15 minutes. The mixture was washed with water, dried over MgSO_4 , filtered, then the solvents were removed by reduced pressure. The final product was isolated by column chromatography (see isolated yield and enantiomeric excess of the final products below).

Characterization data:

Ethyl (R,E)-2-(2-((3,5-dimethylphenyl)(phenyl) phosphoryl)hydrazineylidene)-2-phenylacetate (57aa'). Appearance: colorless oil, yield=74%, *ee*=55%, $[\alpha]_{\text{D}}^{21}$ -1.8 (c 0.5, CH_2Cl_2) for *ee*=55%. HPLC conditions: Daicel Chiralpak IE column, *n*-hexane/2-propanol (60:40), 1 ml/min flowrate, $23\text{ }^{\circ}\text{C}$ column temperature, major peak (*R*): 23.3

min, minor peak (*S*): 25.8 min. ^1H NMR (400 MHz, CDCl_3) δ 7.95 – 7.81 (m, 2H), 7.64 – 7.39 (m, 8H), 7.37 – 7.27 (m, 3H), 7.19 (s, 1H), 4.23 (q, $J = 7.1\text{ Hz}$, 2H), 2.34 (s, 6H),

1.27 (t, $J = 5.7$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 163.74, 142.58 (d, $J = 13.9$ Hz), 138.18 (d, $J = 13.9$ Hz), 134.25 (d, $J = 2.9$ Hz), 132.30 (d, $J = 2.8$ Hz), 132.10, 132.00, 131.71, 130.87, 130.45, 130.03, 129.68, 129.58, 129.47, 128.65, 128.55, 128.48, 128.34, 61.38, 21.29, 14.12. $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, CDCl_3) δ 26.23. HRMS (+ESI) m/z calcd for $\text{C}_{24}\text{H}_{26}\text{N}_2\text{O}_3\text{P}$ ($\text{M} + \text{H}$) $^+$: 421.1681; found: 421.1685.

Benzhydryl (R,E)-2-(2-((3,5-dimethylphenyl)(phenyl)phosphoryl)hydrazineylidene)-2-phenylacetate (**57ba'**). Appearance: white solid, yield=72%, $ee=54\%$, Mp.: 158 – 162 °C, $[\alpha]_{\text{D}}^{21}$ -2 (c 1.0, CH_2Cl_2) for $ee=54\%$. HPLC conditions: Daicel Chiralpak IE column, *n*-hexane/2-propanol (60:40), 1.2 ml/min flowrate, 23 °C column temperature, major peak (*R*): 29.3 min, minor peak (*S*): 25.8 min. ^1H NMR (500 MHz, CDCl_3) δ 7.93 (dd, $J = 12.5, 7.2$ Hz, 2H), 7.62 – 7.56 (m, 1H), 7.53 (s, 1H), 7.51 – 7.38 (m, 7H), 7.32 – 7.27 (m, 2H), 7.26 – 7.24 (m, 5H), 7.24 – 7.23 (m, 5H), 7.21 (s, 1H), 6.90 (s, 1H), 2.31 (s, 6H). ^{13}C NMR (101 MHz, CDCl_3) δ 162.70, 141.85, 141.71, 140.33 (d, $J = 1.3$ Hz), 138.35, 138.21, 134.28 (d, $J = 3.2$ Hz), 132.33 (d, $J = 2.9$ Hz), 132.20, 132.10, 131.67, 131.02, 130.40, 130.14, 129.76, 129.64, 129.54, 129.46, 128.67, 128.48, 128.41, 128.35, 128.24, 127.78 (d, $J = 1.5$ Hz), 126.81 (d, $J = 4.6$ Hz), 77.52, 29.67, 21.29. $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, CDCl_3) δ 26.96. HRMS (+ESI) m/z calcd for $\text{C}_{35}\text{H}_{32}\text{N}_2\text{O}_3\text{P}$ ($\text{M} + \text{H}$) $^+$: 559.2151; found: 559.2150.

Tert-butyl (R,E)-2-(2-((3,5-dimethylphenyl)(phenyl)phosphoryl)hydrazineylidene)-2-phenylacetate (**57ca'**). Appearance: white solid, yield=69%, $ee=58\%$, Mp.: 162 – 164.5 °C, $[\alpha]_{\text{D}}^{21}$ -2.6 (c 1.0, CH_2Cl_2) for $ee=58\%$. HPLC conditions: Daicel Chiralpak IE column, *n*-hexane/2-propanol (70:30), 1 ml/min flowrate, 23 °C column temperature, major peak (*R*): 22.7 min, minor peak (*S*): 20.9 min. ^1H NMR (400 MHz, CDCl_3) δ 7.90 (dd, $J = 12.4, 7.9$ Hz, 2H), 7.60 – 7.37 (m, 8H), 7.31 – 7.27 (m, 2H), 7.22 (d, $J = 20.5$ Hz, 1H), 7.18 (s, 1H), 2.35 (s, 6H), 1.46 (s, 9H). ^{13}C NMR (101 MHz, CDCl_3) δ 162.86, 143.63 (d, $J = 14.0$ Hz), 138.13 (d, $J = 13.8$ Hz), 134.16 (d, $J = 2.7$ Hz), 132.19 (d, $J = 2.9$ Hz), 132.14, 132.04, 131.82, 131.14, 130.55, 129.85, 129.62, 129.52, 129.34, 128.88, 128.58, 128.37, 128.24, 81.70, 28.01, 21.31. $^{31}\text{P}\{^1\text{H}\}$ NMR

(162 MHz, CDCl₃) δ 25.97. HRMS (+ESI) m/z calcd for C₂₆H₃₀N₂O₃P (M + H)⁺: 449.1994; found: 449.1997.

Tert-butyl (*R,E*)-2-(2-((3,5-diethylphenyl)(phenyl)phosphoryl)hydrazineylidene)-2-phenylacetate (**57cb'**). Appearance: colorless oil, yield=77%, *ee*=78%, [α]_D²¹ -5.2 (c 1.0, CH₂Cl₂) for *ee*=78%. HPLC conditions: Daicel Chiralpak ID column, *n*-hexane/2-propanol (85:15), 1 ml/min flowrate, 23 °C column temperature, major peak (*R*): 14.7 min, minor peak (*S*): 13.6 min. ¹H NMR (500 MHz, CDCl₃) δ 7.91 (dd, *J* = 12.5, 7.2 Hz, 2H), 7.59 – 7.38 (m, 8H), 7.30 – 7.27 (m, 2H), 7.26 – 7.18 (m, 2H), 2.66 (q, *J* = 7.6 Hz, 4H), 1.46 (s, 9H), 1.23 (t, *J* = 7.6 Hz, 6H). ¹³C NMR (126 MHz, CDCl₃) δ 162.88, 144.57 (d, *J* = 13.3 Hz), 143.62 (d, *J* = 13.8 Hz), 132.20, 132.12, 131.86 (d, *J* = 3.0 Hz), 131.74, 131.13, 130.72, 130.12, 129.87, 129.37, 128.95, 128.89, 128.80, 128.72, 128.61, 128.35, 128.25, 81.72, 28.79, 28.01, 15.47. ³¹P{¹H} NMR (162 MHz, CDCl₃) δ 26.08. HRMS (+ESI) m/z calcd for C₂₈H₃₄N₂O₃P (M + H)⁺: 477.2307; found: 477.2311.

Benzhydryl (*R,E*)-2-(2-((3,5-di-*tert*-butylphenyl)(phenyl)phosphoryl)hydrazineylidene)-2-phenyl acetate (**57bc'**). Appearance: white solid, yield=63%, *ee*=60%, Mp.: 77-79 °C, [α]_D²¹ -6.2 (c 1.0, CH₂Cl₂) for *ee*=60%. HPLC conditions: Daicel Chiralpak ID column, *n*-hexane/2-propanol (85:15), 1 ml/min flowrate, 23 °C column temperature, major peak (*R*): 19.4 min, minor peak (*S*): 21.4 min. ¹H NMR (300 MHz, CDCl₃) δ 7.95 (dd, *J* = 12.5, 7.1 Hz, 2H), 7.70 (d, *J* = 1.7 Hz, 1H), 7.66 (d, *J* = 1.6 Hz, 1H), 7.63 (s, 1H), 7.58 (d, *J* = 6.4 Hz, 1H), 7.54 – 7.40 (m, 6H), 7.40 – 7.12 (m, 12H), 6.88 (s, 1H), 1.27 (s, 18H). ¹³C NMR (101 MHz, CDCl₃) δ 162.70, 151.22 (d, *J* = 12.9 Hz), 141.93 (d, *J* = 14.1 Hz), 140.26 (d, *J* = 2.1 Hz), 132.38, 132.28, 132.24, 131.66, 130.41 (d, *J* = 3.4 Hz), 130.09, 129.47, 129.16, 128.65, 128.55, 128.38, 128.23, 127.72 (d, *J* = 2.3 Hz), 126.92, 126.87, 126.70 (d, *J* = 2.8 Hz), 126.20, 126.09, 77.64, 35.01, 31.26. ³¹P{¹H} NMR (162 MHz, CDCl₃) δ 27.67. HRMS (+ESI) m/z calcd for C₄₁H₄₄N₂O₃P (M + H)⁺: 643.3090; found: 643.3087.

Tert-butyl (R,E)-2-(2-((3,5-di-tert-butylphenyl)(phenyl)phosphoryl)hydrazineylidene)-2-phenylacetate (57cc'). Appearance: white solid, yield=77%, *ee*=81%, Mp.: 61 – 63 °C, $[\alpha]_D^{21}$ -7 (c 1.0, CH₂Cl₂) for *ee*=81%. HPLC conditions: Daicel Chiralpak ID column, *n*-hexane/2-propanol (90:10), 1 ml/min flowrate, 23 °C column temperature, major peak (*R*): 14.3 min, minor peak (*S*): 11.0 min. ¹H NMR (400 MHz, CDCl₃) δ 7.98 – 7.89 (m, 2H), 7.70 (dd, *J* = 13.3, 1.7 Hz, 2H), 7.61 (s, 1H), 7.58 – 7.36 (m, 7H), 7.31 – 7.20 (m, 2H), 1.45 (s, 9H), 1.32 (s, 18H). ¹³C NMR (101 MHz, CDCl₃) δ 162.81, 151.07 (d, *J* = 12.8 Hz), 143.49 (d, *J* = 13.7 Hz), 132.27, 132.18, 132.12, 132.09, 131.92, 130.77, 130.66, 129.79, 129.51, 129.33, 129.07, 128.56, 128.23, 128.10, 126.48, 126.46, 126.43, 126.32, 126.12, 126.01, 81.66, 35.04, 31.31, 27.98. ³¹P{¹H} NMR (162 MHz, CDCl₃) δ 26.48. HRMS (+ESI) *m/z* calcd for C₃₂H₄₂N₂O₃P (*M* + *H*)⁺: 533.2933; found: 533.2934.

Tert-butyl (R,E)-2-(2-((4-(tert-butyl)phenyl)(phenyl)phosphoryl)hydrazineylidene)-2-phenylacetate (57cd'). Appearance: white solid, yield=75%, *ee*=33%, Mp.: 60-62 °C, $[\alpha]_D^{21}$ -8.1 (c 0.5, CH₂Cl₂) for *ee*=33%. HPLC conditions: Daicel Chiralpak IE column, *n*-hexane/2-propanol (70:30), 1 ml/min flowrate, 23 °C column temperature, major peak (*R*): 16.5 min, minor peak (*S*): 17.7 min. ¹H NMR (400 MHz, CDCl₃) δ 7.94 – 7.85 (m, 2H), 7.85 – 7.77 (m, 2H), 7.32 – 7.21 (m, 3H), 1.45 (s, 9H), 1.33 (s, 9H). ¹³C NMR (101 MHz, CDCl₃) δ 162.79, 155.88, 143.54 (d, *J* = 14.0 Hz), 132.21, 132.18, 132.13, 132.03, 131.92, 131.82, 130.55, 129.81, 129.32, 128.88, 128.55, 128.38, 128.25, 128.12, 126.82, 125.43 (d, *J* = 13.4 Hz), 81.70, 35.02, 31.04, 27.97. ³¹P{¹H} NMR (162 MHz, CDCl₃) δ 25.94. HRMS (+ESI) *m/z* calcd for C₂₈H₃₄N₂O₃P (*M* + *H*)⁺: 477.2307; found: 477.2308.

Tert-butyl (S,E)-2-(2-(ethyl(phenyl)phosphoryl)hydrazineylidene)-2-phenylacetate (57ce'). Appearance: white solid, yield=19%, *ee*=41%, Mp: 125-126 °C, $[\alpha]_D^{21}$ -3.5 (c 0.1, CH₂Cl₂) for *ee*=41%. HPLC conditions: Daicel Chiralpak IE column, *n*-hexane/2-propanol (85:15), 1 ml/min flowrate, 23 °C column temperature, major peak (*R*): 23.6 min, minor peak (*S*): 24.8 min. ¹H NMR (500 MHz, CDCl₃) δ 7.95 – 7.85 (m, 2H), 7.60 – 7.52 (m, 1H), 7.52 –

7.37 (m, 5H), 7.25 – 7.19 (m, 2H), 7.00 (d, $J = 18.1$ Hz, 1H), 2.50 – 2.35 (m, 1H), 2.29 – 2.16 (m, 1H), 1.52 (s, 9H), 1.19 (dt, $J = 19.1, 7.6$ Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 162.75, 143.10 (d, $J = 13.5$ Hz), 132.25 (d, $J = 2.6$ Hz), 131.34, 131.29, 131.22, 130.41, 129.76, 129.29, 128.94, 128.54, 128.48, 128.44, 81.84, 28.03, 22.02 (d, $J = 90.6$ Hz), 5.27 (d, $J = 5.0$ Hz). $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, CDCl_3) δ 39.78. HRMS (+ESI) m/z calcd for $\text{C}_{20}\text{H}_{26}\text{N}_2\text{O}_3\text{P}$ ($\text{M} + \text{H}$) $^+$: 373.1681; found: 373.1677.

4.4.5 Acidic methanolysis of phosphinic hydrazones

The acidic methanolysis was carried out by the following general procedure:

A round-bottom flask was charged with **57aa'** or **57cb'** (40 μmol) in methanol (2 mL). Then concentrated sulfuric acid was added to the mixture (0.1 mL). The mixture was stirred at room temperature for 15 hours. After the starting material was consumed based on TLC, the mixture was treated with sat. NaHCO_3 followed by extraction with DCM (4x). The combined organic phases were washed with brine, dried over MgSO_4 , filtrated and the solvents were evaporated under reduced pressure. The final products were isolated on column chromatography (see isolated yield below):

Methyl (R)-(3,5-dimethylphenyl)(phenyl)phosphinate (**66a**).

Appearance: colorless oil, yield=91%, ee=54%, $[\alpha]_{\text{D}}^{21}$ -2.5 for ee=54%. HPLC conditions: Daicel Chiralpak ID column, *n*-hexane/2-propanol (85:15), 1 ml/min flowrate, 23 °C column temperature, major peak (*R*): 14.1 min, minor peak (*S*): 13.3 min. ^1H NMR (400 MHz, CDCl_3) δ 7.86 – 7.76 (m, 2H), 7.56 – 7.49 (m, 1H), 7.49 – 7.42 (m, 3H), 7.41 (s, 1H), 7.15 (s, 1H), 3.76 (d, $J = 11.1$ Hz, 3H), 2.33 (s, 6H). ^{13}C NMR (101 MHz, CDCl_3) δ 138.53 (d, $J = 13.8$ Hz), 134.21 (d, $J = 3.0$ Hz), 132.28 (d, $J = 2.8$ Hz), 131.85 (d, $J = 10.1$ Hz), 131.49, 130.90, 130.14, 129.46 (d, $J = 10.1$ Hz), 128.72 (d, $J = 13.1$ Hz), 51.69 (d, $J = 6.0$ Hz), 21.43. $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, CDCl_3) δ 33.96. HRMS (+ESI) m/z calcd for $\text{C}_{15}\text{H}_{18}\text{O}_2\text{P}$ ($\text{M} + \text{H}$) $^+$: 261.1044; found: 261.1045.

Methyl (R)-(3,5-diethylphenyl)(phenyl)phosphinate (**66b**).

Appearance: colorless oil, yield=93%, ee=77%, $[\alpha]_{\text{D}}^{21}$ -3.6 for ee=77%. HPLC conditions: Daicel Chiralpak IC column, *n*-hexane/2-propanol

(80:20), 1 ml/min flowrate, 23 °C column temperature, major peak (*R*): 12.9 min, minor peak (*S*): 16.2 min. ^1H NMR (500 MHz, CDCl_3) δ 7.87 – 7.77 (m, 2H), 7.55 – 7.49 (m, 1H), 7.49 – 7.42 (m, 4H), 7.19 (s, 1H), 3.76 (d, J = 11.1 Hz, 3H), 2.65 (q, J = 7.6 Hz, 4H), 1.22 (t, J = 7.6 Hz, 6H). ^{13}C NMR (126 MHz, CDCl_3) δ 144.69 (d, J = 13.4 Hz), 132.04 (d, J = 2.7 Hz), 131.94, 131.67, 131.64, 131.61, 131.59, 131.16, 130.85, 130.08, 128.54, 128.48, 128.44, 128.40, 51.47 (d, J = 6.1 Hz), 28.71, 15.42. $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, CDCl_3) δ 34.12. HRMS (+ESI) m/z calcd for $\text{C}_{17}\text{H}_{22}\text{O}_2\text{P}$ ($M + \text{H}^+$): 289.1359; found: 289.1359.

4.4.6 X-ray measurement data

Crystallographic data: ligand (*R*)-**57aa**.

Table 22. Sample and crystal data for (*R*)-**57aa**.

Identification code	CCDC 1965254	
Chemical formula	$\text{C}_{24}\text{H}_{25}\text{N}_2\text{O}_2\text{PS}$	
Formula weight	436.49 g/mol	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal size	0.140 x 0.180 x 0.210 mm	
Crystal habit	colorless block	
Crystal system	orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	$a = 8.3139(2)$ Å	$\alpha = 90^\circ$
	$b = 16.3794(3)$ Å	$\beta = 90^\circ$

	$c = 16.6172(4) \text{ \AA}$	$\gamma = 90^\circ$
Volume	$2262.88(9) \text{ \AA}^3$	
Z	4	
Density (calculated)	1.281 g/cm^3	
Absorption coefficient	0.236 mm^{-1}	
Absolute structure parameter	$0.06(3)$	

Crystallographic data: ligand (*R*)-**57ca'**.

Table 23. Sample and crystal data for (*R*)-**57ca'**.

Identification code	CCDC 1965253	
Chemical formula	$\text{C}_{26}\text{H}_{29}\text{N}_2\text{O}_3\text{P}$	
Formula weight	448.48 g/mol	
Temperature	100(2) K	
Wavelength	$0.71073 \text{ \AA}$	
Crystal size	$0.080 \times 0.120 \times 0.200 \text{ mm}$	
Crystal habit	colorless block	
Crystal system	orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	$a = 8.9507(3) \text{ \AA}$	$\alpha = 90^\circ$
	$b = 11.6512(5) \text{ \AA}$	$\beta = 90^\circ$
	$c = 22.9288(9) \text{ \AA}$	$\gamma = 90^\circ$
Volume	$2391.16(16) \text{ \AA}^3$	
Z	4	
Density (calculated)	1.246 g/cm^3	
Absorption coefficient	0.144 mm^{-1}	
Absolute structure parameter	$0.25(16)$	

Crystallographic data: ligand **57ai'**.

Table 24. Sample and crystal data for **57ai'**.

Identification code	CCDC 1965252	
Chemical formula	C ₂₂ H ₂₁ N ₂ O ₃ P	
Formula weight	392.38 g/mol	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal size	0.020 x 0.040 x 0.220 mm	
Crystal habit	colorless needle	
Crystal system	orthorhombic	
Space group	<i>P</i> 2 ₁ 2 ₁ 2 ₁	
Unit cell dimensions	a = 8.4671(2) Å	$\alpha = 90^\circ$
	b = 10.4320(2) Å	$\beta = 90^\circ$
	c = 22.0317(4) Å	$\gamma = 90^\circ$
Volume	1946.03(7) Å ³	
Z	4	
Density (calculated)	1.339 g/cm ³	
Absorption coefficient	0.167 mm ⁻¹	
Absolute structure parameter	0.03(4)	

Crystallographic data: ligand (±)-**57bc'**.

Table 25. Sample and crystal data for (±)-**57bc'**.

Identification code	CCDC 1965255	
Chemical formula	C ₄₁ H ₄₃ N ₂ O ₃ P	
Formula weight	642.74 g/mol	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal size	0.140 x 0.200 x 0.220 mm	
Crystal habit	colorless block	
Crystal system	triclinic	
Space group	<i>P</i> $\bar{1}$	
Unit cell dimensions	<i>a</i> = 11.2032(6) Å	α = 79.7546(18)°
	<i>b</i> = 11.6162(6) Å	β = 79.3863(19)°
	<i>c</i> = 27.3632(15) Å	γ = 80.302(2)°
Volume	3410.2(3) Å ³	
Z	4	
Density (calculated)	1.252 g/cm ³	
Absorption coefficient	0.123 mm ⁻¹	

5. Conclusion and outlook

Since their discovery, phosphine ligands have been gaining continuous interest in organic syntheses, due to the wide application strategies of these compounds. In the last decades, enormous number of research papers have been published about the synthesis of chiral phosphine ligands. Among these works, the asymmetric catalytic protocols provide more favorable and effective transformations, due to the reduced amount of metal sources used for the transformations. However, there are still several challenges in this field, which needs to be examined. For instance, certain substrates do not undergo the expected synthetic routes, because of unwanted chelating interactions to the metal center, which can suppress the catalytic activity during the reaction. Another challenge in this field is the generation of P-stereogenic phosphorus compounds via asymmetric catalysis, which is known to be significantly more difficult compared to the C-chiral phosphine syntheses. The P-H addition reactions have been widely studied in the past and found to be a favorable choice of strategy in phosphine ligand syntheses, due to the atom economic nature of the reaction. However, several synthetic protocols are still less explored in this area, for example diphosphine synthesis via double P-H addition. These few examples (among many others) show, that although various methods have already been established in phosphine ligand syntheses, there is still a demand to extend the synthetic methodologies in the field. In this thesis, various phosphine ligand synthesis strategies were presented via C-P and N-P bond formation reactions.

In chapter 1, the literature background of chiral phosphines and chiral palladacycles were discussed. Several methods for chiral phosphine syntheses were reviewed, focusing mainly on catalytic asymmetric strategies.

In chapter 2, palladium catalyzed asymmetric hydrophosphination of N-chelating enones were investigated. Coordination studies revealed the main challenge of this transformation, the N-chelation properties of the starting materials, which suppressed the catalytic activity of the C(sp²)-P type bidentate catalyst. To overcome this challenge, a P-C(sp²)-P type palladium pincer catalyst was used for the reaction, which found to be intact to the substrate chelation. The generated chiral phosphine ligands were successfully transformed to chiral N-C(sp³)-E type pincer compounds via direct cyclometalation. The new palladium complexes contain

enhanced stereoprojecting groups near the metal center, which might be potentially advantageous in catalytic applications. Study on the catalytic performance of these complexes is a possible future research direction.

In chapter 3, a novel transition metal-free tandem dihydrophosphination process of highly conjugated systems were established. Detailed NMR experimental studies revealed the plausible mechanism of the double hydrophosphination. The generated diphosphine ligands demonstrated an unexpected coordination mode to palladium: instead of the commonly expected P,P-bidentate chelation, the diphosphine ligand developed a P,O-bidentate and a P-monodentate coordination to the metal centers, generating a bimetallic species. Upon separation of the diastereomers, chiral bimetallic complexes were isolated. In the future, the catalytic activity of these compounds may be investigated in asymmetric synthesis scenarios. Another possible research direction is the synthesis of mixed bimetallic compounds, based on the established procedure.

In chapter 4, the palladium-catalyzed asymmetric phosphination of electrophilic diazoesters was established for the first time. In the reaction, enantioenriched P-stereogenic phosphinic hydrazones were produced, which compounds were subsequently transformed to P-stereogenic phosphinates using acidic methanolysis. A plausible catalytic cycle was proposed for the unexpected reaction, based on the experimental coordination studies. This research provides new directions not only in P-stereogenic phosphine ligand synthesis, but also in the research area of electrophilic diazo compounds. In the future, extension of the hydrazone product derivatization may be studied and new synthetic protocols may be investigated to improve the enantioselectivity.

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