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SINGAPORE

**SYNTHETIC PROTOCOLS FOR DESIGNING CHIRAL P,N-
CHELATE COMPLEXES**

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SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

2021

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KATONA DÁVID

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

2021

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The contributions of the co-authors are as follows:

- I prepared the manuscript drafts. The manuscript was revised by Dr. Sumod A. Pullarkat and Prof. Leung Pak-Hing.
- I co-designed the study with Prof Leung Pak-Hing and Dr Sumod A. Pullarkat and performed all the laboratory work at the School of Physical and Mathematical Sciences. I also analyzed the data.
- All spectroscopy, including sample preparation, was conducted by me in the laboratories of Central Facilities, SPMS, NTU.
- Dr. Yunpeng Lu carried out the calculations to obtain the optimized structures and the corresponding energy values.
- Dr. Yongxin Li obtained and provided the X-ray crystallography data and their interpretations.

04.03.2021

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Abstract

A novel, chiral bidentate ligand backbone was designed in order to obtain chelate complexes with various low-oxidation state metals. The heterobidentate P,N coordinating moieties were synthesized via exploiting the asymmetric hydrophosphination protocol: to incorporate the coordinating diphenylphosphine into the nitrogen containing activated substrates in an enantioselective manner. The synthesized P,N ligand proved to be suitable for performing the complexation of Pd(II), Pt(II), Rh(I), Ir(I), Ni(II) and Ru(II) metal sources. Palladium and platinum dimethylmalonate complexes could be achieved in an enantiopure form, and their rhodium and iridium counterparts could be realized as enantioenriched mixtures. Beside the thorough characterization of these compounds, their comprehensive steric and electronic scrutiny was also carried out by X-ray crystallography and by $^{31}\text{P}\{^1\text{H}\}$ NMR spectroscopy through various coordination reactions.

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Nanyang Technological University, 2021.

Abbreviations and Symbols

Abbreviations			
^{13}C -NMR	Carbon NMR spectroscopy	dba	Dibenzylidene acetone ((1E, 4E)-1,5-Diphenylpenta-1,4-dien-3-one)
^1H -NMR	Proton NMR spectroscopy	DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
$^{31}\text{P}\{^1\text{H}\}$ -NMR	Phosphorus NMR spectroscopy with decoupled proton signals	DCM	Dichloromethane
Ac	Acetyl	de	Diastereomeric excess
acac	Acetylacetonate (Pentane-2,4-dione)	DFT	Density Functional Theory
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl	DIOP	2,3-O-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
BINOL	1,1'-Bi(2-naphthol)	DIPAMP	Ethane-1,2-diylbis[(2-methoxyphenyl)phenylphosphane]
BIPHEP	2,2'-Bis(diphenylphosphino)biphenyl (sometimes dpbp)	DIPEA	<i>N,N</i> -diisopropylethylamine
Bn	Benzyl	DKR	Dynamic Kinetic Resolution
BOX	bis(oxazoline) ligand	DMAP	4-dimethylamino pyridine
Bu	Butyl	DME	Dimethoxyethane
CCDC	The Cambridge Crystallographic Data Centre	DMSO	Dimethyl sulfoxide
Cp	Cyclopentadienyl	Dppb	1,4-bis-(diphenylphosphine)butane
Cp*	1,2,3,4,5-Pentamethylcyclopentadienyl	Dppe	1,2-bis-(diphenylphosphine)ethane
Cy	Cyclohexyl		

Dppf	1,1'- <i>bis</i> -(diphenylphosphine)ferrocene	MAP	2'-(diphenylphosphaneyl)- <i>N,N</i> -dimethyl-[1,1'-binaphthalen]-2-amine
Dppm	<i>bis</i> -(diphenylphosphine)methane	Me	Methyl
DPPO	Diphenylphosphine oxide	MOP	2-(Diphenylphosphino)-2'-methoxy-1,1'-binaphthyl
Dppp	1,3- <i>bis</i> -(diphenylphosphine)propane	MS	Mass Spectrometry
dr	Diastereomer ratio	Naph	Naphthyl
DYKAT	Dynamic Kinetic Asymmetric Transformation	NBO	Natural Bond Orbital
EDTA	2,2',2'',2'''-(Ethane-1,2-diyl)dinitrilo)tetraacetic acid	ⁿ Bu	Normal butyl
ee	Enantiomeric excess	NMR	Nuclear Magnetic Resonance spectroscopy
en	Ethylenediamine	NOBIN	2'-Amino-1,1'-binaphthalen-2-ol
ESI	Electrospray Ionization	ONf ⁻	Nonaflate
Et	Ethyl	OTf ⁻ , Tf ₂ O	Triflate, Trifluoroacetic anhydride
HPLC	High Performance Liquid Chromatography	Ph	Phenyl
HRMS	High Resolution Mass Spectrometry	Pr	Propyl
ⁱ Pr	Isopropyl	QUINAP	1-(2-diphenylphosphino-1-naphthyl)isoquinoline
IR	Infrared spectroscopy	<i>R</i> , <i>R</i> _c , <i>R</i> _p , <i>R</i> _a	Right absolute configuration (Latin <i>rectus</i>); c: central; p: planar; a: axial chirality elements.
L-DOPA	L-3,4-dihydroxyphenylalanine	ROESY	Rotating Frame Overhauser Enhancement Spectroscopy
		<i>S</i> , <i>S</i> _c , <i>S</i> _p , <i>S</i> _a	Left absolute configuration (Latin

	<i>sinster</i>); c: central; p: planar; a: axial chirality elements.	ν	Frequency (Hz)
		Symbols	
^s Bu	<i>sec</i> -butyl	BD	Bonding Pair of electrons (in NBO results)
TBHP	<i>tert</i> -Butyl Hydroperoxide		
^t Bu	<i>tert</i> -butyl	d	Doublet (signal in NMR spectroscopy)
TEA	Triethylamine	L	Neutral coordinating ligand
TFA	Trifluoroacetic acid		
TMEDA	<i>N,N,N',N'</i> -Tetramethylethane-1,2-diamine	LP	Lone pair of electrons (in NBO results)
TMS	Tetramethylsilane	m	Multiplet (signal in NMR spectroscopy)
Tol	Tolyl	Ry	Rydberg orbitals (in NBO results)
TS	Transition State		
Physical quantities, constants or functions		s	Singlet (signal in NMR spectroscopy)
$[\alpha]_D^{25}$	Specific rotation at the D-lines of sodium (589 nm) at 25 °C	t	Triplet (signal in NMR spectroscopy)
ln	Natural logarithm	t _{2g} , e _g	Irreducible representations of the O _h point group
ⁿ J	Coupling constant (n indicates the number of bonds between the coupling nuclei)	X	Coordinating ligand with charge
		X(Hlg)	Halogen atom in organic molecules
R	Universal Gas Constant: 8.314 (J*mol ⁻¹ *K ⁻¹)	α	Alpha position from a functional group in organic molecules
$\Delta_r G^\circ$	Standard Gibbs free energy (J*mol ⁻¹)	β	Beta position from a functional group in organic molecules
$\Delta_r H^\circ$	Standard enthalpy (J*mol ⁻¹)		
$\Delta_r S^\circ$	Standard entropy (J*mol ⁻¹ *K ⁻¹)	β	Bite angle of bidentate ligand (in degree)

δ	NMR chemical shift in ppm
η^n	Hapticity of a ligand (n indicates the number of the adjacent coordinating atoms on a ligand)
θ	Bond angle in degree
κ^n	Denticity of a ligand (n indicates the number of the non- adjacent coordinating atoms on a ligand)
μ	Bridging Ligand

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CHAPTER 1: Introduction to the chemistry of bidentate ligands

Abstract

Chapter one details the chemistry of complex formations and the role of bidentate ligands in synthetic chemistry with the emphasis on chiral ligand backbones, such as N-donor bidentates, diphosphines, metallacycles or P,N coordinating moieties. This literature review covers the most widespread bidentate chiral ligands by focusing on their coordinating donor atoms and details their structural key points, their synthesis, and their areas of applications without being perfectly comprehensive.

1.1. Chelates and chelation

A coordination compound consists of an electron deficient Lewis acid (usually metal center) and coordinating, electron rich Lewis bases (ligands) around it. A classical octahedral metal complex, where there is no charge on the ligands, can be depicted as an $[ML_6]^{n+} A^{n-}$ system, where M^{n+} is the metal center, A^{n-} is the counter anion and L-s are the electroneutral ligands that coordinate to the metal via a donor atom.¹

In this model, L coordinates with its lone electron pair(s) as a ‘donation’ of electrons to the metal. This bond is called coordinate bond or dative bond, however, the latter term in this context is considered a bit obsolete nowadays. In this thesis, this type of bond will be consistently indicated with an arrow: $L \rightarrow M$. It is noteworthy to mention that beside lone electron pairs, σ - and π -bonds can coordinate to metals as well, but to understand the main concept of this model, this is less relevant at this stage. The character of the $L \rightarrow M$ coordinate bond varies between a purely dative bond and a dative bond with a slight covalent character depending on the coordinating donor atom.

In several cases, the coordinating ligand is not neutral, but it bears negative charge, hence, the metal-ligand interaction has an electrostatic nature as well. However, these ligands cannot be considered as counter anions as in the classical manner, since the metal-ligand bonds in these situations are positioned in the inner coordination sphere of the complex and show strong covalent characteristics. These kinds of ligands are indicated with X in coordination chemistry, Good examples are the chloro or methyl ligands among others, where the $M-X$ bonds (drawn consistently with bond-lines indicating the covalency) have covalent and ionic characters i.e., polar covalent bonds with an electrostatic nature.²⁻³

L often indicates a so called monodentate ligand, although, several examples exist for ligands with more than one coordinating donor atoms. We can refer to them according to the number of the separate binding sites (denticity) on the ligand, such as (mono-), bi-, tri-, tetra-, pentadentate...etc., ligands, and they are often called chelates. Denticity in the literature is described with κ , thus, κ^2 refers to a bidentate ligand. One of the most well-known chelate complexes in nature is the haem in haemoglobin, where the iron ion center is chelated by the tetradentate porphyrin ligand, which is a macrocyclic organic compound.⁴

Because of the extensive nature of the subject, we must limit our focus on bidentate chelates in this study.

When a complexation (chelation) of a metal by a bidentate ligand takes place, a so-called chelate ring forms. The most favorable chelate ring sizes are the five- and six-membered ones, because smaller rings inherently involve conformational strains, while in the case of larger rings, the several possible ring conformations and increasing steric hindrance (which causes changes in the reaction enthalpy during coordination) and the increasing probability for monocoordination degrades the advantages of a simple and one-step, relatively rigid, low-energy ring formation³. Some of the most common bidentate chelates that are used generally in chemistry are ethylenediamine (en),⁵ EDTA⁶, TMEDA⁷ and the numerous diphosphine derivatives, such as bis(diphenylphosphino)alkanes (dppe, dppp, dppf... etc).⁸ EDTA and 'en' are used in pharmaceutical, analytical, agricultural, and food chemistry, while TMEDA is an important additive that synthetic chemists apply in s-block organometallic chemistry. Diphosphines have crucial role in coordination chemistry, thus, in homogenous catalysis as well.⁹

It is important to mention that chelate ring formation has a significant thermodynamic aspect.^{10, 3} In dilute solutions, when we do not take the charge into consideration, a chelate complex formed by a certain type of ligand has higher thermodynamic stability than that for a complex, where the multidentate ligand is substituted with its monodentate counterparts or close analogues. This phenomenon is called *chelate effect*.¹¹ Let us consider L as a monodentate ligand, then let L-L be the bidentate chelating agent with the same donor atoms and very similar structures. In that case, by occupying only two coordination sites on the metal (not focusing on the other possible

sites), the forming metal complex with coordinating L can be described as ML_2 , while the chelating ligand will form $M(L-L)$ complex.

The concept of the *chelate effect* can be shown on the following, generalised schematic reactions:

where the reaction quotient for eq.1. is: $\beta_L = \frac{[ML_2]}{[M][L]^2}$, and

where the reaction quotient for eq.2. is: $\beta_{L-L} = \frac{[M(L-L)]}{[M][L-L]}$.

β_L and β_{L-L} are the cumulative stability constants for the complexation reactions above. According to numerous experimental observations, chelate effect can be thus described as $\beta_{L-L} > \beta_L$. To explain this, we must take the aforementioned thermodynamic effects into consideration. In equilibrium (under standard conditions), the standard Gibbs free energy of a chemical reaction can be expressed by the equation:

$$\Delta_r G^\circ = \Delta_r H^\circ - T\Delta_r S^\circ = -RT \ln \beta, \quad (\text{eq.3.})$$

where $\Delta_r G^\circ$ is the standard Gibbs free energy, T is the temperature, R is the universal gas constant, $\Delta_r H^\circ$ is the standard enthalpy change, while $\Delta_r S^\circ$ is the standard entropy change of the reaction. Because the enthalpy must be very similar for the two reactions and they must occur at the same temperature, the difference lies in the entropy change of the two processes.

Let us examine a concrete situation via the example of cadmium: let L be methylamine, while L-L be ethylenediamine (en). The quantified reaction parameters at 25 °C are compiled in Table 1.³

Table 1. Values of thermodynamic functions in the case of monodentate coordination and chelation of Cd^{2+} .

Complex formation	$\Delta_r G^\circ /$ kJ/mol	$\Delta_r H^\circ /$ kJ/mol	$T\Delta_r S^\circ /$ kJ/mol	$\ln\beta$
$\text{Cd}^{2+}(\text{aq}) + 4 \text{NH}_2\text{Me}(\text{aq}) \rightleftharpoons [\text{Cd}(\text{NH}_2\text{Me})_4]^{2+}(\text{aq})$ (eq.4.)	-37.41	-57.32	-19.91	15.08
$\text{Cd}^{2+}(\text{aq}) + 2 \text{en}(\text{aq}) \rightleftharpoons [\text{Cd}(\text{en})_2]^{2+}(\text{aq})$ (eq.5.)	-60.67	-56.48	+4.19	24.45

It can be seen that the entropy terms significantly differ in each case. This quantitative difference can be explained with the favored ‘increase of disorder’ during complexation; hence, the entropy increases. In Equation 4., there are three reactants on the left-hand side and one species on the right, while in Equation 5., there are two reactants on the left-hand side and one on the right side. The decrease of entropy is less in the case of Equation 5, thus, this process is preferred to Equation 4.

A more powerful illustration of the effect is when the two equations are combined into a substitution case:

Herein, the difference between the two sides with regard to the number of reactants clearly shows why the chelation is the favorable process.

Nevertheless, we can get to the same conclusion by observing Equations 4 and 5 but taking the solvation (hydration) into consideration (because these processes were investigated in solution). By this means, the metal ion exists as poly-aquo complex, where H_2O molecules are the monodentate ligands which are substituted by the coordinating N donor species. The increase of entropy occurs more significantly during chelation in this case as well.¹⁰

1.2. Bidentate ligands in asymmetric chemistry

While the aforementioned achiral N and P donor bidentates mostly act as spectator ligands or have secondary role in reactions (such as activating the reagent or tuning the electronic properties of the metal centers), chiral, especially axially chiral (C_2 -symmetric) ligands are crucial in conveying chiral information in various kinds of syntheses. These four- or six-electron donor multidentate ligands are capable of powerfully defining the space around the active part (metal) of a catalyst complex, thus, clearly determining the arrangement of a coordinating substrate or reagent (Figure 1).¹² Some of them are also often referred as privileged ligands, as they are capable of providing high selectivity in several different fields of catalysis.

Figure 1. A C_2 symmetric model to depict the spatial arrangement of groups around the metal center.

C_2 symmetry means that these types of molecules have 180° rotational axes, i.e., upon a 180° rotation these molecules remain identical. The axis of rotation in this case points perpendicularly out of the plane of the figure (that is toward the reader).

When we divide the space into four pieces or quadrants, it can be seen in the picture that two quadrants out of four (I. and III.) are sterically crowded or hindered while by the *P*-phenyl groups, the other two (II. and IV.) are empty. By this manner, the arrangement of the entering and coordinating reactant(s) is well-defined. The most famous members of this class among others are the bidentate BINAP, developed by Noyori and co-workers¹³ in , and DIPAMP developed and used by Knowles and

colleagues.¹⁴ for asymmetric hydrogenation. Both had unequivocal contribution in establishing the basis of asymmetric transition metal catalysis.

1.2.1. Chiral bidentates with nitrogen and oxygen donor atoms

Before we cover the seemingly more relevant diphosphine ligands, we must mention those are not bearing phosphorus as donor atoms, but nitrogen or oxygen, because they are of great importance in catalysis as well.

1.2.1.1. Bisoxazoline ligands

The most widespread ligands from this class are the bis(oxazoline)-s or BOX ligands (Figure 2.).

(S,S)-BOX ligands:

Figure 2. Bis(oxazoline) or BOX ligands with coordinating nitrogen atoms.

The BOX and (and the tridentate PyBOX) ligand family is mostly used in the late transition metal mediated or catalyzed synthesis, and among them, the copper catalyzed Lewis acid catalysis is the predominantly researched area.¹⁵ Without being comprehensive, some well-described reactions and research fields are the areas of the Michael-reaction, the ene reaction and the Diels-Alder cyclization reactions.¹⁶⁻¹⁷

A good example for the latter cyclization catalyzed by a Lewis-acidic copper(II)-BOX complex is the one worked out by Evans et al in 1995.¹⁶ This reaction is a Diels-Alder cycloaddition between the dienophile acrylimide and a diene, which is cyclopentadiene in our example (Figure 3.).¹⁸

R:	X:	Yield:	endo/exo:	endo ee:
Ph	OTf ⁻	85%	90:10	99%
Ph	SbF ₆ ⁻	96%	91:9	96%
Cl	OTf ⁻	<10%	93:7	53%
Cl	SbF ₆ ⁻	96	86:14	95%

Figure 3. Diels-Alder cyclization between an acrylimide and cyclopentadiene published by Evans and colleagues.

In the reaction, the electron-rich *oxo* groups of the imide or oxazolidinone coordinate to the ligated, relatively electron-deficient, Lewis-acidic copper(II) center, which activates the α,β -unsaturated olefin (dienophile) moiety by coordination. The activated dienophile then reacts with the diene under mild conditions and in a stereoselective way, as the Cu-BOX moiety controls the steric environment around the center of the reaction. Both the satisfactory *endo/exo* ratio and the high ee-s of the *endo* product are the outcome of using the chiral BOX ligand.

It also can be seen that the employed counteranions have significant effect on the reactivity: The catalyst provides better reaction rates when PF₆⁻ was used as a counteranion over OTf⁻. As an explanation, Evans and his co-workers found that the triflate anion can coordinate to the square planar copper(II) center through a fluorine atom at the axial position. By this manner, the Lewis-acidity of the metal is deteriorated, which leads to lower reaction rates. According to the X-ray crystallographic analysis, the PF₆⁻ anion does not coordinate this way and remains indifferent during the reaction. The geometry of the catalyst-substrate complex can be seen in Figure 4.

Figure 4. Square planar catalyst-substrate complex occurring in the Diels-Alder cyclization.

The metal center in the copper(II) complex has d^9 electron configuration, for which the Jahn-Teller distortion is typical. Thus, the geometry of the copper(II) complexes highly depends on the ligands and varies within a broad range.¹⁵ In this case, the distorted square planar arrangement was proved both by X-ray crystallography, and the stereochemical outcome of the reaction.¹⁶

1.2.1.2. NOBIN and its related derivatives

Another coordinating agent which is worth mentioning is the axially chiral NOBIN ligand (Figure 5.).¹⁹ This type is a so-called hybrid ligand, i.e., a bidentate ligand with different coordinating atoms. We must mention that a common feature of hybrid ligands, especially those bearing coordinating oxygen (hard donor atom) is the hemilability, i.e., the partial decoordination of the ligand, that can occur under particular conditions.¹⁹

Figure 5. The binaphthyl type NOBIN and the partially reduced H₈-NOBIN ligands

The NOBIN family is an N,O coordinating bidentate with a binaphthyl backbone. NOBIN itself is a versatile coordinating agent and moiety, ligand precursor and chiral auxiliary in various syntheses.²⁰⁻²² It can be derived from BINOL, which is an O,O bidentate with similar, or even more important role in the field of C_2 symmetric ligands (1,1'-Bi-2-naphthol, see later).²³⁻²⁴

An intriguing example for NOBIN as an asymmetric ligand precursor is reported by Y. Hu et al. in 2003, where they successfully modified the NOBIN backbone to obtain bidentate phosphite-pyridine derivatives as efficient ligands for catalytic (copper catalyzed) enantioselective 1,4 addition²² (Figure 6.). The addition of the ethyl group takes place between chalcone as an activated olefin and diethylzinc in the presence of copper catalyst where the chiral ligands are the aforementioned NOBIN derivatives. The selectivity of the reaction for *trans*-chalcone proved to be high (above 90% of ee) and the process also provided good yields under mild conditions.

Figure 6. a.) H₈-NOBIN being modified to be an effective ligand (S,S)-L for copper catalyzed asymmetric ethyl group addition to *trans*-chalcone (b.)).

1.2.2. Chiral diphosphine ligands

1.2.2.1. DIOP ligand

The chemistry and history of chiral diphosphines make them crucial to be covered, since their contribution to asymmetric catalysis is beyond dispute. Historically, the first chiral, C₂ symmetric diphosphine ligand was the DIOP, a phosphine derivative of tartaric acid, which had an important role in describing rhodium catalyzed asymmetric reduction²⁵ and the platinum and tin catalyzed hydroformylation.²⁶⁻²⁷ The structures of DIOP and its bis(dibenzophosphole) (DBP) derivative can be seen in Figure 7.

(R,R)-DIOP:

(R,R)-DBP-DIOP:

Figure 7. The structures of DIOP and DBP- DIOP ligands; a pioneer ligand backbone of asymmetric catalysis.

The significance of this ligand family is crucial, and the use of this important coordinating agent led to the evolution of asymmetric ligands and catalyst protocols, i.e., the development of the modern enantioselective catalysis.

The aforementioned hydroformylation of styrene catalyzed by a PtCl_2 – DBP-DIOP system in the presence of SnCl_2 is a good illustration of the importance of DIOP ligands (Figure 8.). The reaction was published by Pittman et al. in 1982.²⁶

Figure 8. Platinum catalyzed asymmetric hydroformylation of styrene with the use of DBP-DIOP as chiral ligand.

The reaction takes place at moderate temperatures and the reaction times are relatively short, however, it requires high pressures. Although the desired product was the branched and chiral 2-phenylpropanal, the normal chained 3-phenylpropanal formed as a side-product, too. According to the authors, the optical yields were calculated based on the $[\alpha]_D^{25} = 238$ reference value for optical rotation. The optical yields and the branched / normal ratio increased with the gas pressure, while higher temperatures caused a decrease in the stereoselectivity. The styrene conversions were more than 90% in each case.

1.2.2.2. Knowles' DIPAMP ligand

One of these milestones in asymmetric catalysis is the development of the asymmetric hydrogenation. Upon the success of the famous Wilkinson's catalyst,²⁸ Knowles and co-workers reported an asymmetric version of hydrogenation of acrylic acids by using monodentate P-chiral phosphines and rhodium.²⁹ However, the use of the bidentate DIPAMP bis-phosphine ligand brought the turn in the field (Figure 9.).

Figure 9. Rhodium phosphine complexes for asymmetric reduction.

The selective reduction of α -acylamino acrylic acids with high ee-s led to potential amino acid derivatives.¹⁴ One of the most important examples of these is the synthesis of L-DOPA (L-dopamine precursor, Figure 10.).³⁰

Figure 10. Selective catalytic synthesis of L-DOPA.

In the case of DIPAMP, the chiral induction stems from the stereogenic phosphorus centers on the one hand, while the ethyl backbone defines the aryl rings' positions by its conformationally favorable layout on the other hand.

1.2.2.3. The role of BINAP ligand in asymmetric catalysis

Another pioneer in the field of stereoselective catalysis is Noyori, who has an inevitable contribution to the organometallic chemistry by developing the BINAP ligand and its derivatives (Figure 11.).^{13, 31} This ligand is the direct derivative of the aforementioned BINOL (Figure 12.): upon the bromine substitution of BINOL, the dibromo binaphthyl intermediate was converted into the racemic mixture of BINAP by the phosphination of the aromatic rings. For the halogen phosphorus substitution, they used *tert*-butyl lithium and Ph_2PCl . The resulting mixture was then resolved with the use of chiral phenylethylamine chloro-palladacycle dimer complex as a chiral auxiliary, coordinated to the racemic BINAP. After coordination, the resulting diastereomers were separated by recrystallization, and the pure BINAP enantiomers could be obtained by the removal of the palladacycle moiety.¹³

The C_2 symmetry and the chiral environment are based on the steric lock between the two naphthyl ring systems (thus, inversion cannot occur), and the maximal angle between the naphthyl rings is defined by the metal to which the ligand is coordinated. This steric lock between two, attached aromatic moieties is called atropisomerism, and the stereochemistry of such molecules can be described as a form of axial chirality.³² BINAP, BINOL, NOBIN, MOP, MAP, QUINAP, etc. binaphthyl ligands (*vide infra*) are perfect examples to molecules with the elements of atropisomerism. Hence, in coordinated BINAP, the *P*-phenyl (or aryl) rings' spatial arrangement is determined.

Figure 11. BINAP ligand: the axially chiral backbone structure and its derivatives.

As shown in the figure, there are many existing derivatives that have been developed depending on the reaction it was meant to be used in.³³ By varying the substituents at *ortho* or *para* positions on the *P*-phenyl rings, the steric and electronic properties of the ligands can be modulated. For instance, in the *p*-chloro and fluoro substituted derivatives the π acidity is significantly higher than in the phenyl-BINAP itself.

Figure 12. The synthesis of racemic BINAP from BINOL, that can be resolved by a chiral auxiliary.

Rhodium BINAP complexes also proved to be suitable for the asymmetric reduction of α -acylaminoacrylic acids with high ee-s,¹³ however the asymmetric hydrogenation of the keto group of β -keto carboxylic esters with ruthenium BINAP catalysts was the real breakthrough (Figure 13.). As can be seen in the figure, both the yields and ee-s are high.³⁴ Compared to Knowles's asymmetric reduction, both of the reactions work smoothly at moderate temperatures, i.e., rt for BINAP catalyzed reactions and 50 °C in the case of Rh-DIPAMP. The reactions catalyzed by rhodium BINAP and DIPAMP to reduce aminoacrylic acids need lower pressure (3-4 atm, or 27 atm in some cases of Knowles protocols), while the reduction using ruthenium-BINAP halogenides for ketoesters (Noyori) requires 70-100 atm. Simultaneously, Noyori and co-workers developed the subsequently more widespread ruthenium BINAP diacetate catalyst precursors (Figure 14.). The structure of the complex is octahedral, and the leaving acetate or AcOH plays a crucial role during the catalytic cycle.^{35, 12}

Figure 13. Asymmetric reduction of β -ketoesters.

Figure 14. Ru(II)-[(*R*)-BINAP](OCOMe)₂ catalyst precursors for asymmetric hydrogenation reactions.

Since its development, BINAP (coordinated to various metals) plays a significant role in other catalytic reactions as well, such as hydrosilylation,³⁶ hydroformylation,³⁷ hydroboration,³⁸ Heck reaction³⁹⁻⁴⁰ or allyl alkylation⁴¹ etc.

The catalytic hydrosilylation (disilylation) is a versatile procedure to generate chiral alcohols at the end (Figure 15.).

Figure 15. Synthesis of chiral alcohols by asymmetric disilylation.

According to the reaction scheme, both hydrosilylation and the TMS (trimethylsilyl) protection takes place simultaneously. The silylation protocol works on other, differently substituted α,β -unsaturated ketones, i.e., the methoxyphenyl moiety can be changed to methyl or phenyl groups, and also the methyl group in the other side of the

molecule can be substituted with phenyl or isopropyl moieties. The TMS protecting group was removed with methyl lithium, which also alkylates the -SiPhCl₂ moiety to -SiPhMe₂ group. The resulting alkyl phenyldimethylsilyl moiety then can be converted to a chiral alcohol by a subsequent acidic and oxidative treatment (H⁺; then HBF₄/H₂O₂).³⁶

Another remarkable example that must be highlighted is in the field of C–C cross coupling reactions, i.e., the enantioselective Heck reaction (Figure 16.).

Figure 16. Asymmetric Heck reaction catalyzed by Pd(0)-BINAP complex.

The coupling occurs at moderate temperature (40 °C) in basic medium. The starting Pd(II) metal is partially converted to palladium(0) in the reaction mixture, which oxidation state of the palladium is ready to take place in the oxidative addition of the aryl–X-type starting materials (X here refers to triflate, but it is often a halogen like iodine or bromine in cross coupling protocols). The dihydrofuran (olefin) in this case inserts in the [Pd] –Ar bond that is formed upon the oxidative addition, thus allowing the arylation to take place.

By this fashion, this example provides an extremely valuable reaction protocol to the practice of chemical and mainly the pharmaceutical synthesis.

1.2.3. The bite angle of bidentate (phosphorus) ligands and other steric and electronic effects

Since non-asymmetric metal catalyzed reactions have wider literature, thus, we have deeper knowledge on such protocols. The role of supporting phosphine ligands has been investigated in a broader scale. Their structural and electronic properties and their effects on reactivity was deeply scrutinized by Chadwick A. Tolman and colleagues. They defined the Tolman cone angle of trivalent phosphines and the Tolman electronic parameter.⁴²

1.2.3.1. The Tolman electronic parameter

The Tolman electronic parameter is related to the π -acidity (or the ability of accepting electron density via backdonation from the metal) of phosphines depending on their substituents. This was quantified by Strohmeier⁴³ and Tolman by coordinating monodentate phosphines to nickel carbonyl complexes (eq.7), and by measuring the $\text{C}\equiv\text{O}$ stretching frequencies by infrared spectroscopy (IR).

The stretching frequencies clearly show the extent of the π -acidity of the coordinating phosphine because the more electron density the PR_3 ligand can accommodate from the metal, the less remains on the carbonyls. Thus, the carbonyl's bond order increases (since the electron density from backdonation fills the antibonding orbitals of the CO ligand) and the carbonyls' vibrational frequencies increase as well (Table 2.).

Table 2. The change of carbonyl CO stretchings with different substituents on the phosphines.

Monodentate, trivalent phosphine ligand (PR_3)	$\nu(\text{CO}) / \text{cm}^{-1}$
P^tBu_3	2056
PCy_3	2056
P^iPr_3	2059
PMe_3	2064
$\text{P}(p\text{-Tol})_3$	2066
PPh_3	2069
PH_3	2083
PCl_3	2097
PF_3	2111

We can observe that the phosphines with aliphatic substituents have the lowest π -acidity. The aromatic phosphine ligands are in the middle region, and the phosphine halogenides can withdraw electrons in the highest extent from the metal.

1.2.3.2. Tolman cone angle

While the electronic parameter describes exclusively the electronic factors and effects the coordinating moiety causes, the Tolman cone angle provides quantified information about the steric properties of the ligand (Figure 17).⁴⁴ This was important because, as it was observed, ligands tend to compete to occupy favorable coordination sites of the metal, and the explanation of which cannot be covered only by electronic effects.⁴²

Figure 17. The definition of the Tolman cone angle and angle values of selected phosphines.

According to Tolman's definition, the cone's top point is 2.28 Å from the center of the phosphorus atom (average P–Ni bond length) toward a hypothetical tetrahedron's vertex (the other 3 vertices of which are the three substituents). The cone's generator lines touch the substituents' Van der Waals edges, thus, defines an angle that called the Tolman cone angle (θ).

The cone angle of phosphine ligands helped us understand their different reactivity, selectivity or even the structure of complexes with unusual geometries. A good example for the latter is the Pd(0)(*t*Bu)₃)₂ complex, which is a 14-electron system with linear ML₂ geometry. While in this case the palladium center is unsaturated both electronically and coordinatively, the tri-*tert*-butylphosphines shield the space around the metal in a so high extent, that a third ligand does not have the chance to approach the center (the cone angle of P(*t*Bu)₃ is 182°).

1.2.3.3. Bite angle of bidentate ligands

The third characteristic feature of ligands we must talk about is their bite angle, which is specifically related to bidentates. With regard to phosphines, the bite angle of a bidentate ligand is the angle defined by the two donor phosphines and the metal (P–M–P; Figure 18.).⁴⁵

Figure 18. The natural bite angle of bidentates.

However, since this angle depends on the coordinating metal and its electronic nature, and also on conformational and steric effects, Charles P. Casey and co-workers defined the term *natural bite angle* (β_n): The angle of chelation determined and based only the ligand backbone's structure and preferred conformation. Thus, although it describes a coordinated state, the metal, as a factor, was omitted from the calculations. For modelling the P–M–P system, P–Rh–P chelate was used, and the P–M distance was defined as 2.30 Å, which is the typical Rh–P distance in complexes.⁴⁶ Some selected diphosphine ligands with their natural bite angle can be seen in Figure 19.^{47, 45}

Figure 19. Natural bite angle of some selected ligands.

The study of the bite angle of ligands is of great importance from the points of view of reactivity and effectivity in catalysis. Casey et al. investigated its effects on the hydroformylation reaction,⁴⁸ while Tamio Hayashi and co-workers also observed and scrutinized that through the example of the Kumada cross coupling reaction.⁴⁹ We are going to use the latter as an example to show the importance of the ligand bite angle. Hayashi and co-workers examined the Kumada cross coupling reaction by observing the effect of various coordinating diphosphine ligands on reactivity and selectivity. In their works, they considered it important to compare both the P–Pd–P and the corresponding Cl–Pd–Cl bond angles on the square planar Pd(II) center.

Figure 20. Palladium catalyzed Kumada coupling of *sec*-butylmagnesium chloride and phenyl bromide.

In this coupling reaction, aryl bromides react with *sec*-butylmagnesium chloride via a palladium catalyzed pathway (Figure 20.).⁴⁹ In their work, they considered it important to examine the angles occurring in the precatalyst complexes around the metal center. While their main goal in this regard was to describe the correlation between the P–Pd–P bite angle and reactivity or selectivity, our aim is only to show that bite angle can itself affect significantly the result of a reaction (Table 3.).⁵⁰

Table 3. The geometry of complexes around the palladium center and its effect on the above-mentioned Kumada coupling.

P–P ligand	P–Pd–P angle / °	Cl–Pd–Cl angle / °	Yield (^s BuPh)	Yield (ⁿ BuPh)
dppe	85.8	94.2	0	0
dppp	90.6	90.8	43	19
dppb	94.51	89.78	51	25
dpbp (BIPHEP)	92.24	88.21	93	1
dppf	99.07	87.8	95	2

However, they previously concluded that the bigger bite angle leads to higher yields with better selectivity (dppf was the most effective ligand),⁴⁹ later they described that

the use of dpbp (BIPHEP) as a ligand with moderate bite angle can provide similar or even better results.⁵⁰ The Cl–Pd–Cl bond angles were also taken into consideration, and it served as a better explanation for understanding the angle dependence in this catalysis. Without going into details, the bite angle, and thus, the geometry of the complexes around palladium center is able to affect the reaction rate of reductive elimination at the expense of other side processes, such as β -hydride elimination or isomerization in this case (this led to the formation of *n*-BuPh product).

Through this example, it can be seen that bite angle of bidentate ligands is an unavoidably important factor in designing catalytic reactions and catalysts.

1.2.4. Chiral metallacycles (C,N; C,P and C,As anionic ligands)

Ligands with coordinating carbon atom along with another heteroatom are often considered as the organometallic derivatives of a certain metal (as they are indeed). However, the organic part attached to the corresponding metal can be deemed as a bidentate coordinating moiety or ligand as well, or in other words, as an X-type ligand which bears a negative charge.⁵¹

The negative charge stems from the nature of formation of the C–M σ -bond. Unlike nitrogen, oxygen or phosphorus donors, the of C–M bond in this case is an M–X type covalent bond, and its formation is in effect a substitution between the metal and a proton (metalation, Figure 21.). For this reason, when we hypothetically separate the organic coordinating part from the metal, we must take the charge into consideration. In metallacycles, C–M bond is usually a polar covalent bond with electrostatic character, while the other donor atom is neutral.

Figure 21. The general and simplified scheme of cyclometallation.

The mechanism of the metalation (so-called directed *ortho* metalation) can be described as C–H activation, which resembles to the aromatic electrophilic substitution reaction: the relatively electron deficient metal coordinates to the directing heteroatom (E) and undergoes into a π electron – metal interaction (π complex), which is followed by the formation of a σ complex, although calculations revealed that agostic M---H interaction is also involved during the process. The last step is the proton abstraction, which may

go via the involvement of either an internal or an external deprotonating agent.⁵¹ When $\text{Pd}(\text{OAc})_2$ is used as a metal source for instance, acetate anion carries out the deprotonation intramolecularly as an internal base, while in other cases, external base is used as an additive in the metalation reaction (intermolecular pathway, see later). The donor atom (E) can be nitrogen, phosphorus or arsenic among others, although, nitrogen is the most widespread in the field of metallacycles. A few examples of five-membered chiral metallacycles reported by Leung and his co-workers can be seen in Figure 22.).⁵²⁻

Figure 22. Examples of metallacycles reported by Leung and co-workers.

In these pallada- and platina-cycles the metal centers are in +2 oxidation state and they form chlorodimer complexes, where their bridging chloro ligands act both as L- and X-type coordinating moieties. In the case of the iridacycle, the metal center is Ir(III), and its geometry is a so-called pseudo-tetrahedral structure (we can hypothetically consider the $\eta^5\text{-Cp}^*$ ligand as three, separate monohapto ligands, as the Ir(III) center tends to form octahedral complexes).⁵⁶

A good example for metalation is the cyclopalladation step in the synthesis of the (diphenylphospha)ethyl-naphthylenyl palladium (C,P-dimer) complex, where external base was used for deprotonation. It can be seen in Figure 23.

Figure 23. Cyclopalladation step during the synthesis of the C,P palladium complex.

The resulting five-membered C,P-palladacycle is an important, highly selective and versatile catalyst in the field of asymmetric hydrophosphination⁵⁷⁻⁵⁹ and also in C–C bond formation reactions.⁶⁰

The aforementioned C,N palladium complex (Figure 22.), which is being cited in this review section several times, is an important chiral auxiliary for the resolution of racemic ligand mixtures. Nevertheless, it has a proven field of application as a chiral reagent in *endo*-selective Diels-Alder reaction⁶¹⁻⁶² and asymmetric hydrophosphination,⁶³ and as a catalyst in Claisen rearrangement providing 79% of ee.⁶⁴

The piano-stool Cp* iridacycle complex (Figure 22.) proved to be effective in catalyzing asymmetric transfer hydrogenation with good selectivity (69% ee).⁵⁵

1.2.5. Chiral P,N bidentate ligands

In comparison with diphosphine ligands, changing one of the donor phosphorus atoms to nitrogen leads to significant electronic modifications on the metal center in complexes. Phosphines are usually σ donor π acceptor type of coordinating moieties, because the trivalent phosphorus atom can donate an electron pair to the metal, while they also can accept electrons from the metal's filled d orbitals to the phosphine group's P–R σ^* antibonding orbitals (the extent of which depends on the substituents of the phosphine group). In this fashion, the phosphorus atom can be described as a soft donor, however, this softness can be tuned in a broad scale. It is known that phosphorus is able to stabilize low valent metal centers.⁶⁵

In contrary, coordinating nitrogen is a hard σ donor or strong Lewis base (this hardness however is lower for sp^2 or aromatic nitrogen donors). In the case of aromatic nitrogen donors, backdonation must be taken into consideration, although, it is significantly weaker than that for phosphines. The strong σ donating ability may lead to the activation of the metal center, thus, for example its increased affinity toward oxidative

addition.⁶⁶ In general, the coordination of bidentate ligands bearing different donor atoms (hybrid ligands) causes unsymmetrical electronic effects on the metal, and consequently, on the coordination sites positioned *trans* to them. It also appears in their unsymmetrical affinity for accepting other coordinating agents, which is crucial when a catalytic reaction is being designed.⁶⁷ Despite nitrogen being a relatively hard donor atom, the aforementioned hemilability is not as common as in the case of P,O or N,O bidentates.¹⁹

Chiral and achiral P,N ligands have an emerging and significant role in catalysis. Achiral P,N bidentates for instance were employed in rhodium catalyzed hydrogenation of arenes,⁶⁸ furthermore, in ruthenium catalyzed transfer hydrogenation and metathesis reactions.⁶⁹

To introduce the importance of chiral P,N ligands in transition metal catalysis we have chosen four types of ligand backbones to depict their structure and their related asymmetric reactions.

1.2.5.1. PHOX ligands and derivatives

The first ligand type is PHOX (phosphinooxazoline) family, where the coordinating nitrogen is a part of an oxazoline ring, and the phosphorus atom coordinates as a diphenylphosphino moiety (Figure 24).⁷⁰

Figure 24. PHOX (phosphinooxazoline), PyrPHOX and FcPHOX ligands.

PHOX ligands have been used in asymmetric hydrogenation,⁷¹⁻⁷² allylation and allylic alkylation⁷³⁻⁷⁴ and Heck reaction⁴⁰ among others.

An interesting example is the asymmetric Tsuji-type allylation published by Stoltz and co-workers, where a cyclic enol carbonate is transformed to allyl cycloalkanones with a stereogenic center in the α position to the carbonyl group (Figure 25.).⁷⁴ The obtained

chiral, quaternary product is a very useful building block that can be utilized in total syntheses of natural products.

Figure 25. Tsuji allylation of a cyclic enol carbonate.

During the optimization process, they tried both chiral P,P and P,N (and even P,O) bidentates, and in spite of the to the success of chiral diphosphines, the heterobidentate ones provided the higher selectivity. The best ee value occurred when *t*-Bu-PHOX was used as a ligand in the Pd(0) catalyzed reaction.

1.2.5.2. Chiral ferrocene P,N ligands (MPFA and PPFA)

The next group of P,N bidentates is in the class of 1,2 disubstituted ferrocene compounds, i.e., the planar chiral MPFA and PPFA ligands developed by Hayashi and Kumada (Figure 26.).⁷⁰

Figure 26. Diphenyl- and dimethylphosphinoferrocenyl ethyldimethylamine ligands (MPFA and PPFA), and Josiphos.

Their structures strongly resemble to the chiral Josiphos ligand, which was found effective for Rh and Ir catalyzed asymmetric hydrogenations.⁷⁵

Both Josiphos⁷⁶ and the PFA ligands⁷⁷ can be synthesized stereoselectively from Ugi's amine as a chiral starting material with the use of *n*-butyl lithium and Ph₂PCl. Ugi's amine is a very versatile building block, which already bears a central chiral carbon atom attached to the dimethylamine moiety (Figure 27.). This enables the selective functionalization of the substituted Cp ring with various electrophiles to obtain planar and central chiral compounds.

Figure 27. Ugi's amine, a versatile chiral building block in ferrocene chemistry.

The two, most important fields of application of MPFA and PPFA ligands are the asymmetric hydrosilylation⁷⁷ and the asymmetric Kumada cross-coupling reactions.⁷⁸ The aforementioned asymmetric reaction described by Kumada and Hayashi and co-workers is a C–C coupling between a racemic Grignard reagent and an aromatic or alkenyl bromide (Figure 28.).⁷⁸

Figure 28. Asymmetric Kumada-coupling reaction by using racemic chiral phenylethyl Grignard reagent and allyl bromide.

Selected entries from their reaction optimization table can be seen in the figure: the optimum condition of the coupling between 1-phenylethylmagnesium chloride and allyl bromide was at -20 °C when catalyzed by the nickel-PPFA complex, providing 68% ee and high yield.

The selectivity of the reaction could be increased to 79% by using Weissensteiner's FcPN ligand (Figure 29.) with palladium chloride at 0 °C under similar conditions.⁷⁹

Figure 29. Weissensteiner's FcPN and Hayashi's chromium arene PN ligands.

Another interesting development based on the design of the PPFA family is the planar chiral (η^6 -arene)chromium half-sandwich carbonyl complex (Figure 29.), that functions as a P,N ligand as well. This ligand system was also developed by Hayashi and co-workers, and was successfully utilized in palladium catalyzed asymmetric allyl alkylation reactions.⁸⁰

1.2.5.3. The binaphthyl-type MAP ligand family

The third relevant class of P,N ligands is the MAP family,⁸¹ which is the analogue of Noyori's BINAP and Hayashi's MOP (P,O) ligands (Figure 30.; MOP derivatives were also applied in enantioselective hydrosilylation and they showed very high selectivity).⁸²

Figure 30. MAP and MOP ligands derived from the axially chiral BINAP.

The MAP ligand family was developed by Pavel Kočovský and colleagues, and they used the already mentioned NOBIN binaphthyl backbone. The enantiopure NOBIN was first *N*-methylated in a modified Eschweiler-Clarke-type reaction, then *O*-acylated by Ti_2O (TFAA) in DCM.

As the third step, the $\text{P}-\text{C}(\text{sp}^2)$ coupling was carried out via a palladium(0) catalyzed pathway to obtain a diphenylphosphine oxide intermediate. In the last step, the resulting phosphine oxide was reduced by using trichlorosilane to afford the enantiopure P,N bidentate. The scheme of the synthesis can be seen in Figure 31.

Figure 31. Synthetic scheme of MAP ligand from enantiopure NOBIN.

An interesting feature of MAP is that in solution, its coordination complex is able to undergo P monocoordination via an alternative P,C metallacycle intermediate from P,N coordination (Figure 32).⁸³ The existence of the P,C intermediate can be explained by the tendency of palladium to form five-membered palladacycles with aromatic systems.⁸⁴

Figure 32. Formation of monocoordinated MAP-Pd complex via P,C palladacycle intermediate from P,N palladium chelate.

This effect, caused by the occurrence of P monocoordinated species, can accelerate various coupling reactions, such as Buchwald-Hartwig amination.⁸³

MAP ligands are of proven application and importance in asymmetric allylic substitution,⁸⁵ Suzuki coupling^{83, 86} and in the already mentioned Buchwald-Hartwig amination reaction.^{81, 83}

An example of asymmetric allylic alkylation is the catalytic reaction between the α,β -unsaturated diphenylallyl acetate and dimethylmalonate (Figure 33.).⁸⁵ The allylation is catalyzed by Pd(0)-MAP catalyst and the reaction takes place at room temperature.

Figure 33. Asymmetric allylic alkylation catalyzed by Pd-MAP catalyst system.

The reaction provided 71% ee under the optimum condition (using Cs₂CO₃ as base in DCM). The use of (R)-MAP led to the formation of (S) diphenylallyl malonate enantiomer. The various challenges and effects occurred during this type of reaction were also scrutinized and described by Kočovský and co-workers.^{83, 87-88}

Also, Kočovský and his colleagues described the utilization of MAP ligands in the C-N cross-coupling (or amination) initially developed by Buchwald and Hartwig. However, the emphasis of their research was not on achieving stereoselectivity, but on using MAP and MOP ligands as accelerating coordinating agents compared to BINAP (Figure 34.).⁸¹

Applied ligands:

BINAP, MOP and MAP

Figure 34. The application of MAP and other bidentates to accelerate the Buchwald-Hartwig amination of NOBIN.

The acceleration of the reaction is unequivocal: while the use of BINAP and MOP ligands led the reaction to take place under 1 or 2 hours to reach high conversion, MAP provided 100% conversion under 5 minutes at 60 °C in toluene. The explanation of the acceleration effect was explained above (Figure 32.).

In 2000, Buchwald and co-workers reported the enantioselective synthesis of axially chiral biaryls with the application of the Suzuki coupling protocol. The coupling reaction took place between a brominated naphthyl-diethyl phosphonate and *o*-tolylboronic acid, where the employed catalyst is Pd(0) with various chiral mono- and bidentate ligands (Figure 35.).⁸⁶

Ligand:

<u>R¹:</u>	<u>R²:</u>	<u>Conversion:</u>	<u>ee:</u>
Bu	Cy	100	54
SiMe ₃	Cy	100	23
NMe ₂	Cy	100	87
NMe ₂	<i>i</i> Pr	61	86
NMe ₂	Ph	76	75
NMe ₂	<i>t</i> Bu	73	81
PPh ₂	Ph	40	N/A

Figure 35. Suzuki coupling for producing functionalized axially chiral biaryls with the use of MAP and other mono-, and bidentates.

According to their results, the use of *P*-dicyclohexyl analogue of MAP ligand showed the highest stereoselectivity (87%) with total conversion, while *P*-diphenyl MAP and its butyl and trimethylsilyl monodentate derivatives and even BINAP was employed. Suzuki coupling is an essential reaction protocol for coupling drug fragments in pharmaceutical industry, thus, the relevance of this catalytic method depicted above is crucial in synthetic chemistry.

1.2.5.4. QUINAP ligand and its congeners

The last example to be covered is the axially chiral quinoline analogue of MAP, i.e., the QUINAP ligand and its derivatives (Figure 36).⁶⁶ The main characteristic difference of this ligand class compared to other classes is the sp^2 aromatic nitrogen as a coordinating moiety. The other donor atom is phosphorus as being part of a diarylphosphine group. The nitrogen atom can be incorporated in various heteroaromatic rings, such as isoquinoline (QUINAP), quinazoline (Quinazolinap), phthalazine (Pinap) or pyridine (PyPHOS)

Figure 36. The bidentate diphenylphosphinonaphthyl isoquinoline (QUINAP) ligand and some of its derivatives.

QUINAP was developed by John M. Brown, David Hulmes and their co-workers, and was reported in 1993.⁸⁹ The most relevant and characteristic type of reaction with regard to QUINAP is the asymmetric hydroboration/amination in which the contribution of Brown and his colleagues was beyond significant.

In 1999, Guiry reported Quinazolinap, as a quinazoline analogue of QUINAP, and it was successfully applied in the field of asymmetric hydroboration, allylic alkylation and of copper catalyzed borylation.⁹⁰⁻⁹¹

Pinap was synthesized and published by Carreira and co-workers in 2004 and was tested in various reactions, such as Rh-catalyzed hydroboration; asymmetric addition of

alkynes to imines catalyzed by copper(I); and in silver(I)-catalyzed enantioselective azomethine cycloaddition with high selectivity in every case.⁹²

The biphenyl type analogue of QUINAP is the also atropisomeric PyPHOS ligand designed by Chan and co-workers in 2002. This ligand first was also applied in enantioselective hydroboration with good yield and selectivity.⁹³

The original synthesis of QUINAP started with a Suzuki coupling between 1-chloroisoquinoline and 2-methoxynaphthalene boronic acid (Figure 37.).⁸⁹ The catalyst of the C-C coupling reaction was tetrakis(triphenylphosphine)palladium(0) and the reaction took place under basic conditions with the use of excess sodium carbonate. The methoxy group of the coupled product was converted to a hydroxyl group first, then to a triflate moiety to become a suitable leaving group. The triflate intermediate was then reacted with the oxide of diphenylphosphine in the presence of a catalytic amount of Pd(OAc)₂ to incorporate the phosphorus donor atom into the biaryl backbone. The last step before the resolution was the reduction of the phosphine oxide by using trichlorosilane to obtain the desired trivalent phosphine compound.

Figure 37. Synthetic scheme of racemic QUINAP via the procedure of Alcock et al.

For the resolution of the resulted QUINAP, chiral dimethylaminoethyl-naphthyl chloropalladacycle dimer complex was employed as an auxiliary compound. Upon the separation of the forming diastereomers via recrystallization, the pure QUINAP enantiomers were obtained by the removal of the chiral auxiliary with the chelating diphosphine ligand dppe in DCM (Figure 38.).

Figure 38. Resolution of racemic QUINAP by using naphthyl ethylamin chiral auxiliary.

It is worth mentioning that this synthetic pathway was later improved by applying different approaches carried out by researchers like Paul Knochel, Brian Stoltz or José Lassaletta.⁶⁶

Knochel's approach was to employ (–)-menthyl-(*S*)-*p*-toluene-sulfinate as an organic chiral auxiliary attached to the atropisomeric naphthyl-isoquinoline backbone and to perform the chromatographic separation of the resulting diastereomers (Figure 39.). This kind of separation is faster, more simple and more common in general laboratory practice compared to fractional recrystallization, which requires more time.⁹⁴

Figure 39. Resolution of the precursor of QUINAP by Knochel's approach.

The resulting enantiopure isomers were converted into phosphine sulfide derivatives afterwards by applying phenyllithium (PhLi), Ph₂PCl and sulfur. Sulfurization was used only to facilitate the subsequent purification processes. The resulting phosphine sulfide was then reduced to obtain the desired QUINAP enantiomers (Figure 40.).

Figure 40. Phosphination of the resolved naphthyl-isoquinoline sulfoxide enantiomer.

Stoltz and Virgil also reported a procedure on the enantioselective synthesis of QUINAP by exploiting dynamic kinetic resolution (DKR)⁹⁵ or more specifically the

dynamic kinetic asymmetric transformation (DYKAT).⁹⁶ This synthetic route is in fact a palladium catalyzed phosphination of the naphthyl moiety based on the atropisomerism of the starting material. The enantiomers of the substrate and the diastereomers of the palladium intermediates can change their chiral configuration during the process. Nevertheless, one of the diastereomers is favored in the phosphination step due to the chiral ligand applied in the P-C coupling. In this way, the enantioenriched QUINAP can be obtained from a racemic mixture in a single step (Figure 41.).⁹⁵

Figure 41. QUINAP synthesis by utilizing dynamic kinetic resolution reported by Stoltz and Virgil.

They employed bromine, triflate (OTf) or methanesulfonylbenzene sulfonate (OSs or sosyl) as starting materials and established that the triflate derivative provided the best results in their study. As it was mentioned, both the biaryl starting material and the palladium intermediate are able to change their configurations, however, in the case of the starting biaryl derivative, that is a much slower process than in that for the palladium compound. The transition state they proposed for the isomerization can be seen in Figure 42, where the isomerization takes place and assisted by the agostic interaction between an aromatic naphthyl hydrogen and the palladium.

Figure 42. The proposed transition state of the isomerization of the arylpalladium intermediate.

The optimized reaction scheme for Stoltz and Virgil's DKR to produce enantiopure QUINAP can be seen in Figure 43. The resolution provided 86% yield and 90% ee, which could be enhanced further by recrystallization.

Figure 43. The optimized resolution process for the synthesis of enantiopure QUINAP.

Lassaletta and colleagues also tackled the aforementioned dynamic kinetic resolution pathway by a similar approach, and they carried out a comprehensive mechanistic investigation on the mechanism of the resolution and isomerization. They broadened the substrate scope of the P,N synthesis, and also supported their observations with DFT calculations.⁹⁷ The phosphine reagent they used was diphenyl(trimethylsilyl)phosphine, of which the activity can be tuned by changing the substituents on the silyl group (Figure 44.).

Figure 44. Lassaletta's approach for the resolution and phosphination of the binaphthyl starting material of QUINAP.

They found that the aromatic nitrogen via its lone electron pair had a crucial role in the isomerization of the palladium intermediate on the one hand, and in the subsequent P-C bond formation itself on the other hand. This observation was proved by control experiments. One was carried out on a binaphthyl triflate substrate (where there was no coordinating aromatic nitrogen atom in the reaction mixture whatsoever), and nor the enantio-enrichment neither the P-C bond formation took place. They repeated the experiment with a NOBIN nonaflate derivative as a starting material, which, despite the presence of a coordinating nitrogen moiety, provided the same results i.e., the racemic hydroxyl product because of the subsequent hydrolysis (Figure 45.).

Figure 45. Control experiments for the mechanistic study of the DYKAT process.

The latter reaction clearly indicates that the presence of the aromatic nitrogen is necessary for the dynamic kinetic resolution step (that is to be able to isomerize), and the activation of palladium for the following, diastereoselective P-C bond formation. The palladium intermediate hence is a reactive five-membered palladacycle, which is

capable of switching its axially chiral configuration by virtue of the bent geometry occurs as a transition state of the isomerization (Figure 46.).

Figure 46. The DYKAT process reported and investigated comprehensively by Lassaletta and colleagues.

Upon the formation of the palladacycle via the addition of the $C(sp^2)$ -OTf to palladium, the P-C bond formation takes place via a transmetalation/ligand exchange step on the Pd(II) center followed by the reductive elimination which affords the enantiopure product.

They further scrutinized the differences between Stoltz's palladium TS with the proposed agostic interaction (Figure 42.) and the palladacycle intermediate. Beyond the experimental investigations, they used DFT analysis at B3LYP/6-31G** (LANL2DZ for Pd) level and among others, they defined the energy barrier for the interconversion of the palladacycle. The barrier turned out to be relatively low: 18.7 kcal/mol compared to the possible isomerization of the triflate starting material (Figure 47. a.)).

Figure 47. Computational analysis of some aspects of the resolution.

In addition, the calculated thermodynamic stability of the palladacycle intermediate is significantly higher (The calculated $\Delta\Delta G$ 9.3 kcal/mol lower) than that of the palladium TS proposed by Stoltz and Virgil (Figure 47. b.)).

Along with a deep computational study they focused on each mechanistic step of the reaction and the actual energy differences between the possible diastereomers and conformers during the transmetalation. Thus, they indeed reported an extensive study on QUINAP synthesis.

QUINAP ligand has numerous fields of application in asymmetric chemistry. The most important area is the hydroboration and amination of alkenes to obtain chiral alcohols and amines. Moreover, it also has crucial role in the fields of enantioselective borylation, allylic alkylation or alkyne addition to enamines for obtaining chiral propargylamines.⁶⁶ Asymmetric hydroboration is an important tool for synthesizing chiral secondary alcohols, as hydroboration itself has a remarkable history in olefin hydrofunctionalization in synthetic organic chemistry. John M. Brown and his co-workers have remarkable contribution in the area since they first published the use of QUINAP in the asymmetric process in 1993. Its advantage over BINAP is that the high selectivity QUINAP provides at room temperature (94% ee with *p*-methoxystyrene substrate) instead of applying -78°C .⁹⁸

In their 1995 paper they employed QUINAP and Phenap ligands in the rhodium catalyzed hydroboration protocol, and in some instances, they compared their performance to the Rh-BINAP catalyst system (Figure 48.).⁹⁹

Figure 48. Rh catalyzed hydroboration with the comparison of the performances of QUINAP, Phenap and BINAP catalyst complexes.

As it can be seen, BINAP provided high selectivity in the case of styrene, while the P,N analogues showed better performance in the hydroboration of other aromatic olefin derivatives. In some cases, the Phenap's phenanthridine backbone conveyed the chiral induction even more efficiently than QUINAP.

An alternative version of this reaction is the amination with the use of the boronic ester intermediate, where the resulting catecholboronate is quenched with amine source instead of basic hydroperoxide anion (Figure 49.).

Figure 49. Amination of olefins with Rh-QUINAP and catecholborane.

The amine source used in this reaction is the hydroxylamine-*O*-sulfonic acid (NH₂OSO₃H). The selective hydroboration and amination was demonstrated on the same set of vinylarene substrates as it was shown in Figure 48., and it provided high selectivity in each case as well.¹⁰⁰

Guiry and co-workers reported the β -borylation of α,β -unsaturated compounds in 2009 by using pinacol borane, Cu-QUINAP and other P,N ligand containing catalyst systems (Figure 50.).⁹⁰

Figure 50. Borylation of activated olefin by B₂Pin₂ and Cu-BINAP.

In this variant of hydroboration, the desired product is the boronate intermediate, that can be utilized further as substrate in various synthetic protocols. The reaction takes place with high conversion and good selectivity to afford chiral pinacol borane derivatives, which is a valuable starting material for Suzuki-Miyaura coupling for instance.

The last example to depict as an application of QUINAP, which is other than a boron-related catalysis, is the enantioselective synthesis of propargylamines reported by Knochel (Figure 51.).¹⁰¹ The C-C coupling was tested first with numerous metal salts, viz., Sc(OTf)₃, Yb(OTf)₃, Zn(OTf)₂ and Cu(I) and Cu(II) salts to establish that the optimum condition with the highest conversion can be achieved by using Cu(I) metal. After the metal source was found, they observed that QUINAP provided the highest selectivity (83 % in our example).

Figure 51. Enantioselective synthesis of chiral propargylamines.

Chiral propargylamines are important building blocks for biologically active compounds, thus, this reaction is a useful tool for the enantioselective synthesis.

1.3. Conclusion and Research Objectives

The evolution of the chemistry of bidentate ligands, and especially of their chiral counterparts made a magnificent contribution to the organometallic chemistry and catalysis. These coordinating agents and their transition metal complexes enabled us to access new reaction routes and catalytic pathways.

In our research group, the development of palladacycle complexes with bi- and tridentate coordinating organic moieties has a significant history. Many of these complexes have noteworthy catalytic activity as well. With this project, we aimed to expand our already established scope of catalyst complexes by switching the coordinating aromatic carbon atom to nitrogen to be able to apply transition metals with a broader range of oxidation states. Rhodium(I) and iridium(I) are the two, most important metal centers we intended to use in complexation reactions to obtain new complex frameworks with potential catalytic activity. Besides, we also considered it essential to synthesize palladium(II) and platinum(II) complexes primarily as model compounds to collect information comprehensively on their chemical features. Their comprehensive steric and electronic investigation has also been among our goals together with the testing of these new complex molecules in catalytic reactions.

CHAPTER 2: Asymmetric synthetic protocols for P,N ligand syntheses

Abstract

This chapter covers the development of the bidentate P,N ligand frameworks, viz., the dialkyl and diaralkyl malonates and the acrylophenone derivatives. The following unit starts with their organic syntheses from common building blocks through the application of enantioselective hydrophosphination reaction protocols to obtain the active phosphine compounds as potential ligands. Finally, the incorporation of the diphenylphosphine group was carried out via catalytic pathways, of which the thorough optimization is detailed in this part along with all the relevant observations and synthetic approaches.

2.1. Introduction – Literature background on asymmetric hydrophosphination

Our aim was to develop a chiral P,N coordinating moiety, so that we chose various enantioselective hydrophosphination protocols to selectively incorporate the coordinating phosphine group. Our group has significant experience in both stoichiometric and catalytic asymmetric hydrophosphination, hence, we considered to employ both approaches during the synthesis of the P,N ligand backbone.

Nevertheless, we had to take into consideration the possibility that these protocols might not afford enantiopure products in the first place, but enantioenriched mixtures, thus, the resolution of a possible P,N ligand had to be incorporated into our set of synthetic tools.

2.1.1. Stoichiometric asymmetric hydrophosphination

Although synthetic protocols for stoichiometric hydrophosphination of nitrogen containing substrates were established by our group in 2009,⁶³ an alternative pathway for obtaining a P,N coordination product via Diels-Alder cyclization was also reported by using DMPP (dimethyl-phenylphosphole) as a phosphorus source.¹⁰² In both cases, the chiral templates were the already mentioned C,N palladacycles (*R*)-**1** and (*S*)-**1a** (Figure 52.).

Figure 52. Syntheses of P,N coordinating moieties with the use of chiral template **1** and with utterly different synthetic approaches ((A) and (B)).

Synthetic pathway (B) is based on the intriguing [4+2]-type *exo*-selective cycloaddition reaction and it can be utilized in P-chiral tertiary phosphine syntheses, albeit pathway (A) is more relevant in this chapter.

The diastereoselective hydrophosphination of enone **2** provided 77.7% selectivity by the employment of **(R)-1** and led to an enriched diastereomer mixture, which could be separated further by column chromatography to afford the pure diastereomer product with 70% isolated yield. The reaction required 4 days to be complete.⁶³

In the reaction, the chiral induction occurs during coordination. The hydrophosphination can be seen in Figure 53. with the more favorable arrangement of reactants.

Figure 53. Favored interchelate arrangement upon coordination of the reactants to the chiral template **1**.

The key to the selectivity of the reaction is the preferred equatorial arrangement of the C(O)Ph moiety, which is positioned spatially remote to the equatorial P-phenyl group. The spatial proximity between the α hydrogen atom of the pyridyl ring (H_6) and the prochiral equatorial *N*-methyl group of the palladacycle **1** is unfavored, but still endurable as a minor steric constraint.⁶³

An interesting development on this synthesis was based on the observation that in the case of the ester and amide derivatives (**5**, **6**) of enone **2**, the regioselectivity can be controlled by the presence of base (Figure 54.).¹⁰³ In the absence of base, the hydrophosphination of ester **5** took seven days at room temperature, however, the same functionalization of amide **6** proved to be significantly slower (5 weeks at 40 °C). Hence, triethylamine was added to the mixture, which resulted in shorter reaction times (3 and four days, respectively for compounds **5** and **6**) and the aforementioned, significant regioselectivity.

Figure 54. Base controlled stoichiometric hydrophosphination of acryl ester **5** acrylamide **6**.

As it can be seen in the figure, the reaction without base resulted in the regioselective formation of the six-membered P,N chelate rings, as the phosphine moiety was incorporated into the α -position with respect to the carbonyl group (diastereomers (R,S)-**7** and (R,S)-**8**). In the case of (R,S)-**7** the diastereoselectivity was above 99% while in the case of palladacycle (R,S)-**8** the dr. was 18.9:1 (90% de).

For the base controlled alternative (when 0.4 equiv. of TEA was added to the reaction mixture) however regioselectively afforded 5-membered P,N chelate rings, as the β -carbon was functionalized (complexes (R,R)-**9** and (R,R)-**10**). The (R,R) diastereomer in the case of complex **9** was stereoselectively formed in the ratio of 1:6 (71% de), which resulted as 89% de in the case of the amide derivative **10**. The base controlled hydrophosphinations were carried out at rt in both cases.

The noteworthy advantages of such use of complexes (R) or (S)-**1** is that the resulting diastereomers or diastereomer mixtures are easier to purify, i.e., to be crystallized or separated by chromatography. Hence, the opportunity for the resolution process is given in these situations and it is less difficult in most of the cases when compared to enantiomeric mixtures. The other advantage is that the C,N palladacycle template **1** can be chemoselectively removed by acidic treatment to afford the desired chloro palladium enantiomer upon resolution.

2.1.2. Catalytic asymmetric hydrophosphination

The catalytic enantioselective hydrophosphination of activated enones (α,β -unsaturated substrates) was described first by Leung and co-workers and Duan and co-workers in 2010 (Figure 55.).¹⁰⁴⁻¹⁰⁵

Figure 55. Catalytic enantioselective hydrophosphination of *trans*-chalcone **11**.

Although, Leung's azapalladacycle catalyst **1** seemingly provides only moderately high selectivity, the resulting phosphines could be recrystallized successfully from DCM/acetone solvent system to obtain enantiopure products. It is also noteworthy that after the screening of various palladacycle catalysts to improve the catalytic performance in the reaction, the application of phosphapalladacycle **14** (Figure 56.) afforded the chalcone derivative **12** with high yield and selectivity (90% yield and 98% ee) by employing the same conditions. The use of *(R)*-**14** reduced the reaction time to 2 h from 23 h.⁵⁸

Figure 56. The C,P phosphapalladacycle applied in the hydrophosphination of *trans*-chalcone.

The mechanism of the Michael-type hydrophosphination catalyzed by palladacycles **1** and **14** can be seen in Figure 57.

Figure 57. The mechanism of the palladacycle catalyzed enantioselective hydrophosphination of activated olefins.

In the first step, the labile acetonitrile ligands are replaced by the coordinating diphenylphosphine molecules. Then, the oxo group of the activated olefin coordinates to the palladium(II) center in a certain position due to the stereodirecting P-phenyl substituents on the donor phosphine moiety (Figure 58.). Thus, the direction of the nucleophile attack of the deprotonated, coordinated diphenylphosphide is determined. The deprotonation of the phosphine is carried by the external base (TEA in this instance). Subsequently, the triethylammonium cation protonates the α carbon of the phosphinated substrate, which step is followed by its decoordination from the palladium center.

Figure 58. Steric interactions of the reactants occur around the Pd(II) center during the Michael-type hydrophosphination.

The enhanced reactivity of C,P complex **14** over C,N catalyst **1** can be attributed to the higher *trans* labilizing effect of the donor phosphorus atom compared to the coordinating nitrogen, and the lability of the occurring *trans* P–Pd–P species, which facilitates the elimination of the P,O-coordinating product.⁵⁸

Chiral catalyst **14** was then tested on a wide scope of similar activated substrates and proved to be very effective in enantioselective catalytic reactions.⁵⁹ According to the gathered experience on the asymmetric, Michael-type hydrophosphination of various activated substrates, the highest activation on a C=C double bond could be achieved by methylenemalonate ester derivatives. In our case, this was necessary to be considered, since we intended to apply the hydrophosphination protocol on a potentially coordinating, nitrogen containing system. In 2012, our group reported the hydrophosphination of benzyldienemalonate **15** with 96% selectivity (**A**, Figure 59.).¹⁰⁶ The enhanced reactivity of the substrate (**15**) resulted in the very low, 3.5 h of reaction time at $-80\text{ }^{\circ}\text{C}$. This finding had a crucial role in carrying out this project with the P,N ligand backbone synthesis.

In 2017, Li Xi-Rui et al. reported the hydrophosphination of the similar naphthylidenemalonate **17** to afford the chiral phosphine **18** with 91% ee under almost the same conditions (**B**, Figure 59.). The reaction time was a bit longer with the naphthyl moiety: it took 48 h with the optimized conditions.¹⁰⁷ The conversion was remarkably high in both cases.

Figure 59. Hydrophosphination unsaturated malonate esters by catalyst complex **14**.

An important example for the hydrophosphination reaction on aromatic nitrogen containing substrates is the synthesis of NC(sp³)E palladium pincer (tridentate) complexes where the starting material was a pyridine substituted diene derivative (Figure 60.).¹⁰⁸ The reaction yielded the phosphine sulfide product in 90% and the phosphine oxide product in 86%, and provided excellent (>99%) enantioselectivity.

Figure 60. Asymmetric hydrophosphination of pyridine derivative **19** by pincer catalyst **21**.

The curiosity of this reaction is the use of a different square planar palladium complex (R,R)-**21**. Based on our group's preliminary findings, the potential chelating substrates are able to lead to catalyst poisoning, which can occur in this case as beside the incorporated phosphine moiety, there is an also coordinating nitrogen atom in the formed product.¹⁰⁹ This factor becomes important when the applied catalyst complex possesses at least two, unoccupied coordination sites, thus, the bidentate chelation can also occur during the course of the catalytic cycle. The latter pincer type complex **21** has only one free, active coordination site during catalysis compared to palladacycle

complexes **1** and **14** with two active and available coordination sites. Thus, the tridentate catalyst complex **21** is not vulnerable to catalyst poisoning via chelation.¹⁰⁹ The other noteworthy feature of the pincer-type catalyst is that the use of that does not require additional or external base, because the coordinated acetate ligand dissociates as acetate anion during the catalytic process and acts as an internal base. This way on the other hand, the one active site becomes free on the palladium center to form the key oxa- π -allylpalladium intermediate.¹¹⁰

This protocol was applied in 2018 on the similar, activated isoquinoline (monoene) derivative with the use of the pincer complex **21**. The catalyst provided 99% of conversion and 96.6% of enantiomeric excess at $-40\text{ }^{\circ}\text{C}$ under 1 h in acetone.¹¹¹

2.2. Results and discussion

2.2.1. Synthesis of the activated, nitrogen-donor containing substrates

In order to build up the P,N coordinating moiety, two types of isoquinoline-based activated olefin structures were proposed. The first one was a dimethyl malonate-type compound and the second one was the isoquinoline acrylophenone (Figure 61.).

Figure 61. Substrates for asymmetric hydrophosphination to form the P,N backbone.

The dimethyl malonate derivative **22a** was used as a substrate in both catalytic and stoichiometric hydrophosphination, while olefin **23** was only applied as a starting material during the catalytic approach.

To build the activated double bond, we proposed to employ condensation reactions schemes, which require the reactive aldehyde functionality in the desired position. For this purpose, we started the synthesis of the P,N backbone with the functionalization of

isoquinoline **24** in a regioselective pathway by applying the Minisci reaction.¹¹² The reaction incorporated the formyl group into the 1st position of the isoquinoline ring with high selectivity via a radical pathway by using 90 equiv. of 1,3,5-trioxane as the formyl source (Figure 62.). It is noteworthy that the use of less trioxane did not provide the desired carbaldehyde.

Figure 62. Regioselective functionalization of isoquinoline.

The reaction required overnight reflux in acetonitrile with the use of $t\text{BuOOH}$ (TBHP), ferrous sulfate and TFA to obtain the cyclic acetal intermediate **25**. This acetal can be considered as a protected or ‘masked’ formyl group. The deprotection was then carried out in 20 w/w% HCl solution for one hour under reflux conditions, and the desired carbaldehyde **26** could be isolated with 49% overall yield.¹¹³

Another approach was reported in 2018 by Ganley et al., where the trioxane underwent a reaction with isoquinoline in the presence of $(n\text{Bu}_4\text{N})_2\text{S}_2\text{O}_8$ at 50 °C in dichloroethane (DCE). The resulting acetal was then deprotected with BCl_3 in 10 min in DCM (Figure 63.).¹¹⁴ The latter procedure was carried out as well but eventually it did not provide higher overall yield than the original pathway.

Figure 63. The recently published, alternative procedure for isoquinoline formylation.

2.2.1.1. Synthesis of malonate substrates **22a-d**

The malonate moieties were incorporated with the application of the original and modified Knoevenagel condensation.

In the case of the dimethyl derivative **22a**, classic Knoevenagel conditions proved to be successful. The procedure applied on carbaldehyde **26** was originally tailored to its carbo-aromatic (naphthyl) analogue, nevertheless smoothly provided the olefin product with acceptable yields (Figure 64.).¹¹⁵

Figure 64. Knoevenagel condensation between isoquinoline carbaldehyde and dimethyl malonate.

The condensation between dimethyl malonate and aldehyde **26** worked in the presence of the mixture of benzoic acid and *N*-methyl piperidine. The reaction mixture was refluxed in benzene overnight with the use of Dean-Stark apparatus, and the condensation trap of which contained molecular sieves to enhance the removal of the formed H₂O. After chromatographic purification, product **22a** was obtained in 52% yield as a brown solid.

The Knoevenagel condensation of the sterically more hindered diethyl, diisopropyl and dibenzyl malonates could only be carried out in the classic way in the case of the diisopropyl derivative **22c**, however, the yield was unsatisfactory. For this reason, it was necessary to look for other approaches. In 2006, Chen et al. reported a modified synthesis on the condensation between naphthaldehyde derivatives and *tert*-butyl malonate by using TiCl₄ as an effective Lewis acid (Figure 65.).

Figure 65. Lewis acid promoted condensation of sterically hindered malonates and aldehyde **26**.

The strong Lewis acid, TiCl_4 provided enough activation to promote the reaction, despite the presence of the potentially coordinating aromatic nitrogen in the starting material. The reaction was carried out at 0 °C when the reactants were added and was stirred further at rt until completion. The diethyl derivative **22b** could be synthesized with 29% yield, the diisopropyl product **22c** could be obtained with 38% yield and the dibenzyl derivative (**22d**) was synthesized with 22% yield after purification.

2.2.1.2. Synthesis of the acrylophenone substrate **23**

The isoquinoline acrylophenone **23** was synthesized with the utilization of the aldol condensation. The desired product was obtained from the reaction of carbaldehyde **26** and acetophenone at room temperature (Figure 66).¹¹⁶

Figure 66. Synthesis of isoquinoline acrylophenone by aldol condensation.

The reaction took place in ethanol in the presence of 10 m/m% aqueous NaOH and a few pieces of crushed ice chunks. After completion of the reaction and the subsequent purification the activated olefin could be obtained with 32% yield.

2.2.2. Asymmetric hydrophosphination of nitrogen containing substrates

2.2.2.1. Catalytic asymmetric hydrophosphination of isoquinoline malonate substrates 22a-d

To incorporate the coordinating diphenylphosphino group into the activated olefins we first applied the catalytic asymmetric hydrophosphination protocol. The applied catalysts were the bidentate ligand containing palladacycles **1** and **14** and the pincer type palladium complex **21** (Figure 67.) as well, to establish the optimum condition of the reaction. We also employed Pd(OAc)₂ as catalyst, which was necessary to obtain the racemic mixture of products, as reference data for the HPLC measurements to determine the ee-s.

Figure 67. The applied palladacycle catalysts in the hydrophosphination of substrates 22a-d.

The screening of conditions was carried out according to a report from 2012 on the catalytic hydrophosphination of methylenemalonate derivatives.¹⁰⁶ The general scheme and the optimization of the reaction can be seen in Table 4. Based on previous experience, we expected the pincer type catalyst **21** to be the more effective one because of the previously discussed considerations. However, C,P catalyst **14** was also employed during the optimization combined with 1.0 equiv. of TEA as an external base. The conversion of the hydrophosphination reactions was monitored by ³¹P{¹H} NMR spectroscopy; the stereoselectivity in each case was determined by chiral HPLC. The yields indicated in the tables are isolated yields obtained after the purification of the products by column chromatography.

Table 4. Optimization of conditions for the hydrophosphination of malonate **22a**.

Entry	Catalyst ^a	Solvent	<i>T</i> / °C	<i>t</i> / h	Quenching	Conversion ^b	Yield ^c	ee ^d
1	Pd(OAc) ₂	DCM	25	1	H ₂ O ₂ (aq)	100%	39%	-
2	(<i>S</i>)- 14	DCM	25	3	H ₂ O ₂ (aq)	100%	52%	-
3	(<i>S</i>)- 14	DCM	-80	45	H ₂ O ₂ (aq)	99%	81%	-
4	Pd(OAc) ₂	DCM	25	2	S ₈	100%	66%	0%
5	(<i>R,R</i>)- 21	THF	-40	96	S ₈	17%	22%	6.1%
6	(<i>R,R</i>)- 21	toluene	-40	96	S ₈	18%	37%	0.1%
7	(<i>R,R</i>)- 21	acetone	-40	144	S ₈	58%	46%	7.7%
8	(<i>R,R</i>)- 21	DCM	25	18	S ₈	100%	57%	1%
9	(<i>R,R</i>)- 21	DCM	-40	24	S ₈	(60%)	50%	2.5%
10	(<i>S,S</i>)- 21	Acetone	-40	116	S ₈	NA	23%	2.3%
11	(<i>S</i>)- 14	DCM	25	5	S ₈	100%	74%	5.5%
12	(<i>S</i>)- 14	THF	-80	55	S ₈	50%	76%	2.0%
13	(<i>S</i>)- 14	toluene	-80	17	S ₈	100%	69%	2.3%
14	(<i>S</i>)- 14	CHCl ₃ / DCM	-80	31	S ₈	100%	95%	3.6%
15	(<i>S</i>)- 14	MeOH	-80	22	S ₈	63%	44%	7%
16	(<i>S</i>)- 14	acetone	-80	192	S ₈	70%	65%	44%
17	(<i>S</i>)- 14	DCM	-80	192	S ₈	78%	86%	82%
18	(<i>S</i>)- 1	acetone	-80	120	S ₈	26%	7%	21%
19	(<i>S</i>)- 14	DCM	-40	240	S ₈	69%	99%	25%
20	(<i>S</i>)- 14	DCM	-60	168	S ₈	61%	72%	49%
21	(<i>R</i>)- 14	DCM	-80	74	S ₈	NA	60%	55%

^aThe catalyst loading was 5 mol% in each case. For catalysts (*S*)-**1** and (*S*)-**14**, TEA was used as external base. ^bBased on ³¹P{¹H} NMR spectroscopy measurements. ^cIsolated yields. ^dDetermined by chiral HPLC.

When the testing of the protocol on substrate **22a** was being carried out (entries 1-3, Table 4.), hydrogen peroxide was used for quenching the air-sensitive phosphine intermediate **27**. Nonetheless, it turned out that the formed phosphine oxide **27a** was so

polar that it made the HPLC measurements and even the preliminary purification by column chromatography very difficult. For this reason, it was decided to apply sulfurization to convert the phosphine **27** to an easily manageable compound (**27b**). The ‘naked’ phosphine intermediate **27** could be observed as a singlet at 3.98 ppm (DCM, 162 MHz), and the conversion was established by the integral ratios of the starting diphenyl phosphine and the product **27**. The $^{31}\text{P}\{^1\text{H}\}$ NMR signal of phosphine oxide **27a** occurred at 30.1 ppm, while the chemical shift of the phosphine sulfide **27b** was at 48.7 ppm (CDCl_3 , 202 MHz).

Since there were serious expectations towards the pincer catalyst’s (**21**) activity and selectivity, a screening was carried out by using various solvents and temperatures. The other advantage of **21** beside the fact that it does not require additional base is that it showed optimum selectivity at rt or 0 °C, thus the use of very low temperature conditions was not necessary.^{117, 108} However, in many cases –40 °C proved to be the best condition for the pincer complex¹¹¹, so that both room temperature and lower were applied. To our surprise, complex **21** neither delivered high yields nor high selectivities (entries 5-10, Table 4.). In contrary, the C,P palladacycle **14** turned out to be more efficient at –80 °C: it provided significantly higher yields and stereoselectivity. Among the various solvents tried out, acetone and DCM proved to be the best two with regard to the ee values. By using acetone, the yield was 65% and the selectivity was 44%, while by using DCM the yield was 86%, and the enantioselectivity was 82% (entries 16-17, Table 4.). Neither the use of highly polar (MeOH, entry 15, Table 4.) or highly apolar (toluene, entry 13) solvents, nor solvent mixtures (chloroform/DCM, entry 14, Table 4.) afforded higher values for the ee or the yield. A possible pattern regarding the effect of solvent polarity on the selectivity of the reaction could not be observed.

In entries 11, 19 and 20 in Table 4. the temperature dependence was screened, and it clearly showed that increasing the temperature proportionally deteriorates the ee, while enhances the conversion possibly due to promotion of non-catalyzed side reactions under basic conditions.

Although, the optimum condition was successfully determined, a few questions regarding the reaction remained unanswered. Such questions are the time dependence of the reaction, the influence of the applied base on the reactivity or the effect of the catalyst loading. For this reason, we continued to scrutinize the hydrophosphination by further evaluating and fine tuning the previously optimized conditions. The optimized

conditions of the reaction allowed us to employ the protocol on modified diester substrates **22b-d** as well (Table 5.).

Table 5. Investigation of the additional effects occurred during the asymmetric hydrophosphination of substrate **22a** and the application of the optimized condition on substrates **22b-d**.

Entry	R	Catalyst loading (<i>(S)</i> -14)	Base	<i>T</i> / °C	<i>t</i> / h	Conversion ^a	Yield ^b	ee ^c
1	Me	10 mol%	TEA	−80	66	57%	75%	71%
					115	67%	91%	67.5%
					167	(44%)	70%	63.5%
2	Me	20 mol%	TEA	−80	19 days	63%	-	-
3	Me	5 mol%	-	−80	-	-	-	-
4	Me	5 mol%	10 mol% NaOAc	−80	-	-	-	-
5	Me	5 mol%	10 mol% TEA	−80	-	-	-	-
6 ^d	Me	5 mol%	TEA + H ₂ O	−80	216	32%	(44%)	57%
7	Me	5 mol%	DBU	−80	72	100%	60%	0%
8	Me	No cat.	TEA	rt	5d	100%	- ^e	0%
9	Et	5 mol%	TEA	−80	264	54%	58%	25%
10	<i>i</i> Pr	5 mol%	TEA	−80	216	<10%	-	-
11	Bn	5 mol%	TEA	−80	288	52%	64%	61%

^aBased on ³¹P{¹H} NMR spectroscopy measurements. ^bIsolated yields. ^cDetermined by chiral HPLC. ^dAt this entry the applied solvent was acetone. ^eNot isolated.

The first observation, which needs greater discussion, is the time-dependence of the reaction. As it can be seen in Table 4., the conversion values based on ³¹P{¹H} NMR spectroscopy are not 100% even in the case of the optimized condition after 192 h. The

highest values for the selectivity at entries 16 and 17 (Table 4.) are 70% and 78%, respectively, which also requires explanation.

To answer this question, we monitored the change of the yield and ee of the reaction by removing and working up aliquot amounts of the reaction mixture after 66 h, 115 h and 167 h (entry 1, Table 5.). Also, in entry 2 (Table 5.), we considered to continue to monitor the reaction for longer times to investigate how the conversion proceeds. Based on these two approaches, we concluded that the reaction reached a maximum conversion value after 66 hours approximately and provided good yield (75%) and selectivity (71%). Longer reaction times cause similar or lower selectivity and fluctuation in the isolated yields. It probably occurs because of not yet clarified side processes during the reaction. Entry 2 in Table 5. revealed that after even extremely elongated reaction times (19 days) the conversion did not change significantly but stagnated. This implies that the catalyst cannot promote the process after a certain conversion value by even applying higher catalyst loadings (10% and 20% in entries 1 and 2, Table 5.). Based on this, we hypothesized that the key to this problem is the forming P,N intermediate **27** itself, which sets back the catalytic cycle by coordination. The P,N compound **27** probably needs to reach a certain concentration to act as a catalyst inhibitor. Later, we modelled this assumption by using the C,N palladacycle **1**, which will be elaborated in Chapter 3.

The screening of the applicable bases was also carried out in entries 3-5 (Table 5.). The substrate (and the formed phosphine) contains a weakly basic aromatic nitrogen, so that the reaction was monitored without the use of base as well, but there was no noticeable conversion in this experiment (Entry 3, Table 5.). Sodium acetate, as a weaker base compared to TEA was also tried out at lower concentration (10 mol%), as its conjugate acid's pK_a value is 4.76, while in the case of the protonated TEA this value is 10.75.¹¹⁸ The 10 mol% of NaOAc could not provide enough basicity to promote the reaction, moreover, the subsequent addition of 10 mol% TEA also proved to be insufficient: the conversion of the reaction reached 20-25% but it failed to proceed beyond this point. The addition of 1.0 equiv. of TEA remarkably increased the conversion. We also intended to use a stronger base than TEA, so that we applied 1.0 equiv. of DBU (entry 7, Table 5.) For comparison, the pK_a value of the protonated DBU is 12.¹¹⁸ The conclusion from the base screening results that at least 1.0 equiv. of TEA is necessary for the reaction to provide reasonable conversion. The use of stronger base (DBU) led

to 100% conversion in 72 h, however, there was no selectivity in the reaction whatsoever. The explanation for that result is the presence of the base catalyzed, non-asymmetric hydrophosphination process, which runs in parallel to the metal-catalyzed selective reaction pathway. This could indeed be observed at room temperature, when no metal catalyst was used: the reaction slowly processed towards full conversion in a few days, in the presence of 1.0 equivalent of TEA only and in the absence of any metal catalyst (entry 8, Table 5). In conclusion, at $-80\text{ }^{\circ}\text{C}$ the 1.0 equiv. of TEA is necessary to promote the reaction by providing the sufficient basicity; however, the reaction at this temperature still remains essentially palladium catalyzed. In the case of DBU, its base strength is significantly higher, so that the base promoted process becomes the dominating one even at $-80\text{ }^{\circ}\text{C}$.

The forming P,N intermediate **27** bears an acidic proton at the α position with respect to the ester groups. We presumed that this acidic proton in the basic medium could potentially lead to side reactions via an acid-base equilibrium. This could affect the conversion or/and the stereoselectivity. For this reason, at entry 6 we added 1.0 equiv. of H_2O to the reaction (in this case the reaction was carried out in acetone). However, this modification did not change the outcome of the reaction significantly, thus, we concluded that the possible effect of an occurring acid-base interaction was not likely.

The established protocol was then employed on differently substituted diesters (**22b-d**) with varying results. In entry 9 (Table 5.), the hydrophosphinated diethyl malonate **27c** formed with relatively good yield (58%), however, the selectivity was low (25%). In the case of the diisopropyl substrate **22c**, reasonable conversion could not be observed even after 9 days under these conditions. However, despite the significant steric hindrance (the bulky benzyl groups) incorporated in substrate **22d**, the dibenzyl malonate product **27d** successfully formed and afforded 64% yield and surprisingly respectable selectivity (ee: 61%).

2.2.2.2. Stoichiometric asymmetric hydrophosphination of malonate **22a**

In order to further improve the selectivity hydrophosphination of substrate **22a**, we intended to apply different approaches to incorporate the phosphine moiety. For this purpose, we considered to try out the stoichiometric hydrophosphination protocol mediated by the C,N palladacycle **1**. The protocol we applied was based on our previous report from 2015 on obtaining the pyridine derived P,N coordinating compounds.¹⁰³ In our case, substrate **22a** was the starting material along with diphenylphosphine, and 1.0 equivalent of azapalladacycle template (*R*)-**1** was employed to promote the reaction in the presence of TEA (Table 6.). It is noteworthy that in the absence of TEA, the reaction did not take place.

Table 6. Stoichiometric hydrophosphination of dimethyl malonate **22a**.

Entry	<i>T</i> / °C	<i>t</i> / days	Conversion ^a	de	(<i>S,R</i>)- 28 : (<i>R,R</i>)- 28 ratio ^a
1	25	1	100%	25%	0.6 : 1
2	0	3	100%	45%	0.38 : 1

^aBased on ³¹P{¹H} NMR measurements.

The reaction led to diastereomer formation ((*R,R*)-**28** and (*S,R*)-**28**), thus, the selectivity of the reaction could be easily determined by the integration of the distinct singlet peaks of the diastereomers by using ³¹P{¹H} NMR spectroscopy. The ³¹P{¹H} chemical shift

of diastereomer (*R,R*)-**28** occurred at 57.75 ppm (CDCl₃, 202 MHz), while the chemical shift of the other diastereomer (*S,R*)-**28** could be observed at 62.8 ppm (DCM, 162 MHz). The reaction was carried out at rt and at 0 °C as well.

At room temperature, the reaction was completed in 1 day with full conversion but provided only 25% diastereomer excess (de). The same reaction at 0 °C took place in 3 days with 100% conversion with 45% de. In conclusion, the reaction did not afford better selectivity in generating the phosphine **27** than the catalytic pathway.

The formed diastereomers (**28**) were used in further studies to carry out the resolution of the P,N compound **27**. The details on the crystallization method, characterization and isolation protocols are described in Chapter 3 together with the identification of diastereomers and the configuration of the stereogenic centers.

2.2.2.3. Catalytic hydrophosphination of the acrylophenone substrate **23**

We attempted to apply the catalytic hydrophosphination reaction on substrate **23** by employing both the bidentate C,P catalyst (*S*)-**14** and the pincer complex (*R,R*)-**21** (Table 7. and Figure 68.). During this scrutiny, we faced a somewhat interesting outcome.

In Chapter 3.2.4.3., we describe the synthesis of the dichloropalladium complex (**54**) derived from the naked P,N coordinating moiety **29a**. Interestingly, the X-ray crystallographic measurement on the palladium complex **54** showed that the addition of the diphenylphosphine group took place on the α -carbon atom with respect to the carbonyl group (Figure 68.).

Figure 68. Catalytic asymmetric hydrophosphination of acrylophenone substrate **23**.

This result is exceptional and unique compared to that we observed during the research of various catalytic hydrophosphination protocols. It was described in Chapter 2.1.1. that stoichiometric hydrophosphination protocols provided six-membered P,N chelate

rings in certain cases via phosphine addition on the α carbon, albeit we have not witness this result under catalytic conditions. It is also surprising that this result was experienced in cases of **5** pyridyl acrylate and **6** acrylamide, but not for the pyridyl acrylophenone derivative (**2**).

Our attempts for the catalytic hydrophosphination of substrate **23** can be seen in Table 7. The reactions were monitored by $^{31}\text{P}\{^1\text{H}\}$ spectroscopy. The product was quenched with S_8 in each case and the enantiomer purity of the sulfurized product (**29**) batches were determined by chiral HPLC.

Table 7. Attempt for the optimization of the catalytic hydrophosphination of **23**.

Entry	Catalyst ^a	Solvent	<i>T</i> / °C	<i>t</i> / h	Conversion ^b	Yield ^c	ee ^d
1	(<i>R,R</i>)- 21	DCM	−40 °C	16 days	>85%	23%	1.5%
2	(<i>S</i>)- 14	DCM	rt	96	100%	53%	3.6%
3	(<i>R,R</i>)- 21	DCM	rt	8-10	100%	47%	1.1%
4	Pd(OAc) ₂	DCM	rt	8-10	100%	40%	0%

^aThe catalyst loading was 5%. ^bBased on $^{31}\text{P}\{^1\text{H}\}$ NMR spectroscopy measurements.

^cIsolated yields. ^dDetermined by chiral HPLC.

Unfortunately, despite the conversion of the reaction being satisfactory in each case, neither of the employed catalysts could deliver high stereoselectivity.

The other hurdles that arose during the beginning of the screening were the overly high reaction times. At entry 3 (Table 7.) the pincer type catalyst (*R,R*)-**21** afforded close to 0% of selectivity in 8-10 hours, at reduced temperature (−40 °C) it provided the same result in 16 days, and the conversion was not 100% either (entry 1).

In the case of (*S*)-**14**, the reaction time was already 96 h at rt, yet it is not remotely the optimum temperature for the C,P catalyst **14** (entry 2, Table 7.). Further cooling of the reaction led to an extremely slow process.

It is also worth mentioning that at entry 4 (Table 7.), Pd(OAc)₂ could only give full conversion at rt in 8-10 hours, although in usually this non-asymmetric catalyst delivers the racemic products rapidly with high yields.

Nevertheless, these findings may lead us to continue to investigate the extraordinary outcome of this reaction, and to overcome the arising obstacles in achieving good selectivity in the future.

2.3. Summary and conclusion

In this section, we described the challenges and different approaches adopted (stoichiometric and catalytic) towards obtaining P,N coordinating moieties in an enantioselective manner. Malonate derivatives, especially the dimethylmalonate one could be achieved with good selectivity and yield, which let us use the established protocol to synthesize enantioenriched metal complexes. The difficulties and surprising results we faced during the selective synthesis of the acrylophenone P,N sulfide derivative are stated and described, however, further investigation on the hydrophosphination of this substrate will be carried out as a future project. It is important to mention that since nitrogen containing substrates proved to be challenging starting materials for catalytic hydrophosphination protocols, our findings on this matter may be valuable to help overcome similar problems in the field.

2.4. Experimental section

For preparing and handling air-sensitive phosphines and complexes, positive nitrogen and argon flow was used (standard Schlenk-techniques). Solvents were degassed previously for all reactions and measurements when it was necessary. Reagents for carrying out synthetic steps were purchased for Sigma Aldrich, TCI, Strem, Alfa Aesar, Acros Organics. Purifications by flash column chromatography were carried out on Merck Silica Gel 60.

For the NMR data Bruker AV500 (¹H 500.1 MHz, ¹³C 125.7 MHz, ¹⁹F 470.6 MHz, ³¹P 202.4 MHz), Bruker AV400 and BBFO 400 (¹H 400.1 MHz, ¹³C 100.6 MHz, ¹⁹F 376.5 MHz, ³¹P 162.0 MHz) instruments were used for the characterization of new compounds and the coordination study. Chemical shifts were reported in ppm by using internal standard TMS for ¹H NMR measurements, CDCl₃ for ¹³C NMR measurements, external standard H₃PO₄ for ³¹P{¹H} NMR-measurements and CCl₃F for ¹⁹F NMR-

measurements. HRMS data was recorded on Waters Q-TOF Premier spectrometer by using ESI positive mode. Elemental Analysis was carried out on PerkinElmer CHNS/O Series II 2400 EA instrument. The determination of ee was performed on Agilent 1200 Series chromatograph with Daicel Chiralpack ID and IF columns in n-hexane-isopropanol solvent system. Optical rotation measurements were performed on Jasco P-1030 polarimeter using the D-lines of sodium (589 nm) as light source.

2.4.1. Preparation of isoquinoline-1-carbaldehyde (26)

Isoquinoline (5.4 mmol, 0.70 g, 1.0 equiv.) was dissolved in 35 ml acetonitrile, then trioxane (488.6 mmol, 44.01 g, 90.0 equiv.), *tert*-butyl hydroperoxide (11.13 mmol, 1.02 g, 2.1 equiv.), trifluoroacetic acid (5.4 mmol, 0.62 g, 1.0 equiv.) and iron(II)sulfate (0.27 mmol, 0.04 g, 0.05 equiv.) were added and the solution was refluxed overnight. After the reaction was complete (monitored by TLC), volatiles were removed by evaporation, saturated sodium bicarbonate solution was poured on the residue and extracted with diethyl ether. The organic layer was then washed with brine, dried and evaporated.

The isolated crude acetal was refluxed at 110 °C in 20 m/m% HCl solution for one hour and neutralized at 0 °C with sodium carbonate. The aqueous solution was extracted with dichloromethane, the organic layer was washed with brine, dried and evaporated. The obtained crude material was purified with flash column chromatography on silica gel (*n*-hexane/ethyl acetate 2:1 to 1:1) to collect the pure product.

26 red-brown solid. Yield: 49%.

¹H NMR (500 MHz, CDCl₃) δ 10.40 (s, 1H, *CHO*), 9.32 (dd, ³*J*_{HH} = 8.4, 4.3 Hz, 1H, *ArH*), 8.76 (d, ³*J*_{HH} = 5.5 Hz, 1H, *ArH*), 7.97 – 7.84 (m, 2H, *ArH*), 7.83 – 7.75 (m, 2H, *ArH*); **¹³C NMR** (126 MHz, CDCl₃) δ 195.68 (s, 1C, *CHO*), 149.85 (s), 142.47 (s), 136.91 (s), 130.79 (s), 130.06 (s), 126.96 (s), 126.36 (s), 125.75 (s), 125.52 (s). **HRMS** (+ESI) *m/z*: (*M* + *H*)⁺ calc'd for C₁₀H₈NO, 158.0606; found, 158.0608. **Anal.** Calc'd for C₁₀H₇NO: C, 76.42; H, 4.49; N, 8.91. Found: C, 75.76; H, 4.77; N, 8.73%.

2.4.2. Preparation of dimethyl 2-(isoquinolin-1-ylmethylene)malonate (**22a**)

26 carbadehyde (5.60 mmol, 0.89 g, 1.0 equiv.) and dimethyl malonate (6.52 mmol, 0.86 g, 1.15 equiv.) were dissolved in 40.0 ml benzene and heated to reflux temperature. *N*-methyl piperidine (0.85 mmol, 0.08 g, 0.15 equiv.) and benzoic acid (0.42 mmol, 0.05 g, 0.075 equiv.) were dissolved in 10.0 ml benzene and added to the boiling solution of the starting material and the malonate. The solution was refluxed overnight with the use of Dean-Stark apparatus and 4 Å molecular sieve. After the reaction was complete, saturated aqueous sodium bicarbonate was added to the solution and extracted with DCM. The combined organic layer was washed with brine, dried and evaporated. The residue was purified with column chromatography on silica gel (*n*-hexane/ethyl acetate 4:1 to 2:1) to afford the pure diester.

22a yellow-brown solid. Yield: 52%.

¹H NMR (500 MHz, CDCl₃) δ 8.57 (s, 1H, ArH), 8.55 (d, ³J_{H-H} = 5.5 Hz, 1H, ArH), 8.31 (d, ³J_{H-H} = 8.4 Hz, 1H, ArH), 7.87 (d, ³J_{H-H} = 8.0 Hz, 1H, C=CHAr), 7.78 – 7.60 (m, 3H, ArH), 3.92 (s, 3H, COOCH₃), 3.90 (s, 3H, COOCH₃); **¹³C NMR** (126 MHz, CDCl₃) δ 167.22 (s, 1C, C=O), 164.43 (s, 1C, C=O), 150.11 (s, 1C, N=C-CH), 142.40 (s), 136.54 (s), 136.11 (s), 130.39 (s), 130.30 (s), 128.23 (s), 127.78 (s), 127.53 (s), 123.89 (s), 122.49 (s), 52.92 (s, 1C, COOCH₃), 52.45 (s, 1C, COOCH₃). **HRMS** (+ESI) *m/z*: (M + H)⁺ calc'd for C₁₅H₁₄NO₄, 272.0923; found, 272.0923. **Anal.** Calc'd for C₁₅H₁₃NO₄: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.15; H, 4.15; N, 5.16%.

2.4.3. General procedure for the preparation of diethyl, diisopropyl and dibenzyl 2-(isoquinolin-1-ylmethylene)malonates (**22b-d**)

TiCl₄ (2.0 mmol, 2.1 equiv.) was dissolved in 1.5 ml CCl₄ and this solution was added dropwise to 12 ml THF at 0 °C. Upon the yellow adduct appeared, **26** carbadehyde (0.95 mmol, 1.0 equiv.) and the corresponding malonate (0.95 mmol, 1.0 equiv.) were dissolved in 2.0 ml THF and added to the TiCl₄ solution dropwise. THF solution of pyridine (16.0 mmol, 16.6 equiv.) was also added to the reaction mixture, which then was stirred under nitrogen at 0 °C for 1 hour and further at rt until the reaction was complete. Upon completion the reaction mixture was quenched with 10.0 ml H₂O, then 20.0 ml ethyl acetate and Na₂CO₃(aq.) were added (to adjust the pH to neutral), and the

solution was extracted with ethyl acetate. The organic layer was further washed with NaHCO_3 and brine, then dried and evaporated. The resulting diester was the purified with column chromatography on silica gel (*n*-hexane/ethyl acetate 5:1 to 1:1) to obtain the pure product.

2.4.3.1. Diethyl 2-(isoquinolin-1-ylmethylene)malonate (**22b**)

22b is a brown oil. Yield: 29%.

^1H NMR (500 MHz, CDCl_3) δ 8.53 (d, $^3J_{\text{H-H}} = 5.6$ Hz, 1H, ArH), 8.52 (s, 1H, ArH), 8.28 (d, $^3J_{\text{H-H}} = 8.5$ Hz, 1H, ArH), 7.85 (d, $^3J_{\text{H-H}} = 8.0$ Hz, 1H, C=CHAr), 7.74 – 7.62 (m, 3H, ArH), 4.39 (q, $^3J_{\text{H-H}} = 7.2$ Hz, 2H, OCH_2CH_3), 4.37 (q, $^3J_{\text{H-H}} = 7.2$ Hz, 2H, OCH_2CH_3), 4.22 (q, $^3J_{\text{H-H}} = 7.15$ Hz, 1H), 1.38 (t, $^3J_{\text{H-H}} = 7.2$ Hz, 3H, OCH_2CH_3), 1.31 (t, $^3J_{\text{H-H}} = 7.15$ Hz, 3H, OCH_2CH_3), 1.24 (t, $^3J_{\text{H-H}} = 7.1$ Hz, 1H). **^{13}C NMR** (126 MHz, CDCl_3) δ 166.57 (1C, C=O), 164.05 (1C, C=O), 150.44 (1C, N=C-CH), 142.21 (s), 136.47 (s), 135.52 (s), 131.17 (s), 130.32 (s), 128.12 (s), 127.68 (s), 127.48 (s), 123.99 (s), 122.29 (s), 61.90 (1C, $\text{COOCH}_2\text{CH}_3$), 61.34 (1C, $\text{COOCH}_2\text{CH}_3$), 14.16 (1C, $\text{COOCH}_2\text{CH}_3$), 14.03 (1C, $\text{COOCH}_2\text{CH}_3$). **HRMS** (+ESI) m/z : ($\text{M} + \text{H}$) $^+$ calc'd for $\text{C}_{17}\text{H}_{18}\text{NO}_4$, 300.1236; found, 300.1236.

2.4.3.2. Diisopropyl 2-(isoquinolin-1-ylmethylene)malonate (**22c**)

22c is a brown oil. Yield: 38%

^1H NMR (400 MHz, CDCl_3) δ 8.52 (d, $^3J_{\text{H-H}} = 5.6$ Hz, 1H, ArH), 8.47 (s, 1H, ArH), 8.29 (d, $^3J_{\text{H-H}} = 8.5$ Hz, 1H, ArH), 7.85 (d, $^3J_{\text{H-H}} = 7.6$ Hz, 1H, ArH), 7.76 – 7.63 (m, 3H, ArH), 5.32 (hept, $^3J_{\text{H-H}} = 6.3$ Hz, 1H, $\text{COOCH}(\text{CH}_3)_2$), 5.22 (hept, $^3J_{\text{H-H}} = 6.2$ Hz, 1H, $\text{COOCH}(\text{CH}_3)_2$), 1.36 (d, $^3J_{\text{H-H}} = 6.3$ Hz, 6H, $\text{COOCH}(\text{CH}_3)_2$), 1.32 (d, $^3J_{\text{H-H}} = 6.2$ Hz, 6H, $\text{COOCH}(\text{CH}_3)_2$), 1.28 – 1.20 (m, 1H), 1.16 (d, $^3J_{\text{H-H}} = 6.3$ Hz). **^{13}C NMR** (126 MHz, CDCl_3) δ 166.00 (s, 1C, C=O), 163.60 (s, 1C, C=O), 150.66 (s, 1C, N=C-CH), 142.05 (s), 136.44 (s), 134.92 (s), 131.97 (s), 130.27 (s), 128.04 (s), 127.63 (s), 127.45 (s), 124.09 (s), 122.16 (s), 69.59 (s), 69.54 (s, 1C, $\text{COOCH}(\text{CH}_3)_2$), 68.77 (s), 68.69 (s, 1C, $\text{COOCH}(\text{CH}_3)_2$), 21.78 (s, 2C, $\text{COOCH}(\text{CH}_3)_2$), 21.61 (s, 2C, $\text{COOCH}(\text{CH}_3)_2$). **HRMS** (+ESI) m/z : ($\text{M} + \text{H}$) $^+$ calc'd for $\text{C}_{19}\text{H}_{22}\text{NO}_4$, 328.1549; found, 328.1548.

2.4.3.3. Dibenzyl 2-(isoquinolin-1-ylmethylene)malonate (**22d**)

22d is a brown solid. Yield: 22%.

¹H NMR (500 MHz, CDCl₃) δ 8.57 (s, 1H, ArH), 8.33 (d, ³J_{H-H} = 5.5 Hz, 1H, ArH), 8.26 (d, ³J_{H-H} = 8.4 Hz, 1H, ArH), 7.84 (d, ³J_{H-H} = 8.1 Hz, 1H, C=CHAr), 7.74 – 7.58 (m, 3H, ArH), 7.42 – 7.33 (m, 5H, ArH), 7.33 – 7.26 (m, 6H, ArH), 5.35 (s, 2H, benzyl CH₂), 5.34 (s, 2H, benzyl CH₂). **¹³C NMR** (126 MHz, CDCl₃) δ 166.44 (s, 1C, C=O), 163.82 (s, 1C, C=O), 150.07 (s, 1C, N=C-CH), 142.29 (s), 136.48 (s), 136.35 (s), 135.59 (s), 135.49 (s), 130.43 (s), 130.35 (s), 128.66 (s), 128.63 (s), 128.50 (s), 128.44 (s), 128.31 (s), 128.20 (s), 128.17 (s), 128.14 (s), 128.05 (s), 128.00 (s), 127.71 (s), 127.51 (s), 127.25 (s), 123.90 (s), 122.42 (s), 67.38 (s, 1C, benzyl CH₂), 67.22 (s, 1C, benzyl CH₂). **HRMS** (+ESI) m/z: (M + H)⁺ calc'd for C₂₇H₂₂NO₄, 424.1549; found, 424.1549.

2.4.4. Preparation of (E)-3-(isoquinolin-1-yl)-1-phenylprop-2-en-1-one (**23**)

Carbaldehyde **26** (1.27 mmol, 200 mg, 1.0 equiv.) and acetophenone (1.27 mmol, 152 mg, 1.0 equiv.) were dissolved in 15.0 cm³ ethanol, then NaOEt (0.25 mmol, 13.7 mg, 0.2 equiv.) dissolved in 3.0 cm³ EtOH and added dropwise to the reaction mixture and stirred at rt. The reaction was complete after 2 h according to TLC. The solvent was removed by evaporation and the crude residue was filtered through silica gel and purified by column chromatography by using hexane/EA 5:1 eluent system.

23 is an off-white solid. Yield: 32%

¹H NMR (500 MHz, CDCl₃) δ 8.75 (s, 1H, ArH), 8.72 (s, 1H, ArH), 8.67 (d, ³J_{H-H} = 5.5 Hz, 1H, ArH), 8.47 (d, ³J_{H-H} = 2.6 Hz, 1H, ArH), 8.45 (d, ³J_{H-H} = 8.75 Hz, 1H, ArCH=CHC(O)), 8.21 (d, ³J_{H-H} = 7.3 Hz, 2H, ArH), 7.91 (d, ³J_{H-H} = 8.75 Hz, 1H, ArCH=CHC(O)), 7.81 – 7.69 (m, 3H, ArH), 7.65 (t, ³J_{H-H} = 7.3 Hz, 1H, ArH), 7.57 (t, ³J_{H-H} = 7.6 Hz, 1H, ArH). **¹³C NMR** (101 MHz, CDCl₃) δ 190.25 (s, 1C, C=O), 152.29 (s, 1C, N=C-CH), 142.58 (s), 137.88 (s), 137.78 (s), 136.77 (s), 133.21 (s), 130.37 (s), 128.78 (d, J = 14.8 Hz), 128.30 – 127.74 (m), 127.41 (s), 124.32 (s), 122.31 (s). **HRMS** (+ESI) m/z: (M + H)⁺ calc'd for C₁₈H₁₄NO, 260.1075; found, 260.1084.

2.4.5. General procedure for catalytic hydrophosphination on dialkyl and diaralkyl 2-((diphenylphosphorothioyl)(isoquinolin-1-yl)methylene)malonates (optimization of conditions; 27a-d)

Diphenylphosphine (0.05 mmol, 9.31 mg, 1.0 equiv.) was weighed into a Schlenk flask under positive N₂ flow and 2.0 ml previously degassed solvent was added. Substrate (0.05 mmol, 1.0 equiv.) and the catalyst (0.0025 mmol, 0.05 equiv.) were added to the solution and then the required temperature was adjusted. Upon the required temperature was reached, base (0.05 mmol, 1.0 equiv.) was added dropwise to the reaction mixture. The reaction was monitored by ³¹P{¹H} NMR spectroscopy. Upon completion of the reaction excess sulfur or H₂O₂(aq) was added and the mixture was allowed to warm up and the volatiles were evaporated. The residue was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate 5:1 to 2:1) to obtain the pure sulfurized phosphine product.

2.4.5.1. Dimethyl 2-((diphenylphosphoryl)(isoquinolin-1-yl)methyl)malonate (27a)

27a is a white crystalline solid. Yield: 81%

¹H NMR (500 MHz, CDCl₃) δ 8.34 (d, ³J_{H-H} = 5.6 Hz, 1H, ArH), 8.04 (d, ³J_{H-H} = 6.8 Hz, 1H, ArH), 7.88 – 7.73 (m, 2H, ArH), 7.66 (d, ³J_{H-H} = 8.1 Hz, 1H, ArH), 7.55 (t, ³J_{H-H} = 7.5 Hz, 1H, ArH), 7.51 – 7.33 (m, 7H, ArH), 7.24 (d, ³J_{H-H} = 6.2 Hz, 1H, ArH), 7.12 (m, 2H, ArH), 5.66 (t, ³J_{H-H}, ³J_{H-P} = 11.35 Hz, 1H, CHCH(P(O)Ph₂)Ar), 5.08 (d, ³J_{H-H} = 11.35 Hz, ²J_{H-P} = 8.3 Hz, 1H, CHCH(P(O)Ph₂)Ar), 3.57 (s, 3H, COOCH₃), 3.40 (s, 3H, COOCH₃). **¹³C NMR** (126 MHz, CDCl₃) δ 168.43 (s, 1C, C=O), 168.26 (s, 1C, C=O), 155.76 (d, ²J_{P-C} = 5.6 Hz, 1C, Ar, N=C-C(H)P), 141.26 (d, J_{P-C} = 2.0 Hz, 1C), 136.05 (s), 131.80 (d, ¹J_{P-C} = 2.8 Hz, 1C, Ar, P-C₆H₅), 131.74 – 131.48 (m, 1C, Ar, P-C₆H₅), 131.41 (s), 129.77 (s), 128.26 (d, J_{P-C} = 11.8 Hz), 127.91 (d, J_{P-C} = 2.9 Hz), 127.66 (d, J_{P-C} = 12.0 Hz), 127.19 (d, J_{P-C} = 9.3 Hz), 120.02 (s), 53.05 (m, 2C, COOCH₃), 52.85 (s, 1C, CHCH(P(O)Ph₂)Ar), 52.65 (s, 1C, CHCH(P(O)Ph₂)Ar). **³¹P{¹H} NMR** (162 MHz, CDCl₃) δ 30.13 (s). **HRMS** (+ESI) m/z: (M + H)⁺ calc'd for C₂₇H₂₅NO₅P, 474.1470; found, 474.1476.

2.4.5.2. Dimethyl 2-((diphenylphosphorothioyl)(isoquinolin-1-yl)methyl)malonate (27b)

27b is a pale yellow solid. Yield: 86%

¹H NMR (500 MHz, CDCl₃) δ 8.40 (d, ³J_{H-H} = 5.6 Hz, 1H, ArH), 8.11 (dd, ³J_{H-H} = 11.6, 7.0 Hz, 2H, ArH), 8.02 (d, ³J_{H-H} = 8.3 Hz, 1H, ArH), 7.57 (d, ³J_{H-H} = 8.1 Hz, 1H, ArH), 7.51 – 7.37 (m, 7H, ArH), 7.35 (d, ³J_{H-H} = 5.0 Hz, 1H, ArH), 7.04 (t, ³J_{H-H} = 6.7 Hz, 1H, ArH), 6.91 (m, 2H, ArH), 5.83 (t, ³J_{H-H}, ³J_{H-P} = 10.2 Hz, 1H, CHCH(P(S)Ph₂)Ar), 5.28 (t, ³J_{H-H}, ²J_{H-P} = 10.7 Hz, 1H, CHCH(P(S)Ph₂)Ar), 3.37 (s, 3H, COOCH₃), 3.36 (s, 3H, COOCH₃). **¹³C NMR** (126 MHz, CDCl₃) δ 168.46 – 168.11 (m, 2C, C=O), 155.43 (d, ²J_{P-C} = 6.6 Hz, 1C, Ar, N=C-C(H)P), 141.29 (d, J_{P-C} = 3.0 Hz, 1C), 135.90, 132.46 (d, ¹J_{P-C} = 9.7 Hz, 1C, Ar, P-C₆H₅), 131.93 (d, ¹J_{P-C} = 10.1 Hz, 1C, Ar, P-C₆H₅), 131.61 (s), 131.10 (s), 130.96 (s), 130.86 (s), 130.48 (s), 130.31 (s), 129.53 (s), 128.21 (d, J_{P-C} = 12.0 Hz), 128.00 (s), 127.40 (s), 127.31 (s), 127.17 (s), 127.14 (s), 124.50 (s), 120.13 (s), 54.40 (d, ²J_{P-C} = 3.0 Hz, 1C, CHCH(P(S)Ph₂)Ar), 52.63 (s, 2C, COOCH₃), 44.84 (d, ¹J_{P-C} = 47.3 Hz, 1C, CHCH(P(S)Ph₂)Ar). **³¹P{¹H} NMR** (202 MHz, CDCl₃) δ 48.73 (s). **HRMS** (+ESI) m/z: (M + H)⁺ calc'd for C₂₇H₂₅NO₄PS, 490.1242; found, 490.1240. **Anal.** Calc'd for C₂₇H₂₄NO₄PS: C, 66.25; H, 4.94; N, 2.86. Found: 65.73; H, 4.80; N, 2.99%.

2.4.5.3. Diethyl 2-((diphenylphosphorothioyl)(isoquinolin-1-yl)methyl)malonate (27c)

27c is a yellow solid. Yield: 58%

¹H NMR (500 MHz, CDCl₃) δ 8.39 (d, ³J_{H-H} = 5.6 Hz, 1H, ArH), 8.10 (dd, ³J_{H-H} = 12.1, ³J_{H-H} = 7.3 Hz, 2H, ArH), 8.05 (d, ³J_{H-H} = 8.4 Hz, 1H, ArH), 7.57 (d, ³J_{H-H} = 8.0 Hz, 1H, ArH), 7.53 – 7.36 (m, 7H, ArH), 7.34 (d, ³J_{H-H} = 5.2 Hz, 1H, ArH), 7.05 (t, ³J_{H-H} = 7.0 Hz, 1H, ArH), 6.94 (d, ³J_{H-H} = 5.2 Hz, 2H, ArH), 5.85 (t, ³J_{H-H}, ³J_{H-P} = 10.3 Hz, 1H, CHCH(P(S)Ph₂)Ar), 5.22 (t, ³J_{H-H}, ²J_{H-P} = 10.8 Hz, 1H, CHCH(P(S)Ph₂)Ar), 3.95 – 3.63 (m, 4H, COOCH₂CH₃), 1.10 (t, ³J_{H-H} = 7.1 Hz, 3H, COOCH₂CH₃), 0.76 (t, ³J_{H-H} = 7.0 Hz, 3H, COOCH₂CH₃). **¹³C NMR** (126 MHz, CDCl₃) δ 167.79 – 167.08 (m, 2C, C=O), 155.79 (d, ²J_{P-C} = 6.0 Hz, 1C, Ar, N=C-C(H)P), 141.31 (d, J_{P-C} = 2.9 Hz), 135.86 (s), 132.45 (d, ¹J_{P-C} = 9.7 Hz, 1C, Ar, P-C₆H₅), 132.03 (d, ¹J_{P-C} = 10.0 Hz, 1C, Ar, P-C₆H₅), 131.50 (s), 130.78 (s), 129.49 (s), 128.11 (d, J_{P-C} = 12.1 Hz), 127.34 (d, J_{P-C} = 12.2 Hz), 124.63 (s), 119.96 (s), 61.82 (s, 1C, COOCH₂CH₃), 61.41 (s, 1C,

COOCH₂CH₃), 54.93 (d, ²J_{P-C} = 2.8 Hz, 1C, CHCH(P(S)Ph₂)Ar), 44.80 (d, ¹J_{P-C} = 47.3 Hz, 1C, CHCH(P(S)Ph₂)Ar), 13.71 (s, 1C, COOCH₂CH₃), 13.65 (s, 1C, COOCH₂CH₃). ³¹P{¹H} NMR (202 MHz, CDCl₃) δ 48.81 (s). HRMS (+ESI) m/z: (M + H)⁺ calc'd for C₂₉H₂₉NO₄PS, 518.1555; found, 518.1555.

2.4.5.4. Dibenzyl 2-((diphenylphosphorothioyl)(isoquinolin-1-yl)methyl)malonate (27d)

27d is a yellow solid. Yield: 64%

¹H NMR (500 MHz, CDCl₃) δ 8.31 (d, ³J_{H-H} = 5.6 Hz, 1H, ArH), 8.05 (dd, ³J_{H-H} = 12.2, ³J_{H-H} = 7.6 Hz, 2H, ArH), 7.97 (d, ³J_{H-H} = 8.3 Hz, 1H, ArH), 7.58 – 7.27 (m, 14H, ArH), 7.25 – 7.19 (m, 2H, ArH), 7.15 (t, ³J_{H-H} = 7.4 Hz, 1H, ArH), 7.07 (t, ³J_{H-H} = 7.5 Hz, 2H, ArH), 7.05 (s, 1H, ArH), 6.92 (m, 2H, ArH), 6.83 (d, ³J_{H-H} = 7.3 Hz, 2H, ArH), 5.87 (t, ³J_{H-H}, ³J_{H-P} = 10.4 Hz, 1H, CHCH(P(S)Ph₂)Ar), 5.39 (t, ³J_{H-H}, ²J_{H-P} = 10.7 Hz, 1H, CHCH(P(S)Ph₂)Ar), 4.85 – 4.77 (m, 2H, benzyl CH₂), 4.72 (s, 2H, benzyl CH₂). ¹³C NMR (126 MHz, CDCl₃) δ 167.79 – 167.08 (m, 2C, C=O), 155.46 (d, ²J_{P-C} = 6.2 Hz, 1C, Ar, N=C-C(H)P), 141.27 (d, ¹J_{P-C} = 3.0 Hz), 135.87 (s), 135.29 (s), 134.86 (s), 132.42 (d, ¹J_{P-C} = 9.4 Hz 1C, Ar, P-C₆H₅), 132.08 (d, ¹J_{P-C} = 9.9 Hz, 1C, Ar, P-C₆H₅), 131.48 (d, ¹J_{P-C} = 2.8 Hz), 130.80 (s), 130.32 (s), 129.46 (s), 128.35 (s), 128.19 (s), 128.07 (s), 127.99 (s), 127.94 (s), 127.90 (s), 127.87 (s), 127.36 (d, ¹J_{P-C} = 12.4 Hz), 127.09 (s), 124.58 (s), 120.03 (s), 67.30 (s, 1C, benzyl CH₂), 67.12 (s, 1C, benzyl CH₂), 54.89 (d, ²J_{P-C} = 3.0 Hz, 1C, CHCH(P(S)Ph₂)Ar), 45.15 (d, ¹J_{P-C} = 45.7 Hz, 1C, CHCH(P(S)Ph₂)Ar). ³¹P{¹H} NMR (202 MHz, CDCl₃) δ 48.66 (s). HRMS (+ESI) m/z: (M + H)⁺ calc'd for C₃₉H₃₃NO₄PS, 642.1868; found, 642.1865. Anal. Calc'd for C₃₉H₃₂NO₄PS: C, 73.00; H, 5.03; N, 2.18. Found: 71.13; H, 3.81; N, 2.32%.

2.4.5.5. (R)-3-(diphenylphosphorothioyl)-3-(isoquinolin-1-yl)-1-phenylpropan-1-one (29)

29 is a bright yellow solid. Yield: 53%.

¹H NMR (500 MHz, CDCl₃) δ 8.52 (d, ³J_{H-H} = 5.6 Hz, 1H, ArH), 8.01 (dd, ³J_{H-H} = 12.2 Hz, 7.4 Hz, 2H, ArH), 7.95 (d, ³J_{H-H} = 7.7 Hz, 3H, ArH), 7.64 (d, ³J_{H-H} = 8.2 Hz, 1H, ArH), 7.60 – 7.51 (m, 3H, ArH), 7.48 (dd, ³J_{H-H} = 12.2 Hz, 6.1 Hz, 3H, ArH), 7.44 – 7.38 (m, 4H, ArH), 7.31 (s, 1H, ArH), 7.21 (dd, ³J_{H-H} = 7.9 Hz, 6.4 Hz, 1H, ArH), 7.09 (td, ³J_{H-H} = 7.7 Hz, 3.1 Hz, 2H, ArH), 5.85 (m, ³J_{H-H} = 16.5 Hz, ²J_{H-P} = 1.2 Hz, 1H, CH₂CH(P(S)Ph₂)), 4.93 (ddd, ³J_{H-H} = 18.15 Hz, ³J_{H-P} = 10.4 Hz, ²J_{H-H} = 3.2 Hz, 1H, CH₂CH(P(S)Ph₂)), 3.72 (ddd, ³J_{H-H} = 18.15 Hz, ³J_{H-P} = 11.9 Hz, ²J_{H-H} = 3.2 Hz, 1H, CH₂CH(P(S)Ph₂)). **¹³C NMR** (101 MHz, CDCl₃) δ 197.59 (d, ³J_{P-C} = 16.5 Hz, 1C, C=O), 155.23 (d ²J_{P-C} = 9.1 Hz, 1C, Ar, N=C-C(H)P), 141.39 (s), 136.35 (s), 135.89 (s), 133.33 (s), 132.25 (d, ¹J_{P-C} = 9.4 Hz, 1C, Ar, P-C₆H₅), 131.94 (d, ¹J_{P-C} = 10.1 Hz, 1C, Ar, P-C₆H₅), 131.76 (d, J_{P-C} = 2.8 Hz), 131.20 (d, J_{P-C} = 2.9 Hz), 130.87 (s), 130.19 – 130.10 (m), 129.33 (s), 128.59 (s), 128.51 (s), 128.47 (s), 128.35 (s), 127.86 (d, J_{P-C} = 12.2 Hz), 126.89 (d, J_{P-C} = 6.1 Hz), 124.73 (s), 120.13 (d, J_{P-C} = 2.4 Hz), 41.09 (d, ¹J_{P-C} = 50.3 Hz, 1C, CH₂CH(P(S)Ph₂)), 39.87 (d, ²J_{P-C} = 2.9 Hz, 1C, CH₂CH(P(S)Ph₂)). **³¹P{¹H} NMR** (162 MHz, CDCl₃) δ 50.84 (s). **HRMS** (+ESI) m/z: (M + H)⁺ calc'd for C₃₀H₂₅NOPS, 478.1394; found, 478.1403.

CHAPTER 3: Synthesis of chiral, square planar P,N metal complexes

Abstract

The synthesis of various P,N metal complexes are carried and described in this unit along with all the synthetic difficulties and challenges we encountered. Based on experiences in this part, a suitable workup procedure was established to obtain these transition metal compounds in a selective (enantiopure or enantioenriched) way. The complexation reactions were then performed by using several metals with diverse oxidation states along with the attempts at tailoring some of the resulting compounds to possible catalytic applications.

3.1. Introduction – The importance of square planar complexes

Even though the chemistry of chiral bidentate ligands and their complexes is covered from the point of view of denticity, we must also scrutinize the geometry of these potential catalyst complexes by focusing on the square planar complexes and their related chemistry.

In homogeneous catalysis, square planar complexes with d^8 electron configuration on the metal have crucial importance, as their behavior in various catalysis show significant similarities.

Square planar geometry can be considered as an extreme case of the Jahn-Teller distortion of the octahedral complex resulting in the complete loss of the axial ligands by extreme axial elongation on the one hand, which occurs at low-spin d^8 electron configuration. On the other hand, this approach proved to be debatable because many researchers explain the square planar geometry solely as a result of the high crystal field splitting energy (Δ_o) between t_{2g} and e_g^* d orbitals in the case that there are eight electrons on the metal (Figure 69.).^{2, 119} In the figure, e_g^* refers to the antibonding orbitals of e_g . By symmetry reasons, e_g orbitals can accept coordinating electrons in axial and equatorial positions, thus, they can participate in bond formation with ligands in octahedral complexes. In metals bearing d^8 configuration, e_g^* , which includes the equatorial $d_{x^2-y^2}$ and axial d_{z^2} orbitals, is partially occupied by two electrons. Regarding the Δ_o splitting energy, these electrons can be unpaired and form – octahedral (or tetrahedral) – paramagnetic complexes, but in most of the cases these electrons are paired and form square planar diamagnetic complexes. This can be crucial during

y^2 and d_z^2) orbitals and leads to a more beneficial energy state.¹²⁰

Figure 69. Electron configuration of square planar d^8 complexes (the relative order of the split orbitals may vary for different complexes).

Square planar complexes are usually stable with 16 electrons on the metal. Metal centers, which typically form 16 electron complexes are e.g., Rh(I), Ir(I), (Ni(II) in some cases), Pd(II), Pt(II), and Au(III).² Some complexes which are of remarkable contribution to chemistry can be seen in Figure 70.

Figure 70. Famous and important square planar complexes in organometallic chemistry.

While most of the examples are famous catalysts in organometallic chemistry, *cis*-platin is an exception as it proved to be a remarkable antitumor drug in Western medicine.¹²¹ The latter rhodium and iridium complexes are well-known for their role in catalysis because they can actively accept hydrogen and other covalent molecules via oxidative addition.¹²²⁻¹²³ Wilkinson's catalyst was a pioneer in homogenous catalysis. It was synthesized by Osborne et al. in 1966 from rhodium(III) chloride hydrate and excess triphenylphosphine.²⁸ The mechanism of the hydrogenation catalyzed by Wilkinson's complex was investigated and established by Halpern and co-workers,¹²⁴ and by Schrock and Osborne.¹²⁵ Its catalytic scheme – as a textbook example – still helps us understand the nature of processes when transition metals are involved. Knowles and his co-workers also improved and extended the reaction: they successfully reported the asymmetric version of the latter hydrogenation, too.¹⁴

Vaska's iridium complex¹²⁶ turned out to be highly active towards the oxidative addition of HCl, Cl₂, H₂ or MeI among other small covalent molecules.¹²⁷ It was crucial to scrutinize and understand the mechanism of the oxidative addition, moreover, Vaska's complex can bind oxygen molecule reversibly.¹²⁸

Crabtree's iridium catalyst was also essential in contributing to the catalytic hydrogenation of organic compounds and functioned as a model catalyst complex for further investigations, developments and improvements to design catalytically more effective iridium derivatives.¹²⁹⁻¹³⁰ These iridium diolefin (COD) complexes found applications in deuteration reaction¹³¹ or in asymmetric catalysis, too.¹³²

By staying at the essential role of rhodium in asymmetric catalysis, we consider it important to illustrate the mechanistic scheme of the asymmetric hydroboration mentioned earlier in Chapter 1.¹³³⁻¹³⁴ The determination of the mechanism of this reaction was simultaneously carried out by T. Hayashi¹³⁵ and J. M. Brown¹³⁶ and their coworkers (Figure 71.). The herein depicted reaction protocol is established as the catalytic B–H addition on styrene(s), where the boron source is catecholborane and the catalyst is a Rh[QUINAP] tetrafluoroborate complex.¹³⁶ It is important by mechanistic point of view that the rhodium center is cationic, and there is no halide ligand attached in the complex's inner coordination sphere.

Figure 71. Mechanistic scheme of the homogenous catalytic hydroboration of styrene by catecholborane and $\text{Rh}^+[\text{QUINAP}]\text{BF}_4^-$ catalyst.

In the first step of the mechanistic scheme, the olefin coordinates to the rhodium center, which is still capable of accepting the B–H bond of the catecholborane via oxidative addition. Upon the borane's addition to the square planar rhodium(I) center, a square pyramidal rhodium complex forms with +3 oxidation state. The next step is the migratory 1,2-insertion of the olefin into the Rh–H bond followed by the formation of a η^3 -benzylrhodium intermediate. According to the mechanistic investigations of Hayashi and his coworkers, a cationic rhodium center – without halide ligands in the inner coordination sphere – is necessary for the formation of the allyl-type intermediate, which requires one more coordination site on the complex.¹³⁵ The formation of this intermediate explains the high regioselectivity of the reaction. The reductive elimination then takes place from the benzylrhodium intermediate resulting in the formation of the chiral 1-phenylethyl catecholborane.

It is also noteworthy that the coordinating olefin prefers occupying the vacant site positioned *trans* to the nitrogen of the QUINAP ligand (Figure 72.). This is beneficial, because this way the substrate is close to the directing diphenylphosphine group (that is the more sterically demanding quadrant around the metal center), by which the chiral induction is conveyed in a more effective manner resulting in high enantioselectivity.¹³⁶

Figure 72. Coordination of olefin to the rhodium center in the favoured position.

The previously detailed catalytic scheme, namely the oxidative addition, insertion then reductive elimination occurs not only in the field of catalytic hydrogenation, but in other areas of organometallic catalysis, such as in hydroformylation¹³⁷ or during the famous C–C coupling reactions.² The Mizoroki-Heck reaction follows a very similar scheme extended with the so-called β -elimination step, during which the product leaves the catalyst center as an olefin.¹³⁸

In the case of Suzuki, Negishi and other cross-coupling reactions, transmetalation (or substitution) step takes place instead of coordination/migratory insertion carried out by various organometallic reagents, such as organoboranes.¹³⁹ While these reactions are catalyzed by palladium and nickel with zero oxidation state, the square planar Pd(II) or Ni(II) species are often the precatalysts for these reactions. Moreover, upon oxidative addition the +2 palladium and nickel center is the active intermediate when the transmetalation occurs.¹³⁸⁻¹³⁹

3.2. Results and discussion

Upon the optimal conditions of the catalytic hydrophosphination were determined and established (82% of ee), we turned our focus on utilizing the forming product in complexation reactions with various transition metals. However, 82% of enantiomeric excess does not mean total selectivity, the 91:9 ratio of the forming enantiomers was considered high enough to obtain enantiopure crystals by recrystallization of the resulting metal complexes.

3.2.1. Synthesis of P,N palladium and platinum complexes

Although, it may seem straightforward to obtain metal complexes from a reaction mixture which already includes the enantioenriched ligand, we faced with several obstacles to get these compounds in an enantiopure or at least a highly enantioenriched fashion.

3.2.1.1. Challenges around the *in situ* complexations by using the P,N ligand

Our first approach toward synthesizing metal complexes was to add metal sources to the reaction mixture *in situ* upon the sufficient formation of the ligand **27**. The *in situ* additions led to immediate complex formations, which was proved by the coordination shift determined by $^{31}\text{P}\{^1\text{H}\}$ NMR spectroscopy. The first metal source applied was $\text{Pd}(\text{MeCN})_2\text{Cl}_2$ complex (1.0 equiv.), that afforded the chiral chelate complex **34** (Figure 73.). The $^{31}\text{P}\{^1\text{H}\}$ signal of the phosphorus atom shifted from 3.8 ppm to 52.1 ppm upon coordination (CDCl_3 , 202 MHz).

Figure 73. *In situ* addition of palladium metal source to the reaction mixture of catalytic hydrophosphination.

Upon the formation of the palladium complex (**34**) the mixture was allowed to reach room temperature for further workup processes. The newly formed chelate complex proved to be air-stable and resistant to moisture. Hence, we continued to carry out the

complexation reactions involving other metal sources, such as $\text{Pt}(\text{MeCN})_2\text{Cl}_2$, K_2PtCl_4 and complexes (*R*)-**1** and (*S*)-**1** (Table 8. and Figure 74.).

Table 8. Coordination of ligand **27** to palladium and platinum sources.

Entry	Catalyst	Solvent	<i>T</i> / °C	<i>t</i> / h	Metal source	Yield
1	(<i>S</i>)- 14	DCM	−80	72	$\text{Pd}(\text{MeCN})_2\text{Cl}_2$	26%
2	(<i>S</i>)- 14	acetone	−80	72	$\text{Pt}(\text{MeCN})_2\text{Cl}_2$	12%
3	(<i>S</i>)- 14	DCM	−80	72	K_2PtCl_4	16%
4	(<i>S</i>)- 14	DCM	−80	72	$\text{Pt}(\text{MeCN})_2\text{Cl}_2$	55%
5	(<i>S</i>)- 14	DCM	−80	72	(<i>S</i>)- 1	NA
6	(<i>S</i>)- 14	DCM	−80	72	(<i>R</i>)- 1	33%

It can be seen that the yields for the first three entries was very low, for which the explanation is that the P,N-metal chelates decompose during column chromatography. The workup procedure for these complexes at that point started with allowing the mixtures to reach rt, then their solutions were deliberately exposed to air when the remaining diphenylphosphine was oxidized. The DCM solutions of the crude materials and side products were washed with water and with brine to remove TEA and the forming diphenylphosphine oxide (DPPO), then dried on MgSO_4 and filtered through a short Celite plug. The purified crude materials were then recrystallized from DCM with diethyl ether (Et_2O) excluding the column chromatography step.

Figure 74. *In situ* complexation of various metal sources with ligand **27**.

The structure of the palladium and platinum complexes (**34** and **35**, respectively) was confirmed by X-ray crystallography (Figure 75.), however, the case of the platinum dichloro complex (**35**) was more challenging.

Figure 75. ORTEP image of palladium complex **34**.

When $\text{Pt}(\text{MeCN})_2\text{Cl}_2$ was added to the mixture, the $^{31}\text{P}\{^1\text{H}\}$ NMR signal shifted to 28.7 ppm, and two satellite signals were detected at 38.2 ppm and 19.3 ppm due to the coupling between the NMR active ^{31}P and ^{195}Pt nuclei ($^1J_{\text{Pt-P}} = 3826.9$ Hz, CDCl_3 , 202 MHz). Nevertheless, we considered the 28.7 ppm chemical shift to be too low when compared to other chelates' $^{31}\text{P}\{^1\text{H}\}$ NMR signals⁵⁴ and hypothesized that only the phosphorus donor atom of ligand **27** coordinated to the platinum and formed a dimer complex **35a** (Figure 76.).

Figure 76. Hypothesized platinum dimer complex upon addition of the platinum source to the forming P,N ligand **27**.

In order to make the coordination of the P,N bidentate complete, we chose to employ K_2PtCl_4 as a more active platinum source instead of $\text{Pt}(\text{MeCN})_2\text{Cl}_2$. The methanol solution of K_2PtCl_4 was added to the DCM solution of the ligand (**27**) at room temperature but owing to solubility differences and the high polarity of the platinum

reagent the two solution did not homogenize. In order to promote the mixing of the two solutions, we warmed the mixture up to its reflux temperature. At this point it must be noted that by employing enhanced temperature, the selectivity deteriorated because of the presence of remaining starting materials and the catalyst. The coordination took place in this case as well, and the coordination shift was 28.7 in the $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum. Upon the successful crystallization of complex **35**, the X-ray structure analysis confirmed the formation of the dichloro chelate complex (Figure 77.).

Figure 77. ORTEP image of platinum complex **35**.

For obtaining diastereomers (*S,R*)-, (*R,R*)-, (*R,S*)-, (*S,S*)-**28** (Figure 74.) the procedure employed was the same as that used for the dichloro derivatives **34** and **35**, and the product could be isolated with 33% yield. The previously determined selectivity of the reaction could be confirmed by the integral ratio of the characteristic signals (57.75 and 62.8 ppm) in $^{31}\text{P}\{^1\text{H}\}$ NMR spectroscopy. The diastereomer excess was ascertained to be 71%. It is noteworthy that this method is only accurate when the reaction is 100% complete at the time of the *in situ* addition of chiral template **1**, as the C,N palladacycle can catalyze the hydrophosphination reaction as well. The effective separation of these diastereomers, which are of key importance in this project, is detailed in the upcoming chapter.

3.2.1.2. Resolution of the enantioenriched P,N ligand by using the chiral template **1**

As it was depicted in the previous chapters, (*R*)- and (*S*)-**1** chiral templates were used as metal sources for complexations and for the stoichiometric hydrophosphination. In both cases, the products were the corresponding diastereomers of complex **28**. This complex, which contains the chiral auxiliary (C,N palladacycle) had key importance because it is suitable for carrying out the resolution of the P,N palladium moiety, moreover, the enantioenriched ligand **27** itself. This was crucial for further structure investigation and to prove the configuration of the stereogenic center of the P,N ligand (**27**) depending on the use of the enantioselective (*R*) and (*S*) catalyst **14**. Since the P,N chelation is sensitive to the column chromatography, we intended to employ recrystallization to obtain pure diastereomers. To recrystallize the crude diastereomer mixtures of **28**, we applied both DCM and CHCl₃ to dissolve the complexes, then tried their possible combinations with toluene, hexane, Et₂O, and MTBE. Two of these combinations proved to be suitable for growing pure crystals: DCM / Et₂O and CHCl₃ / Et₂O, however the CHCl₃ / Et₂O solvent combination afforded smaller crystals. Hence, DCM / Et₂O combination proved the perfect one providing diastereomerically pure crystals with acceptable shape and size. (Simultaneously, it turned out that this solvent system also proved to be applicable for crystallizing the palladium and platinum dichloro complexes **34** and **35**.) The obtained crystals were analyzed by X-ray structure crystallography and ³¹P{¹H} NMR spectroscopy (Figure 78. and 79.).

Figure 78. ORTEP image of diastereomer complex (*R,R*)-**28**.

According to our observations, the chemical shift of (*R,R*) and (*S,S*) diastereomers is 57.75 ppm (CDCl₃, 202 MHz), and for (*S,R*) and (*R,S*) diastereomers, the ³¹P{¹H} NMR signal could be observed at 62.8 ppm (DCM, 162 MHz; Figure 79.). It turned out that only the (*R,R*) and (*S,S*) diastereomers (57.75 ppm) can be crystallized from these solvents, thus, can be characterized thoroughly.

(S,S)-28
 $^{31}\text{P}\{^1\text{H}\}$: δ **57.75 ppm**
 (CDCl₃, 202 MHz)

(R,R)-28
 $^{31}\text{P}\{^1\text{H}\}$: δ **57.75 ppm**
 (CDCl₃, 202 MHz)

(S,R)-28
 $^{31}\text{P}\{^1\text{H}\}$ δ **62.8 ppm**
 (DCM, 162 MHz)

(R,S)-28
 $^{31}\text{P}\{^1\text{H}\}$ δ **62.8 ppm**
 (DCM, 162 MHz)

Figure 79. The possible diastereomers of the P,N palladium complex with the use of (*S*) and (*R*) C,N chiral templates.

It is noteworthy that a singlet peak could be observable at 54.85 ppm in the $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum beside the main singlet at 57.75 ppm, which can be attributed to the possibly occurring *cis-trans* isomerization around the palladium center: beside the favorable *trans* P-Pd-N and *trans* C-Pd-N arrangements the *trans* P-Pd-C and *trans* N-Pd-N arrangements also exist in solution as a minor product ((*R,R*)-**28a**, Figure 80.). This equilibrium could be observed during the synthesis of chloro bridged dimer derivative of C,P complex **14** as well.⁵³

Figure 80. The less favorable isomer (minor product) of diastereomer (*R,R*)-28.

These findings were sufficient to prove that when (*S*)-14 was used in the catalytic hydrophosphination reaction, the major product was selectively the ligand (*R*)-27, since, when (*R*)-1 was added, the forming major diastereomer was (*R,R*)-28.

The next step was to chemoselectively remove the C,N auxiliary to obtain complex 34 in an enantiopure resolved form. This was achieved by using concentrated HCl solution (Figure 81.).⁵³

Figure 81. The selective removal of the C,N chiral auxiliary to obtain complex (*R*)-34.

Based on the previously reported procedure, the cleavage of the C,N moiety from (*R,R*)-28 required 300 equiv. of HCl and refluxing for two hours to afford the pure dichloro palladium complex (*R*)-34 with 85% yield. The pure complex was recrystallized successfully from DCM / Et₂O, and its structure was successfully determined by X-ray crystallography (Figure 82.). The Flack parameter of the complex was 0.03(4), which proved the enantiopurity of the crystal.

Figure 82. The ORTEP image of the resolved palladium complex (*R*)-**34**.

The specific rotation of the resolved complex was also determined: $[\alpha]_{\text{D}}^{25} = -361.4$ (c 2.0, DCM), which could be used as a reference for the further investigations.

In the future, the resulted enantiopure palladium complex can be a starting material for changing the metal center with the extraction of the solution of **34** with KCN solution to describe various enantiopure metal complexes if necessary. The air-sensitive ‘naked’ ligand **27** can also be obtained this way in a highly pure form.

3.2.1.3. Synthesis of the enantiopure *P,N* palladium and platinum complexes (**34** and **35**)

When the *in situ* complexations were carried out, the resulting products were recrystallized via the already established manner. At that point unfortunately, the optical rotation measurements on the crystals did not provide consistent values, which indicated that the applied procedure was not suitable to achieve or maintain the desired enantiopurity consistently. Based on our experiences, we concluded an explanation to that observation: however, the conversion of catalytic hydrophosphination reaction stops at a certain point (by the previously explained reasons), the addition of metal sources to the mixture of unreacted diphenylphosphine and substrate (**22a**) in the presence of base, and its subsequent warm up promotes the reaction to reach completion. Nonetheless, this way the selectivity is continuously being deteriorated, hence, the

afforded product mixtures are not enantioenriched enough anymore. To tackle these problems, a modified workup process was devised to obtain enantiopure metal complexes immediately upon hydrophosphination. During this, several approaches to workup the reaction was adopted to achieve sufficient conversion.

In our first attempt, the mixture was precipitated with degassed (oxygen free) hexane at $-80\text{ }^{\circ}\text{C}$, and subsequently filtered through a short Celite plug to filter the relatively polar product and separate it from diphenylphosphine. The Celite plug was then washed first with hexane, then with DCM to wash off the product, which is soluble in DCM. Unfortunately, hexane washed both the product and diphenylphosphine off the Celite into the same flask, so that the volatiles (TEA and solvent) were removed by vacuum, then the remaining diphenylphosphine was eliminated by triturating the residue with hexane. The residue was then redissolved in degassed DCM and the complexation was performed after this procedure at room temperature. The resulting solution of the product was washed with water, dried and filtered again on Celite plug before crystallization. The crystallization however was unsuccessful, supposedly because of the contaminations remained in the crude mixture.

Another approach was the idea of adding the 1.0 equivalent metal source and then excess sulfur immediately at $-80\text{ }^{\circ}\text{C}$ to carry out the complexation of ligand **27** and transform the remaining diphenylphosphine to diphenylphosphine sulfide in one step. Unfortunately, this method also proved unsuccessful: the product could not be crystallized because of the presence of impurities, moreover, the specific rotation of the crude product was also unsatisfactory.

Finally, based on these experiences we established a workup protocol: to stop the reaction, our first step was the removal of solvent (DCM) and TEA by nitrogen flow and vacuum. The mixture was kept at $-80\text{ }^{\circ}\text{C}$ during this process. After that, the excess diphenylphosphine was removed by trituration with degassed hexane (still at $-80\text{ }^{\circ}\text{C}$), then the air-sensitive residue that contained the product was redissolved in DCM, which then was filtered through a short plug of Celite by applying continuous nitrogen flow and pressure. This way, we could get rid of the remaining catalyst and other impurities. The palladium or platinum source was then added to the naked and purified solution of ligand **27** at $-80\text{ }^{\circ}\text{C}$, the mixture was warmed up and stirred for an hour at rt. The resulting crude product was then subjected to recrystallization with DCM /Et₂O solvents. The specific rotation values were consistent to the reference value at that time:

for complex (*R*)-**34** [$\alpha_D^{25} = -479$ (*c* 2.0, DCM) and for the platinum derivative (*R*)-**35** [$\alpha_D^{25} = -43$ (*c* 2.0, DCM) as the proof for the success of the procedure (Figure 83).

Figure 83. General scheme for the synthesis of enantiopure platinum and palladium complexes.

The use of low temperature for complexation was necessary because in the case of platinum complex we observed an additional singlet peak at 52.12 ppm in the $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum. This can be explained with a possible P,O coordination the ligand to the platinum (**35b**) instead of P,N coordination (Figure 84.) that happens when the complexation took place at rt.

Figure 84. The hypothesized P,O derivative of platinum complex **35**.

However, when the same complexation process was carried out at $-80\text{ }^{\circ}\text{C}$, the additional NMR peak of the P,O coordinating derivative could not be observed.

This workup procedure proved effective and suitable to be used for metal complexations. The resulting solution of the P,N ligand **27** was pure enough to be used in this kind of coordination procedure, and it provided a fundamental approach to synthesize several new P,N-metal complexes.

It is noteworthy that the purification of **27** with column chromatography under nitrogen was not applicable, because the P,N ligand got oxidized on silica gel under

chromatographic conditions. Moreover, silica gel probably induces side-processes which resulted in side-products that could be observed in $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum.

3.2.2. Synthesis of P,N Rh(I) and Ir(I) complexes

3.2.2.1. Synthesis of rhodium and iridium triphenylphosphine complexes

To synthesize rhodium and iridium complexes, our first approach was also the *in situ* addition of metals to the reaction mixture of the hydrophosphination of substrate **22a**. The first attempt was to add $[\text{Rh}(\text{COD})\text{Cl}]_2$ to the reaction mixture at rt, then to try to recrystallize the product complex with DCM / Et₂O after filtration. This approach was based on our preliminary hypothesis that in the forming rhodium complex the metal center was stabilized by the P,N ligand and forms a chloro-dimer compound (**36a**, Figure 85.).

Figure 85. The *in situ* addition of rhodium source to the reaction mixture containing ligand **27** and the hypothesized rhodium chloro-dimer complex **36a**.

Upon coordination, the characteristic signals could be observed in the $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum as a doublet at 45,5 ppm ($^1J_{\text{Rh-P}} = 144.2$ Hz, DCM, 162 MHz) owing to the coupling between the NMR active ^{31}P and ^{103}Rh nuclei. However, applying the typical workup procedures (extraction and filtration), moreover, attempts for crystallizing the product were completely unsuccessful, and it turned out that the forming rhodium compound was highly air sensitive.

To surmount this problem, we concluded to add PPh_3 together with the metal source to further stabilize the rhodium center and occupy all the possible coordination sites in the complex (Figure 86.).

Figure 86. *In situ* addition of rhodium sources and PPh₃ to ligand **27**.

The reaction successfully afforded complex **36**, and according to the splitting pattern and the coupling constants observed in $^{31}\text{P}\{^1\text{H}\}$ NMR, *cis* P-P coordination occurred around the rhodium center: δ 75.16 ppm (dd, $^1J_{\text{Rh-P}_1} = 200.3$ Hz, $^2J_{\text{P}_1\text{-P}_2} = 41.55$ Hz), 46.20 ppm (dd, $^1J_{\text{Rh-P}_2} = 171.9$ Hz, $^2J_{\text{P}_1\text{-P}_2} = 41.55$ Hz) (DCM, 162 MHz) (P₁ indicates the phosphorus atom in ligand **27** and P₂ refers to the coordinating triphenylphosphine).¹⁴⁰⁻¹⁴¹ The crude material was purified by the removal of solvent and the TEA, then triturated by degassed hexane to remove the diphenylphosphine and COD residues. However, the inert crystallization of the product was not successful. The recrystallization attempts were carried out from both DCM and CHCl₃ with Et₂O and MTBE solvents.

The same scheme was applied to describe the iridium(I) analogue of complex **36** (Figure 87.).

Figure 87. *In situ* addition of iridium and PPh₃ to ligand **27**.

The iridium complex **37** also showed *cis* P-P coordination around the metal: in $^{31}\text{P}\{^1\text{H}\}$ NMR spectroscopy the showed doublets at 32.14 ppm (d, $^2J_{\text{P}_1\text{-P}_2} = 32.8$ Hz) and at -30.31 ppm (d, $^2J_{\text{P}_1\text{-P}_2} = 32.8$ Hz) (162 MHz, DCM).¹⁴² The crude material was prepared for recrystallization in the same way as complex **36**, and the same solvent combinations were tried out to obtain single crystals, but none of the attempts afforded actual crystals.

In general, the synthesized triphenylphosphine chloro-complexes **36** and **37** proved to be highly air-sensitive and unstable. Even the procedure for preliminary purification of ligand **27** (detailed in Chapter 3.2.1.3.) was tried out to obtain the crude complexes in a suitable condition for a successful recrystallization. However, according to our experiences these complexes decomposed during filtration, hence, the thorough characterization could not be carried out in the desired way. Nevertheless, the information regarding the coordination behavior of these complexes turned out to be highly valuable, so that it will be further elaborated in Chapter 4.

3.2.2.2. Synthesis of rhodium and iridium COD complexes

In light of the experiences and challenges gathered during the syntheses of complexes **36** and **37**, we concluded to change the ancillary ligands around the metal center. Our choice fell on the cyclooctadiene containing rhodium and iridium complexes as model structures with employing of tetrafluoroborate (BF_4^-) counteranion in the in the outer coordination sphere.¹⁴³ For these syntheses, the well-established preliminary workup procedure of **27** were applied, thus, the purified solutions of **27** were used as starting materials for the complexation steps. The scheme of the synthesis for rhodium and iridium complexes can be seen in Figure 88.

Figure 88. Our scheme established for the synthesis of various metal complexes using **27** as a starting material (S here indicates solvent molecules).

The procedure started with the removal of the chloro-ligands from complexes **38** and **41** by using silver tetrafluoroborate (AgBF_4). This step was carried out in degassed solvents under nitrogen because rhodium(I) and iridium(I) metals are sensitive to oxygen. To the DCM solution of the starting $[\text{M}(\text{COD})\text{Cl}_2]$ complexes (**38** and **41**) the methanol solution of AgBF_4 was added, then the mixture was stirred in the dark for 3 hours. The use of methanol was necessary for better solubility of the silver reagent.

After completion, the resulting COD complex intermediates **39** and **42** were filtered through short Celite plugs with the use of positive nitrogen flow and pressure.

In the next step, the previously purified malonate ligand **27** was added to the solutions of **39** and **42**. The complexations were carried out at $-80\text{ }^{\circ}\text{C}$ to avoid the previously explained P,O coordination and afford the desired complexes **40** and **43**. Their solutions were filtered through short Celite plugs, and upon the removal of solvents they could be smoothly stored in gas-tight storage flasks. We attempted to recrystallize these complexes as well, but crystals could not be grown despite the numerous attempts, so that they only could be obtained in an enantioenriched form. The applied solvent combinations were CHCl_3 and DCM with hexane, MTBE and Et_2O .

On the other hand, this procedure proved to be good enough to afford these complexes (**40** and **43**) in a satisfactory form for characterization. Both rhodium and iridium tetrafluoroborate complexes (**40** and **43**) could be obtained with $>99\%$ 'nominal' yields, which are the yields of the crude materials and not isolated ones. Complex **40** showed a doublet signal in the $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum at 49.7 ppm because of the spin-spin coupling of ^{31}P - ^{103}Rh nuclei. The coupling constant was $^1J_{\text{Rh-P}} = 156.2\text{ Hz}$, which is in accordance with the literature.¹⁴⁰ For iridium complex **43** the chemical shift of the phosphorus nucleus was at 41.5 ppm (s) (202 MHz, CDCl_3).

3.2.3. Synthesis of P,N allylpalladium tetrafluoroborate complex (46)

The scheme established in the previous chapters allowed us to design other potential catalyst complexes, too. QUINAP's chemistry was detailed deeply in the Introduction section and it was also applied in asymmetric allylic alkylation reactions as chiral ligand. Brown et al. reported a QUINAP allylpalladium(II) tetrafluoroborate complex as a catalyst for the reaction.¹⁴⁴

Based on this example, we aimed to synthesize the allylpalladium derivative of complex **34** with the same approach we used for the synthesis of iridium and rhodium COD complexes (Figure 89.).

Figure 89. Synthesis of allylpalladium tetrafluoroborate complex **46** (S here indicates solvent molecules).

The methanol solution of AgBF_4 was added to the DCM solution of starting complex **44**, then the mixture was stirred for 3 hours in the dark under nitrogen atmosphere. The resulting intermediate **45** was then filtered through a short Celite plug by using positive nitrogen flow and pressure, and the previously purified DCM solution of **27** was added at $-80\text{ }^\circ\text{C}$ to afford allylpalladium complex **46**. The mixture was allowed to warm up to rt, then filtered through a Celite plug. The crude mixture contained side-products but did not prove to be air-sensitive. For this reason, the crude product was attempted to be recrystallized first from DCM with Et_2O , then with hexane. Subsequent attempts at crystallization was successful and gave colorless crystals, however, due to the significant amount of side-products, the yield was relatively low (18.4%). There was no sign of the formation of enantiopure crystals, thus, the product (**46**) probably remained enantioenriched similarly as in the case of complexes **40** and **43**. The allyl complex could be observed at 49.23 ppm as a doublet of doublets in the $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum. The ORTEP image of the complex can be seen in Figure 90.

Figure 90. ORTEP image of allylpalladium complex **46**.

In the future, the complex will be suitable for testing in catalytic allylic alkylation reactions.

3.2.4. Syntheses and attempts for obtaining other P,N metal complexes

3.2.4.1. Syntheses of palladium(0), ruthenium(II) and nickel(II) complexes

The previously developed procedure was applied in complexation reactions with metals like Pd(0), Ru(II) and Ni(II), too.

We intended to synthesize a ruthenium(II) centered complex, so that we used $[\text{Ru}(\text{COD})\text{Cl}_2]_n$ metal source to be coordinated by the purified P,N moiety **27** (the complexations in these cases were carried out at rt). Our hypothesis was that the forming complex would possess octahedral geometry,^{35, 145} so that we concluded to add 2.0 equiv. of PPh_3 to the mixture together with the metal (Figure 91.). The $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum however showed significant amount of ‘free’ triphenylphosphine, and complex **47** in traces, with *trans* P-P arrangement around the ruthenium center. The chemical shifts could be seen as two doublets at 35.2 ppm and at -23.2 ppm (d, $^2J_{\text{P1-P2}} = 225.8$ Hz) (162 MHz, DCM; P₁ is the phosphorus atom of ligand **27**, P₂ is the

phosphorus atom of PPh₃). The assumed complex **47a** could not be observed in the ³¹P{¹H} NMR spectrum. Nevertheless, product **47** probably exist as an octahedral COD complex, as there are numerous examples of octahedral, 5-membered chelate complexes of ruthenium with coordinating phosphines in the literature.¹⁴⁶ It must be highlighted that without thorough structural analyses these are only proposed structures.

Figure 91. Synthesis of a P,N ruthenium complex with the hypothesized octahedral geometry.

Because of this consideration, we also tried to synthesize a ruthenium compound which in structure is similar to palladium complex **34** (Figure 92.).

Figure 92. Synthesis of P,N ruthenium chloro-complex **48** (proposed structure).

The ³¹P{¹H} NMR spectroscopy showed a singlet peak at 24.3 ppm. Product **48** is probably an octahedral COD complex as well. Our experience was that neither of complex **47** nor **48** could be isolated and prepared for proper characterization or recrystallization: both compounds decomposed during filtration on Celite plugs.

We also employed this procedure to obtain palladium(0) and nickel(II) complexes: Pd₂(dba)₃ and Ni(MeCN)₂Cl₂ were added to the solutions of ligand **27** at rt (Figure 93.).

Figure 93. Attempts for synthesizing P,N Pd(0) and Ni(II) complexes.

The $^{31}\text{P}\{^1\text{H}\}$ NMR spectroscopy measurements did not provide any observable peaks or information in either case.

For the P,N palladium(0) dba complex **49** we could not be sure if the coordination took place, moreover, the successful isolation of this complex could not be carried out either. The resulting mixture, which contained significant amount of undissolved material, was filtered several times before NMR measurements but the $^{31}\text{P}\{^1\text{H}\}$ NMR spectroscopy did not provide any information about the coordination. A possible explanation for this might be the observation that palladium in $\text{Pd}_2(\text{dba})_3$ metal source may contain paramagnetic palladium nanoparticles. Despite palladium metal bears a noble gas electron configuration with closed 4d subshell, in which all electrons are paired, on the surface of these nanoparticles 5s subshell may overlap with the 4d subshell to induce a $4\text{d}^{10-\xi} 5\text{s}^\xi$ configuration ($\xi \approx 0$) with unpaired electrons that causes the paramagnetism of palladium(0) compounds.¹⁴⁷⁻¹⁴⁹ Because of this, carrying out proper NMR measurements may be difficult.

In the case of nickel complex **50**, a more easily conceivable explanation is that for Ni(II) ions, square planar geometry and low-spin d^8 (diamagnetic) configuration is less common: nickel is also likely to form paramagnetic tetrahedral and octahedral complexes with unpaired d^8 electrons depending on the ligands.¹¹⁹ In this case, the

preferred geometry was probably the paramagnetic tetrahedral arrangement with unpaired d electrons. The product could be observed in the mass spectrum obtained by HRMS, however, X-ray crystallographic data could not be obtained because the complex could not be crystallized from DCM neither by the use of Et₂O nor by hexane. The yield of the crude product was 44.8 mg.

3.2.4.2. Modification of palladium and platinum chloro-complexes **34** and **35**

Previously, it was detailed that palladacycle complexes **1** and **14** proved to be highly effective in catalytic and stoichiometric enantioselective hydrophosphinations. The structures of these complexes consist of bidentate C,N and C,P anionic coordinating moieties on the one side, and labile ancillary ligands (N-coordinating acetonitriles) on the other side. These labile acetonitrile ligands can easily be substituted with the coordinating diphenylphosphines and the activated substrates during catalysis.

For this reason, we intended to synthesize the P,N analogue of these bis(acetonitrile)metal complexes by removing the chloro ligands from the dichloro complexes **34** and **35**. The removal was attempted with the use of silver perchlorate reagent as an analogous procedure to the one used in the case of complex **14**.⁵⁷

When the *in situ* P,N-metal addition reactions were carried out, first we were unsure about the coordination of platinum in complex **35**, and we assumed that only phosphorus coordination takes place (**35a**, Chapter 3.2.1.1.). To induce the complete bidentate coordination to take place, we decided to remove the chloro ligands from the hypothesized dimer complex **35a**. However, the reaction was set up based on this assumption, the actual starting material was complex **35**. Thus, excess amount of AgClO₄ was applied (Figure 94.).

Figure 94. Unsuccessful attempts for the removal of chloro ligands from complexes **34** and **35**.

Unfortunately, the reaction did not provide the desired bisacetonitrile product (**51**). The same procedure was carried out with the previously assumed (and hypothetical) rhodium dimer complex **36a** (Chapter 3.2.2.1.), but there was no product formation in that reaction either. (At this point, we were unaware that the P,N rhodium(I) system was highly air-sensitive.)

Nevertheless, this approach seemed to be more promising in the case of palladium complex **34** (Figure 94.). After the reaction was being stirred overnight, the crude mixture was filtered through Celite and recrystallized from acetonitrile with Et₂O. According to the X-ray structure analysis the reaction did not prove to be successful, and to our surprise, the structure formed was a dimer complex (diphenylphosphine(bisacetonitrile)palladium perchlorate) as a side product (Figure 95.) instead of complex **52**.

Figure 95. Ball-stick model based on the crystallographic data of the diphenylphosphine(bisacetonitrile)palladium perchlorate dimer (side) product.

This side product probably formed due to a possible yet unexplored dehydrophosphination process. Thorough X-ray crystallographic analysis could not be carried out in the case of this compound.

Another attempt to obtain a catalytically more applicable P,N complex was to substitute the chloro ligands with the anionic acac ligand. Because the treatment with the silver

reagent resulted in side reactions in the case of product **52**, we first tried to skip the use of AgClO_4 and expected the chelate formation to happen via a simple substitution (**53a** and **53b**) (procedure A, Figure 96.). The treatment of complex **34** with sodium acetylacetonate hydrate could not cause any change on the starting material.

Figure 96. Attempts to synthesize P,N palladium(acac) complexes **53a** and **53b**.

Hence, we also tried to use silver perchlorate to remove the chloro ligands to promote the ligand substitution (procedure B, Figure 96.). According the $^{31}\text{P}\{^1\text{H}\}$ NMR spectroscopy, the starting material remained intact in this case as well.

3.2.4.3. Synthesis of the palladium chloro acrylophenone complex **29a**

Although, the enantioselectivity of the hydrophosphination of substrate **23** resulted to be low, the *in situ* addition of $\text{Pd}(\text{MeCN})_2\text{Cl}_2$ to the reaction mixture also led to the racemic mixture of palladium dichloro complex **54**. As it was mentioned, the X-ray crystallographic measurement revealed that forming complex contains a six-membered P,N chelate ring (Figure 97.).

Figure 97. *In situ* addition of palladium source to the hydrophosphinated acrylophenone ligand **29a**.

The product showed a singlet peak at 51.9 ppm in the $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum. The square planar complex could be isolated and could be recrystallized from DCM with hexane upon filtration. The yield of the crude product was 71 mg, however, only 22 mg of complex **54** was recrystallized with 40% of yield. The ball-stick model obtained based on the X-ray crystallographic data of the complex can be seen in Figure 98.

Figure 98. Ball-stick model based on the crystallographic data of complex **54**. Hydrogen atoms are omitted for clarity.

3.3. Summary and Conclusion

During this chapter, we could achieve and describe several metal complexes as potential catalyst compounds beside the attempts at modifying their structure when necessary. Our starting approach, the *in situ* addition of metal sources to the freshly formed P,N ligand needed to be improved in order to keep the selectivity during complexation. Hence, a novel work-up protocol of the catalytic reaction step was developed to be able to prior purify and 'isolate' the forming P,N ligand before the addition of the various metal sources as far as possible. Then, when the metal sources were added, the complexes could be worked up and isolated. This method may provide a good example for overcoming such difficulties occurring around similar catalytic reactions. Especially, when the reaction does not take place utterly and active species remain in the reaction mixture encumbering the subsequent synthetic steps.

In this part, we got insight into the chemistry of palladium, platinum, rhodium, iridium, nickel and ruthenium metals to certain extent. In the case of palladium(II) and platinum(II) chloro complexes, we could obtain potential catalyst precursor and model compounds, while in the case of rhodium(I) and iridium(I) and also of palladium(II) metals, we could design possible metal catalyst frameworks, which structures can be subjects in catalyst testing reactions in the future.

3.4. Experimental Section

3.4.1. General procedure for generating dichloro P,N palladium and platinum complexes ((*R*)-**34** and (*R*)-**35**)

Diphenylphosphine (0.17 mmol, 0.032 g, 1.0 equiv.) was weighed into a Schlenk flask under positive N₂ flow and 7.0 ml previously degassed DCM was added. Substrate **22a** (0.17 mmol, 0.046 g, 1.0 equiv.) and (*S*)-**14** catalyst (0.0085 mmol, 0.005 g, 0.05 equiv.) were added to the solution and then the mixture was cooled down to -80 °C. Upon the required temperature was reached, triethylamine (0.17 mmol, 0.017 g, 1.0 equiv.) was added dropwise to the reaction mixture. After the reaction reached the desired conversion, TEA and the solvent was removed by using nitrogen flow and vacuum while the low temperature was permanently maintained. The residue was then triturated four times with degassed hexane to remove excess diphenylphosphine. The crude material was redissolved in DCM and filtered through a short celite plug under Schlenk conditions. MCl₂(MeCN)₂ (0.17 mmol, 1.0 equiv.) was then added to the free P,N ligand **27** at -80 °C, stirred for an hour and allowed to rt. Each of the resulting air-stable complex was filtered through short Celite plug and recrystallized from DCM with diethyl ether to afford enantiopure crystals.

3.4.1.1. (*R*)-(κ^2 -P,N)-(dimethyl 2-((diphenylphosphaneyl)(isoquinolin-1-yl)methyl)malonate)-dichloropalladium(II) ((*R*)-**34**)

34 is a yellow solid. Yield: 85%. $[\alpha]_D^{25} = -479$ (*c* 1.0, CH₂Cl₂).

¹H NMR (500 MHz, CDCl₃) δ 9.79 (d, $^3J_{H-H} = 6.6$ Hz, 1H, ArH, HC=CH-N), 8.29 (d, $^3J_{H-H} = 8.6$ Hz, 1H, ArH), 8.02 – 7.86 (m, 7H, ArH), 7.81 – 7.70 (m, 2H, ArH), 7.59 (t, $^3J_{H-H} = 6.9$ Hz, 2H, ArH), 7.53 (t, $^3J_{H-H} = 7.6$ Hz, 2H, ArH), 7.48 (td, $^3J_{H-P} = 7.7$ Hz, $^3J_{H-H} = 2.7$ Hz, 2H, P-C₆H₅), 7.43 (td, $^3J_{H-P} = 7.7$ Hz, $^3J_{H-H} = 2.5$ Hz, 2H, P-C₆H₅), 5.89 (dd, $^3J_{P-H} = 14.8$ Hz, $^3J_{H-H} = 9.4$ Hz, 1H, CHCH(PPh₂)Ar), 4.49 (dd, $^2J_{P-H} = 15.6$ Hz, $^3J_{H-H} = 9.4$ Hz, 1H, CHCH(PPh₂)Ar), 3.30 (s, 3H, COOCH₃), 3.25 (s), 2.76 (s), 2.73 (s, 3H, COOCH₃). **¹³C NMR** (126 MHz, CDCl₃) δ 166.89 (s, 1C, Ar, HC=CH-N), 166.17 (d, $^3J_{P-C} = 12.0$ Hz, 1C, C=O), 161.97 (d, $^3J_{P-C} = 8.1$ Hz, 1C, C=O), 145.40 (s), 136.54 (s), 136.29 (d, $^2J_{P-C} = 11.3$ Hz, 1C, Ar, N=C-C(H)P), 133.44 (s), 133.10 (d, $J_{P-C} = 2.8$ Hz), 132.74 (d, $J_{P-C} = 2.9$ Hz), 132.61 (d, $^1J_{P-C} = 10.5$ Hz, 1C, Ar, P-C₆H₅), 129.93 (s), 129.71

(d, $^1J_{\text{P-C}} = 11.4$ Hz, 1C, Ar, P- C_6H_5), 128.62 (d, $J_{\text{P-C}} = 12.1$ Hz), 126.71 (d, $J_{\text{P-C}} = 10.6$ Hz), 125.04 (d, $J_{\text{P-C}} = 53.6$ Hz), 123.27 (s), 122.60 (d, $J_{\text{P-C}} = 56.0$ Hz), 53.22 (s, 1C, COOCH_3), 53.17 (d, $^2J_{\text{P-C}} = 5.3$ Hz, 1C, $\text{CHCH}(\text{PPh}_2)\text{Ar}$), 52.71 (s, 1C, COOCH_3), 47.08 (d, $^1J_{\text{P-C}} = 30.4$ Hz, 1C, $\text{CHCH}(\text{PPh}_2)\text{Ar}$), 30.93 (s), 29.69 (s). **$^{31}\text{P}\{^1\text{H}\}$ NMR** (202 MHz, CDCl_3) δ 52.13 (s). **HRMS** (+ESI) m/z : ($\text{M} + \text{H}$) $^+$ calc'd for $\text{C}_{27}\text{H}_{25}\text{Cl}_2\text{NO}_4\text{PPd}$, 635.9937; found, 635.9931. **Anal.** Calc'd for $\text{C}_{27}\text{H}_{24}\text{Cl}_2\text{NO}_4\text{PPd}$: C, 51.09; H, 3.81; N, 2.21. Found: C, 48.51; H, 3.61; N, 2.03%.

3.4.1.2. (*R*)-(κ^2 -*P,N*)-(dimethyl 2-((diphenylphosphaneyl)(isoquinolin-1-yl)methyl)malonate)-dichloroplatinum(II) (*R*)-35****

35 is a light brown solid. Yield: 67%. $[\alpha]_{\text{D}}^{25} = -43$ (c 0.5, CH_2Cl_2).

^1H NMR (500 MHz, CDCl_3) δ 10.03 (d, $^3J_{\text{H-H}} = 6.7$ Hz, 1H, ArH, $\text{HC}=\text{CH-N}$), 8.30 (d, $^3J_{\text{H-H}} = 8.5$ Hz, 1H, ArH), 8.08 – 7.94 (m, 5H, ArH), 7.93 (s, ArH), 7.91 (s, 1H, ArH), 7.90 (s, 1H, ArH), 7.73 (m, 1H, ArH), 7.69 (d, $^3J_{\text{H-H}} = 6.8$ Hz, 1H, ArH), 7.57 (m, 2H, ArH), 7.53 – 7.41 (m, 6H, ArH), 5.83 (dd, $^3J_{\text{P-H}} = 12.3$, $^3J_{\text{H-H}} = 9.9$ Hz, 1H, $\text{CHCH}(\text{PPh}_2)\text{Ar}$), 4.52 (dd, $^2J_{\text{P-H}} = 14.7$, $^3J_{\text{H-H}} = 9.9$ Hz, 1H, $\text{CHCH}(\text{PPh}_2)\text{Ar}$), 3.30 (s), 3.27 (s, 3H, COOCH_3), 2.74 (s), 2.69 (s, 3H, COOCH_3). **^{13}C NMR** (126 MHz, CDCl_3) δ 166.98 (s, 1C, Ar, $\text{HC}=\text{CH-N}$), 166.34 (d, $^3J_{\text{P-C}} = 12.2$ Hz, 1C, $\text{C}=\text{O}$), 162.84 (d, $^3J_{\text{P-C}} = 5.7$ Hz, 1C, $\text{C}=\text{O}$), 144.38 (s), 141.96 (s), 139.29 (s), 136.26 (d, $^2J_{\text{P-C}} = 11.7$ Hz, 1C, Ar, $\text{N}=\text{C}-\text{C}(\text{H})\text{P}$), 135.95 (s), 133.18 (s), 132.94 (s), 132.66 (d, $^1J_{\text{P-C}} = 10.9$ Hz, 1C, Ar, P- C_6H_5), 132.45 (s), 130.16 (s), 129.50 (d, $^1J_{\text{P-C}} = 11.5$ Hz, 1C, Ar, P- C_6H_5), 128.51 (d, $J_{\text{P-C}} = 12.4$ Hz), 127.56 (d, $J_{\text{P-C}} = 48.2$ Hz), 126.99 (d, $J_{\text{P-C}} = 8.7$ Hz), 124.60 (d, $J_{\text{P-C}} = 62.1$ Hz), 123.34 (s), 120.84 (d, $J_{\text{P-C}} = 63.8$ Hz), 53.14 (s, 1C, COOCH_3), 52.56 (s, 1C, COOCH_3), 52.12 (d, $^2J_{\text{P-C}} = 4.3$ Hz, 1C, $\text{CHCH}(\text{PPh}_2)\text{Ar}$), 46.23 (d, $^1J_{\text{P-C}} = 37.1$ Hz, 1C, $\text{CHCH}(\text{PPh}_2)\text{Ar}$), 33.82 (s), 31.93 (s), 29.70 (s), 29.36 (s), 22.69 (s), 14.12 (s). **$^{31}\text{P}\{^1\text{H}\}$ NMR** (202 MHz, CDCl_3) δ 28.71 (s), 28.72 (d, $^1J_{\text{Pt-P}} = 3826.9$ Hz). **HRMS** (+ESI) m/z : ($\text{M} + \text{H}$) $^+$ calc'd for $\text{C}_{27}\text{H}_{25}\text{Cl}_2\text{NO}_4\text{PPt}$, 723.0546; found, 723.0544. **Anal.** Calc'd for $\text{C}_{27}\text{H}_{24}\text{Cl}_2\text{NO}_4\text{PPt}$: C, 44.83; H, 3.34; N, 1.94. Found: C, 44.67; H, 3.45; N, 2.10%.

3.4.2. General procedure for synthesizing P,N rhodium and iridium COD tetrafluoroborate complexes (40 and 43)

$[M(\text{COD})\text{Cl}]_2$ (0.04 mmol, 0.5 equiv.) was dissolved in 5.0 ml degassed DCM and stirred under nitrogen. AgBF_4 (0.08 mmol, 1.0 equiv.) was dissolved in degassed methanol and the solution was added to the DCM solution. This mixture was stirred at rt in the dark for 3 hrs.

The resulting $M^+(\text{COD})^- \text{BF}_4$ complex was filtered through a short Celite plug under nitrogen and immediately added to the DCM solution of **27** P,N ligand (0.08 mmol, 1.0 equiv) (obtained in the aforementioned way) at -80°C , stirred for an hour under nitrogen and allowed to rt. The forming (P,N) $M^+(\text{COD})^- \text{BF}_4$ complex was filtered through a short celite plug under Schlenk conditions and the solvent was removed by vacuum.

3.4.2.1. $[(\kappa^2\text{-P,N})\text{-(dimethyl 2-((diphenylphosphaneyl)(isoquinolin-1-yl)methyl)malonate)}][(\eta^1\text{-1Z,5Z-cycloocta-1,5-diene})\text{-rhodium(I)}]\text{tetrafluoroborate (40)}$

40 is a brown solid. Yield: 99.6 % (crude).

^1H NMR (500 MHz, CDCl_3) δ 8.18 (d, $^3J_{\text{H-H}} = 8.7$ Hz, 1H, ArH), 8.07 (d, $^3J_{\text{H-H}} = 6.5$ Hz, 1H, ArH), 7.96 (t, $^3J_{\text{H-H}} = 9.1$ Hz, 1H, ArH), 7.89 (d, $^3J_{\text{H-H}} = 6.4$ Hz, 1H, ArH), 7.86 (d, $^3J_{\text{H-H}} = 8.3$ Hz, 1H, ArH), 7.77 (d, $^3J_{\text{H-H}} = 7.3$ Hz, 1H, ArH), 7.74–7.69 (m, 3H, ArH), 7.68 – 7.63 (m, 1H, ArH), 7.55 – 7.49 (m, 1H, ArH), 7.48 – 7.38 (m, 5H, ArH), 7.33 – 7.27 (m, 3H, ArH), 5.88 (dd, $^3J_{\text{P-H}} = 13.2$ Hz, $^3J_{\text{H-H}} = 8.1$ Hz, 1H, $\text{CHCH}(\text{PPh}_2)\text{Ar}$), 5.67 (dd, $^3J_{\text{H-H}} = 15.1$ Hz, $^2J_{\text{Rh-H}} = 1.4$ Hz, 2H, COD $\text{HC}=\text{CH}$), 4.65 (dd, $^2J_{\text{P-H}} = 15.0$ Hz, $^3J_{\text{H-H}} = 8.1$ Hz, 1H, $\text{CHCH}(\text{PPh}_2)\text{Ar}$), 4.38 (d, $^3J_{\text{H-H}} = 55.1$ Hz, $^2J_{\text{Rh-H}} = 5.5$ Hz, 2H, COD $\text{HC}=\text{CH}$), 3.70 – 3.60 (m), 3.46 (s, 3H, COOCH_3), 3.24 – 3.14 (m, 1H), 2.81 (s, 3H, COOCH_3), 2.74 – 2.53 (m, 2H, COD CH_2), 2.37 (m, 3H, COD CH_2), 2.10 – 1.99 (m, 2H, COD CH_2). **^{13}C NMR** (126 MHz, CDCl_3) δ 167.26 (s, 1C, Ar, $\text{HC}=\text{CH-N}$), 166.16 (d, $^3J_{\text{P-C}} = 9.4$ Hz, 1C, $\text{C}=\text{O}$), 162.56 (d, $^3J_{\text{P-C}} = 9.3$ Hz, 1C, $\text{C}=\text{O}$), 142.02 (s), 136.68 (s), 133.84 – 133.40 (m), 133.55 (d, $^2J_{\text{P-C}} = 10.8$ Hz, 1C, Ar, $\text{N}=\text{C}-\text{C}(\text{H})\text{P}$), 133.16 (d, $^1J_{\text{P-C}} = 10.8$ Hz, 1C, Ar, $\text{P}-\text{C}_6\text{H}_5$), 132.51 (d, $J_{\text{P-C}} = 2.4$ Hz), 132.33 (d, $J_{\text{P-C}} = 2.1$ Hz), 130.07 (s), 129.63 (dd, $^2J_{\text{Rh-C}} = 20.9$ Hz, $^1J_{\text{P-C}} = 10.3$ Hz, 1C, Ar, $\text{P}-\text{C}_6\text{H}_5$), 128.01 (s), 128.00 (s), 127.68 (s), 127.09 (s), 127.02 (s), 126.97 (s), 124.62

(d, $J_{P-C} = 2.2$ Hz), 124.45 (s), 124.32 (d, $J_{P-C} = 2.7$ Hz), 114.05 (s), 109.30 – 108.82 (m, 1C, COD, HC=CH), 107.50 (d, $J = 7.8$ Hz), 106.60 – 106.16 (m, 1C, COD, HC=CH), 79.44 (dd, $^2J_{P-C} = 10.8$ Hz, $^1J_{Rh-C} = 4.9$ Hz, 1C, COD, HC=CH), 78.07 (s), 76.47 – 76.24 (m, 1C, COD, HC=CH), 55.89 (d, $^2J_{P-C} = 8.4$ Hz, 1C, CHCH(PPh₂)Ar), 53.46 (s, 1C, COOCH₃), 52.85 (s, 1C, COOCH₃), 47.75 (s), 47.59 (d, $^1J_{P-C} = 25.2$ Hz, 1C, CHCH(PPh₂)Ar), 35.55 (s), 33.81 (s), 31.91 (s), 30.88 (s), 29.34 (s), 29.14 (s), 28.97 (s), 26.03 (s), 22.67 (s), 18.36 (s), 14.10 (s), 9.13 (s), 1.00 (s). **¹⁹F NMR** (376 MHz, CDCl₃) δ -153.06 (s). **³¹P{¹H} NMR** (202 MHz, CDCl₃) δ 49.69 (d, $^1J_{Rh-P} = 156.2$ Hz). **HRMS** (+ESI) m/z: (M + H – BF₄)⁺ calc'd for C₃₅H₃₇NO₄PRh, 669.1515; found, 669.1519.

3.4.2.2. [(κ²-P,N)-(dimethyl 2-((diphenylphosphaneyl)(isoquinolin-1-yl)methyl)malonate)][(1,2,5,6-η)(1Z,5Z)-cycloocta-1,5-diene]-iridium(I) tetrafluoroborate (43**)**

43 is a dark-red solid. Yield: >99.9% (crude).

¹H NMR (500 MHz, CDCl₃) δ 8.49 (d, $^3J_{H-H} = 6.5$ Hz, 1H, ArH), 8.20 (d, $^3J_{H-H} = 8.7$ Hz, 1H, ArH), 8.08 (d, $^3J_{H-H} = 6.4$ Hz, 1H, ArH), 7.93 (d, $^3J_{H-H} = 8.1$ Hz, 1H, ArH), 7.83 – 7.79 (m, 2H, ArH), 7.72 – 7.61 (m, 4H, ArH), 7.53 (d, $^3J_{H-H} = 3.9$ Hz, 2H, ArH), 7.50 – 7.43 (m, 4H, ArH), 7.36 (d, $^3J_{H-H} = 5.2$ Hz, 3H, ArH), 7.16 (s, ArH), 6.97 (d, $^3J_{H-H} = 9.2$ Hz, 1H, ArH), 6.09 (dd, $^3J_{P-H} = 12.2$ Hz, $^3J_{H-H} = 9.05$ Hz, 1H, CHCH(PPh₂)Ar), 5.62 (s, 1H, COD HC=CH), 5.36 (s, 1H, COD HC=CH), 4.56 (dd, $^2J_{P-H} = 14.1$ Hz, $^3J_{H-H} = 9.05$ Hz, 1H, CHCH(PPh₂)Ar), 4.20 (s, 1H, COD HC=CH), 3.82 (s, 1H, COD HC=CH), 3.42 (s), 3.40 (s, 3H, COOCH₃), 3.19 – 3.10 (m), 2.73 (s, 3H, COOCH₃), 2.58 (s, 4H, COD CH₂), 2.32 – 2.16 (m, 2H, COD CH₂), 1.82 – 1.65 (m, 2H, COD CH₂). **¹³C NMR** (126 MHz, CDCl₃) δ 167.03 (s, 1C, Ar, HC=CH-N), 166.09 (d, $^3J_{P-C} = 10.3$ Hz, 1C, C=O), 165.17 (d, $^3J_{P-C} = 7.4$ Hz, 1C, C=O), 164.54 (s), 142.34 (s), 136.85 (s), 134.22 – 133.81 (m), 133.62 (d, $^2J_{P-C} = 10.6$ Hz, 1C, Ar, N=C-C(H)P), 132.72 (d, $^2J_{P-C} = 19.0$ Hz, 1C, Ar, P-C₆H₅), 131.12 (d, $J_{P-C} = 9.0$ Hz), 130.54 (s), 129.86 (d, $^2J_{P-C} = 10.7$ Hz, 1C, Ar, P-C₆H₅), 129.50 (d, $J_{P-C} = 10.5$ Hz), 129.01 (d, $J_{P-C} = 9.9$ Hz), 128.15 (s), 127.62 (s), 127.49 (s), 127.18 – 126.79 (m), 125.19 (s), 122.49 (d, $J_{P-C} = 46.8$ Hz), 99.76 (s), 97.35 (d, $^2J_{P-C} = 7.7$ Hz, 1C, COD, HC=CH), 96.87 (d, $^2J_{P-C} = 8.9$ Hz, 1C, COD, HC=CH) 65.79 (d, $^2J_{P-C} = 10.4$ Hz, 1C, COD,

HC=CH), 63.06 (d, $^2J_{P-C} = 13.8$ Hz 1C, COD, HC=CH), 55.28 (d, $^2J_{P-C} = 6.8$ Hz, 1C, CHCH(PPh₂)Ar), 53.43 (s, 1C, COOCH₃), 52.86 (s, 1C, COOCH₃), 49.59 (s), 48.22 (d, $^1J_{P-C} = 30.3$ Hz, 1C, CHCH(PPh₂)Ar), 47.73 (s), 43.77 (d, $J = 8.6$ Hz), 36.80 (s), 32.60 (s), 31.91 (s), 29.68 (s), 29.34 (s), 28.94 (s), 25.75 (s), 25.14 (s), 23.24 (d, $J = 4.3$ Hz), 23.04 (s), 22.68 (s), 14.10 (s), 9.13 (s). **^{19}F NMR** (376 MHz, CDCl₃) δ -153.26 (s). **$^{31}\text{P}\{^1\text{H}\}$ NMR** (202 MHz, CDCl₃) δ 41.49 (s). **HRMS** (+ESI) m/z : (M + H - BF₄)⁺ calc'd for C₃₅H₃₇NO₄PIr, 759.2090; found, 759.2097.

3.4.3. Preparation of {(*R*)-($\kappa^2\text{-C}^2,\text{N}$)-1-[1-(dimethylamino)ethyl]naphthyl}-{(*R*)-($\kappa^2\text{-P,N}$)-(dimethyl 2-((diphenylphosphaneyl)(isoquinolin-1-yl)methyl)malonate)}-palladium(II) perchlorate ((*R,R*)-**28**)

Diphenylphosphine (0.08 mmol, 0.015 g, 1.0 equiv.) was weighed into a Schlenk flask under positive N₂ flow and 3.0 ml previously degassed DCM was added. Malonate substrate **22a** (0.08 mmol, 0.022 g, 1.0 equiv.) and (*S*)-**14** catalyst (0.004 mmol, 0.0025 g, 0.05 equiv.) were added to the solution and then the mixture was cooled down to -80 °C. Upon the required temperature was reached, triethylamine (0.08 mmol, 0.009 g, 1.0 equiv) was added dropwise to the reaction mixture. After the completion of the reaction, (*R*)-**1** complex (0.08 mmol, 0.042 g, 1.0 equiv.) was added and the mixture was allowed to warm up to rt. The solution was washed with water and brine, dried, filtered through short celite plug, then the solvent was evaporated. The crude complex was recrystallized from DCM with diethyl ether to afford diastereomerically pure crystals.

(*R,R*)-**28** is a bright-yellow solid. Yield: 33%. [α]_D²⁵ = -247 (c 2.0, CH₂Cl₂).

^1H NMR (500 MHz, CDCl₃) δ 8.72 (d, $^3J_{H-H} = 6.1$ Hz, 1H, ArH, HC=CH-N), 8.32 (d, $^3J_{H-H} = 8.6$ Hz, 1H, ArH), 8.25 (d, $^3J_{H-H} = 6.1$ Hz, 1H, ArH), 7.99 (d, $^3J_{H-H} = 8.2$ Hz, 1H, ArH), 7.89 – 7.76 (m, 5H, ArH), 7.74 (d, $^3J_{H-H} = 8.1$ Hz, 1H, ArH), 7.58 – 7.47 (m, 5H, ArH), 7.47 – 7.40 (m, 3H, ArH), 7.30 (t, $^3J_{H-H} = 6.9$ Hz, 2H, ArH), 7.20 (d, $^3J_{H-H} = 8.4$ Hz, 1H, ArH), 6.97 – 6.91 (m, 1H, ArH), 5.91 (dd, $^3J_{H-P} = 13.7$, $^3J_{H-H} = 8.6$ Hz, 1H, CHCH(PPh₂)Ar), 4.74 – 4.60 (m, 2H, NCHCH₃, CHCH(PPh₂)Ar), 3.31 (s, 3H, COOCH₃), 3.28 (s), 3.19 (s), 3.13 (d, $^4J_{P-H} = 3.0$ Hz, 3H, NCH₃), 3.09 (s, 3H, NCH₃), 2.85 (s, 3H, COOCH₃), 2.22 (d, $^3J_{H-H} = 6.2$ Hz, 3H, NCHCH₃), 1.29 (s), 1.26

(s). ^{13}C NMR (126 MHz, CDCl_3) δ 166.60 (s, 1C, Ar, $\text{HC}=\text{CH}-\text{N}$), 165.95 (d, $^3J_{\text{P-C}} = 11.3$ Hz, 1C, $\text{C}=\text{O}$), 158.91 (d, $^3J_{\text{P-C}} = 5.4$ Hz, 1C, $\text{C}=\text{O}$), 150.18 (s), 146.55 (s), 142.29 (s), 137.27 (d, $^2J_{\text{P-C}} = 12.6$ Hz, Ar, $\text{N}=\text{C}-\text{C}(\text{H})\text{P}$), 137.02 (s), 135.44 (d, $^1J_{\text{P-C}} = 12.0$ Hz, Ar, $\text{P}-\text{C}_6\text{H}_5$), 133.17 (s), 133.07 (s), 132.96 (t, 1C, $J_{\text{P-C}} = 2.8$ Hz, Ar), 131.81 (s), 130.06 (s), 129.96 (d, $J_{\text{P-C}} = 4.5$ Hz, 1C, Ar), 129.01 (d, $^1J_{\text{P-C}} = 11.2$ Hz, Ar, $\text{P}-\text{C}_6\text{H}_5$), 128.91 (d, $J_{\text{P-C}} = 3.9$ Hz), 128.37 (s), 127.11 (d, $J_{\text{P-C}} = 6.0$ Hz), 126.66 (d, $J_{\text{P-C}} = 7.2$ Hz), 126.30 (s), 125.39 (s), 125.18 (s), 124.80 (s), 123.27 (s), 123.17 (s), 122.82 (s), 74.33 (d, $^3J_{\text{P-C}} = 2.8$ Hz, 1C, NCH_3), 55.02 (d, $^2J_{\text{P-C}} = 9.4$ Hz, 1C, $\text{CHCH}(\text{PPh}_2)\text{Ar}$), 53.23 (s, 1C, COOCH_3), 52.89 (s, 1C, COOCH_3), 52.09 (d, $^3J_{\text{P-C}} = 2.4$ Hz, 1C, NCH_3), 47.29 (s, 1C, NCHCH_3), 46.08 (d, $^1J_{\text{P-C}} = 32.3$ Hz, 1C, $\text{CHCH}(\text{PPh}_2)\text{Ar}$), 29.69 (s), 24.51 (s, 1C, NCHCH_3). $^{31}\text{P}\{^1\text{H}\}$ NMR (202 MHz, CDCl_3) δ 57.75 (s), 54.85 (s). HRMS (+ESI) m/z : $(\text{M} + \text{H})^+$ calc'd for $\text{C}_{41}\text{H}_{41}\text{ClN}_2\text{O}_8\text{PPd}$, 861.1324; found, 861.1301. Anal. Calc'd for $\text{C}_{41}\text{H}_{40}\text{ClN}_2\text{O}_8\text{PPd}$: C, 57.15; H, 4.68; N, 3.25. Found: 57.24; H, 4.38; N, 3.13%.

3.4.4. Preparation of $[(\kappa^2\text{-P,N})\text{-(dimethyl 2-((diphenylphosphaneyl)(isoquinolin-1-yl)methyl)malonate)}][(\text{1,2,3-}\eta\text{-allyl})\text{-palladium(II) tetrafluoroborate (46)}$

$[\text{Pd}(\text{allyl})\text{Cl}]_2$ (0.04 mmol, 0.5 equiv.) was dissolved in 5.0 ml degassed DCM and stirred under nitrogen. AgBF_4 (0.08 mmol, 1.0 equiv.) was dissolved in degassed methanol and the solution was added to the DCM solution. This mixture was stirred at rt in the dark for 3 hrs.

The resulting $\text{Pd}^+(\text{allyl}) \text{BF}_4^-$ complex was filtered through a short Celite plug under nitrogen and immediately added to the DCM solution of **27** P,N ligand (0.08 mmol, 1.0 equiv) (obtained in the aforementioned way) at -80°C , stirred for an hour under nitrogen and allowed to rt. The forming $(\text{P,N})\text{Pd}^+(\text{allyl}) \text{BF}_4^-$ complex was filtered through a short celite plug under Schlenk conditions and the solvent was removed by vacuum. The crude material was recrystallized from DCM with hexane.

46 is a colorless crystalline solid. Yield: 18.4%.

^1H NMR (500 MHz, CDCl_3) δ 8.98 (d, $^3J_{\text{H-H}} = 6.2$ Hz, 1H, ArH , $\text{HC}=\text{CH}-\text{N}$), 8.44 (d, $^3J_{\text{H-H}} = 8.6$ Hz, 1H, ArH), 8.10 (d, $^3J_{\text{H-H}} = 12.7$ Hz, 1H, ArH), 8.00 (d, $^3J_{\text{H-H}} = 8.2$ Hz, 1H, ArH), 7.94 (d, $^3J_{\text{H-H}} = 6.2$ Hz, 1H, ArH), 7.93 – 7.89 (m, 2H, ArH), 7.87 – 7.81 (m, 2H, ArH), 7.71 (dd, $^3J_{\text{H-H}} = 10.8$ Hz, 8.3 Hz, 2H, ArH), 7.66 (s, 1H, ArH), 7.65 – 7.62 (m, 2H, ArH), 7.58 (dd, $^3J_{\text{H-H}} = 7.6$ Hz, 1.8 Hz, 2H, $\text{P}-\text{C}_6\text{H}_5$),

7.56 (s, 1H, ArH), 7.44 (d, $^3J_{\text{H-H}} = 7.8$ Hz, 3H, P-C₆H₅), 7.15 (dd, $^3J_{\text{H-H}} = 11.4$ Hz, 8.8 Hz, 2H, ArH), 6.85 (dd, $^3J_{\text{H-H}} = 10.1$ Hz, 9.0 Hz, 1H, CH(CH₂)₂), 6.23 (m, 1H, CH(CH₂)₂), 6.17 (dd, $^3J_{\text{H-H}} = 13.1$ Hz, $^3J_{\text{H-P}} = 8.6$ Hz, 1H, CH₂CH(PPh₂)Ar), 5.50 (dd, $^3J_{\text{H-H}} = 18.5$ Hz, 5.7 Hz, 1H, CH(CH₂)₂), 5.34 – 5.28 (m, 1H, CH₂CH(PPh₂)Ar), 3.33 (s, 3H, COOCH₃), 3.23 (dd, $^3J_{\text{H-H}} = 13.9$ Hz, 6.8 Hz, 1H, CH(CH₂)₂), 2.83 (s, 3H, COOCH₃), 2.76 (s, 1H), 2.06 (d, $^3J_{\text{H-H}} = 10.9$ Hz, 1H, CH(CH₂)₂). **¹³C NMR** (126 MHz, CDCl₃) δ 167.03 (s, 1C, Ar, HC=CH-N), 166.19 (d, $^3J_{\text{P-C}} = 9.8$ Hz, 1C, C=O), 161.27 (d, $^3J_{\text{P-C}} = 9.0$ Hz, 1C, C=O), 148.30 (s), 136.83 (s), 135.38 (d, $^2J_{\text{P-C}} = 14.8$ Hz, 1C, Ar, N=C-C(H)P), 133.24 (s), 132.98 (d, $J_{\text{P-C}} = 2.5$ Hz), 132.86 (d, $^1J_{\text{P-C}} = 13.5$ Hz, 1C, Ar, P-C₆H₅), 132.33 (d, $J_{\text{P-C}} = 1.7$ Hz), 130.11 (s), 129.93 (d, $^1J_{\text{P-C}} = 10.8$ Hz, 1C, Ar, P-C₆H₅), 129.64 (d, $J_{\text{P-C}} = 14.5$ Hz), 129.38 (d, $J_{\text{P-C}} = 11.4$ Hz), 128.20 (s), 127.83 (s), 127.32 (d, $J_{\text{P-C}} = 6.4$ Hz), 126.36 (s), 125.72 (d, $J_{\text{P-C}} = 37.9$ Hz), 124.45 (s), 123.23 (s), 114.06 (s), 54.25 (d, $^2J_{\text{P-C}} = 8.6$ Hz, 1C, CHCH(PPh₂)Ar), 53.19 (s, 1C, COOCH₃), 52.78 (s, 1C, COOCH₃), 45.67 (s, 1C, CHCH(PPh₂)Ar), 31.05 (s). **¹⁹F NMR** (376 MHz, CDCl₃) δ -152.72 (s), -152.77 (s). **³¹P{¹H} NMR** (162 MHz, CDCl₃) δ 49.23 (dd, $^2J_{\text{P-C}} = 291.5$, 8.1 Hz). **HRMS** (+ESI) m/z: (M + H – BF₄)⁺ calc'd for C₃₀H₃₀NO₄PPd, 604.0967; found, 604.0885.

3.4.5. Preparation of (κ²-P,N)-(dimethyl 2-((diphenylphosphaneyl)(isoquinolin-1-yl)methyl)malonate)-dichloronickel(II) (50)

Diphenylphosphine (0.08 mmol, 0.015 g, 1.0 equiv.) was weighed into a Schlenk flask under positive N₂ flow and 3.0 ml previously degassed DCM was added. Malonate substrate **22a** (0.08 mmol, 0.022 g, 1.0 equiv.) and (*S*)-**14** catalyst (0.004 mmol, 0.0025 g, 0.05 equiv.) were added to the solution and then the mixture was cooled down to –80 °C. Upon the required temperature was reached, triethylamine (0.08 mmol, 0.009 g, 1.0 equiv) was added dropwise to the reaction mixture. After the completion of the reaction, Ni(MeCN)₂Cl₂ complex (0.08 mmol, 0.042 g, 1.0 equiv.) was added and the mixture was allowed to warm up to rt. The solution was washed with water and brine, dried, then filtered through a short celite plug. The crude complex could not be recrystallized.

50 is a yellow solid. Yield: 44.8 mg (crude, >100%).

HRMS (+ESI) m/z : $(M + H)^+$ calc'd for $C_{27}H_{25}Cl_2NNiO_4P$, 588.0221; found, 588.0223 (significantly fragmented).

3.4.6. Preparation of (κ^2 -P,N)-(3-(diphenylphosphaneyl)-3-(isoquinolin-1-yl)-1-phenylpropan-1-one)-dichloropalladium(II) (**54**)

Diphenylphosphine (0.08 mmol, 0.015 g, 1.0 equiv.) was weighed into a Schlenk flask under positive N_2 flow and 3.0 ml previously degassed DCM was added. Acrylophenone substrate **23** (0.08 mmol, 0.022 g, 1.0 equiv.) and (*S*)-**14** catalyst (0.004 mmol, 0.0025 g, 0.05 equiv.) were added to the solution and then the mixture was cooled down to $-80^\circ C$. Upon the required temperature was reached, triethylamine (0.08 mmol, 0.009 g, 1.0 equiv) was added dropwise to the reaction mixture. After the completion of the reaction, $Pd(MeCN)_2Cl_2$ complex (0.08 mmol, 0.042 g, 1.0 equiv.) was added and the mixture was allowed to warm up to rt. The solution was washed with water and brine, dried, filtered through short celite plug, then the solvent was evaporated. The crude complex was recrystallized from DCM with hexane to afford pure yellow crystals.

54 is a yellow crystalline solid. Yield: 40%.

1H NMR (500 MHz, $CDCl_3$) δ 9.75 (d, $^3J_{H-H} = 6.5$ Hz, 1H, ArH, HC=CH-N), 9.02 (d, $^3J_{H-H} = 15.8$ Hz, 1H, ArH), 8.77 (dd, $^3J_{H-H} = 15.6$ Hz, 8.4 Hz, 1H, ArH), 8.57 (d, $^3J_{H-H} = 6.4$ Hz, 1H, ArH), 8.26 (d, $^3J_{H-H} = 8.6$ Hz, 2H, ArH), 8.09 – 7.97 (m, 4H, ArH), 7.95 – 7.83 (m, 5H, ArH), 7.75 (ddd, $^3J_{H-H} = 25.3$ Hz, 14.5 Hz, 7.8 Hz, 4H, ArH), 7.64 – 7.53 (m, 6H, ArH), 7.49 (t, $^3J_{H-H} = 6.1$ Hz, 3H, P- C_6H_5), 7.37 (t, $^3J_{H-H} = 7.7$ Hz, 3H, P- C_6H_5), 7.12 (d, $^3J_{H-H} = 5.1$ Hz, 4H, ArH), 6.07 (dd, $^3J_{H-H} = 14.4$ Hz, $^2J_{H-P} = 9.9$ Hz, 1H, $CH_2CH(PPh_2)$), 4.50 (ddd, $^3J_{H-H} = 18.4$ Hz, $^3J_{H-P} = 15.6$ Hz, $^2J_{H-H} = 9.9$ Hz, 1H, $CH_2CH(PPh_2)$), 3.11 (dd, $^3J_{H-H} = 21.0$ Hz, $^3J_{H-P} = 19.8$ Hz, 1H, $CH_2CH(PPh_2)$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 206.99 (s, 1C, C=O), 193.67 (s), 189.56 (s), 165.91 (d, $^2J_{P-C} = 9.1$ Hz, 1C, Ar, N=C-C(H)P), 159.13 (s), 144.88 (s), 143.78 (s), 139.91 (s), 137.25 (s), 136.98 (s), 135.75 (d, $J_{P-C} = 11.1$ Hz), 134.69 (s), 134.24 (d, $J_{P-C} = 21.0$ Hz), 133.76 (s), 133.35 (s), 132.85 (s), 132.71 (d, $^1J_{P-C} = 10.3$ Hz, 1C, Ar, P- C_6H_5), 132.60 – 132.50 (m), 130.48 (s), 129.62 (d, $^1J_{P-C} = 11.4$ Hz, 1C, Ar, P- C_6H_5), 129.49 (s), 129.10 (s),

128.37 (dd, $J_{P-C} = 12.7$ Hz, 10.2 Hz), 127.95 (s), 127.18 (s), 126.60 (s), 126.26 (s), 126.07 (s), 125.54 (s), 125.29 (d, $J_{P-C} = 11.1$ Hz), 123.10 (t, $J_{P-C} = 29.5$ Hz), 122.70 (s), 44.43 (d, $^1J_{P-C} = 33.0$ Hz, 1C, CH₂CH(PPh₂)), 41.73 (d, $^2J_{P-C} = 3.8$ Hz, 1C, CH₂CH(PPh₂)), 30.93 (s). **$^{31}\text{P}\{^1\text{H}\}$ NMR** (162 MHz, CDCl₃) δ 51.9 (s). **HRMS** (+ESI) m/z : (M + H)⁺ calc'd for C₃₀H₂₅Cl₂NOPPd, 624.0164; found, 624.0151.

3.5. Crystallographic data

3.5.1. Crystallographic data of complex (R)-34

Figure 99. Structure of complex (R)-34 with the thermal ellipsoids.

Table 9. Crystal Data of palladium complex (R)-34.

Crystal data	
Identification code	CCDC 1968108
Chemical formula	C ₂₇ H ₂₄ Cl ₂ NO ₄ PPd
Formula weight	634.74 g/mol
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal size	0.060 x 0.100 x 0.220 mm
Crystal habit	yellow block
Crystal system	orthorhombic

Space group	P 21 21 21	
Unit cell dimensions	a = 10.1645(14) Å	$\alpha = 90^\circ$
	b = 10.1645(14) Å	$\beta = 90^\circ$
	c = 17.932(3) Å	$\gamma = 90^\circ$
Volume	2712.2(7) Å ³	
Z	4	
Density (calculated)	1.555 g/cm ³	
Absorption coefficient	0.974 mm ⁻¹	
F(000)	1280	

Data collection

Theta range for data collection	2.27 to 26.42°
Index ranges	-12 ≤ h ≤ 9, -18 ≤ k ≤ 18, -22 ≤ l ≤ 22
Reflections collected	16735
Independent reflections	5536 [R(int) = 0.0933]
Coverage of independent reflections	99.7%
Absorption correction	Multi-Scan
Max. and min. transmission	0.9440 and 0.8140
Structure solution technique	direct methods
Structure solution program	XT, VERSION 2014/5

Refinement

Refinement method	Full-matrix least-squares on F ²
Refinement program	SHELXL-2016/6 (Sheldrick, 2016)
Function minimized	$\sum w(F_o^2 - F_c^2)^2$
Data / restraints / parameters	5536 / 0 / 327
Goodness-of-fit on F²	1.020
Final R indices	3717 data; I > 2σ(I)
	R1 = 0.0566, wR2 = 0.1094
	R1 = 0.1028, wR2 = 0.1307
Weighting scheme	w = 1/[σ ² (F _o ²) + (0.0484P) ²] where P = (F _o ² + 2F _c ²)/3
Absolute structure parameter	0.03(4)
Largest diff. peak and hole	0.864 and -0.582 eÅ ⁻³
R.M.S. deviation from mean	0.119 eÅ ⁻³

3.5.2. Crystallographic data of complex 35

Figure 100. Structure of complex **35** with the thermal ellipsoids.

Table 10. Crystal Data of platinum complex **35**.

Crystal data	
Identification code	CCDC 1968110
Chemical formula	C ₂₇ H ₂₄ Cl ₂ NO ₄ PPt
Formula weight	723.43 g/mol
Temperature	250(2) K
Wavelength	0.71073 Å
Crystal size	0.040 x 0.060 x 0.100 mm
Crystal habit	yellow plate
Crystal system	triclinic
Space group	P -1
Unit cell dimensions	a = 11.0515(12) Å α = 116.404(3)° b = 11.2817(12) Å β = 96.725(3)° c = 11.9017(12) Å γ = 93.542(3)°
Volume	1309.1(2) Å ³
Z	2
Density (calculated)	1.835 g/cm ³

Absorption coefficient	5.659 mm ⁻¹
F(000)	704

Data collection

Theta range for data collection	2.76 to 30.55°
Index ranges	-15 ≤ h ≤ 15, -16 ≤ k ≤ 16, -16 ≤ l ≤ 17
Reflections collected	19663
Independent reflections	7915 [R(int) = 0.0489]
Coverage of independent reflections	98.7%
Absorption correction	Multi-Scan
Max. and min. transmission	0.8050 and 0.6010
Structure solution technique	direct methods
Structure solution program	XT, VERSION 2014/5

Refinement

Refinement method	Full-matrix least-squares on F ²
Refinement program	SHELXL-2016/6 (Sheldrick, 2016)
Function minimized	$\Sigma w(F_o^2 - F_c^2)^2$
Data / restraints / parameters	7915 / 0 / 327
Goodness-of-fit on F²	1.040
$\Delta/\sigma_{\max}$	0.001
Final R indices	6611 data; R1 = 0.0369, wR2 = 0.0875 I > 2σ(I)
	all data R1 = 0.0505, wR2 = 0.0953
Weighting scheme	w = 1/[σ ² (F _o ²) + (0.0470P) ² + 0.2195P] where P = (F _o ² + 2F _c ²)/3
Largest diff. peak and hole	1.747 and -1.975 eÅ ⁻³
R.M.S. deviation from mean	0.161 eÅ ⁻³

3.5.3. Crystallographic data of complex (*R,R*)-28

Figure 101. Structure of complex (*R,R*)-28 with the thermal ellipsoids.

Table 11. Crystal Data of palladium complex (*R,R*)-28.

Crystal data		
Identification code	CCDC 1968111	
Chemical formula	$C_{44.40}H_{48.40}Cl_{1.40}N_2O_{8.80}PPd$	
Formula weight	937.85 g/mol	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal size	0.100 x 0.220 x 0.240 mm	
Crystal habit	yellow block	
Crystal system	orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	$a = 10.0501(2)$ Å	$\alpha = 90^\circ$
	$b = 11.1476(3)$ Å	$\beta = 90^\circ$
	$c = 38.2901(11)$ Å	$\gamma = 90^\circ$
Volume	$4289.81(19)$ Å ³	
Z	4	
Density (calculated)	1.452 g/cm ³	

Absorption coefficient	0.614 mm ⁻¹
F(000)	1936

Data collection

Theta range for data collection	2.43 to 34.97°
Index ranges	-16 ≤ h ≤ 9, -17 ≤ k ≤ 17, -61 ≤ l ≤ 40
Reflections collected	55340
Independent reflections	18695 [R(int) = 0.0557]
Coverage of independent reflections	99.6%
Absorption correction	Multi-Scan
Max. and min. transmission	0.9410 and 0.8670
Structure solution technique	direct methods
Structure solution program	XT, VERSION 2014/5

Refinement

Refinement method	Full-matrix least-squares on F ²
Refinement program	SHELXL-2016/6 (Sheldrick, 2016)
Function minimized	$\sum w(F_o^2 - F_c^2)^2$
Data / restraints / parameters	18695 / 317 / 613
Goodness-of-fit on F²	1.029
$\Delta/\sigma_{\max}$	0.003
Final R indices	15734 data; R1 = 0.0419, wR2 = 0.0749 I > 2σ(I) all data R1 = 0.0581, wR2 = 0.0825
Weighting scheme	w = 1/[σ ² (F _o ²) + (0.0239P) ² + 0.6303P] where P = (F _o ² + 2F _c ²)/3
Absolute structure parameter	0.007(9)
Largest diff. peak and hole	0.691 and -0.888 eÅ ⁻³
R.M.S. deviation from mean	0.090 eÅ ⁻³

3.5.4. Crystallographic data of complex 46

Figure 102. Structure of complex 46 with the thermal ellipsoids.

Table 12. Crystal data of palladium complex 46.

Crystal data

Identification code	leung1173m	
Chemical formula	$C_{30}H_{29}BF_4NO_4PPd$	
Formula weight	691.72 g/mol	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal size	0.040 x 0.220 x 0.280 mm	
Crystal habit	colorless plate	
Crystal system	monoclinic	
Space group	P 1 21/n 1	
Unit cell dimensions	$a = 10.3716(5)$ Å	$\alpha = 90^\circ$
	$b = 24.6474(15)$ Å	$\beta = 94.945(2)^\circ$
	$c = 11.8186(7)$ Å	$\gamma = 90^\circ$

Volume	3010.0(3) Å ³
Z	4
Density (calculated)	1.526 g/cm ³
Absorption coefficient	0.730 mm ⁻¹
F(000)	1400

Data collection

Theta range for data collection	2.39 to 29.59°
Index ranges	-14 ≤ h ≤ 13, -34 ≤ k ≤ 27, -16 ≤ l ≤ 16
Reflections collected	29554
Independent reflections	8378 [R(int) = 0.0908]
Coverage of independent reflections	99.0%
Absorption correction	Multi-Scan
Max. and min. transmission	0.9710 and 0.8220
Structure solution technique	direct methods
Structure solution program	XT, VERSION 2014/5

Refinement

Refinement method	Full-matrix least-squares on F ²
Refinement program	SHELXL-2018/3 (Sheldrick, 2018)
Function minimized	Σ w(F _o ² - F _c ²) ²
Data / restraints / parameters	8378 / 91 / 409
Goodness-of-fit on F²	1.067
Final R indices	5381 data; R1 = 0.0615, wR2 = 0.1205 I > 2σ(I)
	all data R1 = 0.1152, wR2 = 0.1422
Weighting scheme	w = 1/[σ ² (F _o ²) + (0.0391P) ² + 5.6840P] where P = (F _o ² + 2F _c ²)/3
Largest diff. peak and hole	1.223 and -1.145 eÅ ⁻³
R.M.S. deviation from mean	0.119 eÅ ⁻³

3.5.5. Crystallographic data of complex 54

Figure 103. ORTEP image of palladium complex 54.

Table 13. Crystal data of palladium complex 54.

Crystal data		
Identification code	leung1174m	
Chemical formula	C ₃₁ H ₂₅ Cl ₅ NO ₃ Pd	
Formula weight	742.14 g/mol	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal size	0.180 x 0.200 x 0.220 mm	
Crystal habit	yellow block	
Crystal system	monoclinic	
Space group	P 1 21/n 1	
Unit cell dimensions	a = 9.8533(3) Å	$\alpha = 90^\circ$
	b = 22.8442(7) Å	$\beta = 94.1748(14)^\circ$
	c = 13.1558(5) Å	$\gamma = 90^\circ$
Volume	2953.39(17) Å ³	
Z	4	
Density (calculated)	1.669 g/cm ³	
Absorption coefficient	1.163 mm ⁻¹	
F(000)	1488	

Data collection

Theta range for data collection	2.26 to 33.77°
Index ranges	-14≤h≤15, -33≤k≤35, -20≤l≤20
Reflections collected	36019
Independent reflections	11771 [R(int) = 0.0650]
Coverage of independent reflections	99.4%
Absorption correction	Multi-Scan
Max. and min. transmission	0.8180 and 0.7840
Structure solution technique	direct methods
Structure solution program	XT, VERSION 2014/5

Refinement

Refinement method	Full-matrix least-squares on F ²
Refinement program	SHELXL-2018/3 (Sheldrick, 2018)
Function minimized	$\Sigma w(F_o^2 - F_c^2)^2$
Data / restraints / parameters	11771 / 0 / 361
Goodness-of-fit on F ²	1.039
$\Delta/\sigma_{\max}$	0.002
Final R indices	8519 data; R1 = 0.0474, wR2 = 0.0897 I>2σ(I) all data R1 = 0.0772, wR2 = 0.1030
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0283P)^2+1.7294P]$ where $P=(F_o^2+2F_c^2)/3$
Largest diff. peak and hole	0.693 and -1.084 eÅ ⁻³
R.M.S. deviation from mean	0.142 eÅ ⁻³

CHAPTER 4: Structural and Electronic Investigation of the P,N Complexes

Abstract

The comprehensive electronic and structural investigation of the metal complexes obtained in Chapter 3. is being performed in this chapter via thorough crystallographic scrutiny, coordination studies and computational analysis. Upon the deep structural analysis of these compounds, their coordination behaviour was understood, and the electronic effects around the metal centers ligated with the bidentate P,N moiety were quantified by utilizing the Natural Bond Orbital DFT tool. The catalyst testing of P,N palladium complex (*R*)-**34** is also carried out in various catalytic reactions.

4.1. Introduction – Examples for structural and electronic analyses of catalyst complexes

The thorough and deep scrutiny of transition metal catalyst complexes by structural and electronic points of views is crucial in order to better understand the catalytic processes and to be able to propose their mechanisms step by step.

The electronic influences of the coordinating ligands, such as the extents of donation and backdonation can have significant effects on the reactivity of a metal catalysts. This principle is based on the electron density on the metal which varies according to the different coordinating moieties.

This effect was clearly shown by Amatore et al. by investigating the rate of the oxidative addition of phenyl iodide (PhI) to palladium(0) triarylphosphine complexes. The different *para* substituents on the triarylphosphine ligands unambiguously influenced the reaction rate of the oxidative addition (Figure 104.).¹⁵⁰⁻¹⁵¹

Figure 104. Rate-dependence of oxidative addition of PhI to Pd(0) with various triarylphosphine ligands.

The explanation behind this observation is that the different *para* substituents (some of them are more electron-donating, some of them are more electron-withdrawing) cause different electron densities on the coordinating phosphorus atoms by influencing the donation-backdonation capabilities of the ligands. This determines the overall electron density on the metal, thus activity of the palladium(0) center.

Reiersølmoen and Csokas et al. reported a comprehensive study on the electronic effects occur in pyridine gold complexes and their influences on a gold(III) catalyzed cyclopropanation reaction (Figure 105).¹⁵² The influence of the different substituents (R groups) of the pyridine ligands on the cyclopropanation of styrene (**56**) with propargylester (**55**) was scrutinized from electronic and steric points of views. In their paper, they successfully proved that the Au(III) complex **58** remained in +3 oxidation state instead of being the pre-catalyst of an active Au(I) species. They also determined that the two pyridine ligands stayed in the less common *trans* positions to each other during the catalytic process.

Figure 105. Cyclopropanation of styrene at rt with propargylester catalyzed by Au(III) pyridine complexes (**58a-d**).

As it can be seen in the figure, the conversion, thus, the reactivity depends on the electron-withdrawing or donating nature of the R substituents: CF_3 , which is the most electron-withdrawing group in this instance, increases the conversion the most. This indicates that the less electron density on the Au(III) center causes higher activity in the reaction. They employed various DFT methods, such as calculating the stabilization energies of the complexes or applying the Natural Atomic Populations Analysis to

quantify the electron density on the coordinating nitrogen in these gold complexes. Latter was supported by ^{15}N NMR spectroscopy as well.

In our group, there are several examples reported on structural and electronic scrutiny of the reported palladacycle complexes. Joseph Ng et al. carried out and reported a deep conformational analysis on phospho- and arsapalladacycles via Sawhorse and Newman projections.¹⁵³ Similar study was done by Jeremy Chen et al. on the C,N iridacycle they synthesized (Figure 22, Chapter 1.2.4.).⁵⁵ These analyses were based on the obtained X-ray crystallographic data and on two-dimensional ^1H - ^1H ROESY correlation NMR spectroscopy. Latter provides information on the protons' spatial positions by exploiting the Nuclear Overhauser Effect.¹⁵⁴

From the electronic point of view, Huang Yinhua et al. carried out a coordination study to prove their proposed synthesis of the asymmetric hydrophosphination catalyzed by C,N palladacycle complex **1**.¹⁰⁵ In their study, they used diphenylphosphine (HPPH_2) to show its extent of lability especially when positioned *trans* to the aromatic carbon. This reaction helped them determine which coordination site was occupied by the substrate and which one by the reagent (HPPH_2) (Figure 106.).

Figure 106. Selected part of the coordination study carried out by Huang et al. in their paper in 2010.

In this scheme, the diphenylphosphine molecules coordinate to both sites of the palladium complex ((*R*)-**59**) and substitutes the labile acetonitrile ligands. However, when another equivalent of compound (*R*)-**1** was applied, only complex (*R*)-**60** could be observed, in which the coordinating diphenylphosphine is positioned *cis* to the aromatic carbon. This implies that ligand in *trans* position to the carbon are more labile and its coordination is less favorable, hence, it can be removed more easily to be substituted by a substrate molecule. This study successfully revealed the kinetic trans effects (KTE) occurred in the palladacycle complex **1**.

Also, in our research group, Yu-Xiang et al. synthesized the platinum analogues of palladacycle complexes **1** and **14**.⁵⁴ The platinum complexes were then complexed by the dppe (achiral diphosphine) ligand, which afforded (*R*)-**61** and (*R*)-**62** derivatives along with tremendous pieces of information on the electronic features of these compounds (Figure 107.).

Figure 107. Dppe derivatives of the platinum analogues of complexes **1** and **14**.

Complexes (*R*)-**61** and (*R*)-**62** enabled them to gather information on the structural trans effects (or influences in other words) occurring in these molecules. Beyond the X-ray structure analysis, which provided information on bond lengths, the diphosphine complexes were analyzed by $^{31}\text{P}\{^1\text{H}\}$ NMR spectroscopy. The ^{31}P and ^{195}Pt nuclei are both NMR active, thus, the $^1J_{\text{Pt-P}}$ coupling constants clearly showed the strength of each coordination bond.¹⁵⁵ In the case of (*R*)-**61** azaplatinacycle, they found that the $^{31}\text{P}\{^1\text{H}\}$ NMR signal of the dppe phosphorus atom in *trans* position to the aromatic carbon exhibited significantly lower spin-spin coupling ($^1J_{\text{Pt-P}} = 1791$ Hz) compared to the one in *cis* position ($^1J_{\text{Pt-P}} = 3640$ Hz). This shows that the Pt–P bond positioned *trans* to the carbon is significantly weaker because of the carbo-aromatic naphthyl ring's strong π acidity and trans influence. This was also manifested in the elongated Pt–P bond length *trans* to the carbon atom (structural trans influence or STE). In phosphaplatinacycle (*R*)-**62** the trend resulted as the same: the dppe ligand's phosphorus atom positioned *trans* to the aromatic coordinating carbon showed $^1J_{\text{Pt-P}} = 1723$ Hz, which value was lower than that measured in the case of the *cis* dppe phosphorus atom ($^1J_{\text{Pt-P}} = 2770$ Hz). This means that the electron-withdrawing effect of the aromatic carbon atom is even stronger than that for the coordinating phosphorus. This effect of the coordinating sp^2 carbon atom was quantified by DFT calculations in their report as well by scrutinizing the interaction between the aromatic $\pi^*(\text{C}=\text{C})$ and the metal $\text{d}(\text{Pt})$ orbitals. It also can be seen that the difference between the coordinating nitrogen and phosphorus on the

naphthyl ligand backbones is significant regarding this aspect, and worth to be taken into consideration during catalyst designing.

4.2. Results and Discussion

The P,N bidentate coordination causes different electronic effects around the central metal atom than that manifests in palladacycle complexes. Beyond the structural scrutiny of complexes (*R*)-**34** and **35**, we intended to investigate the π acidity of the coordinating heteroaromatic isoquinoline moiety, moreover, the occurring kinetic and structural trans influence on coordinating monodentate ligands in the case of various metals.

At the end of the chapter we will show attempts for catalyst testing, which yet are the starting points for further and more thorough screenings of catalytic activities of these complexes.

4.2.1. Structural investigation of P,N palladium and platinum complexes

Palladium and platinum complexes (*R*)-**34** and **35** were successfully recrystallized from DCM with Et₂O, thus, significant amount of valuable data could be obtained on their structure. The ORTEP image of complex (*R*)-**34** can be seen in Figure 108.

Figure 108. ORTEP image of complex (*R*)-**34** for comprehensive structure analysis.

The determined and selected bond lengths and angles are compiled in Table 14. The measured Flack's parameter of the enantiopure complex was 0.03(4).¹⁵⁶

Table 14. Selected bond length and bond and torsion angles occurring in complex (*R*)-**34**.

Bond	<i>d</i> / Å	Bond	<i>d</i> / Å
Pd(1)–N(1)	2.054(8)	Pd(1)–P(1)	2.200(3)
Pd(1)–Cl(1)	2.370(3)	Pd(1)–Cl(2)	2.290(3)
C(9)–C(10)	1.510(13)	C(9)–N(1)	1.344(12)
C(10)–P(1)	1.849(10)		
Bond	α / °	Bond	α / °
N(1)–Pd(1)–P(1)	83.20(2)	N(1)–Pd(1)–Cl(1)	95.40(3)
P(1)–Pd(1)–Cl(1)	173.48(11)	N(1)–Pd(1)–Cl(2)	169.70(3)
P(1)–Pd(1)–Cl(2)	90.13(11)	Cl(1)–Pd(1)–Cl(2)	92.11(12)
C(9)–N(1)–Pd(1)–P(1)	-3.22	C(10)–C(9)–N(1)–Pd(1)	-24.17
C(11)–C(10)–P(1)–C(22)	-158.60	Pd(1)–P(1)–C(10)–C(11)	80.58

Bonds that include palladium are significantly longer than the bonds occur in the coordinating ligand in average, which explains the slightly elongated geometry of the five-membered chelate ring. The bite angle of the P,N ligand is close to the preferred 90° in bidentate complexes, however, it shows that the shape of the metal center somewhat differs from the ideal square planar arrangement of the low spin d^8 complexes. Another important observation is that the Pd(1)–Cl(1) bond length in the position *trans* to the nitrogen is significantly smaller than in the analogous P,C chlorodimer complexes.^{53, 107} By observing the chelate ring from the aspect of bond angles it has an envelope-like conformation (similarly to the cyclopentane C_s conformer), which is supported by the relatively large torsion angle (–24.17°) observed between C(10)–C(9)–N(1)–Pd(1). This indicates that C(10) is out of the mean coordination plane (m.c.pl., defined by P–Pd–N atoms). Since this carbon atom bears the dimethyl malonate moiety, the torsion values between C(11)–C(10)–P(1)–C(22) atoms (158.60°) and especially between Pd(1)–P(1)–C(10)–C(11) (80.58°) support the fact that the bulky malonate group is positioned axial with respect to the m.c.pl. Based on these observations we concluded that the P,N complex **34** with (*R*) configuration prefers the δ conformation (Figure 109.)

Figure 109. The favored δ conformation of palladium complex (R)-34 shown by Newman and Sawhorse projections.

To support this conclusion, (R)-34 was investigated further in solution by performing 2D ^1H - ^1H ROESY NMR spectroscopy. The 2D spectrum of the complex can be seen in Figure 110.

Figure 110. The two-dimensional ^1H - ^1H ROESY NMR spectrum of complex (R)-34.

Selected NOE interactions: **A**, $\text{H}_a - \text{H}_c$; **B**, $\text{H}_a - \text{H}_b$; **C**, $\text{H}_a - \text{H}$ (eq. phenyl *ortho* protons); **D**, $\text{H}_b - \text{H}$ (ax. phenyl *ortho* protons); **E**, $\text{H}_c - \text{H}$ (eq. phenyl *ortho* protons); **F**, $\text{H}_d - \text{H}$ (ax. phenyl *ortho* protons).

According to the ROESY correlations, we can observe that there are five major interactions occurring in the complex. Correlation **A** is not surprising at all since those protons are in vicinal coupling to each other. Cross-peak **B** between H_a and H_b is important; it means that although the bulky malonate moiety in the axial position can rotate along the C-C bond, a steric block exists between that and the isoquinoline ring. Cross-peak **F** (interaction of H_d and the *ortho* protons of the axial phenyl group ($\text{H}_{\text{ax-ortho}}$)) can be explained by the conformational changes in solution. Nonetheless, the spatial proximity between H_a and the equatorial phenyl group's *ortho* protons ($\text{H}_{\text{eq-ortho}}$; **C**), H_b and the *ortho* protons of the axial phenyl group ($\text{H}_{\text{ax-ortho}}$; **D**) and H_c and the *ortho* protons of the equatorial phenyl group ($\text{H}_{\text{eq-ortho}}$; **E**) also confirms that δ -conformation is more likely in solution. Furthermore, NOE cross-peak **E** points at it unambiguously, since, if λ conformation had any probability of occurring in solution, H_c would have

had a correlation peak with the *ortho* protons of the axial phenyl group, which is clearly absent in the spectrum.

The exact conformation of the coordinating ligand backbone has been determined by NMR and crystallographic methods, however, the successfully crystallized platinum complex **35** is also worth a scrutiny. The comparison of the palladium and platinum complexes (**34** and **35**) provides further valuable information on their structure. The X-ray structure of platinum complex **35** can be seen in Figure 111.

Figure 111. The ORTEP image of platinum complex **35**.

The selected bond lengths and angles can be seen in Table 15.

Table 15. Selected bond length and bond and torsion angles occurring in complex **35**.

Bond	<i>d</i> / Å	Bond	<i>d</i> / Å
Pt(1)–N(1)	2.062(4)	Pt(1)–P(1)	2.1940(9)
Pt(1)–Cl(2)	2.2825(13)	Pt(1)–Cl(1)	2.3640(11)
C(1)–C(2)	1.516(5)	C(2)–N(1)	1.347(5)
C(1)–P(1)	1.849(4)		
Bond	α / °	Bond	α / °
N(1)–Pt(1)–P(1)	84.26(9)	N(1)–Pt(1)–Cl(2)	174.07(9)
P(1)–Pt(1)–Cl(2)	91.78(4)	N(1)–Pt(1)–Cl(1)	94.42(9)
P(1)–Pt(1)–Cl(1)	178.66(4)	Cl(2)–Pt(1)–Cl(1)	89.52(5)
C(2)–N(1)–Pt(1)–P(1)	-2.01	C(1)–C(2)–N(1)–Pt(1)	-22.29
C(11)–C(1)–P(1)–C(22)	-153.04	Pt(1)–P(1)–C(1)–C(11)	87.68

The Pt(1)–N(1) and Pt(1)–P(1) bonds in complex **35** are slightly longer but looks very similar to the palladium analogue **34**. The lengths of the platinum-chlorine bonds also have similar values, and it can be seen that that Pt(1)–Cl(1) is significantly longer than Pt(1)–Cl(2). This shows well the difference in structural trans effect between nitrogen and phosphorus: because of the trans influence of the coordinating phosphorus the Pt(1)–Cl(1) bond is elongated compared to Pt(1)–Cl(2), which is positioned *trans* to the coordinating nitrogen. This observation was the same for both **34** and **35** complexes. Regarding the bond angles occur in the complex, the bite angle in the P,N platinum complex **35** is higher by approximately 1° compared to complex **34**. Another difference between the two is the different geometry of the square planar centers. In the case of complex **35**, the platinum center approximates the ideal planar geometry (the 180° in the case of P–M–Cl and N–M–Cl bond angles) more then the palladium center in complex (*R*)-**34**. However, these values highly depend on the crystal frame and actual arrangement in the crystal, which, in a low extent, varies in every single crystal. The same palladium center in another crystal batch (Figure 75., Chapter 3.2.1.1.) showed to reach the regular and theoretical 180° for P–M–Cl and N–M–Cl bond angles than the platinum center in complex **35**. Nonetheless, the torsion values determined in Table 14. for complex (*R*)-**34** show very similar numbers for platinum complex **35**, which indicates no difference in conformation between the two compounds.

4.2.2. Coordination study and the electronic scrutiny of P,N complexes

The investigation of the electronic features of the obtained P,N complexes was carried out by coordination reactions, which provided information on the nature of the different coordination sites. These reactions were carried out by applying various coordinating phosphines. To define the difference between the P,N and C,P metal complexes with regard to their electronic characteristics and coordination behaviour, we compared our P,N complexes to their exact C,P palladium analogue (palladacycle) and its derivatives reported by Li Xi-Rui et al.^{107, 157}

4.2.2.1. Attempts to synthesize dppe P,N coordination compounds

In the beginning, our aim was to synthesize the dppe derivatives of the P,N platinum and palladium complexes **34** and **35**, since these compounds could provide valuable electronic information on the P,N metal coordination. Disappointingly, the synthesis of these complexes could not be carried out by this method.

Despite the numerous kinds of approaches, the platinum dppe derivatives **63a** and **b** did not form, and no valuable side product could be isolated or recrystallized from the mixtures (Figure 112.). One of the approaches was to remove the chloro ligands from complex **35** by using AgClO₄ (procedure A), however, according to the ³¹P{¹H} NMR spectroscopy, the expected coupling pattern of the coordinating phosphorus atoms could not be observed.

Figure 112. Addition of diphosphine dppe ligand to platinum complex **35**.

Since the desired product could not be seen in $^{31}\text{P}\{^1\text{H}\}$ NMR spectroscopy, we added NH_4PF_6 to the mixture to carry out an anion change. Then, the solvent was evaporated, and the crude mixture was redissolved in MeOH. The hypothesis behind this was that the PF_6^- salts of organometallic complexes are usually not soluble in methanol, thus, all the impurities and side products can be removed by MeOH and the product would remain as a precipitate.¹⁵⁸⁻¹⁵⁹ To our disappointment, this approach did not provide the product either.

The other approach was to skip the silver reagent and add only the dppe in order to substitute the chloro ligands (procedure **B**, Figure 112.). The problem with the process revealed at this point: decomposition products of the platinum complex and ligand **27**, moreover, the $\text{Pt}(\text{dppe})_2$ complex itself could be seen in the $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum. This means that the dppe removes the platinum center from **35**, thus, the complex decomposes.

This could be clearly seen on the example of the same reaction with palladium complex **34** as well (Figure 113.). Our aim was to obtain complex **64**. Upon addition, the $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum exhibited that the palladium center was ‘removed’ from the P,N complex and formed the $\text{Pd}(\text{dppe})_2$ side product. The phosphine oxide (**27a**) derivative

of ligand **27** could also be seen in the spectrum. In this instance, the treatment with silver perchlorate was not tried because according to our experiences, Ag(I) induced yet unexplored side processes in every case this reagent was used in this manner.

Figure 113. Addition of diphosphine *dppe* ligand to palladium complex **34**.

The overall conclusion on these experiments is that the *dppe* bidentate ligand is a stronger coordinating agent than the P,N ligand **27**. This can be attributed to the competing chelate effects in case of the different bidentates, and also to the differences between the strengths of M–P and M–N coordinate bonds. Thus, it can be concluded that P,N metal complexes synthesized by us are sensitive to strong coordinating agents.

4.2.2.2. Successful coordination study on P,N complexes

In light of the experience and observations detailed above, we concluded to use the monodentate PPh_3 as a ligand to gather information on the coordination behavior of our complexes. The first attempt was to use 2.0 equiv. of PPh_3 instead of the bidentate *dppe* (Figure 114.).

Figure 114. Addition of 2.0 equiv. of PPh_3 to palladium complex **34**.

The $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum showed that at the beginning, the complete coordination did not occur (the signals of PPh_3 and the starting material **34** could be seen as well among side products). After a few hours of stirring the $^{31}\text{P}\{^1\text{H}\}$ NMR singlet of the SM

disappeared, however, the excess amount of PPh_3 could be still observed. Our explanation to that is that besides the P,N metal coordination complexes are sensitive to strong coordinating agents (as it was explained above), a forming P,N metal complex with only neutral ligands in the internal coordination sphere is presumably not stable in the case of palladium and platinum. The expected complex **65** would have been a dichloride complex with external counteranions, however, we could not observe the formation of any similar dianion salts of these complexes during this project.

Nonetheless, using strictly 1.0 equivalent of PPh_3 in these coordination reactions without the application of silver reagents led to the anticipated products with valuable information on the coordination behavior of these systems. In the case of palladium and platinum coordination complexes, these reactions were carried out with the use of recrystallized starting materials (complexes **34** and **35**). To the DCM or MeOH solution of these complexes, 1.0 equiv. of PPh_3 was added, then the resulting mixtures were stirred for 1 hour at rt, then product formations were monitored by $^{31}\text{P}\{^1\text{H}\}$ NMR spectroscopy (DCM, 162 MHz). In the following figures P_1 indicates the donor phosphorus of the P,N ligand **27**, P_2 indicates the coordinating PPh_3 phosphorus atom.

We started our study on the palladium complex **34** (Figure 115.).

Figure 115. Coordination of PPh_3 to the palladium center of complex **34**.

According to the determined coupling constants from $^{31}\text{P}\{^1\text{H}\}$ spectroscopy (Figure 116.), only *cis*-coordination (the PPh_3 ligand prefers *cis* position to the phosphorus of the chelate ligand **27**) occurred upon addition of triphenylphosphine ($^2J_{\text{P}_1-\text{P}_2} = 7.3 \text{ Hz}$ (**66**)).⁵⁴

Figure 116. $^{31}\text{P}\{^1\text{H}\}$ spectrum of the coordination product of complex **34**. $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, MeOH) δ 60.00 (d, $^2J_{\text{P1-P2}} = 7.25$ Hz), 32.16 (d, $^2J_{\text{P1-P2}} = 7.25$ Hz).

Nevertheless, in the case of platinum, the obtained $^{31}\text{P}\{^1\text{H}\}$ spectrum requires greater scrutiny: besides the starting material (**35**) and the coordination of triphenylphosphine (*cis*-**67**, $^2J_{\text{P1-P2}} = 13.25$ Hz), significant dimerization occurred to give complex **68** as a major product (Figure 117.).

Figure 117. Coordination of PPh_3 to the platinum center of complex **35**.

The coupling constants between the ^{31}P nucleus of the chelating ligand **27** and ^{195}Pt were generally high ($^1J_{\text{Pt-P1}} = 3693.6$ Hz in the case of *cis*-**67** and $^1J_{\text{Pt-P}} = 3680.6$ Hz for complex **68**), which indicates strong bonding between these atoms¹⁵⁵. Although, the

coupling constant value observed between the phosphorus nucleus of triphenylphosphine and the Pt center was slightly lower ($^1J_{\text{Pt-P2}} = 3445.6$ Hz).

Figure I18. $^{31}\text{P}\{^1\text{H}\}$ spectrum of the coordination product of complex **35**. $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, DCM) δ 39.76 (d, $^2J_{\text{P1-P2}} = 13.25$ Hz), 39.74 (d, $^1J_{\text{Pt-P1}} = 3693.6$ Hz, 13.2 Hz); 28.72 (s), 28.72 (d, $^1J_{\text{Pt-P}} = 3798.0$ Hz); 14.00 (s), 14.00 (d, $^1J_{\text{Pt-P}} = 3680.0$ Hz); 6.35 (d, $^1J_{\text{Pt-P2}} = 3445.6$ Hz), 6.31 (d, $^2J_{\text{P1-P2}} = 13.25$ Hz).

It is worth mentioning that we observed that the concentration of the dimer complex (**68**) and the starting material (**35**) slowly increased in the mixture with respect to the coordination compound **67**.

To further investigate the electronic effects of the P,N ligand (**27**) in regard to other transition metals, let us consider the coordination behavior of rhodium and iridium complexes **36** and **37** covered in Chapter 3.2.2.1. These complexes were synthesized by the addition of 0.5 equivalent $[\text{Rh}(\text{ethylene})_2\text{Cl}]_2$ and $[\text{Ir}(\text{COD})\text{Cl}]_2$ to ligand **27** to form the respective P,N complexes. Then, 1.0 equiv. of triphenylphosphine was subsequently added to their mixtures at rt and they were stirred for 1.0 h to observe the coordination behavior (**36** and **37**, Figure I19).

Figure 119. Preparation of complex **36**.

In the case of rhodium (**36**), the coupling between the three NMR-active nuclei (^{103}Rh and the two ^{31}P nuclei) caused a characteristic pattern (doublet of doublets) in the NMR spectrum. The $^{31}\text{P} - ^{31}\text{P}$ coupling constants were $^2J_{P1-P2} = 41.6 \text{ Hz}$ (75.2 ppm, doublet of doublets and 46.2 ppm, doublet of doublets; 162 MHz, DCM), which are typical values when *cis*-coordination occurs¹⁴¹. The $^{103}\text{Rh} - ^{31}\text{P}$ couplings are also consistent with the literature values: $^1J_{Rh-P1} = 200.3$ and $^1J_{Rh-P2} = 171.9 \text{ Hz}$ ¹⁴⁰⁻¹⁴¹. The resulting spectrum can be seen in Figure 120.

Figure 120. $^{31}\text{P}\{^1\text{H}\}$ spectrum of coordination product **36**. $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, DCM) δ 75.16 (dd, $^1J_{\text{Rh-P1}} = 200.3$ Hz, $^2J_{\text{P1-P2}} = 41.55$ Hz), 46.20 (dd, $^1J_{\text{Rh-P2}} = 171.9$ Hz, $^2J_{\text{P1-P2}} = 41.55$ Hz).

Iridium complex **27** also showed *cis*-coupling with $^2J_{\text{P1-P2}} = 32.8$ Hz (32.1 ppm, doublet and -30.3 ppm, doublet; 162 MHz, DCM)¹⁴² with respect to the coordinating phosphorus atoms, which is not surprising if we consider the electronic effects discussed earlier (Figures 121. and 122.)

Figure 121. Preparation of complex **37**.

Figure 122. $^{31}\text{P}\{^1\text{H}\}$ spectrum of coordination product **37**. $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, DCM) δ 32.14 (d, $^2J_{\text{P1-P2}} = 32.8$ Hz), -30.31 (d, $^2J_{\text{P1-P2}} = 32.8$ Hz).

The last example in this series of experiments is the ruthenium(II) complex **47** detailed in Chapter 3.2.4.1. (Figure 123.).

Figure 123. Preparation of complex **47**.

The addition was the same as in the previous cases: the ruthenium source and triphenylphosphine were added to the solution of **27** in DCM, and the mixture was stirred at rt. The resulting $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum showed *trans* P₁–P₂ coupling in the ruthenium complex, which is surprising (Figure 124.) but a plausible explanation will be provided in Chapter 4.2.2.4.

Figure 124. $^{31}\text{P}\{^1\text{H}\}$ spectrum of coordination product **47**. $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, DCM) δ 35.21 (d, $^2J_{\text{P1-P2}} = 225.8$ Hz), -23.20 (d, $^2J_{\text{P1-P2}} = 225.8$ Hz).

4.2.2.3. Coordination study on the C,P palladium analogues of the P,N complexes

We carried out the same series of experiments by using the exact C,P palladium analogue (**69**) and its derivatives to investigate the differences in coordination compared to the P,N complexes.

The P,C analogue **69** of complex **34** (Figure 125.) showed a dynamic equilibrium between *cis* and *trans* $\text{P}_1\text{-Pd-P}_2$ coordination ($^2J_{\text{P1-P2, trans}} = 427.2$ Hz and $^2J_{\text{P1-P2, cis}} = 26.5$ Hz), although, *trans* arrangement proved to be the favored (**70**, Figure 126.). The ratio of the minor and major isomers is 0.12:1.

Figure 125. Coordination of PPh_3 to the palladium center of C,P complex **69**.

Figure 126. $^{31}\text{P}\{^1\text{H}\}$ spectrum of coordination products *trans*-**70** and *cis*-**70**.
 $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, DCM) δ 63.65 (d, $^2J_{\text{P1-P2}} = 26.45$ Hz), 54.69 (d, $^2J_{\text{P1-P2}} = 427.2$ Hz), 26.36 (d, $^2J_{\text{P1-P2}} = 427.2$ Hz), 17.72 (d, $^2J_{\text{P1-P2}} = 26.45$ Hz).

1.0 equiv. of PPh_3 was also added to the methoxy (**71**) and to the fluoro derivatives (**73**) of palladacycle **69** (Figure 127.).

Figure 127. Coordination of PPh₃ to the palladium centers of C,P complexes **71** and **73**.

It is intriguing that fluorine as a substituent induces higher ratio for the *cis* isomer (complex **74**) than the hydrogen and methoxy substituents in complexes **70** and **72**. It can probably be attributed to the observation that in some cases fluorine acts as an activating group in aromatic systems,¹⁶⁰ thus its +M effect probably competes with the methoxy group's +M effect in this particular case. Nevertheless, the trend, which can be observed is that the *trans* P–M–P geometry is still more favored than the *trans* C(sp²)–M–P arrangement. The ³¹P{¹H} NMR data obtained on the coordination reactions can be seen in Figures 128. and 129.

Figure 128. $^{31}\text{P}\{^1\text{H}\}$ spectrum of the coordination products of complex **71** and triphenylphosphine. $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, DCM) δ 57.01 (d, $^2J_{\text{P1-P2}} = 33.3$ Hz), 52.11 (d, $^2J_{\text{P1-P2}} = 382.25$ Hz), 25.77 (d, $^2J_{\text{P1-P2}} = 381.25$ Hz), 22.46 (dd, $^2J_{\text{P1-P2}} = 33.3$, (5.2 Hz)), 12.86 (t, $^2J_{\text{P-P}} = 32.9$ Hz).

Figure 129. $^{31}\text{P}\{^1\text{H}\}$ spectrum of the coordination products of complex **73** and triphenylphosphine. $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, DCM) δ 63.31 (d, $^2J_{\text{P1-P2}} = 25.2$ Hz), 54.52 (d, $^2J_{\text{P1-P2}} = 431.55$ Hz), 26.60 (d, $^2J_{\text{P1-P2}} = 431.55$ Hz), 18.24 (dd, $^2J_{\text{P1-P2}} = 25.2$ Hz, 7.5 Hz).

It was an interesting case that when we accidentally added 2.0 equiv of PPh₃ to methoxy complex **71**, the following coupling pattern could be observed in the $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum (Figure 130.). In the figure, P₃ refers to the phosphorus atom positioned *cis* to both P₁ and P₂.

Figure 130. $^{31}\text{P}\{^1\text{H}\}$ spectrum of the coordination products of complex **71** and 2.0 equiv. of triphenylphosphine. $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, DCM) δ 58.02 (dd, $^2J_{\text{P1-P2}} = 359.6$, $^2J_{\text{P1-P3}} = 30.9$ Hz), 53.09 (dd, $^2J_{\text{P1-P2}} = 404.2$, 355.6 Hz), 26.16 (dd, $^2J_{\text{P1-P2}} = 405.1$, 165.4 Hz), 21.25 (dd, $^2J_{\text{P2-P1}} = 359.6$, $^2J_{\text{P2-P3}} = 37.25$ Hz), 12.76 (dd, $^2J_{\text{P3-P2}} = 37.25$, $^2J_{\text{P3-P1}} = 30.9$ Hz).

The $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum clearly shows that the main product (**75**) consists of two coordinating triphenylphosphines, thus, the three phosphorus nuclei exhibit a characteristic pattern of multiplets. The structure based on the $^{31}\text{P}\{^1\text{H}\}$ NMR measurement can be seen in Figure 131.

Figure 131. Coordination compound **75**.

4.2.2.4. Interpretation of the observations and DFT calculations

Our findings about the coordination experiments on each P,N complex can be explained by the difference between the *trans* influences of coordinating nitrogen and the sp^2 carbon atoms. Phosphorus and carbon atoms are both at the end of the *trans* influence series and have strong labilizing effect⁶⁷ when compared to nitrogen. In a P,N complex, *trans* P–M–P arrangement is less favorable than P–M–N, hence, despite the significant steric repulsion we could observe the *cis* isomers being formed.

However, ruthenium(II) has d^6 electron configuration, which is completely different from that occurs in the aforementioned and detailed d^8 complexes (Figure 69.). Metals like ruthenium often form octahedral complexes, thus, the *trans* influences of the coordinating ligands in these complexes result in slightly different manners. In this particular case, a probable explanation being that the steric effects between the PPh_3 's and ligand **27**'s phenyl groups dominate the electronic effects. By this reason, the electronically less but sterically more favored *trans* P–M–P coordination took place in the possibly octahedral complex **47**.

Regarding the C,P palladium complexes (**70**, **72** and **74**), carbon has even stronger labilizing effect at the *trans* position than the phosphorus, thus P–M–P (*trans*) arrangement is still benign. Moreover, it is also preferred from the point of view of steric effects.

To support this explanation, we investigated the difference in π acidity between the coordinating carbon and nitrogen (as part of aromatic moieties) with the use of DFT calculations performed by applying Gaussian 09¹⁶¹. For this purpose, we carried out NBO¹⁶² analysis on complexes **34**, **35** and **69**, and examined the HOMO-LUMO interaction energies between the metals' corresponding d orbitals (HOMO) and the aromatic C=N and C=C aromatic π^* antibonding (LUMO) orbitals (Figure 132.).

Figure 132. Selected interaction between $d(\text{Pt}) - \pi^*(\text{C}=\text{N})$ orbitals in complex **35**.

The DFT calculations were performed by using B3LYP functional¹⁶³⁻¹⁶⁶. On palladium and platinum atoms, SDD effective core potential was used. On other atoms, 6-31G* basis set was applied¹⁶⁷⁻¹⁶⁸. The calculated interaction energies can be seen in Table 16.

Table 16. The sum of the $d(\text{metal}) - \pi^*(\text{aromatic})$ interaction energies in P,N and P,C complexes.

Metal complex	$E_{d - \pi^* \text{ interaction}} / \text{kcal/mol}$
34	1.94
35	4.45
69	4.72

According to the analysis, the aforementioned interactions are more significant in the case of palladacycle **69** than for the P,N palladium complex **34**, which means that the π acidity of the coordinating carbo-aromatic naphthyl moiety is more significant. This in turn explains the stronger trans influence of the coordinating aromatic carbon observed in the coordination study. In the case of platinum complex **35**, this energy is relatively high compared to its P,N palladium analogue (**34**), but it can be explained by the difference between the palladium and platinum atoms: platinum's 5d atomic orbitals are at higher energy levels and more diffuse than palladium's 4d orbitals. Thus, they are able to donate more efficiently to the heteroaromatic ligand's antibonding orbitals.

The whole data obtained by the NBO analysis can be seen in Tables 17-19. In our investigation, $d(\text{metal})$ to $\pi^*(\text{C}=\text{N})$ interaction was split into two pairs, thus, we defined the sum of energies for these pairs as π -electron delocalization energy.

Table 17. Second-order interaction energy (E^2 , kcal/mol) between donor and acceptor orbitals in complex **34**.

NBO Donor	NBO Acceptor	Type of NBO	E^2 / kcal/mol
NBO132: LP of Pd NBO147: BD* of C-N	1.94
NBO132	NBO147		

Table 18. Second-order interaction energy (E^2 , kcal/mol) between donor and acceptor orbitals in complex **35**.

NBO Donor	NBO Acceptor	Type of NBO	E^2 / kcal/mol
NBO134: LP of Pt NBO147: BD* of C-N	3.10
NBO134	NBO147
NBO134: LP of Pt NBO147: BD* of C-N	1.35
NBO138	NBO147		

Table 19. Second-order interaction energy (E^2 , kcal/mol) between donor and acceptor orbitals in complex **69**.

NBO Donor	NBO Acceptor	Type of NBO	E^2 / kcal/mol
NBO242: LP of Pd NBO298: BD* of C-C	4.72
NBO242	NBO298		

XYZ coordinates of the optimized geometries (Å)

Complex **34**

```

C   1.845310 -2.821550 -0.751908
H   1.370247 -3.621901 -1.307161
C   3.140243 -2.881026 -0.313429
H   3.735879 -3.765362 -0.518359
C   3.692987 -1.801303  0.413588
C   5.018907 -1.823925  0.919946
H   5.629907 -2.704780  0.742650
C   5.516392 -0.750943  1.622327
H   6.530821 -0.775129  2.010229
C   4.707845  0.390392  1.844105
H   5.108513  1.231969  2.401727
C   3.417975  0.444226  1.363983
H   2.830521  1.338549  1.535340
C   2.868821 -0.652298  0.636676
C   1.531652 -0.667873  0.122824
C   0.630098  0.539159  0.298198
H   0.862170  1.021990  1.246731
C   0.792302  1.646058 -0.795362
H   0.096510  1.470192 -1.620017
C   0.482079  3.012144 -0.177287
C  -0.118483  5.234375 -0.665161
H  -0.982107  5.226329  0.003578
H  -0.333168  5.810759 -1.564655
H   0.748101  5.642844 -0.139531
C   2.171523  1.652120 -1.470961
C   4.273717  2.712849 -1.593848
H   4.842994  1.809325 -1.363157

```

H	4.742269	3.589111	-1.146161
H	4.193737	2.824934	-2.677411
C	-2.254163	1.300175	-0.137971
C	-2.733164	2.263511	0.764229
H	-2.471759	2.208789	1.815338
C	-3.561508	3.292934	0.315552
H	-3.935926	4.027318	1.023636
C	-3.918881	3.370088	-1.032870
H	-4.570421	4.168703	-1.377415
C	-3.455427	2.408806	-1.932726
H	-3.748679	2.449618	-2.977683
C	-2.635596	1.371422	-1.488699
H	-2.320882	0.596029	-2.180172
C	-1.473716	-0.378092	2.159300
C	-2.253581	-1.493628	2.507152
H	-2.647848	-2.138250	1.726730
C	-2.527637	-1.761966	3.849144
H	-3.130575	-2.627231	4.109336
C	-2.026857	-0.927304	4.849734
H	-2.237652	-1.142142	5.893863
C	-1.254247	0.185597	4.509257
H	-0.866252	0.839670	5.285313
C	-0.977170	0.463695	3.170140
H	-0.387831	1.342273	2.921574
Cl	-0.776612	-3.778129	-2.368879
Cl	-3.347759	-2.043278	-1.097531
N	1.044935	-1.735222	-0.520584
O	0.160609	3.898263	-1.125556
O	0.534791	3.263989	1.010083
O	2.961747	2.636053	-1.001657
O	2.500194	0.863477	-2.325140
P	-1.161554	-0.077451	0.380717
Pd	-1.032408	-1.908945	-0.942597

Complex 35

Pt	-1.194929	-1.605089	-0.711959
C	0.836635	0.625626	0.318597
C	1.543005	-0.709921	0.195058
C	2.886350	-0.865475	0.664344
C	3.618802	0.178784	1.301822
C	4.904829	-0.037317	1.745380
C	5.528568	-1.297102	1.574579
C	4.851769	-2.324206	0.958389
C	3.525144	-2.134594	0.492199
C	2.791132	-3.160545	-0.146690
C	1.502639	-2.938771	-0.546198
C	1.101628	1.615503	-0.863237
C	2.452991	1.393744	-1.558098
C	4.676274	2.149356	-1.775558

C	0.981446	3.053331	-0.351961
C	0.649450	5.288462	-1.008827
C	-1.944658	1.752080	-0.053981
C	-2.367520	1.804900	-1.393249
C	-3.071546	2.913524	-1.863681
C	-3.375755	3.968557	-1.001880
C	-2.975842	3.913674	0.335650
C	-2.264345	2.811408	0.810546
C	-1.279460	0.122507	2.310560
C	-0.645140	0.964938	3.240524
C	-0.888633	0.807587	4.605587
C	-1.765053	-0.184321	5.052122
C	-2.401156	-1.019682	4.132100
C	-2.160321	-0.872442	2.765181
Cl	-1.252105	-3.576622	-2.066671
Cl	-3.526907	-1.448329	-0.875145
N	0.875502	-1.732965	-0.360125
O	2.657091	0.511478	-2.357982
O	3.376865	2.292924	-1.168656
O	1.087973	3.387427	0.811066
O	0.758042	3.896862	-1.365158
P	-1.015956	0.273659	0.504805
H	1.181271	1.130543	1.219970
H	3.176510	1.159300	1.432655
H	5.445658	0.767327	2.235066
H	6.542951	-1.448461	1.932540
H	5.319415	-3.295153	0.819910
H	3.241438	-4.134078	-0.314195
H	0.896552	-3.692530	-1.033210
H	0.366315	1.461253	-1.657280
H	5.132906	1.207738	-1.461329
H	5.258272	2.998427	-1.417467
H	4.590365	2.166738	-2.864173
H	-0.202342	5.436519	-0.341228
H	0.497775	5.816520	-1.949877
H	1.564420	5.626856	-0.516556
H	-2.175842	0.963883	-2.051883
H	-3.399432	2.939189	-2.898795
H	-3.937264	4.824644	-1.366431
H	-3.226830	4.723310	1.015585
H	-1.970672	2.777321	1.853856
H	0.028808	1.750361	2.907915
H	-0.393230	1.460593	5.318891
H	-1.950108	-0.305643	6.115995
H	-3.083223	-1.792359	4.475197
H	-2.652357	-1.522462	2.047479

Complex 69

C	-3.129586	1.312792	-1.234563
C	-3.218977	2.512869	-1.994133
H	-2.450040	2.742057	-2.722546
C	-4.265209	3.385820	-1.815064
H	-4.320358	4.299037	-2.404305
C	-5.296796	3.113625	-0.879816
C	-6.396959	3.996404	-0.718073
H	-6.425456	4.901620	-1.320487
C	-7.410392	3.717376	0.170804
H	-8.249281	4.399230	0.281330
C	-7.357951	2.530307	0.937031
H	-8.162681	2.300721	1.630995
C	-6.298490	1.655739	0.809711
H	-6.285000	0.761632	1.422505
C	-5.228046	1.913607	-0.095645
C	-4.108556	1.029070	-0.280774
C	-3.991097	-0.253406	0.519962
H	-4.968607	-0.680486	0.746965
C	-3.222972	-0.150481	1.875179
H	-2.144756	-0.200152	1.703709
C	-3.425552	1.188958	2.590410
C	-4.815423	2.406185	4.057579
H	-3.954508	2.745408	4.638345
H	-5.659282	2.181598	4.710027
H	-5.089213	3.168705	3.324691
C	-3.622891	-1.305601	2.796506
C	-3.001797	-2.502966	4.726118
H	-3.976508	-2.364797	5.201015
H	-2.201382	-2.450040	5.464129
H	-2.983118	-3.463382	4.205509
C	-2.287140	-2.777271	0.261791
C	-0.990513	-2.572888	0.763297
H	-0.468762	-1.644449	0.553535
C	-0.342256	-3.568553	1.495098
H	0.660246	-3.383612	1.868754
C	-0.980860	-4.790682	1.715311
H	-0.474607	-5.575588	2.271422
C	-2.263035	-5.012417	1.205374
H	-2.757405	-5.967102	1.364637
C	-2.916020	-4.013125	0.483405
H	-3.910219	-4.201100	0.093408
C	-4.403208	-2.156653	-1.690521
C	-4.194037	-2.287612	-3.072056
H	-3.267750	-1.928652	-3.511911
C	-5.173781	-2.868514	-3.878753
H	-5.003206	-2.962051	-4.947572
C	-6.369352	-3.318243	-3.315705
H	-7.133670	-3.764991	-3.945851

C	-6.584936	-3.190180	-1.941571
H	-7.514820	-3.537656	-1.499735
C	-5.608128	-2.613087	-1.129117
H	-5.784226	-2.528524	-0.060224
C	3.129866	-1.312483	-1.234676
C	3.219398	-2.512318	-1.994594
H	2.450584	-2.741303	-2.723199
C	4.265628	-3.385298	-1.815635
H	4.320878	-4.298339	-2.405139
C	5.297076	-3.113349	-0.880171
C	6.397238	-3.996155	-0.718543
H	6.425826	-4.901197	-1.321214
C	7.410556	-3.717362	0.170533
H	8.249444	-4.399232	0.280970
C	7.358000	-2.530512	0.937092
H	8.162644	-2.301110	1.631216
C	6.298535	-1.655932	0.809898
H	6.284955	-0.762006	1.422953
C	5.228197	-1.913555	-0.095659
C	4.108696	-1.029003	-0.280663
C	3.991035	0.253243	0.520433
H	4.968472	0.680244	0.747895
C	3.222439	0.149837	1.875341
H	2.144278	0.199209	1.703444
C	3.425163	-1.189685	2.590398
O	4.511426	-1.170463	3.385957
C	3.621675	1.304821	2.797140
C	2.999518	2.501463	4.726864
H	3.973760	2.363082	5.202671
H	2.198415	2.448582	5.464131
H	2.981491	3.461926	4.206335
C	4.403744	2.156994	-1.689563
C	4.194849	2.288134	-3.071130
H	3.268668	1.929194	-3.511220
C	5.174737	2.869173	-3.877550
H	5.004379	2.962850	-4.946391
C	6.370185	3.318853	-3.314197
H	7.134618	3.765717	-3.944121
C	6.585496	3.190596	-1.940040
H	7.515286	3.538026	-1.497970
C	5.608541	2.613367	-1.127860
H	5.784447	2.528636	-0.058949
C	2.287214	2.777333	0.262356
C	0.990495	2.572870	0.763573
H	0.468796	1.644451	0.553618
C	0.342068	3.568460	1.495335
H	-0.660503	3.383455	1.868777
C	0.980594	4.790585	1.715779
H	0.474204	5.575431	2.271852
C	2.262864	5.012401	1.206110

H	2.757181	5.967082	1.365555
C	2.916017	4.013185	0.484189
H	3.910285	4.201225	0.094402
Cl	-0.024050	1.655254	-2.519373
Cl	0.024442	-1.654719	-2.519666
O	-4.511774	1.169764	3.386025
O	-2.697577	2.147203	2.463925
O	-2.738211	-1.434725	3.798546
O	-4.601621	-2.008265	2.657743
O	2.736644	1.433331	3.798955
O	4.600186	2.007885	2.658893
P	-3.083382	-1.406493	-0.667180
P	3.083677	1.406681	-0.666669
Pd	-1.670651	0.003408	-1.715137
Pd	1.670988	-0.002976	-1.715071
O	2.697269	-2.147994	2.463837
C	4.815239	-2.406919	4.057385
H	5.659093	-2.182294	4.709827
H	3.954378	-2.746285	4.638144
H	5.089090	-3.169326	3.324408

4.2.2.5. Catalyst testing reactions with palladium complex (R)-34

P,N palladium complex **34** was being tested in two kinds of catalytic reactions: in asymmetric hydrophosphination¹⁰⁵ and in enantioselective arylation of imines.¹⁶⁹

In the former case, we followed the previously established and detailed protocol for the hydrophosphination of *trans*-chalcone **11** established by Huang et al. and Xu et al. (Table 20.).^{105, 58}

Table 20. Screening the conditions for hydrophosphination of *trans* chalcone with complex **34**.

Entry	Catalyst	Catalyst loading	Solvent	<i>T</i> / °C	<i>t</i> / h	Yield ^a	ee ^b
1	(<i>rac</i>)- 34	5 mol%	DCM	rt	20	50%	0%
2	(<i>R</i>)- 34	5 mol%	DCM	rt	48	57%	0%
3	(<i>R</i>)- 34	5 mol%	DCM	−40	48	82% ^c	5.5%
4	(<i>R</i>)- 34	5 mol%	DCM	−80	48	71% ^c	0%

^aIsolated yields. ^bDetermined by chiral HPLC. ^cThe purified product batches contained side-products.

To our disappointment, the P,N palladium complex **34** could not provide selectivity in the reaction, however, it could generate significant extents of yields. Based on the observation gathered in the coordination study in this chapter, the P,N chelate is sensitive to the strong coordinating agents, thus, to the coordination of the starting material (HPPH₂) molecules as well. The probable explanation to the good conversion with no selectivity is that the P,N ligand **27** was substituted by the diphenylphosphine molecules. The reaction was then basically promoted by the *in situ* forming PdCl₂, which catalyzed the addition of diphenylphosphines to the chalcone's double bond.

The other catalytic reaction the palladium dichloro complex (R)-**34** was tested in was the enantioselective arylation of N-tosyl imine **76**. The notion to apply the dichloro complex **34** in this catalysis was based on the analogous catalytic reaction (reported by

Huang et al.)¹⁶⁹ where the chloro dimer derivative of complex **14** was used ((*R,R*)-CP dimer, Figure 22., Chapter 1.2.4.). In their paper, the proposed mechanism implies that a possible Cl-OH substitution took place owing to the use of the significant extent of base. The best condition they found was the use of KOH as a base at room temperature in toluene. The scheme, in which complex (*R*)-**34** was applied can be seen in Table 21 along with the screening conditions.

Table 21. Arylation of imine **76** catalyzed by complex (*R*)-**34**.

Entry	Catalyst	Catalyst loading	Base (0.5 equiv.)	Solvent	<i>t</i> / days	Yield	Remark ^c
1	(<i>R</i>)- 34	5 mol%	KOH	Toluene	7 ^{a,c}	N/A	No Prod.
2	(<i>R</i>)- 34	5 mol%	K ₂ CO ₃	Toluene	7 ^{a,c}	N/A	Traces
3	(<i>R</i>)- 34	5 mol%	K ₃ PO ₄	Toluene	7 ^{a,c}	N/A	Traces
4	(<i>R</i>)- 34	5 mol%	K ₃ PO ₄	DCM	6 ^{b,d}	N/A	Traces
5	(<i>R</i>)- 34	5 mol%	K ₃ PO ₄	THF	6 ^{b,d}	N/A	No Prod.
6	(<i>R</i>)- 34	5 mol%	K ₃ PO ₄	Acetone	3	N/A	No Prod.
7	(<i>R</i>)- 34	5 mol%	K ₃ PO ₄	MeOH	3	N/A	No Prod.

^a0.5 equiv. of H₂O was added after two days. ^b0.5 equiv. of H₂O was added after one day. ^c0.5 equiv. of TEA was added after 6 days. ^d0.5 equiv. of TEA was added after 5 days. ^eObserved by TLC.

The reactions were monitored by thin-layer chromatography (TLC). After observing no significant product formation, we attempted to add 0.5 equiv. of H₂O, then 0.5 equiv. of the more easily soluble TEA to enhance the formation of the hydroxide anions in the reaction mixture (entries 1-5). However, the reactions did not provide the desired conversion yet. The screening of conditions in this promising catalytic reaction is still being carried out as a part of our future projects.

4.3. Summary and Conclusion

To perform the thorough structural and electronic scrutiny of our coordination compounds, we exploited the advantages of X-ray crystallography, two-dimensional ROESY and the one-dimensional $^{31}\text{P}\{^1\text{H}\}$ NMR spectroscopies beside carrying out coordination reactions on P,N and P,C transition metal complexes. This study was then supported with NBO (DFT) analysis to obtain quantitative data on the electronic effects occurring in the carbo-aromatic and heteroaromatic coordination compounds.

The structural analysis revealed that the synthesized P,N complexes possess relatively rigid and well-defined (δ) conformation around the metal centers, which is suitable to convey chiral information during a potential catalytic process. Moreover, ROESY correlations proved that this geometry remains intact in solution as well.

The coordination experiments supported our hypothesis that the trans influences of the coordinating atoms follow the $\text{C}(\text{sp}^2) > \text{phosphine} > \text{N}(\text{sp}^2)$ pattern regarding their strength in our case. This observation, along with the quantified (computed) results, provides a deeper understanding on the electronic effects occurring around these metal centers.

We also carried out the testing of the obtained P,N dichloro palladium complex in asymmetric hydrophosphination and in the enantioselective arylation of imines. The testing of our newly synthesized complexes in novel organometallic catalytic reactions is one of the most important research directions among the planned future projects regarding this thesis.

CHAPTER 5: Thesis Summary and Future Outlook

5.1. Summary of the thesis

This thesis is based on our desire to extend the already colorful and broad chemistry of transition metal complexes established in our group.^{59, 110} The chemistry of metallacycles is very intriguing and diverse, and their features have been deeply scrutinized in the past decades. Besides their proven performance as highly effective catalysts or chiral reagents, the metallacycle structure bears a crucial limitation from synthetic point of view: metals in the center must be relatively electron deficient. It means that in metallacycles the soft Lewis-acidic late transition metals are generally at higher oxidation states. To be able to broaden the scope of applicable metals for our complexes, which would undoubtedly result in new opportunities in potential catalyst design, we considered changing the nature of the coordination of our ligands. This was achieved by changing the coordinating carbon atom to nitrogen, by which the chiral ligand does not necessarily bear a negative charge (Figure 133.).

Figure 133. The C,P phosphapalladacycle dimer complex and the similar, newly developed P,N dichloropalladium compound.

Unlike the C,P ligand, which is attached to the metal via metalation forming a polar covalent bond, the interaction between the P,N ligand and the metal is neutral, as it is connected via purely coordinate bonds. This allows us to apply a wider range of metals and oxidation states.

In the beginning of the thesis, the first chapter introduces the chemistry of chelate complexes, the process of chelation and bidentate ligands in general. Beyond that, this part focuses on the chemistry of chiral bidentate ligands and their role in asymmetric synthesis. This chapter details their key structural and electronic features, their syntheses, and their roles within the field of organometallic chemistry. Our aim was to

exhibit these bidentate coordinating moieties via their relevance to this work with mentioning their evolution in time when necessary as well. The last part of the introduction describes the nature of chiral P,N ligands, which bear especially great importance to this work.

Our synthetic approaches that we employed to obtain novel P,N ligand scaffolds are described in the second chapter of the thesis. We applied both stoichiometric and catalytic enantioselective methodologies with the aid of chiral palladacycle reagents. The asymmetric hydrophosphination was performed on a series of activated malonate diesters with alkyl and aryl substituents to establish a scope of substrates and to scrutinize the effect of bulkiness on the reaction. Besides, the enantioselective P-H addition was carried out on the α,β unsaturated isoquinoline acrylophenone substrate, where the outcome was rather surprising: in contrast to our expectations, the phosphine addition took place on the α carbon atom adjacent to the carbonyl group. All things considered, the optimized conditions of the catalytic hydrophosphination let us synthesize a set of new transition metal complexes.

The third chapter of this thesis covers the difficulties and observations around the syntheses of chiral chelate complexes by employing various transition metals. Since the *in situ* addition of metal sources to the P,N ligand did not turn out to be applicable, we established a workout procedure to get rid of the active catalyst and other residues in the reaction mixture before complexation. This let us perform the addition of Pd(II), Pd(0), Pt(II), Rh(I), Ir(I), Ni(II) and Ru(II) metals in an enantioenriched manner. By applying crystallization, palladium and platinum dichloro complexes could be obtained in enantiopure forms. Rhodium and iridium COD complexes could be isolated too in enantioenriched ways, while the resulting palladium(0) and nickel(II) P,N complexes proved to be paramagnetic causing serious obstacles during characterization. In the case of ruthenium, the forming compound did not occur to be stable enough for characterization, either. In brief, palladium and platinum complexes are suitable for structural and electronic investigations as model compounds and precatalysts, while their modified rhodium, iridium COD and palladium allyl counterparts were designed as potential catalyst molecules for asymmetric synthesis.

The fourth chapter details the thorough scrutiny of the synthesized transition metal complexes by electronic and steric points of views. Because the application of strong

coordinating agents (dppe or triphenylphosphine) could not or could only be used in a limited extents, applying 1.0 equiv. of triphenylphosphine proved to be suitable to investigate the coordination chemistry of the P,N system with various metals. Even the comparison of this framework with its P,C analogue was performed providing valuable information and a broader view on this matter. Our observations were quantified and supported by Natural Bond Orbital (DFT) calculations by determining the extent of backdonation of the carbo-aromatic and heteroaromatic systems to palladium and platinum metal centers.

In this part, catalytic test reactions involving complex (*R*)-**34** as the active catalyst are also illustrated. The aforementioned palladium complex was tested in asymmetric hydrophosphination and in an enantioselective arylation reaction. Although these attempts did not provide valuable results yet, both are worth to be subjects of deeper investigation as a separate project in the future.

Generally, the synthesis of P,N ligands via catalytic hydrophosphination is a very intriguing and also challenging area. One, obvious obstacle that we immediately faced is the presence of the aromatic nitrogen atom on the substrates because it acts as a potential coordinating donor atom towards the Lewis-acidic transition metals. This makes the possible catalytic approaches highly difficult because the forming P,N product can immediately coordinate to the active metal catalyst.¹⁰⁹ This can disrupt the catalytic cycle due to the chelate effect described at the beginning of Chapter 1.

As it is a common practice when synthesizing bidentate ligands, resolution is often involved in their synthetic pathways.⁶⁶ The resolution step can be carried out by using resolving agents (chiral auxiliaries) and various separation techniques such as column chromatography or fractional recrystallization. More recently, dynamic kinetic resolution (DKE) based procedures were also reported in numerous papers to facilitate these methods. However, catalytic pathways to form these kinds of ligands from an achiral substrate is less reported. With the highly versatile C,P (**14**), P,C,P (**21**) and C,N (**1**) palladacycle catalysts in hand, we could effectively utilize the well-established protocols to carry out hydrophosphination on the activated **22a** dimethyl malonate substrate. This allowed us to use the forming bidentate ligand in various complexation reactions and led us to carry out further attempts in catalyst designing.

In summary, we could extend our scope of complex materials, and with this project, we could provide valuable experience, information, and data for designing such catalyst complexes for our group in the future. Besides, this synthetic route and these novel protocols altogether provide a good example as a new approach to obtain chiral P,N coordinating agents.

5.2. Future outlook based on our findings

This thesis can also be a starting point of various projects in the future. The enantiopure P,N ligand was obtained as the chiral part of the palladium and platinum dichloro complexes via recrystallization or via classic resolution. However, P,N ligand **27** can be liberated from its metal complexes by using saturated potassium cyanide solution (Figure 134.).⁶³

Figure 134. Liberation of resolved enantiopure P,N ligand **27** from its palladium complex by using potassium cyanide.

Coordinating agent **27** then can be either used for synthesizing the Rh(I) (**40**) and Ir(I) (**43**) COD and Pd(II) allyl (**46**) complexes in an enantiopure manner or applied as a novel, free and accessible ligand directly in existing catalytic reactions where chiral bidentate ligands were already employed (Figures 134. and 135.).

Complexes **40** and **43** have significant potentials to be used in rhodium or iridium catalyzed hydrofunctionalization reactions because of the compelling and well-described catalytic activity these metals show in their +1 oxidation state.

Figure 135. Potential transition-metal catalyst complexes developed within this project.

Nonetheless, allylpalladium complex **46** has been intentionally tailored to be able to be employed in allylic alkylation reactions in a similar manner that Brown et al. have reported with high selectivity (Figure 136.).¹⁴⁴

Figure 136. Asymmetric allylic alkylation by allylpalladium(II) QUINAP catalyst.

This reaction requires mild conditions and only 2% of catalyst loading. That may be the first comparison between the catalytic performances of our novel P,N moiety (**27**) and a well-known and successfully used bidentate, the QUINAP ligand.

Further aspect on expanding the present project is the modification of the P,N ligand via its phosphine group: the stereodirecting phosphinophenyl groups can be substituted with bulkier or electronically different aryl rings (Figure 137.).¹⁵⁰⁻¹⁵¹ This may consist in including e.g., *tert*-butyl, halogen or methoxy substituents in particular positions on the phenyl rings to finetune them to be more electron withdrawing or electron deficient. These kinds of modifications usually induce significant effects on the catalytic activities of the applied metal centers.

Figure 137. Modification of the structure of chiral ligand **27** by adjusting the phosphinophenyl groups with different substituents.

Moreover, employing different aryl substituents in the same phosphinoaryl group leads to P-chiral compounds.⁵⁸ Along with the well-defined chirality on the adjacent carbon atom, this may result in a highly efficient exploitation of the thoroughly fashioned chiral medium in a newly designed catalyst complex.

Upon a possibly established catalytic performance and track record of ligand **27**, these derivatives may provide better catalytic effectivity, new opportunities, and new observations in the field of organometallic catalysis.

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