Synthesis of New N-Based Ligands, and Pd-Complexes, and Applications in the Cross-Coupling Reactions

Thesis Submitted for the Partial Fulfilment of the

Degree of

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By

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Abstract

The main purpose of this doctoral thesis is to synthesize new efficient N-based ligands, and catalysts, and to explore their applications in the Pd-catalysed cross-coupling reactions. In addition, we aim to study the mechanistic pathways involved in the cross-coupling reactions through this work. Therefore, this thesis is comprised of four chapters including a general introduction on catalysis, focusing organometallic catalysis in Chapter 1, followed by synthesis and characterization of new N-based ligands and their potential as ligands in Suzuki-Miyaura cross-coupling reaction in Chapter 2, glycerol as an efficient reaction medium for Suzuki-Miyaura cross-coupling reactions in Chapter 3, and finally, Suzuki-Miyaura cross-coupling reaction of aryl halides and aryl boronic acids using a new ionophillic iminophosphine-Pd-complex and insights about the mechanism of the reaction has been studied in Chapter 4.

Chapter 2 provides some insights about synthesis of mono- and bis-pyrazoles bearing flexible *p*-tolyl ether and rigid 2,7-di-*tert*-butyl-9,9-dimethyl-9*H*-xanthene backbones, as pyrazolyl analogues of DPEphos and Xantphos ligands, respectively. The synthesis of the new pyrazolyl analogues was accomplished by following an Ullmann coupling protocol and the resulting products were isolated in good overall yields. In addition, a hybrid imidazolyl-pyrazolyl analogue and selanyl-pyrazolyl analogue bearing xanthene backbone were also synthesized in 78% and 58% yields, respectively. The compounds were found active as potential ligands in the Pd-catalysed Suzuki-Miyaura cross-coupling of aryl halides with aryl boronic acids. A simple catalytic system based on $Pd(OAc)_2$/pyrazolyl analogues, efficiently catalyzes the Suzuki-Miyaura cross-coupling reactions and provides moderate to excellent yields of the corresponding cross-coupling products.

In chapter 3, the use of glycerol as an efficient reaction medium for the Pd-catalyzed Suzuki-Miyaura cross-coupling of aryl bromides with arylboronic acids has been discussed. A simple catalytic system based on $PdCl_2(PPh_3)_2$ in glycerol offers an environmentally benign, cheap, and practical protocol for the synthesis of substituted biaryls. The reaction proceeded smoothly with low catalyst loadings (0.5 mol%) providing excellent yields (up to 99%), and the cross-coupling products were isolated easily by simply extracting the reaction mixture with a glycerol-immiscible solvent. Since, the use of glycerol provides the advantage of using the catalytic system to recycle. Thus, the glycerol recycling experiments by using 2 mol% of Pd loading revealed that

the catalytic medium is recyclable up to 8 cycles with a slight loss of catalytic activity after 8^{th} cycle due to formation of solid inorganic salts, preventing the reaction mixture from a smooth magnetic stirring. Furthermore, we also have provided some details regarding the role of glycerol as an *in situ* source for phosphinte ligand formation by reaction with PPh_2Cl. A very good yield of the cross-coupling product was obtained using PPh_2Cl as a phosphine source in glycerol that can form a phosphinite ligand *in situ* by reaction with glycerol. Moreover, we also have provide some details regarding the role of glycerol as *in situ* source for oxolone ligand formation by reaction with Pd(diphenylphosphine-2-benzaldehyde)$_2$. A moderate yield of the cross-coupling product was obtained using Pd(diphenylphosphine-2-benzaldehyde)$_2$ in glycerol that can form a oxolone ligand *in situ* by reaction with glycerol.

Finally, in chapter 4, we intended to study the mechanistic pathway of Suzuki-Miyaura cross-coupling reaction by identification of key reactive intermediates through ESI mass spectrometry technique. For this purpose, we have synthesized a new ionophillic imino-phosphine Pd-catalyst and has been characterized fully using different spectroscopic and spectrometric technique including the X-ray crystallography. The new imino-phopsphine-Pd-complex demonstrates an excellent catalytic activity for catalyzing the Suzuki-Miyaura cross-coupling reactions of aryl halides and aryl boronic acids. Since, the beneficial aspect of installing charged tag on the catalyst displays an extraordinary high level of sensitivity towards the electrospray ionization mass spectrometry (ESI-MS), we were able to detect and identify several reactive intermediates including a Pd(0) species for the first time through ESI.

Portuguese Abstract

O principal objetivo desta tese de doutorado é a síntese eficiente de novos ligantes e catalisadores nitrogenados, aplicá-los nas reações de acoplamento cruzado catalisadas por Pd. Além disso, neste trabalho pretendemos estudar os mecanismos envolvidos nas reações de acoplamento cruzado. Portanto, esta tese é composta por quatro capítulos. No capítulo 1, uma introdução geral sobre catálise focada em organometálicos. No capítulo 2, a síntese e caracterização de novos ligantes nitrogenados e seu potencial como ligantes na reação de acoplamento cruzado de Suzuki-Miyaura. No capítulo 3, a utilização de glicerol como um meio eficiente para a reação de acoplamento cruzado Suzuki-Miyaura e, finalmente, no capítulo 4, a reação de acoplamento cruzado do tipo Suzuki com halotos de arila e ácidos aril borônicos usando um novo complexo ionofílico de iminofosfina-Pd e as propostas de mecanismo das reações que foram estudadas.

O Capítulo 2 fornece algumas ideias sobre a síntese de mono e bis-pirazóis com éter *p*-tolil flexível e 4,5-dibromo-2,7-di-terc-butil-9,9-dimetil-9H-xanteno, como análogos pirazois dos ligantos DPEphos e Xantphos, respectivamente. A síntese dos novos derivados de pirazois foi realizada seguindo um protocolo de acoplamento Ullmann e os produtos resultantes foram isolados com satisfatórios rendimentos. Além disso, um híbrido de imidazo-pirazo xanteno e selenil-pirazo xanteno também foram sintetizados com rendimentos de 78% e 58%, respectivamente. Os compostos foram considerados ativos como potenciais ligantes no acoplamento cruzado Suzuki-Miyaura catalisado por Pd e haletos de arila com ácidos aril borônicos. Um sistema catalítico simples baseado em $Pd(OAc)_2$/pirazoil catalisa eficientemente a reação Suzuki-Miyaura e fornece rendimentos moderados a excelentes dos produtos correspondentes do acoplamento cruzado.

No capítulo 3, o uso de glicerol como meio de reação eficiente para o acoplamento cruzado Suzuki-Miyaura catalisado por Pd de brometos de arila com ácidos aril borônicos foi discutido. Um sistema catalítico simples baseado em $PdCl_2(PPh_3)_2$ em glicerol oferece um protocolo ambientalmente correto, de baixo custo e prático para a síntese de bis-arílicos substituídos. A reação prosseguiu sem problemas com baixa quantidade de catalisador (até 0,5 mol%), proporcionando excelentes rendimentos (até 99%), e os produtos de acoplamento foram isolados facilmente, extraindo-os da reação com solvente imiscível em glicerol. Sendo assim, o uso de glicerol fornece a vantagem

de reciclos do sistema catalítico. Assim, o reuso do glicerol usando 2% molar de Pd revelou que o meio catalítico é reciclável até 8 ciclos, com uma leve perda de atividade catalítica após o 8º ciclo devido à formação de sais inorgânicos sólidos. Além disso, também fornecemos alguns detalhes sobre o papel do glicerol como fonte *in-situ* para a formação de ligantes de phosphinito por reação com PPh_2Cl. Um rendimento muito bom do produto de acoplamento cruzado foi obtido usando PPh_2Cl em glicerol que pode formar um ligante de phosphinito *in-situ* por reação com glicerol. Além disso, também fornecemos alguns detalhes sobre o papel do glicerol como fonte *in-situ* para a formação de ligantes de oxolona por reação com Pd(difenilfosfina-2-benzaldeído)$_2$. Um rendimento muito bom do produto de acoplamento cruzado foi obtido usando Pd(difenilfosfina-2-benzaldeído)$_2$ em glicerol que pode formar um ligante de oxolona *in-situ* por reação com glicerol.

Finalmente, no capítulo 4, pretendemos estudar o mecanismo da reação de acoplamento cruzado Suzuki-Miyaura, identificando os principais intermediários reativos através da técnica de espectrometria de massa ESI. Para isso, sintetizamos um novo catalisador ionofílico de imino-fosfina-Pd e foi totalmente caracterizado utilizando diferentes técnicas espectroscópicas e espectrométricas, incluindo a cristalografia de raios-X. O novo complexo imino-fosfofina-Pd demonstra uma excelente atividade catalítica para a reação de acoplamento cruzado Suzuki-Miyaura de haletos de arila e ácidos aril borônicos. Com a possibilidade da adição de carga no catalisador, é possível ter um alto nível de sensibilidade na espectrometria de massa de ionização por eletropulverização (ESI-MS), assim, conseguimos detectar e identificar vários intermediários reativos, incluindo uma espécie de Pd(0) pela primeira vez através do ESI.

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List of Schemes

List of Abbreviations and Formulas

Ac	Acetyl
Ana	Analytical
Ar	Aryl
Bu	Butyl
calcd.	Calculated
CC	Cross coupling
CH_3CN	Acetonitrile
COD	1,5-Cyclooctadiene
Cy	Cyclohexyl
d	doublet
DABCO	Diazabisdicylcooctane
Dba	dibenzylideneacetone
δ (delta)	Chemical shift
DCM	Dichloromethane
DCE	1,2-Dichloroethane
DIBAL	di*iso*butylaluminium hydride
DIPEA	di*iso*propylethylamine
DMA	*N*,*N*-dimethylacetaamide
DMF	*N*,*N*-dimethylformamide
DMSO	Dimethylsulfoxide
dppe	1,2-bisdiphenylphosphinoethane
dppp	1,3`-bisdiphenylphosphinopropane

dppb	1,4`-bisdiphenylphosphinobutane
dppf	1,1`-bisdiphenylphosphinoferrocene
EI	Electron ionization
eq.	Equivalents
ESI	Electrospray Ionization
GC	Gas chromatography
HC	Homo-coupling
HR	High resolution
i	Iso
IR	Infra-red
J	Coupling constant
L	Ligand (s)
Lit.	Literature
M^+	Molecular ion
m	multiplet
Me	Methyl
Mes	Mesityl
mp	melting point
NBS	N-bromosuccinamide
NMR	Nuclear magnetic resonance
$PdCl_2(CH_3CN)_2$	Bis(acetonitrile)palladium (II) chloride
$PdCl_2$(COD)	Dichloro(1,5-cyclooctadiene)palladium (II)
$Pd_2(dba)_3$	Tris(benzylideneacetone)palladium (0)
$PdCl_2$(dppf)	[1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)

$PdCl_2(PhCN)_2$	Bis(benzonitrile)palladium (II) chloride
$PdCl_2(PPh_3)_2$	Bis(triphenylphosphine)palladium (II) chloride
Ph	Phenyl
q	Quartet
rt	Room temperature
s	Singlet
t	Triplet
t	Tertiary
T	Temperature
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Tetramethylsilane
Tol	Tolyl
TPPMS	Triphenylphosphine monosulfonate sodium salt

Chapter 1 Introduction and Objectives

1.1 Introduction

The fact that all of the materials and the products that make the foundation of a modern society, all the way from fuels to fertilizers, materials to pharmaceuticals, all of that relies on our ability to transform cheap and readily available starting materials into model products or fine chemicals.[1] The transition metal catalyzed reactions are among the best protocols in this context, because they offer broad substrate selectivity and tolerance, improved product yields, provides opportunity to induce or to obtain regio- and stereo-controlled organic compounds, *etc*. Various transition metals have been used to catalyze a variety of organic reactions in one way or the other, provided the transition metals have less harmful impact on the human health and the environment.[2-5] These metal-catalyzed reactions in the last three to five decades have extended a remarkable level of superiority. Precisely, the Nobel Prize winning research of Knowles, Noyori and Sharpless in 2001 (**Figure 1**),[6-12] and Chauvin, Grubs and Schrock in 2005 (**Figure 2)**,[13-17] for the development and designing of the metal-catalyzed reduction and oxidation reactions, and the olefin metathesis reactions, respectively, have completely altered the notions of the present day scientist.

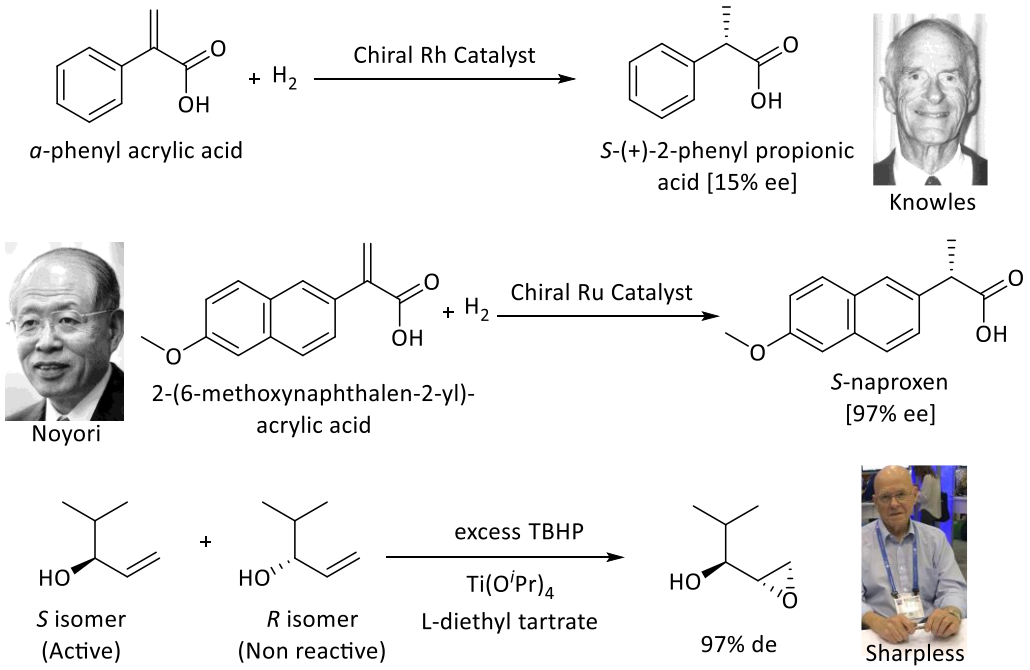


Figure 1. The 2001 Nobel Prize winning research based on transition metals.

Since, they offer an extraordinary astonishing reactivity and selectivity towards the substrates and products, therefore, the transition metals have been widely used as catalysts in both academia and industry, ruthlessly.[18, 19]

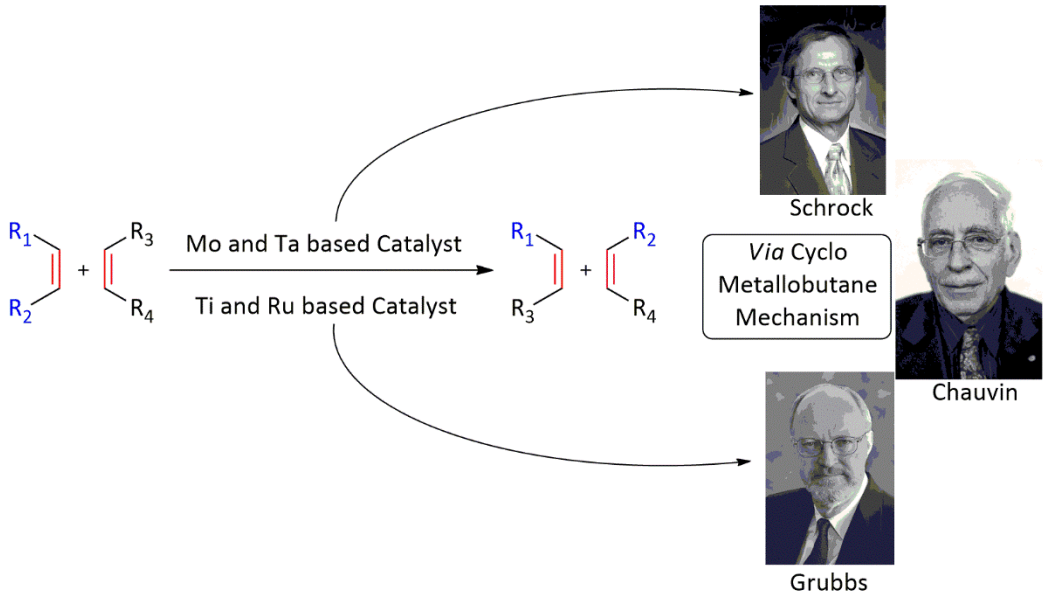


Figure 2. The 2005 Nobel Prize winning research based on transition metals.

The unique capability of the transition metals to catalyze a variety of organic reactions is believed to be due to their intrinsic ability of activating organic molecules *via* oxidative addition and back donation. Through this activation, the transition metals can catalyze a variety of reactions for the formation of new *C*-*C* or *C*-*X* (X = heteroatom) bonds, which in turn are of profound significance in chemical and life sciences. The fashionable assembly of these carbon atoms can then be customized to design and create building blocks and chains and most importantly the lifesaving drugs.[20] Thus, one can say that the transition metal catalysis is playing a vital role in the current world by extending its applications in almost every field of science.

As far as the history of this remarkable field is concerned, dating back into centuries ago, researchers were using these procedures to obtain useful organic molecules. To be more precise, the Glaser homo-coupling of metal acetylides in 1869 is considered to be among the first examples of transition-metal-promoted coupling reactions. Using copper as catalyst, Glaser was able to synthesize diphenyldiacetylene from silver phenylacetylide as coupling partner *via* oxidative dimerization.[21, 22] The development of this new *Csp*-*Csp* bond was well appreciated by the synthetic community

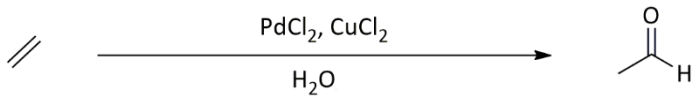
in the following years. Following Glaser, Ullmann successfully reported the dimerization of 2-bromo-nitrobenzene in 1901, using stoichiometric amounts of copper.[23-25]

The significance of catalysis and its role in various fields can be concluded by citing the following statement in *Nature Catalysis*.[26]

"**Historically catalysis has evolved as a set of different fields linked together by a unifying concept. While the distinctions between the various areas serve a purpose, exciting work is happening at the interface**."

1.2 The Advent of Palladium Catalysis

The major event that was responsible for the boosting of research into the palladium chemistry was the discovery of Pd-catalyzed air oxidation of ethylene into acetaldehyde, popularly known as the Wacker process,[27] **Scheme 1**. Even though Pd was discovered in 1802, the importance of Pd in catalyzing organic reactions was realized a century later, after World War II. This discovery and its subsequent refinements and applications on commercial scale, laid the foundation of Pd chemistry as one of the most powerful tool for the synthesis of a variety of organic molecules.[28, 29]



Scheme 1. The Wacker Process.

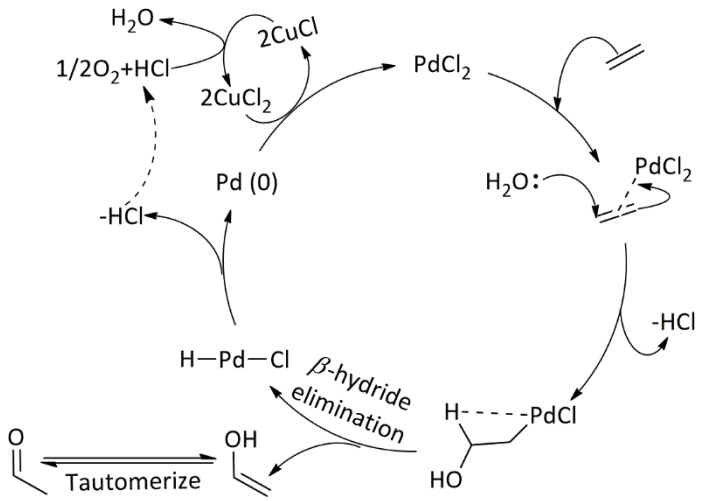


Figure 3. Mechanism of Wacker Oxidation.

Research on Pd-catalyzed new reactions for the formation of carbon-carbon bonds by Heck who was deeply inspired by Wacker process,[30] led to the beginning of a new era in the domain of palladium chemistry, followed by Negishi and Suzuki. That's why the 2010 noble prize in Chemistry was awarded to Heck,[31-33] Negishi,[34-36] and Suzuki[37-39] for their outstanding research on palladium catalyzed cross-coupling reactions,[40, 41] (**Figure 4**).

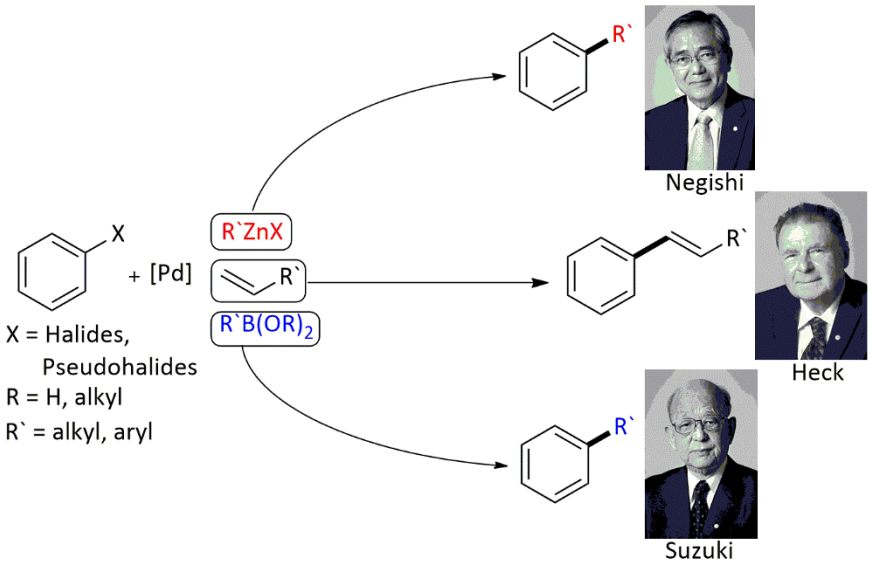


Figure 4. The 2010 Nobel Prize winning research based on palladium metal.

Subsequently, the palladium catalyzed cross-coupling reactions with organo-copper (the Sonogashira),[42-44] organo-tin (the Stille),[45, 46] organo-silicon (the Hiyama)[47, 48] and many other important Pd-catalyzed reactions,[49-53] were developed along with excellent achievements of broad substrate selectivity, functional group tolerance and versatility (**Figure 5**). A multiple fold increase in the research involving Pd-catalyzed reaction can be evidenced by a single SciFinder® search using the keyword palladium which finds more than 354324 research items, whereas the keywords palladium and coupling reactions together shows 47825 hits, further refining the search to the keywords palladium, cross-coupling and Suzuki shows 11500 hits, since then.

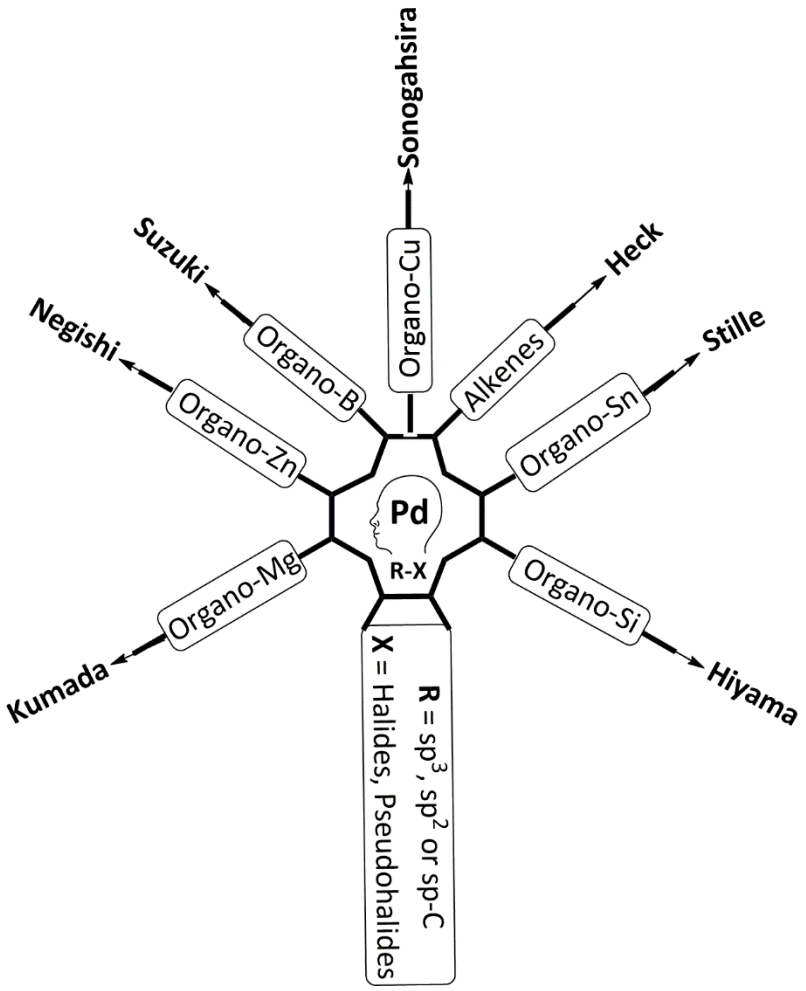


Figure 5. Well-known Pd-catalyzed coupling reactions.

1.3 Mechanism of the Pd-Catalysed Cross-Coupling Reactions

The catalytic specie that is responsible for the initiation of the catalytic cycle in the palladium catalysed reactions has been proposed to be the $L_nPd(0)$ species,[54] where L = any ligand backbone and n = 2, in typical palladium catalysed reactions. The most commonly accepted mechanism for the Pd-catalyzed coupling reactions is showed in **Figure 6**. In general, the aryl halide (or pseudo halide) adds to the catalytically active $L_nPd(0)$ species *via* oxidative addition and generates $L_nPd(II)$ intermediate.[55] This $L_nPd(II)$ intermediate then undergoes transmetalation with an organometallic coupling partner and generates a new $L_nPd(II)$ specie bearing two organic coupling fragments at the same Pd centre.[56] Depending on the situation, the two organic fragments undergo isomerization, followed by the final reductive elimination step which results in the

formation of new C-C bond with the regeneration of the initial $L_nPd(0)$.[57, 58] This catalytically active $L_nPd(0)$ species then re-enters into the second catalytic cycle. It is for the sake of simplicity, the catalytic cycle is commonly described in three major steps, otherwise further micro-steps exist within the individual steps.

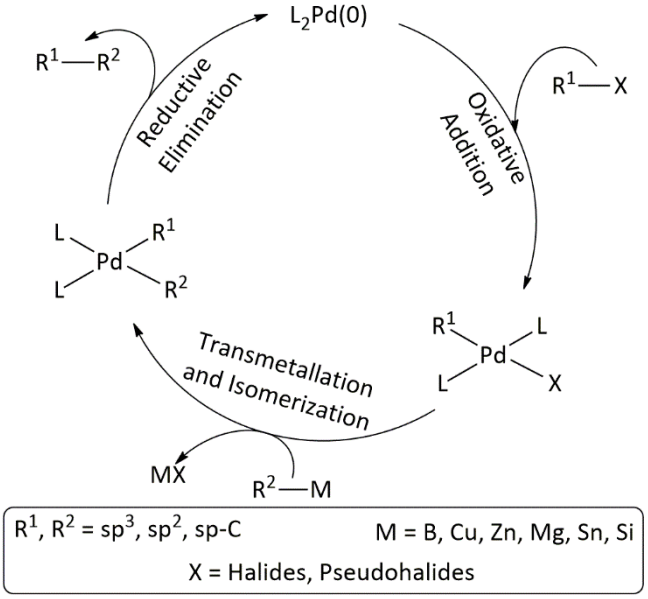


Figure 6. Proposed catalytic cycle for Pd-catalyzed cross coupling reactions.

It is important to mention that the Heck coupling,[36] differs from the other cross-coupling reaction by the fact that the reaction proceeds by the coordination of the alkene to the $L_nPd(II)$ species (**Figure 7**), after oxidative addition. The alkene itself then undergoes an intramolecular *syn*-migratory insertion rather than intermolecular trans-metalation with an organometallic coupling partner. The regioselective outcome of the Heck reaction largely depends on this insertion step and also depends on the type of catalyst, the nature of alkene, and reaction conditions used. Finally, the intermediate generated after migratory insertion step undergoes a *syn* β-hydride elimination to form the coupling product and regenerates the $L_nPd(0)$ specie, which re-enters into the second catalytic cycle.

As the majority of this thesis has been dedicated to the study of cross coupling reactions, therefore, the individual steps involved in the catalytic cycle will be discussed in detail in the following section.

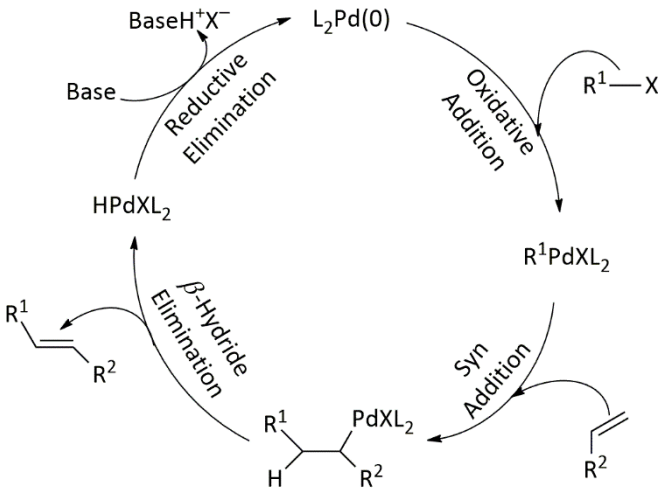
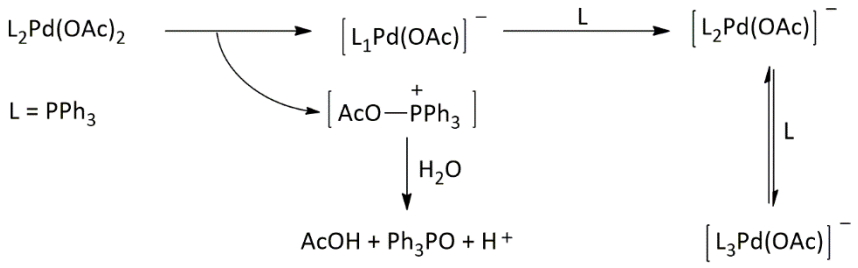


Figure 7. Mechanism of Heck reaction.

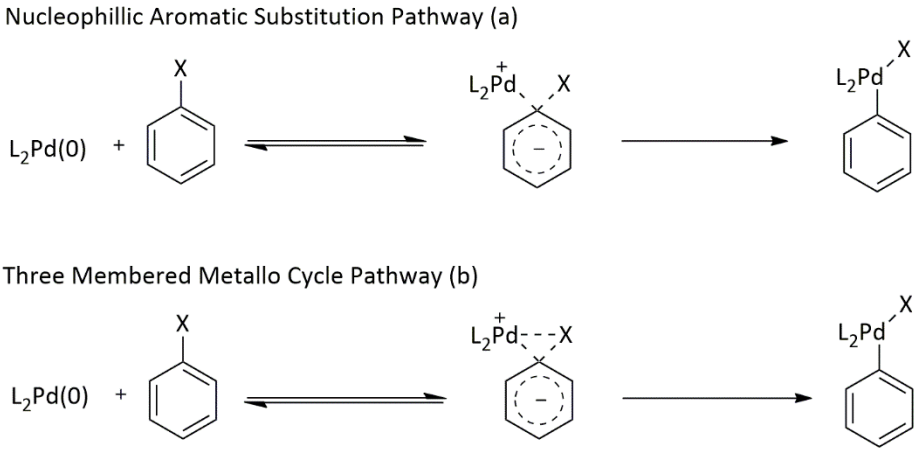
1.3.1 Oxidative addition

The catalytic cycle begins with the oxidative addition step *via* a redox process, followed by insertion of the organo-halides (pseudo halides).[59, 60] Various factors are responsible to speculate the tendency of transition metals to undergo oxidative addition; however, the presence of transition metals in zero or low valent oxidation states is a must criterion for this step to proceed forward smoothly. In addition, the metal must act as a nucleophile or as a reducing agent. The coordination number and the ligand framework also strongly influence the course of the oxidative addition step. For example, ligands can easily dissociate from the metal centre to create vacant sites for the organo-halides to undergo oxidative addition. Steric factors are other major contributing factor which facilitates a smooth oxidative addition step. For instance, bulky ligands with large cone angles helps oxidative addition by easy dissociation from the metal center.[60] Formation of anionic $L_nPd(0)$ species *in situ* are known to catalyze the cross-coupling reactions. For example, Jutand and Amatore reported that the anionic tricoordinated species such as $[PdL_2(OAc)]^-$ are the active species responsible for the oxidative addition when $Pd(OAc)_2$ and PPh_3 are used as the catalytic system (**Scheme 2**).[61]



Scheme 2. Formation of active anionic $L_nPd(0)$ specie from $Pd(OAc)_2$ and PPh_3.

As far as the organo-halides are concerned, aryl halides undergoe undergo oxidative addition to the $L_nPd(0)$ specie *via* two pathways *i.e., via* a nucleophilic aromatic substitution pathway, or a three membered metallo-cycle pathway,[60, 62, 63] (**Scheme 3**). These pathways have been supported by the DFT studies as well.[64] Moreover, an electron transfer pathway has also been suggested for oxidative addition, however, such pathways are not common for the Pd-catalyzed cross-coupling reactions.[65] In contrast, the Cu, Ni, Ir, and Pt catalyzed reactions have been found to follow such pathways. Evidences for the formation of 5 membered coordinated species have also been proposed for the oxidative addition.[63] Regardless of the pathways, the addition of organic halides to the metal proceeds either in a concerted or a stepwise addition mechanism manner.[66]



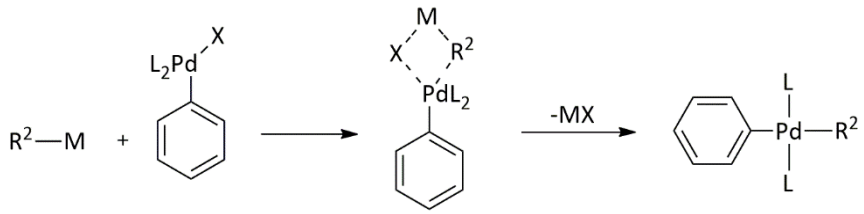
Scheme 3. Mechanistic pathways for oxidative addition.

Among the aryl halides, the relative ease of oxidative addition follows the general order, ArI > ArBr >> ArCl >>> ArF.[67] This classical order of oxidative addition can be reversed *i.e.*, ArCl > ArBr > ArI, if electronically rich and bulky ligands such as NHC's, $P(Bu^t)_3$, Buchwald and Hartwig ligands, *etc*, containing Pd catalysts are used.[68] It is for

this reason, on the basis of the relative affinity of the aryl halides to undergo oxidative addition, the oxidative addition is the rate determining step of the catalytic cycle in many cases. Finally, the addition of aryl halides to the Pd metal initially forms a *cis*-species which undergo isomerization to a *trans*-species at different rates and sometimes the rate of isomerization is extremely fast. In case, when the rate is extremely fast, the isomerization step becomes fast too, as a result the initial *cis*-species cannot be observe and only the final stable *trans*-species has been observed.[63]

1.3.2 Transmetalation and Isomerization

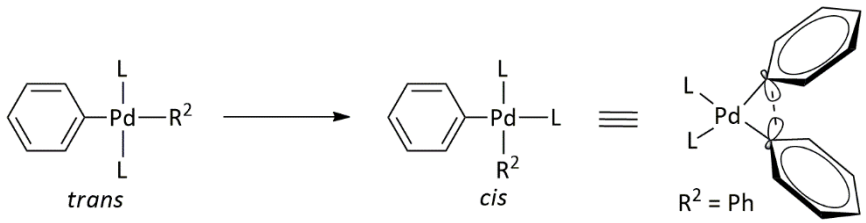
Once the metal undergoes oxidative addition with the organo halides exchange of organic coupling partners occurs between the formed $L_nPd(II)R^1X$ species and the organometallic reagent (R^2M).[56] The difference in the electronegativity of the two metals is considered to be the driving force responsible for a successful transmetalation step. In general, the electronegativity of the metal of the organometallic reagent used for the cross coupling reaction must be less than that of Pd metal for the catalytic cycle to proceed forward.[69] A four-membered cyclic associative pathway has been proposed for the transmetalation step which after cleavage forms a specie containing both the organic coupling partners on the Pd metal, *i.e.*, $L_nPd(II)\ R^1R^2$ species (**Scheme 4**). In addition, dissociative open pathway has also been proposed for the Stille cross-coupling reaction.[70] On the basis of kinetic and spectroscopic studies including the nature of the substrate and the reaction conditions, the transmetalation has also been proposed to be the rate determining step of the catalytic cycle in some cases.[71, 72]



Scheme 4. Proposed four membered cyclic pathway for transmetalation.

The species formed after cleavage of the four membered intermediate initially produces a specie with both the organic coupling partners *trans* to each other *i.e.*, *trans*-$L_nPd(II)R^1R^2$, yet evidence for the direct *cis*-$L_nPd(II)R^1R^2$ species formation are also present in the literature.[63] The *trans*-$L_nPd(II)R^1R^2$ specie then undergoes isomerization

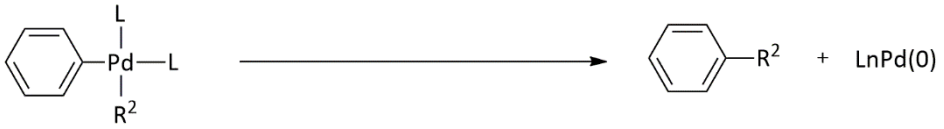
to form a *cis*-$L_nPd(II)R^1R^2$ intermediate, that is why, isomerization has been added additionally in the title here along with the transmetalation step. Nonetheless, in most of the catalytic cycles the isomerization step has not been discussed separately mainly because such events occur in all of the major steps of the catalytic cycle. The preference of the *cis*- over *trans*- before reductive elimination is proposed to be due to the fact that *cis*-intermediate allows preferred π-orbital interaction for the new C-C bond formation (**Scheme 5**).[73]



Scheme 5. *Cis-trans* Isomerization.

1.3.3 Reductive Elimination

Reductive elimination provides the cross-coupling product in the final step of the catalytic cycle by the simultaneous detachment of the organic coupling partners from the Pd metal and regeneration of the $L_nPd(0)$ specie.[73, 74] Since, the organic coupling partners eliminate and the Pd metal is reduced from $L_nPd(II)$ to $L_nPd(0)$, this step is named reductive elimination (**Scheme 6**). The $L_nPd(0)$ specie after reductive elimination renters into the second cycle and begins the next catalytic cycle. The use of sterically crowded ligands containing electron donating groups is the major driving force for a smooth reductive elimination step.[75-78] A unimolecular decomposition pathway has been proposed for the reductive elimination step.[79, 80]



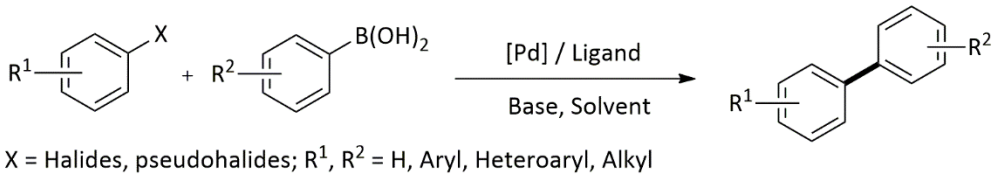
Scheme 6. Proposed pathway for reductive elimination.

The β-hydride elimination and the homocoupling product formation are the common competing side reactions in the catalytic cycle along with the cross-coupling

reaction. The *β*-hydride elimination side reaction can be prevented by the use of *β*-substituted substrates including use of bulky ligands containing strong electron releasing groups. In the same way, the homo-coupling side reactions are due to the scrambling of ligands and organic coupling partners on Pd and also can be avoided or at least minimize by using bulky ligands containing strong electron releasing groups.[81-83] Depending on the rate of detachment of organic groups from the Pd-metal, the reductive elimination has also be proposed to be the rate-determining step by many researchers.[84, 85]

1.4 A Brief Literature Survey of Suzuki-Miyaura Cross-coupling Reaction using Nitrogen (*N*)-based Ligands

The palladium-catalyzed cross-coupling reaction between aromatic halides or pseudohalides and organoboronic compounds, is generally known as Suzuki cross coupling reaction or Suzuki-Miyaura cross coupling reaction. Primarily this method was introduced as a powerful tool for the construction of substituted biaryl motifs.[86] It gain much attention in both academia and industries, with the passage of time and advancements in knowledge and techniques (**Scheme 7**). Today, this method has deepened its roots in various fields including materials, pharmaceuticals, agricultural pesticides, dyes and polymer industry, *etc*. The Suzuki-Miyaura cross-coupling reaction protocol has been widely studied due to several notable reasons. The mild reaction conditions, broad accessibility and stability of organoboron coupling partners, display a wide range of functional group tolerance; and relatively less toxic starting materials and by-products, are among few of them.[26, 87, 88]



Scheme 7. General protocol for Suzuki-Miyaura reaction.

Although several factors influence the outcome of the cross-coupling reaction, the most significant factor influencing the successful execution of a cross-coupling reaction depends largely on the nature and type of ligand used. That is why a huge amount of efforts have been put in research by both academia and industries to develop novel

and efficient ligands.[89-94] Despite the use of original phosphine based ligands, including PPh_3, electronically rich sterically bulky dialky biarylphosphines and trialkyl phosphines, ferrocenyl phosphines, palladacycles, *etc*, in cross-coupling reactions,[95] efforts to synthesize modified and more efficient phosphine based ligands is still active part of ongoing research (**Figure 8**).[96-98] Nevertheless, synthesis of modified ligands based on phosphines is still part of ongoing research, promising efforts for the development of phosphine free ligand systems for cross-coupling reactions and other reactions has also been seen rapidly growing during last 3-5 decades.[99-102]

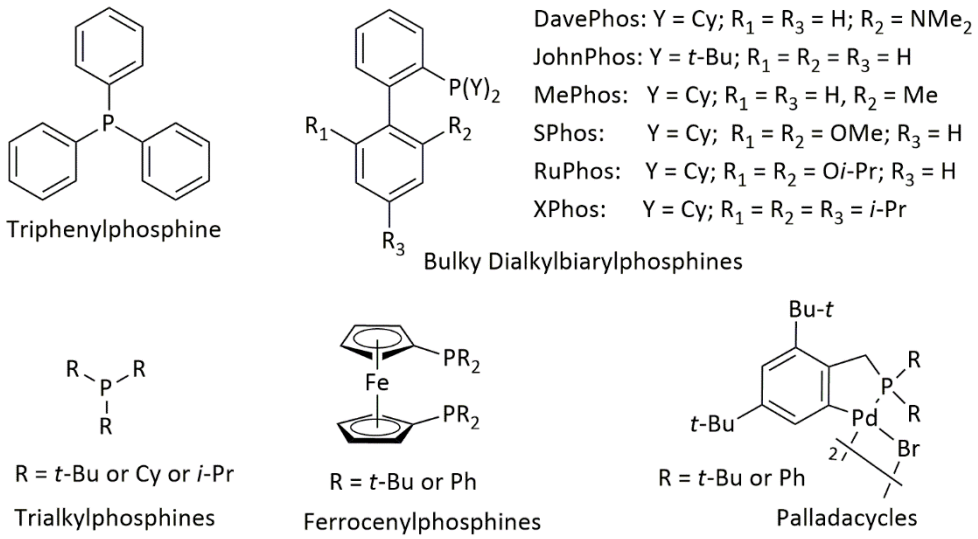


Figure 8. Representative phosphine based ligands and palladacycles.

A variety of phosphine-free *N*-based ligands have been synthesized and reported in literatures.[103-105] One of the several beneficial aspect of using phosphine-free catalytic systems is to overcome the difficulty associated with catalyst instability and their impact on human health and environment, which have been commonly encountered while using phosphine based catalytic systems.[103] These difficulties increase by many folds when such catalytic systems are used for the industrial scale production of chemicals and other useful products. Therefore, development of stable catalytic systems having no or at least minimum impact on human health and environment are much needed challenges and tasks for chemists nowadays. One solution chemists have provided so far is the phosphine-free catalytic systems. The use of *N*-based ligands and catalytic systems is a useful alternative in this aspect, thus they are gaining substantial attention currently. Phosphine free *N*-based ligands used to achieve such shortcomings includes the simple

N-based alkyl amines,[103] aromatic systems containing *N*- as heteroatom such as pyridine,[104] bis-pyridines, phenanthroline,[105] *C*-based *N*-heterocyclic carbenes and ionic liquids,[106-108] *N*-based 2-aryl-2-oxazolines,[109, 110] *C^N*-based aryloxime palladacylces,[111] *N*-based alky or arylimines,[112] *N^N*-based diimines, *N^N^N*- and *N^C^N*-based pincer type ligands, and their hybrids (**Figure 9**).[113] Since the use of *N*-based ligands for the cross coupling reactions exhibit distinctive benefits over corresponding phosphine ligands, especially considering health and environmental restrictions, their sensitivity towards air and moisture, sometimes cost issues among other factors.[114-117] Therefore, one of the objectives of this thesis was aimed for the synthesis of *N*-based ligands and catalysts, and to explore their applications in the cross-coupling reactions. Hence, the following section has been mainly dedicated for the literatures related to *N*-based ligands used for the Pd-catalyzed Suzuki-Miyaura cross-coupling reactions.

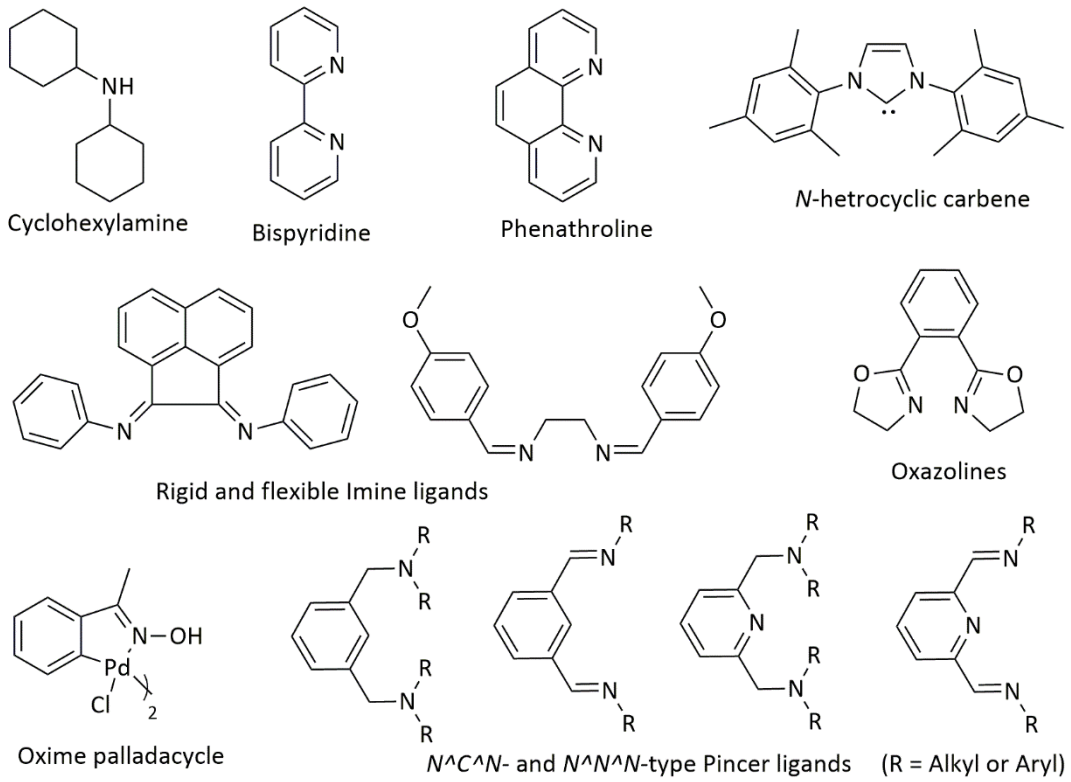


Figure 9. Representative phosphine-free ligands and palladacycles.

The alkyl amine based ligand systems are the simplest *N*-based ligand systems in terms of both cost and stability used for the cross coupling reactions (**Figure 10**). Alkyl and aryl amines have generally been utilized as bases in the cross coupling reactions, nevertheless they display characteristics of ligands as well by stabilizing the reactive

metal intermediates. Tao and Boykin have used a simple alkyl amine system based on amines/$Pd(OAc)_2$ to obtain substituted biaryls form aryl bromides and aryl boronic acids at room temperature. Excellent yields of the cross coupling products were achieved by using Dicyclohexylamine and 1-Adamantylamine as ligands.[103] Likewise, Li and Leu have demonstrated that DABCO/ $Pd(OAc)_2$ can be used as an inexpensive and highly efficient catalytic system for the cross-coupling of aryl halides with aryl boronic acids.[118, 119]

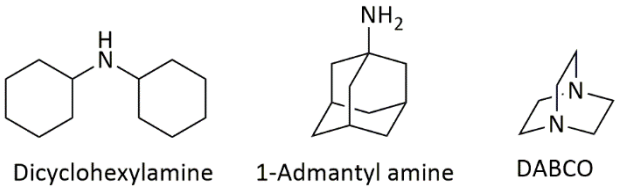


Figure 10. Representative amine based ligands for Suzuki cross-coupling reaction.

The *C*-based *N*-heterocyclic carbenes (*NHC's*) have emerged as a remarkable new class of ligands for cross coupling reactions since last couple of decades.[120] So far, the most promising contestants to replace the corresponding phosphine ligands in cross-coupling reactions are the *NHC's* based ligands and catalytic systems.[121] Some *NHC*-based catalytic systems display outstanding catalytic efficiencies that one can perform extremely challenging cross-coupling reaction with ease and at room temperature.[122] For example, Gereon and co-workers were able to successfully synthesize the highly sterically hindered tetra-*ortho*-biphenyl in excellent yield by using a simple catalytic system based on $Pd(OAc)_2$/Ibox5+HOTf, n = 8 (**Figure 11**).[123]

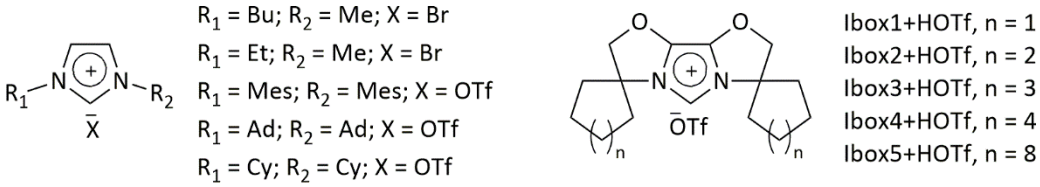


Figure 11. Representative precursors for C-based NHC ligands used for the Pd-catalyzed Suzuki-Miyaura cross-coupling reaction.

Another fascinating aspect of *NHC's* is that the cross-coupling products can be obtained in excellent yields by using a very low catalyst loading, even ppm scale catalyst loadings are known to catalyze cross coupling reactions using *NHC* based catalytic systems. The excellent efficiency of *NHC* based catalytic systems is due to the strong

NHC-Pd bond, which prevents the inactive palladium black formation. Moreover, the facile electron donating capability of *NHC's* facilitates a very smooth oxidative addition step, while the presence of bulky aryl groups such as mesityl group or bulky alkyl groups such as adamantyl or cyclohexyl groups helps in the smooth reductive elimination step of the catalytic cycle.[124] Likewise, imidazole based ionic liquids have been used as solvent medium and ligands for the Suzuki-Miyaura cross-coupling reaction.[108] For example, Xiao and Shreeve have shown that using 2,2`-biimidazole as solvent medium and ligand and $PdCl_2$ as Pd precursor, very good yields of the cross coupling products can be obtained. In addition, they have demonstrated that the developed catalytic system can be recycled up to 4 times without any loss in the catalytic activity.[125]

The aromatic systems containing *N*- as heteroatom such as pyridine, bis-pyridines and phenanthroline though are not so active in catalyzing the Suzuki-Miyaura cross-coupling reaction directly, nevertheless derivatives of pyridine, bis-pyridine and phenanthroline have shown excellent results in this regard (**Figure 12**). Wu and co-workers have used a 2,2`-bipyridyl system to obtain cross coupling products in excellent yields, they further showed that the catalytic system can be recycled various times.[126] In the same way, a variety of di(2-pyridyl)methylamine based ligand system have been successfully utilized for Suzuki-Miyaura cross-coupling reaction. These ligands have the advantage of using water as the solvent medium, since they are soluble in water, therefore, the probability to recycle the catalytic system maximizes.[105, 127] In the context of phenanthroline, Yang and co-workers have described a Merrifield resin supported phenanthroline for Suzuki-Miyaura cross-coupling reaction in water. The catalytic system was recyclable up to 10 cycles with a slight loss in the activity.[128, 129]

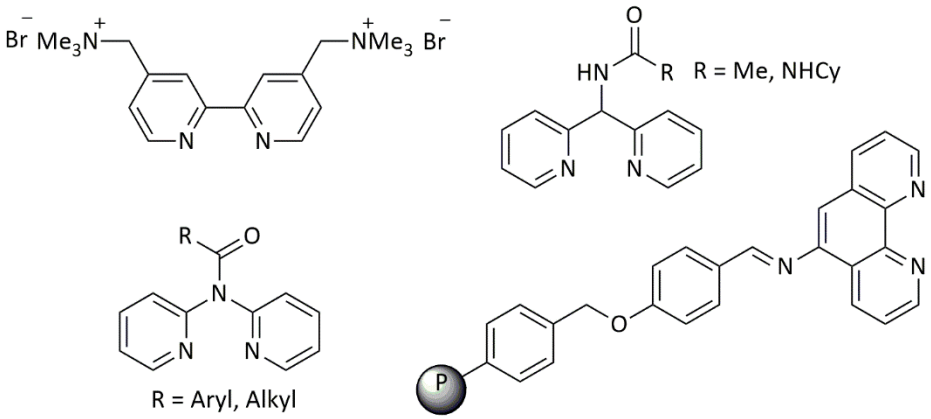


Figure 12. Representative bis-pyridine and phenanthroline based ligands.

Another attractive class of ligands that has fascinated the outcome of the Pd-catalyzed cross-coupling reactions are imine based ligands. Both mono- and di-imine based ligands have been successfully utilized in the Suzuki cross coupling reaction (**Figure 13**). Yang and co-workers have prepared various Pd complexes derived from a rigid mono-imine ligands and evaluated their potential in the Suzuki cross coupling of aryl bromides and aryl boronic acids.[130] The diimine dialkyl or diaryl substituted ligands patented by Nolan and Grasa, have been successfully used in Suzuki-Miyaura cross-coupling reactions.[131] For instance, very good yields were obtained when *N*,*N*'-dicyclohexyl-1,4-diazabutadiene was used as the ligand, while the corresponding aromatic diimines, were slightly inactive and only poor results for the Suzuki-Miyaura cross-coupling reactions were obtained.[69, 132, 133]

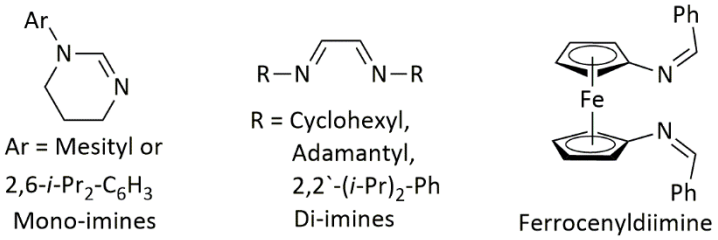


Figure 13. Representative imine based ligands.

Other families of *N*-based ligands used for Suzuki-Miyaura cross-coupling reaction includes oxazoline, imine and oxime based palladacycles (**Figure 14**). Oxazoline ligands and the palladacyles derived from oxazolines have been used to perform Suzuki-Miyaura cross-coupling by Ibrahim and co-workers.[134] *N*-based palladacycles such as oxime and fluorinone based palladacylces were used by Alonso and co-workers as versatile and efficient catalysts to perform a variety of C-C bond-synthesis reactions including Suzuki cross coupling reaction.[135] Moreover, Weissman and Milstein have used an air and thermally stable cyclometallated imine palladacycle to perform Suzuki-Miyaura cross-coupling reaction.[112] On the other hand, Luo and co-workers have demonstrated that novel bis(oxazole) pincer type palladacylces are robust catalysts for Suzuki cross coupling reaction. The Suzuki-Miyaura cross-coupling reactions were performed under aerobic conditions with low catalyst loadings and the corresponding cross-coupling products were obtained in moderate to excellent yields.[136]

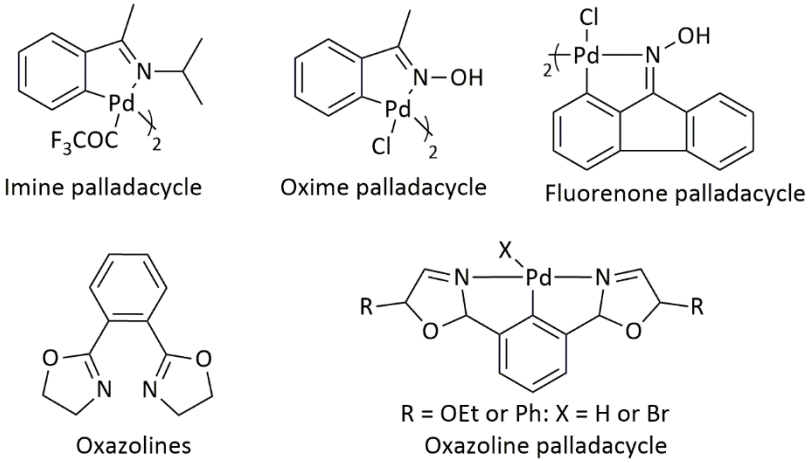


Figure 14. Representative imine, oxime and oxazoline palladacycles.

Lastly, several *N^N^N*- and *N^C^N*-type Pincer ligands have been describe in literatures to perform Suzuki-Miyaura cross-coupling reaction under mild reaction conditions (**Figure 15**).[137] For instance, Yadav *et. al.*, reported new phosphine-free 2,6-bis(pyrrolyl)pyridine based *N^N^N*-type Pincer ligands and their corresponding Pd (II) complexes which competently catalyze the Suzuki- cross-coupling reaction of aryl bromides and phenylboronic acid in aqueous medium.[138] In the same way, Jerome *et. al.*, have synthesize new phosphine-free *N^N^N*-type Pincer ligands and their corresponding Pd (II) complexes. Their efficiency in the Suzuki- cross-coupling reaction of aryl bromides and aryl boronic acid in a 1:1 mixture of ethanol and aqueous medium was evaluated, as a result a moderate to excellent yields of the cross coupling product were obtained.[139] As far as the *N^C^N*-type Pincer ligands are concerned, several bis(oxazoline- and bis(thiazole)-*N^C^N*-type Pincer ligands and their corresponding Pd complexes by Luo and co-workers showed excellent activities in the Suzuki−Miyaura coupling of aryl halides with aryl boronic acids for the synthesis of biaryls. They further demonstrated that the catalytic system was scalable for the green synthesis of the key intermediates of bioactive LUF5771 and its analogues.[140]

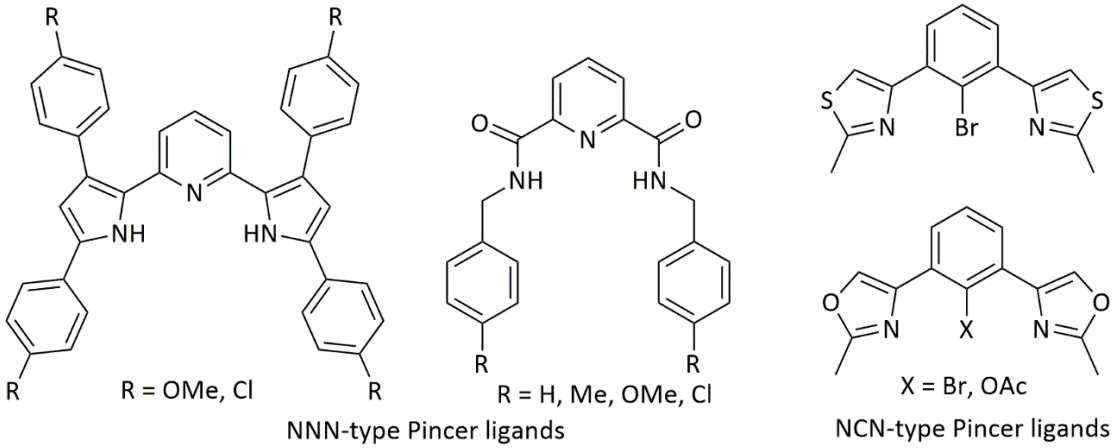


Figure 15. Representative Pincer type ligands.

In conclusion, the use of phosphine-free *N*-based ligands surely demonstrate distinct benefits over the corresponding phosphine based ligand system, in particular when the reactions are performed for large-scale production of fine chemicals and pharmaceuticals. Therefore, one part of this doctoral thesis has been aimed for the synthesis of *N*-based ligand and to explore their application in the cross-coupling reactions and other challenging organic transformations. In addition, we aimed to achieve the following objectives through this doctoral study.

1.5 Objectives

We have aimed to achieve the following objectives;

1- Synthesis of new and efficient N-based ligands and Pd-catalysts.
2- Characterization of ligands and catalysts.
3- Scope of the ligands and catalysts for the Pd-catalyzed cross-coupling reactions, focusing Suzuki-Miyaura cross-coupling reaction.
4- Mechanistic studies of the Suzuki-Miyaura cross-coupling reaction by identification of key intermediates *via* ESI mass spectrometry technique.

Chapter 2 Synthesis of Mono- and Bis-Pyrazoles Bearing Flexible *p*-Tolyl Ether and Rigid Xanthene Backbones, and their Potential as Ligands in the Pd-Catalyzed Suzuki-Miyaura Cross-coupling Reaction

2.1 Introduction

The transition metal complexes of phosphorous (*P*), nitrogen (*N*), sulphur (*S*), and oxygen (*O*)-based ligands and their hybrids have provided the chemist a wide opportunity and a quasi-exhaustive tool to create *C*-*C* bonds of significant interest.[141, 142] The reactivity and the catalytic behavior of these complexes largely depend on the nature of the coordinating atoms, their relative position within the molecular architecture, and the relative flexibility or rigidity of the ligand backbone, as they greatly influence the steric and electronic properties of the resulting complex.[143, 144] Therefore, the fine-tuning of these properties in order to synthesize ligands of particular interest has been an interesting strategy, since decades.

In this perspective, a plethora of ligands with flexible backbones such as *DPEphos* and rigid backbones containing bulky substituents such as *^{t}Bu-Xantphos* and other xanthene scaffolds have been widely described in literature.[145-147] In addition to the diphosphines bearing xanthene backbone, the corresponding diamido,[148] diamine,[149] disilyl,[150] dithiolates[151] as coordination units have also been described. Moreover, these xanthene-derived ligands possess wide bite angles, they can coordinate with a variety of metals and the corresponding metal complexes have been successfully applied to a wide variety of reactions, such as: hydroformylation, alkoxy-carbonylation, hydrocyanation, cross-coupling reactions (for *C–C* and *C–X* bond formation) and carbonylative coupling reactions.[152]

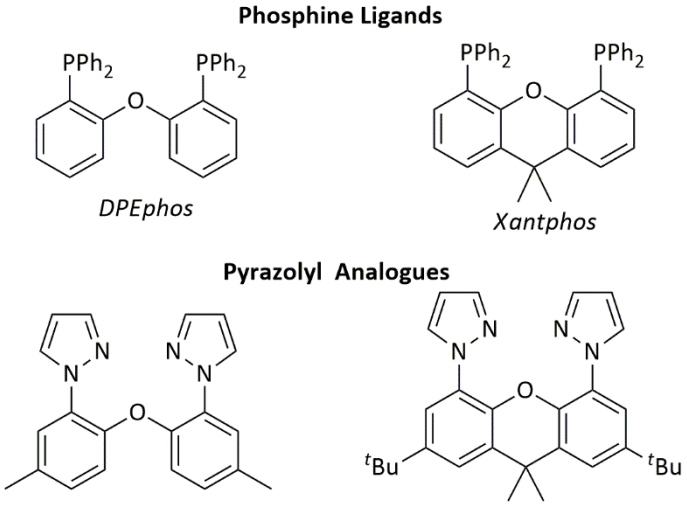


Figure 16. Pyrazolyl analogues of *DPEphos* and *Xantphos*.

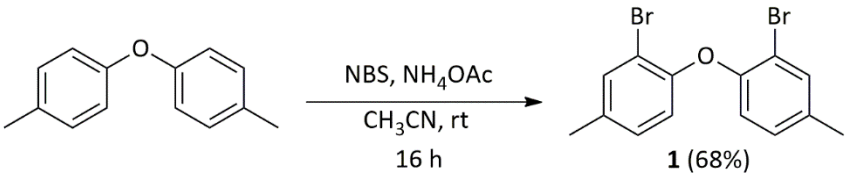
Regardless of the undisputed extraordinary and effective tendency of the phosphine ligands in the Pd-catalyzed cross-coupling reactions, the search for the synthesis of equally efficient alternate ligands has become indispensable due to the relative high cost and difficulties associated with their synthesis, handling and moisture sensitivity, among other factors.[102, 153] Among the cross coupling reactions, the Suzuki-Miyaura (SM) cross-coupling reaction has been widely explored as a powerful tool for the *C-C* bond synthesis due to several reasons.[41, 154-157] A huge amount of effort for the further fine tuning of this protocol by using greener reaction conditions, including the designing of new nitrogen-based ligands and catalytic systems, has been dedicated in both academia and industry worldwide.[158, 159]

Thus far, the majority of the *N*-based ligands for the Pd-catalyzed *C-C* bond synthesis are based on alkyl or aryl amines,[118, 160] pyridines,[161] imines,[162] imidazoles in the form of *N*-heterocyclic carbenes (*NHC's*),[163] oxazolines,[134] and their hybrids,[164] while the corresponding pyrazole based ligands have been relatively less explored.[165, 166] Among the few examples reported in the literature, hybrid unsymmetrical benzimidazolium-pyrazolyl *N,N*-ligands, pyridine-pyrazolyl *N,N*-ligands and bulky monodentate pyrazolyl ligands have been successfully applied for the *Pd*-catalysed Suzuki cross-coupling reactions.[167-169] Nevertheless, the pyrazole based catalysts have been employed in other important *C-C* bond forming reactions such as oligomerizations,[170] polymerizations and copolymerizations.[171] Previously, we have reported some palladium complexes of bis-pyrazolyl tridentate ligands and demonstrated their application in the Suzuki cross-coupling reaction.[172] To the best of our knowledge, pyrazole ligands based on a flexible *p*-tolyl ether and rigid xanthene backbone have not been described in the literatures, inspiring us to synthesize pyrazolyl analogues of the *DPEphos* and *Xantphos*, respectively (**Figure 16**), and to explore their potential as ligands in the Pd-catalyzed Suzuki-Miyaura cross-coupling of aryl halides with aryl boronic acids.

2.2 Results and Discussion

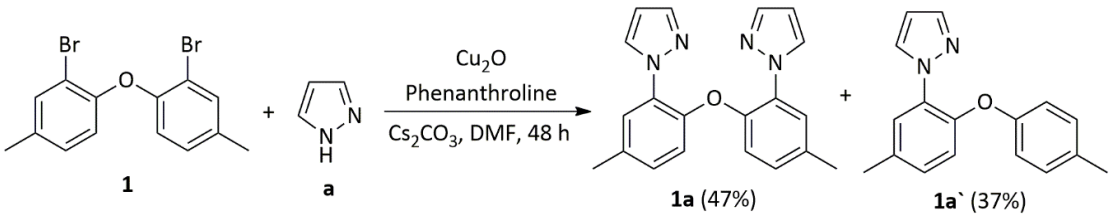
A two-step bromination/Ullmann coupling reaction sequence was designed in order to achieve the synthesis of new pyrazolyl analogue of *DPEphos*. *p*-tolyl ether was chosen as the starting material to avoid the *o*/*p* selectivity issues in the bromination step

through blockage of the *p*-position. The dibromination of *p*-tolyl ether was successfully accomplished by treating it with *NBS* using 20 mol% of ammonium acetate as catalyst in acetonitrile at room temperature, (**Scheme 8**).[173] After chromatographic separation followed by recrystallization in n-pentane, the titled dibromo product, 1,1'-oxybis(2-bromo-4-methylbenzene) (**1**) was obtained in 68% yield. It is important to mention that this dibromination strategy is a much milder and simpler approach as compared to the only other protocol reported in literature, which employs an *ortho*-lithiation strategy.[174]



Scheme 8. Bromination of *p*-tolyl ether.

Then **1** was used as substrate for the Ullmann coupling reaction with 1*H*-pyrazole (**Scheme 9**). The reaction of **1** with *1H*-pyrazole (**a**) using a *Cu_2O*/phenanthroline catalytic system in DMF at 140 ^oC for 48 hours of magnetic stirring provided the symmetrical bis-pyrazolyl analogue **1a** in 47% isolated yield, along with 37% of the dehalogenated mono-pyrazolyl derivative **1a`** as a byproduct (**Table 1**, Entry 5). Attempts to optimize the catalytic system by using different Cu catalysts, and base screenings provided no significant improvements in the selectivity for compound **1a** and are summarized in **Table 1** (Entries 1-4). Despite the moderate yield for **1a**, this protocol additionally allows the isolation of the mono-pyrazolyl derivative **1a`**, which will be useful as a part of a library of pyrazole-based compounds for further investigation in our group, such as photophysical studies.



Reaction conditions: Cu_2O (20 mol%), phenanthroline (44 mol%), **1** (1.0 eq.). **a** (3.2 eq.), Cs_2CO_3 (3.0 eq.), DMF (4 mL), 140-160 ^oC, 48 h.

Scheme 9. Synthesis of flexible bis-pyrazolyl ligands **1a** and **1a`**.

Table 1: Ullmann coupling reaction between **1** and 1*H*-Pyrazole.

Entry	[Cu] (mol%)	Ligand (mol%)	Base	T (ºC)	Yield (%)[b]	
					1a	**1a`**
1	CuI (20)	-	Cs_2CO_3	120	19	-
2	CuI (20)	Phenanthroline (44)	Cs_2CO_3	130	28	21
3	Cu_2O (20)	-	Cs_2CO_3	130	29	23
4	Cu_2O (20)	Phenanthroline (44)	K_2CO_3	130	31	22
5[c]	Cu_2O (20)	Phenanthroline (44)	Cs_2CO_3	130	47	37
6[c]	Cu_2O (10)	Phenanthroline (22)	Cs_2CO_3	140	33	27

a) Reaction conditions: [Cu] (x mol%), Phenanthroline (x mol%) **1** (1.0 eq., 0,5 mmoles scale), 1*H*-pyrazole (3.2 eq.), Base (3.2 eq.), DMF (4 mL), 120 - 140 ºC, 24 h. b) Isolated yield. c) 48 h.

Single crystals suitable for *X-ray* diffraction study were collected from concentrated pentane and ethyl acetate:hexane (10:90) solutions for compounds **1** and **1a**, respectively. The single crystal *X-ray* diffraction study revealed that **1** crystallizes in the triclinic *P(-1)* space group, whereas **1a** crystallizes in the monoclinic *P*(2_1/*c)* space group. The solid-state structures of **1** and **1a** are shown in **Figure 17** and the main crystallographic data and structure refinement parameters are summarized in **Table 2**.

1 **1a**

Figure 17. Molecular structures of **1** and **1a** with the key atoms labelled (thermal ellipsoids drawn at 50% probability). For clarity, hydrogen atoms have been omitted.

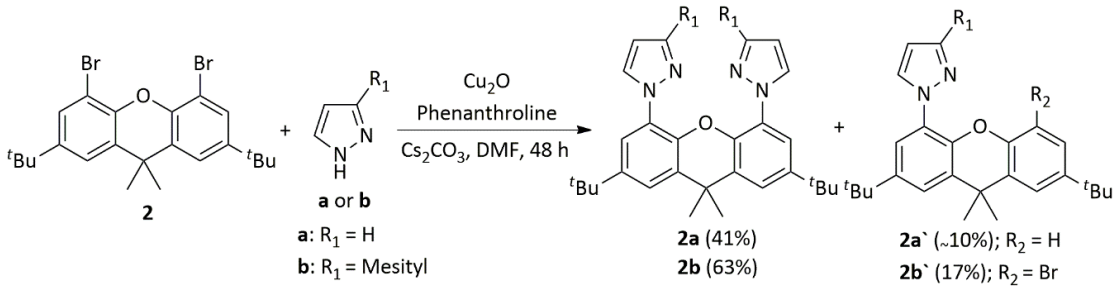
Next, we have used the commercially available 4,5-dibromo-2,7-di-tert-butyl-9,9-dimethyl-9*H*-xanthene (**2**) as a substrate in the Ullmann coupling step to obtain the rigid pyrazolyl analogues of ^{t}*Bu-Xantphos*, **2a-2b`**. When the same reaction conditions,

Table 2. Crystallographic data and structure refinement parameters for **1** and **1a**.

	1	**1a**
Molecular formula	$C_{14}H_{12}Br_2O$	$C_{20}H_{18}N_4O$
Formula weight (g mol^{-1})	356.06	330.38
T (K)	293(2)	293(2)
Wavelength (Å)	0.71073	1.54178
Crystal system	Triclinic	Monoclinic
Space group	P(-1)	$P2_1/c$
a, b, c (Å)	7.439, 7.977, 12.439 (5)	13.5819(2), 8.27900(10), 15.9832(3)
α, β, γ (°)	98.873, 100.877, 108.201 (5)	90, 106.8260 (10), 90
V (Å^3)	670.4(7)	1720.28(5)
Z'	2	4
ρ_{calcd} (g cm^{-3})	1.764	1.276
μ (mm^{-1})	6.027	0.652
F(000)	348	696
Crystal size (mm)	0.26 x 0.19 x 0.14	0.28 x 0.21 x 0.14
θ range (°)	2.979 – 27.545	3.399 – 78.912
Limiting indices (h, k, l)	$-9 \le h \le 9$	$-17 \le h \le 17$
	$-10 \le k \le 10$	$-10 \le k \le 10$
	$-16 \le l \le 16$	$-20 \le l \le 18$
Reflections collected	28840	30475
Reflections unique (R_{int})	3091 (0.0412)	3688 (0.0463)
Completeness to θ_{max} (%)	99.8	100.0
Data/restraints/param.	3091 / 0 / 154	3688 / 0 / 226
Absorption correction	Gaussian	Gaussian
Min. and max. trans.	0.5529 and 0.7456	0.8612 and 0.9389
R_1 [$I > 2\sigma(I)$]	0.0363	0.0450
wR_2 [$I > 2\sigma(I)$]	0.0943	0.1246
R_1 (all data)	0.0519	0.0585
wR_2 (all data)	0.1036	0.1365
S on F^2	1.055	1.044
Largest diff. peak and hole (e Å^{-3})	0.693 and -0.683	0.257 and -0.209

described above for the synthesis of compound **1a** were applied, an incomplete conversion was observed for the reaction between **2** and **a**. Therefore, a slight higher temperature (160 ^{o}C) was used, as a result the reaction of **2** with **a** as the nucleophile delivered the symmetrical bis-pyrazolyl analogue **2a** in 41% isolated yield (**Scheme 9**).

Single crystals suitable for X-ray diffraction study of **2a** were obtained by slow diffusion of hexane into the concentrated DCM solution of **2a**. Moreover, two independent molecules were found in the asymmetric unit of **2a**. Both of them were identical, therefore, only one of the molecular structures is represented below in **Figure 17**. In addition, as observed for the dibromo derivative **1**, the mono-pyrazolyl debrominated byproduct **2a`** was also obtained. Unfortunately, the difficulty in chromatographic separation between **2a** and **2a`** prevented an accurate quantification of **2a`**, nevertheless, a combined yield of approx. 10% for 4 reactions was roughly calculated (**Scheme 10**). A lower Cu_2O loadings (10 mol%) for the reaction also led to an incomplete conversion. At this point, it is worthy to mention that the only reported example of an Ullmann reaction between a related aryl-bridged tetra-bromo-xanthene scaffold and 1*H*-pyrazole (**a**) was achieved by using Cu_2O under ligand free and microwave irradiation conditions.[175]



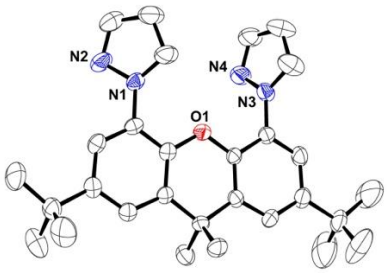
Reaction conditions: Cu_2O (10-20 mol%), phenanthroline (22-44 mol%), **2** (1.0 eq.). **a** or **b** (3.2 eq.), Cs_2CO_3 (3.0 eq.), DMF (4 mL), 140-160 ^{o}C, 48 h.

Scheme 10. Synthesis of pyrazolyl analogues of ^{t}*Bu-Xanphos* **2a - 2b`**.

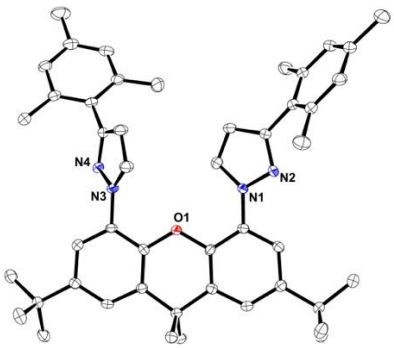
Surprisingly, the scenario was different when we used 3-mesityl-1*H*-pyrazole (**b**) as the nucleophile. The synthesis of the symmetrical bis-mesitylpyrazolyl ligand **2b** by reaction of **2** with **b** was thus accomplished by using a lower *Cu_2O* loading. **2b** was obtained in exceptionally higher yield (63%). Another difference noticed for this reaction is that the debrominated mono-pyrazolyl byproduct was not obtained. In contrary, the

byproduct **2b`** was isolated in 17% yield and also retained the bromine atom in its structure (**Scheme 10**). This result clearly indicated that 3-mesityl-1*H*-pyrazole (**b**) is a better coupling partner for the Ullmann reaction than 1*H*-pyrazole (**a**). Hence, the reaction proceeded under milder conditions, especially with low Cu_2O loadings, providing both better selectivity and yield of the **2b** and preventing the *C-Br* reduction after the first Ullmann coupling.

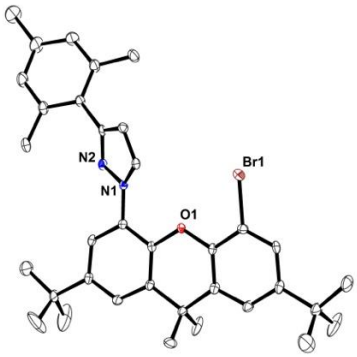
Single crystals suitable for X-ray diffraction of **2b** and **2b`** were collected from concentrated 10% ethyl acetate and hexane solutions of the pure compounds. Both **2b** and **2b`** crystallizes in the triclinic *P(-1)* space group. The solid-state structures are shown in **Figure 18** below and the main crystallographic data and the structure refinement parameters are summarized in the **Table 3**. Moreover, two independent molecules were found in the asymmetric unit of **2b`**. Both of them were quite similar, therefore, only one of the molecular structures is represented below in **Figure 18**.



2a



2b



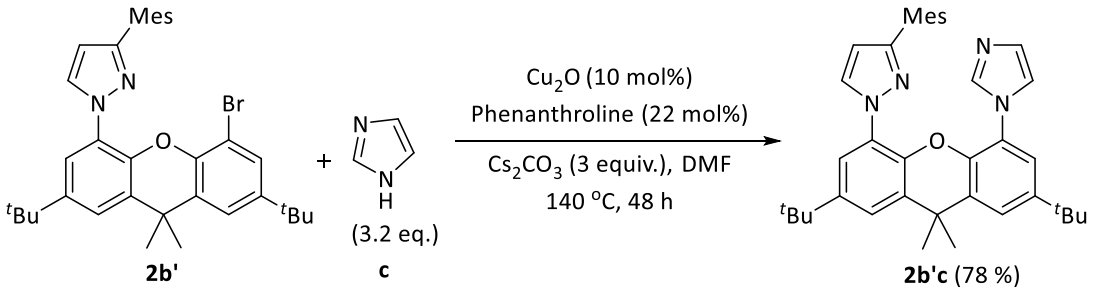
2b`

Figure 18. Molecular structures of **2a**, **2b** and **2b`** with the key atoms labelled (thermal ellipsoids drawn at 50% probability). For clarity, hydrogen atoms have been omitted.

Table 3. Crystallographic data and structure refinement parameters for **2a**, **2b** and **2b`**.

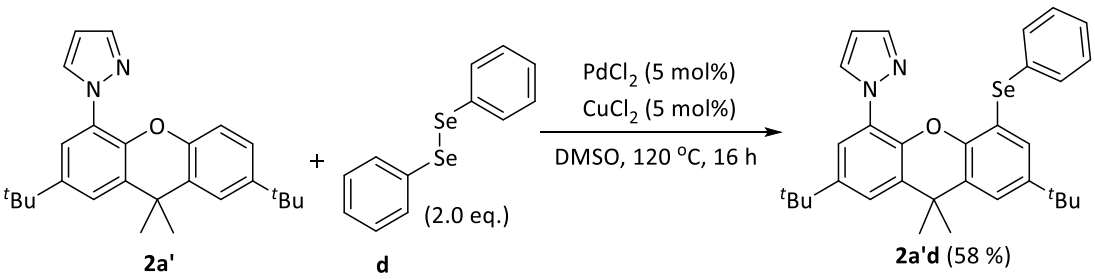
	2a	**2b**	**2b`**
Molecular formula	$C_{29}H_{34}N_4O$	$C_{47}H_{54}N_4O$	$C_{35}H_{41}BrN_2O$
Formula weight (g mol^{-1})	454.60	690.94	585.61
T (K)	292(2)	100(2)	100(2)
Wavelength (Å)	0.71073	1.54178	0.71073
Crystal system	Triclinic	Triclinic	Triclinic
Space group	P(-1)	P(-1)	P(-1)
a, b, c (Å)	12.8681(16), 14.6221 (18), 14.7167(17)	12.1744(3), 12.8278 (3), 14.9523(4)	12.3909(4), 15.3171 (5), 17.5440(6)
α, β, γ (°)	75.649, 72.959, 89.887(4)	100.7726(14), 103.3895 (13), 114.1532(12)	70.7230, 79.9150, 76.2150(10)
V (Å^3)	2557.4(5)	1965.65(9)	3035.57(18)
Z'	4	2	4
ρ_{calcd} (g cm^{-3})	1.181	1.167	1.281
μ (mm^{-1})	0.073	0.535	1.384
F(000)	976	744	1232
Crystal size (mm)	0.394 x 0.175 x 0.126	0.14 x 0.14 x 0.12	0.23 x 0.15 x 0.10
θ range (°)	2.956 to 27.266	3.204 – 62.381	2.656–26.372
Limiting indices (h, k, l)	-16<=h<=16,	$-13 \leq h \leq 13$	$-15 \leq h \leq 15$
	-18<=k<=18,	$-14 \leq k \leq 14$	$-19 \leq k \leq 19$
	-18<=l<=18	$-17 \leq l \leq 17$	$-21 \leq l \leq 21$
Reflections collected	118038	18591	106878
Reflections unique (R_{int})	11384 (0.1467)	6210 (0.0416)	12409 (0.0618)
Completeness to θ_{max} (%)	99.8	99.0	99.9
Data/restraints/param.	11384 / 0 / 613	6210 / 0 / 469	12409 / 0 / 725
Absorption correction	Gaussian	Gaussian	Gaussian
Min. and max. trans.	0.7455 and 0.6524	0.8412 and 0.9402	0.6987 and 0.8279
R_1 [$I > 2\sigma(I)$]	0.0991	0.0595	0.0455
wR_2 [$I > 2\sigma(I)$]	0.2433	0.1497	0.1168
R_1 (all data)	0.1825	0.0819	0.0598
wR_2 (all data)	0.3028	0.1643	0.1256
S on F^2	n/a	1.044	1.022
Largest diff. peak and hole (e Å^{-3})	0.721 and -0.368	0.577 and -0.576	5.650and -1.896

The isolation of the byproduct derivative **2b`** opens the possibility of expanding the scope of the reaction, allowing us to synthesize a hybrid imidazolyl-pyrazolyl xanthene derivative **2b`c**. In order to demonstrate this, **2b`** was treated with 1*H*-imidazole (**c**) under similar conditions described for the synthesis of **2b**, as a result hybrid **2b`c** was obtained in 78% isolated yield (**Scheme 11**).



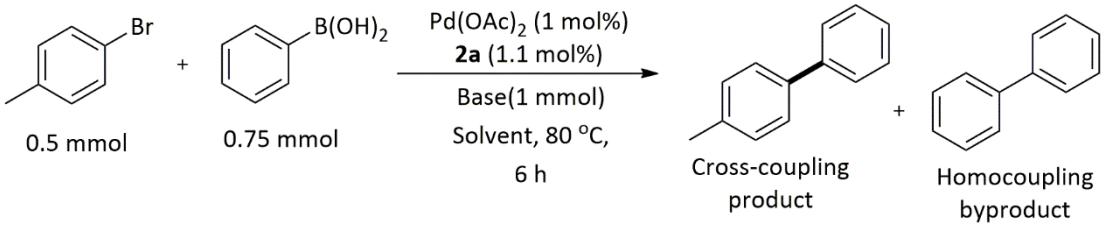
Scheme 11. Synthesis of hybrid analogue **2b`c** from **2b`**.

In addition to this, a selanyl-pyrazolyl hybrid analogue **2a`d** was synthesized by using a *C-H* activation protocol, recently described in the literature.[176] Using 5 mol% of $PdCl_2$ and 5 mol% $CuCl_2$, the reaction between **2a`** and diphenyl diselenide (**d**) in DMSO delivered the hybrid analogue **2a`d** in 58% isolated yield (**Scheme 12**).



Scheme 12. Synthesis of hybrid analogue **2a`d** from **2a`**.

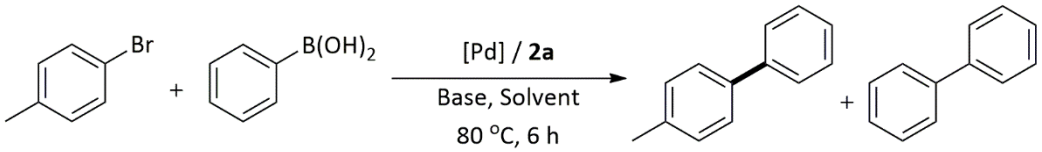
With the new pyrazolyl analogues in hand, we then moved to evaluate their potential as ligands in the Suzuki-Miyaura cross-coupling reaction of aryl halides and aryl boronic acids using $Pd(OAc)_2$ as palladium source. For this purpose, we have selected the symmetrical bis-pyrazolyl analogue **2a** for the Pd-catalyzed SM cross-coupling reaction between 4-bromotoluene and phenylboronic acid as our model ligand and substrates, respectively (**Scheme 13**).



Scheme 13. Model SM reaction used for optimization and ligand evaluation.

We started to optimize the reaction conditions for the $Pd(OAc)_2$/**2a**, by screening different solvent and base combinations (**Scheme 13** and **Table 4**).

Table 4. Solvent, base and Pd-source effects on the model SM cross-coupling reaction.

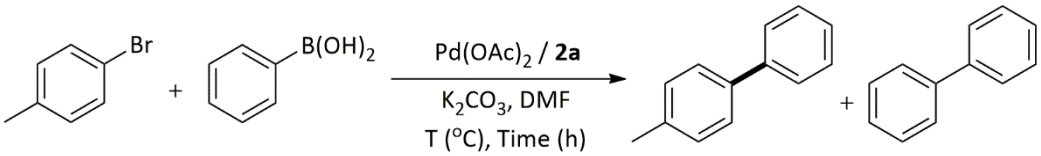


Entry	[Pd]	Base	Solvent	Conversion (%)[b]	CC Yield (%)[b]	HC Yield (%)[b]
1	$Pd(OAc)_2$	KOH	MeOH	74	66	1
2	$Pd(OAc)_2$	K_3PO_4	Dioxan	48	7	1
3	$Pd(OAc)_2$	Cs_2CO_3	DMF	87	61	1
4	$Pd(OAc)_2$	K_2CO_3	DMF	99	98	1
5	$Pd(OAc)_2$	K_2CO_3	MeOH	75	44	1
6	$Pd(OAc)_2$	K_2CO_3	THF:MeOH	65	4	2
7	$Pd(OAc)_2$	K_2CO_3	THF	49	1	2
8	$Pd(OAc)_2$	K_2CO_3	Dioxan	48	2	1
9	$PdCl_2$	K_2CO_3	DMF	97	88	4
10	$PdCl_2(COD)$	K_2CO_3	DMF	72	55	3
11	$PdCl_2(PhCN)_2$	K_2CO_3	DMF	93	92	2

a) Reaction conditions: [Pd] (1 mol%), **2a** (1.1 mol%), 4-Bromotoluene (0.5 mmol), phenylboronic acid (0.75 mmol), Solvent (4 mL), 80 °C, 6 h. b) GC conversion and yield based on 4-bromotoluene c) Homo-coupling (HC) yield based on phenylboronic acid.

Initially, we used KOH as base and methanol as solvent based on our studies for the SM cross-coupling reaction of aryl bromides with an alkyl palladium complex containing 1,1-(2,2'-oxybis(ethane-2,1-diyl)-bis(3,5-dimethyl-*1H*-pyrazole).[172] Under these conditions the cross-coupling product was obtained in 66% yield (**Table 4**, entry 1). It is important to mention that a control experiment under ligand-free conditions using KOH as base and methanol as solvent gave high conversion but low yield for the cross-coupling product (>17%). Therefore, we moved to investigate other common base/solvent combinations for the SM cross-coupling reaction and we were delighted to see that by using DMF as solvent and a cheap base such as K_2CO_3, after 6 hours of magnetic stirring at 80 ^oC, delivers the cross-coupling product in almost quantitative yield (**Table 4**, entry 4). Biphenyl homocoupling byproduct was obtained in very low yield (<2%) for all the reaction conditions evaluated. All the other solvents provided very low yields of the cross-coupling product (**Table 4**, entries 2, 6-8), and most of the 4-bromotoluene converted was reduced into toluene.

Table 5. Temperature effect on the model SM cross-coupling reaction using ligand **2a**.

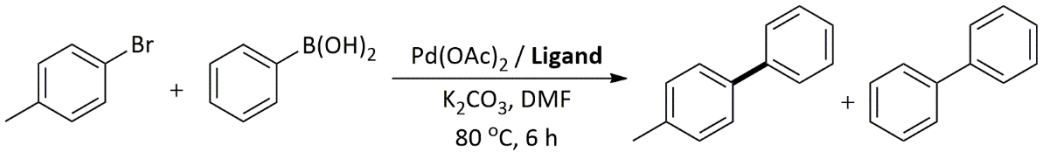


Entry	Temp. (^oC)	Time (h)	Conversion (%)[b]	CC Yield (%)[b]	HC Yield (%)[c]
1	25	24	73	59	1
2	50	12	92	70	1
3	80	6	99	98	1
4	110	3	90	75	1
5[d]	80	12	87	82	1
6[e]	80	24	98	86	16

a) Reaction conditions: $Pd(OAc)_2$ (1 mol%), **2a** (1.1 mol%), 4-Bromotoluene (0.5 mmol), phenylboronic acid (0.75 mmol), temperature, time, K_2CO_3 (2 eq.) and DMF (4 mL). b) GC conversion and yield based on 4-bromotoluene. c) HC yield based on phenylboronic acid. d) 0.5 mol% $Pd(OAc)_2$/**2a**. e) Aerobic conditions.

Then we investigated the effect of the temperature. When the reaction was performed at room temperature, a low yield of the cross-coupling product was obtained (**Table 5**, Entry 1). Hence, increased reaction temperatures were tested, as a result an improved conversion and yield was observed, providing the best result at 80 ^{o}C (**Table 5**, Entries 2 and 3). A further increase in the temperature of the reaction to 110 ^{o}C led to both decreased conversion and yield, indicating partial decomposition of the catalytic system (**Table 5**, Entry 4). A lower catalyst loading of 0.5 mol% also led to a lower conversion and yield (**Table 5**, entry 5).

Table 6: Screening of new pyrazolyl ligands for the SM cross-coupling.



Entry	Ligand	Conversion (%)[b]	CC Yield (%)[b]	HC Yield (%)[c]
1	**2a**	99	98	1
2	**2b**	>99	98	1
3	**2b`c**	99	98	1
4	**2a`**	87	86	1
5	**2a`d**	46	5	1
6	**1a**	83	47	1
7	**1a`**	62	29	1
8	**-**	68	44	2
9	**Xantphos**	93	92	6

a) Reaction conditions: $Pd(OAc)_2$ (1.0 mol%), Ligand (1.1 mol%), K_2CO_3 (2 eq.), DMF (4 mL), 80 ^{o}C, and 6 h. b) GC conversion and yield based on 4-bromotoluene. c) HC yield based on phenylboronic acid.

We concluded that the SM cross-coupling reaction between 4-bromotoluene and phenylboronic acid proceeds smoothly under reaction conditions of 1 mol% of

$Pd(OAc)_2$/**2a**, K_2CO_3 as base, DMF as solvent at 80 ^oC for 6h. With the best reaction conditions established, we then moved to evaluate the potential of the other pyrazolyl ligands **1a**, **1a`**, **2a**, **2a`**, **2b**, **2b`c** and **2a`d** on the model SM cross-coupling reaction. The results are summarized in **Table 6**. The symmetrical ligands **2a** and **2b**, and the hybrid analogue **2b`c** were found very active and selective by providing the corresponding cross-coupling product in excellent yields (98-99%) (**Table 6**, Entries 1-3). A slightly lower conversion (87%) and yield (86%) was observed in case of the mono-pyrazolyl ligand **2a`** (**Table 2.2**, Entry 4). In contrast, the hybrid ligand **2a`d** was not active in catalyzing the reaction (**Table 6**, Entry 5), probably due to the C-Se bond cleavage by Pd, as it is well known that majority of the C-Se bonds are very sensitive towards Pd and undergo oxidative addition with Pd metal.[177]

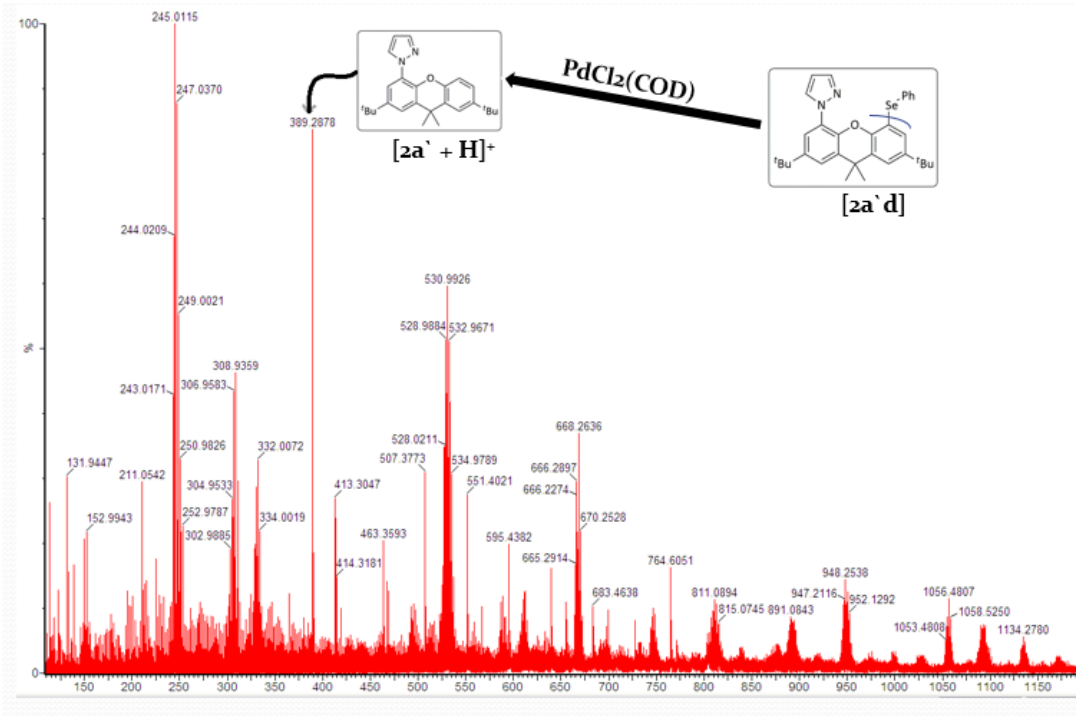


Figure 19. Oxidative cleavage of ligand **2a`d** to **2a`** in the presence of $Pd(COD)Cl_2$.

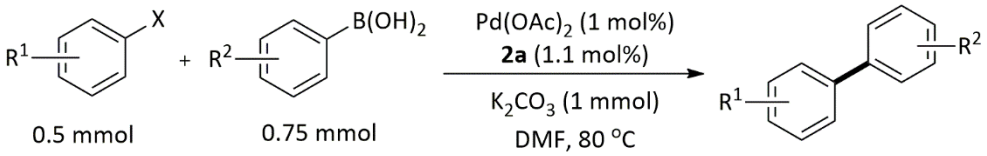
To support this hypothesis, a 1:1 mixture of the hybrid ligand **2a`d** and $PdCl_2(COD)$ in methanol were mixed and allowed to magnetically stir at room temperature for 2 hours. The resulting mixture rapidly turned into a black-green solution, which was then analysed through ESI-MS. The ESI-MS analysis showed several singly charged ionic species including a species with m/z 389 which was assigned to the $[\mathbf{2a`+H}]^+$ and other singly charged ionic Pd-species (**Figure 19**). This observation clearly

demonstrated that the Pd-metal after oxidative addition with **2a`d** undergoes reductive elimination to **2a`**. Likewise, the flexible ligands **1a** and **1a`** were also not so active and provides only low yield of the cross-coupling products (**Table 6**, Entry 6 and 7). We hypothesized that the high conformational freedom around the central oxygen atom of ligand **1a** and **1a`** prevents effective chelation with Pd, leading to a much less efficient catalyst compared to those derived from the ligands with the rigid xanthene backbone.

Finally, we have evaluated the scope of the SM cross-coupling reaction using the $Pd(OAc)_2$/**2a** catalytic system under optimized conditions, employing different haloarenes and arylboronic acids with varying electronic and steric characteristics. The results are summarized in **Table 7**. In general, both electron rich and poor bromoarenes were well tolerated, and provided the corresponding cross-coupling products with phenylboronic acid in good to excellent yields (**Table 7**, entries 1-5). Moreover, the reaction of an electron-rich and an electron-poor arylboronic acid with 4-bromotoluene was also tested. In both cases, the coupling products were obtained with good yields of approximately 80% (**Table 7**, entries 6 and 7). Other two combinations of arylbromides and arylboronic acids of opposite electronic characters demonstrated no considerable outcome on the observed yields of the cross-coupling products (**Table 7**, entries 8 and 9).

Thus, electron-withdrawing substituents on the aryl halide and electron-donating substituents on the arylboronic acids facilitates smooth SM cross-coupling reaction, owing to the easy oxidative addition and transmetallation steps, respectively.[178] Since, the developed catalytic system was not drastically influenced by the electronic nature of the *p*-substituents, however, it was sensitive towards the steric effects. The steric hindrance tolerance was thus evaluated by employing some *o*-substituted substrates. The introduction of methyl substituents in this position, on either of the coupling partners, led to a decreased yield of the cross-coupling products (**Table 7**, entries 10-12). Considering the similarities in the results obtained with the introduction of *o*-substituents on the arylbromide (58% yield, **Table 7**, entry 10) and on the aryl boronic acid (54% yield, **Table 7**, entry 11), one might speculate that the oxidative addition step was not severely affected, and that the observed decreased yield was probably due to a more difficult transmetalation or reductive elimination step.

Table 7: Substrate scope using ligand **2a** under optimized reaction conditions.[a]



Entry	R^1	X	R^2	Yield (%)[b]
1	4-Me	Br	H	94
2	4-CF_3	Br	H	82
3	4-Ac	Br	H	92
4	4-OMe	Br	H	91
5	2-bromonaphthalene		H	91
6	4-Me	Br	4-OMe	82
7	4-Me	Br	4-Ac	78
8	4-OMe	Br	4-Ac	73
9	4-Ac	Br	4-Me	81
10	2-Me	Br	H	58
11	4-Me	Br	2-Me	54
12	4-Me	Br	2,6-diMe	46
13	4-CF_3	I	H	78
14	4-OMe	I	H	80
15	4-Ac	Cl	H	75
16	4-Ac	Cl	H	3[c]
17	4-Me	Cl	H	25

a) Reaction conditions: $Pd(OAc)_2$ (1 mol%), **2a** (1.1 mol%), K_2CO_3 (2 eq), DMF (4 mL), 80 °C, and overnight. b) Isolated yields (average of two reactions). c) Ligand free conditions, GC yield after 24 h.

Even though aryl iodides are generally more active than aryl bromides due to the easy oxidative addition step, we observed slightly lower yields for aryl iodides (80% vs 91%, Entries 14 and 4; and 78% vs 82%, Entries 13 and 2). Also, the homocoupling byproduct was obtained in less than 2% yield, extensive dehalogenation side reaction in case of aryl iodides was responsible for the relatively low isolated yields. As far as the aryl chlorides are concerned, we were pleased to see that *p*-chloroacetophenone reacted smoothly under optimized conditions as well (**Table 7**, Entry 15) and even the deactivated *p*-clorotoluene offered the cross-coupling product in 25% yield. A control experiment for the coupling of *p*-chloroacetophenone with phenylboronic acid under ligand-free conditions gave only 3% of the cross-coupling product after 24 h (**Table 7**, entry 16). The *in situ* formation of *PdL* species must be assumed to explain these results. There is no direct evidence for their formation, since we were unable to isolate or characterize any palladium complex with these ligands until now, however, *in situ* formation of *PdL* species responsible for catalyzing the *SM* reaction can be evidenced by comparing the results obtained with $Pd(OAc)_2$/**2a** catalytic system and under ligand-free condition. These results clearly demonstrate the positive effect of the ligands on the cross-coupling reaction.

2.3 Experimental

2.3.1 Materials and Methods

All the reagents were purchased from commercial suppliers and used without further purification. *p*-tolyl ether, **2** and aryl halides were purchased from Sigma Aldrich. Aryl boronic acids were purchased from Alfa Aesar. The Ullmann and Suzuki-Miyaura coupling reactions were performed using standard Schlenk tube techniques under an argon atmosphere. The solvents used for these reactions were degassed by purging with argon for 20 to 30 minutes prior to each experiment. The progress of the reactions were monitored by GC. The GC analyses were performed using a Shimadzu GC-2010 plus equipment fitted with a 30 m DB-17 column and FID detector, while the GC/MS measurements were performed using a Shimadzu GC/MS-QP2010 SE, (EI 70 eV) equipped with 30 m Rxi-1ms® column. Column chromatography purifications were

performed using silica gel (230-400 mesh) and mixtures of hexanes/acetate as eluents. All compound names were assigned using ChemBioDraw Ultra 12.0 software.

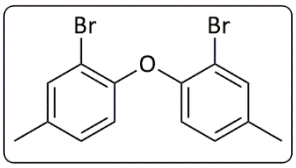
Nuclear magnetic resonance (NMR) spectra were recorded in $CDCl_3$ solutions unless noted otherwise, on MR-400-Varian 400 MHz, Bruker Avance-IIIHD 400 MHz and Bruker Fourier 300 MHz instruments. The Infrared (IR) spectra were obtained using attenua-ted total reflectance (ATR) technique, on a Bruker Alpha-*P* spectro-meter, with scans between 4000 and 650 cm^{-1}, and 4 cm^{-1} resolution. The compounds were analyzed in its pure form and the maximum absorbing frequencies are reported in cm^{-1}. The HRMS data were obtained on Waters micromass Q-ToF microTM instrument, operating on positive mode. Finally, the melting points were measured on the Quimis® instrument and are uncorrected.

2.3.2 Synthesis of Pyrazolyl Analogues

Dibromination of p-tolyl ether (Preparation of 1)

To a stirring solution of NH_4OAc (20 mol%, 2 mmol) and *p*-tolyl-ether (1 eq., 10 mmol) in 35 mL of CH_3CN, was added NBS (2.5 eq., 25 mmol) portion wise over a period of 10-15 minutes and left for overnight stirring (16 hours) at room temperature. After completion of the reaction, the crude reaction mixture was taken in ethyl acetate and washed with distilled water (3x). The organic phase was then dried over $MgSO_4$ and evaporated in vacuo. The crude mixture was purified by using flash silica gel column chromatography (10% ethyl acetate and hexane). Recrystallization in n-pentane furnishes colourless crystals of dibrominated product (**1**) in 68% yield.

4,4'-oxybis(3-bromo-1-methylbenzene) (1)

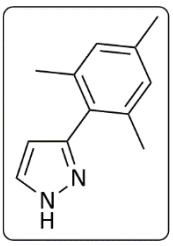


White crystalline solid (m.p. = 74-75 ^{o}C); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.45 (dd, J = 2.1, 0.6 Hz, 1H), 7.03 (ddd, J = 8.3, 2.1, 0.6 Hz, 1H), 6.72 (d, J = 8.3 Hz, 1H), 2.32 (s, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 151.41, 134.97, 134.25, 129.30, 119.29, 113.89, 20.56; **IR (ATR)**: 1477, 1247, 1041, 826, 808; **HRMS** (ESI-TOF): *m/z* calcd for $C_{14}H_{12}Br_2ONa$ $(M+Na)^+$; 376.9153, found 376.9140.

Preparation of 3-Mesityl-1H-pyrazole (adapted from literature)[179, 180]

To a chilled dry toluene solution in a round bottom flask maintained at 0 ^{o}C on an ice bath, Na metal (2 eq., 200 mmol) was added in portions, followed by dropwise addition of 2,4,6-trimethyl acetophenone (1 eq., 100 mmol) and allowed to stir for 1.5 h. To this yellowish reaction mixture, ethyl formate (3.4 eq., 340 mmol) was added dropwise over a period of 15-20 minutes and left overnight for stirring at room temperature. After, the reaction was cooled to 0 ^{o}C on an ice bath and distilled water was added dropwise to quench the unreacted Na metal **(Caution!)**. After all the unreacted Na metal was quenched, additional 200 mL of distilled water was added and allowed the resulting suspension under magnetic stirring for one hour. The resulting mixture was then transferred to a separatory funnel, and the aqueous layer obtained was washed with hexanes (3x). *The first organic phase and washes contain mainly the byproducts, thus, can be discarded.* The aqueous layer was then acidified with 10 % HCl, followed by extraction with DCM (3x). Finally, the combined organic phases were dried over $MgSO_4$ and evaporated under reduced pressure, furnishing yellowish solid product. This crude product without further purification was treated with hydrazine chloride (1.5 eq. 150 mmol) in ethanol and left under reflux for 2.5 h. After, the reaction mixture was concentrated under reduced pressure to half of its initial volume, followed by addition of 2 M NaOH solution (1:1 ratio of reaction mixture and NaOH solution). The aqueous layer was extracted with DCM (3 times). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. Recrystallization from hot hexane furnished yellowish crystals of the desired compound in 35% overall yield. The spectroscopic properties of the compound were consistent with the data available in the literature.

3-Mesityl-1H-pyrazole

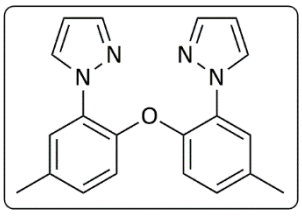


Yellow crystalline needles; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 10.77 (br s, 1H), 7.53 (d, J = 1.7 Hz, 1H), 6.91 (s, 2H), 6.19 (d, J = 1.5 Hz, 1H), 2.34 (s, 3H), 2.06 (s, 6H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 143.93, 138.01, 137.71, 135.75, 128.04, 105.61, 21.07, 20.23.

Synthesis of ligands 1a and 1a`

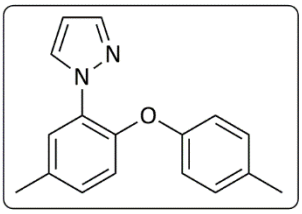
A resealable Schlenk flask evacuated and back-filled with argon (3x) was charged with Cu_2O (21.5 mg, 0.15 mmol), 1,10-phenanthroline (59.5 mg, 0.33 mmol), **1** (267.1 mg, 0.75 mmol), 1*H*-pyrazole (**a**) (163.5 mg, 2.4 mmol) and Cs_2CO_3 (733.1 mg, 2.25 mmol), followed by addition of 4 mL of degassed DMF. The Schlenk was sealed under inert atmosphere and the reaction was left under magnetic stirring for 20 hours at 140 ^{o}C, on an oil bath. After, the reaction was cooled to room temperature and filtered through a short plug of celite, followed by washing with CH_2Cl_2. The filtrate was then washed with distilled water (3x) and the organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was subjected to column chromatography purification using 10% AcOEt in hexanes as eluent, furnishing bis-pyrazole **1a** in 47% yield along with the mono-pyrazole byproduct **1a`** in 37% yield.

1,1'-(oxybis(5-methyl-2,1-phenylene))bis(1H-pyrazole) (1a)



White crystalline solid (m.p. = 124-125 ^{o}C); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.88 (d, J = 2.5 Hz, 1H), 7.68 (d, J = 1.7 Hz, 1H), 7.62 (d, J = 1.7 Hz, 1H), 7.03 (ddd, J = 8.4, 1.5, 0.6 Hz, 1H), 6.85 (d, J = 8.4 Hz, 1H), 6.36 (dd, J = 2.4, 1.9 Hz, 1H), 2.36 (s, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 145.71, 140.35, 134.70, 131.41, 131.07, 129.07, 126.22, 119.30, 107.05, 20.81; **IR** ν_{max} (neat): 1497, 1221, 1034, 809, 761; **HRMS** (ESI-TOF): *m/z* calcd for $C_{20}H_{18}N_4ONa$ $(M+Na)^+$: 353.1378, found 353.1369.

1-(5-methyl-2-(p-tolyloxy)phenyl)-1H-pyrazole (1a`)

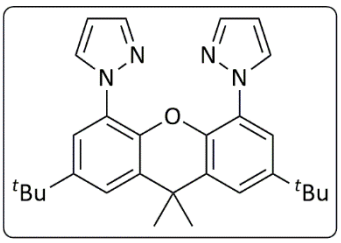


Pale yellow liquid; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 2.5 Hz, 1H), 7.73 (d, *J* = 1.8 Hz, 1H), 7.68 (d, *J* = 1.5 Hz, 1H), 7.09 (d, *J* = 8.3 Hz, 2H), 7.06 (dd, *J* = 8.5, 1.9 Hz, 1H), 6.93 (d, *J* = 8.3 Hz, 1H), 6.85 (d, *J* = 8.5 Hz, 2H), 6.37 (t, *J* = 2.4 Hz, 1H), 2.40 (s, 3H), 2.31 (s, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 154.76, 145.55, 140.24, 134.26, 132.70, 131.78, 131.12, 130.20, 128.27, 125.35, 120.47, 117.69, 106.67, 20.70, 20.58. **IR ν_{max}** (neat): 1522, 1496, 1228, 809, 748; **HRMS** (ESI-TOF): *m/z* calcd for $C_{17}H_{16}N_2ONa$ $(M+Na)^+$: 287.1160, found 287.1450.

Synthesis of Ligands 2a and 2a`

1*H*-pyrazole (**a**) and 4,5-dibromo-2,7-di-tert-butyl-9,9-dimethyl-9*H*-xanthene (**2**) were reacted under similar conditions described above for the synthesis of ligand **1a**, except the reaction was magnetically stirred at 160 ^{o}C. The crude residue obtained after work up was purified using 10% AcOEt and hexanes as eluent, furnishing the bis-pyrazolyl ligand **2a** in 41% yield, along with the mono-pyrazolyl byproduct **2a`** in approx. 10% yield.

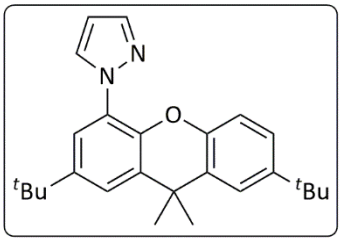
1,1'-(2,7-di-tert-butyl-9,9-dimethyl-9H-xanthene-4,5-diyl) bis (1H-pyrazole) (2a)



Crystalline solid (154 ^{o}C - decompose); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 1.8 Hz, 2H), 7.56 (d, *J* = 2.3 Hz, 2H), 7.51 (d, *J* = 2.4 Hz, 2H), 7.46 (d, *J* = 2.3 Hz, 2H), 6.28 (t, *J* = 2.1 Hz, 2H), 1.74 (s, 6H), 1.37 (s, 18H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 146.70, 140.81, 140.33, 132.10, 131.13, 128.26, 121.82, 121.56, 106.75, 35.32, 34.87, 32.20, 31.54; **IR ν_{max}** (neat): 2953, 1469, 1453, 1259, 750; **HRMS** (ESI-TOF): *m/z* calcd for $C_{29}H_{35}N_4O$ $(M+H)^+$: 455.2811, found 455.2831.

1-(2,7-di-tert-butyl-9,9-dimethyl-9H-xanthen-4-yl)-1H-pyrazole (2a`)

White powder (m.p. = 139-140 ^{o}C); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 8.15 (d, *J* = 2.4 Hz, 1H), 7.76 (d, *J* = 1.7 Hz, 1H), 7.64 (d, *J* = 2.3 Hz, 1H), 7.43 (d, *J* = 2.3 Hz, 1H), 7.41 (t, *J* = 2.6 Hz, 1H), 7.21 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.94 (d, *J* = 8.5 Hz, 1H), 6.50 (t,

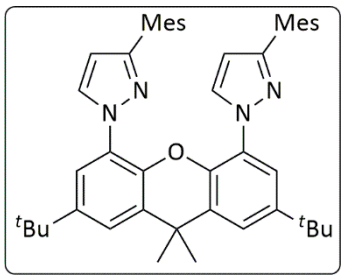


J = 2.1 Hz, 1H), 1.69 (s, 6H), 1.37 (s, 9H), 1.33 (s, 9H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 147.89, 146.39, 145.88, 140.66, 140.21, 131.92, 131.36, 129.29, 127.92, 124.54, 122.55, 121.51, 120.57, 115.88, 106.44, 34.97, 34.82, 34.66, 32.25, 31.68, 31.58; **IR** ν_{max} (neat): 2960, 1455, 1269, 850, 761; **HRMS** (ESI-TOF): *m/z* calcd for $C_{26}H_{33}N_2O$ $(M+H)^+$: 389.2593, found 389.2622.

Synthesis of Ligands 2b and 2b`

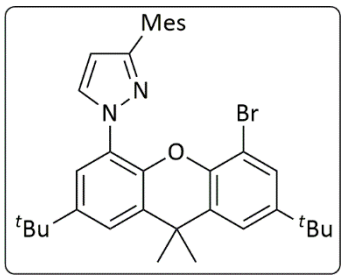
3-mesityl-*1H*-pyrazole (**b**) and **2** were allowed to react under identical conditions described above for the synthesis of ligand **1a**, except that the reaction was performed using a lower catalyst loading (10 mol%). The residue obtained after work up was then purified using silica-gel column chromatography eluting 5% AcOEt and hexanes. Ligand **2b** was isolated in 63% yield, whereas the byproduct **2b`** was obtained in 17% yield.

1,1'-(2,7-di-tert-butyl-9,9-dimethyl-9H-xanthene-4,5-diyl) bis (3-mesityl-1H-pyrazole) (2b)



White crystalline solid (m.p. = 209-210 ^oC); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 2.3 Hz, 2H), 7.64 (d, *J* = 2.3 Hz, 2H), 7.46 (d, *J* = 2.3 Hz, 2H), 6.96 (s, 4H), 6.19 (d, *J* = 2.3 Hz, 2H), 2.33 (s, 6H), 2.24 (s, 12H), 1.77 (s, 9H), 1.37 (s, 18H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 151.43, 146.59, 139.84, 137.49, 137.43, 132.57, 130.81, 130.64, 128.14, 128.04, 121.39, 121.32, 107.98, 35.07, 34.68, 32.35, 31.37, 21.09, 20.65; **IR** ν_{max} (neat): 2959, 1458, 1266, 1238, 849, 761, 741; **HRMS** (ESI-TOF): *m/z* calcd for $C_{47}H_{55}N_4O$ $(M+H)^+$: 691.4376, found 691.4397.

1-(5-bromo-2,7-di-tert-butyl-9,9-dimethyl-9H-xanthen-4-yl) 3-mesityl-1H-pyrazole (2b`)



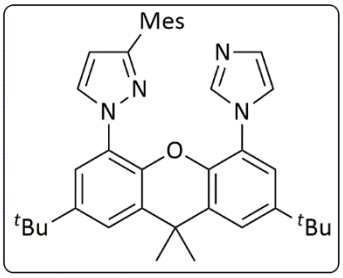
White crystalline solid (m.p. = 189-191 ^oC); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 8.62 (d, *J* = 2.4 Hz, 1H), 7.81 (d, *J* = 2.1 Hz, 1H), 7.48 (d, *J* = 1.9 Hz, 1H), 7.40 (d, *J* = 2.2 Hz, 1H), 7.38 (d, *J* = 2.5 Hz, 1H), 6.97 (s, 2H), 6.41 (d, *J* = 2.4 Hz, 1H), 2.34 (s, 3H), 2.25 (s, 6H), 1.71 (s, 6H), 1.37 (s, 9H), 1.34 (s, 9H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 151.26,

147.29, 146.43, 144.98, 139.75, 137.68, 137.35, 133.29, 131.17, 130.99, 130.65, 128.46, 128.16, 128.07, 121.79, 120.66, 120.45, 109.98, 107.39; **IR** ν_{max} (neat): 2960, 1455, 1269, 850, 761; **HRMS** (ESI-TOF): *m/z* calcd for $C_{35}H_{42}BrN_2O$ $(M+H)^+$: 585.2480, found 585.2461.

Synthesis of hybrid Ligand 2b`c

2b`** and 1*H*-imidazole (**c**) as coupling partners were allowed to react under the reaction conditions described above for the synthesis of ligand **2b** to obtain **2b`c. The crude mixture after work up was purified by silica gel column chromatography using 10% AcOEt in hexanes as eluent, furnishing the hybrid pyrazole-imidazolyl derivative **2b`c** in 78% yield.

1-(2,7-di-tert-butyl-5-(1H-imidazol-1-yl)-9,9-dimethyl-9H-xanthen-4-yl)-3-mesityl-1H-pyrazole (2b`c)



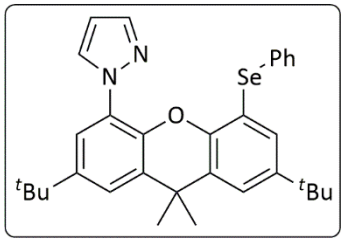
White powder (m.p. = 263-265 ºC); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.69 – 7.65 (m, 2H), 7.53 (d, *J* = 2.3 Hz, 1H), 7.44 (d, *J* = 2.4 Hz, 1H), 7.39 (d, *J* = 2.4 Hz, 1H), 7.20 (d, *J* = 2.3 Hz, 1H), 7.11 – 7.08 (m, 1H), 7.04 (t, *J* = 1.3 Hz, 1H), 6.95 – 6.93 (m, 2H), 6.19 (d, *J* = 2.4 Hz, 1H), 2.32 (s, 3H), 2.20 (s, 6H), 1.75 (s, 6H), 1.37 (s, 9H), 1.34 (s, 9H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 151.41, 146.83, 146.72, 142.11, 139.56, 137.56, 137.33, 131.82, 131.56, 130.92, 130.65, 129.48, 128.31, 128.09, 124.94, 122.67, 121.94, 120.87, 120.75, 108.26, 35.23, 34.72, 34.70, 32.05, 31.40, 31.39, 21.11, 20.65; **IR** ν_{max} (neat): 2953, 1497, 1456, 1271, 760; **HRMS** (ESI-TOF): *m/z* calcd for $C_{38}H_{45}N_4O$ $(M+H)^+$: 573.3588, found 573.3580.

Synthesis of Hybrid Ligand 2a`d

Ligand **2a`d** was synthesized following a recently reported method.[181] An overn dried schelnk flask, evacuated and backfilled with argon 3 times was charged with $PdCl_2$ (5 mol%), $CuCl_2$ (5 mol%), **2a`** (0.2 mmol), and diphenyl diselenide, **d** (0.4 mmol). Finally, added 2 mL of degassed DMSO and allowed the reaction for overnight magnetic stirring at 120 ºC. After cooling to room temperature, the reaction mixture was taken up in 5 mL of ethyl acetate and filtered through a small plug of celite. The organic phase

obtained was dried over $MgSO_4$, and evaporation under vacuum provided a crude solid product. The crude product was then chromatographed using 10% ethyl acetate and hexanes, to obtain the titled compound **2a`d**, in 58% yield.

1-(2,7-di-tert-butyl-9,9-dimethyl-5-(phenylselanyl) -9H- xanthen-4-yl) -1H-pyrazole (2a`d)



White powder (m.p. = 144-146 °C); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 8.32 (d, J = 0.3 Hz, 1H), 7.83 (s, 1H), 7.66 (d, J = 2.3 Hz, 1H), 7.44 (d, J = 2.3 Hz, 1H), 7.42 (d, J = 2.3 Hz, 1H), 7.40 (d, J = 1.7 Hz, 1H), 7.38 (t, J = 1.3 Hz, 1H), 7.25 – 7.28 (m, 2H), 7.24 – 7.17 (m, 3H), 6.86 (d, J = 8.5 Hz, 1H), 1.68 (s, 6H), 1.57 (H_2O), 1.38 (s, 9H), 1.33 (s, 9H): δ 147.75, 146.60, 146.07, 145.81, 140.72, 137.87, 133.49, 131.57, 129.41, 129.31, 129.22, 127.43, 126.31, 124.62, 122.56, 122.06, 120.29, 115.89, 101.95, 35.01, 34.88, 34.69, 32.25, 31.68, 31.59.; **IR** ν_{max} (neat): 2958, 2867, 1497, 1511, 1393, 940, 766; **HRMS** (ESI-TOF): *m/z* calcd for $C_{32}H_{36}N_2OSeNa$ $(M+Na)^+$: 567.1918, found 567.0428.

X-ray Crystallography of 1, 1a, 2a, 2b and 2b`

Bruker *D8* Venture Photon 100 dual source diffractometer was used to collect *X-ray* data for the structural analysis of the compounds. Data were collected using *Cu-Kα* (λ = 1.54178 *Å*) or Mo-*Kα* (λ = 0.71073 *Å*) radiations, and a combination of ϕ and ω scans was carried out to obtain at least one unique data set. The crystal structures were solved using direct methods in the *SHELXS* program.[182] The final structures were refined using *SHELXL*, where the remaining atoms were located from difference Fourier synthesis in which anisotropic displacement parameters were applied to all non-hydrogen atoms, followed by full-matrix least-squares refinement based on F^2. All hydrogen atoms were placed in ideal positions and refined as riding atoms with relative isotropic displacement parameters. Crystallographic data for the structures were deposited in the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 1893376 (**1**), 1893381 (**1a**), 1938492 (**2a**), 1893386 (**2b**) and 1893396 (**2b`**). Copies of the data related to the crystals can be obtained *via* www.ccdc.cam.ac.uk/data_request/cif.

General procedure for SM cross-coupling reaction

For a typical SM cross-coupling reaction, an oven dried resealable Schlenk flask, evacuated and refilled with argon (3 times) was charged with $Pd(OAc)_2$ (1.0 mol%), and **5a** (1.1 mol %) and stirred at room temperature in DMF (2 mL) for 15 minutes, until a yellow solution appears .Then, aryl halide (0.5 mmol), aryl boronic acid (0.75 mmol), and K_2CO_3 (1.0 mmol) were added, finally, l DMF (2 mL) was added and sealed under argon atmosphere. The reaction mixture was heated at 80 ^oC for 6 hours. After, the reaction mixture was cooled to room temperature, filtered through a plug of celite and washed with ethyl acetate, dried over $MgSO_4$ followed by evaporation under reduced pressure. The crude product obtained was then purified using flash silica gel column chromatography.

2.4.3 Spectroscopic Data for Suzuki-Miyaura Cross-coupling Products

4-methyl-1,1'-biphenyl

White powder: m.p. = 48-50^oC (Literature 49-50); **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.57 (dd, J = 7.8, 1.6 Hz, 2H), 7.51 – 7.46 (m, 2H), 7.39 – 7.42 (m, 2H), 7.25 – 7.33 (m, 1H), 7.24 (d, J = 7.9 Hz, 2H), 2.39 (s, 3H); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 141.15, 138.35, 136.99, 129.46, 128.69, 126.98, 126.95, 21.09.

4-(trifluoromethyl)-1,1'-biphenyl

White powder: m.p. = 59-60 ^oC; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.69 (m, 4H), δ 7.62 – 7.58 (m, 2H), 7.50 – 7.44 (m, 2H), 7.43 – 7.38 (m, 1H); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 144.74, 139.76, 128.97, 128.17, 127.41, 127.27, 125.71, 125.68.

1-([1,1'-biphenyl]-4-yl)ethan-1-one

White powder: m.p. = 113-114^oC (Literature 110-111); **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.04 (dd, J = 8.4, 2.0 Hz, 2H), 7.66 – 7.71, (m, 4H), 7.53 – 7.35 (m, 3H), 2.64 (s, 3H); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 197.89, 145.92, 140.01, 135.99, 129.09, 129.05, 128.37, 127.41, 127.36, 26.81.

4-methoxy-1,1'-biphenyl

Yellow powder: m.p. = 79-81 (Literature = 77-78); **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.57 – 7.50 (m, 4H), 7.44 – 7.35 (m, 2H), 7.34 – 7.27 (m, 1H), 7.01 – 6.94 (m,

2H), 3.84 (s, 3H); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 159.13, 140.81, 133.77, 128.70, 128.14, 126.72, 126.64, 114.19, 55.33.

2-phenylnaphthalene

White powder: m.p. = 88-90 ^{o}C; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.04 (d, J = 1.8 Hz, 1H), 7.94 – 7.83 (m, 3H), 7.78 – 7.69 (m, 3H), 7.54 – 7.45 (m, 4H), 7.38 (t, J = 7.4 Hz, 1H); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 141.12, 138.55, 133.67, 132.61, 128.84, 128.40, 128.18, 127.63, 127.42, 127.33, 126.27, 125.91, 125.79, 125.58.

4-methoxy-4'-methyl-1,1'-biphenyl

White powder: m.p. 106-108 (Literature 107-108); **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.54 – 7.48 (m, 2H), 7.44 (d, J = 8.1 Hz, 2H), 7.22 (d, J = 7.9 Hz, 2H), 6.98 – 6.93 (m, 2H), 3.84 (s, 3H), 2.38 (s, 3H); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 158.92, 137.96, 136.33, 133.74, 129.42, 127.94, 126.57, 114.15, 55.34, 21.05.

1-(4'-methyl-[1,1'-biphenyl]-4-yl)ethan-1-one

White powder: m.p. 122-123 (Literature 118-120); **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 8.02 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 8.1 Hz, 2H), 7.28 (d, J = 7.9 Hz, 2H), 2.63 (s, 3H), 2.41 (s, 3H); **^{13}C-NMR (75 MHz, $CDCl_3$)**: δ 197.78, 145.71, 138.23, 136.93, 135.56, 129.67, 128.90, 127.09, 126.94, 26.66, 21.17.

1-(4'-methoxy-[1,1'-biphenyl]-4-yl)ethan-1-one

Yellow powder: m.p. = 146-148; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.04 – 7.97 (m, 2H), 7.67 – 7.53 (m, 4H), 7.03 – 6.96 (m, 2H), 3.86 (s, 3H), 2.62 (s, 3H); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 197.70, 159.92, 145.36, 135.29, 132.25, 128.94, 128.36, 126.61, 114.41, 55.39, 26.62.

2-methyl-1,1'-biphenyl

Pale yellow oil; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.40 – 7.34 (m, 2H), 7.32 – 7.27 (m, 3H), 7.23 – 7.19 (m, 4H), 2.25 (s, 3H); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 142.09, 142.05, 135.41, 130.41, 129.91, 129.30, 128.17, 127.36, 126.87, 125.88, 20.59.

2,4'-dimethyl-1,1'-biphenyl

Pale yellow oil; **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 7.22 - 7.25 (m, Hz, 8H), 2.40 (s, 3H), 2.28 (s, 3H); **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 141.84, 138.99, 136.36, 135.38, 130.26, 129.83, 129.05, 128.75, 127.04, 125.72, 21.17, 20.51.

2,4',6-trimethyl-1,1'-biphenyl

Yellowish oil; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.22 (d, J = 7.5 Hz, 2H), 7.08 – 7.16 (m, 3H), 7.02 (d, J = 7.9 Hz, 2H), 2.40 (s, 3H), 2.03 (s, 6H); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 141.82, 138.00, 136.20, 136.04, 129.09, 128.86, 127.21, 126.85, 21.23, 20.88.

2.4 Conclusions

In conclusion, this work highlights synthesis of new mono- and bis-pyrazoles bearing a flexible *p*-tolyl ether or a rigid xanthene backbone, as pyrazolyl analogues of *DPEphos* and *Xantphos* ligands, respectively, as well as their application in the Suzuki-Miyaura cross-coupling reaction as active ligands. The synthesis of the mono-pyrazaloyl analogues **1a`**, **2a`**, and **2b`** and the bis-pyrazolyl analogues **1a**, **2a**, and **2b**, was achieved by following an Ullmann coupling protocol in good yields. In addition, the hybrid pyrazolyl-imidazolyl analogue **2b`c** was also synthesized in a very good yield of 76% following Ullmann coupling protocol, while the pyrazolyl-selanyl hybrid anaolgue **2b`d** was synthesized using a *C-H* activation protocol in 58% yield. The new ligands were then evaluated for their potential as effective ligands in the Pd-catalyzed Suzuki-Miyaura cross-coupling reaction. For this a simple catalytic system based on $Pd(OAc)_2$/**2a** was developed which efficiently catalyzes the Suzuki-Miyaura cross-coupling reaction of aryl iodides and aryl bromides bearing electron rich and poor substituents and provides the corresponding cross-coupling products in good to excellent yields. In addition, moderate yields were obtained for the aryl chlorides containing electron-withdrawing groups at *p*-position, whereas only poor yields were obtained for the electron-poor substituents. Furthermore, the developed catalytic system was not severely affected by the electronic nature of the *p*-substituents and delivers good to excellent yields of the cross-coupling products, however, the steric factors prominently affects the outcome of the reaction and only moderate yields of the cross-coupling products were obtained.

Chapter 3 Pd-Catalyzed Suzuki-Miyaura Cross-coupling Reaction in Glycerol; A Green and Non-Innocent Solvent.

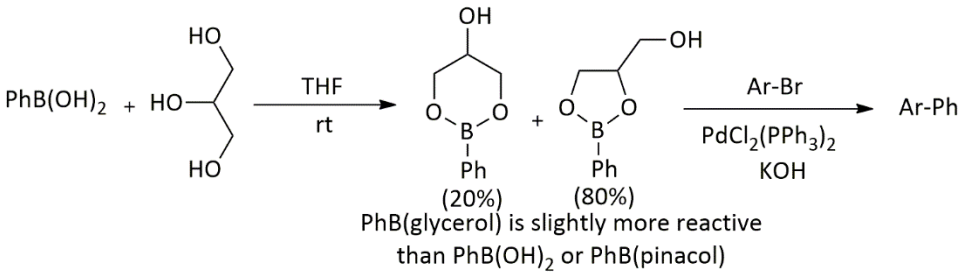
3.1 Introduction

The palladium catalyzed Suzuki-Miyaura cross-coupling reaction are the most powerful and versatile protocols for the construction of Csp^2-Csp^2 bonds because they are simple, cost effective, display tolerance for a variety of functional groups, and often high yielding.[26, 183] Research on the fine tuning of this protocol for industrial purposes for the manufacture of fine chemicals, and useful drugs by using an environmentally benign reaction medium has always remained under the focus of the synthetic chemists.[157] On the other hand, the increasing environmental challenges and difficulty of separation of the desired products from the reaction mixture have restricted the synthetic utility to some extent, as the majority of the waste generated per gram of the product includes the solvent waste, in addition to the inorganic salts.[184] Taking into account the impact of these chemical processes on the environment and the cost of the organic solvents, the search for innovative procedures for the substitution of volatile and expensive organic solvents has become a big challenge in both academia and industry.[185] Therefore, the search for environmentally benign reaction medium has remained an important issue for the Pd-catalyzed Suzuki-Miyaura cross-coupling reactions.[186]

In this context, glycerol provides an attractive alternative, since it offers the desired characteristics of a green solvent including low flammability, high availability, biodegradability, ecofriendly, and ideally can be obtained from renewable sources.[187] With the increased worldwide biodiesel production, the market saturation of glycerol, a co-product of biodiesel production (for every 9 kg of biodiesel produced, about 1 kg of a crude glycerol co-product is formed), is inevitable, especially in Brazil.[188-191] Therefore, the direct utilization of glycerol as a green solvent for organic transformations would be conceptually interesting, since it can provide a sustainable medium with efficiency to drive several organic transformations including hydrophilic and hydrophobic substrates as well as catalysts and also economically affordable.[192] Another valuable aspect of glycerol is that the products can be easily isolated in high yields by simply extracting with a glycerol-immiscible solvent such as hexane, and diethyl ether. Recently, glycerol has been utilize as a green solvent in a variety of organic reactions,[193] including Pd-catalyzed Heck and Suzuki-Miyaura cross-couplings, metal catalyzed transfer hydrogenation reactions and asymmetric reductions.[194, 195] The Pd-catalyzed Suzuki-Miyaura cross-coupling reaction in glycerol was first studied by reacting phenyl iodide

and phenyl boronic acid as coupling partners and very good yields were obtained by using Pd complexes containing water-soluble triphenylphosphine trisulfonate (TPPS) as catalysts.[194] Reports of Suzuki-Miyaura cross-coupling reaction studies using glycerol as solvent medium under ultrasound or microwave irradiations are also found in literature.[196-198] Very recently, a ligand free Suzuki-Miyaura cross-coupling reaction has been studied by using aryltrifluorborates as coupling partners in deep eutectic solvents (choline chloride/glycerol).[199]

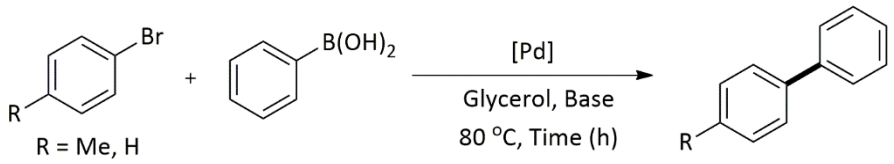
In the research group of Professor Monteiro on the ongoing project on Pd-catalyzed cross-coupling reactions, they have used poly(ethylene oxide) (PEO)/methanol as solvent medium for the Pd-catalyzed Suzuki cross-coupling reaction under mild conditions. After the end of the reaction the product was extracted with heptane and the polar phase was reused several times (up to 12) without any change in the activity.[200] Then, they were interested to evaluate glycerol as an efficient solvent medium for the Pd-catalyzed Suzuki-Miyaura cross-coupling reaction, and observed that it does not only act as a solvent. In fact, the reaction of glycerol with phenylboronic acid provided a mixture of glycerol 1,2-phenylboronate and 1,3-phenylboronate (**Scheme 14**). Usually, arylboronic acids are used in excess to ensure the complete conversion of aryl halides (1.5-2 equivalents). However, excess of glycerol phenylboronates was not required and the coupling products were obtained in high yields. Therefore, beside all other advantages already mentioned, the utilization of glycerol as a solvent can circumvent the use of boronic acid excess in Suzuki-Miyaura cross-coupling reactions.



Scheme 14. Phenylboronic esters from glycerol as active coupling partners for the Suzuki-Miayura cross-coupling reaction.[201]

In this context, our research group has already explored the use of glycerol as a green solvent for the Pd-catalyzed Suzuki-Miyaura cross-coupling reaction.[201] Thus, a typical Suzuki-Miyaura cross-coupling reaction was performed using 4-bromotoluene

and phenyl bromide as model substrates to react with phenyl boronic acid at 80 °C, as it is sufficient enough to engender a homogenize reaction medium of glycerol (**Scheme 15**).



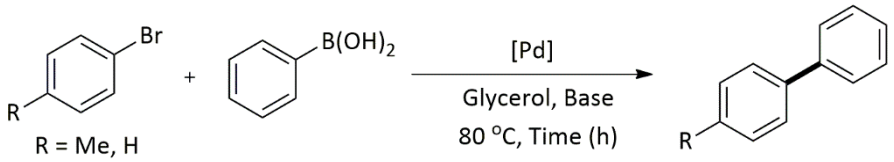
Scheme 15: Model Suzuki-Miyaura cross-coupling reaction in glycerol.

In order to identify the optimum reaction conditions, initially the reaction of aryl bromides (0.5 mmol) with phenylboronic acid (0.55 mmol), using $Pd(dba)_2$ as Pd source without using any ligand was investigated (**Table 8**). Based on the idea previously established in our lab that glycerol despite being solvent and a good source to form glycerol boronates,[201] this study is based on the assumption that glycerol would also act as a ligand and assist Pd in catalyzing the reaction effectively. So, a model reaction of 4-bromotoluene or bromotoluene with phenylboronic acid using 1.0 mol% of $Pd(dba)_2$ was magnetically stirred for 4 hours in the presence of various bases in 4 mL of glycerol under inert conditions. Promising results were obtained with all bases (**Table 8**, Entries 1-4), however, KOH was selected as the base of choice considering its better solubility in glycerol. We believed that the yield of the cross-coupling product could significantly increase if the reaction will be allowed to react for longer reaction time, therefore, the reaction of phenyl bromide with phenyl boronic acid under identical conditions was allowed to stir for 24 hours, as a result a moderate yield was obtained (**Table 8**, Entries 5). We were pleased to see that the GC analysis of the reaction mixture provided the homo-coupling by-product only in negligible amounts of less that 1% yield, when 4-bromotoluene was used as our aryl halide source, suggesting that the observed yield mainly corresponds to the cross-coupling yield.

The ligand free Pd-catalyzed thus motivated us to screen different sources of phosphine based Pd-sources and ligands, including a study based on ^{31}P-NMR for the formation of an *in situ* phoshinite ligand which can be formed from the reaction of PPh_2Cl with glycerol. Furthermore, we also have provide some details regarding the role of glycerol as *in situ* source for oxolone ligand formation by reaction with Pd(diphenylphosphine-2-benzaldehyde)$_2$. A very good yield of the cross coupling

product was obtained using Pd(diphenylphosphine-2-benzaldehyde)$_2$ in glycerol that can form a oxolone ligand *in situ* by reaction with glycerol.

Table 8. Pd-catalyzed Suzuki–Miyaura cross-coupling reaction in glycerol.[201]



Entry	[Pd] (mol%)	R	Base	Time (h)	Yield (%)[b]
1	$Pd(dba)_2$ (1)	Me	K_3PO_4	4	50
2	$Pd(dba)_2$ (1)	Me	Na_2CO_3	4	54
3	$Pd(dba)_2$ (1)	Me	KOH	4	54
4	$Pd(dba)_2$ (1)	H	KOH	4	46
5	$Pd(dba)_2$ (1)	H	KOH	24	70
7	$PdCl_2(PCy_3)_2$ (1)	H	KOH	24	81
8	$PdCl_2(PPh_3)_2$ (1)	H	KOH	24	99

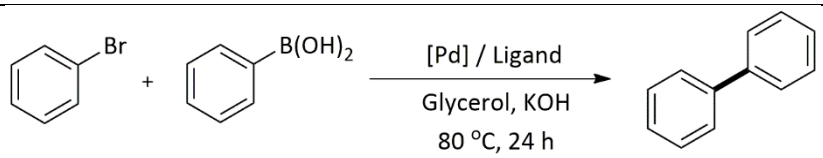
[a] Reaction conditions: 1 mol% $Pd(dba)_2$, 0.5 mmol aryl bromide, 0.55 mmol phenylboronic acid, 1 mmol base, 4 mL glycerol, 80°C. [b] Isolated yield.

3.2 Results and Discussion

Glycerol is an attractive and an alternative green solvent to perform metal catalyzed cross-coupling reactions and provides both economic and eco-friendly benefits. Water has been extensively explored in this regard, however, the necessity of hydrophilic catalysts have restricted the scope of water as an efficient reaction medium. For this purpose, glycerol offers a viable alternative as it can tolerate both hydrophilic and hydrophobic catalysts, and substrates, therefore, we intended to explore the scope and limitations of glycerol as an alternative green reaction medium for the Suzuki-Miyaura cross-coupling reaction.

Our investigation for the Suzuki-Miyaura cross-coupling reaction were started by reproducing and comparing the results above presented in **Table 8**. Identical results were obtained by using the reaction conditions previously established in our lab.[201] For instance, when the model reaction was performed using 1mol% of $Pd(dba)_2$, the cross-coupling product was obtained in81% yield (**Table 9**, entry 1). Similarly, when the model reaction was performed using 1mol% of $PdCl_2(PCy_3)_2$, 81% (**Table 9**, entry 2) yield of the cross-coupling product was obtained, while a quantitative yield was obtained using $PdCl_2(PPh_3)_2$ (**Table 9**, entry 3).

Table 9. Screening of different Pd Sources and Ligands catalyzed Suzuki–Miyaura reaction in glycerol.



Entry	[Pd] (mol%)	Ligand (mol%)	Yield (%)[b]
1	$Pd(dba)_2$ (1)	-	70
2	$PdCl_2(PCy_3)_2$ (1)	-	81
3	$PdCl_2(PPh_3)_2$ (1)	-	99
4	$PdCl_2$(dppf) (2)	-	76[c]
5	$PdCl_2$(dppf) (2)	-	86
6	$PdCl_2$(2-PPh_2-benzaldehyde)$_2$ (1)	-	79
7	$Pd(OAc)_2$ (1)	-	62
8	$Pd(OAc)_2$ (2)	PPh_2Cl (4)	98
9	$Pd(OAc)_2$ (1)	2-PPh_2-benzaldehyde (2)	68

[a] Reaction conditions: 0.5 mmol aryl bromide, 0.55 mmol phenylboronic acid, 1 mmol KOH, 4 mL glycerol, 80°C, 24 h. [b] Isolated yield. [c] 4 h.

In order to compared the results obtained by Wolfson and co-workers,[194] the model reaction was performed under the similar conditions described *i.e.*, using 2 mol% of $PdCl_2$(dppf), only 76% of yield was obtained after 4h (**Table 9**, entry 4). When the

reaction of was allowed for 24 hours of magnetic stirring 86% of yield was obtained (**Table 9**, entry 5). $PdCl_2$(2-PPh_2-benzaldehyde)$_2$ as Pd source provided 89% of isolated yield (**Table 9**, entry 6). To compare the result obtained using ligand free $Pd(dba)_2$, a ligand free $Pd(OAc)_2$ system was also tested, only a yield of 62% cross-coupling product was obtained.

Finally, we were delighted to see that when 2.0 mol% $Pd(OAc)_2$ and PPh_2Cl (4.0 mol%) based catalytic system was used the coupling product was obtained in excellent yield (**Table 9**, entry 8). We assume that the quantitative yield of the cross-coupling product is attributed towards the formation of an *in situ* phosphinate ligand capable of forming a complex *in situ* with the Pd precursor, that's why the cross-coupling product was obtained in quantitative yield. This result further motivated us to use a catalytic system based on the similar assumption that 2-PPh_2-benzaldehyde would form an *in situ* oxolone ligand and would provide a similar result. Thus, a catalytic system based on $Pd(OAc)_2$ and 2-PPh_2-benzaldehyde was also evaluated, however, in contrast to our expectations, only a moderate yield of the cross coupling product was obtained (**Table 9**, entry 9). It is very important to mention that the cross-coupling product was isolated easily by simply extracting the reaction mixture with a glycerol-immiscible solvent such as hexane in this case.

3.2.1 Recycling Studies of Glycerol

The glycerol recycling experiments were studied initially by using the reaction conditions developed previously in our lab. For this, a glycerol-soluble phosphine was investigated, such as the triphenylphosphine monosulfonate sodium salt (TPPMS) based on the hypothesis that it could improve the catalyst homogenization and solubility in the reaction medium. A moderate yield was obtained when 1.0 mol% of $Pd(OAc)_2$/TPPMS was used. Increasing $Pd(OAc)_2$/TPPMS loading to 2.0 mol% although increases the product yield, but sharp deactivation of the catalytic glycerol media after the first cycle was observed again. Interestingly, when 2.0 mol% $PdCl_2$/TPPMS combination was tested, the catalytic glycerol media entered into the fourth cycle, whilst formation of palladium black prevent the reaction medium from further recycling after the fourth cycle.[201]

The glycerol catalytic media recycling experiments were then performed using $PdCl_2(PPh_3)_2$ based under optimized conditions described above. After the extraction of the biaryl product from the first reaction using hexane several times (5 times), the catalytic glycerol medium was dried under vacuum. Then, identical amount of bromobenzene, phenylboronic acid and KOH were added to the glycerol and the reaction was carried out under similar conditions. The results of the recycling catalytic glycerol media experiments are summarized in **Table 10**.

Table 10. Catalyst recycling for Suzuki-Miyaura reaction of bromobenzene with phenylboronic acid in glycerol.[a]

Cycle	**Ph-Ph Yield (%)** [b]		
	$PdCl_2(PPh_3)_2$	$PdCl_2$(dppf)	$PdCl_2(PPh_3)_2$ [c]
1	88	86	89
2	89	28	92
3	85	19	86
4	65	-	99
5	30	-	99
6	-	-	77
7	-	-	62
8	-	-	31

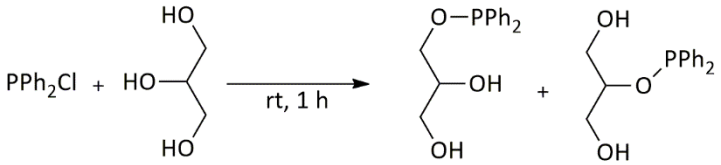
[a] Reaction conditions: [Pd] (2 mol%), 0.5 mmol bromobenzene, 0.55 mmol arylboronic acid, 1 mmol KOH, 4 mL glycerol, 80°C, 24h. [b] Isolated yield. [c] Glycerol:Methanol (1:1).

We started the recycling studies using 1 mol% of $PdCl_2(PPh_3)_2$ that gives a quantitative yield of the cross-coupling product for the first run . Only a 56% yield of the cross-coupling product was obtained for the second cycle of and the reaction stopped in the third cycle. We then increased the $PdCl_2(PPh_3)_2$ loadings to 2.0 mol% and we were delighted to see that under these conditions the catalytic system is recyclable up to 4 cycles smoothly, however a sharp decrease in the yield of the cross-coupling in the 5^{th} cycle stopped us to further recycle the catalytic media due to high excessive inorganic

salt formation, preventing the reaction mixture from smooth magnetic stirring in addition to the high viscosity of glycerol. Therefore, we decided to use a 50:50 solution mixture of glycerol and methanol, to decrease the viscosity and to increase the solubility of the organic substrates in the glycerol catalytic media. Under these conditions we observed a smooth catalytic performance of the catalytic glycerol media. Up to 7 cycles, the catalytic media delivered excellent yields of the cross-coupling products, however, a sharp decreased in the yield of the cross-coupling product in the 8th cycle. We observed formation of solid inorganic salts which prevent the reaction mixture from a smooth magnetic stirring, in addition to the catalyst decomposition after the 8th cycle.

In addition to this, the catalyst decomposition might be another reason for the observed low yield of the cross-coupling product in the 8th run. One of the drawbacks is the lixiviation of the organic part of catalyst to the non-polar organic phase during extraction causing a sharp decrease in the catalytic activity of the catalyst, which in turn might affect the number of recycles. It has been reported that in the presence of $PdCl_2$(dppf) (2 mol%) the reaction between iodobenzene and phenyl boronic acid in glycerol kept the catalytic activity for 3 cycles.[194] However, we did not find similar behaviour for the coupling with bromobenzene, and the yield drops to only 28% for the second cycle.

The reaction of chlorodiphenylphosphine (PPh_2Cl) with alcohols (ROH) to give the corresponding phosphinite (Ph_2POR) ligands is already a known reaction.[202, 203] So, we expected that the treatment of PPh_2Cl with glycerol would form an *in situ* phosphinite ligand (Ph_2P-Glycerol) with two free hydroxyl groups, improving the solubility of the catalyst in the glycerol phase and subsequently will offer a better catalyst recycling (**Scheme 16**).



Scheme 16. Expected reaction of PPh_2Cl with glycerol.

To support this assumption, PPh_2Cl (20 mol%) and glycerol (4 mL) were mixed

directly under argon and allowed to magnetically stir for 1 hour at room temperature. All of the PPh_2Cl was consumed within the first hour, supported by the up field shift of the PPh_2Cl signal from 81.8 ppm (**Figure 20-a**) to 21.7 and 25.9 ppm in the ^{31}P-NMR of the crude reaction mixture (**Figure 20-b**). Then a mixture of glycerol and PPh_2Cl under inert atmosphere were magnetically stirred for 1 hour, followed by addition of 1 mol% of $Pd(OAc)_2$, and stirred for additional 3 hours. The ^{31}P-NMR of the crude reaction mixture showed some downfield signals at 36.3, 33.1 and 28.5 ppm including the signals for the tagged glycerol-PPh_2 signals at 21.7 and 25.9 ppm supporting a partial *in situ* complex formation with Pd (**Figure 20-c**).

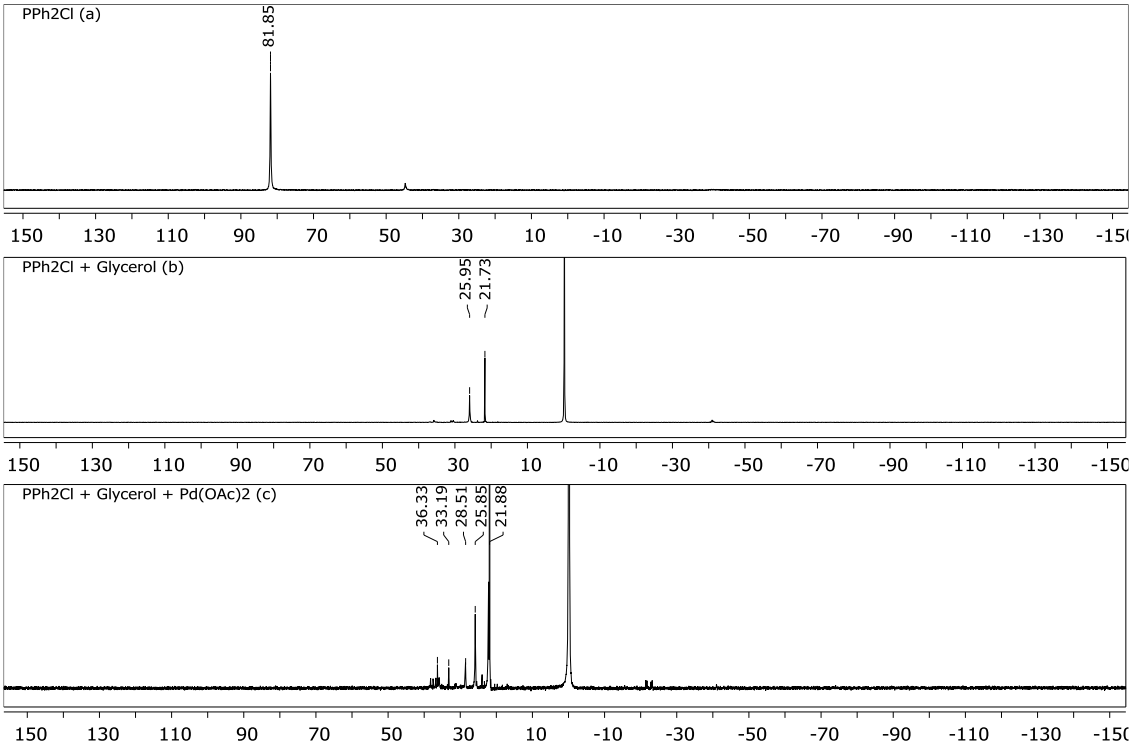
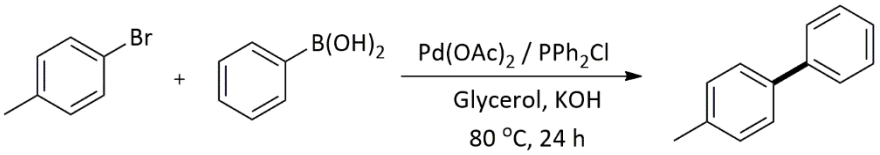


Figure 20: ^{31}P-NMR of PPh_2Cl (**a**), PPh_2Cl + Glycerol (**b**), and PPh_2Cl + Glycerol + $Pd(OAc)_2$ (**c**).

Although, we tried many times to isolate the phosphinte ligand and Pd-complex formed *in situ*, but our attempts remained unsuccessful, nevertheless, our objective here was to increase the number of recylces by improving the solubility of the catalyst in the glycerol phase and not the isolation of the phosphine ligand and the corresponding Pd catalyst formed *in situ*. Hence, for the glycerol recycling experiment, PPh_2Cl (2 mol%) and the glycerol (4 mL) were directly mixed and allowed to stir for 1 hour at room temperature before starting the cross-coupling reaction. Then 4-bromotoluene (0.5

mmol), phenylboronic acid (0.55 mmol), 1 mol% $Pd(OAc)_2$, 1 mmol KOH were added and magnetically stirred under argon at 80°C during 24 h. The coupling products were obtained in 98% and 83% yield in the first and second run respectively, but the yield was dropped to only 10% in the third cycle, (**Table 10a**). The sharp decrease in the yield of the cross-coupling product after the third cycle was attributed towards the formation of palladium black and catalyst decomposition. Since, glycerol does have water in small quantities even after careful drying, therefore, the observed sharp decrease in the yield might also be due to presence of water, preventing the reaction of PPh_2Cl and the glycerol to proceed as proposed.

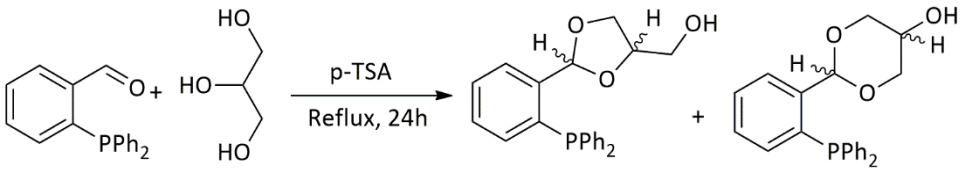
Table 10a. Catalyst recycling in the Suzuki-Miyaura reaction using $Pd(OAc)_2/PPh_2Cl$ system in glycerol.



Cycle	**1**	**2**	**3**
CC Yield (%) [b]	98	83	10

Reaction Conditions: 1 mol% $Pd(OAc)_2$, 20 mol% PPh_2Cl, 0.5 mmol 4-bromotoluene, 0.55 mmol phenylboronic acid, 4 mL glycerol, 1 mmol KOH, 4 mL glycerol, 80°C, 24 h; **[b]** Isolated yield.

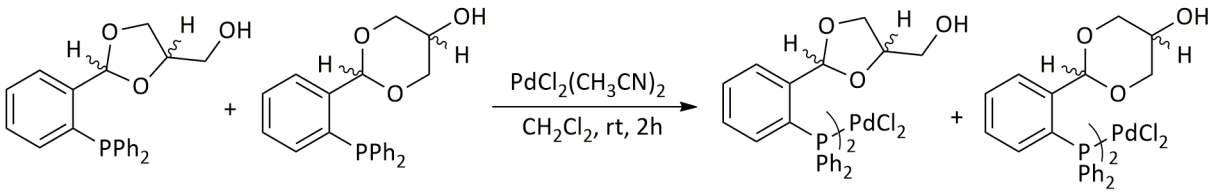
Furthermore, we also have provide some details regarding the role of glycerol as *in situ* source for oxolone ligand formation by reaction with 2-PPh_2-benzaldehyde, (**Scheme 17**). Again we have used the ^{31}P-NMR to follow the *in situ* ligand formation. For this, we first mixed glycerol and diphenylphosphine-2-benzaldehyde in presence of catalytic amounts of *p*-toluene sulphonic acid.



Scheme 17. Reaction of glycerol and 2-PPh_2-benzaldehyde.

The reaction after 24 hours of magnetic stirring using a Dean-Stark apparatus was filtered and analyzed the crude reaction mixture directly by using ^{31}P-NMR which

suggested formation of oxolone intermediates (**Figure 21-a**). The formation of oxolone ligand was confirmed by comparing the literature data related to oxolone ligands with the observed values.[204, 205]



Scheme 18. Reaction for oxolone ligands with $PdCl_2(CH_3CN)_2$.

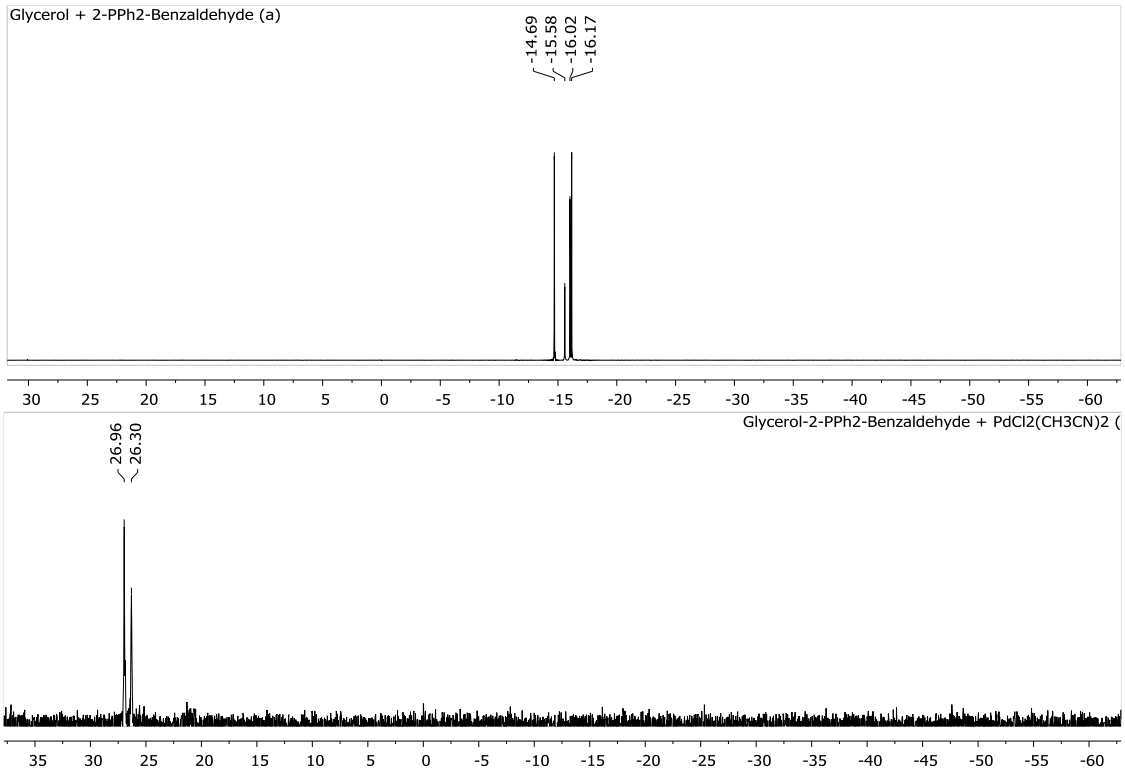


Figure 21. ^{31}P-NMR of 2-PPh_2-benzaladehyde + Glycerol (**a**), and 2-PPh_2-benzaladehyde-Glycerol + $PdCl_2(CH_3CN)_2$ (**b**).

To this reaction mixture we then added $PdCl_2(CH_3CN)_2$ and allowed to magnetically stir for 2 hours in dichloromethane under argon atmosphere at room temperature (**Scheme 18**). The reaction mixture on overnight standing undisturbed produced fine yellowish crystals. The crystals were washed with minimum amount of dichloromethane and submitted for X-ray crystallography and ^{31}P-NMR. The ^{31}P-NMR suggested presence of two phosphorous signals (**Figure 21-b**), while the X-ray analysis though suggested complex formation with Pd, however, the X-ray crystal data was not

completely resolved and revealed co-crystallization of five and six-membered oxolone ligands attached to the Pd-centre. When the Suzuki-Miyaura cross-coupling reaction was performed under optimized conditions using 2-PPh_2-benzaladehyde as ligand, only a moderate yield was obtained, therefore, we stopped the reaction for further evaluation in the glycerol recycling experiments.

3.3 Experimental

3.3.1 Materials and Methods

All reactions were carried out under an argon atmosphere in resealable Schlenk tubes. All the chemicals were purchased from commercial sources and used without further purification. Glycerol was degassed by purging a layer of argon for 15 to 20 minutes before using in a reaction. ^{1}H-, and ^{13}C-NMR spectra of the cross coupling products were recorded on a Varian XL300 and Varian 400 MHz NMR spectrometer. Chemical shifts are reported in ppm downfield to TMS. Mass spectrometry analyses were performed on the GC-MS Shimadzu QP-5050 (EI, 70 eV) equipped with a 30 m long DB-5 column. Gas chromatography analyses were performed on a HP-5890A instrument fitted with a FID detector and a 30 m long DB-17 column.

3.3.2 General Procedure for the Suzuki-Miyaura cross-coupling reaction

For a typical Suzuki-Miyaura experiment, an oven-dried resealable Schlenk flask capacity 10 mL was evacuated and back-filled with argon and charged with $PdCl_2(PPh_3)_2$ (0.5 mol%; 1.8 mg), aryl bromide (0.5 mmol), followed by addition of arylboronic acid (0.55 mmol), KOH (1.0 mmol, 56 mg), and glycerol (4.0 mL). The reaction mixture was allowed to magnetically stirr at 80°C for 24h. After, the solution was cooled to room temperature and was extracted 3 times with a glycerol-immiscible solvent, in this case, hexane. The hexane phase was separated, dried over $MgSO_4$, and concentrated under vacuum. The products were then purified by using silica gel flash chromatography eluting hexane only. The spectral data of the obtained products were in agreement with those described in the literature.

3.3.3 Glycerol Recycling Experiments

Recycling of catalytic glycerol media containing different Pd sources

For the recycling experiment, an oven-dried resealable Schlenk flask was evacuated and refilled with argon and charged with [Pd] (1.0 or 2.0 mol%), and ligand (2.0 or 4.0 mol%). Then aryl bromide (0.5 mmol), followed by addition of aryl boronic acid (0.55 mmol), KOH (1.0 mmol), and glycerol (4.0 mL). The Schlenk tube was then sealed and the reaction mixture was allowed to magnetically stirr at 80°C for 24h. After 5 times extraction with hexane, the resulting glycerol phase was then dried under vacuum, reused for next reaction without further purification. Then, equal amounts of aryl bromide (0.5 mmol), arylboronic acid (0.55 mmol) and potassium hydroxide were added and the reaction was stirred under optimized conditions for further 24 hours.

Recycling of $PdCl_2(PPh_3)_2$ catalytic glycerol media

For the recycling experiment with, an oven-dried resealable Schlenk flask was evacuated and refilled with argon and charged with $PdCl_2(PPh_3)_2$ (2.0 mol%). Then aryl bromide (0.5 mmol), followed by aryl boronic acid (0.55 mmol), and KOH (1.0 mmol), were added in 1:1 mixture of glycerol and methanol (2 + 2 mL). The Schlenk tube was then sealed under argon and the reaction mixture was allowed to magnetically stirr at 80°C for 8h. After 5 times extraction with hexane, the resulting glycerol and methanol based catalytic medium was then evacuated and backfilled with argon three times to make sure oxygen free catalytic medium, and reused for next reaction. Then, equal amounts of aryl bromide (0.5 mmol), arylboronic acid (0.55 mmol) and potassium hydroxide were added and the reaction was stirred for overnight. In this way, alternative 8 and 16 hours cycles *i.e.*, two cycles per day were performed up to 8 cycles.

Recycling of catalytic glycerol media using $Pd(OAc)_2/PPh_2Cl$

To an oven dried resealable Schlenk tube, evacuated and back filled with argon, PPh_2Cl (2.0 mol%) and the glycerol (4 mL) were directly mixed before starting the cross-coupling reaction and magnetically stirred for 1 hour at room temperature. Then 4-bromotoluene (0.5 mmol), phenyl boronic acid (0.55 mmol), 1 mol% $Pd(OAc)_2$, and 1.0 mmol KOH were added and stirred at 80^{o}C for 24 h. The reaction was allowed to achieve room temperature, after 3 times extraction with hexane, the resulting glycerol phase was

then dried under vacuum and reused for next reaction without further purification. Then, equal amounts of 4-bromotoluene (0.5 mmol), phenyl boronic acid (0.55 mmol) and 1.0 mmol KOH were added and the reaction was stirred for further 24 hours.

Recycling of Glycerol using $Pd(OAc)_2$ / 2-PPh_2-benzaldehyde

An oven dried resealble Schlenk tube was evacuated and back filled with argon, was charged with $Pd(OAc)_2$ (1 mol%) and 2-PPh_2-benzaldehyde (2 mol%) and the glycerol (4 mL) were mixed and magnetically stirred for 1 hour at room temperature. Then 4-bromotoluene (0.5 mmol), phenyl boronic acid (0.55 mmol), 1 mol% $Pd(OAc)_2$, and 1.0 mmol KOH were added and stirred at 100^{o}C for 6 h. The reaction was allowed to achieve room temperature, after 3 times extraction with hexane. A moderate yield of cross-coupling product in the first cycle forced us to stop the catalytic media for further recycles.

3.4 Conclusions

In conclusion, a simple catalytic system based on $PdCl_2(PPh_3)_2$ in glycerol efficiently catalyzes the Suzuki-Miyaura cross-coupling reaction of aryl bromides with aryl boronic acids. The cross-coupling products were obtained in good to excellent yields and the products were easily isolated by extraction with hexane. Since, the use of glycerol provides the advantage of using the glycerol catalytic media to recycle, therefore, recycling studies using a 50:50 solution mixture of glycerol and methanol demonstrates a smooth catalytic performance of the catalytic glycerol media. Up to 7 cycles the catalytic media delivered excellent yields of the cross-coupling products, however, a sharp decreased in the yield of the cross-coupling product in the 8th cycle was observed due to formation of solid inorganic salts which prevent the reaction mixture from a smooth magnetic stirring. In addition to this, the catalyst decomposition might be another reason for the observed low yield of the cross-coupling product in the 8th run. We also attempted to study the recycling of glycerol by using a mixture of $Pd(OAc)_2$ and chlorodiphenylphosphine in glycerol which also catalyzes the reaction efficiently. We believe that in the presence of glycerol, Ph_2PCl can be converted *in situ* into a phosphinite ligand. The attempts to recycle the catalytic system suggested that it is recyclable up to

3 cycles and rapidly loss its catalytic activity in the fourth cycle. Furthermore, we also have studied role of glycerol as an *in situ* source for oxolone ligand formation by reaction of glycerol with Pd(diphenylphosphine-2-benzaldehyde)$_2$. Only a good yield of the cross coupling product was obtained using Pd(diphenylphosphine-2-benzaldehyde)$_2$ in glycerol that can form a oxolone ligand *in situ* by reaction with glycerol. However, the catalytic system was not so effective for further evaluation, therefore, we did not explored it for the recycling studies.

Chapter 4 Suzuki-Miyaura Cross-Coupling Reaction of Aryl Halides and Aryl Boronic Acids Catalyzed by Using a New Ionophllic Imino-phosphine-Pd-Complex and Mechanistic Insights Using ESI Mass Spectrometry

4.1 Introduction

Introduction of charged tags (ionophillic fragments) at remote sites as a strategy, in order to immobilize the catalyst enhances the retention and stability of the catalyst vividly and prevents lixiviation from the reaction medium.[206-209] In addition, the catalytic behaviour enhances several folds, facilitates improved solubility in a variety of polar and green solvents including water, along with the beneficial aspects of facile product separation from the reaction mixture and catalyst recyclability.[210-214] The physicochemical properties like thermal stability and electrochemical properties of the catalyst also modify dramatically by using ionic tags. Thus, the use of inherent ionophillic tag provides a well-designed and straightforward pathway for the fine-tuning of the properties of a catalyst which in turn display an enhanced catalytic behavior as a payoff.[215] Therefore, strategic functionalization of ligands and catalysts using charged tags for the stereoselective reactions, and cross-coupling reactions has gained much popularity among the scientific community during the last few decades.[216-220]

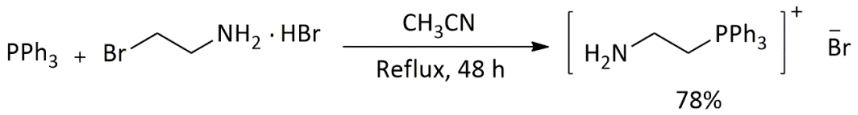
The use of ionophillic tags bestowed upon the catalyst provides the unique advantage of their detection easily and rapidly with a high level of sensitivity in the ESI mass spectrometry analysis, then their corresponding neutral counterparts.[221-225] Introduced for the first time by Adlhart and Chen, the charged tagged catalysts as fishhooks are powerful tools in organometallic catalysis for the detection of key intermediates formed during the reaction.[226] Since, ESI is a soft ionisation technique and the probability of neutral intermediates to undergo ionisation in many cases might be rare, the use of ionic tag ensures a permanent charge which in turn allows the facile detection of the key intermediates involved in the reaction.[221, 227] In addition, the ionisation process in ESI transfers only a limited amount of energy into the probed ions and does not significantly alter the nature of the species detected. That is why ionophillic charged tag catalysts have been widely employed as ionic probes to get insights about the mechanism for several catalytic reactions using ESI mass spectrometry as a fishing tool.[228-233]

There are several reports described in literature about the Suzuki cross-coupling reaction catalyzed by using charged-tagged ligands and ionophillic Pd-catalysts.[125, 219, 234-236] Likewise, several reports on the use of charged-tagged catalysts to get insights

about the mechanism through detection of key intermediates of Suzuki cross-coupling reactions using ESI mass spectrometry are also described.[225, 235, 237, 238] Majority of these reports have provided a significant information about the key intermediates related to oxidative addition step of aryl halides or pseudo-halides to the very reactive Pd (0) specie, transmetalation step and reductive elimination step, however, to the best of our knowledge there is no report that provides the direct evidence for the formation of a stable Pd (0) specie using ESI-MS yet. Therefore, in continuation of our research work on finding active Pd-catalysts for cross-coupling reactions and understanding the mechanistic pathways involved in the Pd-catalyzed cross-coupling reactions using ESI-MS,[239, 240] we herein describe synthesis and characterization of an ionophillic imino-phosphine-Pd catalyst previously synthesized in our research group which demonstrates an excellent catalytic activity in catalyzing the Suzuki-Miyaura cross-coupling reaction. The ionophillic Pd-catalyst was further used as an ionic probe to get some insights about the mechanism of Suzuki-Miyaura cross-coupling reaction through detection of key reactive intermediates using ESI mass spectrometry technique.

4.2 Results and Discussion

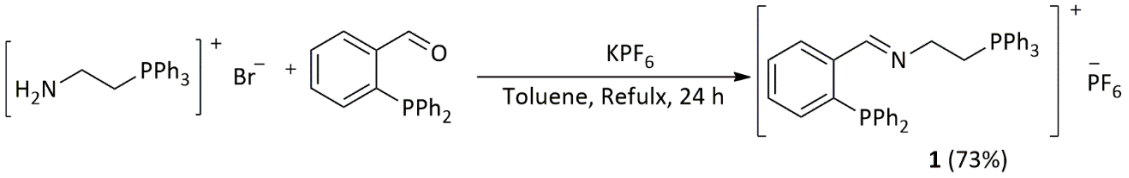
In order to obtain the ionophillic imino-phosphine-Pd-complex **2** previously synthesized in our lab, first 2-aminoethyl-triphenylphosphonium bromide was synthesized by following the same protocol described and cited with a slight modification.[241, 201] By refluxing a mixture of 2-aminoethyl bromide-HBr salt and triphenylphosphine in acetonitrile for 48 hours delivered 76% yield of desired product, **Scheme 19**.[201]



Scheme 19. Synthesis of 2-aminoethylphosphonium bromide.

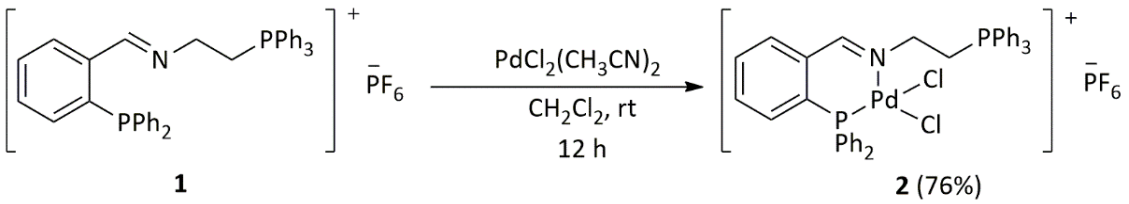
Then a mixture of 2-aminoethyl-triphenylphosphonium bromide (2.9 mmol), 2-diphenylphosphino-benzaldehyde (2.9 mmol), KPF_6 (5,8 mmol) and a pinch of Na_2SO_4 as a dehydrating agent in 50 mL toluene was magnetically stirred under reflux for 24 hours by using a typical Dean-Stark apparatus (**Scheme 20**). The titled compound 2-

diphenylphosphino-1-iminoethyltriphenylphosphonium hexafluorophosphate (**1**), after work up was obtained as a yellow powder in 73% yield.



Scheme 20. Synthesis of Ionophillic Iminophosphine Ligand **1**.

Then a mixture of **1** (2.4 mmol) and $PdCl_2(CH_3CN)_2$ (2.4 mmol) were mixed to a Schlenk tube under argon in 50 mL of dry CH_2Cl_2 and magnetically stirred at room temperature for 12 h (**Scheme 21**). The crude product obtained was filtered through a plug of celite followed by solvent evaporation under argon atmosphere. Washing with several fractions of Et_2O and solvent evaporation, delivered the desired complex **2** in 76% yield.



Scheme 21. Synthesis of Ionophillic Iminophosphine-Pd Complex, **2**.

The formation of the complex was confirmed first by using ^{1}H- and ^{31}P-NMR, followed by HR-ESI mass spectrometry and by comparing the spectroscopic data with the data reported by our research group.[201] In the ^{1}H-NMR spectrum, the characteristic proton singlet resonating at 8.33 ppm was assigned to the imine proton, while the two signals at 4.63 (dt, J = 10.4, 5.0 Hz, 2H), and 3.57 – 3.33 (m, 2H) were assigned to the two methylene group protons, respectively. Other proton signals were assigned to the aromatic protons. In the ^{31}P-NMR, the signals at 22.7, and 31.3 ppm were assigned to the PPh_2 and PPh_3 groups, respectively, while the signals resonating at -154.7, -148.9, -143.0, -137.2, -131.8 ppm were assigned to the PF_6 group. The HRESI-MS in the positive-ion mode ESI mass spectrum showed the molecular ion peak at m/z 756.0596 which was in consistent with the proposed molecular formula $C_{39}H_{34}Cl_2NP_2Pd$ (calcd. 756.0598) (**Figure 22**).

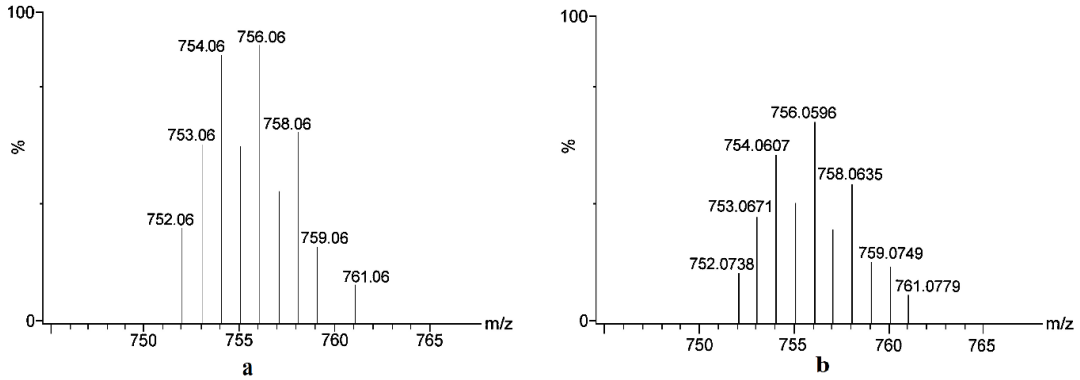


Figure 22. HRESI-MS and Isotopic distribution of **2**: **a**) Experimental, **b**) Simulated.

Finally, the X-ray diffraction data reported by our research group previously revealed that the new ionophillic iminophosphine Pd-complex (**2**) crystallizes in a triclinic *P-1* space group.[201] The solid-state structure of **2** is shown in **Figure 23 (**Adapted from ref. 201).

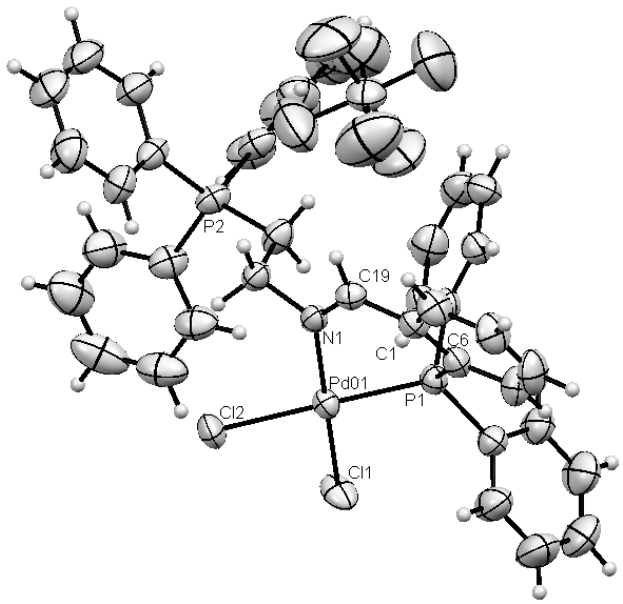


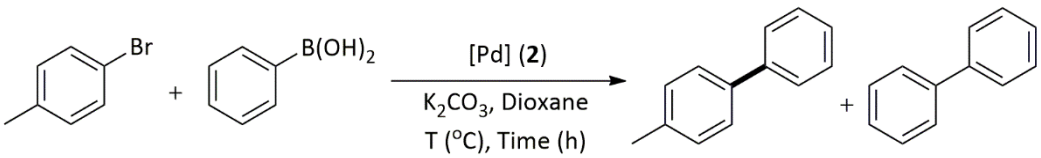
Figure 23. Molecular structure of Ionophillic Iminophosphine-Pd-complex, **2** with the key atoms labelled (thermal ellipsoids drawn at 50% probability) (Adapted from ref. 201).

The complex was then evaluated for its catalytic efficiency in the Suzuki-Miyaura cross-coupling reaction. For this, 4-bromotoluene and phenyl boronic acid were chosen as our model substrates and diphenyl ether was used as internal standard for GC analysis. The investigation for the Suzuki-Miyaura cross-coupling reaction was initially started by

using the reaction conditions optimized in our group for the Suzuki-Miyaura cross-coupling reaction of aryl halides and arylboronic acids using 1 mol% of Pd.

We started our investigation by performing the model reaction at 80 ^{o}C using dioxane as the solvent after 24 hours of magnetic stirring, as a result the model reaction provided a 98% conversion with a cross-coupling yield of 81% (**Table 11**, entry 1). The result motivated us to increase the reaction time under similar conditions, an improved conversion of 98% along with a cross-coupling yield of 94% was obtained (**Table 11**, entry 2). We were very delighted to see that under similar reaction conditions with an increase in reaction time, an excellent yield of the cross-coupling product was obtained after 24 hour of magnetic stirring along with the complete conversion of aryl bromide (**Table 11**, entry 3). Then, we expected that allowing the reaction to stir for 4 hours with a slight increase in the reaction temperature (100 ^{o}C) will also provide better results, however, in contrary to our expectations, both the conversion and the yield of the cross-coupling product decreased (**Table 11**, entry 4).

Table 11: Temperature and time effect on the model SM cross-coupling reaction.



Entry	Temp. (^{o}C)	Time (h)	Conversion (%)[b]	CC Yield (%)[b]	HC Yield (%)[c]
1	80	8	90	81	1
2	80	16	98	94	1
3	80	24	100	96	2
4	100	4	90	80	1
5	100	8	94	85	1
6	100	16	100	96	2

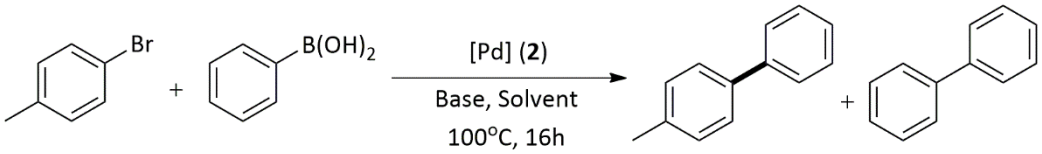
a) Reaction conditions: K_2CO_3 (2 eq.) and Dioxane (4 mL). b) Determined by GC, based on 4-bromotoluene. c) HC biphenyl product yield based on phenyl boronic acid.

When the reaction was allowed for 8 hours of magnetic stirring at 100 ^{o}C, a 94% conversion of the aryl halides with 85% yield of the cross-coupling product was observed (**Table 11**, entry 5). Further increasing the reaction time for 16 hours, presented 100%

conversion of aryl halide with an excellent cross-coupling yield *i.e.*, 96% (**Table 11**, entry 6). A similar result to entries 3 and 6 (**Table 11**) was observed when the temperature of the reaction was increased i.e., 100 ^{o}C (**Table 11**, entry 7). Therefore, we concluded that the model reaction after 16 hours at 100 ^{o}C provides best results.

We then investigated the effect of different solvent and base combinations on the model Suzuki-Miyaura cross-coupling reaction. All the bases evaluated provided a complete conversion and excellent yields of the cross-coupling product (**Table 12**, entries 1-3), however, K_2CO_3 and Cs_2CO_3 showed the best result, (**Table 12**, entry 2).

Table 12: Base and solvent effect on the model SM cross-coupling reaction.



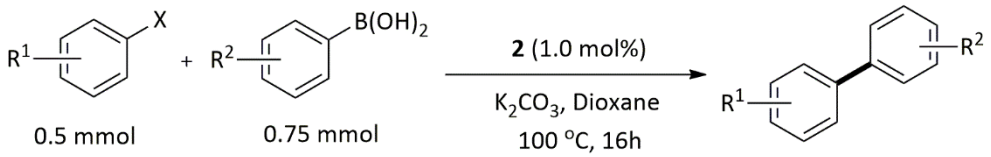
Entry	Base	Solvent	Conversion (%)[b]	CC Yield (%)[b]	HC Yield (%)[c]
1	K_2CO_3	Dioxane	100	96	2
2	Cs_2CO_3	Dioxane	100	97	2
3	KOH	Dioxane	100	92	5
4	KOH	MeOH	99	98	4
5	K_2CO_3	MeOH	99	85	2
6	KOH	Glycerol	67	58	5
7[d]	K_2CO_3	Dioxane	92	89	2

a) Reaction conditions: 0.5 mmol aryl bromide, 0.65 mmol arylboronic acid, 1 mol% Pd, 4 mL Solvent, 1 mmol base, 100 ^{o}C, 16h; b) Determined by GC, based on aryl bromide. c) HC biphenyl product yield based on phenyl boronic acid. d) 0.5 mol% Pd.

The effect of different solvents on the reaction showed that both dioxane and methanol can be used as solvent, as the conversion and yield of the cross-coupling product is high in both cases (**Table 12**, entries 1 and 5). The reaction with glycerol as a solvent provided a low conversion and yield (**Table 12**, entry 6). A low Pd loading (0.5 mol%) was also tested and observed a relative low yield and conversion, (**Table 12**, entry 7). The Suzuki-Miyaura cross-coupling reaction using 1 mol% Pd loading, K_2CO_3 as

base, dioxane as solvent at 100 °C for overnight magnetic stirring was therefore concluded as the optimized conditions to explore the scope of the reaction.

Table 13: Substrate scope under optimized reaction conditions.



Entry	R^1	X	R^2	Conv. (%)[b]	CC Yield (%)[b]	HC Yield (%)[b]
1	4-Me	Br	H	100	96 (95)	2
2	4-Me	I	H	100	96	2
3	4-Me	Cl	H	0	0	8
4	4-OMe	Br	H	100	91	2
5	4-Ac	Br	H	100	98	2
6	4-Me	Br	2-Me	100	77	1
7	4-Me	Br	4-Ac	100	96	2
8	4-Me	Br	4-OMe	100	94	2

a) Reaction conditions: 0.5 mmol aryl bromide, 0.65 mmol arylboronic acid, 1 mol% **2**, 4 mL Dioxane, 1 mmol K_2CO_3, 100 °C, 16h; b) Determined by GC (Isolated yield), based on aryl bromide. c) HC biphenyl product yield based on phenyl boronic acid.

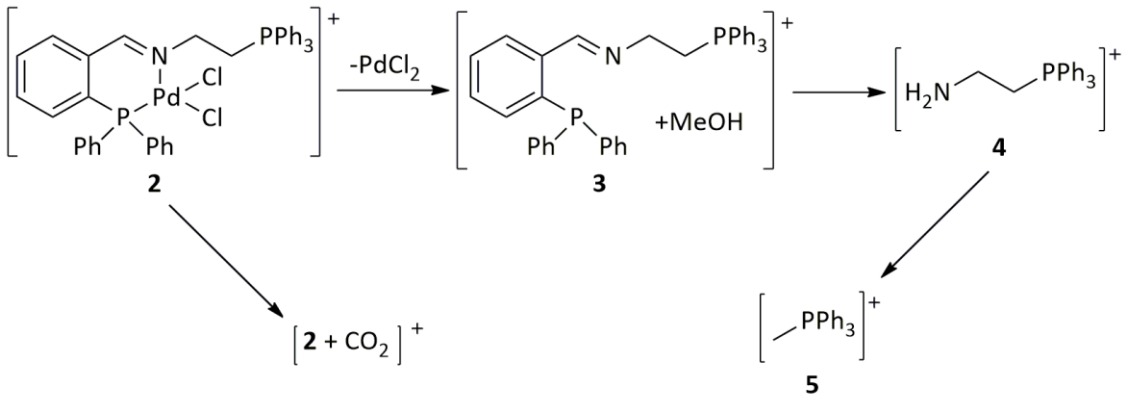
By employing different haloarenes and arylboronic acids with varying electronic and steric characteristics, we observed that both electron rich and poor bromoarenes were well tolerated, providing the excellent conversions and yields of the corresponding cross-coupling products (**Table 13**, entries 2, 3, 7, 8). The reaction was however sensitive towards the steric effects (**Table 13**, entries 6). Unfortunately, the catalyst was inactive for the cross-coupling reaction between aryl chlorides and aryl boronic acids (**Table 13**, entries 3). In conclusion, the new ionophillic Pd-catalyst (**2**) is an efficient catalyst for the Suzuki-Miyaura cross-coupling of aryl iodides and bromides with aryl boronic acids and gives excellent yields of the cross coupling products however, the catalyst was

inactive in catalyzing the reaction when aryl chlorides were as aryl halide equivalents of aryl iodides and bromides.

Finally, we have attempted to obtain some insights about the mechanism of the Suzuki-Miyaura cross-coupling reaction through detection of the key intermediates involved in the catalytic cycle. The catalytic reactions performed for the positive-ion ESI based experiments were performed using an oven dried Schlenk flask evacuated and backfilled with argon and charged with **2** (5 mg, 2 mol%) and 0.25 mmol scale reagents in 3 mL methanol. After 2 hours of magnetic stirring at room temperature or 50 ^{o}C, the reaction mixture was introduced into the mass spectrometer directly by a syringe filled with argon at a rate of 30 mL.min^{-1} initially, which was reduced to 5.0 mL.min^{-1} soon after characteristic ionic species were acquired by the mass spectrometer.

First we investigated the behavior of ionophillic Pd-catalyst (**2**) in methanol. A solution mixture of 2 mol% ionophillic Pd-complex (**2)** in 2 mL methanol stirred at room temperature for 1 hour was injected in the ESI mass spectrometer. **Figure 24** presents the ESI mass spectrum of **2** in methanol at room temperature that displays several singly charged ionic species. Structural assignments were therefore established on the basis of exact mass measurements and similarities in the characteristic isotopic distribution patterns for the different ionic species. For simplification purposes, the m/z value without decimal point values for the ionic species has been adopted here. The proposed hydrolytic pathway of the Pd-complex **2** in methanol is shown in **Scheme 22**.

The species with m/z 756 corresponds to the precursor ionophillic Pd-complex, **2** used here as a probe for ESI detection of ionic species. An adduct species of the **2** with CO_2 ([**2** + CO_2]$^{+}$) was assigned for the m/z 800. The methanolic solution of **2** also contains species with m/z 306 which corresponds to the 2-aminoethyl-triphenylphosphonium ion (**4**) which undergo further cleavage to the species with m/z 277 that corresponds to the methyl-triphenylphosphonium ion (**5**). The species with m/z 610 is consistent with the mass of a methanol adduct of ionophillic ligand (**3**) indicating leaching of $PdCl_2$ from **2** in methanol.



Scheme 22. Proposed hydrolytic pathway of **2** in methanol at room temperature.

Then, mixing **2** (2 mol%) with 4-bromotoluene (0.25 mmol) in 3 mL methanol at 50ºC acquired after 2h showed three key reaction intermediates in the ESI mass spectrum. **2** and $[\mathbf{2} + CO_2]^+$ as observed for the mixing of **2** and methanol at room temperature, including a species at m/z 321 corresponding to **7**. The mass spectra acquired after 2 hours of mixing **2** and K_2CO_3 in methanol afforded a complex mixture of products and showed species related to **7**, and no other species related to the Pd-complex or ionophillic ligand were observed.

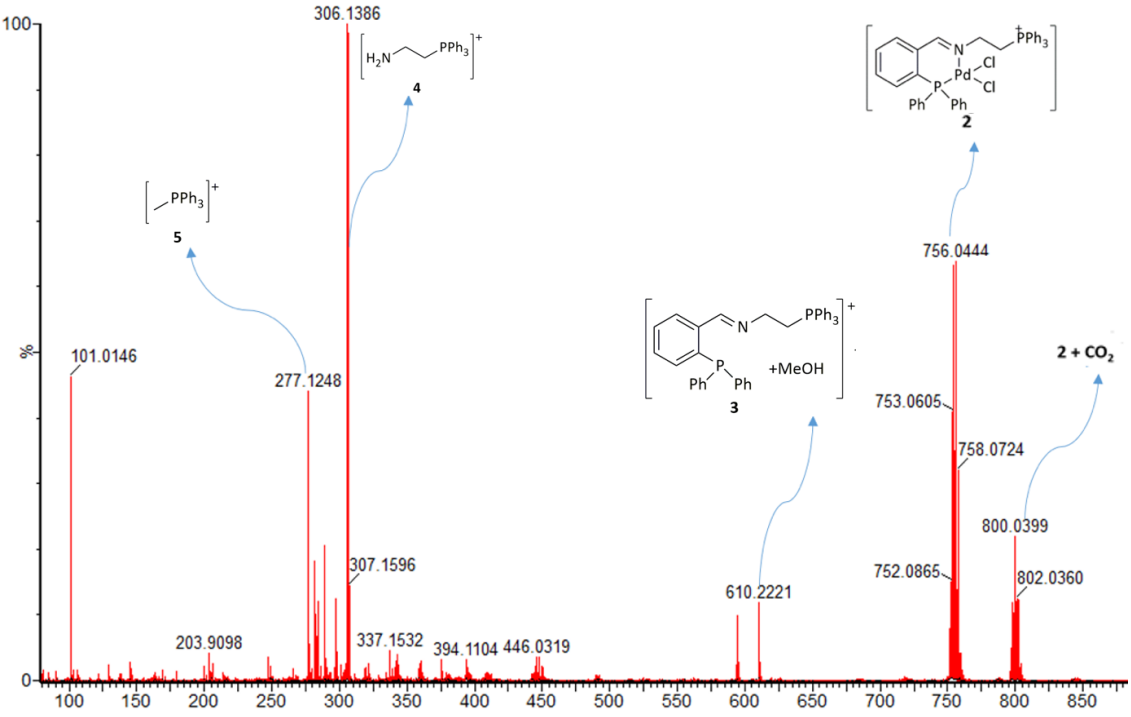


Figure 24. Positive-ion ESI mass spectrum of **2** in methanol acquired after 2h at room temperature.

Figure 25 shows the ESI mass spectrum acquired after 2h reaction of **2** with phenyl boronic acid in the presence of base in methanol at 50°C. We were delighted to see an unprecedented key intermediate (**6**), a Pd(0) specie analogous to m/z 684. The characteristic m/z ratios and isotopic distribution patterns were in complete consistence with the proposed structure as shown in **Figure 26**. In addition to this, the positive ESI mass spectrum also showed two additional reaction intermediates containing ionophillic backbone at m/z 699 and 760. The species with m/z 699 was in consistent to an adduct of [**1** + **B_3O_3HK**], while the species with m/z 760 corresponds to an *ortho*-metalation intermediate, **8**.

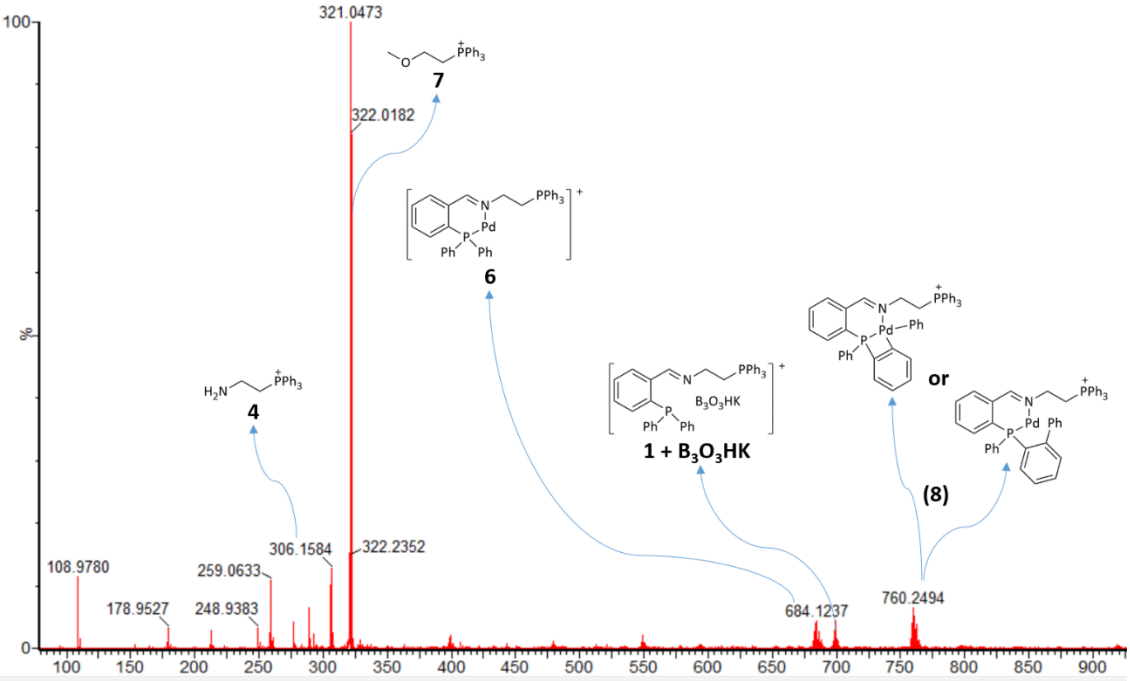
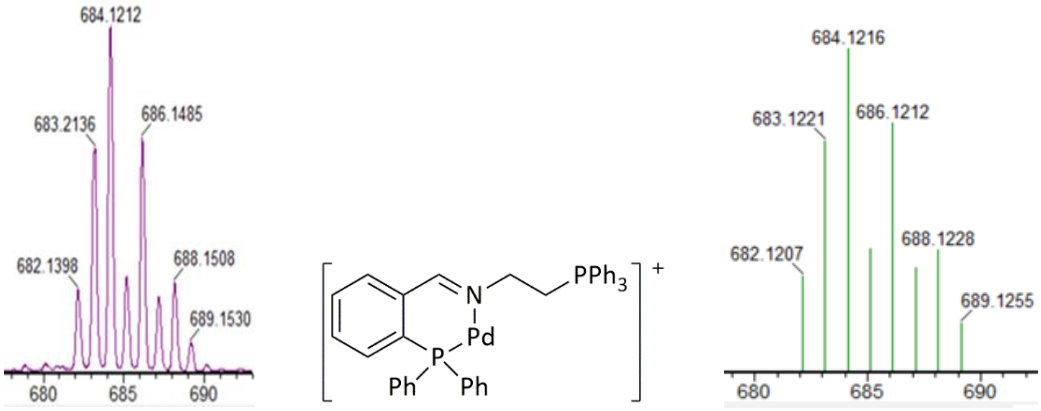


Figure 25. Positive-ion ESI mass spectrum of **2** and phenylboronic acid in methanol acquired after 2h at 50°C.

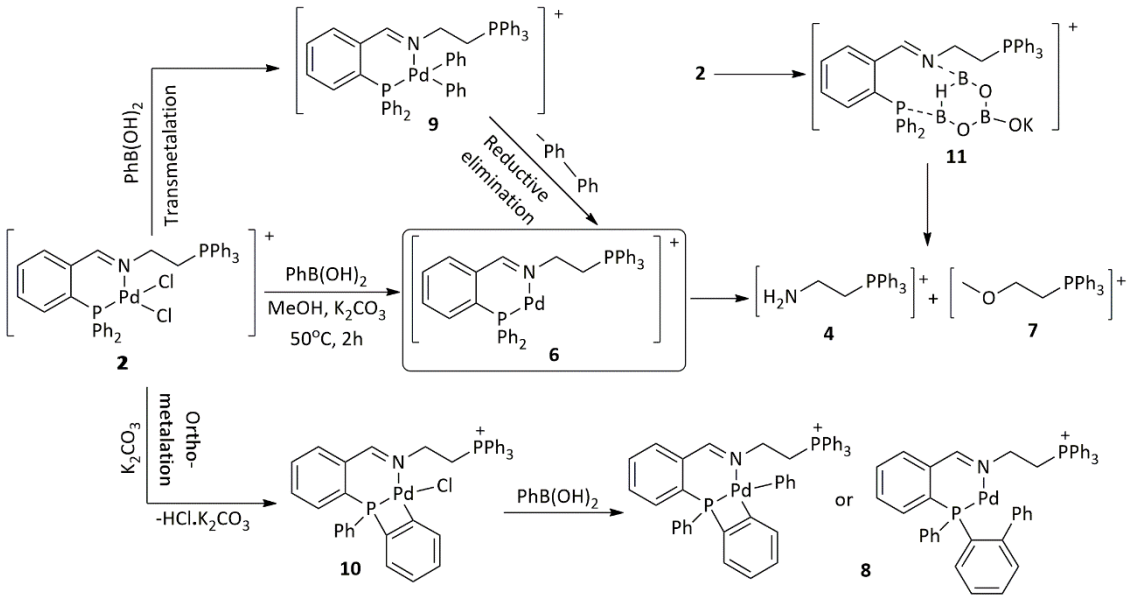
The following pathway has been thus proposed for the formation of Pd(0) specie (**6**) and other related species during the reaction based on the positive-ion ESI mass spectrum, **Scheme 24**. We believe that transmetalation with phenylboronic acid in the presence of base initially forms a very reactive intermediate **9**, which might undergo a fast reductive elimination to the stable Pd(0) species (**6**). In addition, the species with m/z 760 is proposed to be form *via* an *ortho*-metalation pathway. Two different structures have been proposed for the formation of the species with m/z 760 *i.e.*, **8**. We expect that

the Pd-complex **2** first forms a very unstable reactive intermediate **10**, which then undergoes transmetalation in the presence of phenylboronic acid to **8**.



a **6** **b**

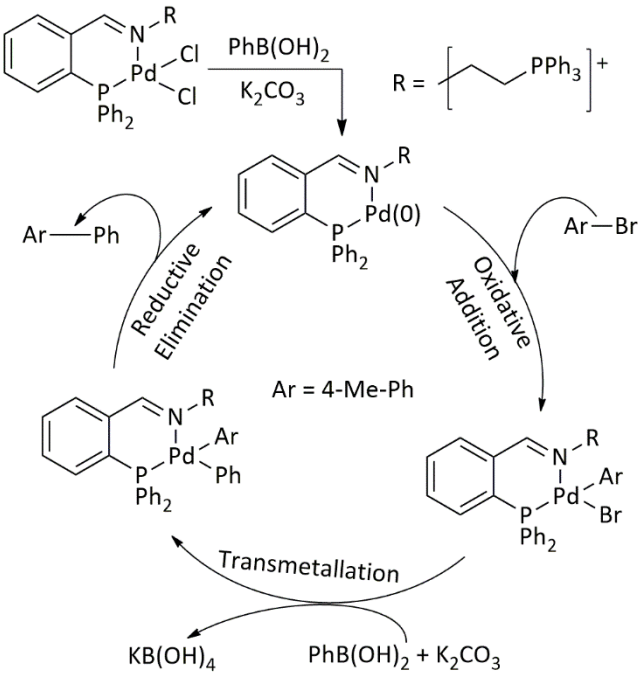
Figure 26. Positive-ion ESI mass spectrum of **6**, **a**) Experimental and **b**) Simulated.



Scheme 23. Proposed pathways for the formation of stable Pd(0) (**6**) intermediate.

Based on these observations, we propose the following catalytic cycle for the ionophillic imino-phopshine Pd-catalyzed Suzuki-Miyaura cross-coupling of aryl halides and aryl boronic acids (**Scheme 24**). According to the proposed mechanism, the Pd-complex **2** (Pd-II) in the presence of K_2CO_3 and phenylboronic acid first undergoes reduction into the active Pd(0) specie, followed by oxidative addition of aryl halide. The Pd(II)-complex after oxidative addition then undergoes transmetalation in the presence

of phenylboronic acid. Finally, the active Pd(0) specie is regenerated through reductive elimination of the desired cross-coupling product and re-enters into the second catalytic cycle.



Scheme 24. Proposed catalytic cycle for the Suzuki-Miyaura cross-coupling reaction.

4.3 Experimental

4.3.1 Materials and Methods

All reactions were carried out under an argon atmosphere in oven-dried resealable Schlenk tubes. All the chemicals were purchased from commercial sources and used without further purification. ^{1}H-, ^{13}C-, and ^{31}P-NMR spectra were recorded on a Varian XL300 MHz and 400 MHz spectrometer. Chemical shifts are reported in ppm downfield to TMS. Melting points were determined by using the Quimis apparatus. Gas chromatography analyses were performed on a HP-5890A fitted with a FID detector and a 30 m long DB-17 column. ESI mass spectra were obtained in both negative and positive ion mode on a Micromass Q-TOF instrument with a 7000 mass resolving power in the TOF mass analyzer.

Preparation of Ionophilic Imino-phosphine-Pd-Complex (**3**)

Synthesis of 2-aminoethyltriphenylphosphonium bromide (1)

A Schlenk flask equipped with a magnetic stirrer was charged with 16 mmols of triphenylphosphine (3.3 g) and 16 mmols of 2-bromoethylamine bromohidrated (4.2 g). This reaction mixture was refluxed in acetonitrile for 48 h. After cooling to room temperature, the white precipitate formed was filtered, dissolved in water and treated with saturated Na_2CO_3 solution until pH = 11. The resulting solution was washed with $CHCl_3$ (3 x 50 mL) and the organic phase was dry with anhydrous $MgSO_4$ and filtered. The solvent was evaporated in a vacuum and the 2-aminoethyltriphenylphosphonium bromide was obtained as a white solid in 76 % yield (4.7 g).

2-aminoethyltriphenylphosphonium bromide

Melting point: 222-228 °C; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ (ppm) 2.1 (s, 2H), 3.1 (m, 2H, dt, 2H, *J* = 7.0 e 13.7 Hz), 3.9 (dt, 2H, *J* = 7.0 e 13.7 Hz), 7.2-7.5 (m, 3H), 7.4-8.0 (m, 12H); **^{13}C-NMR** (APT) (75 MHz, $CDCl_3$): δ (ppm) 26.1, 26.8, 36.7, 118.5, 119.6, 128.6, 128.7, 128.8, 130.3, 130.5, 133.7, 133.9, 134.9; **^{31}P-NMR** (121 MHz, $CDCl_3$, H_3PO_4, 25 °C): δ (ppm) 23.7

Synthesis of 2-diphenylphosphino-1-iminoethyltriphenylphosphonium hexafluoro-phosphate ligand (1)

A mixture of 2-aminoethyltriphenylphosphonium bromide (2.9 mmol, 1.1 g), 2-diphenylphosphinobenzaldehyde (2.9 mmol, 842 mg), KPF_6 (5,8 mmol; 1,1 g) and a small amount of Na_2SO_4 in toluene (50 mL) was stirred under reflux for 24 h by using a typical Dean-Stark apparatus. After the reaction was cool to room temperature, the orange precipitate formed was filtered and washed with Et_2O several times. The crude solid product was then dried under vacuum to obtain 2-diphenylphos-phino-1-iminoethyltriphenylphosphonium hexafluorophosphate (**1**) as a yellow solid in 73 % yield (1.7 g).

2-diphenylphosphino-1-iminoethyltriphenylphosphonium hexafluorophosphate (1)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 8.62 (s, 1H), 7.95 (dd, *J* = 7.8, 4.1 Hz, 1H), 7.86 – 7.80 (m, 3H), 7.73 (td, *J* = 7.8, 3.6 Hz, 7H), 7.63 (m, 5H), 7.52 (dd, *J* = 12.0, 7.8

Hz, 7H), 7.44 (d, *J* = 2.7 Hz, 5H), 6.80 (dd, *J* = 11.0, 7.6 Hz, 1H), 4.64 (dt, *J* = 10.5, 4.7 Hz, 2H), 3.38 – 3.17 (m, 2H); **^{31}P-NMR** (121 MHz, $CDCl_3$, H_3PO_4): δ (ppm) -156.0, -150.1, -144.2, -138.4, -132.5, 14.4, 24.7; **ESI-MS (+)** : Anal. Calcd. for $C_{39}H_{34}NP_2$: 578.2166. Found: 578.2179 [M^+].

Synthesis of Ionophilic Iminophosphine-Pd-Complex (2)

A mixture of **1** (2.4 mmol, 1.7 g) and $PdCl_2(CH_3CN)_2$ (2.4 mmol, 0.7 g) were added to a resealable Schlenk flask evacuated and back-filled with argon. Then 50 mL of dry CH_2Cl_2 was added and magnetically stirred at room temperature for 12 h. The crude product was filtered and washed with Et_2O several times. The desired complex **2** was obtained as a yellow pale solid in 76 % yield (1.6 g).

Ionophilic Iminophosphine-Pd-Complex (2)

^{1}H-NMR (400 MHz, CD_3CN): δ (ppm) 8.33 (s, 1H), 7.94 – 7.84 (m, 4H), 7.78 – 7.64 (m, 17H), 7.57 – 7.46 (m, 7H), 7.08 (dd, *J* = 10.7, 7.6 Hz, 1H), 4.63 (dt, *J* = 10.4, 5.0 Hz, 2H), 3.57 – 3.33 (m, 2H); **^{31}P-NMR** (121 MHz, CD_3CN, H_3PO_4): δ(ppm) -154.7, -148.9, -143.0, -137.2, -131.8, 22.7, 31.3; **ESI-MS (+)** [$PdCl_2$(P^N)$^+$]: Anal. Calcd. for $C_{39}H_{34}Cl_2NP_2Pd$: 756.0598. Found: 756.0596 [M^+].

4.3.2 General procedure for the Suzuki-Miyaura cross-coupling reaction

An oven-dried resealable Schlenk flask was evacuated and back-filled with argon and charged with ionophillic imino-phosphine Pd-complex **2** (1 mol%), followed by addition of aryl bromide (0.5 mmol), arylboronic acid (0.75 mmol), base (1 mmol, 56 mg), and solvent (4 mL). 20 uL diphenyl ether was used as an internal as an internal standard. The reaction mixture was allowed to magnetically stir at 100°C for specified time. After, the solution mixture was cooled to room temperature, analyzed by GC to calculate conversions and yields. For purification, the organic phase was filtered, treated with aqueous 10% KOH solution and brine solution and extracted by dichloromethane. The organic phase obtained after extraction was then dried over $MgSO_4$ and concentrated under vacuum. The pure product was obtained by performing flash silica gel flash chromatography eluting 5% ethyl acetate and hexanes.

4.3.3 General procedure for the ESI based experiments

All the mass spectra experiments were performed on a Micromass Q-ToF micro hybrid Quadrupole/Time-of-Flight mass spectrometer in positive-ion mode using a pneumatically assisted electrospray ionisation. Conditions used; Capillary voltage: 3500 V. Cone voltage: 35 V. Extraction voltage: 3.0 V. Source temperature: 80 ^{o}C. Desolvation temperature: 80 ^{o}C. Cone gas flow: 50 L h^{-1}. Desolvation gas flow: 500 L h^{-1}. For each experiment, Pd-complex (**2**) (5 mg, 2 mol%) and aryl halide (0.25 mmol), aryl boronic acid (0.3 mmol), K_2CO_3 (0.5 mmol) were added in an oven dried Schlenk flask evacuated and backfilled with argon, in 3 mL methanol. After 2 hours of magnetic stirring at room temperature or 50^{o}C, the reaction mixture was introduced into the mass spectrometer directly by a syringe filled with argon at a rate of 30 mL min^{-1} initially, which was reduced to 5.0 mL min^{-1} as soon as appropriate peaks were detected by the ESI spectrometer.

4.4 Conclusions

In conclusion, the current study describes synthesis and characterization of a new ionophillic imino-phosphine-Pd-complex (**2**) and its catalytic efficiency in the Suzuki-Miyaura cross-coupling reaction of aryl halides with aryl boronic acids. The complex demonstrates an excellent catalytic activity for the reaction and provides excellent yields of the cross coupling products. Since, the beneficial aspect of installing charged tags on the catalyst displays an extraordinary high level of sensitivity towards the electrospray ionization mass spectrometry (ESI-MS). Therefore, the complex was further utilized to study the mechanism of the Suzuki cross-coupling reaction. We were able to fish out and characterize several reactive intermediates based on exact mass measurements and characteristic isotopic distribution patterns, including a stable Pd(0) specie for the first time using ESI mass spectrometry. A direct or transmetalation/reductive elimination n pathway has thus been proposed for the formation of the stable Pd(0) species based on our ESI based experiments.

Conclusion and Future Prospective

In conclusion, we have demonstrated the synthesis and characterization of new N-based ligands and their potential as effective ligands in Suzuki-Miyaura cross-coupling reaction. The synthesis of the new pyrazolyl analogues and the hybrid imidazolyl-pyrazolyl analogue were thus synthesize by following an Ullmann coupling protocol as a result overall good yields of the products were obtained. In addition, a hybrid selanyl-pyrazolyl analogue was also synthesized 58% yields using a *C-H* activation protocol. Some of the ligands were found very active among the synthesized ligands in the Pd-catalyzed Suzuki-Miyaura cross-coupling reaction. Thus, a catalytic system based on $Pd(OAc)_2$/pyrazolyl ligands catalyzes the Suzuki-Miyaura cross-coupling reaction of aryl halides and aryl boronic acids efficiently and delivered moderate to excellent yields of the cross-coupling products. We further intend to explore the photophysical properties, biological activity studies, applications in other challenging organic transformations, and coordination chemistry of these compounds, including the isolation of palladium complexes and its structural correlation with catalytic activities as a sequence of this work. We also have extended the work of one of our senior lab member who demonstrated that glycerol is an efficient reaction medium for the Pd-catalyzed Suzuki-Miyaura cross-coupling reactions of aryl bromides and aryl boronic acids and explored the scope of glycerol by synthesizing a variety of substituted biaryls of different electronic nature. Since, the recycling studies were not well studied, therefore, we attempted to improve the glycerol catalytic media recycles in our study. Thus, we demonstrated successfully that a 50:50 solution mixture of glycerol and methanol can effectively tolerate the recycling of the catalytic media up to 7 cycles, however, a sharp decreased in the yield of the cross-coupling product in the 8^{th} cycle was observed due to formation of solid inorganic salts which prevent the reaction mixture from a smooth magnetic stirring. Further studies on the development of novel ligands, catalytic precursors and binders for the use of glycerol as a green solvent for cross coupling reactions are the future prospects of our lab. Finally, the Suzuki-Miyaura cross-coupling reaction of aryl halides and aryl boronic acids using a new ionophillic iminophosphine-Pd-complex already synthesized by our group has been described. In addition, by taking advantage of the ionophillic charge on the Pd-complex, we have demonstrated some insights about the mechanism of the Suzuki-Miyaura cross-coupling reaction through detection of the key intermediates formed during the reaction via ESI mass

spectrometery. We fished out and characterized several reactive intermediates based on exact mass measurements and characteristic isotopic distribution patterns, including a stable Pd(0) specie for the first time using ESI mass spectrometry. Based on our ESI mass spectrometry studies, we have proposed a direct or transmetalation/reductive elimination pathway for the formation of the stable Pd(0) species. We further intend to explore the applications of this ionophillic charged Pd-catalyst in other catalytic reactions and mechanistic studies using ESI or NMR.

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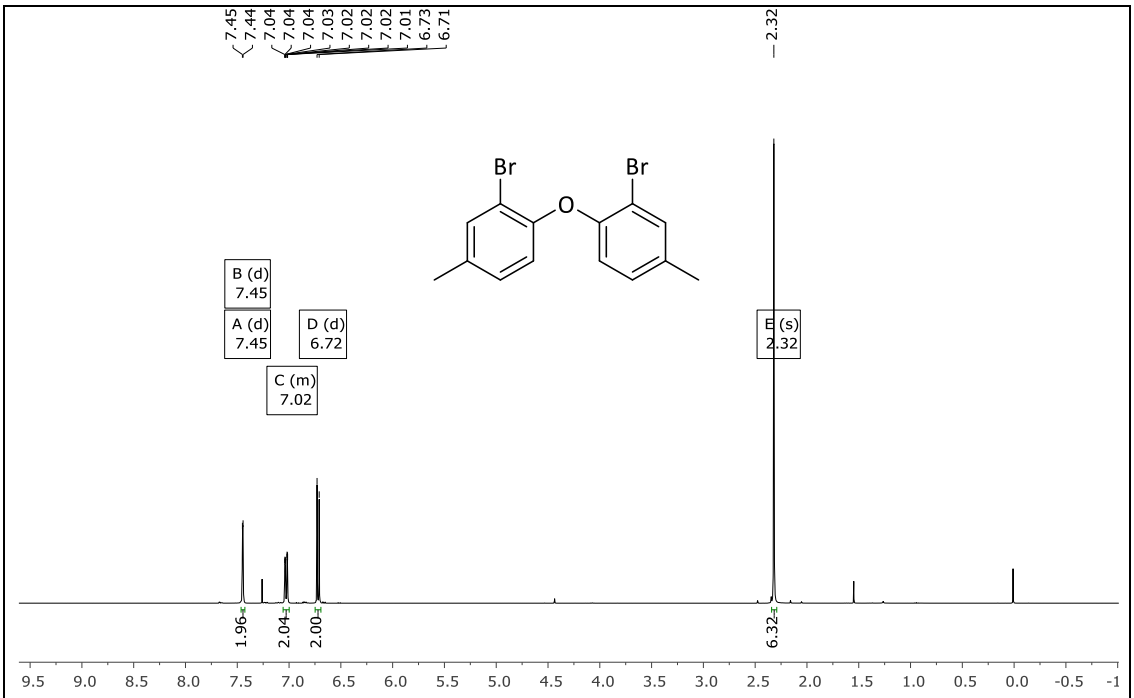
List of Publications

1. **Hussain, Z.,** Schwalm, C. S., Dias, R. F. C., Rambo, R. S., Stieler, R., and Monteiro, A. L., (**2019)**. "Synthesis of mono- and bis-pyrazoles bearing flexible *p*-tolyl ether and rigid xanthene backbones and their potential as ligands in the *Pd*-catalysed Suzuki-Miyaura cross-coupling reaction." ***Catalysts***, 9: 718.
2. **Hussain, Z.,** Schwalm, C. S., Dias, Rambo, R. S., Stieler, R., and Monteiro, A. L., Poster presentation at "Pd-catalysed Suzuki cross-coupling of aryl halides and aryl boronic acids by using new phenoxypyrazole-based *N^O^N*-type bis-pyrazole ligands." ***American Chemical Society (ACS) Spring 2019 National Meeting & Expo***", held at Orlando, Florida, United States, in 2019.
3. **Hussain, Z.,** Schwalm, C. S., Dias, Rambo, R. S., Stieler, R., and Monteiro, A. L., Poster presentation at "Synthesis of *N,O,N* bis-pyrazole ligands through Ullmann Coupling." ***12th Brazilian Meeting on Organic Synthesis***", held at Salvador, Bahia, Brazil, in 2018.

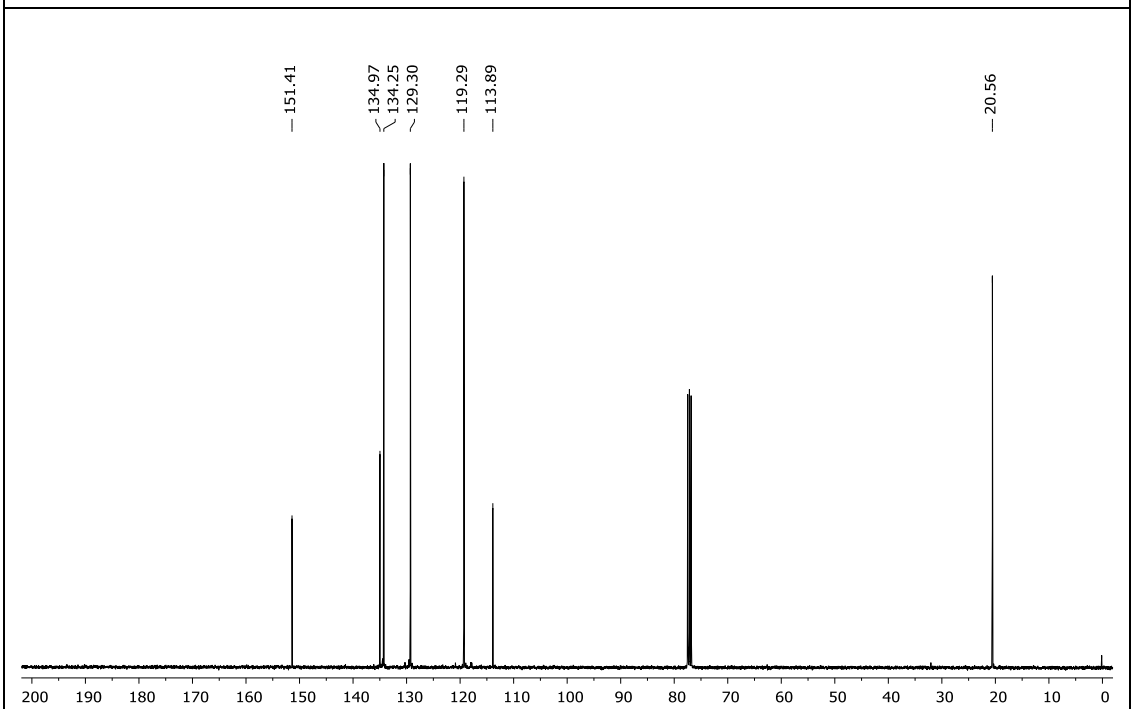
Annexes

[1]H- and [13]C-NMR Spectra for Synthetic Precursors and Pyrazolyl Ligands

1.1 [1]H- and [13]C-NMR Spectra of 1

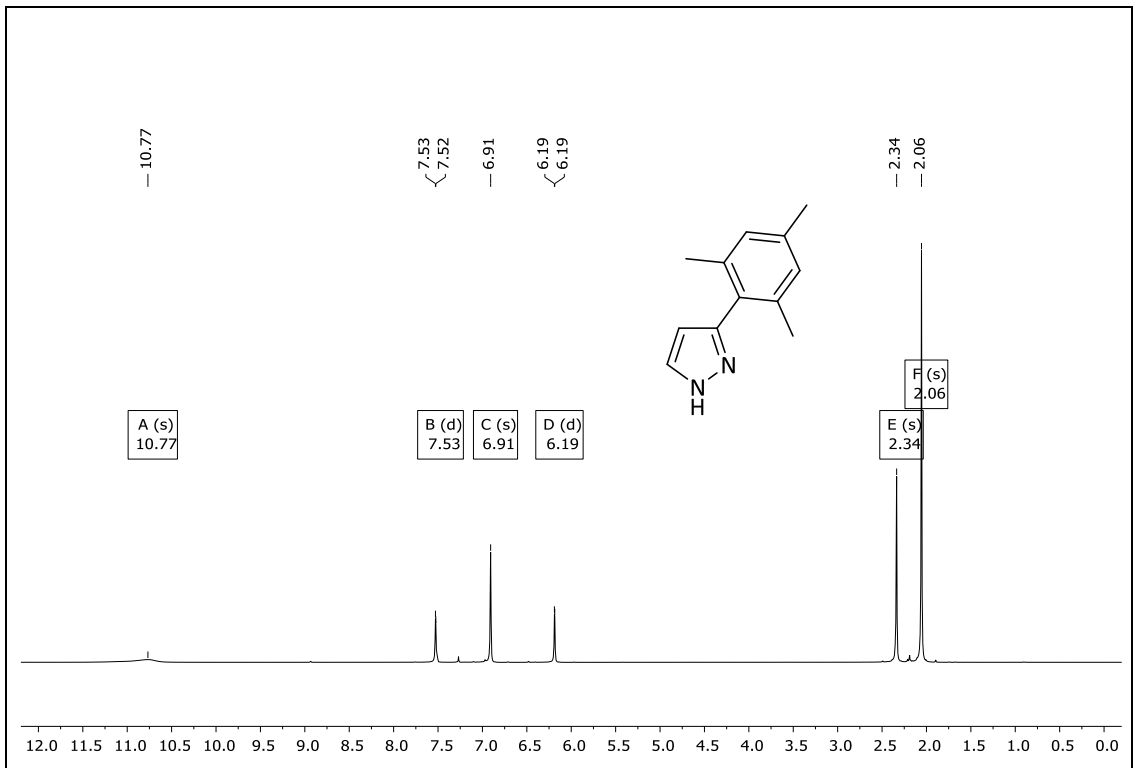


[1]H-NMR Spectrum of **1** ($CDCl_3$, 400 MHz)

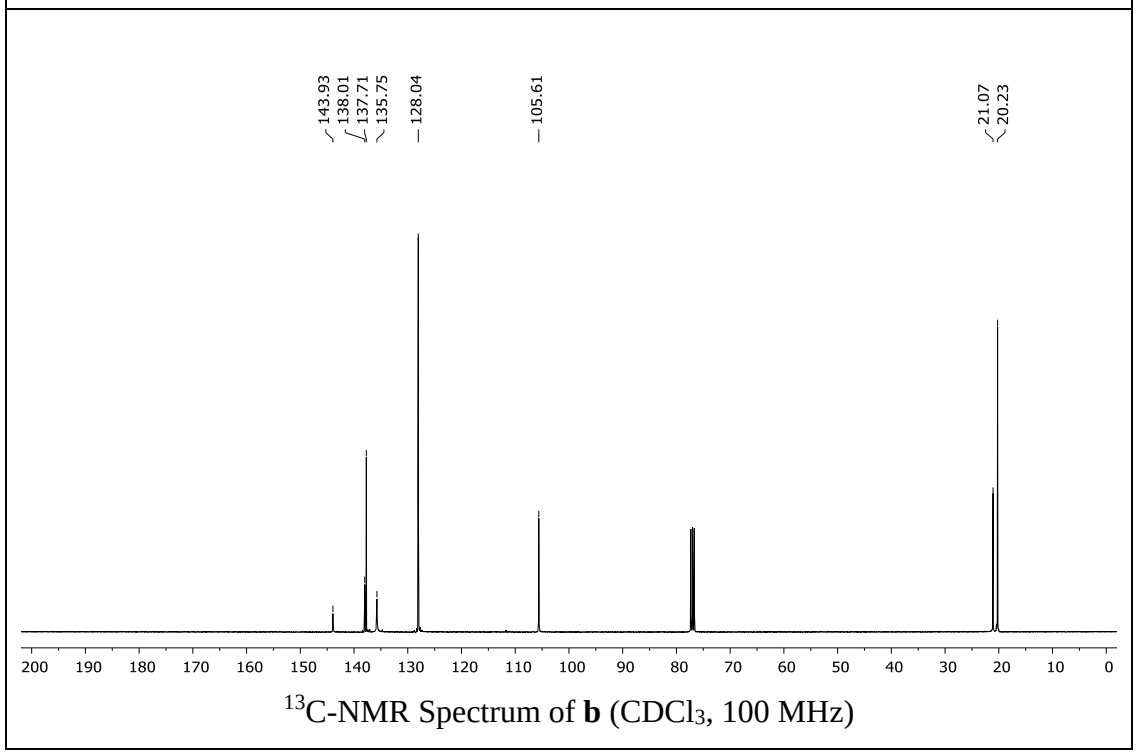


[13]C-NMR Spectrum of **1** ($CDCl_3$, 100 MHz)

1.2 ^{1}H- and ^{13}C-NMR Spectra of 3-Mesityl-1H-pyrazole (b)

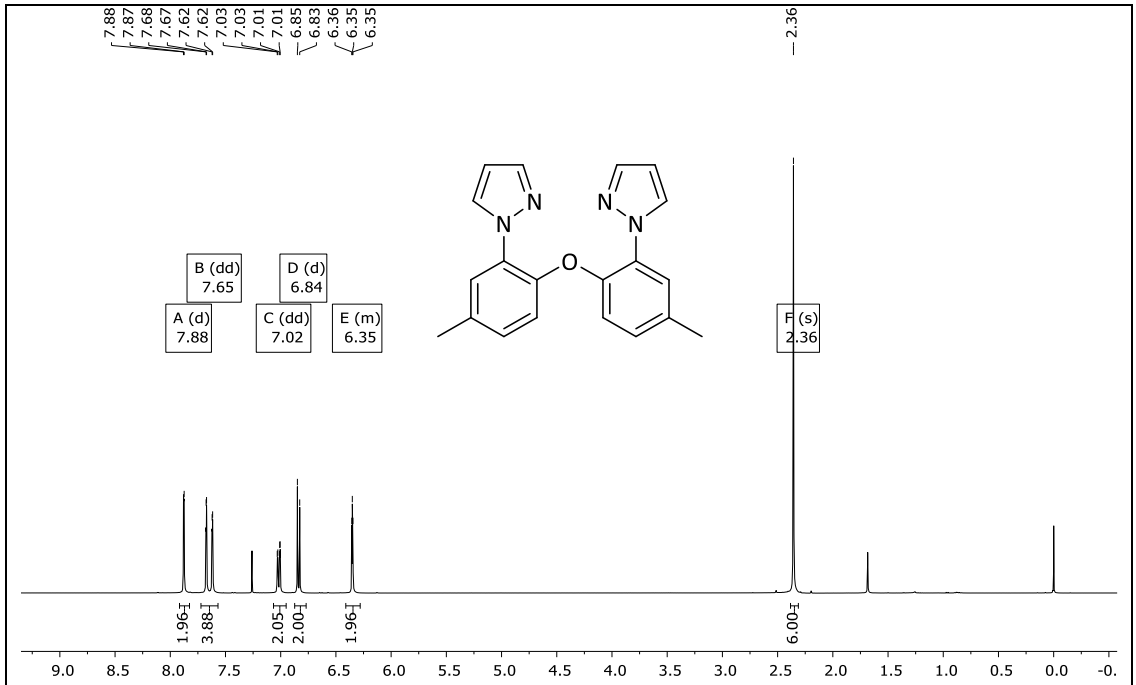


^{1}H-NMR Spectrum of **b** ($CDCl_3$, 400 MHz)

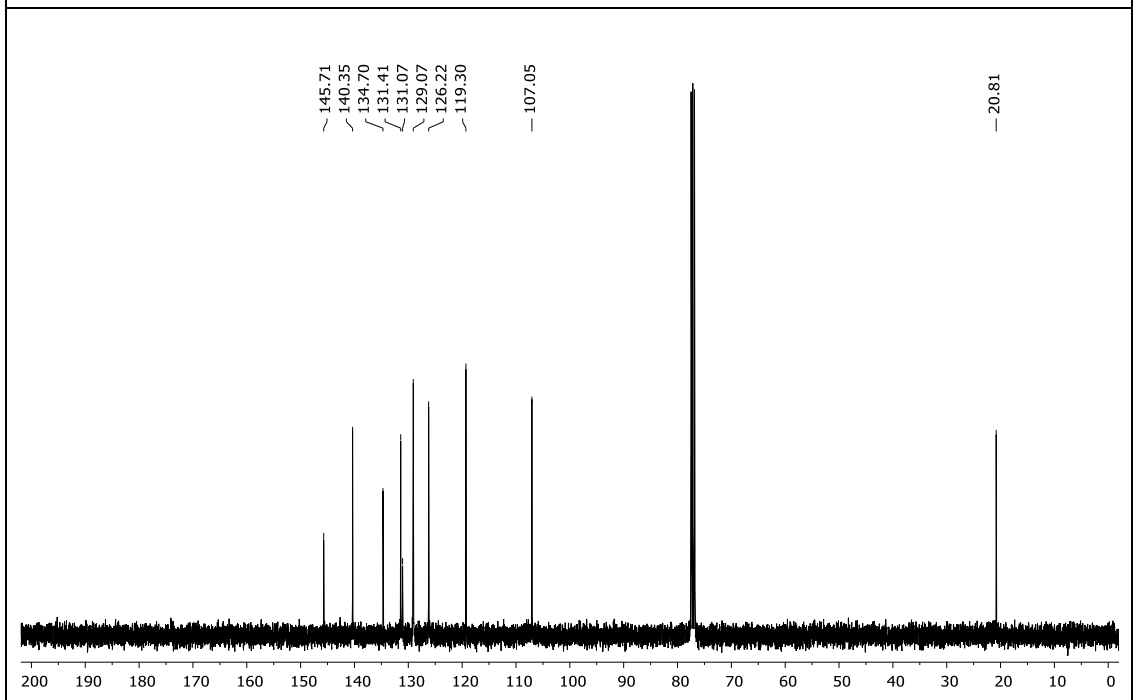


^{13}C-NMR Spectrum of **b** ($CDCl_3$, 100 MHz)

1.3 ^{1}H- and ^{13}C-NMR Spectra of 1a

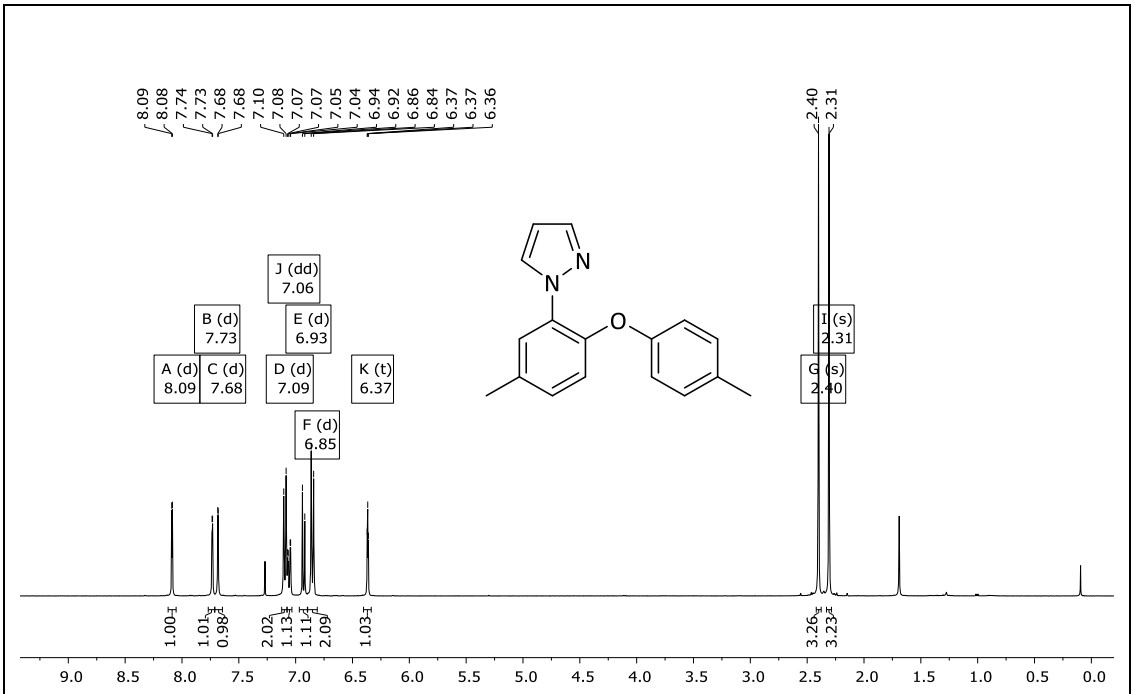


^{1}H-NMR Spectrum of **1a** ($CDCl_3$, 400 MHz)

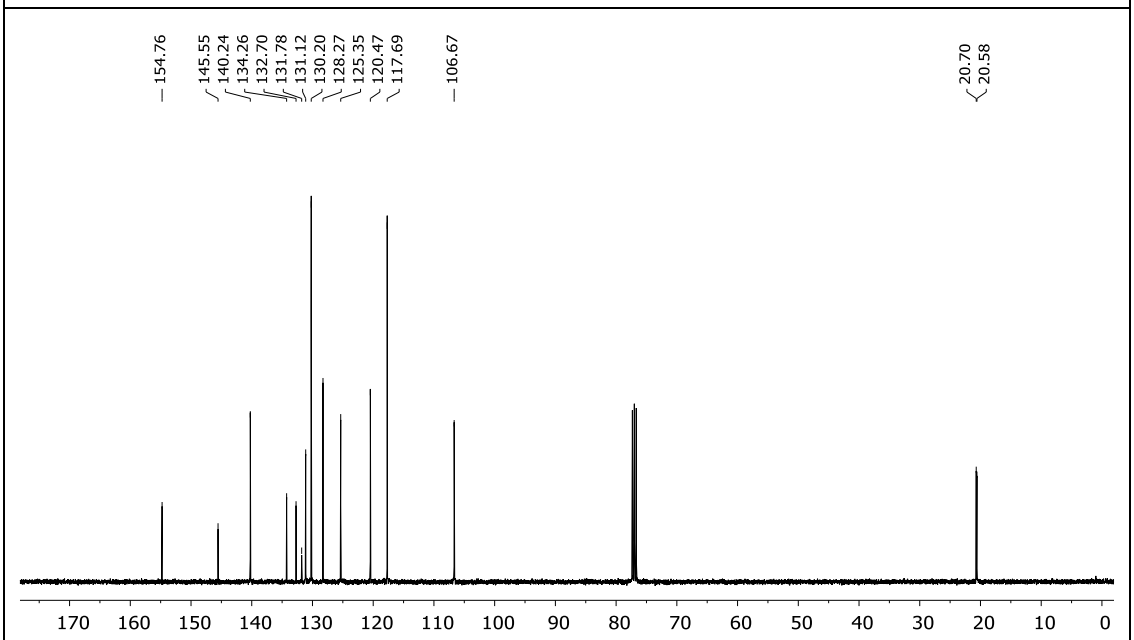


^{13}C-NMR Spectrum of **1a** ($CDCl_3$, 100 MHz)

1.4 ^{1}H- and ^{13}C-NMR Spectra of 1a`

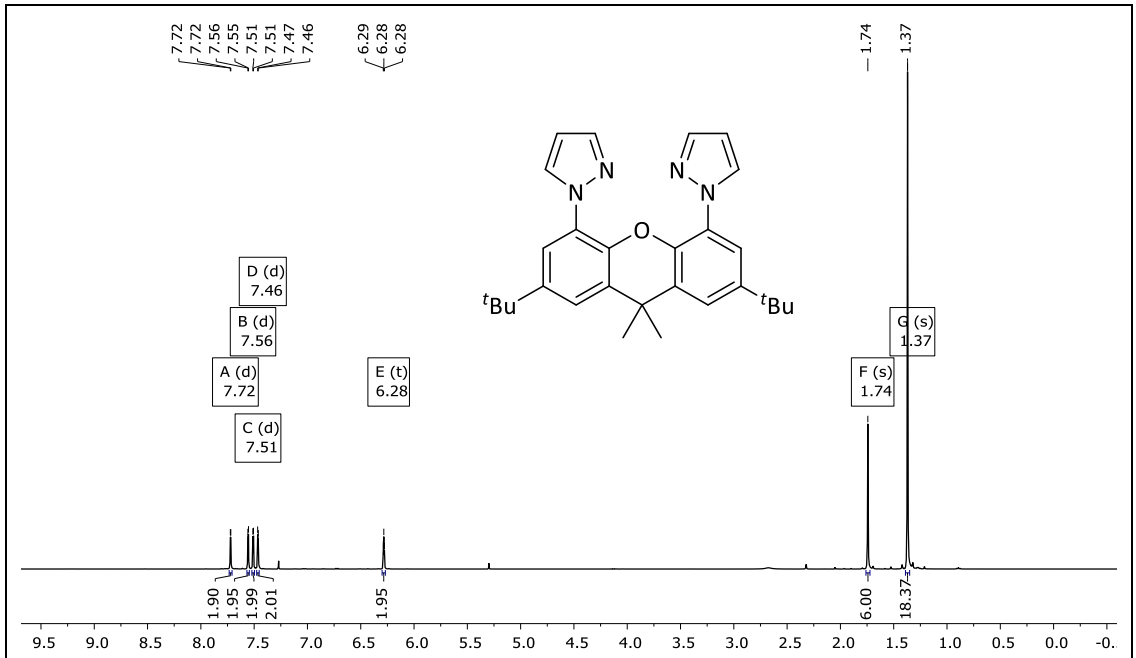


^{1}H-NMR Spectrum of **1a`** ($CDCl_3$, 400 MHz)

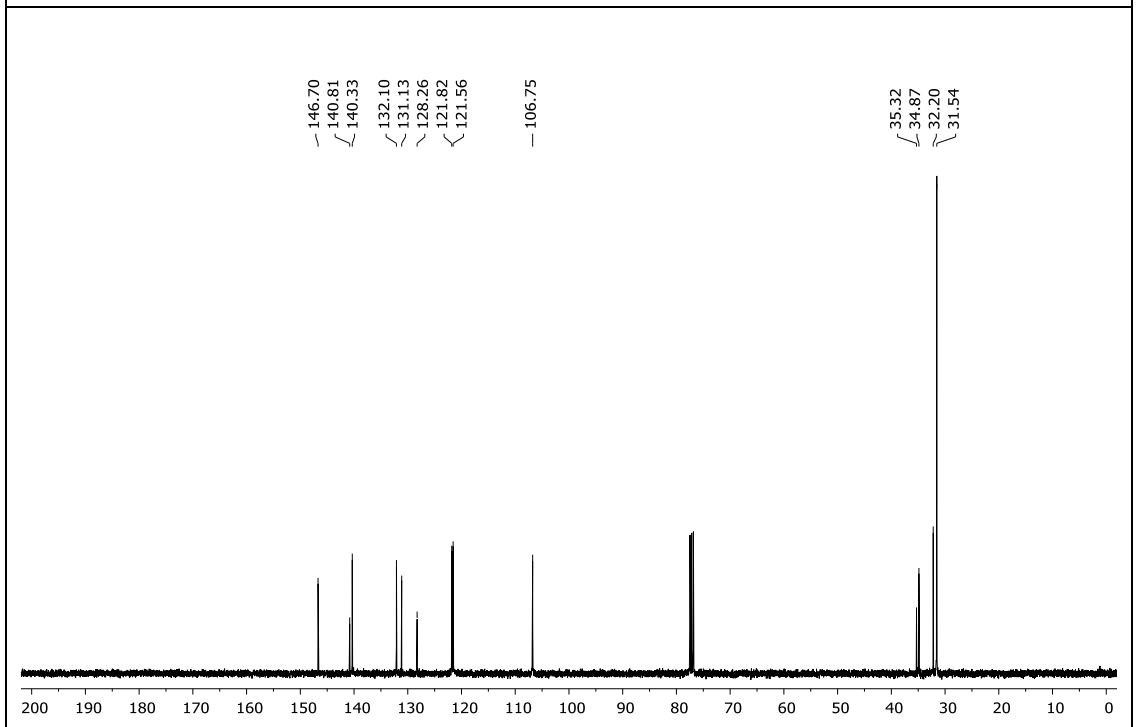


^{13}C-NMR Spectrum of **1a`** ($CDCl_3$, 100 MHz)

1.5 ^{1}H- and ^{13}C-NMR Spectra of 2a

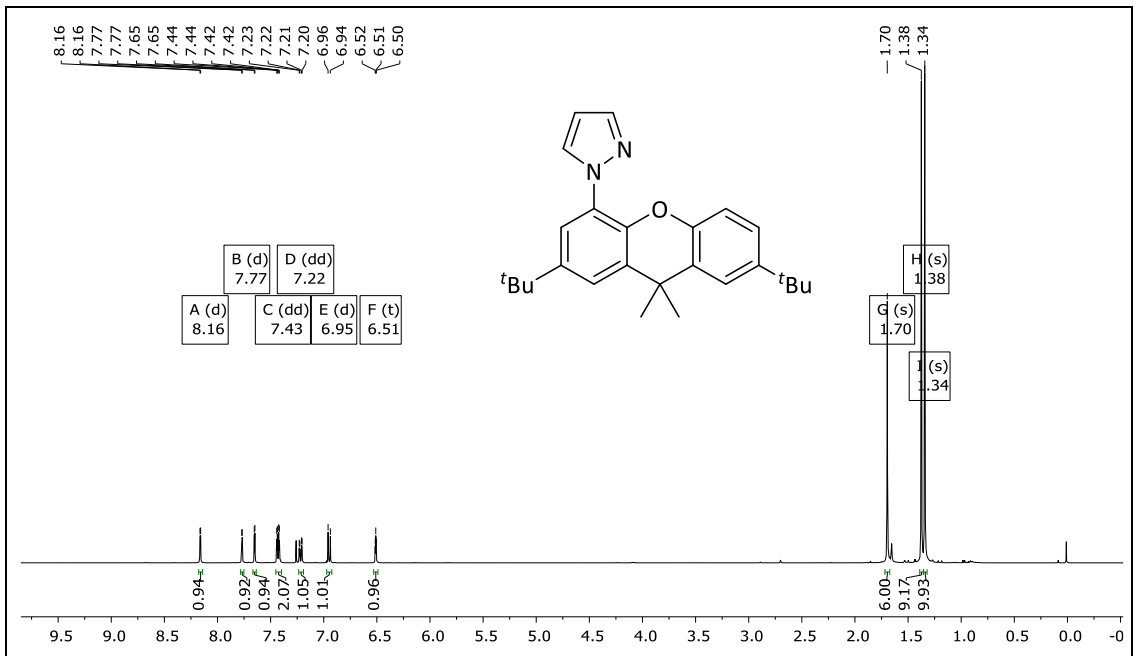


^{1}H-NMR Spectrum of **2a** ($CDCl_3$, 400 MHz)

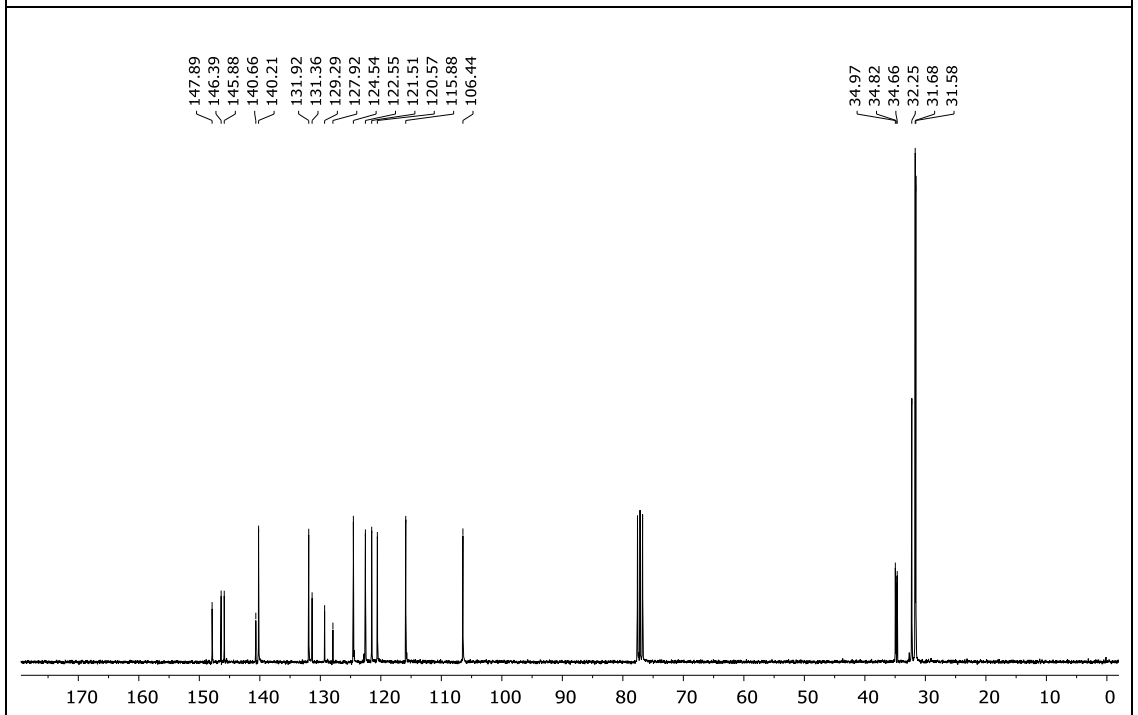


^{13}C-NMR Spectrum of **2a** ($CDCl_3$, 100 MHz)

1.6 ^{1}H- and ^{13}C-NMR Spectra of 2a`

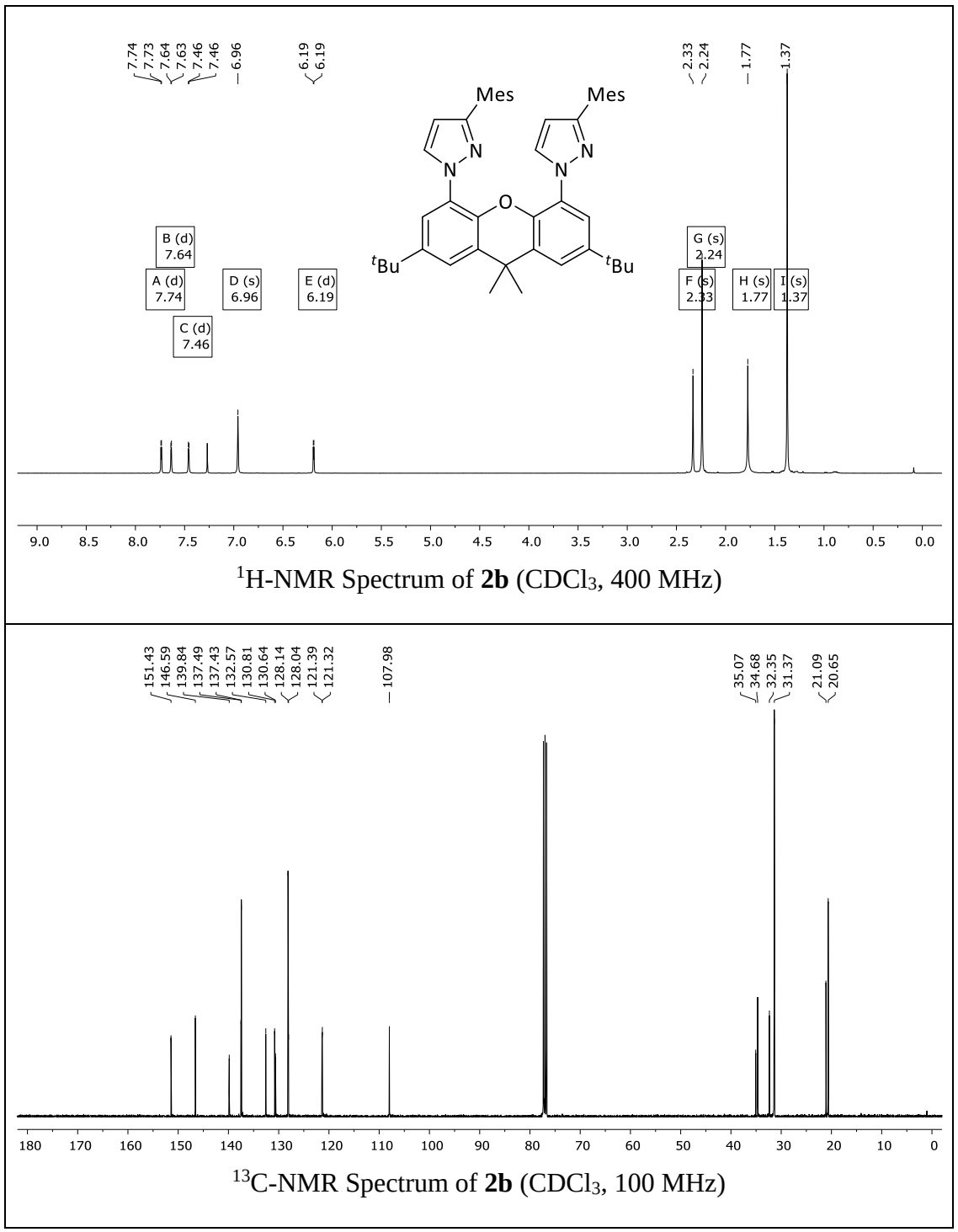


^{1}H-NMR Spectrum of **2a`** ($CDCl_3$, 400 MHz)



^{13}C-NMR Spectrum of **2a`** ($CDCl_3$, 100 MHz)

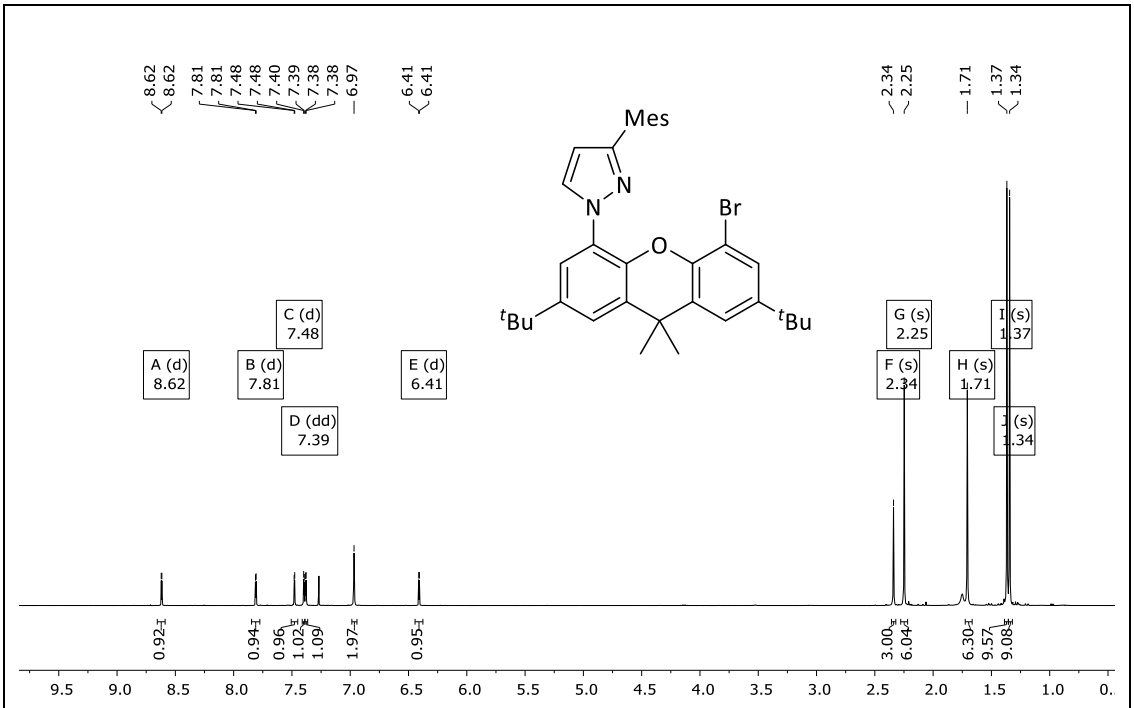
1.7 ^{1}H- and ^{13}C-NMR Spectra of Ligand 2b



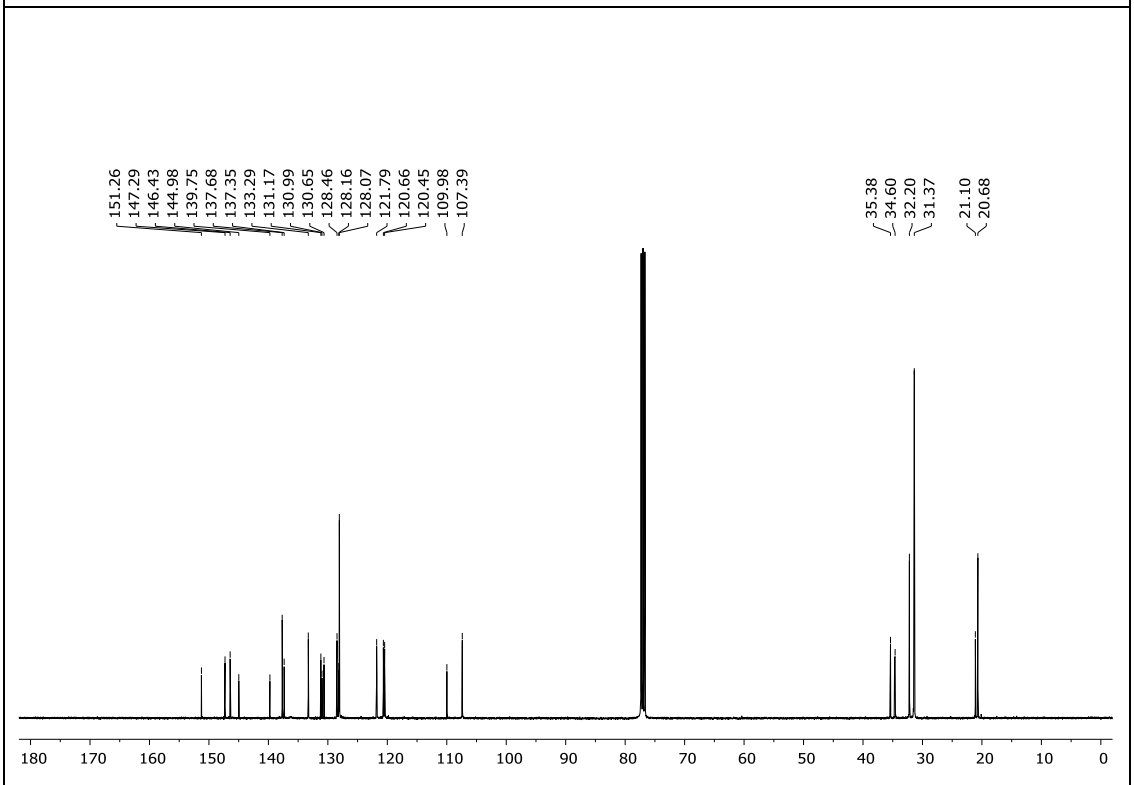
^{1}H-NMR Spectrum of **2b** ($CDCl_3$, 400 MHz)

^{13}C-NMR Spectrum of **2b** ($CDCl_3$, 100 MHz)

1.8 ^{1}H- and ^{13}C-NMR Spectra of 2b`

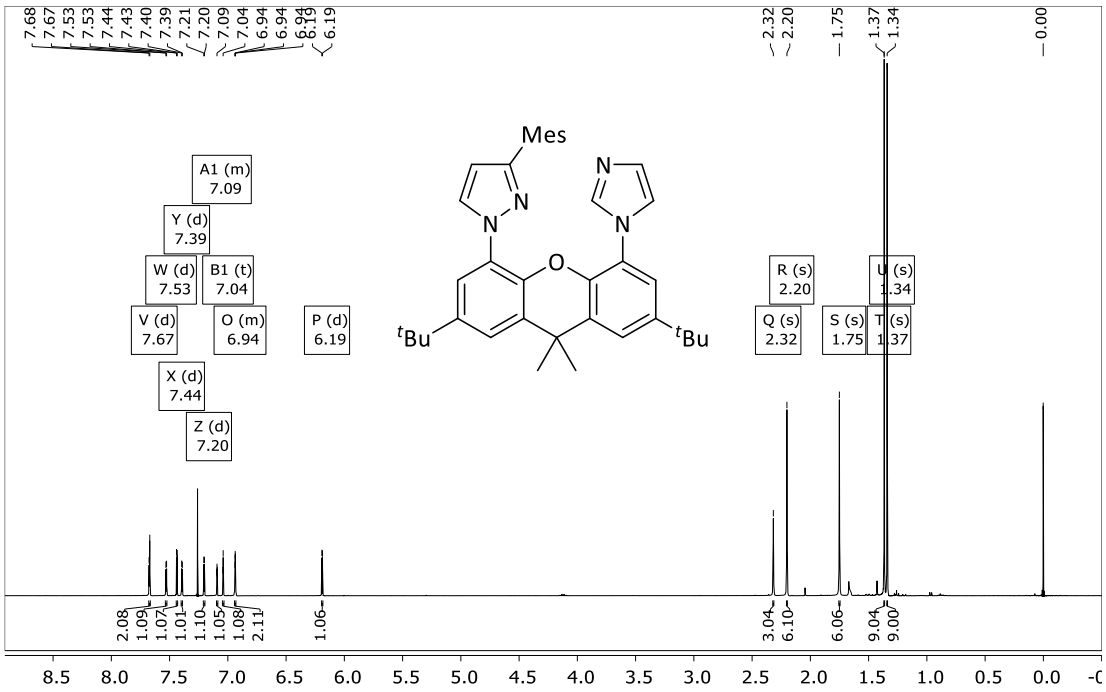


^{1}H-NMR Spectrum of **2b`** ($CDCl_3$, 400 MHz)

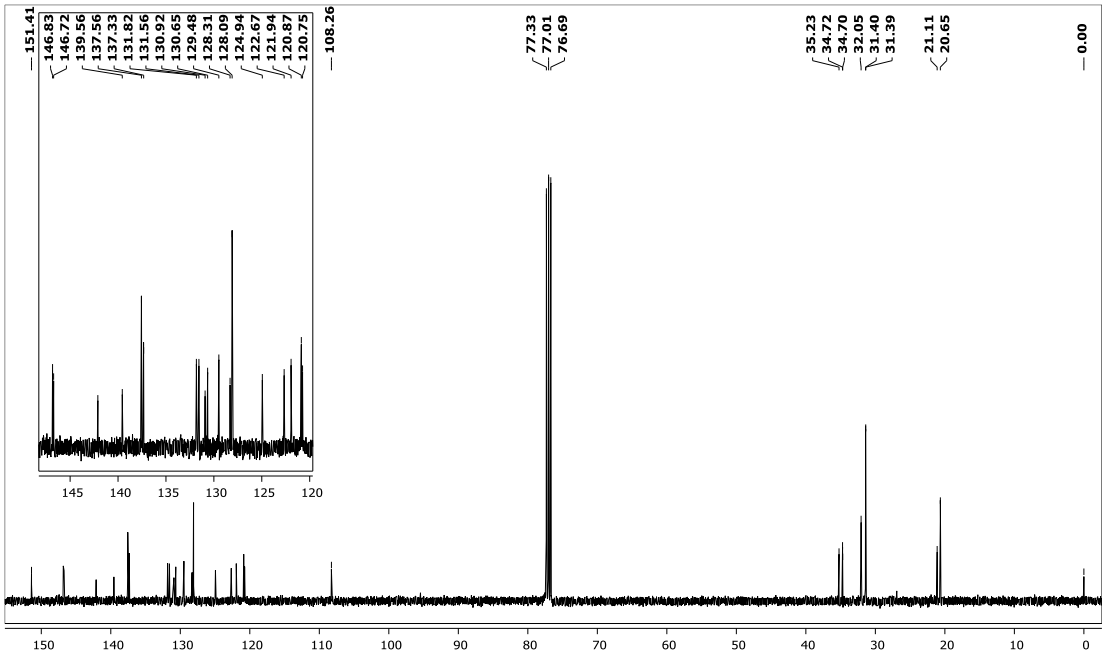


^{13}C-NMR Spectrum of **2b`** ($CDCl_3$, 100 MHz)

1.9 ^{1}H- and ^{13}C-NMR Spectra 2b`c

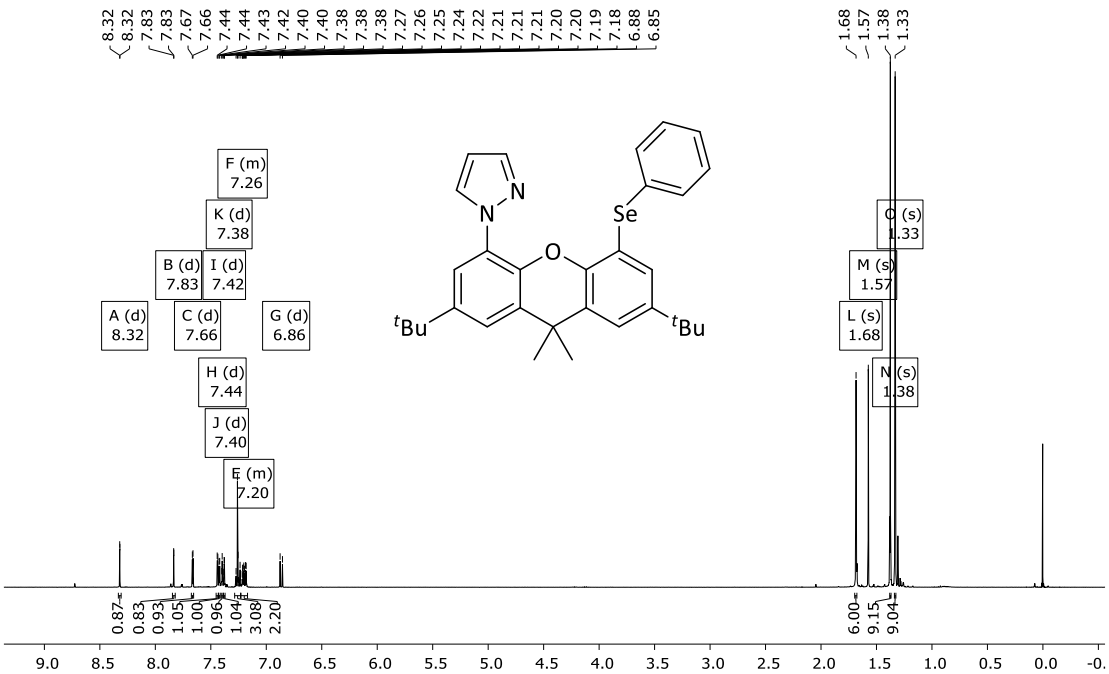


^{1}H-NMR Spectrum of **2b`c** ($CDCl_3$, 400 MHz)

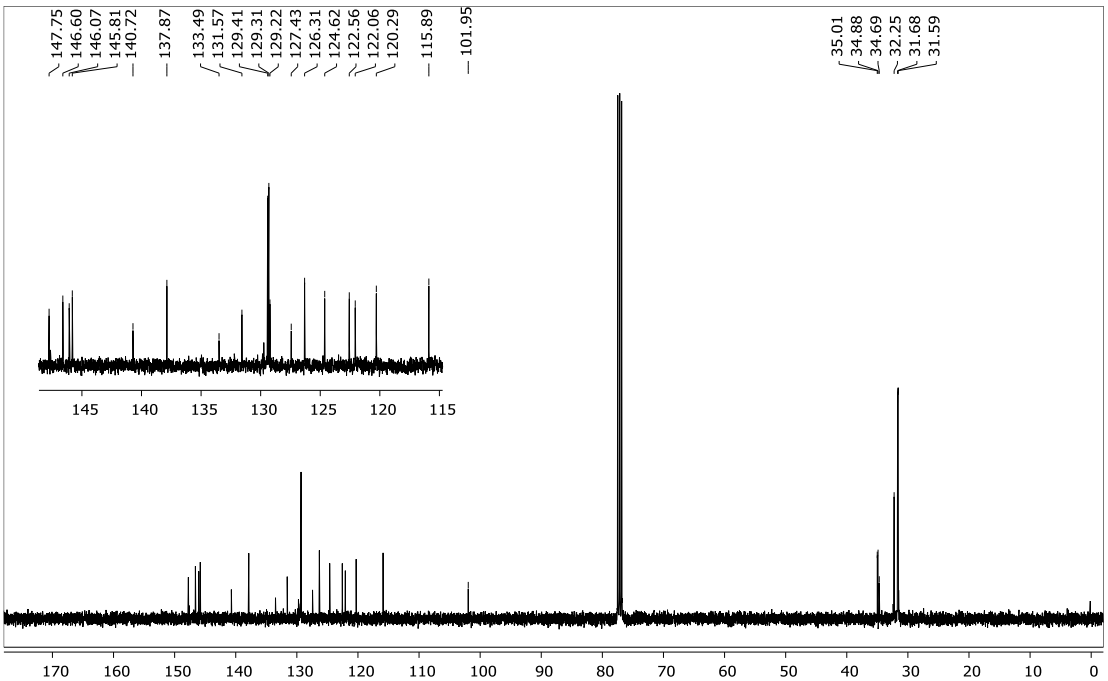


^{13}C-NMR Spectrum of **2b`c** ($CDCl_3$, 100 MHz)

1.10 ^{1}H- and ^{13}C-NMR Spectra of 2a`d



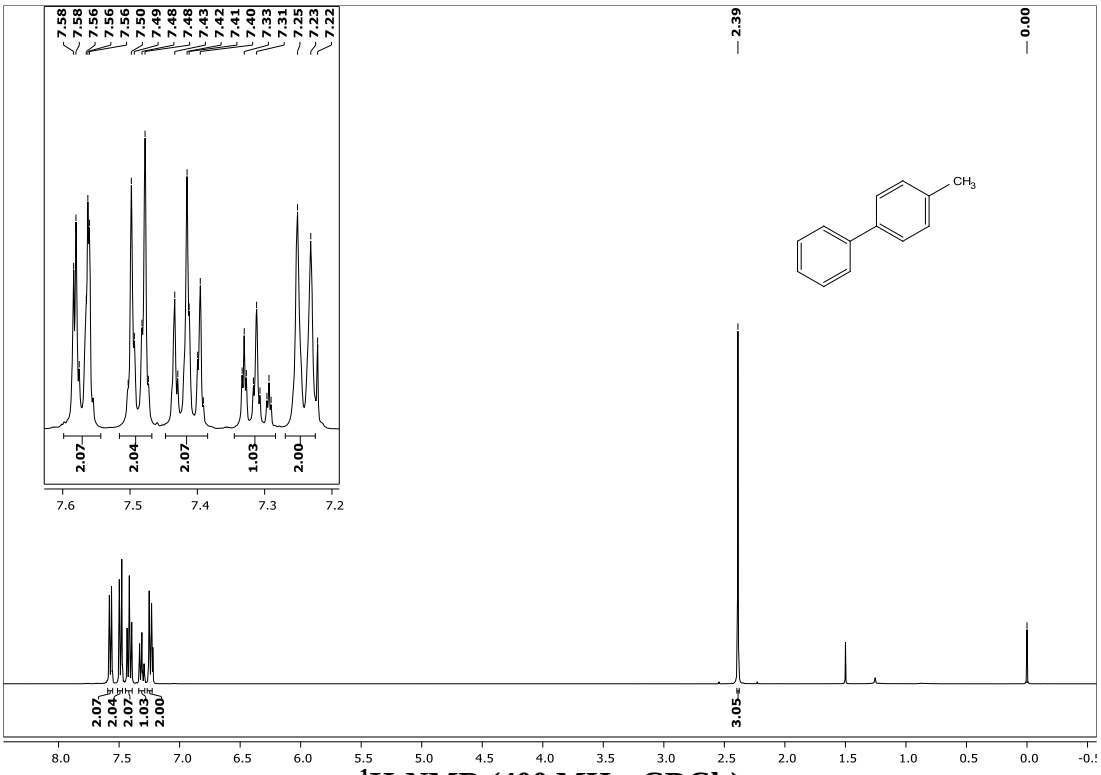
^{1}H-NMR Spectrum of **2a`d** ($CDCl_3$, 100 MHz)



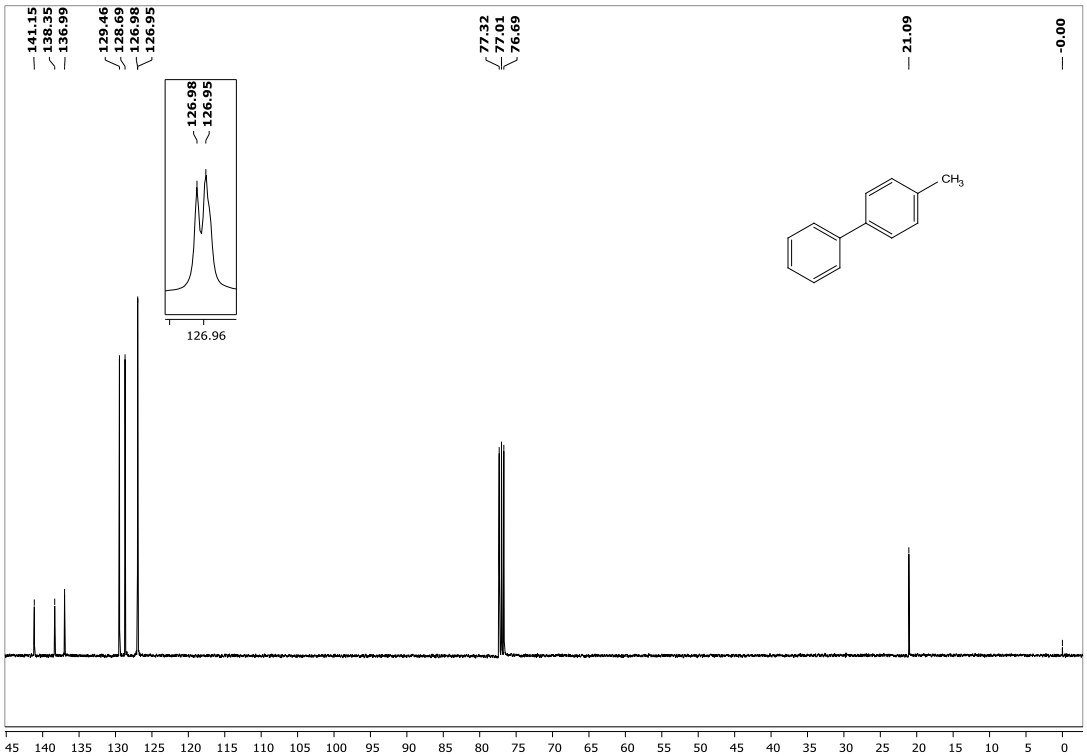
^{13}C-NMR Spectrum of **2a`d** ($CDCl_3$, 100 MHz)

Spectroscopic Data of Cross-Coupling Products

^{1}H- and ^{13}C-NMR of 4-methyl-1,1'-biphenyl:

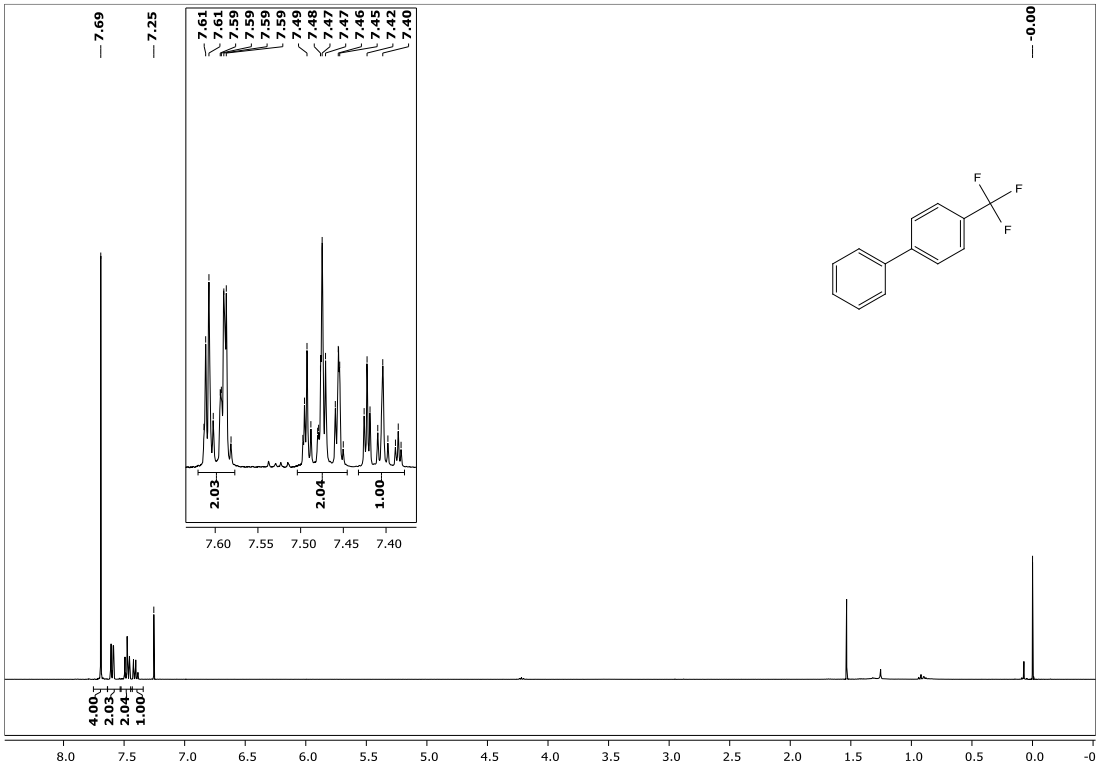


^{1}H-NMR (400 MHz, $CDCl_3$)

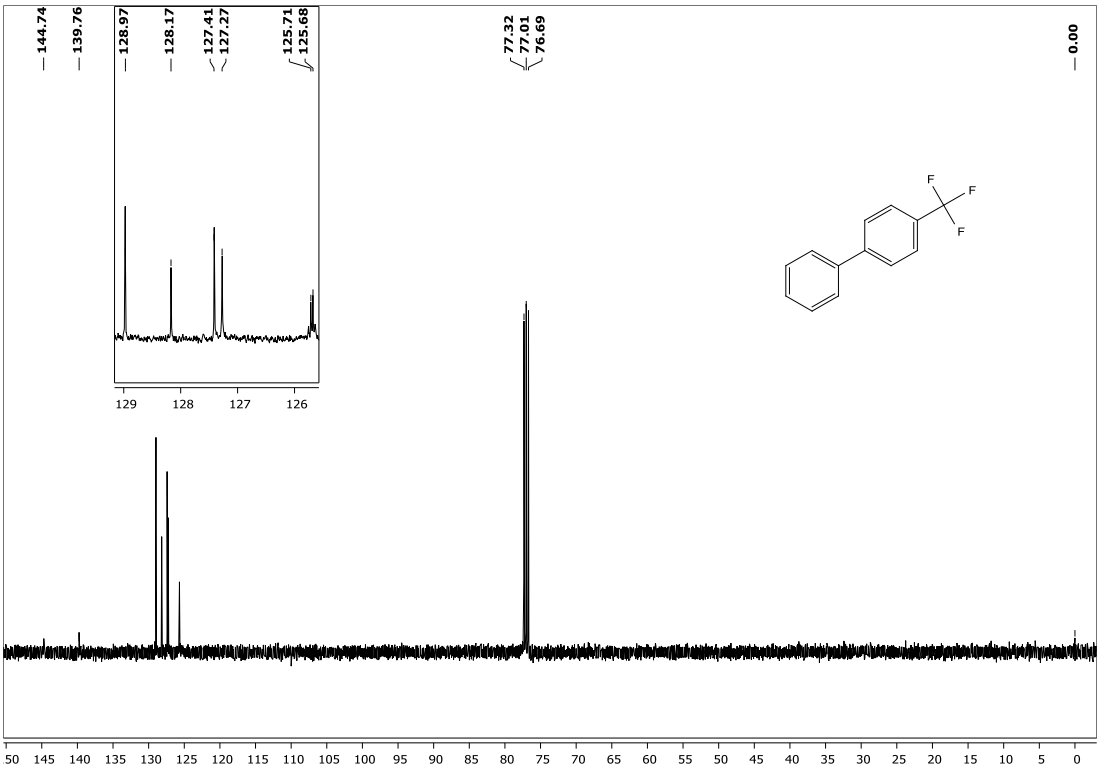


^{13}C-NMR (100 MHz, $CDCl_3$)

^{1}H-) and ^{13}C-NMR of 4-(trifluoromethyl)-1,1'-biphenyl.

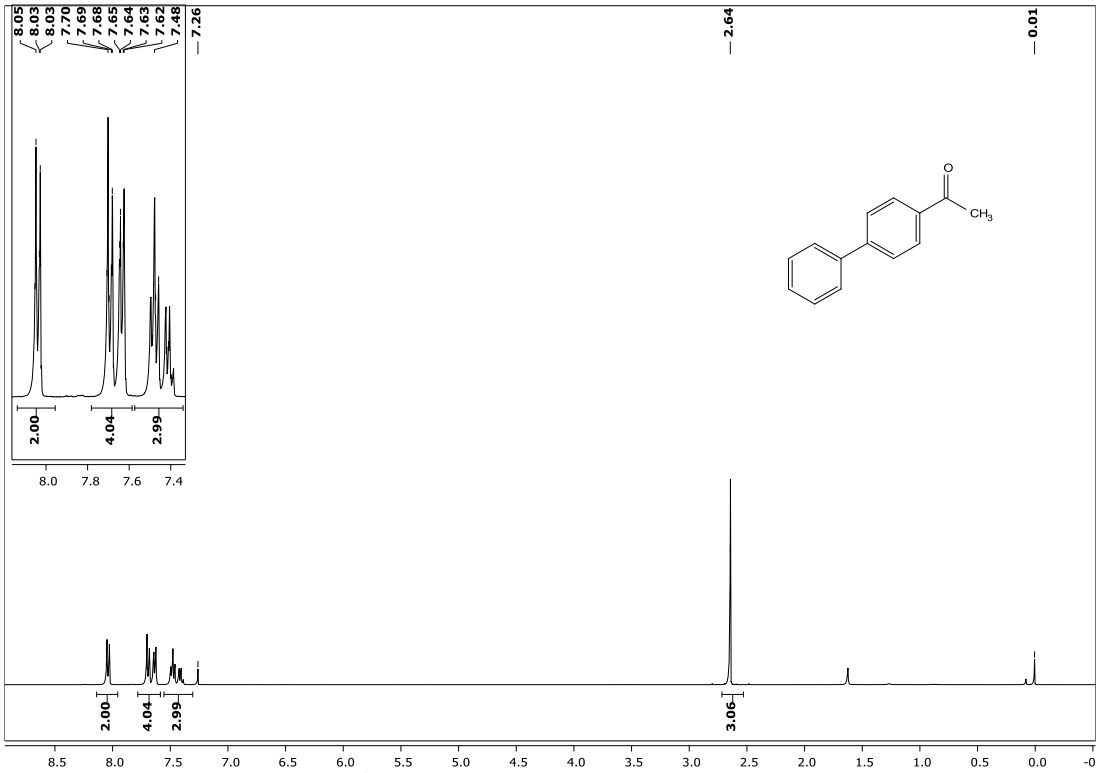


^{1}H-NMR (400 MHz, $CDCl_3$)

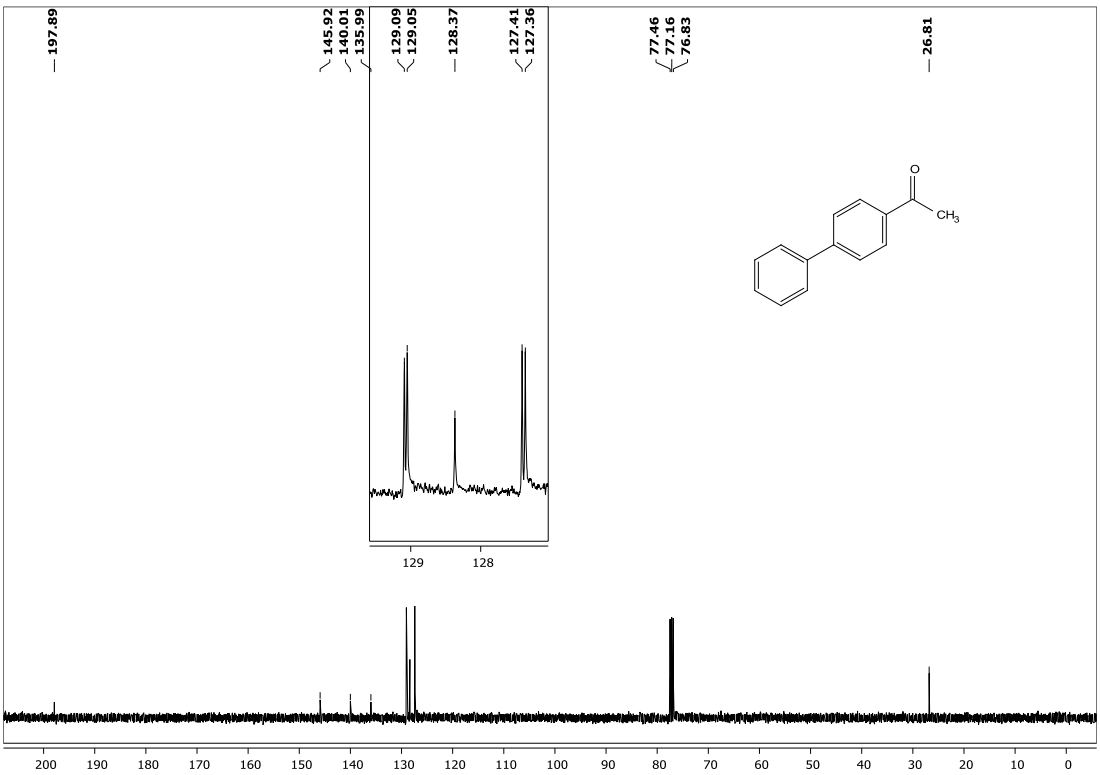


^{13}C-NMR (100 MHz, $CDCl_3$)

^{1}H- and ^{13}C-NMR of 1-([1,1'-biphenyl]-4-yl)ethan-1-one.

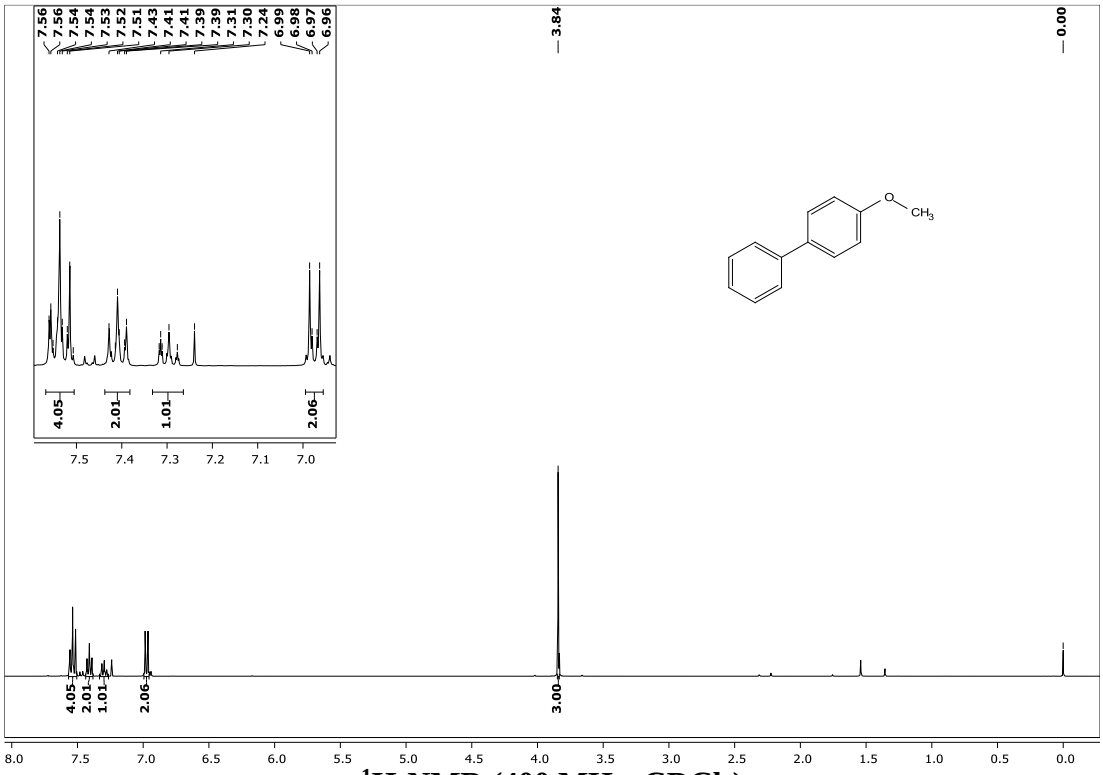


^{1}H-NMR (400 MHz, $CDCl_3$)

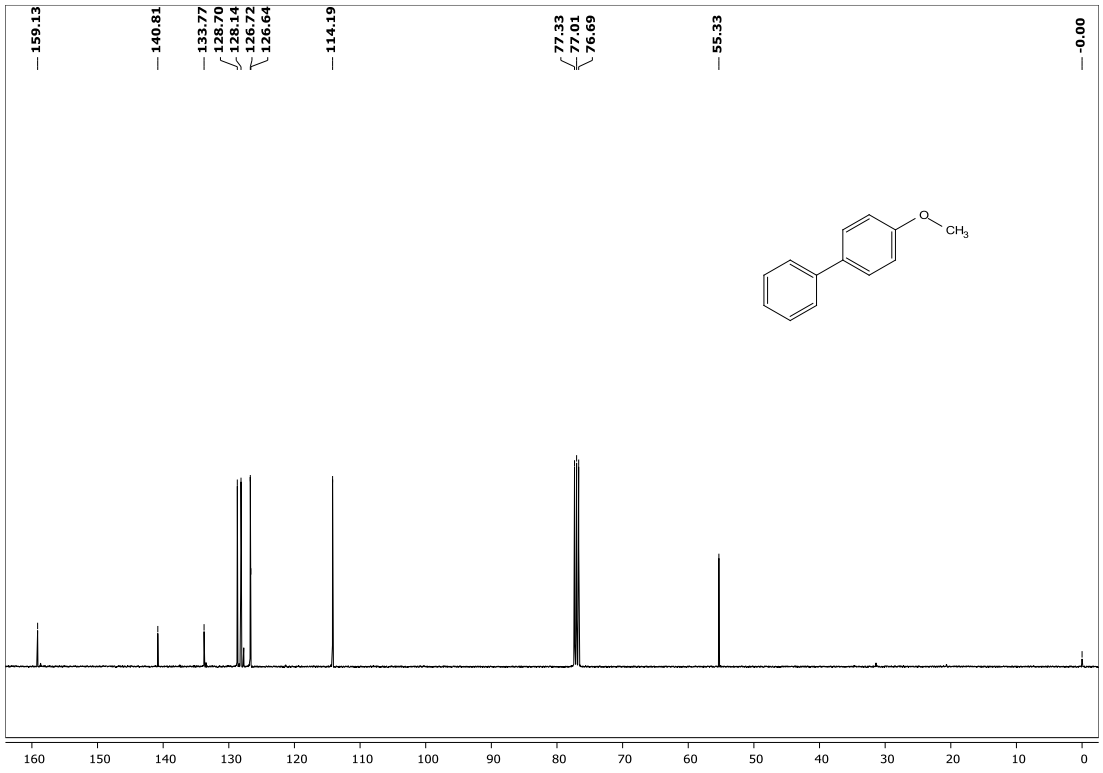


^{13}C-NMR (100 MHz, $CDCl_3$)

^{1}H- and ^{13}C-NMR of 4-methoxy-1,1'-biphenyl.

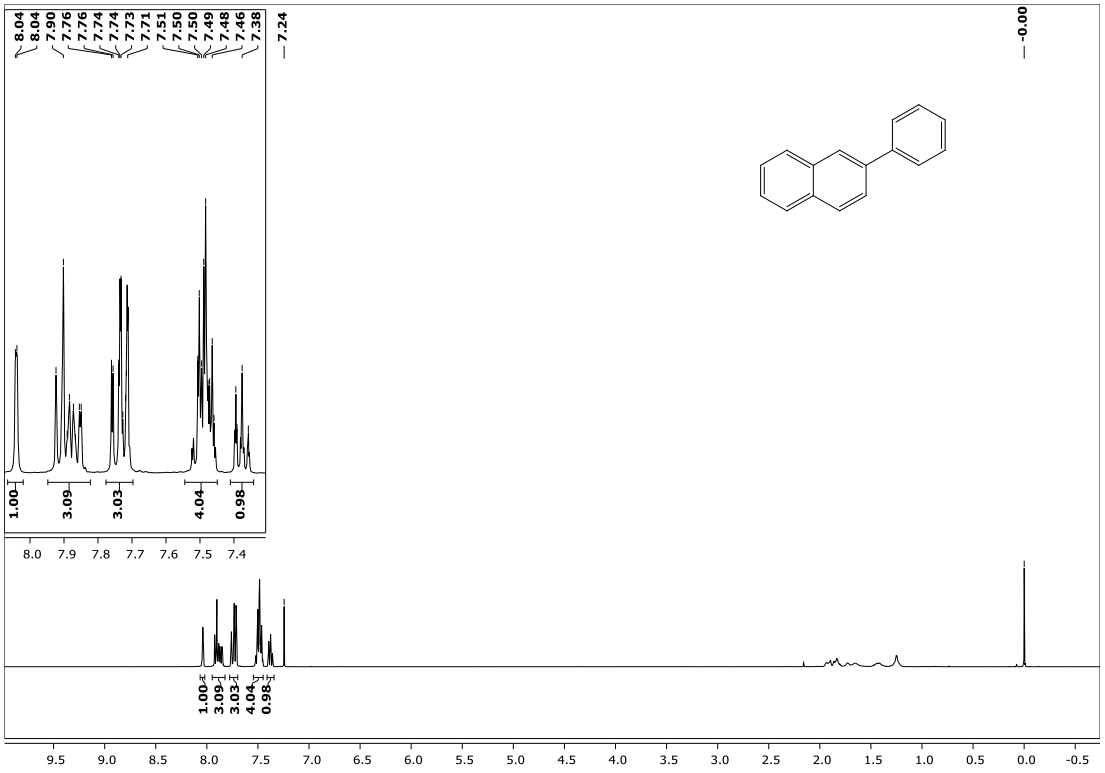


^{1}H-NMR (400 MHz, $CDCl_3$)

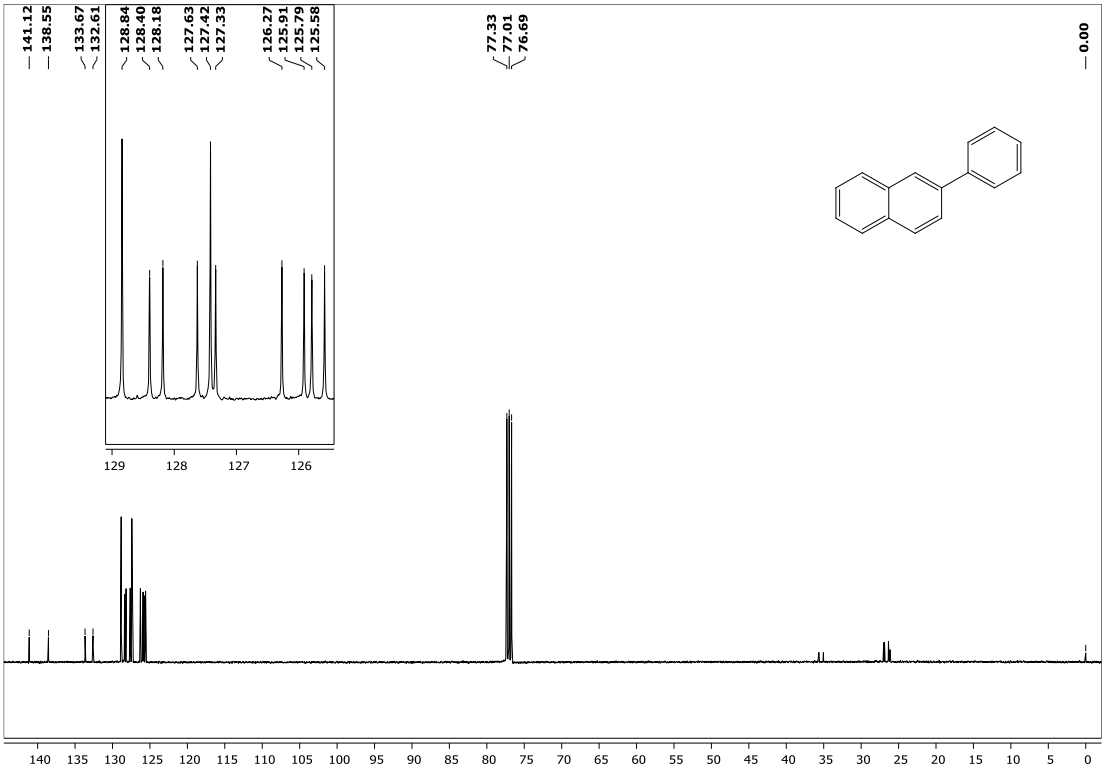


^{13}C-NMR (100 MHz, $CDCl_3$)

^{1}H- and ^{13}C-NMR of 2-phenylnaphthalene.

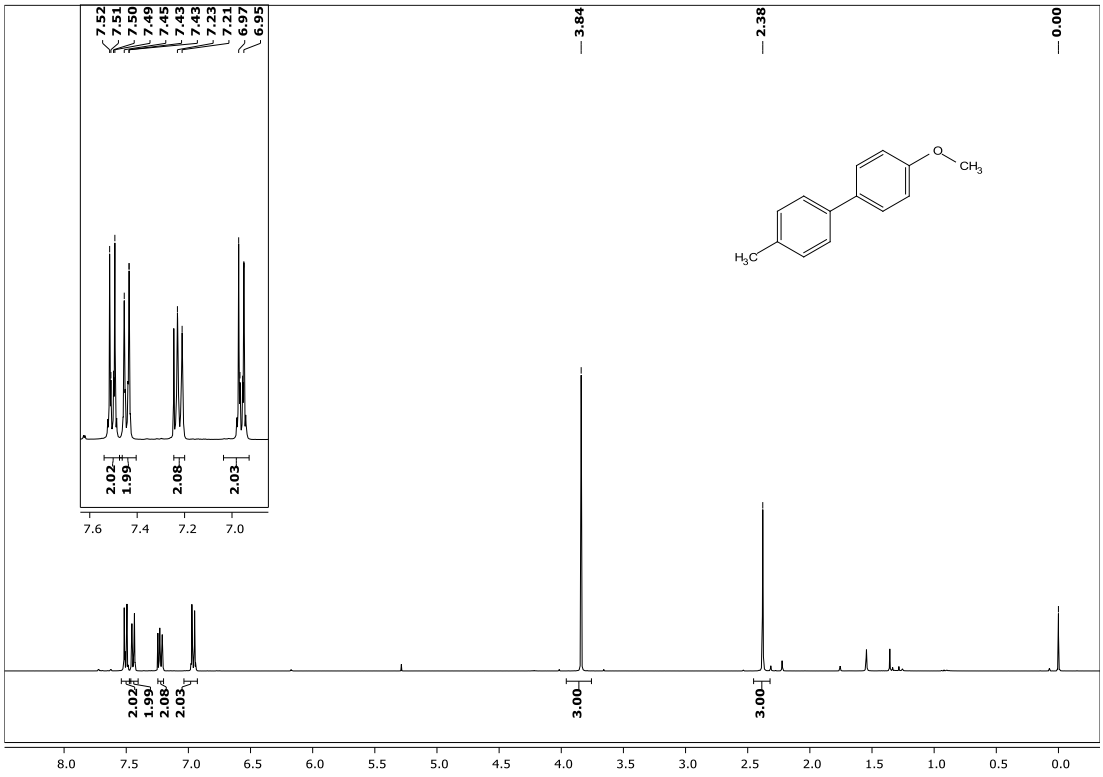


^{1}H-NMR (400 MHz, $CDCl_3$)

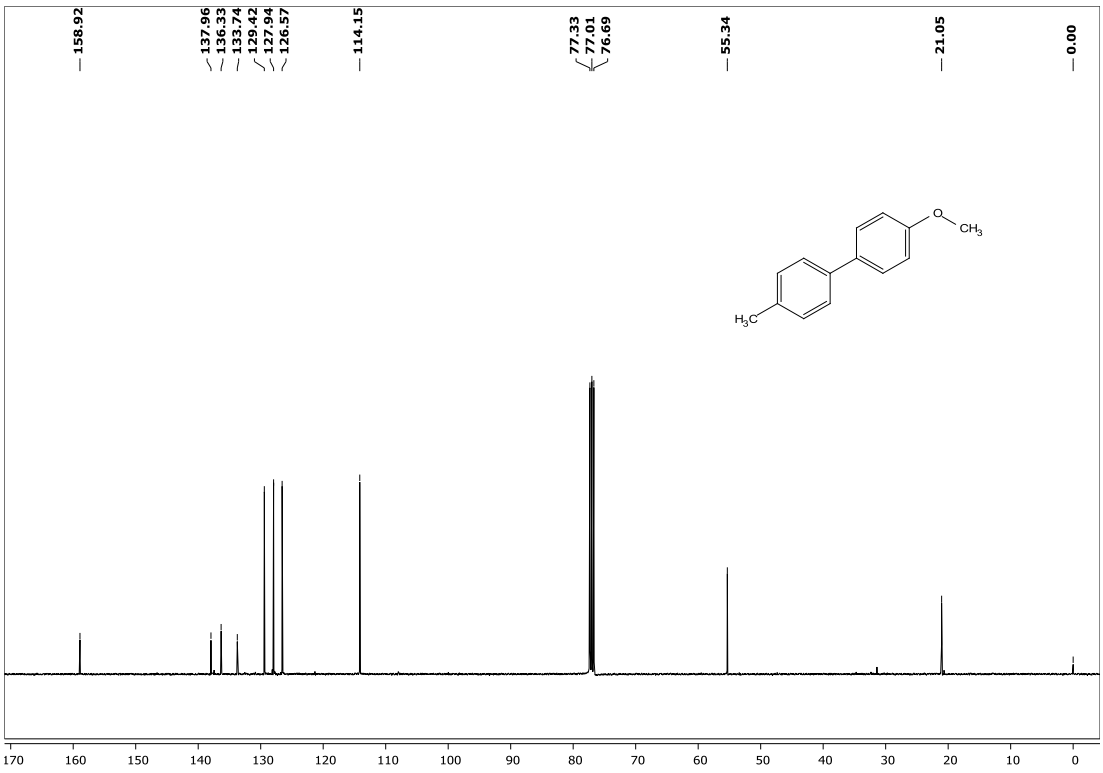


^{13}C-NMR (100 MHz, $CDCl_3$)

^{1}H- and ^{13}C-NMR of 4-methoxy-4'-methyl-1,1'-biphenyl.

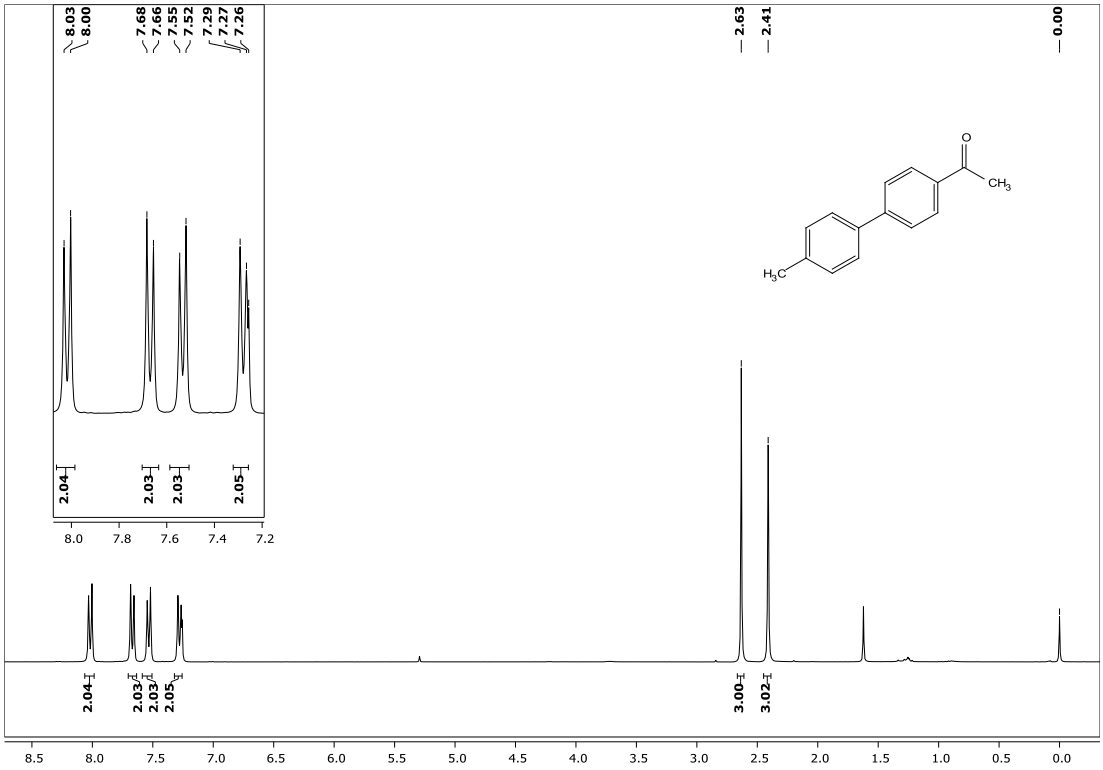


^{1}H-NMR (400 MHz, $CDCl_3$)

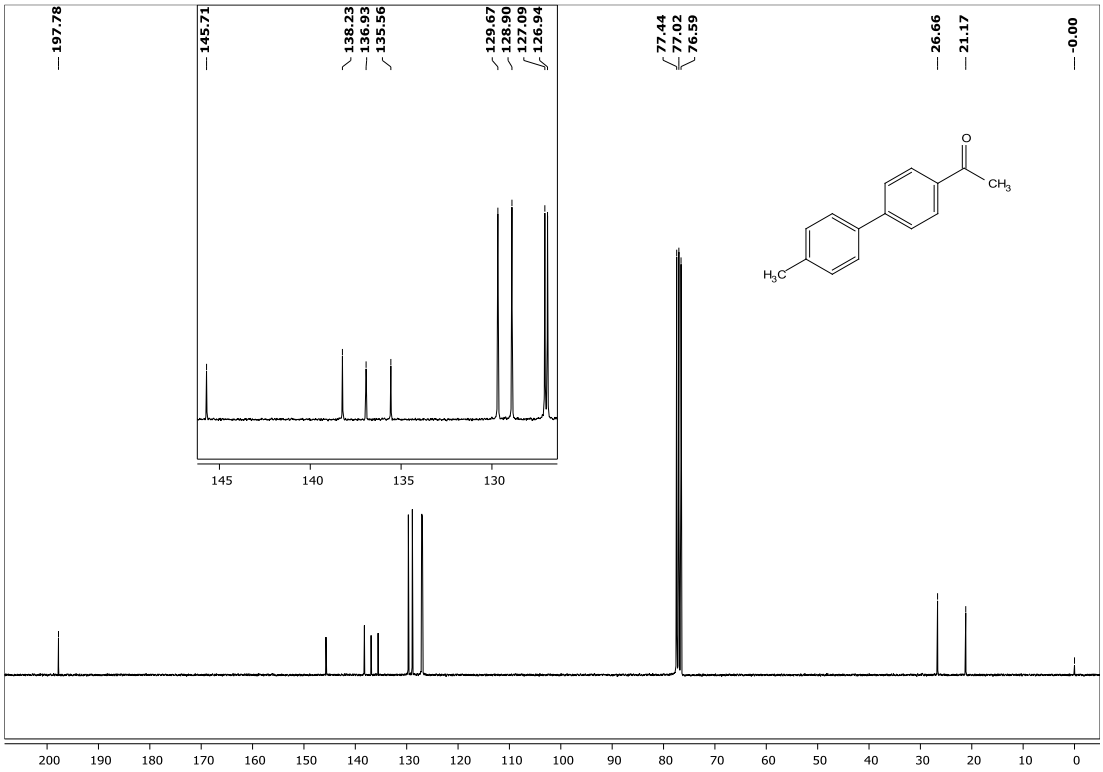


^{13}C-NMR (100 MHz, $CDCl_3$)

^{1}H- and ^{13}C-NMR) of 1-(4'-methyl-[1,1'-biphenyl]-4-yl)ethan-1-one

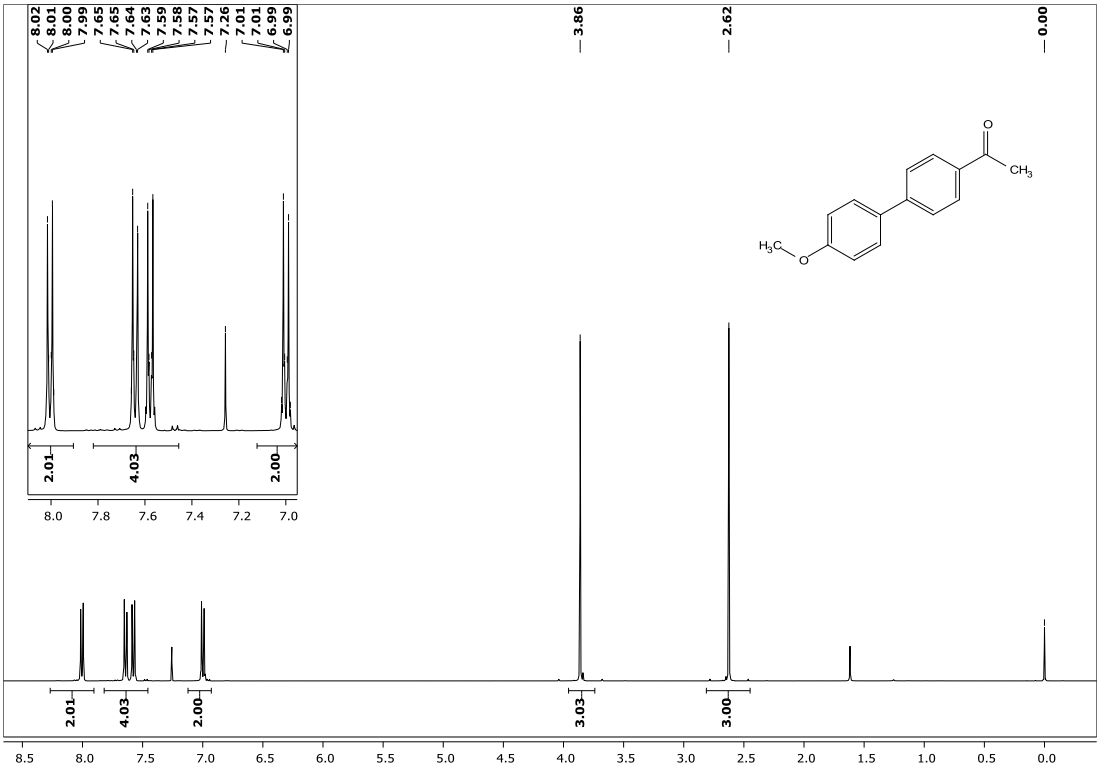


^{1}H-NMR (300 MHz, $CDCl_3$)

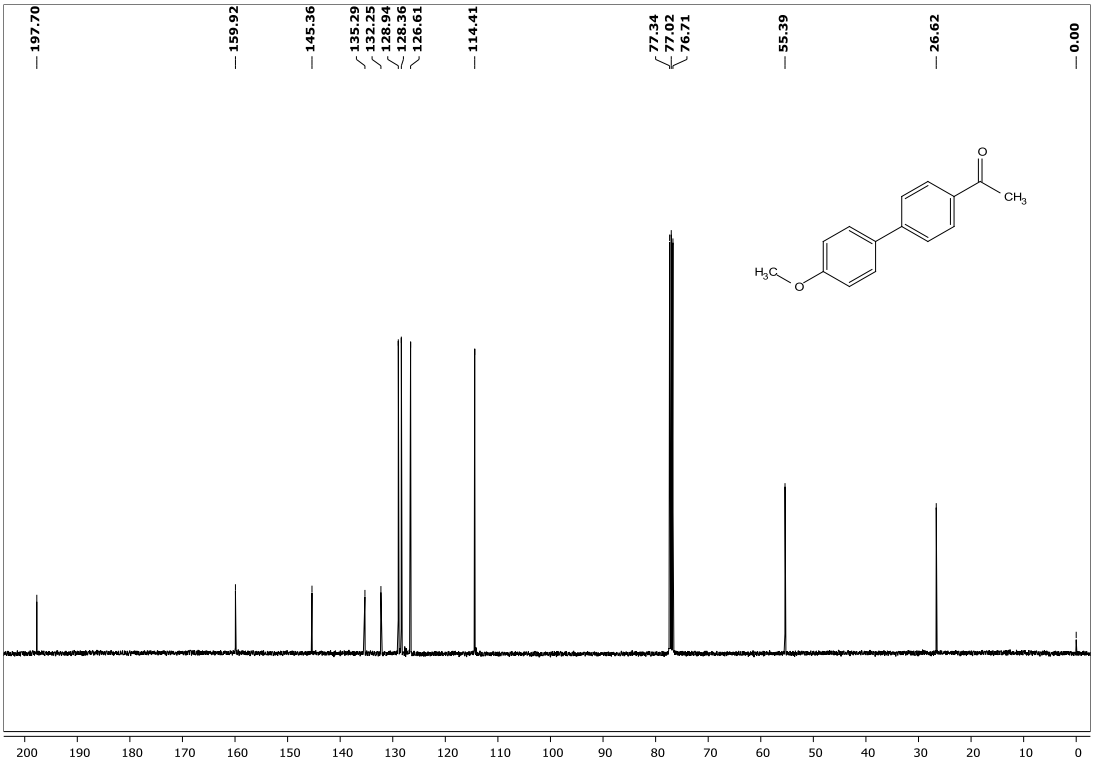


^{13}C-NMR (75 MHz, $CDCl_3$)

^{1}H- and ^{13}C-NMR of 1-(4'-methoxy-[1,1'-biphenyl]-4-yl)ethan-1-one

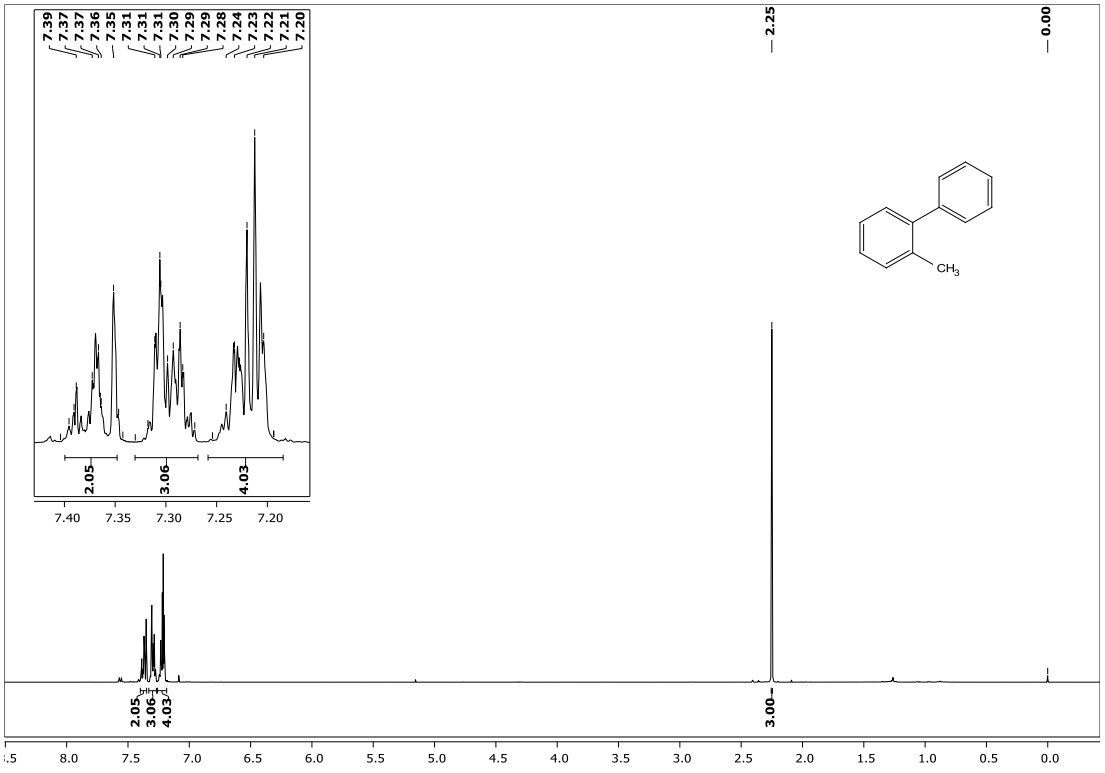


^{1}H-NMR (400 MHz, $CDCl_3$)

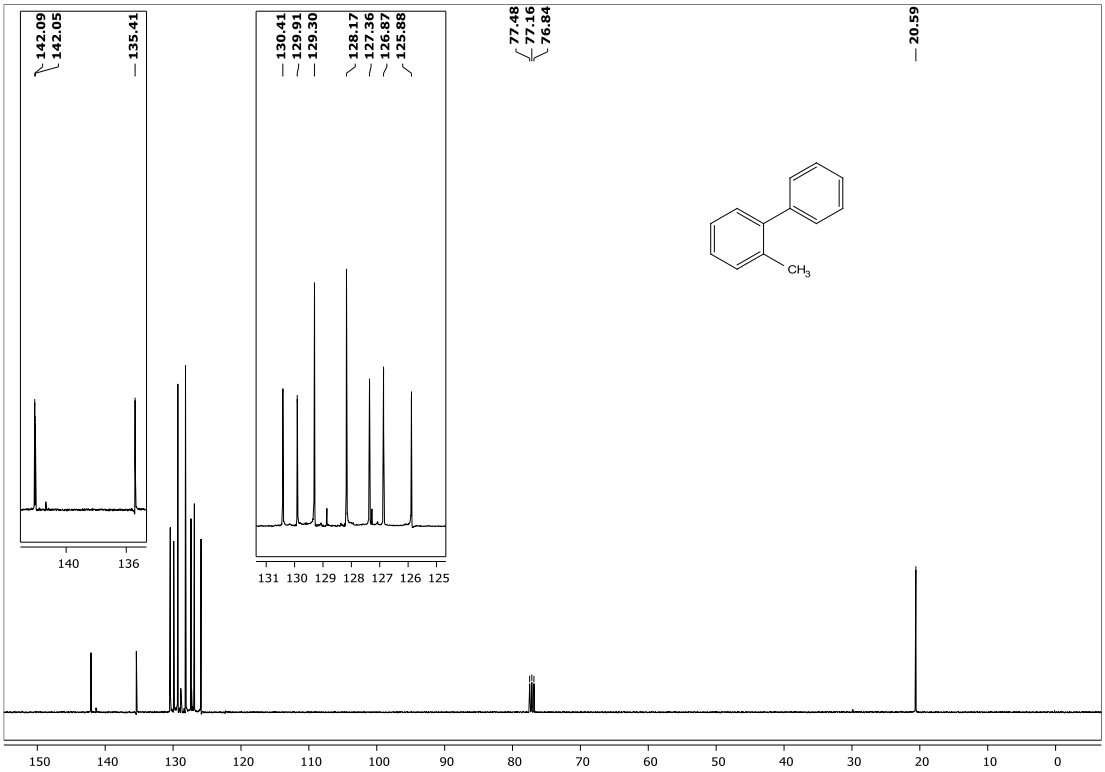


^{13}C-NMR (100 MHz, $CDCl_3$

^{1}H- and ^{13}C-NMR of 2-methyl-1,1'-biphenyl.

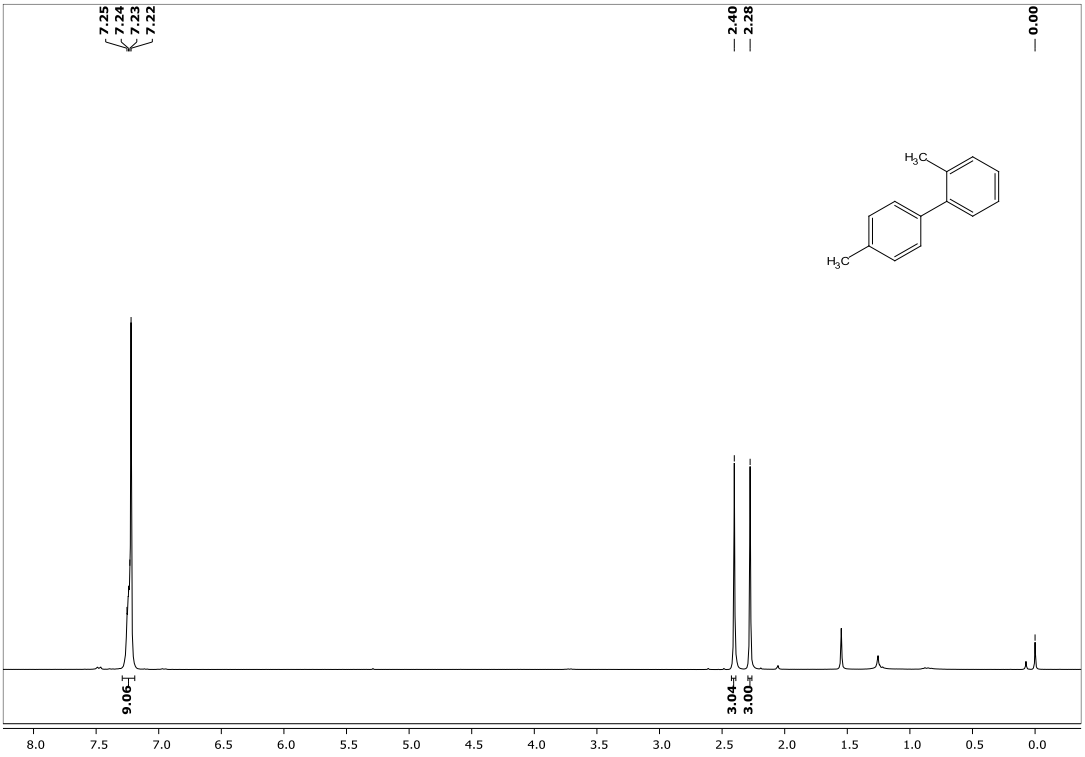


^{1}H-NMR (400 MHz, $CDCl_3$)

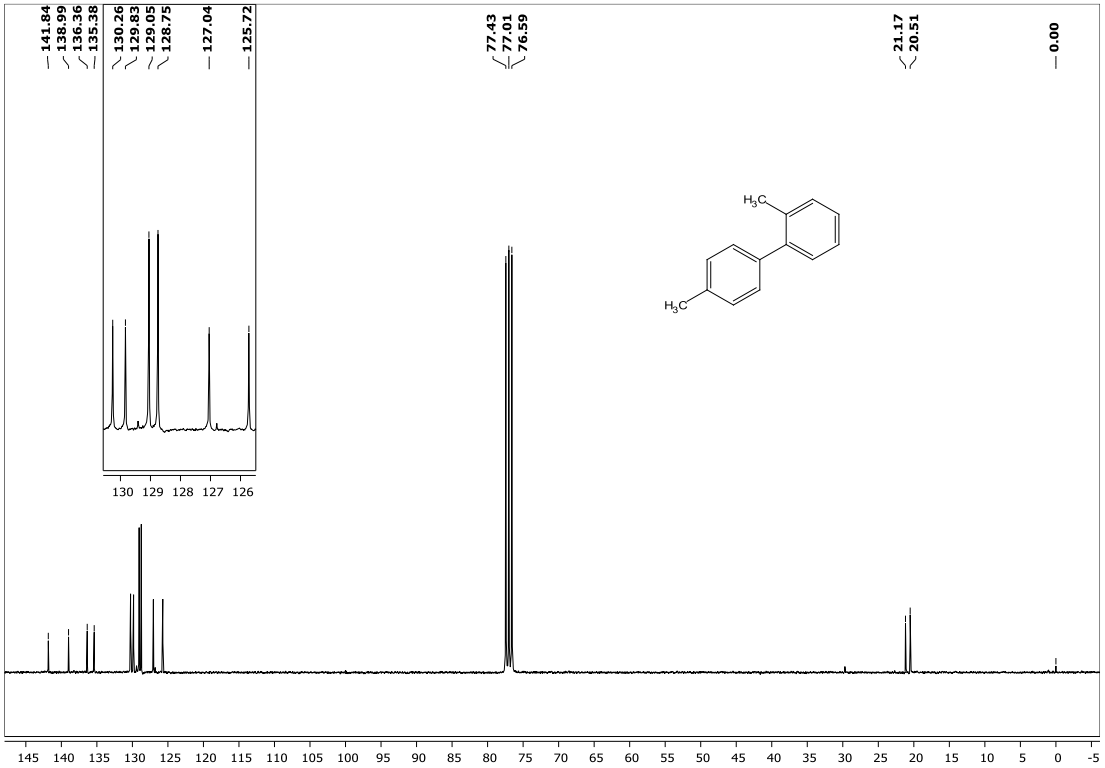


^{13}C-NMR (100 MHz, $CDCl_3$)

^{1}H- and ^{13}C-NMR of 2,4'-dimethyl-1,1'-biphenyl.

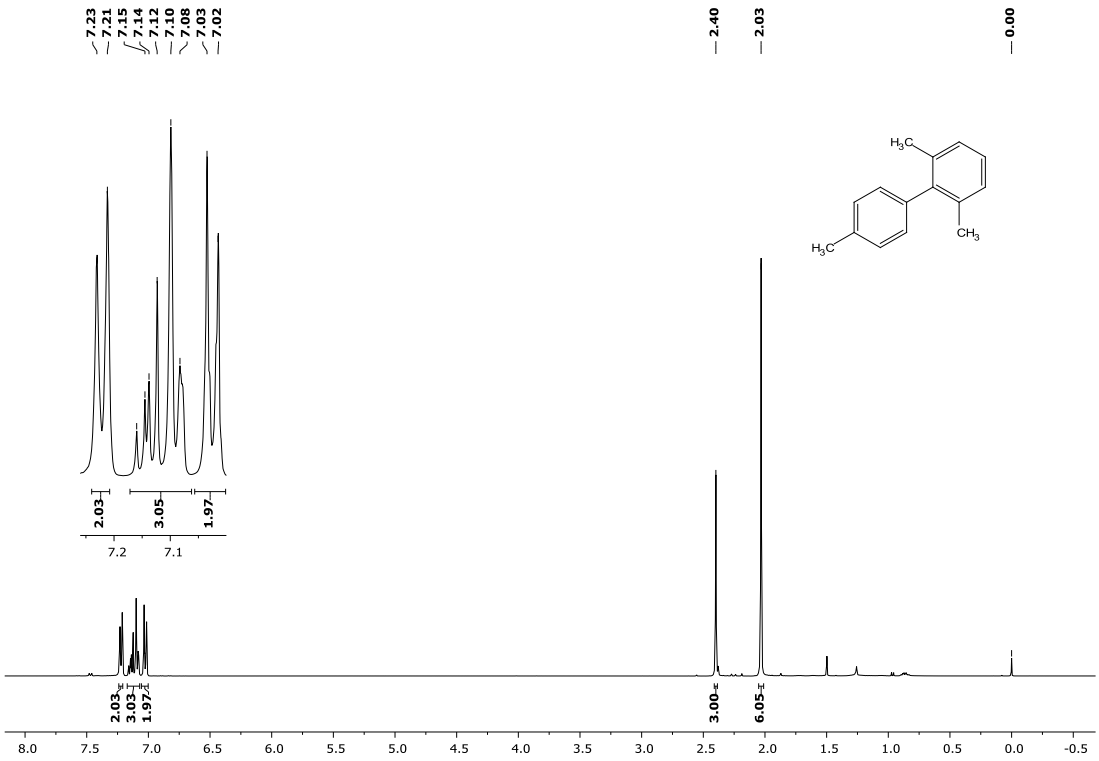


^{1}H-NMR (300 MHz, $CDCl_3$)

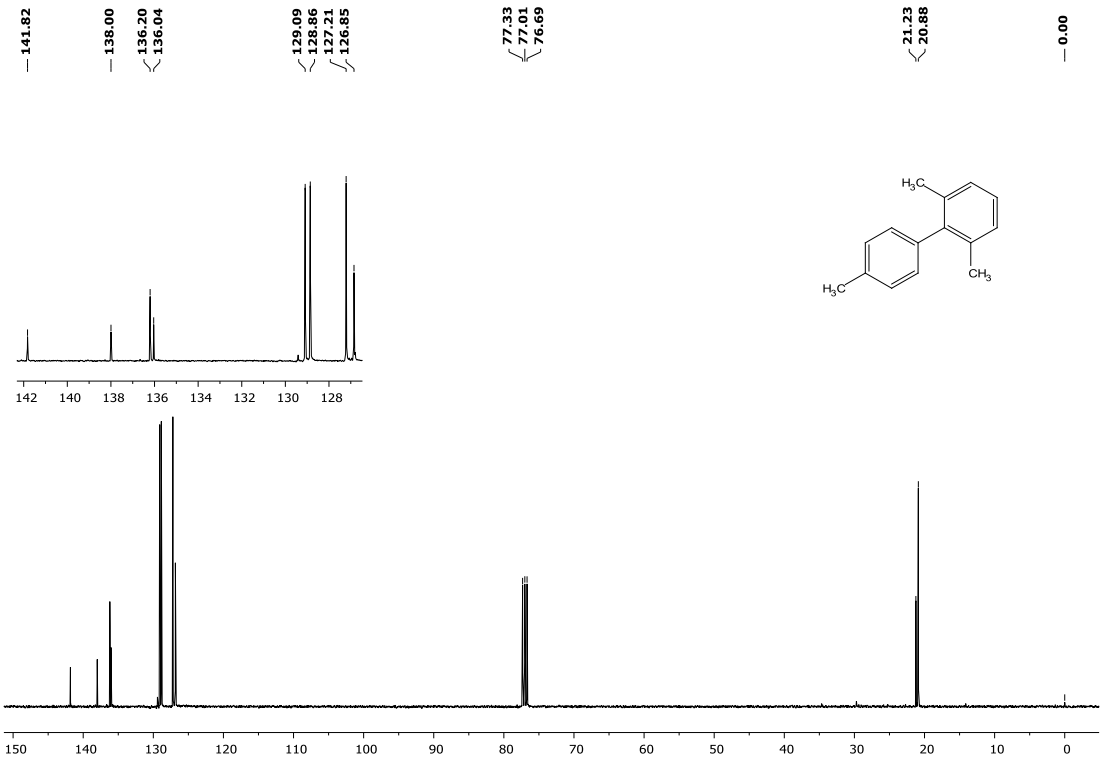


^{13}C-NMR (75 MHz, $CDCl_3$)

^{1}H- and ^{13}C-NMR of 4,2',6'-trimethyl-1,1'-biphenyl.

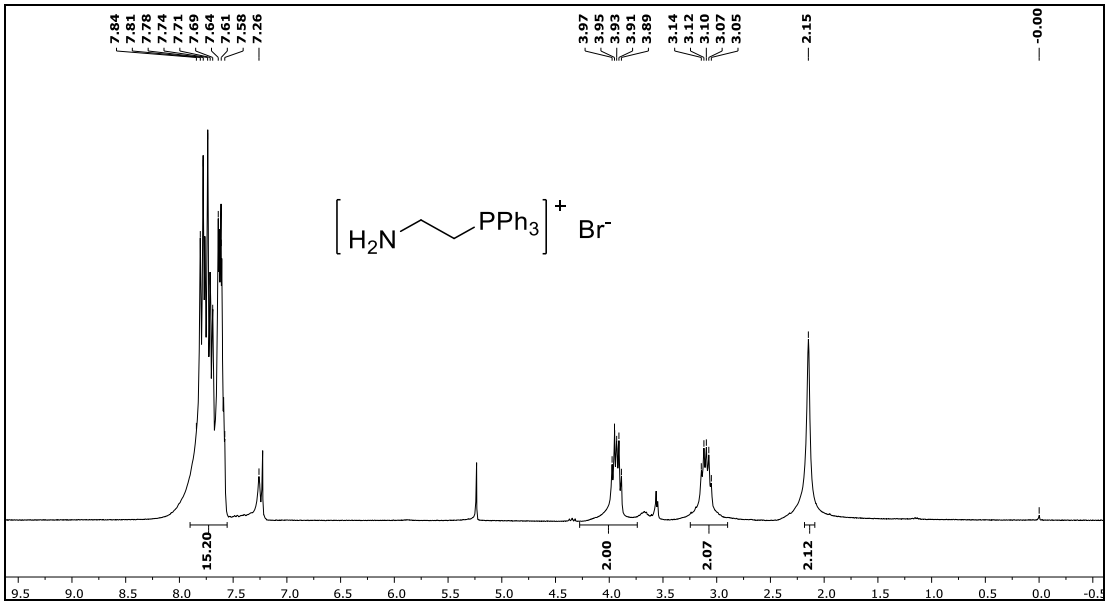


^{1}H-NMR (400 MHz, $CDCl_3$)

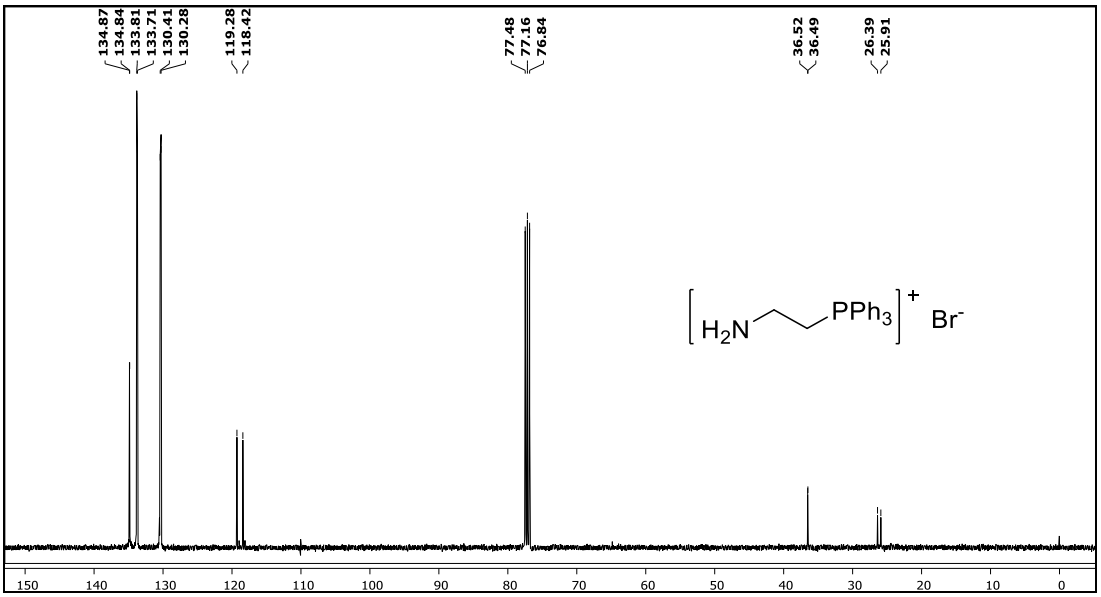


^{13}C-NMR (100 MHz, $CDCl_3$)

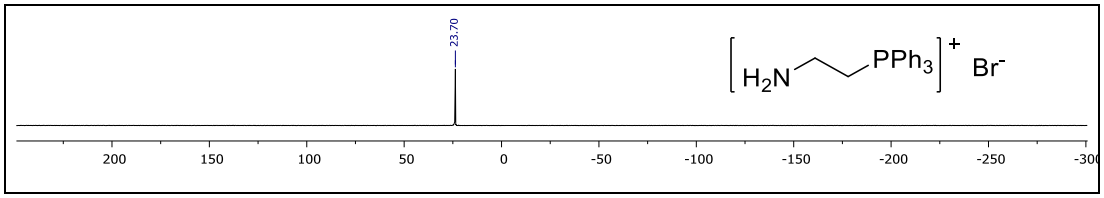
^{1}H-, ^{13}C- and ^{31}P-NMR of 2-aminoethyltriphenylphosphonium bromide.



^{1}H-NMR of 2-aminoethyltriphenylphosphonium bromide.

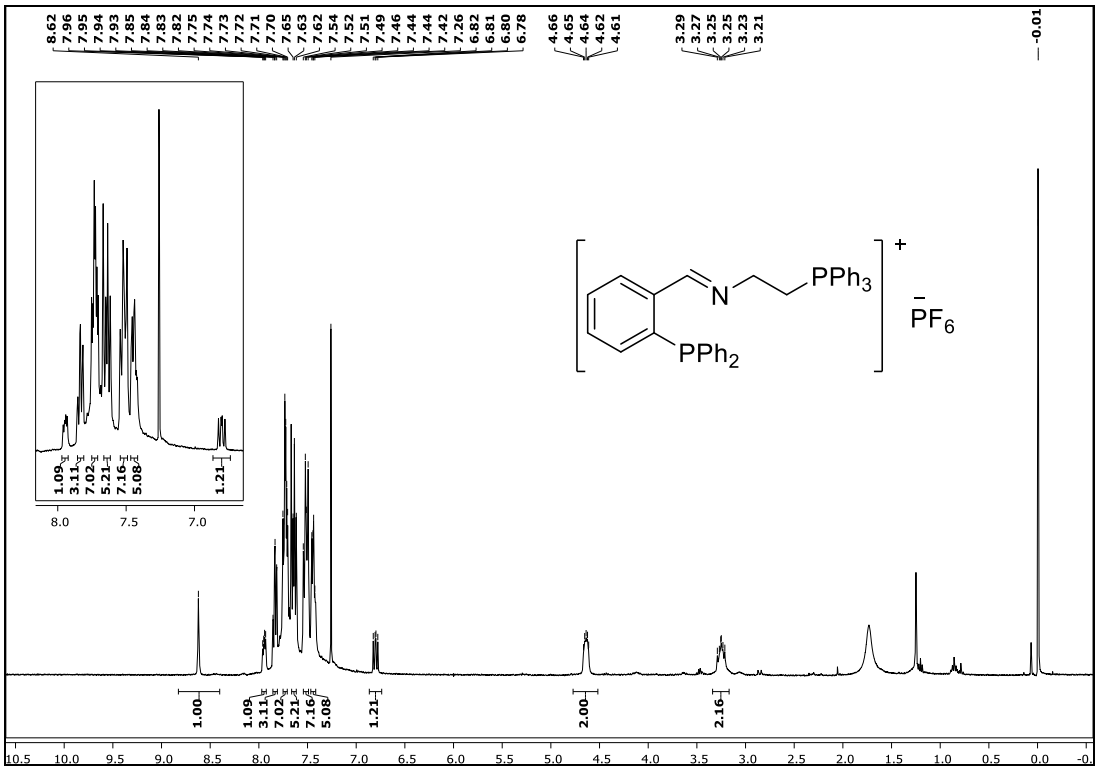


^{13}C-NMR of 2-aminoethyltriphenylphosphonium bromide.

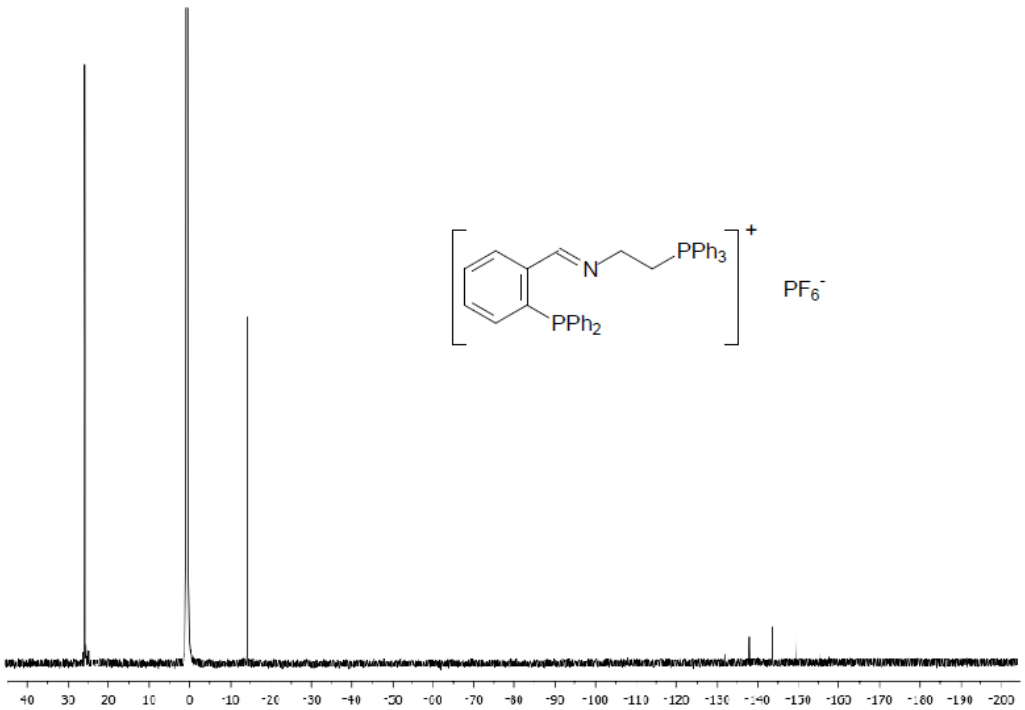


^{31}P-NMR of 2-aminoethyltriphenylphosphonium bromide.

^{1}H- and ^{31}P-NMR spectra of 2-diphenylphosphino-1-iminoethyltriphenylphosphonium hexafluorophosphate.

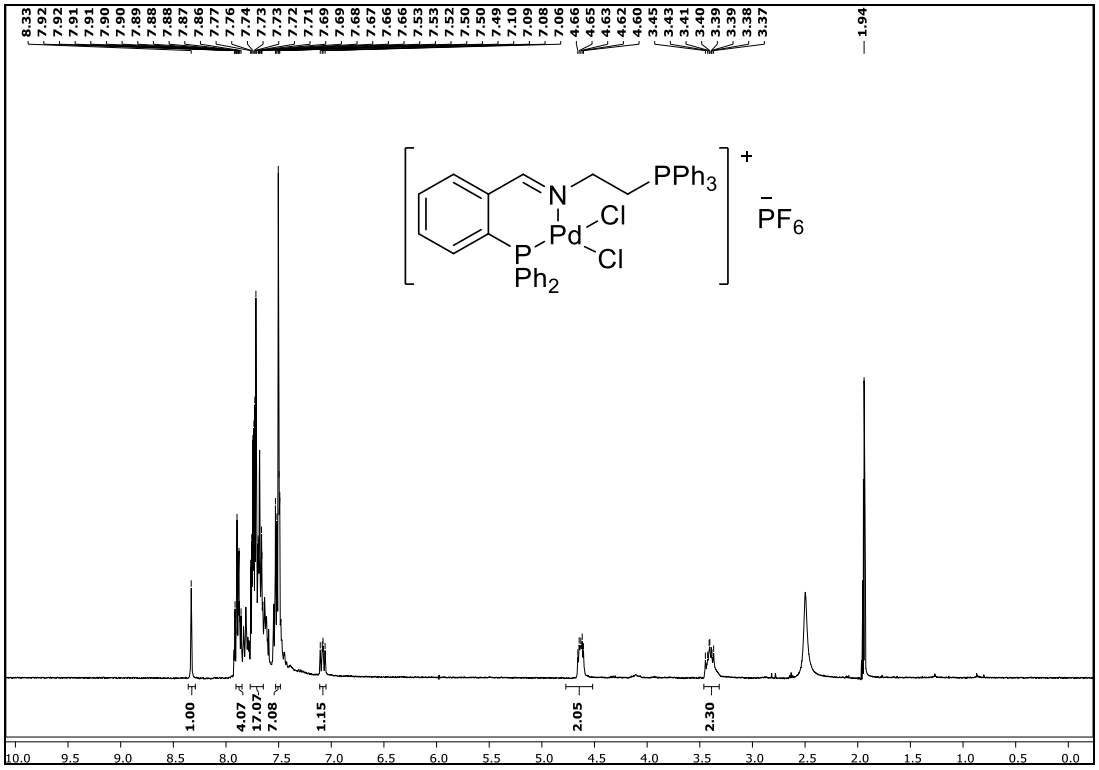


^{1}H-NMR of 2-diphenylphosphino-1-iminoethyltriphenylphosphonium hexafluorophosphate.

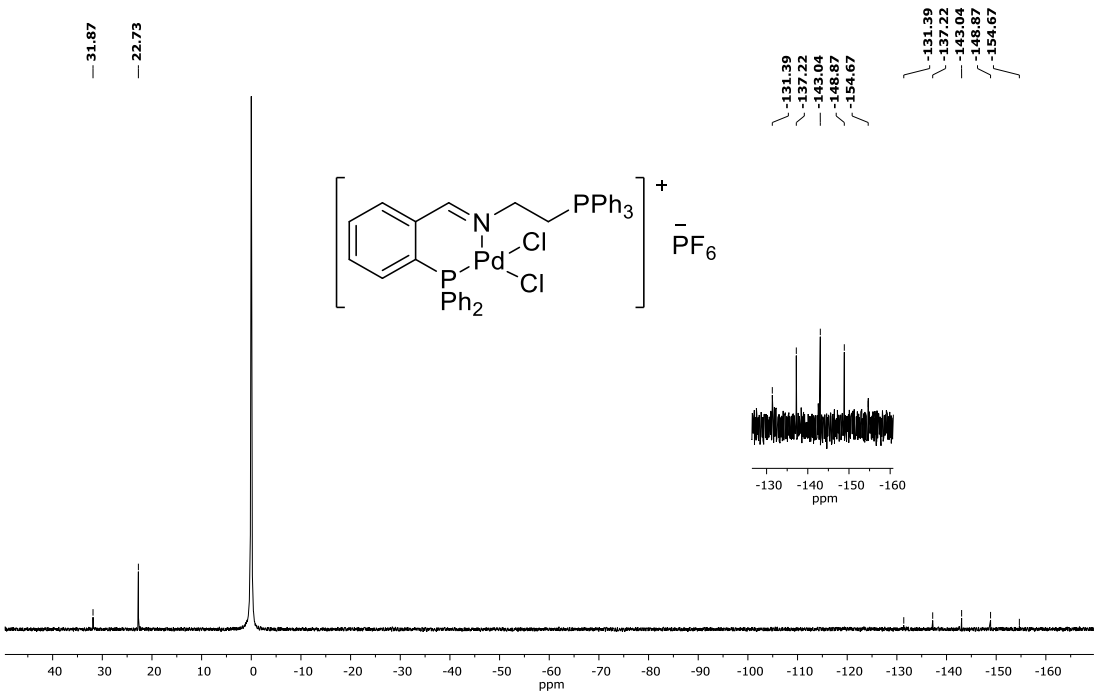


^{31}P-NMR spectra of 2-diphenylphosphino-1-iminoethyltriphenylphosphonium hexafluorophosphate.

^{1}H-and ^{31}P-NMR spectra of Ionophillic Pd-Complex.

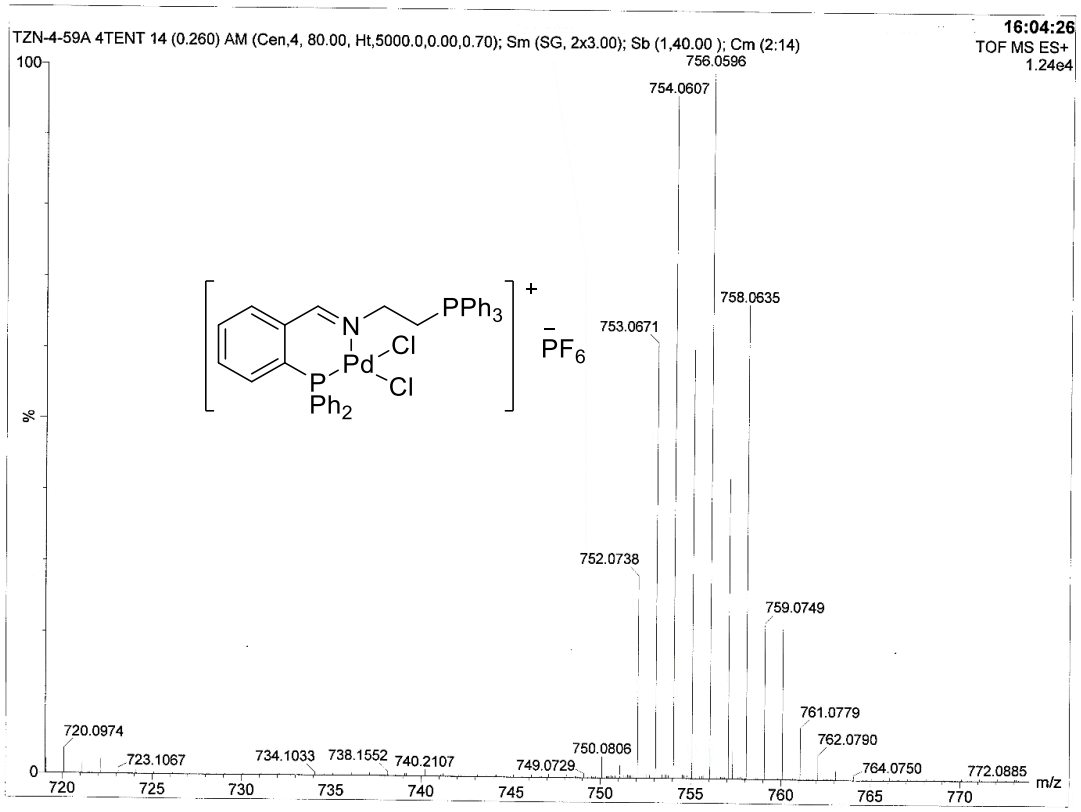


^{1}H-NMR spectra of Ionophillic Pd-Complex.



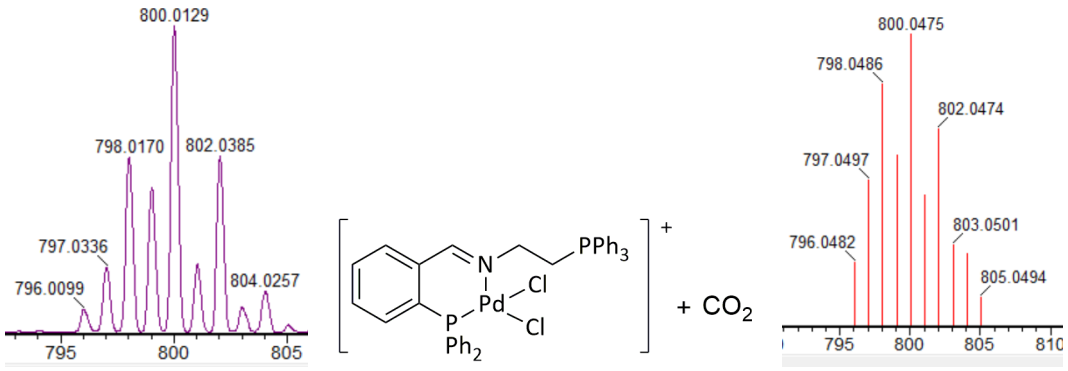
^{31}P-NMR spectra of Ionophillic Pd-Complex.

Positive mode ESI-MS Spectra of Ionophillic Pd-Complex (2)



Experimental Isotopic Distribution Pattern of Ionophillic Pd-Complex **(2)**

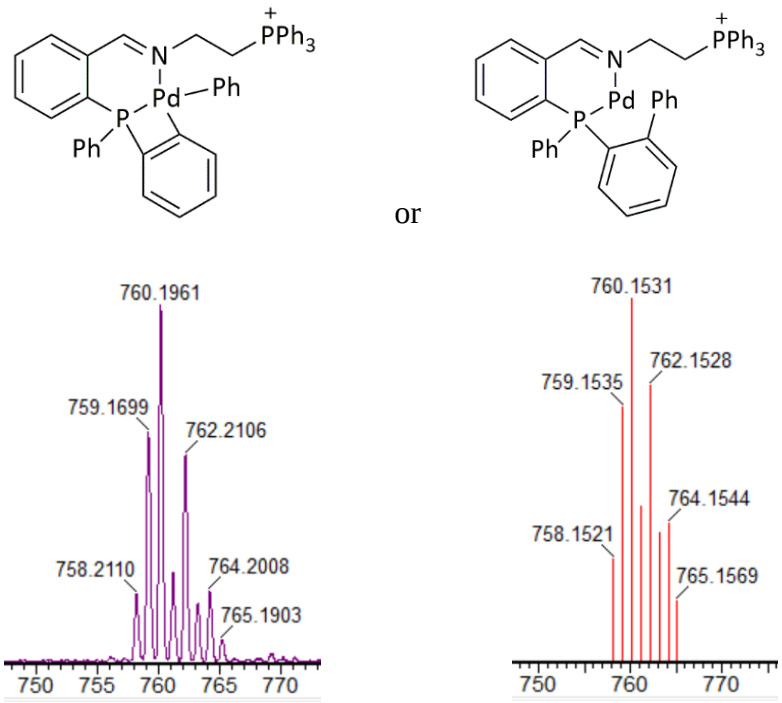
Positive ion ESI-MS Spectra of Ionic Specie Corresponding to m/z 800 (**[2 + CO_2]$^+$**).



a **[2 + CO_2]$^+$** **b**

Positive-ion ESI mass spectrum of [**2 + CO_2]$^+$**, **a**) Experimental and **b**) Simulated.

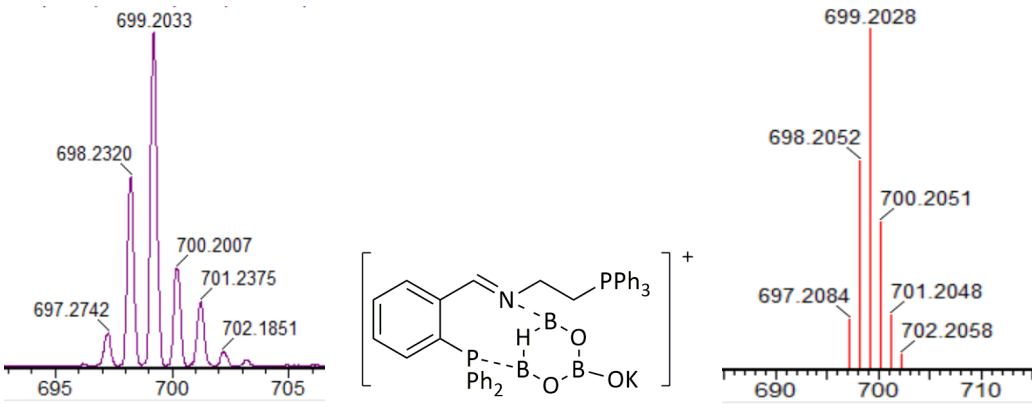
Positive ion ESI-MS Spectra of Ionic Specie Corresponding to m/z 760 (**10**).



a **b**

Positive-ion ESI mass spectrum of **10**, **a**) Experimental and **b**) Simulated.

Positive mode ESI-MS Spectra of Ionic Specie corresponding to m/z 699 (**11**).



a **11** **b**

Positive-ion ESI mass spectrum of **11**, **a**) Experimental and **b**) Simulated.