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

Doctorate in Chemistry

By

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# Table of Contents

Abstract ........................................................................................................................................ VI
Portuguese Abstract ................................................................................................................. VIII
List of Tables .............................................................................................................................. X
List of Figures ............................................................................................................................. XI
List of Schemes ........................................................................................................................ XIII
List of Abbreviations and Formulas ......................................................................................... XV

Chapter 1  Introduction and Objectives ..................................................................................... 1
  1.1  Introduction ......................................................................................................................... 2
  1.2  The Advent of Palladium Catalysis ..................................................................................... 4
  1.3  Mechanism of the Pd-Catalysed Cross-Coupling Reaction .................................................. 6
      1.3.1  Oxidative Addition ........................................................................................................ 8
      1.3.2  Transmetalation and Isomerization ............................................................................. 10
      1.3.3  Reductive Elimination ............................................................................................... 11
  1.4  A Brief Literature Survey of Suzuki-Miyaura Cross-Coupling Reaction using Nitrogen (N)-based Ligands ................................................................................................. 12
  1.5  Objectives ........................................................................................................................... 20

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 ......................................................... 21
  2.1  Introduction ......................................................................................................................... 22
  2.2  Results and Discussion ....................................................................................................... 23
  2.3  Experimental ....................................................................................................................... 37
      2.3.1  Materials and Methods ............................................................................................... 37
      2.3.2  Synthesis of Pyrazolyl Analogues .............................................................................. 38
      2.4.3  General Procedure for Suzuki-Miyaura Cross-Coupling Reaction ......................... 45
  2.4  Conclusions ......................................................................................................................... 47

Chapter 3  Pd-Catalyzed Suzuki-Miyaura Cross-coupling Reaction in Glycerol; A Green and Non-Innocent Solvent ................................................................................................................ 48
  3.1  Introduction ......................................................................................................................... 49
  3.2  Results and Discussion ....................................................................................................... 52
      3.2.1  Recycling Studies of Glycerol .................................................................................... 54
  3.3  Experimental ....................................................................................................................... 60
      3.3.1  Materials and Methods ............................................................................................... 60
Contents

3.3.2 General Procedure for Suzuki-Miyaura Cross-Coupling Reaction ............ 60
3.3.3 Glycerol Recycling Experiments ....................................................... 60
3.4 Conclusions .......................................................................................... 62

Chapter 4 Suzuki-Miyaura Cross-coupling Reaction of Aryl Halides and Aryl Boronic Acids Catalyzed by using a New Ionophillic Imino-phosphine-Pd-complex and Mechanistic Insights Using ESI Mass Spectrometry ............................................. 64
4.1 Introduction ............................................................................................ 65
4.2 Results and Discussion ........................................................................... 66
4.3 Experimental .......................................................................................... 75
  4.3.1 Materials and Methods ................................................................. 76
  4.3.2 General Procedure for Suzuki-Miyaura Cross-Coupling Reaction .... 77
  4.3.3 General Procedure for the ESI-MS Based Experiments ............... 78
4.4 Conclusions ............................................................................................ 79

Conclusion and Future Prospective ............................................................. 80
References ..................................................................................................... 82
List of Publications ....................................................................................... 106
Annexes ........................................................................................................ 107
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-9H-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
Abstract

the catalytic medium is recyclable up to 8 cycles with a slight loss of catalytic activity after 8th 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 phosphinite ligand formation by reaction with PPh₂Cl. A very good yield of the cross-coupling product was obtained using PPh₂Cl 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-phoshpine Pd-catalyst and has been characterized fully using different spectroscopic and spectrometric technique including the X-ray crystallography. The new imino-phosphine-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 pirazóis dos ligantes DPEphos e Xanthphos, respectivamente. A síntese dos novos derivados de pirazóis 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 halitos 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-aryllicos 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
Abstract

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 PPh₂Cl. Um rendimento muito bom do produto de acoplamento cruzado foi obtido usando PPh₂Cl 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-fosfina-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.
## List of Tables

<table>
<thead>
<tr>
<th>Table</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ullmann coupling reaction between 1 and 1H-Pyrazole.</td>
<td>25</td>
</tr>
<tr>
<td>2</td>
<td>Crystallographic data and structure refinement parameters for 1 and 1a.</td>
<td>28</td>
</tr>
<tr>
<td>3</td>
<td>Crystallographic data and structure refinement parameters for 2a, 2b and 2b’.</td>
<td>29</td>
</tr>
<tr>
<td>4</td>
<td>Solvent, base and Pd-source effects on the model SM cross-coupling (CC) reaction.</td>
<td>31</td>
</tr>
<tr>
<td>5</td>
<td>Temperature effect on the model SM cross-coupling reaction using ligand 2a.</td>
<td>32</td>
</tr>
<tr>
<td>6</td>
<td>Screening of new pyrazolyl ligands for the SM cross-coupling reaction.</td>
<td>33</td>
</tr>
<tr>
<td>7</td>
<td>Substrate scope using ligand 2a under optimized reaction conditions.</td>
<td>36</td>
</tr>
<tr>
<td>8</td>
<td>Pd-catalyzed SM cross-coupling reaction in glycerol.</td>
<td>52</td>
</tr>
<tr>
<td>9</td>
<td>Screening of different Pd Sources and Ligands catalyzed Suzuki-Miyaura reaction in glycerol.</td>
<td>53</td>
</tr>
<tr>
<td>10</td>
<td>Catalyst recycling for Suzuki-Miyaura reaction of bromobenzene with phenylboronic acid in glycerol.</td>
<td>55</td>
</tr>
<tr>
<td>11</td>
<td>Temperature and time effect on SM cross-coupling reaction.</td>
<td>68</td>
</tr>
<tr>
<td>12</td>
<td>Base and solvent effect on the model SM cross-coupling reaction.</td>
<td>69</td>
</tr>
<tr>
<td>13</td>
<td>Substrate scope under optimized reaction conditions.</td>
<td>70</td>
</tr>
</tbody>
</table>
## List of Figures

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The 2001 Nobel Prize winning research based on transition metals.</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>The 2005 Nobel Prize winning research based on transition metals.</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>Mechanism of Wacker oxidation.</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>The 2010 Nobel Prize winning research based on Pd-metal.</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>Well-known Pd-catalyzed coupling reactions.</td>
<td>6</td>
</tr>
<tr>
<td>6</td>
<td>Proposed catalytic cycle for Pd-catalyzed cross-coupling reactions.</td>
<td>7</td>
</tr>
<tr>
<td>7</td>
<td>Mechanism of Heck reaction.</td>
<td>8</td>
</tr>
<tr>
<td>8</td>
<td>Representative phosphine based ligands and palladacycles.</td>
<td>13</td>
</tr>
<tr>
<td>9</td>
<td>Representative phosphine-free ligands and palladacycles.</td>
<td>14</td>
</tr>
<tr>
<td>10</td>
<td>Representative amine based ligands for Suzuki cross-coupling reaction.</td>
<td>15</td>
</tr>
<tr>
<td>11</td>
<td>Representative C-based NHC ligands used for Suzuki cross-coupling reaction.</td>
<td>15</td>
</tr>
<tr>
<td>12</td>
<td>Representative bis-pyridine and phenanthroline based ligands.</td>
<td>16</td>
</tr>
<tr>
<td>13</td>
<td>Representative imine based ligands used for Suzuki cross-coupling reaction.</td>
<td>17</td>
</tr>
<tr>
<td>14</td>
<td>Representative imine, oxime and oxazoline based palladacycles.</td>
<td>18</td>
</tr>
<tr>
<td>15</td>
<td>Representative Pincer type ligands used for Suzuki cross-coupling reaction.</td>
<td>19</td>
</tr>
<tr>
<td>Figure</td>
<td>Description</td>
<td>Page</td>
</tr>
<tr>
<td>--------</td>
<td>-----------------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>16</td>
<td>Pyrazolyl analogues of DPEphos and Xantphos.</td>
<td>22</td>
</tr>
<tr>
<td>17</td>
<td>Molecular structures of 1 and 1a with the key atoms labelled (thermal ellipsoids drawn at 50% probability). For clarity, hydrogen atoms have been omitted.</td>
<td>25</td>
</tr>
<tr>
<td>18</td>
<td>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.</td>
<td>28</td>
</tr>
<tr>
<td>19</td>
<td>Oxidative cleavage of ligand 2a'd to 2a` in the presence of Pd(COD)Cl₂.</td>
<td>34</td>
</tr>
<tr>
<td>20</td>
<td>³¹P-NMR of PPh₂Cl (a), PPh₂Cl + Glycerol (b), and PPh₂Cl+Glycerol + Pd(OAc)₂ (c).</td>
<td>57</td>
</tr>
<tr>
<td>21</td>
<td>³¹P-NMR of 2-PPh₂-benzaldehyde + Glycerol (a), and 2-PPh₂-benzalade-hyde-Glycerol + PdCl₂(CH₃CN)₂ (b).</td>
<td>59</td>
</tr>
<tr>
<td>22</td>
<td>HRESI-MS and Isotopic distribution of 2: a) Experimental, b) Simulated.</td>
<td>67</td>
</tr>
<tr>
<td>23</td>
<td>Molecular structures of Ionophillic imino-phosphine Pd-complex (2a) with the key atoms labelled (thermal ellipsoids drawn at 50% probability).</td>
<td>67</td>
</tr>
<tr>
<td>24</td>
<td>Positive-ion ESI mass spectrum of 2 in methanol acquired after 2h at room temperature.</td>
<td>72</td>
</tr>
<tr>
<td>25</td>
<td>Positive-ion ESI mass spectrum of 2, and phenyl boronic acid in methanol acquired after 2h at 50°C.</td>
<td>73</td>
</tr>
<tr>
<td>26</td>
<td>Positive-ion ESI mass spectrum of 6, a) Experimental, and b) Simulated.</td>
<td>74</td>
</tr>
<tr>
<td>Scheme</td>
<td>Description</td>
<td>Page</td>
</tr>
<tr>
<td>--------</td>
<td>------------------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>1</td>
<td>The Wacker process.</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>Formation of active anionic LnPd(0) specie from Pd(OAc)$_2$ and PPh$_3$</td>
<td>9</td>
</tr>
<tr>
<td>3</td>
<td>Mechanistic pathways for oxidative addition.</td>
<td>9</td>
</tr>
<tr>
<td>4</td>
<td>Proposed four membered cyclic pathway for transmetalation.</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td><em>Cis-trans</em> Isomerization.</td>
<td>11</td>
</tr>
<tr>
<td>6</td>
<td>Proposed pathway for reductive elimination.</td>
<td>11</td>
</tr>
<tr>
<td>7</td>
<td>General protocol for Suzuki-Miyaura cross-coupling reaction.</td>
<td>12</td>
</tr>
<tr>
<td>8</td>
<td>Bromination of $p$-tolyl ether.</td>
<td>24</td>
</tr>
<tr>
<td>9</td>
<td>Synthesis of flexible mono- and bis-pyrazolyl ligands 1a and 1a`.</td>
<td>24</td>
</tr>
<tr>
<td>10</td>
<td>Synthesis of pyrazolyl analogues of 'Bu-Xanphos, 2a - 2b`.</td>
<td>27</td>
</tr>
<tr>
<td>11</td>
<td>Synthesis of hybrid ligand 2b<code>c from 2b</code>.</td>
<td>30</td>
</tr>
<tr>
<td>12</td>
<td>Synthesis of hybrid ligand 2a<code>d from 2a</code>.</td>
<td>30</td>
</tr>
<tr>
<td>13</td>
<td>Model SM reaction used for optimization and ligand evaluation.</td>
<td>31</td>
</tr>
</tbody>
</table>
### List of Schemes

<table>
<thead>
<tr>
<th>No.</th>
<th>Scheme Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>Phenylboronic esters from glycerol as active coupling partners for the Suzuki-Miyaura cross-coupling reaction.</td>
<td>50</td>
</tr>
<tr>
<td>15</td>
<td>Model Suzuki-Miyaura cross-coupling reaction in glycerol.</td>
<td>51</td>
</tr>
<tr>
<td>16</td>
<td>Expected reaction of PPh&lt;sub&gt;2&lt;/sub&gt;Cl with glycerol.</td>
<td>56</td>
</tr>
<tr>
<td>17</td>
<td>Reaction of 2-PPh&lt;sub&gt;2&lt;/sub&gt;-benzaldehyde and glycerol.</td>
<td>58</td>
</tr>
<tr>
<td>18</td>
<td>Reaction of oxolone ligands and PdCl&lt;sub&gt;2&lt;/sub&gt;(CH&lt;sub&gt;3&lt;/sub&gt;CN)&lt;sub&gt;2&lt;/sub&gt;.</td>
<td>58</td>
</tr>
<tr>
<td>19</td>
<td>Synthesis of 2-aminoethylphosphonium bromide.</td>
<td>65</td>
</tr>
<tr>
<td>20</td>
<td>Synthesis of ionophillic iminophosphine ligand, 1</td>
<td>65</td>
</tr>
<tr>
<td>21</td>
<td>Synthesis of ionophillic iminophosphine-Pd Complex, 2.</td>
<td>65</td>
</tr>
<tr>
<td>22</td>
<td>Proposed hydrolytic pathway of 2 in methanol at room temperature.</td>
<td>72</td>
</tr>
<tr>
<td>23</td>
<td>Proposed pathways for the formation of stable Pd(0) (6) intermediate.</td>
<td>74</td>
</tr>
<tr>
<td>24</td>
<td>Proposed catalytic cycle for the Suzuki-Miyaura cross-coupling reaction.</td>
<td>75</td>
</tr>
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<td>dppp</td>
<td>1,3`-bisdiphenylphosphinopropane</td>
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<td>dppf</td>
<td>1,1′-bisdiphenylphosphinoferrocene</td>
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<td>Tris(benzylideneacetone)palladium (0)</td>
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<td>Abbreviation</td>
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<td>Bis(benzonitrile)palladium (II) chloride</td>
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<tr>
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<tr>
<td>Tol</td>
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</tr>
<tr>
<td>TPPMS</td>
<td>Triphenylphosphine monosulfonate sodium salt</td>
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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](image1.png)

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

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.\textsuperscript{18, 19}

![Diagram of catalytic reaction](image)

**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 \textit{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.\textsuperscript{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 \textit{via} oxidative dimerization.\textsuperscript{21, 22} The development of this new $C_{sp}-C_{sp}$ 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.\textsuperscript{23-25} 

The significance of catalysis and its role in various fields can be concluded by citing the following statement in Nature Catalysis.\textsuperscript{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,\textsuperscript{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.\textsuperscript{28,29}

\begin{center}
\textbf{Scheme 1.} The Wacker Process.
\end{center}
Chapter 1

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).

![Diagram of palladium catalyzed cross-coupling reactions](image)

**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\textsuperscript{®} 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.
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 $\text{L}_n\text{Pd}(0)$ species,$^5\text{4}$ where $\text{L} = \text{any ligand backbone and } n = 2$, in typical palladium catalysed reactions. The most commonly accepted mechanism for the Pd-catalysed coupling reactions is showed in Figure 6. In general, the aryl halide (or pseudo halide) adds to the catalytically active $\text{L}_n\text{Pd}(0)$ species via oxidative addition and generates $\text{L}_n\text{Pd}(\text{II})$ intermediate.$^5\text{5}$ This $\text{L}_n\text{Pd}(\text{II})$ intermediate then undergoes transmetalation with an organometallic coupling partner and generates a new $\text{L}_n\text{Pd}(\text{II})$ specie bearing two organic coupling fragments at the same Pd centre.$^5\text{6}$ 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 LnPd(0). This catalytically active LnPd(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 differs from the other cross-coupling reaction by the fact that the reaction proceeds by the coordination of the alkene to the LnPd(II) species (Figure 7), after oxidative addition. The alkene itself then undergoes an intramolecular syn-migratory insertion rather than intermolecular transmetalation 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 LnPd(0) species, 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.
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). 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. Formation of anionic LnPd(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 [PdL2(OAc)]− are the active species responsible for the oxidative addition when Pd(OAc)2 and PPh3 are used as the catalytic system (Scheme 2).
Chapter 1

Scheme 2. Formation of active anionic $\text{L}_n\text{Pd}(0)$ specie from $\text{Pd(OAc)}_2$ and $\text{PPh}_3$.

As far as the organo-halides are concerned, aryl halides undergo undergo oxidative addition to the $\text{L}_n\text{Pd}(0)$ specie via two pathways i.e., via a nucleophilic aromatic substitution pathway, or a three membered metallo-cycle pathway,\textsuperscript{60, 62, 63} (Scheme 3). These pathways have been supported by the DFT studies as well.\textsuperscript{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.\textsuperscript{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.\textsuperscript{63} Regardless of the pathways, the addition of organic halides to the metal proceeds either in a concerted or a stepwise addition mechanism manner.\textsuperscript{66}

Scheme 3. Mechanistic pathways for oxidative addition.

Among the aryl halides, the relative ease of oxidative addition follows the general order, $\text{ArI} > \text{ArBr} > > \text{ArCl} >>> \text{ArF}$.\textsuperscript{67} This classical order of oxidative addition can be reversed \textit{i.e.}, $\text{ArCl} > \text{ArBr} > \text{ArI}$, if electronically rich and bulky ligands such as NHC’s, $\text{P(Bu')}_3$, Buchwald and Hartwig ligands, \textit{etc}, containing Pd catalysts are used.\textsuperscript{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 $\text{L}_n\text{Pd(II)}R^1X$ species and the organometallic reagent $(R^3M)$.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., $\text{L}_n\text{Pd(II)}R^1R^2$ 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.](image)

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-$\text{L}_n\text{Pd(II)}R^1R^2$, yet evidence for the direct cis-$\text{L}_n\text{Pd(II)}R^1R^2$ species formation are also present in the literature.63 The trans-$\text{L}_n\text{Pd(II)}R^1R^2$ 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).

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. 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. A unimolecular decomposition pathway has been proposed for the reductive elimination step.

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 $\beta$-hydride elimination side reaction can be prevented by the use of $\beta$-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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{26, 87, 88}

\begin{center}
\includegraphics[width=\textwidth]{scheme7.png}
\end{center}

\textbf{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. Despite the use of original phosphine based ligands, including PPh$_3$, electronically rich sterically bulky dialky biaryl phosphines andtrialkyl phosphines, ferrocenyl phosphines, palladacycles, etc, in cross-coupling reactions, efforts to synthesize modified and more efficient phosphine based ligands is still active part of ongoing research (Figure 8). 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.

**Figure 8.** Representative phosphine based ligands and palladacycles.

A variety of phosphine-free N-based ligands have been synthesized and reported in literatures. 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. 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
Chapter 1

$N$-based alkyl amines\textsuperscript{103} aromatic systems containing $N$- as heteroatom such as pyridine,\textsuperscript{104} bis-pyridines, phenanthroline,\textsuperscript{105} $C$-based $N$-heterocyclic carbenes and ionic liquids,\textsuperscript{106-108} $N$-based 2-aryl-2-oxazolines,\textsuperscript{109, 110} $C^N$-$N$-based aryl oxide palladacycles,\textsuperscript{111} $N$-based alky or arylimines,\textsuperscript{112} $N^N$-$N$-based diimines, $N^N$-$N$-$N$- and $N^C$-$N$-based pincer type ligands, and their hybrids (\textbf{Figure 9}).\textsuperscript{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.\textsuperscript{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.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{ligands.png}
\caption{Representative phosphine-free ligands and palladacycles.}
\end{figure}

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 (\textbf{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.$^{118}$

![Dicyclohexylamine, 1-Adamantylamine, DABCO](image)

**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).$^{123}$

![Representative precursors for C-based NHC ligands used for the Pd-catalyzed Suzuki-Miyaura cross-coupling reaction.](image)

**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
Chapter 1

*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.\textsuperscript{124} Likewise, imidazole based ionic liquids have been used as solvent medium and ligands for the Suzuki-Miyaura cross-coupling reaction.\textsuperscript{108} For example, Xiao and Shreeve have shown that using 2,2’-biimidazole as solvent medium and ligand and PdCl\textsubscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{128,129}

![Figure 12. Representative bis-pyridine and phenanthroline based ligands.](image-url)
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.\textsuperscript{130} The diimine dialkyl or diaryl substituted ligands patented by Nolan and Grasa, have been successfully used in Suzuki-Miyaura cross-coupling reactions.\textsuperscript{131} For instance, very good yields were obtained when \(N,N^{\prime}\)-dicyclopentadienyl-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.\textsuperscript{69, 132, 133}

![Imine ligands](image)

**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 palladacycles derived from oxazolines have been used to perform Suzuki-Miyaura cross-coupling by Ibrahim and co-workers.\textsuperscript{134} \(N\)-based palladacycles such as oxime and fluorinone based palladacycles 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.\textsuperscript{135} Moreover, Weissman and Milstein have used an air and thermally stable cyclometallated imine palladacycle to perform Suzuki-Miyaura cross-coupling reaction.\textsuperscript{112} On the other hand, Luo and co-workers have demonstrated that novel bis(oxazole) pincer type palladacycles 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.\textsuperscript{136}
Lastly, several $N^N$-$N^N$- and $N^C$-$N^N$-type Pincer ligands have been described in literatures to perform Suzuki-Miyaura cross-coupling reaction under mild reaction conditions (Figure 15). For instance, Yadav et al., reported new phosphine-free 2,6-bis(pyrrolyl)pyridine based $N^N$-$N^N$-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. In the same way, Jerome et al., have synthesized new phosphine-free $N^N$-$N^N$-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. As far as the $N^C$-$N^N$-type Pincer ligands are concerned, several bis(oxazoline- and bis(thiazole)-$N^C$-$N^N$-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.

![Figure 14. Representative imine, oxime and oxazoline palladacycles.](image)
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.

**Figure 15.** Representative Pincer type ligands.
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
Chapter 2

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.\textsuperscript{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.\textsuperscript{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 'Bu-Xantphos and other xanthene scaffolds have been widely described in literature.\textsuperscript{145-147} In addition to the diphosphines bearing xanthene backbone, the corresponding diamido,\textsuperscript{148} diamine,\textsuperscript{149} disilyl,\textsuperscript{150} dithiolates\textsuperscript{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.\textsuperscript{152}

![Phosphine Ligands](image1)

![Pyrazolyl Analogues](image2)

**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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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,\textsuperscript{118,160} pyridines,\textsuperscript{161} imines,\textsuperscript{162} imidazoles in the form of \( N \)-heterocyclic carbenes (NHC’s),\textsuperscript{163} oxazolines,\textsuperscript{134} and their hybrids,\textsuperscript{164} while the corresponding pyrazole based ligands have been relatively less explored.\textsuperscript{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.\textsuperscript{167-169} Nevertheless, the pyrazole based catalysts have been employed in other important \( C-C \) bond forming reactions such as oligomerizations,\textsuperscript{170} polymerizations and copolymerizations.\textsuperscript{171} Previously, we have reported some palladium complexes of bis-pyrazolyl tridentate ligands and demonstrated their application in the Suzuki cross-coupling reaction.\textsuperscript{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 \textit{DPEphos} and \textit{Xantphos}, respectively (\textbf{Figure 16}), and to explore their potential as ligands in the Pd-catalyzed Suzuki-Miyaura cross-coupling of aryl halides with aryl boronic acids.

\section*{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 \textit{DPEphos}. \( p \)-tolyl ether was chosen as the starting material to avoid the \( olp \) 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). 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.

\[
\text{Scheme 8. Bromination of} \ p\text{-tolyl ether.}
\]

Then \( 1 \) was used as substrate for the Ullmann coupling reaction with \( 1H \)-pyrazole (Scheme 9). The reaction of \( 1 \) with \( 1H \)-pyrazole \( (\text{a}) \) using a \( \text{Cu}_2O/\text{phenanthroline} \) catalytic system in DMF at 140 °C for 48 hours of magnetic stirring provided the symmetrical bis-pyrazolyl analogue \( 1\text{a} \) in 47\% isolated yield, along with 37\% of the dehalogenated mono-pyrazolyl derivative \( \text{1a}^- \) 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 \( \text{1a} \) and are summarized in Table 1 (Entries 1-4). Despite the moderate yield for \( \text{1a} \), this protocol additionally allows the isolation of the mono-pyrazolyl derivative \( \text{1a}^- \), which will be useful as a part of a library of pyrazole-based compounds for further investigation in our group, such as photophysical studies.

\[
\text{Scheme 9. Synthesis of flexible bis-pyrazolyl ligands} \ \text{1a} \ \text{and} \ \text{1a}^-.
\]

Reaction conditions: \( \text{Cu}_2O \) (20 mol\%), phenanthroline (44 mol\%), \( 1 \) (1.0 eq.), \( \text{a} \) (3.2 eq.), \( \text{Cs}_2\text{CO}_3 \) (3.0 eq.), DMF (4 mL), 140-160 °C, 48 h.
**Table 1:** Ullmann coupling reaction between 1 and 1H-Pyrazole.

<table>
<thead>
<tr>
<th>Entry</th>
<th>[Cu] (mol%)</th>
<th>Ligand (mol%)</th>
<th>Base</th>
<th>T (°C)</th>
<th>Yield (%)</th>
<th>1a</th>
<th>1a'</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuI (20)</td>
<td>-</td>
<td>Cs₂CO₃</td>
<td>120</td>
<td>19</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>CuI (20)</td>
<td>Phenanthroline (44)</td>
<td>Cs₂CO₃</td>
<td>130</td>
<td>28</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Cu₂O (20)</td>
<td>-</td>
<td>Cs₂CO₃</td>
<td>130</td>
<td>29</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Cu₂O (20)</td>
<td>Phenanthroline (44)</td>
<td>K₂CO₃</td>
<td>130</td>
<td>31</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Cu₂O (20)</td>
<td>Phenanthroline (44)</td>
<td>Cs₂CO₃</td>
<td>130</td>
<td>47</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Cu₂O (10)</td>
<td>Phenanthroline (22)</td>
<td>Cs₂CO₃</td>
<td>140</td>
<td>33</td>
<td>27</td>
<td></td>
</tr>
</tbody>
</table>

a) Reaction conditions: [Cu] (x mol%), Phenanthroline (x mol%) 1 (1.0 eq., 0.5 mmoles scale), 1H-pyrazole (3.2 eq.), Base (3.2 eq.), DMF (4 mL), 120 - 140 °C, 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(2₁/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**.

**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-9H-xanthene (2) as a substrate in the Ullmann coupling step to obtain the rigid pyrazolyl analogues of ‘Bu-Xantphos, 2a-2b’. When the same reaction conditions,
### Table 2. Crystallographic data and structure refinement parameters for 1 and 1a.

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>1a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular formula</td>
<td>C_{14}H_{12}Br_{2}O</td>
<td>C_{20}H_{18}N_{4}O</td>
</tr>
<tr>
<td>Formula weight (g mol⁻¹)</td>
<td>356.06</td>
<td>330.38</td>
</tr>
<tr>
<td>T (K)</td>
<td>293(2)</td>
<td>293(2)</td>
</tr>
<tr>
<td>Wavelength (Å)</td>
<td>0.71073</td>
<td>1.54178</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Triclinic</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P(-1)</td>
<td>P2₁/c</td>
</tr>
<tr>
<td>a, b, c (Å)</td>
<td>7.439, 7.977, 12.439(5)</td>
<td>13.5819(2), 8.27900(10), 15.9832(3)</td>
</tr>
<tr>
<td>α, β, γ (°)</td>
<td>98.873, 100.877, 108.201(5)</td>
<td>90, 106.8260 (10), 90</td>
</tr>
<tr>
<td>V (Å³)</td>
<td>670.4(7)</td>
<td>1720.28(5)</td>
</tr>
<tr>
<td>Z'</td>
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<td>4</td>
</tr>
<tr>
<td>ρ_{calc} (g cm⁻³)</td>
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<td>1.276</td>
</tr>
<tr>
<td>μ (mm⁻¹)</td>
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<td>0.652</td>
</tr>
<tr>
<td>F(000)</td>
<td>348</td>
<td>696</td>
</tr>
<tr>
<td>Crystal size (mm)</td>
<td>0.26 x 0.19 x 0.14</td>
<td>0.28 x 0.21 x 0.14</td>
</tr>
<tr>
<td>θ range (°)</td>
<td>2.979 – 27.545</td>
<td>3.399 – 78.912</td>
</tr>
<tr>
<td>Limiting indices (h, k, l)</td>
<td>-9 ≤ h ≤ 9</td>
<td>-17 ≤ h ≤ 17</td>
</tr>
<tr>
<td></td>
<td>-10 ≤ k ≤ 10</td>
<td>-10 ≤ k ≤ 10</td>
</tr>
<tr>
<td></td>
<td>-16 ≤ l ≤ 16</td>
<td>-20 ≤ l ≤ 18</td>
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<td>Reflections collected</td>
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<td>30475</td>
</tr>
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<td>Reflections unique (R_{int})</td>
<td>3091 (0.0412)</td>
<td>3688 (0.0463)</td>
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<tr>
<td>Completeness to θ_{max} (%)</td>
<td>99.8</td>
<td>100.0</td>
</tr>
<tr>
<td>Data/restraints/param.</td>
<td>3091 / 0 / 154</td>
<td>3688 / 0 / 226</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>Gaussian</td>
<td>Gaussian</td>
</tr>
<tr>
<td>Min. and max. trans.</td>
<td>0.5529 and 0.7456</td>
<td>0.8612 and 0.9389</td>
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<tr>
<td>R₁ [I &gt; 2σ(I)]</td>
<td>0.0363</td>
<td>0.0450</td>
</tr>
<tr>
<td>wR₂ [I &gt; 2σ(I)]</td>
<td>0.0943</td>
<td>0.1246</td>
</tr>
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<td>R₁ (all data)</td>
<td>0.0519</td>
<td>0.0585</td>
</tr>
<tr>
<td>wR₂ (all data)</td>
<td>0.1036</td>
<td>0.1365</td>
</tr>
<tr>
<td>S on F²</td>
<td>1.055</td>
<td>1.044</td>
</tr>
<tr>
<td>Largest diff. peak and</td>
<td>0.693 and -0.683</td>
<td>0.257 and -0.209</td>
</tr>
<tr>
<td>hole (e Å⁻³)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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 °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 Cu₂O 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 1H-pyrazole (a) was achieved by using Cu₂O under ligand free and microwave irradiation conditions.¹⁷⁵

![Reaction conditions: Cu₂O (10-20 mol%), phenanthroline (22-44 mol%), 2 (1.0 eq.), a or b (3.2 eq.), Cs₂CO₃ (3.0 eq.), DMF (4 mL), 140-160 °C, 48 h.](image)

**Scheme 10.** Synthesis of pyrazolyl analogues of 'Bu-Xanphos 2a - 2b`.

Surprisingly, the scenario was different when we used 3-mesityl-1H-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 Cu₂O 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 \(2b^\prime\) 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 \(2b^\prime\) were collected from concentrated 10\% ethyl acetate and hexane solutions of the pure compounds. Both \(2b\) and \(2b^\prime\) 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 \(2b^\prime\). Both of them were quite similar, therefore, only one of the molecular structures is represented below in Figure 18.

\[
\text{Figure 18. Molecular structures of } 2a, 2b \text{ and } 2b^\prime \text{ with the key atoms labelled (thermal ellipsoids drawn at 50\% probability). For clarity, hydrogen atoms have been omitted.}
\]
### Table 3. Crystallographic data and structure refinement parameters for 2a, 2b and 2b'.

<table>
<thead>
<tr>
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<th>2a</th>
<th>2b</th>
<th>2b’</th>
</tr>
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<tbody>
<tr>
<td>Molecular formula</td>
<td>C29H34N4O</td>
<td>C37H42N4O</td>
<td>C35H41BrN2O</td>
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<tr>
<td>Formula weight (g mol⁻¹)</td>
<td>454.60</td>
<td>690.94</td>
<td>585.61</td>
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<tr>
<td>T (K)</td>
<td>292(2)</td>
<td>100(2)</td>
<td>100(2)</td>
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<tr>
<td>Wavelength (Å)</td>
<td>0.71073</td>
<td>1.54178</td>
<td>0.71073</td>
</tr>
<tr>
<td>Crystal system</td>
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<td>Triclinic</td>
<td>Triclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P(-1)</td>
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<td>a, b, c (Å)</td>
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<td>(18), 14.7167(17)</td>
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<td></td>
</tr>
<tr>
<td>a, β, γ (°)</td>
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<td>Z’</td>
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<td>4</td>
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<tr>
<td>ρcalcd (g cm⁻³)</td>
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<td>μ (mm⁻¹)</td>
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<td>Crystal size (mm)</td>
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<td>0.14 x 0.14 x 0.12</td>
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<td>3.204 – 62.381</td>
<td>2.656–26.372</td>
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<td>-14 ≤ k ≤ 14, -19 ≤ k ≤ 19</td>
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<tr>
<td>Completeness to θmax (%)</td>
<td>99.8</td>
<td>99.0</td>
<td>99.9</td>
</tr>
<tr>
<td>Data/restraints/param.</td>
<td>11384 / 0 / 613</td>
<td>6210 / 0 / 469</td>
<td>12409 / 0 / 725</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>Gaussian</td>
<td>Gaussian</td>
<td>Gaussian</td>
</tr>
<tr>
<td>Min. and max. trans.</td>
<td>0.7455 and 0.6524</td>
<td>0.8412 and 0.9402</td>
<td>0.6987 and 0.8279</td>
</tr>
<tr>
<td>R1 [I &gt; 2σ(I)]</td>
<td>0.0991</td>
<td>0.0595</td>
<td>0.0455</td>
</tr>
<tr>
<td>wR2 [I &gt; 2σ(I)]</td>
<td>0.2433</td>
<td>0.1497</td>
<td>0.1168</td>
</tr>
<tr>
<td>R1 (all data)</td>
<td>0.1825</td>
<td>0.0819</td>
<td>0.0598</td>
</tr>
<tr>
<td>wR2 (all data)</td>
<td>0.3028</td>
<td>0.1643</td>
<td>0.1256</td>
</tr>
<tr>
<td>S on F²</td>
<td>n/a</td>
<td>1.044</td>
<td>1.022</td>
</tr>
<tr>
<td>Largest diff. peak and hole (e Å⁻³)</td>
<td>0.721 and -0.368</td>
<td>0.577 and -0.576</td>
<td>5.650 and -1.896</td>
</tr>
</tbody>
</table>
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 $1H$-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. 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).
Chapter 2

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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>[Pd]</th>
<th>Base</th>
<th>Solvent</th>
<th>Conversion (%)$^b$</th>
<th>CC Yield (%)$^b$</th>
<th>HC Yield (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)$_2$</td>
<td>KOH</td>
<td>MeOH</td>
<td>74</td>
<td>66</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)$_2$</td>
<td>K$_3$PO$_4$</td>
<td>Dioxan</td>
<td>48</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)$_2$</td>
<td>Cs$_2$CO$_3$</td>
<td>DMF</td>
<td>87</td>
<td>61</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)$_2$</td>
<td>K$_2$CO$_3$</td>
<td>DMF</td>
<td>99</td>
<td>98</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OAc)$_2$</td>
<td>K$_2$CO$_3$</td>
<td>MeOH</td>
<td>75</td>
<td>44</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>Pd(OAc)$_2$</td>
<td>K$_2$CO$_3$</td>
<td>THF:MeOH</td>
<td>65</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>Pd(OAc)$_2$</td>
<td>K$_2$CO$_3$</td>
<td>THF</td>
<td>49</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>Pd(OAc)$_2$</td>
<td>K$_2$CO$_3$</td>
<td>Dioxan</td>
<td>48</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>PdCl$_2$</td>
<td>K$_2$CO$_3$</td>
<td>DMF</td>
<td>97</td>
<td>88</td>
<td>4</td>
</tr>
<tr>
<td>10</td>
<td>PdCl$_2$(COD)</td>
<td>K$_2$CO$_3$</td>
<td>DMF</td>
<td>93</td>
<td>92</td>
<td>2</td>
</tr>
</tbody>
</table>

$^a$ 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-diy1)-bis(3,5-dimethyl-1H-pyrazole). 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$_2$CO$_3$, after 6 hours of magnetic stirring at 80 °C, 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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Conversion (%)$^b$</th>
<th>CC Yield (%)$^b$</th>
<th>HC Yield (%)$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25</td>
<td>24</td>
<td>73</td>
<td>59</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>12</td>
<td>92</td>
<td>70</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>80</td>
<td>6</td>
<td>99</td>
<td>98</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>110</td>
<td>3</td>
<td>90</td>
<td>75</td>
<td>1</td>
</tr>
<tr>
<td>5$^d$</td>
<td>80</td>
<td>12</td>
<td>87</td>
<td>82</td>
<td>1</td>
</tr>
<tr>
<td>6$^e$</td>
<td>80</td>
<td>24</td>
<td>98</td>
<td>86</td>
<td>16</td>
</tr>
</tbody>
</table>

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$_2$CO$_3$ (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 observed (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 °C (Table 5, Entries 2 and 3). A further increase in the temperature of the reaction to 110 °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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Conversion (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>CC Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>HC Yield (%)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>99</td>
<td>98</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>2b</td>
<td>&gt;99</td>
<td>98</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>2b`c</td>
<td>99</td>
<td>98</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>2a`</td>
<td>87</td>
<td>86</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>2a`d</td>
<td>46</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>1a</td>
<td>83</td>
<td>47</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>1a`</td>
<td>62</td>
<td>29</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>-</td>
<td>68</td>
<td>44</td>
<td>2</td>
</tr>
<tr>
<td>9</td>
<td>Xantphos</td>
<td>93</td>
<td>92</td>
<td>6</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction conditions: Pd(OAc)<sub>2</sub> (1.0 mol%), Ligand (1.1 mol%), K<sub>2</sub>CO<sub>3</sub> (2 eq.), DMF (4 mL), 80 °C, and 6 h. <sup>b</sup> GC conversion and yield based on 4-bromotoluene. <sup>c</sup> 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$_2$CO$_3$ as base, DMF as solvent at 80 °C 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 monopyrazolyl 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.\textsuperscript{177}

![Figure 19. Oxidative cleavage of ligand 2a'd to 2a' in the presence of Pd(COD)Cl$_2$.](image)

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 [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’\textsuperscript{`d}. Likewise, the flexible ligands 1a and 1a’\textsuperscript{`d} 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’\textsuperscript{`d} 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)\textsubscript{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.\textsuperscript{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.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>(R^1)</th>
<th>(X)</th>
<th>(R^2)</th>
<th>Yield (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-Me</td>
<td>Br</td>
<td>H</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>4-CF(_3)</td>
<td>Br</td>
<td>H</td>
<td>82</td>
</tr>
<tr>
<td>3</td>
<td>4-Ac</td>
<td>Br</td>
<td>H</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>4-OMe</td>
<td>Br</td>
<td>H</td>
<td>91</td>
</tr>
<tr>
<td>5</td>
<td>2-bromonaphthalene</td>
<td></td>
<td>H</td>
<td>91</td>
</tr>
<tr>
<td>6</td>
<td>4-Me</td>
<td>Br</td>
<td>4-OMe</td>
<td>82</td>
</tr>
<tr>
<td>7</td>
<td>4-Me</td>
<td>Br</td>
<td>4-Ac</td>
<td>78</td>
</tr>
<tr>
<td>8</td>
<td>4-OMe</td>
<td>Br</td>
<td>4-Ac</td>
<td>73</td>
</tr>
<tr>
<td>9</td>
<td>4-Ac</td>
<td>Br</td>
<td>4-Me</td>
<td>81</td>
</tr>
<tr>
<td>10</td>
<td>2-Me</td>
<td>Br</td>
<td>H</td>
<td>58</td>
</tr>
<tr>
<td>11</td>
<td>4-Me</td>
<td>Br</td>
<td>2-Me</td>
<td>54</td>
</tr>
<tr>
<td>12</td>
<td>4-Me</td>
<td>Br</td>
<td>2,6-diMe</td>
<td>46</td>
</tr>
<tr>
<td>13</td>
<td>4-CF(_3)</td>
<td>I</td>
<td>H</td>
<td>78</td>
</tr>
<tr>
<td>14</td>
<td>4-OMe</td>
<td>I</td>
<td>H</td>
<td>80</td>
</tr>
<tr>
<td>15</td>
<td>4-Ac</td>
<td>Cl</td>
<td>H</td>
<td>75</td>
</tr>
<tr>
<td>16</td>
<td>4-Ac</td>
<td>Cl</td>
<td>H</td>
<td>3(^c)</td>
</tr>
<tr>
<td>17</td>
<td>4-Me</td>
<td>Cl</td>
<td>H</td>
<td>25</td>
</tr>
</tbody>
</table>

\(^{a}\) Reaction conditions: \(\text{Pd(OAc)}\(_2\) (1 mol%), 2a (1.1 mol%), \text{K}_2\text{CO}_3\ (2 eq), \text{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-chlorotoluene 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 CDCl₃ 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 attenuated 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 NH₄OAc (20 mol%, 2 mmol) and p-tolyl-ether (1 eq., 10 mmol) in 35 mL of CH₃CN, 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 MgSO₄ 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.
Chapter 2

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

White crystalline solid (m.p. = 74-75 °C); $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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$_2$ONa (M+Na)$^+$; 376.9153, found 376.9140.

Preparation of 3-Mesityl-1H-pyrazole (adapted from literature)\textsuperscript{179,180}

To a chilled dry toluene solution in a round bottom flask maintained at 0 °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 °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\(_3\)) \(\delta\) 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\(_3\)) \(\delta\) 143.93, 138.01, 137.71, 135.75, 128.04, 105.61, 21.07, 20.23.

Synthesis of ligands 1a and 1a\(^\prime\)

A resealable Schlenk flask evacuated and back-filled with argon (3x) was charged with Cu\(_2\)O (21.5 mg, 0.15 mmol), 1,10-phenanthroline (59.5 mg, 0.33 mmol), 1 (267.1 mg, 0.75 mmol), 1H-pyrazole (a) (163.5 mg, 2.4 mmol) and Cs\(_2\)CO\(_3\) (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 °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\(_2\)Cl\(_2\). 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\(^\prime\) in 37% yield.

1,1\(^\prime\)-(oxybis(5-methyl-2,1-phenylene))bis(1H-pyrazole) (1a)

White crystalline solid (m.p. = 124-125 °C); \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) 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\(_3\)) \(\delta\) 145.71, 140.35, 134.70, 131.41, 131.07, 129.07, 126.22, 119.30, 107.05, 20.81; IR \(\nu_{\text{max}}\) (neat): 1497, 1221, 1034, 809, 761; HRMS (ESI-TOF): \(m/z\) calcd for C\(_{20}\)H\(_{18}\)N\(_4\)O\(_2\)Na (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\(_{3}\)) \(\delta\) 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), 6.37 (t, J = 2.4 Hz, 1H), 2.40 (s, 3H), 2.31 (s, 3H). \(^{13}C\)-NMR (100 MHz, CDCl\(_{3}\)) \(\delta\) 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 \(\nu\)\(_{\text{max}}\) (neat): 1522, 1496, 1228, 809, 748; HRMS (ESI-TOF): \(m/z\) calcd for C\(_{17}\)H\(_{16}\)N\(_{2}\)ONa (M+Na\(^{+}\)): 287.1160, found 287.1450.

Synthesis of Ligands 2a and 2a’

1H-pyrazole (a) and 4,5-dibromo-2,7-di-tert-butyl-9,9-dimethyl-9H-xanthene (2) were reacted under similar conditions described above for the synthesis of ligand 1a, except the reaction was magnetically stirred at 160 °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 °C - decompose); \( ^{1}H\)-NMR (400 MHz, CDCl\(_{3}\)): \(\delta\) 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\(_{3}\)): \(\delta\) 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 \(\nu\)\(_{\text{max}}\) (neat): 2953, 1469, 1453, 1259, 750; HRMS (ESI-TOF): \(m/z\) calcd for C\(_{29}\)H\(_{35}\)N\(_{4}\)O (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 °C); \( ^{1}H\)-NMR (400 MHz, CDCl\(_{3}\)): \(\delta\) 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$_3$): $\delta$ 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 $\nu$$_{\text{max}}$ (neat): 2960, 1455, 1269, 850, 761; HRMS (ESI-TOF): m/z calcld for C$_{26}$H$_{33}$N$_{2}$O (M+H)$^+$: 389.2593, found 389.2622.

Synthesis of Ligands 2b and 2b$^\prime$

3-mesityl-1$H$-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$^\prime$ 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 °C); $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 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 $\nu$$_{\text{max}}$ (neat): 2959, 1458, 1266, 1238, 849, 761, 741; HRMS (ESI-TOF): m/z calcld for C$_{47}$H$_{55}$N$_{4}$O (M+H)$^+$: 691.4376, found 691.4397.

1-(5-bromo-2,7-di-tert-butyl-9,9-dimethyl-9H-xanthene-4-yl) 3-mesityl-1H-pyrazole (2b$^\prime$)

White crystalline solid (m.p. = 189-191 °C); $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 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; \textbf{IR }\nu_{\text{max}} \textup{ (neat): } 2960, 1455, 1269, 850, 761; \textbf{HRMS} (ESI-TOF): m/z calcd for C_{35}H_{42}BrN_{2}O (M+H)^{+}: 585.2480, found 585.2461.

\textbf{Synthesis of hybrid Ligand }2b`c

\(2b^\circ\) and 1\textup{H}-imidazole (c) as coupling partners were allowed to react under the reaction conditions described above for the synthesis of ligand 2\textup{\textit{b}}\textit{ 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.

\textbf{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 °C); \textbf{\textup{\textit{1}}}H-NMR (400 MHz, CDCl\textsubscript{3}): \(\delta \) 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);

\textbf{\textup{\textit{1}}}C-NMR (100 MHz, CDCl\textsubscript{3}): \(\delta \) 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; \textbf{IR }\nu_{\text{max}} \textup{ (neat): } 2953, 1497, 1456, 1271, 760; \textbf{HRMS} (ESI-TOF): m/z calcd for C_{38}H_{45}N_{4}O (M+H)^{+}: 573.3588, found 573.3580.

\textbf{Synthesis of Hybrid Ligand }2a`d

Ligand \(2a`d\) was synthesized following a recently reported method.\textsuperscript{181} An overn dried schelnk flask, evacuated and backfilled with argon 3 times was charged with PdCl\textsubscript{2} (5 \textup{mol%}), CuCl\textsubscript{2} (5 \textup{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 °C. 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$_3$): $\delta$ 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$_2$O), 1.38 (s, 9H), 1.33 (s, 9H): $\delta$ 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 $\nu_{\text{max}}$ (neat): 2958, 2867, 1497, 1511, 1393, 940, 766; HRMS (ESI-TOF): m/z calcd for C$_{32}$H$_{36}$N$_2$OSeNa (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 ($\lambda$ = 1.54178 Å) or Mo-Kα ($\lambda$ = 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$_2$CO$_3$ (1.0 mmol) were added, finally, 1 DMF (2 mL) was added and sealed under argon atmosphere. The reaction mixture was heated at 80 °C 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°C (Literature 49-50); $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 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°C; $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 7.69 (m, 4H), $\delta$ 7.62 – 7.58 (m, 2H), 7.50 – 7.44 (m, 2H), 7.43 – 7.38 (m, 1H); $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 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°C (Literature 110-111); $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 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$_3$): $\delta$ 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$_3$): $\delta$ 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 °C; $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 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$_3$): $\delta$ 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$_3$): $\delta$ 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$_3$): $\delta$ 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$_3$): $\delta$ 197.78, 145.71, 136.23, 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$_3$): $\delta$ 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$_3$): $\delta$ 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$_3$): $\delta$ 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$_3$): $\delta$ 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$_3$): $\delta$ 7.22 - 7.25 (m, Hz, 8H), 2.40 (s, 3H), 2.28 (s, 3H); $^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 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$_3$): $\delta$ 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 analogue 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.
Chapter 3

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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{185} Therefore, the search for environmentally benign reaction medium has remained an important issue for the Pd-catalyzed Suzuki-Miyaura cross-coupling reactions.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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,\textsuperscript{193} including Pd-catalyzed Heck and Suzuki-Miyaura cross-couplings, metal catalyzed transfer hydrogenation reactions and asymmetric reductions.\textsuperscript{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.\textsuperscript{194} Reports of Suzuki-Miyaura cross-coupling reaction studies using glycerol as solvent medium under ultrasound or microwave irradiations are also found in literature.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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-Miyaura cross-coupling reaction.\textsuperscript{201}](image)

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.\textsuperscript{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 ³¹P-NMR for the formation of an in situ phosphinite ligand which can be formed from the reaction of PPh₂Cl 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.$^{201}$

<table>
<thead>
<tr>
<th>Entry</th>
<th>[Pd] (mol%)</th>
<th>R</th>
<th>Base</th>
<th>Time (h)</th>
<th>Yield (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(dba)$_2$ (1)</td>
<td>Me</td>
<td>K$_3$PO$_4$</td>
<td>4</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>Pd(dba)$_2$ (1)</td>
<td>Me</td>
<td>Na$_2$CO$_3$</td>
<td>4</td>
<td>54</td>
</tr>
<tr>
<td>3</td>
<td>Pd(dba)$_2$ (1)</td>
<td>Me</td>
<td>KOH</td>
<td>4</td>
<td>54</td>
</tr>
<tr>
<td>4</td>
<td>Pd(dba)$_2$ (1)</td>
<td>H</td>
<td>KOH</td>
<td>4</td>
<td>46</td>
</tr>
<tr>
<td>5</td>
<td>Pd(dba)$_2$ (1)</td>
<td>H</td>
<td>KOH</td>
<td>24</td>
<td>70</td>
</tr>
<tr>
<td>7</td>
<td>PdCl$_2$(PCy)$_3$ (1)</td>
<td>H</td>
<td>KOH</td>
<td>24</td>
<td>81</td>
</tr>
<tr>
<td>8</td>
<td>PdCl$_2$(PPh)$_3$ (1)</td>
<td>H</td>
<td>KOH</td>
<td>24</td>
<td>99</td>
</tr>
</tbody>
</table>

$^a$ 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.\textsuperscript{201} For instance, when the model reaction was performed using 1mol\% of Pd(dba)_2, the cross-coupling product was obtained in 81\% 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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>[Pd] (mol%)</th>
<th>Ligand (mol%)</th>
<th>Yield (%)\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(dba)_2 (1)</td>
<td>-</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>PdCl_2(PCy_3)_2 (1)</td>
<td>-</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>PdCl_2(PPh_3)_2 (1)</td>
<td>-</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td>PdCl_2(dpff) (2)</td>
<td>-</td>
<td>76\textsuperscript{e}</td>
</tr>
<tr>
<td>5</td>
<td>PdCl_2(dpff) (2)</td>
<td>-</td>
<td>86</td>
</tr>
<tr>
<td>6</td>
<td>PdCl_2(2-PPh_3-benzaldehyde)_2 (1)</td>
<td>-</td>
<td>79</td>
</tr>
<tr>
<td>7</td>
<td>Pd(OAc)_2 (1)</td>
<td>-</td>
<td>62</td>
</tr>
<tr>
<td>8</td>
<td>Pd(OAc)_2 (2)</td>
<td>PPh_2Cl (4)</td>
<td>98</td>
</tr>
<tr>
<td>9</td>
<td>Pd(OAc)_2 (1)</td>
<td>2-PPh_3-benzaldehyde (2)</td>
<td>68</td>
</tr>
</tbody>
</table>

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

In order to compared the results obtained by Wolfson and co-workers,\textsuperscript{194} the model reaction was performed under the similar conditions described \textit{i.e.}, using 2 mol\% of PdCl_2(dpff), 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$_2$Cl (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.\textsuperscript{201}
The glycerol catalytic media recycling experiments were then performed using PdCl₂(PPh₃)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

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Ph-Ph Yield (%) b</th>
<th>PdCl₂(PPh₃)₂</th>
<th>PdCl₂(dppe)</th>
<th>PdCl₂(PPh₃)₂ c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>88</td>
<td>86</td>
<td>89</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>89</td>
<td>28</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>85</td>
<td>19</td>
<td>86</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>65</td>
<td>-</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td>-</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>-</td>
<td>-</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>-</td>
<td>-</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>-</td>
<td>-</td>
<td>31</td>
<td></td>
</tr>
</tbody>
</table>

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 PdCl₂(PPh₃)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 PdCl₂(PPh₃)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 5th 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$_2$Cl) with alcohols (ROH) to give the corresponding phosphinite (Ph$_2$POR) ligands is already a known reaction.$^{202, 203}$ So, we expected that the treatment of PPh$_2$Cl with glycerol would form an in situ phosphinite ligand (Ph$_2$P-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](image)

**Scheme 16.** Expected reaction of PPh$_2$Cl with glycerol.

To support this assumption, PPh$_2$Cl (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 PPh₂Cl was consumed within the first hour, supported by the up field shift of the PPh₂Cl signal from 81.8 ppm (Figure 20-a) to 21.7 and 25.9 ppm in the ³¹P-NMR of the crude reaction mixture (Figure 20-b). Then a mixture of glycerol and PPh₂Cl 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 ³¹P-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-PPh₂ signals at 21.7 and 25.9 ppm supporting a partial in situ complex formation with Pd (Figure 20-c).

![Figure 20](image_url)

**Figure 20:** ³¹P-NMR of PPh₂Cl (a), PPh₂Cl + Glycerol (b), and PPh₂Cl + Glycerol + Pd(OAc)₂ (c).

Although, we tried many times to isolate the phosphinite ligand and Pd-complex formed in situ, but our attempts remained unsuccessful, nevertheless, our objective here was to increase the number of recycles 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, PPh₂Cl (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$_2$Cl and the glycerol to proceed as proposed.

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

<table>
<thead>
<tr>
<th>Cycle</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC Yield (%)$^b$</td>
<td>98</td>
<td>83</td>
<td>10</td>
</tr>
</tbody>
</table>

Reaction Conditions: 1 mol% Pd(OAc)$_2$, 20 mol% PPh$_2$Cl, 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 oxo lone 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.\textsuperscript{204, 205}

Scheme 18. Reaction for oxolone ligands with PdCl\(_2\)(CH\(_3\)CN)\(_2\).

Figure 21. \(^{31}\)P-NMR of 2-PPh\(_2\)-benzaldehyde + Glycerol (a), and 2-PPh\(_2\)-benzaldehyde-Glycerol + PdCl\(_2\)(CH\(_3\)CN)\(_2\) (b).

To this reaction mixture we then added PdCl\(_2\)(CH\(_3\)CN)\(_2\) 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$_2$-benzaldehyde 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 aryloboronic acid (0.55 mmol), KOH (1.0 mmol, 56 mg), and glycerol (4.0 mL). The reaction mixture was allowed to magnetically stir 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 stir 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 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 stir 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$_2$Cl

To an oven dried resealable Schlenk tube, evacuated and back filled with argon, PPh$_2$Cl (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°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°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 8$^{th}$ 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 8$^{th}$ 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$_2$PCL can be converted *in situ* into a phosphinite ligand. The attempts to recycle the catalytic system suggested that it is recyclable up to
Chapter 3

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 Ionophlllic 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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. 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, 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. 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.


Then a mixture of 2-aminoethyl-triphenylphosphonium bromide (2.9 mmol), 2-diphenylphosphino-benzaldehyde (2.9 mmol), KPF₆ (5.8 mmol) and a pinch of Na₂SO₄ 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.


Then a mixture of 1 (2.4 mmol) and PdCl\(_2\)(CH\(_3\)CN)\(_2\) (2.4 mmol) were mixed to a Schlenk tube under argon in 50 mL of dry CH\(_2\)Cl\(_2\) 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\(_2\)O and solvent evaporation, delivered the desired complex 2 in 76% yield.


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\(_2\)NP\(_2\)Pd (calcd. 756.0598) (Figure 22).
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 $P\bar{1}$ space group.\textsuperscript{201} The solid-state structure of 2 is shown in Figure 23 (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 °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 °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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Conversion (%)b</th>
<th>CC Yield (%)b</th>
<th>HC Yield (%)c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>80</td>
<td>8</td>
<td>90</td>
<td>81</td>
<td>1</td>
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<tr>
<td>2</td>
<td>80</td>
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<td>80</td>
<td>24</td>
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<tr>
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<tr>
<td>6</td>
<td>100</td>
<td>16</td>
<td>100</td>
<td>96</td>
<td>2</td>
</tr>
</tbody>
</table>

a) Reaction conditions: K₂CO₃ (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 °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 °C (Table 11, entry 7). Therefore, we concluded that the model reaction after 16 hours at 100 °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, K₂CO₃ and Cs₂CO₃ showed the best result, (Table 12, entry 2).

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Solvent</th>
<th>Conversion (%)$^b$</th>
<th>CC Yield (%)$^b$</th>
<th>HC Yield (%)$^c$</th>
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<tbody>
<tr>
<td>1</td>
<td>K₂CO₃</td>
<td>Dioxane</td>
<td>100</td>
<td>96</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>Cs₂CO₃</td>
<td>Dioxane</td>
<td>100</td>
<td>97</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>KOH</td>
<td>Dioxane</td>
<td>100</td>
<td>92</td>
<td>5</td>
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<tr>
<td>4</td>
<td>KOH</td>
<td>MeOH</td>
<td>99</td>
<td>98</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>K₂CO₃</td>
<td>MeOH</td>
<td>99</td>
<td>85</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>KOH</td>
<td>Glycerol</td>
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<td>58</td>
<td>5</td>
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<tr>
<td>7$^d$</td>
<td>K₂CO₃</td>
<td>Dioxane</td>
<td>92</td>
<td>89</td>
<td>2</td>
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</table>

a) Reaction conditions: 0.5 mmol aryl bromide, 0.65 mmol arylboronic acid, 1 mol\% Pd, 4 mL Solvent, 1 mmol base, 100 °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, K₂CO₃ 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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>X</th>
<th>R²</th>
<th>Conv. (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>CC Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>HC Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-Me</td>
<td>Br</td>
<td>H</td>
<td>100</td>
<td>96 (95)</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>4-Me</td>
<td>I</td>
<td>H</td>
<td>100</td>
<td>96</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>4-Me</td>
<td>Cl</td>
<td>H</td>
<td>0</td>
<td>0</td>
<td>8</td>
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<tr>
<td>4</td>
<td>4-OMe</td>
<td>Br</td>
<td>H</td>
<td>100</td>
<td>91</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>4-Ac</td>
<td>Br</td>
<td>H</td>
<td>100</td>
<td>98</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>4-Me</td>
<td>Br</td>
<td>2-Me</td>
<td>100</td>
<td>77</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>4-Me</td>
<td>Br</td>
<td>4-Ac</td>
<td>100</td>
<td>96</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>4-Me</td>
<td>Br</td>
<td>4-OMe</td>
<td>100</td>
<td>94</td>
<td>2</td>
</tr>
</tbody>
</table>

<sup>a)</sup> Reaction conditions: 0.5 mmol aryl bromide, 0.65 mmol arylboronic acid, 1 mol% 2, 4 mL Dioxane, 1 mmol K₂CO₃, 100 °C, 16h; <sup>b</sup>) 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 °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 CO₂ ([2 + CO₂])⁺ 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 PdCl₂ 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 50°C acquired after 2h showed three key reaction intermediates in the ESI mass spectrum. 2 and [2 + CO2]+ 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 K2CO3 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 ionophilic backbone at m/z 699 and 760. The species with m/z 699 was in consistent to an adduct of [1 + B3O3HK], 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.

**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-phosphine 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 K₂CO₃ 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$_2$CO$_3$ 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$_3$): $\delta$ (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$_3$): $\delta$ (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$_3$PO$_4$, 25 °C): $\delta$ (ppm) 23.7

Synthesis of 2-diphenylphosphino-1-iminoethyltriphenylphosphonium hexafluorophosphate 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$_2$SO$_4$ 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$_2$O 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$_3$) $\delta$ (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$_3$PO$_4$): $\delta$ (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$_3$CN)$_2$ (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$_2$Cl$_2$ was added and magnetically stirred at room temperature for 12 h. The crude product was filtered and washed with Et$_2$O 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$_3$CN): $\delta$ (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$_3$CN, H$_3$PO$_4$): $\delta$(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$_2$NP$_2$Pd: 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 °C. Desolvation temperature: 80 °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), K₂CO₃ (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°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 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 synthesized 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 8th 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
spectrometry. 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


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

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

![1H-NMR Spectrum of 1 (CDCl3, 400 MHz)](image1)

![13C-NMR Spectrum of 1 (CDCl3, 100 MHz)](image2)
1.2 $^1$H- and $^{13}$C-NMR Spectra of 3-Mesityl-1H-pyrazole (b)
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`
1.5 $^1$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$^\ddagger$

$^1$H-NMR Spectrum of 2a$^\ddagger$ (CDCl$_3$, 400 MHz)

$^{13}$C-NMR Spectrum of 2a$^\ddagger$ (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\textsuperscript{c}
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-phenynaphthalene.

$^1$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-, $^{13}$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.
\[^1\text{H}-\text{and}~^{31}\text{P}-\text{NMR spectra of}~2\text{-diphenylphosphino-1-iminoethyltriphenylphosphonium hexafluorophosphate.}\]

\[^1\text{H}-\text{NMR of}~2\text{-diphenylphosphino-1-iminoethyltriphenylphosphonium hexafluorophosphate.}\]

\[^{31}\text{P}-\text{NMR spectra of}~2\text{-diphenylphosphino-1-iminoethyltriphenylphosphonium hexafluorophosphate.}\]
$^{1}$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 + CO₂]⁺).

Positive-ion ESI mass spectrum of [2 + CO₂]⁺, a) Experimental and b) Simulated.
Positive ion ESI-MS Spectra of Ionic Specie Corresponding to m/z 760 (10).

or

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).

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