

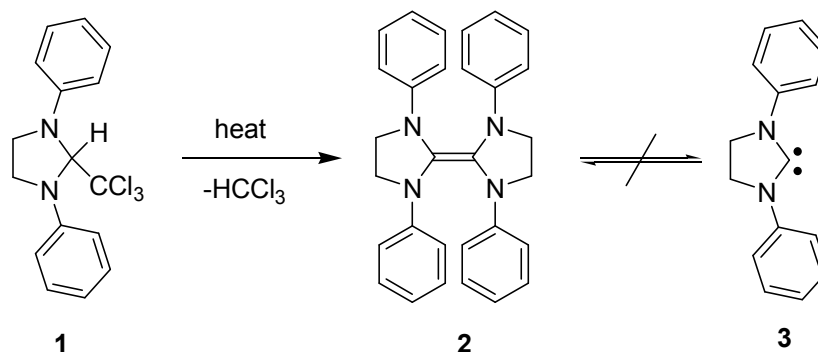
CHAPTER I

INTRODUCTION

INTRODUCTION

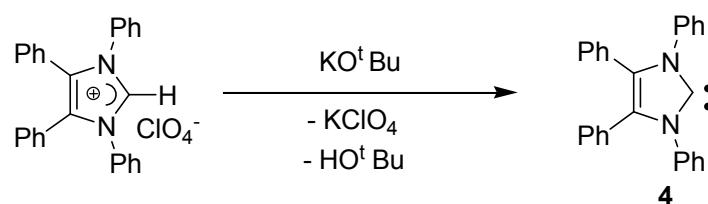
I.A. *N*-heterocyclic carbene

Carbenes are organic molecules containing an electron deficient, divalent carbon atom with two non-bonding electrons and has the general formula: CR_2 . Although the existence of simplest carbene $:\text{CH}_2$ (methylene), was proposed in 1930, the definite evidence for its existence came much later.¹ In ground-state, two unshared electrons may either be in the same orbital with antiparallel spins (singlet state) or in two degenerate orbitals with parallel spins (triplet state), accordingly, carbene can be of linear or bent geometry. *N*-heterocyclic carbenes (NHCs) are neutral compounds which also have a divalent carbon atom with two non-bonding electrons like simple carbenes.² In 1960, initiative attempt for the synthesis of *N*-heterocyclic carbene was done by Wanzlick and the α -elimination method was used for the elimination of chloroform from **1**. Wanzlick, however, could never isolate the postulated imidazolidin-2-ylidene (**3**); instead he always obtained the dimer, the electron rich alkene (**2**) (scheme-I.1).



Scheme-I.1: Wanzlick's Carbene Dimer

Initially Wanzlick postulated equilibrium between dimer (**2**) and monomer/*N*-heterocyclic carbene (**1**). But, the cross-metathesis experiment with differently substituted dimers excluded any equilibrium between monomer and dimer forms. These results were therefore not in support of the Wanzlick's earlier postulate.⁴ The tendency of dimerization was a major stumbling block in achieving isolated NHCs. Although the isolation of free NHC proved difficult, Wanzlick attempted to prepare the free carbene (**4**) by direct deprotonation of tetraphenylimidazolium perchlorate with KO^tBu (scheme-I.2).



Scheme-I.2: Deprotonation of tetraphenylimidazolium perchlorate

The free carbene could not be isolated but he managed to capture it by the isolation of mercury-complex upon treatment with $\text{Hg}(\text{OAc})_2$.⁵ Ofele also prepared NHC complexes *via* the thermolysis of dimethylimidazolium hydridopentacarbonylchromate(II)⁶. In 1970s, Lappert used NHC dimer alkenes to produce carbene complexes of Mo and Fe, the first complexes with saturated NHCs.⁷ Although chemists across the world were trying to isolate a free stable carbene, and in 1988 Bertrand *et al.* first synthesized isolable carbene (figure-I.1).

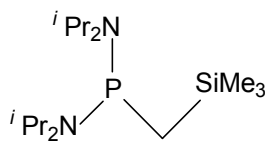
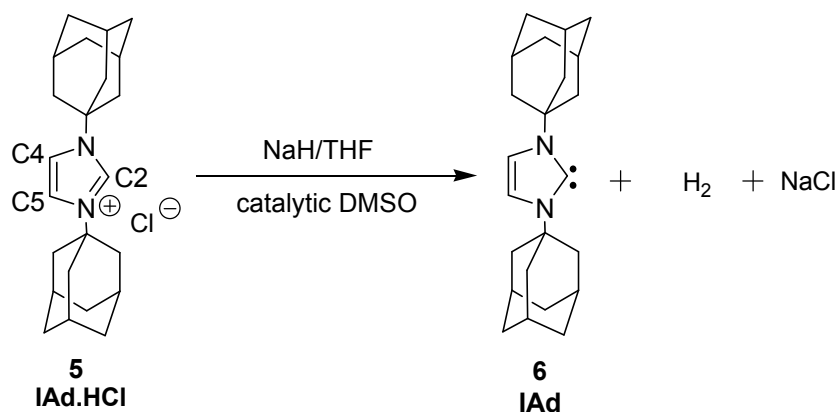


Figure-I.1: Bertrand's carbene.

Unfortunately, these carbene proved to be poor ligands due to strong $\text{P-C}_{\text{carbene}}$ multiple bond character.⁹ However, no diaminocarbene had been isolated with relatively high stability, *i.e.* without tendency to dimerize until the ground-breaking discovery came in 1991 when Arduengo *et al.* isolated the first singlet NHC **6** (scheme-I.3)¹⁰.



Scheme-I.3: Synthesis of Arduengo's carbene (**6**)

Characterisation data for **6** were meticulously gathered by Arduengo. X-ray crystallography showed that N-C-N bond angle to be around $100\text{-}102^\circ$ which is smaller than that in imidazolium ion (**5**) and N-C_{carbene} bond lengths are longer. The ¹³C-NMR showed the imidazolium carbon had shifted significantly downfield in the line with the de-shielded nature

of carbene carbon, C2, typically between 200-250 ppm whilst the signal of the C2 in imidazolium salt is between 130-160 ppm. In the $^1\text{H-NMR}$ spectrum, the acidic proton on C2 of the imidazolium salt, found between 8-12 ppm depending on salt, is no longer been observed.

I.A.1. Synthesis and characteristics of NHCs

The diadamantyl-substituted imidazol-2-ylidene (IAd, **6**) was prepared by deprotonation of the corresponding imidazolium salt with sodium or potassium hydride in the presence of catalytic amounts of DMSO (scheme-I.3). The free carbene was isolated and found to be remarkably stable. Initially, it was believed that the steric effect from the sterically bulky adamantyl groups flanking the imidazolium backbone were play main role for the stability of the carbene preventing the dimerization. However, later it was observed that the replacement of the bulky adamantyl groups by methyl groups led to formation of a less stable but isolable carbene.¹¹ This suggested that steric interactions did not have major influence in determining the stability of the carbene. Resonance stabilization is also not a very important factor in determining the stability of the carbenes, especially since NHCs with saturated imidazolium framework were synthesized and isolated.¹² A whole family of imadazol-2-ylidenes bearing different substituents (**7**) as well as NHC with their saturated counterparts (**8**) (figure-I.2) were prepared following similar methods.^{11,13}



Figure-I.2: Unsaturated and saturated *N*-heterocyclic carbenes.

The main contribution to the stability of NHC or Wanzlick's and Arduengo's carbenes comes from a combination of the large electron withdrawing effect of electronegative nitrogen atom on the σ -electrons of C-N bond paired with a $\Pi_{\text{N}} \rightarrow \Pi_{\text{C}}$ back-donation *via* the p-orbital.^{1,14} The presence of a C=C double bond in the backbone provides additional thermodynamic stabilisation of at least 20 Kcal/mol.¹⁵ Overall, it has been concluded that the decisive factor in

determining the stability of NHCs is the push-pull synergistic effect of the amino groups (figure-I.3).

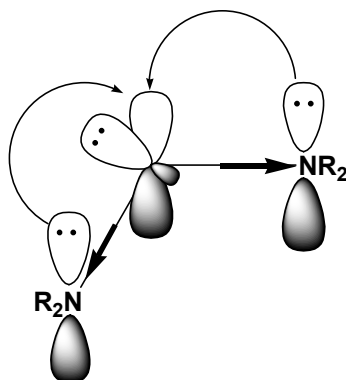
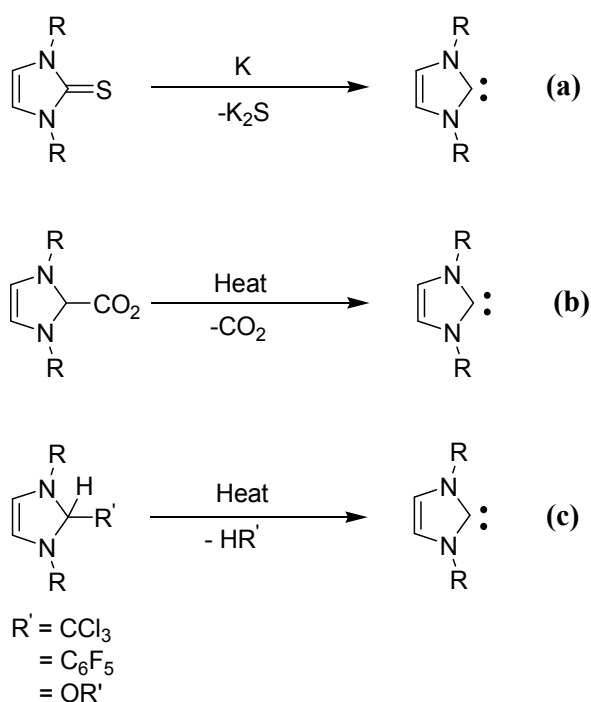


Figure-I.3: Push-pull synergistic effect.

Hermann *et al.* later developed an exceptionally mild method for the preparation of thermally sensitive NHCs. They demonstrated that NHCs could be generated much faster from imidazolium precursors at lower temperature by employing liquid ammonia as co-solvent.^{13b,16} Consequently, other methods were developed for the synthesis of free carbenes as through the reduction of the thione with molten potassium (scheme-I.4a) or through thermal decomposition of alcohols,¹⁷ carbon dioxide,¹⁸ (scheme-I.4b) methylene chloride^{5a} or pentafluorobenzene¹⁹ adducts (scheme-I.4c).



Scheme-I.4: Methods for synthesis of *N*-heterocyclic carbenes.

However, after the development of various methods for the synthesis of *N*-heterocyclic carbene (NHC), they have become ubiquitous ligands in organometallic chemistry proving to be more than just phosphine mimics.²⁰ The structural flexibility of NHCs renders this class of ligands exceptionally intriguing and versatile as evidenced by numerous applications ranging from homogeneous catalysis to material and medicinal sciences. So as the need of chemists, they have synthesized variety of heterocyclic and acyclic carbenes including some mixed heterocyclic carbenes as shown in figure-I.4.

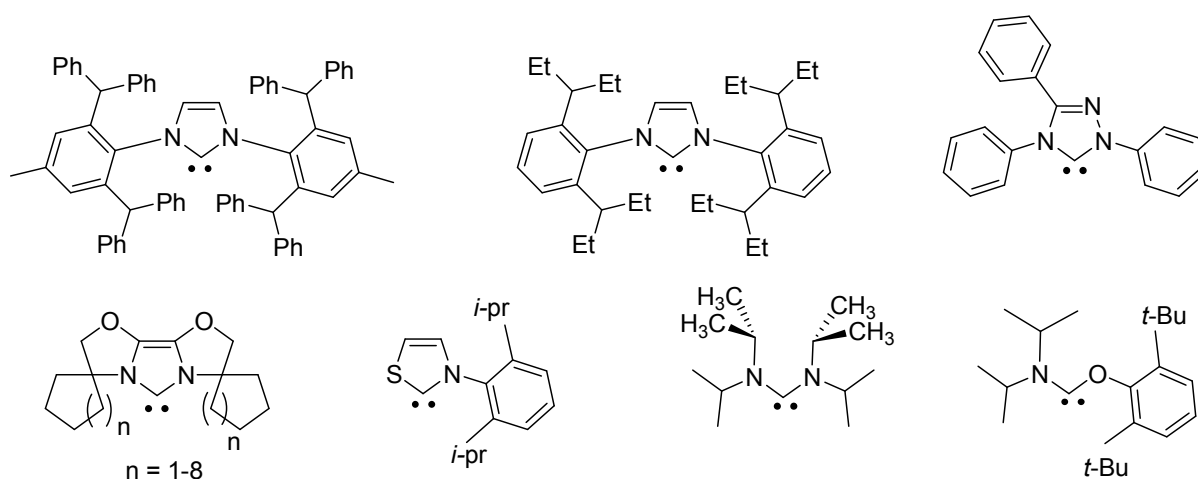


Figure-I.4: Examples of selected *N*-heterocyclic carbenes.^{2,21}

I.A.2. Reactivity and ligand properties of NHCs

For a long while, NHCs were considered to be strong σ -donors only with very little π -back bonding from the metal taking place. After that, it has been recognised that NHCs can take part in π -back bonding, accepting electron density from the metal d-orbitals into π^* orbital. It has also been found that with electron deficient metal centres, NHCs will take part in π -d electron donation so the NHCs are also able to transfer electron density to the metal centre more readily than phosphines (figure-I.5).

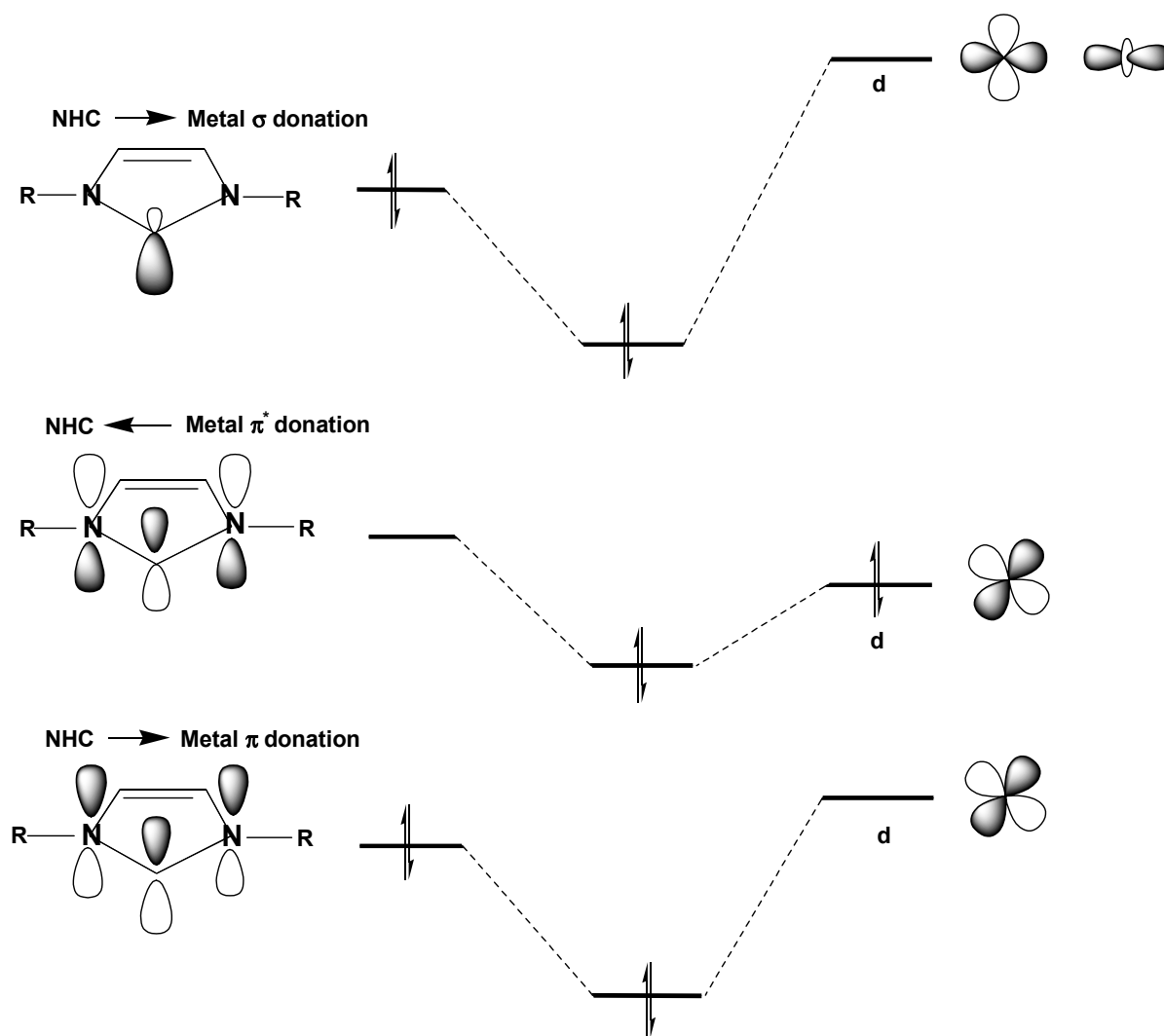


Figure-I.5: Bonding modes of NHCs with metals.²²

Khramov *et al.* investigated the π -acidity of various Rh-complexes of the type (NHC)Rh(COD)Cl. He found that the π -acidity of NHC's was between the high π -acidity of CO and the π -acidity of alkenes.²³ He also found that back-bonding in NHCs is tunable. The steric and electronic properties of carbenes can be influenced by various substituents on the heterocyclic nitrogens and the backbone carbons, C4 and C5, and by different bond saturation on the backbone. This offers the possibility to vary the catalyst's properties by fine tuning of the NHC ancillary ligand to find the optimal system for a process. Thus producing more highly specialised (target only specific reactions) catalysts which are more efficient.²⁴

I.A.3. Electronic character of NHCs

An important characteristic feature of NHCs is their extraordinary electron richness. Various methods have been developed for understanding of electron-donor properties of NHCs (ligands), that is, the ability to measure the effect a ligand exhibits upon the electronic nature of a metal complex.²⁵ The arguably most recent method utilizes the ¹³C chemical shift of carbene carbon atom in palladium (II)-benzimidazolylidene complexes as a probe for the measurement of the donor strength of the additional ligand of interest (figure-I.6, left side). By using this method, Huynh *et al.* analyzed ten different NHC ligands by the formation of the corresponding hetero-bis(carbene)/ Pd(II) complex and their ¹³C NMR spectra.^{25c}

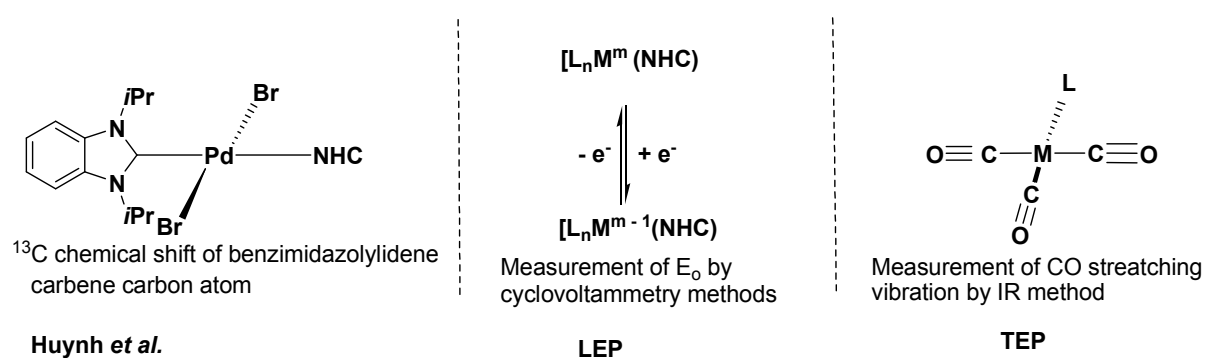


Figure-I.6: Different methods for the determination of the donor strength of NHC ligand.

Another useful method, developed by Lever *et al.*, is based on the electrochemical E_0 values for various redox couples in series of Ru^{III}/Ru^{II} complexes containing the ligands of interest (figure-I.6, middle). The data are deconvoluted into Level electronic parameter (LEP) for individual ligands.²⁶

By far the most commonly-utilised method to evaluate the electronic properties of NHCs is Tolman's electronic parameter (TEP), which was originally developed to describe the electronic properties of tertiary phosphine ligand. In this method, $[Ni(CO)_3(L)]$ ($L=NHC$) complexes has been used for the measuring the electron donating capability of ligands (figure-6, right side). This method makes use of the fact that electron density from a ligand cannot only be passed to the metal, but also on to the π^* orbital of CO ligands. Thus, the frequency A_1 of $[Ni(CO)_3(L)]$ complexes is direct probed to quantify the level of electron donation of ligands. Lower the stretching frequency of CO, stronger the σ -donating ability of NHC ligand. This frequency is known as Tolman's electronic parameter (TEP).²⁷ It was

developed by Tolman after the pioneering works by Strohmeir *et al.*²⁸ as well as Bigorgne *et al.*²⁹

Despite the nickel system being the parent system for TEP determination, the high toxicity of nickel carbonyl precursor has resulted in more accessible and user-friendly rhodium- and iridium-based system being much more widespread. A wide range of complexes of the form $[\text{IrCl}(\text{CO})_2(\text{NHC})]$ have been prepared and characterised since the linear regression analysis was performed to link systems of this type to the $[\text{Ni}(\text{CO})_3(\text{NHC})]$ systems.³⁰ The first $[\text{IrCl}(\text{CO})_2(\text{NHC})]$ complexes were reported by Chianese *et al.*,^{30a} and were prepared from reaction of corresponding $[\text{IrCl}(\text{COD})(\text{NHC})]$ complexes with carbon monoxide. It was observed that there was a linear correlation between $\gamma_{\text{av}}(\text{CO})$ for $[\text{IrCl}(\text{CO})_2(\text{PR}_2\text{R})]$ complexes and TEP value determined from the corresponding $[\text{Ni}(\text{CO})_3(\text{PR}_2\text{R})]$ complexes. The use of $[\text{RhCl}(\text{CO})_2(\text{NHC})]$ to measure TEPs was proposed by Plenio *et al.*³¹ and they have nicely correlated the averaged carbonyl frequencies of several dicarbonylchloroiridium and dicarbonylchlororhodium carbene complexes. Afterwards Glorius also re-evaluated this correlation.³²

I.A.4 Steric effect in the M-(NHC) bond

Determination of steric demand of NHCs is significantly more challenging than the measurement of the electronic properties. Tolman cone angle is used to define the steric requirements of monodentate phosphine ligands. In Tolman cone angle, the metal is placed in the vertex and the atoms on the perimeter of the cone (figure-I.7, left).²⁷

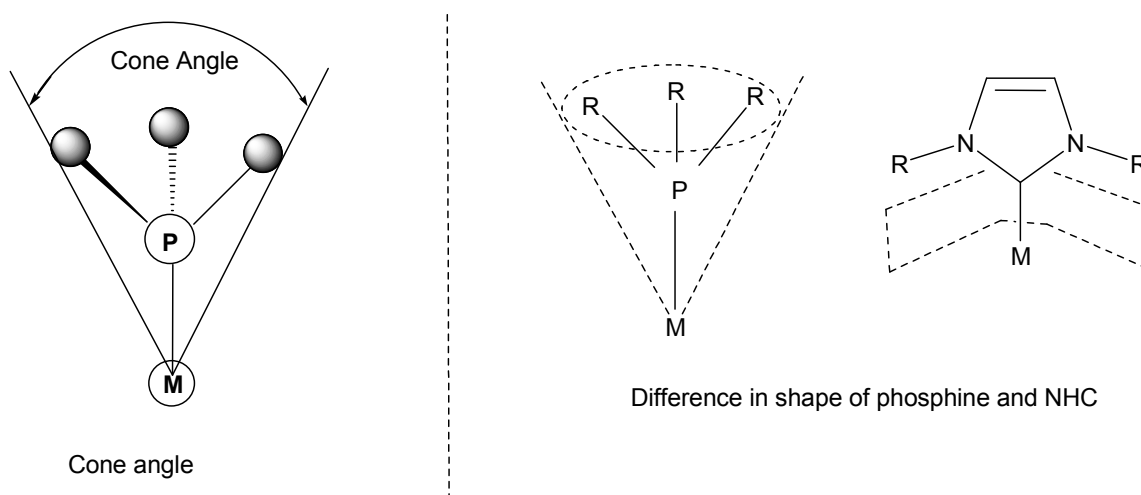


Figure-I.7: Cone angle during the phosphine-metal adduct (left); differences in shape of phosphine- and metal-adduct (right).

It can be seen that R group in phosphines are located away from the metal centre whereas they angle towards the metal centre in a “fan-like” manner in NHCs³³, almost wrapping the metal centre in a pocket (figure-I.7, right). However, this model is not sufficient to determine the steric environment of NHC ligands due to their unique and unsymmetrical structure, and other parameters have therefore been explored. Nolan *et al.* have proposed a new model to define the steric requirement of NHC ligands, known as the “percent buried volume” or % V_{bur} .³⁴ The buried volume % V_{bur} represents the part of a sphere around the metal (with a certain radius r) that is buried by atoms of the ligands under investigation (figure-I.8). This value is defined as the percentage of the total volume of a sphere centered upon the metal atom that is occupied by the ligand.

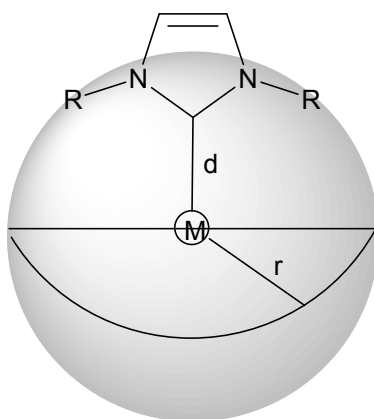


Figure-I.8: Percent buried volume (% V_{bur})

Initial studies with this model demonstrated a strong correlation between % V_{bur} values and the bond dissociation energy (BDE) of metal-ligand bond for $[C_p^*Ru(NHC)Cl]$ complexes.^{34a} The bond dissociation energies of NHC, calculated from a series of Ru and Ni complexes, are reported.^{34a,35} When comparing NHCs, it is interesting to note that in the presence of N-alkyl substituted carbenes appear to have fixed % V_{bur} values whereas for N-aryl substituted carbenes the % V_{bur} values are altered which demonstrate significant steric flexibility. It has been observed that IAd and *t*Bu are more sterically demanding than IPr and SIPr in high coordination number metal complexes whereas reversed trend is followed by low coordination number metal complexes.

I.A.5. NHCs as ligands and replacement of phosphines

Electron rich and bulky phosphines are most employed ligands in transition metal catalyzed C-C bond forming reactions especially with palladium. Prime motivation for their

employment as ligand in a wide array of cross-coupling reaction is because of their tendency to stabilize Pd(0) intermediate in catalytic cycle.³⁶ It has been proposed that electron-rich nature of sterically bulk phosphines such as P(^tBu)₃ and P(*o*-tol)₃ promotes oxidative addition³⁷ whereas the steric bulk around the metal centre facilitates reductive elimination³⁸ (figure-I.9).

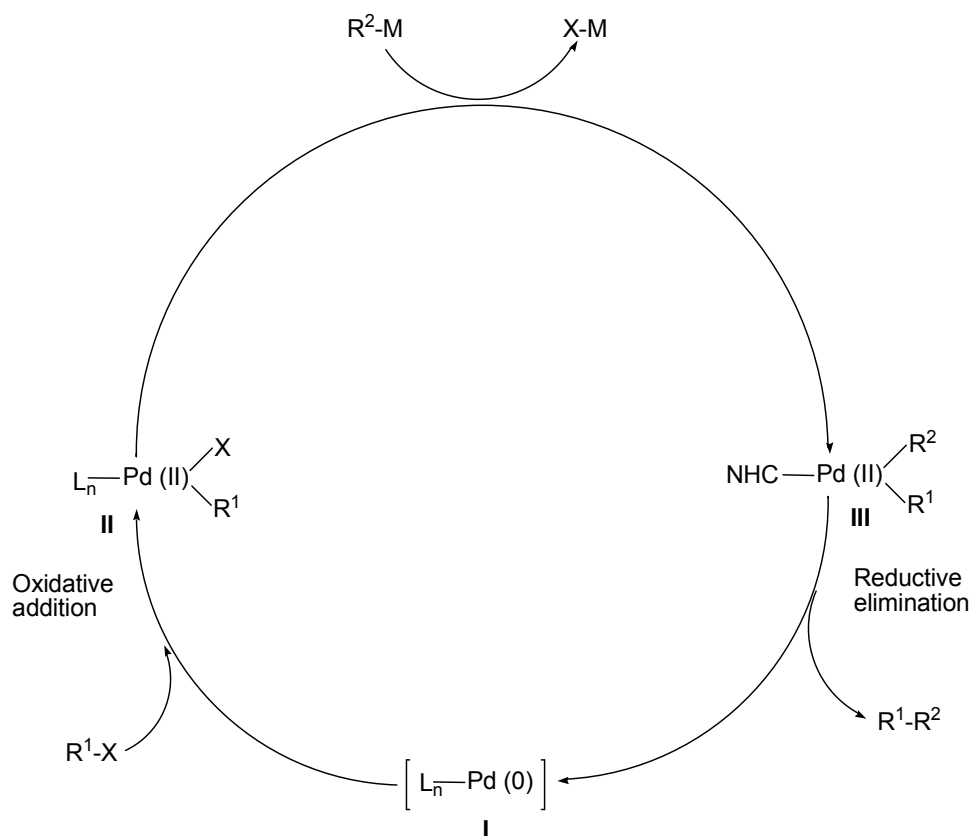


Figure-I.9: Mechanistic cycle for metal catalyzed cross-coupling reaction.

Mild reaction conditions and coupling of less reactive halides like chloride have been achieved with bulky phosphines ligated palladium complexes as their significant advancement.³⁹ An air-stable phosphine-ligated-palladium-dimer complex $[(SPhos-Pd)_2.(BF_4)_2]$ was reported by Barder⁴⁰ as the catalyst in C-C coupling reaction.

However, Phosphines suffer from a number of drawbacks.⁴¹ They are generally air-sensitive and have a tendency to undergo degradation at higher temperature via P-C bond cleavage. To overcome these shortcomings, excess ligand concentration is required. Employment of higher phosphine concentrations not only have direct consequences on the economics of the catalytic process but also have a negative effect on the environment due to the unrecoverable nature of the ligand.

Additionally, in comparison to NHCs the tuning of the steric and electronic properties of phosphine ligands is not suitable due to the direct attachment of its substituents to the donor atom in phosphines. On the other hand, the steric and electronic properties of NHCs are independent from each other because the substituents are attached to the nitrogens of the heterocycle hence in principle are less direct in affecting the electron density of the species.⁴² A change of substituents changes only the steric nature of the NHC. It has been proposed that in order to affect an electronic nature in an NHC ligand, it is best to modify the azole ring.⁴³ Due to their strong σ -donor properties and usually large steric requirements, NHC ligands are able to stabilize low-valent transition-metal complexes that can be used in many catalytic processes.⁴⁴ Therefore NHCs provide a more flexible approach to incorporate a certain set of required properties in a ligand.⁴⁵ One of the important key factors of NHCs is their pronounced donor properties which makes them superior performers as catalysts. Experimentally it has been confirmed that typical NHCs are more electron-releasing than even the most basic phosphines.⁴⁶ In light of all drawbacks of phosphine ligands,⁴⁷ focus was turned towards employing NHCs in transition metal catalyzed C-C bond forming reactions. The potentiality of NHCs as spectator ligands in transition-metal catalyzed C-C coupling reactions was recognized in 1995 by Herrmann *et al.*⁴⁸ Grubbs *et al.* recognized the electron-donating potential of these carbenes and replaced the phosphine ligand in their first generation Grubbs catalyst with a NHC ligand. Consequently, the second generation Grubbs catalyst showed higher catalytic activity in comparison to their first generation catalyst in olefin metathesis and contributed to the Nobel Prize in 2005.⁴⁹ In light of the vast numbers of applications and their distinctive advantages, NHCs have now become a guiding “concept” in organometallic catalysis.

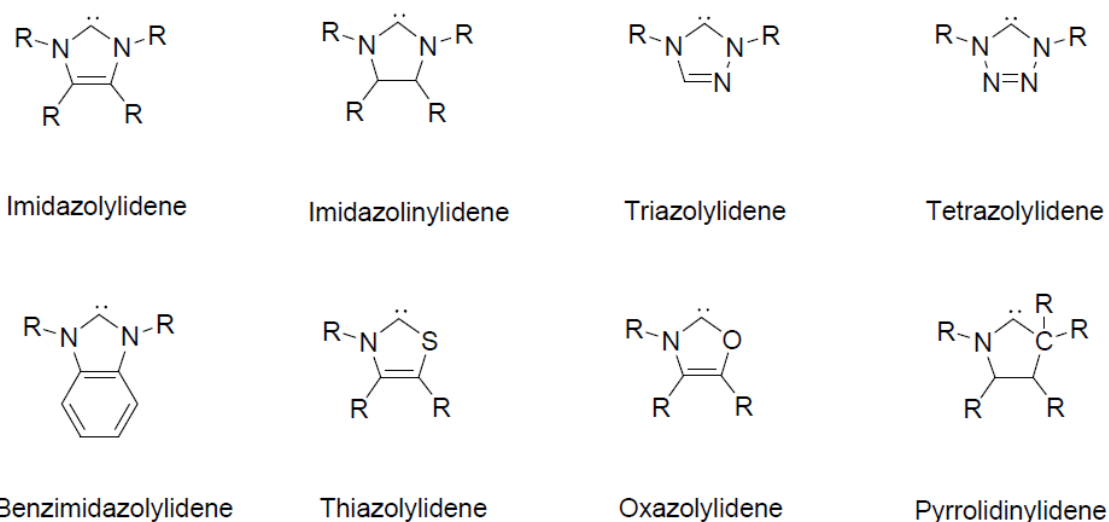


Figure-I.10: Common types of 5-membered heterocyclic carbenes.⁵⁰

Five membered NHCs have been the most commonly researched types so far, in particular, imidazolylidenes and imidazolidinyliidenes, but 3-, 4-, 6-, 7-, 8-membered carbenes as well as acyclic diaminocarbenes have also been synthesised and used in transition metal complexes as ligands.⁵¹

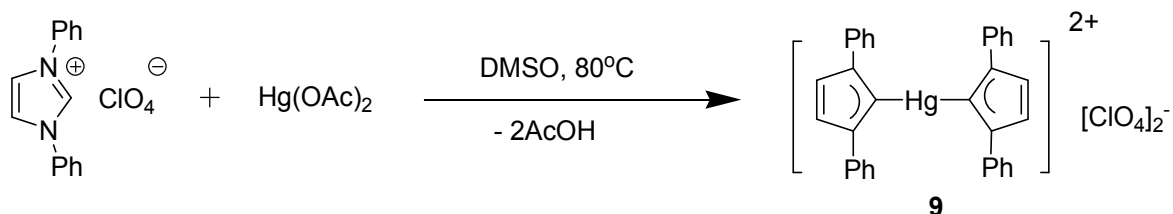
I.B. Synthesis and catalytic activity of Pd-NHC complexes

I.B.1. Synthesis of Pd-NHC complexes

A huge library of early⁵² and late⁵³ transition metal complexes containing mono- and poly-ligating NHCs, pincer-NHCs and mixed donor systems have been generated and extensively utilized in homogeneous catalysis.⁵⁴ Palladium catalyzed cross-coupling reactions are now commonly used in organic synthesis. This was recognised when the 2010 Nobel Prize in chemistry was awarded jointly to Richard F. Heck, Ei-ichi Negishi and Akira Suzuki for “palladium-catalysed cross-coupling in organic synthesis”.⁵⁵

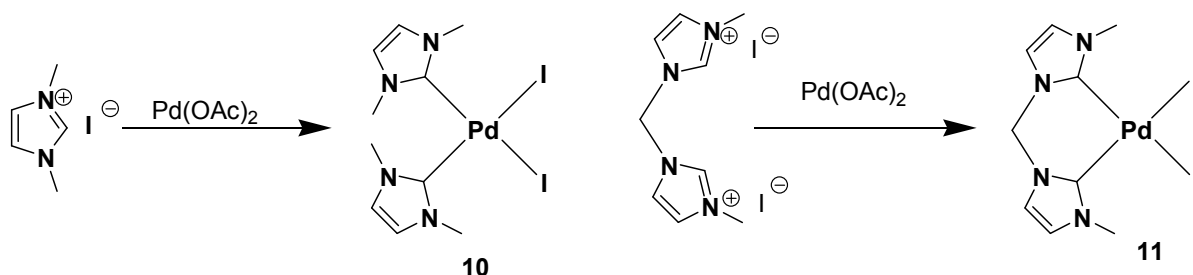
Many new catalysts have been produced which efficiently performed in reactions necessary to a target molecules synthesis. One of the reasons for arrival of many new catalysts is that there has been a significant increase in the number of ligands available, of which NHCs make up a significant part. These ligands are used to synthesis Pd-NHC complexes which can then be assessed for catalytic activity.

The first organometallic NHC complexes were formed from the imidazolium salt.⁵⁶ Wanzlick *et al.* prepared bis(1,3-diphenylimidazolio)mercury diperchlorate from the imidazolium salt and $[\text{Hg}(\text{OAc})_2]$ in DMSO (scheme-I.5).^{56b}



Scheme-I.5: Wanzlick's Hg-NHC complex.

Herrmann and co-workers first prepared $[\text{PdI}_2(\text{NHC})_2]$ complexes^{48,57} through an analogous method to that of Wanzlick (scheme-I.6).



Scheme-I.6: Herrmann's Pd-NHC complexes.

They have first introduced these Pd-NHC complexes in cross-coupling reaction and the use of Pd-NHC complexes in organic reactions has steadily increased almost over the past two decades.

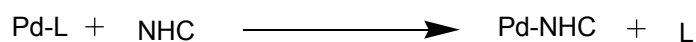
Pd-NHC complexes are synthesized in three general methods (scheme-I.7).

Method-A: Substitution reaction of a labile ligand with the free carbene.

Method-B: *In-situ* generation of the free carbene from a diamino salt in the presence of Pd source.

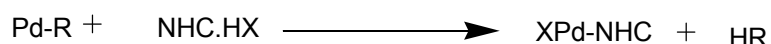
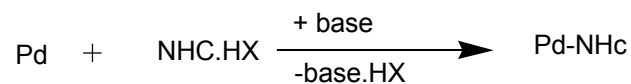
Method-C: Transmetallation from Ag-complexes.

Substitution of labile ligand(L): Method-A



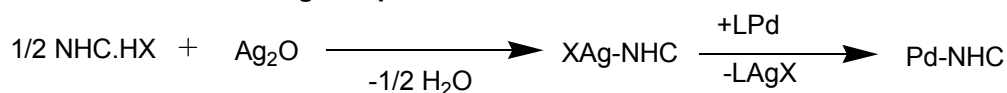
L = Labile ligand such as cod, dba, PPh₃ etc.

In-situ generation of free carbene: Method-B



R = basic organic group such as OAc

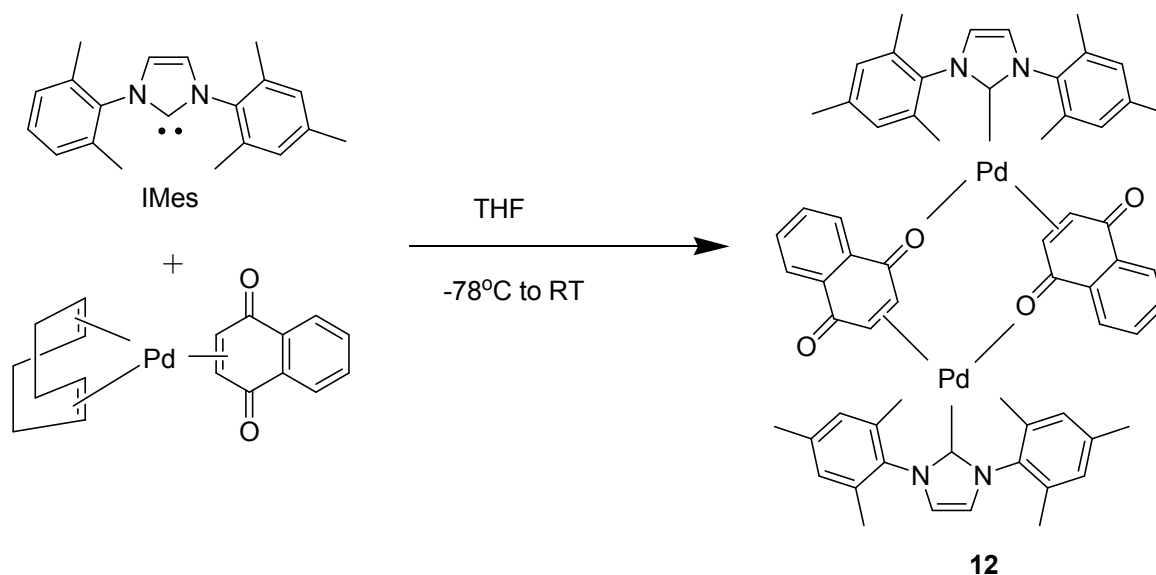
Transmetalation for Ag-complex: Method-C



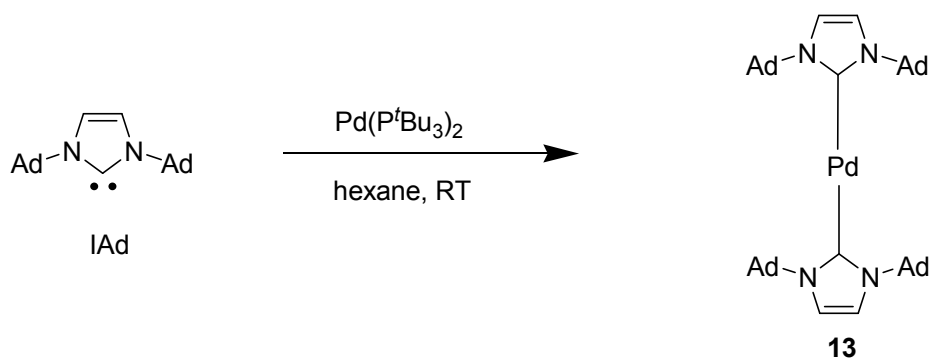
Scheme-I.7: Common synthetic methods to Pd-NHC complexes.

I.B.1.1 Method-A

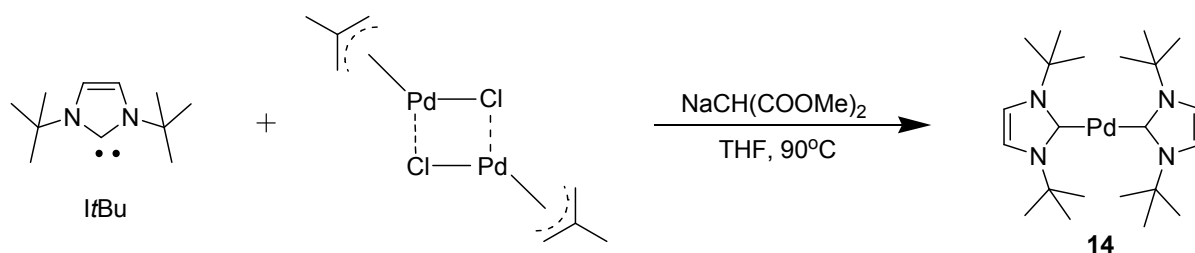
In case of method A, direct substitution of labile ligands such as cod (cod = 1,5-cyclooctadiene), dba (dba = dibenzylideneacetone), bridging halide and weakly bonding phosphines can lead to desired Pd-NHC complex⁵⁸ (scheme-I.8 to I.10).



Scheme-I.8: Synthesis of complex 12

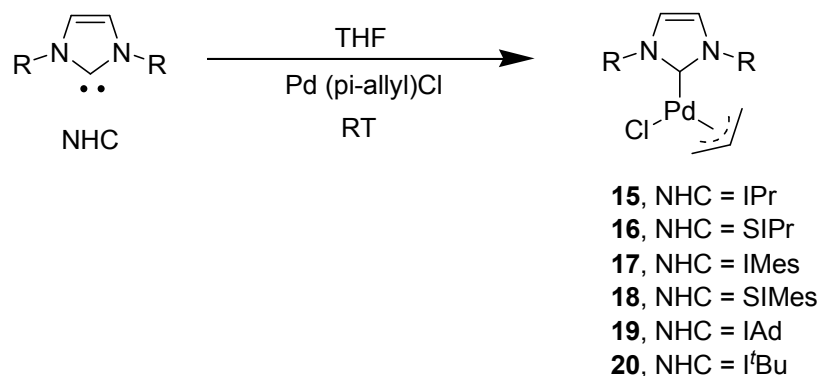


Scheme-I.9: Synthesis of complex **13**



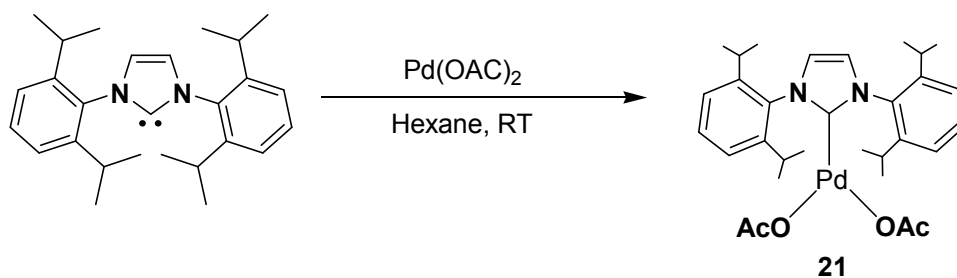
Scheme-I.10: Synthesis of complex **14**

Nolan and co-workers have described the development of [(NHC)Pd(π -allyl)Cl] complexes. Treatment of the corresponding π -allylpalladium chloride dimers with free carbenes at room temperature resulted in the formation of monomeric Pd-NHC species in high yields⁵⁹ (scheme-I.11).



Scheme-I.11: Synthesis of [(NHC)Pd(π -allyl)Cl] complexes.

Monomeric IPr complexes of Pd(OAc)₂ was prepared by treatment of the Pd salt with the free carbene under anhydrous conditions⁶⁰ (scheme-I.12).



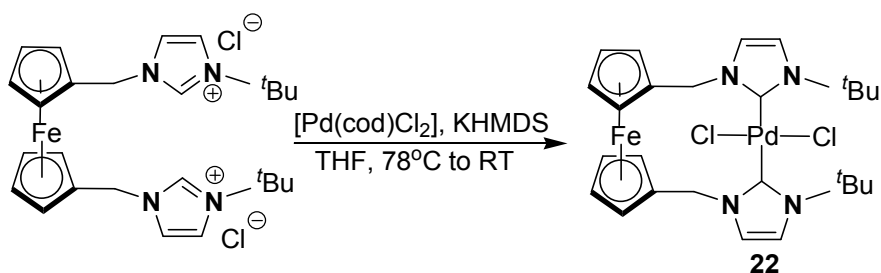
Scheme-I.12: Synthesis of monomeric IPr-Pd complex **21**

I.B.1.2. Method-B

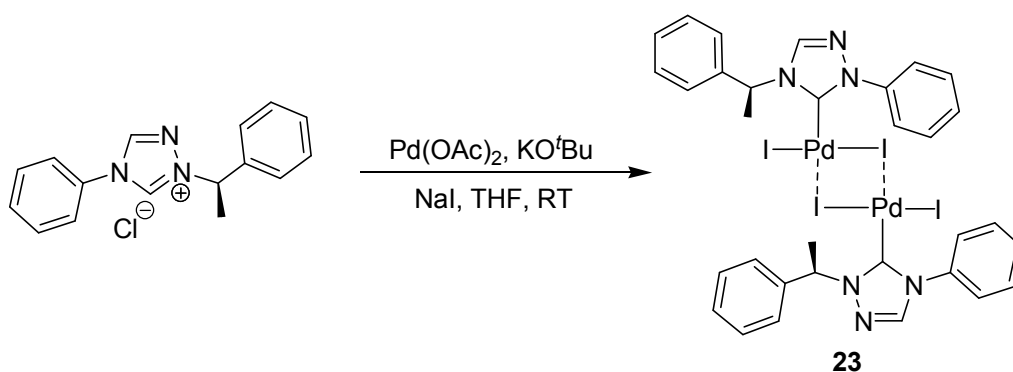
In case of method B, *in-situ* generation of free carbene can be an effective strategy for employing NHCs, which are unstable in free state. Even though stronger external base such as KHMDS⁶¹ and KO^tBu⁶² are effective, more often K₂CO₃,⁶³ Cs₂CO₃⁶⁴ or even NaOAc⁶⁵ are used. *In-situ* generated free carbenes are captured by palladium and finally stable Pd-NHC complexes are formed.

On the other hand, Pd-NHC complexes can be formed without any external base. In this case, ligands directly bonded to the palladium source. A common source for the latter is Pd(OAc)₂. Addition of one or two NHCs can be accomplished depending on the reaction stoichiometry with release of HOAc. An added advantage of this technique is that often reactions can be performed under an ambient atmosphere.

I.B.1.2a. Synthesis of Pd-NHCs with external bases



Scheme-I.13: Synthesis of complex-**22** using KHMDS as base.



Scheme-I.14: Synthesis of complex **23** using KO^tBu as base.

The first generation pre-catalyst in the Pd-PEPPSI (PEPPSI = pyridine enhanced precatalyst preparation, stabilization and initiation) series are prepared by using their precursors azolium salt, PdCl_2 and K_2CO_3 as external base in neat 3-chloropyridine to provide the corresponding Pd-PEPPSI complexes.⁶³

Gradually various PEPPSI themed Pd-NHC complexes have been developed including *N/O*-functionalized carbene complexes⁶⁶ (figure-I.11).

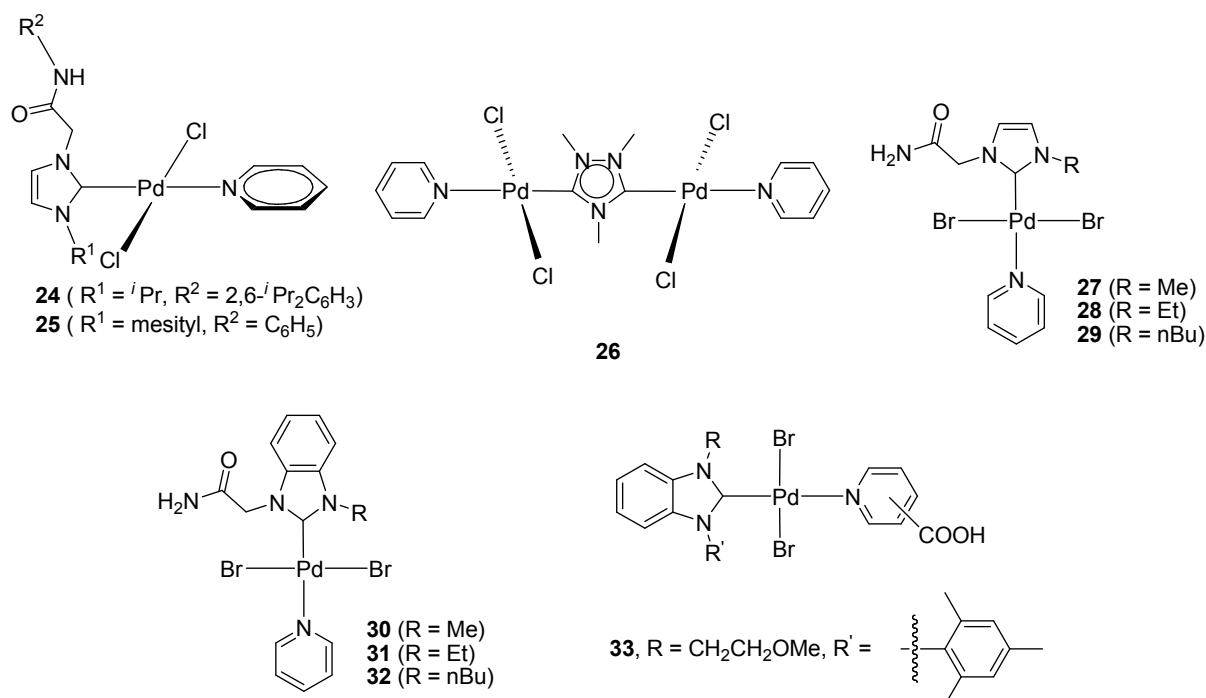
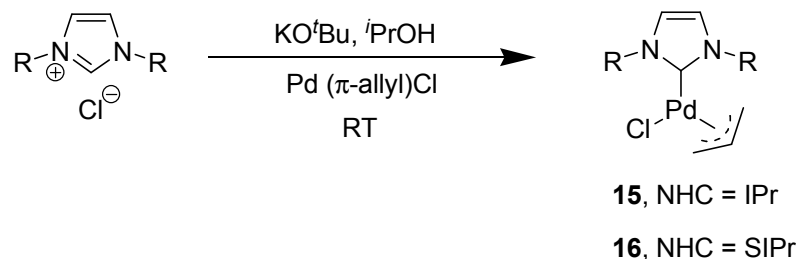


Figure-I.11: PEPPSI themed Pd-NHC complexes.

Various $[(\text{NHC})\text{Pd}(\pi\text{-allyl})\text{Cl}]$ complexes prepared by Nolan *et al.* by method-A (scheme-I.12) which is already described. As the handling of the sensitive free carbene limits the practicality and the scale of the precatalyst preparation, Nolan and co-workers have then addressed this concern by developing a one-pot procedure: the carbene was generated on a

large scale from the imidazolium salt and KO^tBu in technical grade 2-propanol followed by addition of [$\{Pd(\pi\text{-allyl})Cl\}_2$](scheme-I.15).⁶⁷

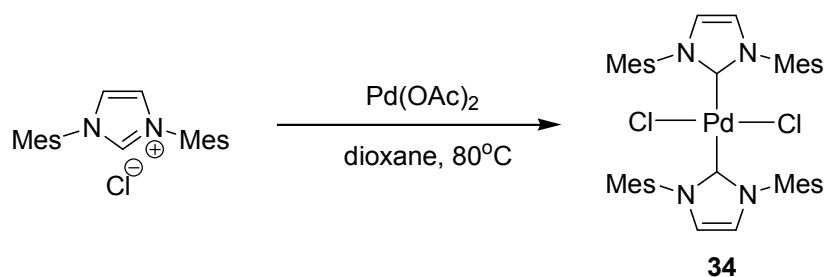


Scheme-I.15: Synthesis of [(IPr)Pd(allyl)Cl] and [(SIPr)Pd(allyl)Cl]

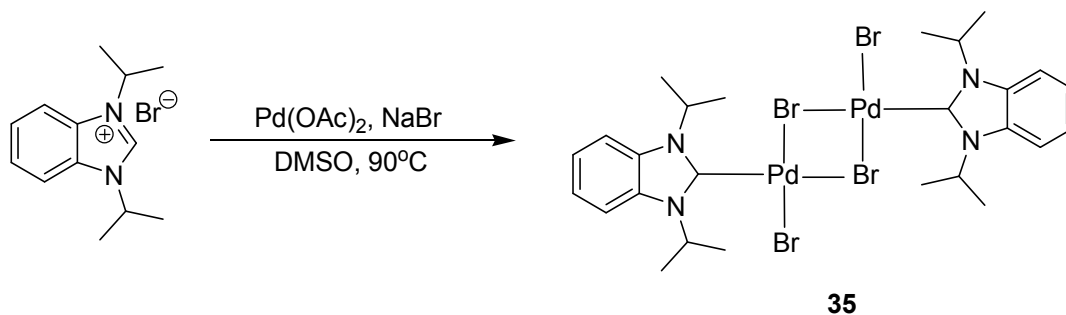
I.B.1.2b. Synthesis of Pd-NHC complexes without using external base

Initially, Herrmann et al. reported the synthesis of Pd-NHC complexes **10** and **11** (scheme-I.6) using only Pd(OAc)₂ without any external base. Pd(OAc)₂ as both the Pd source and base is especially attractive from an atom economical point of view.

In case of Pd-NHC halide complexes, halides can be introduced either as the counterion to the azolium salt or from an additive are incorporated in the coordination sphere of the Pd atom (scheme-16 to 19). This method was not restricted in imidazolium salt as Huynh *et al.* synthesized a benzimidazolyl-2-ylidene-PdBr₂ dimer in 93% yield by heating benzimidazolium salt, Pd(OAc)₂, and NaBr in DMSO⁶⁸ (scheme-I.17).

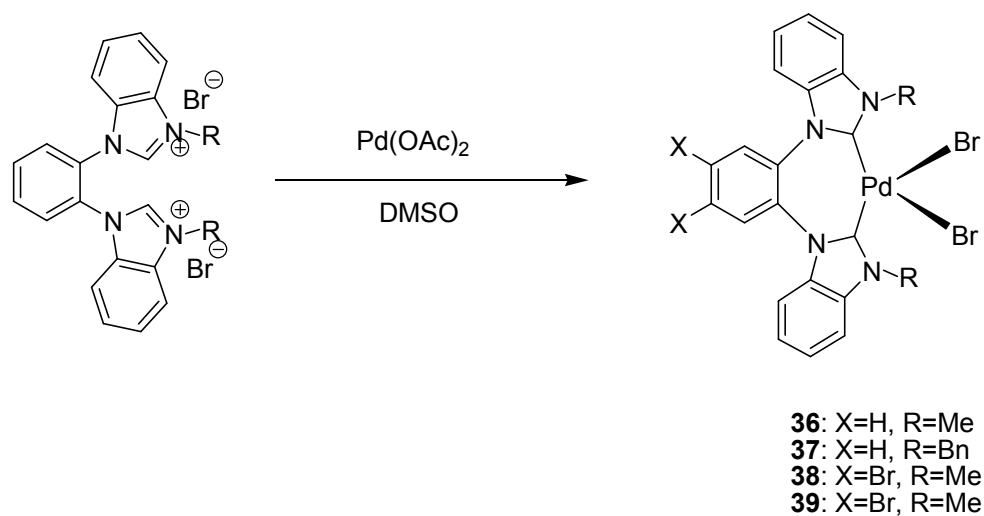


Scheme-I.16: Synthesis of complex **34**



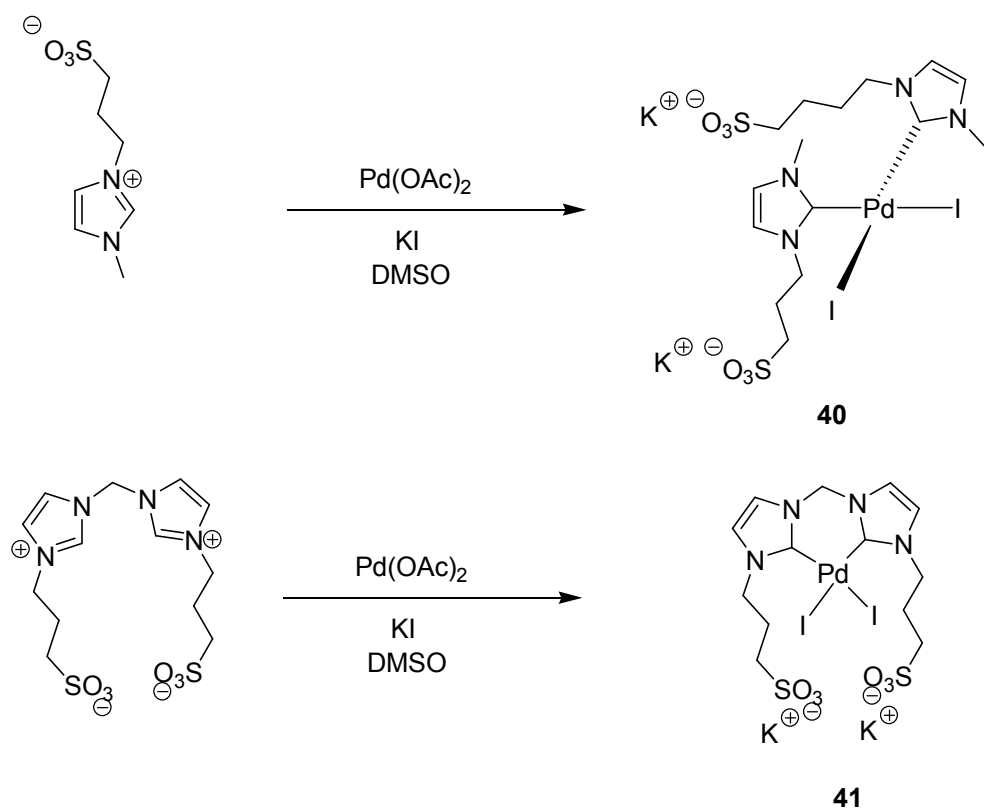
Scheme-I.17: Synthesis of benzimidazole based Pd-NHC complex **35**

Bridged palladium-bis-NHC complexes are also synthesised without external base where $\text{Pd}(\text{OAc})_2$ was used as Pd source ⁶⁹ (scheme-I.18).



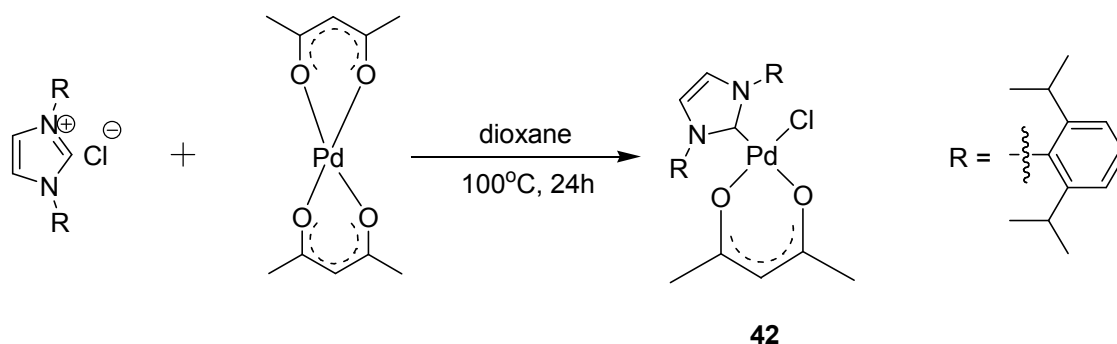
Scheme-I.18: Synthesis of bridged Pd-NHC complexes.

Pd-NHC complexes with sulfonate-functionalized-NHC also prepared where KI was used as additive ⁷⁰ (scheme-I.19).



Scheme-I.19: Synthesis of sulfonate-functionalized Pd-NHC complex **40** and **41**.

Nolan *et al.* reported the synthesis of [(NHC)Pd(acac)Cl] complex and it was prepared directly from [Pd(acac)₂] and azolium salt in refluxing dioxane, by relying on the inherent basicity of acetylacetonate ligand⁷¹ (scheme-I.20).



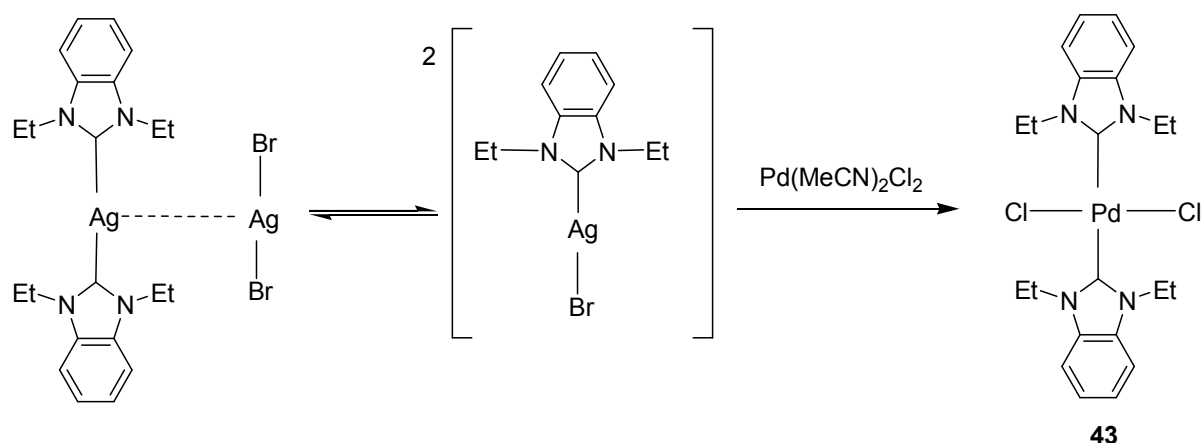
Scheme-I.20: Synthesis of [(IPr)Pd(acac)Cl] complex.

I.B.1.3. Method-C

Ag₂O can be used as base to directly form [AgX(NHC)] when reacted with azolium salts. These complexes can be isolated and sequentially reacted with the Pd source. The result of which is transmetalation of the NHC from Ag to Pd. Alternatively, one-pot reaction, in which the Pd-source is added directly to the Ag₂O/NHC.HX mixture can lead to the desired Pd-NHC complex. The main disadvantage, besides the cost, is that the silver complexes are often light-sensitive.

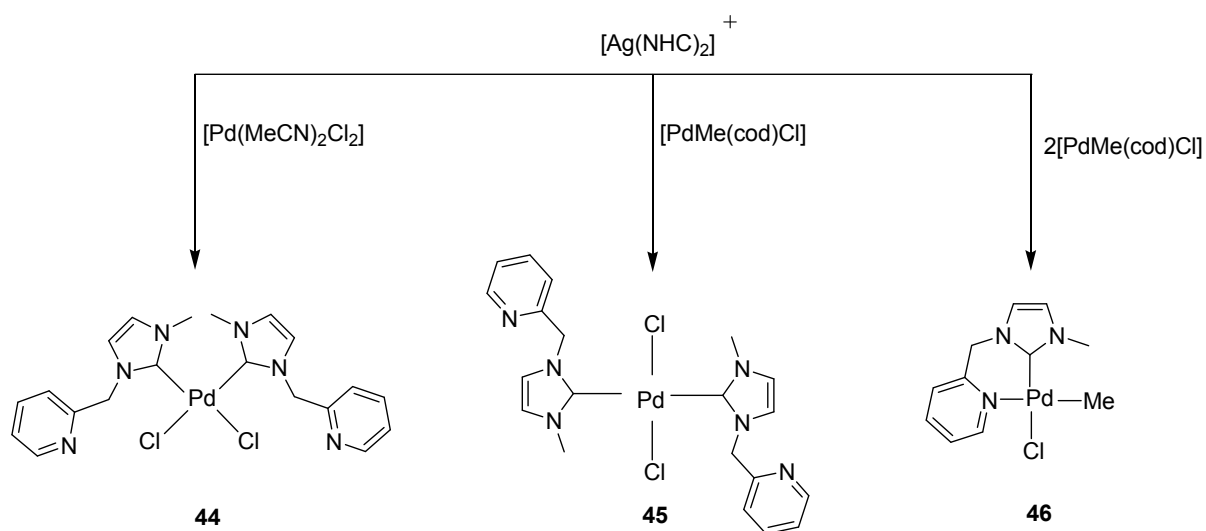
However, in early as 1993, Arduengo reported the first Ag(I)-NHC complex by the reaction of Ag(I)-salt with free NHC.⁷² The reaction of Ag₂O with azolium salts to afford Ag(I)-NHC was first reported in 1998 by Lin and co-worker.⁷³ While using different bases for deprotonation of azolium salts, in an attempt to synthesize Au(I)-NHCs, the employment of Ag₂O as mild base effectively produced the Au(I)-NHCs. This study elaborates the generation of Ag(I)-NHC *in-situ*, and their role as transmetalating agents to prepare other metal-NHC complexes.

With non-functionalized NHCs (only with N-alkyl or N-aryl substituents), transmetalation normally produced simple [Pd(NHC)₂Cl₂] complexes as shown in scheme-I.21.⁷⁴

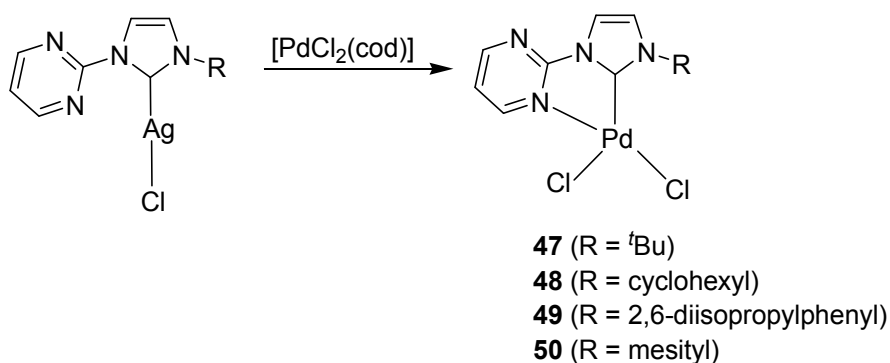


Scheme-I.21: Synthesis of [(NHC)₂PdCl₂] complex **43**.

Whereas, with the functionalized NHCs, Pd(II)-NHCs of different structures were obtained, depending on the nature of Pd(II) precursor, the reaction conditions, and the stoichiometry of the reactants. For example, Cavell and co-workers showed that equimolar reactions between a picolyl substituted Ag(I)-NHC and [Pd(MeCN)₂Cl₂] or [PdMe(cod)Cl] produce non-chelated Pd(II)-NHC complexes whereas, a chelated mono-carbene complex was obtained upon reaction of Ag(I)-NHC with two equivalents of [PdMe(cod)Cl]⁷⁵ (scheme-I.22). Pyrimidine functionalized chelated Pd-NHC complexes were also synthesised by Strassner *et al.* using same methodology⁷⁶ (scheme-I.23).



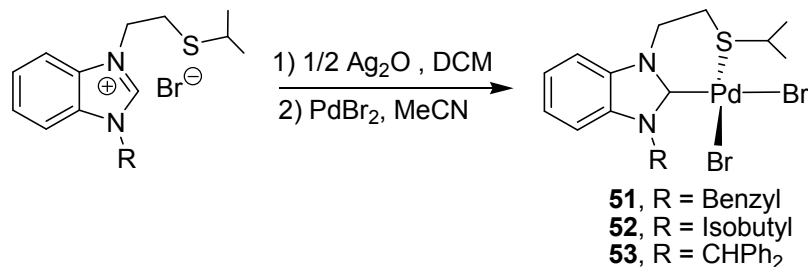
Scheme-I.22: Synthesis of picolyl Pd-NHC complexes.



Scheme-I.23: Synthesis of pyrimidine functionalized chelated Pd-NHC complexes.

Several chelated Pd(II)-NHC complexes of achiral tridentate amino-NHC-amino,^{77a} achiral tridentate NHC-amino-NHC,^{77b} bidentate amino-NHC^{77c} ligands have been prepared via carbene transfer technique. A chiral motive-bridge,^{78a} pyridine bridged CNC linked chelated,^{78b} benzimidazole based bearing 1,6-hexylene linker^{78c} and benzimidazole-functionalized imidazole based chelated^{78d} Pd-NHC complexes were also prepared adopting Ag-transmetallation method.

Recently, Huynh and co-worker have developed benzimidazole based thioether-functionalized palladium(II)-NHC complexes through this method (scheme-I.24)⁷⁹ and novel sulfinyl NHC-Pd complexes are also prepared by Tada *et. al.*⁸⁰



Scheme-I.24: Synthesis of thioether-functionalized Pd-NHC complexes.

I.B.2. Abnormal Pd-NHC complexes

Coordination of 5-membered NHCs usually occurs via the C2 carbon, although there is also a possibility of so-called “abnormal” coordination at the C4 carbon and a remote coordination when the carbene carbon is β to any nitrogen (figure-I.12).

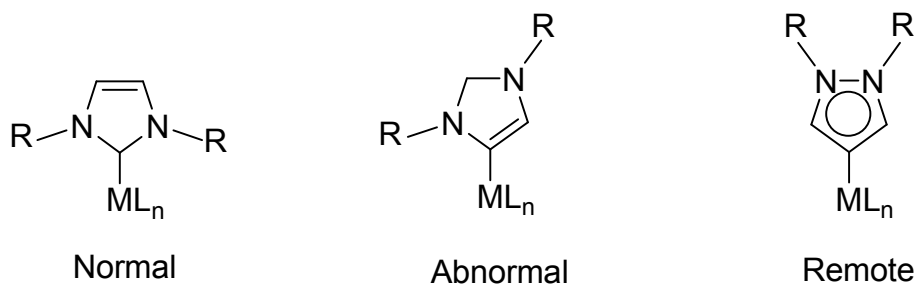
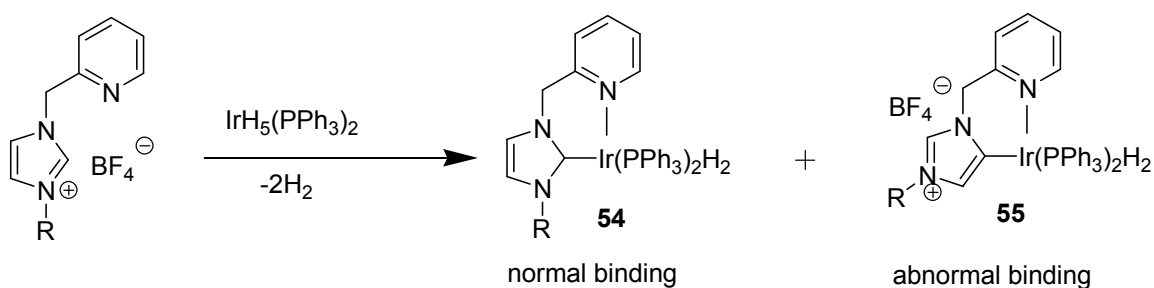


Figure-I.12: Normal, abnormal and remote NHC-metal complexes.⁸¹

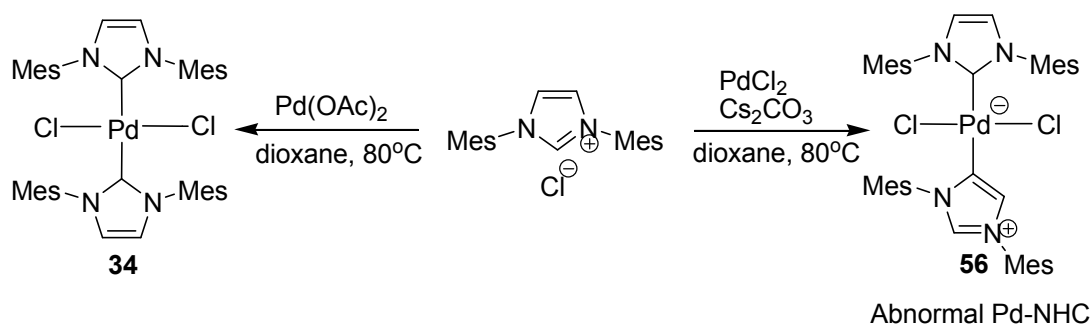
Grundemann *et al.* reported a pyridine functionalized imidazolium ligand that, on reacting with $\text{IrH}_5(\text{PPh}_3)_2$, gave a mixture of two carbene complexes: one with regular binding at C-2 and one with binding at C-4 as shown in scheme-I.25.⁸³ This binding mode was coined abnormal binding.



SchemeI.-25: Abnormal binding mode in NHC coordination.

Once the normal or abnormal compounds have formed they do not easily interconvert, even after prolong heating in DMSO. IR-spectroscopy data suggest that abnormal C-4 bound NHCs would be substantially stronger electron donor than normal C-2 carbenes,⁸³ which may be beneficial for some catalytic applications.

For instance, it was shown that palladium complexes bearing two NHCs (IMes), one in the normal and another in abnormal binding mode, could be used as active catalyst in C-C coupling reactions.⁶⁴ When the two ligands are in the normal binding mode the catalyst is inactive. Whether the normal or abnormal complex is obtained depends on the reaction conditions “when cesium carbonate is used as a base, abnormal binding occurs more frequently.” (Scheme-I.26)



Scheme-I.26: Synthesis of normal and abnormal Pd-NHC complex.

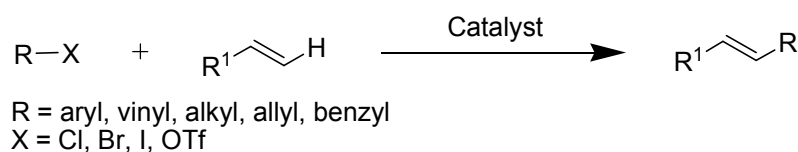
Recently, Mandal *et al.* have reported the synthesis of halo bridged abnormal Pd-NHC complexes through the C-H activation using 1,3-bis(2,6-diisopropylphenyl)-2,4-diphenyl imidazolium salt. They have also shown the catalytic activity of this Pd-NHC towards Suzuki coupling of aryl chlorides at room temperature.⁸⁴

Several review articles have nicely explained the abnormal binding of NHCs with various transition metals.⁸⁵

I.B.3. Catalytic activity of Pd-NHC complexes

I.B.3.1.C-C bond formation

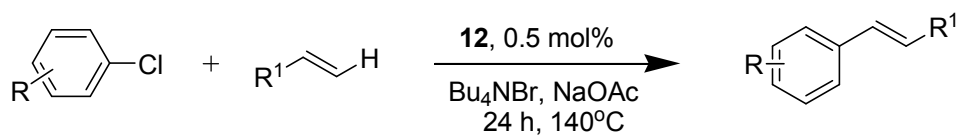
I.B.3.1.a. Mizoroki-Heck reaction



Scheme-I.27: General scheme for Heck reaction.

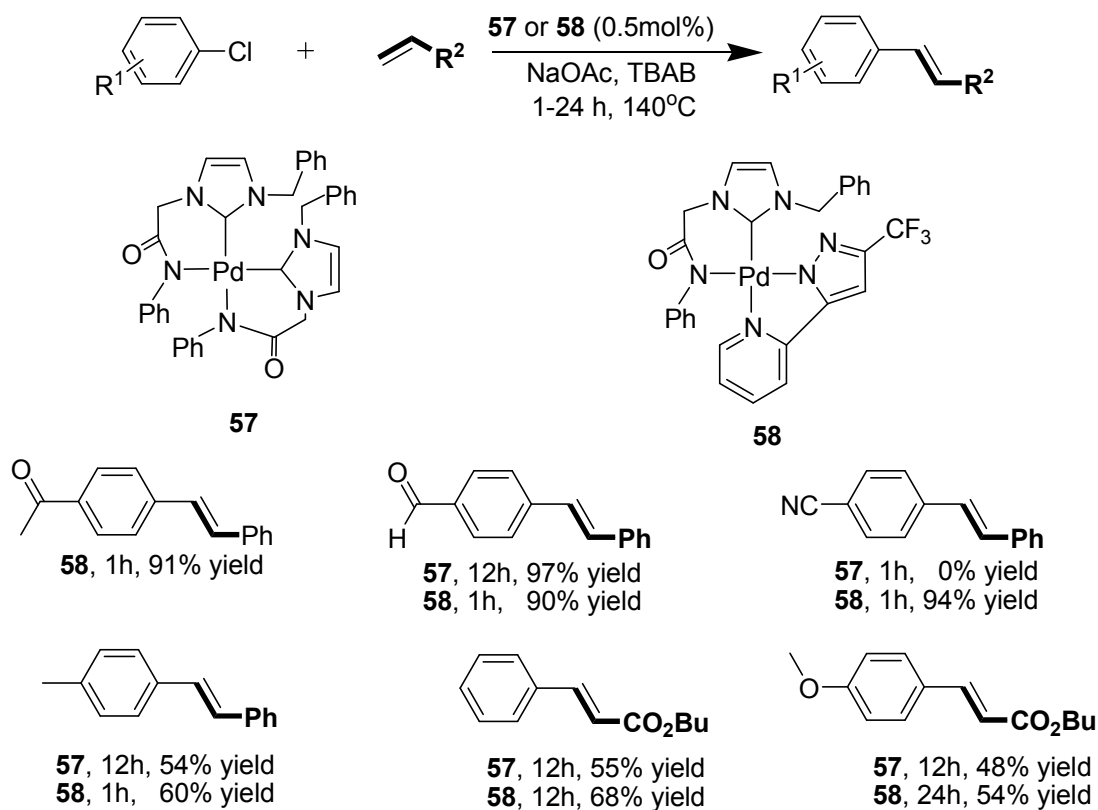
The Mizoroki-Heck cross-coupling reaction is one of the most attractive and versatile cross-coupling reactions used to date.⁸⁶ Herrmann *et al.* first used Pd-NHC complexes **10** and **11** in Heck coupling reaction of aryl bromides and aryl chlorides with n-butyl acrylate.^{48,57} Since then, several strategies of catalyst design have been employed for Mizoroki-Heck cross-coupling reaction.^{54b} Various Pd-NHC complexes like bridged dipalladium complexes, tridentate pincer ligated complexes, palladacycles, bis-NHC-Pd complexes have been used as catalyst for this reaction. However, in case of aryl chlorides, most of them show poor catalytic activity. Beller *et al.* have developed a reaction system that shows good activity with aryl chlorides. It involves an ionic liquid as solvent and a Pd-NHC naphthquinone complex (**12**) as catalyst⁸⁷ (table-I.1). Yields were unfortunately greatly diminished when using catalyst loading lower than 0.5 mol%.

Table-I.1: Pd-NHC naphthquinone complex (**12**) catalyzed Heck coupling reactions.



R	R ¹	Yield(%)
H	Ph	62
4-NO ₂	Ph	92
4-COCH ₃	Ph	96
2-CN	Ph	94
2-CN		99
4-CF ₃		90
4-COCH ₃		99

Lee and co-workers have prepared some of the most active Pd-NHC catalysts for Heck coupling reaction.⁸⁸ These are shown in scheme-28. It was found that activated aryl chlorides could be coupled in high yields within hours and deactivated aryl chlorides gave moderate yields within 24 h. In addition, the replacement of one NHC/amide ligand in **57** with an anionic weaker bonding ligand, catalytic activity has improved as shown in scheme-I.28.



Scheme-I.28: Pd-NHC complex **57** and **58** catalyzed Heck coupling reactions.

Huynh *et al.* have recently reported palladium(II) sulfonate-NHC complexes (figure-I.13) catalyzed Mizoroki-Heck reactions in aqueous medium but this protocol is not suitable for aryl chlorides.⁸⁹

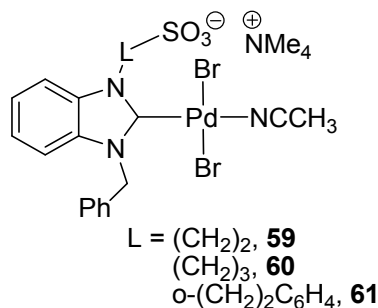
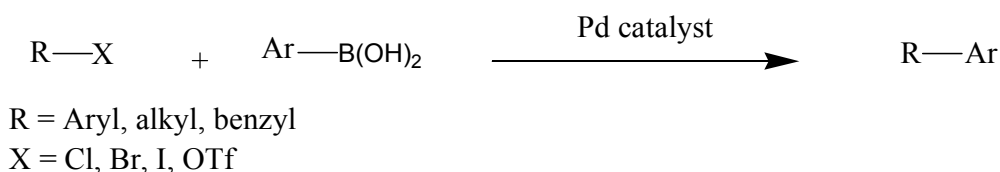


Figure-I.13: Sulfonate-NHC-Pd(II) complexes for Mizoroki-Heck reaction.

A series of triazole MIC (mesoionic carbene)-derived-Pd-PEPPSI complexes have been developed⁹⁰ and Pd-MIC-PEPPSI complexes also have been introduced in Heck-coupling reaction.⁹¹

I.B.3.1b. Suzuki-Miyaura cross-coupling

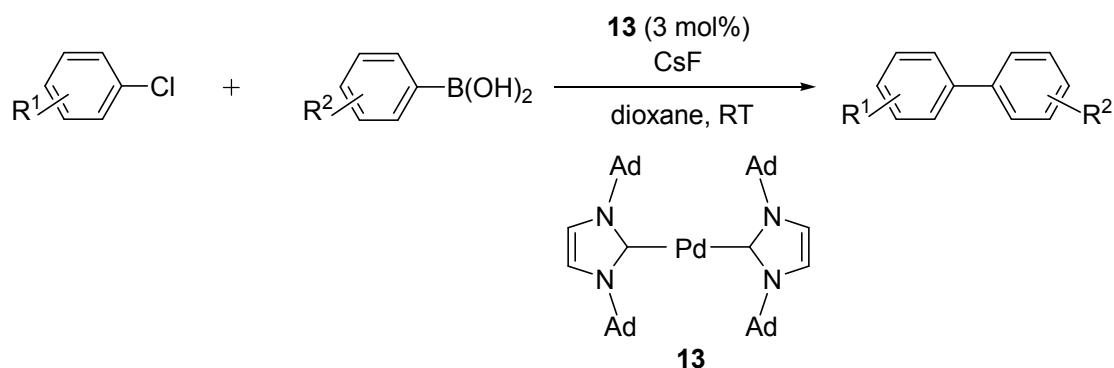


Scheme-I.29: General scheme for Suzuki coupling reaction.

Suzuki-Miyaura cross-coupling is the most studied cross-coupling reaction. In this coupling reaction, a great number of *in-situ* generated Pd-NHC and well-defined Pd-NHC complexes have been utilized.

An early example of the use of a well-defined Pd-NHC catalyst used for Suzuki-Miyaura cross-coupling was reported by Herrmann *et al.* in 2002. Most impressively, [Pd(IAd)₂] (**13**) catalyzed the Suzuki coupling reaction of aryl chlorides and arylboronic acids at room temperature^{58b} (table-I.2).

Table-I.2: [Pd(IAd)₂] (**13**) catalyzed Suzuki coupling reaction of aryl chlorides.



R ¹	R ²	Time	Yield(%)
4-CH ₃	H	6h	>99
4-OCH ₃	H	6h	>99
4-CF ₃	H	6h	>99
4-CF ₃	3-OCH ₃	24h	97
4-COCH ₃	3-OCH ₃	24h	95

Palladacyclic complex [(IPr)PdCl(η³-N,C-C₁₂H₁₇NMe₂)] (**90**) (figure-I.20) showed high activity in Suzuki-Miyaura coupling of aryl chlorides in formation of di and tri-ortho-substituted biaryls at room temperature. Additionally, **90** was shown to be active in the coupling of heteroaryl chlorides and aryl triflates also.⁹²

The Organ group has studied NHC-Pd-PEPPSI complexes in Suzuki-Miyaura cross-coupling reaction.^{63a}

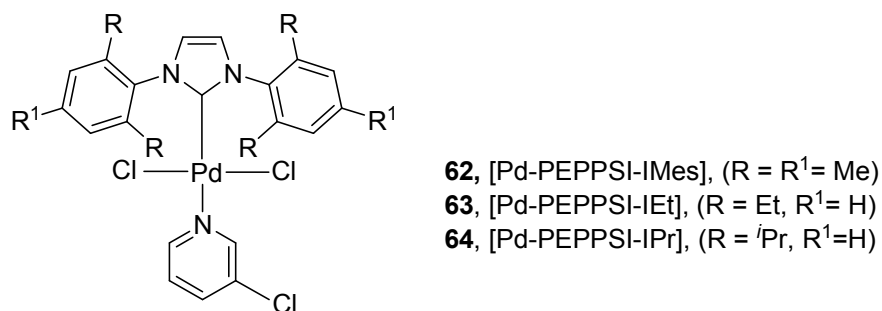


Figure-I.14: Pd-PEPPSI-NHC complexes used in Suzuki-coupling reaction.

Another very successful NHC-Pd pre-catalyst is the [PdCl(η^3 -allyl)(NHC)] complexes. Some of this type of complexes have shown highest activity of Pd-NHC well defined catalysis. Initial simple allyl group containing pre-catalysts of this family was used for the Suzuki-Miyaura coupling reaction.⁹³

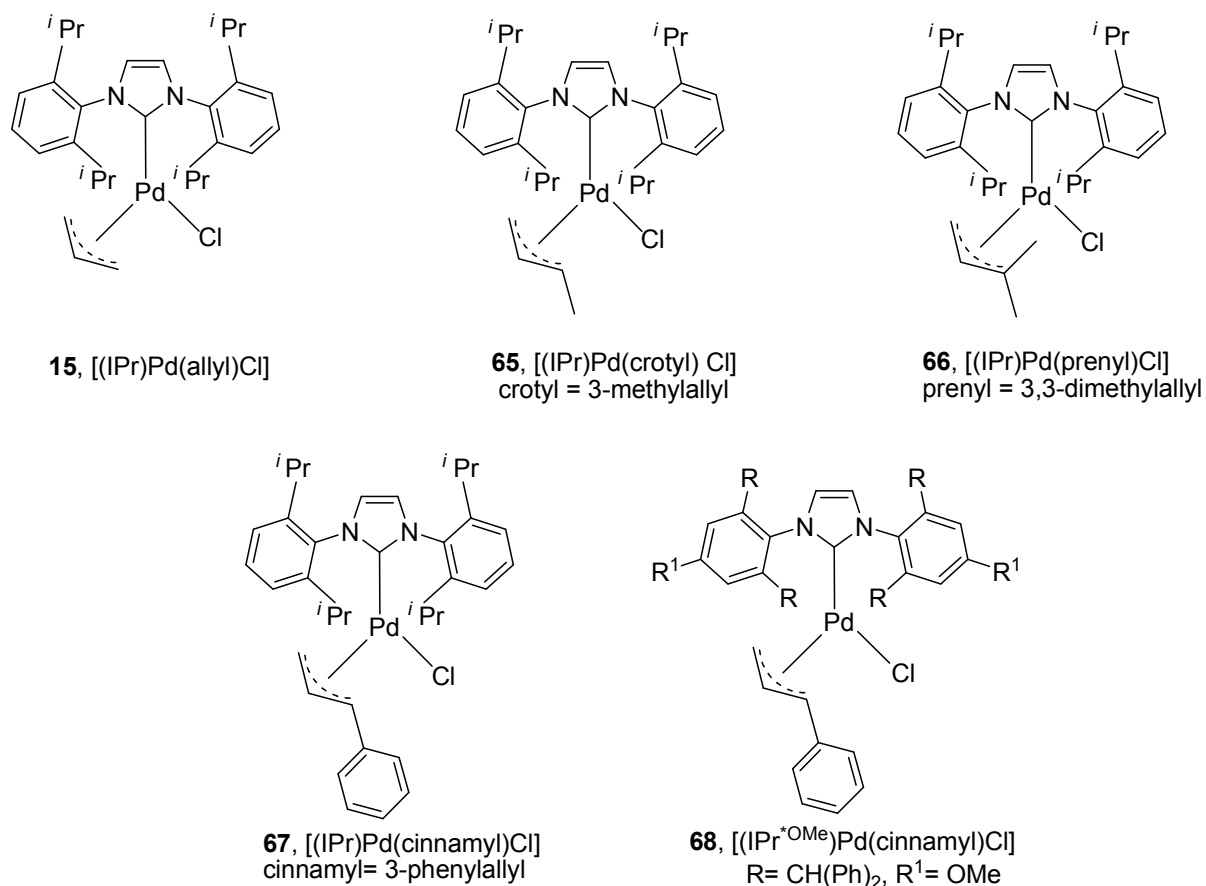


Figure-I.15: [PdCl(R-allyl)(NHC)] complexes for Suzuki coupling reaction.

Replacement of the η^3 -allyl group by crotyl, prenyl or cinnamyl groups increased the catalytic activity of the $[\text{PdCl}(\eta^3\text{-allyl})(\text{NHC})]$ complexes.^{59b} Tabel-I.3 shows the conversion for a series of $[\text{PdCl}(\eta^3\text{-R-allyl})(\text{IPr})]$ pre-catalysts.

Table-I.3: Effect of substitution at the allyl moiety on pre-catalyst performance in the Suzuki-Miyaura coupling of simple substrates.

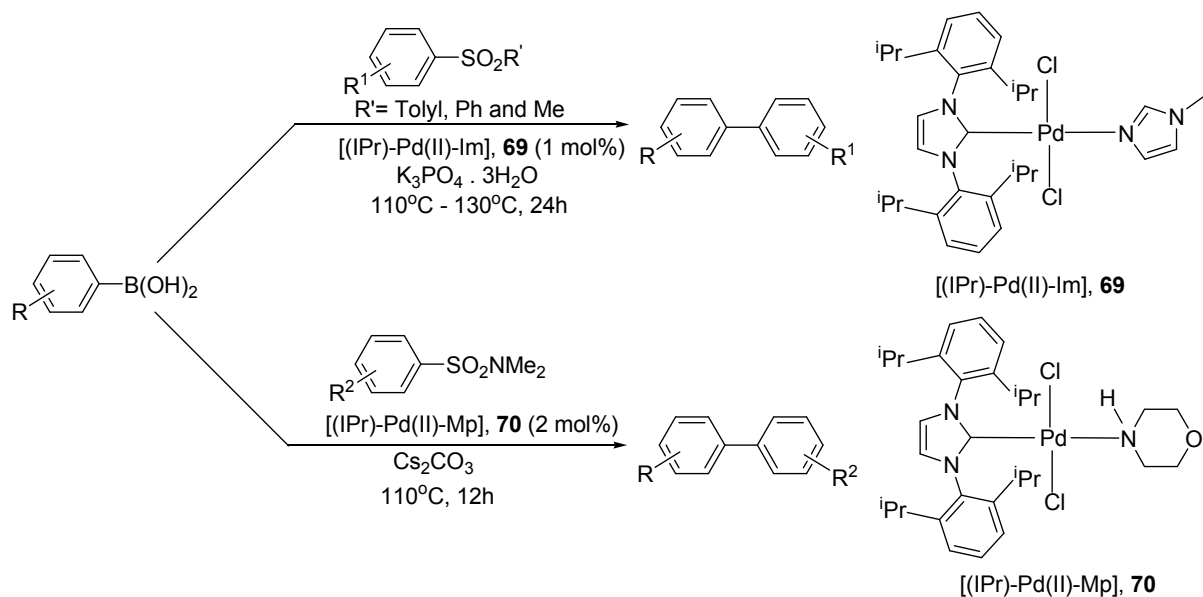
Entry	Catalyst	GC yield (%)
1	$[(\text{IPr})\text{Pd}(\text{allyl})\text{Cl}]$	12
2	$[(\text{IPr})\text{Pd}(\text{crotyl})\text{Cl}]$	86
3	$[(\text{IPr})\text{Pd}(\text{prenyl})\text{Cl}]$	90
4	$[(\text{IPr})\text{Pd}(\text{cinnamyl})\text{Cl}]$	90

Nolan *et al.* have very recently disclosed the catalytic activity of $[(\text{IPr}^{\text{OMe}})\text{Pd}(\text{cinnamyl})\text{Cl}]$ (**68**) in Suzuki cross-coupling as well as C-N bond forming reaction.⁹⁴

Although studies of Suzuki-Miyaura cross-coupling reaction in water is performed since the 1990's,⁹⁵ it has only been relatively recent that this condition has been utilized in Pd-NHC catalyzed reactions.^{70, 96, 78c}

Recently the Cazin group has examined the use of a series of mixed *trans*- $[\text{PdCl}_2(\text{PR}_3)(\text{NHC})]$ complexes in aqueous Suzuki coupling of aryl chlorides with aryl boronicacids. Reactions were carried out with 0.03 mol% Pd in $\text{H}_2\text{O}/i\text{PrOH}$ (9:1) mixture at 100°C. Very interestingly, tri-*ortho*-substituted biaryls and heteroaromatic biaryls have also been obtained in moderate to good yields.⁹⁷

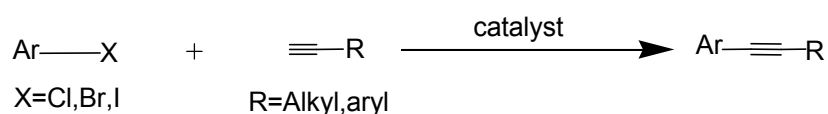
Shao *et al.* performed the Suzuki coupling reaction of aryl sulfonates with aryl boronicacids using $[(\text{IPr})\text{-Pd}(\text{II})\text{-Im}]$ complex (**69**)⁹⁸ as well as coupling of aryl sulfamates and aryl boronicacids utilizing $[(\text{IPr})\text{-Pd}(\text{II})\text{-Mp}]$ (**70**)⁹⁹ (scheme-I.30).



Scheme-I.30: Suzuki coupling of aryl sulfonates and aryl sulfamates.

However, [(IPr)-Pd(II)-Im] catalyzed Suzuki cross-coupling of aryl chlorides and aryl boronicacids have also been carried out at room temperature.¹⁰⁰

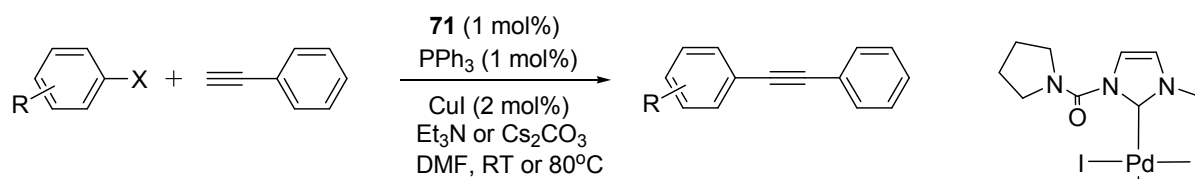
I.B.3.1c. Sonogashira cross-coupling reaction



Scheme-I.31: General reaction scheme of Sonogashira cross-coupling

Early attempts of Sonogashira reaction featuring NHC-Pd complexes were overwhelmed with production of the alkyne homo-coupling product (Glaser product),¹⁰¹ or activated aryl bromides were required to achieve moderate to poor yields.^{57a,78}

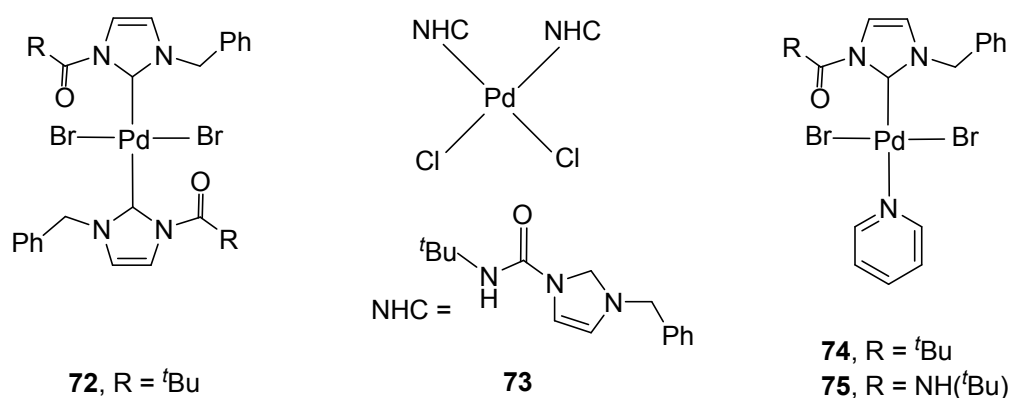
Caddick and Cloke published the first example of well-defined catalyst [Pd(*t*Bu)₂] (**14**) used in Sonogashira cross-coupling reaction.¹⁰² Batey *et al.* developed N-carbamoyl-substituted NHC-Pd(II) complex (**71**) which effectively catalyzed Sonogashira cross-coupling reaction under mild condition¹⁰³ (table-I.4).

Table-I.4: Sonogashira reaction catalyzed by Batey's Pd-NHC complex.

Entry	R	X	Base	Temp(°C)	Yield(%)
1	4-COCH ₃	I	Et ₃ N	RT	95
2	4-CH ₃	I	Et ₃ N	RT	Quant.
3	4-OCH ₃	I	Et ₃ N	RT	98
4	4-COCH ₃	Br	Et ₃ N	80°C	99
5	4-CHO	Br	Et ₃ N	80°C	89
6	4-NMe ₂	Br	Cs ₂ CO ₃	80°C	95
7	4-OCH ₃	Br	Cs ₂ CO ₃	80°C	85

Glorius then disclosed a comparison between the catalytic activity of [PdCl₂(IBiox7)]₂ complex and *in-situ* generated species from [Pd(allyl)Cl₂] and IBiox7.HOTf salt in Sonogashira reaction. This result showed the well-defined complex to be superior and developed system proved tolerant of many functional groups including epoxide and acetate groups.¹⁰⁴

Ghosh *et al.* have published an intriguing example of catalytic system that works under aqueous medium.¹⁰⁵ They successfully demonstrated the Sonogashira coupling of Ar-X (X = I, Br) with aryl, pyridinyl and alkyl acetylenes generally in 2h at 110°C. They also observed that catalyst **72** and **73** (figure-I.16) showed comparable activity to one another but were much more active than their corresponding mono-NHC-Pd-PEPPSI analogues **74** and **75** (figure-I.16).^{66a,b}

**Figure-I.16:** Pd-NHC catalysts for Sonogashira coupling developed by Ghosh *et al.*

Cao and Shi have very recently developed a series of chiral NHC-Pd complexes (figure-I.17). They have performed Cu-free Sonogashira cross-coupling reaction as well as Sonogashira/hydroarylation sequential reactions using their developed chiral NHC-Pd complexes.¹⁰⁶

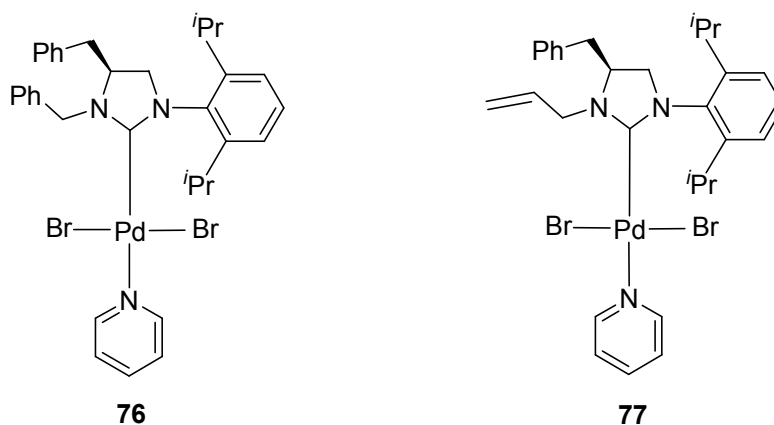
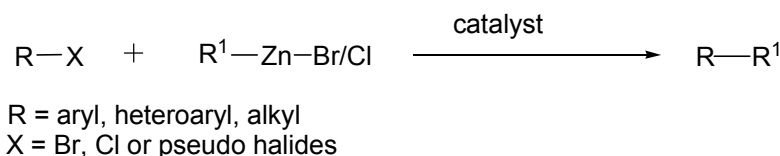


Figure-I.17: Chiral NHC-Pd complexes for Sonogashira coupling developed by Cao and Shi.

I.B.3.1d. Negishi cross-coupling reaction

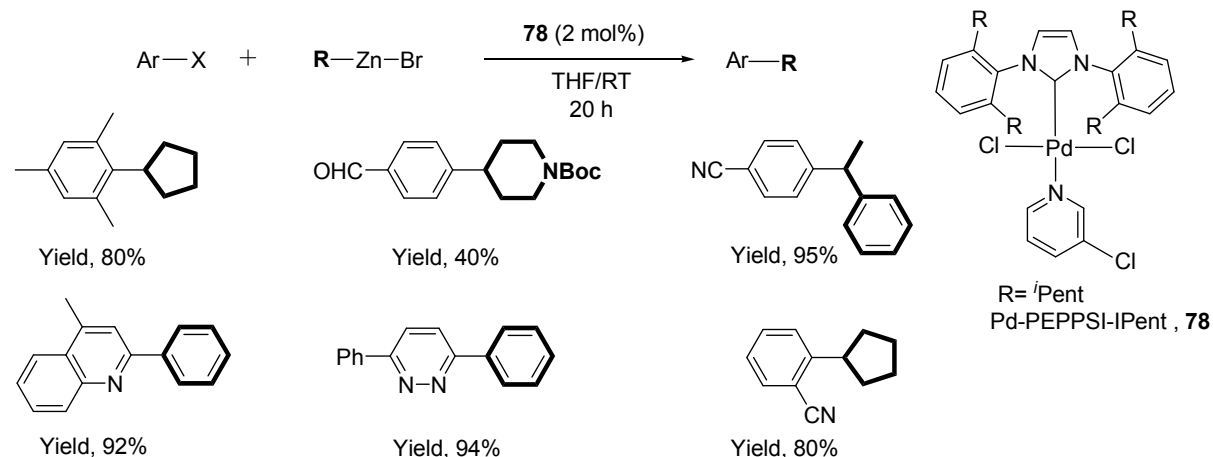


Scheme-I.32: General scheme for Negishi cross-coupling reaction.

Negishi coupling is potentially, an extremely useful cross-coupling reaction. Although, organozinc compounds are highly sensitive to air and water but high tolerance to functional groups makes it powerful synthetic tool. Initially, various *in-situ* generated Pd-NHC catalytic system were successfully utilized in Negishi cross-coupling reaction.¹⁰⁷ Organ *et al.* showed the superiority of well-defined NHC-Pd catalysts over *in-situ* generated catalyst in Negishi coupling reaction.^{63a,108} In 2006, they used [PdCl₂(IPr)(3-Cl-Py)] (Pd-PEPPSI-IPr, **64**) complex which successfully catalyzed the coupling of organozinc reagent with that of alkyl and aryl halides or pseudo halides.¹⁰⁹ Knochel and co-workers also developed a protocol for [Pd-PEPPSI-IPr] (**64**) catalyzed one-pot Negishi cross-coupling reaction of *in situ* generated zinc reagent with aryl halide and aryl triflate.¹¹⁰ Pd-PEPPSI-IPent (**78**) also have been used

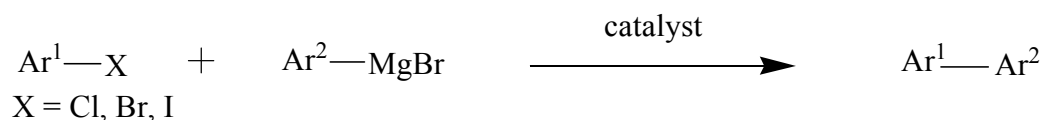
for preparation of highly functionalized, tetra-*ortho*-substituted biaryls through the Negishi cross-coupling reaction.¹¹¹

Organ *et al.* have recently published Negishi cross-coupling of secondary alkyl zinc reagents with aryl/heteroaryl halides using **78** (scheme-I.33).¹¹²



Scheme-I.33: Pd-PEEPSI-IPent catalyzed Negishi cross-coupling of secondary alkyl zinc reagents.

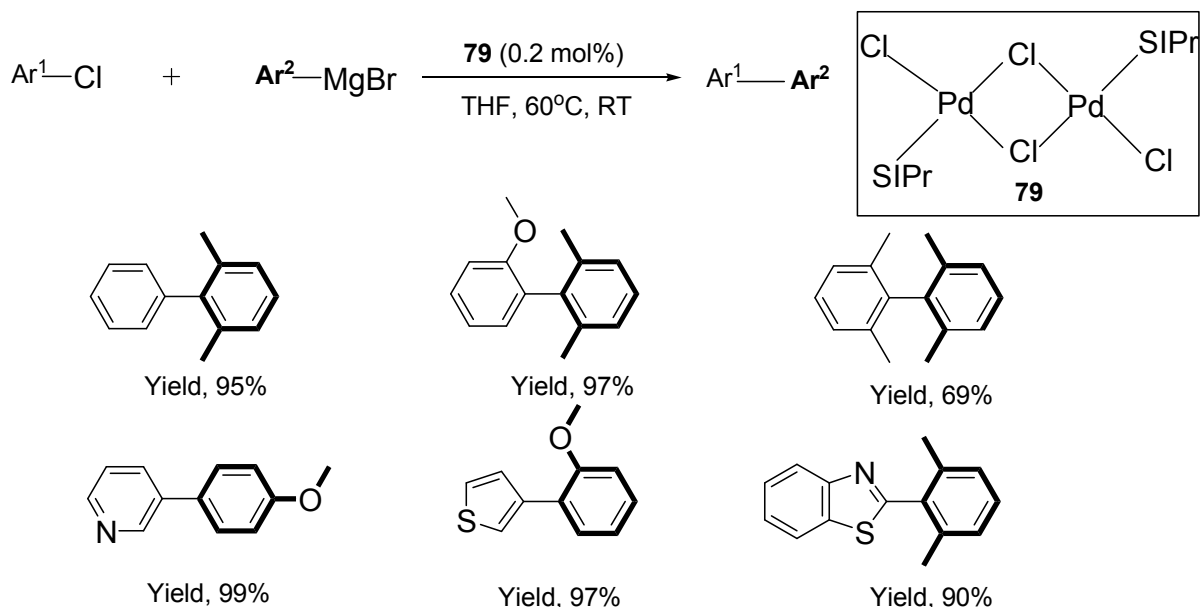
I.B.3.1e. Kumada-Tamao-Corriu cross-coupling



Scheme-I.34: General reaction Scheme for Kumada-Tamao-Corriu cross-coupling.

Coupling reactions of alkenyl or aryl halides with Grignard reagent using Ni-catalyst were first reported by Kumada and Tamao,¹¹³ and also separately by Corriu *et al.* in 1972.¹¹⁴ Similar to many of the other types of coupling reaction, *in-situ* generated Pd-NHC catalysts were the first strategies employed in Kumada cross-coupling reaction.¹¹⁵

Cazin *et al.* examined the dimeric pre-catalyst $[\text{Pd}(\mu\text{-Cl})\text{Cl}(\text{NHC})]_2$ complexes in Kumada-Tamao-Corriu cross-coupling reactions of aryl chlorides with aryl Grignards.¹¹⁶ Pd-NHC complex $[\text{Pd}(\mu\text{-Cl})\text{Cl}(\text{SiPr})]_2$ (**79**) successfully catalysed Kumada coupling of heteroaryl chlorides at 60°C and additionally, the synthesis of tri- and terta-*ortho*-substituted biaryls was accomplished (scheme-I.35).

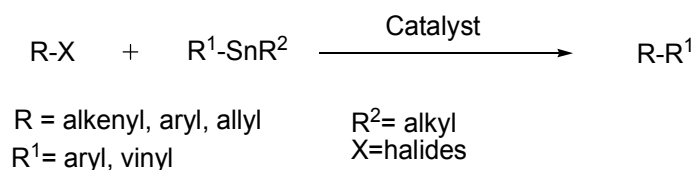


Scheme-I.35: $[\text{Pd}((\mu\text{-Cl})\text{Cl}(\text{SIPr}))_2]$ catalyzed Kumada cross-coupling reaction.

Various Pd-PEPPSI-NHC complexes were introduced in Kumada-Tamado-Corriu cross-coupling reaction by Organ *et al.*¹¹⁷ Jin and Fang have also disclosed successful Kumada coupling using the air stable $[\text{PdCpCl}(\text{NHC})]$ complexes.¹¹⁸

Liu *et al.* developed Pd-NHC catalyzed protocol for Kumada-Tamao-Corriu cross-coupling that involved an alkyl magnesium bromide substrate and the coupling partners were predominately aryl bromides.¹¹⁹

I.B.3.1f. The Stille reaction

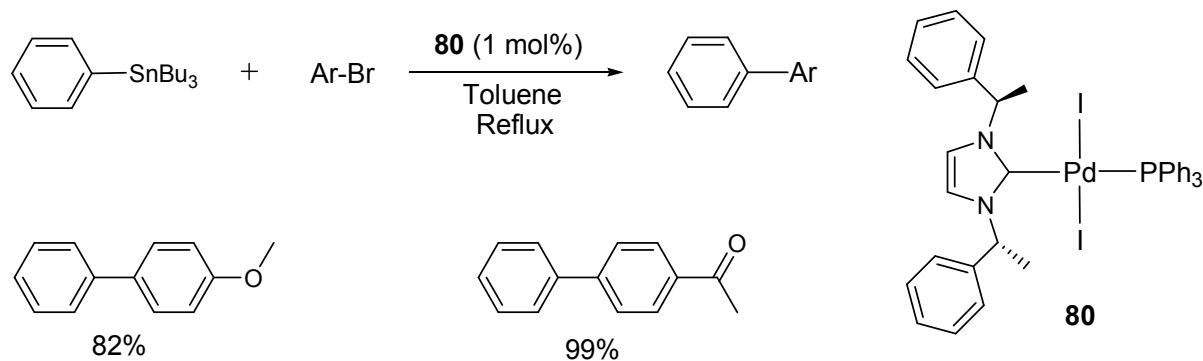


Scheme-I.36: General reaction scheme for the Stille reaction.

The Stille reaction has developed as an effective protocol for the formation of C-C bonds due to the air- and moisture-stability as well as functional group compatibility of organostannanes. Despite its efficiency, it has fallen out of favour recently because of the high toxicity of organostannanes.

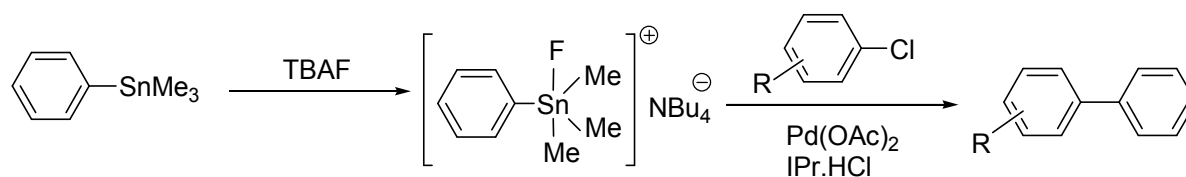
The first example of NHC-Pd catalyzed Stille reaction between aryl bromides and aryl stannanes was reported by Herrmann *et al* in 1999.¹²⁰

Summarised in scheme-I.37 are the best results obtained when the well-defined pre-catalyst (**80**) was employed. Unfortunately, the coupling of aryl chlorides was not possible.



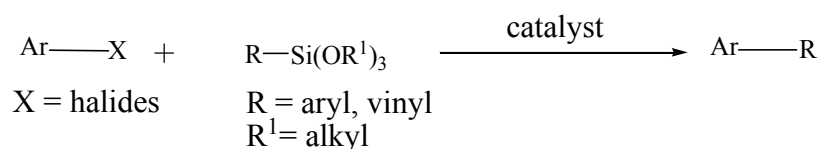
Scheme-I.37: First example of Pd-NHC catalyzed Stille reaction.

An *in-situ* Pd(OAc)₂-imidazole salt mixture has developed by Nolan and Grasa. The addition of fluorine anion source, TBAF (tetrabutylammonium fluoride) gave improved result in the coupling of aryl chlorides to vinyl and aryl stannanes. The fluoride is thought to coordinate to tin in order to facilitate the transmetalation step¹²¹ (scheme-I.38).



Scheme-I.38: Stille reaction in presence of TBAF.

I.B.3.1g. Hiyama cross-coupling reaction



Scheme-I.39: General reaction scheme for Hiyama cross-coupling reaction.

The use of silyl species in reaction is desirable as they are easily available, easily synthesised and stable. Another advantage is that their by-products are biodegradable, thus reducing detrimental impact on environment. Typically the C-Si bond needs to be activated either by electronegative substituent on the aryl/vinyl siloxane or by external fluoride anions.

Pd-NHC catalyzed Hiyama reaction was reported by Nolan using an *in-situ* generated catalytic protocol by mixing Pd(OAc)₂ and IPr. HCl for the formation of catalyst.¹²²

Ghosh *et al.* have examined a number of NHC-Pd-PEPPSI type complexes in fluorine-free Hiyama cross-coupling reaction in aqueous medium.^{66b}

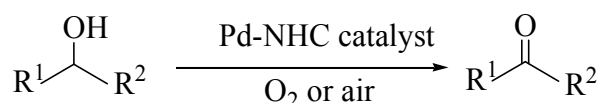
Penafiel and co-workers have recently disclosed hydroxyl-functionalized-NHC-palladium complex catalyzed microwave-accelerated fluorine-free Hiyama reaction.¹²³

I.B.3.2. Miscellaneous reactions

Apart from above described Pd-NHC catalyzed C-C bond forming reactions, many other types of reactions like oxidation, reduction, C-H bond arylation, hydroarylation, allylic alkylation reactions have also been carried out by using well-defined Pd-NHC complexes as well as with *in-situ* generated catalysts.

I.B.3.2a. Oxidation of alcohol

The oxidation of alcohols to the corresponding carbonyl compounds is one of the key reactions in synthesis. Many metals have been used in such oxidation reactions, among which palladium is mostly preferred. Like other reactions, Pd-NHC complexes are also introduced in oxidation of alcohol as efficient catalysts.



Scheme-I.40: General reaction scheme for Pd-NHC catalyzed oxidation of alcohols.

Sigman and co-workers reported that complex **81** promotes the aerobic oxidation of alcohols.¹²⁴ Interestingly, the scope of the reaction using [(IPr)Pd](μ-Cl)Cl₂ (**82**) catalyst can be extended to oxidative kinetic resolution of secondary alcohols by using (-)-sparteine as a base.¹²⁵

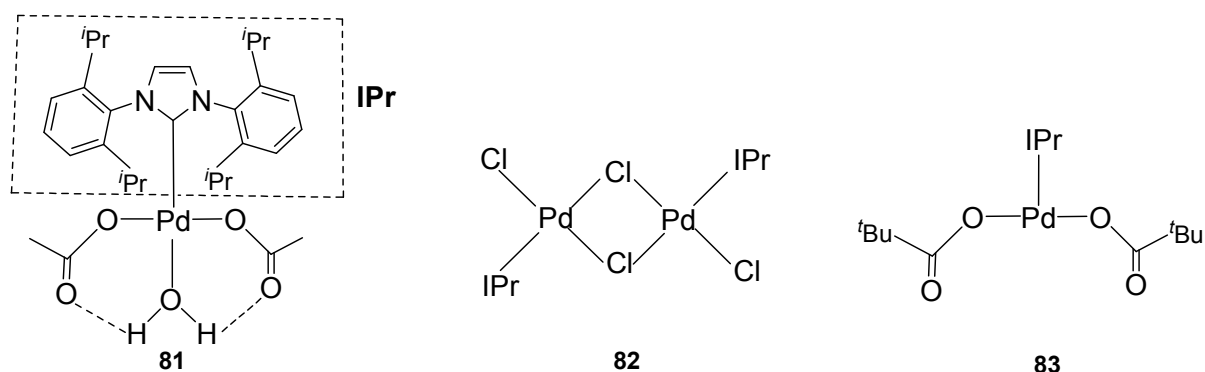
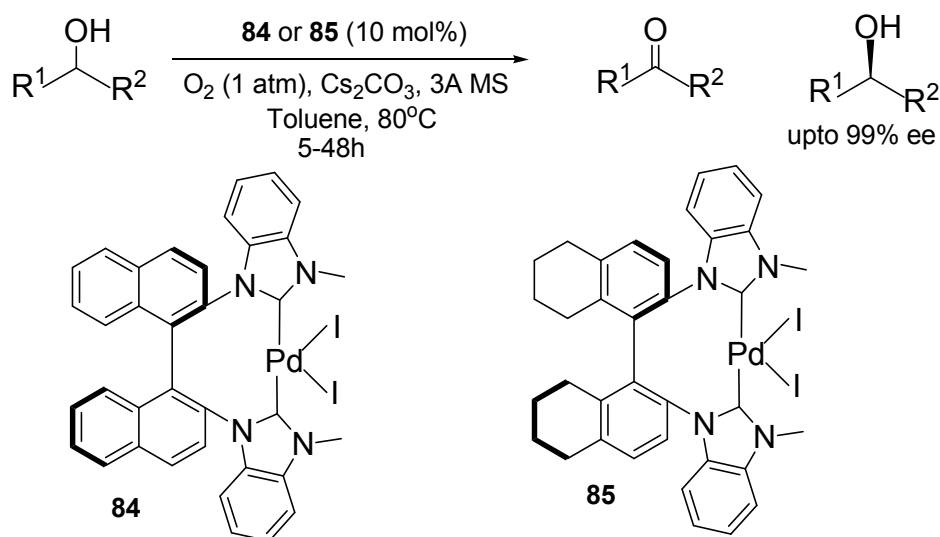


Figure-I.18: Pd-NHC complexes used in alcohol oxidation by Sigman.

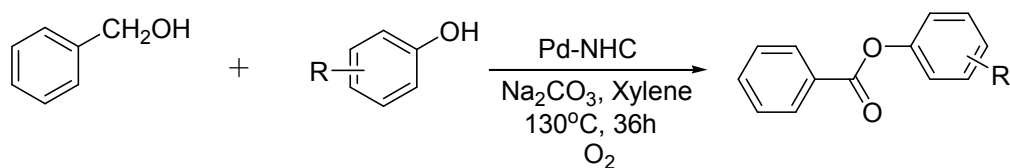
Afterwards, Sigman's group also reported [Pd(IPr)(OPiv)₂] (**83**) catalysed alcohol oxidation under room temperature but with a more limited substrate scope.¹²⁶ Axially chiral Pd-NHC complexes reported by Shi *et al.* have shown high selectivity in the oxidative kinetic resolution of alcohols without addition of chiral base (scheme-I.41).¹²⁷ Recently, Cazin and co-workers have also reported [Pd(NHC)(PR₃)] catalyzed alcohol oxidation using molecular oxygen.¹²⁸



Scheme-I.41: Oxidative kinetic resolution of alcohols using chiral bis-NHC-Pd complexes.

I.B.3.2b. Oxidative esterification

Pd-NHC catalyzed oxidative esterification of benzylic alcohol and aldehydes with phenols have been developed. Chen *et al.* have disclosed *in-situ* generated Pd-NHC catalyzed tandem oxidative esterification of benzylic alcohol with phenols¹²⁹ (scheme-I.42).



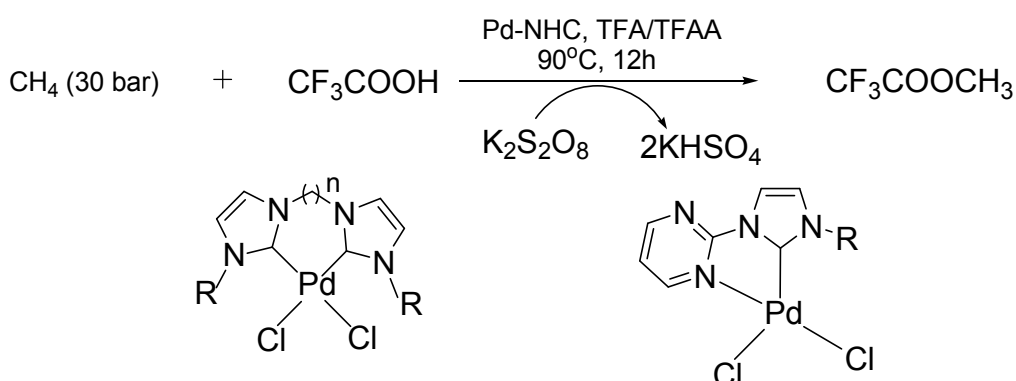
Scheme-I.42: Oxidative esterification of benzyl alcohol.

Zhang and co-workers have also disclosed Pd-NHC catalyzed oxidative esterification of aldehydes with phenols in presence of air.¹³⁰

I.B.3.2c. Oxidation of methane

The oxidation of C-H bonds represent one of the major challenges in organic chemistry. C-H bond oxidations are often performed in strongly acidic media (such as oleum) in order to enhance the electrophilicity of the metal centre. This indeed requires catalysts that are stable under very challenging conditions.

Early work by Strassner and co-workers showed that the chelating bis-NHC-Pd complexes were capable of promoting the oxidation of methane, whilst the iodo-analogues of such complexes were inactive under the same reaction condition.¹³¹ Indeed, trifluoroacetic acid methyl ester is produced from mixture of TFA and TFAA, in the presence of potassium peroxodisulfate under 20-30 bar of methane. In a more recent work, the authors disclosed the use of pyrimidine-NHC-Pd complexes for the same reaction⁷⁶ (scheme-I.43).

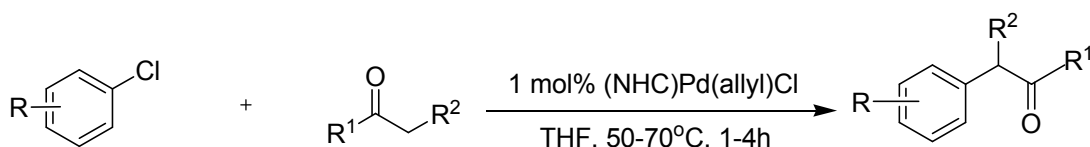


Scheme-I.43: Pd-NHC catalyzed oxidation of methane.

I.B.3.2d. α -Arylation of ketones

The synthesis of α -aryl ketones has received attention since the discovery of direct coupling between simple ketones and aryl halides without the use of tin or silicon intermediates.¹³²

In the year of 2002, Nolan *et al.* reported a well-defined Pd-NHC catalyzed α -arylation of ketones using aryl chlorides as reactive partners. A numbers of [(NHC)Pd(allyl)Cl] complexes were found as active catalysts for arylation of ketones¹³³ (scheme-I.44).



Scheme-I.44: [(NHC)Pd(allyl)Cl] catalyzed α -arylation of ketones.

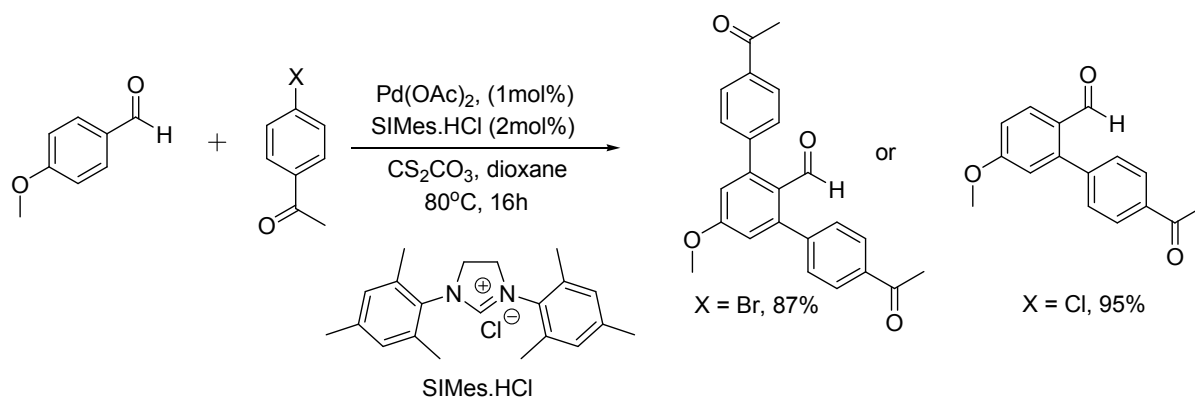
They have also successfully introduced palladacycle/NHC complexes (**90** and **91**, figure-I.20 in C-N bond formation) as well as [(IPr)Pd(acac)Cl] (**42**) in α -arylation of ketones.¹³⁴

I.B.3.2e. Direct C-H arylation

While cross-coupling methods are extremely useful and of easy and common use, several drawbacks for these reactions could be pointed out, like the need of prefunctionalisation of both coupling partners and the use of the organometallic partner in stoichiometric amounts, with the corresponding generation of toxic waste. Alternative methods have emerged and the direct arylation through C-H bond activation is most attractive procedure for arylation.

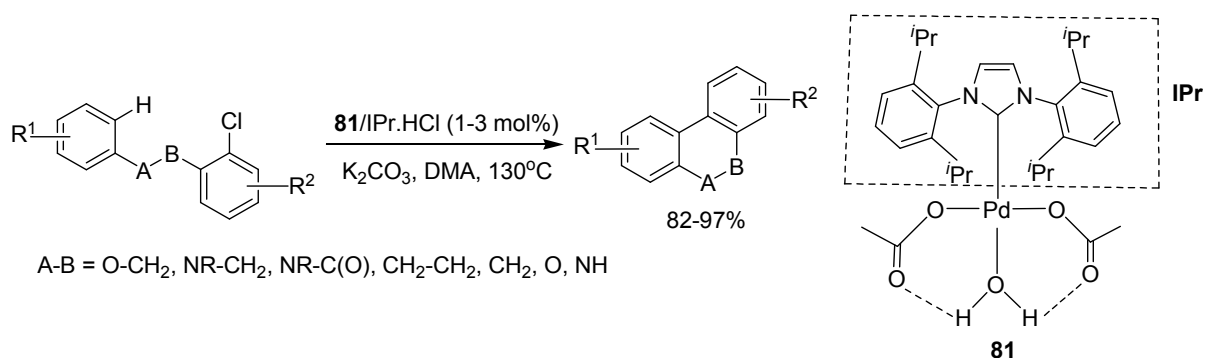
Like various other type of reactions, Pd-NHC catalysts have proved their efficiency in C-H arylation reactions also.

Çetinkaya and co-workers have described the Pd-catalysed *ortho*-arylation of benzaldehyde derivatives with aryl bromides and chlorides where aldehyde served as directing group. Good yields were obtained when using Pd(OAc)₂ and SIMes for the arylation of a variety of benzaldehyde derivatives with a wide range of electron-rich and -poor aryl halides¹³⁵ (scheme-I.45).



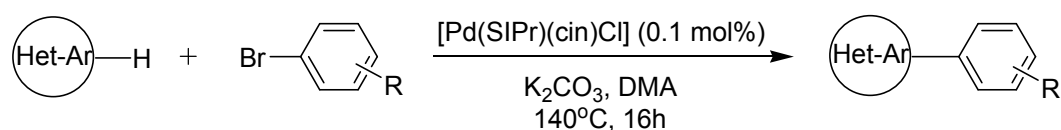
Scheme-I.45: Direct arylation of benzaldehyde.

Fagnou and co-workers reported Pd-NHC complex catalyzed intramolecular direct arylation reaction of arenes with aryl chlorides to form six- and five-membered ring biaryls including different functionalities as ether, amine, amide and alkyl¹³⁶ (scheme-I.46).



Scheme-I.46: Intramolecular direct arylation reactions with aryl chlorides.

Pd-NHC catalyzed direct C-H arylation of heteroarenes have also been developed. Nolan *et al.* have investigated the direct arylation of heterocycles using a series of [Pd(NHC)(cinnamyl)Cl] precatalysts and [Pd(SIPr)(cinnamyl)Cl] proved to be most efficient promoter for C-H arylation of sulfur- or nitrogen-containing heterocycles¹³⁷ (scheme-I.47).



Scheme-I.47: [Pd(NHC)(cinnamyl)Cl] catalyzed C-H arylation of heterocycles.

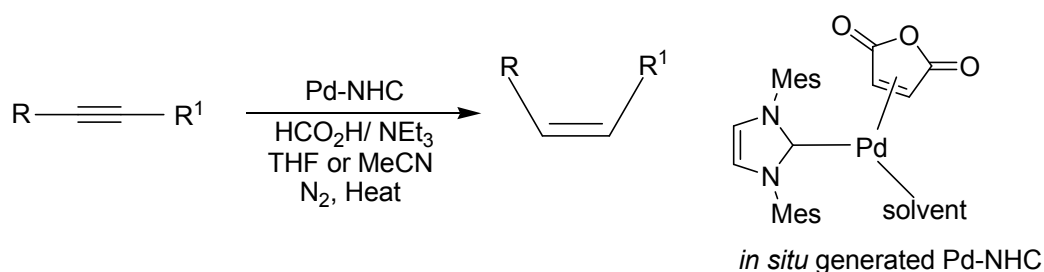
Pd-NHC catalyzed direct arylation of pyrrole derivatives with aryl chlorides as coupling partners is also reported by Ozdemir and co-workers.¹³⁸

Very recently, Grisi *et al.* have reported a palladium complex bearing a hydroxyl-functionalized NHC ligand and it effectively catalyzed the direct arylation of furan and thiophene derivatives with aryl halides.¹³⁹

I.B.3.2f. Semihydrogenation of alkynes

In the year of 2005, Elsevier first reported Pd-NHC catalyzed semihydrogenation of alkynes and *in situ* generated Pd(0)-NHC complex was used as catalyst.¹⁴⁰

Afterwards, Elsevier's group again reported a protocol for transfer semihydrogenation of alkynes to exclusively Z-alkenes and HCO₂H/Et₃N was used as hydrogen donor¹⁴¹ (scheme-I.48).



Scheme-I.48: Pd-NHC catalyzed transfer semihydrogenation.

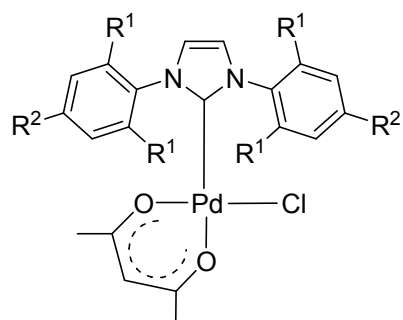
Zerovalent [Pd(NHC)(alkene)_{1,2}] complexes bearing expanded-ring NHC ligand was recently used for transfer hydrogenation of alkynes.¹⁴² Pd(II)-NHC precatalyst, [(IMes)Pd(allyl)Cl] (**17**) has also been recently introduced in transfer semihydrogenation methodology for alkynes by Elsevier and co-workers.¹⁴³

I.B.3.3. Pd-NHC catalyzed C-N bond formation

During the past few years, the palladium-catalyzed amination reaction has become one of the most important and frequently applied methods for the formation of C-N bonds.¹⁴⁴ A variety of phosphine ligands were developed for this purpose, such as Buchwald's biaryl phosphines,¹⁴⁵ Hartwig's ferrocene-based phosphines,¹⁴⁶ Beller's N-substituted heteroaryl phosphines.¹⁴⁷ However, all tertiary phosphine ligands mentioned were used as free ligands with palladium salts; thus, usually addition of excess ligands was necessary in comparison to palladium salts. Recently, in addition to air-sensitive tertiary phosphine ligands, several air

stable NHC-palladium complexes have been developed which have proven to be good catalysts in the amination reactions.

It was shown that less reactive aryl chlorides coupled with amines very effectively at room temperature. [(IPr)Pd(acac)Cl] complex (**42**) showed catalytic activity in N-arylation of aryl bromides and chlorides.^{134b}



42, [Pd(IPr)(acac)Cl]; (R¹ = *i*Pr; R² = H)

86, [Pd(IPr^{*})(acac)Cl]; (R¹ = CH(Ph)₂; R² = Me)

87, [Pd(IPr^{OMe})(acac)Cl]; (R¹ = CH(Ph)₂; R² = OMe)

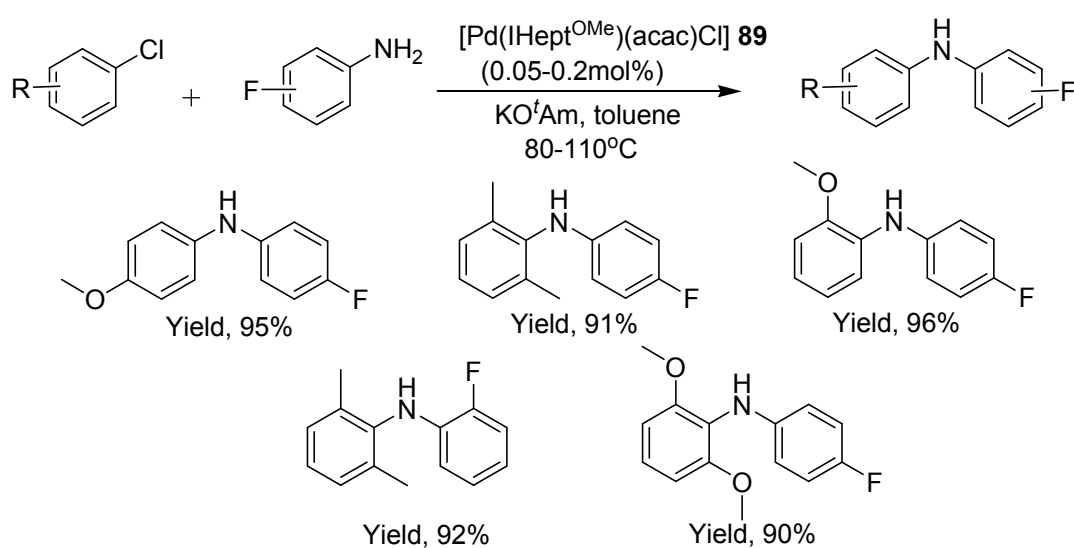
88, [Pd(IPent^{OMe})(acac)Cl]; (R¹ = *i*Pent; R² = OMe)

89, [Pd(IHept^{OMe})(acac)Cl]; (R¹ = *i*Hept; R² = OMe)

Figure-I.19: [Pd(NHC)(acac)Cl] complexes used in C-N coupling reaction.

Nolan and co-workers have recently introduced various [Pd(NHC)(acac)Cl] complexes as effective catalyst in the field of C-N coupling reaction¹⁴⁸ (figure-I.19).

It has been observed that [Pd(IPr^{OMe})(acac)Cl] (**87**) shown better catalytic activity than that of [Pd(IPr^{*})(acac)Cl] (**86**).^{148a} Soon after they also reported that [Pd(IHept^{OMe})(acac)Cl] (**89**) displayed excellent catalytic activity for the coupling of electron-poor anilines with electron-rich aryl chlorides^{148b} (scheme-I.49).



Scheme-I.49: Coupling of electron -poor anilines with electron-rich aryl chlorides.

In the year of 2003, Nolan *et al.* described the catalytic activity of a novel class of palladacycle/NHC complexes (**90** and **91**) in C-N bond formation reaction.^{134a}

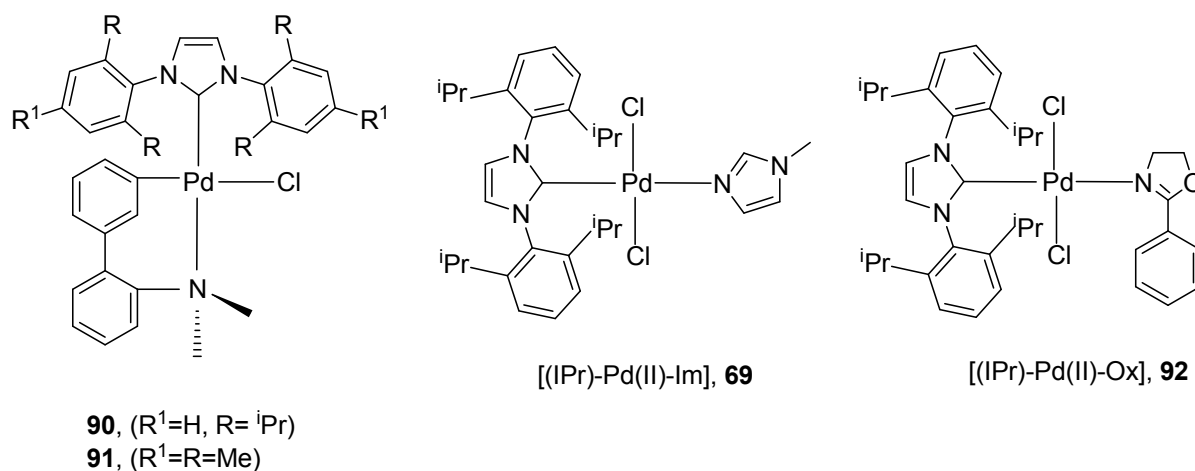
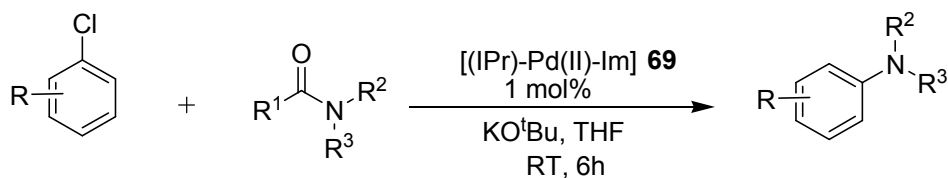


Figure-I.20: Pd-NHC complexes used in amination reaction and/or C-C bond formation.

Shao *et al.* have developed a protocol for amination between aryl chlorides and amides using [(IPr)-Pd-Im] (**69**)¹⁴⁹ (scheme-I.50). Lu and co-workers have very recently introduced [(IPr)-Pd-Ox] (**92**) complex as an effective catalyst for the amination of aryl chlorides.¹⁵⁰



Scheme-I.50: Amination of aryl chlorides with amides.

[Pd(NHC)(3-Cl-pyridinyl)Cl₂] also called [Pd-PEPPSI-NHC] precatalyst introduced by Organ^{63a,111,112,151} and then various Pd-PEPPSI-NHC complexes (figure-I.21) have been applied as efficient catalyst for Buchwald-Hartwig amination reaction by Organ and Nolan.¹⁵²

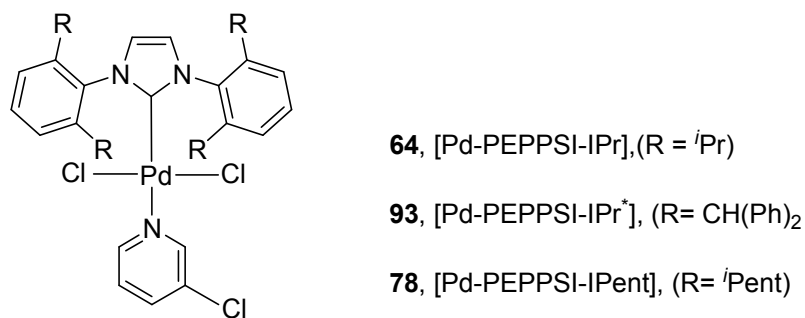


Figure-I.21: Selective Pd-PEPPSI-NHC for Buchwald-Hartwig amination.

A series of [(NHC)Pd(R-allyl)Cl] have also been employed for arylation reaction at room temperature.^{59b,59d,94,153}

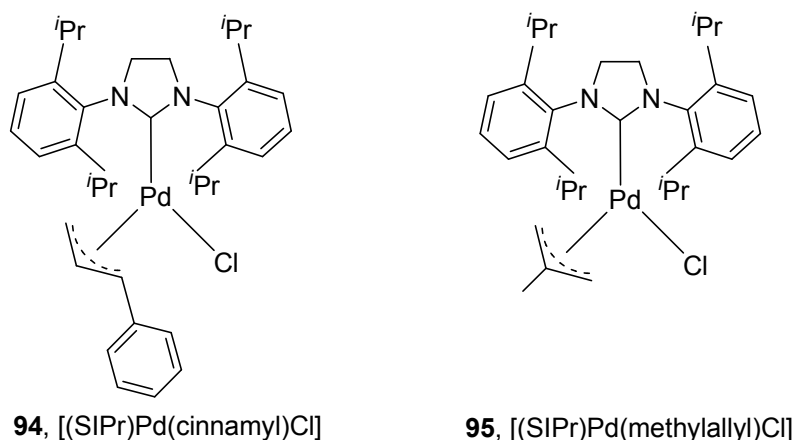
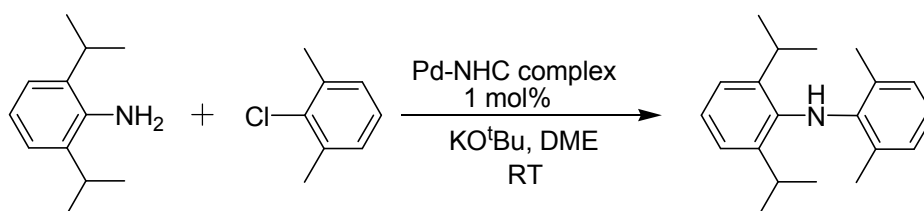


Figure-I.22: NHC-Pd complexes for C-N bond formation reaction.

It has been observed that [(SIPr)Pd(allyl)Cl] (**16**) shows better activity in Buchwald-Hartwig amination than [(IPr)Pd(allyl)Cl] (**15**) at room temperature.^{59d} Nolan *et al.* have made a comparison between **15**, **16**, **67** and **94** regarding their catalytic activity in C-N bond forming amination reaction.^{59b} (Scheme-I.51)



Pd-NHC complex	Time	GC conversion (%)
[(IPr)Pd(allyl)Cl], 15	20h	73
[(SIPr)Pd(allyl)Cl], 16	15h	90
[(IPr)Pd(cinnamyl)Cl], 67	6h	98
[(SIPr)Pd(cinnamyl)Cl], 94	1.5h	97

Scheme-I.51: Comparison of catalytic activity of Pd-NHC complexes in C-N bond formation.

Very recently, it has been disclosed that [(IPr^{*OMe})(cinnamyl)Cl] (**68**) provides high catalytic activity for Buchwald-Hartwig cross-coupling reactions of sterically demanding aryl chlorides with sterically hindered and deactivated aniline derivatives.⁹⁴

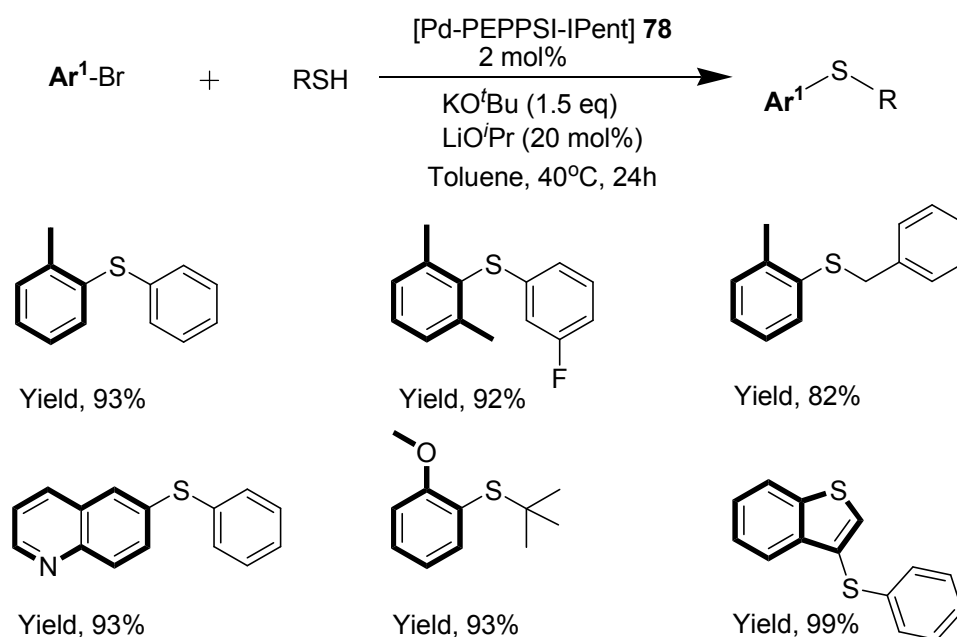
Apart from Buchwald-Hartwig cross-coupling reaction, other types of C-N bond forming reactions are also performed using various Pd-NHC complexes. These include aminocarbonylation,¹⁵⁴ intermolecular direct annulations between *o*-amino arylhalide and cyclic ketones,¹⁵⁵ intramolecular oxidative amination of alkenes¹⁵⁶ and hydroamination of alkynes¹⁵⁷ *etc.*

I.B.3.4. C-S bond formation

The formation of carbon-sulfur bond is of the significant importance in molecular assembly strategies, as several bio-active compounds with wide range of activity contain aryl thioether moieties. Different transition metals are used (e.g. copper, nickel, iron, rhodium, gold and palladium) for the formation of carbon-sulfur bond.¹⁵⁸ In case of palladium, phosphine based catalysts have been successfully used in this field.¹⁵⁹

As Pd-NHC complexes have been found to be an efficient alternative to Pd-phosphines systems in Buchwald-Hartwig amination reaction, they were recently studied for carbon-sulfur bond forming reactions. Some Pd-NHC complexes are commonly used in C-S bond forming reaction as well as C-C coupling reactions and/or amination reaction too e.g. **62**, **64** and **78**.

However, Pd-PEPPSI pre-catalysts are investigated and systematically modified to enable one of the most general mild protocols for C-S bond formation.¹⁶⁰ Organ *et al.* have introduced [Pd-PEPPSI-IPent] (**78**) for the sulfination of aryl halides and heteroaryl halides with variety of aryl as well as alkyl sulfides (scheme-I.52).^{160a}



Scheme-I.52: [Pd-PEPPSI-IPent] catalyzed C-S bond formation reaction of aryl halides and heteroaryl halides with aryl as well as alkyl sulfides.

It is observed that [Pd-PEPPSI-IPent] was found to be more effective at aryl sulfination than its predecessors [Pd-PEPPSI-IPr] (**64**) and [Pd-PEPPSI-IMes] (**62**) due to the increase in steric effect of the NHC ligands.^{160a} Various modifications have been done to achieve more active catalyst such as [Pd-PEPPSI-IPent^{Cl}] (**96**) as well as [Pd-PEPPSI-IPent^{Cl}-*o*-picoline] (**97**)^{160c} (figure-I.23).

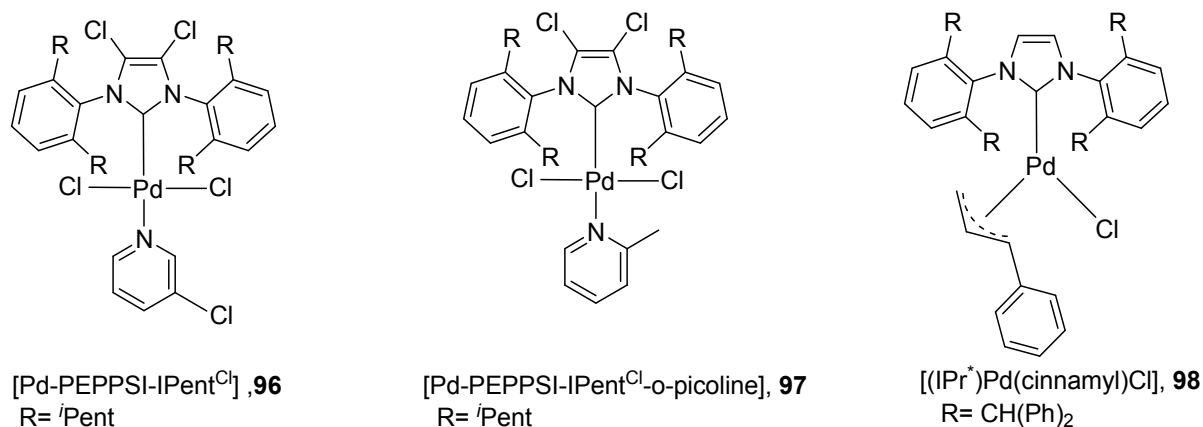
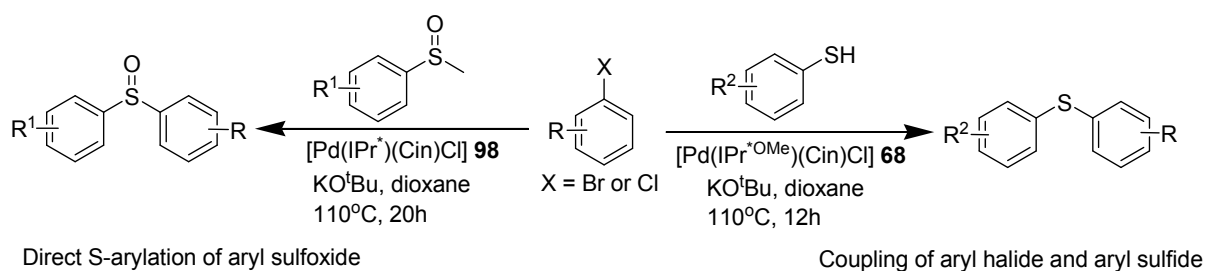


Figure-I.23: Pd-PEPPSI-NHC complexes for C-S bond formation.

[(NHC)Pd(R-allyl)Cl] complexes are also employed in C-S bond forming reaction. Nolan *et al.* have very recently disclosed direct S-arylation of unactivated arylsulfoxides using [Pd(IPr^{*})(cinnamyl)Cl] (**98**) catalyst.¹⁶¹ They have also reported [Pd(IPr^{*OMe})(cinnamyl)Cl] (**68**) catalyzed C-S bond formation between arylhalides and aryl sulfides¹⁶² (scheme-I.53).



Scheme-I.53: [(NHC)Pd(R-allyl)Cl] complex catalyzed C-S bond formation.

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