CHAPTER I

A Brief Review on Cross Coupling Methodologies for Carbon-Carbon and Carbon-Heteroatom Bond Forming Reactions

I.A. Introduction

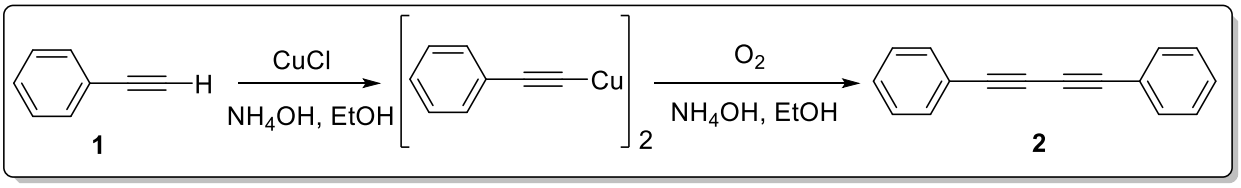
Carbon-carbon (C-C) and carbon-heteroatom (C-X) bond formation reactions are indispensable tools in organic synthesis. Cross coupling reactions are extremely powerful and most widely used for the construction of carbon-carbon and carbon-heteroatom bond in synthetic chemistry.[1] This reaction allows the chemists to connect two organic parts under relatively soft conditions for the manipulation and creation of complex, delicate molecules. In this regard, the metal catalyzed cross coupling reactions between sp^2-hybridized aryl halide; an electrophile with an organometallic nucleophile is an important synthetic methodology.[2]

The potential of cross-coupling reactions can be elucidated through two findings. First, the emergence of these techniques has enabled the evolution of beneficial synthetic routes for the synthesis of molecules with useful industrial applications.[2] Secondly, and possibly even more importantly, cross-coupling reactions have influenced novel schemes for molecules that would not else have been assumed. This can be illustrated through a correlation of the application of the Suzuki−Miyaura reaction. In 2014 it was found to be the second most common reaction while in 1984, there were hardly any example of Suzuki−Miyaura reaction.[3] The efficiently documented "flattening" of pharmaceuticals in this period towards planar structures was also probably somewhat accountable for the substantial switch towards cross-coupling reactions mostly towards the Suzuki−Miyaura reaction.[4] This gives foundation to the theory that progress in dependable synthetic methods can encourage molecular design and highlights the remarkable impact of cross coupling reactions. The influence was recognized in 2010 when the Nobel Prize in Chemistry was awarded to Richard. F. Heck, Ei-ichi Negishi, and Akira Suzuki for the development of palladium-catalyzed cross coupling reactions.[5]

The important factor in the extensive use of cross coupling reactions is their reproducibility and consistency compared with other synthetic methods,[6] remarkably, the high success rates of Suzuki−Miyaura reactions.[3] The knowledge about the nature of the organometallic intermediates and catalyst decomposition pathways and conception of the mechanism of cross coupling reactions has furnished to the reliability of these reactions.[2]

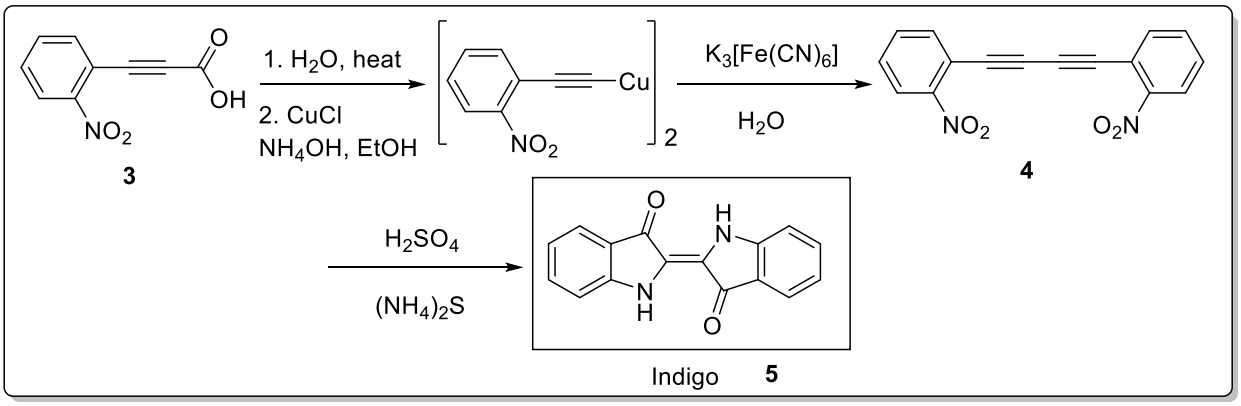
I.A.1. Origin of Cross Coupling Reactions

In 1869 Glaser reported the copper mediated homo coupling of metallic acetylides (**Scheme I.1.**).[7,8] In these groundbreaking studies, Glaser reported the oxidative dimerization of phenyl acetylene to diphenyldiacetylene in presence of Cu-as catalyst in an open flask. Reasonably explosive,[9] copper acetylides was identified as an intermediate of this reaction but the superiority of this new C(sp)–C(sp) bond forming reaction were admired by the synthetic community in the next decades, for the building of several acetylenic compounds.



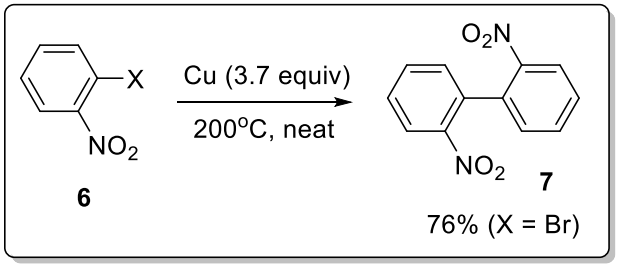
Scheme I.1. The Glaser coupling

In 1882, the synthesis of indigo by Baeyer (**Scheme I.2.**)[10] is an excellent example for the use of the Glaser coupling. This is distinctly a predecessor of the current combined transition-metal-catalyzed Sonogashira–heteroannulation procedure for indoles and related heterocycles.



Scheme I.2. Baeyer's synthesis of indigo

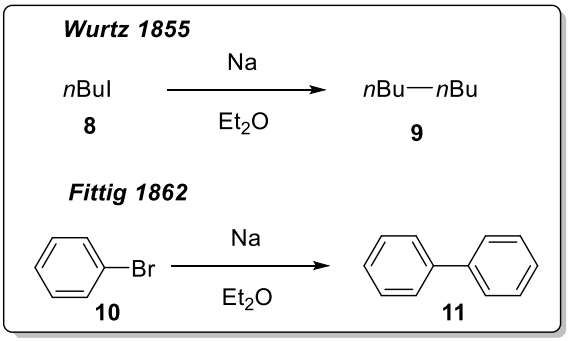
Following the progress of C(sp)-C(sp) homocoupling, the copper method was also reached out to C(sp^2)-C(sp^2) bond formation. Ullmann described the dimerization of 2-bromo- and 2-chloro nitrobenzene assisted by the use of super stoichiometric copper sources in 1901 (**Scheme I.3.**).[11, 12] While the Ullmann dimerization connected to the Glaser-type process that preceded it, differed in one basic point that the dimerization takes place between carbons bearing halogens rather than between simple unfunctionalized carbon systems.[11, 12]



Scheme I.3. The Ullmann reaction

This concept of using carbon atoms bearing halogens for coupling chemistry was simultaneously being flourished in the areas of organomagnesium (Grignard) and organosodium (Wurtz–Fittig) chemistry.

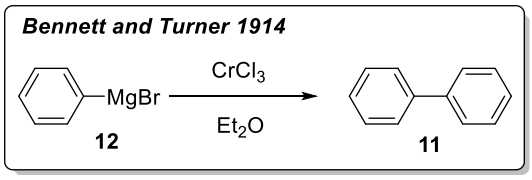
Alongside the promising evolution in copper-mediated processes, improvements were being made in the area of organoalkali-metal reagents. Research on the production of organosodium and organopotassium species had earlier disclosed their pyrophoric character and ferocious reactivity.[13] Wurtz described the homodimerization of alkyl halides in the presence of metallic sodium in 1855[14] and Fittig widened this work to incorporate the homodimerization of aryl halides[15] in extension to his work with Tollens on the reaction of alkyl halides under comparable conditions in 1862 (**Scheme I.4.**).[16] Obviously the violent reactivity of Na and K reagents restricted the application of these reagents and tempted to the exploration and evolution of the softer nucleophilic Grignard reagents [17] in the early part of the 20th century.



Scheme I.4. Sodium-mediated dimerization of alkyl and aryl halides

The reactivity with alkyl and aryl halide derivatives of these milder reagents was restricted due to several side reactions. The construction of $C(sp^2)$-$C(sp^2)$ bonds using Grignard reagents was

unknown prior to the report of Bennett and Turner in 1914[18] who delineated the dimerization of phenylmagnesium bromide using stoichiometric quantities of chromium(III) chloride (**Scheme I.5.**). A few years later, Krizewsky and Turner also described a $CuCl_2$ promoted homocoupling reaction.[19]



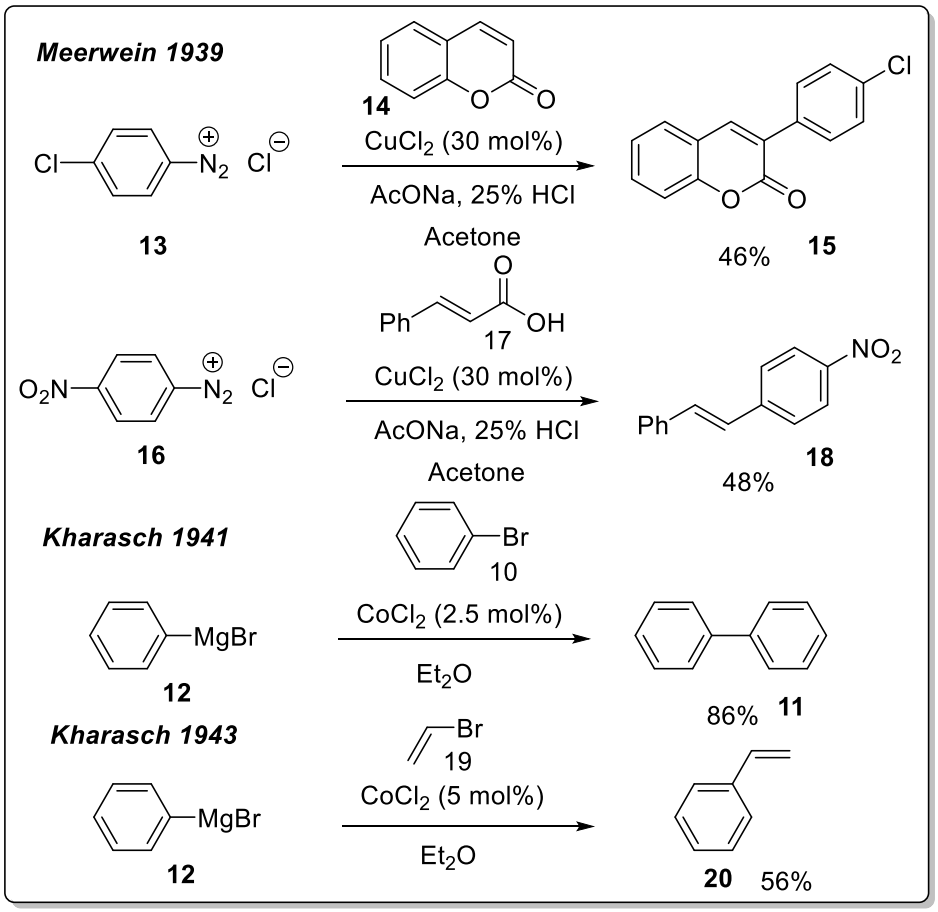
Scheme I.5. Chromium chloride promoted dimerization of Grignard reagents

In spite of these extraordinary accomplishments, the initial metal promoted reactions were restricted in two vital ways: 1) the use of inadequately soluble, stoichiometric or superstoichiometric metal reagents and 2) matter of selectiveness for coupling devil these early procedures. The conversions were restricted to homocoupling and often culminated to several side reactions and undesirable by-products. The first sights of a solution to both these issues emerged during the first half of the 20th century, beginning the new possibilities and, finally, to the robust selective catalytic procedure that we know and value today.

While catalytic quantities of copper had been shown to boost the C-O coupling reaction of phenols with aryl halides as early as 1905 by Ullmann,[20] the use of catalytic metals for the formation of C-C bonds somehow stand an evasive idea through the first part of the 20th century. The beginning of catalysis for the formation of C-C bonds is masked by the fog of World War I. Corriu[21] had attracted concentration to the overlooked work of Job, a French chemist working in the inter-war period, who reported in 1923 the action of $NiCl_2$ on phenylmagnesium bromide in the presence of ethylene, carbon monoxide, hydrogen and other gases—the work which would be broaden into the catalytic empire a year later.[22] In his paper published in 1924, Job aimed to draw the scientific communities' attention to the significance of these observations with an inviting statement:—*"Briefly, we believe that we have made progress by introducing catalysis into the field of organometallics."*[23]

Job's far-sighted findings have been largely forgotten and not recognized by succeeding researchers. A comparable story unraveled for other early findings (Scheme **I.6.**). Meerwein

described the outcome of catalytic copper(II) salts on the coupling of aryldiazonium salts with substituted alkenes in 1939.[24] However, the reactions reported were restricted to coumarins and cinnamic acids, and would themselves be extended in subsequent years, the importance of Meerwein's findings in the field of cross-coupling, mainly decarboxylative coupling, seem to have been lost. The first methodical study of transition-metal-catalyzed $C(sp^2)$-$C(sp^2)$ coupling was seen in a publication by Kharasch[25] in 1941 regarding the study of homocoupling of Grignard reagents, a reaction further delineated in general terms in his historic book on Grignard reagents.[26]



Scheme I.6. The first examples of catalysis in couplings for C-C bond formation: Meerwein and Kharasch couplings.

In 1943,[27] and in succeeding research during the 1940s, this work was expanded to the cross-coupling of vinyl bromide with aryl organomagnesium species utilizing cobalt chloride. These researches delineated the primary information of a cross-coupling product—the utilization of

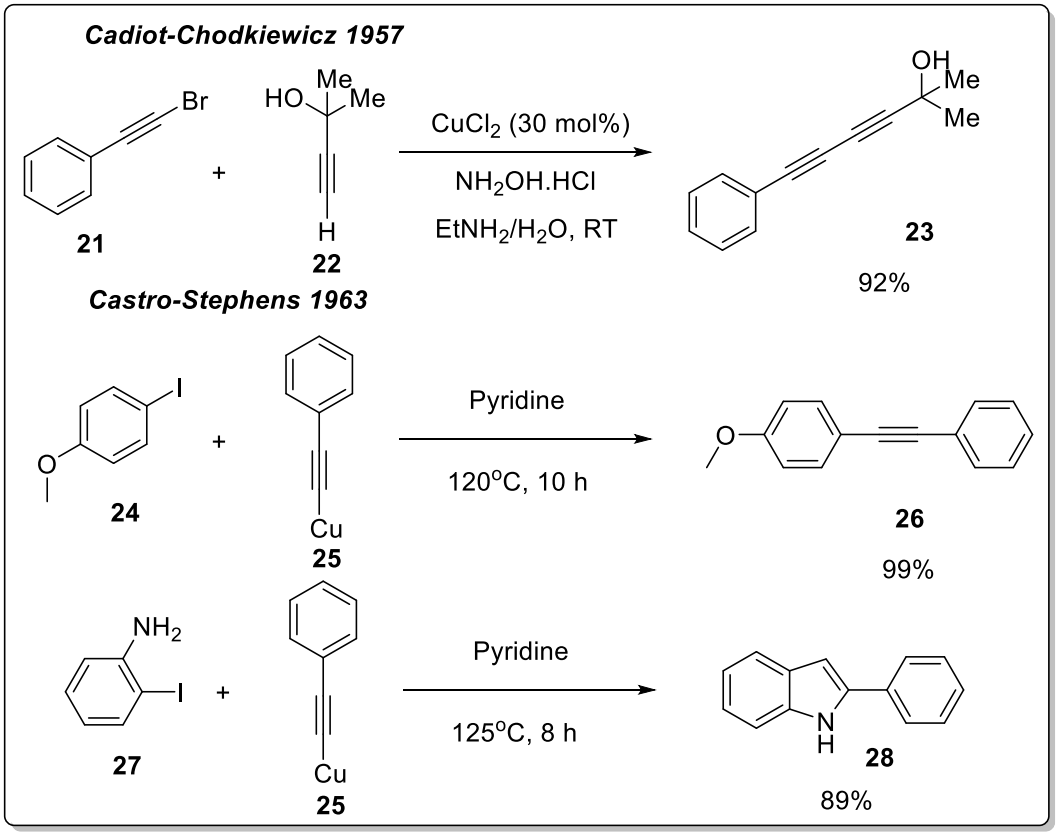
metals to couple two different coupling associates (**Scheme I.6.**) and, as opposed to that of Job, emerged to have tempted, in time, the successive chemistry community. Thus, only in the 1970s Kochi would go on to probe the mechanism of these procedure and also to illustrate Ag,[28] Cu,[29] and Fe[30] salt catalysis under equivalent conditions. Kochi's attentive and penetrating works are of utmost importance to the current interpretation of the mechanistic details of this reactions.[31, 32]

However, the initial Meerwein- and Kharasch-type couplings were highly limited in substrate range and functional-group compatibility. They had illustrated a foundational basis that would provide as the foundation for all of the coupling chemistry to obey i. e transition metals in catalytic quantities could be used to construct C-C bonds. Woefully, the restrictions noted furnished these conditions incompatible for general application in synthesis. Particularly, a basic problem of selectivity attached at the core of the cobalt- and nickel-promoted couplings was the ratio of the homo-coupling to cross-coupling product formed was mainly substrate specific which gave fluctuating yields. Therefore, improvement in the field looked for finding of conditions which increases the selectivity of the cross coupling product.

The copper-catalyzed C(sp)-C(sp) cross-coupling of alkynes with bromoalkynes was reported by Cadiot and Chodkiewicz in 1955[33] followed by a full paper by Chodkiewicz in 1957 (**Scheme I.7.**).[34] In 1963, Castro and Stephens described the C(sp)-C(sp^2) cross-coupling using aryl or vinyl halides with alkynes derivatised as copper salts.[35] Castro and Stephens found that the intermediate acetylene underwent cyclization giving indole or benzofuran products when aryl iodide having a nucleophilic heteroatom in the ortho position. The Cadiot–Chodkiewicz coupling moved under mild conditions and the Castro–Stephens method progress at elevated temperatures and used the poorly soluble copper(I) phenylacetylide. These solubility problems resulted in inconsistent yields and are frequently cited drawback of these methods.[36]

In spite of the experimental issues, the effort by these pioneering chemists gave a strong solution to the selectivity problem for the first time. The framework of the cross-coupling concept began to emerge with these first examples of truly selective C-C bond formation between sp and sp carbon centers (Cadiot–Chodkiewicz) or sp and sp^2 carbon centers (Castro–Stephens). Furthermore a set of standard needs for coupling procedure became ascertainable by this point in the history of coupling chemistry. In the widest sense, any coupling procedure needed three components to fulfill a selective cross-coupling process: 1) an organohalide, usually aryl or

alkynyl, as a coupling participant; 2) organometallic partner in stoichiometric amounts, either prepared in situ (Cadiot–Chodkiewicz coupling) or separately (Kharasch coupling) preventing homocoupling of the halide coupling partner; 3) a transition metal, in stoichiometric or catalytic loading, to carry out the C-C bond formation.



Scheme I.7. The Cadiot–Chodkiewicz and the Castro–Stephens reactions

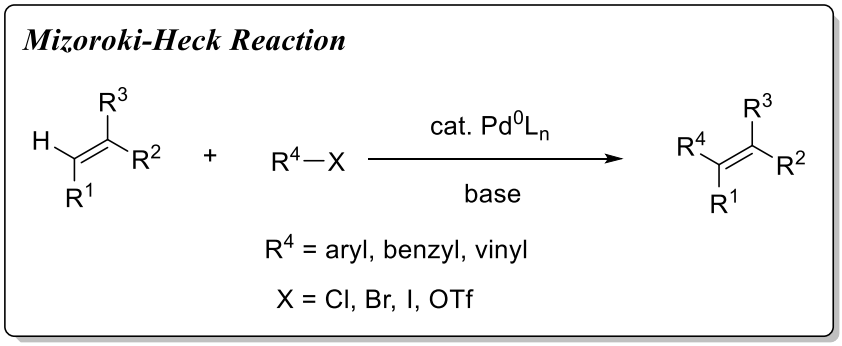
In 1802 Wollaston discovered palladium[37] although his effort to realize financial advantage were categorically ineffective.[38] Though Wollaston could not find a market for his stocks of palladium, founder of Johnson Matthey, the metallurgist Percival Norton Johnson, established a gold refining company, publicized palladium for use in chemistry, medical instruments, and as a replacement for steel.[39] The chemistry of palladium was dominated by its more active cousins, platinum and nickel for the next hundred years, as researchers explored these metals reactivity in oxidations, reductions, and hydrogenations of unsaturated hydrocarbons.[40] Catalysts was emerged which adapted and regulated this activity by emerging the familiar palladium on charcoal[41] and Lindlar[42] catalysts. These two established their place in the laboratory and

production sight. However both the work on palladium and the other platinum group metals confirmed the activity and affinity of palladium for double and triple bonds.

The observation in the 1940s for the homocoupling of Grignard reagents utilizing alkyl or aryl halides as oxidizing agents catalyzed by the first-row transition metal salts, such as $FeCl_3$, $CoCl_2$, $NiCl_2$, $CuCl_2$, or $CrCl_2$ was accelerated the invention of cross-coupling reactions.[43] This follow to pioneering studies by Kochi in the 1970s reporting the cross-coupling of alkenyl halides with Grignard reagents using iron salts.[44] Inspired by Kochi's reports further research accelerated, and over a period of time, palladium became the metal of choice for catalyzing cross-coupling reactions, because of its bench stability and high activity, which are now applied nearly all fields of synthetic chemistry.

I.A.2. Palladium catalyzed different cross coupling reactions

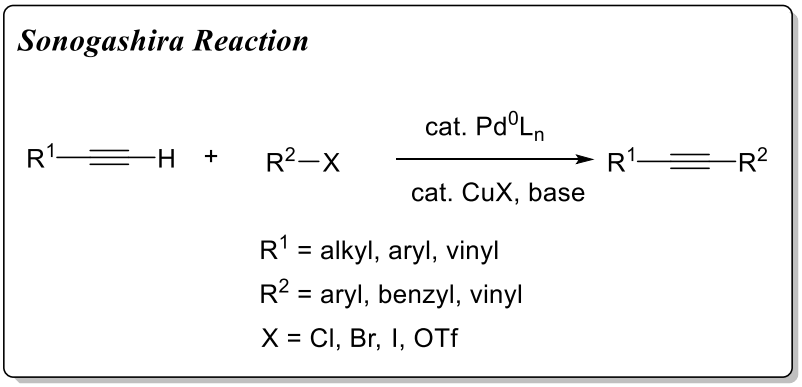
I.A.2.1. Mizoroki-Heck reaction



Scheme I.8. General scheme of Mizoroki-Heck reaction

Mizoroki-Heck reaction is the Pd-catalyzed vinylic substitution reaction in which vinylic hydrogen is substituted by an aryl, alkenyl, or benzyl moiety (**Scheme I.8.**), as we would recognize it today were first independently reported by Mizoroki (1971)[45] and, in a better form, by Heck (1972).[46] In the late 1980s, the evolution of catalytic asymmetric Heck reactions led the way to a additional resurgence of attention in this field.[47] For carbon–carbon bond formation, the Heck reaction now stands as a exceptionally powerful and effective method, mainly in the intramolecular ring formation and generation of tertiary and quaternary stereocenters, and remains a progressing domain of research.

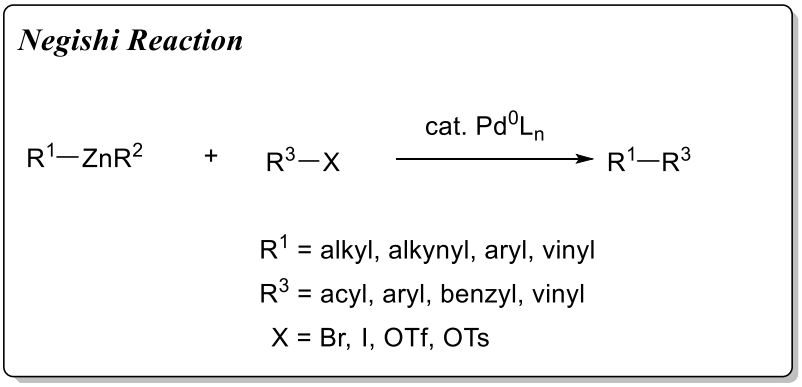
I.A.2.2. Sonogashira Reaction



Scheme I.9. General scheme of Sonogashira Reaction

The cross coupling of terminal alkynes with vinyl or aryl halides catalysed by palladium was first separately and simultaneously described by the groups of Cassar[48] and Heck[49] in 1975. After few months, Sonogashira and co-workers illustrated that, usually, this cross-coupling reaction could be speed up by the addition of CuI salts as co-catalyst to the reaction mixture.[50, 51] This method is known as the Sonogashira reaction (**Scheme I.9.**) and can be described as an alkyne version of the Heck reaction. This can also be viewed as an implementation of palladium catalysis to the renowned Stephens–Castro reaction which described the coupling of vinyl or aryl halides with stoichiometric amounts of copper(I) acetylides.[52]

I.A.2.3. Negishi Reaction

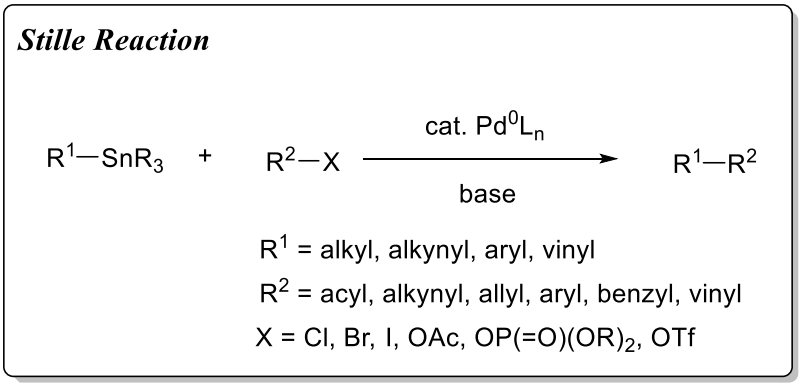


Scheme I.10. General scheme of Negishi Reaction

The use of organozinc reagents as the nucleophilic coupling partner in palladium-catalyzed cross-coupling reactions is known as the Negishi coupling (**Scheme I.10.**) which was first reported in 1977.[53] Organozinc reagents show a very high innate reactivity in palladium-catalyzed cross-coupling reactions. The number of available procedures for the preparation of organozinc reagents and their comparatively low toxicity, fabricated the Negishi coupling an exceptionally useful option to other cross-coupling methods, moreover constituting an influential method for carbon–carbon bond formation in its own prerogative.[54]

I.A.2.4. Stille Reaction

The cross-coupling reaction of vinyl organotin compounds and organic electrophiles catalyzed by palladium is known as the Stille reaction (**Scheme I.11.**),[55] following the late Professor J. K. Stille who introduced (1978)[56] and subsequently developed[57] this reaction, while the seeds of innovation were shown prior by Kosugi and his group, who first reported carbon-carbon bond forming reactions with organotin compounds catalysed by transition-metal a year earlier.[58, 59] The Stille reaction remains one of the most extensively applied carbon–carbon bond-forming reactions catalysed by palladium after 42 years later, in largely due to mild reaction conditions, the proficiency of preparation of a broad spectrum of coupling partners, and the toleration of an extensive variety of fragile functionalities during this transformation.

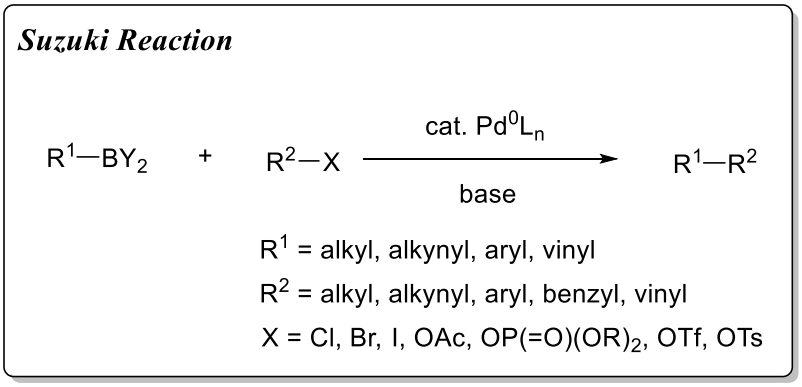


Scheme I.11. General scheme of Stille Reaction

I.A.2.5. Suzuki Reaction

Another useful carbon–carbon bond-forming reaction catalyzed by palladium were described by the Suzuki group in 1979.[60] In the presence of a base, this methodology associates the coupling

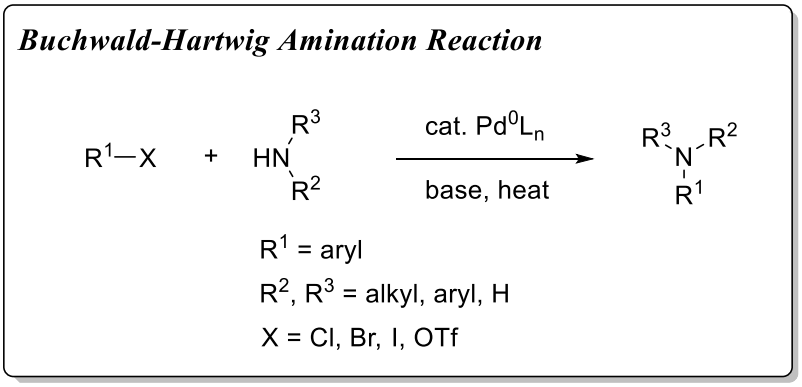
of organic electrophiles (aryl or alkenyl halides and triflates) with organoboron compounds (**Scheme I.12.**).[61] The Suzuki reaction is advantageous as a technique for the making of biaryl and related systems as well as high stereoisomeric pure conjugated dienes and higher polyene systems.



Scheme I.12. General scheme of Suzuki Reaction

The ease of synthesis of organoboron compounds (e.g. aryl, vinyl, alkyl) and their comparative stability to air and water, associated with the comparatively mild conditions for the reaction as well as the formation of nontoxic by-products, established the Suzuki reaction a valued addition to the arsenal of the synthetic organic chemist.

I.A.2.6. Buchwald–Hartwig Amination Reaction



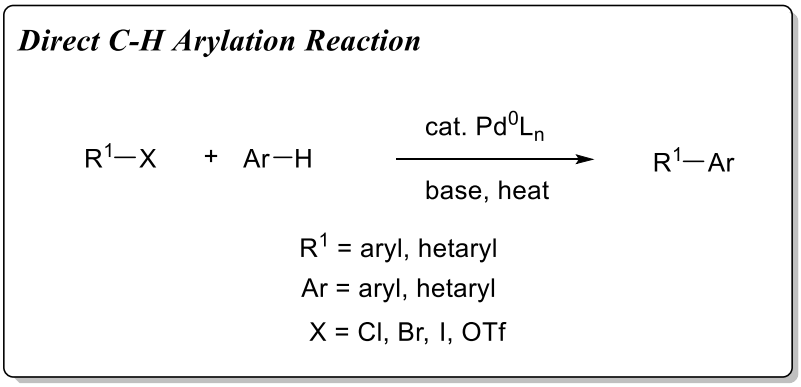
Scheme I.13. General scheme of Buchwald–Hartwig Amination Reaction

The construction of C(sp^2)–N bonds was developed in 1983 by Migita and coworkers, who announced that the formation of aryl amines from aryl bromides and aminostannanes could be

catalysed by palladium complexes of P(*o*-tol)$_3$.[62] The restraint related with both the use of toxic aminostannanes and the limited substrate scope accomplished in this groundbreaking work were later overcame by Stephen L. Buchwald and John F. Hartwig, who separately described a better methodology first in 1994 for the coupling of aryl bromides and aminostannanes[57] and later a tin-free Pd-catalyzed coupling of aryl bromides with amines in 1995.[58a,b] This discovery together with the successive ceaseless attempt from both laboratories towards a general and effective methodology for C–N bond construction and a extensive mechanistic apprehension of the process bring to the establishment of what nowadays is known as the Buchwald–Hartwig amination reaction (**Scheme I.13.**).

I.A.2.7. Direct C−H Arylation Reaction

In current years quite a number of literature reports dealing with the application of Pd metal catalysts to a range of C−H bond functionalization reactions have been published, frequently the direct arylation of arenes and heteroarenes with aryl halides (**Scheme I.14.**). This reaction is obviously connected to cross-couplings, and especially to the Heck reaction, which can own be treated in its outcome as a "C−H functionalization" reaction.

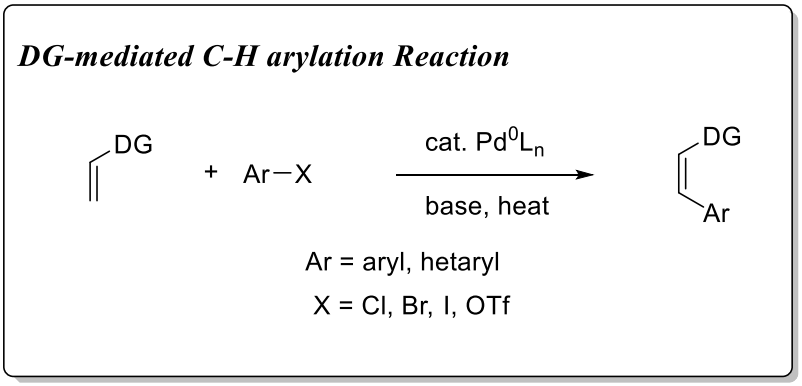


Scheme I.14. General scheme of Direct C−H Arylation Reaction

The catalytic accomplishment of Pd metal catalysts in these reactions ascribe at present way beyond that of homogeneous catalysts (moreover on other noble metals such as Rh or Ru other than Pd), in that (i) in most occasion only heteroarene substrates have been employed, which are the most reactive substrates for these reactions (ii) generally high reaction temperatures (>100 °C) are required and (iii) only aryl bromides and aryl iodides can be employed as substrates.

Only few reports delineated activation of aryl chlorides; the best example is activation of aryl chlorides for the selective arylation of benzo[*b*]thiophenes at the C3 position were furnished by the group of Glorius, though the reaction employs up to 10 mol % Pd/C + CuI as the catalytic system and 150 °C reaction temperature.[63]

I.A.2.8. Directing group (DG) mediated arylation



Scheme I.15. General scheme of Directing group (DG) mediated arylation reaction

Synthetic organic chemists fond that directing group assisted C−H activation (**Scheme I.15.**) is a key instrument for the convenient and site selective formation of C−C and C-X bonds during the past decades. Among the different directing group approaches, bidentate directing groups are now acknowledged as one of the most well organized devices for the selective functionalization of certain positions due to the fact that its metal center permits tunable, fine, and reversible coordination. The family of bidentate directing groups permits several types of assistance to be achieved, such as *N*,*N*-dentate, *N*,*O*-dentate, and *N*,*S*-dentate auxiliaries, which are classified based on the coordination site.[64, 65, 66, 67, 68]

I.A.3. General catalytic cycle of Palladium catalysed cross-coupling reaction

The catalytic cycle of general cross-coupling reaction is shown in **Figure I.1.** The first step, that is oxidative addition, is oxidative with respect to the metal and is slowed by electron-rich substrates and by crowding around the leaving group. The middle step is the transmetalation or heteroatom coordination. This step is charge the nucleophile on the now electron-deficient metal center is/are boost by nucleophiles that are sterically undemanding and electronically rich in nature. The final step is reductive elimination. This step reinstate the metal's oxidation state back

to (0) and is electronically favoured by an electron-poor oxidative addition partner (i.e., the acceptor) and an electron-rich nucleophile (i.e., the donor).[69] Contrarily, this step is generally favored by bulky substrates, as repulsion around the metal is thought to accommodate in favorably aligning the substrates to facilitate bonding while relieving the steric strain around the metal.

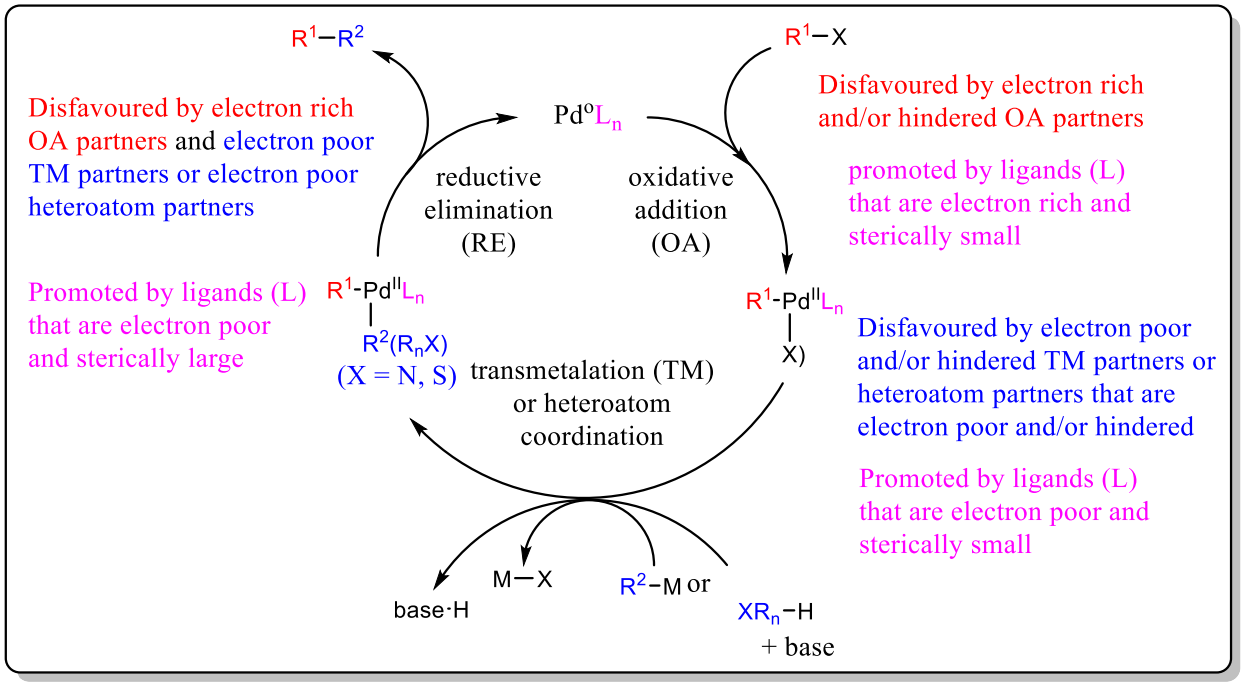


Figure I.1. General Palladium catalyzed catalytic cycle of cross-coupling reaction

These contradictory electronic and steric demands for each step of the catalytic cycle make the evolution of a single catalyst that will have high reactivity across any pairing of starting materials a major obstacle. The ancillary ligand that is used to solubilize the metal, here plays an enormous role. The ligand can be "modified" to be more or less electron-rich, adjusted in size, and have its features directed towards the metal. Balancing these properties is the vital toward finding a catalyst that is truly general and produces desirable results in wide-ranging applications.

Oxidative addition participants that are progressively electron-rich and/or have steric bulk surroundings the point of introduction of the metal into the leaving group bond as being progressively difficult coupling associates. Similarly nucleophiles that are progressively electron

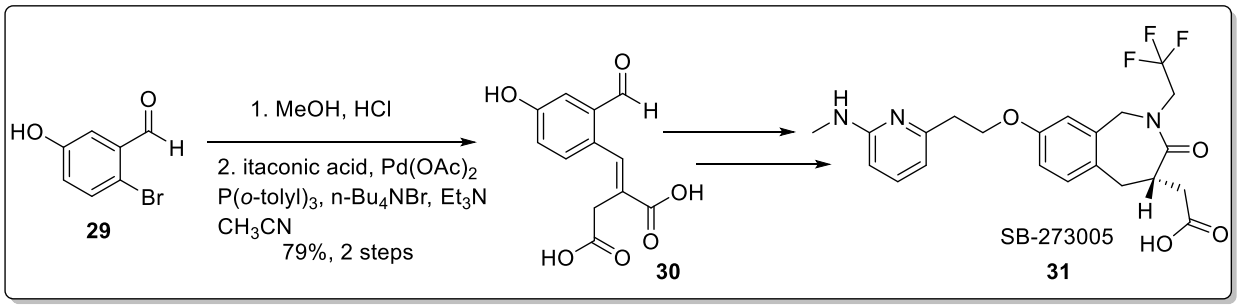
poor having steric bulk around the point of transmetalation or heteroatom coordination as being progressively difficult. Basically, as bulk essentially helps to speed up reductive elimination in the catalytic cycle, there has to be adequate steric footprint in the ligand to promote this step while not deprecate the first two.

In this carbon–carbon/carbon–heteroatom bond-forming two-electron redox cycles processes, the electronic and steric properties of NHCs (**Section I.A.5.2.1.**) assist to improve different steps of the catalytic cycle (**Figure I.1.**). The strong σ–donating carbene enhances the electron density at central metal and accordingly improves the activity towards oxidative addition of carbon-halogen or pseudohalogen bonds of the substrates. This characteristic is particularly essential for the coupling of challenging aryl chloride substrates, as carbon-chlorine bonds relatively less reactive to oxidative addition reaction. On the other hand, large steric effect of NHCs is found to facilitate the reductive elimination step. Moreover, both steric and electronic effects play a crucial role in stabilizing the coordinatively unsaturated low-oxidation-state of active catalyst and reduce the chance of its decomposition which is a major problem in these processes.

I.A.4. Application of Pd-catalyst in cross coupling reactions towards the synthesis of important molecules

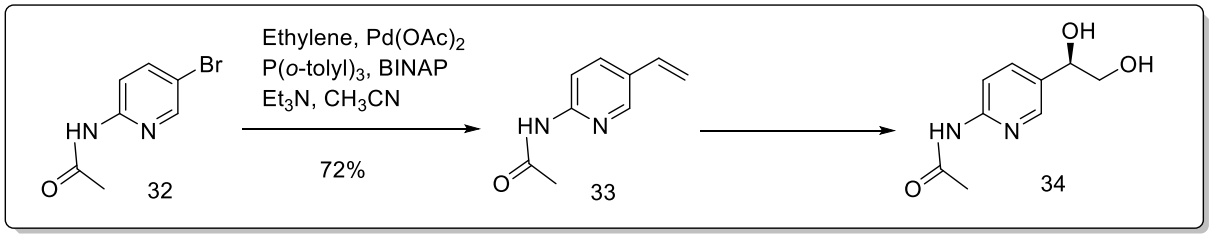
I.A.4.1. Application of Mizoroki-Heck reaction

Researchers at GlaxoSmithKline delineated the multi kilogram scale synthesis of the vitronectin receptor antagonist SB-273005 (**31**) in 2004 involving the coupling of itaconic acid with 4-bromo-4-hydroxybenzaldehyde (**29**) as a crucial step (**Scheme I.16.**).[70] The Heck–Mizoroki coupling was not performed directly with **29** because of an intramolecular aldol side reaction. After treatment with catalytic amounts of acid in methanol obtained corresponding dimethyl acetal. Heck-Mizoroki reaction was performed with this dimethyl acetal to obtained 79% of product **30**. As anticipated for the transformation of such electron-poor alkenes, [71] the reaction was trans-selective.



Scheme I.16. Mizoroki–Heck reaction on the way to SB273005

An effective multikilogram-scale synthesis of **33** was realized at Pfizer laboratories by using the racemic-BINAP ligand in combination with $Pd(OAc)_2$ and P(*o*-tol)$_3$ (**Scheme I.17.**).[72] A key intermediate (**34**) was synthesized by Sharpless dihydroxylation of 2-acetamido-5-vinylpyridine (**33**) for their drug candidates.

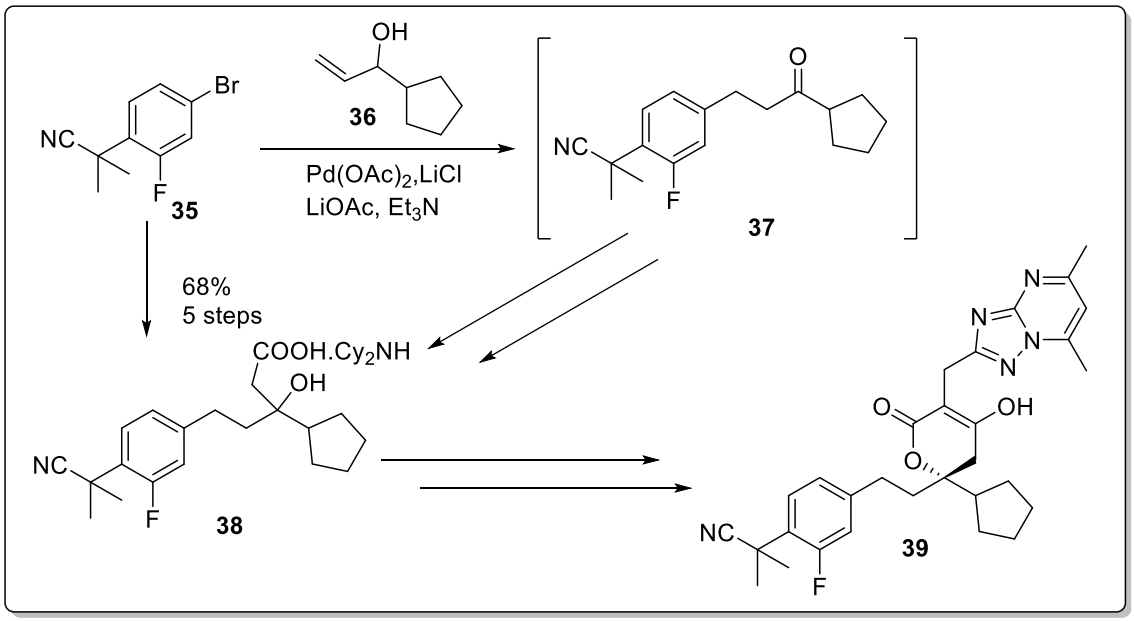


Scheme I.17. Mizoroki–Heck reaction with Ethylene

In Pfizer Global R&D, Scott and co-workers established a kilogram scale beneficial synthetic method for the hepatitis C polymerase inhibitor **39** (**Scheme I.18.**).[73] The early synthesis using Sonogashira coupling was patented in 2004, which was reasonably effective.[74] Although, the entire process did not transit to large-scale production because of the low stability of the alkyne intermediate yielded during the cross-coupling reaction. A Mizoroki–Heck coupling was performed in the new alternate route instead of the alkyne transformation where bromide **35** was reacted with alkene **36** in the presence of $Pd(OAc)_2$, LiCl and triethylamine (Et_3N).

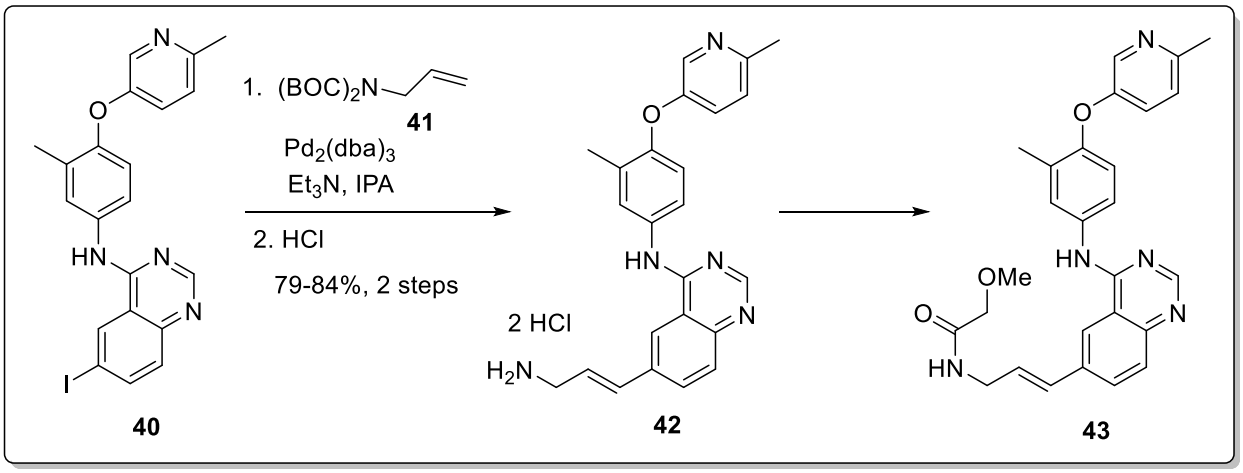
Engrossingly, the amine had to be administered to slow down the reaction. Because of the nature of a high adiabatic temperature rise caused the reaction to be modified. However, due to the amine concentration in the reaction mixture stability problems of the catalyst had been resulted. To overcome this problem, LiOAc was added to the reaction mixture as a co-base, which allowed the execution of the reaction on a 40-kg scale. Although the more electron-rich **36** was

employed, the selectivity towards the trans-β product was very high. After isomerization oily ketone **37** was produced, this was directly transformed to **38** in four steps.



Scheme I.18. Phosphine-free Heck coupling towards synthesis of hepatitis C polymerase inhibitor (**39)**

In industrial scale, allylamines can also have been successfully coupled via the Heck–Mizoroki reaction. During root optimization of oncology candidate CP-724,714 (**43)**, different Pd coupling protocols were explored on the pilot-plant scale, together with Heck couplings next to Suzuki and Sonogashira-type transformations (**Scheme 1.19.**).[75]



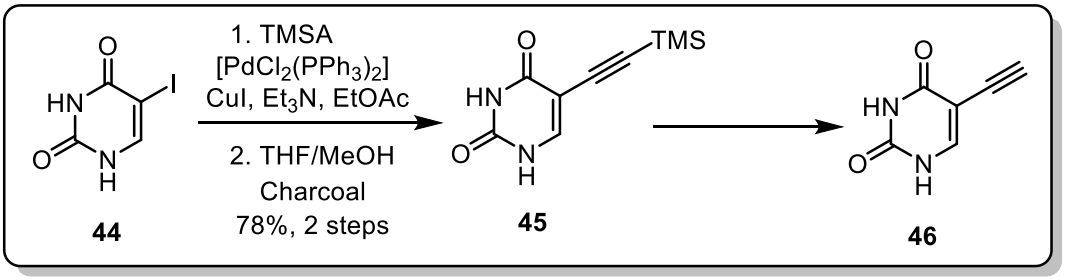
Scheme I.19. Mizoroki–Heck route to oncology candidate CP-724,714 (**43)**

The second-generation Heck–Mizoroki route remained superior among the others with respect to efficiency, safety issues and the amount of waste produced during the whole process. 96 kg of product **42** were obtained by reacting **40** and Boc-protected allylamine (**41**) using a Pd loading of just 1 mol % [$Pd_2(dba)_3$ as catalyst precursor] with followed by deprotection.

I.A.4.2. Application of Sonogashira Reaction

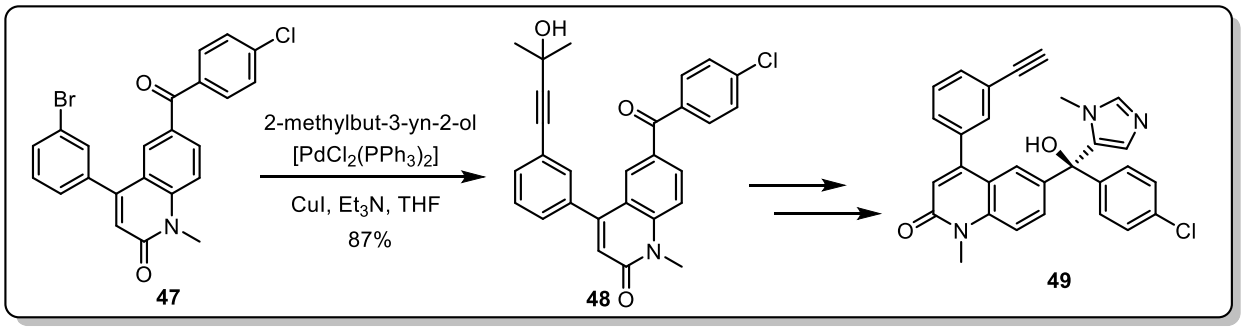
The main cause of bypassing a Sonogashira reaction on industrial scale is the unavailability of the alkyne intermediates, or their high costs, if commercially available. Therefore, the regular variation of this alkyne coupling in industrial-scale synthesis is the reaction of acetylene substitute like 2-methylbut-3-yn-2-ol or trimethylsilylacetylene (TMSA) with aryl halides. The TMS-group or the corresponding acetone moiety is eventually cleaved off. This two-step process gives an easy synthesis to terminal aryl alkynes.

Cooke et al. at GlaxoSmithKline used one of these approaches for the synthesis of Enduracil (**46**), a dehydrogenase inactivator.[76] Accordingly, iodide **44** was transformed to the corresponding TMSA derivative in the presence of 0.5 mol% of CuI and 0.5 mol% of bis(triphenylphosphine)palladium dichloride [$PdCl_2(PPh_3)_2$] giving 52 kg of product (82% yield) on a pilot-plant scale (**Scheme I.20.**). After purification and followed by desilylation using basic conditions they obtained **46** in high purity with a copper content <1 ppm and palladium content <2 ppm.



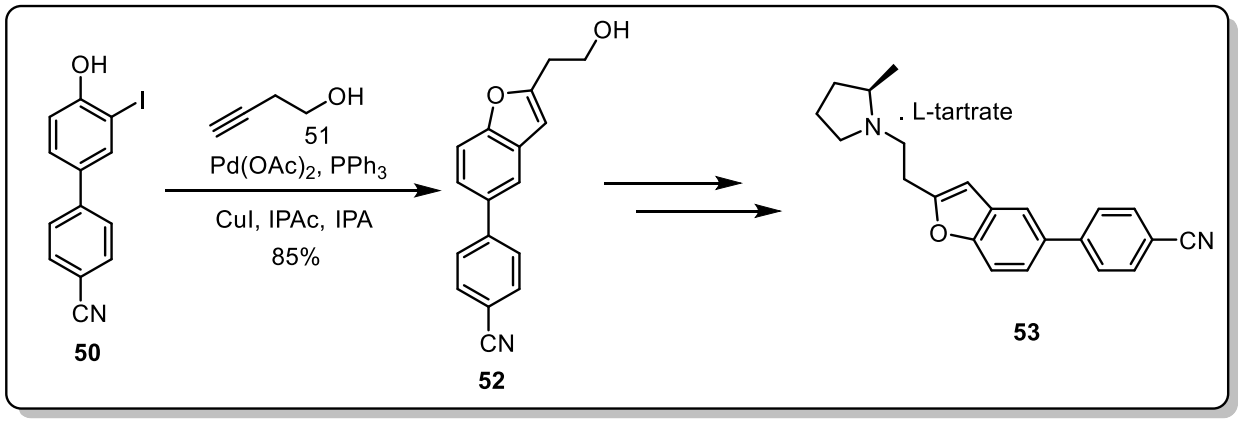
Scheme I.20. Synthesis of Enduracil via Sonogashira coupling

Pfizer's researchers also have shown the application of 2-methylbut-3-yn-2-ol in a Sonogashira reaction on a kg-scale while developing an efficient process for the synthesis of farnesyl transferase inhibitor **49** (**Scheme I.21.**).[77]



Scheme I.21. Sonogashira coupling in the manufacture of farnesyl transferase inhibitor, **49**

The application of a Sonogashira coupling in a large scale reaction cascade was demonstrated by Pu *et al.* in the manufacture of ABT-239 **53**.[78] $[PdCl_2(PPh_3)_2]$ (2.5 mol %) was the catalyst of choice in combination with CuI (2.5 mol %) during this synthesis. ABT-239 is a 2-substitituted benzofuran scaffold and histamine H3 receptor antagonist.



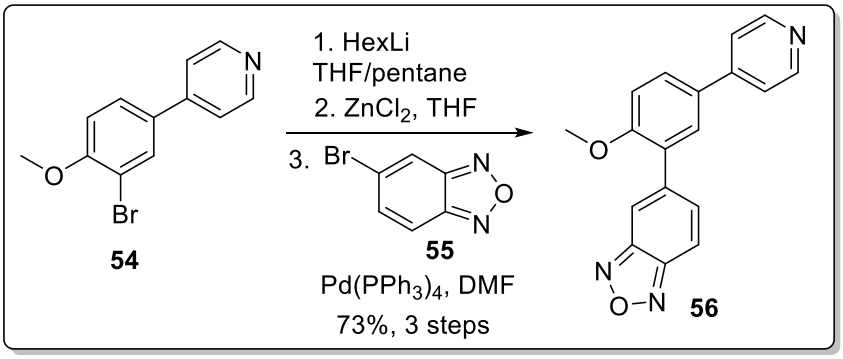
Scheme I.22. Large-scale reaction cascade to give ABT-239 intermediate, **52**

This can be synthesized via coupling of an alkyne with a 2-halo-substituted phenol and subsequent ring formation. For the synthesis of precursor **52** the reaction of **50** with butyn-3-ol (**51**) was successfully applied which was scaled up using a combination of $Pd(OAc)_2$ (1 mol %), PPh_3 (2 mol %) and CuI (2 mol %) (**Scheme I.22.**).

I.A.4.3. Application of Negishi Reaction

In 2003, Manley, Acemoglu, and co-workers from Novartis delineated the application of a Negishi protocol[71a, 79, 80] in the production of the phosphodiesterase type 4D inhibitor PDE472

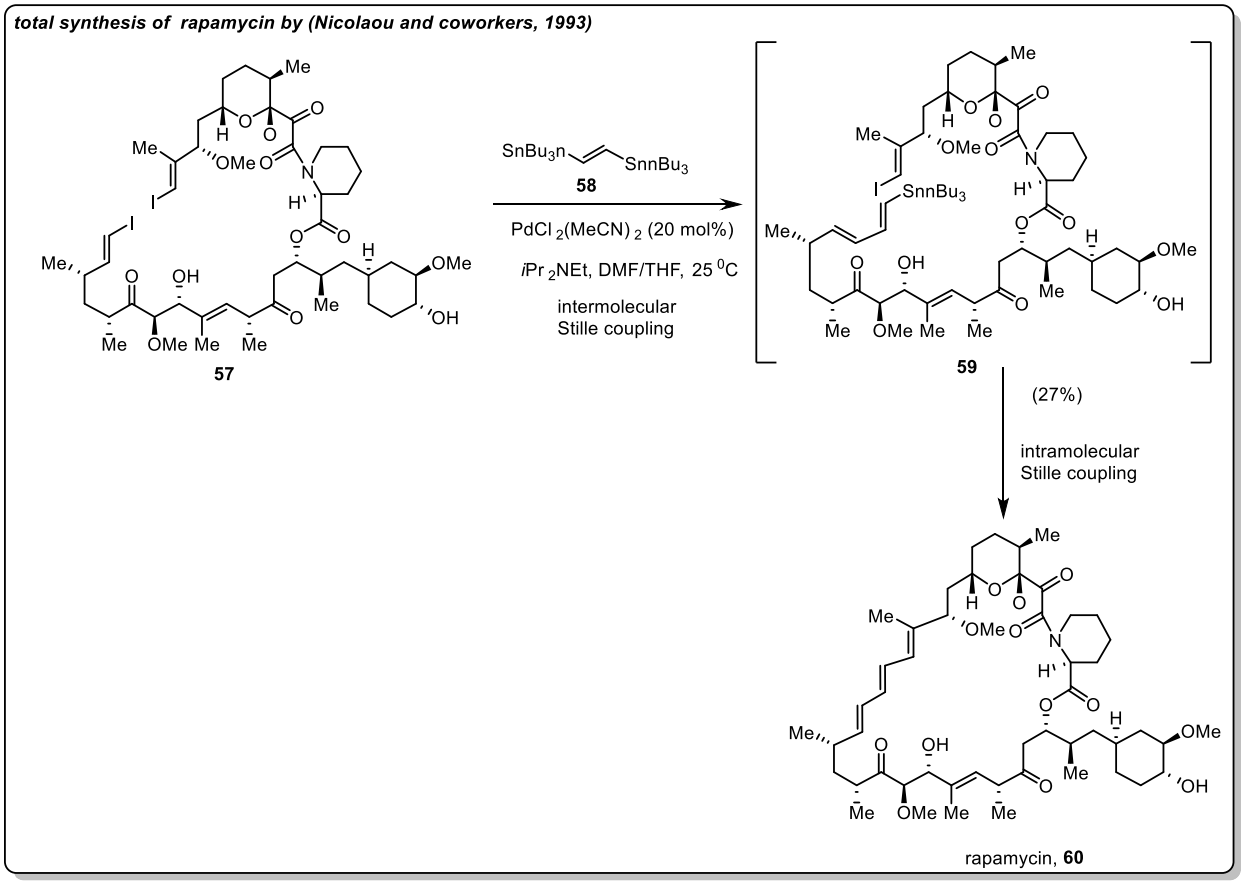
56. On a 4.5-kg scale the Negishi protocol proved to be more successful as an alternative to the analogous Suzuki coupling, yielding the benzoxadiazole (56) in 73% yield using 0.8 mol % tetrakispalladium(triphenylphosphine) $Pd(PPh_3)_4$ as the precatalyst (**Scheme I.23**.).[81] A Pd content <2 ppm was detected in the target compound after crystallization of **53** as the hemi-maleate salt.



Scheme I.23. Negishi coupling in the large-scale production of PDE472, **56**

I.A.4.4. Application of Stille Reaction

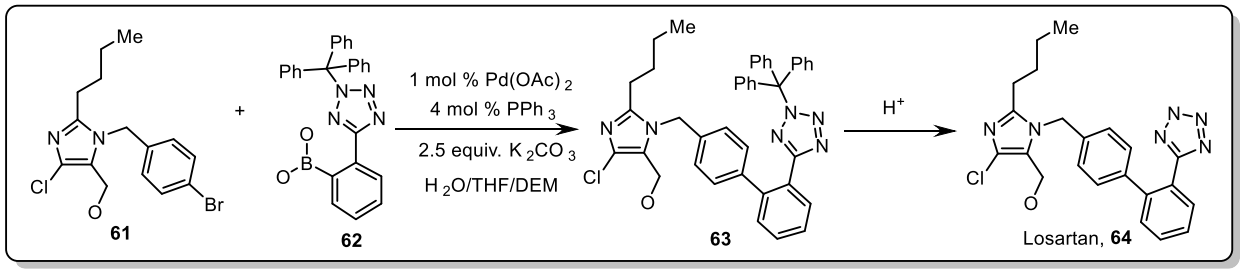
The Nicolaou group developed a stitching-cyclization reaction to synthesized rapamycin (58) from the bis(vinyl iodide) precursor **57** and trans-1,2-distannyl ethylene **58** (**Scheme I.24.**).[82] This is a distinct example of Stille Reaction. In the total synthesis of rapamycin, final step involved a double Stille coupling process and progressed from the naked (no protecting groups) precursor **57** in presence of $[PdCl_2(MeCN)_2]$ (20 mol %) and *i*Pr_2NEt as a dilute solution in DMF/THF at room temperature, apparently through the intermediacy of iodostannane **59**. The 29-membered macrocyclic ring of rapamycin, with its all-trans triene system, was installed from an acyclic precursor just in one fell swoop, and without the need for any protection/deprotection operations. The achievement of this macrocyclization reaction unquestionably relies on the ornamental effect of the palladium center, which brings the two ends of the chain into the required closeness for bond formation.



Scheme I.24. Scheme for total synthesis of rapamycin, **60**

I.A.4.5. Application of Suzuki–Miyaura Reaction

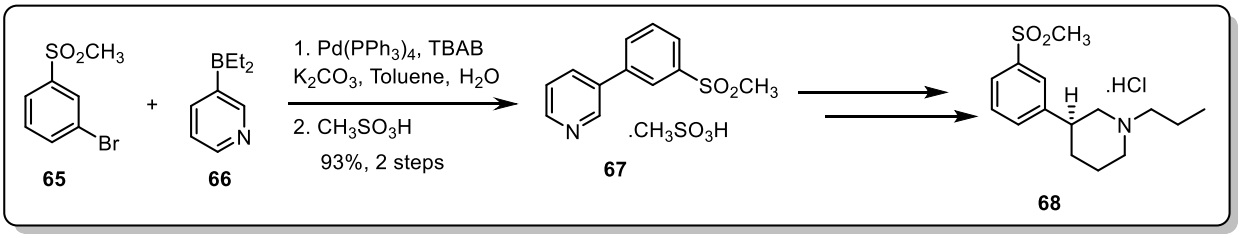
A late-stage Suzuki−Miyaura reaction was involved in the synthesis of the blood pressure drug losartan, **64** (**Scheme I.25.**).[83]



Scheme I.25. Suzuki−Miyaura reaction used in the synthesis of Losartan, **64**

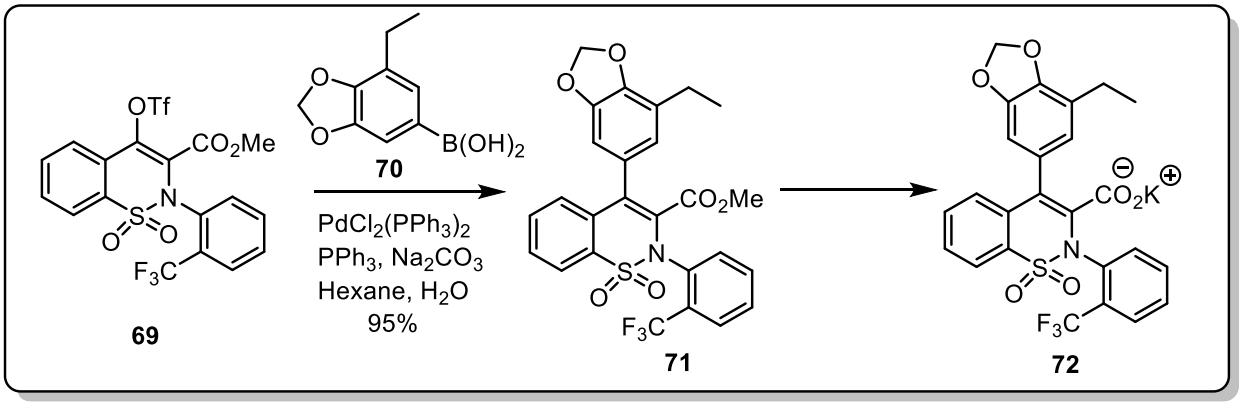
In collaboration with Dow researchers at Pharmacia Corporation were able to scale-up the Suzuki coupling of **65** with pyridine **66** in the synthesis of **68**, a potential CNS agent (**Scheme**

I.26.). The Problems were a high palladium loading required for the reaction in a mixture of water and tetrahydrofuran (THF). Though, the optimization of the solvent system (toluene/ water) significantly improved the process with only 0.7 mol% of Pd catalyst. It was hypothesized that a less polar media is advantageous for the lifetime of the catalyst.[84]



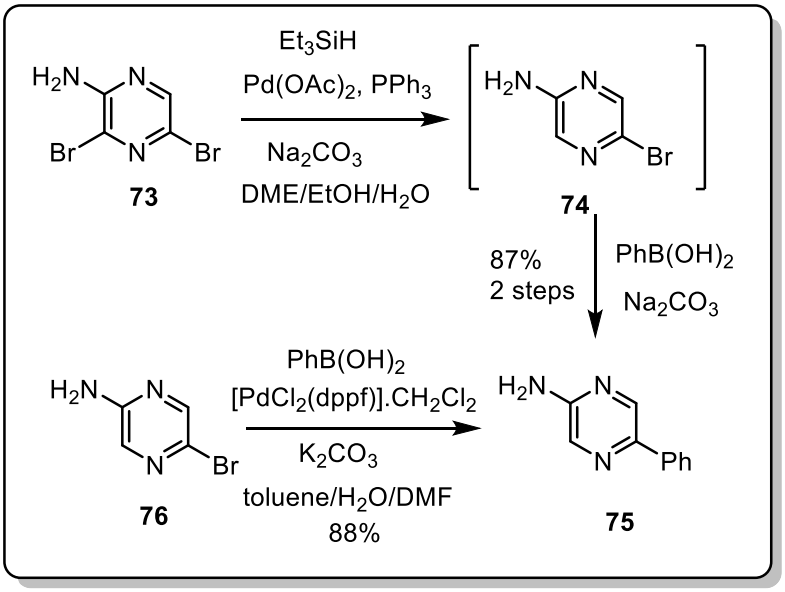
Scheme I.26. Suzuki−Miyaura reaction used in key intermediate synthesis of OSU 6162

In Pfizer, Jacks et al. manifested a dependable mulitkilogram-scale process to Cl-1034 **72** including a Suzuki coupling of triflate **69** with boronic acid **70** as an essential step (**Scheme I.27.**).[85] Cl-1034 is an endothelin antagonist.



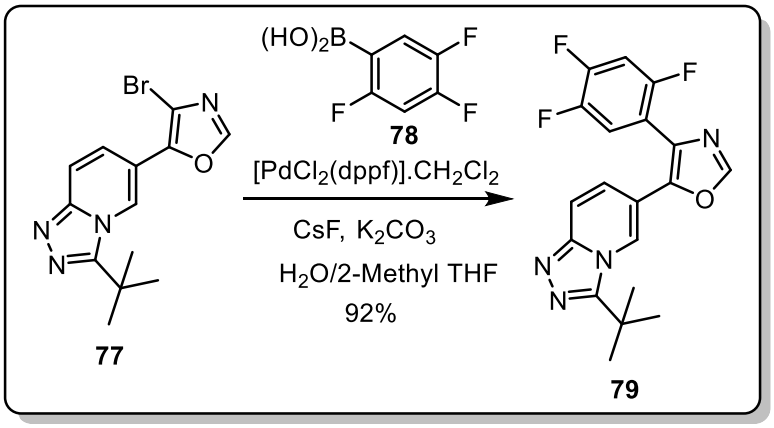
Scheme I.27. Pfizer's route to Cl-1034 using Suzuki−Miyaura reaction

Itho, Zhao *et al.* described a sophisticated one-pot synthesis using two palladium-catalyzed transformations (**Scheme I.28.**).[86] A key intermediate of a selective NPY-5 receptor antagonist, 2- amino-5-phenylpyrazine **75** synthesized via reduction of dibromide **73** and successive Suzuki coupling. 2 kg of product **75** could be synthesized alternatively by coupling of the monobromide **76**. Here the bisphosphine 1,1'-bis(diphenylphosphino)ferrocene (dppf) was used as an ancillary ligand.



Scheme I.28. Synthesis of key intermediate of a selective NPY-5 receptor antagonist using Suzuki−Miyaura reaction

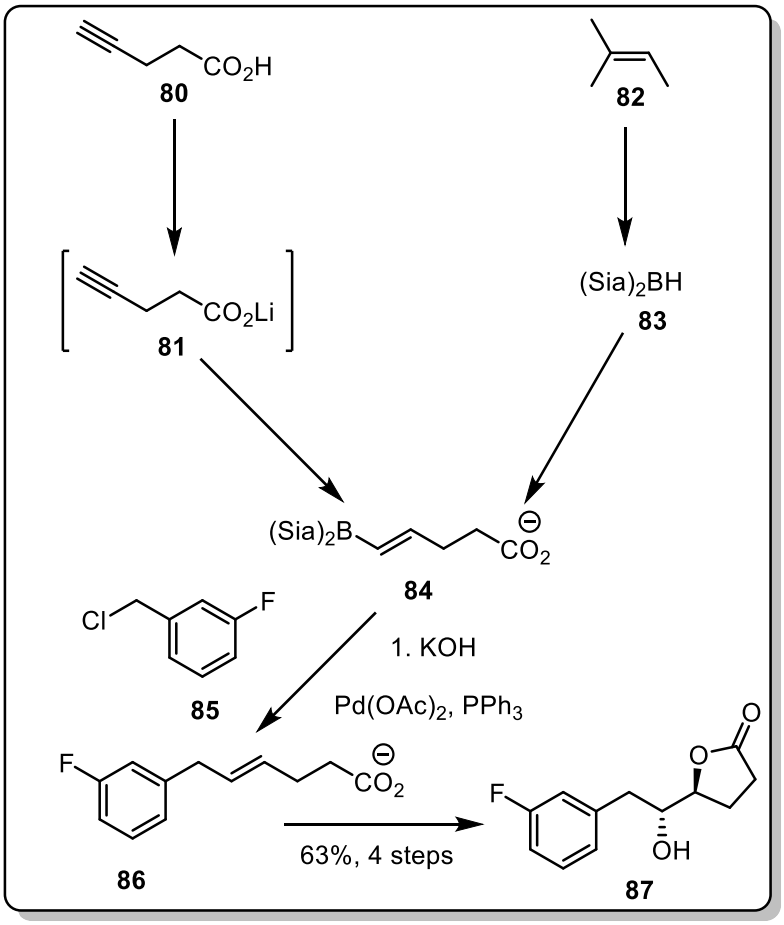
Pfizer's laboratories also used dppf in a Suzuki coupling reaction on an industrial scale in the manufacturing of kinase inhibitor **79**.[87] Suzuki coupling of 77 with 1,3,4-trifluorophenyl-6-boronic acid (78) was carried out successfully on the 3-kg scale (**Scheme I.29.**).



Scheme I.29. Synthesis of kinase inhibitor using Suzuki−Miyaura reaction

The utilization of Suzuki protocols is not only limited to the coupling of arylboronic acids and heteroaryl halides or vice versa. The adaptability of this reaction also permits the formation of $C(sp^2)$-$C(sp^3)$ bond on an industrial scale. At DSM, Ager and co-workers pick out and

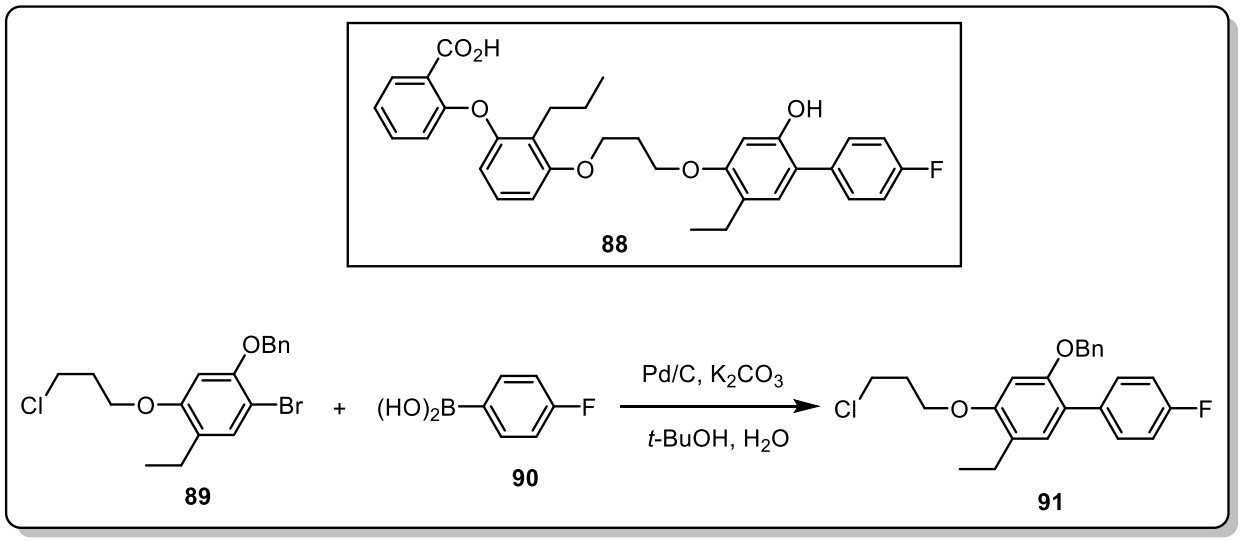
improved an effective process to produce large amounts of lactone **87.** This is a precursor to potential HIV drugs and blood pressure modulation agents.[88] On a production plant scale using the standard precatalyst $Pd(OAc)_2/PPh_3$, the disiamylborane **84** was reacted with 3-fluorobenzyl chloride (**85**) to give **86** (**Scheme I.30**.). After that, the **86** was transformed into **87** via organocatalytic Shi epoxidation.



Scheme I.30. Suzuki benzylation towards synthesis of a precursor to potential HIV drugs and blood pressure modulation agents, **87**

Etalocib (LY293111, VML295), **88** has shown ability to reduce the proliferation of different cancer cells. The synthesis of this was developed at Eli Lilly and Company. The Suzuki coupling is a key-step of the synthesis (Scheme **I.31.**). The Suzuki coupling is between 4-fluorophenylboronic acid (**90**) and an aryl bromide (**89**) to obtain intermediate **91** in gram-scale. Preferable to the homogeneous catalyst (palladium acetate combined with PPh_3), Pd/C has been found to accomplish as the best catalytic system, due to its use confirms a much lower palladium

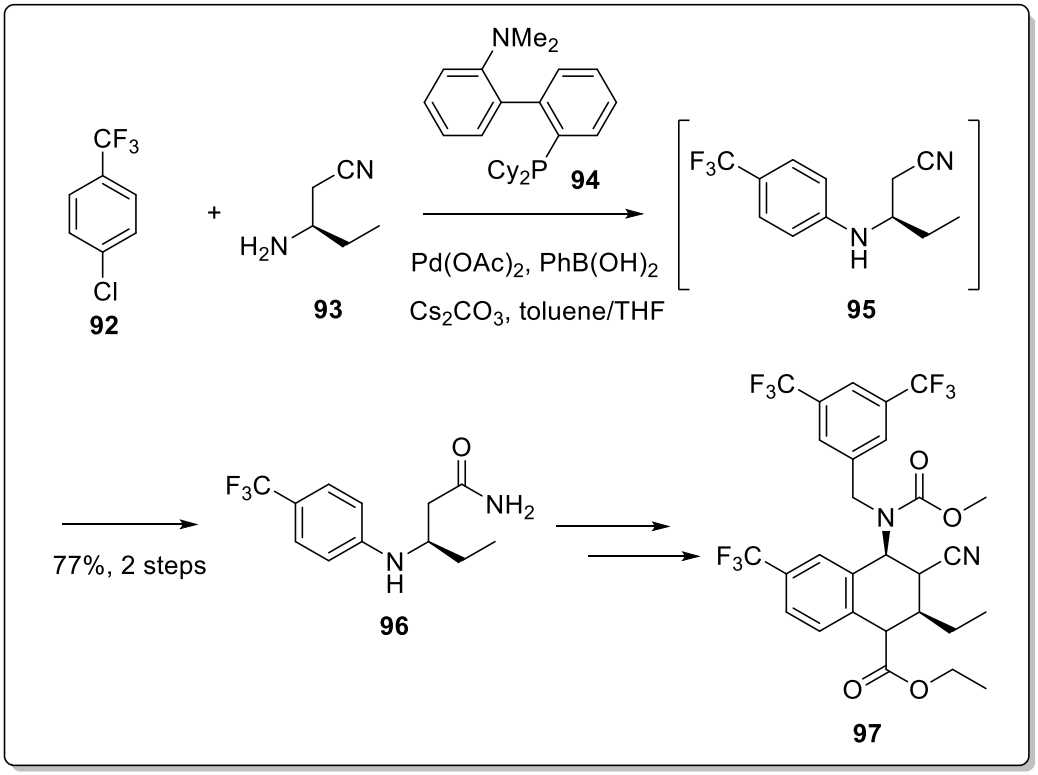
contamination of **91**. Though the reaction can be carried out in different alcohols, aqueous *t*-BuOH was the optimal choice and K_2CO_3 was used as the base.[89]



Scheme I.31. Application of the Suzuki reaction towards the synthesis of Etalocib

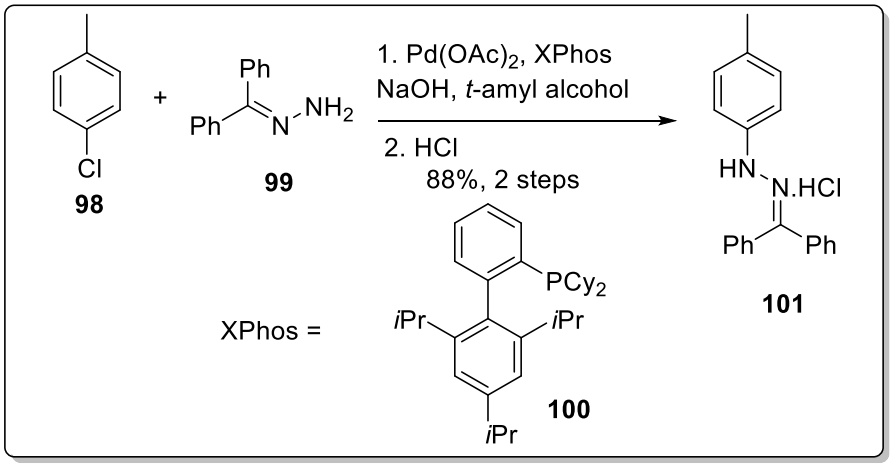
I.A.4.6. Application of Buchwald–Hartwig reaction

Buchwald–Hartwig amination is the good methodology for the synthesis of aryl amines. These aryl amines synthesized via Buchwald–Hartwig amination are important building blocks for industrial products. Therefore commercial interest in the Buchwald–Hartwig amination reaction is high and strong. Recently, this fact was pointed out by Schlummer and Scholz.[90] The authors divulged that although in the literature a somewhat smaller number of processes have appeared but several C-N couplings running in a production scale of multi-hundred kgs. One example is the manufacturing of CETP inhibitor CP 529,414 **97** patented by Pfizer.[91] In this process, intermediate **95** was synthesized by Buchwald– Hartwig coupling applying $Pd(OAc)_2$ and Buchwald's DavePhos **94** on a 3-kg scale (**Scheme I.32.**).[92] Interestingly in this process catalytic amount of phenylboronic acid were required to pre-activate the catalyst.



Scheme I.32. Large-scale Buchwald–Hartwig amination yielding precursor, **95**

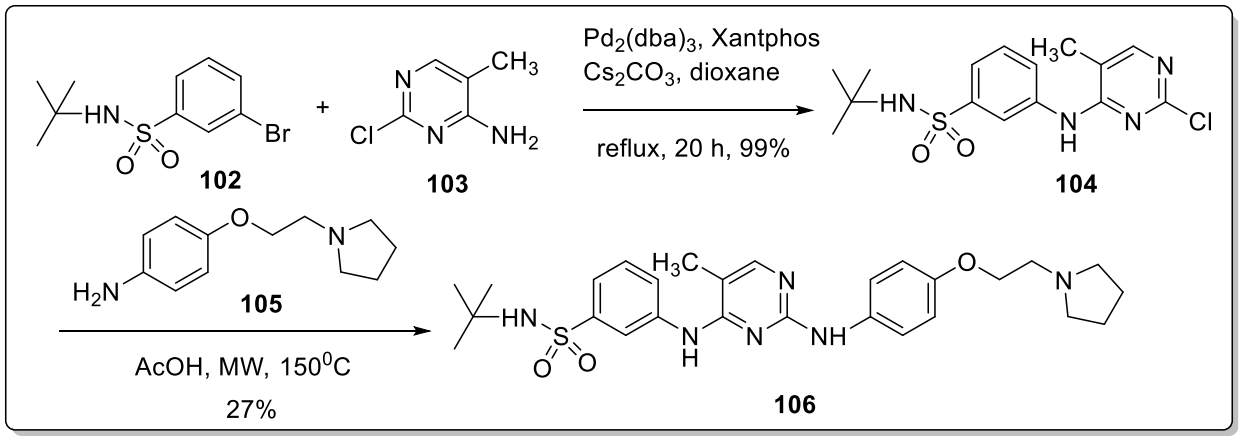
For the synthesis of aryl hydrazones, aryl piperazines and diarylamines, Buchwald et al. delineated the usage of similar bulky biaryl phosphines (Scheme **I.33.**).[93]



Scheme I.33. Coupling of 4-chlorotoluene with hydrazone (**99)**

For example, the reaction of benzophenone hydrazine (**99**) with 4-chlorotoluene (**98**), catalyzed by a complex produced from $Pd(OAc)_2$ (0.5 mol %) and XPhos (1 mol %), was smoothly scaled up and directly transformed into the hydrochloride salt **101** using hydrochloric acid (Scheme **I.33.**). The final compound contaminated with less than 10 ppm of residual palladium.[94]

Fedratinib **106** (**Scheme I.34.**) is a potential inhibitor of Janus kinase 2 (JAK2), which has IC50 values on nanomolar range.[95] It has dual binding nature. It binds to both ATP-binding site and substrate-binding site. The U.S FDA approved fedratinib as remedy for intermediate-2 or high-risk primary or secondary myelofibrosis in adult patients on 16 August 2019. Fedratinib is marketed under the registered name Inrebicr® capsules by Impact Biomedicines, Inc., a wholly owned subsidiary of Celgene Corporation. [96]



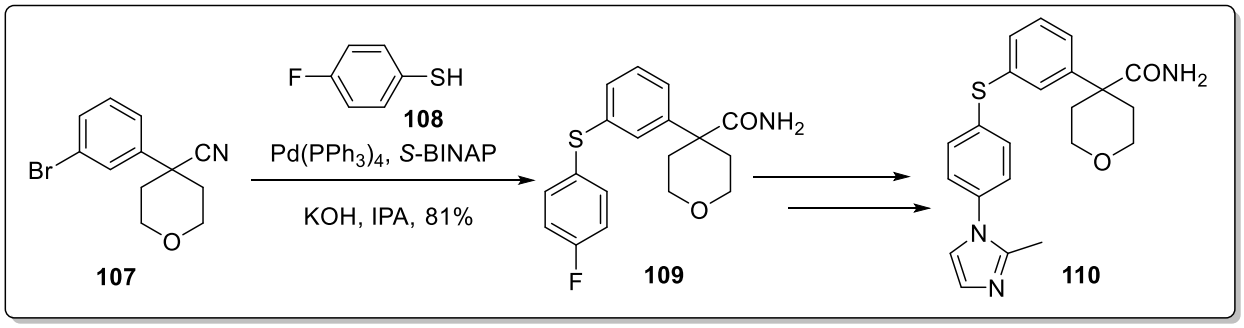
Scheme I.34. Small-scale synthesis of fedratinib *via* Buchwald-Hartwig amination reaction according to TargeGen Inc.

For the formation of C-N bond performed a cross-coupling reaction in the synthetic route for fedratinib[97] (**Scheme I.34.**). Buchwald-Hartwig amination reaction was utilized for the synthesis of sulfonamide compound **104**. A suspension of 3-bromo-N-(tertbutyl)benzenesulfonamide **102**, 2-chloro-5-methyl-pyrimidin-4-ylamine **103**, $Pd_2(dba)_3$ (5 mol %), Xantphos(10 mol %) and Cs_2CO_3 in dioxane were refluxed for 20 h affording crude compound **104** in 99% yield.

I.A.4.7. Application of C-S bond formation

Sulphur nucleophiles can also take part in Pd-catalyzed coupling reactions like nitrogen and carbon counterparts. Migita[98] described a high-yielding route to diaryl thioethers by reaction of

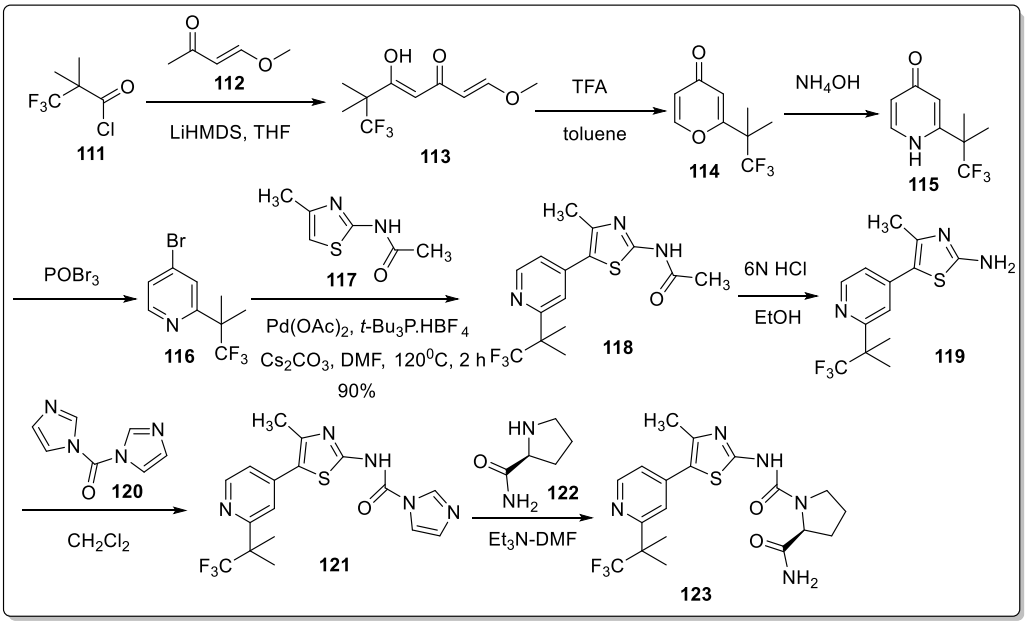
aryl iodides with thiophenols in the presence of catalytic amounts of $Pd(PPh_3)_4$. Researchers at Pfizer reacted nitrile **107** with 4-fluorothiophenol (**108**) furnishing 40 kg of thioether **109** for the large-scale manufacture of the former antiasthma drug candidate **110** (**Scheme I.35.**).[99] It was found that bidentate phosphorus ligands were accelerating the reaction. In the optimized reaction protocol, a mixture of 1 mol % of racemic BINAP and 0.5 mol % $Pd(PPh_3)_4$ constituted the precatalyst. During this step under the strong basic conditions (KOH), the desired hydrolysis of the nitrile group yielding the amide also occurred.



Scheme I.35. Pfizer's Migita protocol for the synthesis of **109**

I.A.4.8. Application of C-H Functionalization

Alpelisib, **123** (**Scheme I.36.**) is a potent antitumor agent and is the first approved PI3K inhibitor prescribed in combination with fulvestrant for the treatment of human epidermal growth factor receptor 2 (HER2)-negative, hormone receptor (HR)-positive, PIK3CA-mutated, metastatic or advanced breast cancer.[100, 101] In May 2019 Alpelisib combination drug was approved by the U.S FDA and sold by Novartis Oncology under the brand name Piqray®. The synthetic route to alpelisib, **123** involves C-C bond formation *via* C-H functionalization. This was designed and developed by Novartis[102] and is represented in Scheme **I.36.** This C-C bond formation reaction *via* C-H functionalization is the key step among the eight steps of the designed synthetic process reported. A mixture of 2-acetamido-4-methylthiazole **117**, 4-bromo-2-(1,1,1-trifluoro-2-methylpropan-2- yl)pyridine **116**, *t*-$Bu_3P.HBF_4$ (20 mol %), $Pd(OAc)_2$ (10 mol %) and Cs_2CO_3 in DMF at 120°C to accomplished **118** after C-C bond formation in 90% yield. The reaction was performed on a laboratory scale, 1.2 g with respect to aryl bromide **116**.



Scheme I.36. Medicinal chemistry route to alpelisib, **123**

I.A.5. Ligands for Cross-Coupling reactions

I.A.5.1. Phosphine and dialkylbiarylphosphine

The one biggest advancement in palladium-catalyzed cross-coupling reaction over the last two decades has been the evolution of specialized ligands those enhanced the rates of the elementary steps in catalysis, like oxidative addition and reductive elimination.[103]

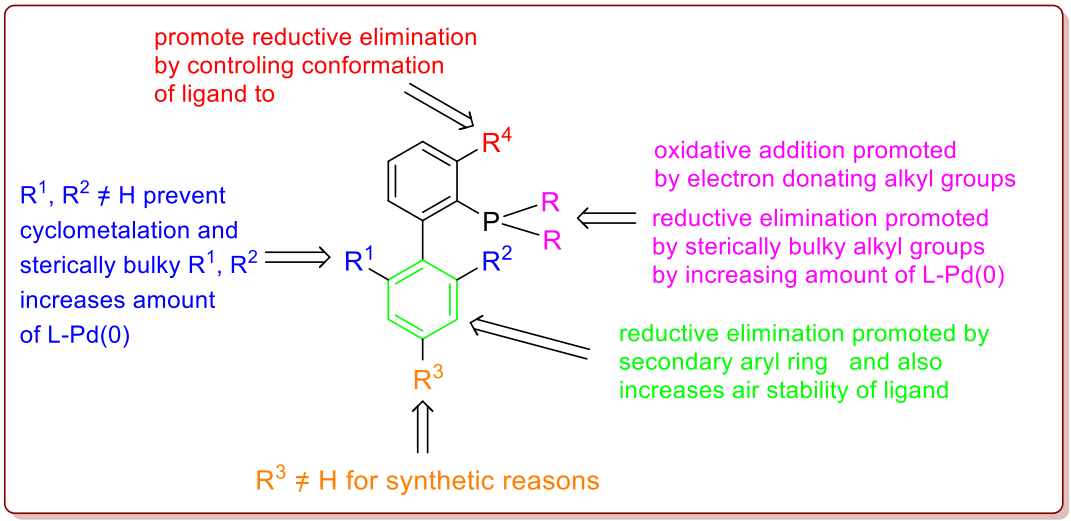


Figure I.2. Generic advantages of Buchwald-type dialkylbiarylphosphine ligands

Initially, simple triarylphosphine ligands were utilized in cross-coupling, but influential work from the Buchwald group revealed that sterically bulky dialkylbiarylphosphine ligands generated catalytic systems with increased efficiency and scope (**Figure I.2.**).[103e]

Due to the development of these ligands the discovery of catalytic systems capable of room-temperature Suzuki−Miyaura reactions involving unactivated aryl chloride substrates was possible[104] and has been key to developments in the opportunity of Buchwald−Hartwig reactions.[105] An extensive variety of Buchwald-type dialkylbiarylphosphine ligands are available commercially, and the universal design principles for boosting both the elementary steps in catalysis and the generation of the active monoligated palladium(0) species are clearly understood (**Figure I.2.**). In general, it is also possible to predict which classes of ligand are suitable for a specific reaction, though not a particular ligand will be suitable for a definite type of reaction, for example, a Suzuki−Miyaura or Buchwald−Hartwig reaction. It is unexpected that there will be at all a "all-round" ligand that is ideal for all cross-coupling reactions, but rather, researchers could choose from a list of specialized ligands, with the "optimal" ligand depending on the particular reaction and conditions. However, for specialized applications, research into more advanced phosphine ligands continues, it seems likely that only small improvements in efficiency for traditional cross-coupling reactions will result. The main development to dialkylbiarylphosphine ligands that can be made is probably to make them less expensive or to design cheaper new ligands that give comparable activity.

I.A.5.2. N-Heterocyclic carbene

Carbenes are defined as neutral compounds containing a divalent carbon atom with a six-electron valence shell. Carbenes are the one of the most interesting class of carbon-containing compounds. Incomplete electron octet and coordinative unsaturation make free carbenes intrinsically unstable and they have been primarily considered as highly reactive transitory intermediates in organic transformations such as cyclopropanation. The isolation and distinct characterization of a free, uncoordinated carbene stand elusive until intensive studies in the late 1980s and early 1990s[106]. In 1988 Bertrand and co-workers described the synthesis of the first isolable carbene stabilized by favourable interactions with adjacent phosphorus and silicon substituents[107]. In 1991 Arduengo *et al.* delineated an isolable and 'bottleable' carbene included into a nitrogen heterocycle[108]. Inspired by earlier insightful studies with structural features by

Wanzlick[109] and Ofele[110] on metal–carbene complexes, the exceptional stability and quite simple synthesis of the first N-heterocyclic carbene (NHC) 1,3-di(adamantyl)imidazol-2-ylidene (**IAd, 124**) led to a surging of experimental and theoretical studies with libraries of novel NHCs being synthesized and analysed (Figure **I.5.**). Due to these investigations, NHCs have been uplifted from barely laboratory curiosities to compounds of huge practical significance as more rich chemistry of these compounds has been divulged and exploited. NHCs have found multiple applications in some of the most important catalytic transformations in the chemical industry as excellent ligands for transition metals.

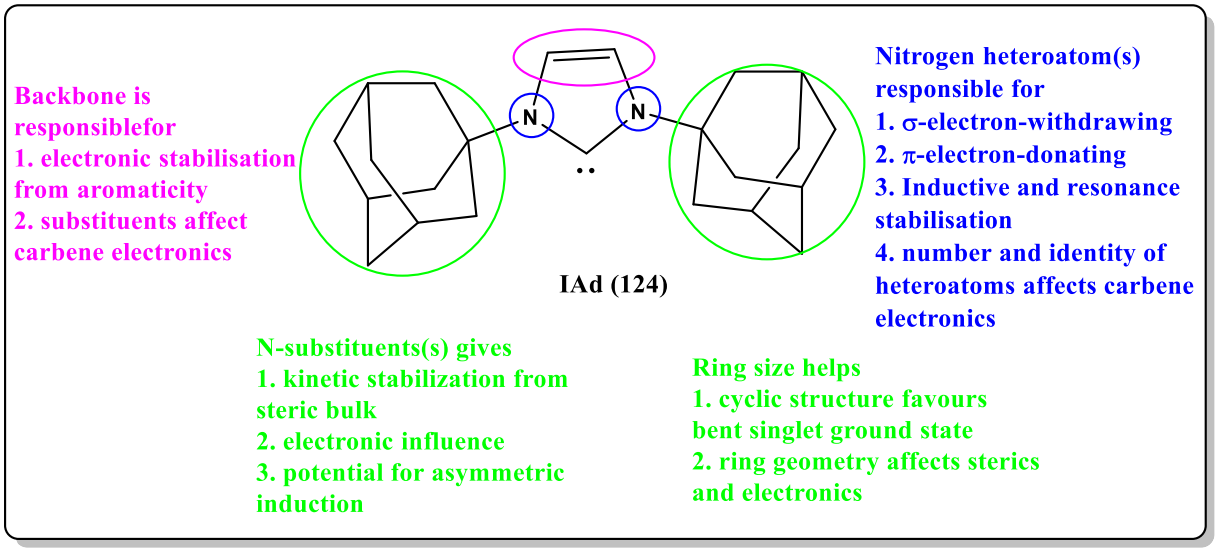


Figure I.3. General structural features of **IAd (124)**

I.A.5.2.1. Structure and general properties of NHCs

NHCs can be defined as heterocyclic species having a carbene carbon and at least one nitrogen atom within the ring structure[111,112]. As represented for the first reported compound **IAd (124)**, general structures of NHCs is shown in (**Figure I.3.**). The general electronic and steric effects of these structural attribute help to explaining the extraordinary stability of the carbene centre C-2. NHCs generally feature bulky substituents adjacent to the carbene carbon, as exhibited by the two adamantyl groups bound to the nitrogen atoms in **IAd (124)**. These bulky substituents disfavouring dimerization to the corresponding olefin (the Wanzlick equilibrium) assist to kinetically stabilize the species. However, the electronic stabilization provided by the nitrogen atoms, is a much more important factor. NHCs such as IAd exhibit a singlet ground-state

electronic configuration with the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) best described as a formally sp^2-hybridized lone pair and an unoccupied p-orbital at the C-2 carbon, respectively (**Figure I.4.**).

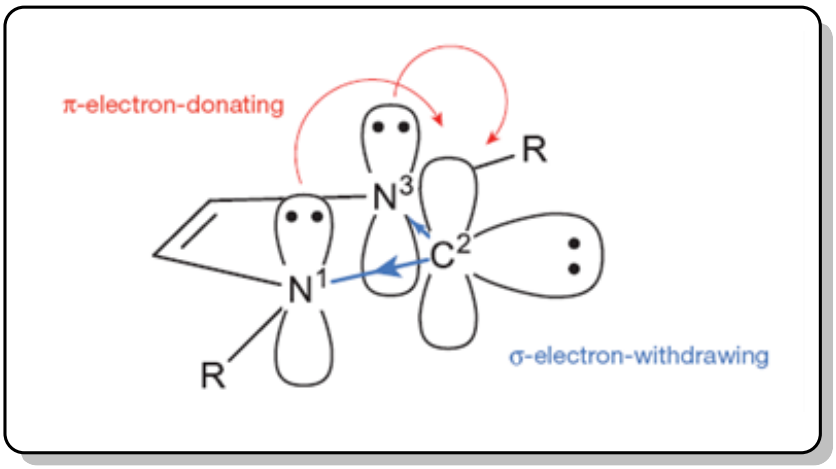


Figure I.4. The σ-withdrawing and π-donating effects of the nitrogen hetero atoms help to stabilize the singlet carbene structure of imidazol-2-ylidenes in ground-state electronic structure.

The adjacent's π-electron-donating and σ-electron-withdrawing nitrogen atoms stabilize this structure both by mesomerically by donating electron density into the empty p-orbital and inductively by lowering the energy of the occupied s-orbital. The cyclic nature of NHCs forced the carbene carbon into a bent, more sp^2-like arrangement. This helps to favour the singlet state. This ground-state structure observed in **IAd (124)** is reflected in the C(2)-N bond lengths (1.37 A˚), which fall in between those of its corresponding imidazolium salt ($IAdH^+$, 1.33 A˚)[108] and its C(2)-saturated analogue (IAdH, 1.49 A˚)[113], signifying that the C(2)-nitrogen bonds possess partial double bond character.

These common principles of carbene stabilization pertain to all classes of NHC while the relative influence of each effect fluctuates from compound to compound (Figure **I.5.**). NHCs obtained from heteroaromatic compounds aid from a greater degree of stabilization by attribute of their partial aromaticity. This effect is calculated to be around 25 kcal mol^{-1} for model imidazol-2-ylidenes[114] which allows for a lesser demand for proximal steric bulk. Therefore the simple methyl-substituted NHC 1,3-di(methyl)imidazol-2-ylidene (**IMe, 125**) is persistent in solution[115]. There are many stable carbenes that do not aid from aromaticity. For example Arduengo and co-workers reported 1,3-di(mesityl)imidazolin-2-ylidene (**SIMes, 129**) in 1995[116]. There is neither a

requirement for two adjacent nitrogen atoms to stabilize the carbene centre[117]. NHCs having alternative heteroatoms such as sulphur (**131**) and oxygen (**132**) are also accessible. Bertrand *et al.* introduced stable carbenes containing only one nitrogen substituent, such as the series of cyclic (alkyl) (amino)carbenes (**CAACs, 135**).[118]

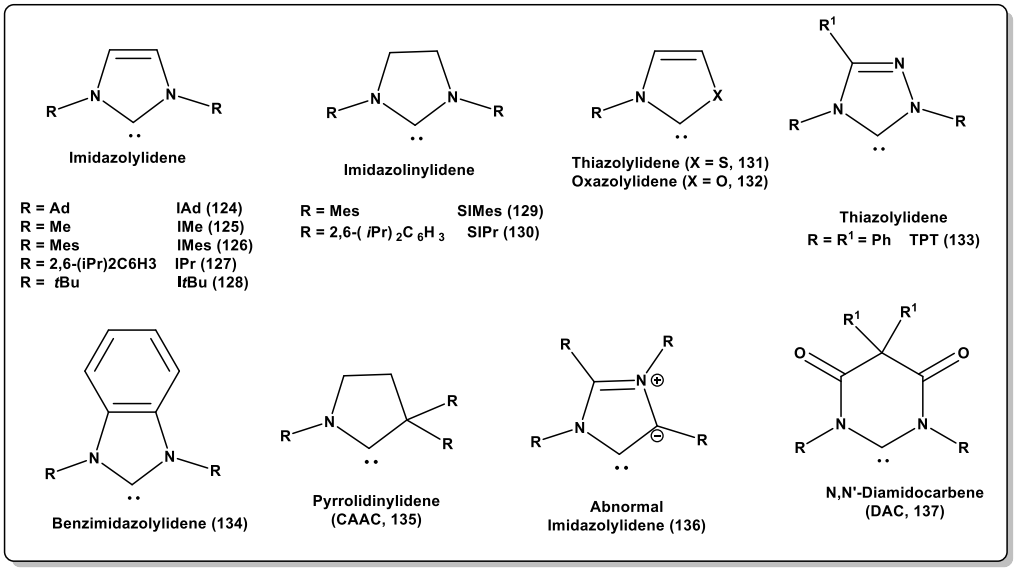


Figure I.5. Structures of some of the most commonly applied classes of NHCs

NHCs can also be formed upon generation of the carbene centre at alternative positions to C2 stabilized by only one nitrogen atom. For these mesoionic or 'abnormal' carbenes 8, a neutral, non-zwitterionic carbene resonance structure cannot be drawn. These are generally more electron-donating than their 'normal' analogues and can display very different properties[119,120]. However, 5-membered rings still make up the largest class of NHCs, examples having smaller or larger ring sizes including N,N′- diamidocarbenes (**DACs, 137**) have also been reported. These compounds having greater N1-2C2-2N3 bond angle lead to increased steric shielding, which successfully pushes the nitrogen substituents closer to the carbene centre.

I.A.5.2.2. Coordination of NHCs to transition metals

The most of applications of N-heterocyclic carbenes associate their coordination to transition metals (**Figure I.6.**). The acceptability of NHCs as ligands for transition metals can be justified by their innate σ–donor ability with a formal sp^2-hybridized lone pair accessible for donation into a σ–accepting orbital of the transition metal. Though σ–donation is the major important

component of metal–ligand binding, the contribution of both π–back-bonding into the carbene p-orbital and π–donation from the carbene p-orbital are also significant. The strong σ–donor and relatively weak π–acceptor properties of NHCs carries similarity to the coordination characteristics of phosphines, and they were primarily considered as mimics for this prevalent class of ancillary ligand in transition-metal coordination chemistry.[121]

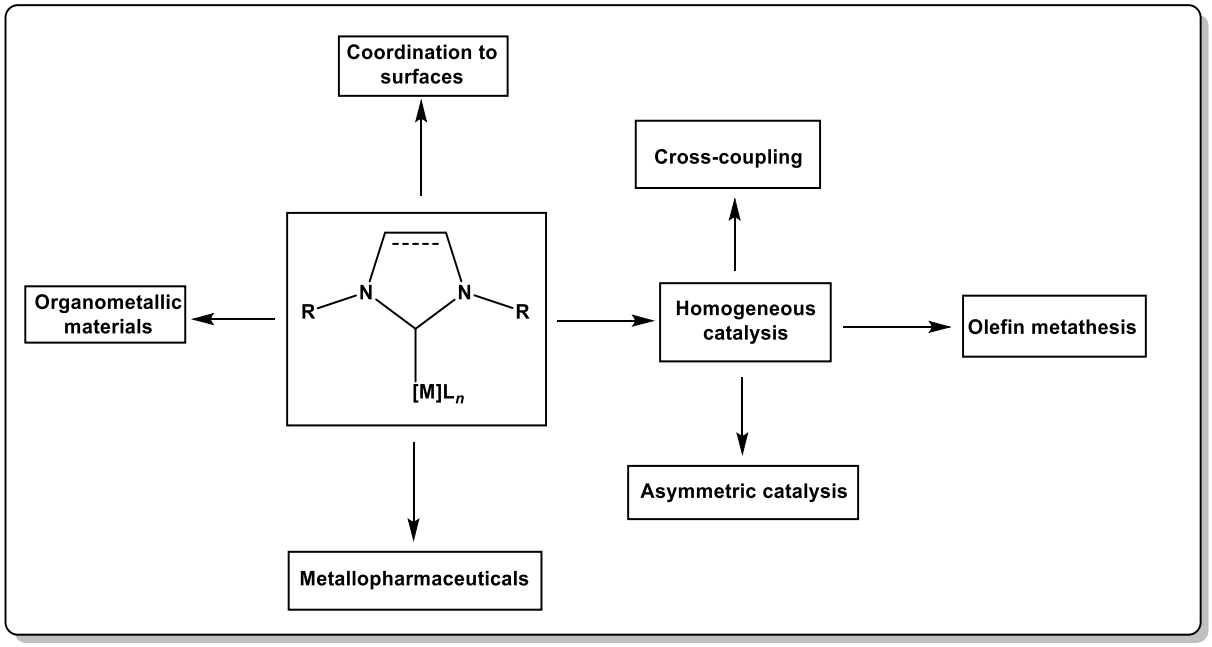


Figure I.6. Applications of NHCs coordinated to transition metals

NHCs are commonly more electron-donating than phosphines. This helps to thermodynamically stronger metal–ligand bonds and is revealed in the typically greater bond dissociation energies and shorter metal–ligand bond lengths witnessed for NHC complexes over their phosphine counterparts. However, excepting the most sterically demanding **IAd (124)**, for all carbene ligands, the bond dissociation energies persisted greater than that of the analogous complex with even the most Lewis-basic phosphine tested (PCy_3). Therefore the stronger metal–ligand interaction provides NHC–metal coordination less labile than metal–phosphine bond and the complexes are more thermally and oxidatively stable.[122] A comparison of the steric properties of NHCs and phosphines also displays remarkable differences. While the sp^3-hybridization of phosphines develops in a cone-shaped spatial orientation of the steric bulk, major classes of NHCs, involving the most commonly used imidazole-based imidazolylidene and imidazolinylidene, can best be depicted as fan- or umbrella-shaped with the nitrogen-substituents

adjacent to the carbene carbon aligned more towards the metal. Consequently, NHCs are commonly treated to be sterically demanding ligands with alterations in the nitrogen substituents and class of heterocycle having a substantial effect on the steric environment at the metal centre. In reverse of phosphines, the steric properties of NHCs are also highly anisotropic and rotation around the metal–carbene bond may occur so as to minimize clashing with other bulky ligands.

The more discrepancy between NHCs and phosphines covers the ease of modifying their steric and electronic properties. To synthesize NHCs employing well established heterocyclic chemistry is known. In case of phosphines synthetic roots for structural variation is limited. Additionally, changing the phosphorus substituents invariably affects both the steric and electronic properties of phosphines. In case of NHCs there is a potential to separately modify the nitrogen substituents, backbone functionality and class of heterocycle for more independent variation of each parameter.

With these interesting characteristics, NHCs presently contender phosphines and cyclopentadienyls as ligands across organometallic chemistry and the substantial range of available complexes continue to grow at an amazing rate.

Several procedures of manufacturing complexes may be used and there is usually no requirement to pre-form the free carbene. Most often, in situ deprotonation of an azolium salt is used in the presence of an appropriate transition-metal precursor, though procedures using α–elimination or oxidative addition at the carbene carbon, carbene transfer from pre-formed NHC-silver(I) or copper(I) complexes and metal-templated formation of the NHC may also be employed. Azolium salts are generally bench-stable solids and precursors for the extensively used NHCs, such as **IPr (127)** and **SIMes (129)** are commercially available. A fascinating group of NHCs includes additional roped coordinating groups into their structure and many examples of bi-, tri- and tetra-dentate ligands appearing multiple NHC moieties have been described. These NHCs may act either as chelating ligands to a single metal or bridge several different metals, regulating on their structure, providing complexes with an array of divergent geometries.[123]

The interesting characteristics of NHC-metal coordination have usher to a broad range of numerous applications of these complexes across the chemical sciences. However, generally, by far the largest application of NHC-transition metal complexes and certainly of NHCs is in the

homogeneous catalysis of organic transformations. First revealed by Herrmann and co-workers in an imidazol-2-ylidene palladium-catalyzed Mizoroki–Heck reaction[124], nowadays, NHC complexes of different transition metals are favoured catalysts for several academically and commercially important processes.

Majority of the success in these transformations of NHC spectator ligands can be ascribed to the increased catalyst stability, and subsequent lower rates of catalyst decomposition accompanying from strong metal–ligand binding. The prominent steric and electronic effect of the NHC on the metal centre may also bring on to improved catalytic activity. These two factors are wonderfully illustrated in the outstanding efficiency of perhaps the most leading NHC–metal complex; Grubbs' second-generation olefin metathesis catalyst **138** (**Figure I.7.**).[125,126] Grubbs' second-generation catalyst, the SIMes–Ru(II) complex **138** exhibits substantially greater thermal stability and remains catalytically active for cross- and ring-closing metathesis, and ring-opening metathesis polymerization (ROMP) reactions at much lower catalyst loadings, compared to the first-generation Grubbs' catalyst **139**, which features two PCy_3 ligands bound to ruthenium.

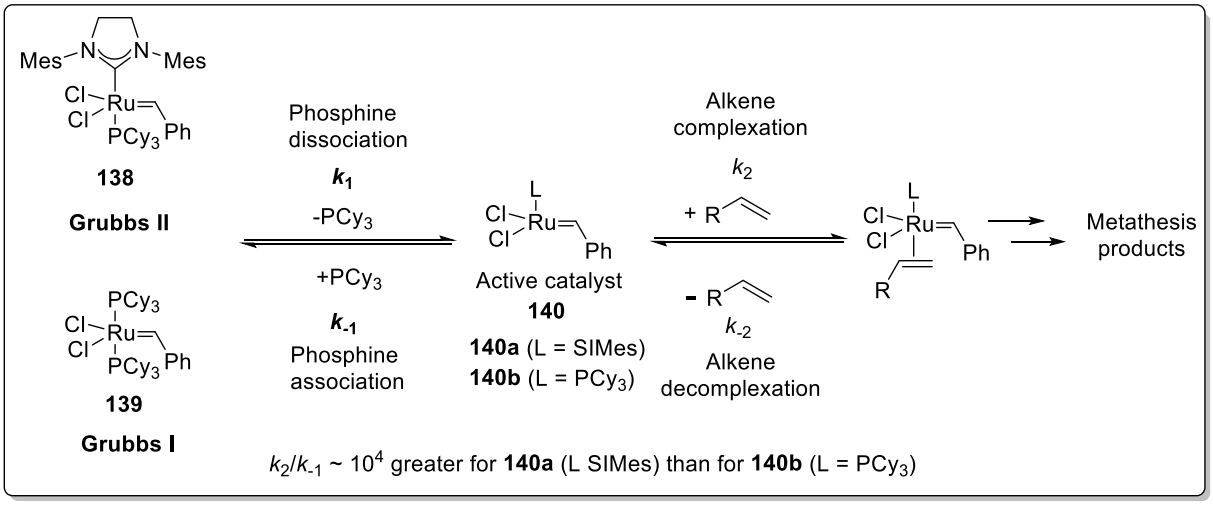


Figure I.7. Comparison of Grubb's first- and second-generation catalysts

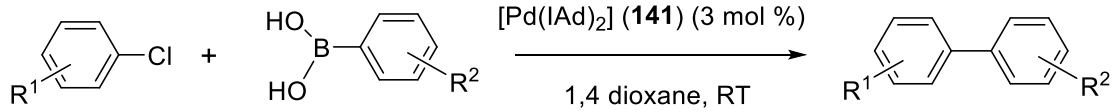
I.A.5.2.3. NHC-Complexes in cross coupling reactions

NHC remained dominant ligands over other many ligands examined for metal catalysed organic transformations. This section is a succinct account for few of those name reactions in the light of literature where Pd-NHC metal complexes have been successfully used as catalyst.

I.A.5.2.3.1. Suzuki–Miyaura Cross-coupling Reaction

Extensive work on Pd–NHC-based catalysts was carried out during the rapid development of NHC chemistry.[127a,b] Some of the challenges associated with cross-coupling reactions have focused on the use of unreactive aryl chlorides as coupling partners in view of their attractive cost and readily available diversity. In 2002 Herrmann *et al*. reported a well-defined Pd-NHC catalyst, [Pd(IAd)$_2$] (**141**) used for Suzuki-Miyaura cross-coupling reaction of aryl chlorides and arylboronic acids at room temperature (**Table I.1.**).[128]

Table I.1. [Pd(IAd)$_2$] (**141**) catalyzed Suzuki coupling reaction of aryl chlorides

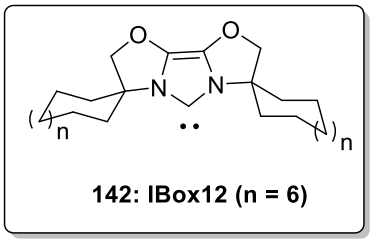


R^1	R^2	Time	Yield (%)
4-CH_3	H	6h	>99
4-OCH_3	H	6h	>99
4-CF_3	H	6h	>99
4-CF_3	3-OCH_3	24h	97
4-$COCH_3$	4-OCH_3	24h	95

Altenhoff *et al*.[129]reported the first example of a NHC ligand used to prepare sterically congested biaryls. Using a sterically bulky, yet flexible derivative of their bioxazoline-derived NHC ligand (IBox12•HOTf) (**142**) with Pd(OAc)$_2$, sterically hindered aryl chlorides and boronic acids were coupled to give a variety of *tetra-ortho*-substituted biaryls in high yield. Although this catalyst system was capable of coupling aryl chlorides, which are less expensive and more readily available than their bromide and iodide analogs, strictly anhydrous conditions were required to avoid proto-deboronation of the boronic acid, a common side reaction observed in Suzuki–

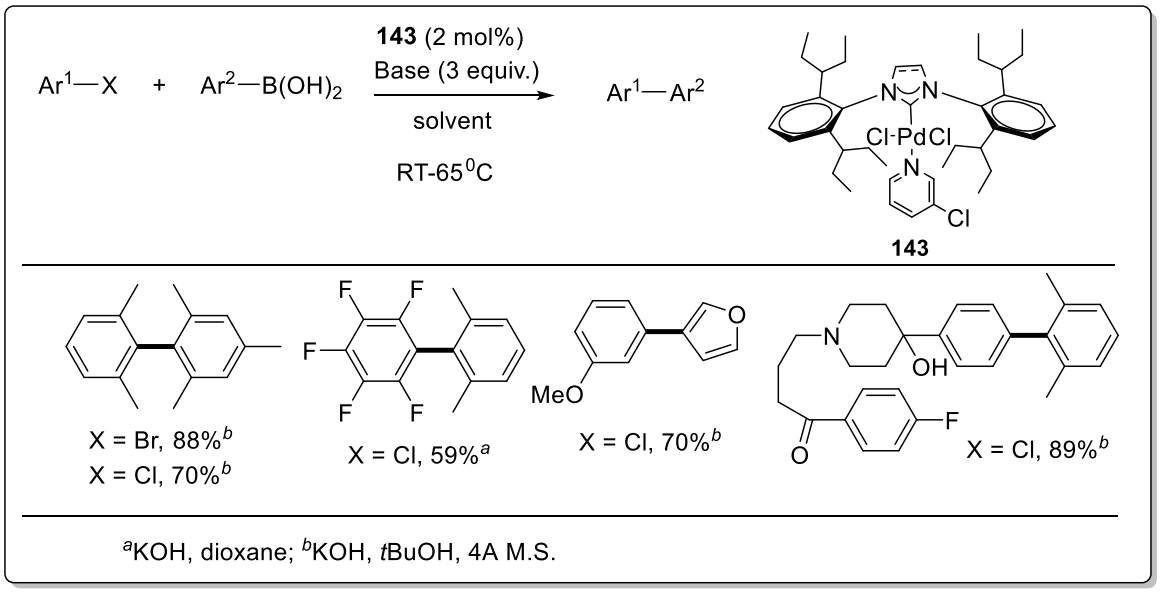
Miyaura coupling. Nevertheless, the report highlighted for the first time the importance of "flexible steric bulk" around the metal center necessary to promote this challenging reaction.

Unfortunately, the need for high reaction temperatures (>100 °C), the use of excess ligand, and high catalyst loadings with the early protocols was a major drawback and placed significant limitations on this useful methodology.



142: IBox12 (n = 6)

In 2009, Organ and co-workers were able to improve on the reaction temperature, coupling a variety of sterically hindered aryl halides with boronic acids at 65°C using their sterically bulky Pd-PEPPSI-IPent pre-catalyst (**143**)(Scheme **I.37.**).[130]



Scheme I.37. Preparation of *tetra-ortho*-substituted and functionalized biaryls

In 2010, Schmidt and Rahimi[131] reported ligand **144** (**Figure I.8.**) to be highly efficient in Suzuki–Miyaura coupling. Combining **144** with $Pd(OAc)_2$, this in situ generated system was able

to generate various hindered biaryls at room temperature and *tetra ortho*-substituted biaryls at elevated temperatures (60–110 °C).

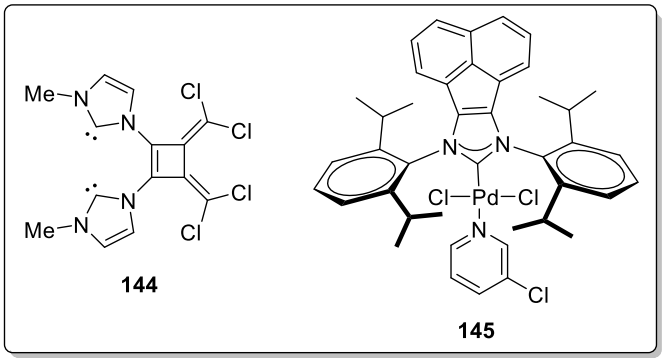


Figure I.8. Structures of NHC ligand **144** and Pd-NHC pre-catalyst **145** used in preparation of *tetra-ortho*-substituted biaryls

In 2011, Wu *et al.*[132]reported the first example of an NHC ligand capable of promoting the construction of sterically encumbered *tetra-ortho* substituted biaryls at room temperature via Suzuki–Miyaura coupling. Employing 2 mol % of complex **146** (**Figure I.9.**) along with *t*BuOK as the base, a variety of bulky *tetra-ortho*-substituted biaryls were formed in high yield (**Scheme I.38.**).

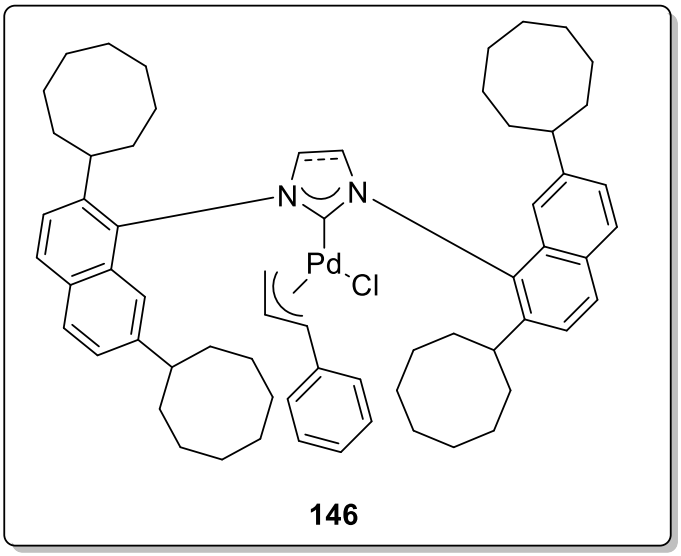
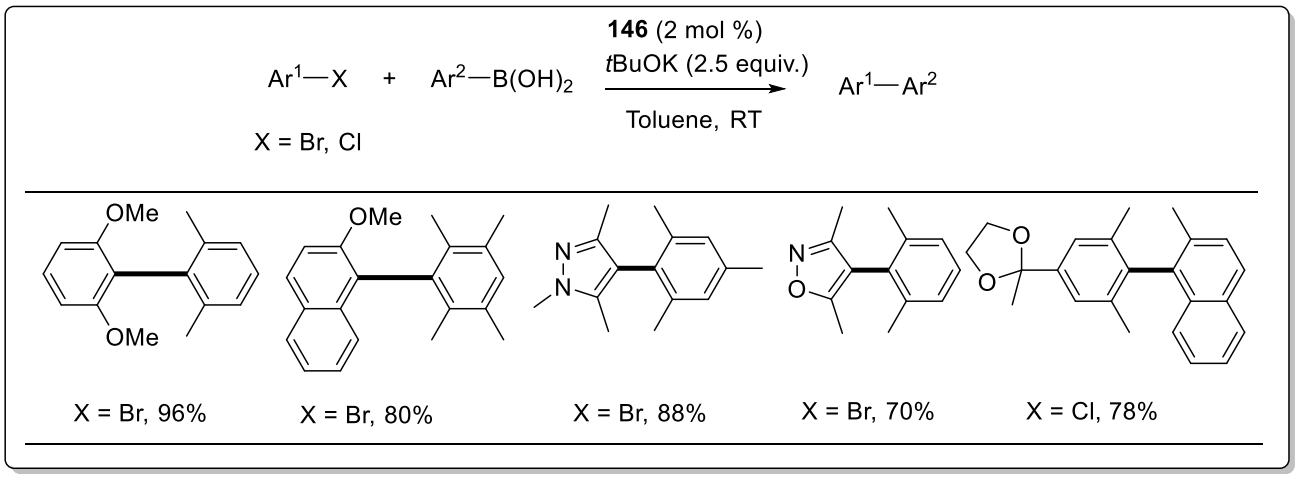
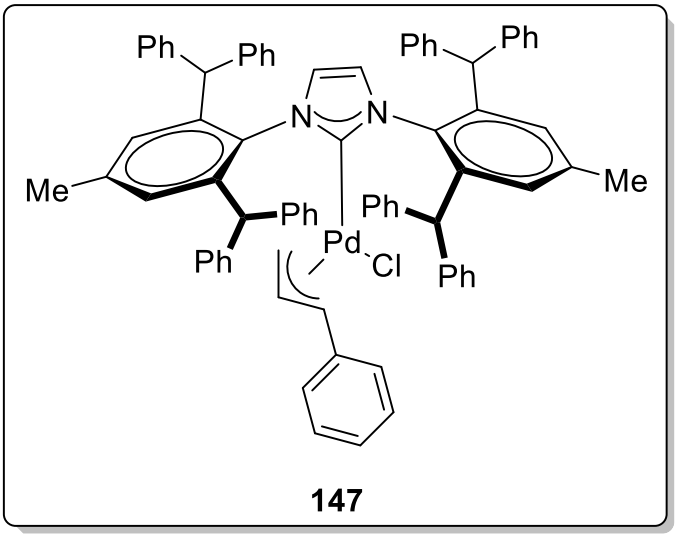


Figure I.9. Structure of [Pd(NapCyoct$_2$)(cin)Cl], **146**



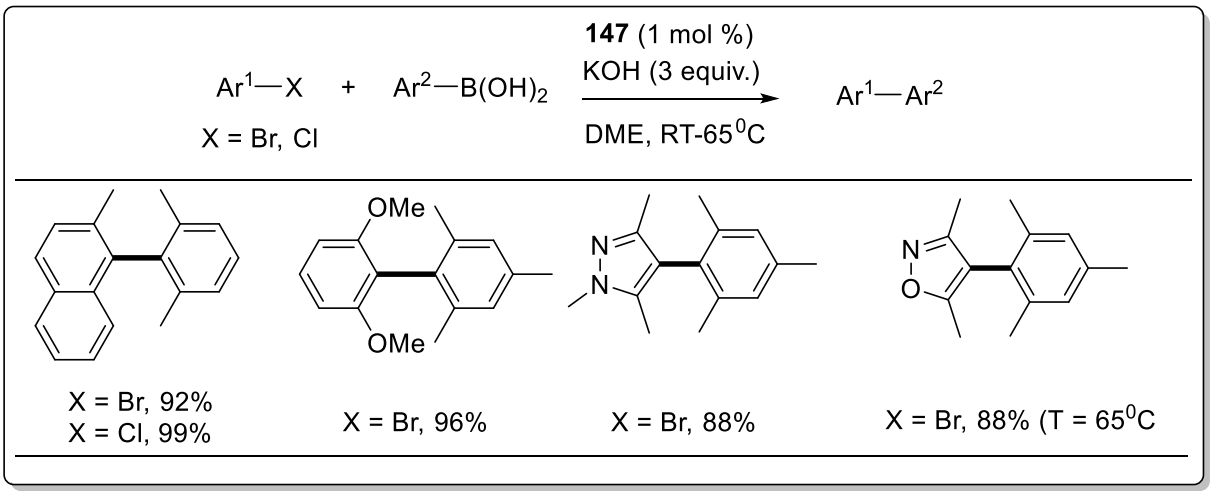
Scheme I.38. Reactivity of **146** in the Suzuki–Miyaura coupling of *tetra-ortho*-substituted Biaryls

In 2012, S. P. Nolan *et al.*[133] reported improvements in catalyst efficiency using [Pd(IPr*)(cin)Cl] (**147**) (**Figure I.10.**). With only 1 mol % of pre-catalyst **147** and KOH as the base, a variety of *tetra-ortho*-substituted biaryls were produced either at room temperature or at 65 °C (**Scheme I.39.**).

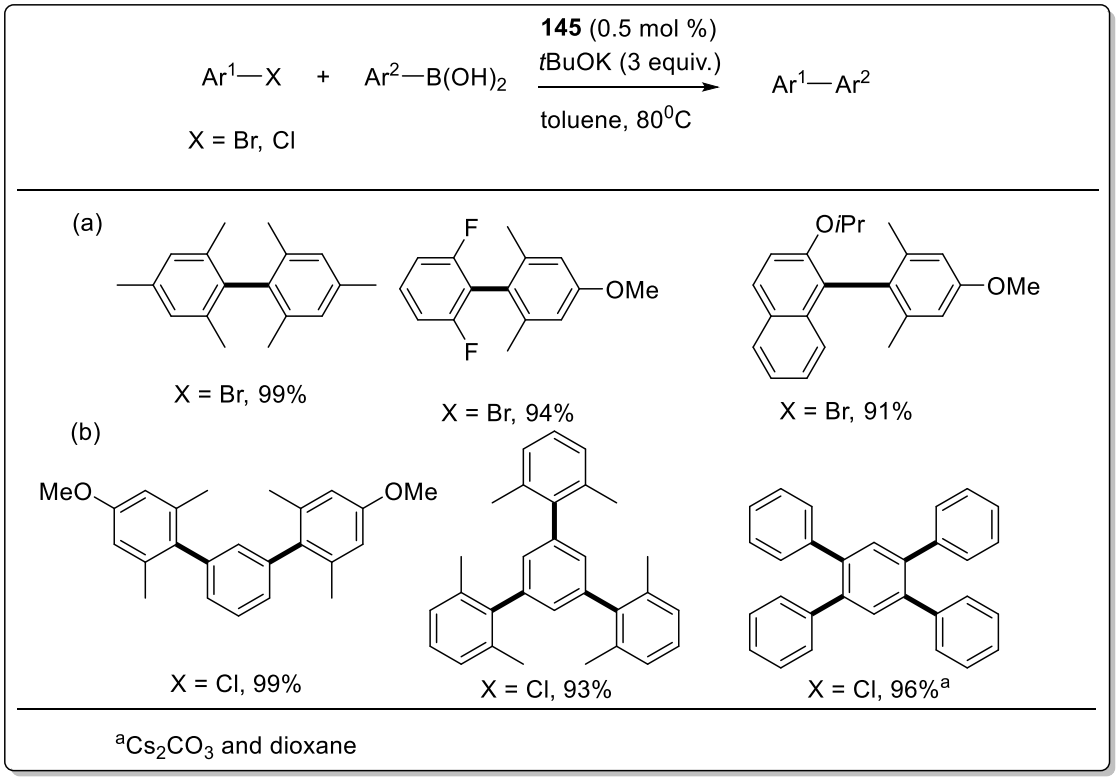


147

Figure I.10. Structure of [Pd(IPr*)(cin)Cl], **147**



Scheme I.39. Preparation of *tetra*-ortho-substituted biaryls using [Pd(IPr*)(cin)Cl] (**147)**

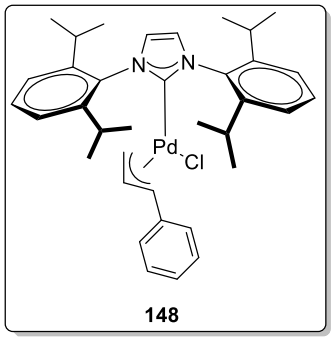


Scheme I.40. Preparation of (a) *tetra*-ortho-substituted biaryls and (b) polyarylbenzenes using **145**

Tu and *et al.* investigated the use of acenaphthoimidazolylidene based PEPPSI pre-catalysts in Suzuki–Miyaura couplings with sterically encumbered substrates.[134]Complex **145** (**Figure I.8.**) was found to be the most efficient, generating *tetra-ortho*-substituted biaryls in excellent yield

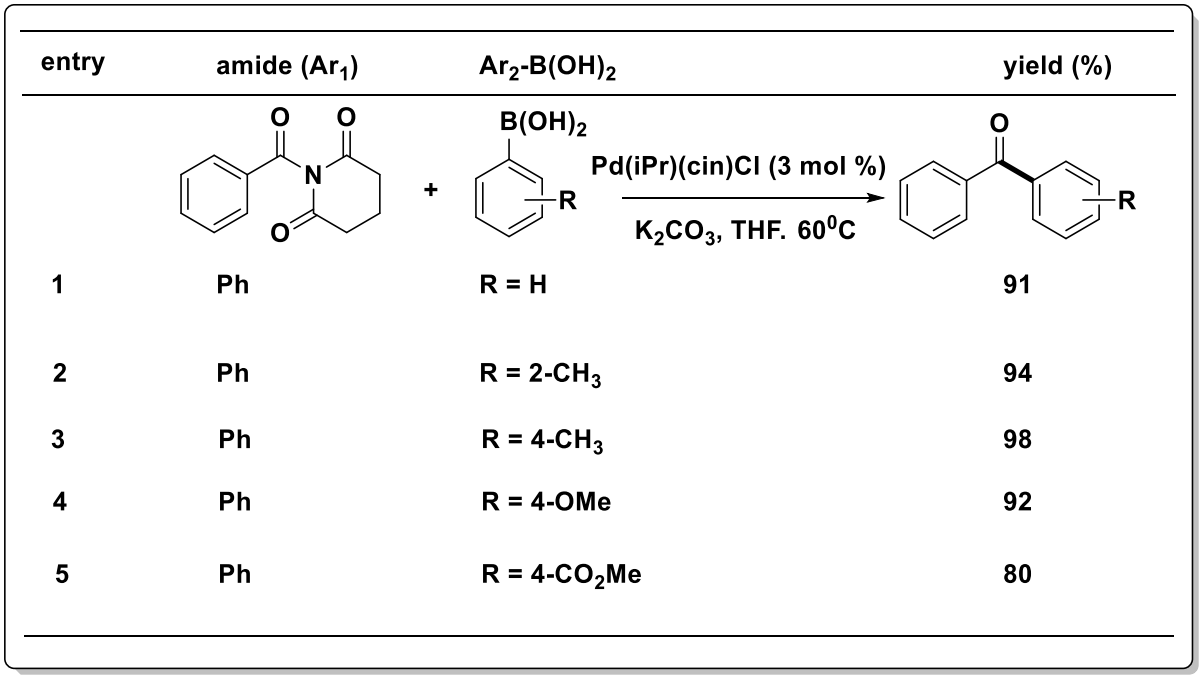
with low catalyst loadings (0.05 mol %); however, elevated temperatures (80°C) and a harsh base (^{t}BuOK) were still required to achieve full conversation. Interestingly, the protocol could also be extended to polychloro aromatics to generate a variety of polyaryl benzenes in good to excellent yields (**Scheme I.40.**).

In 2017, Szostak et *al.*[135] reported the direct Suzuki−Miyaura cross-coupling of amides catalyzed by Pd-NHC complexes [Pd(IPr)(cin)Cl] (**148**). The studies described the use of versatile Pd-NHC complexes as catalysts for transition-metal-catalyzed cross-coupling of amides by N−C bond activation (**Scheme I.41.**). The Pd-NHC catalysts provide a significant improvement over Pd-PR_3 systems employed for the amide N−C bond activation.



148

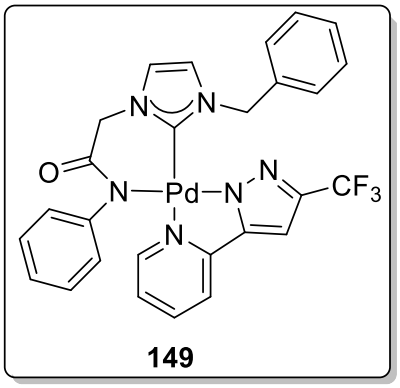
Figure I.11. Structure of [Pd(IPr)(cin)Cl], **148**



Scheme I.41. Pd-NHC-Catalyzed Suzuki−Miyaura Cross-Coupling of Amides

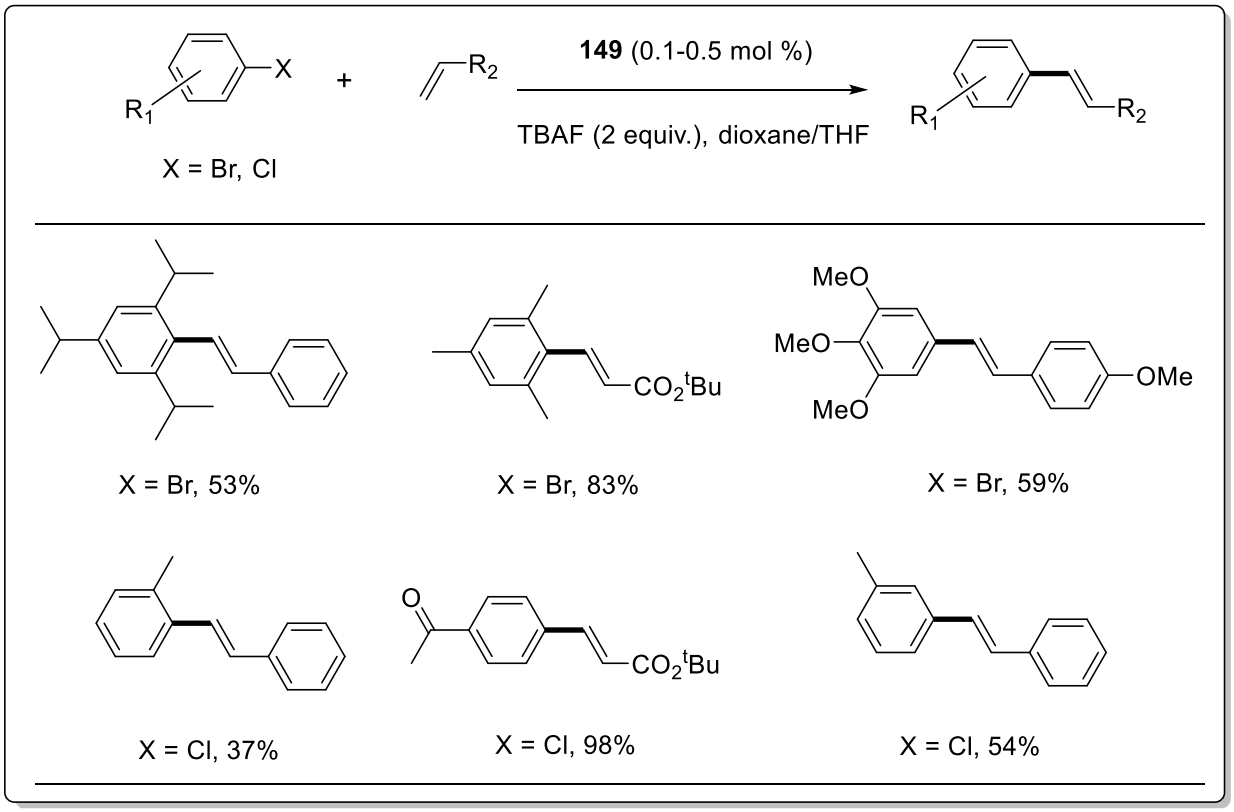
I.A.5.2.3.2. Mizoroki-Heck Reaction

The first NHC-Pd catalyzed reaction, able to couple aryl bromides and aryl chlorides to alkenes in high yields, was applied by Herrmann *et al.* in 1995.[136]



149

Figure I.12. Structure of heteroleptic Pd(II)complex, **149**



Scheme I.42. Heck reaction with heteroleptic Pd(II) complex

Early developments based on mixed NHC-phosphine complexes allowed for significant improvements in comparison to *bis*-NHC or *bis*-phosphine complexes. The steric demand of the NHC was once more crucial for catalytic activity.[137] Changing the reaction media to ionic liquids, more precisely *tetra*-butyl ammonium bromide, was a successful modification allowing for good yields with various aryl chlorides and a well-defined mono carbene-palladium complex.[138] Lee and coworkers developed heteroleptic palladium(II) complexes, **149** (**Figure I.12.**) bearing a bidentate carbene/amido ligand to perform this transformation. In an ionic liquid, this catalyst performed exceedingly well even with unactivated aryl chlorides at catalyst loadings in the range 0.1–0.5 mol % (**Scheme I.42.**). Replacement of a second carbene/amido ligand by a weaker binding ligand is a key for improved catalyst activation.[139]

Huynh *et al*. have 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.[140]

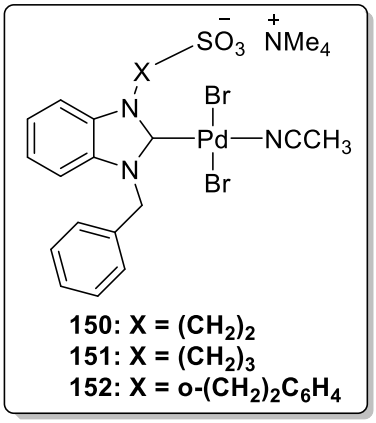


Figure I.13. Sulfonate-NHC-Pd(II) complexes for Mizoroki-Heck reaction

With a focus on an inexpensive and easily synthesized catalyst suitable for demanding aryl iodides and bromides, Ying *et al.* reported the one-pot synthesis of [Pd(IMes)(dmba)Cl] (dmba=dimethylbenzylamine) and its successful use with a series of interesting substrates.[141] Heck reactions conducted in air and in the presence of moisture have been achieved with SIMes-thiourea precursors and $Pd(dba)_2$[142] and various multi dentate carbene palladium catalysts derived *in situ* from imidazolium salts and $Pd(OAc)_2$ even tolerated the presence of oxidants.[143] Turn over numbers (TONs) upto 2000000 with full conversion have been reported when testing a *bis*-NHC palladium (II) complex with 4-bromoacetophenone and butyl acrylate.[144]

I.A.5.2.3.3. Sonogashira Reaction

Room temperature Sonogashira coupling of aryl iodides with an air stable *N*-carbamoyl-substituted heterocyclic carbene Pd-complex was one of the early success demonstrating the potential of NHC complexes in this coupling reaction.[145] A catalyst formed *in situ* from $Pd(OAc)_2$ and IMes.HCl also showed good activity even under copper-free conditions for activated aryl bromides. The first example of Pd-NHC Sonogashira coupling with alkyl bromides bearing *β*-hydrides followed soon afterwards and was performed by Fu and coworkers with $[Pd(\pi\text{-allyl})Cl]_2$ and the sterically demanding IAd.HCl at 45°C.[146]

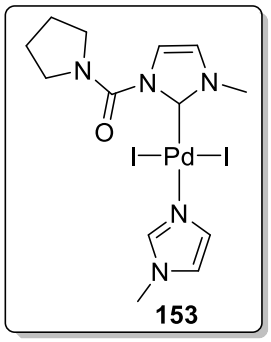
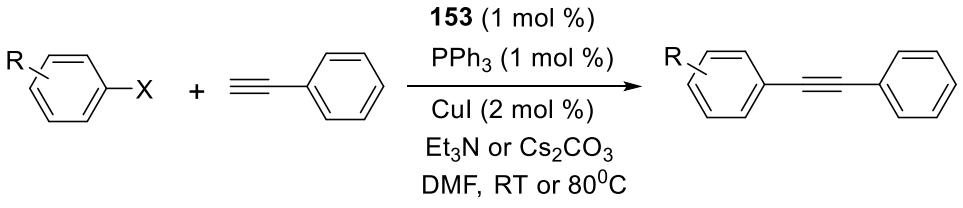


Figure I.14. N-carbamoyl-substituted NHC-Pd(II) complex for Sonogashira cross-coupling reaction



entry	R	X	base	Temp (^{0}C)	Yield (%)
1	4-$COCH_3$	I	Et_3N	RT	95
2	4-CH_3	I	Et_3N	RT	Quantitative
3	4-OCH_3	I	Et_3N	RT	98
4	4-$COCH_3$	Br	Et_3N	80	99
5	4-CHO	Br	Et_3N	80	89
6	4-NMe_2	Br	Cs_2CO_3	80	95
7	4-OCH_3	Br	Cs_2CO_3	80	85

Scheme I.43. Sonogashira reaction catalyzed by Batey's Pd-NHC complex (**153**)

Batey *et al*. developed N-carbamoyl-substituted NHC-Pd(II) complex, **153** (**Figure I.14.**) which effectively catalyzed Sonogashira cross-coupling reaction under mild condition (**Scheme I.43.**).[145]

Another important contribution was made by Gosh who developed a NHC-based catalyst (**154)** suitable for Sonogashira couplings under amine-free conditions in air and in aqueous solvent mixtures (**Scheme I.44.**). The scope is, however, limited to aryl iodides[147], but sulfonated NHCs coordinated to palladium permitted couplings with aryl bromides in water/isopropanol.[148] PEPPSI catalysts achieved the amine-and copper-free coupling of both aryl iodides and bromides in air.[149a, b]

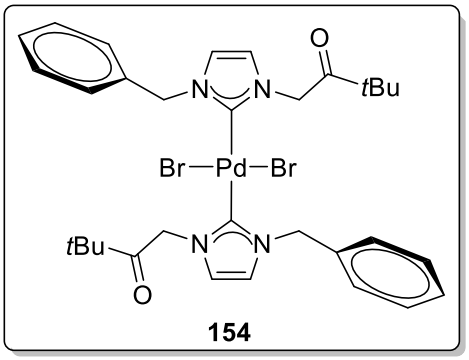
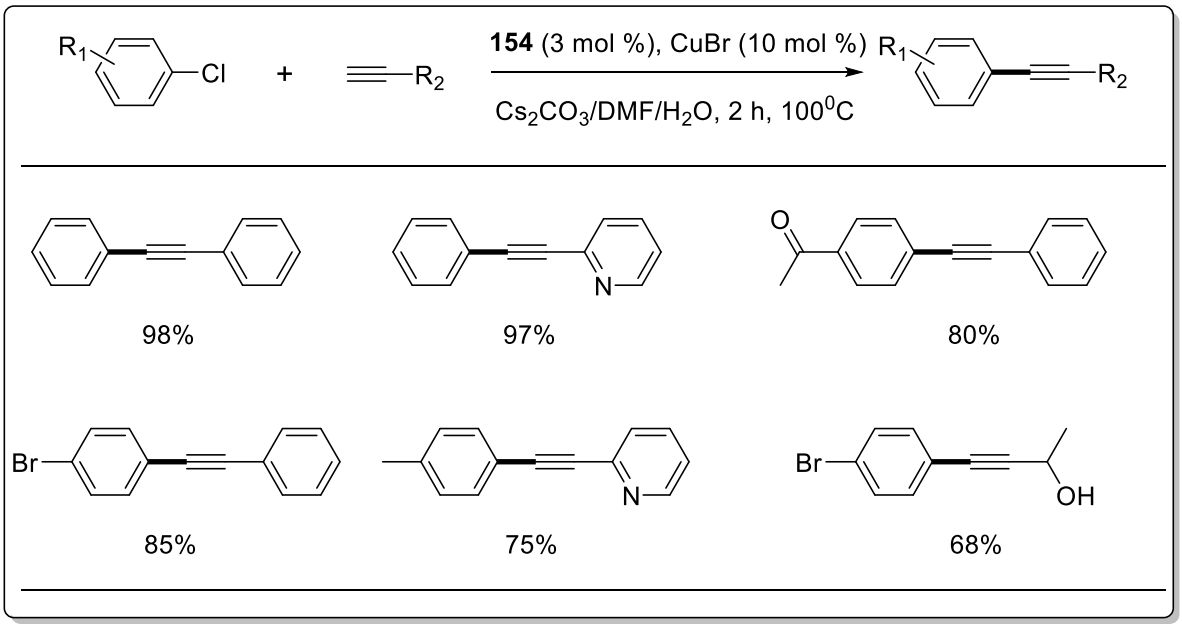


Figure I.15. NHC-Pd(II) complex for amine-free Sonogashira cross-coupling reaction



Scheme I.44. Sonogashira reaction in air under amine-free conditions

I.A.5.2.3.4. Direct C-H arylation

The area of direct C(sp^2)−H arylation of heterocycles by Pd−NHC complexes remained dormant until 2010 when Özdemir and co-workers synthesized a series of Pd−NHC benzimidazolylidene complexes **155−159** (**Figure I.16.**) bearing different N side chains and employed them as catalysts for the direct C(sp^2)−H arylation of furan, thiophene, and thiazole derivatives with aryl bromides (**Scheme I.45.**).[150]

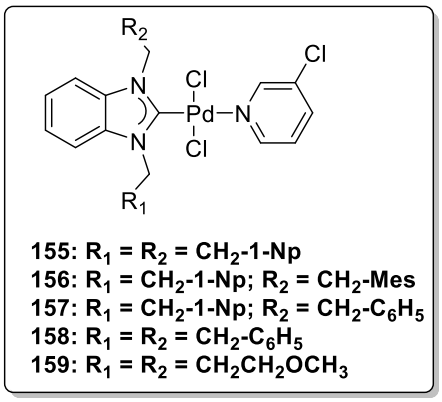
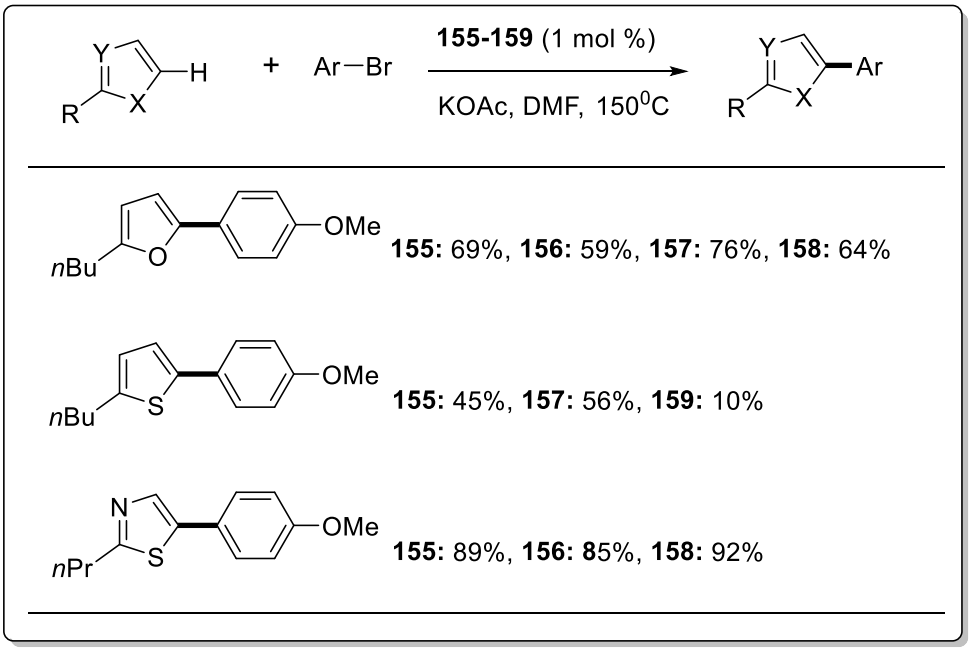


Figure I.16. Pd−NHC benzimidazolylidene complexes for the direct C(sp^2)−H arylation



Scheme I.45. Pd−NHC-Catalyzed Direct C−H Arylation of Furans, Thiophenes, and Thiazoles by Özdemir

Notably, only 1.0 mol % of air-stable Pd(II)−NHC precatalysts was required for this transformation. This represented a major practical advantage over the procedures employing air-sensitive phosphine ligands. In addition, this procedure generates KOAc and HBr as major by-products instead of metal salts.

In 2014, Akkoc and co-workers reported bis-Pd−NHC benzimidazolylidene complexes **160-162** (**Figure I.17.**) for the direct C(sp^2)−H C5 arylation of furans, thiophenes, and thiazoles (**Scheme I.46.**).[151]The procedure was compatible with both electron deficient and electron-rich aryl halides as coupling partners. High catalytic activity was observed using 0.5 mol % of Pd−NHC complexes in DMA at 130 °C.

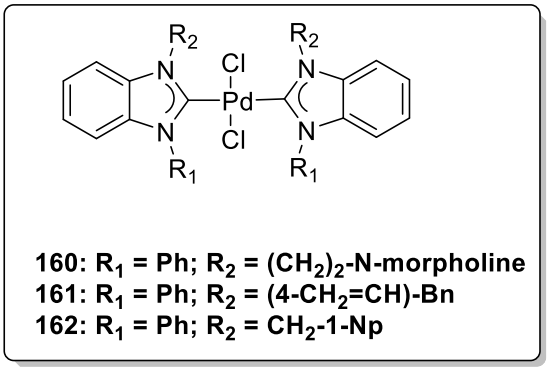
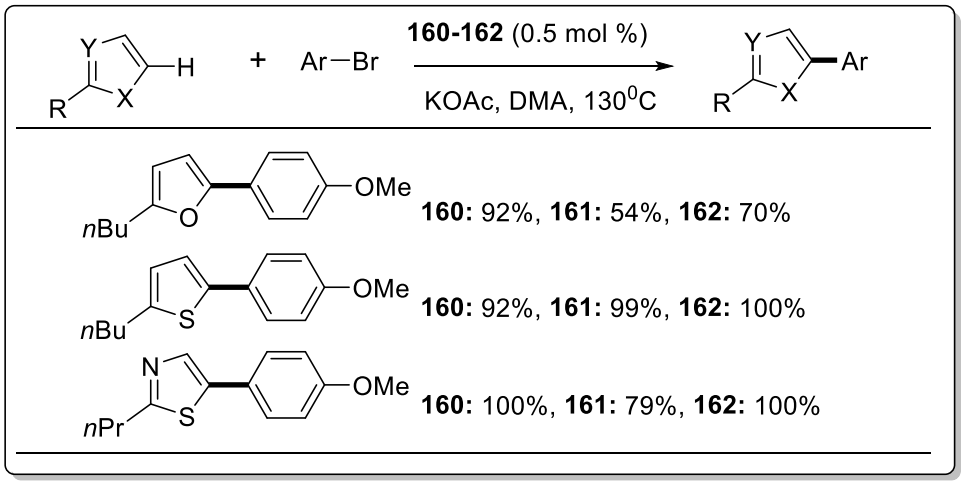


Figure I.17. Pd−NHC benzimidazolylidene complexes for the direct C(sp^2)−H arylation by Akkoc



Scheme I.46. Pd−NHC-Catalyzed Direct C−H Arylation of Furans, Thiophenes, and Thiazoles by Akkoc

In 2015, the Yang group described a chelating [Pd(NHC)-Cl_2] complex containing N-2-pyrimidine and N-2-hydroxyalkyl side chains (**163**) (**Figure I.18.**) as an efficient catalyst for the direct C(sp^2)−H arylation of benzoxazoles (**Scheme I.47.**).[152]The optimized reaction conditions utilized ^{t}BuOLi as a base in DMF at 130 °C. This protocol was applied to a broad range of substrates and achieved TON of 40.

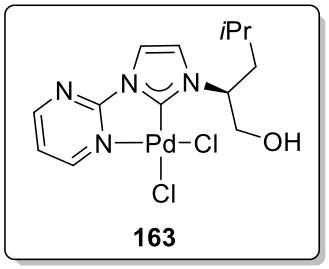
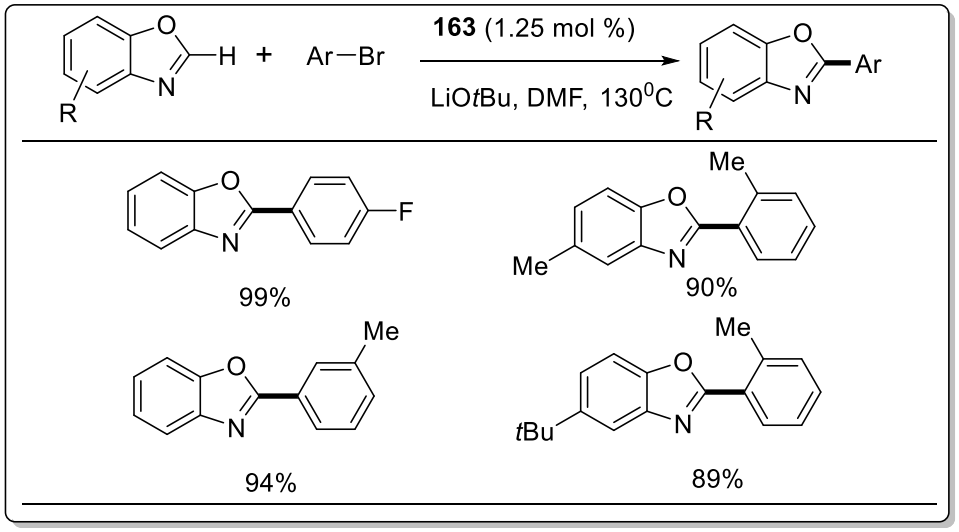


Figure I.18. [Pd(NHC)-Cl_2] complex containing N-2-pyrimidine and N-2-hydroxyalkyl side chains



Scheme I.47. Pd−NHC-Catalyzed Direct C−H Arylation of Benzoxazoles by Yang

In 2018, the Gandhi group developed N-4-dibenzofurylfunctionalized Pd−PEPPSI-type catalyst **164** (**Figure I.19.**) for the direct C(sp^2)−H arylation of benzoxazoles (**Scheme I.48.**).[153]The C−H arylation was achieved in DMF at 120°C. These N-dibenzofuryl Pd−NHC precatalysts also showed high activity in the Suzuki−Miyaura cross-coupling of aryl bromides.

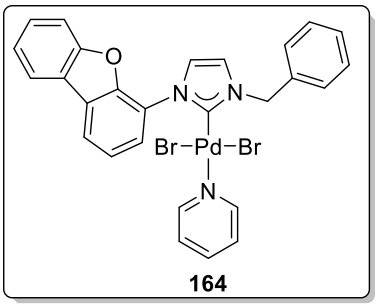
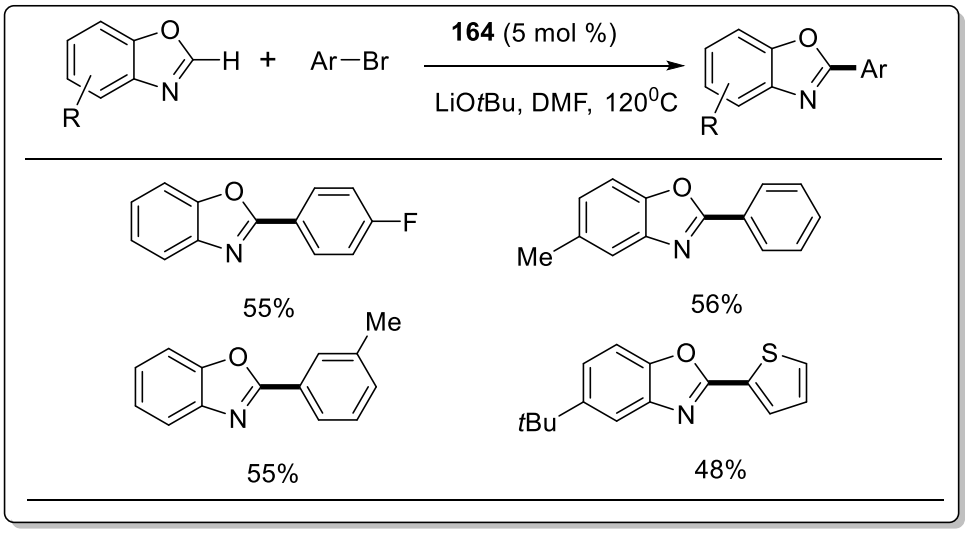


Figure I.19. Dibenzofuryl functionalized Pd−PEPPSI-type catalyst



Scheme I.48. Pd−NHC-Catalyzed Direct C−H Arylation of Benzoxazoles by Gandhi

The direct arylation could be conducted under aerobic conditions in the presence of pivalic acid (30 mol %) and K_2CO_3 as a mild base in DMA at 130 °C. Liu and co-workers identified bulky BIAN-type Pd−NHC complexes (BIAN =bis(imino)acenaphthene) (**165**) (**Figure I.20.**) for the direct C(sp^2)−H arylation of a broad range of azoles with aryl bromides (**Scheme I.49.**).[154]These impressive reactions proceed efficiently with only 0.05−0.5 mol % catalyst loading and are performed under aerobic conditions. A wide variety of heterocycles, including imidazoles, thiazoles, isoxazoles, and pyrazoles, provided the direct C−H activation products in good to excellent yields.

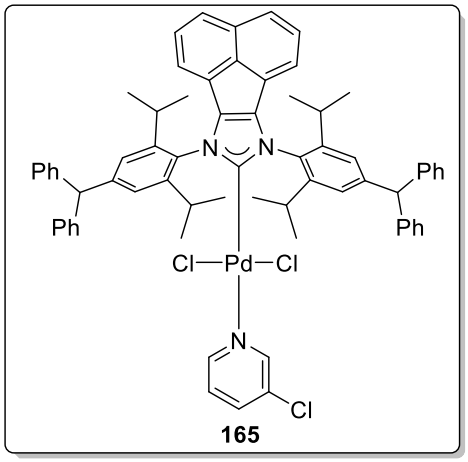
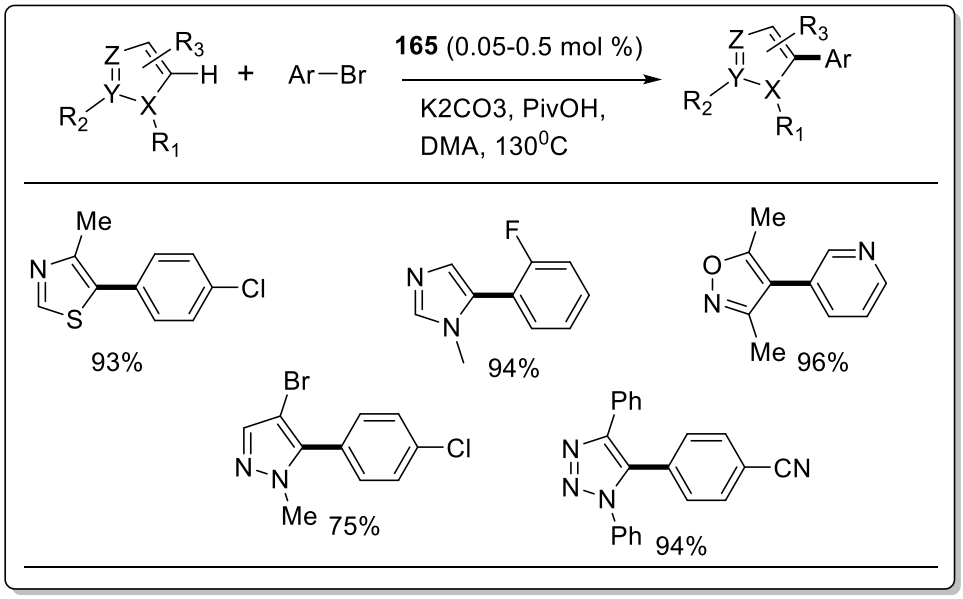


Figure I.20. Bis(imino)acenaphthene Pd−NHC complex

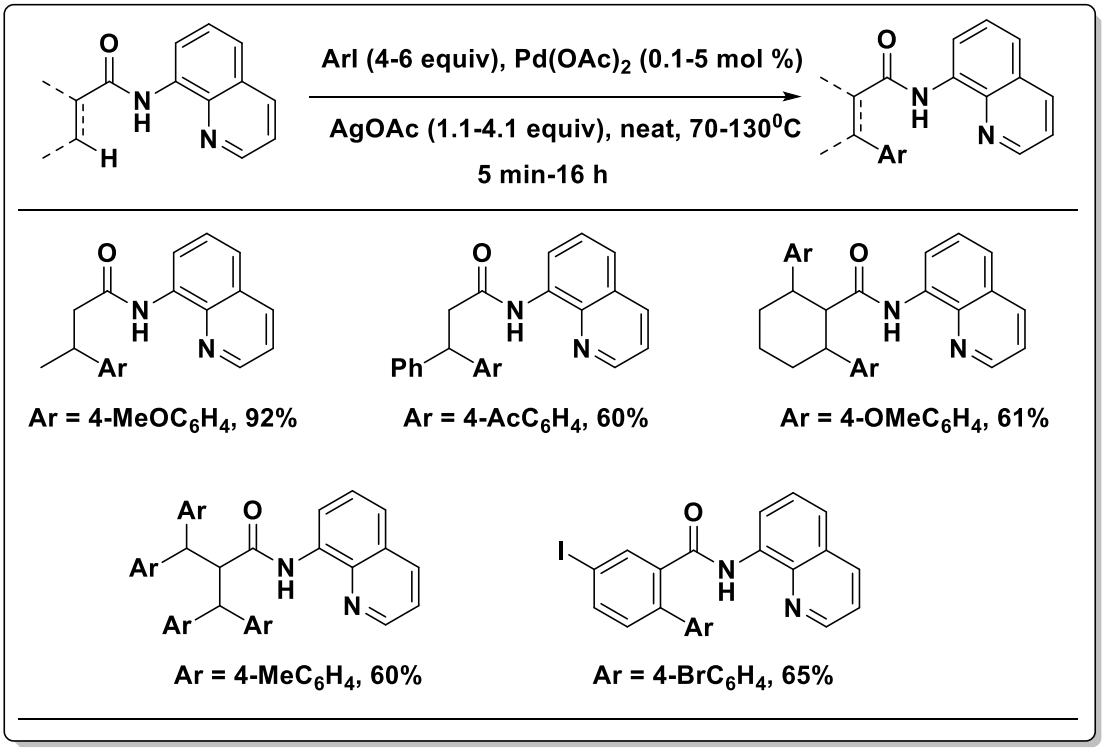


Scheme I.49. Direct C(sp^2)−H arylation using Bis(imino)acenaphthene Pd−NHC complex

Lee group reported decarboxylative C(sp^2)−H arylation of electron-deficient azoles using the Pd(0)−NHC complex.[155]This approach offers an alternative strategy to the direct C(sp^2)−H arylation of heterocycles using Pd−NHC catalysts.

I.A.5.2.3.5. Directing group (DG) mediated arylation

For directing group (DG) mediated arylation 8-amino quinoline (8-AQ) appears as a main DG. In 2005 Douglas first reported C(sp^2)−H and C(sp^3)−H arylation of amides using 8-AQ as directing group (**Scheme I.50.**).[156] This protocol was found to be applicable for a number of unreactive C(sp^3)−H bonds including primary and secondary C−H bonds.



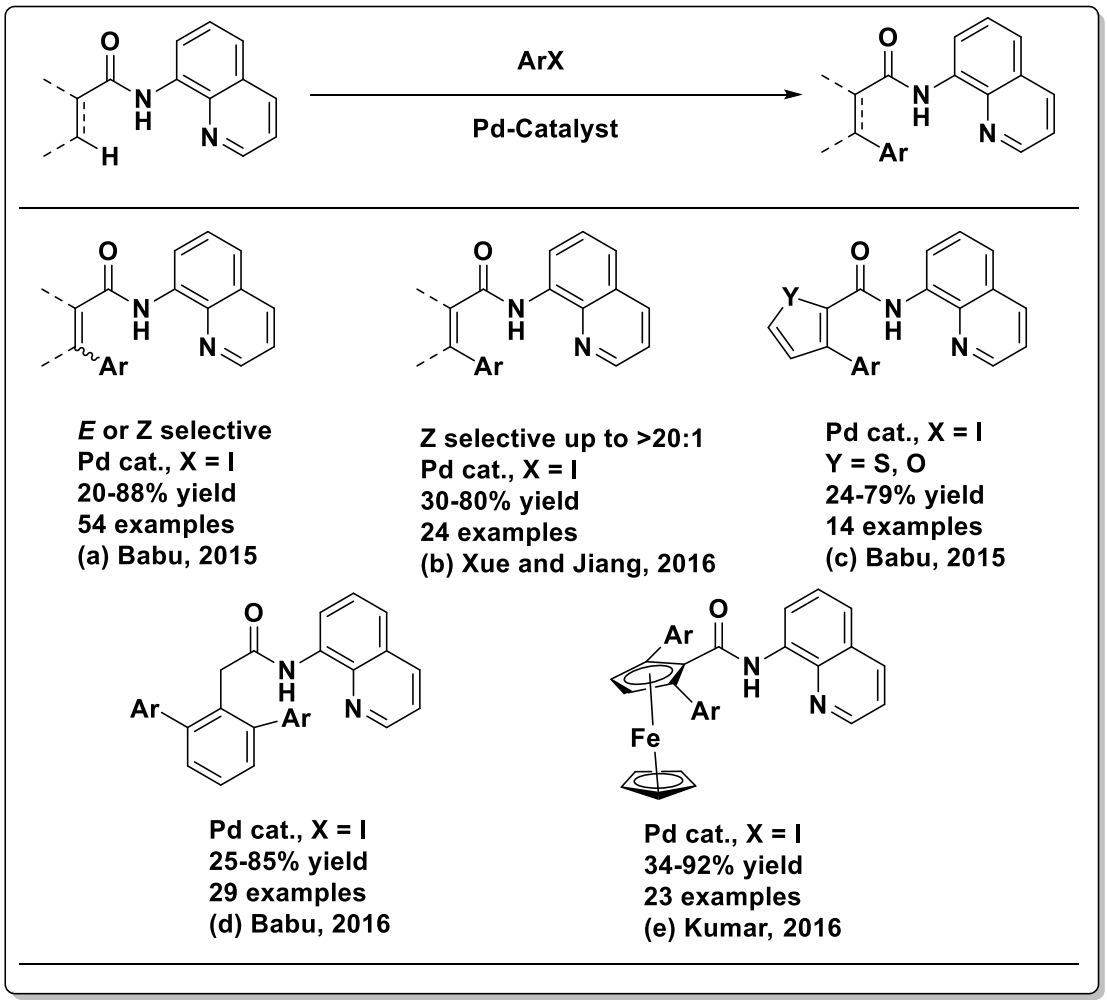
Scheme I.50. Pd-Catalyzed C(sp^2)−H and C(sp^3)−H Arylation Assisted by an 8-AQ Auxiliary (Daugulis, 2005)

In terms of Pd-catalyzed C(sp^2)−H arylation, the E- or Z selective arylation of acrylamides was reported by Babu[157](**Scheme I.51a.**) and by Xue and Jian[158] (**Scheme I.51b.**) using aryl iodides with the assistance of an 8-AQ auxiliary.

Babu also reported the use of the same directing group in the Pd-catalyzed C3-arylation of thiophene and furan-2-carboxamides[159](**Scheme I.51c.**).

Babu even showed that arylacetamides containing an 8-AQ auxiliary provided the ortho arylation product of arylacetamides[160] (**Scheme I.51d.**).

The use of an 8-AQ directing group in the Pd-catalyzed C−H functionalization of ferrocene carboxamides was reported, which provided a range of diarylated ferrocene carboxamide derivatives[161] (**Scheme I.51e.**).



Scheme I.51. C(sp^2)−H Arylation Assisted by an 8-AQ Auxiliary

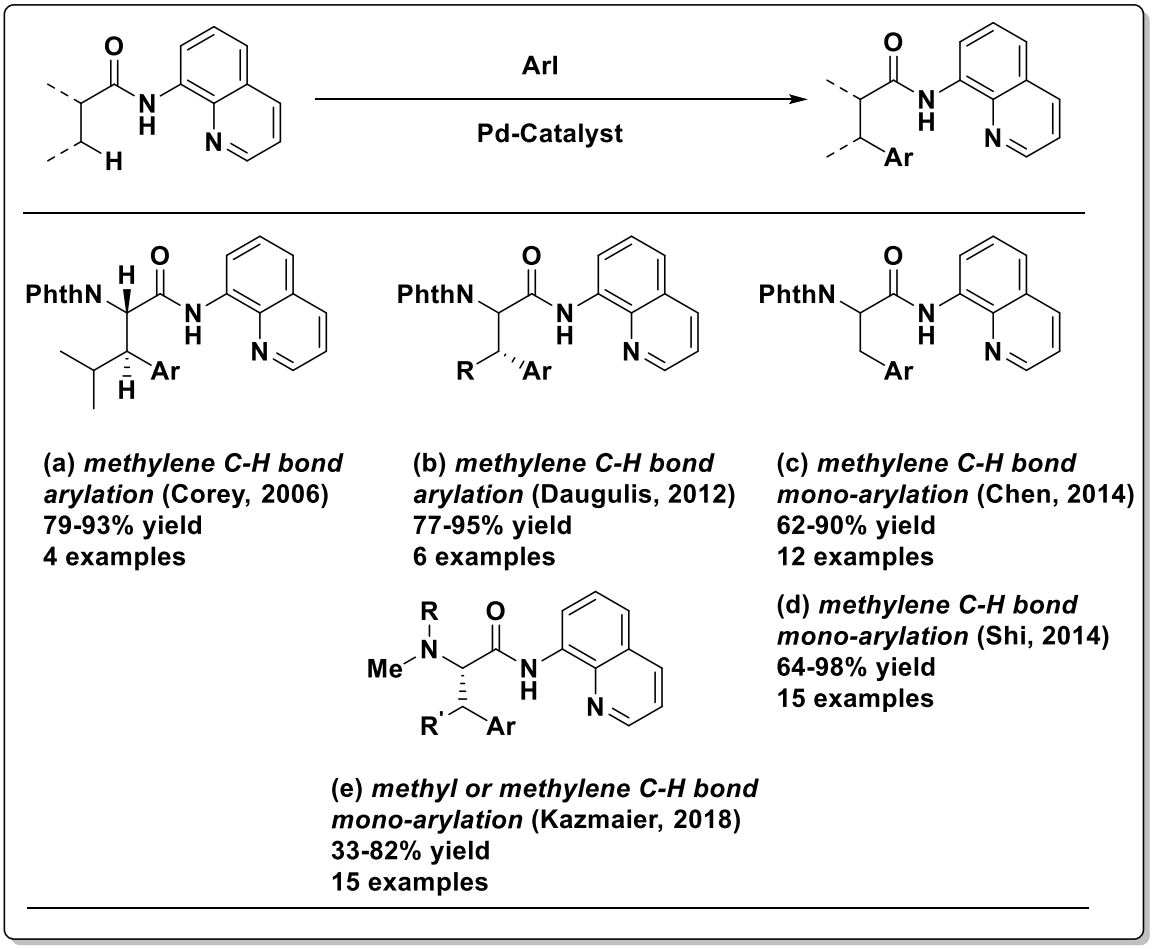
Because of the inertness of C(sp^3)−H bonds, researchers are more interested in the functionalization of such bonds rather than C(sp^2)−H bonds. Hence, a vast number of studies have appeared in the field of the C(sp^3)−H arylation of amides using Pd-catalyst and an 8-AQ auxiliary.

It is noteworthy that the second report on an N,N-bidentate directing group assisted C−H functionalization was reported by Corey in 2006 for the Pd-catalyzed *β*-C(sp^3)−H arylation of amino acid derivatives with the aid of an 8-AQ auxiliary (**Scheme I.52a.**).[162] Especially, the arylation proceeded at the unactivated methylene moiety.

A similar transformation was also examined by Daugulis for the stereoselective methylene C−H bond arylation of alanine derivatives[163] (**Scheme I.52b.**).

Later, Chen[164] (Scheme **I.52c.**) and Shi[165a,b,c](**Scheme I.52d.**) independently reported the methyl C−H mono arylation of alanine derivatives.

Kazmaier recently reported the *β*-C−H arylation of N-methylated amino acids and peptides[166] (**Scheme I.52e.**). This protocol is an effective tool for synthesizing natural products such as abyssenine A and mucronine E.

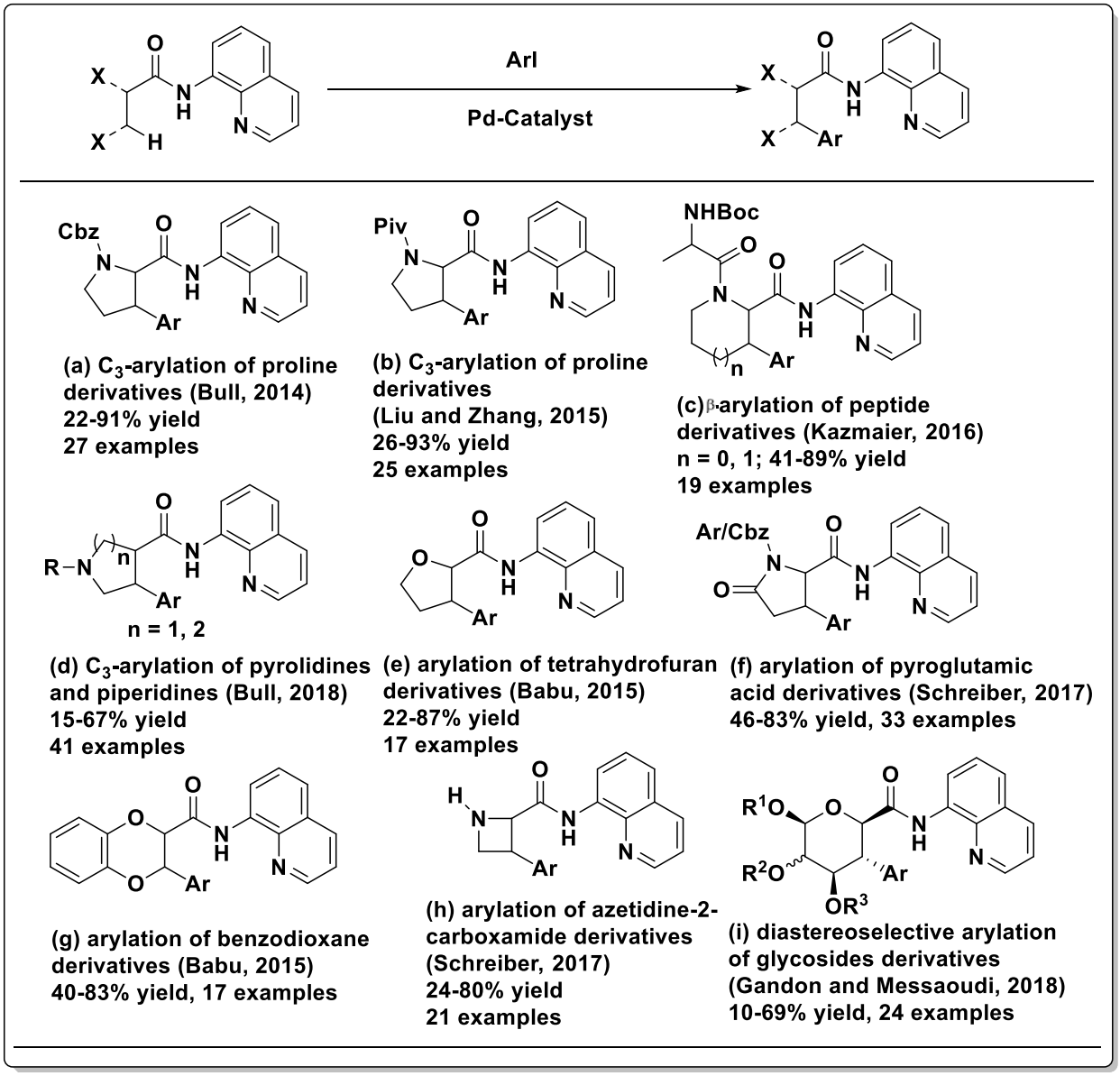


Scheme I.52. C(sp^3)−H Arylation of Amino Acid Derivatives Assisted by an 8-AQ Auxiliary

Because of the importance of saturated heterocycles in biological and medical chemistry, numerous reports on the Pd-catalyzed C(sp^3)−H arylation of aliphatic heterocyclic amides with the assistance of an 8-AQ auxiliary have been reported.

Bull[167a,b], and Liu/Zhang[168]separately delineated the C3-arylation of Cbz- or Piv-protected proline derivatives, respectively (**Scheme I.53a.**, **I.53b.**). The C(sp^3)−H arylation of further heterocyclic amides[169]includes the stereoselective *β*-arylation of peptide derivatives[170] (**Scheme**

I.53c.), the regio- and stereoselective C3-arylation of pyrrolidine and piperidine derivatives[171](**Scheme I.53d.**), the selective arylation of tetrahydrofuran[172](**Scheme I.53e.**), C3-arylation of pyroglutamic acid derivatives[173](**Scheme I.53f.**), and 1,4-benzodioxane derivatives[172](**Scheme I.53g.**).



Scheme I.53. C(sp^3)−H Arylation of Aliphatic Heterocyclic Amides Assisted by an 8-AQ Auxiliary

The expansion of Pd-catalyzed C(sp^3)−H arylation was implemented for the selective arylation of azetidine-2-carboxamides[174](**Scheme I.53h.**) for preparing a bicyclic azetidine derivative that has *in vivo* antimalarial activity.

Gandon and Messaoudi delineated the diastereoselective C−H arylation of glycosides[175] (**Scheme I.53i.**). A broad range of α- and β-glycosides participated in selective coupling with aryl iodides to fabricate a range of 3-arylglycosylamides.

I.B. Conclusion

Tremendous advances have taken place using transition-metal−NHC complexes to promote C-C cross coupling and C−H functionalization reactions. The unique electronic and steric properties of NHC ligands, in particular, their greater σ-donation than phosphine ligands and capacity to form well-defined complexes with diverse transition metals, combined with the stability to oxidative conditions have enabled the development of an array of novel C-C cross coupling and C−H functionalization reactions which resulted in significant improvements of the existing C-C cross coupling and C−H functionalization methods. There is a scarcity of types of NHC-Pd complex that have been tested both in C-C cross coupling and C−H activation reactions.

In spite of the significant research done in the area of DG mediated C-H arylation over the last two decades, a few but important limitations remain, such as the reactions require inert / dry atmosphere and the removal of DGs after the C-H activation step. Therefore, the development of structurally in-built (which itself can constitute a part of the target molecule), unique bidentate directing groups is always attractive strategy for various types of organic transformations especially at late stage to synthesize new molecular entities that might be employed in medicinal chemistry research.

We have tried to develop a catalyst which is effective for cross coupling reactions and C-H functionalization and also we have tried to find new directing group assisted reaction which would have the significance in terms of late-stage functionalization of biologically important motifs through diverse C-H activation, that too in industry-appealing, environmentally friendly solvent water (as in a typical process the solvent accounts for 50–60% of the entire mass).

I.C. References

References are given in the BIBLIOGRAPHY under chapter I (pp-181-190)