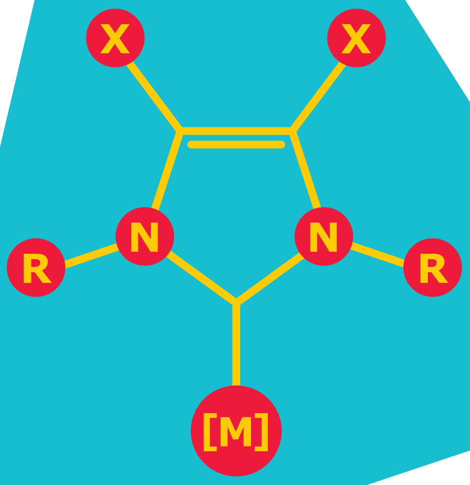
Buchwald–Hartwig and Suzuki–Miyaura Cross-Coupling using Pd–NHC (NHC = N-Heterocyclic Carbene) Complexes

Desk Reference

Sourav S. Bera and Michal Szostak



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Cross-Coupling using Pd–NHC Complexes

Desk Reference

Sourav Sekhar Bera. Sourav Sekhar Bera was raised in Haldia, India. Sourav received his Bachelor's degree in 2012 from the University of Calcutta. He completed his Master's degree in 2014 at the Indian Institute of Technology Kharagpur under Prof. Dipakranjan Mal. He then joined the Ph.D. program at the same institution under the supervision of Dr. Modhu Sudan Maji. His thesis title was 'High-Valent Cp*Co(III)-Catalyzed C–C and C–N Bond Formation via Directed C–H Functionalization'. In 2020, he moved to RWTH Aachen, Germany for his first postdoctoral study under Prof. Rene M. Koenigs, where he worked on metal-catalyzed carbene transfer reactions. Currently, he is working with Prof. Michal Szostak at Rutgers University-Newark. His research interests include the synthesis of new types of carbenes and their use in transition-metal-catalysis.

Michal Szostak. Szostak received his Ph.D. from the University of Kansas in 2009. After postdoctoral stints at Princeton University and University of Manchester, in 2014, he joined the faculty at Rutgers University, where he is currently Professor of Chemistry. His research group developed the concept of acyclic twisted amide bond activation. In 2022, he edited the book "Amide Bond Activation: Concepts and Reactions". His research group is focused on the development of new synthetic methodology based on transition-metal-catalysis, NHC ligands, inert bond activation, and application to the synthesis of biologically active molecules. He is the author of over 250 publications.

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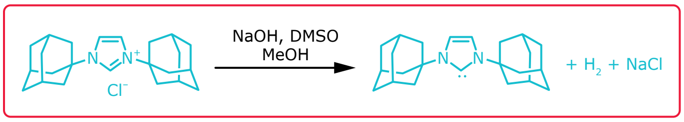
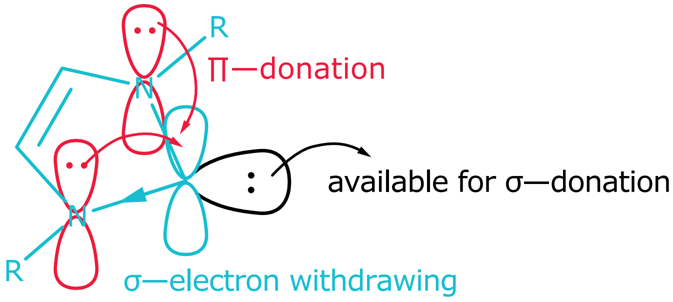
I. Introduction

N-Heterocyclic carbenes (NHCs) are singlet carbenes in which the divalent carbenic centre is directly associated with at least one nitrogen atom within the heterocycle. Although Wanzlick,[1] Öfele[2] and Lappert[3] studied NHCs in organometallic chemistry as early as in the 1960s, the renaissance of applications of NHCs commenced after the seminal report by Arduengo[4] on the extraordinary stability, isolation and storage of crystalline IAd.



In terms of electronic properties, N-heterocyclic carbenes are electron-rich and nucleophilic in nature. This is in sharp contrast to other carbenes, which are usually electrophilic. In the case of NHCs, the carbene center is stabilized by the combined effects of σ-electron-withdrawing and π-electron-donating nitrogen atoms.[5] In terms of steric properties, Arduengo-type NHCs are described as umbrella shaped vs. cone shaped phosphine ligands, which leads to vastly distinct effects in transition-metal-catalysis.[5-7]



Considering electronic and steric properties, NHCs are broadly classified into several subgroups:

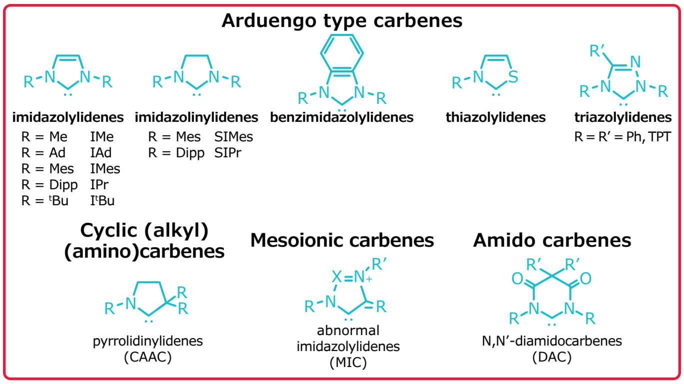
(1) Arduengo type carbenes—NHCs bearing two heteroatoms adjacent to the carbene centre.

(2) Cyclic amino carbenes—cyclic carbenes bearing only one nitrogen atom adjacent to the carbene centre.

(3) Mesoionic carbenes—carbenes where canonical resonance structures are mesoionic.

(4) Amido carbenes—carbenes where one of the nitrogen atoms is attached to a carbonyl group.

Electronic properties of Arduengo type carbenes can be tuned by varying the nature of the azole ring in the following order of electron-donicity: imidazoline > imidazole > benzimidazole.

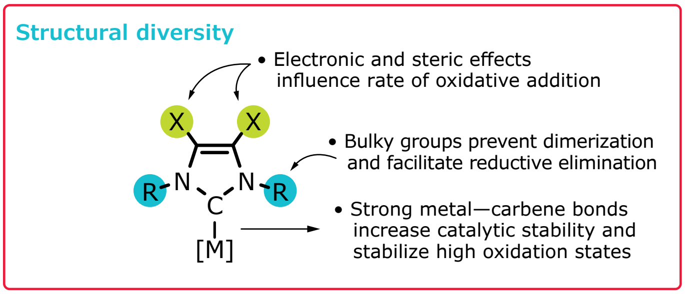


In this guide, our focus is on NHCs and NHC–metal complexes that are commercially available and readily accessible to a wide range of interested synthetic chemists. For discussion of other classes of carbenes, the reader is encouraged to consult several excellent reviews on these topics.[6]

2. Properties of NHCs

2.1. Coordination of NHCs to Transition Metals

Metal–NHCs have become one of the most popular classes of catalysts in modern chemical synthesis due to strong metal–carbene bonds, ease of synthesis and structural diversity. The strong σ-donor properties of NHCs supersede phosphines, which are the most prevalent class of ancillary ligands in transition-metal-coordination chemistry.



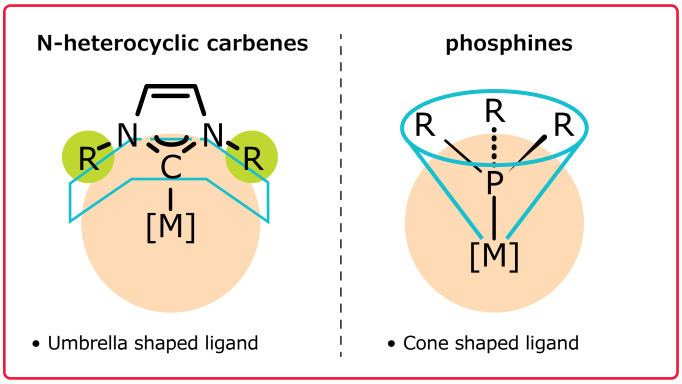
Structural diversity

- Electronic and steric effects influence rate of oxidative addition
- Bulky groups prevent dimerization and facilitate reductive elimination
- Strong metal—carbene bonds increase catalytic stability and stabilize high oxidation states

2.2. Difference in Steric Properties

N-heterocyclic carbenes are sterically distinct from phosphines. The steric effect of phosphines can be generalized as cone-shaped. In this geometric arrangement, the steric bulk expands away from the metal centre and away from the coordination sphere. In contrast, in most cases, NHCs can be described as umbrella-shaped. In this geometry, N-wingtips are expanded towards the metal centre and towards the coordination sphere, providing a significantly higher steric impact than phosphine ligands. The pendant

N-wingtip groups play a major role on the reactivity of metal centers due to the intrinsic geometry of NHCs. The NHC architecture provides additional opportunities to tailor ligand properties in catalysis. Furthermore, in contrast to phosphines, bulky NHCs are highly anisotropic and rotation around the N-wingtips can often happen to minimize the steric clash of the metal–carbene bond with substituents.[7]



2.3. Difference in Electronic Properties

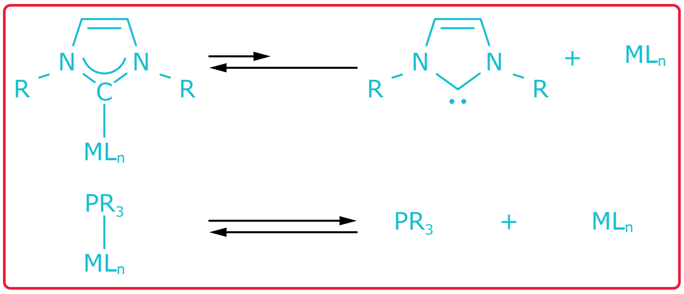
N-heterocyclic carbenes are characterized by stronger bonds with metals than phosphines. In NHCs, the electron donating ability depends on three factors: (1) L → M σ-donation, (2) M → L π*-backbonding, (3) L → M π-donation. L–M π-donation accounts for about 15–20% of the overall contribution. σ-Donation is the key factor in establishing the strength of metal–carbene bonds. NHCs are generally much better σ-donors than even the most basic phosphines. The electronic parameters of NHCs are quantified through TEP values (TEP = Tolman Electronic Parameter). TEP values of NHCs can be compared with representative phosphine ligands to determine the electronic contribution to the metal centre.

L = NHC	ν_{CO} (E) (cm^{-1})	L = phosphine	ν_{CO} (E) (cm^{-1})
IMes	2051	PPh3	2069
IPr	2052	PMe3	2064
IPr*	2053	P^tBu3	2056

Table 1. Carbonyl Bands (cm^{-1}) in $[Ni(CO)_3L]$ Complexes in CH_2Cl_2.[5,8]

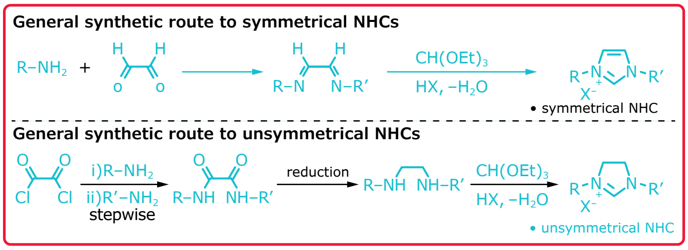
2.4. Stability of Metal–NHC Complexes

Since metal–carbene bonds are more stable than metal–phosphine bonds, metal–ligand dissociation in metal–NHC complexes is minimized. The high stability of metal–NHC bonds is an important consideration in catalysis.



2.5. Synthesis of NHC Salts

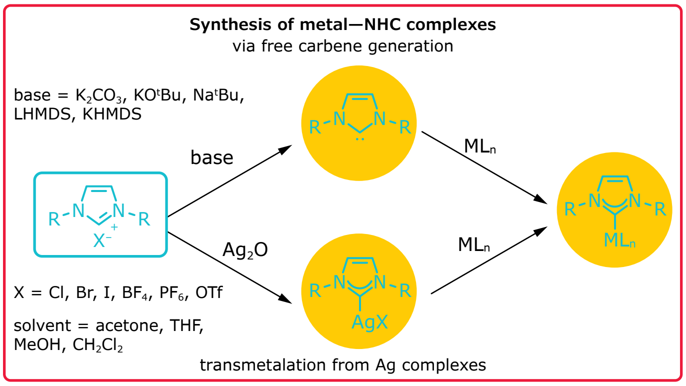
The vast majority of common NHC ligand precursors are now commercially available (see List of NHC Ligands). These ligands are also readily accessible by several synthetic routes, including the synthesis of symmetrical and unsymmetrical imidazolium salts.[9]



2.6. Synthesis of Metal–NHC Complexes

Metal–NHC complexes are conveniently synthesized via free carbene route from the corresponding azolium salts using suitable base followed by the addition of a metal precursor. In an alternative popular and operationally-simple route, metal–NHC complexes are synthesized by transmetallation from silver–NHCs.[10] More recently, "weak base route" using weak bases has gained significant attention due to practical advantages of this protocol.[11]

At present, a range of accessible NHC complexes continues to grow at an impressive rate due to the ease of synthesis and the diversity of accessible metal–NHC complexes. In 2023, a wide range of NHC–metal complexes is accessible for all transition metals relevant to modern catalysis and the toolbox has been expanding to main group elements.[12]



3. Palladium–NHC Complexes in Catalysis

Palladium–NHC complexes can be classified according to their structure.[13] There are three main classes from the standpoint of cross-coupling:

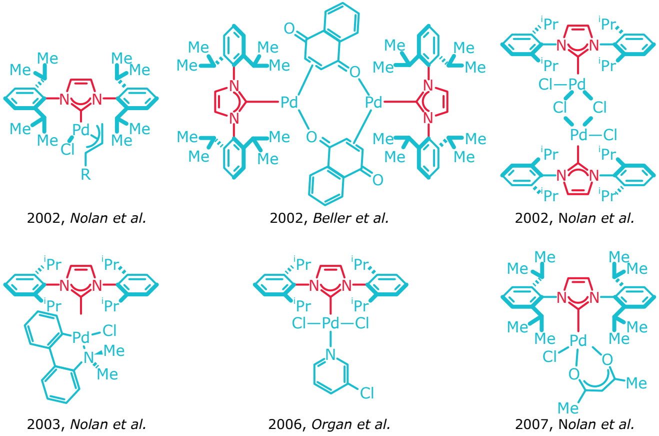
(1) Well-defined, air- and moisture-stable Pd(II)–NHCs. This method is recommended for all applications in cross-coupling.

(2) In situ generated Pd–NHC complexes. This method is recommended for rapid screening of NHC salt precursors.

(3) Well-defined and highly reactive Pd(0)–NHCs. This method is recommended for advanced users to tailor the reactivity in select cases.

The most useful are well-defined Pd(II)–NHCs. These complexes are stabilized by spectator ancillary ligands, such as allyl, amines, heterocycles, and activated in situ to monoligated Pd(0)–NHCs. Well-defined Pd(II)–NHCs permit for an operationally-simple, bench-top reaction set-up using the optimal 1:1 Pd to ligand ratio. These Pd(II)–NHC complexes routinely allow one to use low catalyst loading at a range of temperatures in different solvents. Crucially, Pd(II)–NHC complexes typically show higher reactivity in cross-coupling reactions than the in situ formed Pd–NHCs.

Examples of Pd(II)—NHC and Pd(0)—NHC catalysts



2002, Nolan *et al.*

2002, Beller *et al.*

2002, Nolan *et al.*

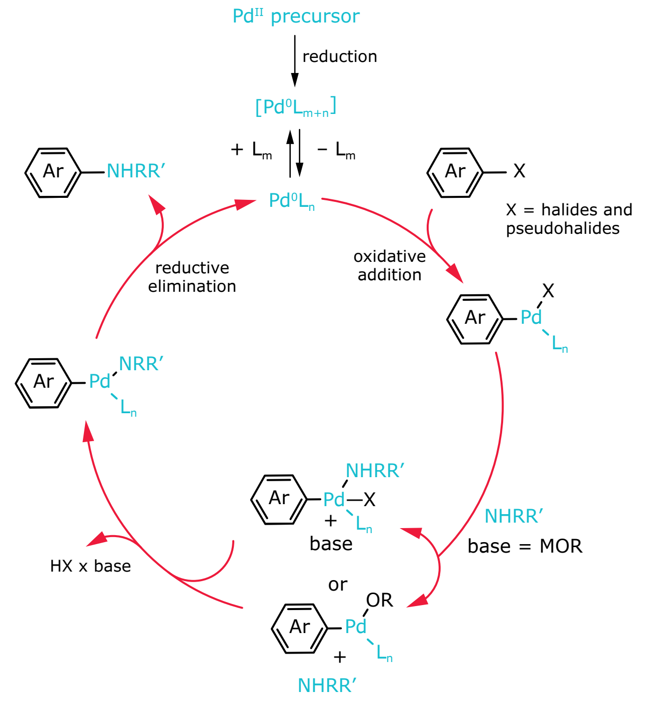
2003, Nolan *et al.*

2006, Organ *et al.*

2007, Nolan *et al.*

4. Pd–NHC Complexes in Buchwald-Hartwig Cross-Coupling

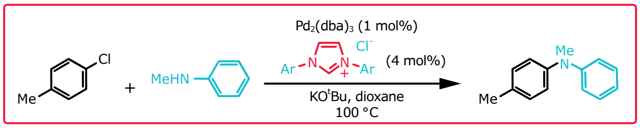
The palladium-catalyzed cross-coupling of organohalides with amines (Buchwald–Hartwig amination) is recognized as one of the most useful methods for the synthesis of amines.[14] In the last two decades, Pd–NHC complexes have provided synthetically useful and complementary reactivity to Pd–phosphine complexes in Buchwald–Hartwig amination.

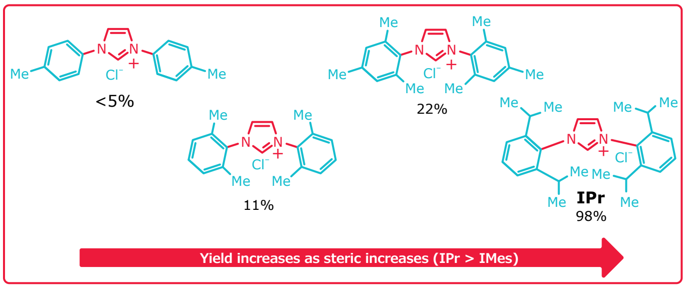


4.1. Mechanism

After the initial activation of Pd(II) to Pd(0), the monoligated Pd–NHC complex becomes the main active catalyst.[15] Oxidative addition of the aryl halide to Pd(0)–NHC occurs, which is followed by ligation of the amine. Deprotonation in the presence of a base produces the Pd–amide complex. Subsequently, reductive elimination takes place to provide the amination product and regenerate the active Pd(0)–NHC species. Common side reactions include β-hydride elimination, followed by reductive elimination to produce the hydro-dehalogenated arene and the corresponding imine. The strongly s-donating NHCs are advantageous over Pd–phosphine systems in that they allow to engage challenging electrophiles under mild reaction conditions.

4.2. First Example of Buchwald-Hartwig Amination using Pd–NHCs





The first highly reactive Pd–NHC catalyst system in Buchwald-Hartwig cross-coupling was reported by the Nolan group in 1999.[16] They identified sterically hindered NHCs to replace the well-established at that time phosphine ligands. This study reported general and efficient conditions (KOᵗBu, dioxane, 100 °C) for the amination of challenging aryl chlorides, bromides and iodides using Pd–NHC system formed in situ from $Pd_2(dba)_3$ and IPr·HCl in the presence of potassium tert-butoxide as a base. The yield of the coupling product increased with the steric bulk of the NHC wingtips, and IPr was the most reactive ligand for the cross-coupling. In terms of scope, primary and secondary aromatic and aliphatic amines were coupled selectively with an aryl partner. This was also the first report of amination of aryl chlorides with acyclic primary and secondary alkylamines, attesting to the high reactivity of Pd–NHC complexes in this amination manifold.

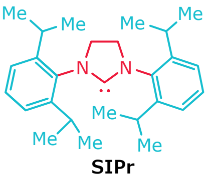
4.3. Catalytic Improvements using Pd–SIPr

Subsequently, the Hartwig group developed a mild amination of aryl chlorides by identifying 1,3-bis(2,6-diisopropylphenyl)4,5-dihydroimidazolium salt, SIPr·HBF_4, as an effective ligand precursor.[17] The use of saturated imidazolinylidene NHC significantly increased the catalytic efficiency of the reaction. At elevated temperatures (100 °C), turnover numbers as high as 5,000 were obtained for the cross-coupling of morpholine with chlorotoluene as a representative unactivated aryl chloride. The dimeric Pd catalysts, $Pd_2(dba)_3$ and $Pd(dba)_2$, were equally effective as precursors for this amination. Milder bases such as Cs_2CO_3 and K_3PO_4 were not efficient under these conditions. For interested users, it should be noted that imidazolin-2-ylidene NHCs are typically less stable than the corresponding imidazol-2-ylidenes.

$$\text{ArCl} + \text{NHRR'} \xrightarrow[\text{NaO}^t\text{Bu, DME; rt – 100 °C}]{\text{Pd(dba)}_2\ (0.02–2\ \text{mol\%}),\ \text{NHC x HBF}_4\ (0.08–2\ \text{mol\%})} \text{Ar—NRR'}$$

- Ar = unactivated aryl, heteroaryl
- NHRR′ = 1° and 2° aryl, 2° acyclic and cyclic alkyl; imino
- TON up to 5,000

NHC =



SIPr

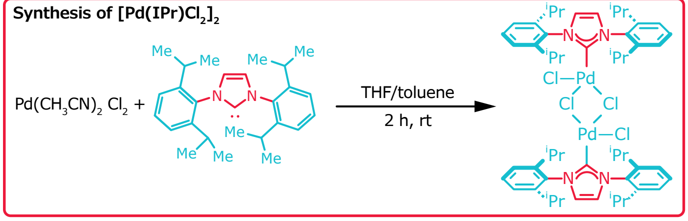
4.4. Well-Defined Air-Stable Pd(II)–NHC Precatalysts

In 2002, the Nolan group reported well-defined, air-stable Pd(II)–NHC complex, $[Pd(IPr)Cl_2]_2$, for the amination of aryl chlorides and bromides using primary and secondary amines.[18] This Pd(II)–NHC dimer showed outstanding activity even under air using DME as a solvent and KOtAm as a base. This catalyst was found to be air- and moisture-stable, and the reactions could be carried out with undried solvents. In addition to aromatic amines, heterocyclic amines, such as chloropyridines were also efficient substrates.

$$\text{ArX} + \text{NHRR'} \xrightarrow[\text{KO}^t\text{Am, DME; 80 °C}]{[\text{Pd(IPr)Cl}_2]_2\ (0.5\ \text{mol\%})} \text{Ar—NRR'}$$

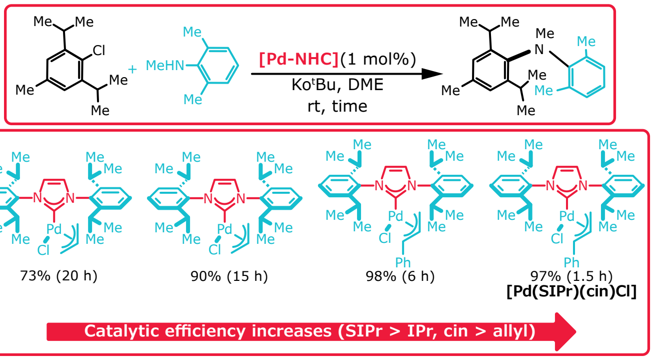
X = Cl, Br

Synthesis of $[Pd(IPr)Cl_2]_2$



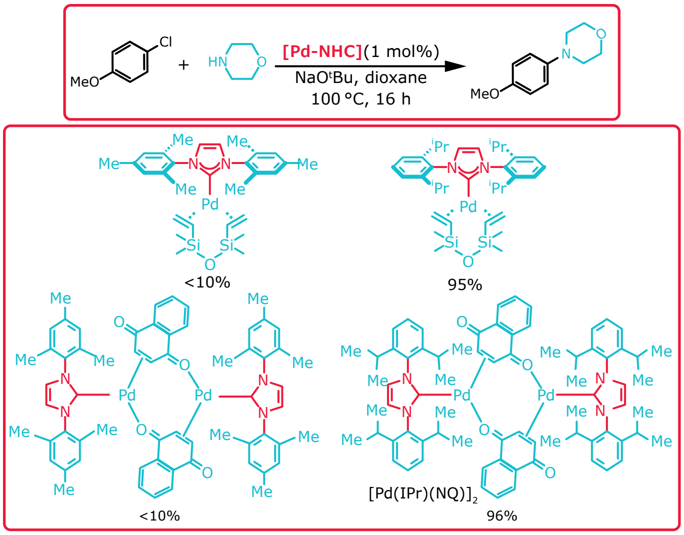
4.5. Palladium-Allyl Complexes

At the same time, the Nolan group introduced a series of air- and moisture-stable [Pd(NHC)(allyl)Cl] complexes bearing 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene and 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene NHC ligands.[19] Substitution of the allyl ligand was also varied, including allyl, crotyl, prenyl and cinnamyl. The catalytic efficiency of these Pd(II)–NHC complexes in Buchwald Hartwig amination depended on both ligands, namely the type of NHC and the allyl group. [Pd(SIPr)(cin)Cl] was found to be the most active catalyst in Buchwald-Hartwig amination. Notably, these allyl complexes showed extraordinary efficiency in Buchwald-Hartwig aminations. Reactions of heterocyclic halides were possible at 0.001 mol% loading at room temperature. These catalysts were also highly effective for aminations of sterically-hindered substrates.



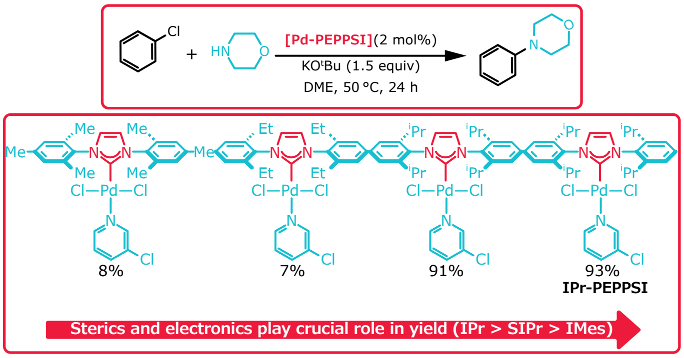
4.6. Pd(0)–NHC Complexes

In 2005, the Gooβen group reported that naphthoquinone-supported Pd(0)–NHC complexes, $[Pd(NHC)(NQ)]_2$, were highly effective catalysts for amination of aryl halides.[20a] These catalysts were originally developed by the Beller group for the Suzuki–Miyaura cross-coupling of aryldiazonium salts.[20b] Complexes containing sterically-demanding IPr ligand with 2,6-diisopropyl N-wingtips gave excellent yields in Buchwald-Hartwig amination at 0.5% catalyst loading using KOH in dioxane at 100 °C. Complexes with less bulky IMes ligands were significantly less reactive, mirroring the effects observed by Nolan in the in situ formed Pd–NHCs. These Pd(0)–NHC complexes are air- and moisture-stable and should be considered as an alternative to other classes of Pd–NHCs in Buchwald-Hartwig amination. However, in most cases, well-defined Pd(II)–NHCs show higher reactivity.



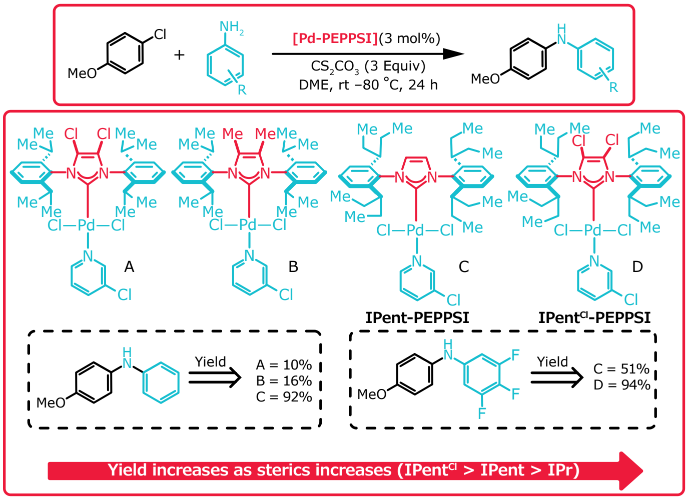
4.7. Pd–PEPPSI Complexes

In 2008, the Organ group reported the use of their Pd–PEPPSI complexes in Buchwald-Hartwig amination reactions.[21] The efficiency of these readily available and user-friendly catalysts increases with the steric bulk at the NHC wingtips. These catalysts were compatible with highly electron-rich aryl halides and highly hindered coupling partners. Typical conditions involved 2 mol% catalyst loading in DME in the presence of tBuOK at 23–50 °C. The authors also demonstrated the cross-coupling using mild carbonate base, Cs_2CO_3, in DME at 80 °C for select substrates.



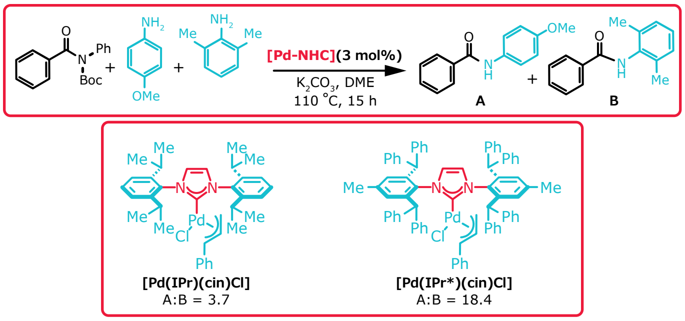
4.8. Room Temperature Amination of Deactivated Anilines

In 2014, as a further modification of their Pd–PEPPSI complexes, the Organ group developed Pd–PEPPSI–IPent catalysts (IPent = 1,3-bis-(2,6-di-3-pentylphenyl)-imidazol-2-ylidene) featuring ortho-sterically-branched aromatic N-wingtips.[22] This strategy was employed to further increase the steric bulk of NHC ligands. The Pd–PEPPSI–IPent system worked impressively well for the amination of highly deactivated anilines using mild carbonate Cs_2CO_3 base at 80 °C. Furthermore, the analogue bearing chloro-substitution at the NHC backbone, Pd–PEPPSI–IPentCl was so effective that it promoted cross-coupling of highly deactivated fluoroanilines at room temperature. Owing to the high reactivity, the IPent class of catalysts should be included in screening of challenging substrates in Buchwald-Hartwig amination. Related classes of catalysts with ortho-branching of aromatic wingtips include ITent[22b,c] and IPr*/IPr# Pd(II)–NHC catalysts. Note that in select cases BIAN catalysts provide additional advantages.[22c,d]



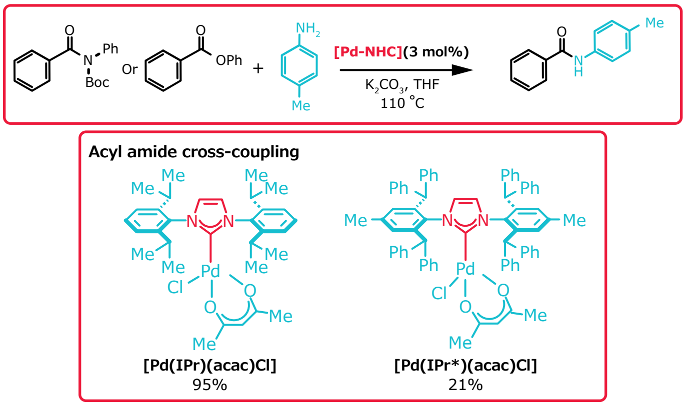
4.9. Acyl Buchwald-Hartwig Amination of Amides

Acyl Buchwald-Hartwig cross-coupling of amides represents an expedient route to higher order amides in a formal transamidation of the amide bond via versatile acyl-metal intermediates.[23a-d] Szostak, Nolan, Poater et al reported Buchwald-Hartwig amination of sterically-hindered amides using air- and moisture-stable [Pd(NHC)(allyl)Cl] complexes.[23c] It was observed that the steric bulk of the NHC ligand played an important role in product formation.[23e,f] The use of sterically-demanding [Pd(IPr*)(cin)Cl] resulted in the selective coupling of deactivated anilines in the presence of sterically hindered anilines. The acyl Buchwald-Hartwig cross-coupling of amides works well with Pd(II)–NHC allyl[23a] and Pd–PEPPSI systems.[23b]



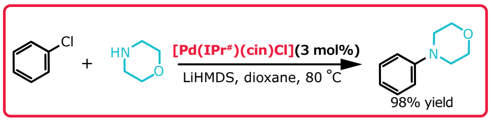
4.10. [Pd(IPr)(acac)Cl] Complexes

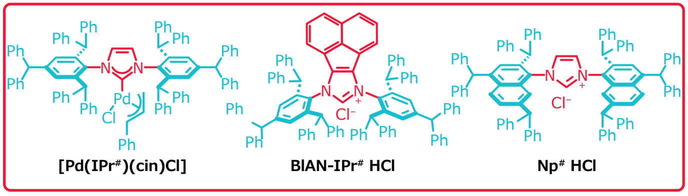
In 2007, the Nolan group reported a practical synthesis of [Pd(NHC)(acac)Cl] complexes featuring acetylacetonate ligand.[24a,b] These air- and moisture-stable complexes are readily prepared on >10 g scale by reacting the imidazolium precursors and $Pd(acac)_2$ in dioxane at 100 °C. [Pd(IPr)(acac)Cl] showed high reactivity in large scale (10 mmol) Buchwald-Hartwig aminations using KO^{t}Bu and DME at 50 °C.[24b] In 2019, Szostak, Nolan et al showed the utility of [Pd(IPr)(acac)Cl] in acyl Buchwald-Hartwig cross-coupling of amides and esters.[24c] These catalysts have specific advantages, including mild carbonate bases and water-free reaction conditions, thus eliminating hydroxide formation. Furthermore, the facile synthesis of [Pd(NHC)(acac)Cl] permits for in situ ligand screening to identify the optimal NHC for a specific set of substrates in Buchwald-Hartwig amination.



4.11. IPr# Ligands in Buchwald-Hartwig Cross-Coupling

Szostak group reported IPr# family of ligands based on direct peralkylation of anilines.[25] These ligands are modular, sterically-hindered and flexible around the metal center. These [Pd(IPr#)(cin)Cl] and IPr#–PEPPSI complexes are air- and moisture-stable and show excellent reactivity in Buchwald Hartwig cross-coupling reactions.

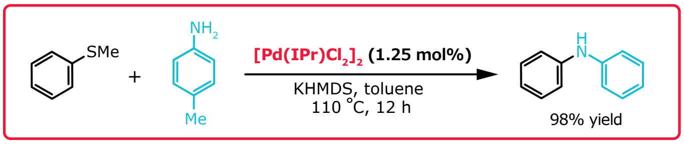


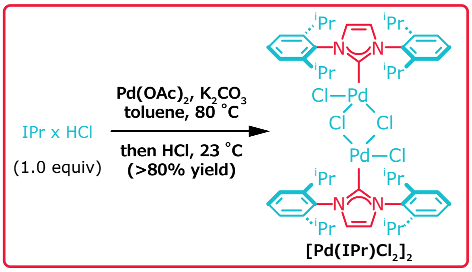


[Pd(IPr#)(cin)Cl] **BIAN-IPr# HCl** **Np# HCl**

4.12. Buchwald-Hartwig Amination of Aryl Thioethers

The cross-coupling of readily available C–S electrophiles is a powerful alternative to aryl halides in Buchwald-Hartwig amination reactions.[26a,b] Szostak, Nolan, Poater et al reported activation of C–S bonds for Buchwald-Hartwig amination using [Pd(NHC)Cl2]2 complexes.[26c] [Pd(IPr)Cl$_2$]$_2$ can be easily synthesized from Pd(OAc)$_2$ and IPr·HCl in a one-pot operation.[26d] These catalysts showed excellent reactivity in the cross-coupling of aryl sulfides through the oxidative addition of aryl C–S bonds. Notably, alkyl thiols could also be used as cross-coupling partners to replace the amine counterpart under similar conditions.



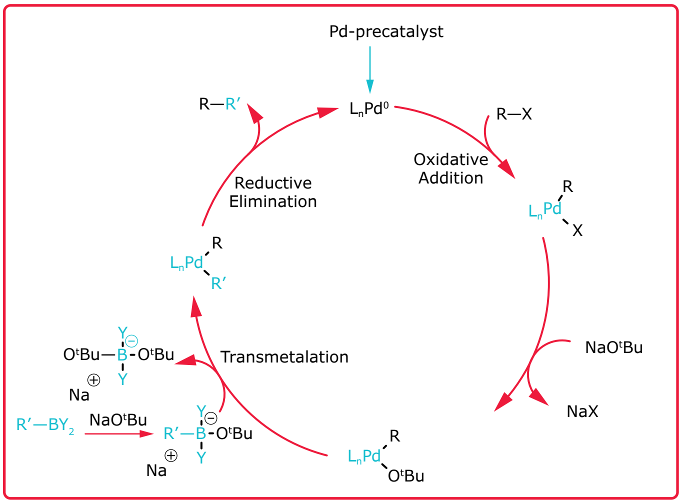


[Pd(IPr)Cl$_2$]$_2$

5. Pd–NHC Complexes in Suzuki–Miyaura Cross-Coupling

The palladium-catalyzed Suzuki-Miyaura cross-coupling is the most powerful and synthetically useful cross-coupling method in academic and industrial research.[27] In this reaction, Pd–NHCs provide distinct advantages over other catalytic systems, including Pd–phosphines.

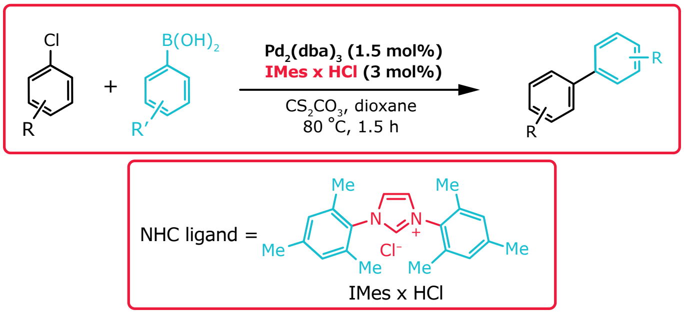
5.1. Mechanism



The Suzuki-Miyaura cross-coupling involves C–C bond formation between an organoboron compound and an organic halide. The active catalyst is a Pd(0) species which is typically generated in situ from a Pd(II) precursor. The reaction is initiated by oxidative addition of the organohalide. This species reacts with a base, followed by transmetallation with the organoboron compound. Reductive elimination affords the cross-coupling product and regenerates the Pd(0) precatalyst. It is generally accepted that the monoligated Pd(0)–NHCs are the active catalytic species in the Suzuki-Miyaura reactions catalyzed by Pd–NHCs.[28]

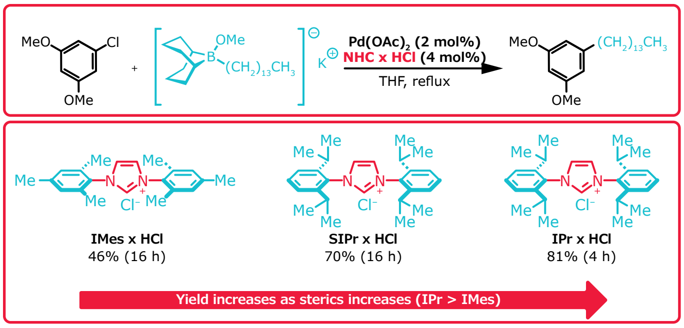
5.2. First Example of Suzuki–Miyaura Cross-Coupling using Pd–NHCs

The use of N-heterocyclic carbenes as ancillary ligands in the Suzuki-Miyaura cross-coupling was first reported by the Nolan group in 1999.[29] The catalyst generated in situ from IMes·HCl and $Pd_2(dba)_3$ or $Pd(OAc)_2$ was proved to be a highly efficient system for the cross-coupling of aryl chlorides with aryl boronic acids. Cesium carbonate was identified as the optimal base. Organic bases were ineffective for this reaction as precipitation of palladium black was immediately observed.



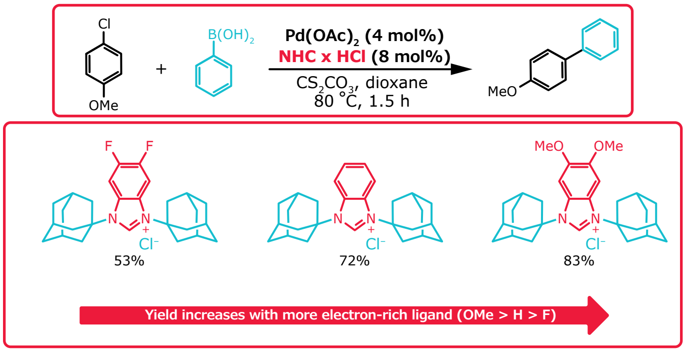
5.3. Suzuki–Miyaura Cross-Coupling with Alkyl-9-BBN Reagents

In 2001, the Fürstner group reported the Suzuki-Miyaura cross-coupling of aryl halides with alkyl organoboranes using 9-R-9-BBN reagents.[30] Optimization of different NHCs identified IPr·HCl as the most reactive NHC ligand in the presence of KOMe as a base. This method was extended to allyl and alkynyl 9-BBN reagents. The reaction was compatible with different electron-poor and electron-rich electrophiles, attesting the high reactivity of Pd–NHCs.



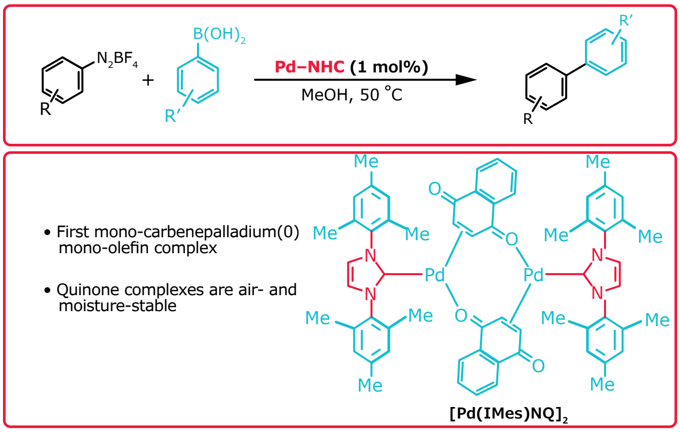
5.4 Electronic Effects of NHCs in Suzuki–Miyaura Cross-Coupling

In 2005, the Organ group reported the Suzuki-Miyaura cross-coupling promoted by a series of electronically-differentiated N-heterocyclic carbene ligands derived from N,N-di-adamantyl-benzimidazolium.[31] More electron-rich NHCs were more effective due to enhancing the rate of oxidative addition. The reductive elimination step was dependent on the steric environment rather than the electronic nature of the NHC ligand.



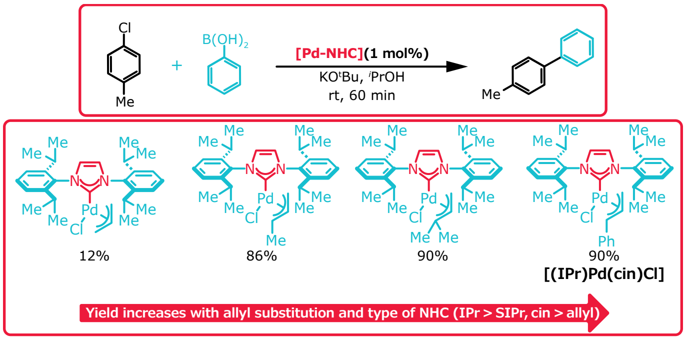
5.5. Pd(0)–NHC Complexes

In 2002, the Beller group reported monocarbene–palladium(0) complexes using benzoquinone and naphthoquinone as ancillary ligands.[20b] The quinone moiety showed bidentate bonding, which contributed to the air- and moisture-stability of these Pd(0)–NHC complexes. These $[Pd(IMes)BQ]_2$ and $[Pd(IMes)NQ]_2$ complexes were highly effective in the Suzuki-Miyaura cross-coupling of arenediazonium salts with aryl boronic acids in MeOH at 50 °C.



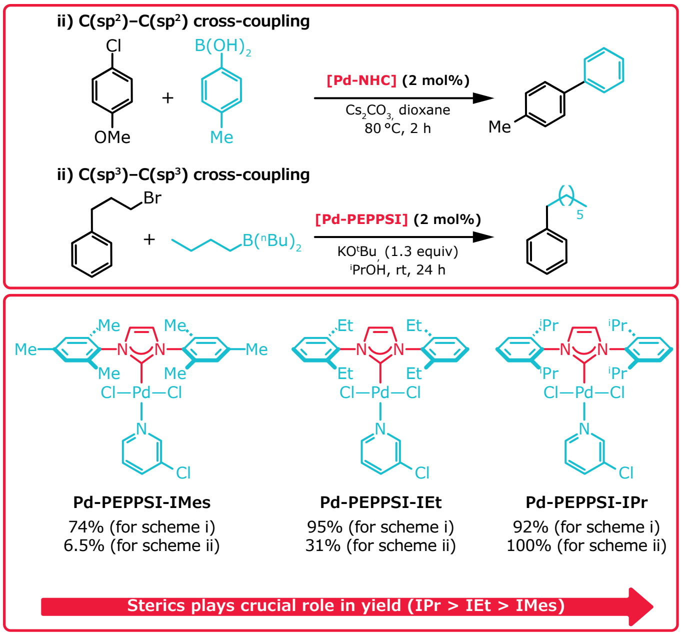
5.6. Palladium-Allyl Complexes

In 2006, the Nolan group reported a series of air- and moisture-stable [(NHC)Pd(allyl)Cl] complexes for the Suzuki-Miyaura cross-coupling of aryl chlorides.[32] Substitution at the allyl ligand played a significant role in improving the catalytic efficiency in the cross-coupling. The authors proposed that increasing the dissymmetry of the allyl moiety vs. the palladium centre resulted in the more facile activation step to give the monoligated Pd(0). The reactivity of [(IPr)Pd(cin)Cl] complex was impressive, allowing for the Suzuki-Miyaura cross-coupling of a wide range of aryl chlorides, bromides and triflates at room temperature at low catalyst loading (0.05 mol%). These catalysts were also found to be compatible with the cross-coupling of highly sterically-hindered aryl chlorides and aryl boronic acids even with 50 ppm catalyst loading at 80 °C.



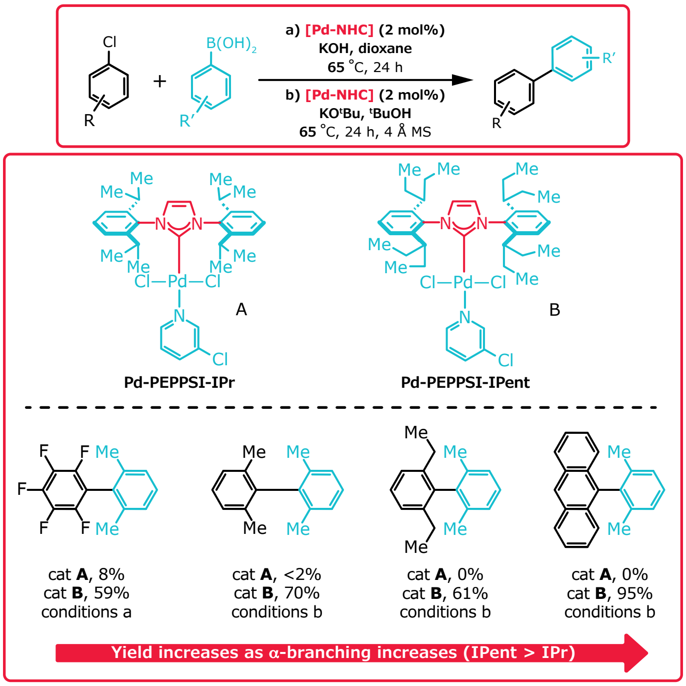
5.7. Pd–PEPPSI Complexes

In 2006, the Organ group reported air- and moisture-stable Pd–PEPPSI complexes featuring 3-chloropyridine as an ancillary ligand for the Suzuki-Miyaura cross-coupling of aryl halides.[33a] The most reactive complex contained IPr as the NHC ligand. Optimization of different Pd–PEPPSI catalysts showed that sterics played a crucial role in catalytic efficiency. This class of catalysts is distinguished by facile synthesis from NHC salts, $PdCl_2$ and 3-Cl-py, air- and moisture-stability and high reactivity after activation to monoligated Pd(0)–NHC. Later, the same group reported a protocol for the challenging alkyl–alkyl Suzuki-Miyaura cross-coupling catalyzed by IPr–Pd–PEPPSI.[33b]

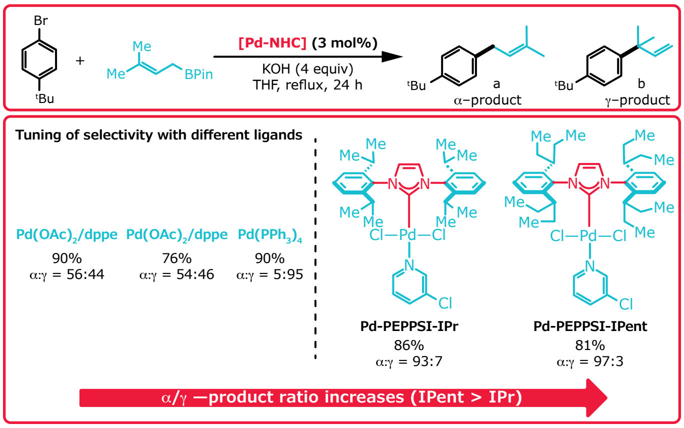


5.8. Pd–PEPPSI–IPent Complexes

In 2009, the Organ group developed Pd–PEPPSI–IPent complexes featuring flexible steric bulk at the ortho-substituted wingtips.[34] Flexible sterics by the branched sec-pentyl group is important for accommodating oxidative addition and reductive elimination steps of the cross-coupling. The IPent catalyst was found to be more reactive than other Pd–PEPPSI complexes. In particular, the Pd–PEPPSI–IPent was effective for highly challenging cross-coupling of sterically hindered aryl halides with aryl boronic acids to form tetra-ortho-substituted biaryls.

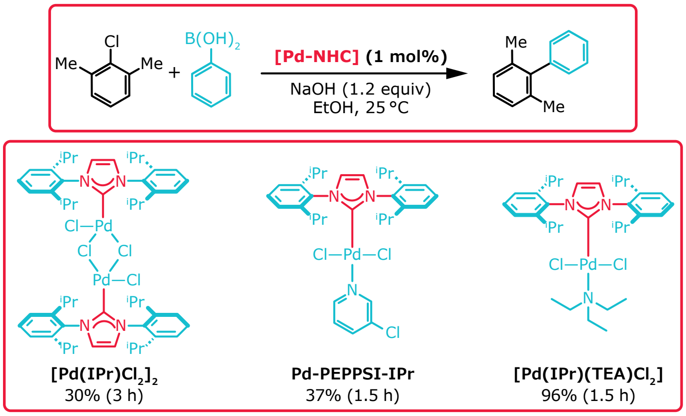


The same group reported highly selective Suzuki-Miyaura allylation of aryl bromides using Pd–PEPPSI–IPent. This catalyst provided high α/γ-selectivity in the cross-coupling using allyl boronic acid pinacol esters.[35] In contrast, Pd–phosphine catalytic systems afforded the mixture of isomers or γ-selectivity. The observed regioselectivity of Pd–PEPPSI–IPent was attributed to the significant steric bulk of the NHC ligand.

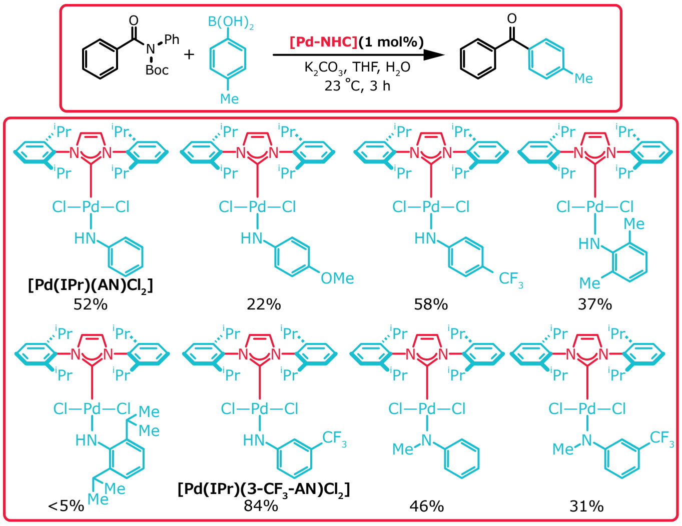


5.9. [Pd(NHC)(amine)Cl$_2$] Complexes

In 2011, the Navarro group reported Pd(II)–NHC complexes supported by triethylamine (TEA). These [Pd(NHC)(TEA)Cl$_2$] complexes were successfully employed in the Suzuki-Miyaura cross-coupling.[36a] A comparative study showed that [Pd(NHC)(TEA)Cl$_2$] complexes exhibited higher activity than the corresponding Pd–PEPPSI. The improved catalytic activity was attributed to faster dissociation of TEA and stabilization of monoligated Pd(0)–NHC by recoordination of amine under the reaction conditions used.

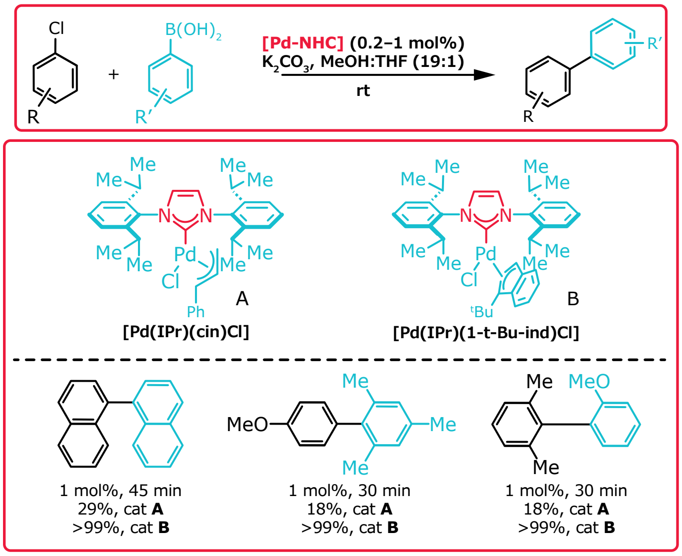


In 2021, the Szostak group reported air- and moisture-stable [Pd(NHC)(AN)Cl$_2$] complexes based on anilines (AN = aniline) as an unexplored class of stabilizing ligands in Pd–NHC cross-coupling catalysis.[36b] These precatalysts show significantly higher stability than [Pd(NHC)(TEA)Cl$_2$] complexes and can be activated in situ under both mild and strong base conditions. The high activity of [Pd(NHC)(AN)Cl$_2$] has been demonstrated in the Suzuki-Miyaura cross-coupling of aryl halides and aryl ammonium salts, where the most reactive is the analogue bearing 3-CF3-aniline as ancillary ligand, ([Pd(IPr)(3-CF3-AN)Cl$_2$]). This catalyst showed higher reactivity than the corresponding Pd–PEPPSI complexes.[36c,d]



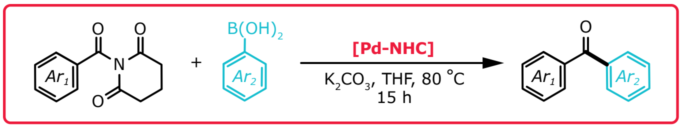
5.10. [Pd(IPr)(1-t-Bu-ind)Cl] Complex

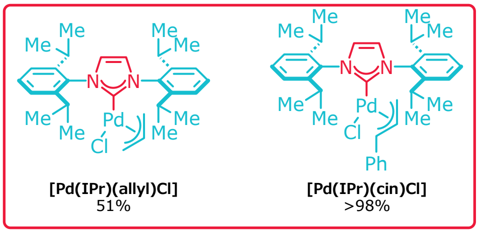
In 2015, the Hazari group reported [Pd(IPr)(1-t-Bu-ind)Cl] as an air- and moisture-stable allyl-based Pd(II)–NHC precatalyst for the Suzuki-Miyaura cross-coupling.[37a,b] The authors showed that this catalyst is more effective than [(IPr)Pd(cin)Cl] under tested reaction conditions. This improvement in catalytic activity was attributed to the avoidance of inactive Pd(I) dimers, (μ-1-t-Bu-ind)(μ-Cl)Pd$_2$(IPr)$_2$, formed in situ from [Pd(IPr)(1-t-Bu-ind)Cl], compared to (μ-cin)(μ-Cl)Pd$_2$(IPr)$_2$ from [(IPr)Pd(cin)Cl]. A subsequent study by Szostak, Nolan, Poater et al determined the relative reactivity of [(IPr)Pd(cin)Cl], [Pd(IPr)(1-t-Bu-ind)Cl] and [(IPr)PdCl]$_2$ precatalysts, showing that the commercially available Pd dimer, [(IPr)PdCl]$_2$, is the most reactive under tested strong and mild base conditions.[37c]



5.11. Acyl Suzuki-Miyaura Cross-Coupling of Amides

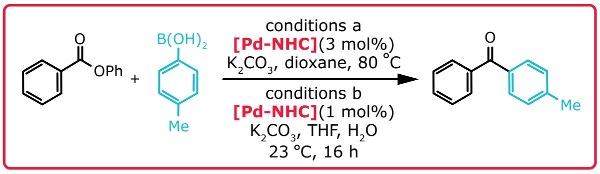
Acyl Suzuki-Miyaura cross-coupling represents a valuable approach to the catalytic synthesis of ketones.[38a] In 2017, the Szostak group reported an the Suzuki-Miyaura cross-coupling of N-acyl-glutarimides by N–C bond activation using Pd(II)–NHC complexes.[38b] Air- and moisture-stable [Pd(IPr)(cin)Cl)] was identified as the most reactive allyl-based Pd(II)–NHC complex.[38b-d] The method provided a significant advantage over Pd–phosphine systems in amide N–C bond activation in terms of substrate scope generality, mild reaction conditions and low catalyst loading. Subsequently, Pd–PEPPSI and [Pd(IPr)(1-t-Bu-ind)Cl] catalysts were found highly reactive in the same reaction manifold with differences in catalyst activation and reaction scope.[38e-f]

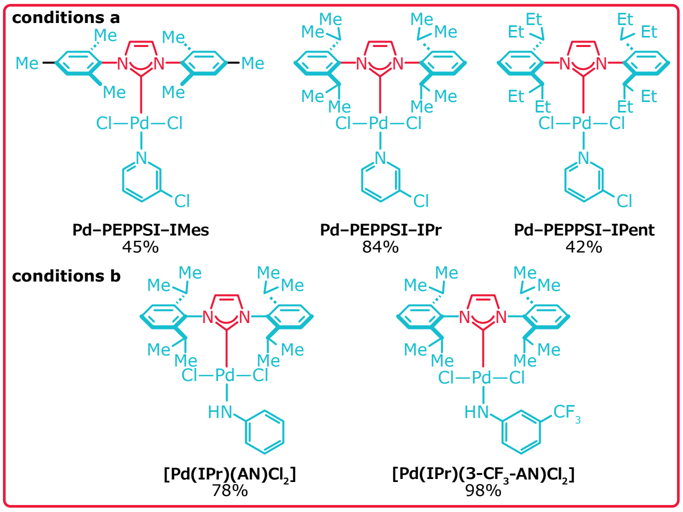




5.12. Acyl Suzuki–Miyaura Cross-Coupling of Esters

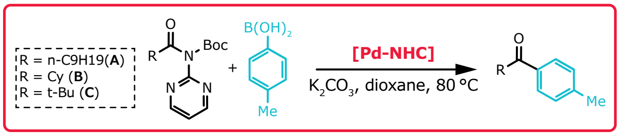
In 2017, the Newman group reported acyl Suzuki-Miyaura cross-coupling of phenolic esters.[39a] They identifed [Pd(IPr)(cin)Cl)] as the optimal catalyst for the cross-coupling in THF at 90 °C. Phenolic esters represent an attractive class of acyl electrophiles for cross-coupling reactions with reactivity complementary to activated amide derivatives.[39b] Later, the Szostak group reported Suzuki-Miyaura cross-coupling of the same class of substrates using Pd–PEPPSI catalysts.[39c,d] It was observed that Pd–PEPSI–IPr was more efficient than both less sterically-demanding Pd–PEPPSI–IMes and bulky Pd–PEPPSI–IPent. The optimized conditions featured mild base K_2CO_3, which allowed tolerance of a variety of functional groups. Comparative study between [Pd(IPr)(cin)Cl)], Pd–PEPPSI and [Pd(IPr)(1-t-Bu-ind)Cl] revealed that these precatalysts may react through the common palladium hydroxy dimers, $[Pd(IPr)(m\text{-}OH)Cl]_2$, under aqueous conditions. $[Pd(IPr)(AN)Cl_2]$ are another class of Pd(II)–NHC precatalysts that are highly effective for the cross-coupling of amide and ester electrophiles.[36b]

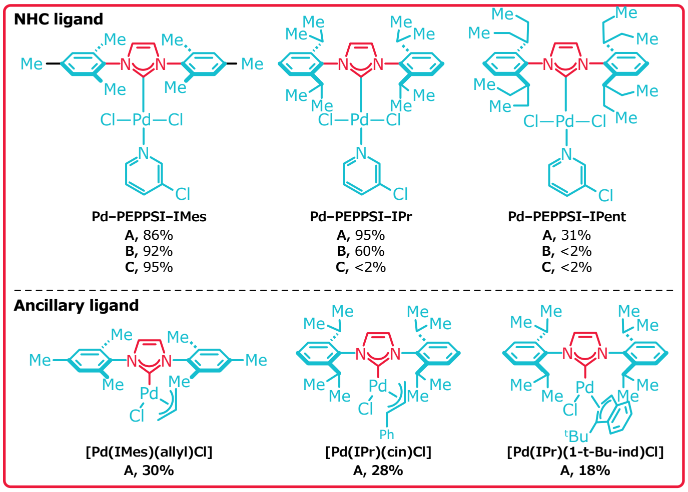




5.13. Acyl Suzuki–Miyaura Cross-Coupling of Alkyl Amides

The challenging Suzuki-Miyaura acyl cross-coupling of aliphatic amides was reported by the Szostak group.[40] Among different classes of Pd–NHC catalysts tested, Pd–PEPPSI–IPr and Pd–PEPPSI–IMes proved to be the best for this reaction. The reactivity of electrophiles was correlated with the steric demand of NHC ligands. More sterically hindered 2° and 3° amides gave significantly better results with Pd–PEPPSI–IMes, while Pd–PEPPSI–IPr was the best catalyst for 1° electrophiles. This reaction is an example of reactivity tuning by steric match between the substrate and NHC ligands as well as the importance of selecting an appropriate spectator ancillary ligand in acyl Suzuki-Miyaura cross-coupling.





6. Pd–NHCs in Other Cross-Coupling Reactions

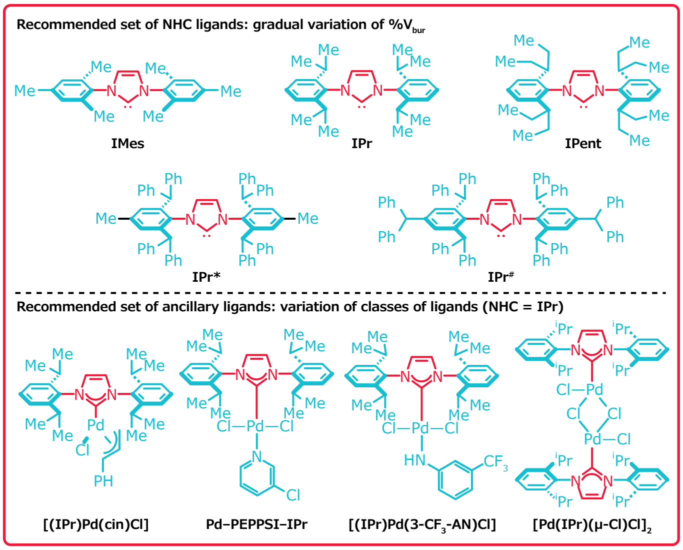
Apart from Buchwald-Hartwig and Suzuki-Miyaura reactions, Pd–NHC catalysts have been employed in a range of other cross-couplings, such as Sonogashira,[41] Heck,[42] Negishi,[43] Hiyama,[44] Kumada[45] and Stille[46] cross-coupling. The reader is encouraged to consult leading references[41–46] and excellent reviews[47,13] on these topics.

7. Recommendation

The development of "universal catalysts" that can efficiently catalyze cross-coupling reactions of challenging substrates in a variety of reactions using air-, moisture-stable catalysts under operationally-simple conditions and at low catalyst loading has been the central topic of chemistry research in the past five decades. To date, there is a consensus that there is not a single catalyst that is equally effective for all palladium-catalyzed cross-coupling reactions. The use of Pd–NHC catalysts is significantly advantageous compared to other ligands owing to electronic and steric properties of NHCs that are distinct from the most commonly used phosphine ligands.[5–7]

NHC Ligand. The use of bulky NHC ligands should be a regular practice for developing palladium-catalyzed Buchwald-Hartwig and Suzuki-Miyaura cross-coupling reactions. Strongly s-donating, bulky NHCs ligands prevent dimerization of the active catalyst and contribute to making the catalyst stable. Electron-rich, bulky NHC ligands are responsible for faster oxidative addition and reductive elimination steps. This design is particularly effective with "bulky-yet-flexible-ligands" that accommodate to the catalytic pocket for specific steps of the catalytic cycle. However, it is also well-recognized that some cross-coupling reactions and specific substrates require lower steric demand of NHC ligands.

A general recommendation is to screen several different NHC ligands with varying steric demand, as measured by buried volume (%Vbur).[7,48] For example, a standard set for screening should include IMes, IPr, IPent, IPr*, IPr#, or a simplified set of IMes, IPr, IPr#, where the range of buried volume extends from low to high in the presence of ortho-substitution of the aromatic wingtips that are critical for effective cross-coupling reactions.



Throw-Away Ligand. Another critical selection is the spectator, "throw-away" ligand that stabilizes the Pd–NHC complex. These ligands render the cross-coupling reactions more effective due to more reactive preformed Pd(II)–NHCs and considerably more user-friendly conditions by permitting operationally-simple, bench-top set-up. In principle, these "throw-away" ligands are removed under the reaction conditions to give the same catalytically active monoligated Pd(0)–NHC species. However, it is now well-recognized that there are considerable variations in the reaction efficiency using different "throw-away" ligands. The ease of formation of Pd(0) affects the overall catalytic efficiency. Activation of Pd(II)–NHC precursors proceeds with different efficiency depending on base, solvent, additives, and temperature. Re-coordination of the ancillary ligand affects the stability of the active Pd(0) species, depending on the reaction and the reaction conditions.

A general recommendation is to screen Pd(II)–NHCs with various classes of ancillary ligands with different donors. A standard set for screening should include allyl, heterocycle and halide-based Pd(II)–NHCs, for example, [Pd(IPr)(cin)Cl], [Pd–PEPPSI], [Pd(IPr)(3-CF3-AN)Cl$_2$] and [Pd(NHC)(μ-Cl)Cl]$_2$. These catalysts are characterized by different stability, activation pathways and rates of activation. These Pd(II)–NHCs allow for highly practical reaction set-up in moisture and air-insensitive conditions at room temperature with low catalyst loadings, often with deactivated substrates.

8. Conclusions

The development of new Buchwald-Hartwig and Suzuki-Miyaura cross-coupling reactions always demands extensive screening of catalysts and reaction conditions. We hope this manual will encourage the range of interested chemists to take a full advantage of all classes of Pd–NHC catalysts to promote their desired cross-coupling transformations.

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