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Latest Developments in Palladium and Nickel-Catalyzed Cross-Couplings for Aryl Chlorides: Suzuki-Miyaura and Buchwald-Hartwig Reactions

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Abstract:

Palladium- and nickel-catalyzed cross-couplings are powerful methods for constructing C-C and C-N bonds, particularly through Suzuki-Miyaura and Buchwald-Hartwig reactions. Although aryl iodides, bromides, and triflates are the most commonly used substrates, aryl chlorides are less frequently utilized due to their lower reactivity. However, they are appealing because they are readily available and inexpensive. This short review highlights recent developments in Suzuki-Miyaura and Buchwald-Hartwig cross-couplings of aryl chlorides, using both homogeneous and heterogeneous catalysis with palladium and nickel.

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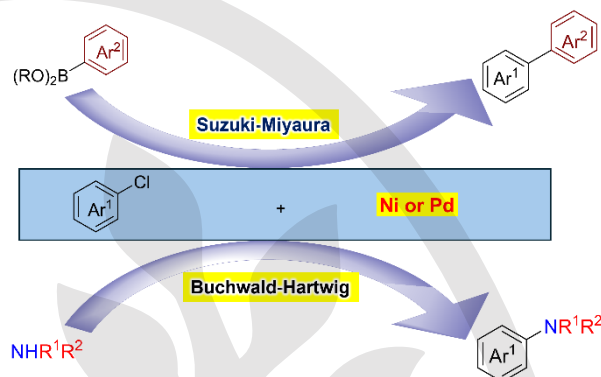
Latest Developments in Palladium and Nickel-Catalyzed Cross-Couplings for Aryl Chlorides: Suzuki-Miyaura and Buchwald-Hartwig Reactions

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Abstract: Palladium- and nickel-catalyzed cross-couplings are powerful methods for constructing C-C and C-N bonds, particularly through Suzuki-Miyaura and Buchwald-Hartwig reactions. Although aryl iodides, bromides, and triflates are the most commonly used substrates, aryl chlorides are less frequently utilized due to their lower reactivity. However, they are appealing because they are readily available and inexpensive. This short review highlights recent developments in Suzuki-Miyaura and Buchwald-Hartwig cross-couplings of aryl chlorides, using both homogeneous and heterogeneous catalysis with palladium and nickel.

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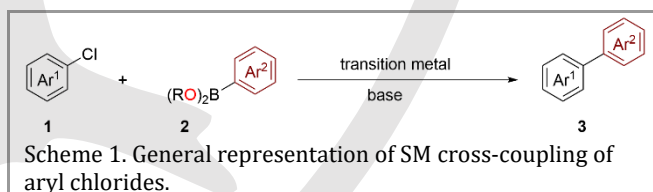
Key words: Palladium catalysis, nickel catalysis, Cross-coupling, Aryl chloride, Buchwald-Hartwig amination, Suzuki-Miyaura coupling, homogeneous catalysis, heterogeneous catalysis

1. Introduction

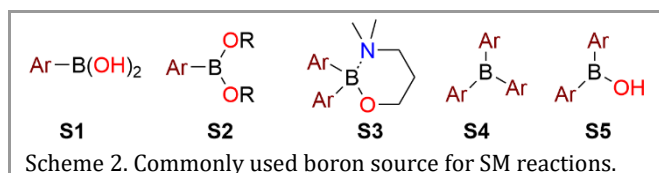
Cross-coupling reactions are extensively studied and are critical in chemical synthesis. Among these reactions, Suzuki-Miyaura (SM)¹, which forms C-C bonds, and Buchwald-Hartwig (BHA)², which forms C-N bonds, are widely used in both academia and industry. Palladium and nickel are the primary transition metals used in these two cross-coupling processes. Although SM and BHA reactions are among the most significant, they are mainly applied to aryl iodides, bromides, and triflates as substrates. Aryl chlorides, despite being more readily available and cost-effective,

are less reactive, limiting their application in cross-coupling reactions. However, because they are cheap and easily sourced, their use in cross-couplings is highly desirable, particularly for industrial applications. Indeed, there are reports of aryl chlorides in these reactions. Earlier studies (pre-2013) on SM and BHA reactions with aryl chlorides focused primarily on electron-deficient substrates, as summarized by Fu,^{1a} Buchwald,^{1b} Hartwig,^{2l} and Han^{1j}. Significant advancements in cross-couplings involving electron-rich, electron-neutral, electron-deficient, and heteroaryl chlorides have been made over the last decade. This short review summarizes recent (2013 onward) reports on SM and BHA reactions with aryl chlorides using both homogeneous and heterogeneous palladium and nickel catalysis.

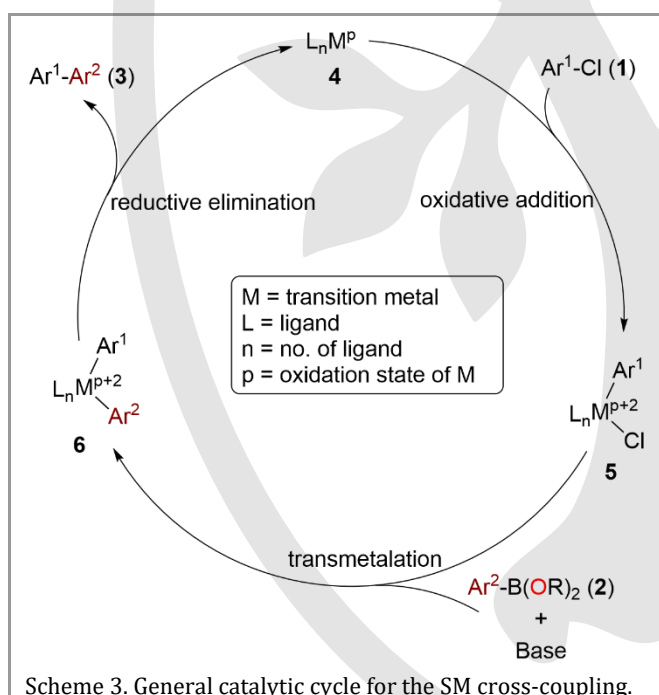
2. Suzuki-Miyaura Cross-Coupling



A transition metal-catalyzed Suzuki-Miyaura (SM) cross-coupling of aryl chlorides with arylboronic acids/esters is emerging as a powerful tool for constructing biaryl compounds (Scheme 1).¹ The SM cross-coupling is highly valuable because many arylboronic acids used as reactants are commercially available, inexpensive, and non-hazardous. Additionally, arylboronic acids are stable under heat, air, and moisture. Although arylboronic acids **S1** and their esters **S2** are typical coupling partners in the SM cross-coupling of aryl chlorides, many other boron sources are also listed in the literature, such as aryl borinates **S3**, triarylborane **S4**, and diarylborinic acid **S5** (Scheme 2).



SM cross-coupling involves three mechanistic steps: i) oxidative addition, ii) transmetalation, and iii) reductive elimination (Scheme 3). Owing to the low reactivity of aryl chlorides (BDE: 330 kJ/mol), the oxidative process becomes difficult; thus, oxidative addition typically becomes the rate-limiting step. To overcome the low reactivity of aryl chlorides, researchers have developed highly active transition-metal catalysts using bulky ligands. The addition of additives, such as TBAB or NaI, to the reaction mixture is another way to solve the issue of the low reactivity of aryl chlorides. TBAB can act as a phase transfer catalyst, and it could stabilize the transition metal nanoparticles by avoiding aggregation.³ The addition of NaI is reported to facilitate the reaction of aryl chlorides via the halide exchange.⁴ Additionally, the ligand designing might also assist in overcoming the low reactivity issue; for example, electron-rich ligands usually perform better in the oxidative addition of aryl chlorides than electron-deficient ligands.⁵ The presence of a suitable base makes the transmetalation step more accessible. Similarly, the presence of bulky ligands usually favors reductive elimination. In Section 2, recent examples of the SM cross-coupling of aryl chlorides using homogeneous (2.1, 2.3) and heterogeneous (2.2, 2.4) palladium (2.1-2) and nickel (2.3-4) catalysts are presented.

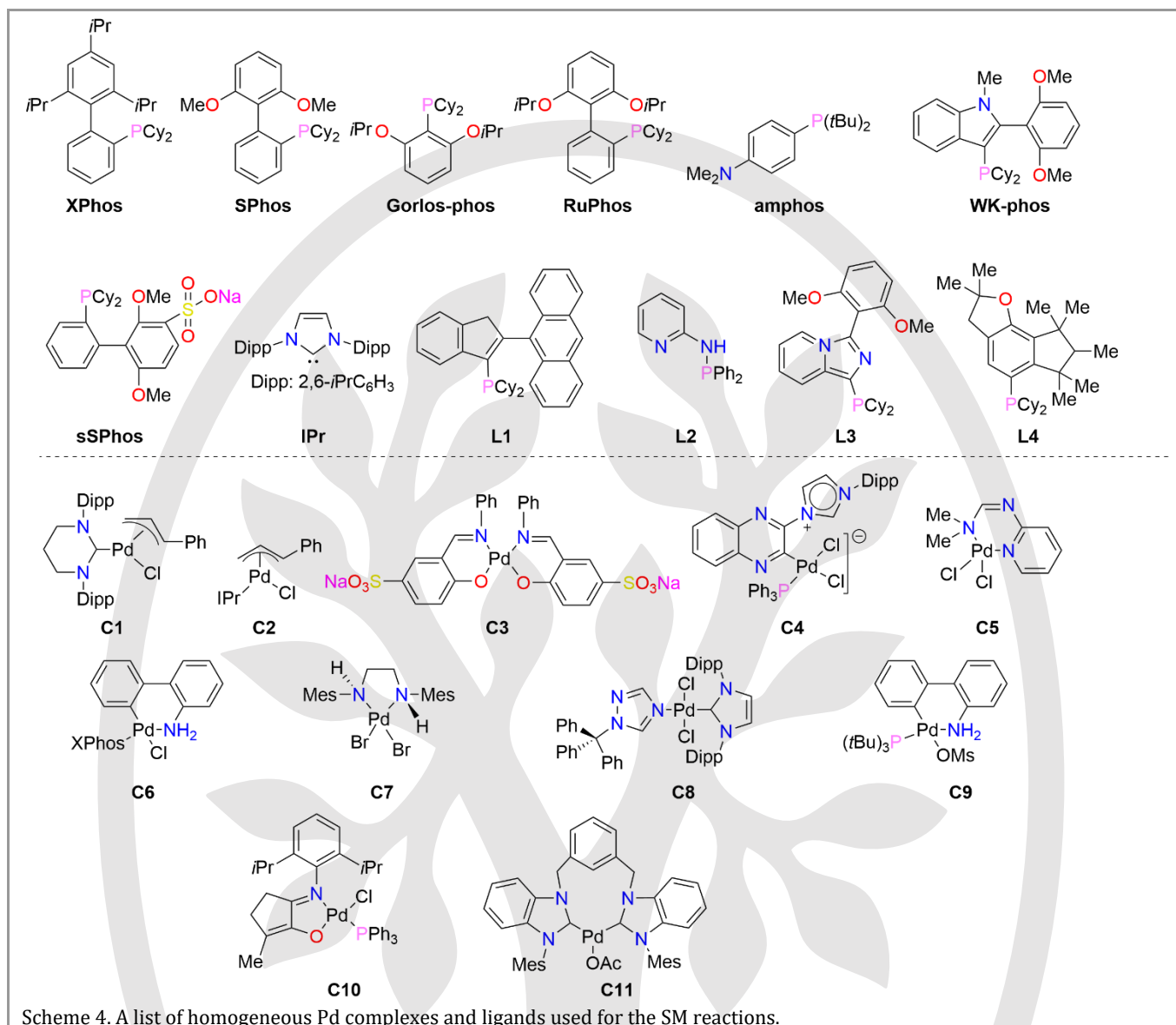


2.1. Homogeneous palladium catalysis

In 2013, Nechaev et al. developed a diaminocarbene palladium complex **C1** (Scheme 4) for the SM reaction.⁶ They performed the reaction of 2-chloropyridine and arylboronic acids in the presence of 0.5 mol% of **C1**. The addition of TBAB is essential for this transformation. The coupling products were obtained in 99% yield. In 2014, Balcells, Hazari, and Tilset group developed

Pd(IPr)(η^3 -cinnamyl)Cl complex **C2**.⁷ The SM coupling of tolyl chloride with phenylboronic acid proceeded in >99% yield within 30 min at 30 °C using 1 mol% of the palladium complex **C2**. During their mechanistic studies, they observed Pd(I)-dimeric complex **10**, which originated from the comproportionation reaction of Pd(II) and Pd(0) complexes (Scheme 5). This Pd(I)- μ -allyl dimer **10** was less reactive and provided only a 4% yield of biaryls under the same conditions using **C2**.

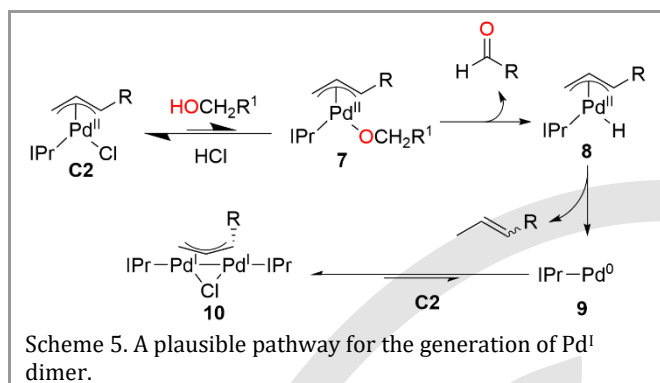
In 2015, Ayogu et al. prepared antimicrobial compounds via the SM cross-couplings using Pd₂(dba)₃ (1 mol%) and SPhos (2 mol%), and the corresponding products **13a** or **13b** were obtained in both 43% yields (Scheme 6).⁸ Li and Zhong et al. reported the SM cross-couplings of aryl chlorides with trialkyl- and triaryl-borane derivatives **S4**.⁹ They used Pd(OAc)₂ (2.5 mol%) as a metal source and RuPhos (5 mol%) as a ligand. They prepared the trialkyl boranes from the corresponding olefin and BF₃.Et₂O, and used them in the SM cross-couplings in one-pot. In this one-pot process, the products were obtained in an 86% yield. Das and coauthors applied a hydrophilic salen-Pd(II) complex **C3** (1 mol%) to the cross-couplings of aryl chloride and aryl boronic acid in water at 100 °C.¹⁰ The reaction of an electron-rich 4-chloroanisole with phenylboronic acid afforded 4-methoxybiphenyl in 93% yield, whereas the reaction of electron-deficient 4-chloronitrobenzene and phenylboronic acid gave only 45% yield of 4-nitrobiphenyl. This was improved by adding a phase-transfer catalyst, cetyltrimethylammonium bromide (CTAB), to afford the desired product in 96% yield. Zou, Tang, et al. used *O,N*-chelate-stabilized diarylborinates **S3** (Scheme 2) as reactants for SM coupling reactions. They used a mixture of Pd(OAc)₂/IPr/P(OPh)₃ in a 1:1:5 ratio as a catalyst precursor (Pd: 0.1 mol%).¹¹ The reaction of electron-rich or electron-deficient aryl chlorides and diarylborinates afforded the corresponding products in 70–99% yield, indicating that the reaction is less sensitive to an electronic variation on benzene rings. Unfortunately, the chemical yield decreased because of the steric hindrance of the substrates. For example, the reactions of 2-chlorotoluene and 2,6-dimethylchlorobenzene with diphenylborinate afforded biaryl compounds in 72 and 42% yields, respectively, with 1 mol% catalyst. Yu et al. reported the SM coupling by Pd(OAc)₂ (0.02 mol%) and a ligand **L1** (0.04 mol%) in toluene/*i*-PrOH/H₂O.¹² Heterocyclic aryl chlorides such as 2-chloropyridine, 3-chloropyridine, and 2-chloropyrazine were converted to the 84–95% yield. An intermediate for the synthesis of Boscalid **16** was produced in 91% yield via SM, and the TON of the catalyst reached 4550 (Scheme 7). Ren, Young, and Lang used *N*-diphenylphosphanyl-2-aminopyridine **L2** as a ligand and PdCl₂ (1.5 mol%) for the palladium-catalyzed SM cross-couplings of aryl chlorides.¹³ This reaction is applied to electron-deficient aryl chlorides only while the products were given in up to 98% yield. Reddy et al. developed a Zwitterionic Pd(II) complex **C4** (0.5 mol%) and utilized it for SM coupling of aryl or heteroaryl chlorides,¹⁴ where triphenylphosphine (PPh₃) was used as an additional ligand (2 mol%). The reaction of multiple heterocyclic aryl chlorides, including pyridine, pyrazine, quinoline, isoquinoline, and thiophene, afforded cross-coupling products **17–24** in 80–95% yield (Scheme 8).



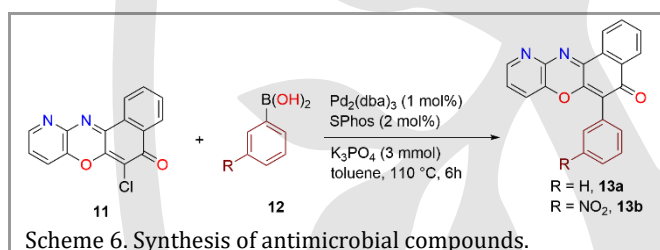
Scheme 4. A list of homogeneous Pd complexes and ligands used for the SM reactions.

The SM coupling of chlorobenzene and phenylboronic acid using a pyridylformidine-based Pd(II)-complex **C5** was given quantitatively in water at 100 °C.¹⁵ The addition of TBAB was essential for facilitating this reaction. The reactions of chlorobenzene, 4-chlorophenol, and 4-chloroaniline afforded the product in quantitative yield (three examples). Ji et al. reported one-pot Miyaura borylation and SM coupling at room temperature.¹⁶ They used XPhos-Pd-G2 **C6** (0.5 mol%) and XPhos (0.5 mol%) as a metal source and a ligand. The reaction of electron-rich and electron-deficient aryl chlorides with arylboronic acid produced 56–96% yield. Heteroaryl chlorides and heteroaryl boronic acids were tolerated in the reaction. Similarly, Ma et al. reported another one-pot Miyaura borylation and SM coupling using Pd(OAc)₂/Gorlos-Phos (up to 95% yield of the products).¹⁷ Liu, Huang, Wang, et al. reported a diamine-based palladium complex **C7**.¹⁸ The use of 0.05 mol% of **C7** led to a 96% yield of SM reactions. Unfortunately, the reactions of heteroaryl chlorides and sterically hindered aryl chlorides failed to produce the coupling products. The authors detected the Pd⁰, Pd^{II}, and Pd^{IV} species using XPS. Thus, they proposed two simultaneous reaction pathways: conventional Pd⁰/Pd^{II} and

Pd^{II}/Pd^{IV} catalysis (Scheme 9). In addition, they confirmed the possibility of a Pd^{II}/Pd^{IV} catalytic pathway using DFT studies. The DFT studies suggested that transmetalation is the rate-determining step in this catalytic cycle. Schmidt et al. reported that the oxidative addition of aryl chloride to ligand-free Pd species is a reversible process.¹⁹ Thus, under ligand-free conditions, oxidative addition is not the rate-determining step. In 2020, Zeng and Liu reported an NHC-Pd(II)-azole complex **C8** as a pre-catalyst for the SM reaction.²⁰ The reaction using sterically hindered 2,6-dimethylchlorobenzene with different aryl boronic acids afforded the corresponding products in 78–98% yield. This reaction can tolerate steric hindrance but cannot tolerate heteroaryl chlorides. The monophosphine ligand WK-phos was reported by Kwong et al.²¹ Using this WK-phos ligand and Pd(OAc)₂, palladium loading was reduced to 10 mol ppm without dropping the reaction yield (>99%) with up to 100,000 TON. Electron-rich and electron-deficient aryl chlorides were tolerated under these conditions. Yet et al. prepared 3-aryl-1-phosphinoimidazo[1,5-a]pyridine ligand **L3** and Pd(OAc)₂ (2.5 mol %) for the SM reaction.²² They obtained up to 92% yield of the biaryl derivatives.

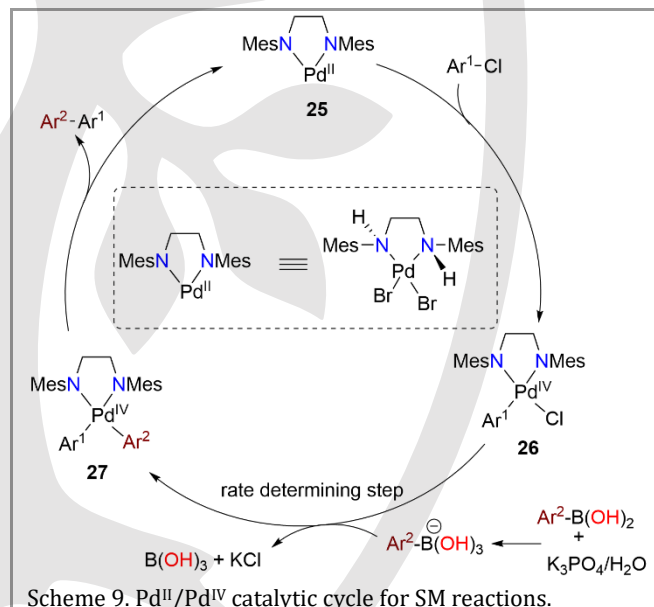
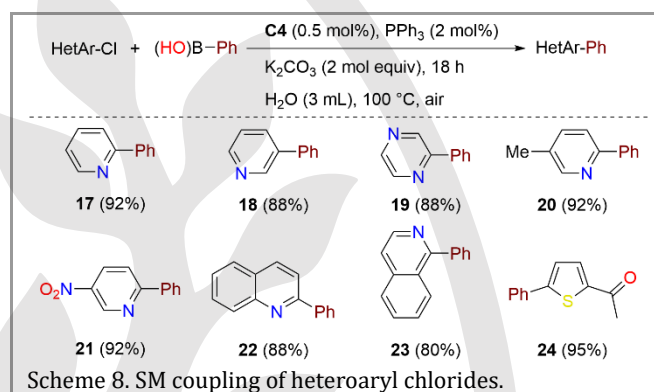
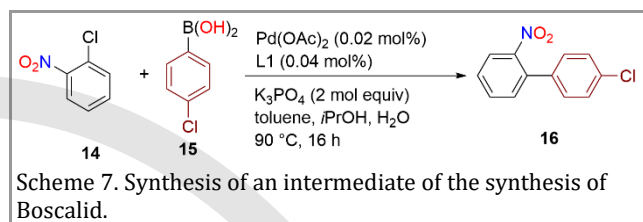


Niwa and Uetake reported a Lewis acid-assisted SM coupling under base-free conditions.²³ In the conventional SM coupling, a base facilitates the transmetalation step. Thus, a base-free SM coupling of aryl chloride is unique.²⁴ The base-free SM coupling is mainly reported with cationic organopalladium(II) intermediate, which is thermally unstable and limits the application.²⁵ The role of Lewis acid is to mask and stabilize the cationic intermediate. Zinc complex **29**, which is used as a Lewis acid, interacts with palladium complex **28** to produce **28'** (Scheme 10). The palladium intermediate **28'** underwent transmetalation with borates. Although the authors mainly focused on the reactivity of aryl bromides, they also showed that the reaction of aryl chlorides afforded the corresponding products in up to 86% yield.



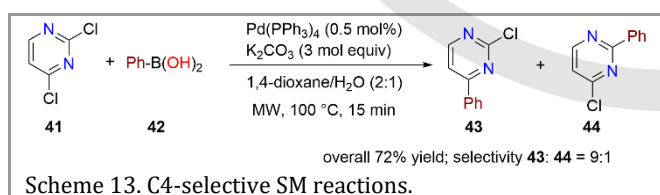
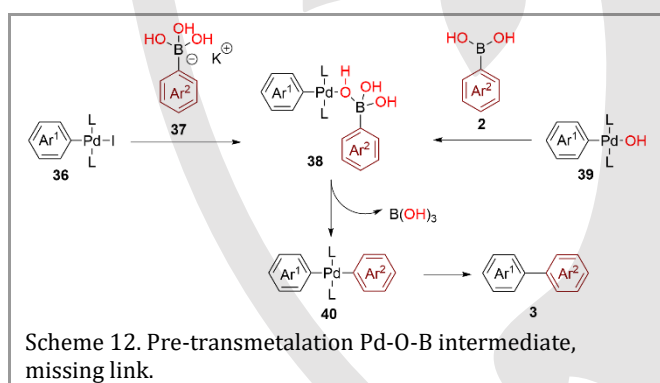
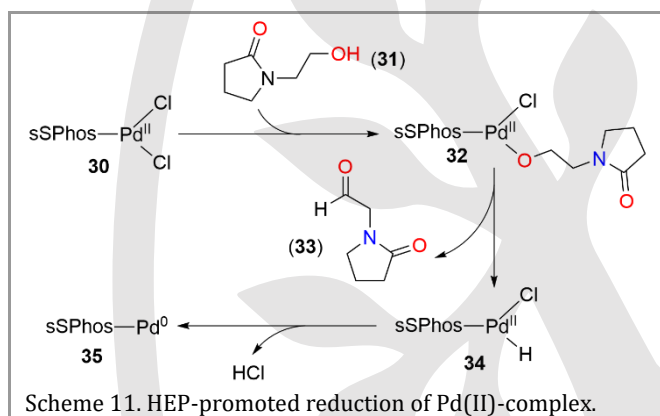
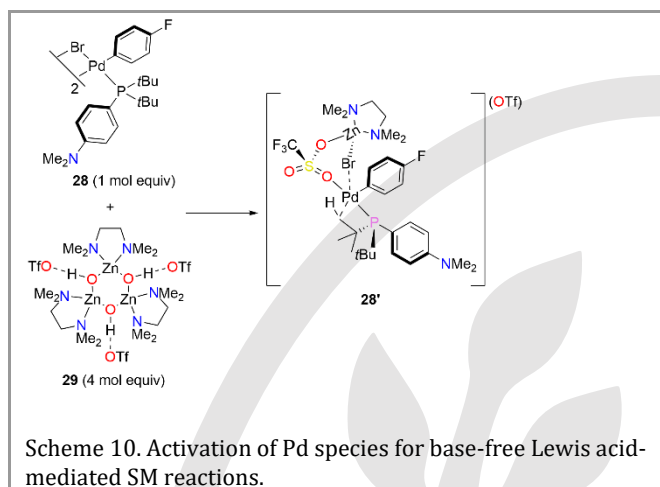
An HEP **31**-promoted reduction of the Pd(II) complex was reported by Fanatoni and Carbi.²⁶ The proposed mechanism of HEP-promoted Pd⁰ formation from Pd^{II} is shown in Scheme 11. This Pd⁰ species efficiently catalyzed SM coupling to produce a product yield of up to 95%. In this study, PdCl₂(MeCN)₂ (0.05 mol%) and sSPhos (0.15 mol%) were used as metal and ligand, respectively. Leyva-Peréz et al. introduced an indomuscone-based sterically encumbered phosphine ligand **L4** for the Pd-catalyzed SM reaction.²⁷ The use of Pd(OAc)₂ in 2.5 mol% and **L4** in 5 mol% provided biaryl derivatives in up to 80% yield. Schaub et al. reported a Pd(OAc)₂ (50 ppm)-catalyzed SM coupling of aryl chlorides and aryl boronic acid in water.²⁸ As a ligand, they used P(*t*Bu)Cy₂ in 0.02 mol% in this reaction, where the corresponding products with up to quantitative yield were obtained. Additionally, they synthesized several industrially important fungicides, such as Boscalid, Fluxapyroxad, and Bixafen. In this reaction, they achieved up to 20000 of TON and 2000 h⁻¹ of TOF. Denmark et al. reported that the transmetalation of arylboronic esters was faster than that of arylboronic acids.^{29a} They reported the SM coupling of arylboronic esters with aryl halides in the presence of **C9** (2 mol%). They used potassium trimethylsilylanolate (TMSOK) as a base, and the reaction was performed at 23 °C. The reaction of aryl chlorides with aryl neopentyl esters afforded products in up to 91% yield. The same authors also found a pre-transmetalation Pd-O-B intermediate

38, which they called a missing link.^{29b} This intermediate was formed before the transmetalation step, as shown in Scheme 12.



A microwave-assisted regioselective SM coupling of 1,4-dihydropyridines and aryl/heteroaryl boronic acid using Pd(PPh₃)₄ (0.5 mol%) was reported by Sova et al.³⁰ The reaction was completed within 15 mins under the microwave irradiation conditions at 100 °C. This reaction afforded C4-substituted pyrimidines. They obtained products **43** and **44** with selectivities up to 9:1 and an overall yield of 72% (Scheme 13). McIntosh and Mansell reported the SM cross-coupling of aryl chlorides and aryl boronic acid at room temperature using Pd(II)-complex **C10** (1 mol%) and monoanionic [*N*, *O*] ligands.³¹ The authors observed that the rate of the reaction increased significantly with increasing reaction temperature. They proposed that the decomposition of **C10** at higher temperatures resulted in the

generation of active Pd nanoparticles, which accelerated the reaction rate.

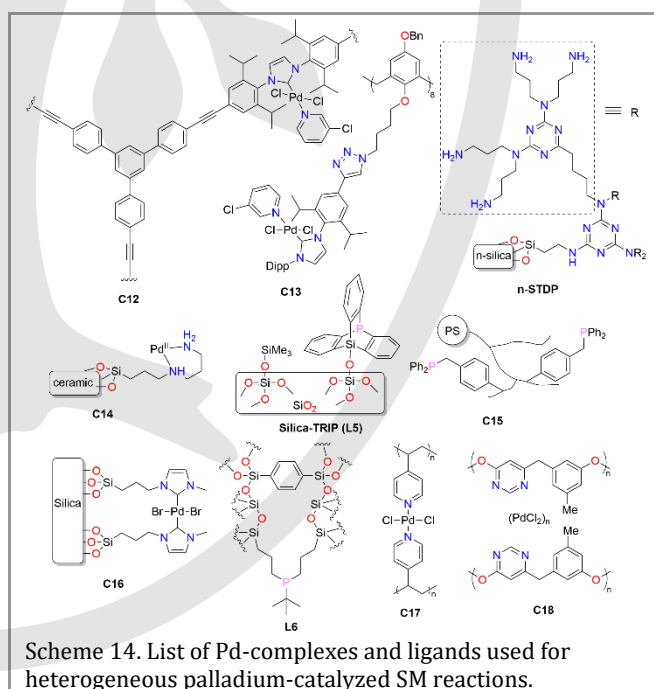


Lee et al. developed a xylyl-linked bis-benzimidazolium-based palladium complex **C11**.³² Using 1 mol% of **C11**, biaryl

derivatives were obtained in up to 97% yield. While the reaction was mainly limited to electron-deficient aryl chlorides, 2-methyl chlorobenzene and phenylboronic acid afforded 2-methylbiphenyl in 95% yield, whereas 3- and 4-chlorobenzene afforded 27% and 17% yields, respectively. In summary, significant progress has been made during the last decades, which includes base-free SM couplings and finding the pre-transmetalation intermediates. Additionally, researchers have shown that the choice of ligand (electron-rich) and base (to prevent substrate decomposition) is crucial for SM reactions of aryl/heteroaryl chlorides.

2.2. Heterogeneous palladium catalysis

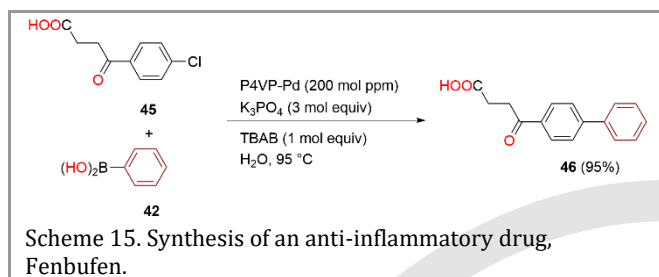
Sureshbabu et al. reported SM couplings catalyzed by poly(vinyl chloride) (PVC)-supported palladium nanoparticles at room temperature.³³ They obtained biaryls in up to 99% yield using 1 mol% of Pd. The catalyst was recycled four times in the reaction, and the yield decreased from 99% to 90% during the 4th reuse. ICP-OES analysis suggested that the Pd loading decreased during recycling. The Pd loading after 4th reuse was 11.81%, whereas the original loading (fresh catalyst) was 13%. Mohammadpoor-Baltork and Mirkhani developed a nano-silica triazine dendritic polymer (nSTDP) supported palladium complex (Pd-nSTDP).³⁴ Using this Pd-nSTDP complex (60 mol ppm), up to 96% yield of the couplings were obtained under microwave irradiation. Although the authors mainly focused on the reaction of aryl bromides and iodides, they found that the reactions of chlorobenzene, 4-chloroacetophenone, and 4-chlorobenzaldehyde with phenylboronic acid proceeded in up to 94% yield. The recyclability of the catalyst was investigated in a reaction using aryl bromide as the substrate. During catalyst recycling, 2% Pd leaching was observed.



Metin and Sun prepared bimetallic Ni/Pd core/shell nanoparticles supported on graphene (G-Ni/Pd).³⁵ The SM cross-couplings of aryl chlorides and heteroaryl chlorides with phenylboronic acid afforded up to 96% yield of the products using 0.91 mol% of Pd. A catalyst reusability test was performed

for the reaction of an aryl iodide, revealing no loss of catalytic activity after 5th reuse. TEM observation showed that there were no changes in the nanoparticle morphology, and ICP-AES analysis suggested no change in the Ni/Pd composition after the SM coupling reaction. Firouzabadi et al. reported a phosphinite-functionalized clay composite-stabilized Pd nanoparticles.³⁶ The cross-coupling of chlorobenzene and phenylboronic acid proceeded with 720 mol ppm of Pd (from clay composite) in water to give 88% yield of biphenyl at 80 °C. The SM couplings of 4-chloronitrobenzene and 4-chlorotoluene with phenylboronic acid also proceeded. Inductively coupled plasma (ICP) analysis suggested a 7% loss of Pd in the recovered catalyst. Sawamura et al. developed a silica-supported triptycene-type phosphine (Silica-TRIP, **L5**).³⁷ The authors used this Silica-TRIP as a ligand (0.5 mol%) for the SM coupling of aryl chlorides using PdCl₂(py)₂ as a metal source (0.5 mol%). While the reaction using in-situ generated PdCl₂(py)₂/**L5** provided 5% yield of biaryls, pre-complexed PdCl₂(py)₂/**L5** gave a 56% yield. The yield further improved to 93% when the metal source was changed from PdCl₂(py)₂ to Pd(OAc)₂. The recovered Pd(OAc)₂/**L5** catalytic system afforded the product in 28% yield on 2nd run and 3% yield on 3rd run. The authors proposed that Pd leaching occurred because of the moderate coordination ability of the phosphine center of **L5**. In 2015, an interesting discovery by Lipshutz et al. was reported, where they found that FeCl₃, which contains Pd as a contaminated metal species, promotes the SM reaction.³⁸ They used 5 mol% FeCl₃ (97% purity), and 300 - 350 ppm of Pd contamination was detected by ICP analysis. Grignard reagents (MeMgCl, 10 mol %) were added to prepare the Pd nanoparticles (Fe-ppm-Pd). Without the Grignard treatment, SM coupling did not proceed. In addition, Fe is essential for this transformation. The choice of the ligand is also crucial, as SPhos or XPhos are the only ligands that promote this reaction. The reaction of aryl chlorides with commercially available surfactant TPGS-750-M in water afforded the corresponding products in 85% yield. The reusability test was performed in the reaction of a more reactive aryl bromide; however, reactivity loss was observed: the yield dropped to 87% in the 4th run while the yield was 95% in the 1st run using a fresh catalyst. Andrés and Flores developed a silica-supported bis-(NHC) complex of palladium **C16**.³⁹ This palladium catalyst was immobilized on γ -Fe₂O₃. This catalyst provided an 89% yield of the product in the reaction of 4-chlorotoluene and phenylboronic acid using 0.024 mol% Pd. The catalyst was magnetically recovered after the reaction. The catalyst exhibited a gradual decrease in yield, and Pd leaching from the catalyst was observed. The ICP-MS analysis showed 10 ppm of Pd contamination in the product. Li and Chen reported Pd and Co bimetallic hybrid nanocrystal (Pd-Co₃[Co(CN)₆]₂ with a Pd: Co ratio of 3:1.⁴⁰ This nanocrystal (0.45 mol% Pd) affords biphenyl in 86% yield. The catalyst was recovered and reused eight times. The Pd content of the solution after the 1st and 5th cycles was less than 100 ppb. The Pd-to-Co ratio of Pd and Co remained unchanged after the reaction. Friedrich et al. prepared PdCuCeO by substituting Pd²⁺ and Cu²⁺ in the CeO₂ lattice.⁴¹ PdCuCeO as a catalyst promoted the SM reaction in the presence of tetrapropyl ammonium bromide (TPAB). SM coupling of electron-deficient aryl chlorides using 2.3 mol% Pd proceeded to provide the product in quantitative yield. This catalyst failed to cross-couple arylboronic acids with the electron-rich aryl chlorides. Sajiki et al. developed an anatase-type TiO₂-supported Pd catalyst,

Pd/TiO₂.⁴² The SM coupling of an electron-deficient aryl chloride proceeded with a 5 mol% Pd/TiO₂ catalyst to give the product in 98% yield. Electron-rich aryl chlorides were not tolerated under these conditions. The products and reaction mixture showed traces of Pd contamination, and the catalyst was not reusable. The authors suggested that this was likely due to catalyst deactivation. SM coupling of aryl chlorides using a glass-supported palladium nanoparticles (SGIPd, 0.35 mol%) under microwave irradiation was reported by Arisawa et al.^{43a} In this reaction, the TON reached 28571, and the TOF reached 1120 h⁻¹. The catalyst was used 10 times, and the yield dropped to 90% on the 10th use from 98% on the 1st use. Electron-rich, electron-deficient, and heteroaryl chlorides led the reaction to yield products in up to 98%. Motokura et al. observed an unexpected formation of triphenyl borane (Ph₃B) during a palladium-catalyzed SM coupling reaction.⁴⁴ They used mesoporous silica-supported Pd complex catalyst Pd/MS. Ph₃B is an active intermediate in the SM coupling of aryl chlorides and phenylboronic acids. Bai et al. reported an effective photothermal dual-responsive Pd₁Cu₄/Ce_xO_y catalyst (1 mg/mmol substrate).⁴⁵ The SM reaction of aryl chlorides and arylboronic acid proceeded under thermal heating at 70 °C. Additionally, SM cross-coupling proceeded under visible-light irradiation at room temperature to afford biaryls in up to 99% yield. The catalyst was reused five times with a gradual loss of catalytic activity. Phan and Zhang reported graphene oxide-supported palladium nanoparticle-catalyzed (Pd/rGO-60, 0.5 mol%) SM coupling in water under microwave irradiation.⁴⁶ The reaction of electron-rich and electron-deficient aryl chlorides afforded the products in up to 95% yield. Microwave irradiation reduced the reaction time from 20 h to 2.5 h. The presence of tetrabutylammonium bromide (TBAB) was essential in this reaction. Abdallah and Huc developed a palladium PEPSI-IPr complex supported on Calix[8]arene **C13** (0.2 mol% - 1 mol%).⁴⁷ The cross-coupling reaction of electron-rich and electron-deficient aryl chlorides and heteroaryl chlorides to give the products in up to 98% yield. ICP-MS analysis of the reaction solution showed trace amounts of Pd contamination, indicating the heterogeneous nature of the catalyst. We developed a convoluted poly(4-vinylpyridine) supported palladium catalyst, P4VP-Pd **C17**^{48a}, using our molecular convolution method.⁴⁸ P4VP-Pd showed high catalytic activity (up to 99% yield), even at a 40-ppm level, toward the SM coupling of aryl chlorides and aryl boronic acids in water. Electron-rich and electron-deficient heteroaryl chlorides were tolerated by the P4VP-Pd catalysts. The non-steroidal anti-inflammatory drug Fenbufen was directly synthesized using P4VP-Pd catalysis (Scheme 15). The catalyst was recovered and reused without a significant loss of catalytic activity, with 92% yield at 1st use and 91% yield at 4th use. No Pd contamination was observed in the reaction mixture during ICP-MS analysis. We also developed a convoluted poly(*meta*-phenylene oxide) palladium catalyst, Pd@poly(*m*PO)_n (**C18**),^{48e} with a 400 ppb Pd loading, providing SM coupling in water. The TON and TOF reached 1900000 and 95000 h⁻¹, respectively.

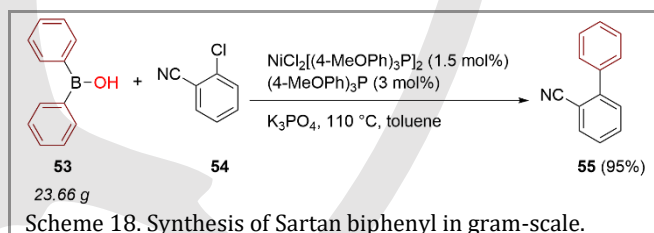
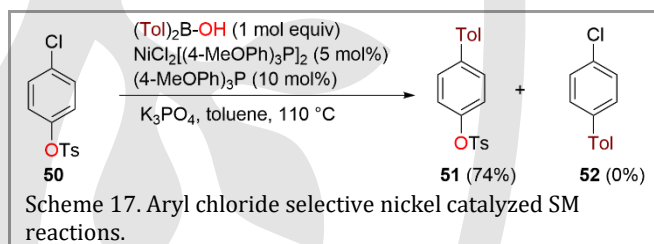
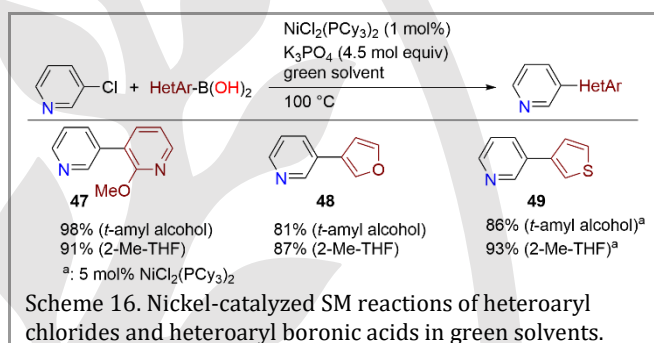


Farinola et al. utilized a silk fibroin-supported palladium catalyst (Pd/SF) for the SM coupling of aryl chlorides.^{49a} The reaction of chlorobenzene and 4-methoxy benzoic acid took place in the presence of Pd/SF with 3.8 mol% Pd for 3 h in aqueous ethanol to give the product quantitatively. The authors reused the catalyst 25 times in the reaction of an aryl iodide.^{49b} After the 25th reuse, the biaryl product was obtained in 42% yield. The authors proposed that palladium cluster formation segregates catalytically active metal atoms. In 2022, Wang and Liu reported SM coupling reactions using a Pd-PEPPSI-embedded conjugated microporous polymer-supported complex, Pd-PEPPSI-CMP **C12**.⁵⁰ The catalyst reusability test showed a gradual catalytic activity loss until the 3rd reuse (the yield changed from 96% to 91%), followed by a sudden decrease to 56% during the 4th reuse. Wu and Chen reported flow-through SM coupling using a Pd-loaded functionalized ceramic membrane **C14** (1.9 mol% Pd).⁵¹ The catalyst showed no significant loss of catalytic activity until 5th reuse. Nakajima et al. reported the SM coupling using a Pd catalyst supported on phosphine periodic mesoporous organosilica **L6**.⁵² They used Pd(dba)₂ (2.5 mol% Pd) as a transition metal source. Under these conditions, the SM reaction using 4-chlorophenol and 4-(mercapto)chlorobenzene as substrates did not proceed. Dai and Sun reported a porous supramolecular-assembled palladium catalyst that was utilized for the SM reaction of aryl chlorides.⁵³ Irrespective of the steric and electronic nature of the aryl chloride, the reaction provided a quantitative yield under 0.5 mol% of Pd. The ICP-MS analysis showed that the reaction mixture contained less than 0.1 ppb Pd, which indicates that the Pd catalyst is stable and leaching of Pd does not occur. The catalyst was reused five times, affording the product in 95% in 5th reuse. Lee and Joung reported an ordered mesoporous polymeric phosphine (Meso-PPh₂)-supported palladium catalyst **C15**.⁵⁴ The reaction of electron-deficient aryl chlorides using 4 mol% of **C15** afforded the products in up to 93% yield. The reaction of electron-rich aryl chlorides produced biaryls in 19–43% yield. **C15** was not reusable, and inactive palladium black formation was observed in the recovered catalyst by TEM. In addition, Pd leaching was observed. In summary, there are multiple reports of heterogeneous palladium-catalyzed SM reactions of aryl chlorides. However, in most reports, either palladium leaching or palladium catalyst deactivation was observed. A convoluted polymer-supported palladium catalyst might be helpful for this purpose.

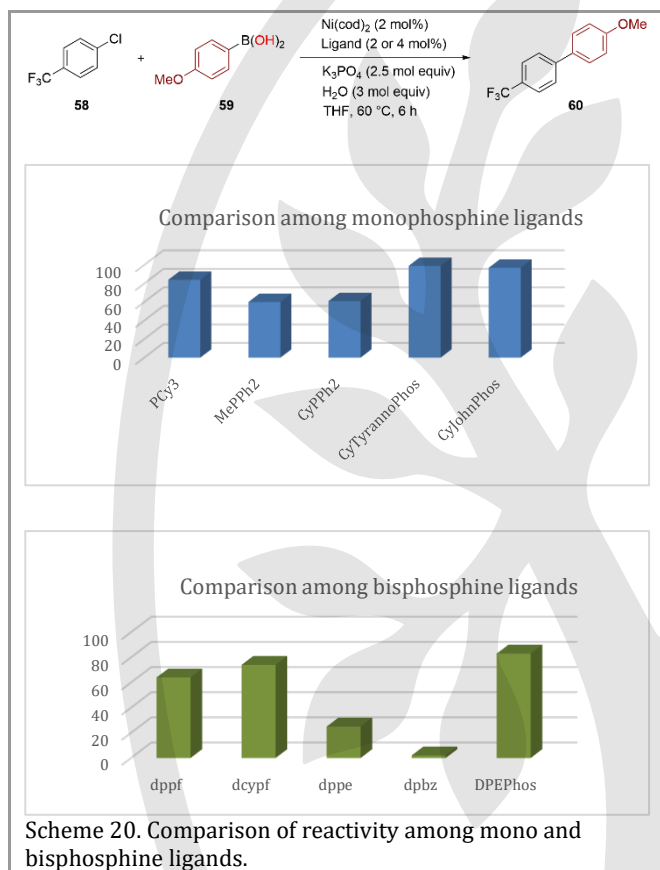
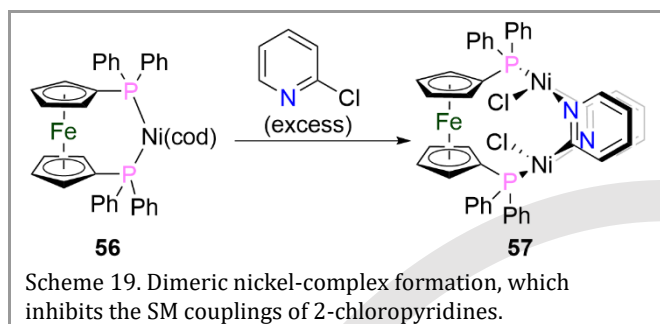
2.3. Homogeneous nickel catalysis

Since Suzuki-Miyaura coupling is the reaction of organic halides (and their equivalents) with organic boronic acids (and their equivalents) using Pd catalysts, the reaction using Ni catalysts should be described as a Suzuki-Miyaura type reaction (coupling). To simplify the description, we use the word of the SM reaction (SM coupling) in the Ni-catalyzed reaction.

In 2013, Garg et al. reported nickel-catalyzed SM couplings in *t*-amyl alcohol or 2-Me-THF as green solvents.⁵⁵ The SM couplings of 3-chloropyridine and phenylboronic acid proceeded quantitatively using NiCl₂(PCy₃)₂ (1–5 mol%). Several heteroaryl boronic acids were converted to the products in 81–98% yield (Scheme 16). In the same year, Lei et al. reported the SM reaction of aryl chlorides using the Ni(II) σ -aryl complex **C20**.⁵⁶ The SM coupling proceeded with 5 mol% **C20** and 10 mol% PPh₃. Although the reactions of electron-rich 4-chlorotoluene and 4-chloroanisole with phenylboronic acid gave the corresponding products in 97 and 86% yields, respectively, those of electron-deficient 4-chloronitrobenzene and phenylboronic acid did not proceed at all. Additionally, electron-deficient aryl boronic acids or heteroaryl boronic acids were not suitable for this reaction (trace to 8% yield).

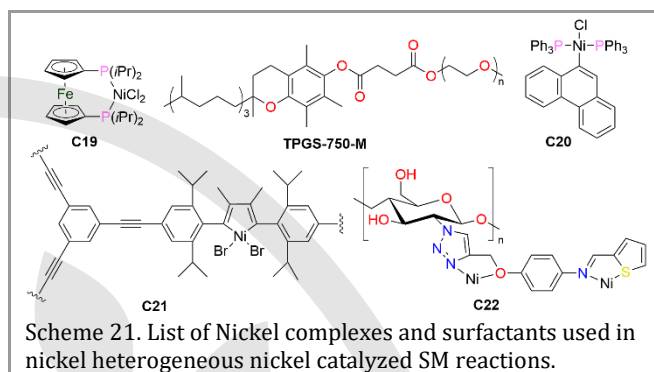


In 2014, Zou et al. reported the SM coupling of aryl chlorides with diarylboronic acids **S5** using NiCl₂[(4-MeOPh)₃P]₂ (5 mol%).⁵⁷ Interestingly, in this reaction, a chloride moiety selectively underwent the SM coupling with diarylboronic acid in the presence of tosylate (Scheme 17). Additionally, they synthesized 2-cyanobiphenyl (**55**), a key intermediate for the synthesis of Sartans (a medicine for hypertension), on a 24 g scale (Scheme 18).



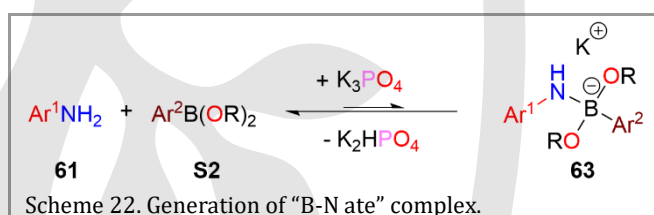
In 2021, Nelson et al. reported the SM coupling of 3- and 4-chloropyridines using Ni(cod)(dppf).⁵⁸ They found that 2-chloropyridine underwent dimerization (Scheme 19). A similar dimerization proceeded in the reaction of α -halo-*N*-heterocycles (2-chloropyridine, 2-chloroquinoline). Dimeric nickel complex **57** was inactive in the SM reactions. Kumar et al. reported the SM coupling reaction of aryl halides using NiBr₂ as a catalyst (8 mol%).⁵⁹ Although their work provided up to 92% yield for aryl bromides and iodides, it could only provide up to 42% yield for aryl chlorides. Doyle et al. reported comparison studies of monophosphine and bisphosphine ligands for the Ni-catalyzed SM reaction of aryl chlorides (Scheme 20).⁶⁰ Although bisphosphine-type ligands are usually used for nickel-catalyzed SM reactions, their results suggested that monomeric phosphine ligands (e.g., CyTyrannoPhos) might outperform bisphosphine ligands depending on the substrates. They proposed that monophosphine ligands enabled challenging oxidative addition and transmetalation steps, whereas bisphosphine ligands prevented off-cycle reactivity and catalyst deactivation. In summary, the use of electron-rich and sterically hindered ligands

is suitable for SM couplings of aryl chlorides under homogeneous nickel catalysis.



2.4. Heterogeneous nickel catalysis

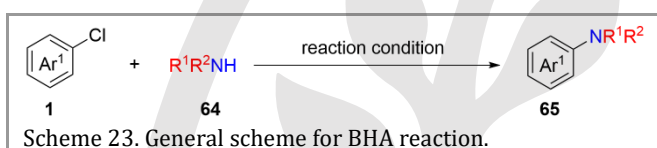
In 2015, Lipshutz et al. reported a nickel-nanoparticle-catalyzed SM reaction in water.⁶¹ They used the **C19** complex (3 mol%) as the nickel source and performed SM coupling reactions in the presence of TPGS-750-M as a surfactant (Scheme 21). They prepared Ni nanoparticles in situ by adding MeMgBr (3 mol%). ICP-MS analysis of the isolated products revealed nickel contamination of less than or equal to 5 ppm. The authors mainly focused on aryl iodides, bromides, and triflates, but also provided a few examples of aryl chlorides. Electron-rich, electron-deficient, and heteroaryl chlorides provided the SM coupling products in up to 93% yield.



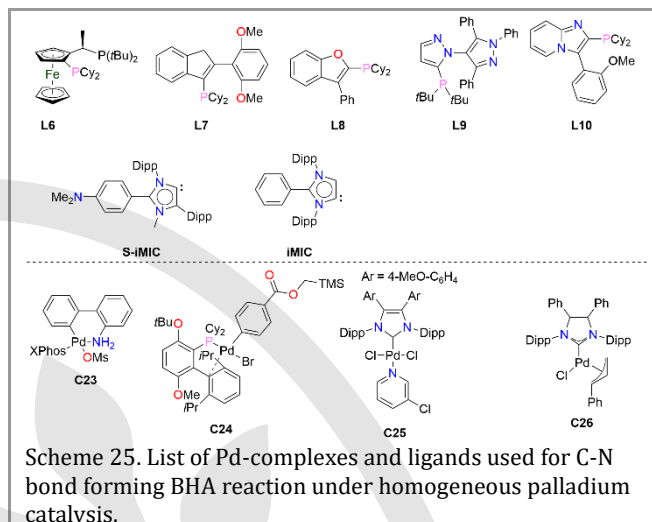
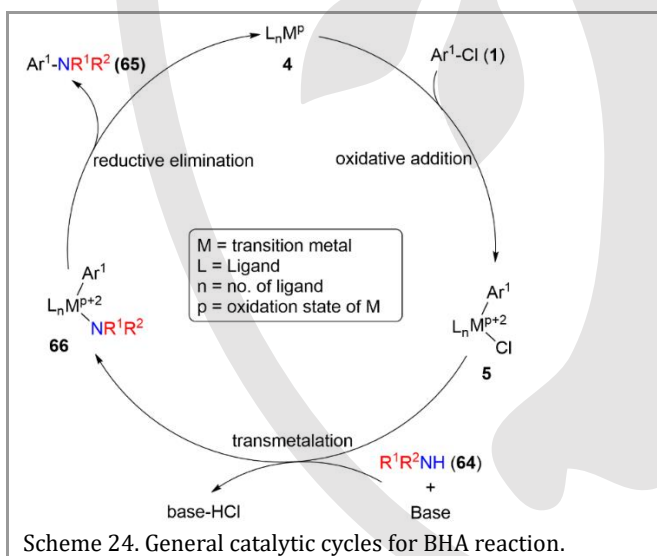
In 2017, Hajipour et al. developed chitosan-supported nickel nanoparticles (**C22**).⁶² The SM couplings of electron-rich and electron-deficient aryl chlorides proceeded well with 0.2 mol% of the catalyst and afforded products in up to 87% yield. Catalyst reusability tests were performed using aryl bromide substrates. A gradual decrease in the yield of the SM reaction products was observed, and the reaction solution showed only 0.04 ppm nickel contamination. Cai et al. developed a recyclable and efficient NiCl₂(dppp)/PEG-400 catalytic system for the SM reactions of aryl chlorides and aryl boronic acids.⁶³ Using 2 mol% catalyst loading, they obtained up to 95% yield from electron-rich, electron-deficient, and heteroaryl chlorides. The NiCl₂(dppp)/PEG-400 system was recovered and reused 6 times. The biaryl formation yield was 92% at 6th use, whereas the fresh catalytic reaction provided a 95% yield. The nickel contamination test using ICP-MS showed only 0.8 ppm nickel contamination in the products. In 2020, we developed activator-promoted aryl halide-dependent C-C and C-N bond-forming reactions where aryl chloride provided C-C bond formation and aryl iodide favored C-N bond formation.⁶⁴ This chemoselective reaction was catalyzed by NiI₂ (0.5 mol%). The presence of an aryl amine as an activator is essential for SM coupling between aryl chlorides and arylboronic acids. The Ni species were stabilized on the surface of the base (K₃PO₄). The SM couplings using the K₃PO₄-supported heterogeneous nickel species

provided 99% yield. The ^{15}N - and ^{11}B -NMR studies suggested that a B-N ate complex was formed (Scheme 22), which further underwent transmetalation to produce a C-C bond. Hot-filtration tests revealed the heterogeneous nature of the catalysts. The catalyst was recovered and reused. The yield of the SM coupling dropped to 89% when the recovered catalyst was used, whereas the yield was 98% for the fresh catalyst. Dong and Dong reported a diimine-based nickel complex, **C21**.⁶⁵ The SM cross-coupling between chlorobenzene and phenylboronic acid provided biphenyl in 26% yield. In the reported (2013-2024) heterogeneous nickel catalysts, leaching was observed. Thus, further development of a new, more stable, and reusable heterogeneous nickel catalyst is still in demand for SM couplings of aryl chlorides.

3. Buchwald-Hartwig Amination Reaction

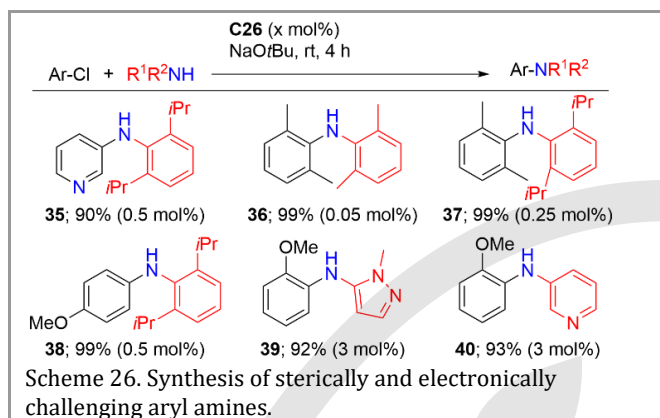


Starting in 1995,⁶⁶ Buchwald-Hartwig amination (BHA) of aryl halides and pseudohalides has become a fundamental tool for forming C-N bonds (Scheme 23). Several natural products, pharmaceuticals, and agrochemicals contain nitrogen heterocycles, which could be synthesized using BHA reactions.² Mechanistically, BHA follows three significant steps: i) oxidative addition, ii) ligand exchange or transmetalation, and iii) reductive elimination (Scheme 24). The rate-determining step usually varies among these three steps depending on the reaction conditions, such as transition metals, ligands, bases, and additives.

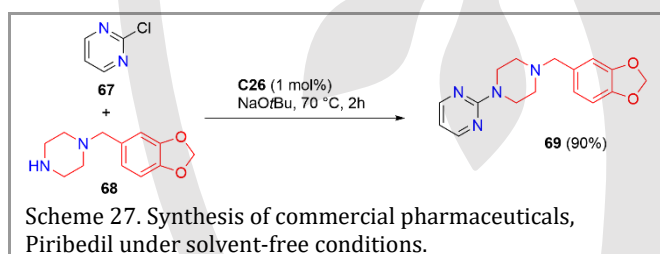


3.1. Homogeneous palladium catalysis

In 2013, Buchwald et al. developed a new palladium complex, XPhos-Pd-G3 (**C23**, Scheme 25), and applied it in SM and BHA reactions.^{67a} In the BHA reactions of aryl chlorides, 0.01–0.5 mol% of **C23** was used, and up to 97% yield was observed. Electronic and steric variations of the aryl chlorides had minimal effects on these reactions. In 2020, they also developed another Pd catalyst (GPhos-Pd-G6, **C24**) for the BHA reaction.^{67b} This Pd catalyst has unique features, such as the *t*BuO group improving the catalyst stability, the OMe group increasing the reaction rate, and the free *p*-position of diisopropyl substituted benzene ring expanding the substrate scope. Using this Pd-complex in 0.2–0.5 mol%, the authors performed the BHA reactions of base-sensitive amines,^{67c} electron-deficient amines, and electron-rich amines at room temperature. In 2017, Yu et al. reported a $\text{Pd}(\text{dba})_2/\text{L7}$ catalyzed BHA reaction under solvent-free conditions. The reaction also proceeded in an aqueous medium.⁶⁸ Under solvent-free conditions, several diarylamines were obtained in up to 89% yield using $\text{Pd}(\text{dba})_2$ in 1 mol%. Although the authors used **L7** as the ligand, the control experiment showed that XPhos and RuPhos produced similar results. Li et al. synthesized a series of 3-arylbenzofuran-2-ylphosphines (**L8**) and applied them as a ligand in BHA reactions.⁶⁹ The BHA reactions of aryl chlorides and primary, secondary, and aromatic amines proceeded in the presence of $\text{Pd}(\text{OAc})_2$ (2.5 mol%) and **L8** (7.5 mol%) to produce the C-N coupling products in up to 90% yields. In 2021, Hartwig et al. reported the BHA reactions of aryl chlorides and hydrazine using 800 mol ppm of $\text{Pd}[\text{P}(o\text{-tolyl})_3]_2$ and $\text{CyPF-}t\text{Bu}$ (800 mol ppm).^{70a} They used KOH as the base. Because of the use of KOH as the base, the reaction using base-sensitive functional groups, such as ester- or amide-bearing aryl chlorides, provided only 45% and 56% yields, respectively. Hydrazine deprotonation is the rate-determining step in this reaction. The same group reported the BHA reactions of aryl chlorides and ammonium salts using the same catalytic system.^{70b}



Xu et al. reported a dianisole-decorated Pd-NHC complex, Pd-PEPSSI-IPr^{OMe} (**C25**), for the BHA reactions (**C25**, 0.1 mol%).⁷¹ Although the BHA reactions of electron-rich aryl chlorides and primary, secondary, and aryl amines proceeded to provide 54–98% yield, the same of electron-deficient aryl chlorides didn't proceed. Gevorgyan et al. performed BHA reactions in lipids and lipid impurities under XPhos-Pd-G3 catalysis (**C23**, 2 mol%) and obtained diarylamines from aryl chlorides in 99% yield.⁷² Qiu et al. reported a solvent-free BHA reaction using an NHC-Pd complex ((SIPr)^{Ph}Pd(cin)Cl), **C26** at room temperature.⁷³ The presence of two phenyl rings at the backbone of the NHC ligand is supposed to be essential, according to the control experiments they reported. The authors proposed that the electron-donating ability and steric hindrance created by these phenyl groups increase the catalytic activity. Several sterically challenging diaryl amines were obtained under this solvent-free condition using Pd loading 0.05–3 mol% (Scheme 26). They also synthesized the commercial pharmaceutical Piribedil directly from heteroaryl chlorides (Scheme 27).

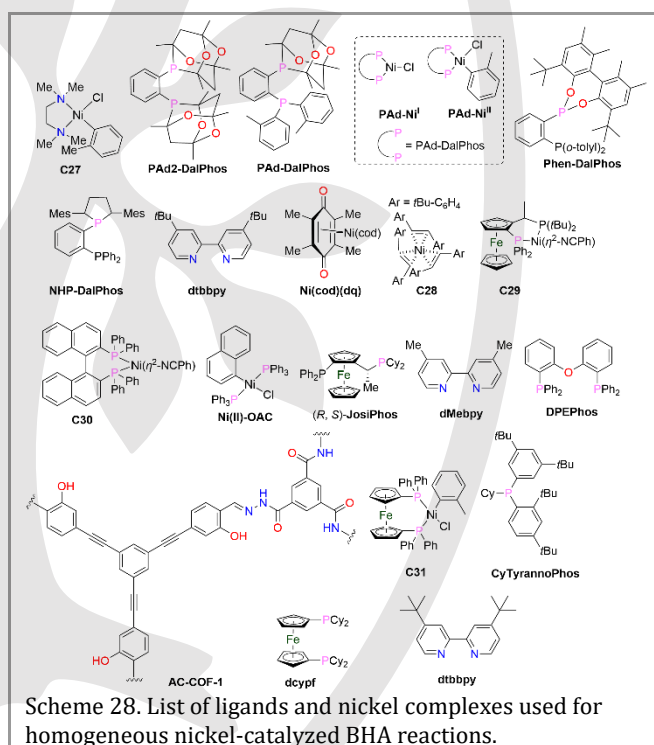


Recently, Yet et al. reported a BHA reaction using Pd(OAc)₂ (2.5 mol%) and JagPhos II (**L10**, 5 mol%).⁷⁴ The reaction using aryl amines and secondary amines with aryl chlorides provided BHA products with 7–98% yields, but in general, the primary and benzylic amines provided poor yields (2–27%). A super bulky mesoionic carbene (S-iMIC, “i” represents the 1,3-imidazole-derived) was reported by the Ghadwal et al.⁷⁵ They utilized this super bulky mesoionic carbene in BHA-type reactions between tolyl chlorides and morpholines in the presence of Pd(OAc)₂ (2.5 mol%). The reaction using S-iMIC ligands produced C-N coupling products in up to 99% yield, whereas the reactions using IPr or iMIC as ligands produced only 7 or 9% yields. In summary, the use of bulky ligands in homogeneous palladium catalysis seems beneficial for the C-N bond-forming BHA reactions of aryl chlorides.

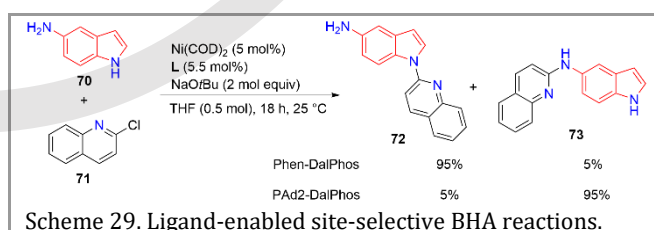
3.2. Heterogeneous palladium catalysis

In 2021, Sobhani et al. reported a Pd-Co bimetallic alloy encapsulated in a melamine-based dendrimer supported on

magnetically active $\gamma\text{-Fe}_2\text{O}_3$ named $\gamma\text{-Fe}_2\text{O}_3\text{@MBD/Pd-Co}$.⁷⁶ The ICP-MS analysis suggested that the bimetallic alloy contains 0.75 and 3.15 mmol of Pd and Co, respectively, per Kg of the catalyst. The Pd: Co molar ratio was 1:4.2. Using this bimetallic alloy as the catalyst (in 500 mol ppm Pd) for the BHA reaction between chlorobenzenes and aryl amines, biaryl amines were obtained in 91% yield. The authors also applied the bimetallic catalyst to the Mizoroki-Heck reaction and examined the catalyst reusability for that reaction only. In 2024, Lipshutz et al. reported a BippyPhos ligand-assisted Pd-catalyzed BHA reaction of aryl chlorides and aliphatic amines in micellar conditions.⁷⁷ They used [Pd(crotyl)Cl]₂ as a metal source in 0.25 mol% of Pd loading. In addition, BippyPhos ligand (**L9**, 2 mol%) was used. 2 wt% Savie/water (0.5 M) was used to generate micelles. BHA reactions using primary, secondary, and benzylic amines produced C-N bond-forming products in 55–99% yields. The catalyst was recovered and recycled three times. The yield of BHA decreased from 98% to 90% on 3rd reuse. ICP-MS analysis of the BHA product showed only 0.78 ppm of Pd contamination. In summary, only a few works have been reported within this time frame (2013–2024). Thus, there is a demand for highly active and reusable heterogeneous palladium catalysts for the BHA reactions of aryl chlorides.

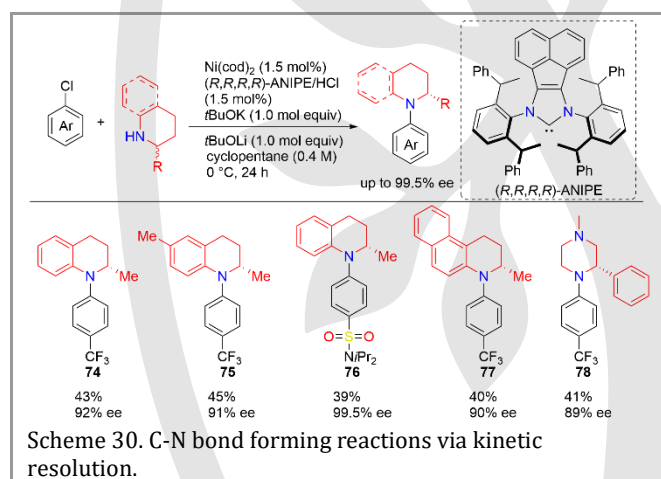


3.3. Homogeneous nickel catalysis



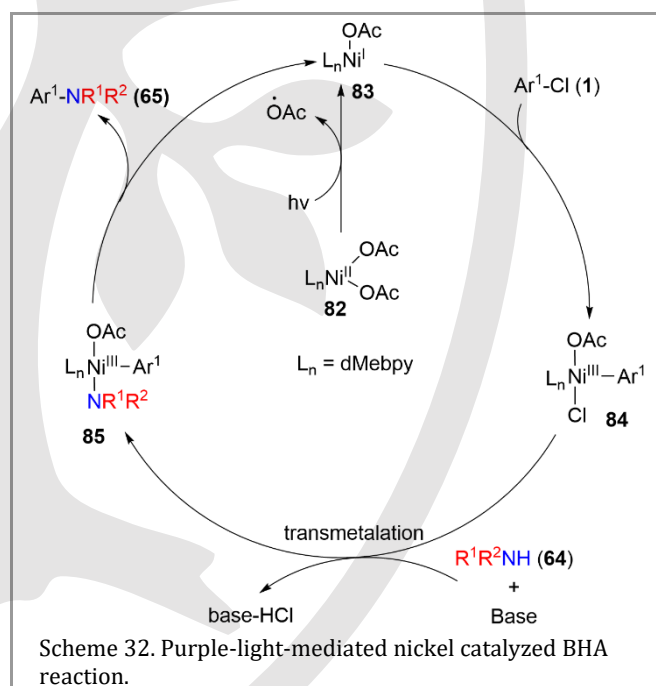
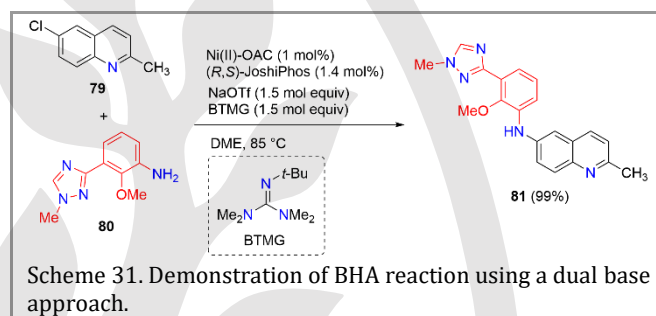
In 1997, Buchwald et al. reported a nickel-catalyzed BHA reaction of aryl chlorides and amines where they used Ni(COD)₂ as a transition metal source.^{78a} In continuation of their previous work,

in 2013, they prepared a new air-stable nickel catalyst named $(\text{dppf})\text{Ni}(\text{o-tolyl})\text{Cl}$ (**C31**, Scheme 28).^{78b} They used this nickel complex (5 mol%) for the BHA reaction of aryl chlorides at 100 °C. The amination of aliphatic secondary amines and aryl amines afforded products in up to 98% yield. Amination using a secondary aryl amine required an increased catalyst loading (10 mol%) and increased the reaction temperature (130 °C). Stradiotto et al. reported a nickel-catalyzed monoarylation of ammonia using $\text{Ni}(\text{COD})_2/\text{JosiPhos}$.⁷⁹ Hartwig et al. reported a $(\text{BINAP})\text{Ni}(\eta^2\text{-NCPH})$ catalyst (**C30**) for the BHA reactions of primary amines and aryl chlorides.^{80a} The use of this BINAP-supported nickel catalyst in 1 mol% provided up to 96% yield. This reaction was highly selective for primary amines. If the substrate contains both primary and secondary amines, then only the primary amines react, leaving the secondary amines intact. The same group also reported the BHA reaction of ammonia.^{80b} They prepared a new nickel complex (**C29**) by combining $\text{Ni}(\text{cod})_2$, JosiPhos, and benzonitrile (PhCN). This **C29** nickel complex was used at 2–4 mol% for the coupling of ammonia or ammonium sulfate with aryl chlorides to produce primary aryl amines in up to 58–84% yield. Ammonia performed better than $(\text{NH}_4)_2\text{SO}_4$, in general. Ammonia, methylamine hydrochloride (MeNH_2HCl), and ethylamine hydrochloride (EtNH_2HCl) were reacted with aryl chlorides, resulting in the production of secondary aryl amines in 52–99% yield.



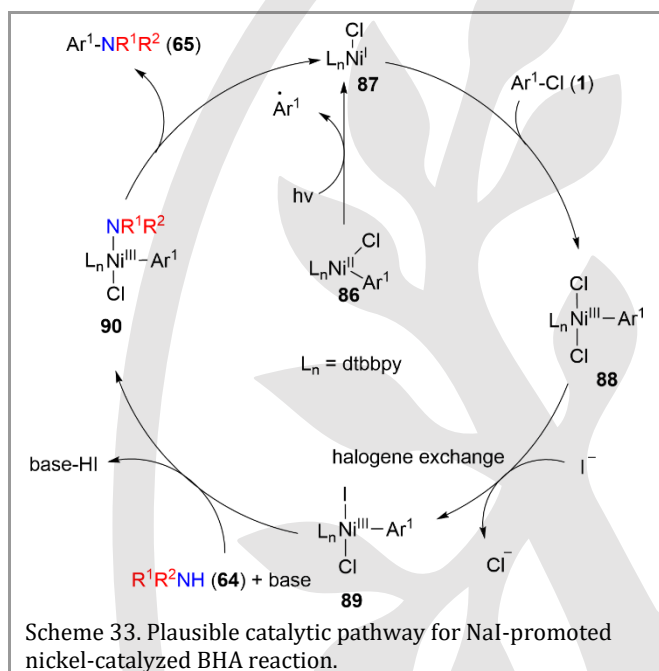
In 2015, Monfette et al. prepared a tetramethylethylenediamine (TMEDA) ligated nickel complex **C27**.⁸¹ This **C27** is not air and moisture-sensitive. It is easily applied to multi-gram-scale nickel complex preparation. Using this **C27** nickel complex (5 mol%), cross-coupling of morpholine and electron-deficient aryl chlorides afforded the amination product in 91% yield. In the same year, Doyle et al. prepared the same catalyst independently and applied it to the SM and BHA reactions.⁸² Unlike Monfette who used $\text{Ni}(\text{cod})_2$ for the synthesis of **C27**, Doyle et al. used $\text{Ni}(\text{acac})_2$ and $\text{Al}(\text{OEt})\text{Me}_2$. In the field of nickel-catalyzed BHA reactions, the Stradiotto group has made a major contribution during the last decades.⁸³ They developed a series of DalPhos ligands for nickel-catalyzed BHA reactions, such as PAdDalPhos,^{83b} NHP-DalPhos,^{83c} PhPAdDalPhos,^{83g} PAd2DalPhos,^{83e} and PhenDalPhos^{83f} (Scheme 28). They also compared the reactivities of Ni(I) (PAD-Ni^I) and Ni(II) (PAD-Ni^{II}) complexes for the BHA reactions of aryl chlorides.^{83a} Using their DalPhos-type ligand, the Ni(II) complex generally performs better than the Ni(I) complex. A computational study suggested

that reductive elimination was the rate-limiting step in the Ni(0)/Ni(II) catalytic cycle. Oxidative addition is the rate-limiting step in the Ni(I)/Ni(III) catalytic system. The authors also reported ligand-enabled site-selective reactions (Scheme 29). The reaction using PhenDalPhos as the ligand promoted the amination of indoles to provide **72**, whereas that using PAd2DalPhos promoted the amination of anilines to produce **73**. Baran et al. reported BHA reactions using electrochemistry.⁸⁴ This electrochemical reaction utilized an RVC anode and a nickel foam cathode. LiBr (4 mol equiv) was used as the electrolyte. They used $\text{NiBr}_2\cdot\text{glyme}$ complex (10 mol%) as a nickel source. Although they mainly focused on aryl bromides, they also showed that electron-deficient aryl chlorides were tolerated (up to 73% yield) for the BHA reactions under these conditions.



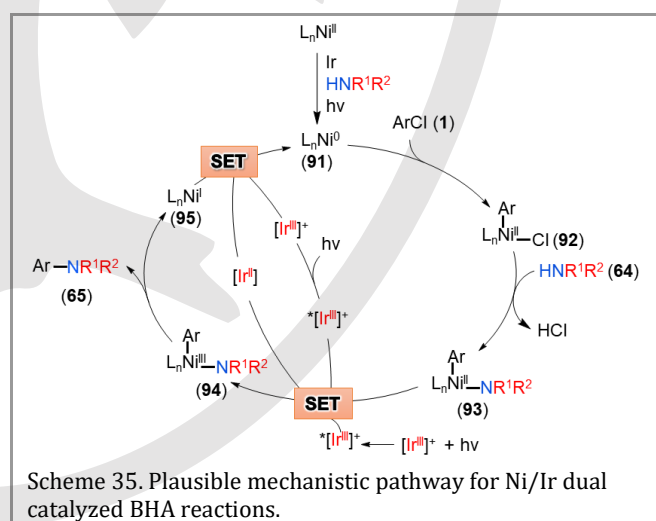
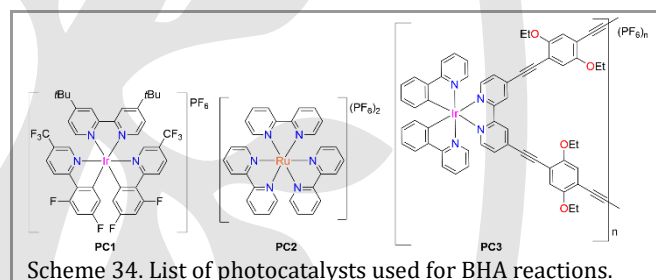
In 2020, the Engle et al. reported an air-stable 18-electron nickel(0)-olefin complex named $\text{Ni}(\text{cod})(\text{dq})$ catalyzed BHA and SM reactions.⁸⁵ This catalyst was prepared in an 8 g scale with a 79% yield. This $\text{Ni}(\text{cod})(\text{dq})$ complex was initially reported by Schrauzer in 1962.⁸⁶ Engle et al. applied $\text{Ni}(\text{cod})(\text{dq})$ in cross-coupling reactions and compared its reactivity with that of $\text{Ni}(\text{cod})_2$. The $\text{Ni}(\text{cod})(\text{dq})$ complex (5 mol%) showed improved reactivity toward aryl chlorides (BHA reaction); however, in the case of heteroaryl chlorides, $\text{Ni}(\text{cod})_2$ performed better. In the same year, Cornella et al. reported a 16-electron-nickel(0)-olefin complex (**C28**) derived from *trans*-stilbene.⁸⁷ The *t*-Bu

substituent increased the thermal stability of this complex. The authors claimed that this 16-electron Ni complex (**C28**) could be stored in open air at room temperature for at least 1 month. The BHA reaction of aryl chlorides and amines using this nickel complex provided the amination product in 90% yield, whereas Ni(cod)₂ provided the product in 96% yield. In 2021, we used a machine learning approach to find suitable reaction conditions for the BHA reactions of tolyl chloride and toluidine under nickel(II) catalysis.⁸⁸ The machine learning approach suggested that a combination of Ni(acac)₂ and XPhos could provide the maximum yield (35%), and laboratory experiments showed a 33% yield under the proposed conditions.



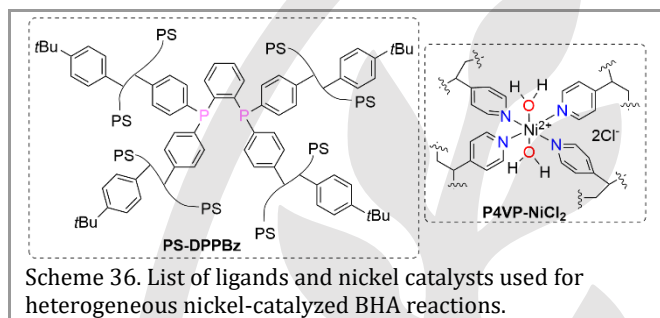
A C-N bond forming amination via kinetic resolution enabled by flexible and bulky chiral ligands was reported by Hong and Shi (Scheme 30).⁸⁹ As a chiral ligand, they used (*R,R,R,R*)-ANIPE (1.5 mol%) in the presence of Ni(cod)₂ (1.5 mol%). Multiple sterically hindered α -branched amines successfully underwent amination with up to 99.5% ee value. Computational studies suggested that oxidative addition has an energy barrier of 8.9 kcal/mol, whereas reductive elimination has an energy barrier of 14.7 kcal/mol. The transmetalation has an energy barrier of 14.0 kcal/mol. Thus, reductive elimination is the rate-determining step. Reductive elimination is also an enantioselectivity-determining step. Computational studies also suggested that the Ni(I)/Ni(III) catalytic cycle is unlikely to occur because of the high energy barrier. Hernandez, Garlets, and Frantz used a dual-base approach for BHA reactions to overcome functional group compatibility issues under strong alkoxide-type bases.⁹⁰ The alkoxide bases are poorly soluble and challenging to utilize in large-scale reactions. They collaborated with the industry and academia to develop a general method that could be applied to heteroaryl chlorides and amines (both aliphatic and aromatic). They found the reaction using a combination of NaOTf (1.5 mol equiv) and BTMG (1.5 mol equiv) provided amination of several heteroaryl and aryl chlorides in up to 99% yield (Scheme 31). They also performed a 20-gram-scale reaction of amine **79**, which is found in the TYK2 inhibitor Deucravacitinib, to obtain coupling product **81** in 99% yield (Scheme 31). Ananikov et al.

developed NiCl₂Py₂ (10 mol%)-and IPr (20 mol%)-catalyzed BHA reactions of aryl chlorides and amines.⁹¹ They obtained *N*-arylation products in 14–95% yield. Xue et al. developed purple LED light (390–395 nm)-assisted nickel-catalyzed BHA reactions.⁹² They used Ni(OAc)₂ (10 mol%) and dMeppy (10 mol%) for C-N bond-forming cross-coupling of aryl chlorides with ammonium bromide (NH₄Br),^{92a} aliphatic amines,^{92b} and hydrazine.^{92c} Recently, they used Warner salt ([Ni(NH₃)₆]Cl₂) as a catalyst for the BHA reaction of aqueous ammonia.^{92d} The purple LED light irradiation generates the Ni(I)-OAc complex via the generation of acetate radical, and then the reaction follows a Ni(I)/Ni(III) catalytic pathway (Scheme 32). These visible-light-promoted photocatalyst-free nickel-catalyzed reactions are limited to ammonia and primary and secondary amines. Lin et al. reported the sodium-iodide-promoted nickel-catalyzed C-N cross-coupling of aryl chlorides and aryl amines under visible-light irradiation (455 nm).⁴ The light irradiation generated Ni(I) species via the generation of aryl radicals. Halogen exchange was a critical step in this reaction (Scheme 33). The control experiments suggested that the addition of NaI was essential. Although the reaction provided a yield of up to 99%, it was limited to electron-deficient aryl chlorides. This reaction followed the Ni(I)/Ni(III) catalytic pathway. Xue et al. also found that the addition of KI was beneficial for the BHA reactions of aryl chlorides.^{92b}



MacMillan et al. reported a ligand-free nickel-iridium dual-catalyzed BHA reaction of aryl bromides.⁹³ They used NiCl₂.glyme (5 mol%) and iridium photocatalyst (**PC1**, Scheme 34). The main role of the Ir photocatalyst is to destabilize the nickel-amido intermediate via single-electron transfer (SET) and facilitate reductive elimination (Scheme 35). Additionally, the

photocatalyst assisted in the in-situ generation of Ni (0) species. Unfortunately, the BHA reaction of aryl chlorides did not proceed under these reaction conditions. Catalytically inactive nickel black was observed during the reaction, which limited the application of this reaction to aryl chlorides. Pieber et al. reported nickel-catalyzed BHA reactions of aryl chlorides by using CN-OA-m as a photocatalyst.⁹⁴ NiBr₂·3H₂O (5 mol%) was used as a nickel source. Using this NiBr₂/CN-OA-m system, the BHA reaction of electron-deficient aryl chlorides was performed. Electron-rich aryl chlorides such as 4-methoxy anisole coupled with pyrrolidine were obtained in only 2% yield, even after 168 h.



Buchwald et al. reported a BHA reaction using nickel/ruthenium dual catalysis in flow.⁹⁵ As a photocatalyst, they used PC2. They obtained a yield of 65–93% using electron-deficient aryl chlorides, whereas coupling between chlorobenzene and pyrrolidine provided only a 22% yield. Yasuran and Zhang reported nickel-catalyzed BHA reactions in the presence of an acetylene-based hydrazone-linked covalent organic framework (AC-COF-1, Scheme 28) and blue LED (440 nm) irradiation.⁹⁶ Like Pieber, they also used NiBr₂·3H₂O (7.5 mol%) as a nickel source. Using this Ni/AC-COF-1 dual-catalytic system, the authors performed BHA reactions of electron-deficient and electron-rich aryl chlorides and obtained a yield of up to 99%. In this study, pyrrolidine was used as the only amine source. In summary, the utilization of a dual nickel-photocatalyst system appears to be effective for the BHA reactions of aryl chlorides. The use of electron-rich ligands in nickel catalysis under photo-redox-free conditions would be an alternative pathway.

3.4. Heterogeneous nickel catalysis

Sawamura et al. reported a polystyrene-cross-linking bisphosphine (PS-DPPBz, Scheme 36) as a ligand for the nickel-catalyzed amination reaction.⁹⁷ As a nickel source, they used Ni(cod)₂ in 1 mol%. The in situ-generated polymer-supported nickel complex catalyzed the BHA reactions of electron-deficient and electron-rich aryl chlorides and primary aliphatic amines to produce C-N bond-forming products in 97% yield. Hot-filtration and mercury poisoning experiments confirmed the heterogeneous nature of the catalysts. The PS-DPPBz-Ni catalyst was recovered and reused. The catalytic activity decreased to 73% in the 3rd run compared to 90% in the 1st run. The ICP-AES analysis of the reaction mixture confirmed the leaching of Ni. There are a few reports on light-assisted heterogeneous nickel-catalyzed BHA reactions of aryl halides.⁹⁸ Unfortunately, these reactions are highly restricted to aryl iodides and bromides. We recently prepared a linear polymeric iridium photocatalyst, PC3 (Scheme 34).⁹⁹ This newly developed polymeric iridium photocatalyst was used for the nickel-iridium dual-catalyzed BHA reactions of aryl chlorides. As the nickel catalyst, we used

poly(4-vinylpyridine), a convoluted polymeric nickel complex (P4VP-NiCl₂, 0.2 mol%; Scheme 36). In this reaction, dual irradiation with visible light (430 nm) and microwaves was essential. The addition of TBAB is necessary for this reaction. Several electron-rich and electron-deficient aryl chlorides (**96–102**) were used in this reaction to produce quantitative yields (Scheme 37). Cyclic primary amines, cyclic secondary amines, linear primary amines, branched primary amines, and aryl amines all produced BHA reactions in 43–91% yields (**103–106**). Molecules with antimalarial (**107**), anticancer, anti-HIV (**108**), and antiviral (**109**) properties were synthesized under these conditions. The polymer-supported Ni and Ir catalysts could be recovered and reused at least five times without any loss of catalytic activity (Table 1). In summary, a reusable nickel-photocatalyst dual catalytic system is a promising catalytic system for the BHA reactions of aryl chlorides.

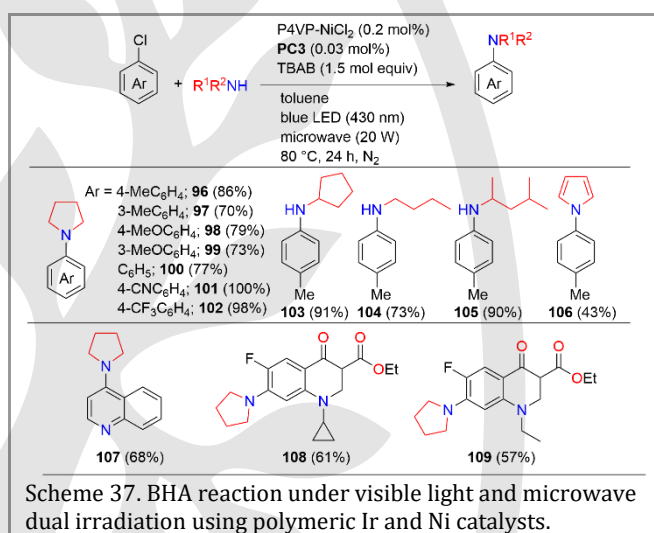


Table 1. Catalyst reusability for dual nickel/iridium catalysis.

Entry	Number of times used (Ni and Ir)	Yield of 101 (%)
1	1 st	>99
2	2 nd	99
3	3 rd	99
4	4 th	99
5	5 th	99
6	6 th	99

4. Conclusion

In the past decade, significant advancements have been made to overcome the low reactivity of readily available and inexpensive aryl chlorides in nickel and palladium catalysis. The selection of

the appropriate ligand—particularly those that are sterically bulky and electron-rich—can be critical for successful cross-coupling of aryl chlorides. The use of photocatalyst-assisted metal-catalyzed cross-coupling is another viable option. The studies discussed above indicate that, depending on the metal catalyst and ligand, the rate-determining step for the cross-coupling of aryl chlorides could be oxidative addition, transmetalation, or reductive elimination. Several

pharmaceutical products have been synthesized on a large-scale using aryl chlorides, underscoring the industrial relevance of this approach. Despite the significant progress made, there remains room for further improvements, such as discovering cross-coupling reactions of aryl chlorides at room temperature using highly stable and reusable metal catalysts under additive-free conditions.

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Conflict of Interest

The authors declare no conflict of interest.

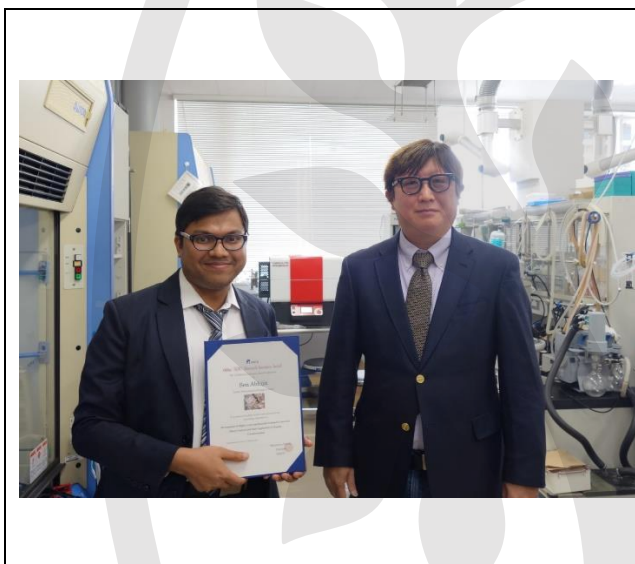
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Biosketches



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