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Latest Developments on Palladium- and Nickel-Catalyzed Cross-Couplings Using Aryl Chlorides: Suzuki–Miyaura and Buchwald–Hartwig Reactions

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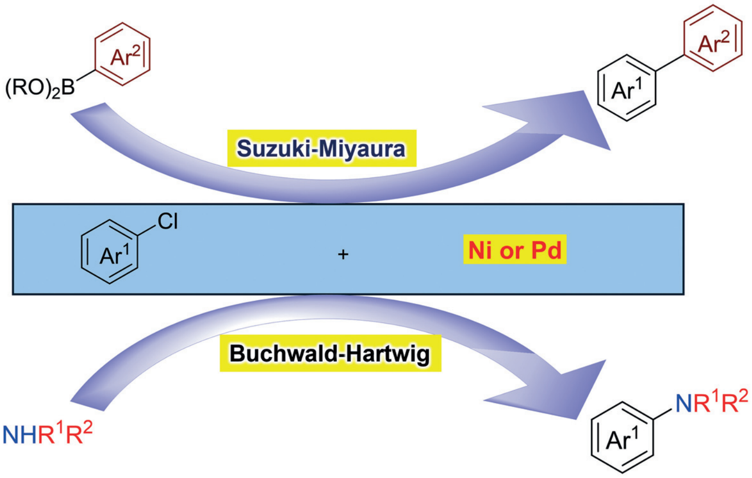

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Abstract Palladium- and nickel-catalyzed cross-couplings are powerful methods for constructing C–C and C–N bonds, particularly through Suzuki–Miyaura and Buchwald–Hartwig reactions. Although aryl iodides, bromides, and triflates are the most commonly 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 on the Suzuki–Miyaura and Buchwald–Hartwig cross-couplings of aryl chlorides, using both homogeneous and heterogeneous catalysis with palladium and nickel.

Key words palladium catalysis, nickel catalysis, cross-coupling, aryl chloride, Buchwald–Hartwig amination, Suzuki–Miyaura coupling, homogeneous catalysis, heterogeneous catalysis

1 Introduction

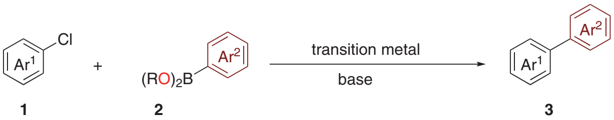
Cross-coupling reactions are extensively studied and are very important processes in chemical synthesis. Among these, Suzuki–Miyaura (SM) reactions,[1] which form C–C bonds, and Buchwald–Hartwig (BHA) reactions,[2] which form C–N bonds, are widely used in both academia and industry. Palladium and nickel 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, which limits 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 the application of aryl chlorides in SM and BHA 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 reports (since 2013) on SM and BHA reactions with aryl chlorides using both homogeneous and heterogeneous palladium and nickel catalysis.

Abhijit Sen (left) earned his master's degree from the University of Hyderabad, India, in 2015. He then pursued doctoral studies at Osaka University, Japan, under the supervision of Prof. Hiroaki Sasai. His doctoral research focused on palladium-catalyzed aza-Wacker-type reactions. After receiving his Ph.D. in 2018, he joined RIKEN as a postdoctoral fellow under the guidance of Dr. Yoichi M. A. Yamada in 2019. In 2022, he was promoted to the position of research scientist at the same institute. He is currently engaged in developing highly active and reusable polymer-supported metal catalysts and applying them to organic transformations.

Yoichi M. A. Yamada (right) earned his Ph.D. from the University of Tokyo, Japan, in 1999. Following positions at Teikyo University, Japan, The Scripps Research Institute, USA, and the Institute for Molecular Science, Japan, he became Deputy Team Leader at RIKEN, Japan. In 2018, he was appointed Team Leader of the Green Nanocatalysis Research Team at the RIKEN Center for Sustainable Resource Science. His research focuses on developing highly active and reusable heterogeneous catalysts for batch and flow organic transformation reactions, with interests in microwave and light-irradiation applications.

2 Suzuki–Miyaura Cross-Coupling

The transition-metal-catalyzed Suzuki–Miyaura (SM) cross-coupling of aryl chlorides with arylboronic acids/esters has emerged 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 arylborinates **S3**, triarylboranes **S4**, and diarylborinic acids **S5** (Figure 1).



Scheme 1 General representation of the Suzuki–Miyaura cross-coupling of aryl chlorides

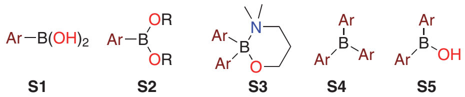
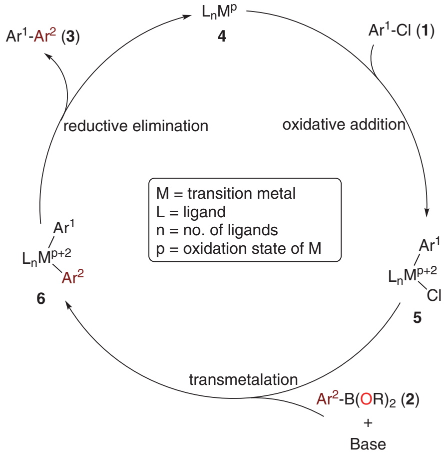


Figure 1 Commonly used boron sources for SM reactions

SM cross-coupling involves three mechanistic steps: (i) oxidative addition, (ii) transmetalation, and (iii) reductive elimination (Scheme 2). Owing to the low reactivity of aryl chlorides [bond-dissociation energy (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 can stabilize transition-metal nanoparticles by avoiding aggregation.[3] The addition of NaI is reported to facilitate the reaction of aryl chlorides via halide exchange.[4] Additionally, the ligand design 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 SM cross-couplings of aryl chlorides using homogeneous (2.1 and 2.3) and heterogeneous (2.2 and 2.4) palladium (2.1 and 2.2) and nickel (2.3 and 2.4) catalysts are presented.



Scheme 2 General catalytic cycle for the SM cross-coupling

2.1 Homogeneous Palladium Catalysis

In 2013, Nechaev et al. developed a diaminocarbene palladium complex **C1** (Figure 2) 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

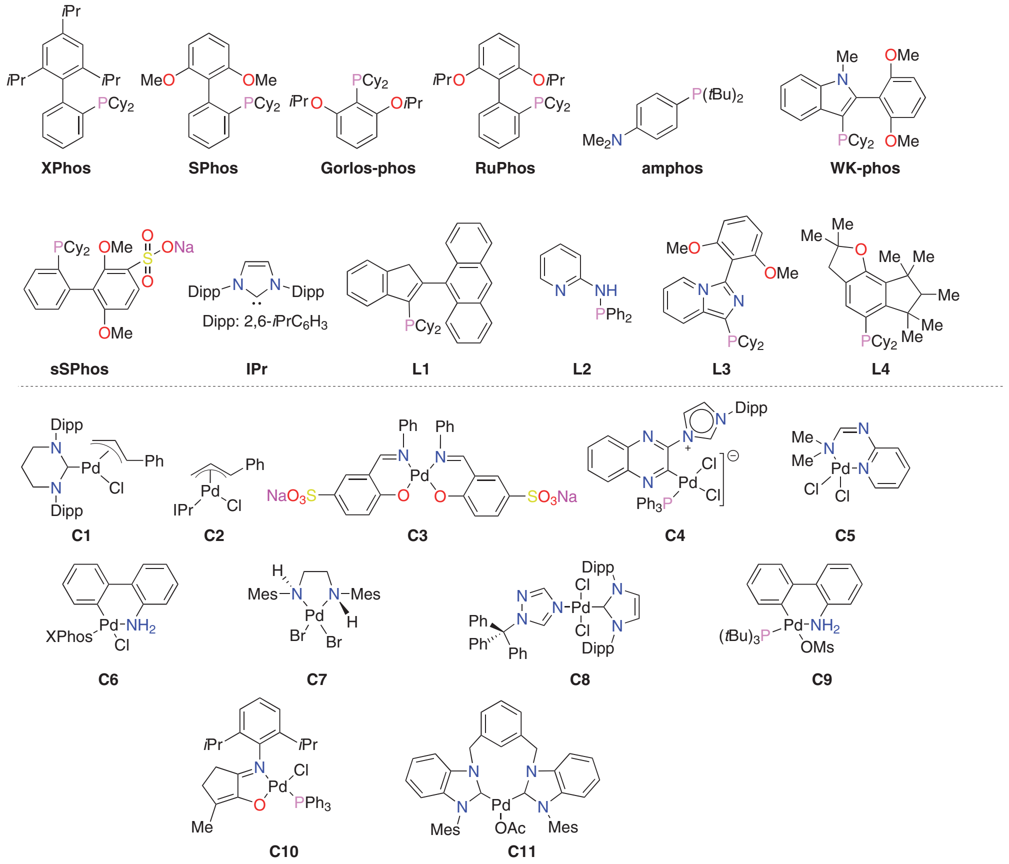
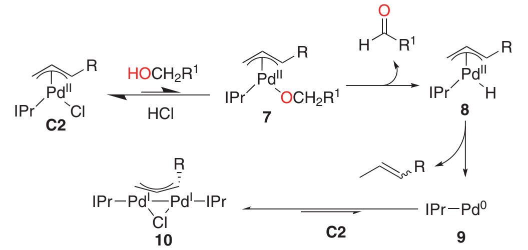


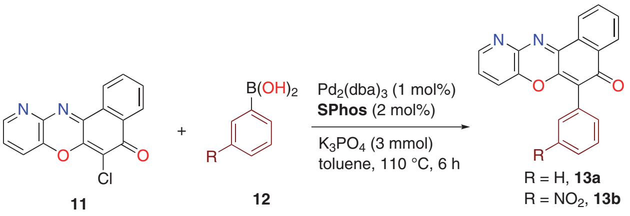
Figure 2 Homogeneous Pd complexes and ligands used for the SM reactions

TBAB was essential for this transformation and the coupling products were obtained in up to 99% yield. In 2014, the group of Balcells, Hazari, and Tilset 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 minutes 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 3). This Pd(I)-μ-allyl dimer **10** was less reactive and provided only a 4% yield of the biaryl product under the same conditions using **C2**.

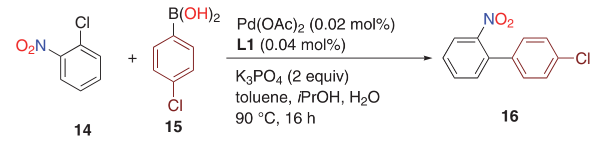


Scheme 3 A plausible pathway for the generation of a Pd^{I} dimer

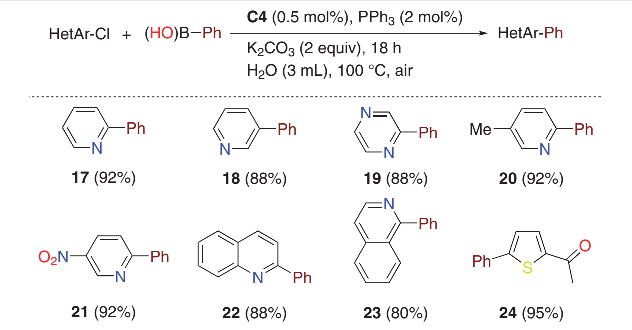
In 2015, Ayogu et al. prepared antimicrobial compounds via SM cross-couplings using $Pd_2(dba)_3$ (1 mol%) and SPhos (2 mol%), and the corresponding products **13a** or **13b** were both obtained in 43% yield (Scheme 4).[8] Li, Zhong and co-workers reported the SM cross-couplings of aryl chlorides with trialkyl- and triaryl-borane derivatives **S4**.[9] They used $Pd(OAc)_2$ (2.5 mol%) as the metal source and RuPhos (5 mol%) as the ligand. They prepared the trialkylboranes from the corresponding olefin and $BF_3{\cdot}Et_2O$, and used them in the SM cross-couplings in one-pot. In this one-pot process, the products were obtained in up to 86% yield. Das and co-workers applied the hydrophilic salen-Pd(II) complex **C3** (1 mol%) to the cross-couplings of aryl chlorides and arylboronic acids 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 a 45% yield of 4-nitrobiphenyl. This was improved by adding a phase-transfer catalyst, cetyltrimethylammonium bromide (CTAB), leading to the desired product in 96% yield. Zou, Tang and co-workers used *O*,*N*-chelate-stabilized diarylborinates **S3** (Figure 1) 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 reactions of electron-rich or electron-deficient aryl chlorides and diarylborinates afforded the corresponding products in 70–99% yield, indicating that the reaction was less sensitive to electronic variation on the benzene rings. Unfortunately, the chemical yield decreased because of steric hindrance in 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% of the catalyst. Yu et al. reported SM couplings by using Pd(OAc)$_2$ (0.02 mol%) and ligand **L1** (0.04 mol%) in toluene/*i*-PrOH/H$_2$O.[12] Heterocyclic aryl chlorides such as 2-chloropyridine, 3-chloropyridine, and 2-chloropyrazine were converted into the desired products in yields of 84–95%. The intermediate **16** for the synthesis of boscalid was produced in 91% yield via a SM reaction, and the TON of the catalyst reached 4550 (Scheme 5). Ren, Young, and Lang used *N*-diphenylphosphanyl-2-aminopyridine (**L2**) as a ligand and PdCl$_2$ (1.5 mol%) for the palladium-catalyzed SM cross-couplings of aryl chlorides.[13] This reaction was applied to electron-deficient aryl chlorides only, while the products were obtained in up to 98% yield. Reddy et al. developed a zwitterionic Pd(II) complex **C4** (0.5 mol%) and utilized it for SM couplings of aryl or heteroaryl chlorides,[14] where triphenylphosphine (PPh$_3$) (2 mol%) was used as an additional ligand. The reactions of multiple heterocyclic aryl chlorides, including pyridine, pyrazine, quinoline, isoquinoline, and thiophene, afforded cross-coupling products **17**–**24** in yields of 80–95% (Scheme 6).



Scheme 4 Synthesis of antimicrobial compounds

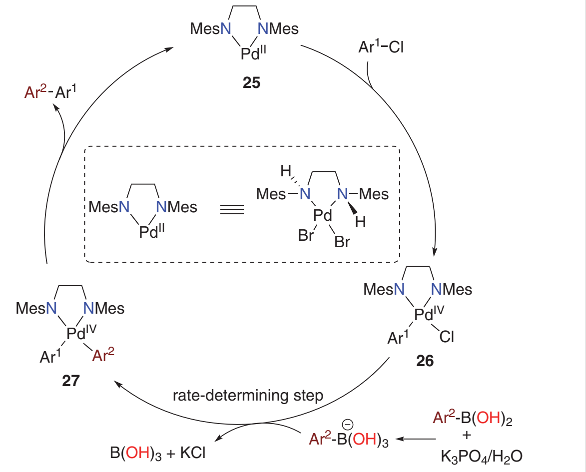


Scheme 5 Synthesis of an intermediate for the preparation of boscalid



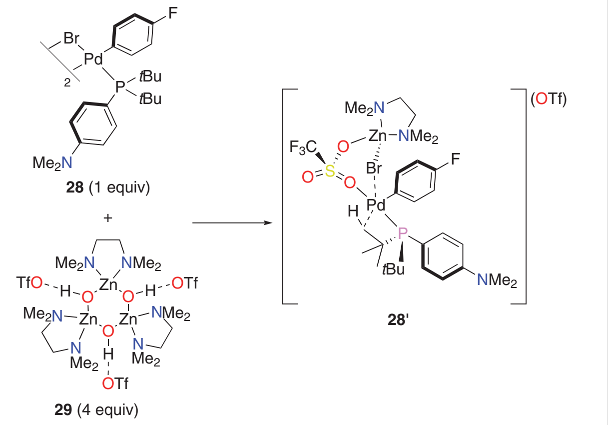
Scheme 6 SM couplings of heteroaryl chlorides

The SM coupling of chlorobenzene and phenylboronic acid using a pyridylformidine-based Pd(II)-complex **C5** proceeded 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 corresponding products in quantitative yields (three examples). Ji et al. reported the 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 the metal source and the ligand, respectively. The reactions of electron-rich and electron-deficient aryl chlorides with arylboronic acids produced the coupled products in 56–96% yield. Heteroaryl chlorides and heteroarylboronic 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, with product yields of up to 95%.[17] Liu, Huang, Wang and co-workers reported the diamine-based palladium complex **C7**.[18] The use of 0.05 mol% of **C7** led to yields of up to 96% in SM reactions. Unfortunately, the reactions of heteroaryl chlorides and sterically hindered aryl chlorides failed to produce the coupling products. The authors detected Pd^0, Pd^{II}, and Pd^{IV} species using XPS. Thus, they proposed two simultaneous reaction pathways: conventional Pd^0/Pd^{II} and Pd^{II}/Pd^{IV} catalysis (Scheme 7). In addition, they confirmed the possibility of a Pd^{II}/Pd^{IV} catalytic pathway using DFT studies, which suggested that transmetalation was the rate-determining step in this catalytic cycle. Schmidt et al. reported that the oxidative addition of aryl chlorides to ligand-free Pd species was a reversible process.[19] Thus, under ligand-free conditions, oxidative addition was not the rate-determining step. In 2020, Zeng and Liu reported the 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 arylboronic acids afforded the corresponding products in 78–98% yield. This reaction tolerated steric hindrance but did not tolerate heteroaryl chlorides. The monophosphine ligand WK-phos was reported by Kwong et al.[21] Using this WK-phos ligand and Pd(OAc)$_2$, the palladium loading was reduced to 10 mol ppm without dropping the reaction yield (>99%), with a TON of up to 100,000. 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 utilized it with Pd(OAc)$_2$ (2.5 mol%) for SM reactions.[22] They obtained yields of up to 92% of the desired biaryl derivatives.



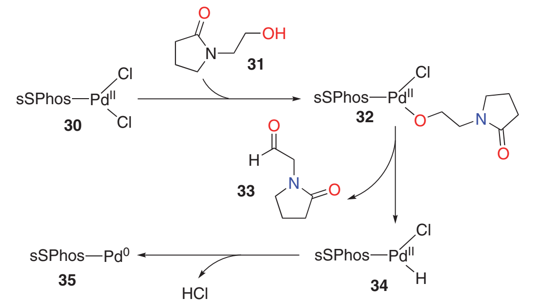
Scheme 7 A Pd^{II}/Pd^{IV} catalytic cycle for SM reactions

Niwa and Uetake have 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 chlorides is unique.[24] The base-free SM coupling is mainly reported with a cationic organopalladium(II) intermediate, which is thermally unstable and limits the applications.[25] The role of the 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 8). 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.



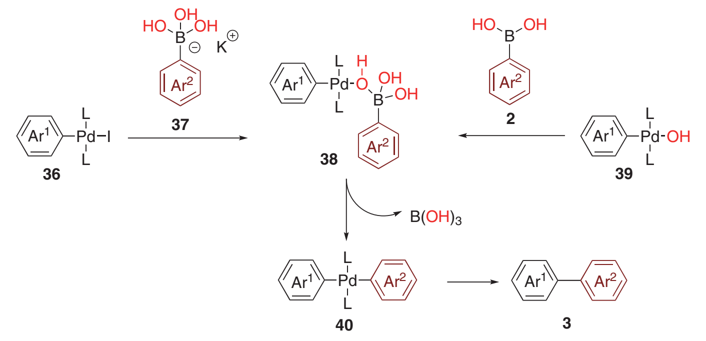
Scheme 8 Activation of a Pd species for base-free Lewis acid mediated SM reactions

The *N*-hydroxyethylpyrrolidone (HEP) (**31**) promoted reduction of a Pd(II) complex was reported by Fanatoni and Carbi.[26] The proposed mechanism for HEP-promoted Pd^0 formation from Pd^{II} is shown in Scheme 9. This Pd^0 species efficiently catalyzed the SM coupling to produce products in yields of up to 95%. In this study, PdCl$_2$(MeCN)$_2$ (0.05 mol%) and sSPhos (0.15 mol%) were used as the metal and the 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)$_2$ (2.5 mol%) and **L4** (5 mol%) provided biaryl derivatives in up to 80% yield. In 2021, Schaub et al. reported a Pd(OAc)$_2$ (50 ppm)-catalyzed SM coupling of aryl chlorides and arylboronic acids in water.[28] As the ligand, they used P(*t*Bu)Cy$_2$ (0.02 mol%), and the corresponding products were obtained in up to quantitative yield. Additionally, they synthesized several industrially important fungicides, such as boscalid, fluxapyroxad, and bixafen. In this reaction, they achieved a TON of up to 20,000 and a TOF of 2,000 h^{-1}. 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 trimethylsilanolate (TMSOK) as the base, and the reaction was performed at 23 °C. The reactions of aryl chlorides with aryl neopentyl esters afforded the products in up to 91% yield. The same group also reported 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 10.

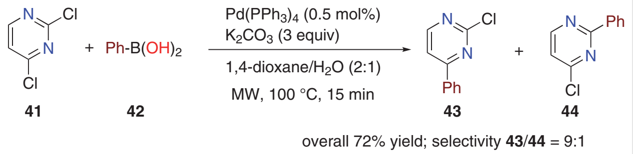


Scheme 9 HEP-promoted reduction of a Pd(II) complex

A microwave-assisted regioselective SM coupling of 1,4-dihydropyridines and aryl/heteroarylboronic acids using Pd(PPh$_3$)$_4$ (0.5 mol%) was reported by Sova et al.[30] The reaction was completed within 15 minutes under microwave irradiation conditions at 100 °C. This reaction afforded C4-substituted pyrimidines. The products **43** and **44** were obtained with a selectivity of 9:1 and an overall yield of 72% (Scheme 11). McIntosh and Mansell reported the SM cross-couplings of aryl chlorides and arylboronic acids at room temperature using the Pd(II) complex **C10** (1 mol%) and monoanionic [*N*,*O*] ligands.[31] The authors observed that the rate of the reaction increased significantly on increasing the 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.



Scheme 10 A pre-transmetalation Pd–O–B intermediate: a missing link



Scheme 11 C4-selective SM reactions

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-methylchlorobenzene 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 the discovery of pre-transmetalation intermediates. Additionally, researchers have shown that the choice of ligand (electron-rich) and base (to prevent substrate decomposition) are 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 fourth reuse. ICP-OES analysis suggested that the Pd loading decreased during recycling. The Pd loading after the fourth 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) (Figure 3).[34] Using this Pd-nSTDP complex (60 mol ppm), up to 96% coupling yields were obtained under microwave irradiation. Although the authors mainly focused on the reactions 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 an 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] They performed SM cross-couplings of aryl chlorides and heteroaryl chlorides with phenylboronic acid to afford the desired products in up to 96% yield by 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 the fifth reuse. TEM observations showed that there were no changes in the nanoparticle morphology, and ICP-AES analysis indicated no change in the Ni/Pd composition after the SM coupling reaction. Firouzabadi et al. have reported phosphinite-functionalized clay-composite-stabilized Pd nanoparticles.[36] In their studies, the cross-coupling of chlorobenzene and phenylboronic acid proceeded with 720 mol ppm of Pd (from the clay composite) in water to give an 88% yield of biphenyl at 80 °C. The SM couplings of 4-chloronitrobenzene and 4-chlorotoluene with phenylboronic acid also proceeded successfully. 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**) (Figure 3).[37] The authors used this Silica-TRIP as a ligand (0.5 mol%) for the SM coupling of aryl chlorides using $PdCl_2(py)_2$ as a metal source (0.5 mol%). While the reaction using in situ generated $PdCl_2(py)_2$/**L5** provided a 5% yield of the biaryl product, precomplexed $PdCl_2(py)_2$/**L5** gave a 56% yield. The yield further improved to 93% when the metal source was changed from $PdCl_2(py)_2$ to $Pd(OAc)_2$. The recovered $Pd(OAc)_2$/**L5** catalytic system afforded the product in 28% yield on the second run and in 3% yield on the third 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 $FeCl_3$, which contained Pd as a contaminating metal

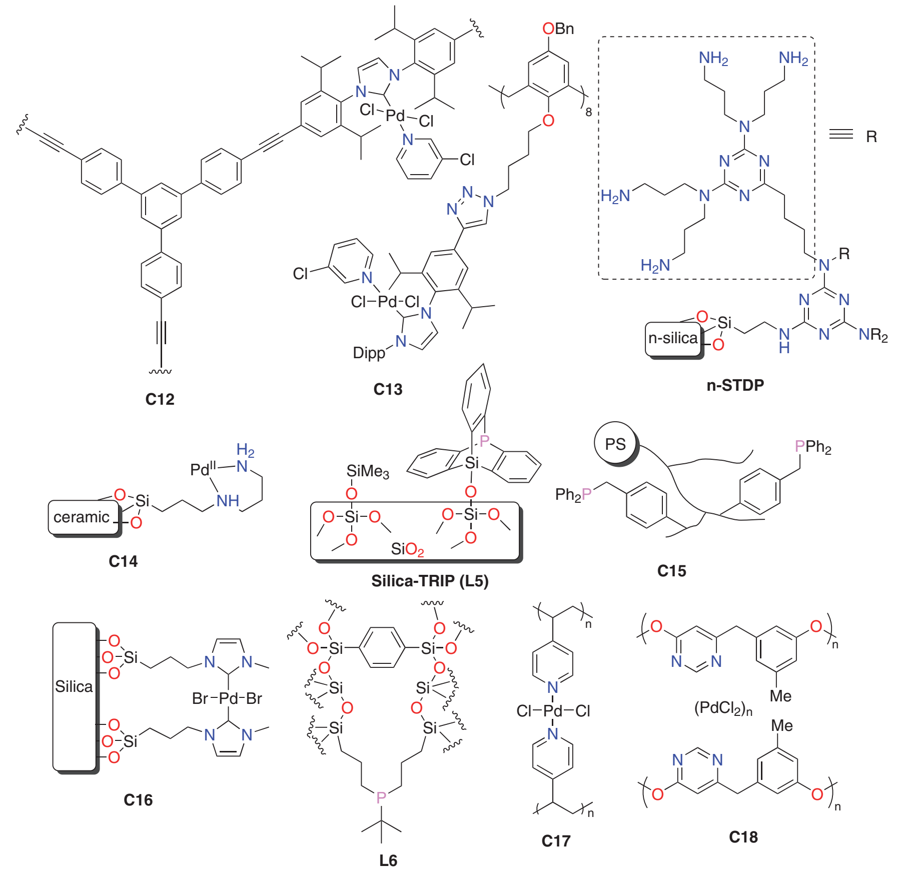


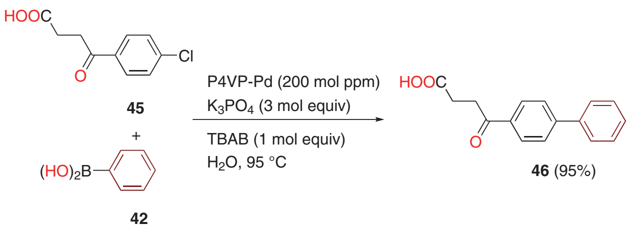
Figure 3 Pd complexes and ligands used for heterogeneous palladium-catalyzed SM reactions

species, promotes SM reactions.[38] They used $FeCl_3$ (5 mol%, 97% purity), in which 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 was also crucial, as SPhos or XPhos were the only ligands that promoted this reaction. The reactions of aryl chlorides with the commercially available surfactant TPGS-750-M in water afforded the corresponding products in 85% yield. A reusability test was performed with a more reactive aryl bromide; however, a loss in reactivity was observed: the yield dropped to 87% in the fourth run while the yield was 95% in the first run using fresh catalyst. Andrés and Flores developed the silica-supported bis-(NHC) complex **C16** containing palladium (Figure 3).[39] This palladium catalyst was immobilized on γ-Fe_2O_3 and provided an 89% yield of the product in the reaction of 4-chlorotoluene and phenylboronic acid using 0.024 mol% of Pd. The catalyst was magnetically recovered after the reaction. However, the catalyst exhibited a gradual decrease in yield, and Pd leaching from the catalyst was observed. ICP-MS analysis showed 10 ppm of Pd contamination in the product. Li and Chen reported a Pd and Co bimetallic hybrid nanocrystal ($Pd\text{-}Co_3[Co(CN)_6]_2$) with a Pd/Co ratio of 3:1.[40] This nanocrystal (0.45 mol% Pd) afforded biphenyl in 86% yield. The catalyst was recovered and reused eight times. The Pd content of the solution after the first and fifth cycles was less than 100 ppb, whilst the Pd-to-Co ratio remained unchanged after the reaction.

Friedrich et al. prepared PdCuCeO by substituting Pd^{2+} and Cu^{2+} in the CeO_2 lattice.[41] PdCuCeO as a catalyst promoted the SM reaction in the presence of tetrapropylammonium bromide (TPAB). SM coupling of electron-deficient aryl chlorides using 2.3 mol% Pd proceeded to provide the products in quantitative yields. However, this catalyst failed to cross-couple arylboronic acids with electron-rich aryl chlorides. Sajiki et al. developed an anatase-type TiO_2-supported Pd catalyst, Pd/TiO_2.[42] The SM coupling of an electron-deficient aryl chloride proceeded with the Pd/TiO_2 (5 mol%) 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 glass-supported palladium nanoparticles (SGIPd) (0.35 mol%) under microwave irradiation was reported by Arisawa et al.[43] In this reaction, the TON reached 28,571, and the TOF reached 1,120 h^{-1}. The catalyst was used 10 times, and the yield dropped to 90% on the tenth use from 98% on its first use. Electron-rich, electron-deficient, and heteroaryl chlorides reacted to yield the corresponding products in up to 98% yield.

Motokura et al. observed the unexpected formation of triphenylborane (Ph_3B) during a palladium-catalyzed SM coupling reaction using a mesoporous silica-supported Pd complex catalyst Pd/MS.[44] Ph_3B is an active intermediate in the SM coupling of aryl chlorides and phenylboronic acids. Meanwhile, Bai et al. reported an effective photothermal dual-responsive Pd_1Cu_4/Ce_xO_y catalyst (1 mg/mmol substrate).[45] The SM reactions of aryl chlorides and arylboronic acids with this catalyst 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 have reported graphene oxide supported palladium-nanoparticle-catalyzed (Pd/rGO-60) (0.5 mol%) SM coupling in water under microwave irradiation.[46] The reactions of electron-rich and electron-deficient aryl chlorides afforded the products in up to 95% yield. Microwave irradiation reduced the reaction time from 20 hours to 2.5 hours, and the presence of tetrabutylammonium bromide (TBAB) was essential in this reaction. Abdellah and Huc developed a palladium PEPPSI-IPr complex supported on calix[8]arene **C13** (0.2 mol% to 1 mol%) (Figure 3).[47] The cross-coupling reactions of electron-rich and electron-deficient aryl chlorides and heteroaryl chlorides proceeded 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**) (Figure 3),[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 arylboronic acids in water. Electron-rich and electron-deficient heteroaryl chlorides were tolerated by this P4VP-Pd catalyst. Interestingly, the non-steroidal anti-inflammatory drug fenbufen (**46**) was directly synthesized using P4VP-Pd catalysis (Scheme 12). The catalyst was recovered and reused without a significant loss of catalytic activity, with a 92% yield on the first use and a 91% yield on the fourth 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(mPO)$_n$ (**C18**),[48e] with a 400 ppb Pd loading, which enabled SM coupling in water. The TON and TOF reached 1,900,000 and 95,000 h^{-1}, respectively.



Scheme 12 Synthesis of the anti-inflammatory drug fenbufen

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-methoxybenzoic acid took place in the presence of Pd/SF with 3.8 mol% Pd over 3 hours 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 twenty-fifth 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**) (Figure 3).[50] A catalyst reusability test showed a gradual catalytic activity loss until the third reuse (the yield changed from 96% to 91%), followed by a sudden decrease to 56% during the fourth 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 the fifth reuse. Nakajima et al. reported SM couplings using a Pd catalyst supported on phosphine periodic mesoporous organosilica **L6**.[52] They used $Pd(dba)_2$ (2.5 mol% Pd) as the 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 SM reactions of aryl chlorides.[53] Irrespective of the steric and electronic nature of the aryl chloride, the reactions provided quantitative yields of products by utilizing 0.5 mol% of Pd. ICP-MS analysis showed that the reaction mixture contained less than 0.1 ppb Pd, which indicated that the Pd catalyst is stable and that leaching of Pd does not occur. The catalyst was reused five times, affording the product in 95% yield on the fifth reuse. Lee and Joung reported an ordered mesoporous polymeric phosphine (Meso-PPh_2)-supported palladium catalyst **C15** (Figure 3).[54] The reaction of electron-deficient aryl chlorides using 4 mol% of **C15** afforded the products in up to 93% yield. The reactions of electron-rich aryl chlorides produced biaryls in 19–43% yield. Catalyst **C15** was not reusable, and inactive palladium black formation was observed in the recovered catalyst by TEM. In addition, Pd leaching was observed.

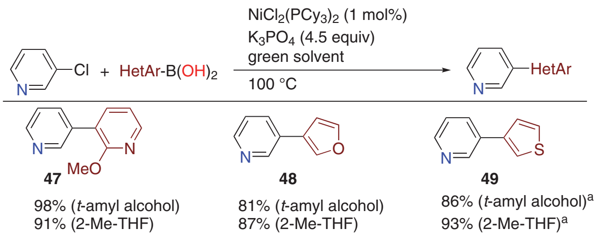
In summary, there are multiple reports of heterogeneous palladium-catalyzed SM reactions of aryl chlorides. However, in most of these reports, either palladium leaching or deactivation of the palladium catalyst was observed. A convoluted polymer-supported palladium catalyst might be helpful for this purpose.

2.3 Homogeneous Nickel Catalysis

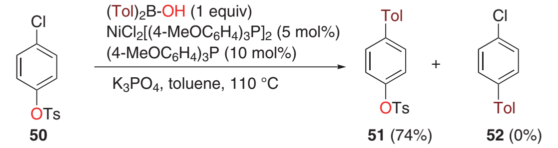
Since the Suzuki–Miyaura coupling is the reaction of organic halides (and their equivalents) with organic boronic acids (and their equivalents) using Pd catalysts, the reaction using Ni catalysts should be described as a Suzuki–Miyaura-type reaction (coupling). To simplify the description, we also use the term ‘SM reaction (SM coupling)’ for the Ni-catalyzed reactions described herein.

In 2013, Garg et al. reported nickel-catalyzed SM couplings in *t*-amyl alcohol or 2-Me-THF as green solvents.[55] The SM coupling of 3-chloropyridine and phenylboronic acid proceeded quantitatively using $NiCl_2(PCy_3)_2$ (1–5 mol%). Several heteroarylboronic acids were converted into the corresponding products in 81–98% yield (Scheme 13). In the same year, Lei et al. reported the SM reaction of aryl chlorides using the Ni(II) σ-aryl complex **C20** (Figure 4).[56] The SM coupling proceeded with 5 mol% of **C20** and 10 mol% of PPh_3. 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 arylboronic acids or heteroarylboronic acids were not suitable for this reaction (trace to 8% yields).

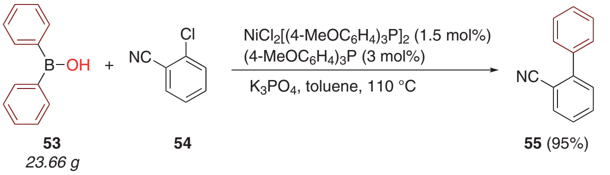
In 2014, Zou et al. reported the SM coupling of aryl chlorides with diarylborinic acids **S5** using $NiCl_2[(4\text{-}MeOC_6H_4)_3P]_2$ (5 mol%).[57] Interestingly, in this reaction, a chloride moiety selectively underwent the SM coupling with the diarylborinic acid in the presence of a tosylate (Scheme 14). Additionally, the same authors synthesized 2-cyanobiphenyl (**55**), a key intermediate for the synthesis of a sartan (a medicine for hypertension), on a scale of ca. 24 g (Scheme 15).



Scheme 13 Nickel-catalyzed SM reactions of heteroaryl chlorides and heteroarylboronic acids in green solvents. [a] 5 mol% $NiCl_2(PCy_3)_2$.



Scheme 14 Aryl chloride selective nickel-catalyzed SM reactions



Scheme 15 Synthesis of a biphenyl sartan on gram scale

In 2021, Nelson et al. reported the SM coupling of 3- and 4-chloropyridines using Ni(cod)(dppf).[58] They also found that 2-chloropyridine underwent dimerization (Scheme 16). 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. Meanwhile, Kumar et al. reported the SM coupling reaction of aryl halides using $NiBr_2$ (8 mol%) as the catalyst.[59] Although their method provided yields of up to 92% with aryl bromides and iodides, it only provided yields of up to 42%

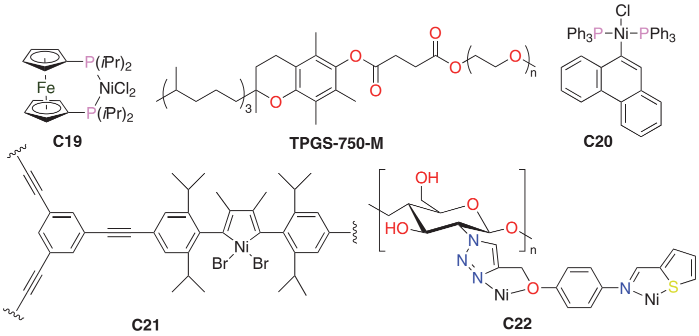
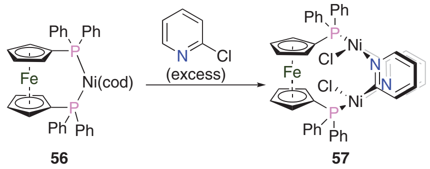


Figure 4 Nickel complexes and surfactants used in heterogeneous nickel-catalyzed SM reactions

with aryl chlorides. Doyle et al. have reported comparison studies of monophosphine and bisphosphine ligands for the Ni-catalyzed SM reactions of aryl chlorides (Scheme 17).[60] Although bisphosphine-type ligands are typically used for nickel-catalyzed SM reactions, the results suggested that monomeric phosphine ligands (e.g., CyTyrannoPhos) might outperform bisphosphine ligands depending on the nature of the substrates. They proposed that monophosphine ligands enabled challenging oxidative addition and transmetalation steps, whereas bisphosphine ligands prevented off-cycle reactivity and catalyst deactivation.

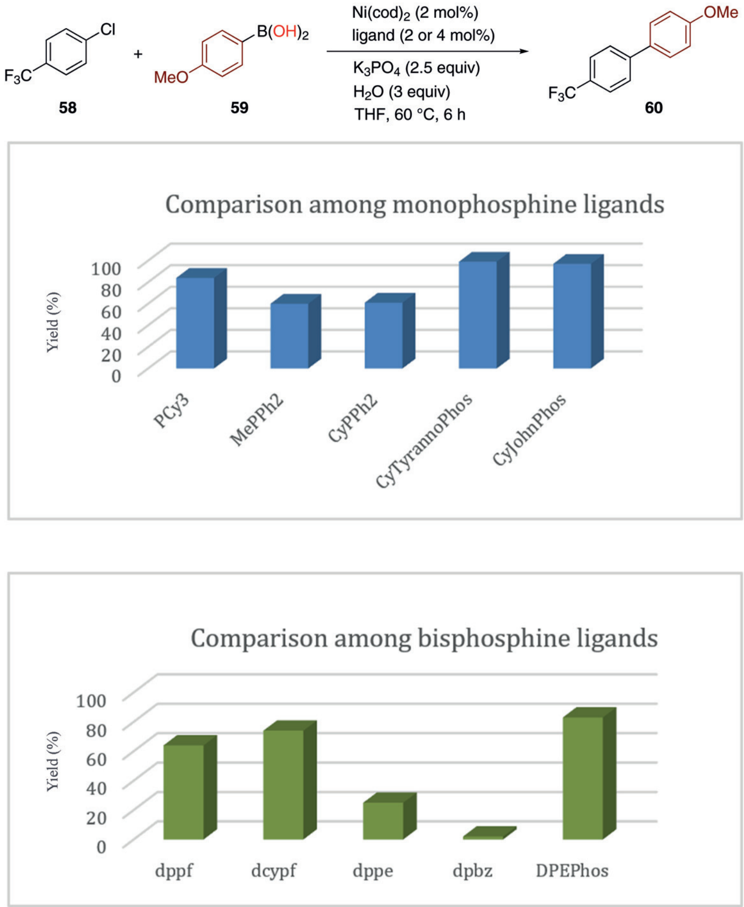


Scheme 16 Dimeric nickel-complex formation, which inhibits the SM coupling of 2-chloropyridine

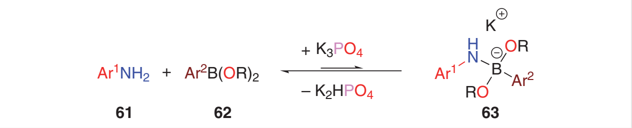
In summary, electron-rich and sterically hindered ligands are suitable for SM couplings of aryl chlorides under homogeneous nickel catalysis.

2.4 Heterogeneous Nickel Catalysis

In 2015, Lipshutz et al. reported a nickel-nanoparticle-catalyzed SM reaction in water.[61] They used complex **C19** (3 mol%) as the nickel source and performed SM coupling reactions in the presence of TPGS-750-M as a surfactant (Figure 4). 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.



Scheme 17 Comparison of the reactivity of monophosphine and bisphosphine ligands



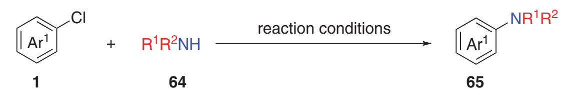
Scheme 18 Generation of a B–N ate complex

In 2017, Hajipour and Abolfathi developed chitosan-supported nickel nanoparticles **C22** (Figure 4).[62] The SM couplings of electron-rich and electron-deficient aryl chlorides proceeded well with 0.2 mol% of the catalyst and afforded the 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 of nickel contamination. Cai et al. have developed a recyclable and efficient NiCl$_2$(dppp)/PEG-400 catalytic system for the SM reactions of aryl chlorides and arylboronic acids.[63] Using a catalyst loading of 2 mol%, they obtained yields of up to 95% from electron-rich, electron-deficient, and heteroaryl chlorides. The NiCl$_2$(dppp)/PEG-400 system was recovered and reused 6 times. The yield of biaryl formation was 92% on the sixth use, whereas the fresh catalytic reaction provided a 95% yield. A nickel contamination test using ICP-MS showed only 0.8 ppm of nickel contamination in the products. In 2020, we developed activator-promoted aryl-halide-dependent C–C and C–N bond-forming reactions, where aryl chlorides led to C–C bond formation and aryl iodides favored C–N bond formation.[64] This chemoselective reaction was catalyzed by NiI$_2$ (0.5 mol%). The presence of an aryl amine as an activator was essential for SM coupling between aryl chlorides and arylboronic acids, whilst the Ni species were stabilized on the surface of the base (K$_3$PO$_4$). The SM couplings using this K$_3$PO$_4$-supported heterogeneous nickel species provided yields of up to 99%. ^{15}N and ^{11}B NMR studies suggested that a B–N ate complex was formed (Scheme 18), which further underwent transmetalation to produce a C–C bond. Hot-filtration tests revealed the heterogeneous nature of the catalyst, which 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. Y. Dong and Y.-B. Dong reported a diimine-based nickel complex, **C21**,[65] which was utilized in the SM cross-coupling between chlorobenzene and phenylboronic acid to provide biphenyl in 26% yield.

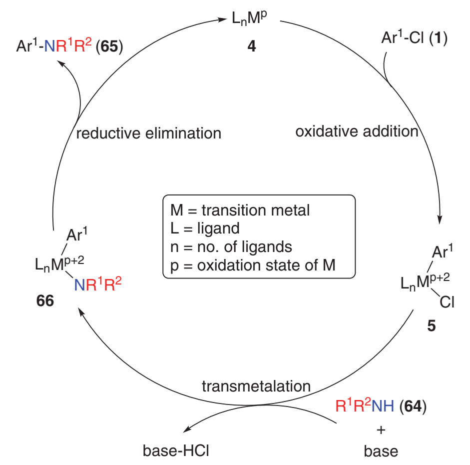
On utilizing these reported (2013–2024) heterogeneous nickel catalysts, leaching was observed. Thus, further development of new, more stable, and reusable heterogeneous nickel catalysts is still in demand for SM couplings of aryl chlorides.

3 Buchwald–Hartwig Amination Reactions

Since 1995,[66] the Buchwald–Hartwig amination (BHA) of aryl halides and pseudohalides has become a fundamental tool for forming C–N bonds (Scheme 19). Several natural products, pharmaceuticals, and agrochemicals containing nitrogen heterocycles can be synthesized using BHA reactions.[2] Mechanistically, the BHA follows three significant steps: (i) oxidative addition, (ii) ligand exchange or transmetalation, and (iii) reductive elimination (Scheme 20). The rate-determining step usually varies among these three steps depending on the reaction conditions, which include the transition metal, ligand, base, and additive.



Scheme 19 General scheme for the BHA reaction



Scheme 20 General catalytic cycle for the BHA reaction

3.1 Homogeneous Palladium Catalysis

In 2013, Buchwald et al. developed a new palladium complex, Xphos-Pd-G3 (**C23**) (Figure 5), and applied it in SM and BHA reactions.[67a] In BHA reactions of aryl chlorides, 0.01–0.5 mol% of **C23** was used, and product yields of up to 97% were observed. Electronic and steric variations on the aryl chlorides had minimal effects on these reactions. In 2020, Buchwald 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 the diisopropyl-substituted benzene ring expanding the substrate scope. Using this Pd complex (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 Pd(dba)$_2$/**L8** catalyzed BHA reac-

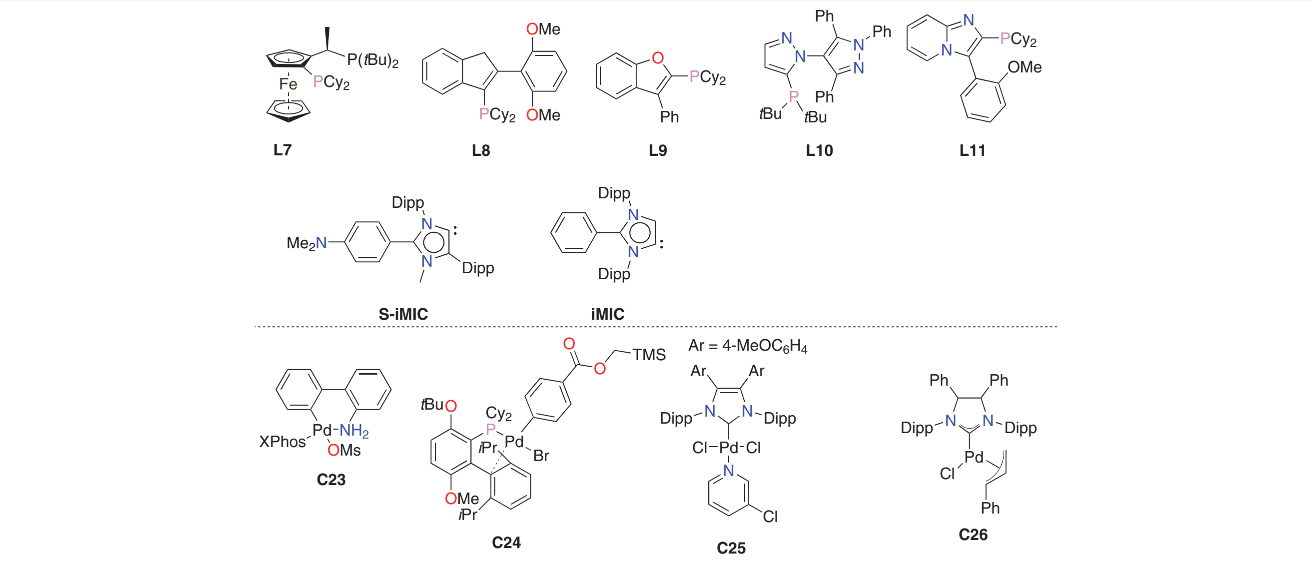
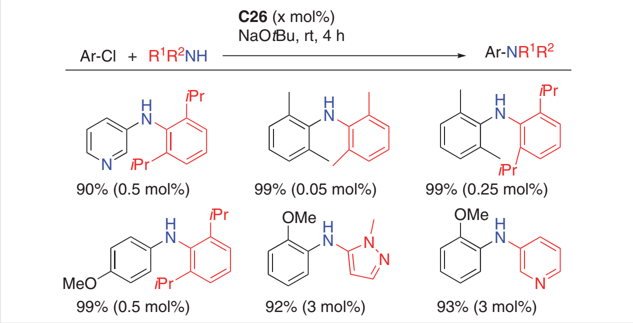


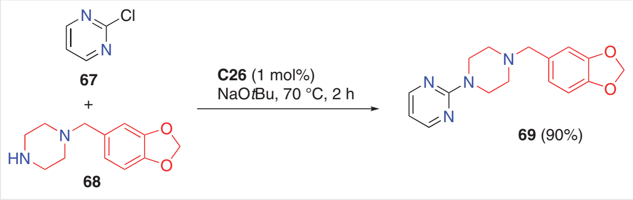
Figure 5 Pd complexes and ligands used for C–N bond-forming BHA reactions under homogeneous palladium catalysis

tion 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 Pd(dba)$_2$ (1 mol%). Although the authors used **L8** as the ligand, control experiments showed that XPhos and RuPhos produced similar results. Li et al. synthesized a series of 3-arylbenzofuran-2-ylphosphines (e.g., **L9**) and applied them as ligands in BHA reactions.[69] The BHA reactions of aryl chlorides and primary, secondary, and aromatic amines proceeded in the presence of Pd(OAc)$_2$ (2.5 mol%) and **L9** (7.5 mol%) to produce the C–N coupling products in yields of up to 90%. In 2021, Hartwig et al. reported the BHA reactions of aryl chlorides and hydrazine using 800 mol ppm of Pd[P(*o*-tolyl)$_3$]$_2$ and CyPF-*t*Bu (800 mol ppm) in the presence of KOH as the base.[70a] However, reactions using base-sensitive functional groups, such as ester- or amide-bearing aryl chlorides, provided yields of only 45% and 56%, respectively. Hydrazine deprotonation is the rate-determining step in this reaction. Furthermore, the same group reported the BHA reactions of aryl chlorides and ammonium salts using the same catalytic system.[70b]

Xu et al. have reported a dianisole-containing Pd-NHC complex, Pd-PEPPSI-IPr^{OMe} (**C25**) (Figure 5), for BHA reactions.[71] Although the BHA reactions of electron-rich aryl chlorides and primary, secondary, and aryl amines using **C25** (0.1 mol%) proceeded to provide yields of 54–98%, the same reaction with electron-deficient aryl chlorides did not occur. Gevorgyan et al. performed BHA reactions in lipids and lipid impurities under XPhos-Pd-G3 (**C23**) (2 mol%) catalysis and obtained diarylamines from aryl chlorides in up to 99% yield.[72] Qiu and co-workers have reported a solvent-free BHA reaction using an NHC-Pd complex [(SIPr)^{Ph2}Pd(cin)Cl (**C26**)] at room temperature.[73] The presence of two phenyl rings on the backbone of the NHC ligand is thought to be essential, according to the reported control experiments. The authors proposed that the electron-donating ability and steric hindrance created by these phenyl groups increases the catalytic activity. Several sterically challenging diaryl amines were obtained under these solvent-free conditions using a Pd loading of 0.05–3 mol% (Scheme 21). They also synthesized the commercial pharmaceutical piribedil (**69**) directly from a heteroaryl chloride (Scheme 22).



Scheme 21 Synthesis of sterically and electronically challenging aryl amines



Scheme 22 Synthesis of the commercial pharmaceutical piribedil under solvent-free conditions

Recently, Yet et al. reported a BHA reaction using $Pd(OAc)_2$ (2.5 mol%) and JagPhos II (**L11**) (5 mol%).[74] The reaction using aryl amines and secondary amines with aryl chlorides provided BHA products in 7–98% yields, but in general, primary and benzylic amines provided poor yields (2–27%). A super bulky mesoionic carbene (S-iMIC, 'i' represents the 1,3-imidazole unit) (Figure 5) 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%). Reactions using the S-iMIC ligand produced C–N coupling products in up to 99% yield, whereas reactions using IPr or iMIC as ligands produced yields of only 7% and 9%, respectively.

In summary, the use of bulky ligands in homogeneous palladium catalysis appears 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 γ-Fe_2O_3 that was named γ-Fe_2O_3@MBD/Pd-Co.[76] 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 (500 mol ppm Pd) for the BHA reaction between chlorobenzenes and aryl amines, biaryl amines were obtained in up to 91% yield. The authors also applied this 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 under micellar conditions.[77] They used $[Pd(crotyl)Cl]_2$ as the metal source with a 0.25 mol% Pd loading. In addition, the BippyPhos ligand (**L10**) (2 mol%) (see Figure 5) was used along with 2 wt% Savie/water (0.5 M) to generate micelles. BHA reactions using primary, secondary, and benzylic amines produced products containing newly formed C–N bonds in 55–99% yields. The catalyst was recovered and recycled three times. The yield of the BHA decreased from 98% to 90% on the third reuse. ICP-MS analysis of the BHA product showed only 0.78 ppm of Pd contamination.

In summary, only a few reports on this topic have been published within the time frame (2013–2024) of this short review. Thus, there is still 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 previous work, in 2014, Buchwald prepared a new air-stable nickel catalyst named (dppf)Ni(*o*-tolyl)Cl (**C31**) (Figure 6).[78b] They used this nickel complex (5 mol%) for the BHA reaction of aryl chlorides at 100 °C. The aminations 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 an increased reaction temperature (130 °C). In 2015, Stradiotto et al. reported a nickel-catalyzed monoarylation of ammonia using $Ni(COD)_2$/JosiPhos.[79] Hartwig et al. reported a (BINAP)Ni(η^2-NCPh) catalyst (**C30**) for the BHA reactions of primary amines and aryl chlorides.[80a] The use of this BINAP-supported nickel catalyst (1 mol%) provided yields of up to 96% and was highly selective for primary amines. If the substrate contained both primary and secondary amines, then only the primary amines reacted, leaving the secondary amines intact. The same group also reported the BHA reaction of ammonia.[80b] They prepared the new nickel complex **C29** by combining $Ni(COD)_2$, JosiPhos, and benzonitrile (PhCN), which they used with 2–4 mol% loading for the coupling of ammonia or ammonium sulfate with aryl chlorides to produce primary aryl amines in yields of up to 58–84%. In general, ammonia performed better than $(NH_4)_2SO_4$. In addition, ammonia, methylamine hydrochloride ($MeNH_3Cl$), and ethylamine hydrochloride ($EtNH_3Cl$) were reacted with aryl chlorides, resulting in the production of secondary aryl amines in yields of 52–99%.

In 2015, Monfette and Magano prepared the tetramethylethylenediamine (TMEDA)-ligated nickel complex **C27** (Figure 6).[81] This complex was not air- or moisture-sensitive and was easily prepared on multigram scale. Using nickel complex **C27** (5 mol%), the cross-coupling of morpholine and electron-deficient aryl chlorides afforded the desired amination products in up to 91% yield. In the same year, Doyle et al. prepared the same catalyst independently and applied it to SM and BHA reactions.[82] Unlike Monfette who used $Ni(cod)_2$ for the synthesis of **C27**, Doyle used $Ni(acac)_2$ and $Al(OEt)Me_2$. In the field of nickel-catalyzed BHA reactions, the Stradiotto group has made major contributions over recent decades.[83] They developed a series of DalPhos ligands, including Pad-DalPhos,[83b] NHP-DalPhos,[83c] PhPAd-DalPhos,[83g] PAd2-DalPhos,[83e] and Phen-DalPhos,[83f] for nickel-catalyzed BHA reactions (Figure 6). 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. Meanwhile, oxidative addition is the rate-limiting step in the Ni(I)/Ni(III) catalytic system. The same authors also reported ligand-enabled site-selective reactions (Scheme 23). The reaction using Phen-DalPhos as the ligand promoted the amination of indoles to provide products **72**, whereas that using PAd2-DalPhos promoted the amination of anilines to

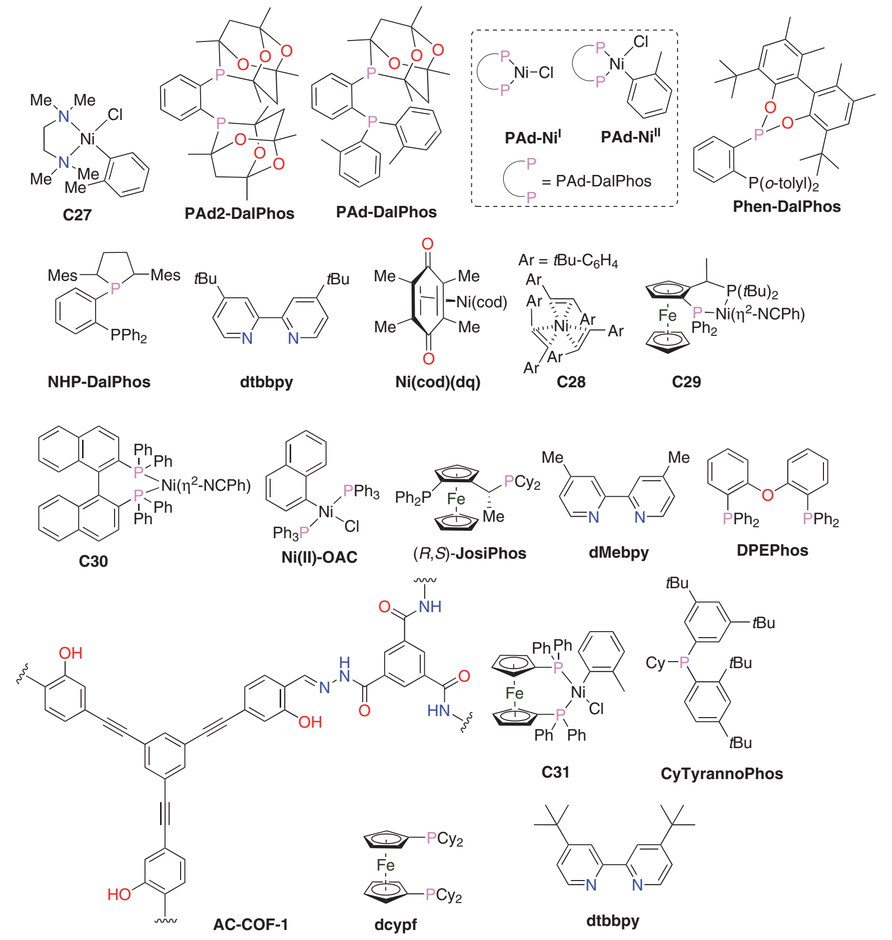
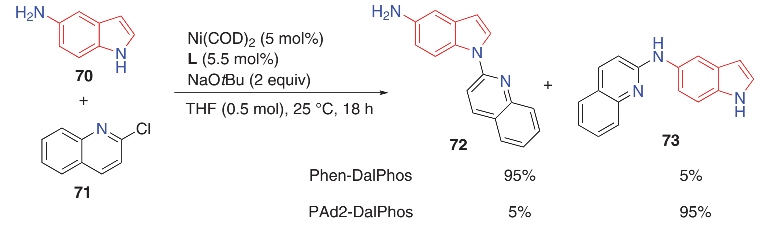


Figure 6 Ligands and nickel complexes used for homogeneous nickel-catalyzed BHA reactions

produce compounds **73**. Interestingly, Baran et al. have reported BHA reactions using electrochemistry.[84] This electrochemical reaction utilized an RVC anode and a nickel foam cathode, with LiBr (4 mol equiv) being used as the electrolyte. They used $NiBr_2$·glyme complex (10 mol%) as the nickel source. Although they mainly focused on aryl bromides, they also showed that electron-deficient aryl chlorides were tolerated (up to 73% yield) in BHA reactions under these conditions.

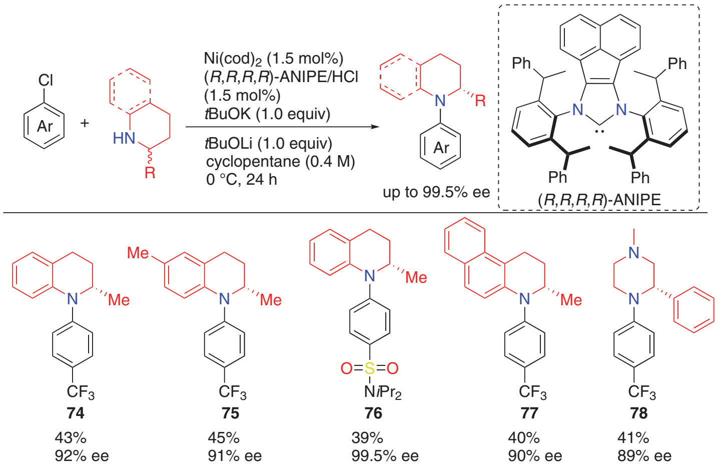
In 2020, Engle et al. reported an air-stable 18-electron nickel(0)-olefin complex named Ni(cod)(dq) that catalyzed BHA and SM reactions.[85] This catalyst was prepared on an 8 g scale in 79% yield. This Ni(cod)(dq) complex was initially reported by Schrauzer in 1962.[86] Engle et al. applied Ni(cod)(dq) in cross-coupling reactions and compared its reactivity with that of $Ni(cod)_2$. The Ni(cod)(dq) complex (5 mol%) showed improved reactivity toward aryl chlorides (BHA reaction); however, in the case of heteroaryl chlorides, $Ni(cod)_2$ performed better. In the same year, Cornella



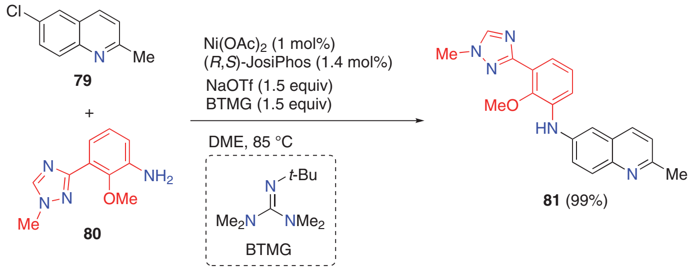
Scheme 23 Ligand-enabled site-selective BHA reactions

and Nattmann reported a 16-electron-nickel(0)-olefin complex (**C28**) derived from *trans*-stilbene (Figure 6).[87] The *t*Bu substituent increased the thermal stability of this complex. The authors claimed that complex **C28** could be stored open to air at room temperature for at least 1 month. The BHA reactions of aryl chlorides and amines using this nickel complex provided the amination products in up to 90% yield, whereas $Ni(cod)_2$ provided the products in up to 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] This approach suggested that a combination of $Ni(acac)_2$ and XPhos would provide the maximum yield (35%), and laboratory experiments showed this to be the case with a 33% yield being obtained under the proposed conditions.

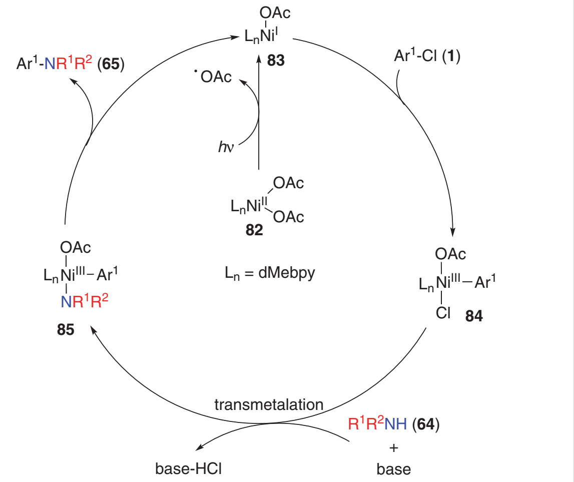
A C–N bond-forming amination via kinetic resolution enabled by flexible and bulky chiral ligands was reported by Hong and Shi (Scheme 24).[89] As a chiral ligand, they used (*R*,*R*,*R*,*R*)-ANIPE (1.5 mol%) in the presence of $Ni(cod)_2$ (1.5 mol%). Multiple sterically hindered α-branched amines successfully underwent amination with ee values of up to 99.5%. Computational studies suggested that the oxidative addition had an energy barrier of 8.9 kcal/mol, whereas the reductive elimination had an energy barrier of 14.7 kcal/mol. The transmetalation had an energy barrier of 14.0 kcal/mol. Thus, reductive elimination is the rate-determining step as well as the 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 in the presence of strong alkoxide-type bases.[90] Alkoxide bases are poorly soluble and challenging to utilize in large-scale reactions. The authors collaborated with industry and academia to develop a general method that could be applied to heteroaryl chlorides and amines (both aliphatic and aromatic). They found that the reaction using a combination of NaOTf (1.5 mol equiv) and BTMG (1.5 mol equiv) enabled the amination of several heteroaryl and aryl chlorides in up to 99% yield (Scheme 25). 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 25). Ananikov et al. have developed $NiCl_2Py_2$ (10 mol%)- and IPr (20 mol%)-catalyzed BHA reactions of aryl chlorides and amines to obtain *N*-arylation products in yields of 14–95%.[91] Meanwhile, Xue et al. utilized purple LED light (390–395 nm) for nickel-catalyzed BHA reactions.[92] They used $Ni(OAc)_2$ (10 mol%) and dMeppy (10 mol%) for C–N bond-forming cross-couplings of aryl chlorides with ammonium bromide (NH_4Br),[92a] aliphatic amines,[92b] and hydrazine.[92c] Recently, Xue used the Warner salt ($[Ni(NH_3)_6]Cl_2$) as a catalyst for the BHA reactions of aqueous ammonia.[92d] Irradiation with purple LED light generates a Ni(I)-OAc complex via the formation of an acetate radical, and the reaction subsequently follows a Ni(I)/Ni(III) catalytic pathway (Scheme 26). These visible-light-promoted photocatalyst-free nickel-catalyzed reactions are limited to ammonia and primary and secondary amines. Lin et al. reported nickel-catalyzed C–N cross-couplings of aryl chlorides and aryl amines promoted by sodium iodide under visible-light irradiation (455 nm).[4] The light irradiation generated a Ni(I) species via the formation of aryl radicals, with halogen exchange being a critical step in this reaction (Scheme 27). Control experiments suggested that the addition of NaI was essential. Although the reaction provided yields of up to 99%, it was limited to electron-deficient aryl chlorides. Furthermore, 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]



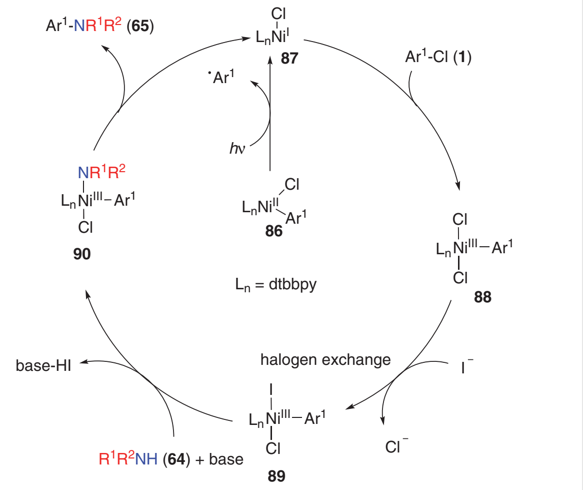
Scheme 24 Formation of C–N bonds via kinetic resolution



Scheme 25 Demonstration of the BHA reaction using a dual-base approach



Scheme 26 Mechanism of the purple-light-mediated nickel-catalyzed BHA reaction



Scheme 27 A plausible catalytic pathway for NaI-promoted nickel-catalyzed BHA reactions

MacMillan et al. have reported a ligand-free nickel-iridium dual-catalyzed BHA reaction of aryl bromides.[93] They used $NiCl_2$·glyme (5 mol%) and the iridium photocatalyst **PC1** (Figure 7). The main role of the Ir photocatalyst was to destabilize the nickel-amido intermediate via single-electron transfer (SET) and facilitate reductive elimination (Scheme 28). Additionally, the photocatalyst assisted in the in situ generation of the Ni(0) species. Unfortunately, the BHA reaction of aryl chlorides did not proceed under these reaction conditions due to the formation of catalytically inactive nickel black during the reaction. Pieber et al. have reported nickel-catalyzed BHA reactions of aryl chlorides by using CN-OA-m as a photocatalyst.[94] $NiBr_2·3H_2O$ (5 mol%) was used as a nickel source. Using this $NiBr_2$/CN-OA-m system, the BHA reactions of electron-deficient aryl chlorides were performed. However, electron-rich aryl chlorides, such as the chloride of 4-methoxyanisole, coupled with pyrrolidine in only 2% yield, even after 168 hours.

Buchwald et al. reported a BHA reaction using nickel/ruthenium dual catalysis in flow in the presence of photocatalyst **PC2**.[95] They obtained yields of 65–93% using electron-deficient aryl chlorides, whereas the coupling between chlorobenzene and pyrrolidine provided only a 22% yield. In 2023, Yasuran and Zhang reported nickel-catalyzed BHA reactions in the presence of an acetylene-based hydrazone-linked covalent organic framework (AC-COF-1) (Figure 6) and blue LED (440 nm) irradiation.[96] Like Peiber, they also used $NiBr_2·3H_2O$ (7.5 mol%) as the 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 product yields of up to 99%. In this study, pyrrolidine was used as the only amine source.

In summary, the utilization of dual nickel-photocatalyst systems has proven to be effective for BHA reactions of aryl chlorides. The use of electron-rich ligands in nickel catalysis under photoredox-free conditions would represent an alternative pathway.

3.4 Heterogeneous Nickel Catalysis

Sawamura et al. reported a polystyrene-cross-linking bisphosphine (PS-DPPBz) (Figure 8) as a ligand for nickel-catalyzed amination reactions.[97] As a nickel source, they used $Ni(cod)_2$ (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 the corresponding products in up to 97% yield. Hot-filtration and mercury-poisoning experiments confirmed the heterogeneous nature of the catalysts. The PS-DPPBz-Ni catalyst was recovered and reused.

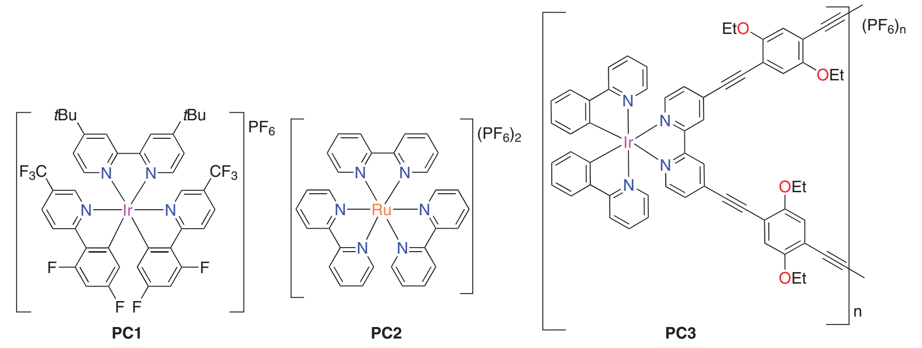
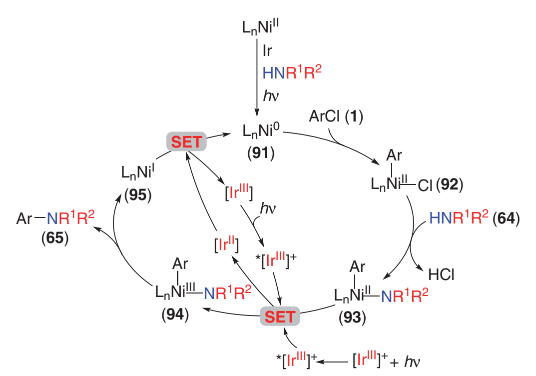
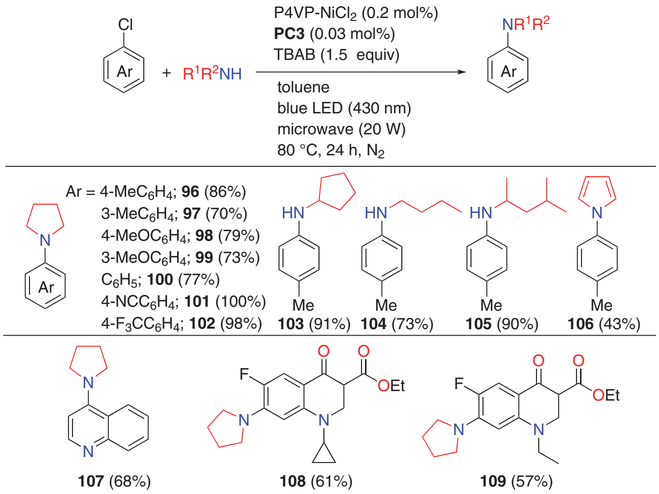


Figure 7 Photocatalysts used for BHA reactions



Scheme 28 Plausible mechanistic pathway for Ni/Ir dual catalyzed BHA reactions

The catalytic activity decreased to 73% in the third run compared to 90% in the first run, with ICP-AES analysis of the reaction mixture confirming the leaching of Ni. There are a few reports on light-assisted heterogeneous nickel-catalyzed BHA reactions of aryl halides.[98] Unfortunately, these reactions were restricted to aryl iodides and bromides. We recently prepared the linear polymeric iridium photocatalyst **PC3** (Figure 7).[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) (P4VP-NiCl$_2$) (0.2 mol%), a convoluted polymeric nickel complex (Figure 8). In this reaction, dual irradiation with visible light (430 nm) and microwaves was essential. The addition of TBAB was also necessary for this reaction. Several electron-rich and electron-deficient aryl chlorides (**96**–**102**) were used in this reaction to produce high to quantitative yields of the products (Scheme 29). Cyclic primary amines, cyclic secondary amines, linear primary amines, branched primary amines, and aryl amines produced BHA reaction products **103**–**106** in yields of 43–91%. 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 the catalytic activity (Table 1).



Scheme 29 BHA reactions under visible light and microwave dual irradiation using polymeric Ir and Ni catalysts

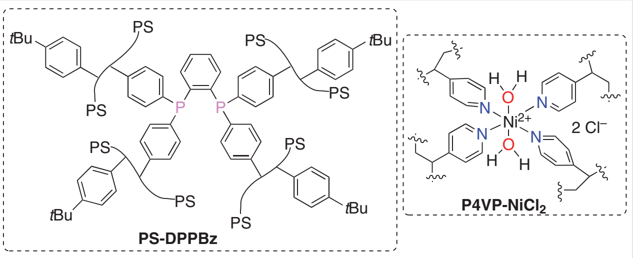
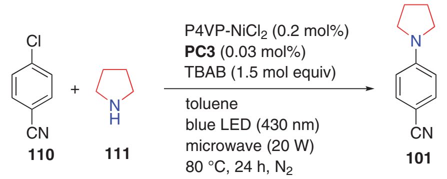


Figure 8 A ligand and nickel catalyst used for heterogeneous nickel-catalyzed BHA reactions

Table 1 A Catalyst Reusability Study on the Dual Nickel/Iridium Catalysis



Entry	Catalytic run	Yield of **101** (%)
1	1st	>99
2	2nd	99
3	3rd	99
4	4th	99
5	5th	99
6	6th	99

In summary, a reusable nickel-photocatalyst dual catalytic system serves as a promising catalytic system for the BHA reactions of aryl chlorides.

4 Conclusion

In the past decade, significant advancements have been made to overcome the low reactivity of readily available and inexpensive aryl chlorides under nickel and palladium catalysis. The selection of an 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 can 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 such an approach. Despite the significant progress made, there remains room for further improvements, such as the development of cross-coupling reactions of aryl chlorides at room temperature using highly stable and reusable metal catalysts under additive-free conditions.

Conflict of Interest

The authors declare no conflict of interest.

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