Recent Progress Towards Transition-Metal-Catalyzed Direct Arylation of Heteroarenes

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Abstracts: In this short review, the direct intermolecular cross-coupling reactions of heteroarenes with aryl (pseudo)halides catalyzed by transition metals via C-H bond cleavage in recent years are described. The fundamental emphasis has been given to the synthetic aspects of different intermolecular direct cross-coupling reaction. Much attention is drawn to the palladium-catalyzed arylation reactions due to their important utility at present. Meanwhile, the procedures employed other transition metals are also presented.

Keywords: Aryl (pseudo)halides, C-H activation/functionalization, direct arylation, heteroarenes, and transition metals.

1. INTRODUCTION

The direct construction of aryl–aryl bonds has been a goal of numerous organic chemists for many years as it can avoid the use of stoichiometric organometallic reagents also along with any troubles concerned with their preparations, functional group compatibility and stability, as well as it reduces the number of steps to prepare these compounds. In the last two decades, much attention has been paid to the direct synthesis of arylheteroarenes and unsymmetrical biheteroaryls through transition metal-catalyzed non-chelation assisted direct arylations of heteroarenes with aryl halides or pseudohalides by C–H bonds cleavage [1]. In 1982, this procedure had been demonstrated feasible by Nakamura and coworkers [2]. Later on, the area of transition-metal-catalyzed direct intermolecular and intramolecular arylation has earned much more attention and undergone rapid development since it can directly construct the central structural motifs of pharmaceuticals, natural products, agrochemicals, polymers, and feedstock commodity chemicals. Transition metal-catalyzed C-H functionality represents an atom-economically and environmentally more attractive strategy, and crucially it not only takes the advantage of minimizing the overall by-products, but also allows for streaming organic synthesis. However, some fundamental challenges still exist: (i) the inherent high strength of most carbon-hydrogen bonds and (ii) since organic molecules usually contain diverse C-H bonds with comparable dissociation energies; the requirement to control site selectivity in them is a major challenge. With the persevering effort of organic chemists, these two challenges have been partly solved. To meet the first challenge, a majority of researches has been carried out by demonstrating that the transition metals, including Pd, Ru, Rh, Cu, Ni and Co, can insert into the C-H bonds to produce C-M bonds, and the resulting compounds are more reactive than their original ones. The biaryls can be acquired when the resulting compounds were heated under nitrogen in anhydrous solvents [3]. As for the second major challenge, the selective functionalization of a single C-H bond is achieved within a complex molecular. A number of approaches have been employed to address this problem, including: (i) the use of substrates containing weaker or activated C–H bonds (e.g., 3^oor benzylic/allylic systems), or the deprotonation of substrates can be achieved with application of the strong base such as *t*BuOK [4], fortunately, if the pKa values of C–H bonds in aromatic heterocyclic compounds in DMSO is below certain value, the weaker base can be used such as K_3PO_4 [5]. Some pioneering work of kinetic acidity of substrates and deprotonation energies has been done by Schlosser and Marzi [6]. (ii) the use of coordinating ligands within a substrate as directing groups, (iii) carrying out intramolecular functionalization reactions via favorable five- or six-membered transition states, (iv) the use of supramolecular chemistry to position a specific C–H bond near the catalyst active site, and (v) the use of the transition metal catalysts/ligands to control selectivity [7].

This critical review aims at giving a brief introduction in transition metal-catalyzed direct arylations of heteroarenes through the C-H cleavage in recent years. The fundamental emphasis has been given to the synthetic aspects of different intermolecular arylation procedures; meanwhile, crucial mechanistic proposals have also been briefly reported and discussed. This review can be divided as following: i) transition metal-catalyzed intermolecular direct (hetero) arylations of five membered heteroarenes. Furthermore, this part can be subdivided according to the species of transition metals applied again; ii) transition metal-catalyzed intermolecular direct (hetero) arylations of six membered heteroarenes. Also this section can be further subdivided based on the different metals; iii) the conclusion and perspective.

2. TRANSITION METAL-CATALYZED INTERMOLECULAR DIRECT (HETERO) ARYLATION OF FIVE-MEMBERED HETEROARENES

2.1. Pd-Catalyzed Direct Arylation of Imidazole, Benzothiophene, Benzothiazole, Benzoxazole, Indole, Indazole, Purine, Furan, Thiophene, Pyrrole, Thiazole and Oxazole Ring System

Palladium has been applied as the main transition metal catalyst in carbon–carbon construction reactions [8]. Palladium complexes have several reasons to be the attractive catalysts for such conversions. Firstly, ligand-directed C-H functionalization at Pd centers can be used to install many diverse species of bonds, such as carbon-carbon, carbon-nitrogen, carbon-sulfur, and carbon-halogen bonds [9]. Few other transition metals allow such diverse bond constructions, and this ability is mainly the results of two important characteristics: (i) the compatibility of diverse Pd(II) catalysts with many oxidants, and (ii) the capability to selectively functionalize the cyclopalladated intermediates. Secondly, unlike other transition metals, palladium can form cyclometalation with a large number of directing groups, so this can easily and readily activate both the sp^2 and sp^3 C-H bonds. Thirdly, even the ambient air and moisture atmosphere allow most of the Pd-catalyzed direct C-H functionalization reactions, which is significantly practical in the organic synthesis [1b]. Lastly, the application of palladium-catalyzed direct C-H functionalization in the construction of sp^2 C-C bonds would be a tremendous advantage for the sustainable development, due to its lower mass, lower cost as well as the easier treatment of the relatively non-toxic by-products. The five-membered heteroarenes have already been found wide applications in the pharmaceuticals and agrochemicals. As mentioned above the direct construction of the sp^2 C-C bonds among them will be a tremendous advantage as well as attractive methodology, and it can accelerate the development in these areas. It occurs that most of these direct arylations are catalyzed by palladium, so in the following part, the recent advances achieved in

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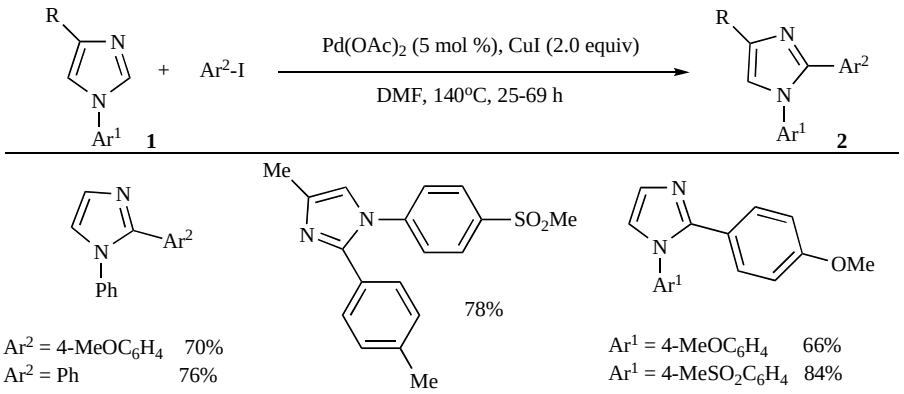
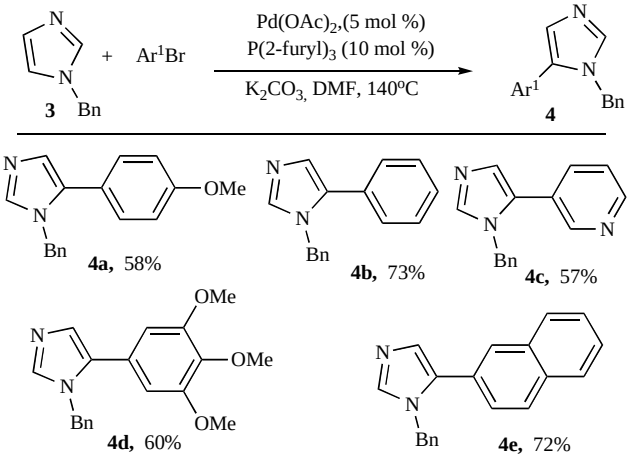


Scheme 1. Pd- and Cu-mediated C-2 arylation of 1-aryl-1H-imidazoles with **1** aryl iodides.

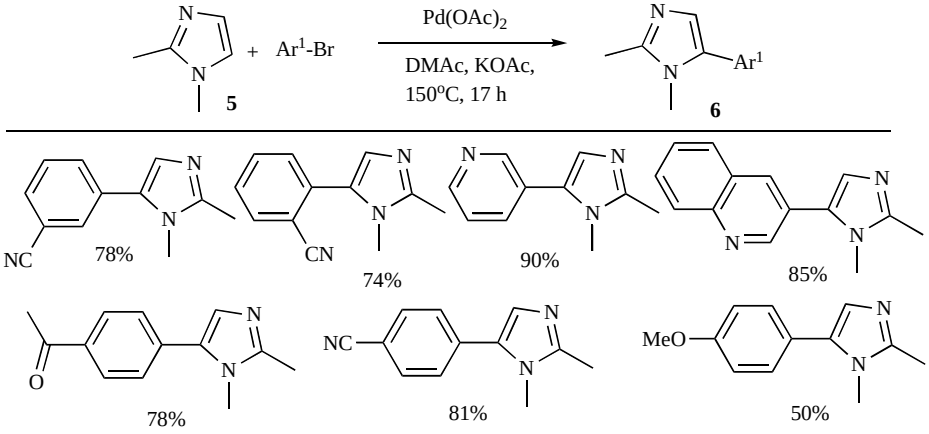
the connection of five-membered heteroarenes catalyzed by palladium are presented.

Among the synthetic approaches of 2-aryl-1-H-imidazoles, the most attractive and atom-economical one is intermolecular azolyl-aryl bonds formation between imidozales and aryl halides or pseudohalides catalyzed by palladium with the assistant of a proper ligand also an inorganic base. Rossi [10] and coworkers in 2007 developed an efficient and regioselective approach to prepare 1, 2-diaryl-1H-imidazoles **2** through the direct C-2 arylation of 1-aryl-1H-imidazoles **1** with aryl iodides in the presence of CuI and catalytic $Pd(OAc)_2$ in DMF at 140°C without ligand (Scheme **1**).

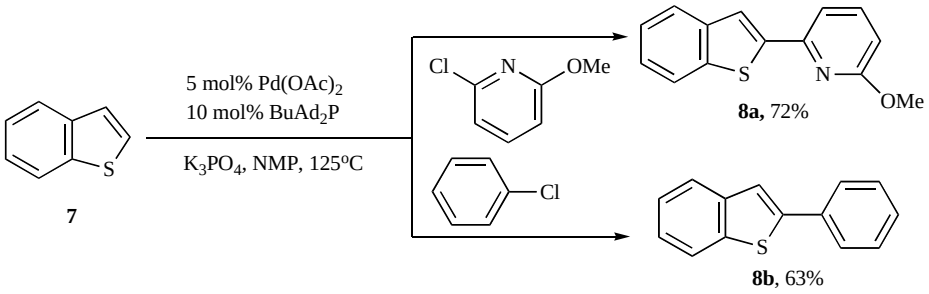
In 2008 Rossi and coworkers established a simplified procedure [11] that a diverse of 4(5)-aryl-1-benzyl-1H-imidazoles **4** can be prepared by the direct arylations of 1-benzyl-1H-imidazoles **3** with electron-deficient and electron-neutral aryl bromides in the presence of catalytic $Pd(OAc)_2$ and 2 equiv of K_2CO_3 in DMF at 140°C with P(2-furyl)$_3$ as ligand (Scheme **2**). They found that the procedure showed good to excellent regioselectivity, and gave satisfactory to good yields which are not much lower than those obtained in the Suzuki-type reactions between 4(5)-bromo-1H-imidazole and arylboronic acids. Even the strongly deactivated 3, 4, 5-trimethyloxylphenyl bromide can give the desired compound **4d** with satisfactory yield.



Scheme 2. Pd-catalyzed regioselective synthesis of 5-aryl-1-benzyl-1H-imidazoles.

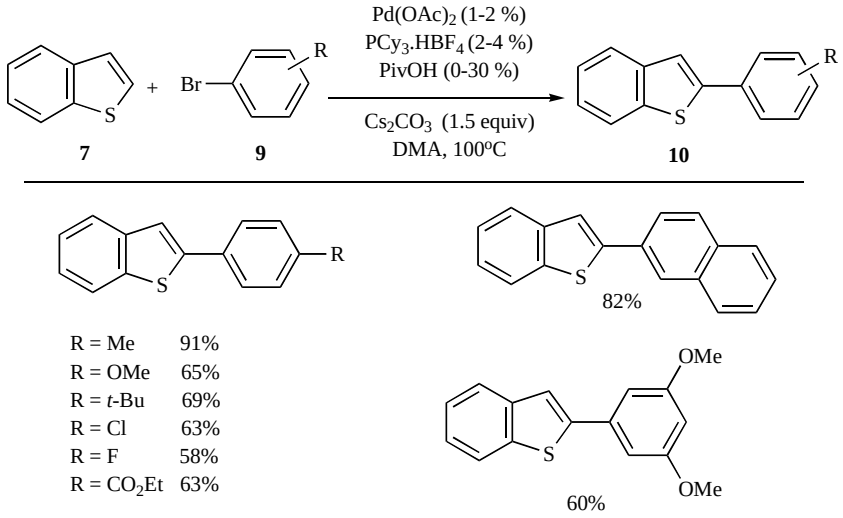


Scheme 3. Palladium catalysed arylation of 1,2-dimethylimidazole **5** with aryl bromides.



Scheme 4. Benzothiophene **7** arylation by aryl chlorides.

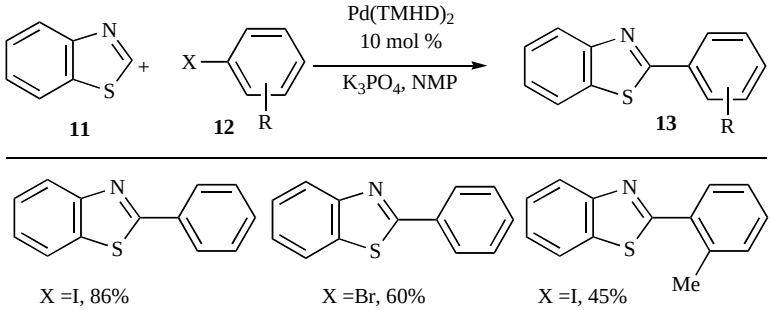
In 2009 Roger [12] and coworkers also established an atom-economical and simple method that 5-arylimidazole derivatives **6** can be highly regioselectively prepared by the direct arylations of 1, 2-dimethylimidazole **5** with several para-substituted aryl bromides in the presence of $Pd(OAc)_2$ as catalyst under ligandless condition. The scheme shows that the activated aryl bromides proceeded effectively with imidazole derivatives, offering the good to excellent yields (Scheme **3**). Under this condition, a great deal of functionalities such as benzoyl, formyl, fluoro, acetyl, nitrile or carboxylate on the aryl bromides are compatible. The methodology is of practical advantage due to there is no need to remove phosphine derivatives at the end of reaction and a very diverse of aryl bromides are commercially available. The aryl bromides bearing electron-deficient functionalities favor the arylations under this protocol.



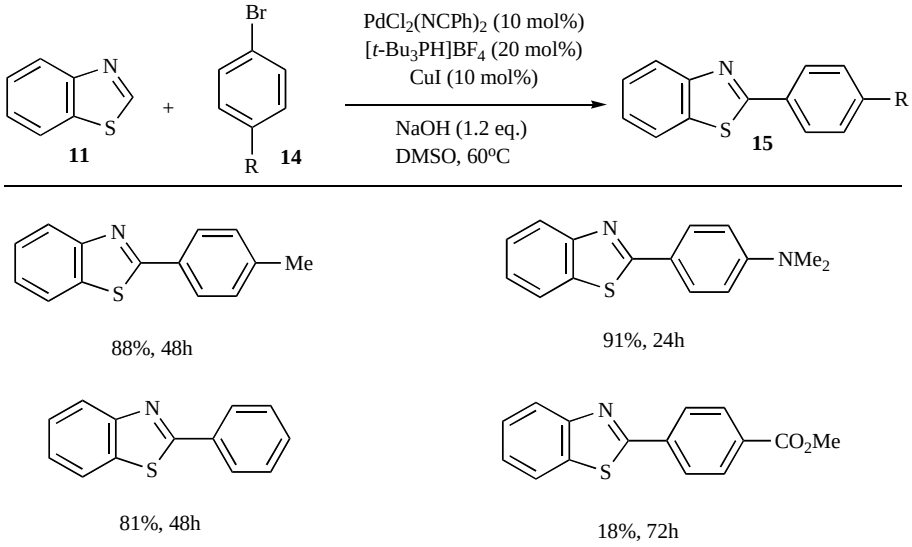
Scheme 5. Direct arylation of benzothiophene **7** with aryl bromides **9**.

Nowadays, most of the aryl halides used in the palladium-catalyzed direct arylations are aryl iodides or bromides, whereas the cheap and commercially available aryl chlorides are seldom applied. The direct arylations of aryl chlorides with heteroarenes will be of an immense benefit for sustainable development because of its atom-economy and a wide variety of commercially available aryl chlorides, also due to the formation of HCl associated to a base as by-product as well as the reduction of steps to obtain the required compounds. The oxidative addition of Pd (0) to aryl chlorides usually needs an electron-rich, bulky phosphine, an N-heterocyclic carbine (NHC) or a secondary phosphine oxide [13]. Chiong and coworkers [14] in 2007 reported a general procedure for such direct arylation, which did not require the stoichiometric amounts of copper salt as additives. After the extensive screening, they obtained the optimal condition, including $Pd(OAc)_2$, butyldi-1-adamantylphosphine, K_3PO_4 and NMP (Scheme **4**).

Unsubstituted benzothiophene **7** underwent direct arylations with numerous aryl bromides under the catalytic system comprising $Pd(OAc)_2$(2mol%), $PCy_3{\cdot}HBF_4$ (4mol %), PivOH (30mol %), and K_2CO_3 (1.5 equiv) in DMAc (0.3M) at 100°C. It offers the corresponding 2-arylbenzothiophenes derivatives **10** in synthetically



Scheme 6. Arylation of benzothiazoles **11** with aryl halides.



Scheme 7. Reaction between benzothiazole **11** with various aryl bromides **14**.

useful yields (Scheme **5**) [15]. Even the electron-rich 5-bromo-2-acetoxythiophene can furnish the required product in 22% yield. The addition of pivalic acid was found to accelerate the direct arylation and improve the reaction results.

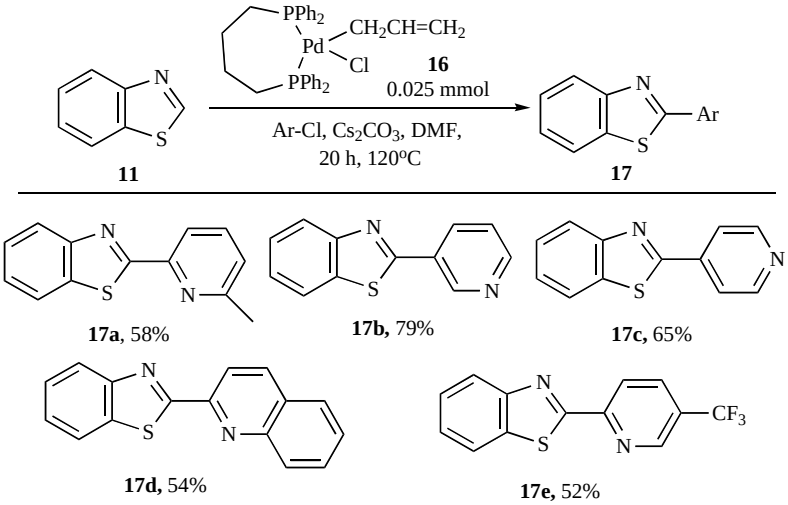
In 2008 Nandurkar [16] and coworkers used 2, 2, 6, 6-tetramethyl-3, 5-heptanedione (TMHD) as the ligand of palladium-catalyzed direct arylation, avoiding the use of expensive, air-sensitive and toxic phosphine ligands as well as the addition of stoichiometric amounts of copper salt additives, which resulted in excellent yields of desired products. The delicate balance that coexists between the electronic and steric properties of TMHD makes a great contribution to its reactivity. $Pd(TMHD)_2$ is significantly advantageous for the direct C-2 arylation of benzothiazole **11** due to its easy preparation, stability towards air, high solubility in organic solvents and compatibility with a great diversity of substrates. Benzothiazole **11** can efficiently arylate bromobenzene or aryl iodides derivatives **12** using K_3PO_4 and catalytic $Pd(TMHD)_2$ in NMP, providing good yields of the desired products **13** (Scheme **6**).

A catalytic system applying $PdCl_2(NCPh)_2$ as catalyst, [*t*-$Bu_3PH]BF_4$ as ligand, CuI as additive and sodium hydroxide as an activator for the direct cross coupling between benzothiazole **11** and aryl bromides was disclosed by Mori and Miyaoku [17]. Bromides containing electron-rich substituents such as NMe_2, Me furnished the target compounds in good yield; on the contrary, methyl 4-bromobenzoate resulted in a poor yield (18%). Sodium hydroxide was of great advantage as an activator toward other additives such as TBAF in the cost of synthesis. Significantly, the reaction temperature is lower than that of other procedures [1] (Scheme **7**).

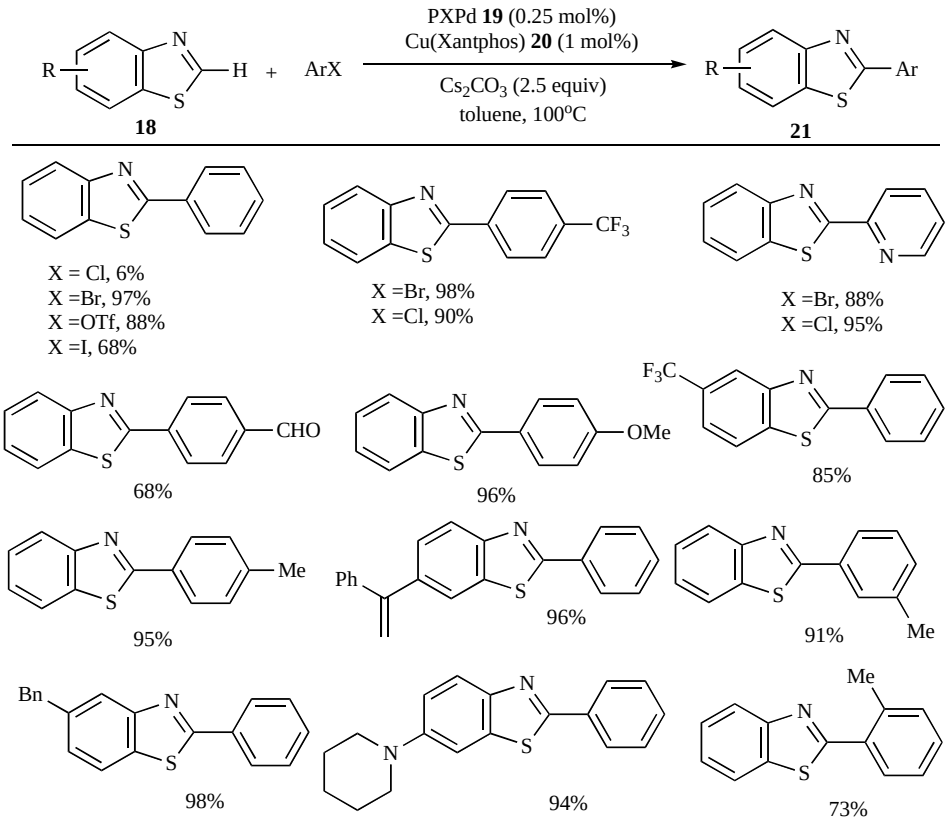
After extensive screening and optimization, Roger and coworkers [18] in 2009 proved that the complex $PdCl(dppb)(C_3H_5)$ **16** was an efficient catalyst for the direct arylations of chloropyridines and benzothiazole **11** in the presence of Cs_2CO_3 in DMF at 120°C. The study also showed that the position of chloro substitute on pyridines had a minor influence on the yields (Scheme **8**).

Palladium-catalyzed direct C-H functionalization still required high catalyst loadings, strong base and high temperature [1, 19]. After enormous screening, Huang and coworkers in 2010 finally obtained an excellent cocatalyst system consisting of the air-stable and commercially available PXPd(dichlorobis(chloro-di-tert-butylphosphine)palladium) complex **19** and Cu(Xantphos) **20** (9,9-dimethyl-4,5-bis(diphenylphosphine)xanthene). The optimal combination of **19** (0.25%) and **20** (1 mol %) has been found to be effective and efficient for the direct arylations of benzothiazole and a wide diversity of aryl halides (Scheme **9**) [20].

Electron-rich or -deficient aryl bromides containing functionalities such as trifluoromethyl, nitrile, ester, vinyl or aldehyde as well as pyridinyl rings are well-tolerated in the reactions. Electron-



Scheme 8. Benzothiophene **11** arylation by aryl chlorides.

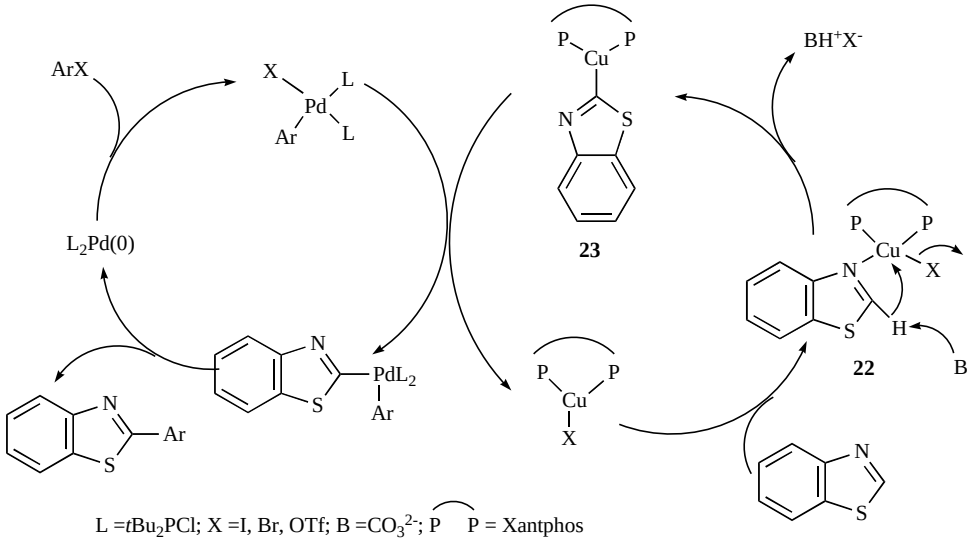


Scheme 9. PXPd/Cu(Xantphos)-catalyzed benzothiazole direvatives **18** arylation.

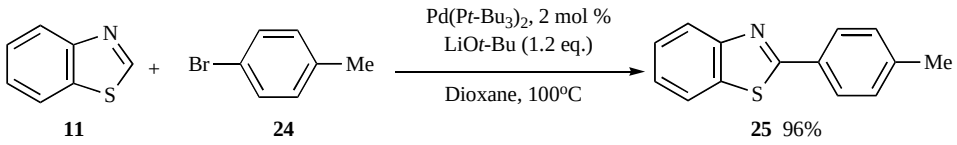
rich benzothiazoles can offer higher yields than that of their electron-deficient counterparts. And they also proposed a mechanism in which copper complex takes part in the crucial transmetalation step in the Pd/Cu cocatalytic cycles (Scheme **10**). The copper center can combine to the lone pair on the nitrogen atom in benzothiazole to form tetrahedral complex **22**. Then, the subsequent deprotonation and re-arrangement of complex **22** would give 2-benzothiazole-copper complex **23**. Transmetalation of **23** to catalytic palladium (II) followed by reductive elimination would afford the desired product and release both the palladium and copper catalysts.

In 2010, Mori's group [21] had shown that the cross coupling between benothiazole **11** and 4-bromotoluene **24** could proceed with Pd(P*t*-Bu_3)$_2$ as catalyst, LiO-*t*-Bu as base in dioxane, affording the product in excellent yield (Scheme **11**). Unfortunately, this procedure was unviable in the previous widely reported solvent-DMF. Beneficially, this methodology was better than their previous ones applying NaOH or TBAF as an additive and copper as cocatalyst [17, 22].

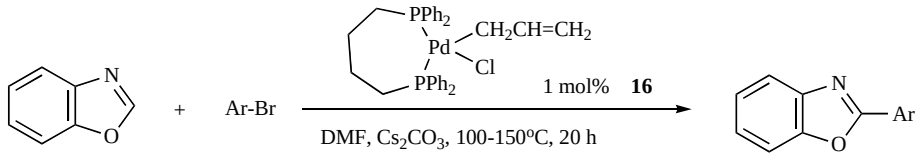
Palladium-catalyzed cross-coupling reactions between aryl bromides and benzoxazole **26** represent a powerful access to 2-arylbenzoxazole derivatives **27**. The direct arylations of benzoxazole **26** with a wide diversity of sterically and electronically aryl bromides and chlorides or heteroaryl halides catalyzed by PdCl(dppb)(C_3H_5) **16** in the presence of Cs_2CO_3 in DMF, furnishing the desired products in 73% to 88% yields were reported by Derridj and coworkers [23] in



Scheme 10. Proposed mechanism for the direct C-H arylation.



Scheme 11. The reaction of benzothiazole **11** with 4-bromotoluene **24**.



Ar	Yield (%)
4-$CF_3C_6H_4$	84
3,5-$(CF_3)_2C_6H_3$	82
4-FC_6H_4	78
4-$OMeC_6H_4$	85
2-naphthyl	88
3-CNC_6H_4	81
2-MeC_6H_4	79
2-thienyl	73
3-thienyl	79
3-pyridyl	84
4-pyridyl	82
5-pyrimidiyl	82

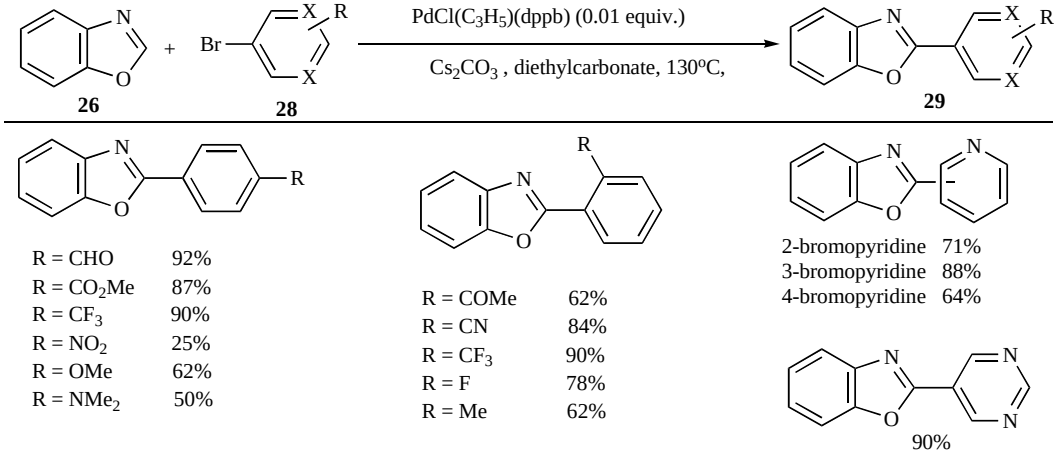
Scheme 12. Palladium-catalyzed arylation of benzoxazole **26** using aryl bromides.

2008. They also carried out several studies on the reactivity of various *para*- *meta*- and *ortho*-substituted aryl bromides with benzoxazole (Scheme **12**). Some substituted functional groups such as trifluoromethyl, fluoro, methoxy, acetyl, carboxylate, amino, nitrile or nitro on the aryl bromides are tolerated.

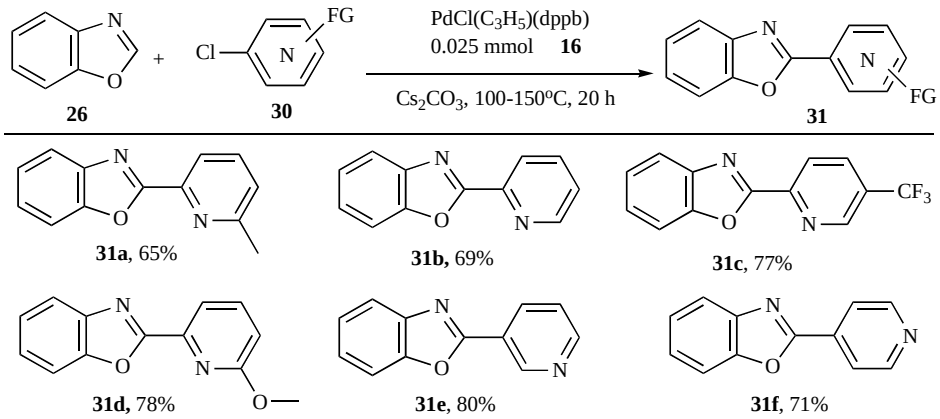
In 2009, diethylcarbonate was first employed as solvent for the direct C2-arylation of benzoxazole derivatives **26** with aryl bromides **28** catalyzed with PdCl(dppb)(C_3H_5), and this was reported by Doucet and coworkers [24]. This solvent was considered to be an environmental and cost-effective alternative to the widely used ones, for it is nontoxic and biodegradable. This protocol is tolerant for both electron-donating and electron-withdrawing groups including methoxy, formyl, acetyl, propionyl, ester, nitrile, trifluoromethyl and fluoro (Scheme **13**). The low yields could be due to the partial poisoning of the palladium such as 4-bromonitrobenzene.

In 2009 Doucet and coworkers [18] established an efficient, economical attractive and simple catalytic system comprising complex PdCl(dppb)(C_3H_5) **16**, DMF or DMAc, Cs_2CO_3 or KOAc, for the direct couplings of chloropyridines **30** with benzoxazole **26**, offering satisfactory to good yields. 2-, 3- or 4-chloropyridine derivatives are suitable substrates for this reaction (Scheme **14**). The position of chloro substituent on the pyridines seems to have a minor influence on the yields.

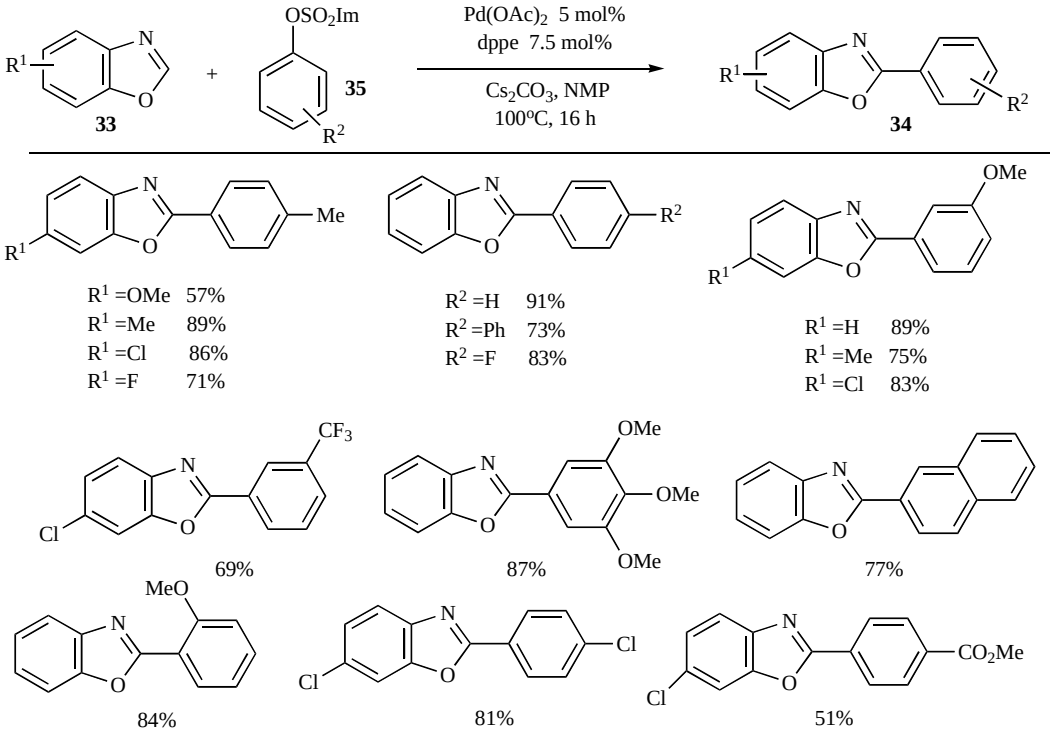
In 2010 Ackermann and coworkers [25] developed a very attractive and user-friendly arylating reagent-imidazolysulfonates because of their moisture-stable nature, properties of the cross-coupling byproduct imidazolesulfonic acid, along with the self-destruction, thus nongenotoxicity. The direct cross-coupling protocol of benzoxazoles **33** with differently substituted imidazolylsulfonates **35** (Scheme **15**) in the presence of catalytic $Pd(OAc)_2$, using NMP as solvent and Cs_2CO_3 as base, dppe as bidentate phosphine ligand was reported. The electron-rich, electron-poor and ortho- subtituents appeared to have a minor influence on the yields. Furthermore, even the substituted benzoxazoles were viable in the coupling reactions, displaying valuable functional groups for further synthetic elaboration.



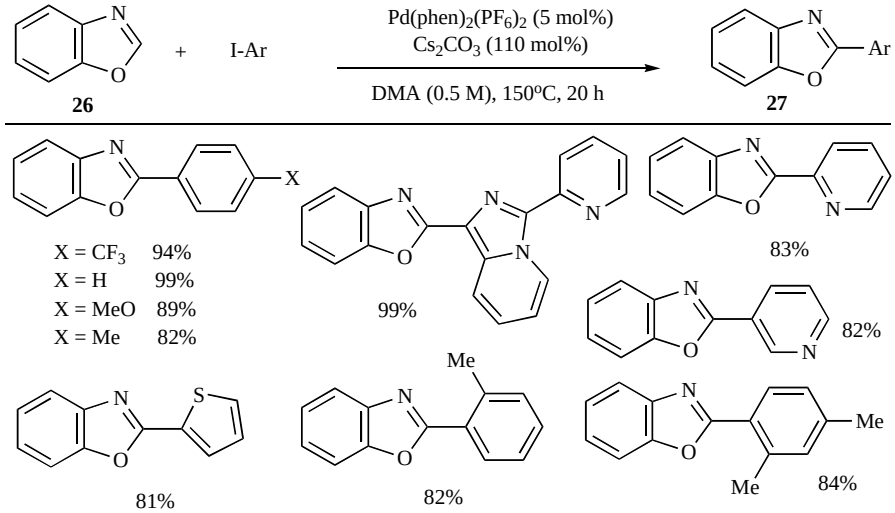
Scheme 13. Arylation of benzoxazole direvatives employing diethylcarbonate as solvent.



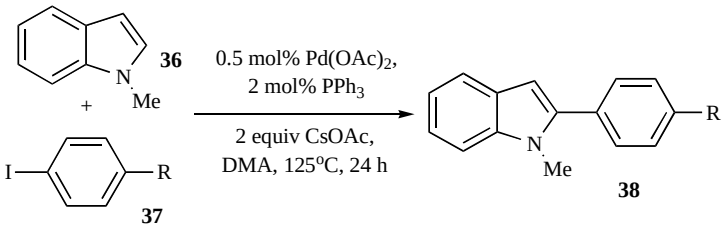
Scheme 14. Palladium-catalyzed arylation of chloropyridine derivatives **30**.



Scheme 15. Direct arylation of benzoxazole derivatives **33** with Imidazolylsulfonates **35**.



Scheme 16. The direct arylation of benzoxazole **26** and aryl iodides.

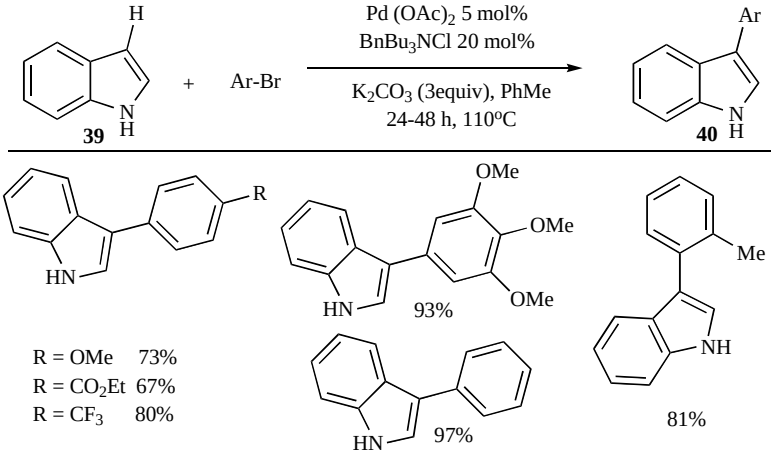


Scheme 17.The selective C-2-arylation of N-methyl indoles **36**.

In 2010 Murai and coworkers [26] developed a moisture-stable cationic palladium complex bearing a nitrogen-based ligand, $Pd(phen)_2(PF_6)_2$, which could efficiently promote the direct arylation of heteroarenes. As a result, reactions can be carried out on a bench-top without using Schlenk techniques. The cross-coupling of benzoxazole **26** and aryl iodides can be performed in the presence of catalytic $Pd(phen)_2(PF_6)_2$, Cs_2CO_3 as base in DMF at 150°C for 20 hours, offering high yields of corresponding products without regard for the nature of the electronic property of substituents on the arenes (Scheme **16**). And the multiple arylation of unsubstituted heteroarenes can be performed highly selective with this catalytic system.

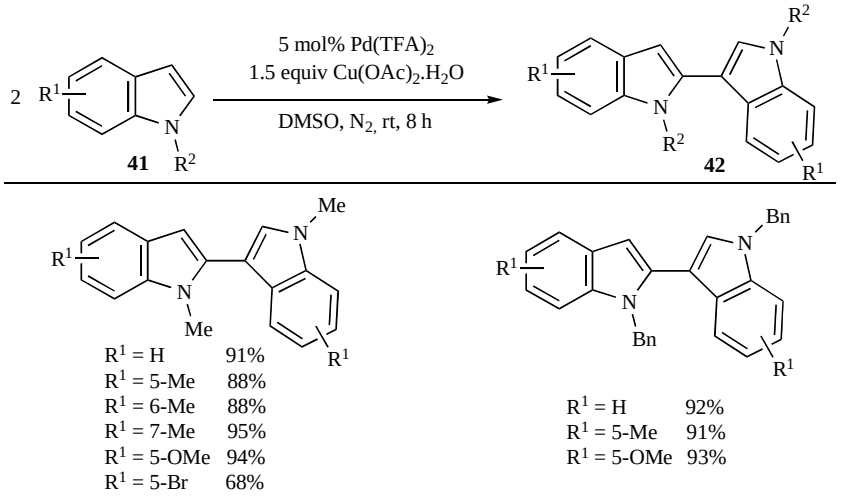
In 2004, Sames and coworkers devised a practical and novel way to arylate N-substituted indoles **36** selectively at the C-2 position with $Pd(OAc)_2$ and PPh_3 as catalytic system, CsOAc as base and DMA as solvent at 125°C for 24h, and offering the desired products in good yields [27]. Both the indoles **36** and aryl iodides **37** containing electron-poor substituted groups favor the arylation, and this method has a good functional group tolerance (Scheme **17**). 4-trifluoromethyl-iodobenzene, 4-cyano-iodoben-zene, 3-iodopyridine and 4-acetyl- iodobenzene can be arylated to offer the yields 62%, 71%, 73% and 52% respectively. The catalyst loading is vital to this methodology, because the reduced catalyst loading can avoid the formation of biphenyl byproduct and enhance the desired product construction.

In 2008, a practical and novel methodology for the regioselective and efficient C-3 arylation of free (NH)-indoles **39** with a small molar excess of activated, unactivated or deactivated aryl bromides under the catalytic system of $Pd(OAc)_2$/$BnBu_3NCl$ and using K_2CO_3 as base in refluxing toluene providing the desired free (NH)-3-arylindoles **40** in satisfactory to good yields was described by Bellina and coworkers

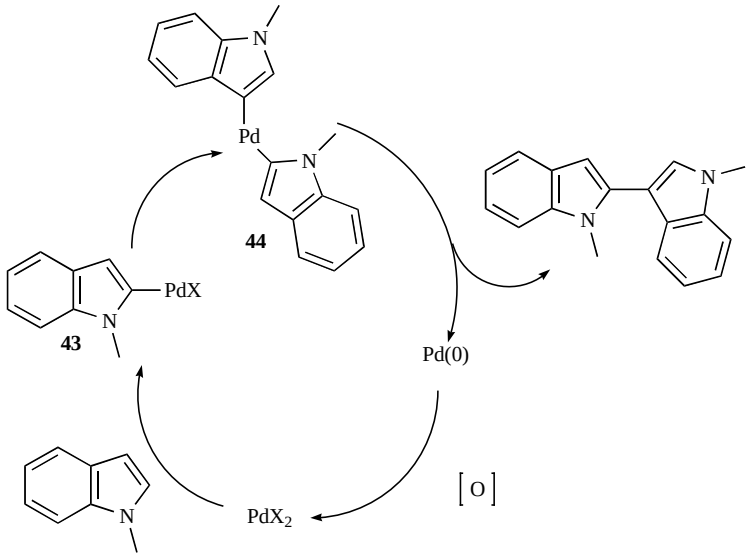


Scheme 18. C-3 Arylation of free (NH)-indoles **39** with aryl bromides.

(Scheme **18**) [28]. Unfortunately, this protocol is not viable for the indoles containing electron-deficient functional groups. However, it is



Scheme 19. Oxidative homocoupling of various substituted indoles **41**.



Scheme 20. Mechanism of palladium-catalyzed regioselective oxidative coupling of Indoles.

worth mentioning that compared with Sames' procedure [27] that for construction of C-2 arylindoles, 1, 2-migration of an intermediate palladium species does not exist and a strongly electron-rich C-3 position is demanded in this new protocol.

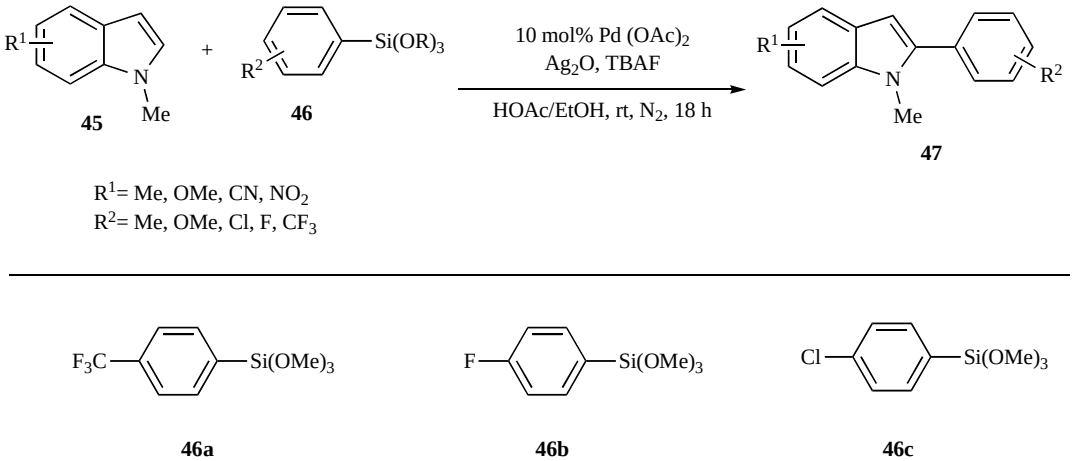
Several indoles **41** underwent the dimerization using the selective and efficient catalytic $Pd(TFA)_2/Cu(OAc)_2{\cdot}H_2O$, offering the 2, 3'-biindolyls **42** with excellent regioslectivity in high yields at room temperature in DMSO (Scheme **19**) [29]. The indoles containing electron-rich substitutes proceeded in high yields. The sterically encumbered indoles just displayed moderate reactivity and performed in satisfactory yields because of steric hindrance.

A plausible Pd (0)/Pd (II) mechanism for the homo-coupling reaction was proposed as shown in Scheme **20** [29]. The electrophilic palladation first occurs at the preferential C3-position of indoles and the subsequent migration of the C3-PdX bond to the 2-position leads to the formation of intermediate **43**, which undergoes the electrophilic palladation with the second indole to form intermediate **44**. The following reductive elimination generates the 2, 3'-dimer of indole, and the formed Pd(0) is oxidized to Pd(II) by Cu(II) or Ag(I) salts in the system to furnish the cycle.

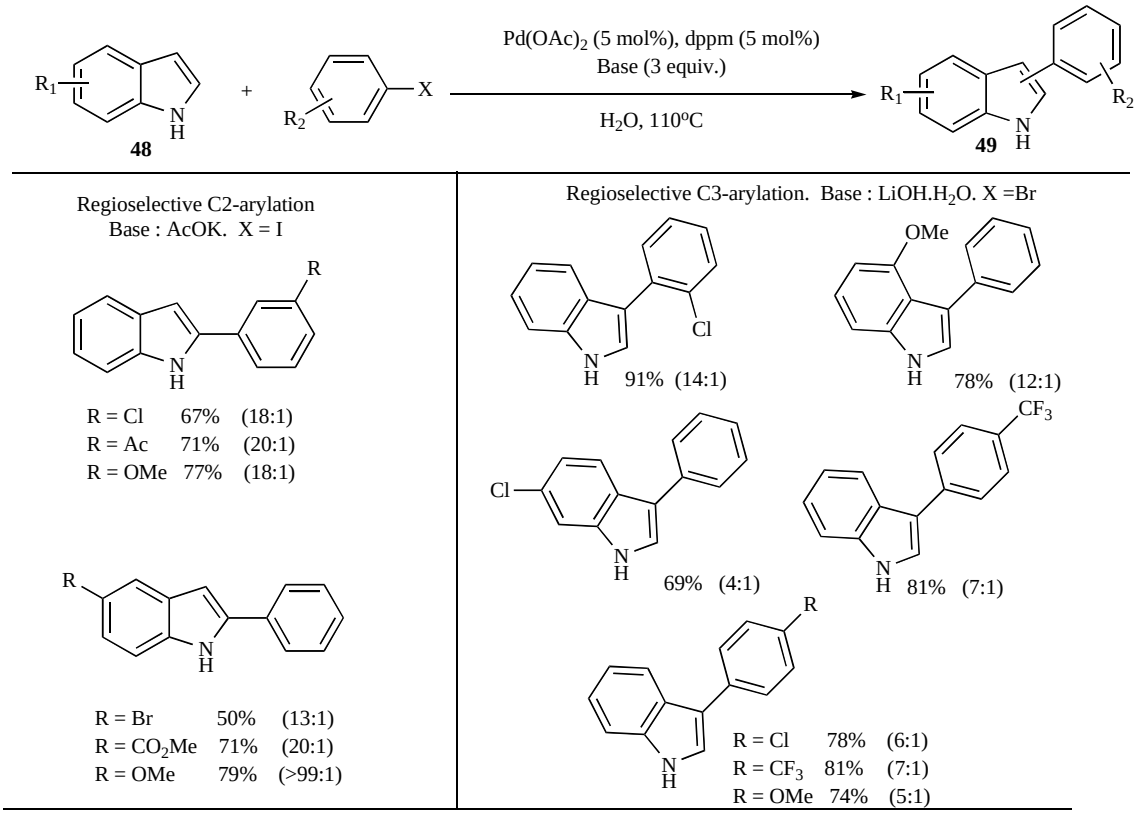
In 2010, a method that 2-aryl-*N*-methylindoles **47** can also be obtained with the $Pd(OAc)_2$-catalyzed cross-coupling reactions between *N*-methylindoles **45** and arylsiloxanes **46** under the condition of TBAF and Ag_2O in acidic medium was depicted by Zhang and coworkers [30]. Arylsilanes containing the electron-deficient group can arylate the indoles, giving the excellent yields (Scheme **21)**. For example, trimethoxy(4-(trifluoromethyl) phenyl)silane **46a**, 4-fluorophenyl-trimethoxysilane **46b** and 4-chlorophenyl-trimethoxysilane **46c** coupled efficiently with indole to offer the desired products in 90%, 91% and 93% respectively. In contrast, arylboranes containing an electron-rich group in the aromatic ring can arylate *N*-methylindoles offering the higher reactivity [31]. Compared with Sames' [27], this methodology takes much more advantage since it can be performed under room temperature and give higher yields.

The protocol that complementary site-selective arylation of (NH)-indoles **48** without protecting or directing groups proceeded in the presence of Palladium (II) acetate/bis(diphenylphosphino)methane $[Pd(OAc)_2/dppm]$ was firstly reported by Djakovitch and coworkers [32]. This procedure is of great significance for it works "on water", offers the C2- and C3-arylation products by employing appropriate base/halide partners, and exhibits high structural versatility with regard to both indoles and aryl moieties. This methodology has good tolerance for both electron-rich and electron-poor groups such as Ac, CO_2Me, OMe, Cl and Br (Scheme **22**).

The report that C2-arylation of indoles derivatives **50** and aryl chlorides **51** catalyzed by palladium(II) acetate applying 2-(dicyclohexylphosphino)-biphenyl as ligand in DMAc was disclosed by Daugulis and coworkers [33] in 2011. Aryl chlorides bearing electron-donating and electron-withdrawing functionalities are viable

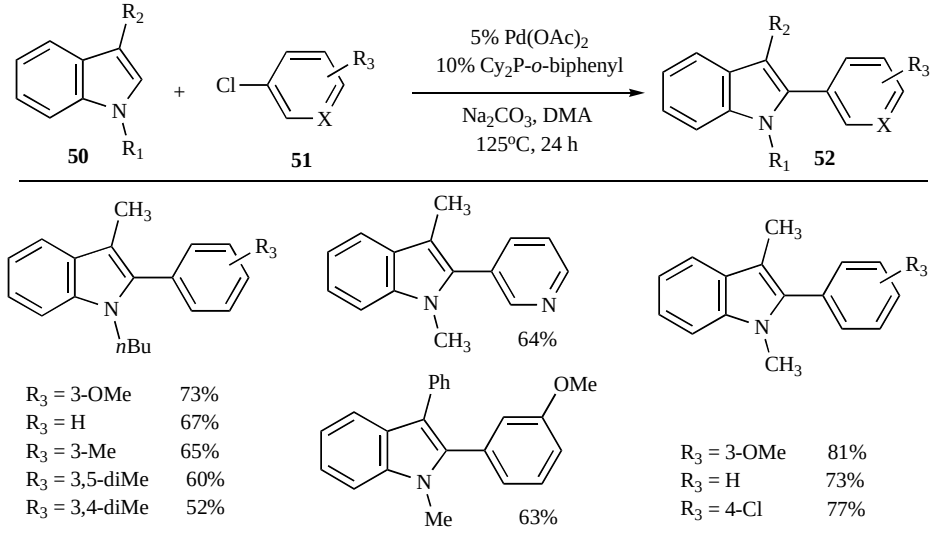


Scheme 21. Regioselective arylation of *N*-methylindoles **45** with arylsiloxane **46**.



Values in brackets refer to 2:3 selectivity of crude material determined by GC.

Scheme 22. "On Water" direct and site-selective Pd-catalysed C-H arylation of (NH)-indoles **49**.

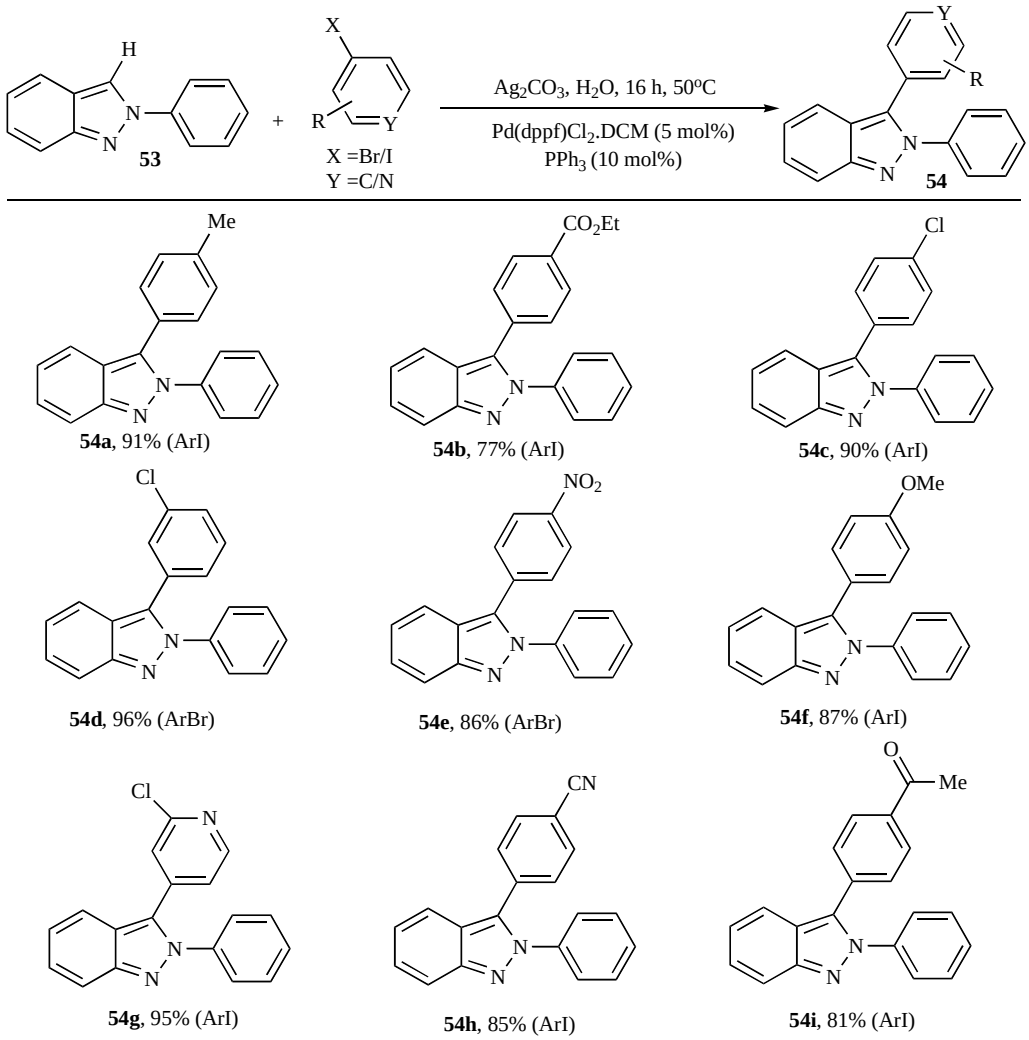


Scheme 23. Palladium-catalyzed indole **50** arylation by aryl chlorides **51**.

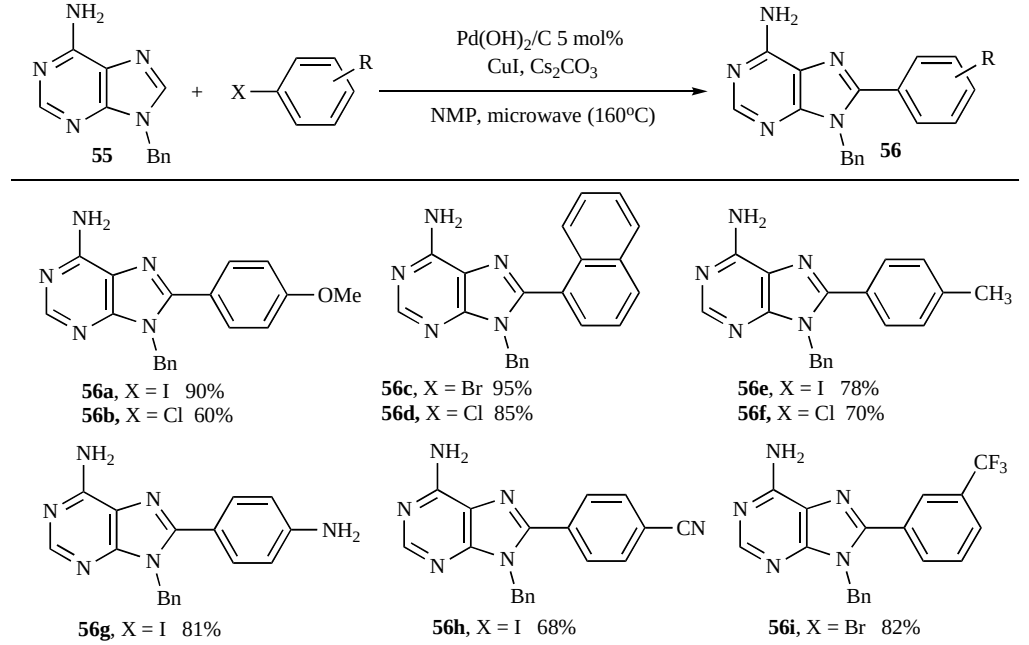
coupling partners, and can offer desired products in moderate to good yields (Scheme **23**). Unfortunately, under this catalytic system, N-arylated products were obtained using unprotected indoles; decomposition of the starting substrates and low conversion to product when the employed indoles bearing electron-poor functionalities on the nitrogen were observed.

The cross-coupling reactions of 2H-indazoles **53** with both aryl iodides and bromides using the catalytic system of $Pd(dppf)Cl_2/PPh_3$ in the presence of an equivalent of Ag_2CO_3 at just 50°C on water and giving good to excellent yields of 2, 3-diarylindazoles **54** was firstly reported by Greaney and coworkers [34] in 2010 (Scheme **24**). Halogen, electron-withdrawing and electron-donating groups on the aryl halides were tolerated at both *para* and *meta* position. 2-chloro-4-iodopyridine gave the desired product **54g** in 95% yield, which can be further functionalized to produce more complicated compound. Successful arylation required both silver salt and ''on water'' conditions.

The direct arylations of free-(NH_2) adenines **55** with a wide range of aryl halides in the presence of $Pd(OH)_2$ (Pearlman's catalyst) and stoichiometric amount of copper iodide under ligand-free microwave activation was reported by Sahnoun and coworkers [35] in 2008. This methodology was proved to be effective for preparation of various 8-aryladenine derivatives **56** without prior protection of the amino substituent. Under this catalytic system, electron-rich and electron-poor aryl iodides, bromides or several chlorides could proceed with good to excellent yields (Scheme **25**). Even the steric aryl halides may offer satisfactory yields of desired products. Although aryl chlorides are less reactive than their corresponding iodo and bromo



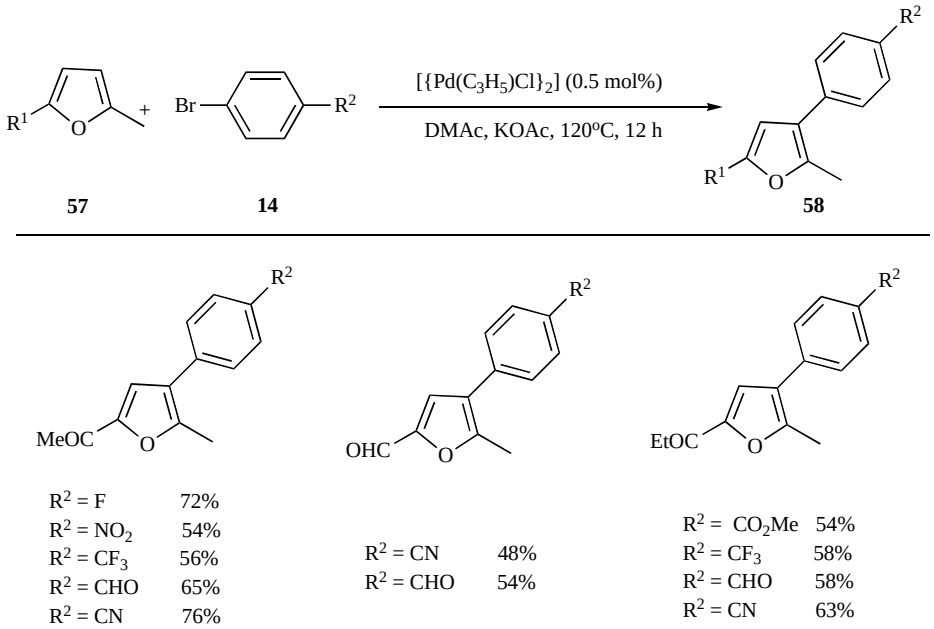
Scheme 24. Palladium-catalyzed direct arylation of 2-phenylindazole **53**.



Scheme 25. Synthesis of C-8 aryladenine derivatives **56** from 6-amino-9-benzylpurine **55**.

derivatives, the similar yields of arylations can be achieved as long as the reaction times (1-2 hours instead of 15 minutes) were prolonged.

An atom-economic and cost-effective procedure for the selective and direct C-4 arylation of 2, 5-disubstituted furans **57** was reported by Doucer and coworkers [36] in 2008. When using a furan

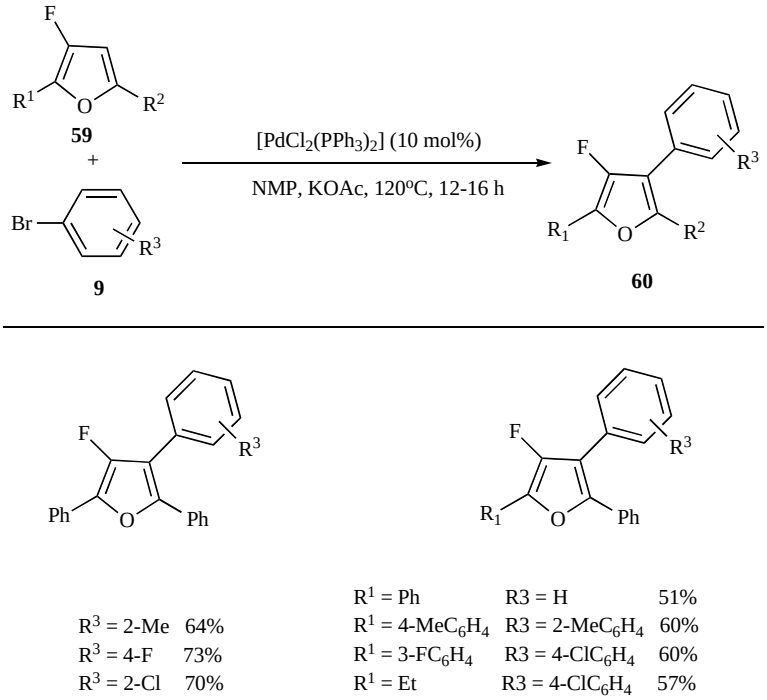


Scheme 26. The direct arylation of furan **57** with aryl bromides **14**.

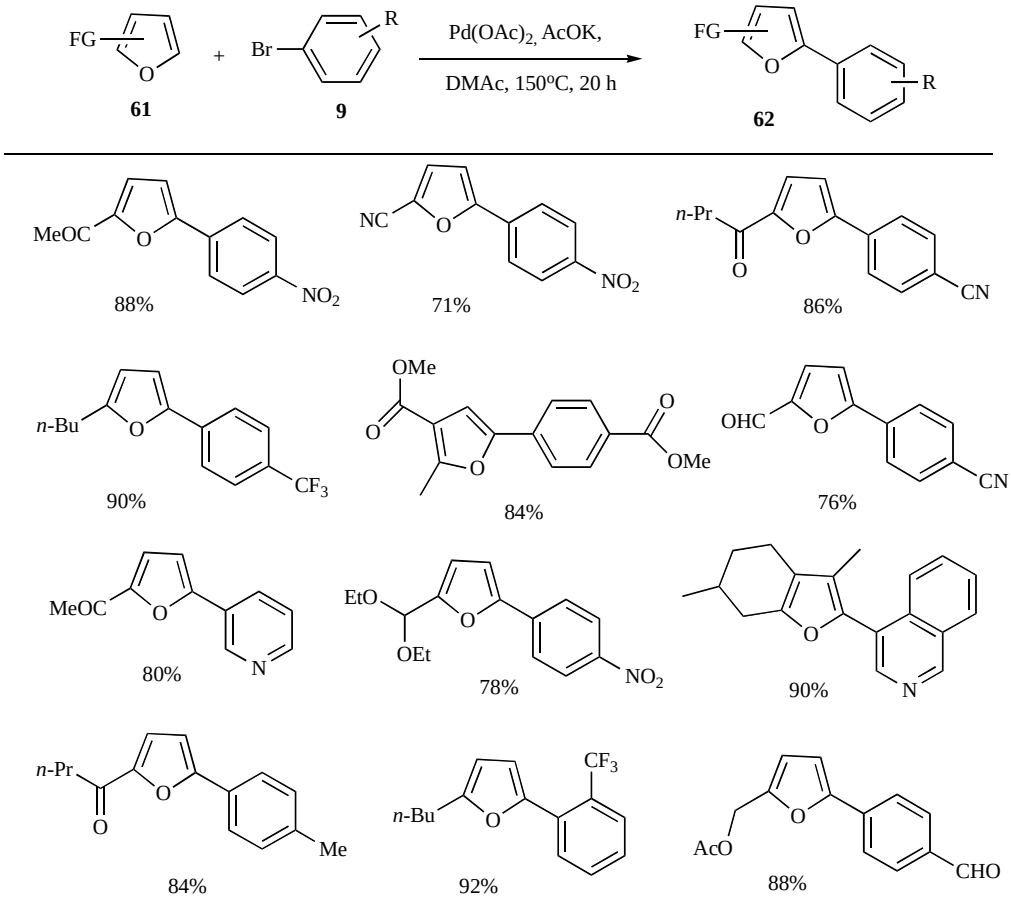
containing an electron-withdrawing functionality such as acetyl and applying KOAc as base, a regioselective C-4 arylated product was observed. The ratio of C-3 arylation and C-4arylation products was strongly dependent on the reaction conditions and catalyst. The C-4 arylated products were formed with high reioselectivity in the presence of the optimized coupling conditions that $[Pd(C_3H_5)Cl]_2$ as catalyst, KOAc as base in DMAc at 120°C for 12 hours (Scheme **26**). The use of other base such as KF, Na_2CO_3 or K_3PO_4 may lead to the formation of C3 arylated or C3 and C4 diarylated products. This method has been proved to be compatible with a wide diversity of functionalities on the aryl bromides such as formyl, alkoxycarbonyl, cyano, acetyl, nitro, fluoro or trifluoromethyl.

Palladium-catalyzed C-4 direct arylations of 2, 5-disubstituted furan **59**, utilizing the neighboring effect of fluorine atom, with a variety of aryl bromides **9**, providing tetrasubstituted monofluoro-furans **60** in moderate to good yields, were reported by Zhu and coworkers [37] in 2009 (Scheme **27**). After extensive screening, the best yields were obtained with catalytic $PdCl_2(PPh_3)_2$, KOAc as base and DMF or DMAc as solvent. It is interesting to notice that neither the position nor the electronic nature of the substituents on the aryl ring exhibited any evident influence on the yields. However, the fluorine atom on the furan ring seemed to facilitate the arylation. Aryl bromides bearing electron-withdrawing functionalities are more reactive and can furnish satisfactory to good yields.

In the same year, Dong and coworkers [38] established a procedure that the direct 5-arylations of furans with aryl bromides proceed in excellent yields at very low amount of catalytic $Pd(OAc)_2$ in the absence of ligand. With such low loading catalyst, it is needless



Scheme 27. Direct 4-arylation of 2,5-diaryl-3-fluorofuran **59**.

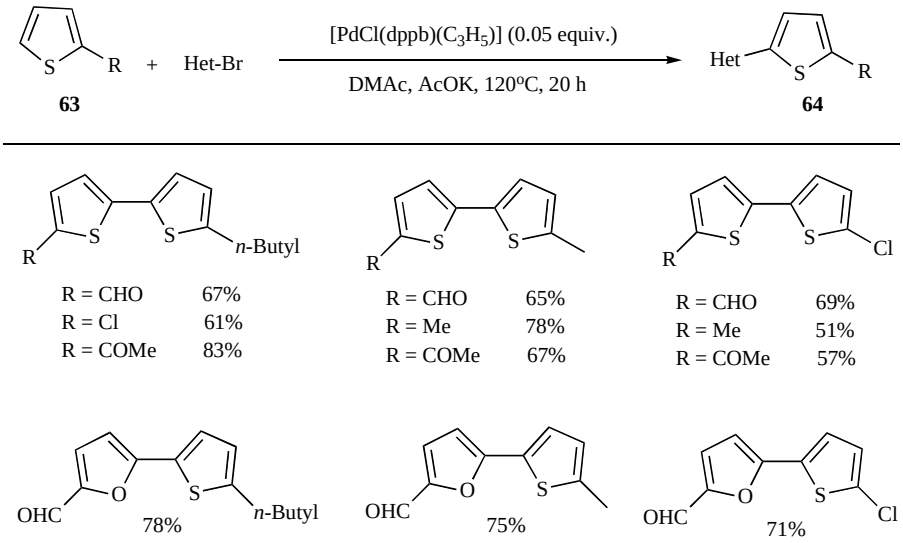


Scheme 28. Palladium catalysed coupling of furan derivatives **61** and aryl bromides **9**.

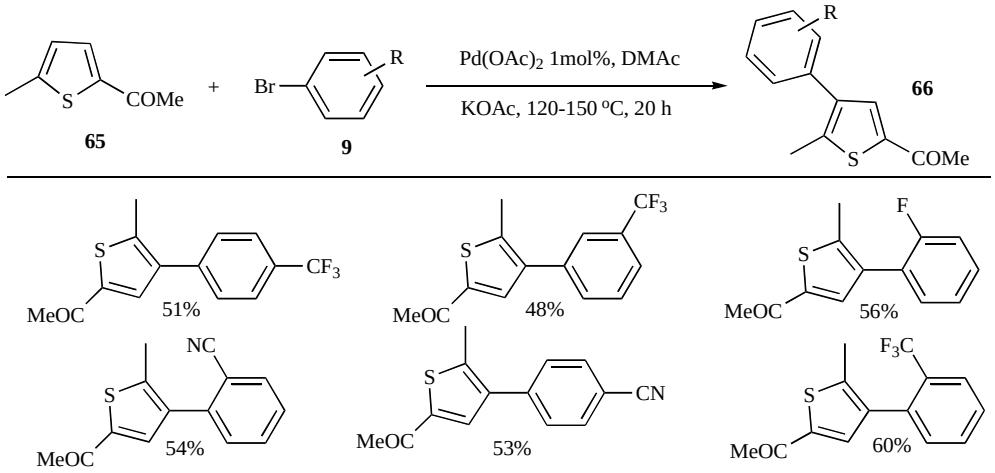
to use the palladium stablizing agents such as ammonium salts which are frequently applied in ligandfree palladium-catalyzed C-H arylation. Unfortunately this method is confined to the arylations between the electron-deficient aryl bromides **9** and furans derivatives **61**. However, it should be pointed out that a wide diversity of functionalities such as ester, formyl, acetyl, nitro, nitile trifluoromethyl or fluoro on the substrates are compatible in this procedure (Scheme **28**).

A wide range of thiophene-containing bi- or polydentate compounds **64** can be conveniently prepared by employing air-stable complex PdCl(dppb)(C_3H_5)] as catalyst [39]. This protocol can offer the desired products in moderate to good yields and a wide range of functional groups are tolerated such as nitrile, formyl, ester or acetyl (Scheme **29**).

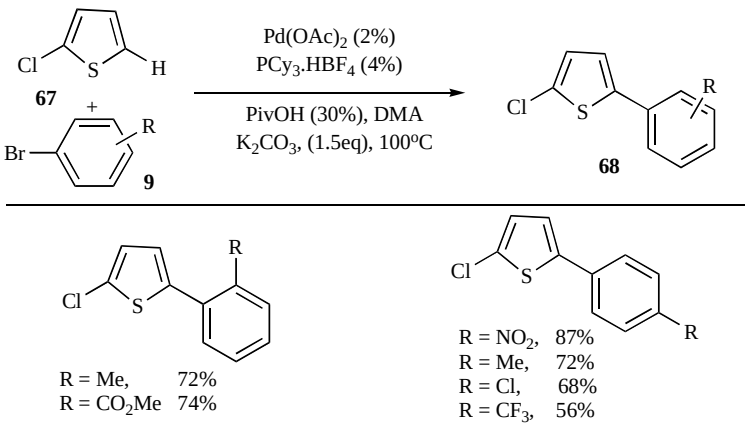
The cross-couplings of 2-acetyl-5-methylthiophene **65** and electron-poor aryl bromides **9** offered higher yields than that of 2, 5-dimethylthiophene with corresponding aryl bromides using $Pd(OAc)_2$ as catalyst, KOAc as base, DMAc as solvent [40] (Scheme **30**). Furthermore, 2-acetyl-5-methylthiophene **65** underwent the arylation reaction with a good regioselectivity on the C-4 position.



Scheme 29. Palladium-catalysed cross-coupling with thiophene derivatives **63**.



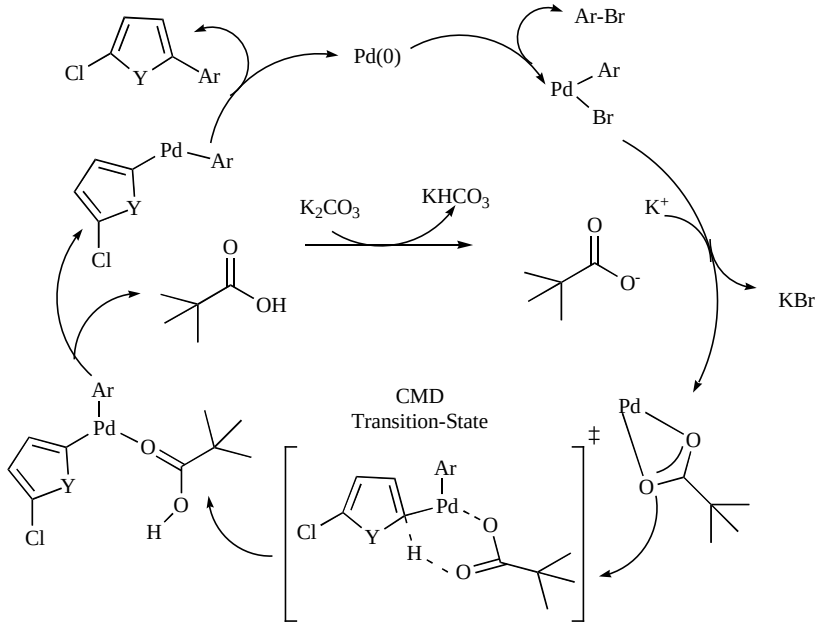
Scheme 30. Palladium-catalysed direct 4-arylations of 2-acetyl-5-methylthiophene **65** with aryl bromides **9**.



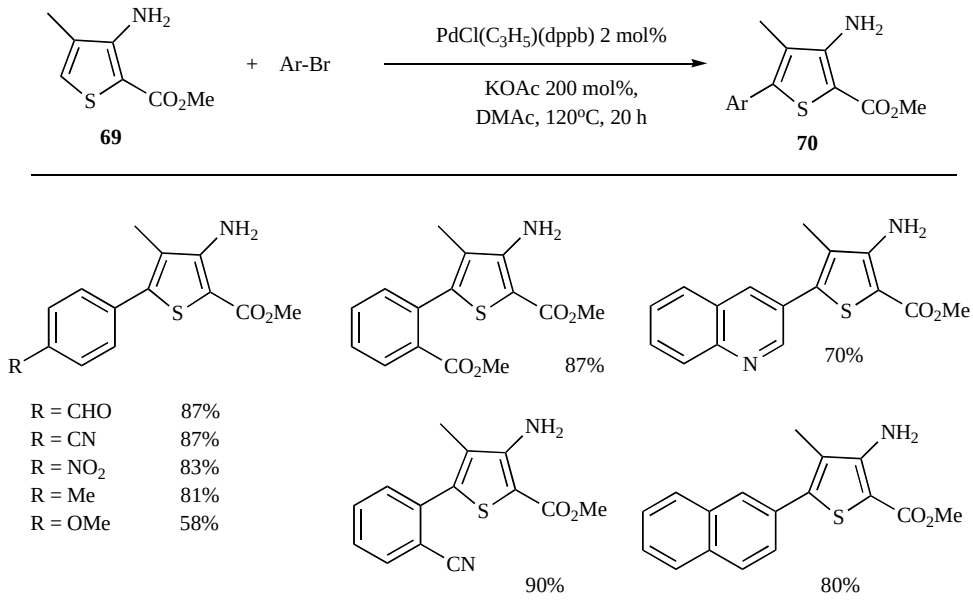
Scheme 31. C-5 direct arylation of 2-chlorothiophene **67** in the presence of a copper additive.

Unfortunately, only aryl bromides can be employed in this procedure. Under the similar conditions, 2, 5-dimethylthiophene could give the C-4 arylated products with moderate to good yields. Another, a wealth of functional groups such as formyl, propionyl, nitro, benzoyl, nitrile, fluoro or trifluoromethyl is tolerated on the aryl bromides.

The introduction of chlorine atom to the heteroarenes can improve the reactivity and offer previously inaccessible direct coupling products through the diversion of typical direct arylation regioselectivity. From the angle of synthesis, this methodology is particularly attractive and advantageous because of the easily introduction of C-Cl bond, and a wide range of highly functionalized



Scheme 32. Proposed catalytic cycle for the palladium-catalyzed direct arylation of heteroaromatics.



Scheme 33. Direct arylation of methyl 3-amino-4-methylthiophene-2-carboxylate **69**.

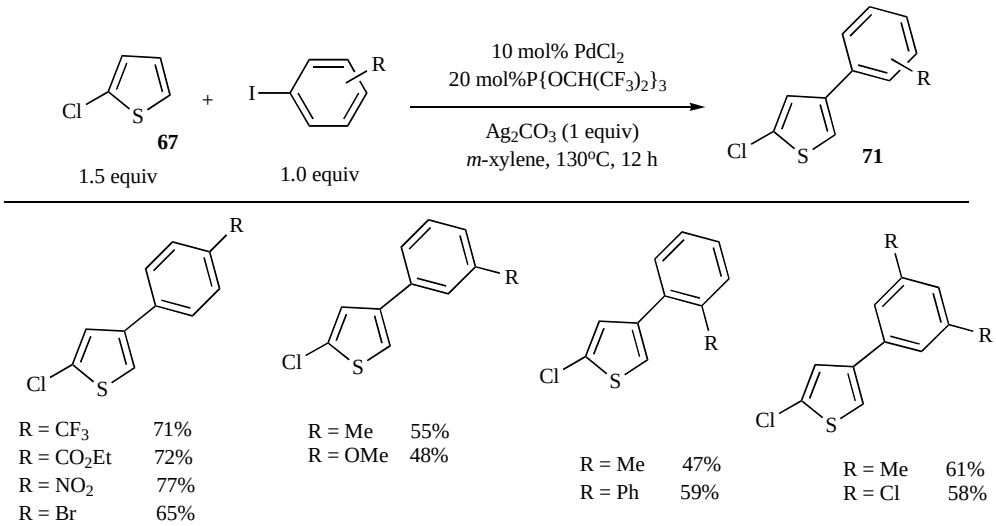
lized aromatics could be prepared through the subsequent conversion of the chlorine-substituted heteroarenes without being preactivated. In 2010 Fagnou and coworkers [41] applied this methodology in the direct arylation of commercially available 2-chlorothiophene **67** with several electron-poor or electron-neutral 4-substituted aryl bromides **9**, offering the corresponding products in good yields (Scheme **31**). Furthermore, the sterically encumbered and unactivated electron-rich aryl halides were suitable in this reaction.

Then, they proposed the catalytic cycle for such arylation. Initial oxidative addition of the palladium(0) species into the aryl halide bond is followed by a bromide/pivalate ligand exchange, the latter being generated in situ from the catalytic pivalic acid and the insoluble stoichiometric carbonate base. Approach of the hetero-aromatic partner leads to a concerted metalation-deprotonation (CMD) transition state, enabled by the pivalate ligand. Subsequent reductive elimination produces the biaryl product and regenerates the active catalytic species (Scheme **32**) [41].

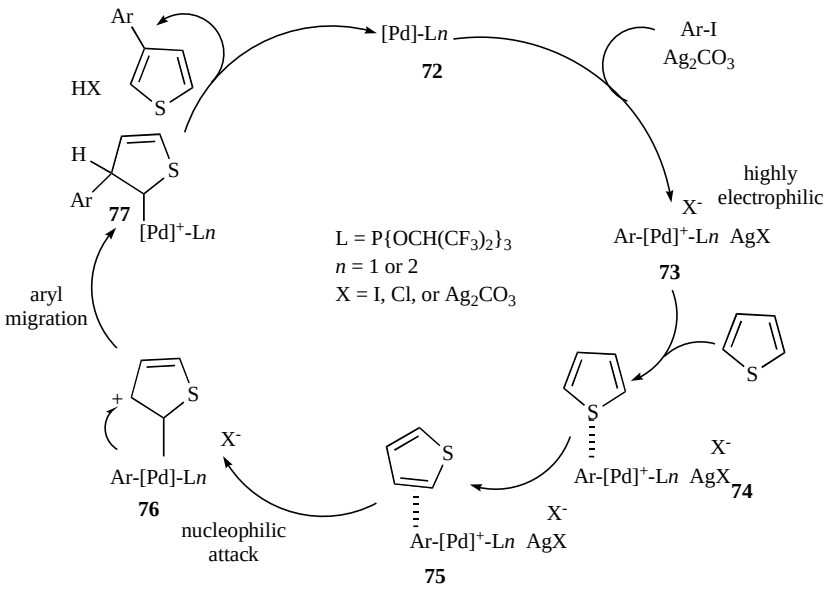
The first protocol for arylations of free NH_2-subsituted thiophene **69** with aryl bromides in the presence of $PdCl(C_3H_5)(dppb)$ with KOAc as base in DMAc was disclosed by Doucet and coworkers [42] in 2010, offering no coupling products of aryl bromides with thiophene NH_2 subsitutent. The electron-deficient or congested aryl bromides give the desired products in excellent yields, while the electron-rich coupling partners furnish moderate yields due to the partial conversions (Scheme **33**). The formation of 2, 5-diarylated product and the decarboxylated product are responsible for the low yields.

After extensively exploring, the first general protocol for β-selective arylation of thiophene **67** occuring by C-H arylation in the presence of $PdCl_2$, using extremely electron-withdrawing $P\{OCH(CF_3)_2\}_3$ as ligand, had been disclosed by Itami and coworkers [43] in 2010. This procedure is extremely of importance, because when the 2-position of thiophene is occupied by ortho/para-directing groups, such as Ph or Cl, the 4-position is least reactive (Scheme **34**). This methodology is complementary for Fagnou's [41], which arylated at α-position of 2-chlorothiophene with $Pd/PCy_3/tBuCO_2H/K_2CO_3$ catalytic system.

They proposed the potential mechanism (Scheme **35**): oxidative addition of ArI to the Pd complex **72** was followed by regeneration of electrophilic and cationic aryl palladium species **73** mediated by silver. After **74** and/or **75** was produced by coordination of thiophene to Pd, C_α-Pd bond formation to give **76**. The formation of β-aryl



Scheme 34. Arylation of 2-chlorothiophene **67** and iodoarene.

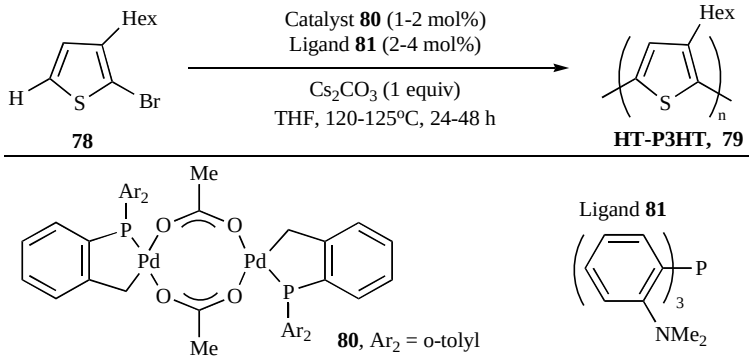


Scheme 35. Possible mechanism.

thiophene with the regeneration of **72** by proton abstraction tailed after the formation of **77** by migration of aryl group from Pd to β carbon atom [43].

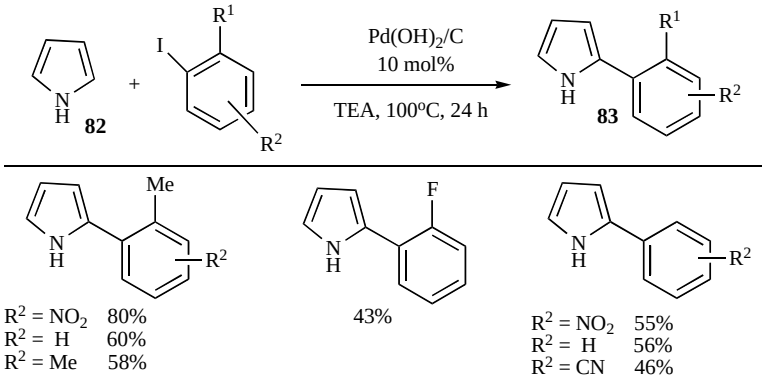
The dehydrohalogenative polycondensation of 2-bromo-3-hexythiophene **78** was successfully and highly efficient catalyzed by Herrmann's catalyst **80**, employing tris(2-dimethylamino-phenyl) phosphine **81** as ligand, furnishing the head-to-tail poly(3-hexylthiophene) **79** in the yield of 99% with high regioregularity, which was performed in a gastight Schlenk tube(Scheme **36**) [44]. This methodology is more advantageous than Kita and coworkers' [45] using hypervalent iodine(III), for it offers higher yield and the latter just can catalyze the dimerization of 3-subsituted thiophene. Another, the procedure is complementary to the head-to-head [46] or tail-to-tail [47] dimerization of β-substituted thiophenes using copper as catalyst.

The catalytic system comprising $Pd(OH)_2/C$ (10 mol%) and triethanolamine (0.2 M) could provide an atom-economical, efficient cost-effective and environmentally attractive route to a wide diversity

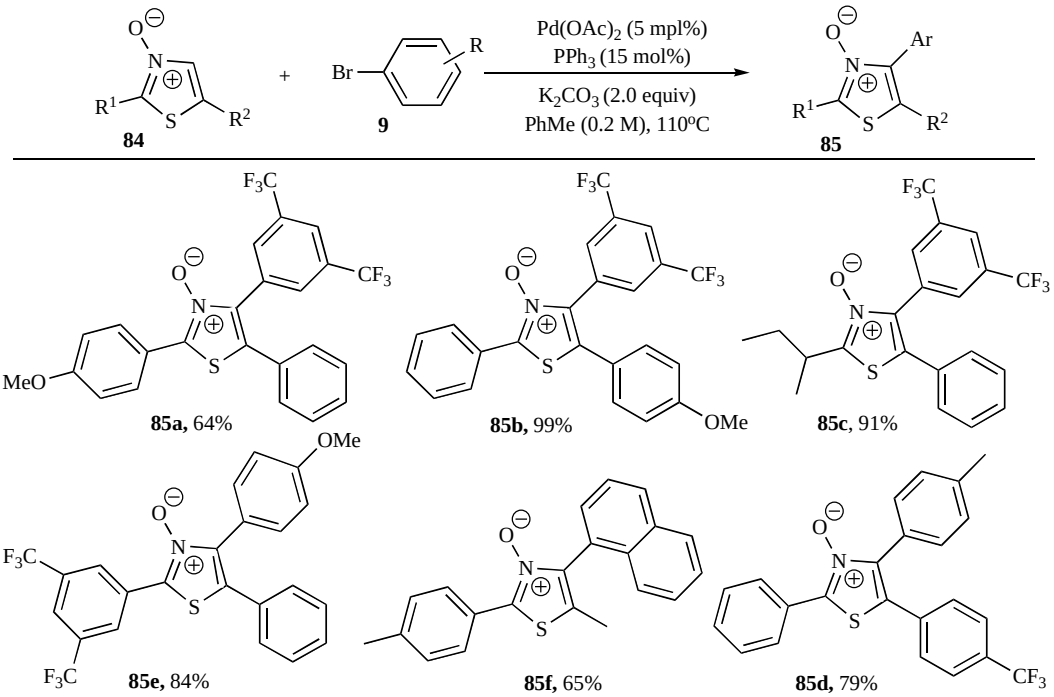


Scheme 36. Polycondensation of 2-bromo-3-hexylthiophene **78**.

of 2-aryl-1H-pyrroles **82** from readily available starting materials, since it eliminates the need for introducing protecting groups and reactive functionalities prior to C-C bond formation (Scheme **37**) [48]. The aryl iodides containing electron-withdrawing or electron-



Scheme 37. Regioselective direct C-2 arylation of free NH-pyrroles **82**.

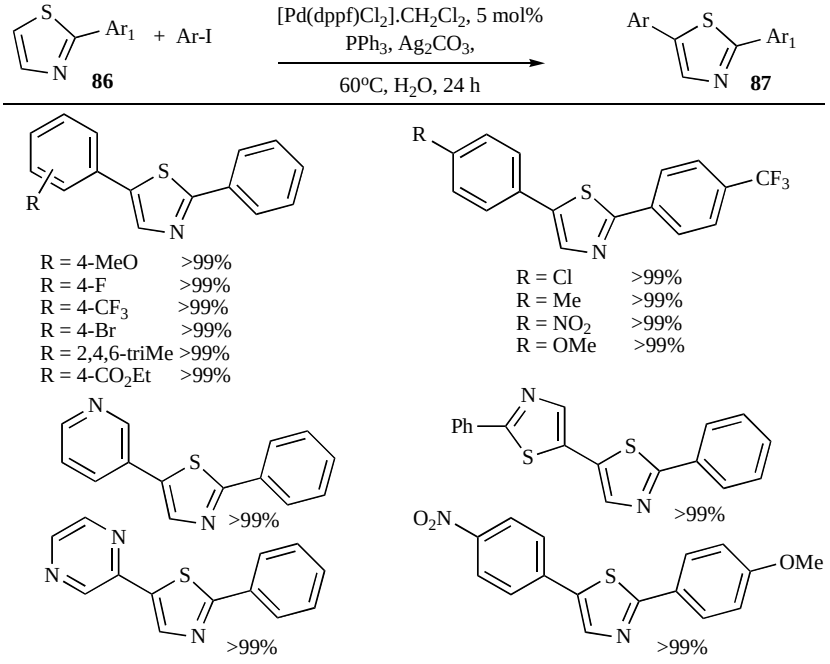


Scheme 38. 4-arylation of thiazole derivatives **84** with aryl bromides **9**.

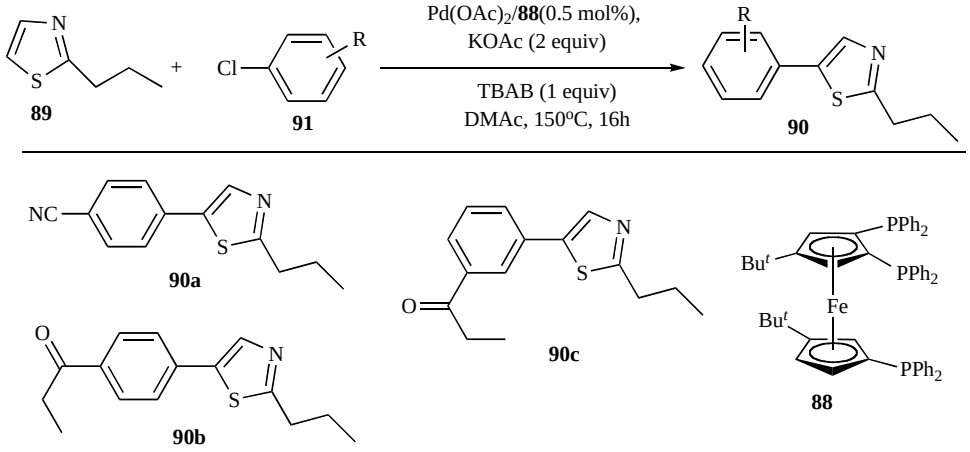
donating subsituents were suitable for such arylation, even the sterically demanding iodoarenes were viable coupling partners under the presented conditions.

The conversion of thiazoles to thiazoles N-Oxides could significantly increase the reactivity of all positions on the thazoles rings as well as change the reactivity profile with respect to the sequence of arylation, which means that the arylation of thiazole N-oxides strictly obey the order that occuring at C2, then at C5 and eventually at C4. The arylation conditions between thiazole N-oxides and aryl halides, comparing with that required for thiazole arylation, were much milder. This provided the method that arylated regioslectively and high-yielding at C4 of thiazoles, so it could offer a unique opportunity for exhausive functionalization of thiazole core. In 2008 Fagnou and coworkers [49] had reported the 4-arylation of thiazole derivatives **84** involving the use of catalytic $Pd(OAc)_2$ (5mol%) in the presence of PPh_3 (15mol%) and 2equiv of K_2CO_3 in toluene at 110 °C. Under such conditions, 2, 5-diarylthiazole N-oxides **85a, 85b, 85d, 85e** or 2-tolyl-5-methylthiazole N-oxides **85f** could arylate a wide range of aryl bromides **9**, offering the yields of 59-99% (Scheme **38**). The resulting thiazole N-oxides can readily convert to thiazole derivatives under mild reductive conditions.

In 2007, Greaney and coworkers [50] established direct arylations of thiazoles **86** and aryl iodides applying $[Pd(dppf)Cl_2]\cdot CH_2Cl_2/PPh_3$ [dppf=(diphenylphosphanyl)ferroce-ne] as an effective catalytic system, characterizing the first direct cross coupling method that



Scheme 39. Arylation of thiazoles derivatives **86** with various aryl iodides.



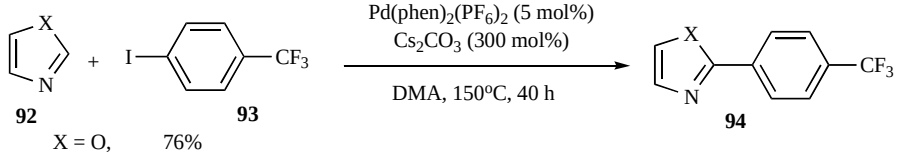
Scheme 40. Direct arylation of heteroarenes thiazole **89** using chloroarenes **91**.

works "on water". This procedure has an excellent tolerance of substituents that is electron-rich (R=Me, OMe) and electron-poor (R=F, NO_2, CN, CF_3, CO_2Et) at each of the *o*, *m* and *p*-position in iodides (Scheme **39**). This "on water" methodology is of substantial benefit: enhanced reaction rate and efficiency; eased of operation and work-up; improved safety profile due to the heat capacity of water, low-cost and eco-friendly of water.

In 2010, the method that efficient couples of substituted thiazoles with chloroarenes detivatives achieved by a catalytic system comprising air-stable, moisture and tempeture tolerant Murai and coworkers (Scheme **41**) [52]. A minor amount of diarylated products are produced in the reaction.

2.2. Cu-Catalyzed Direct Arylation of Benzothiazole, Benzoxazole, Benzimidazole, Indole, Thiophene, Pyrrole and Oxazole Ring System

Recently, most of the catalysts applied in the direct cross-coupling reactions of aromatic compounds catalyzed by transition metals via C-H cleavage are usually the expensive ones such as palladium and rhodium. So taking the cost-efficiency into

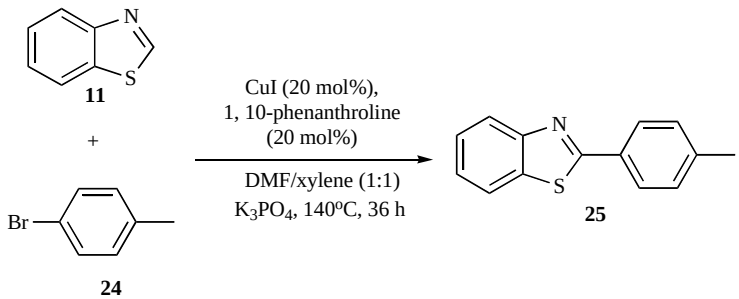


X = O, 76%
X = NMe, 59%

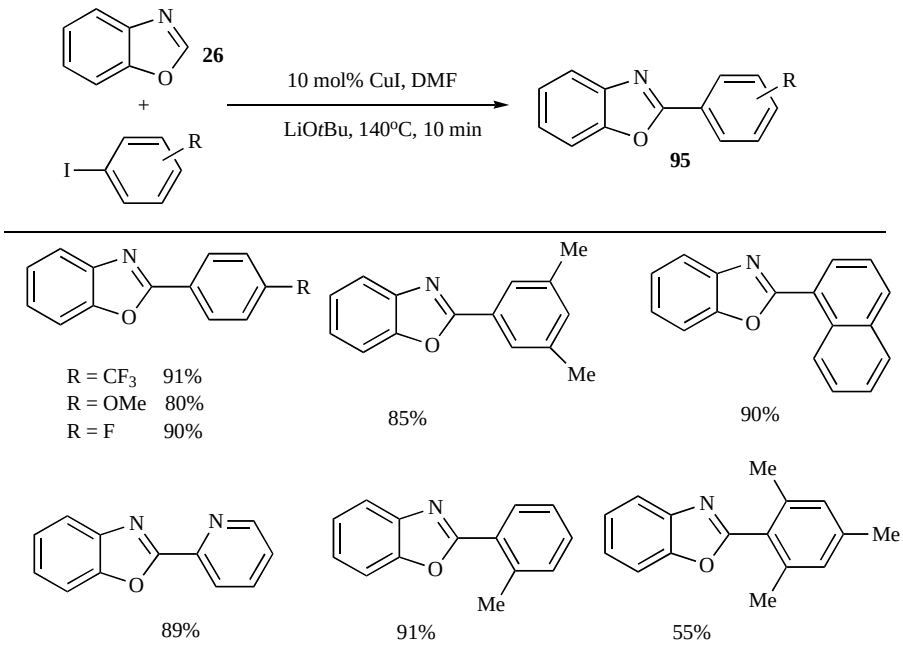
Scheme 41. Triple arylation of simple oxazole and N-methylimidazole.

$Pd(OAc)_2$ and constrained ferrocenyl triphosphane ligand **88**, in the presence of KOAc as base in DMAc, was disclosed by Hierso and coworkers (Scheme **40**) [51]. The addition of tetra-*n*-butylammonium bromide (TBAB) was useful and vital for this procedure. 2-n-propylthiazole **89** can couple with 4-chlorobenzonitrile, 3- or 4-chloropropiophenone employing this procedure, and furnishing the desired products **90a**, **90b** and **90c** respectively, in the yields within the range of 62-92%. This protocol can be carried out with other heterocyclics such as furan, pyrrole and thiophene and is compatible with ester, keto, nitriles, nitro and formyl functionalities in *para*, *meta* or *ortho* positions of substituted chloroarenes.

In 2010, an excellent catalytic reactivity with cationic Pd complex $Pd(phen)_2(PF_6)_2$ (phen = 1,10-phenanthroline) had been firstly demonstrated in the triarylation **92** between oxazole or N-methylimidazole and 4-trifluoromethylphenyl iodide (3 eqiv.) by consideration, it is significantly attractive to replace them with a cheaper one to prepare the biaryls such as copper [53]. In 2009, You and coworkers disclosed a protocol for the arylations of benzothiazole **11** with aryl halides in the presence of catalytic system that was generated in situ from 1, 10-phenanthroline and CuI employing K_3PO_4 as base in DMF/xylene (1:1) furnishing the product in 83% yield (Scheme **42**) [54]. The similar result can be achieved with $Pd(OAc)_2$ as catalyst by the same group [55]. The electron-rich, poor, sterically bulky or heteroaryl bromide were reactive with this procedure, and the functionalities such as cyano, aldehyde, ester and benzyloxy groups on the aryl bromides were compatible. Compared with Miura's [56] or Dangulis' [57], this methodology can avoid any troubles caused by phosphorous-containing ligand during postal treatment or the use of strong base. Another, this method was the first report of copper-catalyzed direct couple of 2-formylthiophene and 2-formylfuran. Diphenyl-[2-(phenylthio)phenyl]amine can be obtained



Scheme 42. Copper-catalyzed direct arylation of benzothiazole **11.**



Scheme 43. The direct arylation of benzoxazole **26** with aryl iodides catalyzed by copper.

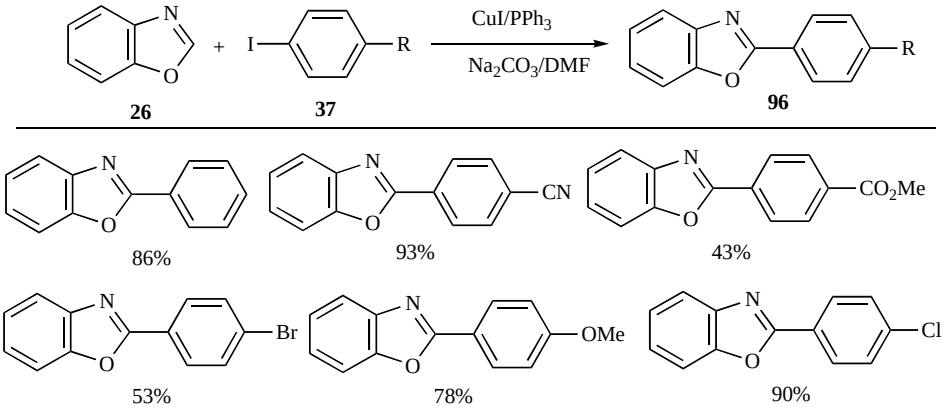
due to the C-2 hydrogen of **11** is relatively more acidic and its anion readily undergoes ring-opening when the strong base was employed or the electron-withdrawing ability of substrate **11** was strong such as bearing CN, NO_2 or pyridine ring [56, 58]. Me-substituted 1, 10-phenanthroline may bring more benefit to this reaction [59].

Due to the observation that the addition of copper salt can influence the regioselectivity of palladium-catalyzed direct arylation of aromatic compounds, Daugulis and coworkers [57] in 2007 first reported that benzoxazole **26** and aryl iodides can undergo the direct cross-coupling reactions using the catalytic system comprising CuI and Li*O*t*Bu in DMF at 140°C just for 10 minutes (Scheme **43**). Electron-deficient, electron-rich or the steric encumbered aryl iodides even the heteroaryl iodides are viable coupling partners under this condition, giving the products in excellent yields with the exception of mesityl iodides.

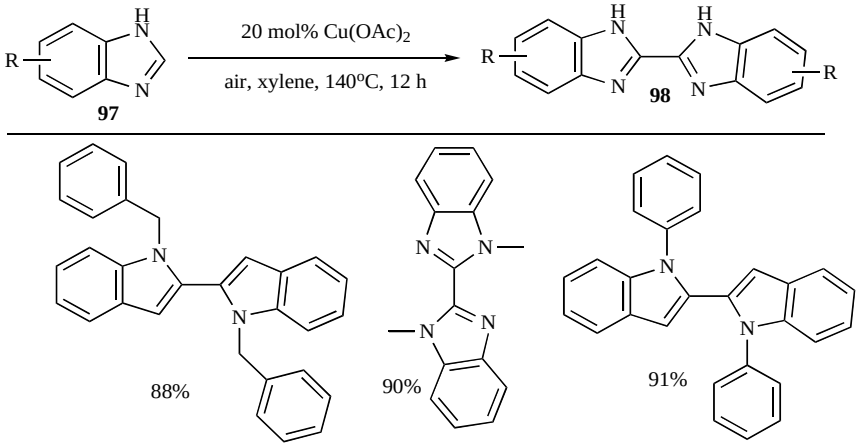
The arylations of benzoxazole **26** with aryl iodides **37** can effectively and selectively proceed at the C-2 position promoted by CuI in the presence of PPh_3 and Na_2CO_3 or K_3PO_4 as ligand and base, respectively, in DMF or DMSO, furnishing the expected products in good yields (Scheme **44**) [56]. Several 4-subsituted aryl iodides containing electron-rich and electron-deficient substituents offered the desired 2-arylbenzoxazoles products **96** in fair to excellent yields. And ester, bromo and nitrile functional groups are compatible under the presented procedure.

The procedure that direct construction of C-C bonds at the 2-position of various benzimidazoles **97** achieved by $Cu(OAc)_2$/air mediated oxidative homo-cross-coupling reaction was uncovered by Bao and coworkers [60] in 2010. This approach is of great significance since the environmentally benign oxygen was used as an terminal oxidant and $Cu(OAc)_2$ can be recovered and recycled although the yield slightly declined as the number of times the catalyst was recycled increased. Another, no methyl will be oxidated and the dimerizations of the substrates regioselectively occurred at the 2-position under this procedure (Scheme **45**).

By comparing with other d^8 species, for instance Pd (II) and Rh (I), Gaunt and coworkers speculated that other d^8 configured transition metals may promote C-H arylation such as Cu(III) which possesses d^8 configuration as well as carry a +3 charge that should render it more reactive. This led to the establishment of the procedure that Cu(II)-catalyzed free (*NH*) - and *N*-alkylindoles direct arylations with a wealth of unsymmetrical [TRIP-i-Ar]OTf salts (TRIP: 2, 4, 6-tri-isopropylphenyl) using $Cu(OTf)_2$ as catalyst and 2,6-di-tert-butylpyridine as ligand which can prevent the dimerization of indole in DCE just at 35°C, furnishing the C3-regioisomer with excellent selectivity and in good yields (Scheme **46**) [61]. It is noteworthy that aryl substrates having C-Br and even C-I bonds are unaffected in this



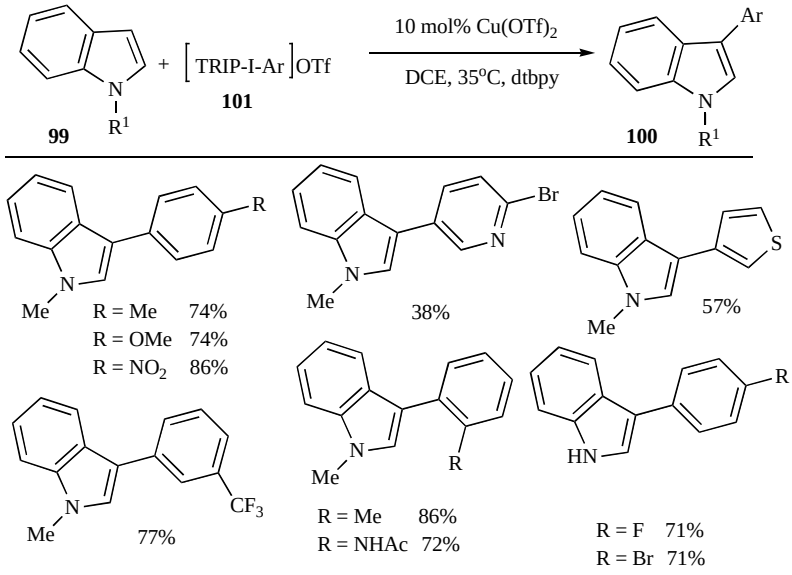
Scheme 44. Reaction of benzoxazole **26** with aryl iodides **37**.



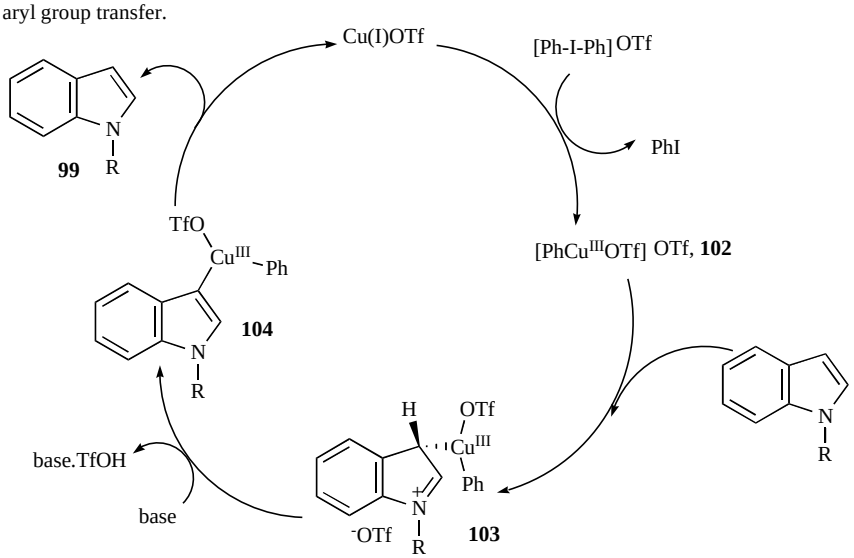
Scheme 45. An effcient and convenient $Cu(OAc)_2$/air mediated oxidative coupling of benzimidazoles **97** via C-H activation.

procedure, offering a complementary platform for further elaboration through traditional Pd(0)-catalyzed arylation.

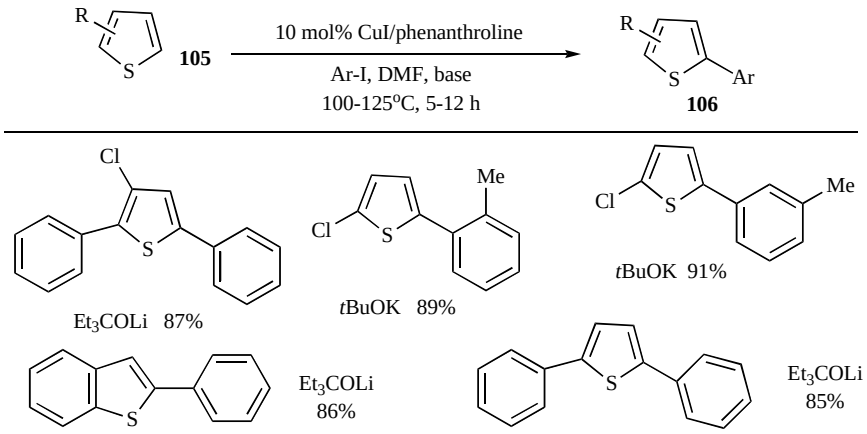
The mechanism of the Cu(II)-catalyzed C-H bond arylation is proposed to begin with reduction of the Cu(II) catalyst to Cu (I) by the indole (Scheme **47**) [61]. Oxidative addition of the diaryliodine(III) reagent to the Cu(I) salt would generate the electrophilic Cu(III)-aryl intermediate **102** that can undergo attack at the C3 position of indole to **103**. Re-aromatization via C-H bond cleavage to **104** would be followed by reductive elimination, delivering the product **100** and re-forming the Cu(I) catalyst.



Scheme 46. Cu(II)-catalyzed aryl group transfer.



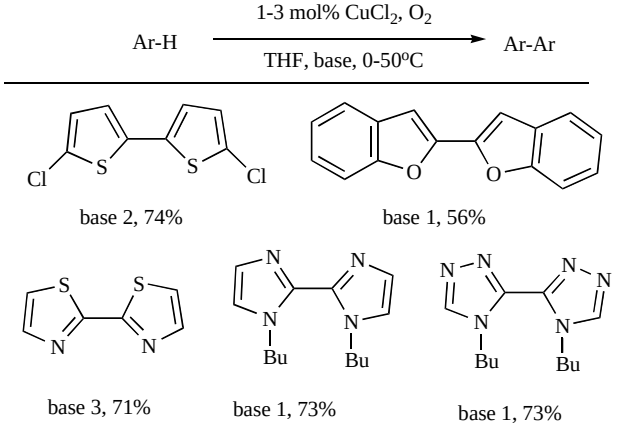
Scheme 47. Proposed catalytic cycle for the Cu(II) catalyzed C-H arylation.



Scheme 48. The direct arylation of thiophene derivatives **105** with aryl iodides.

In 2008, a protocol for the direct arylations of thiophene derivatives **105** and aryl iodides in the presence of hindered Et_3COLi or *t*BuOK as base, DMF as solvent and catalytic system consisting of CuI and phenanthroline, furnishing the required products in good to excellent yields was developed by Daugulis and coworkers [4] (Scheme **48**).

Daugulis and coworkers first developed a general protocol for the deprotonative dimerization of heteroarenes by applying oxygen as terminal oxidant in the presence of $CuCl_2$, employing THF as solvent at 0-50°C, typically at room temperature (Scheme **49**) [62]. Electron-deficient or electron-rich heteroarenes are viable in this catalytic system and some of the functional groups such as cyano, nitro, amino and ester groups are tolerated in the heteroarenes.



Base 1 *i*PrMgCl*LiCl + tetramethylpiperidine (1:1.1)
Base 2 Base 1 + $ZnCl_2$ (1:0.25)
Base 3 Base 1 + $ZnCl_2$ (1:0.5)

Scheme 49. Cu-catalyzed dimerization of heteroarenes.

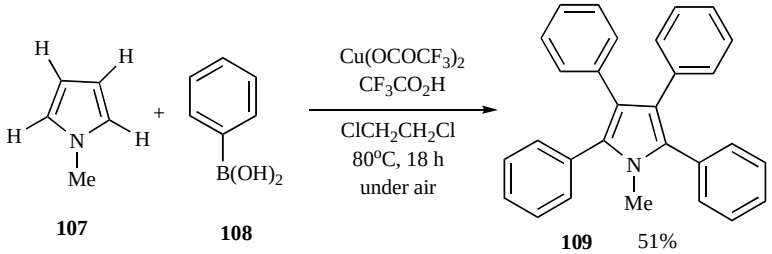
In 2008 Itami and coworkers [63] proved that N-methylpyrrole **107** and phenylboronic acid **108** can undergo multiple C-H bond arylations using catalytic $Cu(OCOCF_3)_2$ in the presence of 1,2-dichloroethane at 80°C for 18 hours under air, furnishing the quadruple phenylation pyrrole **109** in 51% yield. No homocoupling product arising from pyrrole or phenylboronic acids is observed (Scheme **50**).

5-(3, 4-dimethyloxyphenyl)oxazole **110** underwent C-2 direct arylations with diverse iodobenzenes **37** containing an electron-rich or electron-deficient subsituents, using the combination of easily available and tractable reagents $CuI/PPh_3/Na_2CO_3$ as catalytic system, giving the corresponding aryl-substituted oxazole compounds in good yields(Scheme **51**) [64]. Functional groups such as methoxy, methoxycarbonyl, bromo, trifluoromethyl or cyano on the aryl iodides are tolerable.

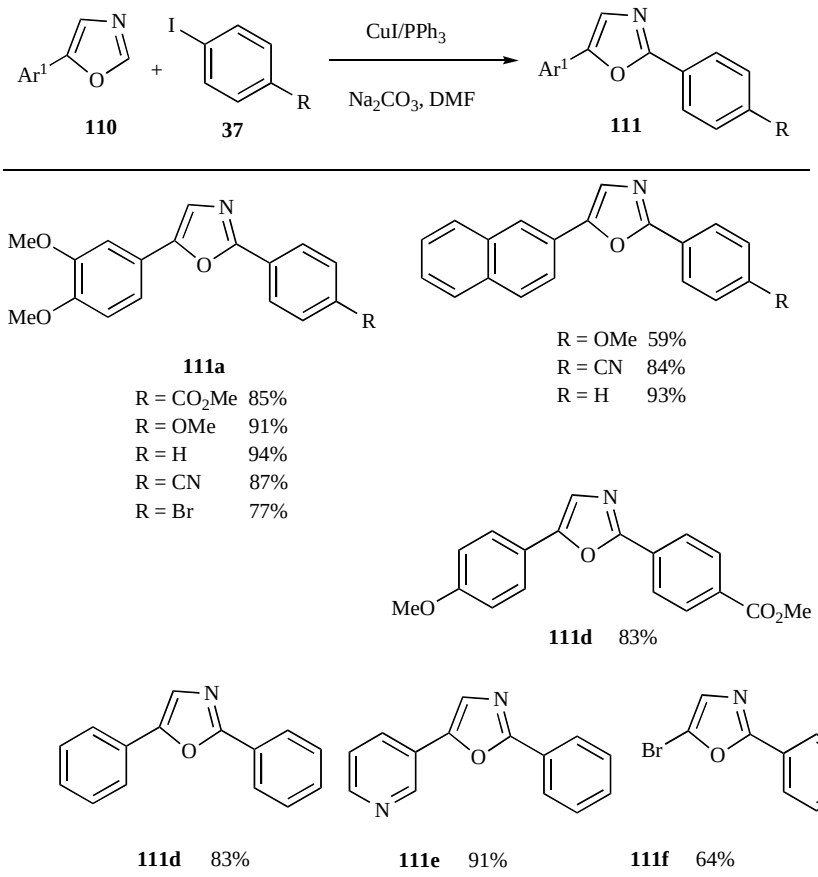
2.3. Rh-catalyzed Direct Arylation of Thiophene and Benzimidazole Ring System

In 2006 Itami and coworkers [65] established an excellect and attractive rhodium complex **112** having a strongly π-accepting ligand, $P[OCH(CF_3)_2]_3$, due to its prominent stability in moisture and air as well as long-bench life. With this catalyst, the arylations of substituted thiophene **105** with a range of aryl or heteroaryl iodides proceeded efficiently in the presence of Ag_2CO_3, furnishing the expected products **106** in good to excellent yields (Scheme **52**). It is worth mentioning that the thiophene bearing electron-donating group can be coupled with electron-rich heteroaromatics, giving the desired product **106b** in satisfactory yield.

After extensively screening, Ellman and coworkers developed a catalytic system including commercially available and much less expensive catalytic $[RhCl(coe)_2]_2$, highly hindered amine base (*i*-Pr_2-*i*-BuN) and (Z)-1-tert-butyl-2,3,6,7-tetrahydrophosphepine **115**. Using such catalytic system, benzimidazole **113** underwent arylations with aryl bromides heated in a microwave reactor, furnishing the expected products **114** in good to excellent yields in two hours (Scheme **53**) [66]. By applying the tetrafluoroborate salt of the corresponding phosphonium, the arylation may undergo outside of glove-box without purification of reagents and solvent. It is noteworthy that sulfinyl, acetamide, free hydroxyl, chloro and free amine groups were well-tolerated. Electron-rich heteroaryl bromides were viable coupling partners **114c**. The remarkable features of this



Scheme 50. Direct phenylation of pyrrole **107** catalyzed by copper.



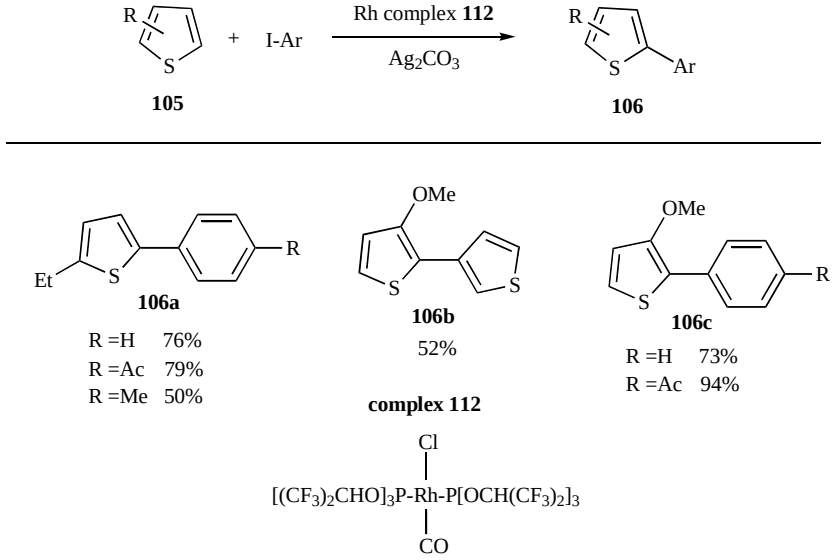
Scheme 51. Reaction of 5-aryloxazole derivatives **110** with aryl iodides.

procedure are the unique selectivity compared with Pd- and Cu-catalyzed methods as well as the extremely high functional group tolerance.

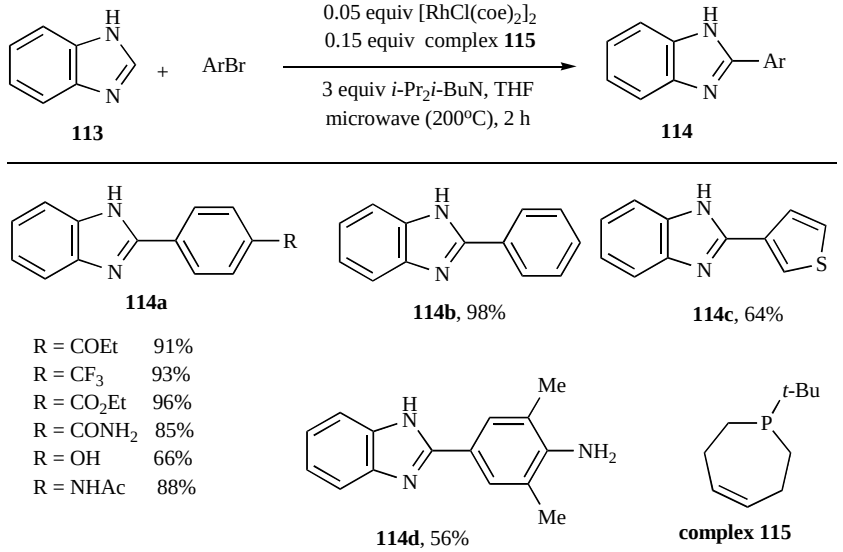
2.4. The Other Transition Metal-Catalyzed Intermolecular Direct (Hetero)Arylation of Benzothiazole,Benzoxazole, Indole, Benzothiophene and Thiazole Ring System

In 2009 Itami and coworkers[67] proved $Ni(OAc)_2$/bipy/LiO*t*-Bu/dioxane/85°C to be an effective catalytic system for the direct cross couping reactions of benzothiazole **11** with aromatic iodides or bromides, giving the desired heterobiaryl products **17** in moderate to excellent yields (Scheme **54**). Electron-rich or electron-poor aryl iodides/bromides were viable aryl electrophiles. Steric encumbered aryl electrophiles and heteroaryl iodides as well as bromides were reactive under this condition. The noticeable features of the catalytic system are efficient, cheap, simple and stable.

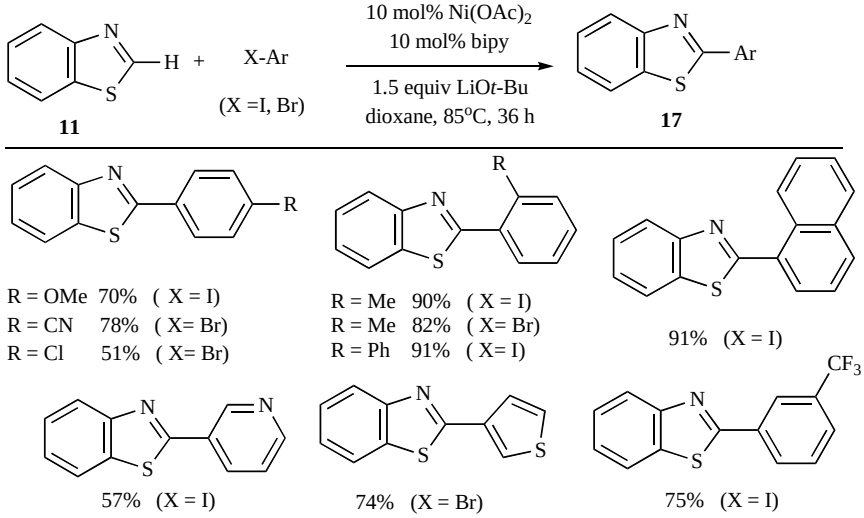
In the same year, the successful arylations between benzoxazole **26** and aryl bromides employing $NiBr_2$.diglyme as precatalyst were achieved by Miura and coworkers [68]. The application of less polar *o*-xylene other than diglyme can suppress the decomposition of benoxazole. The addition of the Zn powder can continuously generate



Scheme 52. Direct C-H arylation of thiophene derivatives **105** catalyzed by complex **112**.



Scheme 53. Direct arylation of benzoimidazole **113** with aryl bromides.



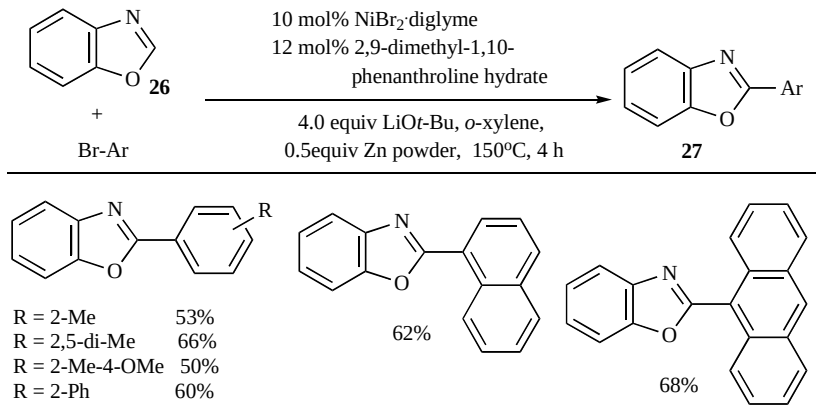
Scheme 54. Ni(OAc)2/bipy-catalyzed arylation of benzothiazole **11** with aryl bromides and Iodides.

the zerovalent nickel species which is necessary for the arylation (Scheme **55**).

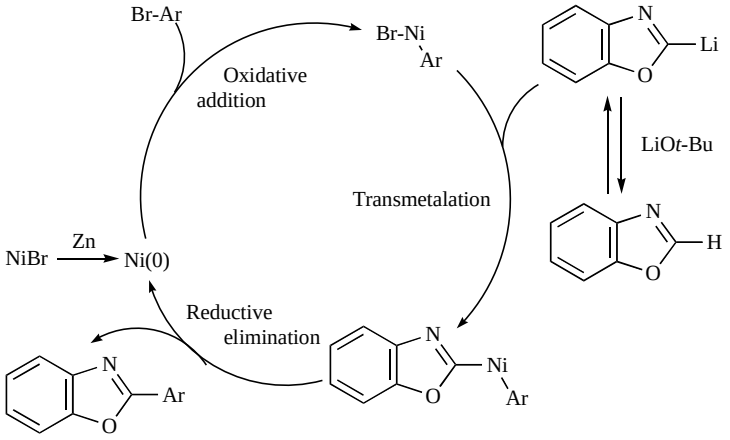
The potential mechanism was proposed with the initial generation of zerovalent nickel specie through the reduction of $NiBr_2$.diglyme and Zn powder. As shown in the scheme **56** [68].

The first example of direct construction heteroaryl–heteroaryl bonds between indole derivatives **116** and various thiophenes **117** based on S_NAr reation without using thiophene bearing electron-withdrawing substituents was reported by Takahashi and coworkers [69] in 2010. This reaction can proceed by employing $In(OTf)_3$ as catalyst in the presence of dioxane and toluene (Scheme **57**).

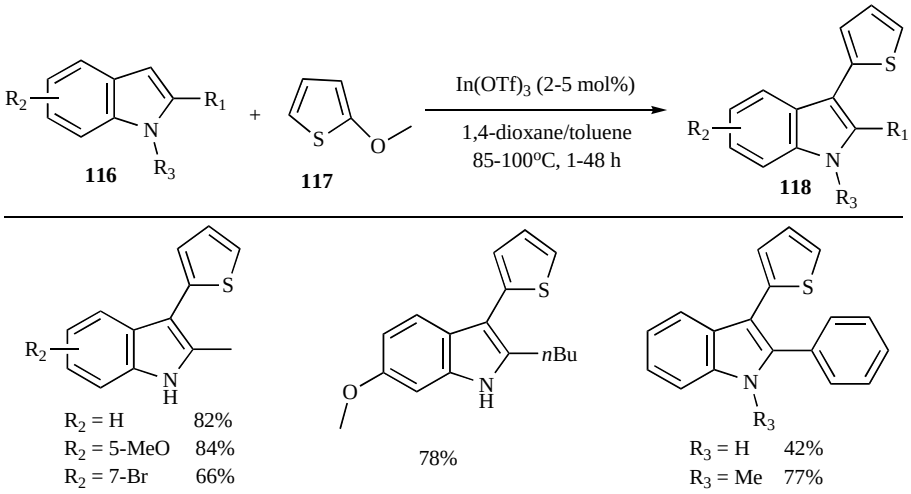
In 2009 Knocheland and coworkers [70] developed a selective complex base TMPZn·LiCl(**119**) allowing the chemoselective zincations at room temperature, thus the subsequent arylation reaction is easily performed by a Negishi cross-coupling or a Sonogashira reaction, furnishing the desired arylated products(Scheme **58**). The



Scheme 55. Nickel-catalyzed direct arylation of benzoxazole **26** with various aryl bromides.



Scheme 56. The proposed mechanism of benzoxazole and aryl bromides.



Scheme 57. Indium-catalyzed indole-thiophene bond formation through nucleophilic aromatic substitution.

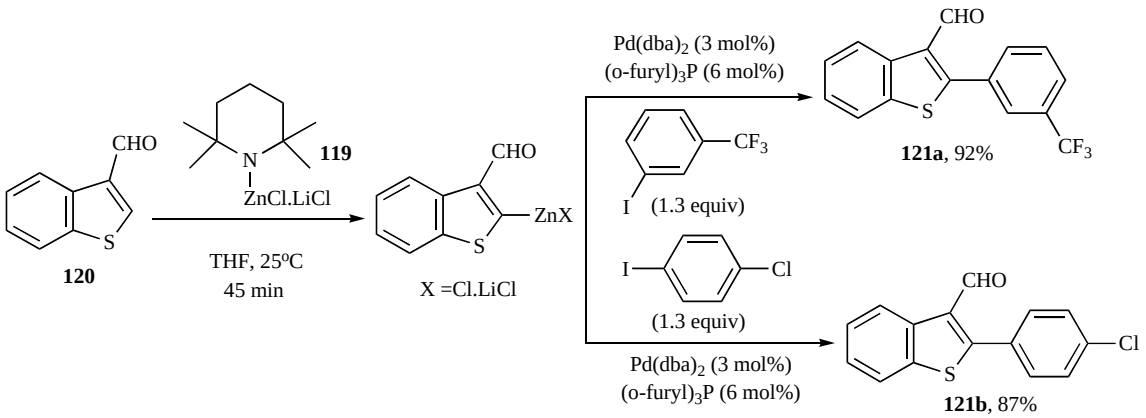
excellent characteristics of this procedure are the functional groups tolerance such as aldehyde and nitro group, provision of a new platform in metalation of aromatic and heterocyclic substrates.

Thiazole **122** underwent direct cross-coupling reaction with iodobenzene in the presence of anhydrous cobalt(II), using 3-bis-mesitylimidazolylcarbene (IMes) **123** or ethylenbis-salicylimine (SALEN) **124** as ligand, cesium carbonate as base [71]. Under this condition, 5-phenylthiophene **125a** was regioselectively prepared as a single product in 64% yield. The addition of CuI can completely divert the regioselectivity from C-5 to C-2, giving 2-phenylthiophene **125b** exclusively in 84% yield (Scheme **59**). Compared with palladium-based procedure, the cobalt-catalyzed method proved superior in terms of both selectivity and yield.

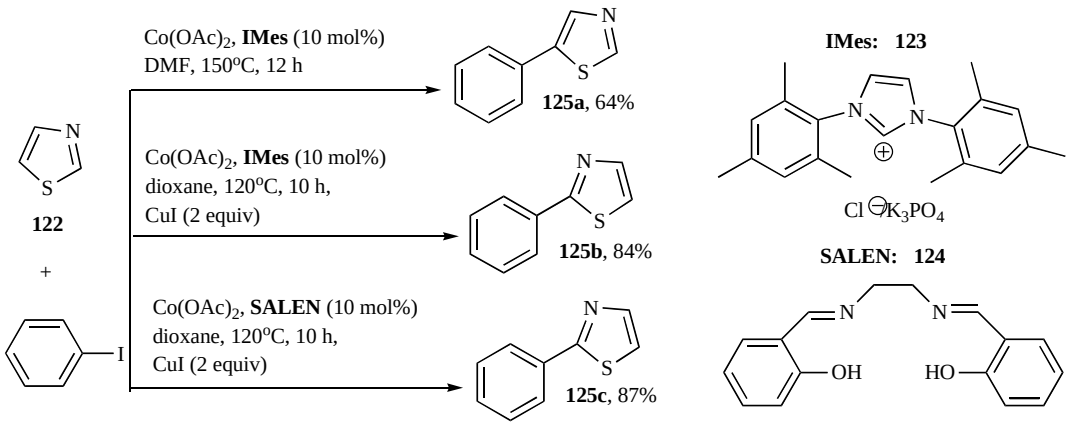
3. TRANSITION METAL-CATALYZED INTERMOLECULAR DIRECT (HETERO) ARYLATION OF SIX-MEMBERED HETEROARENES

3.1. Pd-Catalyzed Intermolecular Direct Arylation of Pyridine, Pyrazine, Benzo[h]Quinoline, Quinoline and 7-Azaindole Ring System

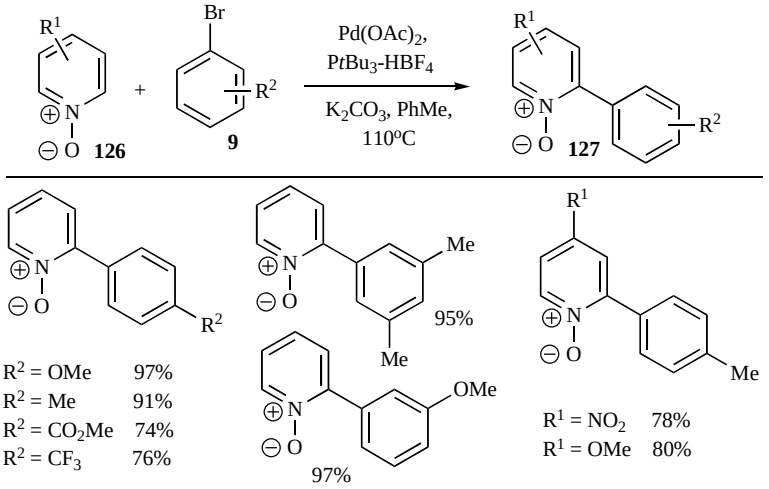
After extensively screening, an attractive and efficient catalytic system comprising the combination of palladium acetate and tri-tert-



Scheme 58. Zincation of benzo[b]thiophene-3-carbaldehyde **120** using TMPZnCl.LiCl (**119**) and trapping with electrophiles.



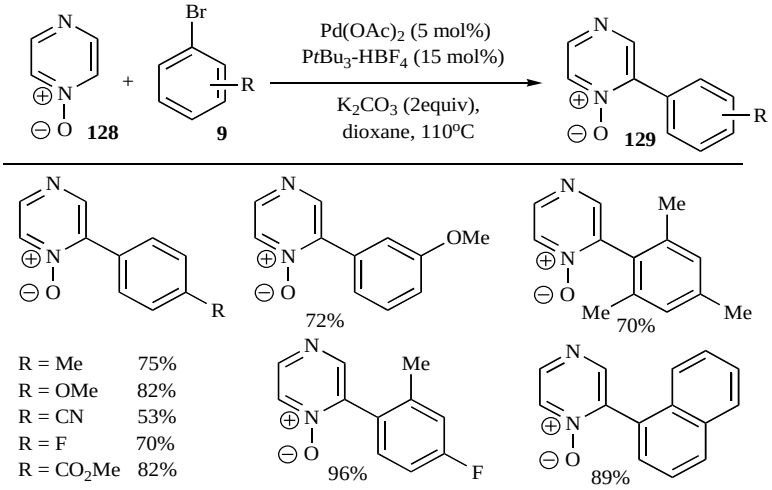
Scheme 59. Cobalt-catalyzed arylation of thiazole **122**.



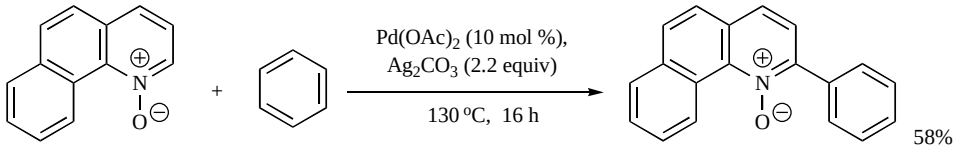
Scheme 60. Regioselective direct arylation of pyridine N-oxides **126**.

butylphosphine (added to the reaction mixture as the commercially available and air-stable HBF_4 salt) applied as optimal catalyst, together with potassium carbonate and toluene emerged as optimized base and solvent respectively was devised to prepare 2-arylpyridines N-oxides **127** by Fagnou and coworkers [72] in 2005. Under this condition, either electron-donating or selectron-withdrawing aryl bromides **9** are viable coupling partners, as for sterically encumbered ortho-substituted arenes (Scheme **60**). The presence of electron-rich and electron-poor substituents emerged on the N-oxides pyridine ring **126** is tolerated and has minor affect on the yields. The significant features of this methodology are the reactions are insensitive to the presence of water and subsequent 2-arylpyridines N-oxides **127** can be readily transformed to corresponding 2-arylpyridines using Pd/C and ammonium formate under mild conditions.

High-yielding arylations of diazine N-oxides **128** are viable with aryl iodides or aryl bromides, even with aryl chlorides. As for aryl iodides, Ag_2CO_3 must be applied as additive. Either electron-rich or electron-poor substituents on the aryl bromides **9** are tolerated. Sterically encumbered aryl bromides can be applied (Scheme **61**) [73].



Scheme 61. Direct arylation of pyrazine N-oxide **128** with aryl bromides **9**.



130 **131**

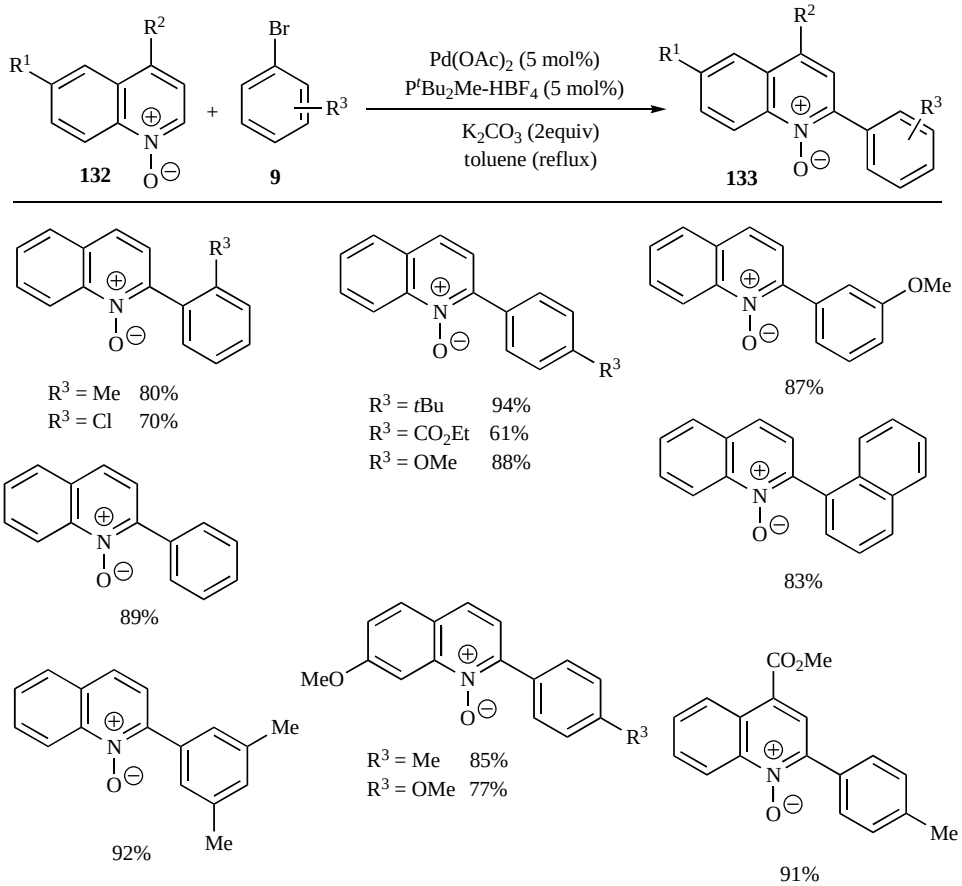
Scheme 62. Pd-catalyzed direct arylation of benzo[h]quinoline N-oxide **130** using benzene.

The direct cross-coupling reaction of benzo[*h*]quinoline *N*-oxide **130** with unactivated benzene in the presence of $Pd(OAc)_2$ and Ag_2CO_3, furnishing the expected product **131** in 58% yield, was devised by Chang and coworkers in 2008 (Scheme **62**) [74]. The arylation proceeded selectively at *ortho* position which offered a useful complementary procedure for the direct arylation of benzo[*h*]quinoline catalyzed by palladium, Rhodium or iron underwent at C-10 position [75]. Therefore, it provided us with an example of regioselective control by the application of different directing groups within the same molecular.

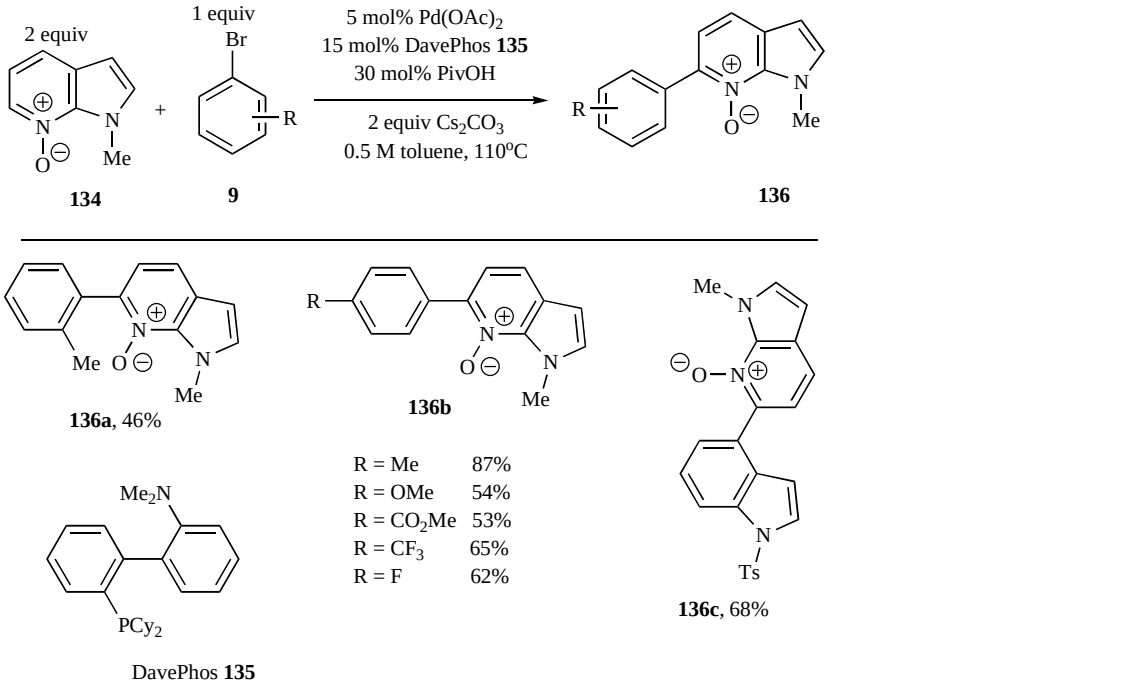
The direct corss-coupling reactions of quinoline N-oxides **132** with a wide variety of aryl halides were devised, using catalytic $Pd(OAc)_2$ in the presence of P^tBu_3-HBF_4 and K_2CO_3 in toluene [76]. The reactions were compatible with activated, unactivated or alkyl substituents on the aryl bromides **9**, another both electron-withdrawing and electron-donating functionalities were tolerated on the quinoline N-oxides (Scheme **63**). It is noticeable that if the arenes contains chlorine and bromine atom, the arylation performed selectively with the C-Br bond. The N-oxides moiety would not be destroyed in the arylation reactions, subsequently the arylated quinoline N-oxides **133** could be further functionalized on the heterocycle core. The presence of N-oxide could promote the efficiency and effectiveness of arylations because of the increased electron-density of electron-poor quinoline ring system.

Although 7-azaindoles bears both electron-poor pyridines and electron-rich pyrroles ring system, it could arylate regioselectively at the pyridine ring system by applying N-oxide activation. In 2009 Fagnou and coworkers [77] explored the direct cross-coupling reactions of N-methyl-7-azaindoles **134** with a wide variety of aryl bromides **9,** using a $Pd(OAc)_2$/DavePhos **135** catalyst system, furnishing the expected products in satisfactory to good yields (Scheme **64**). The reaction was equally compatible with electron-poor and electron-rich substituents on the aryl bromides, additionally sterically encumbered aryl bromides were viable coupling partners under this condition. Even bis-indole substrates could also be performed, providing access to polycyclic heterocyclic products. It is noteworthy that they also reported that palladium-catalyzed direct coupling of N-methyl-7-azaindole was shown to proceed selectively at C-2 position.

The unprecedented procedure that direct arylations of electron-deficient polyfluoropyridines **137** and aryl iodides employing the immiscible mixture of EtOAc and H_2O, which allows complete solubilization of all components of the system, catalyzed by $Pd(OAc)_2$ was uncovered by Renè and coworkers [78] in 2010. Compared with Fagnou's [79], the reaction temperature is of great



Scheme 63. Direct arylations of quinoline N-oxides **132** with aryl bromides **9**.



Scheme 64. Direct arylation of N-methyl-7-azaindole N-oxide **134** with aryl bromides **9**.

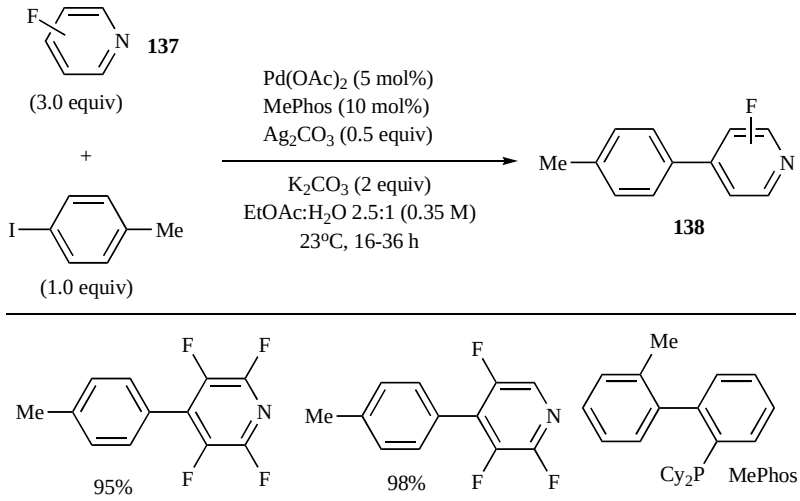
significance for the substrates and work-ups. The ratio of EtOAc and H_2O is proved to be crucial to the conversion. This protocol provided access to a wide range of biaryls at room temperature in excellent yields, and it demonstrated the viability to application of water as a cosolvent in the exploitation of milder condition for direct arylation of thermal-sensitive substrates, such as the natural and pharmaceutical compounds (Scheme **65**).

3.2. The Other Transition Metal-Catalyzed Intermolecular Direct (Hetero) Arylation of Quinoline, Pyrazine, Pyridine and Thiophene Ring System

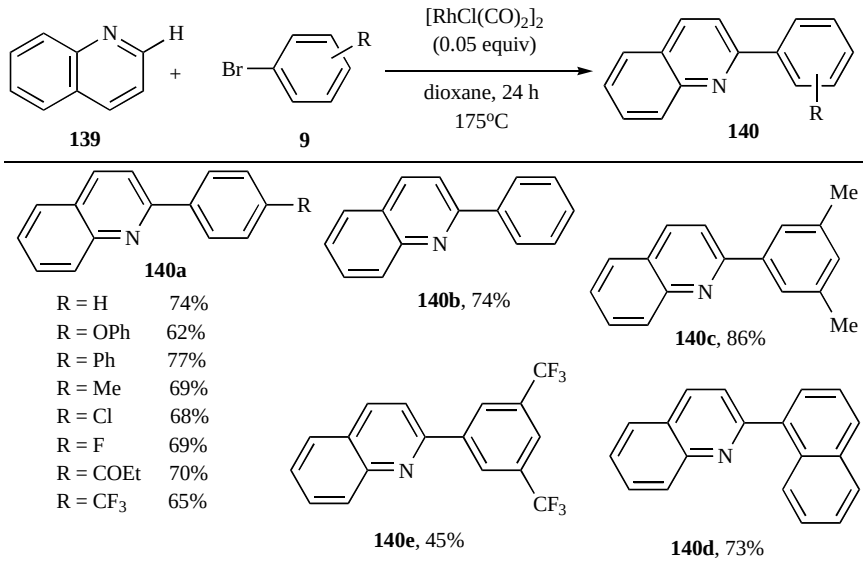
2-arylquinolines **140** can also be prepared through operationally Rh(I)-catalyzed quinolines with a wide range of aryl bromides, furnishing the expected products in similar yields compared with the previous reported Pd-catalyzed direct arylation of quinolines N-oxides [76]. In 2008 Ellman and coworkers explored the direct cross-couplings of quinoline **139** with a array of aryl bromides **9,** using electron-deficient $[RhCl(CO_2)]_2$ as catalyst in ligand-free conditions [80]. Under this condition, both electron-poor and electron-rich aryl bromides were viable coupling partners with equal efficiency, and a wealth of beneficial functionalities on the aryl bromides were tolerated such as ketone, alkyl ethers, and fluoride, chloride and aryl groups (Scheme **66**). The noticeable features of this methodology are that it does not need to activate quinoline starting material and unmask the arylated products as well as eliminate the phosphorous derivatives compared with the procedure using palladium as catalyst by N-oxide activation.

Pyrazine **141** underwent direct arylations with a variety of aryl bromides **9** using catalytic Cy_3PAuCl in the presence of *t*-BuOK at 100°C, and the yields of the desired products depend on the nature of aryl bromides (Scheme **67**) [81]. Pyazine and electron-rich aryl bromides underwent the arylations in good to excellent yields, as for electron-poor aryl bromides, the satisfactory rates and yields of C-H arylation reaction required the addition of $AgBF_4$.

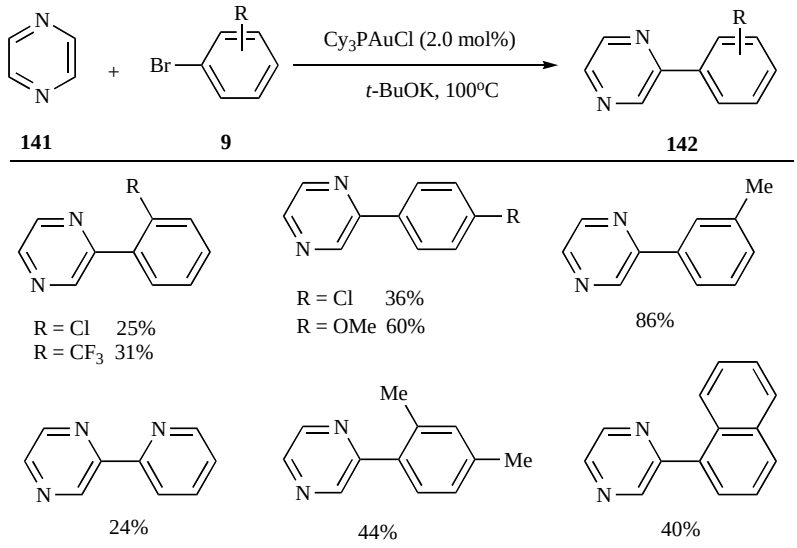
A great variety of functionalized heteroarylzinc compounds can be prepared by employing complex TMPZn·LiCl(**119**), and the resulting zinc organometallics can effectively couple with various classes electrophiles furnishing the required products in high yields (Scheme **68**) [82]. A diversity of sensitive functionalities such as aldehyde, ester, nitro and nitrile group were well-tolerated, another



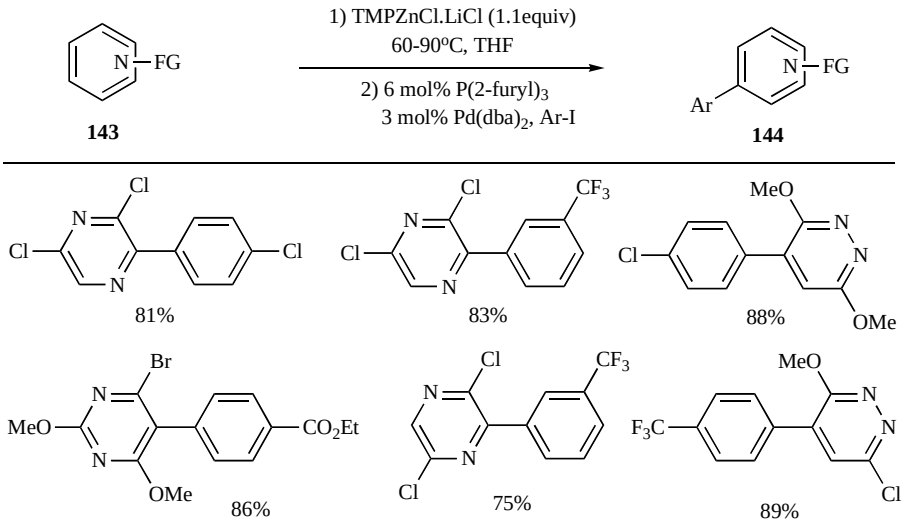
Scheme 65. Direct arylation of polyfluoropyridines with 4-Iodotoluene.



Scheme 66. Rh(I)-catalyzed direct arylation of quinolines **139**.



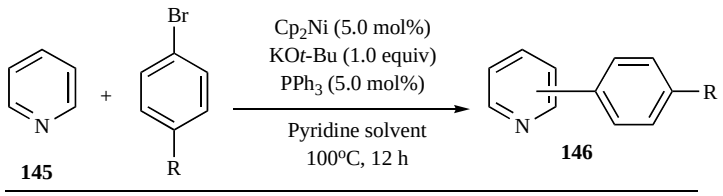
Scheme 67. Cy3PAuCl-catalyzed reactions of pyrazine **141** with aryl bromide **9**.



Scheme 68. Products obtained using TMPZnCl.LiCl **119** and quenching with electrophiles.

the regioselectivity and chemoselectivity can be achieved in this procedure.

In 2009 Yamakawa [83] and coworkers first reported that pyridine **145** could undergo arylation with bromobenzene using

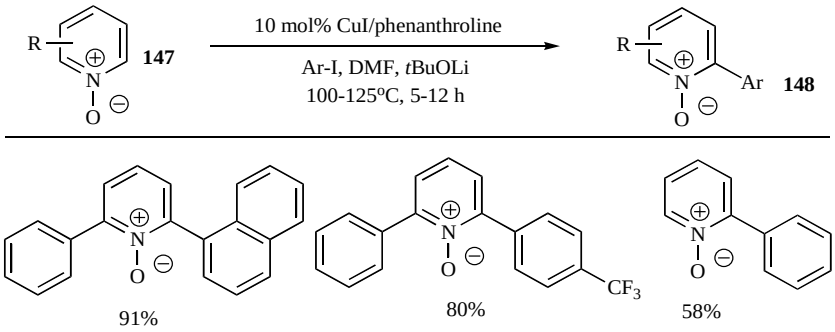


R	Total yield (%)	2-:3-:4- isomer ratio
4-$OMeC_6H_4$	53	48:36:16
Ph	70	46:43:11
4-PhC_6H_4	73	48:41:11
4-^{t}BuC_6H_4	60	46:36:18

Scheme 69. Coupling of pyridine **145** and aryl bromides.

catalytic Cp_2Ni in the presence of KO*t*-Bu and PPh_3 at 100°C for 12 hours (Scheme **69**). Unfortunately, the product was a mixture of 2-, 3-, and 4-arylpyridine. However, this methodology is potentially more attractive and economical than the processes with other transition metal as catalysts such as palladium and rhodium.

The electron-deficient pyridine N-oxides **147** can be arylated with aryl iodides in the presence of CuI/ phenanthroline, employing *t*BuOLi as base and DMF as solvent. This protocol can offer the required products in good to excellent yields (Scheme **70**) [4]. Compared with Fagnou and coworkers' procedure [72] for arylation of pyridine N-oxides, the phosphorous-containing ligand is not needed and the post-treatments of the products are obviously easier.



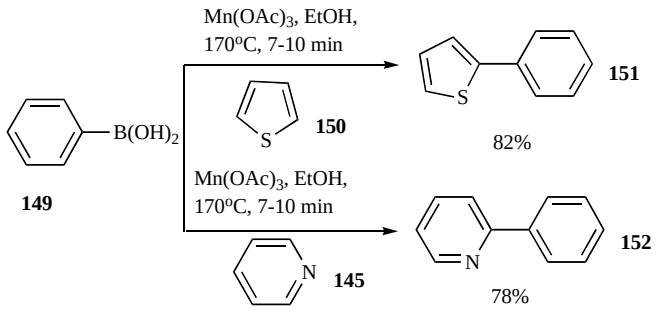
Scheme 70. The direct arylations of pyridine derivatives **147** with aryl iodides.

The single-electron-transfer oxidative direct C-H bond arylation of pyridine with phenylboronic acid **149** catalyzed by $Mn(OAc)_3$ under microwave irradiation and ligand-free condition in ethanol, furnishing regioslectively 2-phenylpyridine in 78% yield was presented [84]. The slight excessive of pyridine **145** was found to be vital in the protocol. Under this condition, electron-poor or electron-rich heterarenes and arylboronic acid could undergo the arylations on the C-H bond *ortho* to the ring heteroatoms due to their relatively higher acidity, exhibited higher reactivity (Scheme **71**). This methodology represents an alternative to the known transition-metal-catalyzed (Pd, Ru and Rh).

4. CONCLUSION AND PERSPECTIVE

This review described the impressive progresses achieved in the last few years in the area of transition metal-catalyzed direct intermolecular (hetero)arylation reactions via the cleavage of C-H bond. This methodology represents the cost-effective and more environmentally attractive protocol for the direct, efficient, regioselective construction of C-C bonds among aromatics to prepare biaryheteroarenes avoiding the application of stoichiometric amounts of organometallic reagents.

As depicted in the review, under certain conditions, π-electron-rich and π-electron-poor heteroarenes are able to undergo this type of C-C bond construction reaction at present. However, several challenges concerning the direct intermolecular arylation reactions of heteroarenes still remain: (i) until very recently, the majority of transition metal-catalyzed arylation reactions have been performed with palladium, rhodium or ruthenium catalysts. However, less-expensive copper, nickel and iron complexes have been employed in the last few years, and have great potential utility in this area due to their highly catalytic reactivity. And the highly efficient, air-,



Scheme 71. Arylation of heteroarenes with phenylboronic acids **149**.

moisture- and heat-stable catalysts will find significant use in the arylation reaction; (ii) The temperature of arylation is still high which is very disadvantageous for the thermal unstable substrates and the catalyst loading is not satisfactory; (iii) At present, most of arylating reagents are aryl iodides, the relative inexpensive and easily commercially available aryl chlorides, tosylates, mesylates which also can be used as electrophilic coupling partners are seldom employed; (iv) The exact mechanisms for any given examples appear to largely depend on the substrates and reaction conditions employed.

With continuous methodology evolution and mechanistic investigation, the procedure of C-H bond functionalization/ activation catalyzed by transition metals will lead to the establishment of highly active catalytic system for the regioselective and mild construction of C-C bond between heteroarenes and aryl (pseudo)halides. Significant research efforts are still necessary to allow further improvement concerning efficiency, simplicity and reaction scope.

ACKNOWLEDGEMENTS

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