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Advances in direct C-H arylation of 5,5, 6,5 and 6,6- fused-heterocycles containing heteroatoms (N, O, S)

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Direct arylation is a useful method for the preparation of (hetero)aryl-aryl systems by C-H bond cleavage. This procedure has several advantages such as the reduction of cost, time and waste. This report aims at reviewing the advances made in C-H arylation of 5,6, 6,6 and 5,5 fused-heterocyclic systems including: indole, azaindole, imidazo[1,2-*a*]pyridine, imidazo[1,2-*a*]pyrimidine, imidazo[1,2-*a*]pyrazine, imidazo[1,2-*b*]pyridazine, pyrazolo[1,5-*a*]pyrimidine, imidazo[1,2-*b*][1,2,4,5]tetrazine, indolizine, pyrrolo[1,2-a]pyrazine, indazole, benzothiadiazole, benzotriazole, benzoxazole, benzofuran, benzothiophene, benzimidazole, benzothiazole, thieno[3,4-b]pyrazine, indolizine-2-carboxylate, thieno[3,4-*b*]pyrazine, quinoline and derivatives, chromanone, coumarin, quinoxaline, thieno[2,3-*b*]thiophene, thieno[3,4-*b*]thiophene, imidazo[2,1-*b*]thiazole, imidazo[1,2-*b*]pyrazole, thiazolo[3,2-*b*][1,2,4]triazoles and pyrrolo[3,2-*b*]pyrrole.

1. Introduction

In the last two decades, the field of C-H activation has undergone rapid growth and much more attention has been paid to the synthesis of aryl-heteroarenes and unsymmetrical bi-heteroaryls via transition metal-catalyzed direct arylation without the need of stoichiometric organometallic activating groups which are often prepared from stannane or boronate coupling partners prior to the cross-coupling reaction. The C-H bond functionalization, developed using various transition metal catalysts such as palladium, copper, ruthenium, nickel, silver, rhodium, manganese and iron provided the synthesis of biologically relevant aryl-(heteroaryl) compounds[1-9]. During the last decade many efforts for the development of direct arylation of 6,5, 6,6 and 5,5 heterocyclic systems have been made offering new protocols. In some cases, the choices of ligands, additives, bases and halide partners were crucial for the achievement of C-H arylation reactions and/or the control of the regioselectivity. Some recent reports involved the use of low catalytic amount of the transition metal and/or avoided the use of ligand and additives. Also, new reaction conditions were investigated including microwave-associated synthesis and heterogeneous catalysis as green procedures. The topic of this review is related to direct arylation reaction and is essentially restricted to the developments reported on 6,5, 6,6 and 5,5 fused- heterocyclic systems.

2. Arylation of 5,6-fused-heterocyclic systems

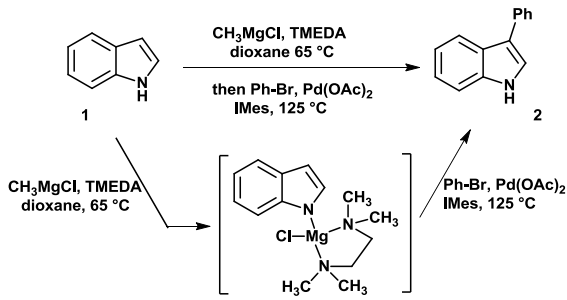
2.1 Indole

2.1.1 C3-arylation of indoles

Indole is the most studied heterocyclic system toward direct arylation and the recent

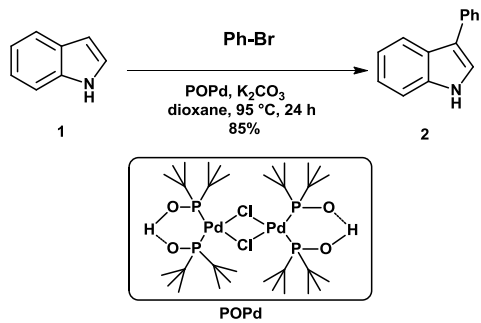
developments have been extensively reviewed in recent reports[10,11]. For this reason, this first section summarizes only the recent development reported in this area and updates the exhaustive reviews reported by Djakovitch et al.[10] and by Larrosa et al.[11]

Regioselective C3-arylation has been developed by few groups due to the lack of reactivity at the C3 position of indole compared to C2 position. Sames's group[12] showed that the use of CH_3MgCl and tetramethylethylenediamine (TMEDA) in the presence of IMes as a sterically hindered ligand instead of Ph_3P and bromobenzene as arylating agent instead of iodobenzene led to highly selective C3-phenylation of indole **1** (C3/C2, 67:1) (Scheme 1). The reaction was conducted in dioxane at 65 °C in the presence of 2.5% $Pd(OAc)_2$ which led to the desired product **2** in 96% yield.



Scheme 1. C3-arylation of indole **1**

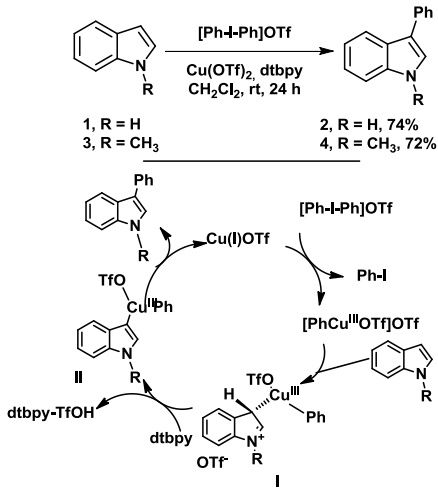
An elegant protocol for regioselective C3-arylation of indole **1** was developed by He and collaborators using air stable palladium catalyst with phophinous acid complex (POPd)[13]. The optimum reaction conditions were found when using POPd, K_2CO_3 in refluxing dioxane for 24 h. The desired 3-phenylindole **2** was isolated in 85% yield (Scheme 2).



Scheme 2. C3-phenylation of (*NH*) indole **1**.

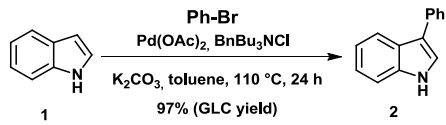
Guant et al. showed that the use of $Cu(OTf)_2$ as catalyst under mild conditions was effective for regioselective C3-arylation of indole[14]. In this study, the coupling reaction of *N*-methyl indole **3** and [Ph-I-Ph]OTf in the presence of $Cu(OTf)_2$ and di-*tert*-butyl bipyridine (dtbpy) led to 3-phenylindole **4** in 72% yield. When free (*NH*) indole **1** was used as starting material under similar reaction conditions, the expected product **2** was isolated in 74% yield (Scheme 3). The plausible mechanism proposed in this report started by the reduction of Cu(II) to Cu(I) by indole then the oxidative addition of the diphenyl-iodine(III) to Cu(I) led to Cu(III)-phenyl. The attack at the

C3 position of indole generated intermediate **I** which was transformed to **II** by rearomatization. Reductive elimination led to C3-phenylated indole (Scheme 3).



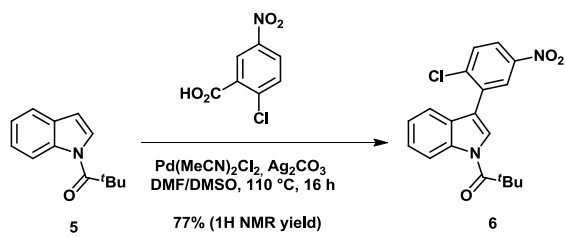
Scheme 3. C3-arylation of indole **1** and **3**.

Ligandless conditions for regioselective C3-arylation of indole **1** was developed by Rossi's group.[15] This method was effective using free (*NH*) indole and bromobenzene as coupling partners in the presence of $Pd(OAc)_2$, $BnBu_3NCl$ and K_2CO_3 in toluene at 110 °C for 24 h. Under these conditions, expected product **2** was obtained in 97% (GLC yield) (Scheme 4).



Scheme 4. Synthesis of 3-phenylindole **1**.

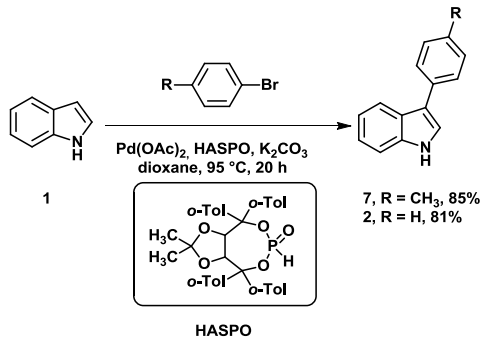
Larrosa et al. described palladium catalyzed decarobxylative C3-arylation of indole using benzoic acids bearing ortho electron-withdrawing substituents as arylating agents[16]. Authors showed that treatment of indole **5** with 2-chloro-5-nitrobenzoic acid in the presence of $Pd(MeCN)_2Cl_2$, Ag_2CO_3 in a mixture of DMF/DMSO at 110 °C for 16 h led to C3-arylated indole **6** in 77% yield (yield was measured by ^1H NMR of crude product using an internal standard) (Scheme 5).



Scheme 5. Direct arylation of indole **5** with 2-chloro-5-nitrobenzoic acid.

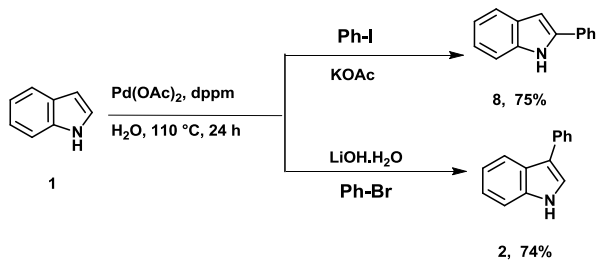
Ackermann et al.[17] reported a highly regioselective C3-arylation of indole using

air stable heteroatom substituted secondary phosphine oxide (HASPO) as preligand. Reaction was conducted using free (*NH*) indole **1**, bromotoluene, $Pd(OAc)_2$, HASPO, K_2CO_3 in dioxane at 95 °C for 20 h. The desired product **7** was isolated in 85% yield. When bromobenzene was used as coupling partner, the C3-phenylated indole **2** was obtained in 81% yield (Scheme 6).



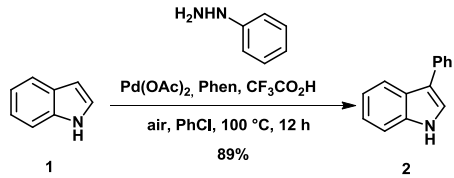
Scheme 6. Regioselective C3-arylation of indole using HASPO as preligand.

Djakovitch group described an interesting study of regioselective arylation of indole[18]. Authors highlighted the crucial effect of base/halide partners on regioselectivity. Thus, when KOAc and iodobenzene were used in the presence of free (*NH*) indole **1**, $Pd(OAc)_2$ and bis(diphenylphosphino)methane (dppm) in H_2O at 110 °C, C2-phenylated indole **8** was obtained with good selectivity (C2/C3, 20:1). However, when LiOH was used instead of KOAc and bromobenzene instead of iodobenzene, C3-phenylated product **2** was obtained with good selectivity (C3/C2, 6.5:1) and in good yield (74%) (Scheme 7).



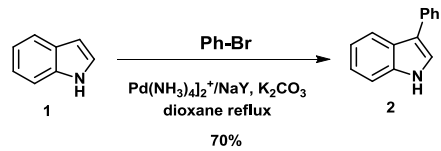
Scheme 7. Regioselective arylation of indole **1**.

Very recently, original direct denitrogenative C3-arylation of (*NH*) indole with arylhydrazines as arylating agents and palladium as catalyst was developed by Chen's group[19]. This method is based on the use of (*NH*) indole **1** and phenylhydrazine as coupling partners in the presence of $Pd(OAc)_2$, 1,10-phenanthroline as ligand, air as oxidant and chlorobenzene as solvent. The reaction mixture was heated at 100 °C for 12 h to provide the expected C3-phenylated indole **2** in 89% yield (Scheme 8).



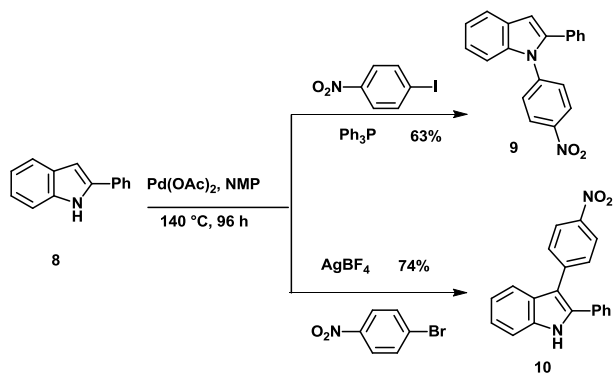
Scheme 8. Denitrogenative C3-arylation of (*NH*) indole with arylhydrazines.

Djakovitch and Cusati reported an heterogeneously palladium-catalyzed regioselective arylation of (*NH*) indole using $Pd(NH_3)_4]^{2+}$/NaY, a heterogeneous catalyst prepared by ion exchange between NaY zeolite and a aqueous solution of $Pd(NH_3)_4^{2+}$, $2Cl^-$. Authors found that the treatment of indole **1** with bromobenzene in the presence of $Pd(NH_3)_4]^{2+}$/NaY and K_2CO_3 in refluxing dioxane for 24 h led to C3-arylated product **2** in 70% isolated yield (Scheme 9)[20].



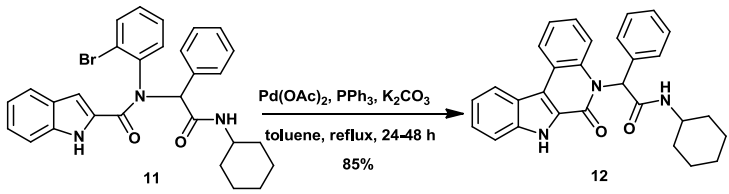
Scheme 9. Heterogeneously palladium-catalyzed arylation of (*NH*) indole **1**.

The same group provided C3-arylation of 2-phenylindole **8**[21]. 4-bromonitrobenzene as coupling partner, instated of 4-iodonitrobenzene, gave total conversion and desired C3 arylated product **10** was isolated in good yield (74%). Reaction was carried out using 2-phenylindole and 4-bromonitrobenzene in the presence of $Pd(OAc)_2$, $AgBF_4$ in NMP at 140 °C for 96 h. It is noticed that, when Ph_3P was added to the reaction mixture instead of $AgBF_4$ and 4-iodonitrobenzene instead of 4-bromonitrobenzene, no C3-arylation reaction was observed only *N*-arylation occurred furnishing compound **9** in 63% yield (Scheme 10).



Scheme 10. C3-arylation of 2-phenylindole **8**.

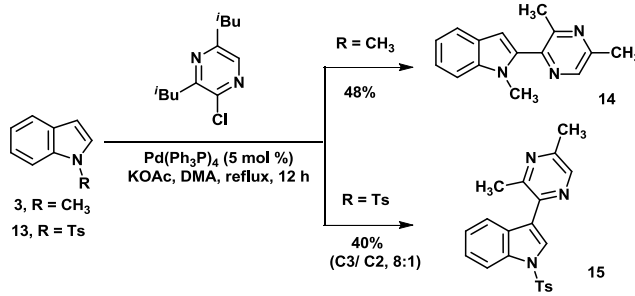
An expedient method was developed by Rasouli and coworkers[22] for the construction of novel indolo[2,3-c]quinolinone derivatives **12** via intramolecular palladium-catalyzed C3-arylation of intermediate **11** using $Pd(OAc)_2$, PPh_3 and K_2CO_3 in refluxing toluene for 24 h. This procedure led to C3-arylated product **12** in 85% isolated yield (Scheme 11).



Scheme 11. Intramolecular arylation of **11.**

2.1.2 C2-arylation of indoles.

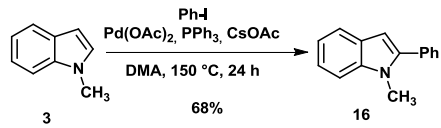
Ohta's group showed that the use of an electron with drawing protecting group, like tosyl, led to selective C3-aryalted product **15** with good selectivity (C3/C2, 8:1) and in 40% yield[23, 24]. However, when using *N*-methylindole **3** as starting material, the reaction with chloropyrazine in the presence of $Pd(PPh_3)_4$ and KOAc in refluxing DMA furnished C2-arylated product **14** in 48% yield.



Scheme 12. C2/ C3 arylation of indole **3** and **13**.

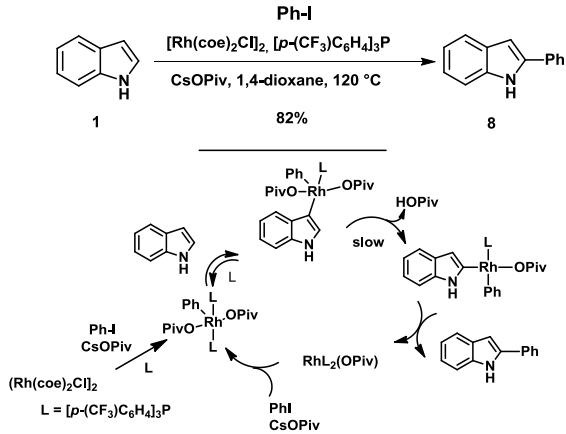
Since the first report on direct C2-arylation of indoles[23, 24], development of selective method for direct C2-arylation of this systems has undergone rapid growth. Thus, in contrast to C3-arylation of indole which had a relatively little development, various examples of regioselectiove C2-aryaltion have been reported. In the following section only few representative examples of C2-arylation of indole are detailed.

Sames's group investigated direct arylation of indole developing thus various methods for regioselective C2-arylation[25]. Authors noticed that, in comparison to other five-membered heteroarenes (furan, pyrrole, oxazole, and related systems), indole does not follow the "electrophilic" regioselectivity. In 2004, the first example of C2-arylation using indole **3** as starting material and iodobenzene as coupling partner in the presence of $Pd(OAc)_2$, Ph_3P and CsOAc in DMA at 150 °C was reported. In that report, authors observed the formation of a biphenyl product due to the homocoupling reaction. This issue was addressed by decreasing the catalyst loading which favored the formation of the arylated product and reduce the formation of homocoupling by-product. The use of 5% mol of $Pd(OAc)_2$ led to the formation of 68% yield of desired product **16** (Scheme 13).



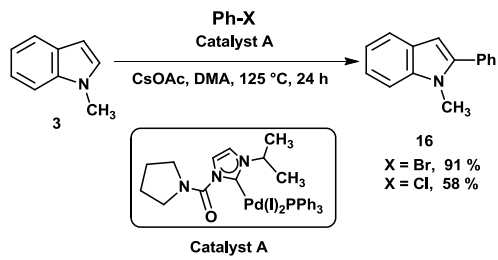
Scheme 13. Regioselective C2-arylation of indole **3**.

The same group provided C2-arylation of free (*NH*) indole **1** using Ar-Rh(III) complexes, formed *in situ*, as catalyst[26]. The reaction was carried out using $[Rh(coe)_2Cl]_2$ as catalyst, $[p\text{-}(CF_3)C_6H_4]_3P$ as ligand in the presence of CsOPiv in dioxane at 120 °C. These conditions led to C2-phenylated indole **8** in 82% isolated yield. A plausible mechanism of C2-arylation catalyzed by $[Rh(coe)_2Cl]_2$ was also suggested (Scheme 14).



Scheme 14. Arylation of free (*NH*) indole **1** catalyzed by $Rh(coe)_2Cl]_2$.

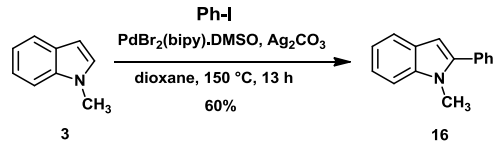
Another interesting report on C2-arylation was described by Sames's group using a new palladium catalyst (catalyst A)[27]. In this case, the reaction was achieved using indole **3** and bromobenzene as coupling partners in the presence of palladium catalyst A and CsOAc in DMA at 125 °C for 24 h. Desired product **16** was isolated in 91%. When using chlorobenzene as arylating agent, the C2-phenylated product **16** was obtained in 58% yield (Scheme 15).



Scheme 15. C2-arylation reaction of **3**.

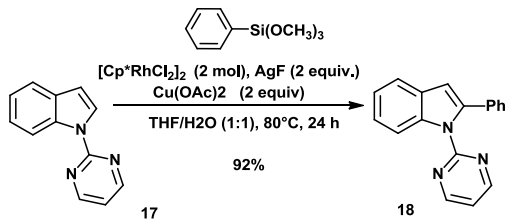
In 2011, Yanagisawa and Itami[28] described the Pd/bipy-based catalytic system for the C-H arylation of *N*-protected indole with aryl iodide (Scheme 16). The 1-methyl-

1*H*-indole **3** (1.5 equiv.) was reacted with 1 equivalent of aryl iodide in 1,4-dioxane at 150 °C in the presence of 10 mol % $PdBr_2$(bipy)DMSO as catalyst and 1 equivalent of Ag_2CO_3 as oxidant to give the corresponding C2-aryl indole **16** in a moderate yield (60%). In the course of this study it was found that benzofuran undergo reaction under the same reaction conditions.



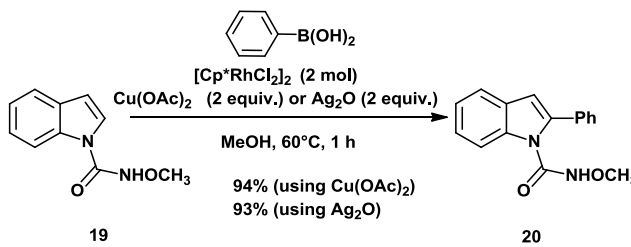
Scheme 16. C2-arylation reaction of **3**.

Very recently, Lu et al.[29] demonstrated that the use of $[Cp^*RhCl_2]_2$ as catalyst precursor was effective for the arylation of *N*-protected indole **17**. Thus, direct C2-arylation with organosilanes in a mixture of THF/H_2O (1:1) at 80°C in the presence of $Cu(OAC)_2$ as oxidant and AgF as activator led to arylated derivative **18** in good yield (92%) (Scheme 17).



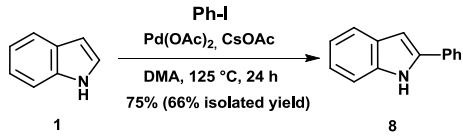
Scheme 17. C2-arylation of **17** with organosilanes.

Similar Rh(III)-catalyst was used by Zheng and coworkers[30] for C2-arylation of indoles. Thus, when employing either Ag_2O or $Cu(OAc)_2$ as oxidant, direct C2-arylation of *N*-methoxy-1*H*-indole carboxamide **19** with aryl boronic acid in methanol as solvent was archived giving desired compound **20** in 94 and 93% yield, respectively (Scheme 18).



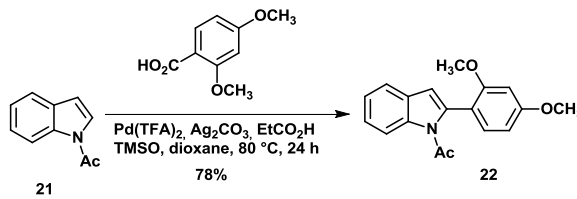
Scheme 18. C2-arylation of **19** with phenyl boronic acid.

A phosphine free C2-arylation of indole was described using indole **1** and iodobenzene as coupling partners in the presence of $Pd(OAc)_2$ as catalyst and CsOAc as base in DMA at 125 °C for 24 h[31]. This method gave the desired product **8** in 75% yield (yield was calculated using GC method calibrated against an internal standard) (Scheme 19).



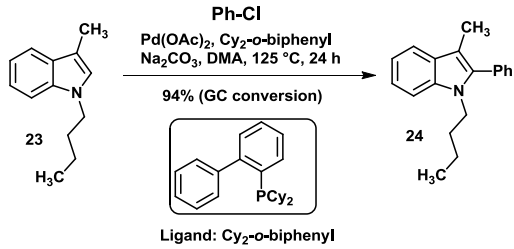
Scheme 19. C2-arylation reaction of **1**.

Similar method to that reported by Larrosa group[16] was developed by Su et al. for the direct arylation of indole with benzoic acids[32]. However, in this case, C2 isomer was the major product. Optimisation studies showed that when indole **21** was treated by benzoic acid derivative in the presence of $Pd(TFA)_2$, Ag_2CO_3, TMSO and $EtCO_2H$ in dioxane at 80 °C for 24 h, C2-arylated product **22** was obtained in 78% isolated yield with C2/C3 ratio of 16.5:1 (Scheme 20).



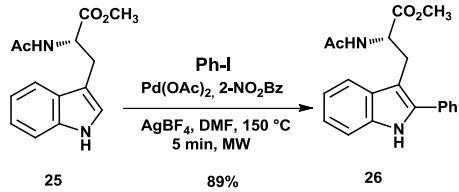
Scheme 20. Direct arylation of indole **21** with benzoic acid.

Daugulis et al. reported C2-arylation of 3-substituted indole using chloroarenes as coupling partners[33]. In a representative example, 1-butyl-3-methyl-1*H*-indole **23** was treated by chlorobenzene in the presence of $Pd(OAc)_2$, 2-(dicyclohexylphosphino)-biphenyl ligand and Na_2CO_3 in DMA at 125 °C for 24 h leading to C2-phenylated indole **24** in 94% GC conversion (Scheme 21).



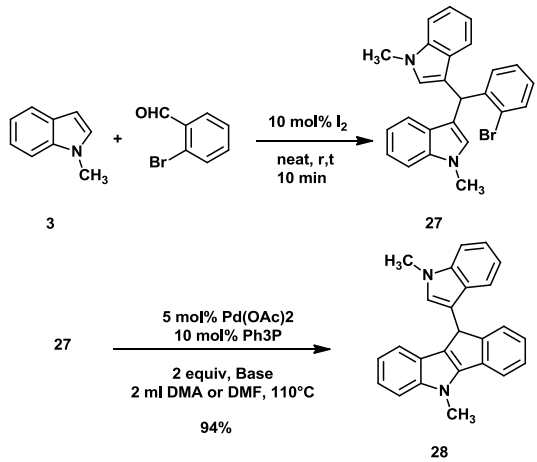
Scheme 21. C2-arylation of 3-substituted indole **23** using chlorobenzene.

Recently, Lavilla et al. described an elegant C2-arylation of indole ring present in amino acids and peptides[34]. A representative example is shown in Scheme 18. In this case, Ac-Trp-OMe **25** was arylated using iodobenzene, $Pd(OAc)_2$, 2-NO_2Bz and $AgBF_4$ at 150 °C in DMF under microwave irradiation for only 5 min. The expected product **26** was isolated in good yield (89%) (Scheme 22).



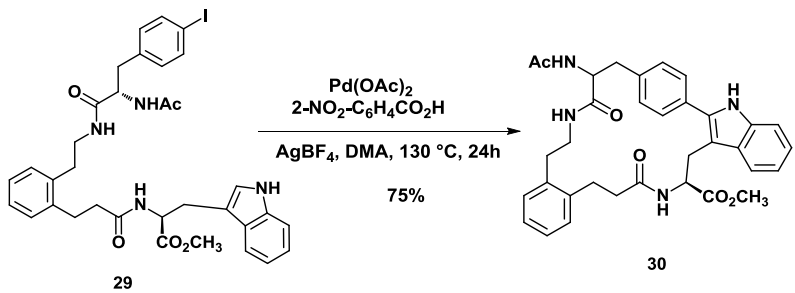
Scheme 22. C2-arylation reaction of **25**.

Recently, Chu and co-workers[35] performed intramolecular indole C2-arylation reactions of bis-indole derivatives **27** obtained from 1-methyl-1*H*-indole and 2-bromobenzaldehyde, the reaction was catalyzed by $Pd(OAc)_2$ in the presence of Ph_3P as ligand and CsOAc as base in either DMA or DMF at 110 °C for 5 h. The desired compound **28** was obtained with good yield (94%) (Scheme 23).



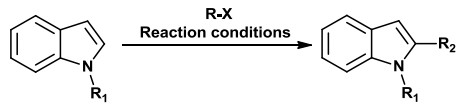
Scheme 23. Intramolecular C2-arylation of **27**.

In another interesting development of C2-arylation, James et al.[36] reported peptide macrocyclization by intramolecular C2-arylation of indole **29**. Thus, the side chain of a phenylalanine derivative containing an iodoaryl and the side chain of tryptophan were connected using $Pd(OAc)_2$ as catalyst in the presence of 2-NO_2-$C_6H_4CO_2H$ and $AgBF_4$ in DMA at 130 °C for 24 h. The desired macrocyclic peptide **30** was isolated in 75% (Scheme 24).



Scheme 24. C2-arylation reaction of **29**.

For the length consideration, table 1 summarizes the most important achievements reported in the last decade on C2-arylation of indole. Reaction conditions, coupling partners, reaction yields as well as references are presented; it is worth noting that only results of studies utilizing non-substituted indoles on the arene ring and on C3 position (Scheme 25) are shown in Table 1.



Scheme 25. C2-arylation of indole **1** and **3** (Table 1)

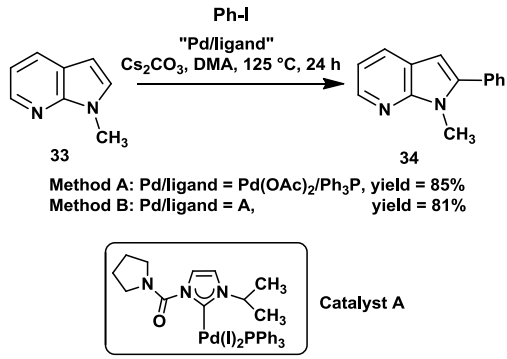
Table 1. Regioselective C2-arylation of indoles

entry	conditions	R_1	R_2-X	Product, yield	ref
1	$Pd(OAc)_2$, AgOAc, H_2SO_4, DMF/CH_3CN, 100 °C, MW, 40 min	H	Ph-SO_2H	**8**, 82 %	[37]
2	$Pd(OAc)_2$, c-$C_6H_{11}CO_2Ag$, H_2O, 4h, 30 °C	CH_3	Ph-I	**16**, 94 %	[38]
3	$Pd(Amphos)_2Cl_2$, NaOH, H_2O/EtOH, 80 °C	H	Ph-I	**8**, 80 %	[39]
4	$Pd(COD)Cl_2$, $CuCl_2$, toluene/dioxane, 110 °C, 24 h	CH_3	CH_3-C_6H_4-SO_2	**31**, 88 % GC yield	[40]
5	Pd/MIL-101(Cr), DMF, CsOAc, 120 °C, 24 h	CH_3	Ph-I	**16**, 85 %	[41]
6	Pd supported fluorous silica gel (FSG), DMA, CsOAc, 120 °C, 24 h	CH_3	Ph-I	**16**, 86 %	[42]
7	$Pd(OAc)_2$, Ag_2O, TBAF, AcOH/EtOH, rt, 18 h	CH_3	Ph-Si$(OMe)_3$	**16**, 82 %	[43]
8	$Pd(OAc)_2$/$Cu(OA)_2$, AcOH, air, rt, 12h	H	Ph-BF_3K	**8**, 81 %	[44]
9	$Pd(OAc)_2$, *o*-O_2N-C_6H_4-CO_2H, Ag_2O, DMF, 25 °C, 18h	CH_3	Ph-I	**16**, 99 % GC yield	[45]
10	$Pd(OAc)_2$, TEMPO, KF, EtCOOH, rt, 1h	H CH_3	Ph-$B(OH)_2$ Ph-$B(OH)_2$	**8**, 81 % **16**, 68 %	[46]
11	$Pd(OAc)_2$, O_2, HOAc, rt, 8h	CH_3	Ph-$B(OH)_2$	**16**, 77 %	[47]
12	$Pd(OAc)_2$, CuI, DMA, 160 °C, 48h	H	*p*-CH_3O-C_6H_4-I *Ph*-I	**32**, 53 % **8**, 29 %	[48]
13	$Pd(OAc)_2$, CuI, DMF, 140 °C, 48h	H	*p*-CH_3O-C_6H_4-I	**32**, 35 %	[49]
14	IMesPd$(OAc)_2$, AcOH, 25 °C, 18h	CH_3	(Ph-I^+-Ph)BF_4^-	**16**, 86 %	[50]

2.2 Azaindole

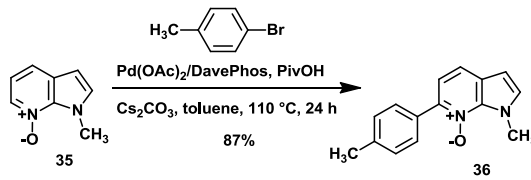
Sames et al. extended reaction conditions, previously optimized for C2-arylation of indole, to direct arylation of 7-azaindole **33**. Two methods were developed (methods A and B, see Scheme 26). In the case of method A[12, 25] the reaction was catalyzed by $Pd(OAc)_2$ in the presence of Ph_3P as ligand and Cs_2CO_3 as base in DMA at 125 °C

for 24 h. Under these reaction conditions, the desired product **34** was isolated in 85% yield (Scheme 26). In the second method (method B), catalyst A was used instead of $Pd(OAc)_2/Ph_3P$ system[27]. In this case, product **34** was isolated in 81% yield (Scheme 26).



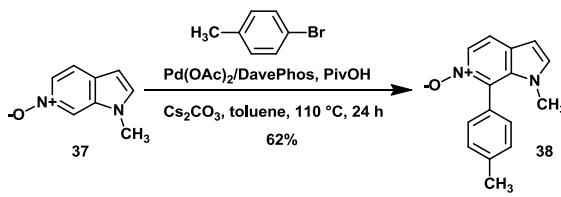
Scheme 26. Synthesis of compound **34** by direct C-arylation of **33**.

Fagnou and Huestis[51] found new protocol for direct C6-arylation of *N*-methyl-7-azaindole *N*-oxide **35** using $Pd(OAc)_2$, DavePhos and PivOH, Cs_2CO_3,in toluene at 110 °C. The desired product **36** was isolated in 87% yield (Scheme 27).



Scheme 27. Synthesis of compounds **36** by direct arylation of **35**.

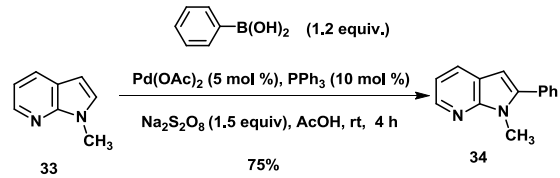
In the same report and under similar reaction conditions, the direct C7-arylation of *N*-methyl 6-azaindole *N*-oxide **37** led to the expected product **38** in 62% yield (Scheme 28).



Scheme 28. Synthesis of compound **38** by direct arylation of **37**.

In a recent report, Das and co-workers showed that $Pd(OAc)_2$ is a suitable catalyst precursor for C2 palladium-catalyzed oxidative arylation between *N*-methyl-7-azaindole **33** and phenylboronic acid (Scheme 29).[52] After various screenings, authors found general oxidative cross-coupling conditions [phenylboronic acid (1.2 equiv.), $Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol %) and the peroxydisulfate salts $Na_2S_2O_8$ as the oxidant (1.5 equiv.) in AcOH at room temperature]. Under these conditions, the oxidative cross-coupling product **34** was obtained with high regioselectivity and

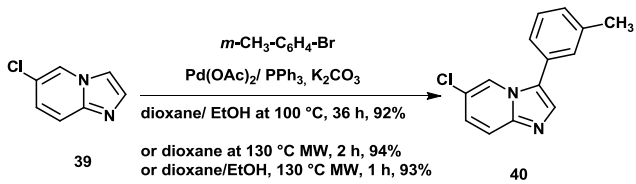
good yield (75%) (Scheme 29).



Scheme 29. Pd-Catalyzed C3-arylation of N-methyl-7-azaindole **33**.

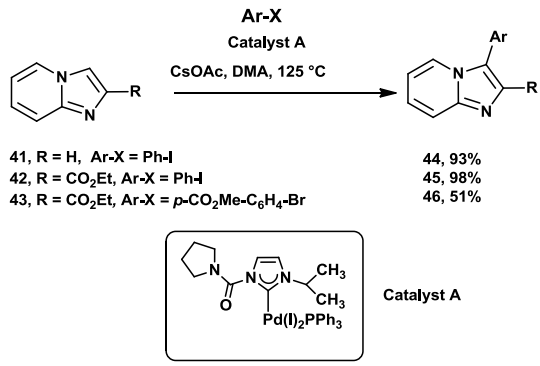
2.3 Imidazo[1,2-*a*]pyridine

Very recently, we reviewed the recent development in the field of cross-coupling reactions applied to functionalize imidazo[1,2-a]pyridines[53]. Our research group described the first regioselective C3-arylation of imidazo[1,2-*a*]pyridine[54, 55]. The reaction was carried out using starting material **39** and 3-bromotoluene in the presence of K_2CO_3, $Pd(OAc)_2$ as catalyst and PPh_3 as ligand. The reactions were carried out using either conventional heating or microwave irradiation. In the first case, (conventional heating in a mixture of dioxane/EtOH for 36 h), the desired product **40** was isolated in 92% yield. In the second case when using microwave irradiation at 130 °C, two different solvents were effective. So, when using dioxane or mixture of dioxane/EtOH, C3 arylated product **40** was obtained in 94 and 93% yields, respectively. The reaction times were 1 h when using dioxane and 2 h when using a mixture of dioxane/EtOH (Scheme 30).



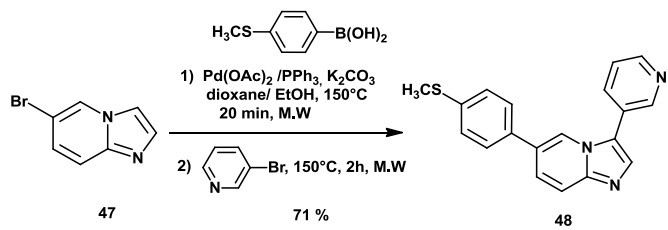
Scheme 30. Synthesis of compound **40** by direct C-arylation of **39**.

Independently, Sames et al[27] prepared three examples of C3 arylated imidazo[1,2-*a*]pyridines using starting materials **41**-**43** and aryl halides (Ar-X) in DMA at 125 °C in the presence of CsOAc as base and a catalytic amount of the NHC–palladium(II) complex (Scheme 31). The desired products **44**-**46** were isolated in moderate to good yields (51 to 93 %).



Scheme 31. C3-arylation of starting materials **41-43**.

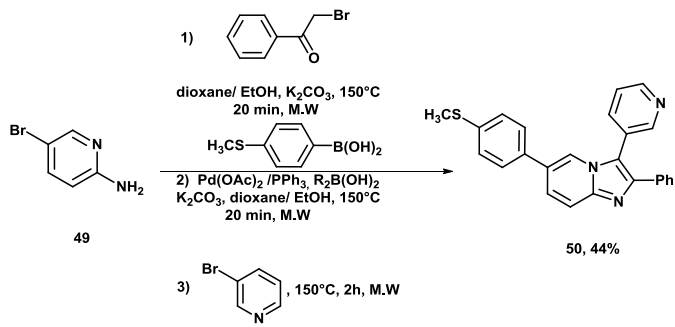
In 2007, our group developed two efficient methods for the synthesis of 3,6-disubstituted imidazo[1,2-*a*]pyridine derivatives[87]. The first method furnished the desired compounds **48** *via* a microwave-assisted one-pot, two-step Suzuki/heteroarylation on 6-bromoimidazo[1,2-a]pyridine **47**. The one-pot cross-coupling between compound **47**, *p*-thiomethylphenylboronic acid, and 3-bromopyridine under optimized reaction conditions [$(Pd(OAc)_2/PPh_3$ as catalyst and K_2CO_3 as base in a mixture of dioxane/EtOH at 150 °C, MW] gave the expected product **48** in 71 % overall yield (Scheme 32).



Scheme 32. One-pot two-step Suzuki/heteroarylation of 6-bromoimidazo[1,2-a]pyridine **47**.

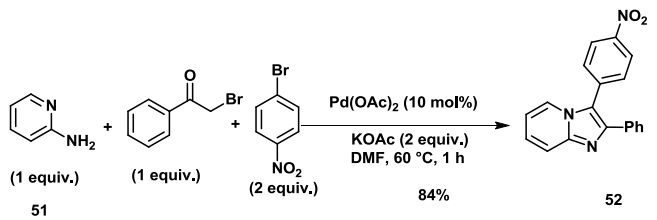
The second method led to 2,3,6-trisubstituted imidazo[1,2-*a*]pyridines in a one-pot, three-step reaction by tandem cyclization/Suzuki cross-coupling/palladium-catalyzed heteroarylation starting from the commercially available 2-amino-5-bromopyridine. In fact, under microwave irradiation, the treatment in the same pot of 2-amino-5-bromopyridine **49** successively with 2-bromo-1-phenylethanone (cyclization), then with palladium acetate, triphenylphosphine and *p*-thiomethylphenylboronic acid (Suzuki coupling), and finally with 3-bromopyridine (heteroarylation reaction), afforded the desired 2,3,6-trisubstituted imidazo[1,2-*a*]pyridine **50** in 44% overall yield (scheme 33).

Interestingly, the $Pd(OAc)_2/PPh_3$ system proved to be the optimal catalyst system for both Suzuki-Miyaura cross-coupling and (hetero)arylation reactions.



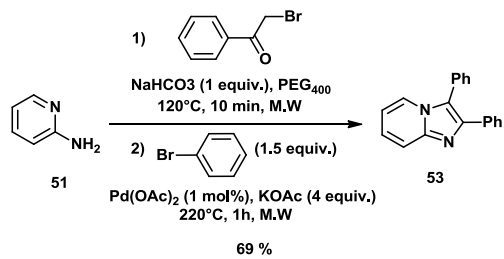
Scheme 33. One-pot three-step cyclization/Suzuki/heteroarylation of 49.

After seven years, Li and co-workers[56] have used the same strategy to prepared 2,3-diarylimidazo[1,2-a]pyridines by one-pot, ligand-Free palladium-catalyzed three-component reaction under microwave irradiation. The one-pot reaction between 2-aminopyridine **51**, 2-bromo-1-phenylethanone, and 1-bromo-4-nitrobenzene under optimized reaction conditions [($Pd(OAc)_2$ as catalyst, KOAc as base, DMF as solvent at 160 °C under MW] led to expected 2,3-diarylated imidazo[1,2-a]pyridine **52** in good yield (Scheme 34).



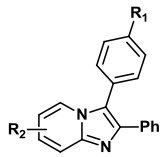
Scheme 34. One-pot two-step cyclization/ heteroarylation of **5**.

Very recently, Berteina and co-workers reported similar microwave-assisted sequential one-pot two-step cyclization/C-H arylation in PEG_{400} medium. Under this new conditions various 2,3-diarylimidazo[1,2-a]pyridines[57] were synthesized. In a representative example, when starting material **51** was treated successively in the same pot with 2-bromo-1-phenylethanone (cyclization), then with $Pd(OAc)_2$ and KOAc in PEG_{400}, the reaction led to 2,3-bisphenylimidazo[1,2-a]pyridines **53** in 69% isolated yield (Scheme 35).



Scheme 35. Synthesis of **53** via one-pot two-step cyclization/C-H arylation in PEG_{400} medium.

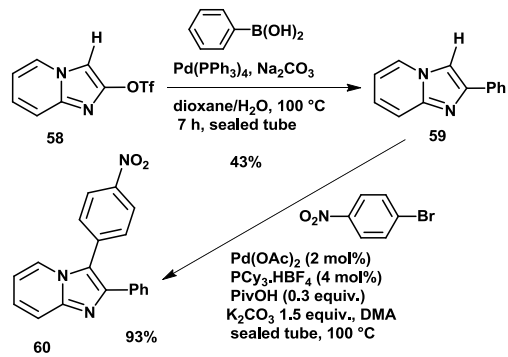
It is noticed that, mild electron-donating and electron-withdrawing groups gave the expected products in moderate to good yields over the two step process. In contrast, no coupling product was observed for **55**, **56** and **57**, and for the synthesis of **54** in which significant degradation was observed. Also, no cleavage of the C–Cl bond was noticed (Figure 1).



	Yields
54, R_1 = H, R_2 = 7-Cl	traces
55, R_1 = H, R_2 = 6-CO_2Me	0%
56, R_1 = H, R_2 = 8-OBn	0%
57, R_1 = CO_2Me , R_2 = H	0%

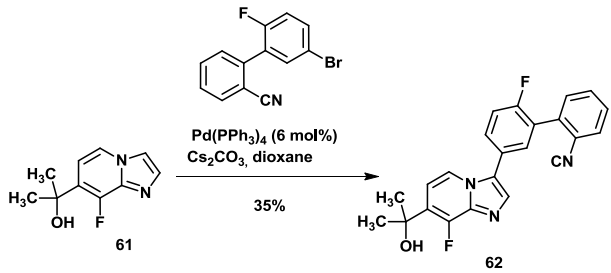
Fig. 1. Limits of one-pot two-step cyclization/C-H arylation in PEG_{400} medium.

In 2012, Marchand et al developed sequential C2 Suzuki-Miyaura/ direct C3-arylation of imidazo[1,2-*a*]pyridines (Scheme 36)[58]. In a representative example, 2,3-diarylimidazo[1,2-*a*]pyridine **60** was prepared starting from imidazo[1,2-*a*]pyridin-2-yl triflate **58** after treatment with phenylboronic acid under Suzuki-Miyaura reaction conditions in a sealed tube [$PhB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, dioxane/H_2O 2:1, sealed tube at 100 °C] giving **59** in 43% yield. Then, C3-arylation reaction was carried out on **59** using 4-bromonitrobenzene in the presence of $Pd(OAc)_2$, $PCy_3.HBF_4$, PivOH and K_2CO_3 in DMA in a sealed tube at 100 °C to give the expected polysubstituted imidazo[1,2-*a*]pyridine analogue **60** in 93% yield (Scheme 36).



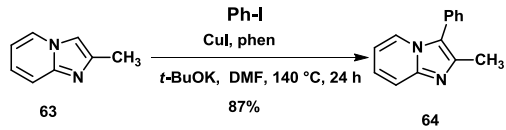
Scheme 36. Sequential C2 Suzuki-Miyaura cross coupling and C3 direct C–H arylation of imidazo[1,2-*a*]pyridines **58**.

Humphries et al. reported the direct arylation of imidazo[1,2-a]pyridine as a key step for the synthesis of potential $GABA_A$ agonist candidates[59-61,62-64]. Authors synthesized C3 arylated imidazo[1,2-*a*]pyridine **62** in 35% yield by treatment of imidazo[1,2-*a*]pyridine **61** in the presence of 5'-bromo-2'-fluorobiphenylcarbonitrile. The reaction was catalyzed by $Pd(PPh_3)_4$ in the presence of Cs_2CO_3 in dioxane (Scheme 37).



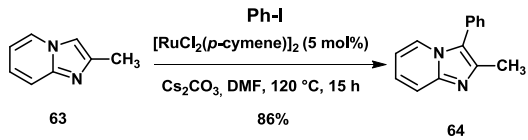
Scheme 37. C3-arylation of imidazo[1,2-*a*]pyridine **61**.

Recently, Jiang et al. [65] reported a new method for C3-arylation of imidazo[1,2-*a*]pyridine **63** using copper iodide as catalyst. Thus, working in DMF at 140 °C, the best reaction conditions were found to be CuI, 1,10-phenantroline as ligand and *t*-BuOK as base. The expected product **64** was isolated in 87% yield (scheme 38).



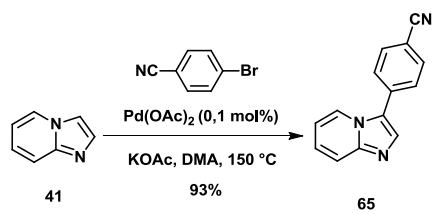
Scheme 38. CuI-catalyzed C3-arylation of **63**.

Developing further the reaction conditions, Yang et al.[66] reported a new Ru-catalyzed C-H activation of imidazo[1,2-*a*]pyridines. The reaction was carried out using imidazo[1,2-*a*]pyridine **63** and iodobenzene in the presence of $RuCl_2(p\text{-cymene})]_2$ and Cs_2CO_3 in DMF at 120 °C which afforded the desired product **64** in 86% (GC yield) (Scheme 39).



Scheme 39. Ru-catalyzed C3-arylation of **63**.

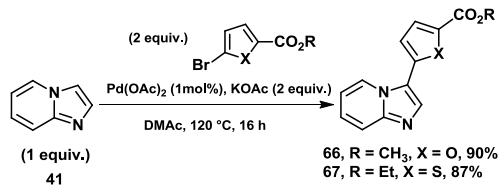
A phosphine-free C3-arylation of imidazo[1,2-*a*]pyridine **41** was recently developed by Doucet et al.[67] using $Pd(OAc)_2$ as catalyst in the presence of KOAc as base in DMA at 150 °C. Only 0.1 mol% of the catalyst efficiently catalyzed the cross-coupling reaction leading to desired product **65** in 93% isolated yield (Scheme 40).



Scheme 40. Phosphine-free C3-arylation of **41**.

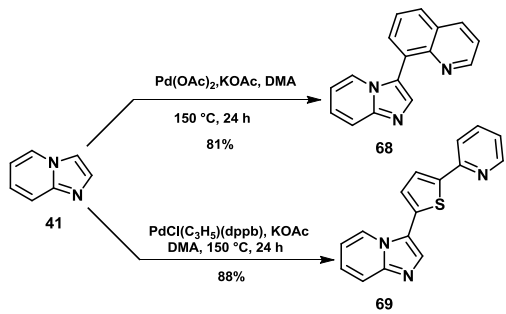
Doucet's group prepared also the 3-furanylimidazo[1,2-a]pyridine and 3-thienyl

imidazo[1,2-*a*]pyridine derivatives **66**, **67** by C3-arylation of imidazo[1,2-*a*]pyridine **41** with methyl 5-bromofuroate (1 equiv.) or ethyl 5-bromothiophene-2-carboxylate (1 equiv) as arylating agents[68]. The reaction was heated for 16 h at 120 °C in DMA in the presence of KOAc as base and 1 mol% of $Pd(OAc)_2$ as catalyst. Under these conditions, the desired heteroarylated products **66** and **67** were isolated in 90% and 87% yields, respectively (Scheme 41). It is noticed that, under the optimized reaction conditions, authors achieved also the C2-arylation of benzothiophene with methyl 5-bromofuroate.



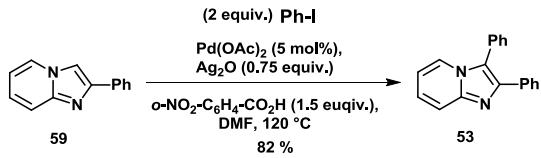
Scheme 41. $Pd(OAc)_2$-catalyzed C3-arylation of imidazo[1,2-a]pyridine **41**.

Recently, the same group reported direct heteroarylation of imidazo[1,2-a]pyridine using either 8-bromoquinoline or 2-(5-bromothiophen-2-yl)-pyridine as arylating agents[69]. In the case of 8-bromoquinoline (1 equiv.) and 2-(5-bromothiophen-2-yl)-pyridine (1 equiv.), the best reaction conditions were found to be $Pd(OAc)_2$ (1 mol%), imidazopyridine **41** (2 equiv.) and KOAc (2 equiv.) in DMA at 120 °C for 16 h. Under these conditions, the expected products **68** and **69** were isolated in 81% and 88% yields, respectively (Scheme 42).



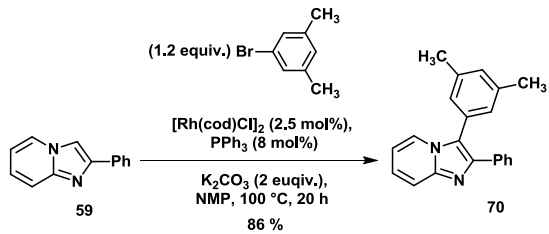
Scheme 42. Phosphine-free C3-arylation of imidazopyridine **41**.

Another phosphine free direct arylation was reported by Chakravarty et al. [70]. In this case, 2-phenylimidazo[1,2-*a*]pyridine **59** and iodophenyl were used as coupling partners in the presence of 5 mol% of $Pd(OAc)_2$, 0.75 equiv of Ag_2O and 1.5 equiv. of *o*-NO_2-C_6H_4-CO_2H in DMF at 120 °C. Under these conditions, the expected product 2,3-bisphenylimidazo[1,2-a]pyridine **53** was isolated in 82% yield (Scheme 43).



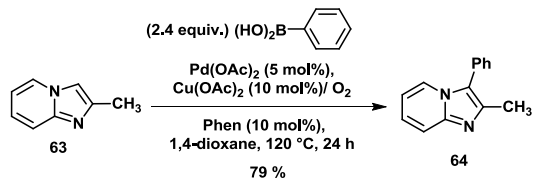
Scheme 43. Phosphine-free C3-arylation of **59**.

In the same year, Liu and co-workers found that the reaction between 2-phenylimidazo[1,2-*a*]pyridine **59** (1 equiv.) and 1-bromo-3,5-dimethylbenzene in the presence of 2.5 mol% $[Rh(cod)Cl]_2$, 8 mol% PPh_3 and 2 equiv. of K_2CO_3 in NMP at 100 °C for 24 h provided 3-aryl-2-phenylimidazo[1,2-*a*]pyridine **70** in 86% yield (Scheme 44)[71].



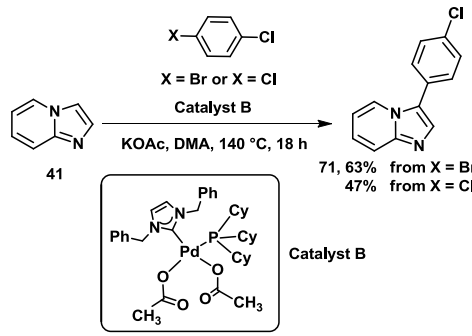
Scheme 44. Rhodium-catalyzed direct arylation of imidazo[1,2-a]pyridines **59**.

In 2014, Cao and co-workers examined whether imidazo[1,2-a]pyridine underwent C3-arylation with arylboronic acids and found that the $Pd(OAc)_2$-catalyzed reactions of 2-methylimidazo[1,2-a]pyridine **63** with 2.4 equiv. of phenylboronic acid using O_2 as oxidant in the presence of 10 mol% of $Cu(OAc)_2$, 10 mol% of phenanthroline in dioxane at 120°C for 20 h, provided compound **64** in 79% yield (Scheme 45)[72].



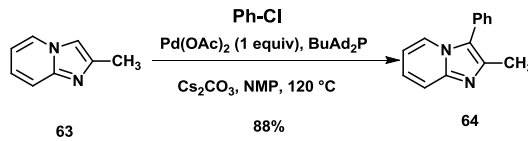
Scheme 45. Arylation of **63** with phenylboronic acid.

Recently, Lee and co-workers[73] prepared 3-arylimidazo[1,2-*a*]pyridine **71** by direct C3-arylation of imidazo[1,2-*a*]pyridine **41** with aryl halides (Br or Cl) in DMA at 140 °C in the presence of KOAc as base and a catalytic amount of palladium(II) acetate complexes bearing phosphines and carbene ligands $[Pd(L)(PR_3)(OAc)_2$ (R = Cy; L = 1,3-dibenzylimidazol-2-ylidene)]. Under these conditions, the desired product **71** was obtained using either aryl bromide or chloride in 63 and 47 % yields, respectively (Scheme 46).



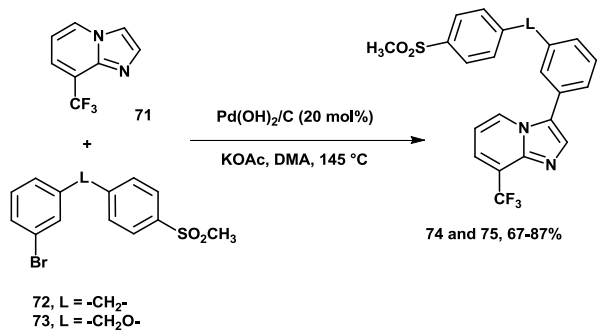
Scheme 46. C3-arylation of imidazo[1,2-*a*]pyridine **41**.

Attempting to use chloroaryls as less expensive alternatives to iodo or bromoaryl coupling partners, Cao and al.[74] developed an efficient Pd-catalyzed regioselective arylation at the C3 position of imidazo[1,2-*a*]pyridine **63** with chlorobenzene. This reaction was catalyzed by $Pd(OAc)_2$ in the presence of $BuAd_2P$ (Ad= adamantyl) and Cs_2CO_3 in NMP at 120 °C (Scheme 47). The expected product **64** was obtained in 88% (GC yield). The authors noticed that when 2-chlorothiophene, 4-chloronitrobenzene and 4-chloromethoxybenzene were used as coupling partners no reaction occurred.



Scheme 47. C3-arylation of imidazo[1,2-*a*]pyridine **63** with chlorobenzene.

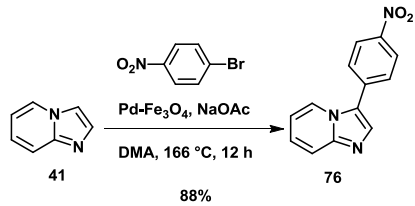
Imidazo[1,2-*a*]pyridines **74** and **75** were reported as agonists of liver X receptor by Singhaus et al.[75] These compounds were prepared by direct arylation of **71** with either **72** or **73** in the presence of $Pd(OH)_2$ on carbon and KOAc in DMA at 145 °C for 24 h. The expected products **74** and **75** were isolated in 67 and 87% yields, respectively (Scheme 48).



Scheme 48. Preparation of compounds **74** and **75** by C3-arylation.

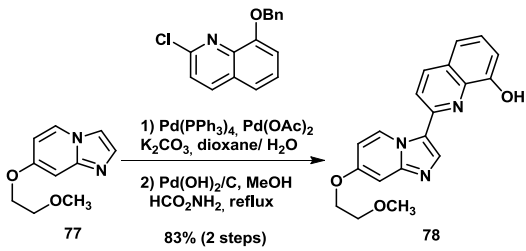
Recently, magnetically recyclable Pd-Fe_3O_4 nanoparticles as catalyst were used by Lee et al.[76] to achieve the direct arylation of imidazo[1,2-*a*]pyridine. Reaction

between **41** and 4-bromonitrobenzene was carried out using Pd-Fe_3O_4 and NaOAc in DMA at 166 °C leading to desired product **76** in 88% yield (Scheme 49).



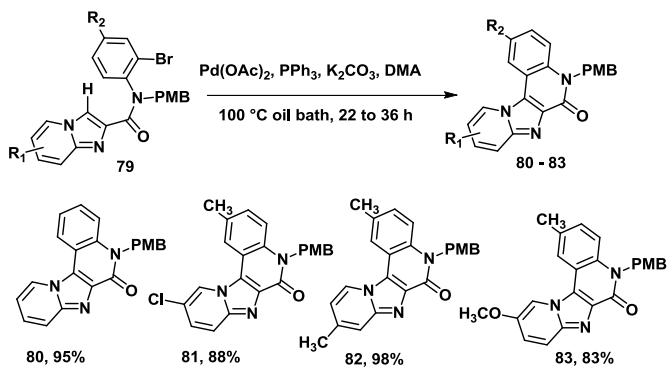
Scheme 49. Direct arylation of imidazo[1,2-*a*]pyridine **41**.

Very recently, Hicken et al. reported the synthesis and biological evaluation of a novel class of imidazo[1,2-*a*]pyridines with potent PDGFR activity and oral bioavailability. Starting from imidazo[1,2-*a*]pyridine derivative **77** and chloroquinoline as coupling partners, $Pd(PPh_3)_4$/ $Pd(OAc)_2$ as a mixed catalyst system and K_2CO_3 as a base in a mixture of dioxane/ H_2O at 100 °C. followed by a treatment with $Pd(OH)_2$ on carbon in the presence of ammonium formate, the expected product **78** was obtained in 83% yield (yield was calculated after two steps) (Scheme 50).



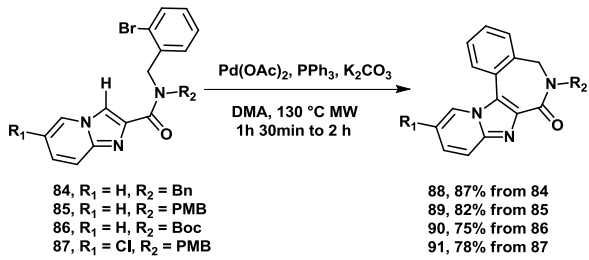
Scheme 50. Cross-coupling reactions imidazo[1,2-a]pyridine derivative **77** and chloroquinoline.

A straightforward preparation of original polycyclic compound libraries via palladium-catalyzed intramolecular C3-arylation of imidazo[1,2-*a*]pyridine **79** was reported by some of us.[77] The expected products **80-83** were achieved using $Pd(OAc)_2/PPh_3$ as catalytic system in the presence of K_2CO_3 in DMA at 100 °C. Yields of isolated products were ranging between 83 and 98% (Scheme 51).



Scheme 51. Intramolecular C3-arylation of **79**.

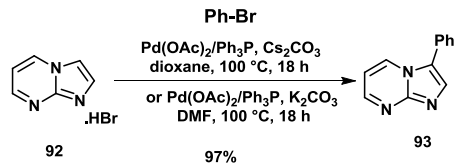
Pursuing the investigation of this new method, seven-membered ring of the azepinone systems were also prepared. Thus, intramolecular arylation reaction was carried out using **84-87** as starting materials in the presence of $Pd(OAc)_2/PPh_3$ and K_2CO_3 in DMA at 130 °C under microwave irradiation. The desired products **88-91** were isolated in yields ranging between 75 and 87% (Scheme 52).



Scheme 52. Intramolecular C3-arylation of **84-87**.

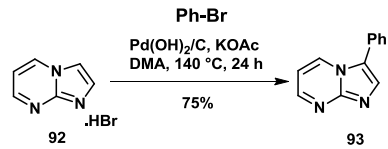
2.4 Imidazo[1,2-*a*]pyrimidines.

Li et al.[78] reported the first example of direct arylation of imidazo[1,2-*a*]pyrimidine **92**. Two reaction conditions were successfully applied using $Pd(OAc)_2/Ph_3P$ as the catalyst/ligand system in the presence of either Cs_2CO_3 in dioxane at 100 °C or K_2CO_3 in DMF at 100 °C. In both cases, the desired product **93** was isolated in excellent yield of 97% (Scheme 53).



Scheme 53. Pd-catalyzed C3-arylation of **92.**

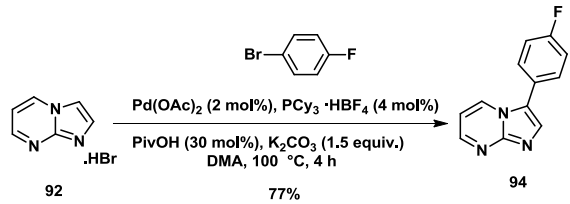
Similar synthesis was achieved by Fagnou et al.[79] using palladium hydroxide on carbon $Pd(OH)_2/C$ (Pearlman's catalyst) as catalyst. The arylation coupling was carried out in the presence of starting matetial **92**, bromobenzene, $Pd(OH)_2/C$ and KOAc in DMA at 140 °C. The phenylated product **93** was isolated in 75% yield (Scheme 54).



Scheme 54. Pd-catalyzed C3-arylation of **92**.

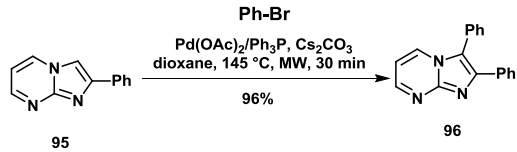
The same group established broadly applicable reaction conditions for the palladium-catalyzed direct arylation of imidazo[1,2-*a*]pyrimidine with arylbromides[9]. Thus, the treatment of **92** with 4-bromofluorobenzene in the presence of $Pd(OAc)_2/PCy_3.HBF_4$ as catalytic system associated with the use of substoichiometric quantities of pivalic acid (which in situ generated potassium pivalate) and K_2CO_3 as base in DMA at 100 °C for 4 h led to desired product **94** in

77% yield (scheme 55).



Scheme 55. Pd-catalyzed C3-arylation of **92**.

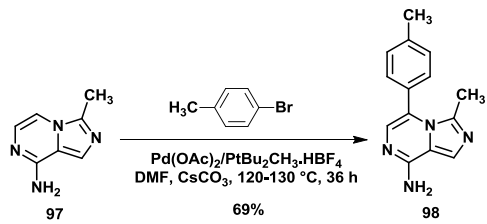
Another study describing imidazo[1,2-*a*]pyrimidine direct arylation was published by Eycken et al.[80]. Using imidazo[1,2-a]pyrimidine **95** and bromobenzene as coupling partners in the presence of $Pd(OAc)_2$ as catalyst, Ph_3P as ligand and Cs_2CO_3 as base in dioxane at 145 °C under microwave irradiation, the expected product **96** was isolated in 96% yield (Scheme 56).



Scheme 56. Pd-catalyzed C3-arylation of **95**.

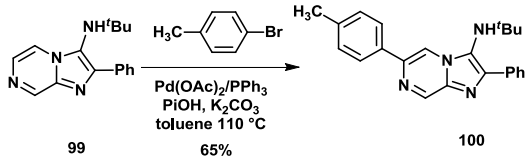
2.5 Imidazo[1,2-*a*]pyrazine

Snieckus and co-workers[81] reported regioselective C5-arylation of imidazo[1,5-*a*]pyrazine catalyzed by palladium. The coupling reaction was carried out using **97** as starting material and 4-bromotoluene as arylating agent in the presence of $Pd(OAc)_2/P^tBu_2CH_3.HBF_4$, and Cs_2CO_3 in DMF at 120-130 °C. The expected product **98** was obtained in 69% HPLC yield using 4-methoxy-benzoic acid as an internal standard (Scheme 57).



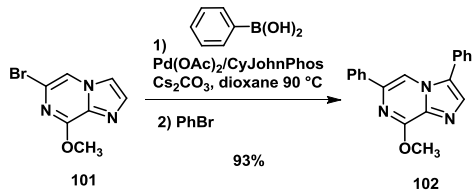
Scheme 57. Pd-catalyzed C3-arylation of **97**.

Guchhait et al. described direct arylation of imidazo[1,2-*a*]pyrazine under concerted metalation-deprotection process (CMD)[82]. After an evaluation of reagents and reaction condition for regioselective C6-arylation of 3-aminoimidazo[1,2-*a*]pyrazine **99**, authors found that $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), PivOH (30 mol%), K_2CO_3 (2 equiv.), in toluene at 110°C were the best conditions providing no traces of C2'-arylated product. The desired product **100** was isolated in 65% yield (Scheme 58).



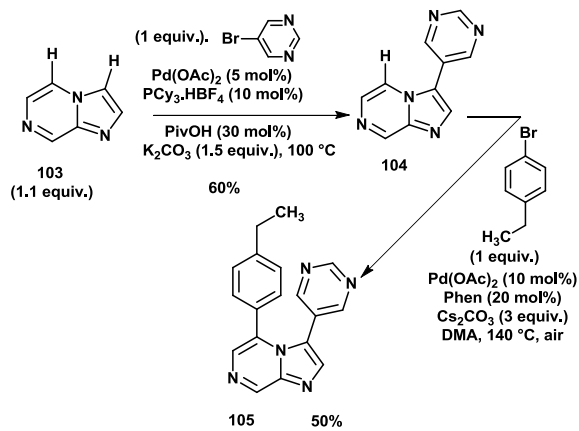
Scheme 58. Pd-catalyzed C6-arylation of **99**.

Recently a one-pot sequential Suzuki/arylation reaction was developed by Hoarau et al.[83]. Thus, C3/C6 functionalization was achieved by treatment of imidazo[1,2-*a*]pyrazine **101** using Suzuki conditions that are [PhB(OH)$_2$, Pd(OAc)$_2$, CyJohnPhos, Cs$_2$CO$_3$, dioxane at 90 °C, 3h]. Then, PhBr was added and the reaction mixture was heated at 120 °C for 18 h. This sequence led to C3, C6-disubstituted imidazo[1,2-*a*]pyrazine **102** in 93% isolated yield (Scheme 59).



Scheme 59. Pd-catalyzed C3-arylation of **101.**

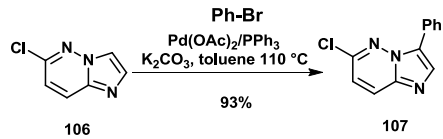
In 2014, a new procedure of double functionalization of imidazo[1,2-*a*]pyrazines using direct C–H arylation at the 3 position followed by a direct arylation at the 5-position was developed by Huestis and Johnson[84]. Thus, 3,5-diarylimidazo[1,2-*a*]pyrazine **105** was prepared starting from imidazo[1,2-*a*]pyrazine **103**. After treatment with 5-bromopyrimidine under reaction conditions [Pd(OAc)$_2$, PCy$_3$.HBF$_4$, PivOH (30 mol%), K$_2$CO$_3$, 100 °C], the desired monoarylated product **104** was isolated in 60 % yield. C5-arylation reaction was then carried out on **104** using *p*-CH$_3$CH$_2$C$_6$H$_4$-Br in the presence of Pd(OAc)$_2$, 1,10-phenanthroline, Cs$_2$CO$_3$ in DMA at 140 °C under atmospheric air which furnished bis-arylated product **105** in 50% (Scheme 60).



Scheme 60. Sequential C3 and C5 direct C–H arylation of imidazo[1,2-*a*]pyrazine **103.**

2.6 Imidazo[1,2-*b*]pyridazines

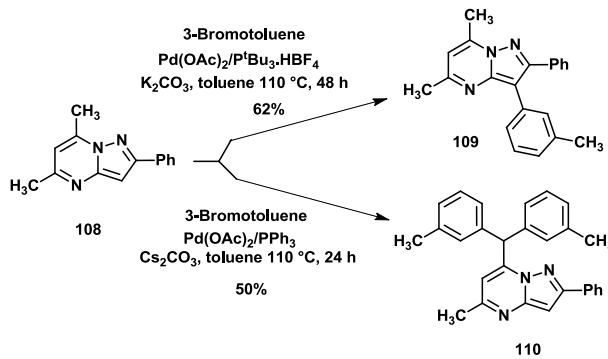
One of us and coworkers developed an elegant C3 direct arylation of imidazo[1,2-b]pyridazines[85]. Optimization of reaction conditions using imidazo[1,2-b]pyridazine **106** and bromobenzene as coupling partners showed that $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%) and K_2CO_3 (2 equiv.), in toluene at 110°C gave the expected product **107** in a very good yield (93%) (Scheme 61). Then, the authors developed a one pot, two step Suzuki/arylation which led to the functionalization of both 3 and 6 positions of imidazo[1,2-*b*]pyridazine.



Scheme 61. Pd-catalyzed C3-arylation of **106**.

2.7 Pyrazolo[1,5-*a*]pyrimidines

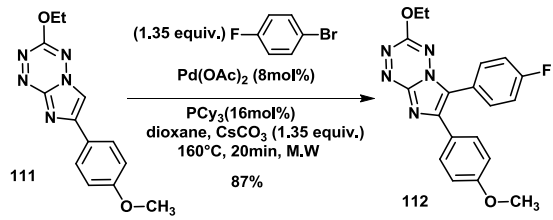
Recently, one of us and coworkers reported direct arylation of pyrazolo[1,5-*a*]pyrimidine system[57]. Thus, when starting material **108** was treated with 3-bromotoluene in the presence of $Pd(OAc)_2$, $P^tBu_3.HBF_4$ and K_2CO_3 in refluxing toluene, the reaction led to sp^2 C3-arylated product **109** in 62% isolated yield. Interestingly, when Ph_3P was used instead of $P^tBu_3.HBF_4$ and Cs_2CO_3 instead of K_2CO_3 the reaction led to sp^3 C-H arylation, the reaction gave exclusively compound **110** in 50% isolated yield (Scheme 62).



Scheme 62. Pd-catalyzed arylation of pyrazolo[1,5-*a*]pyrimidine **108**.

2.8 Imidazo[1,2-b][1,2,4,5]tetrazines

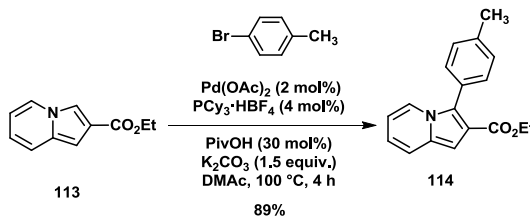
In 2010, Routier and co-workers developed a regioselective palladium-catalyzed (het)arylation as a key step to access to a library of C6-arylated imidazo[1,2-*b*][1,2,4,5]tetrazines[86]. The protocol involved the treatment of ethoxy-7-(4-methoxyphenyl)imidazo[1,2-*b*][1,2,4,5]tetrazine **111** with aryl bromide in dioxane at 160°C for 20 min under microwave irradiation, in the presence of Cs_2CO_3, 8 mol% $Pd(OAc)_2$ and 8 mol% of PCy_3. Under these conditions the arylated compound **112** was obtained in 87% yield (Scheme 63).



Scheme 63. Microwave-assisted palladium-catalyzed C3-arylation of **111**.

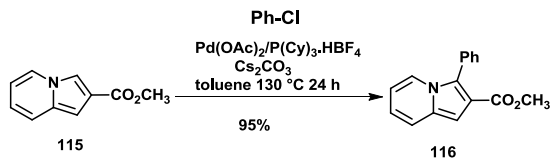
2.9 Indolizine

Recently, Fagnou and co-workers used C-H arylation to introduce various aryls at the C3-position of indolizine-2-carboxylate **113** in order to prepare poly-substituted indolizine[9]. Thus, the reaction between **113** and *p*-bromotoluene in the presence of a catalytic amount of $Pd(OAc)_2/PCy_3.HBF_4$ gave the C–H arylated compound **114** in 89% yield (Scheme 64).



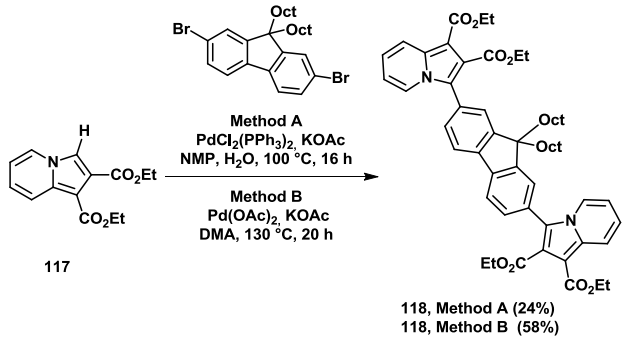
Scheme 64. Pd-catalyzed C3-arylation of **113**.

Lan et al. showed that chloroaryls are suitable coupling partners for direct arylation of indolizine-2-carboxylate **115**[87]. To achieve the arylation reaction, starting material **115** was treated by chlorobenzene in the presence of $Pd(OAc)_2$ and $PCy_3.HBF_4$ as ligand in toluene at 130 °C for 24 h. The expected product **116** was obtained in very good yield of 95% (Scheme 65). The C3-arylation of indolizine-2-carboxylate provided a wide range of heteroarenes library of organic fluorophores which were able to mark successfully A375 cells making them promising bioimaging fluorescence probes.



Scheme 65. Pd-catalyzed C3-arylation of **115**.

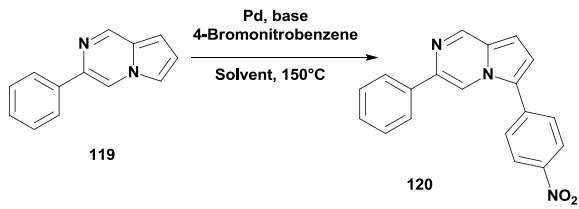
Almost at the same time, Gryko and co-workers reported the arylation of electron-poor indolizines at C3 position with aryl bromides.[88] The authors demonstrated the possibility of efficient preparation of two indolizine units connected with 9,9-dioctylfluorene linkers. Direct coupling of indolizine **117** with 2,7-dibromo-9,9-dioctylfluorene under optimum reaction conditions (Method A or Method B) gave the desired bis-indolizine **118** in satisfactory yields (Schemes 66).



Scheme 66. Preparation of bis-indolizine **118**.

2.10 Pyrrolo[1,2-a]pyrazine

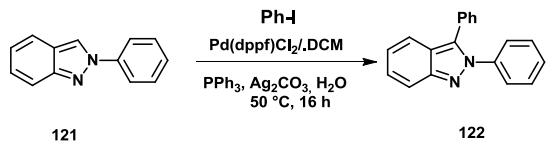
Recently, using pyrrolo[1,2-a]pyrazine system, Park et al.[89] reported that starting material **119** undergo direct C6-arylation when treated by 4-bromonitrobenzene in the presence of KOAc as base, $(PPh_3)_2Pd(Cl)_2$ as a catalyst system in DMA as solvent at 150 °C. The desired product **120** was obtained in 87% yield (Scheme 67). As far as we know, this is the only example reported so far on C6-arylation of pyrrolo[1,2-a]pyrazines.



Scheme 67. C6-arylation of pyrrolo[1,2-a]pyrazine **119.**

2.11 Indazole

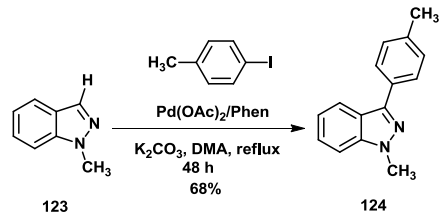
The first example of direct arylation of indazole was reported on (2*H*) indazole serie[90]. The reaction was performed on water using 2-phenylindazole **121** as starting material and iodobenzene as coupling partner in the presence of $Pd(dppf)Cl_2$ as catalyst, PPh_3 as ligand and Ag_2CO_3 as base. The arylated product **122** was obtained in 76% yield (Scheme 68).



Scheme 68. C3-arylation of 2-phenylindazole **121**.

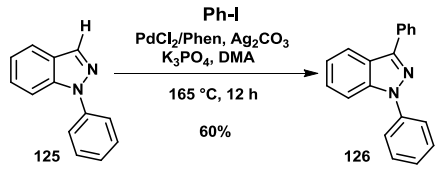
Our group reported the first example of direct arylation of (1*H*) indazole **123** using $Pd(OAc)_2$ as catalyst and 1,10-phenanthroline as ligand in the presence of K_2CO_3 as base and DMA as solvent[91]. The reaction was conducted at reflux for 48 h

leading to desired compound **124** in 68% isolated yield (Scheme 69). Moreover, heteroaryl bromides were also successfully employed leading to expected heteroarylated indazoles.



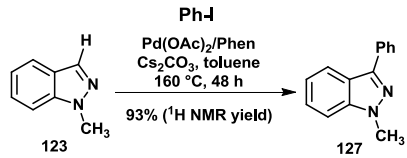
Scheme 69. Direct arylation of (1*H*) indazole **123.**

Independently, Itami's group reported the C3-arylation of (1*H*) indazole **125** using $PdCl_2$ as catalyst, 1,10-phenanthroline as ligand, Ag_2CO_3 as base and K_3PO_4 as additive[92]. The reaction was carried out in DMA at 165 °C for 12 h leading to desired product **126** in 60% isolated yield (Scheme 70).



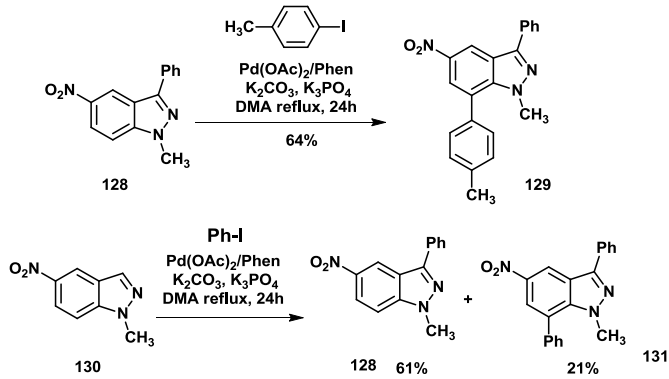
Scheme 70. C3-arylation of (1*H*) indazoles **125.**

Later, Yu et al.[93] reported the C3-arylation on (1*H*) indazoles using indazole **123** as starting material, iodobenzene as coupling partner, $Pd(OAc)_2$ as catalyst, 1,10-phenantroline as ligand and Cs_2CO_3 as base in toluene at 160 °C for 12 h. The expected product **127** was obtained in 93% (yield was determinated by ^{1}H NMR) (Scheme 71).



Scheme71. C3-arylation of (1*H*) indazole **123**.

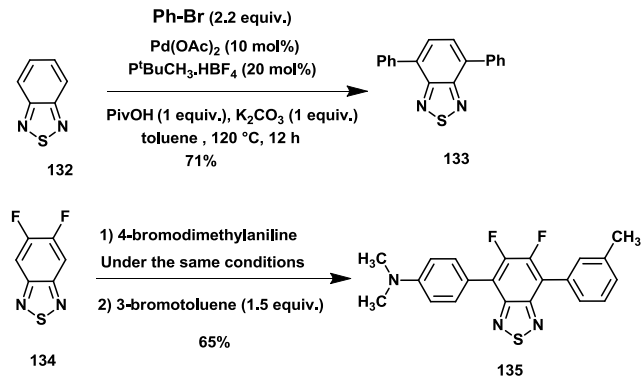
Very recently, we reported the first example of the direct arylation on the arene ring of 6,5 fused heterocyclic system containing no heteroatom on the six-membered ring[94]. Thus, direct C7-arylation was developed using 3-substituted 1*H*-indazoles **128** containing an EWG on the arene ring as starting material and 4-iodotoluene as coupling partner in the presence of $Pd(OAc)_2$, 1,10-phenanthroline, K_2CO_3, and K_3PO_4 in refluxing DMA for 18h. In this case desired C7 arylated product **129** was isolated in 64% yield (Scheme 72). It is noticed that when the 3 position of 1*H*-indazole was not substituted, the arylation reaction of starting material **130** led to a mixture of C3 arylated and C3/C7 diarylated products **128** and **131** in 61 and 21% yields, respectively (Scheme 72).



Scheme 72. C7-arylation and C3/C7diarylation of indazole **128** and **130**.

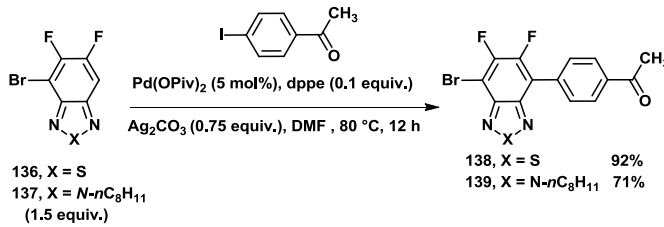
2.12 Benzothiadiazole and benzotriazole

Marder et al. reported an elegant direct arylation of benzothiadiazole through a coupling reaction between **132** and 4-bromobenzene catalyzed by $Pd(OAc)_2$ in the presence of $P^tBu_2CH_3.HBF_4$, PivOH and K_2CO_3 in toluene at 120 °C for 3-5 h[95]. Under these conditions, the symmetricaly diarylated product **133** was isolated in 71% yield (Scheme 73). Authors applied the developed method for the synthesis of symmetrical and unsymmetrical diarylated benzothiadiazole. In a representative example, a one-pot synthesis of an unsymmetrical trial was achieved by the treatment of **134** by 4-bromodimethylaniline (0.8 equiv.) then by 3-bromotoluene (1.5 equiv.) under the optimized reaction conditions indicated obove, diarylated product **135** was isolated in 65% yield (Scheme 73).



Scheme 73. Direct arylation of **132** and **134**.

In an independent study, Zhang and co-workers showed that fluorinated benzothiadiazoles (DFBT, compound **136**) and benzotriazole (DFTAZ, compound **137**) could undergo arylation coupling reaction with aryl and heteroaryl iodides[96]. With the use of a 1-(4-iodophenyl)ethanone reagent, $Pd(OPiv)_2$ as a catalyst and bis(diphenylphosphino)etane (dppe) as ligand, benzothiadiazole **136** and benzotriazole **137** were arylated leading to products **138** and **139** in 92 and 71 % isolated yields, respectively (Scheme 74).

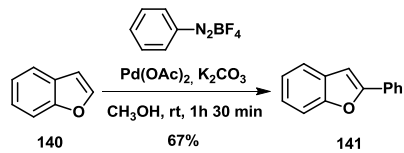


Scheme 74. Direct arylation of DFBT **136** and DFTAZ **139** with -(4-iodophenyl)ethanone.

2.13 Benzofuran

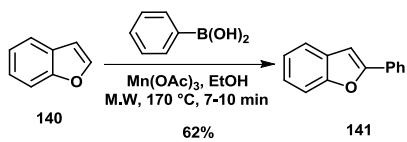
2.13.1 C2-arylation of Benzofuran

Correia and collaborators[97] reported the direct and regioselective palladium catalyzed arylation of benzofuran **140** using aryldiazonium salt as coupling partner. The reaction was carried out between benzofuran and benzendiazonium salt in the presence of $Pd(OAc)_2$ and K_2CO_3 in methanol at room temperature. The expected C2 arylated product **141** was isolated in 67% yield (Scheme 75).



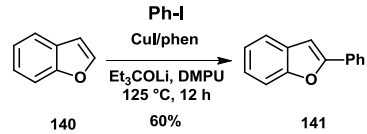
Scheme 75. Regioselective palladium catalysed arylation of benzofuran **140**.

Guchhait and co-workers showed that benzofuran **140** could undergo arylation coupling reaction with arylboronic acid under microwave irradiation[98]. In this case, phenylboronic acid was used as coupling partner and $Mn(OAc)_3$ as catalyst, the reaction was carried out under microwave irradiation in methanol at 170 °C which led to the desired product **141** in 62% yield (Scheme 76).



Scheme 76. C2-direct arylation of benzofuran **140** with phenylboronic acid.

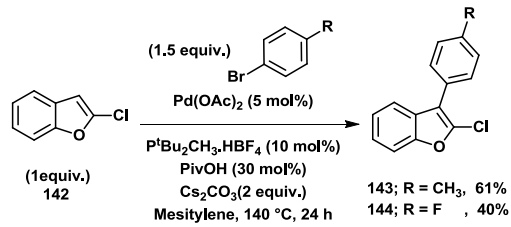
A copper catalysed C2-arylation was also reported by Duagulis et al.[99]. In a representative example C2-direct arylation of benzofuran **140** was achieved by treatment of benzofuran **140** with iodobenzene in the presence of CuI/1,10-phenanthroline and Et_3COLi in DMPU at 125 °C for 12h. This sequence led to desired product **141** in 60% yield (Scheme 77).



Scheme 77. C2-direct arylation of benzofuran **140**.

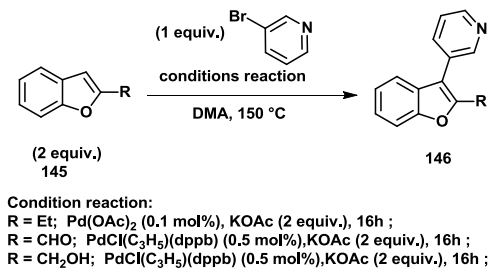
2.13.2 C3-arylation of Benzofuran

Recently, various examples of direct C3-arylation of benzofurans using (het)aryl halides as arylating agents have been reported. In 2010, Fagnou and co-workers prepared two examples of C3-arylation of 2-chlorobenzofuran **142** using eitheir *p*-tolyl bromide or *p*-fluorobenzene bromide as arylating agent[7]. The reaction was catalysed by $Pd(OAc)_2P(t\text{-}Bu)_2Me{\cdot}HBF_4$/PivOH system in the presence of Cs_2CO_3 as base and mesitylene as solvent at 140 °C (Scheme 78). The desired products **143** and **144** were isolated in 61% and 40% yields, respectively.



Scheme 78. C3 arylation of benzofuran **142** with 4-bromo-aryls.

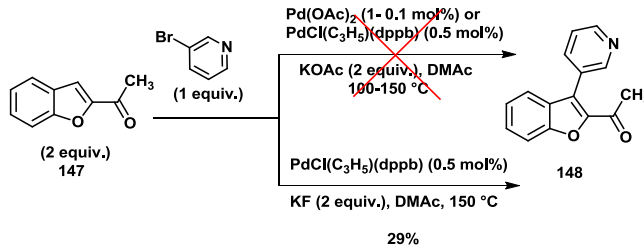
In the same year, Doucet and co-workers explored the reactivity of 2-substituted benzofurans toward C3-arylation reaction[100]. Thus, treatment of benzofurans **145** with aryl bromides in DMA at 150 °C in the presence of either KOAc or KF as base and either $PdCl(C_3H_5)(dppb)$ or $Pd(OAc)_2$ as catalyst led to C3 arylated products **146** in moderate to good yields (Scheme 79). It is noticed that a wide range of functional groups such as ethyl, butyl, formyl, acetyl or hydroxyethyl, on the 2-position of benzofurans were tolerated.



Scheme 79. C3 arylation of 2-substituted benzofurans **145** with 3-bromopyridine.

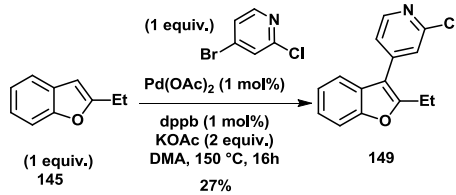
The authors have examined the reactivity of 2-acetylbenzofuran **147** using $PdCl(C_3H_5)(dppb)$ or $Pd(OAc)_2$ as catalyst, KOAc as base at 150 °C in DMA. Under these conditions, an inseparable mixture of unidentified products, which did not contain 3-arylated benzofuran, was obtained. These results might be explained by a partial deprotonation of the acetyl function of this benzofuran derivative by KOAc

to form an enolate. When KF as the base was used instead of KOAc, the coupling product **148** was obtained in 29% yield[100] (Scheme 80).



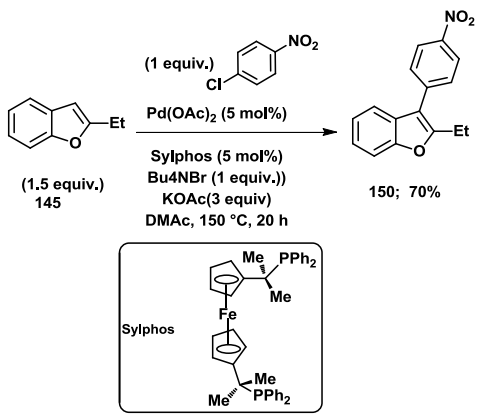
Scheme 80. C3-arylation 2-acetylbenzofuran **147** with 3-bromopyridine.

Recently, Doucet's group reported that the Pd-catalyzed arylation of 2-ethylbenzofuran **145** with 4-bromo-2-chloropyridine using dppb [dppb=1,4-bis(diphenylphosphino)butane] as ligand, KOAc as base and DMA as solvent gave the 3-arylated 2-ethylbenzofuran **149** in 27% yield (Scheme 81)[101]. The optimized reaction conditions were also applied for C2-arylation of benzoxazole and C2-arylation of benzothiophene leading to expected products in modest yields.



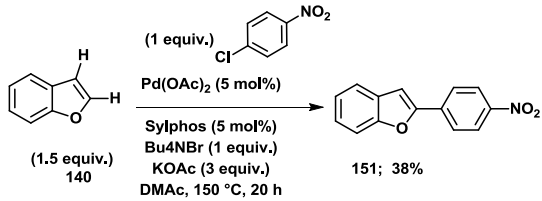
Scheme 81. C3 arylation of benzofuran **145** with 4-bromo-2-chloropyridine.

In 2012, the same group published a novel reaction conditions for C3-arylation of 2-ethylbenzofuran **145**[102]. Thus, treatment of **145** with aryl chlorides in DMA at 150 °C in the presence of KOAc as base, Bu_4NBr as additive and $Pd(OAc)_2$/ferrocenyldiphosphane sylphos as a catalytic system gave 3-aryl-2-ethylbenzofuran **150** in good yield (Scheme 82).



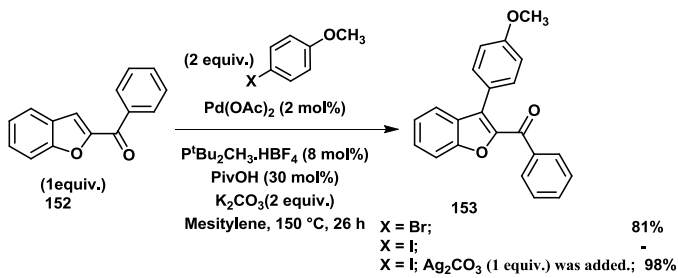
Scheme 82. C3-arylation of 2-ethylbenzofuran **145** with 4-chloronitrobenzene.

When benzofuran **140** did not contain substituents at both the 2 and 3 positions, C2 arylated product **151** was obtained as the major isomer in moderate yield with C2/C3 ratio of 11:6 (Scheme 83).



Scheme 83. C2-arylation of benzofuran **140** with 4-chloronitrobenzene.

In the same year, Bertounesque and co-workers applied the similar reaction conditions to those developed by Fagnou's group[7], for the C3-arylation of 2-benzoylbenzofuran **152**. Thus, using 4-bromomethoxybenzene as arylating agent in mesitylene as solvent at 150 °C in the presence of K_2CO_3 as base and a catalyst system $Pd(OAc)_2$/ $P(^tBu)_2Me{\cdot}HBF_4$/ PivOH gave 3-aryl-2-ethylbenzo[b]furans **153** in good yields (Scheme 84)[103].

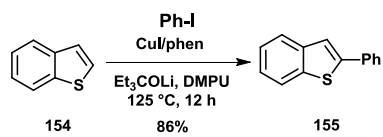


Scheme 84. C3-arylation of 2-benzoylbenzofuran **152** with 4-X-methoxybenzene.

2.14 Benzothiophene

2.14.1 C2-arylation of benzothiophene

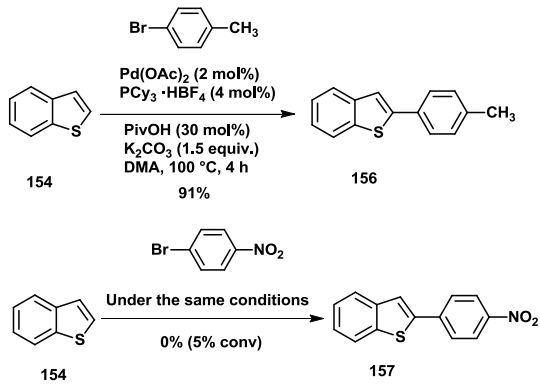
The Duagulis's group applied the optimized reaction conditions developed for directe arylation of benzofuran to regioselective C2-arylation of benzothiophene **154**[99]. The use of iodobenzene, CuI/phen and Et_3COLi in DMPU at 125 °C furnished the desired product **155** in good yield (86%) (Scheme 85).



Scheme 85. C2-arylation of benzothiophene **154**.

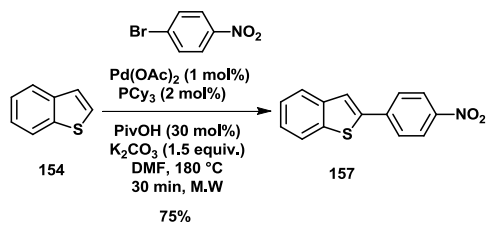
In 2009, Fagnou and collaborators developed a palladium-catalyzed arylation reaction to access to 2-arylbenzothiophene[9]. For example, reaction between benzothiophene **154** and 4-bromotoluene in the presence of $Pd(OAc)_2$, $PCy_3.HBF_4$ and K_2CO_3 in DMA at 100 °C is outlined in Scheme 86. In the absence of pivalic acid, very low conversion was observed (approximately 10% after 3 h). However, the addition of only 10 mol% of PivOH resulted in a dramatic increase in reactivity,

giving 65% conversion after the same reaction time. The yield was further improved by increasing the amount of pivalic acid to 30 mol%, which generated greater than 91% yield of **156**. Furthermore, under the reported conditions, attempts for direct arylation with electron-deficient aryl bromides such as 4-bromonitrobenzene proved to be unsuccessful and only 5% conversion of **157** was observed (Scheme 86).



Scheme 86. C2-arylation of benzothiophene **154**.

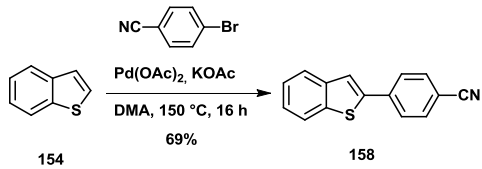
Because reaction times was relatively long (4h), Kappe and co-workers reported a related palladium-catalyzed intermolecular arylation of benzothiophene **154** under microwave irradiation which reduced the reaction times to only 10-60 min[104]. In most examples the use of microwave irradiation allowed reduction in catalyst loading while retaining high coupling efficiencies. Most importantly, by performing the arylation processes at high temperatures under microwave irradiation, the reactivity of some substrates was dramatically increased allowing the preparation of arylated products which were not accessible under classical heating (see the previous Scheme 86). It is particularly noteworthy in this regard that the use of 4-bromonitrobenzene as arylating agent and benzothiophene **154** as starting material led to 75% yield of the desired product **157**. The reaction was carried out under microwave irradiation at 180 °C for 1 h (Scheme 87).



Scheme 87. Pd-catalyzed C-H arylation of benzothiophene **154** with 4-bromonitrobenzene.

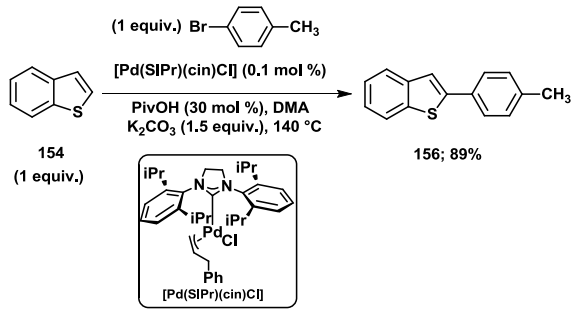
A C2-arylation of benzothiophene **154** using a low amount of ligand-free $Pd(OAc)_2$ was reported by Doucet et al.[105] Thus, the coupling between benzothiophene **154** and 4-bromobenzonitrile was achieved using 0.5 mol% of catalyst and 2 equivalents of KOAc in DMA at 150 °C for 16 h. This procedure led to the expected product **158** in total conversion and 69% yield (Scheme 88). A large library of C2 arylated benzothiophenes was prepared using various aryl or heteroaryl bromides as arylating agents. The best yields were achieved when using electron-

deficient aryl bromides.



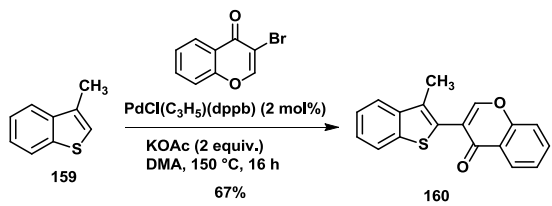
Scheme 88. C2-arylation of benzothiophene **154**.

Recently, Nolan's group described direct arylation of benzothiophene **154** catalyszed by [Pd(SIPr)cin)Cl] [SIPr=1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene][106]. The reactions, carried in DMA at 140 °C, were performed using 0.1 mol% of the catalyst, 1 equiv. of aryl bromide, 30 mol% of PivOH and 1.5 equiv. of K_2CO_3. The expected product **156** was isolated in 89% yield (Scheme 89). Interestingly, the authors demonstrated also the adaptability of reaction conditions initially developed for benzothiophene to direct arylation of imidazo[1,2-*a*]pyridines which produced C3 arylated products in acceptable to high yields (Scheme 68).



Scheme 89. [Pd(SIPr)cin)Cl]-catalyzed C2-arylation of benzothiophene **154**.

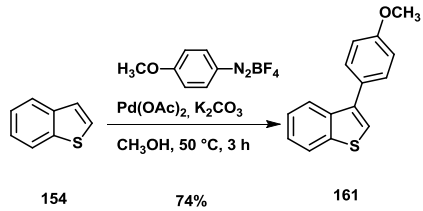
Recently, Doucet et al. reported C2-heteroarylation of benzothiophene **159** using 8-bromoquinoline as arylating agent. Thus, using $PdCl(C_3H_5)(dppb)$ as catalyst in the presence of 2 equiv. of 3-methyl benzothiophene **159**, KOAc (2 equiv.) in DMA at 150 °C, the heteroarylated product **160** was isolated in 67% yield (Scheme 90). The optimized reaction conditions were also effective for C3-arylation of imidazo[1,2-*a*]pyridine.



Scheme 90. C2-hetroarylation of benzothiophene **159**.

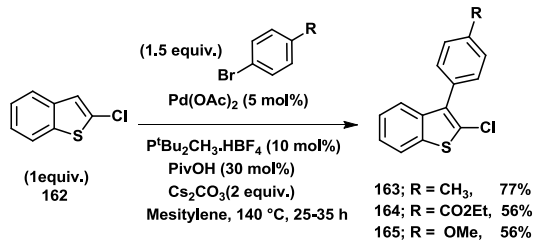
2.14.2 C3-arylation of benzothiophene

Correia's group applied the direct arylation conditions developed for benzofuran to the C3-arylation of benzothiophene **154**[97]. In this case, *p*-methoxybenzendiazonium salt was used as coupling partner in the presence of $Pd(OAc)_2$ and K_2CO_3 in MeOH at 50 °C which afforded good yield (74%) of compound **161** (Scheme 91).



Scheme 91. C3-arylation of benzothiophene **154**.

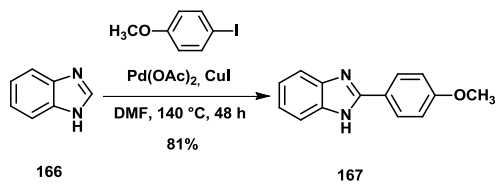
In 2010, Fagnou and co-workers applied the reaction conditions illustrated in Scheme 92 , for C3-arylation reaction of 2-chloro benzothiophene **162** with aryl bromides[7]. The desired products **163-165** were isolated in moderate to good yields (56 to 77 %). The same procedure was successfully used to achieve C2 and C3-arylation of indole.



Scheme 92. C3-arylation of 2-chloro benzofuran **162** with 4-bromo-aryl.

2.15 Benzimidazole

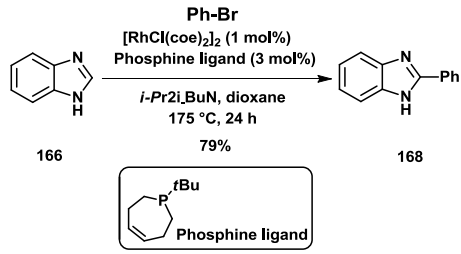
Rossi et al.[48, 49] described direct arylation of benzimidazole **166** using 1-iodo-4-methoxybenzene as coupling partner. The coupling reaction was achieved using $Pd(OAc)_2$ and CuI as catalysts in DMF at 140 °C. The desired product **167** was isolated in a good yield (81 %) (Scheme 93).



Scheme 93. Direct arylation of benzimidazole **166**.

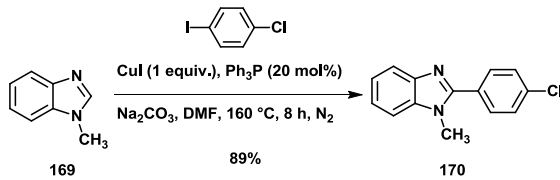
Ellman and collaborators showed that Rh(I) was a suitable catalyst for the arylation of benzimidazole **166**[107]. The reaction was carried out using benzimidazole **166** and bromobenzene as coupling partners and *i*-Pr_2*i*-BuN in dioxane at 175 °C for

24 h in the presence of catalytic amounts of $[RhCl(coe)_2]_2$ (0.01 equiv.) and phosphine ligand (0.03 equiv.). The desired product **168** was isolated in 90% yield (Scheme 94).



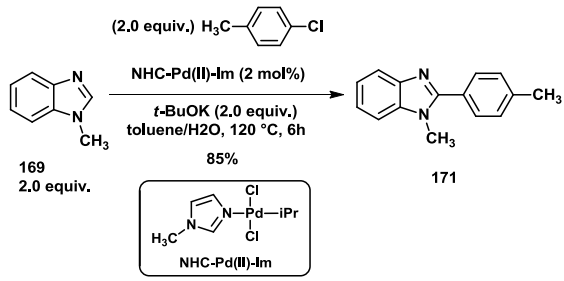
Scheme 94. Rh(I) catalyzed direct arylation of benzimidazole **166**.

In 2008, Miura and co-workers reported the palladium-catalyzed direct arylation of 1-methyl-1*H*-benzimidazole **169** with aryl iodides [108]. The treatment of 1-methyl-1*H*-benzimidazole **169** with 4-chloroiodobenzene in the presence of 1 equivalent of CuI, 0.2 equivalent of Ph_3P and Na_2CO_3 in DMF at 160 °C provided 2-arylated benzimidazole **170** in 89% yield (Scheme 95).



Scheme 95. Copper-mediated direct arylation of 1-methyl-1*H*-benzimidazole **169** with iodoaryl.

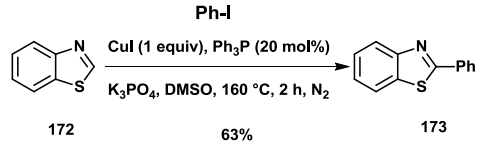
Recently, Shao and co-workers established that the catalyst complex NHC-Pd(II)-Im [heterocyclic carbene-Pd(II)-1-methylimidazole] (2 mol%) in the presence of KOtBu as base promoted the efficient C2-arylation of benzimidazoles **169** with aryl chloride in mixture of toluene/H_2O at 120°C (Scheme 96)[109]. Under the optimal reaction conditions, various activated, unactivated, and deactivated (hetero)aryl chlorides were successfully applied as arylating reagents to prepare the 2-(hetero)aryl (benz)imidazoles in acceptable to high yields. In a representative example, shown in scheme 96, starting material **169** was arylated with chlorotoluene which led to the expected compound **171** in 85% yield.



Scheme 96. NHC-Pd(II)-Im catalyzed direct arylation of **169** with aryl chloride.

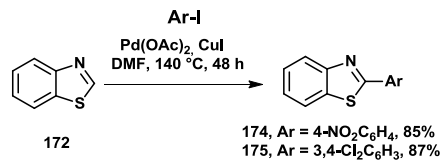
2.16 Benzothiazole

Similar conditions were applied by Muira's group to achieve direct arylation of benzothiazole **172** with iodobenzene[108]. Thus, the coupling reaction between benzothiazole **172** (1 mmol) and iodobenzene (2 equiv.) in the presence of CuI (1 equiv.), PPh_3 (0.2 equiv.), and K_3PO_4 (2 equiv.) in DMSO for 2 h gave the expected 2-phenylbenzothiazole **173** in 63% yield (Scheme 97).



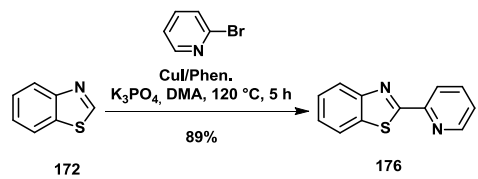
Scheme 97. Copper-mediated direct arylation of benzothiazole **172** with iodobenzene.

Rossi's group demonstrated the adaptability of reaction conditions initially developed for benzimidazole to the direct arylation of benzothiazole **172**[48] . In fact, under these conditions [$Pd(OAc)_2$ and CuI as catalysts in DMF at 140 °C for 48 h], the desired products **174** and **175** were isolated in 85 and 87% yields, respectively (Scheme 98).



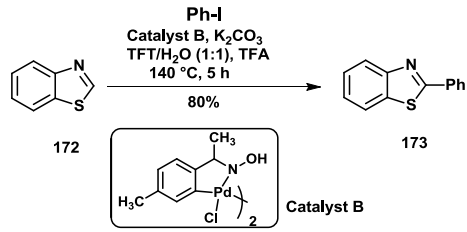
Scheme 98. Cu(I)-catalyzed arylation of benzothiazole **172**.

An example of benzothiazole direct arylation using 2-bromopyridine as arylating agent was reported by Daugulis[99] et al. The reaction was carried out using **172** and 2-bromopyridine in the presence of 10 mol% of CuI/phenanthroline as catalytic system and K_3PO_4 as base in DMF. The reaction mixture was heated at 120 °C for 5 h which afforded C2-phenylated product **176** in 89% isolated yield (Scheme 99).



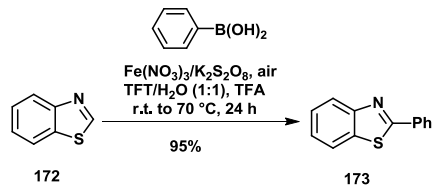
Scheme 99. Arylation of benzothiazole **172** with 2-bromopyridine.

Ding et al. reported a phosphine free direct arylation of benzothiazole **172**[110]. The reaction was carried out using oxime-derived palladacycle **B** as caralyst and iodobenzene in the presence of K_2CO_3 in DMA at 140 °C for 24 h. The arylated product **173** was isolated in 80% yield (Scheme 100).



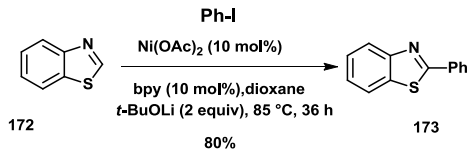
Scheme 100. Direct arylation of benzothiazole **172**.

Maiti et al. reported an iron-catalyzed direct arylation of benzothiazole **172** using boronic acids as arylating agents[111]. The reaction was conducted using $Fe(NO_3)_3$ (20 mol%), $K_2S_2O_8$ (4 equiv.), TFA (2 equiv.) in a mixture of TFT/H_2O (1:1) (Scheme 101). The expected product **173** was obtained in 95% yield. The same procedure was successfully applied to achieve C-H arylation of other heterocyclic systems such as quinoxaline and quinolines.



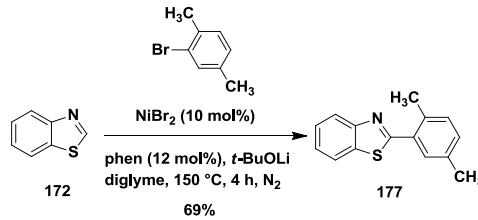
Scheme 101. Iron-catalyzed direct arylation of benzothiazole **172**.

In 2009, Itami and co-workers developed nickel-catalyzed direct C–H arylation of benzothiazole with aryl bromides, aryl iodides, aryl chlorides and aryl triflates (Scheme 72)[112]. For example, in the presence of a catalytic amount of $Ni(OAc)_2$, 2,2'-bipyridine (bpy) and LiOtBu in dioxane, stating material **172** was coupled with iodobenzene to afford regioselectively C2 arylated product **173** in 80% yield (Scheme 102).



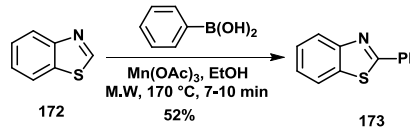
Scheme 102. $Ni(OAc)_2$/bipy-catalyzed arylation of benzothiazole **172** with iodobenzene.

At almost the same time, Miura et al. reported the regioselective nickel-catalyzed arylation of benzothiazole **172**[113]. For example, benzothiazole **172** reacted with 1-bromo-2,5-dimethylbenzene in the presence of a catalytic amount of nickel(II) bromide complex ($NiBr_2$), 1,10-phenanthroline, and *t*-BuOLi afforded the corresponding coupling product **177** in 69% yield (Scheme 103). It is noticed that the use of 1,10-phenanthroline produced better results than 2,9-dimethyl-1,10-phenanthroline (dmphen) and the use of zinc powder as additive was not required.



Scheme 103. Nickel-catalyzed direct arylation of benzothiazole **172** with 1-bromo-2,5-dimethylbenzene.

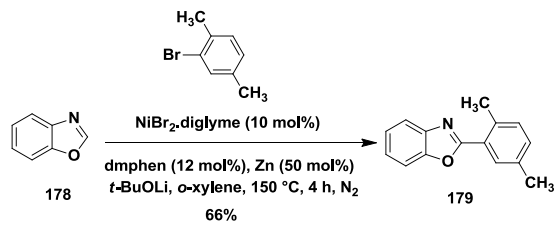
Guchhait and co-workers applied the direct arylation conditions developed for benzofuran to C2-arylation of benzothiazole **172** with phenylboronic acid as arylating agent (Scheme 104)[97]. The reaction was conducted in the presence of $Mn(OAc)_3$ as catalyst under microwave irradiation in EtOH at 170 °C which provided C2 arylated benzothiazole **173** in 52% yield (Scheme 104).



Scheme 104. C2-direct arylation of benzothiazole **170** with phenylboronic acid.

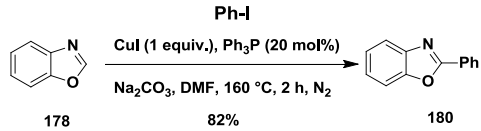
2.17 Benzoxazole

The same group applied the optimized reaction conditions for C2-arylation of benzoxazole **178**[113]. In a demonstrative example, the reaction of benzoxazole **178** with 1-bromo-2,5-dimethylbenzene carried out in the presence of nickel(II) bromide–diglyme complex ($NiBr_2$.diglyme) as catalyst, 2,9-dimethyl-1,10-phenanthroline (dmphen) as ligand, zinc powder and *t*-BuOLi in *o*-xylene at 160 °C gave C2 arylated product **179** in 66% yield (Scheme 105).



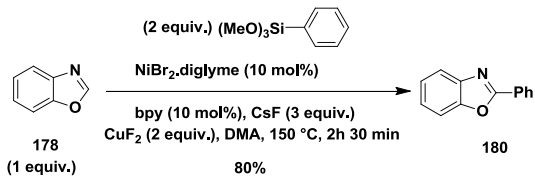
Scheme 105. Nickel-Catalyzed direct arylation of benzoxazole **178** with 1-bromo-2,5-dimethylbenzene.

Benzoxazole **178** was also coupled with iodobenzene using the appropriate choice of catalyst, ligand, base and solvent (CuI, Ph_3P, Na_2CO_3, DMF at 160 °C for 2 h under N_2][108]. Under these conditions, the desired 2-phenylbenzoxazole **180** was isolated in good yield (82 %, Scheme 106).



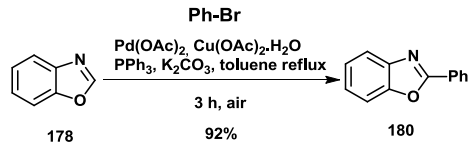
Scheme 106. Copper-catalyzed direct carbon–hydrogen bond arylation of benzoxazole **178**.

Recently, Miura and co-workers synthesized a wide variety of C2 arylated benzoxazole via a novel nickel-catalyzed C–H/C–Si(OMe)$_3$ cross-coupling reaction[114]. After an extensive screening of various reaction parameters, the treatment of benzoxazole **178** with trimethoxyphenylsilane in the presence of NiBr$_2$.diglyme/2,2'-bipyridine (bpy) enabled direct coupling with the aid of a combination of CsF and CuF$_2$ in DMA (Scheme 107). The result showed a good product yield of the expected 2-phenylbenzoxazole **180** (80 %).



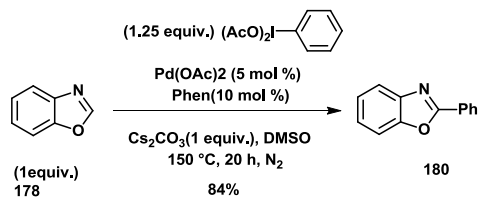
Scheme 107. Nickel-catalyzed direct C-H arylation of benzoxazole **178** with trimethoxyphenylsilane.

Huang et al. reported direct arylation of benzoxazole using Pd(OAc)$_2$/Cu(II)/PPh$_3$ as a cocatalyst system[115]. The treatment of benzoxazole **178** and bromobenzene with a very low catalytic amount of Pd(OAc)$_2$ (1 mol%) and a catalytic amount of PPh$_3$ (20 mol%) in the presence of K$_2$CO$_3$ in refluxing toluene led to expected product **180** in 92% yield (Scheme 108).



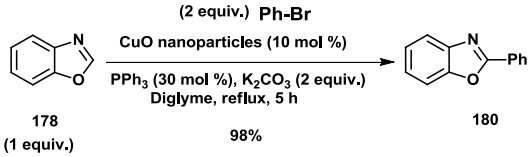
Scheme 108. Direct arylation of benzoxazole **178**.

In 2012, Cheng and co-workers developed a Pd-catalyzed direct C2-arylation of benzoxazole **178** using iodobenzene diacetate as arylation agent[116]. The method (Scheme 109) which involved the treatment of **178** with 1.25 equiv. of iodobenzene diacetates in DMSO at 150 °C for 24 h in the presence of 5 mol% Pd(OAc)$_2$, provided 2-aryl-1*H*-pyrroles **180** in 84% yield. The procedure tolerateed a series of functional groups such as methoxy, nitro, cyano, chloro, and bromo groups.



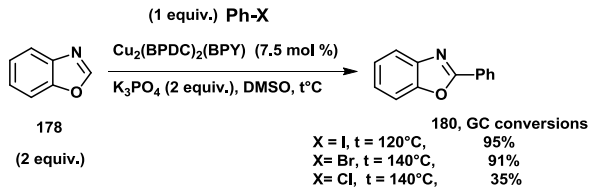
Scheme 109. Pd-catalyzed direct arylation of benzoxazole **178** with iodobenzene diacetates.

Very recently, Wang et al. reported C-H arylation of benzoxazole **178** with bromobenzene using CuO nano particles as catalyst[117]. The reaction was conducted using 10 mol % of CuO nanoparticles, PPh_3 (30 mol %), K_2CO_3 (2 equiv.) in diglyme at reflux for 5 h (Scheme 110). The expected product **180** was obtained in 98% yield. The same procedure was successfully applied to achieve C-H arylation of other heterocyclic systems such as benzothiazole and benzimidazole.



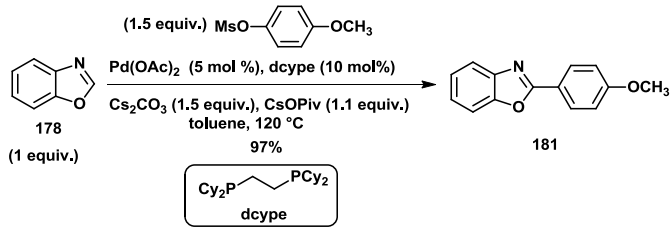
Scheme 110. Nano CuO-catalyzed direct C-H arylation of benzoxazole **178** with bromobenzene.

In the same year, Phan and co-workers published ligand-free direct C2-arylation of benzoxazole **178** with aryl halides in DMSO as solvent in the presence of K_3PO_4 as base and a heterogeneous catalyst $Cu_2(BPDC)_2(BPY)$. This reactions conditions provided 2-phenylbenzoxazole **180** in moderate to good conversion (Scheme 111)[118]. Reaction conditions similar to those illustrated in Scheme 111 were successfully employed by Phan and co-workers for direct C2-arylation of benzothiazole and *N*-methylbenzimidazole.



Scheme 111. $Cu_2(BPDC)_2(BPY)$-catalyzed C-H arylation of benzoxazole **178** with aryl halide.

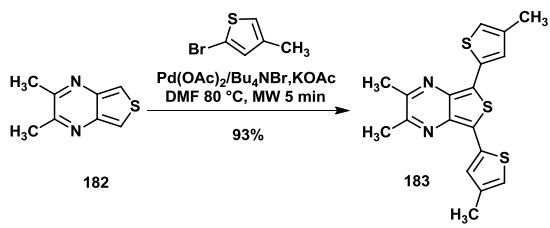
Very recently, Kalyani and co-workers reported the development of Pd-catalyzed direct arylation of benzoxazole **178** using mesylates as arylating agents[119]. They discovered that the reaction between electron-rich mesylate (1.5 equiv. and 1 equiv.) and benzoxazole **178** in toluene at 120 °C in the presence of 1.5 equiv. of Cs_2CO_3, 1.1 equiv. of CsOPiv, 5 mol% $Pd(OAc)_2$ and 10 mol% of dcype, gave 2-arylbenzoxazole **181** in 97% yield (scheme 112). Furthermore, the authors describe a sequential mesylation/arylation protocol using phenols as substrates in very good yields. The same procedure was also applied to intermolecular arylation of benzothiophene and intramolecular arylation of indole using mesylates under optimum C-H arylation conditions.



Scheme 112. Pd-catalyzed C-H arylation of benzoxazole **178** with mesylates.

2.18 Thieno[3,4-*b*]pyrazine

Abdo et al[120] reported an interesting synthesis of oligomeric and polymeric materials using C-H activation as a key step. In a representative example, thieno[3,4-*b*]pyrazine **182** was treated by $Pd(OAc)_2$, Bu_4NBr and KOAc in DMF at 80 °C for 5 min under microwave irradiation. These reaction conditions led to diarylated thieno[3,4-*b*]pyrazine **183** in 93% isolated yield (Scheme 113).

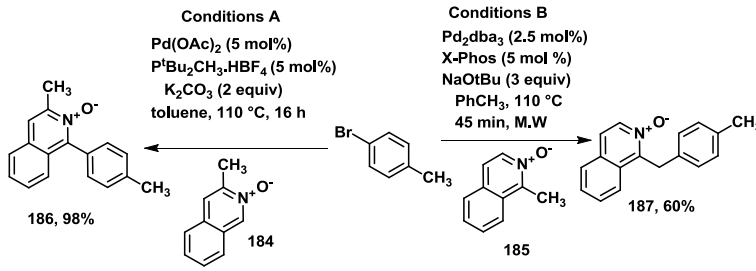


Scheme 113. . Pd-catalyzed C3-arylation of **182**.

3. Direct arylation of 6,6-fused-heterocyclic systems

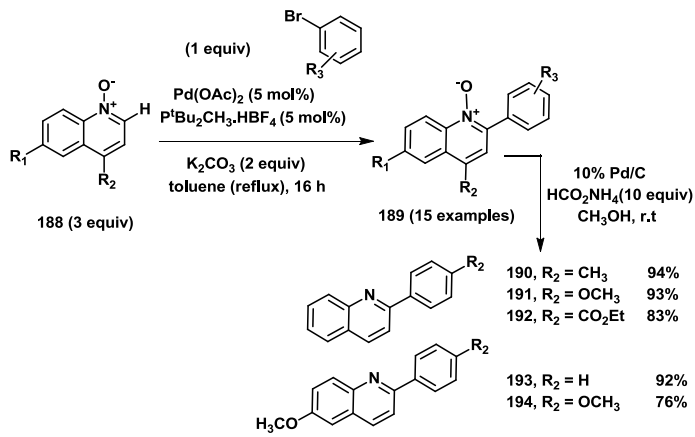
3.1 Quinoline and isoquinoline

In 2008, Fagnou and co-workers made the highly important discovery that the *N*-oxide group imparts a dramatic increase in reactivity in direct palladium-catalysed arylation at either sp^3 or sp^2 C-H bonds of 1-methyl and 3-methyl-isoquinoline[121]. Thus, under conditions A (Scheme 114), high yield of sp^2-arylation at C1 of 3-methyl-isoquinoline-*N*-oxide **184** was achieved. Also, under conditions B, good yield of benzylic sp^3-arylation of 1-methyl-isoquinoline-*N*-oxide **185** under microwave irradiation was obtained. This methodology was validated in both divergent sp^2/sp^3 arylation (Scheme 114).



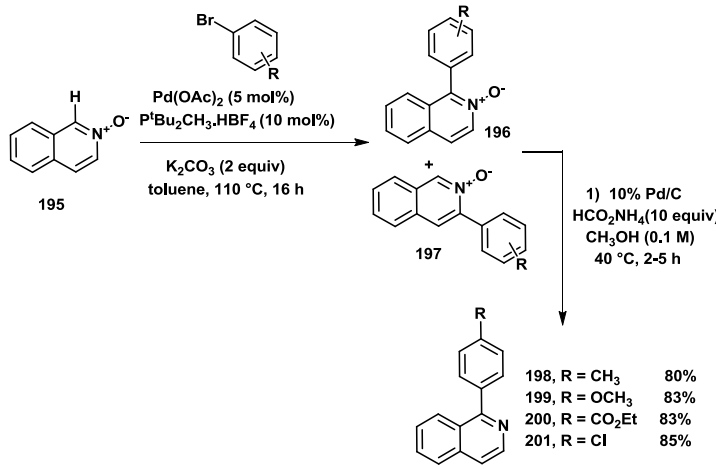
Scheme 114. Divergent sp^2/sp^3 direct arylation of **184** and **185**.

In 2009, the direct arylation of quinoline *N*-oxide compounds was described by the same group[122] employing 3 equivalents of quinoline *N*-oxide **188** in conjunction with an aryl bromide as coupling partner. Thus, 5 mol% of $Pd(OAc)_2$, 5 mol% of $P^tBu_3.HBF_4$ and 2 equivalents of K_2CO_3 were used in refluxing toluene. Under these conditions, the corresponding 2-arylquinoline *N*-oxides **189** was obtained in good to excellent yields. 2-arylquinoline *N*-oxides can be readily reduced to the corresponding 2-arylquinoline **190**-**194** by Pd/C with ammonium formate. Reactions of deoxygenation, achieved at room temperature, proceed in relatively short reaction times, and provided the products **190**-**194** in good to excellent yields (Scheme 115).



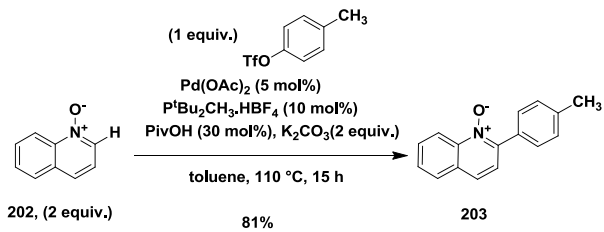
Scheme 115. Direct arylation of quinoline *N*-oxide and illustrative example of *N*-oxide deoxygenation.

The same group investigated the site-selective isoquinoline arylation at the azine ring via *N*-oxide activation[122] and reported that subjecting isoquinoline *N*-oxide **195** to a $Pd(OAc)_2/P^tBu_3.HBF_4$, catalyst system enabled the regioselective direct arylation of the azine ring with aryl bromides. These conditions provided regioisomeric products **196** and **197** in satisfactory to good yields. Isomers **196** and **197** were inseparable by silica gel flash chromatography (Scheme 116). For this reason, the mixtures of these products were subjected to two-pot process of arylation and deoxygenation reactions prior to the separation of the isomers. Following this way, the compounds **198**-**201** were isolated in good overall yields (Scheme 116).



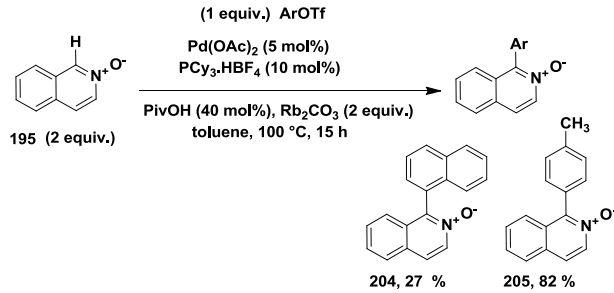
Scheme 116. Direct arylation of isoquinoline *N*-oxide **195** with aryl bromides.

Almost at the same time, C2-selective arylation of quinoline *N*-oxide **202** was achieved using *p*-toluene triflate as coupling partner (Scheme 117). The reaction was carried out using $Pd(OAc)_2/P^tBu_2CH_3.HBF_4$ as a catalytic system in the presence of K_2CO_3 as a base[123]. The reaction mixture was stirred for 15 h at 110 °C to give the desired coupling product **203** in 81% yield.



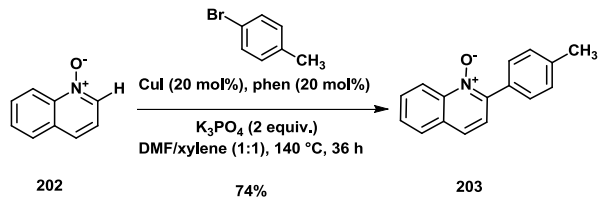
Scheme 117. Direct arylation of quinoline *N*-oxide **202** with *p*-toluene triflate.

To achieve C1 regioselective arylation, authors employed $Pd(OAc)_2/PCy_3.HBF_4$ as the catalytic system in the presence of Rb_2CO_3 as base and PivOH as additive in toluene at 100 °C. Using either tolyl triflate or naphtyl triflate as arylating agents, the C1-regioselective arylation of isoquinoline *N*-oxide **195** led to two final products **204** and **205** which were obtained in 27% and 82% yields, respectively (Scheme 118).



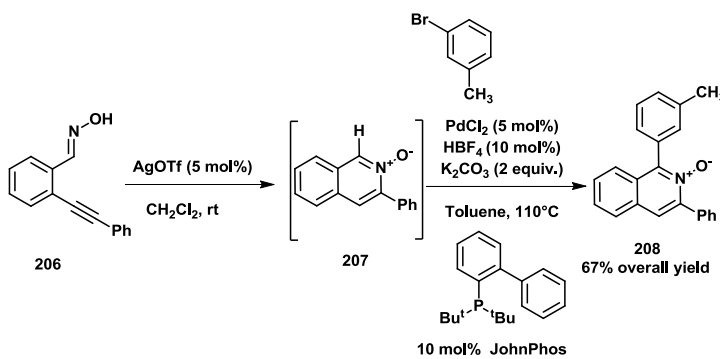
Scheme 118. Direct arylation of isoquinoline *N*-oxide **195** with aryl triflate.

In another report, quinoline *N*-oxide **202** arylation with aryl bromide was developed by You and co-workers[124]. Reaction was carried out using CuI (20 mol%), 1,10-phenanthroline (20 mol%), K_3PO_4 (2.0 equiv.), quinoline *N*-oxide (1.0 equiv.) and aryl bromides (1.5 equiv.) in a mixture of DMF/xylene at 140 °C for 36 h. These conditions afforded the desired product **203** in 74% yield (Scheme 119).



Scheme 119. Catalytic C2-arylation of quinoline *N*-oxide **202** with *p*-toluene bromide.

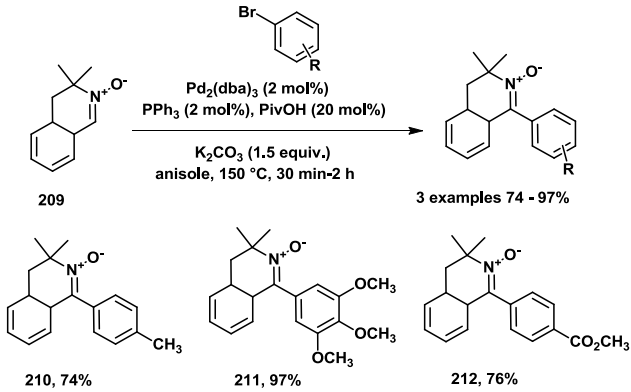
Very recently, Peng and co-workers reported a rapid synthesis of 1,3-disubstituted isoquinoline *N*-oxide **208** using a one-pot cyclization/direct arylation coupling[125]. Employing optimum reaction conditions that are: a toluene solution of 2-alkynylbenzaldoximes **206** (0.6 mmol), AgOTf (5 mol %), 2-phenylisoquinoline *N*-oxide **207** and 3-bromotoluene as coupling partners in the presence of $PdCl_2$ (5 mol %), JohnPhos (10 mol %), HBF_4 (10 mol %) and K_2CO_3 (2.0 equiv.) in toluene at 110 °C. Under these conditions, the desired coupling product **208** was obtained in 67 % overall yield (Scheme 120).



Scheme 120. One-pot two-step cyclization/arylation reactions of oxime **206** and aryl bromide.

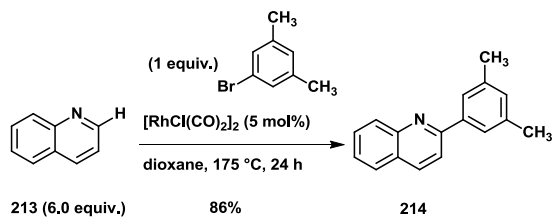
Additional approach toward the direct arylation of activated cyclic nitrones **209**

was reported by Blandin and co-workers using $Pd_2(dba)_3$ as catalyst and pivalic acid as cocatalys[126]. Again, direct arylation was found to occur exclusively at the C1 position of cyclic nitrone. Treatement of **209** with diferent aryl brimides led to compounds **210**-**212** in 74 to 97% isolated yields (Scheme 121).



Scheme 121. Direct arylation of nitrone **209** with aryl bromide.

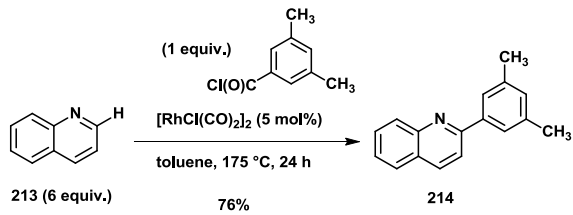
Recently, Bergman and Ellman's groups developed a Rh(I)-catalyzed strategy for the direct C2-arylation of quinoline derivatives. Extensive screening of catalysts and reaction conditions led to the discovery that, while electron-rich rhodium(I) catalysts were inefficient, the electron-deficient $[Rh(CO)_2Cl]_2$ in the absence of other ancillary ligands was a good precatalyst for C2 selective direct arylation of quinolines with bromoarenes (Scheme 122)[127]. The use of various additives such as phosphines, phosphites, Brønsted or Lewis acid and bases did not result in improved yields and in certain cases completely suppressed the catalytic activity. Under typical reaction conditions, the quinoline **213** (6 equiv.), 3,5-dimethylbromobenzene (1 equiv.), and $[Rh(CO)_2Cl]_2$ (0.05 equiv.) are heated at 190 °C in dioxane for 24 h leading to desired product **214** in a very good yield (86%). The catalyst loading can be reduced to 2 mol% Rh while maintaining good yields by conducting the reaction in neat substrates. Comparable yields were obtained for electron-rich and electron-poor bromoarenes. The reaction was however limited in scope to quinolines substituted at the 2-position. Sterically hindered and/or ortho substituted electrophiles are unreactive, however, meta and para substituted electrophiles were well tolerated. Functional group compatibility was also good (aryl chlorides and fluorides, ketones and ethers).



Scheme 122. Rhodium-catalyzed direct arylation of quinoline **213**.

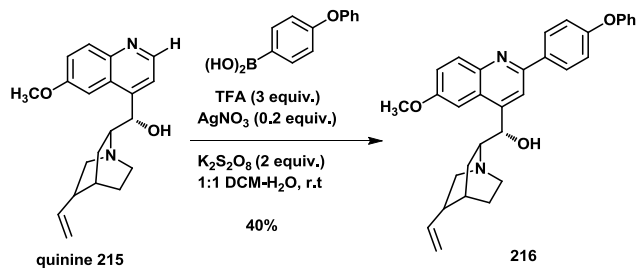
More recently, the same group prepared a variety of 2-aryl-quinolines via Rh(I)-

catalysed C–H arylation[128]. 3,5-dimethylbenzoyl chloride served as an effective quinolone coupling partner to give ortho-arylation product via a decarbonylation pathway. The arylation reaction was conducted using **213** and 3,5-dimethylbenzoyl chloride in the presence of $[RhCl(CO_2)]_2$ as catalyst in toluene at 175 °C for 24 h. These conditions furnished the expected product **214** in high isolated yield (Scheme 123). Electron-rich aroyl chlorides coupled efficiently under these conditions, while the use of electron-poor aroyl chlorides proved to be more challenging. It is noteworthy to mention that, sterically congested 1-naphthoyl and 1-methylbenzoyl chlorides proved to be competent coupling partners.



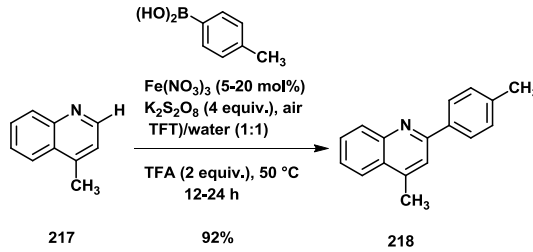
Scheme 123. Direct arylation of quinoline **213** with 3,5-dimethylbenzoyl chloride.

In 2010, Baran et al. reported a general and efficient direct coupling of electron-deficient quinolines, isoquinolines and quinoxalines using arylboronic acids and an inexpensive silver catalyst as also a co-oxidant[129]. The synthetic utility of this method was demonstrated in a highly efficient direct arylation of natural product quinine **215** (Scheme 124). Thus, under ambient conditions, *p*-phenoxyphenylboronic acid was directly coupled to C2 position of **215** which afforded expected compound **216** in 40% isolated yield, avoiding the need of multistep sequences involving protecting groups and prefunctionalization of the heterocyclic system. The same procedure was also successfully applied on other heterocyclic systems such as isoquinolines and quinoxalines using arylboronic acids under optimum C-H arylation condition.



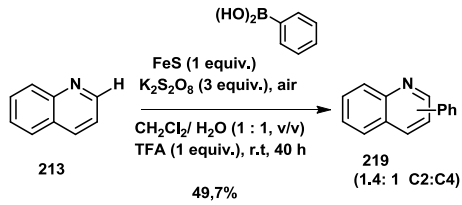
Scheme 124. Direct arylation of quinine **215**.

In the same year, Maiti and co-workers applied the direct arylation conditions developed for benzothiazole to the C2-arylation of 4-methylquinoline **217** using arylboronic acids in the presence of a catalytic amount of inexpensive $Fe(NO_3)_3$ and $K_2S_2O_8$ in a mixture of trifluorotoluene (TFT)/water (1:1) and trifluoroacetic acid (TFA)[111] under ambient air. Under these conditions, C2-arylation of 4-methylquinoline **217** using *p*-toluene boronic acid as coupling partner gave the expected product **218** in 92% yield (scheme 125).



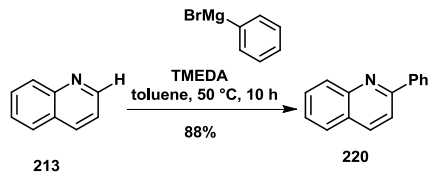
Scheme 125. Arylation of 4-methylquinoline **217** with a *p*-toluene boronic acid.

An example on iron-mediated direct C–H arylation of quinoline **213** with phenylboronic acid was published with the lack of regionselectivity[130]. Only low reaction yield was obtained (49.7%, mixture of regioisomers **219** 1.4: 1 C2:C4) (Scheme 126).



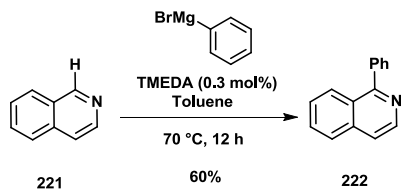
Scheme 126. Arylation of quinoline **213** with a pheny boronic acid.

The intermolecular arylation of quinoline **213** was reported using TMEDA in toluene at 50 °C for 10 h[131]. In this case, ortho arylation of electron-deficient quinoline with inexpensive aryl Grignard reactant afforded the desired arylated product **220** in a very good yield (88%, Scheme 127).



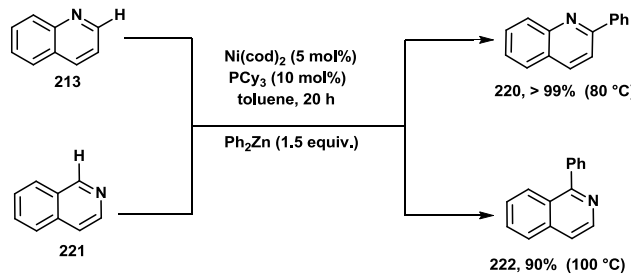
Scheme 127. Phenyl Grignard addition to quinoline **213**.

In continuation of their effort, the authors evaluated the Grignard addition to isoquinoline **221**. The reaction was fully site-specific affording C1-arylation of isoquinoline **221** with aryl Grignard. The highest yield obtained for **222** was 60% when using C_6H_5MgBr as arylating agent (Scheme 128).



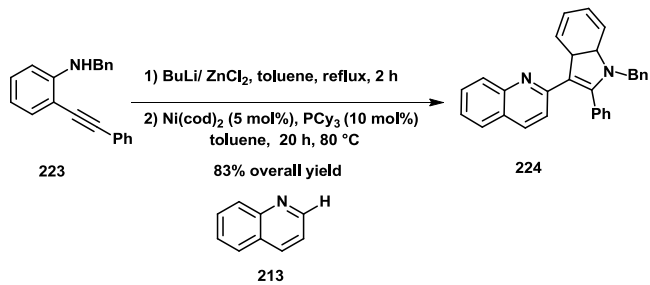
Scheme 128. Phenyl Grignard addition to isoquinoline **221**.

In 2009, Chatani, Tobisu, and co-workers revealed nickel-catalyzed Ar–H/Ar–M coupling of quinoline and isoquinoline[132, 133]. With the use of a diphenylzinc reagent as an aryl nucleophile and $Ni(cod)_2/PCy_3$ as catalyst, quinoline **213** and isoquinoline **221** were regioselectively arylated at C2 and C1, respectively. The desired products **220** and **222** were obtained in 99 and 90% yields, respectively (Scheme 129).



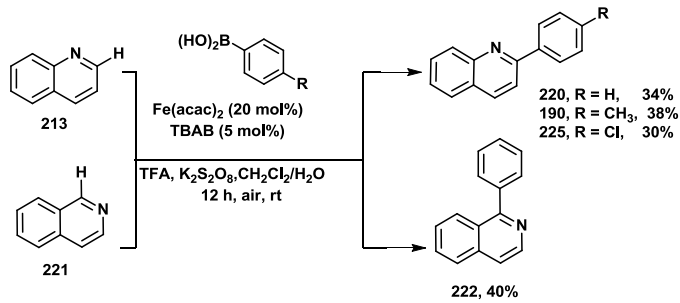
Scheme 129. Nickel-catalyzed direct arylation of quinoline **213** and isoquinoline **221** with diphenylzinc reagent.

After extensive studies, arylzinc reagents proved to be effective aryl donors in *N*i-catalyzed reaction[91]. Thus, treatment of **223** by $BuLi/ZnCl_2$ in refluxing toluene for 2 h followed by a treatment with **213**, $Ni(cod)_2$, PCy_3 in toluene at 80 °C for 20 h afforded the expected product **224** in 83% yield (Scheme 130). Functional groups such as ethers, amines, and chlorides were tolerated under these conditions. Moreover, indolylzinc reagents prepared by Nakamura's procedure[134, 135] could also be employed, further demonstrating the utility of this catalytic arylation.



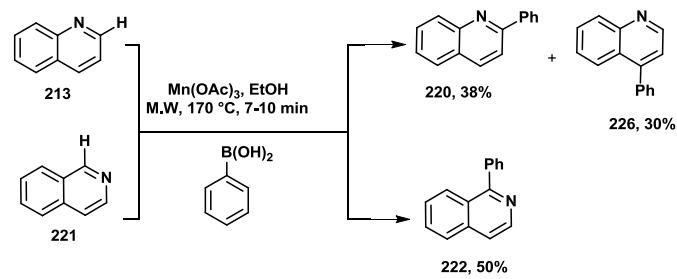
Scheme 130. Nickel-catalyzed direct arylation of quinoline **213** with indolylzinc reagent.

In independent study, Vishwakarma and co-workers reported Fe-catalyzed coupling reaction between quinolone or isoquinoline and arylboronic acids (Scheme 131)[136]. Quinoline **213** treated with phenyl-, *p*-tolyl-, or 4-chlorphenylboronic acids gave products **220**, **190**, and **225** in 34, 38 and 30% yields, respectively. Similarly, isoquinoline **221** under optimized conditions was coupled with phenylboronic acid to give a moderate yield of 40% of monoarylated 1-phenylisoquinoline **222**.



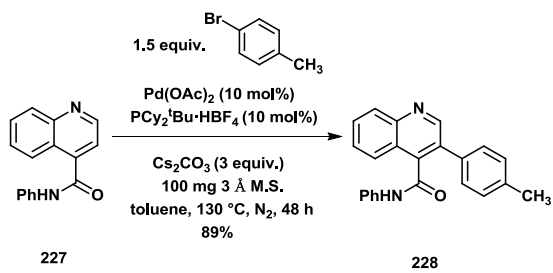
Scheme 131. Fe-catalysed arylation of quinoline **213** and isoquinoline **221** with arylboronic acids.

Guchhait's group demonstrated the adaptability of reaction conditions initially developed for benzofuran and benzothiazole to the direct arylation of quinoline **213** and isoquinoline **221**[48] . With the use of phenylboronic acid as arylation reagent and $Mn(OAc)_3$ as catalyst, quinoline **213** was arylated at both C2 and C4 positions leading to products **220** and **226** in 38 and 30% isolated yields, respectively. Using the same procedure, isoquinoline **221** was regioselectively arylated at C-1 giving compound **222** in 50% yield (Scheme 132)[98].



Scheme 132. Direct C-H arylation of quinoline **213** and isoquinoline **221** with phenylboronic acid.

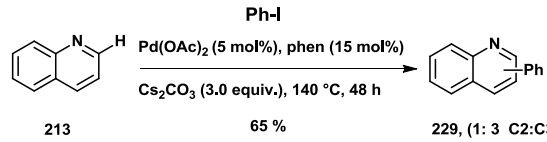
A amide-directed coupling of *p*-bromotoluene with quinoline **227** was recently reported[137]. Reaction optimization demonstrated that the phosphine ligand ($PCy_2tBu{\bullet}HBF_4$) improved the Pd-catalyst activity leading to the best reaction efficiency. Thus, using this catalyst system in the presence of Cs_2CO_3 as base in toluene at 130°C, good yield (89%) was obtained for the C3-arylated product **228** (Scheme 133).



Scheme 133. Arylation of nicotinic derivative **227**.

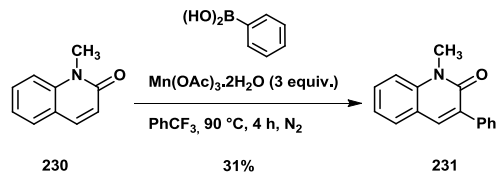
Yu and co-workers described the Pd-catalyzed C-H arylation of quinoline **213** and bromobenzene using 1,10-phenanthroline (15 mol %), $Pd(OAc)_2$ (5 mol %) and

Cs_2CO_3 (3.0 equiv.) for 48 h at 140 °C with the lack of regionselectivity. Thus, a mixture of regioisomers **229** (1:3, C2:C3) was obtained in 65% yield[138, 139] (Scheme 134).



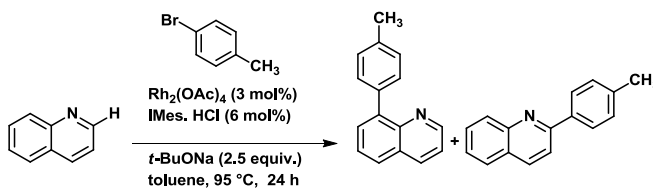
Scheme 134. . Pd-catalyzed coupling of quinoline with iodobenzene.

Very recently, Miura and co-workers developed a Mn(III)-mediated direct C3-arylation of quinolin-2-one with phenylboronic acid (Scheme 135)[140]. The manganese-based reaction occurred regioselectively at the C3 position of the *N*-methyl-quinolin-2-one **230** to furnish the corresponding C3 arylated product **231** in moderate yield.



Scheme 135. Mn(III)-mediated C3-arylation of *N*-methylquinolin-2-one **230** with phenylboronic acid.

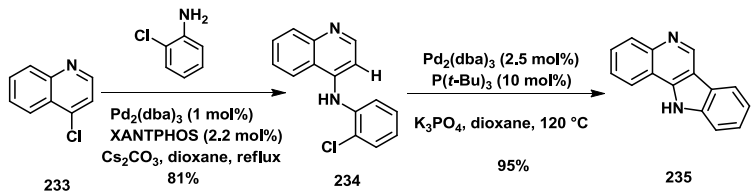
In 2011, Chang and co-workers reported that $Rh_2(OAc)_4$ is a suitable catalyst precursor for the Rh(NHC)-catalyzed C8-arylation of six-membered electron-deficient quinoline **213** with 4-bromotoluene (Scheme 136)[141]. It is noticed that the optimized reaction conditions involved the use of catalytic amount of IMes•HCl as ligand. After the screening various conditions, authors found general conditions with the use of 2 equiv. of quinoline **213**, 1 equiv. of 4-bromoarene, $Rh_2(OAc)_4$ (3 mol%)/ IMes. HCl (6 mol%) and *t*-BuONa (2.5 equiv.) in toluene at 95 °C for 24 h. Under these conditions, the arylated product **232** was obtained with high regioselectivity and good yields (yield of **232** + **190** was determined by ^{1}H NMR using an internal standard and a regioselectivity > 99:1 of **232**/**190** was determined by GC integration).



Scheme 136. Rh(NHC)-catalyzed C8-arylation of quinoline **213**.

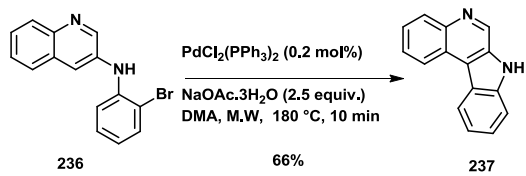
In addition to the intermolecular versions of direct arylation, the entropically favored intramolecular C-H arylation was also extensively explored. For instance, Maes and co-workers published a new method for the synthesis of 11*H*-indolo[3,2-c]quinoline **235** starting from commercially available 4-chloroquinoline **233** and 2-

chloroaniline[142]. The coupling was achieved via two consecutive palladium-catalyzed reactions, a selective Buchwald–Hartwig reaction (chemoselective oxidative addition) leading to intermediate **234** in 81% yield followed by an intramolecular arylation involving C-H activation which afforded **235** in 95% yield (Scheme 137).



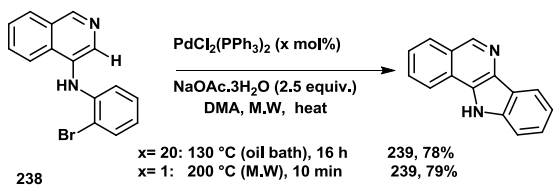
Scheme 137. Synthesis of **235** via consecutive palladium-catalyzed reactions.

The same group utilized a microwave-assisted synthesis in which an intramolecular arylation of 3-(2-bromophenyl)quinolin-3-amine **236** using $PdCl_2(PPh_3)_2$ in DMA at 180 °C for 10 min in the presence of $NaOAc.3H_2O$ led to the facile synthesis of 7H-indolo[2,3-*c*]quinoline **237** in good yield (Scheme 138)[143].



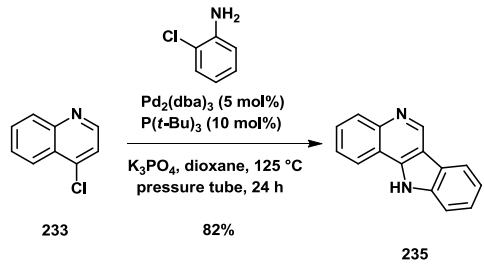
Scheme 138. Microwave-assisted intramolecular arylation of **236**.

Recently, Maes research group reported Pd-catalyzed intramolecular direct arylation of *N*-(2-bromophenyl)isoquinolin-4-amine **238** in the presence of $NaOAc.3H_2O$ in DMA under either conventional heating or microwave irradiation. The synthesis of 11*H*-indolo[3,2-*c*]isoquinolines **239** was achieved in 78% yield, under conventional heating and in 79% yield under microwave irradiation (Scheme 139)[144]. The use of this procedure allowed the facile synthesis of D-ring analogues of isocryptolepine for subsequent SAR screening.



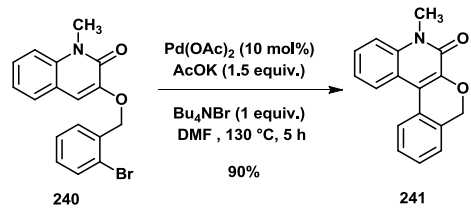
Scheme 139. Synthesis of 11*H*-indolo[3,2-*c*]isoquinoline **239**.

In the same year, an expedient synthesis of D-ring-substituted 11*H*-indolo[3,2-c]quinolines **235** was achieved via an auto tandem consecutive intermolecular Buchwald–Hartwig *N*-arylation and palladium-catalysed arylation of 4-chloroquinoline **233** with *N*-unsubstituted 2-chloroaniline in dioxane at 125 °C. This sequence led to desired product **235** in 82% yield (Scheme 140).



Scheme 140. Synthesis of 11*H*-indolo[3,2-*c*]quinoline **235**.

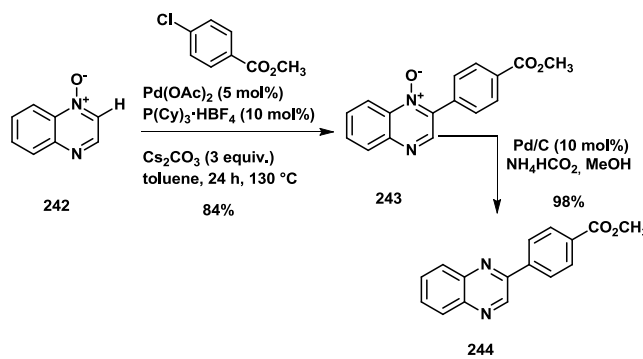
In another interesting report, Majumdar and co-workers employed ligandless intramolecular palladium-catalysed arylation conditions that are : $Pd(OAc)_2$, KOAc, Bu_4NBr, DMF at 130 °C for 5 h for intramolecular arylation of 1-methyl-3-(20-bromobenzyloxy)quinolin-2(1H)-ones **240.** This procedure worked well leading to 5-methyl-5H-[2H]benzopyrano[3,4-c]quinolin-6(8H)-ones **241** in 90% yield (Scheme 141)[145].



Scheme 141. Synthesis of tetracyclic quinolinone **241**.

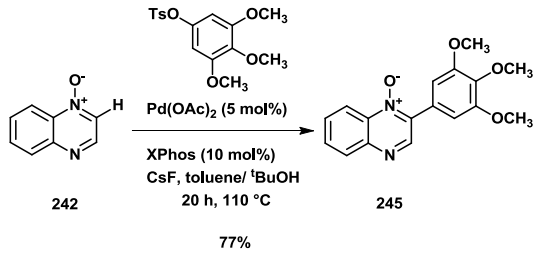
3.2 Quinoxaline

Fagnou and Leclerc,[97] reported the direct and regioselective palladium catalyzed arylation of quinoxaline *N*-oxide using aryl chloride as coupling partner. The reaction was carried out between quinoxaline *N*-oxide **242** and *p*-CO_2CH_3-phenyl chloride in the presence of $Pd(OAc)_2$/ $P(Cy)_3{\cdot}HBF_4$ and Cs_2CO_3 in toluene for 24 h at 130 °C. The expected C2-arylated product **243** was isolated in 84% yield. 2-aryl-quinoxaline *N*-oxide was then reduced to the corresponding 2-aryl-quinoxaline by Pd/C using ammonium formate at room temperature offering the arylated product **244** in a very good yield (Scheme 142).



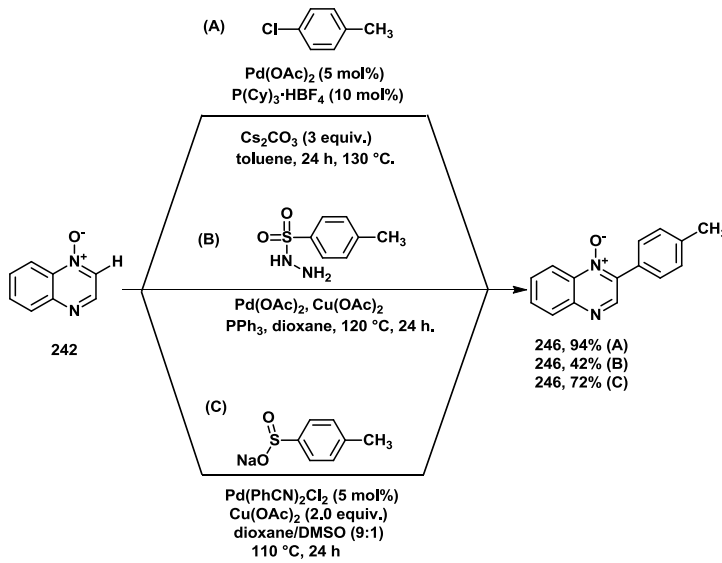
Scheme 142. Synthesis of 2-arylquinazoline **244**.

Recently, Ackermann and Fenner applied a similar arylation method for the C2-arylation of quinoxaline *N*-oxide **242** using 3,4,5-trimethoxybenzene tosylate as coupling partner in the presence of $Pd(OAc)_2$, XPhos and CsF in toluene/tBuOH [146]. In this case, the reaction was carried out at 110 °C for 20 h which formed the desired product **245** in 77% yield (Scheme 143).



Scheme 143. Croos-coupling of quinoxaline *N*-oxide **242** with aryl tosylate.

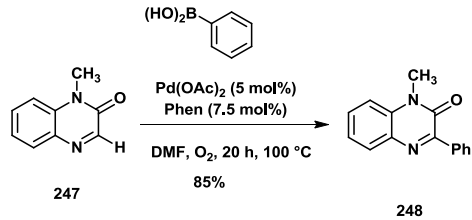
Mono-*N*-oxidized arylquinoxalines can be accessed through the introduction of aryl substituents by metal-catalyzed C–C coupling reactions. The synthetically most useful arylation reactions have been reported for the unsubstituted quinoxaline *N*-oxide **242**, which was coupled with *p*-toluene chloride[87], *p*-tolylsulfonylhydrazide,[147] or even sodium sulfinate,[148] through palladium catalysis. Using either methods A, B or C, expected product **246** was obtained in 94, 42 and 72% yields, respectively (Scheme 144).



Scheme 144. Arylation of unsubstituted quinoxaline *N*-oxide **242**.

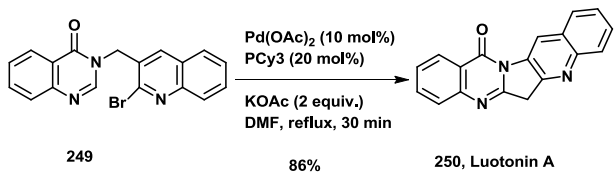
A related palladium-catalyzed intermolecular oxidative arylation approach was also used for the synthesis of 3-aryl-quinoxalin-2(1*H*)-one **248**[149]. The author successfully applied a C-H coupling strategy to starting material **247** involving phenyl boronic acid with catalyst/ligand system ($Pd(OAc)_2$/Phenantroline) in DMF under oxygen which afforded the desired product **248** in 85% yield (Scheme 145). It

is noticed that this protocol is compatible with a wide range of functional groups and allows the construction of various biologically important quinoxalin-2(1*H*)-one backbones (Scheme 145).



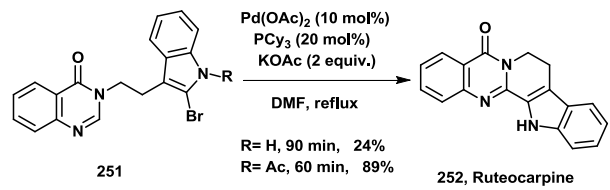
Scheme 145. Synthesis of 3-phenyl quinoxalin-2(1*H*)-one **248**.

Early applications of intramolecular palladium-catalyzed C-H arylation for the synthesis of pyrroloquinazolinoquinoline cytotoxic alkaloid luotonin **250** was published by Harayama research group[150-153]. 3-[(2-Bromoquinol-3-yl)methyl]-4(3H)-quinazolinone **249** was treated with $Pd(OAc)_2/PCy_3$ in DMF under reflux in the presence of KOAc as base to afford luotonin A in 86% yield (Scheme 146)[154].



Scheme 146. Synthesis of Luotonin A **250**.

Harayama and co-workers applied a similar intramolecular C-H coupling for the achievement of a total synthesis of ruteocarpine, an indolopyridoquinazoline alkaloid. The reaction was carried out starting from 3-[2-(*N*-acetyl- 2-bromoindol-3-yl)ethyl]-4(3H)-quinazolinone **251**[150-153] which after treatment with $Pd(OAc)_2$, $P(Cy)_3$, KOAc at refluxing DMF led to desired product **252** in excellent yield (Scheme 147). It is noticed that when R = H, the reaction provided compound **252** in a low (24%).

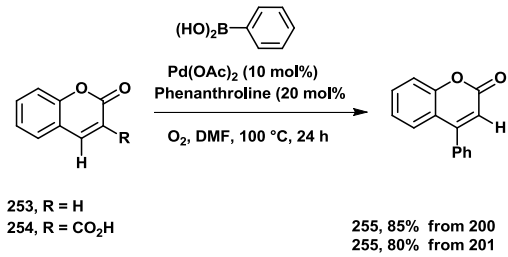


Scheme 147. Synthesis of Ruteocarpine **252**.

3.3 Chromanones and coumarins

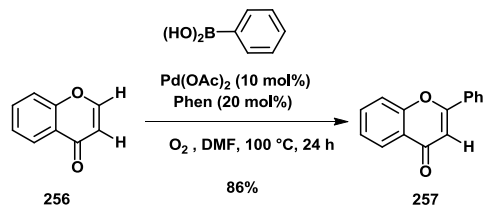
Recently, Jafarpour and co-workers found that C–H arylation reaction of either coumarin **253**[155] or coumarin-3-carboxylic acid **254**[156] with phenyl boronic acid catalyzed by $Pd(OAc)_2$ in the presence of 1,10-phenanthroline as ligand and oxygen as oxidant in DMF at 100°C, provided the desired 4-arylcoumarin product **255** in 85% and 80% yields, respectively (Scheme 148). It is noticed that, C4 arylated product was not detected at all and the reaction proceeded with minimal biphenyl

formation.



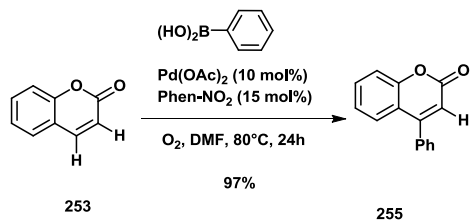
Scheme 148. Pd-catalyzed oxidative arylation of coumarin **253** and coumarin-3-carboxylic acid **254** with phenylboronic acid.

Using the optimized reaction conditions, the authors realized also the Pd-catalyzed direct C2-arylation of chromenone **256** with phenylboronic acid[155]. A final product **257** was obtained in high yield (86%) and excellent regioselectivity (Scheme 149). This protocol is compatible with a wide variety of electron-donating and electron-withdrawing substituents. In contrast, under the optimized reaction conditions, 3-nitrophenylboronic acid was not effective.



Scheme 149. Regioselective C2-arylation of chromenone **256**.

Under reaction conditions similar to those previously used for the synthesis of 4-phenyl-2*H*-chromen-2-one **255**, starting material **253** was transformed to **255**. In his case, phen-NO_2 was used as a ligand instead of 1,10-phenanthroline which afforded the expected compound **255** in 97% yield[157] (Scheme 150).

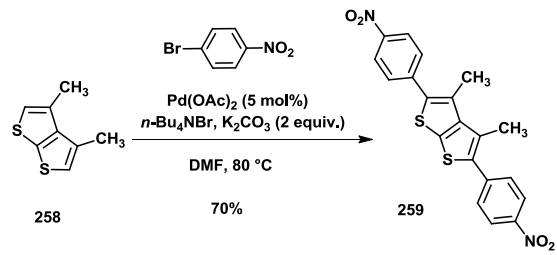


Scheme 150. Synthesis of 4-phenylcoumarins **255**.

4. Direct arylation of 5,5-fused-heterocycles systems

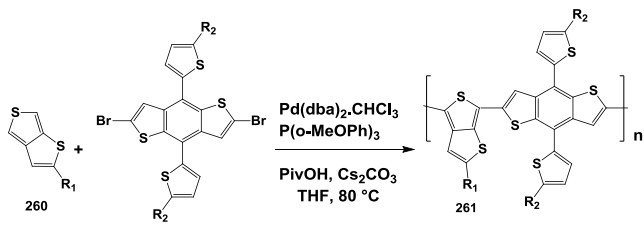
In 2006, Mashraqui and co-workers reported a direct C–H arylation of thieno[2,3-*b*]thiophene **258** with 4-bromonitrobenzene in the presence of catalytic amount of $Pd(OAc)_2$, tetrabutylammonium salt (*n*-Bu_4NBr), a molar excess of K_2CO_3 in DMF

at 80 °C under ligandless conditions. The bis-arylated product **259** was obtained in 70% yield (Scheme 151)[158].



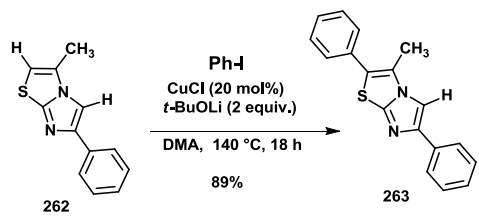
Scheme 151. $Pd(OAc)_2$-catalyzed arylation of **258**.

In 2013, Coughlin and co-workers reported copolymerization with dithienylbenzodithiophene by direct arylation polymerization which afforded novel low bandgap poly(thienothiophene-alt-dithienylbenzodithiophene) (PTB) polymers **261**. Utilizing the activated C−H bonds of the thieno[3,4-b]thiophene **260** monomers and the aryl halide bonds in the dibrominated benzodithiophene monomer, a series of alternating copolymers were synthesized (Scheme 152) via optimized direct arylation polymerization conditions [$Pd_2(dba)_3$·$CHCl_3$ (0.05 mmol), tris(2-methoxyphenyl)phosphine (0.2 mmol), pivalic acid (1 mmol), and Cs_2CO_3 (3 mmol)][159].



Scheme 152. Synthesis of poly(thieno[3,4-b]thiophene-alt-dithienylbenzodithiophene) polymers.

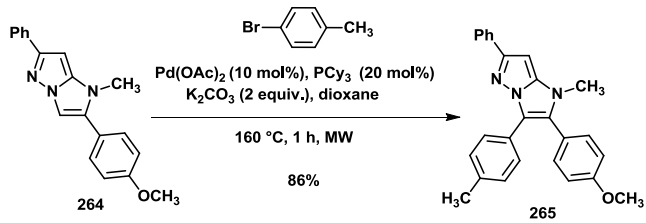
Recently, Jiang and Wang group developed a copper catalyzed C2-arylation of 3-methyl-6-phenylimidazo[2,1-*b*]thiazole **262** with iodobenzene. Using 20 mol% of CuCl as catalyst, *t*BuOLi as base at 140 °C in DMA for 18 h, C2 arylated imidazo[2,1-*b*]thiazole product **263** was obtained in 89% yield[160] (Scheme 153).



Scheme 153. Cu-Catalyzed C2-arylation of Imidazo[2,1-b]thiazole **262**.

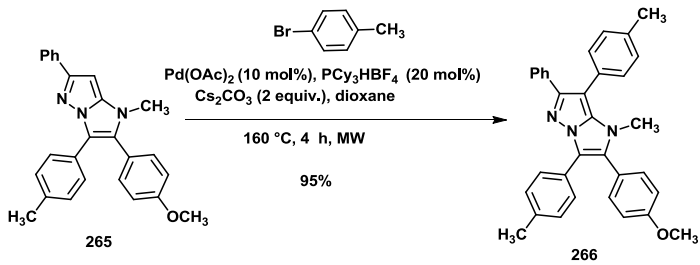
Very recently, one of our collaborators developed an efficient Pd-catalyzed

regioselective arylation at the C3 position of imidazo[1,2-*b*]pyrazoles **264**[161]. Under microwave irradiation, the optimum reaction conditions were found when using $Pd(OAc)_2$ as catalyst, $P(Cy)_3$ as ligand and K_2CO_3 as base in dioxane for 1 h. The desired compound **265** was isolated in 86% yield (Scheme 154).



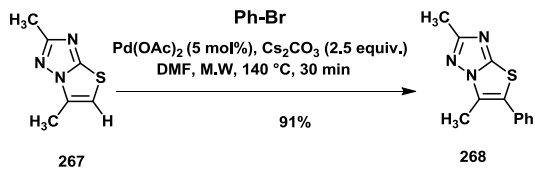
Scheme 154. Pd-catalyzed regioselective C3-arylation of imidazo[1,2-*b*]pyrazole **264**

The same group described a similar synthesis of 2,3,6,7-tetrasubstituted imidazo[1,2-*b*]pyrazole **266** using a microwave-assisted C7-direct arylation of imidazo[1,2-*b*]pyrazole **265**[162]. Thus, under optimum arylation conditions, substrate **265** and 4-bromo-methylbenzene in the presence of $Pd(OAc)_2$, $P(Cy)_3.HBF_4$ and Cs_2CO_3, the desired product **266** was isolated in 95% yield (scheme 155).



Scheme 155. Synthesis of **266** via C7-arylation of imidazo[1,2-*b*]pyrazole **265**.

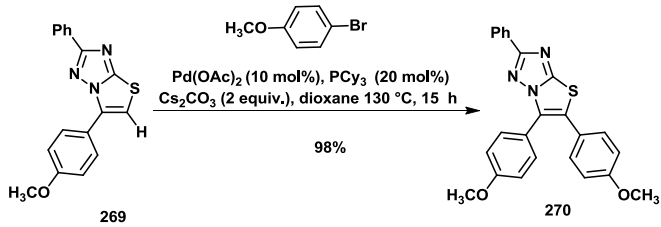
An efficient microwave-assisted Pd-catalyzed direct arylation of thiazolo[3,2-*b*]-1,2,4-triazoles **267** with aryl bromides under ligandless conditions was developed by Wang and collaborators[163]. The phenyl group was introduced at the 5-position using $Pd(OAc)_2$ as catalyst in the presence of Cs_2CO_3 as base under microwave irradiation which led to the desired compound **268** in 91% yield (Scheme 156). This methodology was successfully applied to the synthesis of a variety of substituted thiazolo[3,2-*b*]-1,2,4-triazoles in good yields.



Scheme 156. Microwave-assisted Pd-catalyzed arylation of **267** with bromobenzene.

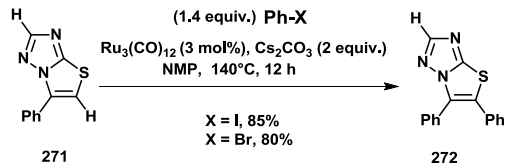
Very recently, one of us and collaborators reported direct C5-arylation of mono and di-substituted thiazolo[3,2-*b*][1,2,4]triazoles[164]. In a representative example, starting material **269** was treated by 4-bromoanisole, $Pd(OAc)_2$, $P(Cy)_3$ and Cs_2CO_3

in dioxane at 130 °C for 15 h (Scheme 157). The C5-arylated product **270** was isolated in very good yield (98%).



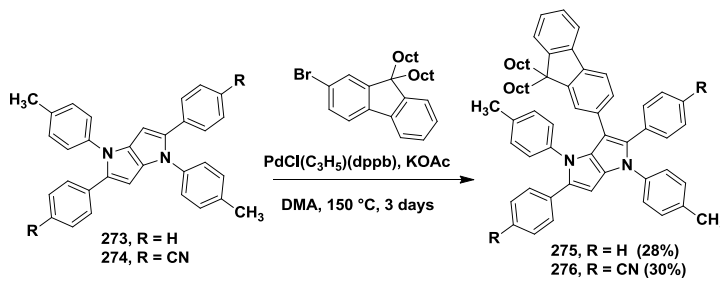
Scheme 157. Direct C5-arylation of thiazolo[3,2-b][1,2,4]triazole **269**.

More recently, Zhang reported that 6-phenylthiazolo[3,2-*b*]-1,2,4-triazole **271** was able to react with phenyl iodide and phenyl bromide in NMP at 140°C in the presence of 2 equiv. of Cs_2CO_3 and 3 mol% $Ru_3(CO)_{12}$ to give arylated derivative **272** in good yields (Scheme 158)[165].



Scheme 158. $Ru_3(CO)_{12}$-catalyzed direct arylation of **271** with iodobenzene.

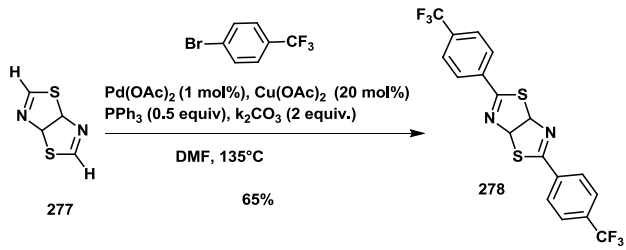
Gryko and co-workers synthesized a wide variety of pentaaryl- and hexaaryl-1,4-dihydropyrrolo[3,2-*b*]pyrroles (Scheme 159)[88]. The result showed moderate product yields of pentaaryl-pyrrolo[3,2-b]pyrroles **275** and **276** prepared from the corresponding tetraaryl-1,4-dihydropyrrolo[3,2-*b*]pyrroles **273** and **274** via direct arylation using 2-bromo-9,9-dioctylfluorene as arylating agent and $PdCl(C_3H_5)(dppb)$ as catalyst in the presence of KOAc in DMA at 150 °C for 3 days. It is noteworthy that in the case of electron-donating bromoarenes, monoarylation products were almost exclusively formed. The bis-arylation emerged when haloarenes with electron-withdrawing substituents were used.



Scheme 159. Direct arylation of pyrrolo[3,2-b]pyrrole **273** and **274**.

In 2014, Blakey and co-workers achieved the arylation of thiazolothiazole by treatment with an excess (4 equiv.) of 1-bromo-4-(trifluoromethyl)benzene in

anhydrous DMF at 135°C in the presence of 1 mol% of $Pd(OAc)_2$, 20 mol% of $Cu(OAc)_2$, 0.5 equiv. of PPh_3 and 2 equiv. of K_2CO_3 (Scheme 160)[166]. The coupling of thiazolothiazole **277** with *p*-trifluoromethylbromobenzene proceeded well, affording the desired product **278** in 65% yield (Scheme 160).



Scheme 160. Direct arylation of thiazolothiazole **277** with *p*-trifluoromethylbromobenzene.

5. Summary and Outlook

The development of new procedures for direct arylation of heterocyclic systems especially 6,5, 6,6 and 5,5 fused-heterocyles containing heteroatoms (N, O, S) has grown considerably during the last two decades. Elegant methods were recently developed which significantly improved the reaction conditions by reducing the amount of the catalyst, recycling the catalyst system, replacing palladium by less expensive catalysts, avoiding in some cases the use of ligands and additives and reducing reaction times using microwave irradiation. As the result, various interesting systems such as indole, azaindole, imidazo[1,2-a]pyridine, imidazo[1,2-a]pyrimidine, imidazo[1,2-a]pyrazine, imidazo[1,2-b]pyridazine, imidazo[1,2-b][1,2,4,5]tetrazine, indolizine, pyrrolo[1,2-a]pyrazine, pyrazolo[1,5-a]pyrimidine, indazole, benzothiadiazole, benzotriazole, benzofuran, benzothiophene, benzimidazole, benzothiazole, benzoxazole, thieno[3,4-b]pyrazine, indolizine-2-carboxylate, thieno[3,4-b]pyrazine, quinoline and derivatives, chromanone, coumarin, quinoxaline, thieno[2,3-*b*]thiophene, imidazo[2,1-b]thiazole, imidazo[1,2-*b*]pyrazole, thiazolo[3,2-b][1,2,4]triazoles among others were efficiently functionalized with less expensive coupling partners and in one single step. Recent efforts have shown that even electron-deficient heteroarenes were able to be arylated using new catalyst/ligand systems. In the most cases, the arylation reactions were achieved via electrophilic aromatic substitution (S_EAr), Heck-like pathway, a concerted metalation–deprotonation (CMD) or via radical pathways. Direct arylation was even applied for the synthesis of new drugs as well as for the achievement of complex heterocyclic systems by intermolecular or intramolecular arylation as well as by peptide or amino acids macrocyclization. Also, polycyclic compounds preparation and total syntheses of alkaloid were achieved using direct arylation reactions as key steps. In addition, the C-H activation was successfully applied for copolymerisation leading to novel organic polymers.

References

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1. D. Alberico, M. E. Scott and M. Lautens, *Chem. Rev.*, 2007, **107**, 174.
2. T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147.
3. I. V. Seregin and V. Gevorgyan, *Chem. Soc. Rev.*, 2007, **36**, 1173.
4. G. P. McGlacken and L. M. Bateman, *Chem. Soc. Rev.*, 2009, **38**, 2447.
5. L. Ackermann, R. Vicente and A. R. Kapdi, *Angew. Chem., Int. Ed.*, 2009, **48**, 9792.
6. J. C. Lewis, R. G. Bergman and J. A. Ellman, *Acc. Chem. Res.*, 2008, **41**, 1013.
7. B. Liegault, I. Petrov, S. I. Gorelsky and K. Fagnou, *J. Org. Chem.*, 2010, **75**, 1047.
8. A. Sharma, D. Vacchani and E. Van der Eycken, *Chem. Eur. J.*, 2013, **19**, 1158.
9. B. Liegault, D. Lapointe, L. Caron, A. Vlassova and K. Fagnou, *J. Org. Chem.*, 2009, **74**, 1826.
10. L. Joucla and L. Djakovitch, *Adv. Synth. Catal.*, 2009, **351**, 673.
11. F. Jafarpour and P. T. Ashtiani, *J. Org. Chem.*, 2009, **74**, 1364.
12. B. S. Lane, M. A. Brown and D. Sames, *J. Am. Chem. Soc.*, 2005, **127**, 8050.
13. Z. Zhang, Z. Hu, Z. Yu, P. Lei, H. Chi, Y. Wang and R. He, *Tetrahedron Lett.*, 2007, **48**, 2415.
14. R. J. Phipps, N. P. Grimster and M. J. Gaunt, *J. Am. Chem. Soc.*, 2008, **130**, 8172.
15. F. Bellina, F. Benelli and R. Rossi, *J. Org. Chem.*, 2008, **73**, 5529.
16. J. Cornella, P. Lu and I. Larrosa, *Org. Lett.*, 2009, **11**, 5506.
17. L. Ackermann and S. Barfuesser, *Synlett*, 2009, 808.
18. L. Joucla, N. Batail and L. Djakovitch, *Adv. Synth. Catal.*, 2010, **352**, 2929.
19. Y. Chen, S. Guo, K. Li, J. Qu, H. Yuan, Q. Hua and B. Chen, *Adv. Synth. Catal.*, 2013, **355**, 711.
20. G. Cusati and L. Djakovitch, *Tetrahedron Lett.*, 2008, **49**, 2499.
21. L. Djakovitch, P. Rouge and R. Zaidi, *Catal. Comm.*, 2007, **8**, 1561.
22. M. A. Rasouli, M. Mandavi, L. Firoozpour, A. Shafiee and A. Foroumadi, *Tetrahedron*, 2014, **70**, 3931.
23. Y. Akita, Y. Itagaki, S. Takizawa and A. Ohta, *Chem. Pharm. Bull.*, 1989, **37**, 1477.
24. Y. Akita, A. Inoue, K. Yamamoto, A. Ohta, T. Kurihara and M. Shimizu, *Heterocycles*, 1985, **23**, 2327.
25. B. S. Lane and D. Sames, *Org. Lett.*, 2004, **6**, 2897.
26. X. Wang, B. S. Lane and D. Sames, *J. Am. Chem. Soc.*, 2005, **127**, 4996.
27. B. B. Toure, B. S. Lane and D. Sames, *Org. Lett.*, 2006, **8**, 1979.
28. S. Yanagisawa and K. Itami, *Tetrahedron*, 2011, **67**, 4425.
29. M.-Z. Lu, P. Lu, Y.-H. Xu and T.-P. Loh, *Org. Lett.*, 2014, **16**, 2614.
30. J. Zheng, Y. Zhang and S. Cui, *Org. Lett.*, 2014, **16**, 3560.
31. X. Wang, D. V. Gribkov and D. Sames, *J. Org. Chem.*, 2007, **72**, 1476.
32. J. Zhou, P. Hu, M. Zhang, S. Huang, M. Wang and W. Su, *Chem. Eur. J.*, 2010, **16**, 5876.
33. E. T. Nadres, A. Lazareva and O. Daugulis, *J. Org. Chem.*, 2011, **76**, 471.
34. J. Ruiz-Rodriguez, F. Albericio and R. Lavilla, *Chem. Eur. J.*, 2010, **16**, 1124.
35. X.-Q. Chu, Y. Zi, X.-M. Lu, S.-Y. Wang and S.-J. Ji, *Tetrahedron*, 2014, **70**, 232.
36. H. Dong, C. Limberakis, S. Liras, D. Price and K. James, *Chem. Comm.*, 2012, **48**, 11644.
37. T. Miao, P. Li, G.-W. Wang and L. Wang, *Chem. Asian J.*, 2013, **8**, 3185.
38. S. Islam and I. Larrosa, *Chem. Eur. J.*, 2013, **19**, 15093.
39. G.-p. Lu and C. Cai, *Synlett*, 2012, 2992.
40. M. Wu, J. Luo, F. Xiao, S. Zhang, G.-J. Deng and H.-A. Luo, *Adv. Synth. Catal.*, 2012, **354**, 335.
41. Y. Huang, Z. Lin and R. Cao, *Chem. Eur. J.*, 2011, **17**, 12706.
42. L. Wang, W.-b. Yi and C. Cai, *Chem. Comm.*, 2011, **47**, 806.
43. Z. Liang, B. Yao and Y. Zhang, *Org. Lett.*, 2010, **12**, 3185.
44. J. Zhao, Y. Zhang and K. Cheng, *J. Org. Chem.*, 2008, **73**, 7428.

45. N. Lebrasseur and I. Larrosa, *J. Am. Chem. Soc.*, 2008, **130**, 2926.
46. S. Kirchberg, R. Froehlich and A. Studer, *Angew. Chem., Int. Ed.*, 2009, **48**, 4235.
47. S.-D. Yang, C.-L. Sun, Z. Fang, B.-H. Li, Y.-Z. Li and Z.-J. Shi, *Angew. Chem., Int. Ed.*, 2008, **47**, 1473.
48. F. Bellina, C. Calandri, S. Cauteruccio and R. Rossi, *Tetrahedron*, 2007, **63**, 1970.
49. F. Bellina, S. Cauteruccio and R. Rossi, *Eur. J. Org. Chem.*, 2006, 1379.
50. N. R. Deprez, D. Kalyani, A. Krause and M. S. Sanford, *J. Am. Chem. Soc.*, 2006, **128**, 4972.
51. M. P. Huestis and K. Fagnou, *Org. Lett.* 2009, **11**, 1357.
52. P. Kannaboina, K. Anilkumar, S. Aravinda, R. A. Vishwakarma and P. Das, *Org. Lett.* 2013, **15**, 5718.
53. J. Koubachi, S. El Kazzouli, M. Bousmina and G. Guillaumet, *Eur. J. Org. Chem.*, 2014, 5119.
54. J. Koubachi, S. El Kazzouli, S. Berteina-Raboin, A. Mouaddib and G. Guillaumet, *Synlett*, 2006, 3237.
55. J. Koubachi, S. El Kazzouli, S. Berteina-Raboin, A. Mouaddib and G. Guillaumet, *J. Org. Chem.*, 2007, **72**, 7650.
56. Y. Wang, B. Frett and H.-y. Li, *Org. Lett.*, 2014, **16**, 3016.
57. I. Bassoude, S. Berteina-Raboin, S. Massip, J.-M. Leger, C. Jarry, E. M. Essassi and G. Guillaumet, *Eur. J. Org. Chem.*, 2012, 2572.
58. S. Marhadour, P. Marchand, F. Pagniez, M.-A. Bazin, C. Picot, O. Lozach, S. Ruchaud, M. Antoine, L. Meijer, N. Rachidi and P. Le Pape, *Eur. J. Med. Chem.*, 2012, **58**, 543.
59. A. C. Humphries, E. Gancia, M. T. Gilligan, S. Goodacre, D. Hallett, K. J. Merchant and S. R. Thomas, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 1518.
60. P. S. Humphries, J. V. Almaden, S. J. Barnum, T. J. Carlson, Q.-Q. T. Do, J. D. Fraser, M. Hess, Y. H. Kim, K. M. Ogilvie and S. Sun, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 6116.
61. P. S. Humphries, S. Bailey, J. V. Almaden, S. J. Barnum, T. J. Carlson, L. C. Christie, Q.-Q. T. Do, J. D. Fraser, M. Hess, J. Kellum, Y. H. Kim, G. A. McClellan, K. M. Ogilvie, B. H. Simmons, D. Skalitzky, S. Sun, D. Wilhite and L. R. Zehnder, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 6120.
62. S. C. Goodacre, L. J. Street, D. J. Hallett, J. M. Crawforth, S. Kelly, A. P. Owens, W. P. Blackaby, R. T. Lewis, J. Stanley, A. J. Smith, P. Ferris, B. Sohal, S. M. Cook, A. Pike, N. Brown, K. A. Wafford, G. Marshall, J. L. Castro and J. R. Atack, *J. Med. Chem.*, 2006, **49**, 35.
63. M. G. N. Russell, R. W. Carling, L. J. Street, D. J. Hallett, S. Goodacre, E. Mezzogori, M. Reader, S. M. Cook, F. A. Bromidge, R. Newman, A. J. Smith, K. A. Wafford, G. R. Marshall, D. S. Reynolds, R. Dias, P. Ferris, J. Stanley, R. Lincoln, S. J. Tye, W. F. A. Sheppard, B. Sohal, A. Pike, M. Dominguez, J. R. Atack and J. L. Castro, *J. Med. Chem.*, 2006, **49**, 1235.
64. R. T. Lewis, W. P. Blackaby, T. Blackburn, A. S. R. Jennings, A. Pike, R. A. Wilson, D. J. Hallett, S. M. Cook, P. Ferris, G. R. Marshall, D. S. Reynolds, W. F. A. Sheppard, A. J. Smith, B. Sohal, J. Stanley, S. J. Tye, K. A. Wafford and J. R. Atack, *J. Med. Chem.*, 2006, **49**, 2600.
65. H. Cao, H. Zhan, Y. Lin, X. Lin, Z. Du and H. Jiang, *Org. Lett.*, 2012, **14**, 1688.
66. H. Yang, L. Yang, Y. Li, F. Zhang, H. Liu and B. Yi, *Catal. Comm.*, 2012, **26**, 11.
67. H. Y. Fu, L. Chen and H. Doucet, *J. Org. Chem.*, 2012, **77**, 4473.
68. H. Y. Fu, L. Zhao, C. Bruneau and H. Doucet, *Synlett*, 2012, 2077.
69. J. Laroche, K. Beydoun, V. Guerchais and H. Doucet, *Catal. Sci. Tech.*, 2013, **3**, 2072.
70. S. Kona, R. S. Ravi, M. Chakravarthy and V. N. R. Chava, *J. Chem.*, 2013, doi:10.1155/2013/205934.
71. Y. Liu, L. He, G. Yin, G. Wu and Y. Cui, *Bull. Kor. Chem. Soc.*, 2013, **34**, 2340.
72. L. Zhao, H. Zhan, J. Liao, J. Huang, Q. Chen, H. Qiu and H. Cao, *Catal.Comm.*, 2014, **56**, 65.
73. P. V. Kumar, W.-S. Lin, J.-S. Shen, D. Nandi and H. M. Lee, *Organometallics*, 2011, **30**, 5160.
74. H. Cao, Y. Lin, H. Zhan, Z. Du, X. Lin, Q.-M. Liang and H. Zhang, *RSC Advances*, 2012, **2**, 5972.
75. R. R. Singhaus, R. C. Bernotas, R. Steffan, E. Matelan, E. Quinet, P. Nambi, I. Feingold, C. Huselton, A. Wilhelmsson, A. Goos-Nilsson and J. Wrobel, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 521.

76. J. Lee, J. Chung, S. M. Byun, B. M. Kim and C. Lee, *Tetrahedron*, 2013, **69**, 5660.
77. J. Koubachi, S. Berteina-Raboin, A. Mouaddib and G. Guillaumet, *Tetrahedron*, 2010, **66**, 1937.
78. W. J. Li, D. P. Nelson, M. S. Jensen, R. S. Hoerrner, G. J. Javadi, D. Cai and R. D. Larsen, *Org. Lett.*, 2003, **5**, 4835.
79. M. Parisien, D. Valette and K. Fagnou, *J. Org. Chem.*, 2005, **70**, 7578.
80. D. S. Ermolat'ev, V. N. Gimenez, E. V. Babaev and E. Van der Eycken, *J. Comb. Chem.*, 2006, **8**, 659.
81. J.-X. Wang, J. A. McCubbin, M. Jin, R. S. Laufer, Y. Mao, A. P. Crew, M. J. Mulvihill and V. Snieckus, *Org. Lett.* 2008, **10**, 2923.
82. S. K. Guchhait, S. Kandekar, M. Kashyap, N. Taxak and P. V. Bharatam, *J. Org. Chem.*, 2012, **77**, 8321.
83. V. Gembus, J.-F. Bonfanti, O. Querolle, P. Jubault, V. Levacher and C. Hoarau, *Org. Lett.*, 2012, **14**, 6012.
84. B. M. Johnson and M. P. Huestis, *Eur. J. Org. Chem.*, 2014, 1589.
85. A. El Akkaoui, S. Berteina-Raboin, A. Mouaddib and G. Guillaumet, *Eur. J. Org. Chem.*, 2010, 862.
86. L. Pellegatti, E. Vedrenne, J.-M. Leger, C. Jarry and S. Routier, *J. Comb. Chem.*, 2010, **12**, 604.
87. B. Liu, Z. Wang, N. Wu, M. Li, J. You and J. Lan, *Chem. Eur. J.*, 2012, **18**, 1599.
88. B. Koszarna, R. Matczak, M. Krzeszewski, O. Vakuliuk, J. Klajn, M. Tasior, J. T. Nowicki and D. T. Gryko, *Tetrahedron*, 2014, **70**, 225.
89. S. Park, Y. Jung and I. Kim, *Tetrahedron*, 2014, **70**, 7534.
90. S. A. Ohnmacht, A. J. Culshaw and M. F. Greaney, *Org. Lett.*, 2010, **12**, 224.
91. A. Ben-Yahia, M. Naas, S. El Kazzouli, E. M. Essassi and G. Guillaumet, *Eur. J. Org. Chem.*, 2012, 7075.
92. K. Hattori, K. Yamaguchi, J. Yamaguchi and K. Itami, *Tetrahedron*, 2012, **68**, 7605.
93. M. Ye, A. J. F. Edmunds, J. A. Morris, D. Sale, Y. Zhang and J.-Q. Yu, *Chem. Sci.*, 2013, **4**, 2374.
94. M. Naas, S. El Kazzouli, E. M. Essassi, M. Bousmina and G. Guillaumet, *J. Org. Chem.*, 2014, **79**, 7286.
95. J. Zhang, W. Chen, A. J. Rojas, E. V. Jucov, T. V. Timofeeva, T. C. Parker, S. Barlow and S. R. Marder, *J. Am. Chem. Soc.*, 2013, **135**, 16376.
96. C.-Y. He, C.-Z. Wu, F.-L. Qing and X. Zhang, *J. Org. Chem.*, 2014, **79**, 1712.
97. A. F. P. Biajoli, E. T. da Penha and C. R. D. Correia, *RSC Advances*, 2012, **2**, 11930.
98. S. K. Guchhait, M. Kashyap and S. Saraf, *Synthesis*, 2010, 1166.
99. H.-O. Do, R. M. K. Khan and O. Daugulis, *J. Am. Chem. Soc.*, 2008, **130**, 15185.
100. M. Ionita, J. Roger and H. Doucet, *Chemsuschem*, 2010, **3**, 367.
101. M. Baloch, D. Roy, S. Bensaid, V. Guerchais and H. Doucet, *Eur. J. Inorg. Chem.*, 2012, 4454.
102. D. Roy, S. Mom, S. Royer, D. Lucas, J.-C. Hierso and H. Doucet, *ACS Catal.*, 2012, **2**, 1033.
103. A. Carrer, D. Brinet, J.-C. Forent, P. Rousselle and E. Bertounesque, *J. Org. Chem.*, 2012, **77**, 1316.
104. M. Baghbanzadeh, C. Pilger and C. O. Kappe, *J. Org. Chem.*, 2011, **76**, 8138.
105. L. Zhao, C. Bruneau and H. Doucet, *Tetrahedron*, 2013, **69**, 7082.
106. A. R. Martin, A. Chartoire, A. M. Z. Slawin and S. P. Nolan, *Beilstein J. Org. Chem.*, 2012, **8**, 1637.
107. J. C. Lewis, A. M. Berman, R. G. Bergman and J. A. Ellman, *J. Am. Chem. Soc.*, 2008, **130**, 2493.
108. T. Yoshizumi, H. Tsurugi, T. Satoh and M. Miura, *Tetrahedron Lett.*, 2008, **49**, 1598.
109. Z.-S. Gu, W.-X. Chen and L.-X. Shao, *J. Org. Chem.*, 2014, **79**, 5806.
110. G. Zhang, X. Zhao, Y. Yan and C. Ding, *Eur. J. Org. Chem.*, 2012, 669.
111. A. Deb, S. Manna, A. Maji, U. Dutta and D. Maiti, *Eur. J. Org.Chem.*, 2013, **2013**, 5251.
112. J. Canivet, J. Yamaguchi, I. Ban and K. Itami, *Org. Lett.*, 2009, **11**, 1733.
113. H. Hachiya, K. Hirano, T. Satoh and M. Miura, *Org. Lett.*, 2009, **11**, 1737.
114. H. Hachiya, K. Hirano, T. Satoh and M. Miura, *Angew. Chem., Int. Ed.*, 2010, **49**, 2202.
115. X.-M. Yan, X.-R. Mao and Z.-Z. Huang, *Heterocycles*, 2011, **83**, 1371.
116. P. Yu, G. Zhang, F. Chen and J. Cheng, *Tetrahedron Lett.*, 2012, **53**, 4588.
117. W. Zhang, Y. Tian, N. Zhao, Y. Wang, J. Li and Z. Wang, *Tetrahedron*, 2014, **70**, 6120.

118. H. T. N. Le, T. T. Nguyen, P. H. L. Vu, T. Thanh and N. T. S. Phan, *J. Mol.Catal. A: Chem.*, 2014, **391**, 74.
119. D. M. Ferguson, S. R. Rudolph and D. Kalyani, *ACS Catal.*, 2014, **4**, 2395.
120. N. I. Abdo, A. A. El-Shehawy, A. A. El-Barbary and J.-S. Lee, *Eur. J. Org. Chem.*, 2012, 5540.
121. L.-C. Campeau, D. J. Schipper and K. Fagnou, *J J. Am. Chem. Soc.*, 2008, **130**, 3266.
122. L.-C. Campeau, D. R. Stuart, J.-P. Leclerc, M. Bertrand-Laperle, E. Villemure, H.-Y. Sun, S. Lasserre, N. Guimond, M. Lecavallier and K. Fagnou, *J. Am. Chem. Soc.*, 2009, **131**, 3291.
123. D. J. Schipper, M. El-Salfiti, C. J. Whipp and K. Fagnou, *Tetrahedron*, 2009, **65**, 4977.
124. D. Zhao, W. Wang, F. Yang, J. Lan, L. Yang, G. Gao and J. You, *Angew. Chem., Int. Ed.*, 2009, **48**, 3296.
125. Q. Ding, D. Wang, X. Sang, Y. Lin and Y. Peng, *Tetrahedron*, 2012, **68**, 8869.
126. E. Demory, D. Farran, B. Baptiste, P. Y. Chavant and V. Blandin, *J. Org. Chem.*, 2012, **77**, 7901.
127. A. M. Berman, J. C. Lewis, R. G. Bergman and J. A. Ellman, *J. Am. Chem. Soc.*, 2008, **130**, 14926.
128. A. M. Berman, R. G. Bergman and J. A. Ellman, *J. Org. Chem.*, 2010, **75**, 7863.
129. I. B. Seiple, S. Su, R. A. Rodriguez, R. Gianatassio, Y. Fujiwara, A. L. Sobel and P. S. Baran, *J. Am. Chem. Soc.*, 2010, **132**, 13194.
130. J. Wang, S. Wang, G. Wang, J. Zhang and X.-Q. Yu, *Chem. Comm.*, 2012, **48**, 11769.
131. F.-F. Zhuo, W.-W. Xie, Y.-X. Yang, L. Zhang, P. Wang, R. Yuan and C.-S. Da, *J. Org. Chem.*, 2013, **78**, 3243.
132. M. Tobisu, I. Hyodo and N. Chatani, *J. Am. Chem. Soc.*, 2009, **131**, 12070.
133. I. Hyodo, M. Tobisu and N. Chatani, *Chem. Asian J.*, 2012, **7**, 1357.
134. M. Nakamura, L. Ilies, S. Otsubo and E. Nakamura, *Angew. Chem., Int. Ed.*, 2006, **45**, 944.
135. M. Nakamura, L. Ilies, S. Otsubo and E. Nakamura, *Org. Lett.*, 2006, **8**, 2803.
136. P. P. Singh, S. K. Aithagani, M. Yadav, V. P. Singh and R. A. Vishwakarma, *J. Org. Chem.*, 2013, **78**, 2639.
137. M. Wasa, B. T. Worrell and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2010, **49**, 1275.
138. K. M. Engle and J.-Q. Yu, *J. Org. Chem.*, 2013, **78**, 8927.
139. M. Ye, G.-L. Gao, A. J. F. Edmunds, P. A. Worthington, J. A. Morris and J.-Q. Yu, *J. Am. Chem. Soc.*, 2011, **133**, 19090.
140. A. Nakatani, K. Hirano, T. Satoh and M. Miura, *J. Org. Chem.*, 2014, **79**, 1377.
141. J. Kwak, M. Kim and S. Chang, *J. Am. Chem. Soc.*, 2011, **133**, 3780.
142. S. Hostyn, B. U. W. Maes, L. Pieters, G. L. F. Lemiere, P. Matyus, G. Hajos and R. A. Dommisse, *Tetrahedron*, 2005, **61**, 1571.
143. S. Hostyn, B. U. W. Maes, G. Van Baelen, A. Gulevskaya, C. Meyers and K. Smits, *Tetrahedron*, 2006, **62**, 4676.
144. G. Van Baelen, C. Meyers, G. L. F. Lemiere, S. Hostyn, R. Dommisse, L. Maes, K. Augustyns, A. Haemers, L. Pieters and B. U. W. Maes, *Tetrahedron*, 2008, **64**, 11802.
145. K. C. Majumdar, A. K. Pal, A. Taher and P. Debnath, *Synthesis*, 2007, 1707.
146. L. Ackermann and S. Fenner, *Chem. Comm.*, 2011, **47**, 430.
147. B. Liu, J. Li, F. Song and J. You, *Chem. Eur. J.*, 2012, **18**, 10830.
148. B. Liu, Q. Guo, Y. Cheng, J. Lan and J. You, *Chem. Eur. J.*, 2011, **17**, 13415.
149. A. Carrer, J.-D. Brion, S. Messaoudi and M. Alami, *Org. Lett.*, 2013, **15**, 5606.
150. Z. Z. Ma, Y. Hano and T. Nomura, *Heterocycles*, 2005, **65**, 2203.
151. Z. Z. Ma, Y. S. Hano, T. Nomura and Y. J. Chen, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 1193.
152. Z. Z. Ma, Y. Hano, T. Nomura and Y. J. Chen, *Heterocycles*, 1997, **46**, 541.
153. A. Cagir, S. H. Jones, R. Gao, B. M. Eisenhauer and S. M. Hecht, *J. Am. Chem. Soc.*, 2003, **125**, 13628.
154. T. Harayama, A. Hori, G. Serban, Y. Morikami, T. Matsumoto, H. Abe and Y. Takeuchi, *Tetrahedron*, 2004, **60**, 10645.
155. M. Khoobi, M. Alipour, S. Zarei, F. Jafarpour and A. Shafiee, *Chem. Comm.*, 2012, **48**, 2985.
156. M. Khoobi, F. Molaverdi, M. Alipour, F. Jafarpour, A. Foroumadi and A. Shafiee, *Tetrahedron*, 2013, **69**, 11164.
157. Y. Li, Z. Qi, H. Wang, X. Fu and C. Duan, *J. Org. Chem.*, 2012, **77**, 2053.
158. S. H. Mashraqui, M. Ashraf and S. G. Ghadigaonkar, *Synlett*, 2006, 2423-2426.

159. P. D. Homyak, J. Tinkham, P. M. Lahti and E. B. Coughlin, *Macromolecules*, 2013, **46**, 8873.
160. G. Huang, H. Sun, X. Qiu, C. Jin, C. Lin, Y. Shen, J. Jiang and L. Wang, *Org. Lett.*, 2011, **13**, 5224.
161. S. Grosse, C. Pillard, S. Massip, J. M. Leger, C. Jarry, S. Bourg, P. Bernard and G. Guillaumet, *Chem. Eur. J.* 2012, **18**, 14943.
162. S. Grosse, C. Pillard, P. Bernard and G. Guillaumet, *Synlett*, 2013, **24**, 2095.
163. S.-H. Wang, W.-J. Liu, H.-Y. Zhan, H. Zhang, Y. Liang and Y. Tian, *RSC Advances*, 2013, **3**, 23972.
164. M. Le Meur, S. Bourg, S. Massip, M. Marchivie, C. Jarry, G. Guillaumet and S. Routier, *Eur. J. Org. Chem.*, 2014, 3704.
165. H. Zhang, *J. Organomet. Chem.*, 2014, **756**, 47.
166. J. L. Bon, D. Feng, S. R. Marder and S. B. Blakey, *J. Org. Chem.*, 2014, **79**, 7766.

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