This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. This Accepted Manuscript will be replaced by the edited, formatted and paginated article as soon as this is available.

You can find more information about Accepted Manuscripts in the Information for Authors.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal’s standard Terms & Conditions and the Ethical guidelines still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.
Advances in direct C-H arylation of 5,5, 6,5 and 6,6- fused-heterocycles containing heteroatoms (N, O, S)

Saïd El Kazzouli,*[a] Jamal Koubachi,[b] Nabil El Brahmi*[a] and Gérald Guillaumet*[c]

DOI: 10.1039/b000000x [DO NOT ALTER/DELETE THIS TEXT]

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, benzoindazole, benzo[d]thiazole, 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. 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\textsuperscript{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.\textsuperscript{10} and by Larrosa et al.\textsuperscript{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. Same’s group\textsuperscript{12} showed that the use of CH\textsubscript{3}MgCl and tetramethylethylenediamine (TMEDA) in the presence of IMes as a sterically hindered ligand instead of Ph\textsubscript{3}P 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)\textsubscript{2} which led to the desired product 2 in 96\% yield.

![Scheme 1. C3-arylation of indole 1](image1.png)

An elegant protocol for regioselective C3-arylation of indole 1 was developed by He and collaborators using air stable palladium catalyst with phosphinous acid complex (PO\textsubscript{3}Pd)\textsuperscript{13}. The optimum reaction conditions were found when using PO\textsubscript{3}Pd, K\textsubscript{2}CO\textsubscript{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.](image2.png)

Guant et al. showed that the use of Cu(OTf)\textsubscript{2} as catalyst under mild conditions was effective for regioselective C3-arylation of indole\textsuperscript{14}. In this study, the coupling reaction of N-methyl indole 3 and [Ph-I-Ph]OTf in the presence of Cu(OTf)\textsubscript{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. This method was effective using free (NH) indole and bromobenzene as coupling partners in the presence of Pd(OAc)$_2$, BnBu$_3$NCl and K$_2$CO$_3$ in toluene at 110 °C for 24 h. Under these conditions, expected product 2 was obtained in 97% (GLC yield) (Scheme 4).


Larrosa et al. described palladium catalyzed decarboxylative C3-arylation of indole using benzoic acids bearing ortho electron-withdrawing substituents as arylating agents. Authors showed that treatment of indole 5 with 2-chloro-5-nitrobenzoic acid in the presence of Pd(MeCN)$_2$Cl$_2$, Ag$_2$CO$_3$ 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 $^1$H 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. 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$_2$CO$_3$ 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 (dpdm) in H$_2$O 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).
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\(_2\)CO\(_3\) in refluxing dioxane for 24 h led to C3-arylated product 2 in 70% isolated yield (Scheme 9\(^{20}\)).

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\(_3\)P 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).

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\(_2\)CO\(_3\) in refluxing toluene for 24 h. This procedure led to C3-arylated product 12 in 85% isolated yield (Scheme 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-arylated product 15 with good selectivity (C3/C2, 8:1) and in 40% yield\textsuperscript{23, 24}. However, when using N-methylindole 3 as starting material, the reaction with chloropyrazine in the presence of Pd(PPh\textsubscript{3})\textsubscript{4} and KOAc in refluxing DMA furnished C2-arylated product 14 in 48% yield.

Since the first report on direct C2-arylation of indoles\textsuperscript{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 regioselective C2-arylation 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\textsuperscript{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)\textsubscript{2}, Ph\textsubscript{3}P 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)\textsubscript{2} led to the formation of 68% yield of desired product 16 (Scheme 13).
The same group provided C2-arylation of free (NH) indole 1 using Ar-Rh(III) complexes, formed in situ, as catalyst. The reaction was carried out using [Rh(coe)2Cl]2 as catalyst, [p-(CF3)C6H4]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).

Another interesting report on C2-arylation was described by Sames’s group using a new palladium catalyst (catalyst A). 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).

In 2011, Yanagisawa and Itami described the Pd/bipy-based catalytic system for the C-H arylation of N-protected indole with aryl iodide (Scheme 16). The 1-methyl-
1H-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 % PdBr₂(bipy)DMSO as catalyst and 1 equivalent of Ag₂CO₃ 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.


Very recently, Lu et al.²⁹ demonstrated that the use of [Cp*RhCl₂]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/H₂O (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 Ag₂O or Cu(OAc)₂ as oxidant, direct C2-arylation of N-methoxy-1H-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 iodosobenzene 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 was developed by Su et al. for the direct arylation of indole with benzoic acids. 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$_2$CO$_3$, TMSO and EtCO$_2$H 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. In a representative example, 1-butyl-3-methyl-1H-indole 23 was treated by chlorobenzene in the presence of Pd(OAc)$_2$, 2-(dicyclohexylphosphino)-biphenyl ligand and Na$_2$CO$_3$ in DMA at 125 °C for 24 h leading to C2-phenylated indole 24 in 94% GC conversion (Scheme 21).


Recently, Lavilla et al. described an elegant C2-arylation of indole ring present in amino acids and peptides. A representative example is shown in Scheme 18. In this case, Ac-Trp-OMe 25 was arylated using iodobenzene, Pd(OAc)$_2$, 2-NO$_2$Bz 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).
Recently, Chu and co-workers\textsuperscript{35} performed intramolecular indole C2-arylation reactions of bis-indole derivatives \textsuperscript{27} obtained from 1-methyl-1\textsubscript{H}-indole and 2-bromobenzaldehyde, the reaction was catalyzed by \textit{Pd(OAc)}\textsubscript{2} in the presence of \textit{Ph}_{3}\textit{P} as ligand and \textit{CsOAc} as base in either DMA or DMF at 110 °C for 5 h. The desired compound \textsuperscript{28} was obtained with good yield (94\%) (Scheme 23).

In another interesting development of C2-arylation, James et al.\textsuperscript{36} reported peptide macrocyclization by intramolecular C2-arylation of indole \textsuperscript{29}. Thus, the side chain of a phenylalanine derivative containing an iodoaryl and the side chain of tryptophan were connected using \textit{Pd(OAc)}\textsubscript{2} as catalyst in the presence of 2-\textit{NO}_{2}-\textit{C}_{6}\textit{H}_{4}\textit{CO}_{2}\textit{H} and \textit{AgBF}_{4} in DMA at 130 °C for 24 h. The desired macrocyclic peptide \textsuperscript{30} was isolated in 75\% (Scheme 24).
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

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>R₁</th>
<th>R₂-X</th>
<th>Product, yield</th>
<th>ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)₂, AgOAc, H₂SO₄, DMF/CH₂CN, 100 °C, MW, 40 min</td>
<td>H</td>
<td>Ph-SO₂H</td>
<td>8, 82 %</td>
<td>37</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)₂, c-C₆H₄CO₂Ag, H₂O, 4h, 30 °C</td>
<td>CH₃</td>
<td>Ph-I</td>
<td>16, 94 %</td>
<td>38</td>
</tr>
<tr>
<td>3</td>
<td>Pd(Anchomos)Cl₂, NaOH, H₂O/ EtOH, 80 °C</td>
<td>H</td>
<td>Ph-I</td>
<td>8, 80 %</td>
<td>39</td>
</tr>
<tr>
<td>4</td>
<td>Pd(COD)Cl₂, CuCl₂, toluene/dioxane, 110 °C, 24 h</td>
<td>CH₃</td>
<td>CH₃-C₆H₄-SO₂</td>
<td>31, 88 % GC yield</td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>Pd/MIL-101(Cr), DMF, CsOAc, 120 °C, 24 h</td>
<td>CH₃</td>
<td>Ph-I</td>
<td>16, 85 %</td>
<td>41</td>
</tr>
<tr>
<td>6</td>
<td>Pd supported fluorous silica gel (FSG), DMA, CsOAc, 120 °C, 24 h</td>
<td>CH₃</td>
<td>Ph-I</td>
<td>16, 86 %</td>
<td>42</td>
</tr>
<tr>
<td>7</td>
<td>Pd(OAc)₂, Ag₂O, TBAB, AcOH/ EtOH, rt, 18 h</td>
<td>CH₃</td>
<td>Ph-Si(O)(OMe)₃</td>
<td>16, 82 %</td>
<td>43</td>
</tr>
<tr>
<td>8</td>
<td>Pd(OAc)₂/Cu(OA)₂, AcOH, air, rt, 12h</td>
<td>H</td>
<td>Ph-BF₃K</td>
<td>8, 81 %</td>
<td>44</td>
</tr>
<tr>
<td>9</td>
<td>Pd(OAc)₂, o-O,N-C₆H₄-CO₂H, Ag₂O, DMF, 25 °C, 18h</td>
<td>CH₃</td>
<td>Ph-I</td>
<td>16, 99 % GC yield</td>
<td>45</td>
</tr>
<tr>
<td>10</td>
<td>Pd(OAc)₂, TEMPO, KF, EtCOOH, rt, 1h</td>
<td>H</td>
<td>Ph-B(OH)₂</td>
<td>8, 81 %</td>
<td>46</td>
</tr>
<tr>
<td>11</td>
<td>Pd(OAc)₂, O₂, HOAc, rt, 8h</td>
<td>CH₃</td>
<td>Ph-B(OH)₂</td>
<td>16, 77 %</td>
<td>47</td>
</tr>
<tr>
<td>12</td>
<td>Pd(OAc)₂, CuI, DMA, 160 °C, 48h</td>
<td>H</td>
<td>p-CH₂O-C₆H₄-I</td>
<td>32, 53 %</td>
<td>48</td>
</tr>
<tr>
<td>13</td>
<td>Pd(OAc)₂, CuI, DMF, 140 °C, 48h</td>
<td>H</td>
<td>p-CH₂O-C₆H₄-I</td>
<td>32, 35 %</td>
<td>49</td>
</tr>
<tr>
<td>14</td>
<td>IMesPd(OAc)₂, AcOH, 25 °C, 18h</td>
<td>CH₃</td>
<td>p-Ph-I²-PhBF₄⁻</td>
<td>16, 86 %</td>
<td>50</td>
</tr>
</tbody>
</table>

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 Ph₃P as ligand and Cs₂CO₃ 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$_3$P 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.](image)

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$_2$CO$_3$, 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.](image)

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.](image)

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$_2$S$_2$O$_8$ 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]pyridines53. Our research group described the first regioselective C3-arylation of imidazo[1,2-a]pyridine54, 55. The reaction was carried out using starting material 39 and 3-bromotoluene in the presence of K2CO3, Pd(OAc)2 as catalyst and PPh3 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 al27 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%).
In 2007, our group developed two efficient methods for the synthesis of 3,6-
disubstituted imidazo[1,2-a]pyridine derivatives\textsuperscript{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)\textsubscript{2}/PPh\textsubscript{3} as catalyst and
K\textsubscript{2}CO\textsubscript{3} as base in a mixture of dioxane/EtOH at 150 °C, MW] gave the expected
product 48 in 71 % overall yield (Scheme 32).

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)\textsubscript{2}/PPh\textsubscript{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 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, 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 PEG400 medium. Under this new conditions various 2,3-diarylimidazo[1,2-a]pyridines 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 PEG400, 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 PEG400 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).

![Diagram](image)

**Fig. 1.** Limits of one-pot two-step cyclization/C–H arylation in PEG400 medium.

In 2012, Marchand et al developed sequential C2 Suzuki–Miyaura/ direct C3-arylation of imidazo[1,2-a]pyridines (Scheme 36). 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(PPh3)4, Na2CO3, dioxane/H2O 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, PCy3-HBF4, PivOH and K2CO3 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](image)

**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. 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(PPh3)4 in the presence of Cs2CO3 in dioxane (Scheme 37).
Scheme 37. C3-arylation of imidazo[1,2-α]pyridine 61.

Recently, Jiang et al.\textsuperscript{65} reported a new method for C3-arylation of imidazo[1,2-α]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-phenanthroline as ligand and t-BuOK as base. The expected product 64 was isolated in 87% yield (scheme 38).

Scheme 38. Cul-catalyzed C3-arylation of 63.

Developing further the reaction conditions, Yang et al.\textsuperscript{66} reported a new Ru-catalyzed C-H activation of imidazo[1,2-α]pyridines. The reaction was carried out using imidazo[1,2-α]pyridine 63 and iodobenzene in the presence of RuCl\textsubscript{2}(p-cymene)\text subscipt{2} and Cs\textsubscript{2}CO\textsubscript{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-α]pyridine 41 was recently developed by Doucet et al.\textsuperscript{67} using Pd(OAc)\textsubscript{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-α]pyridine and 3-thienyl...
imidazo[1,2-α]pyridine derivatives 66, 67 by C3-arylation of imidazo[1,2-α]pyridine 41 with methyl 5-bromofuroate (1 equiv.) or ethyl 5-bromothiophene-2-carboxylate (1 equiv) as arylating agents. 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-α]pyridine 41.](image)

Recently, the same group reported direct heteroarylation of imidazo[1,2-α]pyridine using either 8-bromoquinoline or 2-(5-bromothiophen-2-yl)-pyridine as arylating agents. 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.](image)

Another phosphine free direct arylation was reported by Chakravarty et al. In this case, 2-phenylimidazo[1,2-α]pyridine 59 and iodophenyl were used as coupling partners in the presence of 5 mol% of Pd(OAc)₂, 0.75 equiv of Ag₂O and 1.5 equiv. of o-NO₂-C₆H₄-CO₂H in DMF at 120 °C. Under these conditions, the expected product 2,3-bisphenylimidazo[1,2-α]pyridine 53 was isolated in 82% yield (Scheme 43).
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% PPh₃ and 2 equiv. of K₂CO₃ in NMP at 100 °C for 24 h provided 3-aryl-2-phenylimidazo[1,2-a]pyridine 70 in 86% yield (Scheme 44).

Recently, Lee and co-workers⁷³ 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)(PR₃)(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).
Attempting to use chloroaryls as less expensive alternatives to iodo or bromoaryl coupling partners, Cao and al.\textsuperscript{74} developed an efficient Pd-catalyzed regioselective arylation at the C3 position of imidazo[1,2-\textit{a}]pyridine \textit{63} with chlorobenzene. This reaction was catalyzed by Pd(OAc)$_2$ in the presence of BuAd$_2$P (Ad= adamantyl) and Cs$_2$CO$_3$ in NMP at 120 °C (Scheme 47). The expected product \textit{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.

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

Recently, magnetically recyclable Pd-Fe$_3$O$_4$ nanoparticles as catalyst were used by Lee et al.\textsuperscript{76} to achieve the direct arylation of imidazo[1,2-\textit{a}]pyridine. Reaction
between 41 and 4-bromonitrobenzene was carried out using Pd-Fe$_3$O$_4$ 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.](image)

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$_2$CO$_3$ as a base in a mixture of dioxane/ H$_2$O 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.](image)

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. The expected products 80-83 were achieved using Pd(OAc)$_2$/PPh$_3$ as catalytic system in the presence of K$_2$CO$_3$ in DMA at 100 °C. Yields of isolated products were ranging between 83 and 98% (Scheme 51).

![Scheme 51. Intramolecular C3-arylation of 79.](image)
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$_2$CO$_3$ 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.](image)

2.4 Imidazo[1,2-α]pyrimidines.

Li et al.$^{78}$ reported the first example of direct arylation of imidazo[1,2-α]pyrimidine 92. Two reaction conditions were successfully applied using Pd(OAc)$_2$/Ph$_3$P as the catalyst/ligand system in the presence of either Cs$_2$CO$_3$ in dioxane at 100 °C or K$_2$CO$_3$ 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.](image)

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 material 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.](image)

The same group established broadly applicable reaction conditions for the palladium-catalyzed direct arylation of imidazo[1,2-α]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$_2$CO$_3$ 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-α]pyrimidine direct arylation was published by Eycken et al. Using imidazo[1,2-α]pyrimidine 95 and bromobenzene as coupling partners in the presence of Pd(OAc)$_2$ as catalyst, Ph$_3$P as ligand and Cs$_2$CO$_3$ 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-α]pyrazine

Snieckus and co-workers$^{81}$ reported regioselective C5-arylation of imidazo[1,5-α]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$_2$Bu$_2$CH$_3$.HBF$_4$, and Cs$_2$CO$_3$ 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-α]pyrazine under concerted metalation-deprotection process (CMD)$^{82}$. After an evaluation of reagents and reaction condition for regioselective C6-arylation of 3-aminimidazo[1,2-α]pyrazine 99, authors found that Pd(OAc)$_2$ (10 mol%), PPh$_3$ (20 mol%), PivOH (30 mol%), K$_2$CO$_3$ (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).
Recently a one-pot sequential Suzuki/arylation reaction was developed by Hoarau et al.\textsuperscript{83} Thus, C3/C6 functionalization was achieved by treatment of imidazo[1,2-\textit{a}]pyrazine 101 using Suzuki conditions that are [PhB(OH)\textsubscript{2}, Pd(OAc)\textsubscript{2}, CyJohnPhos, Cs\textsubscript{2}CO\textsubscript{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-\textit{a}]pyrazine 102 in 93% isolated yield (Scheme 59).

In 2014, a new procedure of double functionalization of imidazo[1,2-\textit{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\textsuperscript{84}. Thus, 3,5-diarylimidazo[1,2-\textit{a}]pyrazine 105 was prepared starting from imidazo[1,2-\textit{a}]pyrazine 103. After treatment with 5-bromopyrimidine under reaction conditions [Pd(OAc)\textsubscript{2}, PCy\textsubscript{3}, HBF\textsubscript{4}, PivOH (30 mol%), K\textsubscript{2}CO\textsubscript{3}, 100 °C], the desired monoarylared product 104 was isolated in 60 % yield. C5-arylation reaction was then carried out on 104 using \textit{p}-CH\textsubscript{3}CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}-Br in the presence of Pd(OAc)\textsubscript{2}, 1,10-phenanthroline, Cs\textsubscript{2}CO\textsubscript{3} in DMA at 140 °C under atmospheric air which furnished bis-arylared product 105 in 50% (Scheme 60).

### 2.6 Imidazo[1,2-\textit{b}]pyridazines
One of us and coworkers developed an elegant C3 direct arylation of imidazo[1,2-b]pyridazines. Optimization of reaction conditions using imidazo[1,2-b]pyridazine and bromobenzene as coupling partners showed that Pd(OAc)$_2$ (10 mol%), PPh$_3$ (20 mol%) and K$_2$CO$_3$ (2 equiv.), in toluene at 110°C gave the expected product 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.](image)

2.7 Pyrazolo[1,5-a]pyrimidines

Recently, one of us and coworkers reported direct arylation of pyrazolo[1,5-a]pyrimidine system. Thus, when starting material was treated with 3-bromotoluene in the presence of Pd(OAc)$_2$, P$_3$Bu$_3$.HBF$_4$ and K$_2$CO$_3$ in refluxing toluene, the reaction led to sp$^2$ C3-arylated product in 62% isolated yield. Interestingly, when Ph$_3$P was used instead of P$_3$Bu$_3$.HBF$_4$ and Cs$_2$CO$_3$ instead of K$_2$CO$_3$ the reaction led to sp$^3$ C-H arylation, the reaction gave exclusively compound in 50% isolated yield (Scheme 62).

![Scheme 62. Pd-catalyzed arylation of pyrazolo[1,5-a]pyrimidine 108.](image)

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. The protocol involved the treatment of ethoxy-7-(4-methoxyphenyl)imidazo[1,2-b][1,2,4,5]tetrazine with aryl bromide in dioxane at 160°C for 20 min under microwave irradiation, in the presence of Cs$_2$CO$_3$, 8 mol% Pd(OAc)$_2$ and 8 mol% of PCy$_3$. Under these conditions the arylated compound was obtained in 87% yield (Scheme 63).
This journal is © The Royal Society of Chemistry [year]

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\(^8\)\(^7\). 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.\(^8\)\(^8\) 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.\textsuperscript{89} reported that starting material 119 undergo direct C6-arylation when treated by 4-bromonitrobenzene in the presence of KOAc as base, (PPh\textsubscript{3})\textsubscript{2}Pd(Cl)\textsubscript{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\textsubscript{H}) indazole serie\textsuperscript{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\textsubscript{2} as catalyst, PPh\textsubscript{3} as ligand and Ag\textsubscript{2}CO\textsubscript{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\textsubscript{H}) indazole 123 using Pd(OAc)\textsubscript{2} as catalyst and 1,10-phenanthroline as ligand in the presence of K\textsubscript{2}CO\textsubscript{3} as base and DMA as solvent\textsuperscript{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 (1H) indazole 123.](image)

Independently, Itami’s group reported the C3-arylation of (1H) indazole 125 using PdCl₂ as catalyst, 1,10-phenanthroline as ligand, Ag₂CO₃ as base and K₃PO₄ as additive. 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 (1H) indazoles 125.](image)

Later, Yu et al. reported the C3-arylation on (1H) indazoles using indazole 123 as starting material, iodobenzene as coupling partner, Pd(OAc)₂ as catalyst, 1,10-phenanthroline as ligand and Cs₂CO₃ as base in toluene at 160 °C for 12 h. The expected product 127 was obtained in 93% (yield was determined by ¹H NMR) (Scheme 71).

![Scheme 71. C3-arylation of (1H) indazole 123.](image)

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. Thus, direct C7-arylation was developed using 3-substituted 1H-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, K₂CO₃, and K₃PO₄ 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 1H-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).
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' Bu$_2$CH$_3$:HBF$_4$, PivOH and K$_2$CO$_3$ in toluene at 120 °C for 3-5 h$^{95}$. Under these conditions, the symmetrical 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 above, diarylated product 135 was isolated in 65% yield (Scheme 73).

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 aryl diazonium salt as coupling partner. The reaction was carried out between benzofuran and benzendiazonium salt in the presence of Pd(OAc)\(_2\) and K\(_2\)CO\(_3\) 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\(_3\)COLi in DMPU at 125 °C for 12h. This sequence led to desired product 141 in 60% yield (Scheme 77).
2.13.2 C3-arylation of Benzofuran

Recently, various examples of direct C3-arylation of benzofurans using (het)aryl halides as arylation agents have been reported. In 2010, Fagnou and co-workers prepared two examples of C3-arylation of 2-chlorobenzofuran 142 using either p-tolyl bromide or p-fluorobenzene bromide as arylation agent. The reaction was catalysed by Pd(OAc)$_2$P(t-Bu)$_2$Me·HBF$_4$/PivOH system in the presence of Cs$_2$CO$_3$ 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-aryl.

In the same year, Doucet and co-workers explored the reactivity of 2-substituted benzofurans toward C3-arylation reaction. 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$_5$H$_5$)(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$_5$H$_5$)(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, Bu4NBr 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, 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 K₂CO₃ as base and a catalyst system Pd(OAc)₂/P(°Bu)₂Me·HBF₄/PivOH gave 3-aryl-2-ethylbenzo[b]furans 153 in good yields (Scheme 84).  

**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. The use of iodobenzene, Cul/phen and Et₃COLi 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. For example, reaction between benzothiophene 154 and 4-bromotoluene in the presence of Pd(OAc)₂, PCy₃·HBF₄ and K₂CO₃ 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.](image)

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\textsuperscript{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.](image)

A C2-arylation of benzothiophene 154 using a low amount of ligand-free Pd(OAc)\textsubscript{2} was reported by Doucet et al.\textsuperscript{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.](image)

Recently, Nolan’s group described direct arylation of benzothiophene 154 catalysed by [Pd(SIPr)cin)Cl] [SIPr=1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene]108. 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$_2$CO$_3$. 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-α]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.](image)

Recently, Doucet et al. reported C2-heteroarylation of benzothiophene 159 using 8-bromoquinoline as arylating agent. Thus, using PdCl(C$_3$H$_5$)(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-α]pyridine.

![Scheme 90: C2-heteroarylation of benzothiophene 159.](image)
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]. In this case, p-methoxybenzediazonium salt was used as coupling partner in the presence of Pd(OAc)\(_2\) and K\(_2\)CO\(_3\) in MeOH at 50 °C which afforded good yield (74%) of compound 161 (Scheme 91).

![Scheme 91. C3-arylation of benzothiophene 154.](image)

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.](image)

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.](image)

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-1H-benzimidazole 169 with aryl iodides $^{108}$. The treatment of 1-methyl-1H-benzimidazole 169 with 4-chloroiodobenzene in the presence of 1 equivalent of CuI, 0.2 equivalent of Ph$_3$P and Na$_2$CO$_3$ in DMF at 160 °C provided 2-arylated benzimidazole 170 in 89% yield (Scheme 95).

Scheme 95. Copper-mediated direct arylation of 1-methyl-1H-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$_2$O 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\textsuperscript{108}. Thus, the coupling reaction between benzothiazole 172 (1 mmol) and iodobenzene (2 equiv.) in the presence of CuI (1 equiv.), PPh\textsubscript{3} (0.2 equiv.), and K\textsubscript{3}PO\textsubscript{4} (2 equiv.) in DMSO for 2 h gave the expected 2-phenylbenzothiazole 173 in 63% yield (Scheme 97).

\[ \text{Ph-I} \]
\[ \text{172} \]
\[ \text{Cul (1 equiv), PPh}_3 (20 \text{ mol\%}) \]
\[ \text{K}_3\text{PO}_4, \text{DMSO, 160 }^\circ\text{C, 2 h, N}_2 \]
\[ \text{173} \]
\[ \text{63\%} \]

**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\textsuperscript{48}. In fact, under these conditions [Pd(OAc)\textsubscript{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).

\[ \text{Ar-I} \]
\[ \text{172} \]
\[ \text{Pd(OAc)}_2\text{, CuI in DMF, 140 }^\circ\text{C, 48 h} \]
\[ \text{174, Ar } = \text{4-NO}_2\text{C}_6\text{H}_4, 85\% \]
\[ \text{175, Ar } = \text{3,4-Cl}_2\text{C}_6\text{H}_3, 87\% \]

**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\textsuperscript{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\textsubscript{3}PO\textsubscript{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).

\[ \text{172} \]
\[ \text{CuI/Phen.} \]
\[ \text{K}_3\text{PO}_4, \text{DMA, 120 }^\circ\text{C, 5 h} \]
\[ \text{176} \]
\[ \text{89\%} \]

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

Ding et al. reported a phosphine free direct arylation of benzothiazole 172\textsuperscript{110}. The reaction was carried out using oxime-derived palladacycle B as catalyst and iodobenzene in the presence of K\textsubscript{2}CO\textsubscript{3} in DMA at 140 °C for 24 h. The arylated product 173 was isolated in 80% yield (Scheme 100).
Maiti et al. reported an iron-catalyzed direct arylation of benzothiazole 172 using boronic acids as arylating agents. The reaction was conducted using Fe(NO$_3$)$_3$ (20 mol%), K$_2$S$_2$O$_8$ (4 equiv.), TFA (2 equiv.) in a mixture of TFT/H$_2$O (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.

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). 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).

At almost the same time, Miura et al. reported the regioselective nickel-catalyzed arylation of benzothiazole 172. 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). 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. 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$_3$P, Na$_2$CO$_3$, 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).

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\textsuperscript{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%).


Huang et al. reported direct arylation of benzoxazole using Pd(OAc)_2/Cu(II)/PPh_3 as a cocatalyst system\textsuperscript{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_2CO_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\textsuperscript{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-1H-pyrroles 180 in 84% yield. The procedure tolerated 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. The reaction was conducted using 10 mol % of CuO nanoparticles, PPh3 (30 mol %), K2CO3 (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 K3PO4 as base and a heterogeneous catalyst Cu2(BPDC)2(BPY). This reaction conditions provided 2-phenylbenzoxazole 180 in moderate to good conversion (Scheme 111). 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. Cu2(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. 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 Cs2CO3, 1.1 equiv. of CsOPiv, 5 mol% Pd(OAc)2 and 10 mol% of dctype, 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\textsuperscript{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)\textsubscript{2}, Bu\textsubscript{4}NBr 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\textsuperscript{3} or sp\textsuperscript{2} C-H bonds of 1-methyl and 3-methyl-isoquinoline\textsuperscript{121}. Thus, under conditions A (Scheme 114), high yield of sp\textsuperscript{2}-arylation at C1 of 3-methyl-isoquinoline-N-oxide 184 was achieved. Also, under conditions B, good yield of benzylic sp\textsuperscript{3}-arylation of 1-methyl-isoquinoline-N-oxide 185 under microwave irradiation was obtained. This methodology was validated in both divergent sp\textsuperscript{2}/sp\textsuperscript{3} arylation (Scheme 114).
In 2009, the direct arylation of quinoline N-oxide compounds was described by the same group\textsuperscript{122} employing 3 equivalents of quinoline N-oxide \textbf{188} in conjunction with an aryl bromide as coupling partner. Thus, 5 mol% of Pd(OAc)\textsubscript{2}, 5 mol% of P\textsubscript{t}Bu\textsubscript{3}.HBF\textsubscript{4} and 2 equivalents of K\textsubscript{2}CO\textsubscript{3} were used in refluxing toluene. Under these conditions, the corresponding 2-arylquinoline N-oxides \textbf{189} was obtained in good to excellent yields. 2-arylquinoline N-oxides can be readily reduced to the corresponding 2-arylquinoline \textbf{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 \textbf{190-194} in good to excellent yields (Scheme 115).

The same group investigated the site-selective isoquinoline arylation at the azine ring via N-oxide activation\textsuperscript{122} and reported that subjecting isoquinoline N-oxide \textbf{195} to a Pd(OAc)\textsubscript{2}/P\textsubscript{t}Bu\textsubscript{3}.HBF\textsubscript{4}, catalyst system enabled the regioselective direct arylation of the azine ring with aryl bromides. These conditions provided regioisomeric products \textbf{196} and \textbf{197} in satisfactory to good yields. Isomers \textbf{196} and \textbf{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 \textbf{198-201} were isolated in good overall yields (Scheme 116).

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$_{t}$Bu$_3$CH$_3$.HBF$_4$ as a catalytic system in the presence of K$_2$CO$_3$ 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$_2$CO$_3$ 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\textsuperscript{124}. Reaction was carried out using CuI (20 \text{ mol\%}), 1,10-phenanthroline (20 \text{ mol\%}), \text{K}_3\text{PO}_4 (2.0 \text{ equiv.}), quinoline N-oxide (1.0 \text{ equiv.}) and aryl bromides (1.5 \text{ 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).


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\textsuperscript{125}. Employing optimum reaction conditions that are: a toluene solution of 2-alkynylbenzaldoximes 206 (0.6 mmol), AgOTf (5 \text{ mol \%}), 2-phenylisoquinoline N-oxide 207 and 3-bromotoluene as coupling partners in the presence of PdCl\textsubscript{2} (5 \text{ mol \%}), JohnPhos (10 \text{ mol \%}), HBF\textsubscript{4} (10 \text{ mol \%}) and K\textsubscript{2}CO\textsubscript{3} (2.0 \text{ 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 Pd₂(dba)₃ as catalyst and pivalic acid as cocatalyst. Again, direct arylation was found to occur exclusively at the C1 position of cyclic nitron. Treatment of with different aryl bromides led to compounds in 74 to 97% isolated yields (Scheme 121).

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). 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 (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 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).

More recently, the same group prepared a variety of 2-aryl-quinolines via Rh(I)-
catalysed C–H arylation. 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] 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](image)

**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. 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-phenoxypyhenylboronic 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](image)

**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(NO3)3 and K2S2O8 in a mixture of trifluorotoluene (TFT)/water (1:1) and trifluoroacetic acid (TFA) 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. 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 phenylboronic acid.

The intermolecular arylation of quinoline 213 was reported using TMEDA in toluene at 50 °C for 10 h. 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 C6H5MgBr 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.](image)

After extensive studies, arylzinc reagents proved to be effective aryl donors in Ni-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.](image)

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-chlorophenylboronic 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-catalyzed 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. 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 C1 giving compound 222 in 50% yield (Scheme 132).

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. Reaction optimization demonstrated that the phosphine ligand (PCy₂Bu-HBF₄) improved the Pd-catalyst activity leading to the best reaction efficiency. Thus, using this catalyst system in the presence of Cs₂CO₃ 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...
Cs₂CO₃ (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% yield¹³⁸,¹³⁹ (Scheme 134).

![Scheme 134](image)

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](image)

In 2011, Chang and co-workers reported that Rh₂(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, Rh₂(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 ¹H NMR using an internal standard and a regioselectivity > 99:1 of 232/190 was determined by GC integration).

![Scheme 136](image)

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 11H-indolo[3,2-c]quinoline 235 starting from commercially available 4-chloroquinoline 233 and 2-
chloroaniline. 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 PdCl₂(PPh₃)₂ in DMA at 180 °C for 10 min in the presence of NaOAc.3H₂O led to the facile synthesis of 7H-indolo[2,3-c]quinoline 237 in good yield (Scheme 138).

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.3H₂O in DMA under either conventional heating or microwave irradiation. The synthesis of 11H-indolo[3,2-c]isoquinolines 239 was achieved in 78% yield, under conventional heating and in 79% yield under microwave irradiation (Scheme 139). The use of this procedure allowed the facile synthesis of D-ring analogues of isocryptolepine for subsequent SAR screening.


In the same year, an expedient synthesis of D-ring-substituted 11H-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).
In another interesting report, Majumdar and co-workers employed ligandless intramolecular palladium-catalysed arylation conditions that are: Pd(OAc)$_2$, KOAc, Bu$_4$NBr, 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)$^{145}$.

### 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$_2$CH$_3$-phenyl chloride in the presence of Pd(OAc)$_2$/P(Cy)$_3$·HBF$_4$ and Cs$_2$CO$_3$ 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).
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. 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. Cross-coupling of quinoxaline N-oxide 242 with aryI 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, p-tolylsulfonylhydrazide, or even sodium sulfinate 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(1H)-one 248. 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(1H)-one backbones (Scheme 145).

![Scheme 145. Synthesis of 3-phenyl quinoxalin-2(1H)-one 248.](image)

Early applications of intramolecular palladium-catalyzed C–H arylation for the synthesis of pyrroloquinazolinoquinoline cytotoxic alkaloid luotonin 250 was published by Harayama research group150-153. 3-[(2-Bromoquinol-3-yl)methyl]-4(3H)-quinazolinone 249 was treated with Pd(OAc)2/PCy3 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.](image)

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 251150-153 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.](image)

### 3.3 Chromanones and coumarins

Recently, Jafarpour and co-workers found that C–H arylation reaction of either coumarin 253155 or coumarin-3-carboxylic acid 254156 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
This journal is © The Royal Society of Chemistry [year]

formation.

\[
\text{Scheme 148. Pd-catalyzed oxidative arylation of coumarin 253 and coumarin-3-carboxylic acid 254 with phenylboronic acid.}
\]

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.

\[
\text{Scheme 149. Regioselective C2-arylation of chromenone 256.}
\]

Under reaction conditions similar to those previously used for the synthesis of 4-phenyl-2H-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).

\[
\text{Scheme 150. Synthesis of 4-phenylcoumarins 255.}
\]

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\(_4\)NBr), a molar excess of K\(_2\)CO\(_3\) 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.](image)

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 $[Pd_{2}(dba)_{3} \cdot CHCl_{3} (0.05 \text{ mmol}), \text{tris}(2\text{-methoxyphenyl})\text{phosphine} (0.2 \text{ mmol}), \text{pivalic acid} (1 \text{ mmol}), \text{and Cs$_2$CO$_3$ (3 mmol)}]^{159}$.

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

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, tBuOLi 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.](image)

Very recently, one of our collaborators developed an efficient Pd-catalyzed
regioselective arylation at the C3 position of imidazo[1,2-b]pyrazoles 264\textsuperscript{161}. Under microwave irradiation, the optimum reaction conditions were found when using Pd(OAc)$_2$ as catalyst, P(Cy)$_3$ as ligand and K$_2$CO$_3$ 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](image)

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\textsuperscript{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$_2$CO$_3$, 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.](image)

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\textsuperscript{163}. The phenyl group was introduced at the 5-position using Pd(OAc)$_2$ as catalyst in the presence of Cs$_2$CO$_3$ 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.](image)

Very recently, one of us and collaborators reported direct C5-arylation of mono and di-substituted thiazolo[3,2-b][1,2,4]triazoles\textsuperscript{164}. In a representative example, starting material 269 was treated by 4-bromoanisole, Pd(OAc)$_2$, P(Cy)$_3$ and Cs$_2$CO$_3$
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 Cs₂CO₃ and 3 mol% Ru₃(CO)₁₂ to give arylated derivative 272 in good yields (Scheme 158)²⁶⁵.

Scheme 158. Ru₃(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(C₃H₅)(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.


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$_2$CO$_3$ (Scheme 160). 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-heterocycles 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 ($S_{\text{E}}\text{Ar}$), 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

**Biographies**

Saïd El Kazzouli received his Ph.D. in organic chemistry from the University of Orleans in 2004 under the supervision of Prof. G. Guillaumet and Prof. A. Mouaddib. Then, he worked at the same University as a postdoctoral fellow with Prof. L. Agrofoglio and with Prof. S. Berteina-Raboin. In 2006, he joined the NCI at the NIH in the USA as a postdoctoral fellow for 3 years with Dr. V. E. Marquez. In 2009, he became a researcher (project leader) at INANOTECH (MAScIR Foundation) in Rabat, Morocco. In 2013, he joined the Euro-Mediterranean University of Fes, Morocco as an Associate Professor.

Jamal Koubachi received his Ph.D. degree in organic chemistry in 2008 from the University of Orleans (France) under the direction of Professors G. Guillaumet and A. Mouaddib, working on the development and application of palladium-catalyzed direct arylation and alkenylation for the synthesis of various imidazo[1,2-a]pyridine derivatives. Dr. Koubachi then conducted a postdoctoral fellowship at the Institute of Molecular and Materials Chemistry of Orsay, University of Paris-Sud (France) with Professor D. Bonnaffé for 2 years. In 2010 he has been an Assistant Professor at the Faculty of Polydisciplinaire of Taroudant, University of Ibn Zohr (Agadir), Taroudant, Morocco.

Nabil El Brahmi was born in Taounate (Morocco). He obtained in 2007 his M.Sc. in pharmaceutical chemistry from the University Mohamed V (Rabat, Morocco). In 2013, he received his Ph.D in organic chemistry from the same University in collaboration with the Laboratoire de Chimie de Coordination (LCC) at CNRS of Toulouse (France). From May 2013 to January 2014, he worked as a postdoctoral fellow at the Euro-Mediterranean University of Fes, Morocco (UEMF) in collaboration with the LCC. In 2013 he was appointed Assistant Professor at the UEMF. His current research interests are the synthesis of bioactive molecules and drug delivery.

Gérald Guillaumet studied chemistry at the University of Clermont-Ferrand. He joined the group of Prof. Caubère and received his Ph. D. in 1972 from the University of Nancy. Working first as an assistant at the University of Clermont-Ferrand, he was appointed as Maître-Assistant, then as Maître de Conferences at the
University of Nancy. Nominated as full professor in organic chemistry at the University of Orléans in 1983, he became director of the Institute of Organic and Analytical Chemistry and president of the University of Orléans from 2004-2009. He is author of more than 347 publications and 47 patents.