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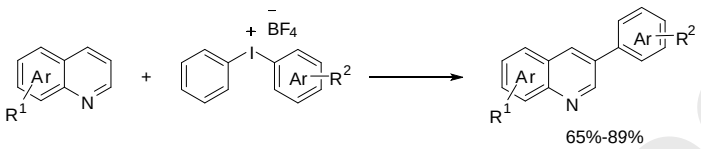

Catalyst: Pd nanoparticles. Oxidant: $Cu(OAc)_2$. No Ligand

R^1 = H, CH_3, NO_2 R^2 = H, CH_3, OCH_3, Cl, F, CF_3, CN

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ABSTRACT

3-Arylquinolines are biologically and medicinally very important compounds. Direct and regioselective C3-H arylation offers a straight forward methodology for their synthesis. In this work, we report their synthesis by a Pd nanoparticle catalyzed reaction with aryliodonium salts as the arylating agent in the presence of stoichiometric oxidant $Cu(OAc)_2$. The reaction works with different quinolines and diaryliodonium salts with both electron donating and electron withdrawing groups. The advantage of the methodology is that it does not require any ligand and the catalyst also is recoverable and recyclable.

Synthesis of 3-arylquinolines and their derivatives has received wide attention in organic synthesis as these form the key framework of several biologically active compounds (Figure 1). For example, 3-arylquinolyl chalcones show potential anticancer activity,[1] 3-aryl substituted 4-chloroquinolines exhibit antiproliferative activity,[2] dimethoxy derivatives of 3-aryl quinolines exhibit inhibitory effects on platelet derived growth factor receptor tyrosine kinase (PDGF-RTK),[3] 3-(2'-fluorophenyl)-*N*,*N*'-dimethylquinoline-2,7-diamine act as promoter for prostate apoptosis response-4 (PAR-4) and was reported to suppress pro-apoptopic tumors,[4] 2,3-diarylquinolines substituted at C4 inhibit cyclooxygenase 1 or 2 selectively[5] and BEZ-235[6] a bis-quinoline ring containing compound, which acts as mTOR-P13K dual inhibitor.

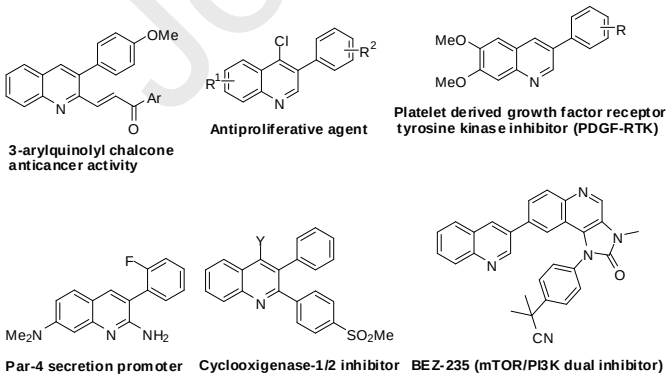

Figure 1. Some biologically and medicinally important 3-arylquinolines.

Synthesis of 3-arylquinolines can be classified according to the following three categories: (i) construction of the quinoline skeleton bearing C3-aryl group from anilines or its derivatives via cyclization (Scheme 1a); (ii) Arylation of C-3 pre-functionalized quinolines (Scheme 1b); (iii) Direct and regioselective C3-H arylation via C-H activation of quinolines. Of these the first and second categories are more explored (Scheme 1c).

Among examples of the first category is one reported by Wang and co-workers involving $FeCl_3$ catalyzed tandem reaction between aryl amines and styrene oxide by means of C-C cleavage.[7] Similarly the reaction of aryl amines or azides with phenylacetaldehyde in presence of CuBr, TfOH or $[Bmim]BF_4$, MW or $PdCl_2$, DMSO, 1-adamentane carboxylic acid was also reported for the synthesis of 3-arylquinolines.[8] Again, Sortais et al. used the reaction between 2-aminobenzyl alcohol and 2-arylacetonitrile in presence of Rhenium PN(H)P catalyst.[9] Similarly, various styrene derivatives have also been reported as the coupling partner with aniline derivatives for the purpose. For example, Kong et al. synthesized 3-aryl quinolines by the reaction between 2-amino benzaldehyde and 2-iodovinyl benzene in presence of CuI catalyst and glycine ligand.[10] Similarly Li et al. and Gattu et al. reported their syntheses by the reaction of β-nitrostyrene with 2-nitro benzaldehyde or α-aminoacetophenone in presence of Fe, AcOH or IBr.[11] In a mechanistically interesting variation, which involved cyclization of the quinoline ring together with opening of the indole ring, Vecchione et al. and Rao et al. reported the synthesis of 2-amino-3-arylquinolines by reacting indole with 2-aminobenzaldehyde or 2-

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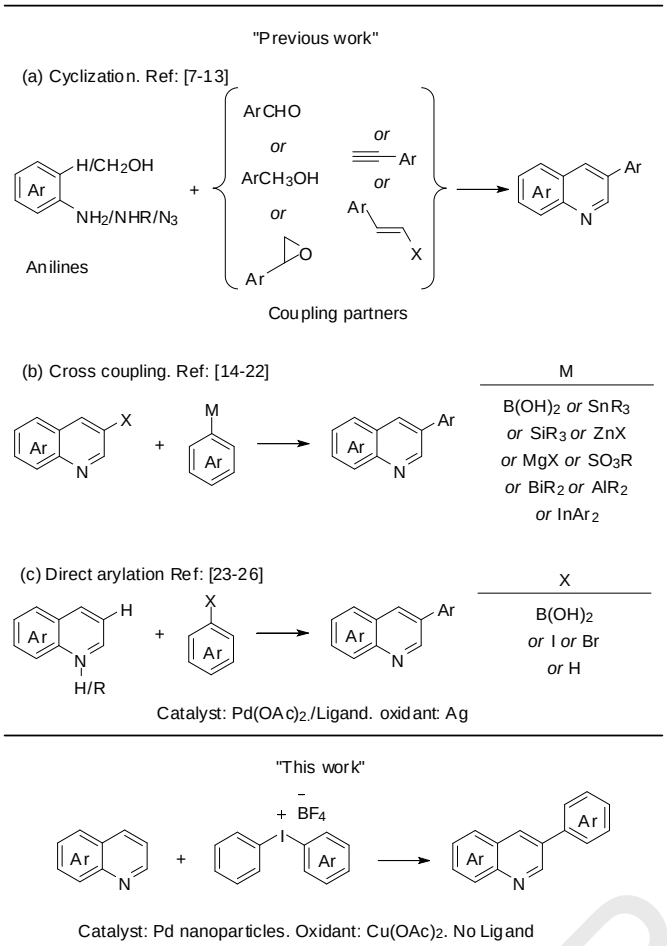


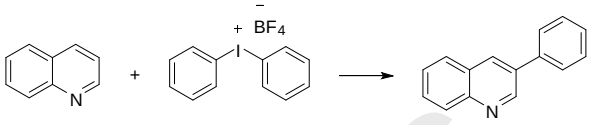
Scheme 1. Previous work and the present work related to the synthesis of 3-arylquinolines.

nitrobenzaldehyde in presence of *p*-TSA or $SnCl_4$ under microwave irradiation.[12] A similar strategy that uses the hetero Diels-Alder reaction was also reported with alkynes and 2-aminobenzyl alcohol or aryl amines, with DMSO as one carbon source for the latter.[13]

Among the examples of the second category are ones that involve the transition-metal-catalyzed cross coupling reactions between 3-haloquinolines with different coupling partners such as aryl boronates,[14] aryl stannates,[15] aryl silane,[16] aryl zinc,[17] aryl magnesium,[18] aryl sulfonates,[19] aryl bismuth,[20] aryl aluminium,[21] and aryl indium.[22]

Among the examples of third category is the report by Yu et al. who reported the direct C3-H activation-based arylation of quinolines with aryl iodides using $Pd(OAc)_2$ as catalyst in presence of ligands and Cs_2CO_3 as base.[23] In the same year, Sames et al. also reported the direct C3-arylation of 4-chloroquinolines using $Pd(OAc)_2$ as catalyst and Ag_2CO_3 as the oxidant in the presence of $PBuAd_2$ as the ligand and several other additives. [24] Kapur and co-workers reported the two step process that involved dearomatization of the heterocyclic ring followed by of heteroatom guided regioselective C3-arylation of quinolines with concomitant rearomatization.[25] Another C-H activation based strategy was reported by Huang and co-workers involved the regioselective C3-arylation of isolated quinolines with chlorobenzenes (usually trichloro or dichloro- benzene) with $Pd(OAc)_2$ catalyst and Ag_2CO_3 as oxidant in the presence of excess adamentane-1-carboxylic acid.[26] However, all the above C-H based strategies present some limitations such as limited scope of the quinoline or the arylating partner or the requirement of an extra step in the form of the protection of the *N*-atom of the and herein we report the regioselective synthesis of 3-aryl quinoline via the direct C-H activation reaction of simple quinolines using preformed, surfactant-free and clean palladium nanocatalyst (PdNC) with $Cu(OAc)_2$ as oxidant in absence of any ligands with diaryliodonium compounds as arylating agent.

Table 1. Optimaziation of the conditions for the C3-arylation of quinolines.

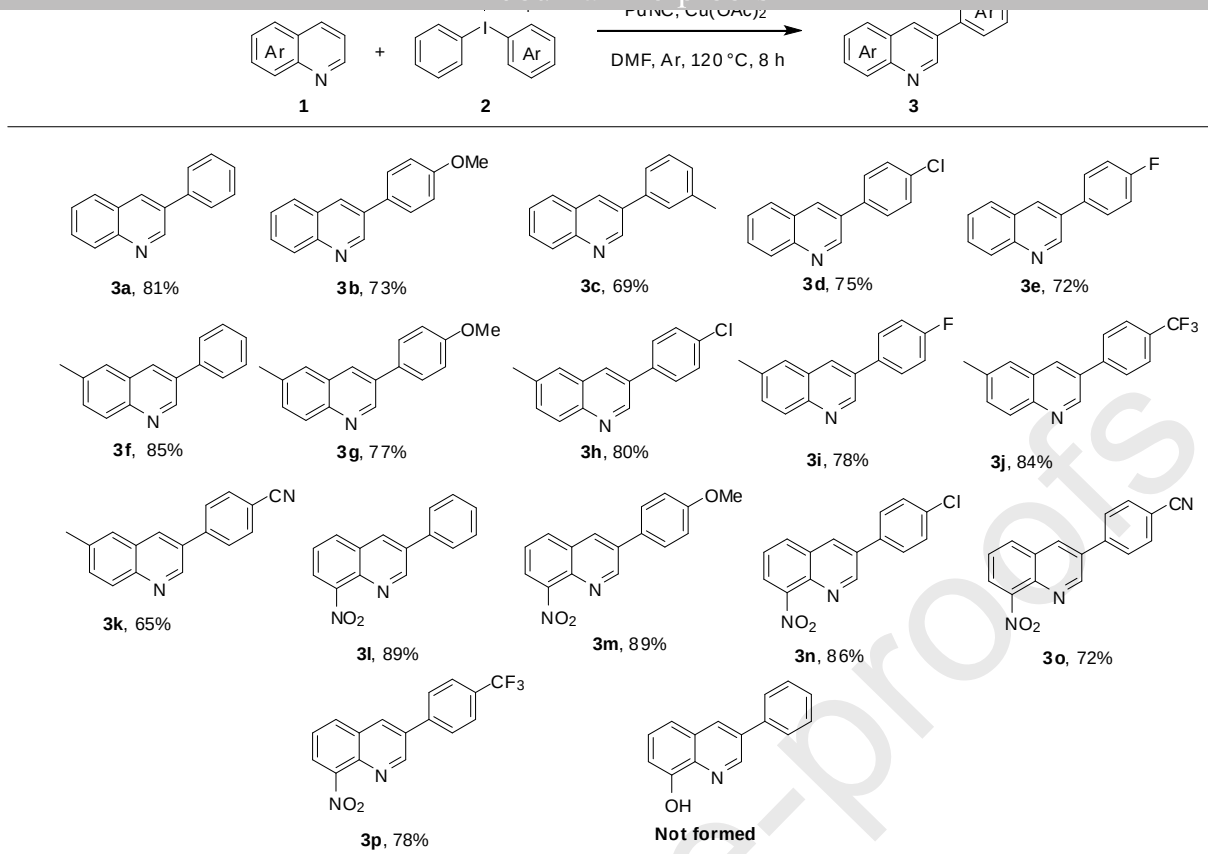


Entry[a]	Oxidant	Solvent	Temp., Time	Yield[b]
1	$Cu(OAc)_2$	MeCN	80 °C, 48 h	21
2	$Cu(OAc)_2$	THF	65 °C, 48 h	39
3	$Cu(OAc)_2$	DMSO	120 °C, 18 h	45
4	$Cu(OAc)_2$	DMF	120 °C, 8 h	81
5	-	DMF	120 °C, 48 h	0
6[c]	$Cu(OAc)_2$	DMF	120 °C, 48 h	0
7	TEMPO	DMF	120 °C, 48 h	0
8	O_2	DMF	120 °C, 48 h	0
9[d]	$Cu(OAc)_2$	DMF	120 °C, 8 h	38

[a] Reaction conditions: **1a** (1 mmol), **2a** (1.2 mmol), oxidant (1.5 mmol) Solvent (5 mL), PdNC (3 mg) was heated under Ar at appropriate temperature for indicated time. [b] Isolated yield. [c] No Pd catalyst was used. [d] $Pd(OAc)_2$ was used as catalyst.

The Pd nanocatalyst (PdNC) used as catalysts was synthesized following a procedure we had previously reported.[27] The synthesized and isolated nanoparticles were thoroughly characterized again through a variety of techniques such as TEM, HRTEM, TEM-EDX and XPS.[27] The TEM analysis showed a particle size distribution of 2.5-5 nm. The TEM-EDX confirmed the nanoparticles as those of Pd. The HRTEM-SAED diffraction image showed the presence of several crystalline phases including those for Pd (0) and PdO. More specifically the crystalline planes (1 1 1), (2 0 0), (2 2 0) having interlayer spacings of 2.27, 1.96, 1.39 Å respectively could be identified for Pd (0) and the crystalline plane (2 1 0) having the interlayer spacing of 1.34 Å corresponding to PdO. XPS spectroscopy confirmed the oxidation state of the nanoparticles. The deconvoluted XPS spectra revealed the peaks for Pd(0) at 334.2 and 339.8 eV corresponding to $3d_{5/2}$ and $3d_{3/2}$ as well as the peaks for PdO at 336.6 and 341.2 eV corresponding to $3d_{5/2}$ and $3d_{3/2}$ for PdO.

Initial optimization reactions for the arylation of the quinolines was carried out by the reaction of quinoline **1a** and diphenyl iodonium tetrafluoroborate **2a** in the presence of 3 mg of the PdNC. Several oxidants as well as the solvents were screened for the reaction (Table 1). The optimization reactions revealed that the reaction was best carried out in the presence of $Cu(OAc)_2$ as oxidant and DMF solvent at 120 °C, affording 3-phenylquinoline **3a** in 81% (Entry 4, Table 1). As a control experiment, the reaction was also carried out in the absence of any PdNC using only 1.5 equivalents of $Cu(OAc)_2$ when it was seen that none of the product **3a** was formed (Entry 5, Table 1). A reaction was also carried out using $Pd(OAc)_2$ without any added ligand in the presence of similar equivalent of $Cu(OAc)_2$ which provided the 3-arylated quinoline only in 38% yield (Entry 9, Table 1).

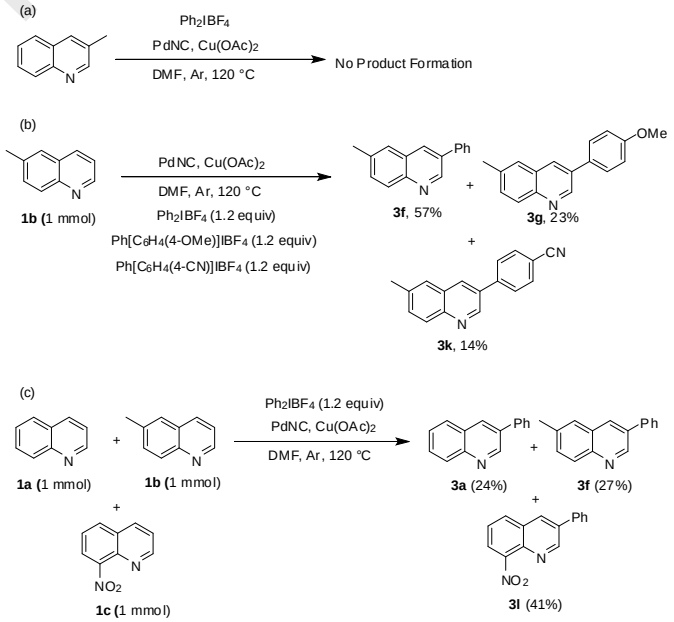


Scheme 2 Substrate scope for the synthesis of the 3-arylquinolines Reactions were carried out with 1 mmol of under the optimized conditions. Isolated yields are reported.

After establishing the optimum conditions for the reaction, the arylation of different quinoline derivatives with different aryliodonium salts were carried out under the standard conditions. The results are summarized in Scheme 2. The reactions were successful, affording the C-3 arylated quinolines regioslectively with substrates having both electron donating and electron withdrawing groups on the quinoline moiety as well as the aryliodonium salts. The reaction was successful with the aryliodonium compounds having substituents like Cl, F, CN OMe and CF_3 groups providing the corresponding C3-arylated quinolines in very good yields. However 8-hydroxyquinoline was inert towards the arylation reaction under the standard conditions.

To investigate and confirm whether the regioselectivity was exclusive or not, a control experiment was carried out using 3-methylquinoline (Scheme 3a). No product was formed in the reaction which provided a confirmation that the methodology was useful only for the selective activation of the quinoline C3-H. In order to investigate the effect of electronic effects on the product formations, a parallel reaction was carried out with three different diaryliodonium salts with **1b** (Scheme 3b). It was found that the reaction with the diaryliodonium salt bearing electron donating group was preferred over the one bearing an electron withdrawing group. Compensating for the statistical factor, it was also found that the yield for the reaction with the diaryliodonium salt bearing electron donating group was slightly more than the one with the diphenyliodonium salt. With respect to the quinolines, it was found that the reaction with quinolines was preferred with a substrate bearing electron withdrawing groups over substrates bearing electron donating group (Scheme 3c). From the above experiments a general understanding of the mechanism of the aryl transfer from the aryliodoniums can be made.

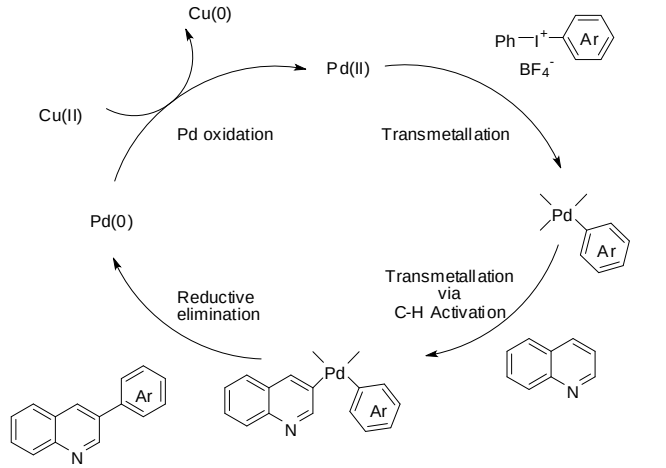
Based on the mechanism of the Pd catalyzed arylation reactions with hypervalent iodonioum salts proposed by Sanford and co-workers, a very plausible mechanism that is also



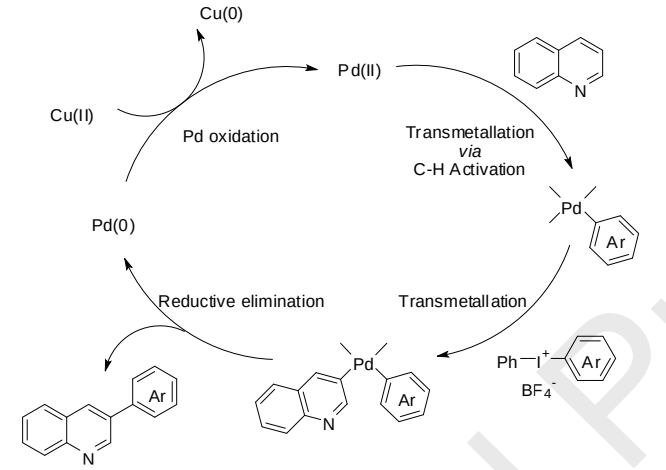
Scheme 3. Control experiments (a) effect of blocking the C3 of the quinoline. (b) Effect of electron donating and withdrawing groups on the aryliodonium salts. (c) Effect of electron donating and withdrawing groups on the quinoline.

consistent with the greater reactivity of the electron rich iodonium salt is depicted in Scheme 4a and involves the Pd(II) as catalyst.[28] It involves initial transmetallation between the iodonium salt and Pd(II) followed by C-H activation based transmetallation with the quinoline moiety and subsequent reductive elimination to generate the product **3**.[28] The reactions of the aryliodonium salts bearing electron deficient groups on the other hand can be explained by mechanism depicted in Scheme 4b which again involves catalysis by Pd(II) species. Due to the

(a) activation (Electron Rich iodonium salts)



(b) C-H activation by Pd(II) Transmetallation to Pd(IV) (Electron deficient iodonium salts)



Scheme 4. Probable mechanism of the arylation of the quinolines.

lower reactivity of the electron deficient aryls towards the oxidative addition to the Pd(0) species, initially the insertion of the quinoline moiety occurs through C-H activation followed by oxidative addition of the aryliodonium salt to generate Pd(IV) intermediate and consequent reductive elimination to generate the product **3**.[28]

The recyclability of the solid PdNC was then verified by the reaction of **1a** with **2a**. The catalyst was recovered by means of centrifugation of the reaction mixture after dilution with water and ethyl acetate and reused as the catalyst for successive reactions for up to 8 cycles (Figure S8, SI). The yields of the reactions dropped very insignificantly up to the 5th cycle and quite rapidly in the subsequent cycles. As a preliminary test to determine whether the actual catalyst was the nanocatalyst or a leached Pd species, the *in situ* ICPMS analysis of the reaction medium (for the reaction between **1a** and **2a**) was also carried out to detect any leached Pd species after removal of the catalyst. A very negligible level of Pd (3.3891 ppb) was detected that indicated that probably the reaction was catalyzed by the PdNC nanoparticles itself.

In conclusion, we have established a new approach towards the direct synthesis of 3-arylquinolines through the nano Pd catalyzed C-H arylation reaction of quinolines and diaryl ates several functional groups on both the moieties. The methodology can be used either for late stage arylations of the quinoline moiety or further modifications on the phenyl ring for applications in medicinal chemistry.

Acknowledgments

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Supplementary Material

Detailed experimental procedures, additional figures and characterization data and NMR spectra are presented.

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Highlights

- Direct synthesis of 3-arylquinolines by the regioselective arylation of quinolines.
- Broad substrate scope of the aryliodonium salts used as arylation agent.
- Electron donating as well as electron withdrawing substituents on quinoline are tolerated.
- Heterogeneous and recyclable catalysis by Pd-nanoparticles.