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Palladium-Catalyzed Selective C–H Activation: A Simple Method to Synthesize C-3 Site Arylated Quinoline Derivatives

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Abstract: A novel protocol for the synthesis of 3-arylated quinoline derivatives has been developed using silver carbonate (Ag_2CO_3) and dioxygen (O_2) as the oxidants. In this method, quinolines acting as the parent reagent react with arenes under palladium acetate [$Pd(OAc)_2$] catalysis along with 1-adamantanecarboxylic acid (Adm). The combination of the 1-adamantanecarboxylic acid ligand and the palladium catalyst is found to be an essential factor for achieving high activity and selectivity, and allows a wide range of 3-arylquinoline derivatives to be obtained in high yields. Moreover, a relevant mechanism is proposed, revealing that un der the palladium(II) catalysis a migratory insertion to C-3–H of quinolines and insertion to the C–H of arenes are key steps in this reaction. Mild reaction conditions and high selectivity of the reactive site provide potential for promising applications in drug discovery and functional materials.

Keywords: C–H activation; one-pot reaction; palladium catalysts; quinolones; selective functionalization

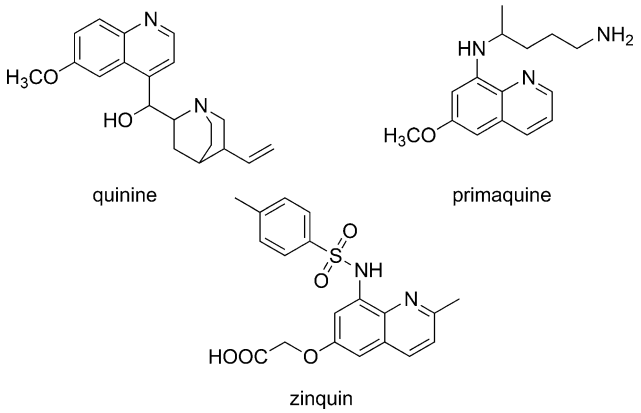
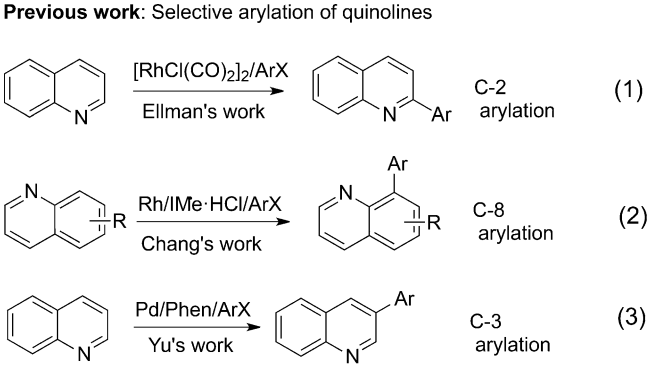
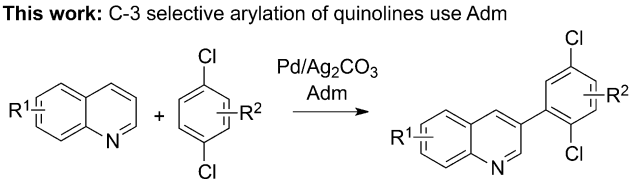


Figure 1. Biologically active quinoline derivatives.





Scheme 1. Selective arylation of quinolones.

Quinoline, as an important skeleton motif involved in many biologically active compounds[1] and functional materials,[2] was often employed for the formation of useful heterocycles, such as quinine, primaquine and zinquin (Figure 1).[3] As a consequence, the selective functionalization of quinolines at different active sites has received considerable attention over the past decades.[4] In the cases reported, transition metal-catalyzed C–H activation leading to C–C bond formation,[5,6] as one of promising approaches, makes the inactive sites of quinolines more simple and easy to be tailored. In 2008, Ellman's group developed a Rh(I)-catalyzed strategy for the direct arylation of pyridines and quinolines at the C-2 position [Scheme 1, Eq. (1)].[7] Chang's group developed a Rh(NHC)-catalyzed arylation of quinolines. Under these Rh(NHC) catalytic condition, a wide range of 8-arylquinoline

derivatives was obtained in high yields for the first time [Scheme 1, Eq. (2)].[8] Yu's group achieved the C-3 selective arylation of quinolines by using the combination of 1,10-phenanthroline (Phen) and a palladium complex as catalyst. The Phen ligand was found to be necessary to access 3-arylquinolines in high selectivity and yield. This was the first report on non-directed C-3 selective arylation of unprotected quinolines and pyridines [Scheme 1, Eq. (3)].[9] However, it is still a tremendous challenge to regioselectively control the active site of quinolines in the construction of C–C bonds.

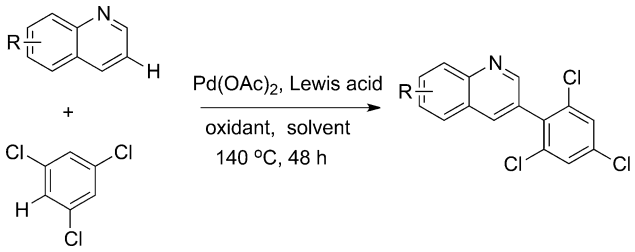
Herein, inspired by our previous work on the development of C-2 selective arylation of quinolines,[10] we examined the feasibility of a direct arylation at the C-3 site of quinolines catalyzed by Pd(II) and used quinolines and chlorobenzenes as substrates. In the formation of chlorphenylquinoline derivatives, Ag_2CO_3 and O_2 were used as the oxidants, the Adm ligand plays a key role in the selective C–H activation. This method would represent a significant advance in the highly selective functionalization of quinolones and, subsequently, it would open up new opportunities in chemical synthesis.

At the outset of our investigations, a combined catalytic system of $Pd(OAc)_2$ (10 mol%), Ag_2CO_3 (3.0 equiv.) as oxidant and PivOH (2.0 equiv.) as additive was employed. When the reaction was accomplished in DMF (1.5 mL) at 140 °C for 72 h, only a 40% isolated yield was obtained. When the amount of PivOH was increased up to 4.0 equiv., the yield of product **3ab** increased to 60%. Subsequently, a variety of additives was screened (Table 1, entries 4–6), the result revealed that Adm offered the better yield and decreased appreciably the reaction time. Exploration of oxidants disclosed that only Ag_2CO_3 was more active as compared to AgOAc, $Cu(OAc)_2$, MnO_2, DDQ and $K_2S_2O_8$, which was in agreement with our previous reports. Screening of solvents showed that DMF was the best choice. Although all of these reaction pathways did not require external oxidants, the addition of O_2 (1 atm) could increase the yield from 60% to 70% (Table 1, entry 16). Additionally, the use of PPh_3, 1,10-phenanthroline (phen), DPPB, DPPE as ligands provided the product in lower yields.

With the optimized reaction conditions in hand, the substrate scope was investigated as shown in Table 2. The quinoline (**1a**) reacts with the 1,3,5-trichlorobenzene (**2b**) to afford **3ab** in 70% isolated yield. Next, a variety of substrates bearing a single substituent on the aryl ring was surveyed, both electron-donating and electron-withdrawing groups, such as methoxy, nitro, halogen, methyl and ester, were compatible with this transformation. The predicted products were formed in moderate to good yields (**3bb–3ib**). It is noteworthy that methoxy and chloride on the ring represent versatile handles for further transformations.[11] Notably, when quinolines possessing a methyl group at the pyridyl ring C-2 and C-4 sites were examined (**3jb**, **3kb**), only trace amounts of products were detected on the silica gel TLC. It was deduced that this result was due to both electronic effects and steric effects. Additionally, compared with quinolines, 5,6,7,8-tetrahydroquinoline and 6,7-dihydro-5*H*-cyclopenta[*b*]pyridine as substrates also exhibited some reactivity to give the desired products 3-(2,4,6-trichlorophenyl)-5,6,7,8-tetrahydroquinoline and 3-(2,4,6-trichlorophenyl)-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine, respectively.

Encouraged by the above results, further exploration of the reactivity of diverse arenes was undertak-

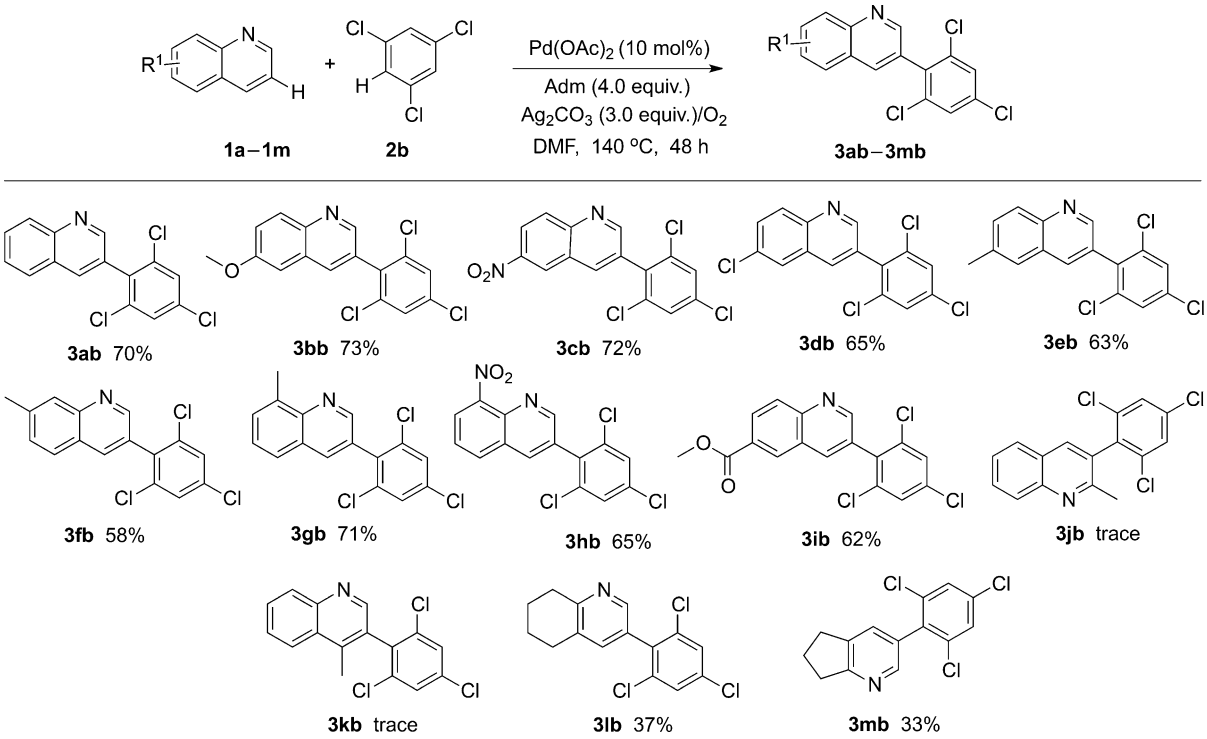
Table 1. Optimization of the reaction conditions.[a]



Entry	Oxidant (equiv.)	Additive (equiv.)	Time [h]	Solvent	Yield[b] [%]
1	Ag_2CO_3 (3.0)	PivOH (2.0)	72	DMF	40
2	Ag_2CO_3 (3.0)	PivOH (3.0)	72	DMF	47
3	Ag_2CO_3 (3.0)	PivOH (4.0)	72	DMF	60
3	Ag_2CO_3 (3.0)	PivOH (5.0)	72	DMF	53
4	Ag_2CO_3 (3.0)	AcOH (4.0)	72	DMF	20
5	Ag_2CO_3 (3.0)	TFA (4.0)	72	DMF	trace
6	Ag_2CO_3 (3.0)	Adm (4.0)	48	DMF	66
7	AgOAc (3.0)	Adm (4.0)	48	DMF	47
8	$Cu(OAc)_2$ (3.0)	Adm (4.0)	48	DMF	0
9	MnO_2 (3.0)	Adm (4.0)	48	DMF	37
10	DDQ (3.0)	Adm (4.0)	48	DMF	42
11	$K_2S_2O_8$ (3.0)	Adm (4.0)	48	DMF	0
12	Ag_2CO_3 (3.0)	Adm (4.0)	48	NMP	35
13	Ag_2CO_3 (3.0)	Adm (4.0)	48	DMSO	15
14	Ag_2CO_3 (3.0)	Adm (4.0)	48	toluene	42
15	Ag_2CO_3 (3.0)	Adm (4.0)	48	DMA	50
16[c]	**Ag_2CO_3 (3.0)**	**Adm (4.0)**	**48**	**DMF**	**70**
17[d]	Ag_2CO_3 (3.0)	Adm (4.0)	48	DMF	33
18[e]	Ag_2CO_3 (3.0)	Adm (4.0)	48	DMF	27
19[f]	Ag_2CO_3 (3.0)	Adm (4.0)	48	DMF	57
20[g]	Ag_2CO_3 (3.0)	Adm (4.0)	48	DMF	50

[a] *Reaction conditions:* quinolines (0.2 mmol), $Pd(OAc)_2$ (10 mol%), 1,3,5-trichlorobenzene (2.0 mmol), oxidant, and additive in DMF (1.5 mL) at 140 °C for 48 or 72 h.
[b] Yields of isolated products.
[c] O_2 (1 atm) was used.
[d] PPh_3 was used as ligand.
[e] 1,10-Phen was used as ligand.
[f] DPPB was used as ligand.
[g] DPPE was used as ligand.

Table 2. Synthesis of 3-(1,3,5-trichlorophenyl)quinolines from substituted quinolines and 1,3,5-trichlorobenzene.[a]



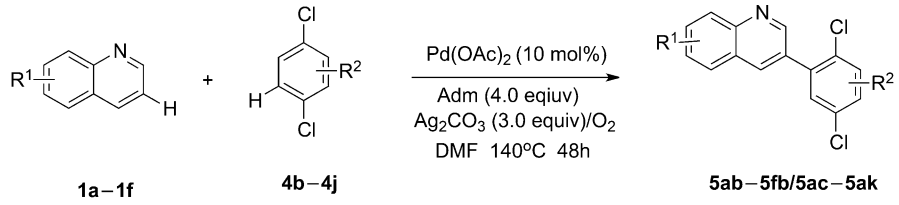
[a] *Reaction condition:* quinolines (0.2 mmol), $Pd(OAc)_2$ (10 mol%), 1,3,5-trichlorobenzene (2.0 mmol), Ag_2CO_3 (0.6 mmol), and Adm (0.8 mmol) in DMF (1.5 mL) at 140 °C for 48 h, O_2 (1 atm).

en. As shown in Table 3, 1,4-dichlorobenzene was suitable to react with a series of quinolines and pyridines, respectively, generating the desired products (**5ab**–**5fb**) in moderate to good yields. Beyond that other dichlorobenzenes such as 1,2-dichlorobenzene and 1,3-dichlorobenzene also furnished the corresponding products in good yields (**5ac**, **5ad**). Furthermore, the reaction of multi-chloro-substituted arenes with quinoline also proceeded smoothly to give the product 3-(2,3,5,6-tetrachlorophenyl)quinoline (**5ae**), albeit in low yield. Furthermore, mono-substituted arenes, like chlorobenzene, generated *m/p* mixtures (**5af**). When the reaction was run with quinoline and 2,6-dichloro-1-methylbenzene, the only product with a specific structure (**5ag**) was isolated in 53% yield. The electronic effect of substituents on the arenes was clearly present, for example, 1,3,5-trifluorobenzene and quinoline were compatible with the reaction conditions and gave the corresponding product 3-(2,4,6-trifluorophenyl)quinoline (**5ah**) in 47% yield, while tribromobenzene and triiodobenzene furnished a trace of product and failure, respectively. Under the standard conditions, benzene methyl ether and nitrobenzene also failed to react. Interestingly, the parent pyridine and 1,2,3,4-tetrachlorobenzene can undergo a dehydrogenative C–C coupling to form the product 3-(2,3,4,5-tetrahlorophenyl)pyridine in 19% yield.

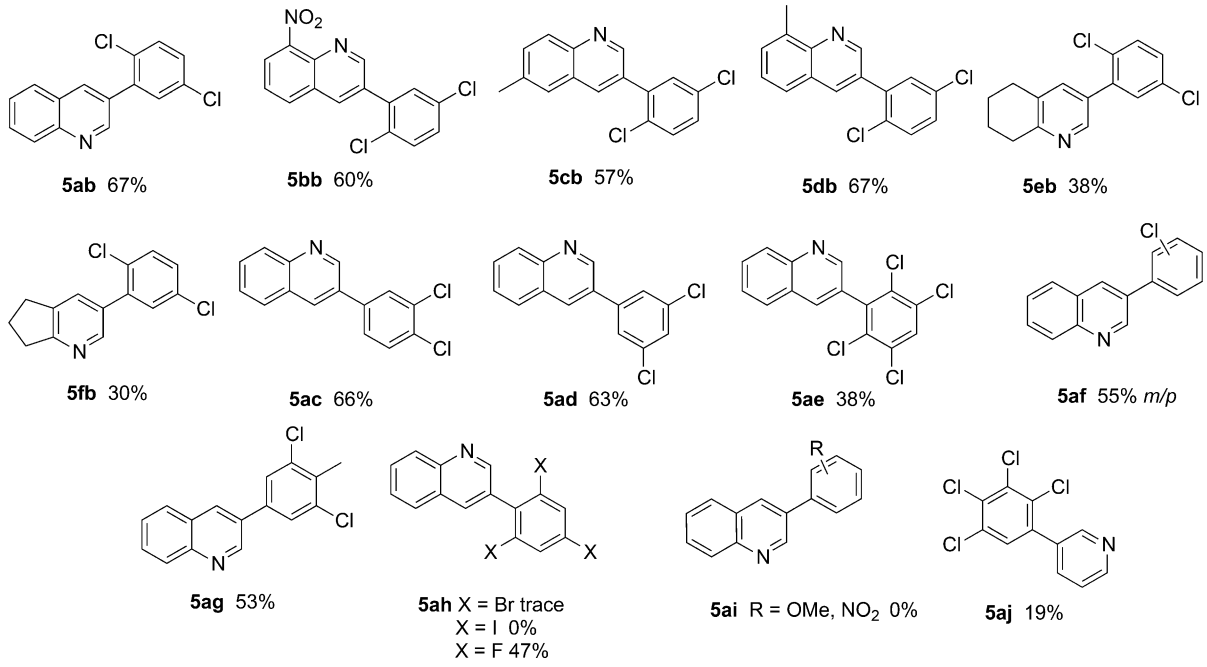
The C-3 arylation probably follows the pathway delineated in Figure 2. The first step involves quinoline (**1a**) which can potentially coordinate with Pd(II) through the N atom to form **A**, assisted by the ligand Adm.[10] Under the steric effect of the Adm ligand, **A** subsequently reorients itself to the π system through a *trans* effect process, which triggers C-3–H activation, and a molecule of Adm leaves to form **B**.[9] Then C–H activation of **2b** by electrophilic palladation, affords an intermediate **C**.[12] The last step is reductive elimination from **C** to furnish the 3-aryl C–C bond. Pd(0) is reoxidized to Pd(II) by Ag(I)/Adm/O_2 to close the catalytic cycle.

In summary, a novel protocol for the effective Pd-catalyzed C-3 arylation of quinolines has been developed using O_2 and Ag_2CO_3 as the oxidants, with Adm as the ligand. The choice of Adm ligand in combination with the poalladium catalyst source was found to be essential in achieving high activity and selectivity, allowing a wide range of 3-arylquinoline derivatives to be obtained in moderate to high yields. This strategy provides a simple and efficient method for quinoline C-3–H bond activation. The resulting C-3 arylated quinolines can be used as building blocks for the synthesis of bioactive alkaloid natural products and drug molecules. Ongoing work seeks to exploit this mechanistic manifold for other synthetically useful

Table 3. Synthesis of 3-arylquinolines from quinolines and substituted chlorobenzenes.[a]



1a–1f + **4b–4j** → **5ab–5fb/5ac–5ak**



[a] *Reaction conditions:* quinolines (0.2 mmol), $Pd(OAc)_2$ (10 mol%), substituted chlorobenzenes (2.0 mmol), Ag_2CO_3 (0.6 mmol), and Adm (0.8 mmol) in DMF (1.5 mL) at 140 °C for 48 h, O_2 (1 atm) was used.

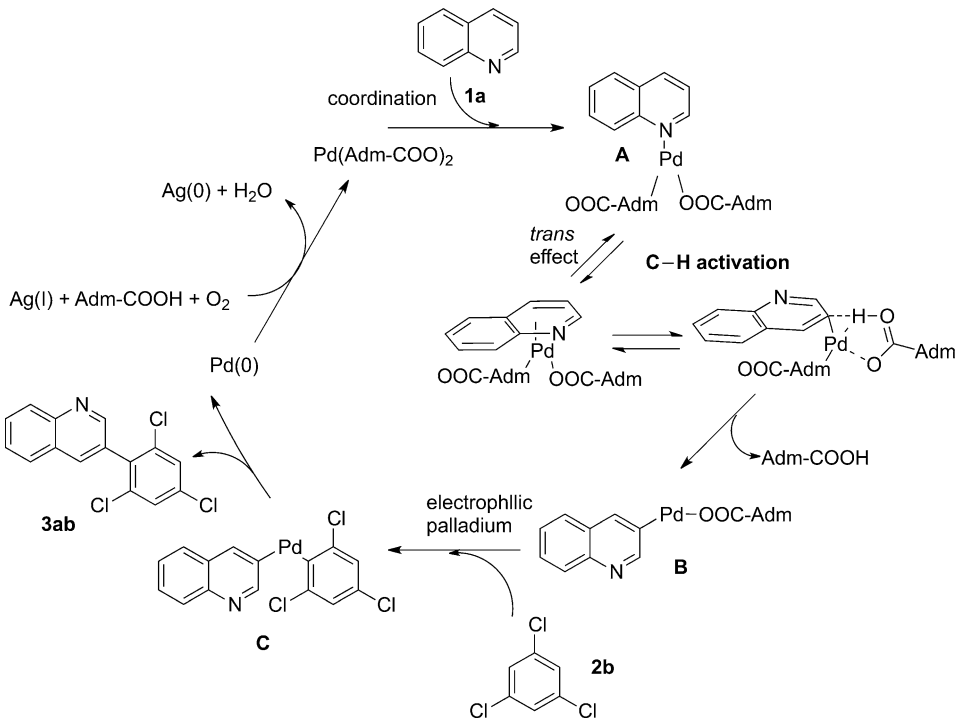


Figure 2. Plausible mechanistic pathway.

cross-coupling reactions as well as to further probe the mechanism of these new transformations.

Experimental Section

General Procedure

A test tube was charged with quinoline (0.2 mmol), $Pd(OAc)_2$ (10 mol%), Ag_2CO_3 (0.6 mmol), 1,3,5-trichlorobenzene (2.0 mmol), and Adm (0.8 mmol) in DMF (1.5 mL). The reaction mixture was stirred at 140 °C under 1 atm of dioxygen (balloon pressure) for 48 h. After cooling to room temperature, the solution was diluted with 10 mL ethyl acetate and washed with 5 mL brine and dried over anhydrous Na_2SO_4. After the solvent was evaporated under vacuum, the residues were purified by column chromatography, eluting with petroleum ether/EtOAc to afford pure 3-(2,4,6-trichlorophenyl)quinolines.

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