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Palladium-Catalyzed C-2 Selective Arylation of Quinolines

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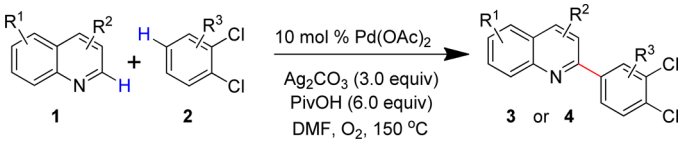
ABSTRACT



An efficient method for the Pd-catalyzed regioselective C-2 arylation of quinolines is presented. Reactions of various substituted quinolines and unactivated arenes have been conducted under mild conditions. The result shows good product yields of 2-arylquinolines, which are highly useful building blocks for the synthesis of bioactive alkaloid natural products and drug molecules.

Biaryl structural motifs are indispensable structures which are frequently found in biologically active molecules, natural products, and organic materials and have been attracting chemists' attention for decades.[1,2] Therefore, transition-metal-catalyzed aryl−aryl bond formation through the coupling of two C−H bonds is of high importance to organic chemists.[3] Direct arylation affords biaryls in fewer steps compared to traditional methods.[4] Consequently, much attention has been given to developing synthetic pathways for creating an aryl−aryl bond via C−H activation.

Quinolines are one of the key components of many synthetic building blocks, natural products, and drug candidates.[5] In the past decades, a variety of methods have been developed to functionalize quinoline compounds. Previous researchers[6−17] have reported several efficient protocols to synthesize C-2 aryl quinolines by transition-metal-catalyzed coupling reactions of its derivatives (e.g., *N*-oxides and *N*-iminopyridinium ylides and heteroaryl

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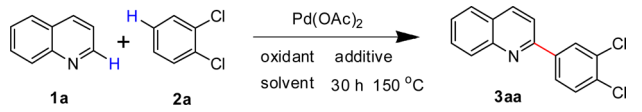
Table 1. Optimization of Reaction Conditions[a]



entry	oxidant (equiv)	addition (equiv)	solvent	yield (%)
1	AgOAc (2.0)	PivOH (2.0)	DMF	32
2	Ag_2CO_3 (2.0)	PivOH (2.0)	DMF	38
3	$Cu(OAc)_2$(2.0)	PivOH (2.0)	DMF	0
4	Ag_2CO_3 (3.0)	PivOH (2.0)	DMF	42
5	Ag_2CO_3 (3.0)	PivOH (4.0)	DMF	45
6	Ag_2CO_3 (3.0)	PivOH (6.0)	DMF	52
7	Ag_2CO_3 (3.0)	PivOH (8.0)	DMF	48
8[b]	Ag_2CO_3 (3.0)	PivOH (6.0)	DMF	60
9	Ag_2CO_3 (3.0)	AcOH (6.0)	DMF	50
10	Ag_2CO_3 (3.0)	TFA (6.0)	DMF	12
11	Ag_2CO_3 (3.0)	PivOH (6.0)	DMAc	58
12	Ag_2CO_3 (3.0)	PivOH (6.0)	NMP	55
13	Ag_2CO_3 (3.0)	PivOH (6.0)	DMSO	46
14	Ag_2CO_3 (3.0)	PivOH (6.0)	Dioxane	23
15	Ag_2CO_3 (3.0)	PivOH (6.0)	AcOAc	0
16[c]	Ag_2CO_3 (3.0)	PivOH (6.0)	DMF	21
17[d]	Ag_2CO_3 (3.0)	PivOH (6.0)	DMF	47
18[e]	Ag_2CO_3 (3.0)	PivOH (6.0)	DMF	11
19[f]	Ag_2CO_3 (3.0)	PivOH (6.0)	DMF	42

[a] Reaction condition: quinolines (0.2 mmol), $Pd(OAc)_2$ (10 mol %), 1,2-dichlorobenzene (1.0 mL), Ag_2CO_3 (0.4 mmol), and PivOH (0.4 mmol) in DMF (0.6 mL) at 150 °C for 30 h. [b] O_2 (1 atm) was used. [c] 1,10-Phen was used as ligand. [d] *i*-Pr_2S was used as ligand. [e] PPh_3 was used as ligand. [f] Run at 130 °C.

halide) and functionalized arylenes. However, these methods required the prefunctionaliztion of one or both coupling partners. In addition, the pioneering works reported by Ong[18] and Nakao[19] have independently demonstrated that, in the presence of Lewis acids and N-heterocyclic carbene nickel complexes, not only the selective activation of the C-3 carbon but also the unprecedented C-8 selectivity alkylation of quinolones were achieved. In addition, Sames and co-workers[20] have developed a new catalytic protocol for high regioselectivity at C-4 and C-6 arylation of quinolines containing electron-withdrawing substituents ($-NO_2$). Recently, Kapur and co-workers disclosed a two-step approach for quinoline C-3 arylation,[21] and You and co-workers described the Pd-catalyzed oxidative C−H/C−H coupling of pyridines and heteroarenes.[22] To date, the oxidative coupling of arenes with quinolines has been quite challenging due to their relatively low reactivity. Furthermore, the stereoselective functionalization is often more difficult. Thus, an efficient and stereoselective synthetic route to aromatic quinolines, which does not required any preactivation, is among the most desireable transformations. Herein, we have developed a novel Pd-catalyzded method for the selective arylation of quinolines.

Inspired by our previous work[23] on C-2 selective C−H olefination of pyridine derivatives via a Pd(II)/Pd(0) catalytic manifold, we investigated the possibility of achieving quinoline C-2 arylation with unactivated arenes through palladium C−H activation chemistry. Our results shows that quinoline (**1a**, 0.2 mmol) and 1,2-dichlorobenzene (**2a**, 1.0 mL) as substrates can efficiently produce the sole meta-selective arylation of 1,2-dichlorobenzene (**3aa**) in the presence of AgOAc (0.4 mmol) and pivalic acid (PivOH) (0.4 mmol) in *N*,*N*-dimethylformamide (DMF) at 150 °C in air. In order to find the best oxidants under $Pd(OAc)_2$ catalysis, we chose AgOAc, Ag_2CO_3, and $Cu(OAc)_2$ as candidates. The results showed that using Ag_2CO_3 as oxidants can give the best yield, followed by AgOAc, but using $Cu(OAc)_2$ leads to no production of **3aa** (Table 1, entries 1−3). Further optimization showed that increasing the amount of Ag_2CO_3 remarkably improved the product yield (Table 1, entry 4). Additionally, we found that increasing the quantity of PivOH to 6.0 equiv would increase the efficiency for the reaction (Table 1, entries 5−7). Although all of these reaction pathways did not require external oxidants, the addition of O_2 (1 atm) can increase the yield from 52% to 60% (Table 1, entry 8). Replacing PivOH with acetic acid (AcOH) or trifluoroacetic acid (TFA) did not improve the yield of the desired product (Table 1, entries 9 and 10). Furthermore, we studied the solvent effect and found that DMF was superior to *N*,*N*-dimethylacetamide (DMA), *N*-methyl-2-pyrrolidone (NMP), dimethyl sulfoxide (DMSO), dioxane, or AcOAc (Table 1, entries 11−15). In addition, the use of 1,10-phenanthroline (phen), i-Pr_2S, PPh_3 as ligand provided the product in lower yield. Thus, quinoline was considered to be a ligand by itself (Table 1, entries 16−18). In addition, the reaction temperature was crucial for the reaction. Compared with the results under the conditions in Table 1, entry 8, the model reaction catalyzed by $Pd(OAc)_2$ at 130 °C gave **3aa** in 42% yield (Table 1, entry 19), suggesting that higher temperature was beneficial for the formation of the target.

With the optimized conditions, we examined the compatibility of the quinoline coupling partners (Scheme 1). Generally, quinoline was arylated smoothly to give the corresponding C-2 arylation product with excellent meta-selectivity with respect to 1,2-dichlorobenzene. At first, compared with electron-rich analogues, electron-deficient C-6 substituted quinolines exhibited high reactivity in the procedure (**3ba**, **ca**). Similarly, substitution at C-5 by the nitro group also gave the desired product in excellent yield (**3da**). Additionally, a number of halogenated quinolines treated with 1,2-dichlorobenzene with high regioselectivity to give the 2-arylated products in moderate to good

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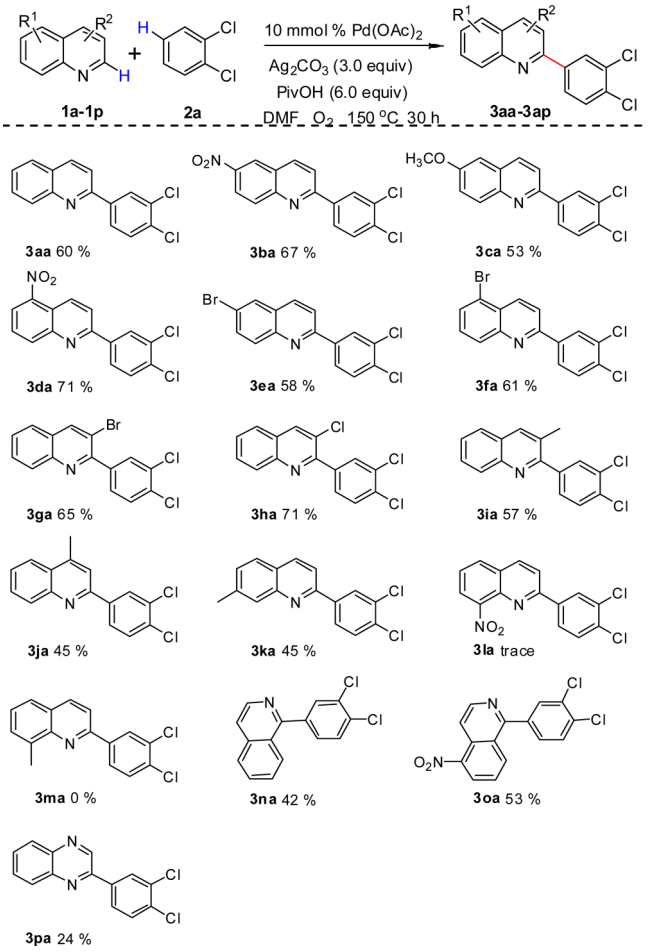
Scheme 1. Synthesis of 2-(3,4-Dichlorophenyl)quinolines from Substituted Quinolines and 1,2-Dichlorobenzene[a]



[a] Reaction condition: quinolines (0.2 mmol), $Pd(OAc)_2$ (10 mol %), 1,2-dichlorobenzene (1.0 mL), Ag_2CO_3 (0.6 mmol), and PivOH (1.2 mmol) in DMF (0.6 mL) under O_2 at 150 °C for 30 h.

yields (**3ea**–**ha**). It was noteworthy that methoxy, chloride, and bromide on the ring were versatile handles for further transformations.[24] When the electron-donating methyl group was presented in quinoline, the yields of desired product were dramatically decreased from those containing electron-withdrawing groups (**3ia**–**ka**). This demonstrated that the position and the electronic properties of the substituents on the rings were more influential than steric effects in the reaction systems. Notably, the quinoline with a nitro group at C-8 may not be suitable for the process as the desired product was not isolated, and only a trace amount of product was detected on the silica gel (**3la**); however, a methyl group at C-8 did not work directly under the standard conditions (**3ma**). Furthermore, exclusive C-1-selectivity was observed. Isoquinoline and 5-NO_2-isoquinoline achieved moderate yields (**3na**,**oa**), and arylation of quinoxaline gave a relatively low yield (**3pa**).

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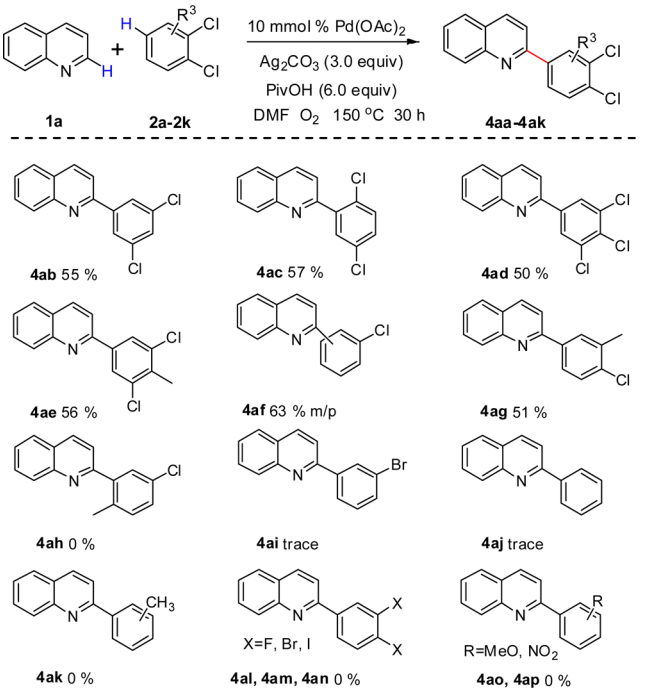
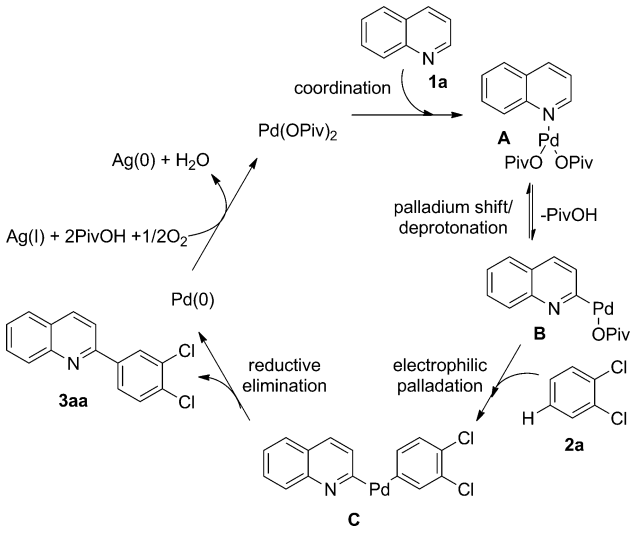
Scheme 2. Synthesis of 2-(3,4-Dichlorophenyl)quinolines from Quinolines and Substituted Dichlorobenzene[a]



[a] Reaction condition: quinolines (0.2 mmol), $Pd(OAc)_2$ (10 mol %), 1,2-dichlorobenzene (1.0 mL), Ag_2CO_3 (0.6 mmol), and PivOH (1.2 mmol) in DMF (0.6 mL) under O_2 at 150 °C for 30 h.

To further explore the applicability of this significant developed method, we examined the scope of dichlorobenzenes. As summarized in Scheme 2, although the acidity of H at C-2 on 1,3-dichlorbenzene was higher than at C-5, we found that 2-(3,5-dichlorophenyl)quinoline was produced as the only product in moderate yield when the reaction was carried out in 1,3-dichlorobenzene at 150 °C (**4ab**). Moreover, reaction of quinoline with 1,4-dichlorobenzene afforded the corresponding ortho-only arylated products in 57% yield (**4ac**). When 1,2,3-trichlorobenzene and 1,3-dichloro-2-methylbenzene were used as substrates, the desired products were detected in moderate yields (**4ad**, **ae**). However, complex mixtures were produced when chlorobenzene was applied in the reaction, indicating the importance of electronic effects on the selectivity (**4af**). Interestingly, quinoline with 1-chloro-2-methylbenzene provided the desired 2-(3-chloro-4-methylphenyl)quinoline as the only product (**4ag**), but 1-chloro-4-methylbenzene failed to generate (**4ah**). It should be noted that when bromobenzene and benzene were applied as coupling partners, only a trace amount of the desired products was detected (**4ai**,**aj**), and then toluene did not react with quinoline (**4ak**), which further indicated that the electronic character of aromatic substituents exhibits the strongest impact on reactivity. Furthermore, when 1,2-difluorobenzene, 1,2-dibromobenzene, and 1,2-diiodobenzene were employed as substrates, we failed to get the 2-arylation product (**4al**–**an**). Other electron-donating or -withdrawing groups

Scheme 3. Plausible Mechanistic Pathway



such as methoxy and nitro groups substituents did not work in this reaction (**4ao**,**ap**). Although other oxidative coupling reactions and undirected C−H activation reactions are not limited to chloroarenes, chlorine is necessary on the aromatic ring in this reaction.

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A plausible reaction mechanism is outlined in Scheme 3. Step i: quinoline (**1a**) can potentially coordinate with Pd(II) through the N atom to form **A**, followed by palladium migration to C-2, which is promoted by electron-withdrawing groups. Step ii: metalation deprotonation[25] at C-2 occurs. Step iii: C−H activation of **2a** by electrophilic palladation[26] affords an intermediate **C**. Step iv: reductive elimination from **C** furnishes the 2-aryl C−C bond. Step v: Pd(0) is reoxidized to Pd(II) by Ag(I)/PivOH/O_2 to close the catalytic cycle.

In summary, a novel protocol of effective Pd-catalyzed C-2 arylation of quinolines has been developed using O_2 and Ag_2CO_3 as the oxidants. This strategy provides a simple and efficient method for quinoline C−H bond activation. The resulting C-2-arylated quinolines can be used as building blocks for synthesis of bioactive alkaloid natural products and drug molecules. Ongoing work seeks to exploit this mechanistic manifold for other synthetically useful cross-coupling reactions as well as to further probe the mechanism of these new transformations.

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Supporting Information Available. Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.