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Original article

$KMnO_4$-mediated direct selective radical cross-coupling: An effective strategy for C2 arylation of quinoline *N*-oxide with arylboronic acids

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Graphical Abstract

$KMnO_4$-mediated direct selective radical cross-coupling: An effective strategy for C2 arylation of quinoline *N*-oxide with arylboronic acids

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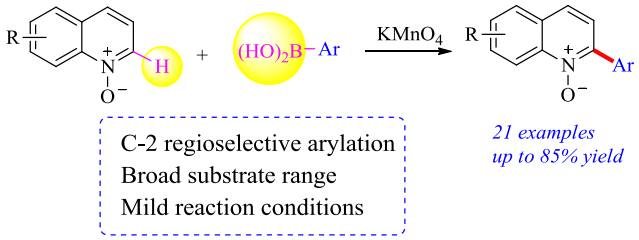

A direct C-H functionalization of quinoline *N*-oxides with arylboronic acids is achieved using $KMnO_4$ as the sole and efficient oxidative system in mild conditions with moderated to good yields.

ABSTRACT

Direct C-H functionalization of quinoline N*-oxides with arylboronic acids is achieved using $KMnO_4$ as the sole and efficient oxidative system. This method provides an efficient protocol to construct regioselectively 2-arylquinoline* N*-oxides* via *radical cross-coupling reaction in moderated to good yields under mild conditions*

Keywords:
Quinoline *N*-oxide
Arylboronic acid
$KMnO_4$-mediated
Radical reaction
Arylation

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1. Introduction

Quinolines and quinoline *N*-oxides as important structural motifs exhibit antitumor and antimalarial activity [1-3]. In addition, the quinoline *N*-oxide core has been found in drugs that activate microsomal Na/K-ATPase [4]. 2-Arylquinoline *N*-oxide derivatives are important structural motifs with applications in the areas of drug discovery [5-7]. Hence, methods that allow for regioselective construction of C-C bonds to quinolines have attracted continuous attention. In particular, introduction of aryl substituent to the C2-position of quinoline derivatives is an important strategy in heterocyclic synthesis that represents a significant synthetic challenge. As a result, considerable efforts have been made towards their synthesis and functionalization [8-10].

Transition-metal catalyzed cross-coupling is now recognized to be one of the most powerful C-C bond forming reactions. Of the methods available for the synthesis of 2-arylquinoline derivatives, the Pd-catalyzed Suzuki-Miyaura type coupling reaction is one of the most convenient methods for preparing biaryl compounds [11-13]. Using aryboronic acids as coupling partners, transition-metal Palladium catalyzed C2 arylations of haloquinolines have recently been reported (Scheme 1, Eq. 1) [14-21]. Nallasamy's group reported that 2-arylquinolines was synthesized *via* ONO pincer type Pd(II) complexes as a catalyst system using 2-chloroquinolines and arylboronic acids as coupling partners [22]. However, employing halogenated quinolines for Suzuki-Miyaura type coupling has its own drawback as it requires pre-functionalization of quinolines. Haloquinolines are hard to access due to chemo and regioselectivity issues. A direct arylation of a variety of electron-deficient heterocycles with arylboronic acids has also been developed using silver nitrate in the presence of persulfate. But this method provided the two regioisomer products in moderated yields with bad regioselectiity when pyridine and quinoline were employed [23]. Moreover, the relatively high price and considerable toxicity of catalysts limit its application. Direct C-H cross-coupling is highly advantageous, as this avoids involvement of prefunctionalized starting materials. Recently, more methods have been developed based on metal-catalyzed or metal-free catalyzed direct C-H bond functionalization in which heteroaromatic *N*-oxides are employed as versatile substrates [24-31]. In 2012, a direct arylation of pyridine *N*-oxides with arylboronic acids through C-H functionalization has been reported by our group, and this reaction was performed at room temperature using catalytic silver(I) nitrate in the presence of potassium persulfate, and a ligand-free $Pd(OAc)_2$-catalyzed selective arylation of pyridine *N*-oxides using potassium (hetero)aryltrifluoroborates as coupling partners *via* C-H bond activation was achieved in the presence of TBAI (Scheme 1, Eq. 2) [32,33]. $Cu(acac)_2$-catalyzed direct C-H arylation of pyridine *N*-oxides with arylboronic esters has been developed by Wu's group, leading to a wide range of 2-arylpyridines in a one-pot synthesis with moderate to good yields without an additional reductant (Scheme 1, Eq. 3) [34]. In 2015, Antonchick's group described a direct C-H bond functionalization of quinoline *N*-oxides to 2-arylated quinoline derivatives by employing quinoline *N*-oxides with arylboronic acids as substrates, and this transformation was realized without metal in DMSO solvent at 110 °C for 2-24 h (Scheme 1, Eq. 4) [35]. Although this method could make a direct arylation of pyridine *N*-oxides, and achieve an improved regioselectivity, a high reaction temperature, long reaction time, and an excess of arylboronic acid (3.0 equiv.) were required. Moreover, the scope of the cross-coupling reaction was limited.

Aryboronic acids are highly stable, even in water and readily available in variety of substituted forms, making it a convenient precursor for building compounds of wide substrate scope. It is known that arylboronic acids decompose to aryl radicals in the presence of some oxidants, such as potassium persulfate ($K_2S_2O_8$), $Mn(OAc)_3$, di-*tert*-butyl peroxide (DTBP), $Mn(acac)_2$, *etc*. [36-46]. Furthermore, we previously reported the direct and regioselective arylation of coumarins employing a wide range of arylboronic acids to produce 3-arylcoumarin using $KMnO_4$/AcOH for an oxidant system [47]. Guided by the recent studies on using arylboronic acids as aryl sources, we turned our attention toward the activation of C-H bonds through a radical transfer pathway. Although direct arylation reaction of quinoline *N*-oxides has been investigated with many coupling partners, methods involving the reaction process of aryl radical are only in scarce. We decided to investigate the modular synthesis for 2-arylquinoline *N*-oxides by this method. Herein, we report such transformations starting from quinoline *N*-oxides with arylboronic acids that lead to 2-arylquinoline *N*-oxide derivatives using $KMnO_4$ as an oxidant (Scheme 1, Eq. 5).

2. Results and discussion

Our studies began with optimization of conditions for the reaction between quinoline *N*-oxide **1a** and arylboronic acid **2a** as a model. Given aryl radical could be generated from arylboronic acids using $K_2S_2O_8$ at higher temperature, quinoline *N*-oxide **1a** reacted with arylboronic acid **2a** in the presence of $K_2S_2O_8$ (0.2 equiv.) as an oxidant in CH_3CN at 90 °C for 1.0 h. Unfortunately, the desired product **3a** was not formed (Table 1, entry 1). Various oxidants including H_2O_2, *tert*-butyl hydroperoxide (TBHP), $Mn(OAc)_3$, $Mn(OAc)_2$, and $KMnO_4$ were investigated. To our delight, the product **3a** could be obtained in 44% and 50% yields when the oxidants $Mn(OAc)_3$ and $KMnO_4$ were used, respectively (Table 1, entries 4 and 6). However, other oxidants were ineffective for the reaction (Table 1, entries 2, 3 and 5). The amount of oxidant was also examined. Increasing the amount of $KMnO_4$ from 0.2 equiv. to 2.0 equiv. had beneficial effect and the product **3a** was obtained in the highest yield (85%). Further, increasing in the quantity of $KMnO_4$ to 3.0 equiv. had no improvement on the yield. When the quantity of $KMnO_4$ was increased to 4.0 equiv., the product yield dropped dramatically (Table S1 in Supporting information, entries 1-5). The ratio of quinoline *N*-oxide **1a** and arylboronic acid **2a** was also screened. The result showed that the ratio of 1:2 was the optimal, and the yield was 85% (Table S2 in Supporting information, entries 1-4). Subsequently, a number of solvents including AcOH, dioxane, DCE, CH_3CN, toluene, C_2H_5OH, and DMSO were examined, and

these tests revealed that CH_3CN was the best solvent (Table 1, entries 7-13). The solvent screening also indicated that the solvent played a key role in the reaction. Increasing the reaction temperature from 20 °C to 100 °C, the optimal was 90 °C and it could provide 85% yield (Table 1, entries 10, 14-18). Finally, various reaction times were also tested, 1.0 h proved to the best appropriate and the yield was 85% (Table 1, entries 10, 19-21). In the absence of $KMnO_4$ no desired product **3a** was formed, which indicated that $KMnO_4$ was crucial to this cross-coupling reaction (Table 1, entry 22).

With the optimized conditions in hand, we next set out to examine the scope of quinoline *N*-oxides and arylboronic acids, and the results are summarized in Fig. 1. Different arylboronic acids with substituents including $-CH_3$, $-C(CH_3)_3$, $-OCH_3$, -F, -Cl, -Br, *etc*. are well tolerated on the aromatic ring and their reactions afforded the target products in good to excellent yields (40%-85%), showing the broad scope of this reaction. Arylboronic acids bearing electron donating groups (**3a-3e**) could give better yields than analogues with electron-withdrawing groups (**3g-3n**). Unfortunately, when 2-methoxylphenyl boronic acid and 2,4,5-trimethylphenyl boronic acid were coupled with quinoline *N*-oxide, even after prolonged reaction time, the target products failed to be formed. These facts suggest that the steric hindrance of arylboronic acids plays a key role for this cross-coupling reaction. It is gratifying to obtain the desired product **3f** with moderate yield (42%) when 1-naphthaleneboronic acid (NBA) was employed. Notably, arylboronic acids containing keto and aldehyde groups were well tolerated and offered **3m** and **3n** in moderate yields. However, arylboronic acid with strong electron withdrawing –CN group on reaction with quinoline *N*-oxide failed to produce the desired product. This may be due to the unstable nature of cyano aryl radical. Gratifying, heteroaromatic boronic acid, 2-furanboronic acid could also react smoothly with quinoline *N*-oxide to provide 2-arylquinoline *N*-oxide **3o**.

As a part of the study we next examined reativity of quinoline *N*-oxide derivatives. Various substituted quinoline *N*-oxides were also found to be amenable to this direct C-H functionalization reaction. Arylation of quinoline *N*-oxides bearing methyl and methoxyl groups proceeded smoothly leading to 2-arylquinoline *N*-oxides scaffolds **3p**, **3q**, and **3t** in 78%-83% yields. It was noteworthy that 6-bromoquinoline *N*-oxide and 3-bromoquinoline *N*-oxide were well tolerated, providing handles for further functionalization. Unfortunately, when quinoline *N*-oxide possessing an electron-withdrawing group $-NO_2$ at the C6 position was employed, the yield (39%) of desired product **3s** dropped dramatically. Pleasingly, the coupling reaction of 3-bromoquinoline *N*-oxides with phenylboronic acid could proceed to afford the product **3u** in 76% yield, which indicated that the steric effect of quinoline *N*-oxides played a weak role in this transformation.

With these impressive results, we further focused on application of the same oxidant system for arylation of other heterocycles such as quinolines (Scheme 2). Quinolines could also react smoothly with arylboronic acids to provide the corresponding products **5a-5c** in 20%-42% yields.

Although a detailed reaction pathway remains to be unclarified, a plausible mechanism for the current $KMnO_4$-mediated direct C2 arylation of quinoline *N*-oxides with arylboronic acids is depicted in Scheme 3, which is based on the radical mechanism proposed [41,42]. Arylboronic acids have been reported to decompose into aryl radicals through a single-electron transfer in the presence of an oxidant [36-46,48]. Initially, phenylboronic acid **A** was oxidized by one-electron oxidation to generate a phenyl radical **B**. The *N*-oxide moiety increases the electron-density of the electron-deficient pyridine ring system, and enhances the Brönsted acidity of the adjacent pyridyl C-H bonds. The given phenyl radical **B** attacked on C2 position of quinoline *N*-oxide to form the corresponding radical **C**. Subsequently, through a single-electron transfer (SET) process, the corresponding cationic intermediate **D** was provided. The generated intermediate **D** aromatized to afford the desired product **E** by a deprotonation step.

3. Conclusion

In summary, we have successfully developed a direct and regioselective C2 arylation of quinoline *N*-oxides with arylboronic acids. This method provides an efficient protocol to construct regioselectively 2-arylquinoline *N*-oxides. The advantage of this reaction is high efficiency, moderated to good yield, and a broad functional groups tolerance.

4. Experimental

General procedure for synthesis of 2-arylquinoline *N*-oxide derivatives **3a-u**: In a 50 mL Schlenk tube, quinoline *N*-oxides **1** (0.3 mmol), arylboronic acids **2** (0.6 mmol), and $KMnO_4$ (0.6mmol, 94.8 mg) in acetonitrile (3.0 mL) were added and the reaction was continued at 90 °C for 1.0 h (monitored by TLC). The reaction mixture was diluted with ethyl acetate, then washed with saturated sodium chloride solution for three times. The resulting organic phase was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product was purified by silica gel column chromatography using ethyl acetate/petroleum ether (1 : 3 to 2 : 1) as eluant to obtain the desired products **3a-u**. All compounds were confirmed by IR, ^{1}H NMR, ^{13}C NMR, and MS.

2-Phenylquinoline 1-oxide **3a**: Colorless solid, mp 145-146 °C (EtOAc) [lit [26] mp 148.5-149.7 °C]. IR (KBr, cm^{-1}): ν 1462, 1377, 1352, 1302. ^{1}HNMR (400 MHz, $CDCl_3$): δ 8.86 (d, 1H, $J_{H\text{-}H}$ = 8.8 Hz), 7.97 (d, 2H, $J_{H\text{-}H}$ = 8.3 Hz), 7.87 (d, 1H, $J_{H\text{-}H}$ = 8.1 Hz), 7.82-7.76 (m, 2H), 7.65 (t, 1H, $J_{H\text{-}H}$ = 7.2 Hz), 7.55-7.45 (m, 4H). ^{13}CNMR (100 MHz, $CDCl_3$): δ 145.1, 142.2, 133.4, 130.6 (CH), 129.6

(CH), 129.5 (CH), 128.4 (CH), 128.3 (CH), 127.9 (CH), 125.4 (CH), 125.3, 123.3 (CH), 120.3 (CH). MS (ESI): *m/z* $[M + H]^+$ found: 222.3, calcd. for $C_{15}H_{12}NO$: 222.1.

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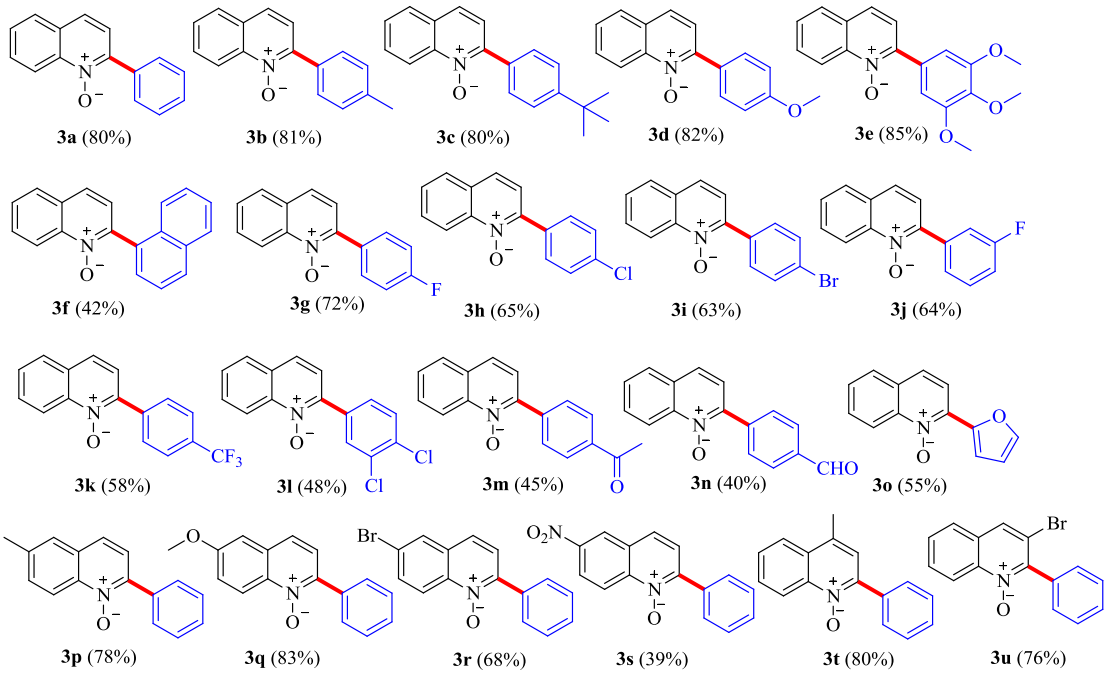
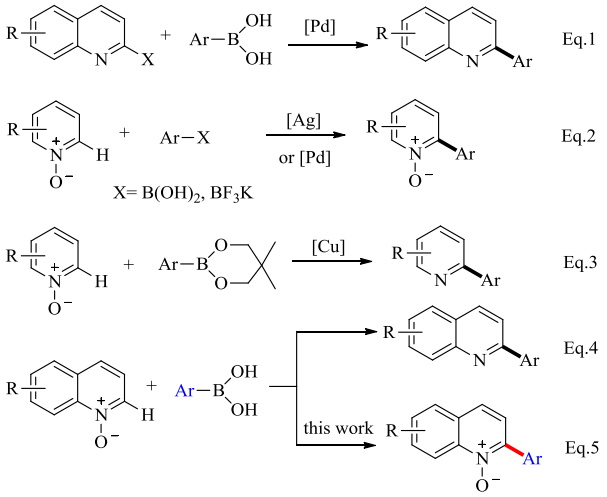
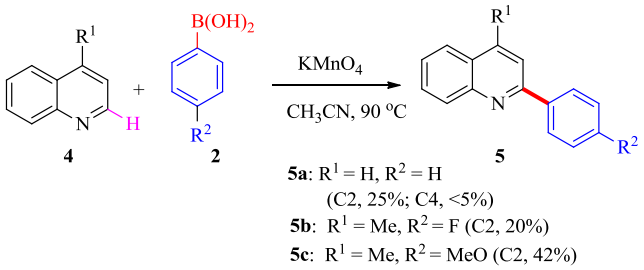


Fig. 1. 2-Arylquinoline *N*-oxides were synthesized from quinoline *N*-oxides and arylboronic acids, and yields are isolated yield.

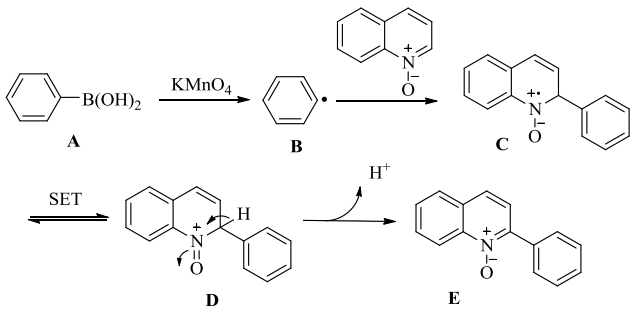


Scheme 1. Synthesis of 2-aryl *N*-heterocycle derivatives with boronic acids.



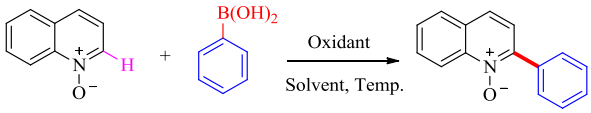
5a: R^1 = H, R^2 = H
(C2, 25%; C4, <5%)
5b: R^1 = Me, R^2 = F (C2, 20%)
5c: R^1 = Me, R^2 = MeO (C2, 42%)

Scheme 2. Synthesis of 2-arylquinolines from quinolines and arylboronic acids. Reaction conditions: Quinolines **4** (0.3 mmol), arylboronic acid **2** (0.6 mmol), $KMnO_4$ (0.6 mmol, 94.8 mg) in 3.0 mL CH_3CN solvent, 90 °C for 1.0 h. Yield are isolated yield.



Scheme 3 Proposed reaction mechanism.

Table 1
Optimization of reaction conditions.[a]



1a **2a** **3a**

Entry	Oxidant (equiv.)	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	$K_2S_2O_8$ (0.2)	CH_3CN	90	1.0	0
2	H_2O_2 (0.2)	CH_3CN	90	1.0	0
3	TBHP (0.2)	CH_3CN	90	1.0	0
4	$Mn(OAc)_3$ (0.2)	CH_3CN	90	1.0	44
5	$Mn(OAc)_2$ (0.2)	CH_3CN	90	1.0	0
6	$KMnO_4$ (0.2)	CH_3CN	90	1.0	50
7	$KMnO_4$ (2.0)	AcOH	90	1.0	42
8	$KMnO_4$ (2.0)	Dioxane	90	1.0	54
9	$KMnO_4$ (2.0)	DCE	90	1.0	0
10	$KMnO_4$ (2.0)	CH_3CN	90	1.0	85
11	$KMnO_4$ (2.0)	Toluene	90	1.0	20
12	$KMnO_4$ (2.0)	C_2H_5OH	90	1.0	22
13	$KMnO_4$ (2.0)	DMSO	90	1.0	50
14	$KMnO_4$ (2.0)	CH_3CN	20	1.0	45
15	$KMnO_4$ (2.0)	CH_3CN	40	1.0	48
16	$KMnO_4$ (2.0)	CH_3CN	60	1.0	73
17	$KMnO_4$ (2.0)	CH_3CN	80	1.0	80
18	$KMnO_4$ (2.0)	CH_3CN	100	1.0	83
19	$KMnO_4$ (2.0)	CH_3CN	90	0.5	52
20	$KMnO_4$ (2.0)	CH_3CN	90	1.5	83
21	$KMnO_4$ (2.0)	CH_3CN	90	2.0	80
22[c]	/	CH_3CN	90	2h	0

[a] Reaction conditions: Quinoline *N*-oxide **1a** (0.3 mmol, 43.5 mg), phenylboronic acid **2a** (0.6 mmol, 73.2 mg), oxidant and solvent (3.0 mL).

[b] Isolated yield.

[c] No $KMnO_4$ is added.