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# C8-Selective Acylation of Quinoline *N*-Oxides with *α*-Oxocarboxylic Acids via Palladium-Catalyzed Regioselective C–H Bond Activation

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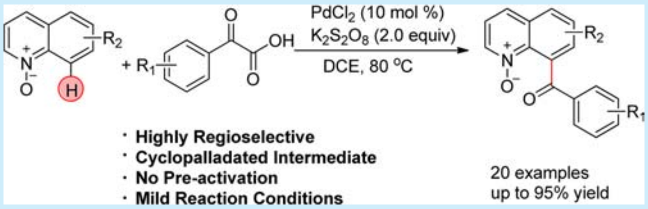
*Supporting Information*

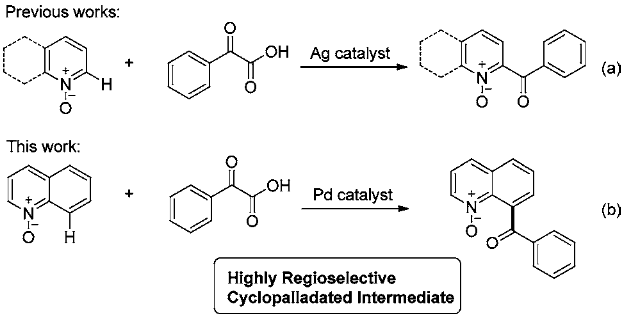
**ABSTRACT:** A facile and efficient protocol for palladium-catalyzed C8-selective acylation of quinoline *N*-oxides with *α*-oxocarboxylic acids has been developed. In this approach, *N*-oxide was utilized as a stepping stone for the remote C–H functionalization. The reactions proceeded efficiently under mild reaction conditions with excellent regioselectivity and broad functional group tolerance.



Quinoline is an important structural motif in natural products,[1] drugs,[2] and advanced functional materials.[3] Accordingly, the development of efficient methods for accessing substituted quinoline is a subject of considerable importance.[4] In particular, streamlining the synthetic process through the introduction of site-selective direct functionalization of a quinoline C–H bond is highly desirable. *N*-Oxide as a directing group has recently attracted great attention in the past years, which has been used to achieve the desired regioselective control.[5] A significant number of methods exist for transition-metal-catalyzed functionalization at C2 of quinoline *N*-oxides, such as olefination,[6] sulfonylation,[7] alkylation,[8] acetoxylation,[9] phosphonation,[10] arylation,[11] and amination.[12] In contrast, only a few examples have been reported for the selective C-8 functionalization of quinoline *N*-oxides.[13] The elegant work by Chang and co-workers developed two catalytic procedures to 8-iodinated and 8-aminated quinolines using rhodium and iridium catalytic systems.[13a] Rh- and Co-catalyzed redox-neutral coupling with alkynes in the C8 position of quinoline *N*-oxides was disclosed by the Li, Chang, and Sundararaju groups.[13b−d] Larionov reported on the palladium-catalyzed C8 arylation and selective homocoupling of quinoline *N*-oxides.[13g,h] Very recently, we realized the synthesis of 8-acylated 2-quinolinones in a one-pot manner through palladium-catalyzed selective C8–H activation of quinoline *N*-oxides with aldehydes.[14]

On the other hand, transition-metal-catalyzed decarboxylative coupling[15] is an attractive synthetic method for C–C bond formation since it does not require the use of stoichiometric organometallic coupling reagents and produces $CO_2$ as the sole waste. In 2014, Muthusubramanian and co-workers achieved a silver-catalyzed decarboxylative acylation of pyridine *N*-oxides with *α*-oxocarboxylic acids[15b] (Scheme 1, a), which was only found to provide C2-acylated products of quinoline *N*-oxides. Therefore, our interest in transition-metal-catalyzed C–H functionalization of quinoline *N*-oxides spurred us to test the feasibility of direct C8-acylation for such a transformation. Herein, we report a highly efficient and mild Pd-catalyzed regioselective C8 acylation of quinoline *N*-oxides with *α*-oxocarboxylic acids (Scheme 1, b). The mechanistic investigations indicated that the high regioselectivity was also achieved through the smooth formation of *N*-oxide chelated palladacycle.

**Scheme 1. Site-Selective C–H Acylation of Quinoline *N*-Oxides with *α*-Oxocarboxylic Acids**



We initiated our investigation on the model reaction of quinoline *N*-oxide (**1a**) with 2-oxo-2-phenylacetic acid (**2a**) to optimize various reaction parameters. The results are summarized in Table 1. Only a trace amount of the desired product **3a** was obtained when $PdCl_2$ was used as a catalyst and 70% *tert*-butyl hydroperoxide (TBHP) in decane was used as an oxidant (entry 1). The molecular structure of product **3a** was confirmed by NMR spectra. To our delight, a 95% yield of **3a** was obtained in the presence of $K_2S_2O_8$ (entry 3). However,

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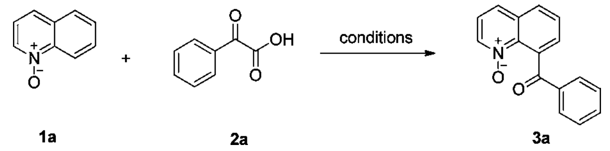
### Table 1. Optimization of the Various Parameters for the Reaction of Quinoline *N*-Oxide with 2-Oxo-2-phenylacetic Acid[a]



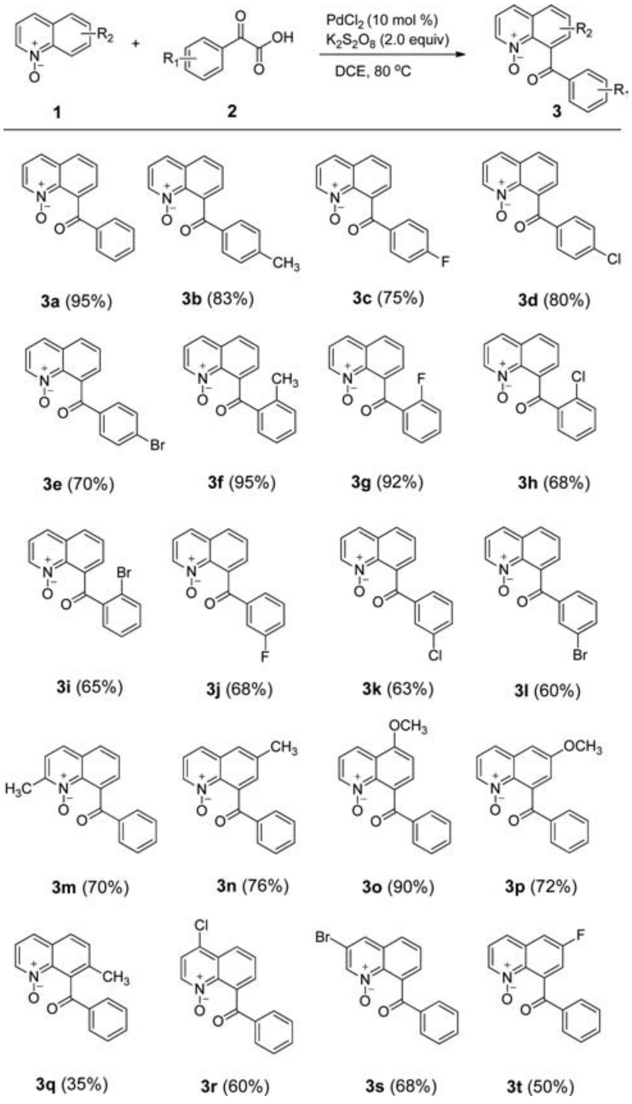
| entry | catalyst | oxidant | temp (°C) | yield[b] (%) |
|---|---|---|---|---|
| 1 | $PdCl_2$ | TBHP[c] | 80 | trace |
| 2 | $PdCl_2$ | DTBP | 80 | trace |
| 3 | $PdCl_2$ | $K_2S_2O_8$ | 80 | 95 |
| 4 | $PdCl_2$ | AgOAc | 80 | nd[e] |
| 5 | $PdCl_2$ | $AgCO_3$ | 80 | nd[e] |
| 6 | $PdCl_2$ | DDQ | 80 | nd[e] |
| 7 | $PdCl_2$ | BQ | 80 | nd[e] |
| 8 | $PdCl_2$ | $O_2$ | 80 | 15 |
| 9 | $Pd(OAc)_2$ | $K_2S_2O_8$ | 80 | 94 |
| 10 | $Pd(TFA)_2$ | $K_2S_2O_8$ | 80 | 92 |
| 11 | CuI | $K_2S_2O_8$ | 80 | nd[e] |
| 12 | $Cu(OAc)_2$ | $K_2S_2O_8$ | 80 | nd[e] |
| 13 | $PdCl_2$ | $K_2S_2O_8$ | 50 | 41 |
| 14 | $PdCl_2$ | $K_2S_2O_8$ | rt | nd[e] |
| 15[d] | $PdCl_2$ | $K_2S_2O_8$ | 80 | 90 |

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), catalyst (10 mol %), oxidant (2.0 equiv), DCE (1.5 mL), under air, 80 °C, 24 h. [b] Isolated yields. [c] TBHP (5−6 M in decane). [d] Under $N_2$. [e] nd = not detected.

the use of di-*tert*-butyl peroxide (DTBP) as an oxidant did not improve the yield of **3a** (entry 2). Other oxidants, such as AgOAc, $AgCO_3$, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), and benzoquinone (BQ), were found to be ineffective in the reaction (entries 4−7). Only a 15% yield of **3a** was obtained when the reaction was carried out under $O_2$ atmosphere (entry 8). The effect of the palladium and copper salts on the reaction were also examined. The results demonstrated that $Pd(OAc)_2$ and $Pd(TFA)_2$ also gave high yields of **3a** (entries 9 and 10), while no acylated product was observed with CuI and $Cu(OAc)_2$ (entries 11 and 12). Decreasing the reaction temperature resulted in a significant decrease in the yield (entries 13 and 14). When the reaction was protected by nitrogen, the desired product **3a** was obtained in 90% yield (entry 15), which indicated that the oxygen molecule from air was tolerated. Finally, the optimized reaction conditions were identified as follows: 10 mol % of $PdCl_2$ as the catalyst and $K_2S_2O_8$ as the oxidant in DCE at 80 °C under air atmosphere for 24 h.

With these optimal reaction conditions in hand, we turned our attention to embarking on the generality and scope of the substrates for this transformation. The results are summarized in Scheme 2. It was found that substrates with both electron-donating and electron-withdrawing groups on the benzene ring of 2-oxo-2-arylacetic acids were tolerated and afforded the corresponding acylated products in good to excellent yields (**3a**−**e**). 2-Oxo-2-arylacetic acids bearing electron-donating groups, for example, 2-oxo-2-(*p*-tolyl)acetic acid, gave the target product **3b** in 83% yield. Halogens in 2-oxo-2-arylacetic acids were tolerated well; for example, 2-(4-fluorophenyl)-2-oxoacetic acid, 2-(4-chlorophenyl)-2-oxoacetic acid, and 2-(4-bromophenyl)-2-oxoacetic acid provided the desired products in 75% (**3c**), 80% (**3d**), and 70% (**3e**) yields, respectively.

### Scheme 2. Scope of Quinoline *N*-Oxides and α-Oxocarboxylic Acids[a,b]

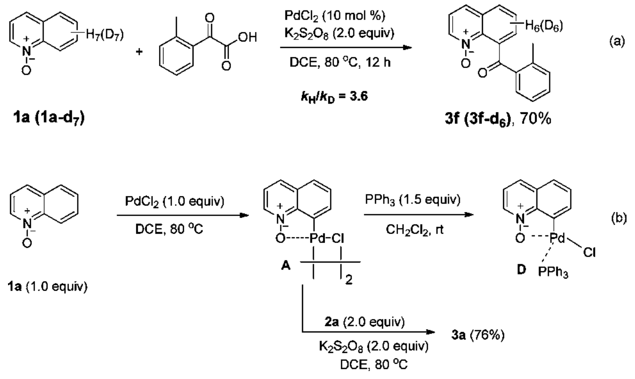


[a] Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), $PdCl_2$ (10 mol %), $K_2S_2O_8$ (2.0 equiv), DCE (1.5 mL), under air, 80 °C, 24 h. [b] Isolated yield.

Steric hindrance on the aryl group of 2-oxo-2-arylacetic acids had no significant effect. In particular, the acylation of 2-oxo-2-(*o*-tolyl)acetic acid (**2f**) with quinoline *N*-oxide (**1a**) gave an excellent yield of 95%. *Ortho* and *meta* halogen-substituted compounds worked well and gave the desired products in moderate to good yields (**3g**−**l**), which makes this reaction particularly attractive for further transformation by transition-metal-catalyzed coupling reactions. To expand the scope of this method, some quinoline *N*-oxides were evaluated using 2-oxo-2-phenylacetic acid (**2a**) as the coupling partner. Various substituents at the 2-, 3-, 4-, 5-, and 6-positions on the quinoline *N*-oxides were well tolerable, affording the corresponding 8-acylated quinoline *N*-oxides in moderate to excellent yields with excellent regioselectivity. The efficiency of the acylation was slightly affected by the electronic variation of substrates. In general, quinoline *N*-oxides with electron-donating groups (**3m**−**p**) gave slightly higher yields than those with electron-withdrawing groups (**3r**−**t**). However, 7-methylquinoline *N*-oxide exhibited low efficiency in this transformation, perhaps because of the steric hindrance (**3q**).

To clarify the reaction mechanism, some control experiments were carried out (Scheme 3). Parallel competition reactions between **1a** and its deuterated analogue **1a**-$d_7$ were performed under the standard reaction conditions and revealed a notable kinetic isotope effect ($k_H/k_D$ = 3.6, Scheme 3, a), indicating that the C−H bond cleavage would be rate-limiting in the overall process.

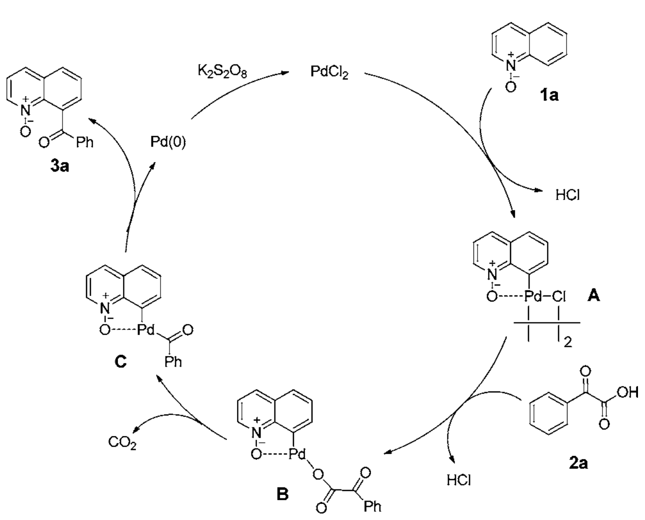
**Scheme 3. Control Experiments**



Furthermore, the reaction of quinoline *N*-oxide with stoichiometric $PdCl_2$ gave the chloride-bridged palladacycle dimer **A**, which produced the corresponding triphenylphosphine ($PPh_3$) adduct **D** treated with triphenylphosphine ($PPh_3$) in dichloromethane at room temperature (Scheme 3, b). The structure of mono palladium complex **D** was confirmed by single-crystal X-ray diffraction.[14] The reaction of complex **A** with 2-oxo-2-phenylacetic acid (**2a**) afforded the desired product **3a** in 76% yield, which implied the possible intermediacy of a five-membered complex in the catalytic cycle.

On the basis of the results obtained above and previous literature reports,[15f−k] the reaction mechanism was proposed as shown in Scheme 4. First, the palladacycle[16] dimer intermediate **A** was formed via coordination of the palladium atom to the *N*-oxide and subsequent electrophilic attack at the C8. Then, the obtained **A** underwent an anion exchange with 2-oxo-2-phenylacetic acid (**2a**) to generate a cyclopalladated complex **B** along with release of HCl. Decarboxylation of the complex **B** followed by reductive elimination provides the desired product **3a**. Finally, the Pd(0) can be reoxidized to the active Pd(II) with $K_2S_2O_8$. Alternatively, the Pd(III) or Pd(IV) intermediate could not be absolutely ruled out in the system.[15c,d]

**Scheme 4. Proposed Reaction Mechanism**



In conclusion, we have developed an efficient palladium-catalyzed direct acylation of quinoline *N*-oxides with an excellent regioselectivity at the C8 position using $\alpha$-oxocarboxylic acids as the acylated reagent. In this approach, *N*-oxide was utilized as a stepping stone for the remote C−H functionalization. Further exploration of the synthetic potential of this regioselective C−H bond functionalization platform is underway in our laboratory.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01746.

$^1H$ NMR and $^{13}C$ NMR spectra of compounds **3a−t** (PDF)

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### Notes

The authors declare no competing financial interest.

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