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From Ketones, Amines, and Carbon Monoxide to 4-Quinolones: Palladium-Catalyzed Oxidative Carbonylation

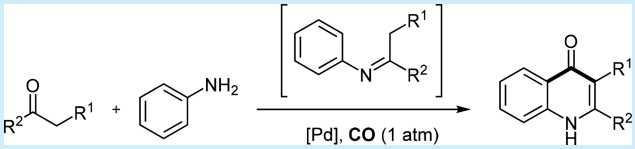
Jiwei Wu,[†] Yuchen Zhou,[†] Ting Wu,[†] Yi Zhou,[†] Chien-Wei Chiang,[†] and Aiwen Lei*[,†,‡]

[†]The Institute for Advanced Studies (IAS), College of Chemistry and Molecular Sciences, Wuhan University, Wuhan 430072, P. R. China

[‡]State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou 730000, P. R. China

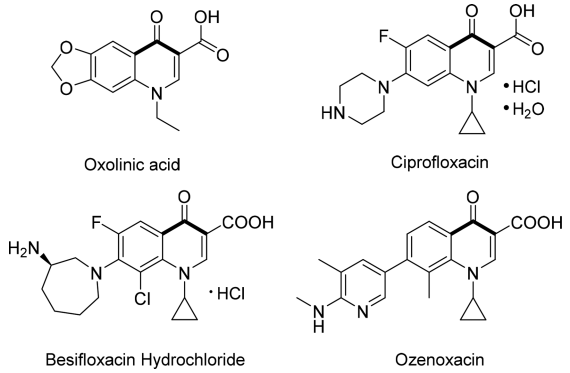
Supporting Information

ABSTRACT: A novel method of palladium-catalyzed oxidative carbonylation of ketones, amines, and carbon monoxide for the synthesis of 4-quinolones has been developed. This protocol provides a straightforward route to construct useful 4-quinolone derivatives from inexpensive chemicals.



4-Quinolones represent one of the major classes of nitrogen-containing heterocycles and is widely found in natural products and biological active molecules.[1] Furthermore, compounds containing 4-quinolone scaffolds exhibit various pharmaceutical activities such as antiviral,[2] antimalarial,[3] or anticancer.[4] Many 4-quinolone derivatives, such as oxolinic acid, ciprofloxacin, besifloxacin hydrochloride, ozenoxacin, etc., have emerged as potent antibiotics and have been used in daily life (Scheme 1).[5]

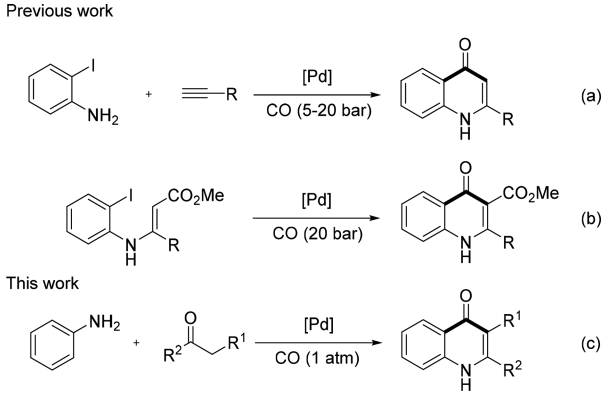
Scheme 1. Representative Drug Compounds Containing 4-Quinolone Scaffolds



The synthesis of 4-quinolone scaffolds has attracted considerable interest, and various methods for the synthesis of 4-quinolone scaffolds have been documented, such as Camps cyclizations,[6] Conrad–Limpach reaction,[7] Niementowski reaction,[8] etc.[9] However, these methods usually required harsh reaction conditions, such as high temperatures and strong bases or acids, which dramatically limit its application. Therefore, a more efficient and straightforward method for the synthesis of 4-quinolones is highly desired.

Carbon monoxide (CO), the simplest carbonyl source, has been widely used in the synthesis of carbonyl compounds,[10] which meets the requirements of atom economy,[11] step economy,[12] and green chemistry.[13] Recently, palladium-catalyzed carbonylation[14] for constructing 4-quinolones by using CO as carbonyl source have been reported (Scheme 2a,b).[15] However, these reactions use aryl halogen (usually synthesized from C–H compounds) as raw material, which do not meet step economy. In addition, these methods also suffer from the requirement of high pressures of CO gas, which made them hazardous for large-scale industrial applications. To overcome these obstacles and on the basis of a continuous interest in the synthesis of heterocycles via oxidative carbonylation in our group,[16] we envisioned that the goal of constructing 4-quinolones could be achieved via palladium-catalyzed oxidative carbonylation using CO as carbonyl source at atmospheric pressure (Scheme 2c).

Scheme 2. Palladium-Catalyzed Carbonylative Synthesis of 4-Quinolinones



In light of retrosynthetic analysis, we know that 4-quinolones could be constructed by enamine **B** with CO. Enamine **B** is

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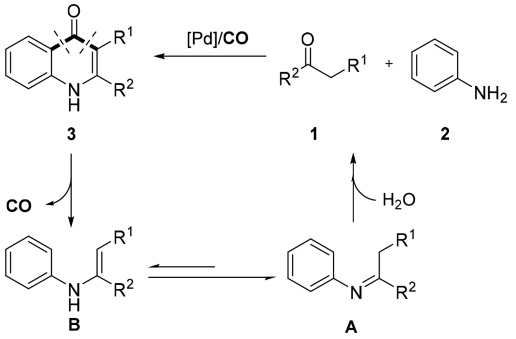
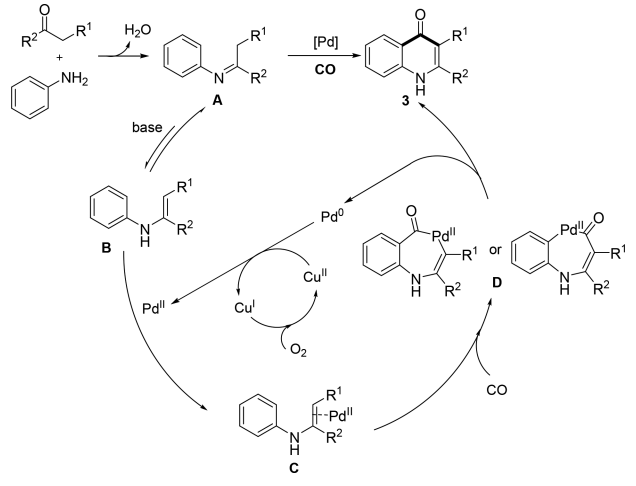
generated via tautomerization of imine **A**. Imine **A** was formed from ketone and amine by dehydration condensation. Ketones and amines, as simple and commercially available chemical materials, were the ideal raw material for synthesis of 4-quinolones. Thus, oxidative carbonylation between simple ketones, amines, and CO for the synthesis of 4-quinolones was designed (Scheme 3). To the best of our knowledge, the oxidative carbonylation for the synthesis of 4-quinolones from simple ketones, amines, and CO has not been reported.

Scheme 3. Reaction Design of the Oxidative Carbonylation for the Synthesis of 4-Quinolones from Ketones, Amines, and CO



We propose that the palladium-catalyzed oxidative carbonylation of ketones, amines, and CO for syntheses of 4-quinolones proceeds through the catalytic cycles shown in Scheme 4. First,

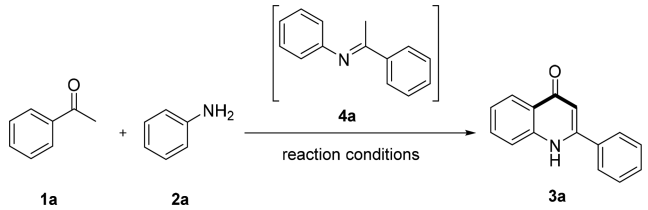
Scheme 4. Proposed Catalytic Cycles



imine **A** is formed from ketone and amine by dehydration condensation. Then, enamine **B** derived from imine/enamine isomerization can be electrophilically attacked by Pd(II) to form intermediate **C**. Intermediate **C** would then undergo intramolecular C−H activation and CO insertion to generate intermediate **D**. Subsequently, reductive elimination of **D** affords the final product **3** and releases a Pd(0), which is oxidized by copper and O_2 to regenerate Pd(II) and complete the catalytic cycle.

On the basis of the above speculation, acetophenone (**1a**) and aniline (**2a**) in the presence of 1 atm of CO were chosen as the model substrates to test this reaction. The desired product (**3a**) was obtained in 75% yield with the following procedure: first, **1a** reacted with **2a** for 6 h in the presence of molecular sieves, then $Pd(dba)_2$, Xantphos, KI, $CuBr(Me_2S)$, and PhCOONa were added in the presence of 1 atm of CO to react another 24 h (Table 1, entry 1). Unfortunately, when they were all added into

Table 1. Optimization of the Reaction Conditions[a]



entry	variation from the standard conditions	yield (%)
1	none	75
2[b]	none	n.d.
3	no 4 Å MS	21
4	no $Pd(dba)_2$	n.d.
5	no KI	17
6	no Xantphos	54
7	no $CuBr(Me_2S)$	trace
8	no PhCOONa	trace
9	$Pd(PPh_3)_4$ instead of $Pd(dba)_2$	62
10	$Pd(OAc)_2$ instead of $Pd(dba)_2$	54
11	$PdCl_2$ instead of $Pd(dba)_2$	53
12	CuBr instead of $CuBr(Me_2S)$	47
13	$Cu(OAc)_2$ instead of $CuBr(Me_2S)$	58
14	K_2CO_3 instead of PhCOONa	trace
15	DABCO instead of PhCOONa	17
16	0.01 mmol $Pd(dba)_2$ instead of 0.02 mmol	60
17	CO/O_2 = 15/1 instead of CO/O_2 = 3/1	59

[a]Reaction conditions: **1a** (0.24 mmol), **2a** (0.2 mmol), 4 Å MS (200 mg), in 0.5 mL of $PhCH_3$, at 110 °C for 6 h, then $Pd(dba)_2$ (0.02 mmol), Xantphos (0.02 mmol), KI (0.2 mmol), $CuBr(Me_2S)$ (0.2 mmol), PhCOONa (0.3 mmol), in 2 mL of $PhCH_3$ and 0.4 mL DMSO, at 110 °C under CO/O_2 = 3/1 for 24 h. Yields shown are of isolated products. [b]All added together in 2 mL of $PhCH_3$ and 0.4 mL of DMSO, at 110 °C under CO/O_2 = 3/1 for 24 h. n.d. = not detected.

the reaction together for 24 h, no desired product was obtained (Table 1, entry 2). Without molecular sieves, the yield of **3a** was reduced to 21% due to the low reactivity of **1a** and **2a** to form imine (Table 1, entry 3). Control experiments indicate that $Pd(dba)_2$, $CuBr(Me_2S)$, and PhCOONa were necessary for this reaction (Table 1, entries 4, 7, and 8). KI also played a critical role in this transformation;[17] without KI, only 17% yield of **3a** was obtained (Table 1, entry 5). Xantphos as a ligand can improve the yield of **3a** from 54% to 75% (Table 1, entry 6). Then, different palladium salts such as $Pd(PPh_3)_4$, $Pd(OAc)_2$, and $PdCl_2$ were studied, and the results showed that $Pd(dba)_2$ was still the best choice (Table 1, entries 9−11). CuBr and $Cu(OAc)_2$ were not suitable for this reaction as that afforded the desired product in lower yield (Table 1, entries 12−13). Further base study revealed that PhCOONa was the best choice for this reaction (Table 1, entries 14−15). The reaction could also proceed smoothly to give the desired product **3a** in 59% yield under nonexplosive conditions (CO/O_2 = 15/1) (Table 1, entry 17). Furthermore, a 77% yield of **3a** was observed when imine **4a** was directly used under standard conditions (Scheme 5).

With the optimal reaction conditions in hand, we turned our attention to test the substrate scope of this transformation. First, various ketones (**1**) were evaluated in the reaction with aniline **2a**

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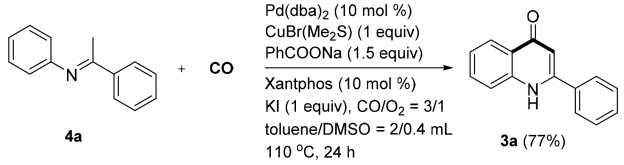
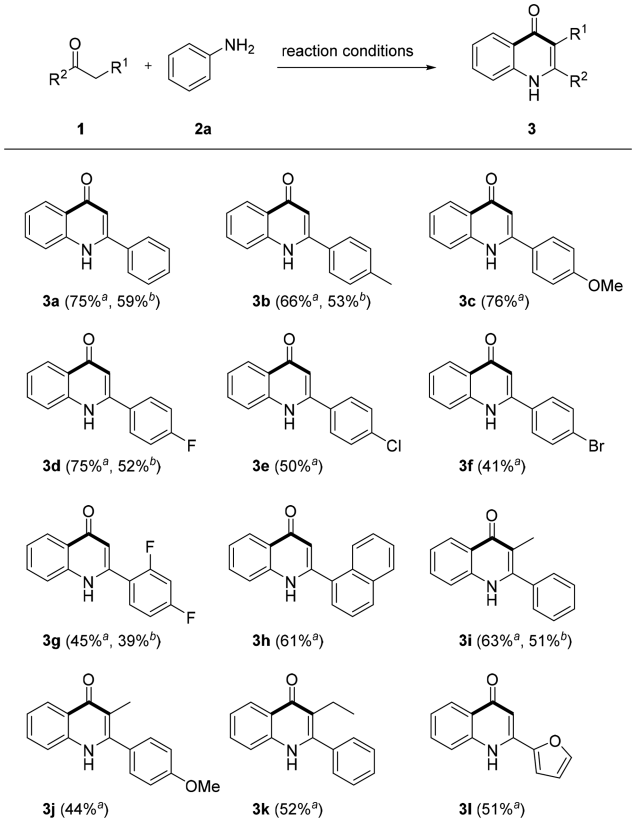
Scheme 5. Oxidative Carbonylation for the Synthesis of 4-Quinolones from Imine



under the standard conditions. As shown in Scheme 6, a wide range of functional groups were well tolerated, and the desired

Scheme 6. Substrate Scope of Oxidative Carbonylation of Ketones with Aniline

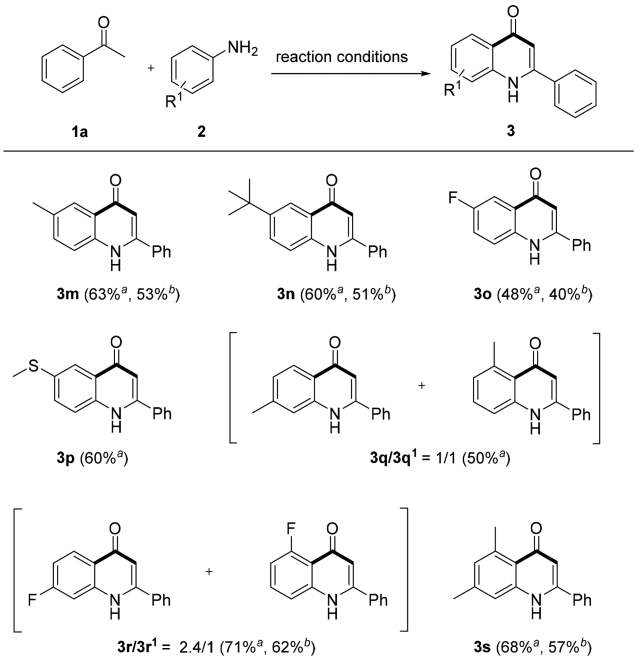


[a]Reaction conditions: **1** (0.24 mmol), **2a** (0.2 mmol), 4 Å MS (200 mg), in 0.5 mL of $PhCH_3$, at 110 °C for 6 h, then $Pd(dba)_2$ (0.02 mmol), Xantphos (0.02 mmol), KI (0.2 mmol), $CuBr(Me_2S)$ (0.2 mmol), PhCOONa (0.3 mmol), in 2 mL of $PhCH_3$ and 0.4 mL of DMSO, at 110 °C under CO/O_2 = 3/1 for 24 h. Yields shown are of isolated products. [b]CO/O_2 = 15/1.

coupling products were obtained in moderate to good yields. Acetophenone with electron-rich groups such as *p*-Me and *p*-OMe afforded the corresponding 4-quinolones in good yields (Scheme 6, **3b,c**). Halogen substituents such as F, Cl, and Br were well tolerated, affording the desired products in moderate to good yields (Scheme 6, **3d−g**). Fortunately, the reaction with 1-(naphthalen-1-yl)ethan-1-one also proceeded smoothly, resulting in the desired product with 61% yield (Scheme 6, **3h**). Propiophenone and 1-phenylbutan-1-one were also tolerated, affording the corresponding products in 63% and 52% yield, respectively (Scheme 6, **3i,k**). It is noteworthy that 1-(furan-2-yl)ethan-1-one showed good reactivity and afforded the desired product with 51% yield (Scheme 6, **3l**).

Then, several anilines (**2**) were explored as substrates by reaction with acetophenone **1a**. In general, the reactions proceeded well to afford the desired products in moderate to good yields. As shown in Scheme 7, anilines with an electron-rich

Scheme 7. Substrate Scope of Oxidative Carbonylation of Acetophenone with Anilines



[a]Reaction conditions: **1a** (0.24 mmol), **2** (0.2 mmol), 4 Å MS (200 mg), in 0.5 mL of $PhCH_3$, at 110 °C for 6 h, then $Pd(dba)_2$ (0.02 mmol), Xantphos (0.02 mmol), KI (0.2 mmol), $CuBr(Me_2S)$ (0.2 mmol), PhCOONa (0.3 mmol), in 2 mL of $PhCH_3$ and 0.4 mL of DMSO, at 110 °C under CO/O_2 for 24 h. Yields shown are of isolated products. [b]CO/O_2 = 15/1.

p-Me and *p*-^{t}Bu (Scheme 7, **3m,n**) substituent or halogen such as *p*-F (Scheme 7, **3o**) all gave the desired products in moderate yields. It is noteworthy that 4-(methylthio)aniline (Scheme 7, **3p**) could be tolerated under the current conditions. For *m*-substituted anilines, the reactions also proceeded smoothly with acetophenone to give the desired products in moderate to good yields (Scheme 7, **3q,r**) but with poor selectivity. Furthermore, 3,5-dimethylaniline reacted smoothly with acetophenone to give the desired **3s** in 68% yield (Scheme 7, **3s**).

In conclusion, we have developed a novel method for palladium-catalyzed oxidative carbonylation of ketones, amines, and CO for the synthesis of 4-quinolones. This protocol provides a straightforward route to the synthesis of useful 4-quinolone derivatives from inexpensive chemicals. Various kinds of ketones, even heterocyclic ketones, and amines were shown to be workable substrates, generating the corresponding 4-quinolones in good yields. Detailed mechanistic studies and the synthetic application of this method are currently ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedure, characterization data, and copies of ^{1}H and ^{13}C NMR spectra (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: aiwenlei@whu.edu.cn.

ORCID

Aiwen Lei: 0000-0001-8417-3061

Notes

The authors declare no competing financial interest.

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