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Copper-Catalyzed Aerobic Oxidation and Oxygenation of Anilines and Acetaldehydes with Dioxygen for the Concise Synthesis of 2-Aroylquinolines

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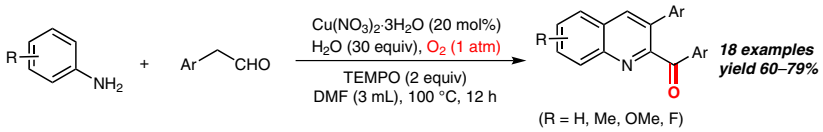

- efficient construction of 2-aroylquinolines from simple building blocks
- molecular oxygen serves as the environmentally-benign oxygen donor

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Abstract A concise and efficient aerobic oxidation and oxygenation approach for the construction of 2-aroylquinolines has been developed through copper-catalyzed annulation of anilines, acetaldehydes, and dioxygen. 2,2,6,6-Tetramethylpiperidine-1-oxyl was employed to direct the selectivity toward the desired 2-aroyl products. Molecular oxygen was used in this transformation as an environmentally benign source of oxygen.

Key words 2-aroylquinolines, oxygenation, anilines, acetaldehydes, copper catalysis, aerobic oxidation, annulation

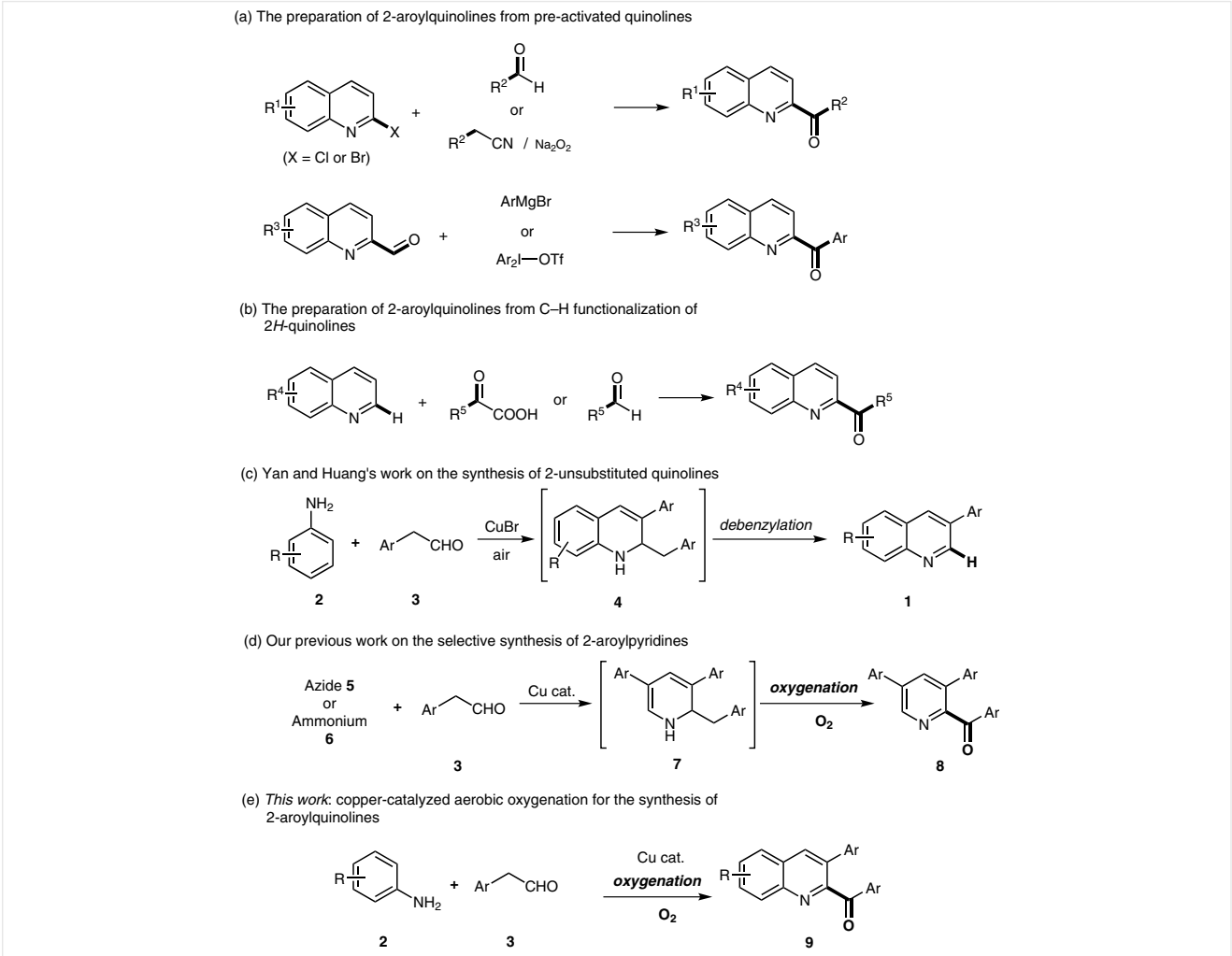
Quinoline is among the most significant nitrogen-containing heterocyclic moieties that are important structural fragments in natural products, pharmaceuticals, functional materials, and have been widely applied in medicinal chemistry and organic synthesis.[1] In particular, 2-aroyl derivatives of quinoline are widely present in biologically active compounds.[2] Through conventional quinoline syntheses, including the Combes reaction,[3] the Skraup reaction,[4] and the Friedländer reaction,[5] 2-aroylquinolines have generally been prepared by functionalization of preactivated quinolines, for example, by cross-coupling reactions of 2-haloquinolines[6] or quinoline-2-carbaldehydes[2,7] [Scheme 1 (a)]. Alternatively, 2-aroylquinolines can also be prepared by direct C–H functionalization of 2-unsubstituted quinolines with aldehydes or α-oxo carboxylic acids [Scheme 1 (b)].[8] All these methods require the corresponding quinoline substrates to be prepared in advance, and these necessitate multiple steps from simple building blocks. In recent years, much effort has been spent on developing novel methods for the preparation of heterocyclic molecules by transition-metal-catalyzed multicomponent coupling and tandem annulation from simple and readily available building blocks.[9–11] However, to our knowledge, the synthesis of 2-aroylquinolines has not previously been realized through such a strategy.

Recently, Yan et al. reported a copper-catalyzed aerobic synthesis of 3-phenylquinolines **1** from anilines **2** and acetaldehydes **3** through debenzylation of the corresponding 2-benzyldihydroquinoline intermediates **4** [Scheme 1 (c)].[12] In our previous report on the selective construction of 2-aroylpyridines **8** from acetaldehydes **3** and ammonium salts **6** or azides **5**, a similar 2-benzyldihydropyridine intermediate **7** was also involved in a subsequent oxygenation process with molecular oxygen [Scheme 1 (d)].[13] Inspired by these works, we surmised that the desired 2-aroylquinoline might be obtained through a 2-benzyldihydroquinoline intermediate if the debenzylation process could be suppressed while an oxygenation process, similar to that in our previous work, could be promoted [Scheme 1 (e)]. Here, we report a copper-catalyzed, concise, and efficient aerobic oxidative construction of 2-aroylquinolines **9** from simple anilines **2**, acetaldehydes **3**, and molecular oxygen [Scheme 1 (e)]. To the best of our knowledge, this is the first example of a single-step protocol for the construction of 2-aroylquinolines from simple and readily available building blocks.

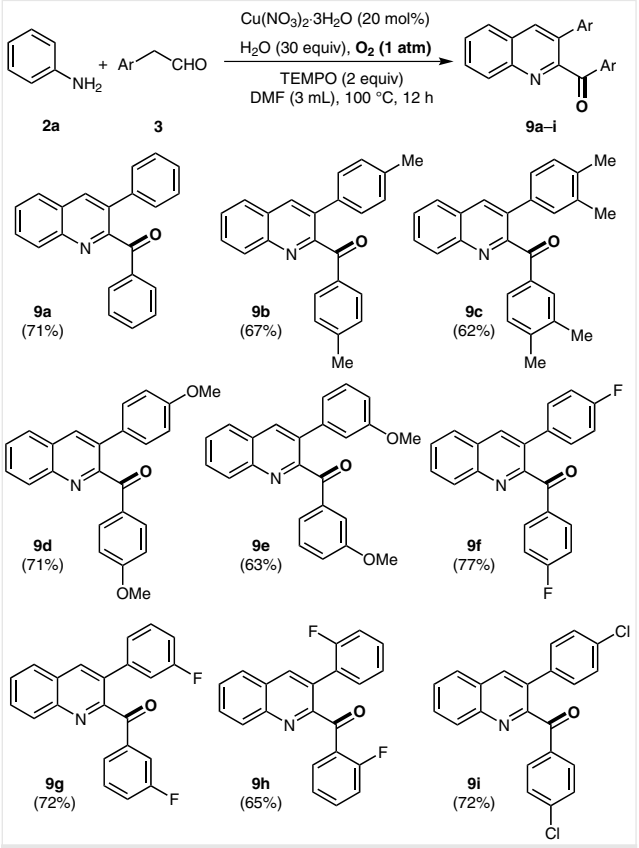
Our investigations commenced with the optimization of the reaction conditions (Table 1). A preliminary trial with aniline (**2a**) and phenylacetaldehyde (**3a**) as model building blocks under reaction conditions similar to those described in our previous report[13] gave both the desired 2-aroylquinoline **9a** and the debenzylated byproduct **1a** in very low yields and with poor selectivity (Table 1, entry 1). Adding 30 equivalents of water markedly facilitated the transformation into **9a**, elevating its yield to 44% while slightly in-

creasing the yield of the byproduct **1a** (entry 2). Screening of the reaction temperature suggested that either increasing or reducing the temperature is detrimental to the yield of **9a** (entries 3 and 4). The yield of the desired product **9a** decreased under air (entry 5). The reaction did not work in the absence of a copper catalyst (entry 7) or under argon, even with 1 equivalent of the copper catalyst in the presence of 30 equivalents of water (entry 6). These results show that the copper catalyst is required for this transformation, and that molecular oxygen is essential as an oxygen source for the generation of the 2-benzoylquinoline. Subsequently, our attention was turned to the screening of the copper catalysts (entries 7–10).[14] With $Cu(NO_3)_2{\cdot}3H_2O$ as the catalyst, the aniline substrate **2a** was completely consumed and the yield of quinoline **9a** increased to 58%, although 26% of the byproduct **1a** was also generated (entry 10). Subsequent optimization focused on suppressing the generation of byproduct **1a**. To our delight, after screening of various additives,[14] this byproduct was suppressed by the addition of two equivalents of TEMPO, providing the desired **9a** in 71% yield (entry 11). It is reasonable that TEMPO might inhibit the radical process of debenzylation, as proposed by Yan and Huang,[12] while the aerobic oxidation process prevailed under copper catalysis. Further screening of the solvent failed to offer better results. Finally, the reaction conditions of entry 11were selected for further investigations on the substrate scope.[15]

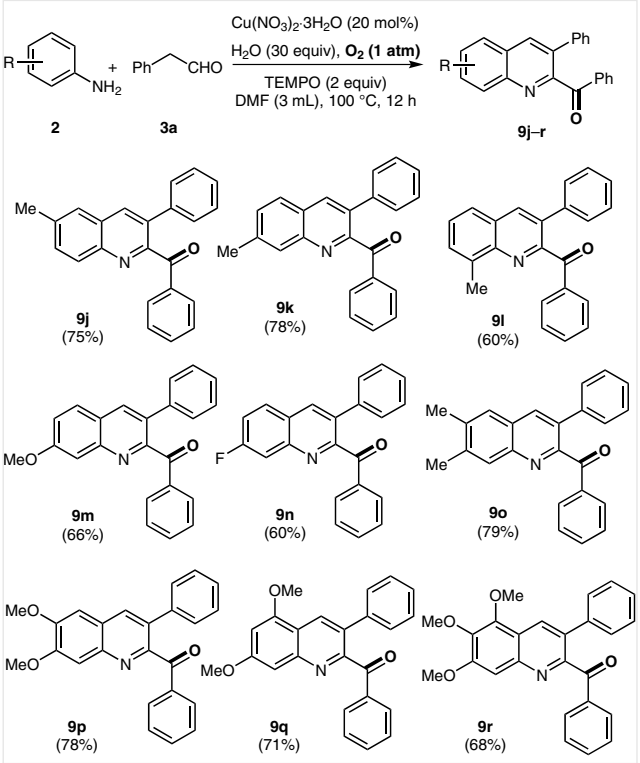
With the optimal conditions in hand, the scope of the arylacetaldehyde was first explored, as shown in Scheme 2. A variety of arylacetaldehydes were investigated for the construction of 2-aroylquinolines. Generally, both electron-deficient and electron-rich aldehydes gave the corresponding 2-aroylquinolines in moderate to good yields, although the yields from electron-deficient ones (**9f** and **9g**) were slightly higher than those from electron-rich ones (**9d** and **9e**). Meanwhile, the steric hindrance also showed a slight influence on the yield, since the yields from *ortho*- or *meta*-



Scheme 1 Construction of 2-aroylquinolines from simple and readily available building blocks



Scheme 2 The arylacetaldehyde scope for the construction of 2-aroylquinolines. *Reagents and conditions*: aniline (**2a**; 0.25 mmol), arylacetaldehyde **3** (1 mmol, 4 equiv), $Cu(NO_3)2{\cdot}3H_2O$ (0.05 mmol, 20 mol%), TEMPO (0.5 mmol, 2 equiv), DMF (3 mL), under O_2 (1 atm), 100 °C, 12 h. Reported yields are isolated yields after column chromatography (silica gel).



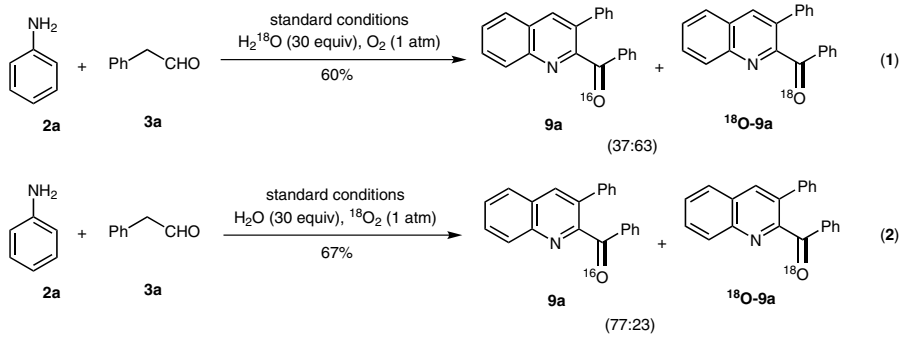
Scheme 3 The aniline scope for the construction of 2-aroylquinolines. *Reagents and conditions*: aniline **2** (0.25 mmol), phenyacetaldehyde (**3a**; 1 mmol, 4 equiv), $Cu(NO_3)_2{\cdot}3H_2O$ (0.05 mmol, 20 mol%), TEMPO (0.5 mmol, 2 equiv), DMF (3 mL), under O_2 (1 atm), 100 °C, 12 h. Isolated yield after column chromatography in silica gel.

substituted aldehydes (**9e**, **9g**, and **9h**) were lower than those from *para*-substituted ones (**9d** and **9f**).

The reactions of various substituted anilines were then explored under the optimized conditions (Scheme 3). Unlike the pattern observed with aldehydes, electron-deficient 3-fluoroaniline provided the corresponding quinoline **9n** in a lower yield than those obtained from electron-rich anilines. Steric hindrance also showed some effect on this reaction. A sterically hindered *ortho*-substituted aniline provided the corresponding product **9l** in a lower yield than the *meta*- or *para*-substituted ones (**9j** and **9k**). In addition, the annulation took place at the less-hindered site on the aniline substrate. For instance, all *meta*-substituted anilines provided the less sterically hindered quinolines predominantly (**9k**, **9m**, and **9n**), whereas no C5-substituted product of higher hindrance was generated. Such patterns were also observed for the polysubstituted quinolines **9o** and **9p**.

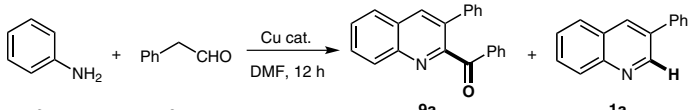
During the optimization of the reaction conditions, we found that molecular oxygen is crucial to this transformation (Table 1, entries 2, 5, and 6). We therefore conducted isotope-labeling experiments by using $H_2{}^{18}O$ and $^{18}O_2$, and we found that the ^{18}O-**9a** product was detected under both the $H_2{}^{18}O$ and $^{18}O_2$ conditions (Scheme 4, eqs 1 and 2). These results, together with the control experiments in Table 1 (entries 5 and 6) demonstrate that the molecular oxygen is essential and that the oxygen source participates in this transformation for the construction of 2-aroylquinolines. Isotope exchange between the 2-aroylquinolines and $H_2{}^{18}O$ occurred, with generation of the ^{18}O-product (Scheme 4, eq 1), which explains the low ratio of the ^{18}O-product in the control reaction under $^{18}O_2$ (Scheme 4, eq 2). These results are in accordance with our previous work on O-exchange between 2-aroylpyridines and H_2O.[13]

In conclusion, we have developed a copper-catalyzed concise and selective aerobic oxidation and oxygenation approach for the construction of 2-aroylquinolines from simple, inexpensive, and readily available anilines, acetaldehydes, and dioxygen. Unlike our previous work, in which the selectivity was controlled by nitrogen donors,[13] TEMPO was employed in this efficient annulation to suppress the generation of the debenzylated byproduct, affording the de-



Scheme 4

Table 1 Optimization of the Reaction Conditions[a]



Entry	Catalyst (20 mol%)	Additive (equiv)	Gas	Temp (°C)	Yield[b] (%) of **9a**	Yield[b] (%) of **1a**
1	$Cu(TFA)_2{\cdot}xH_2O$	–	O_2	100	9	7
2	$Cu(TFA)_2{\cdot}xH_2O$	H_2O (30)	O_2	100	44	10
3	$Cu(TFA)_2{\cdot}xH_2O$	H_2O (30)	O_2	80	22	trace
4	$Cu(TFA)_2{\cdot}xH_2O$	H_2O (30)	O_2	120	36	11
5	$Cu(TFA)_2{\cdot}xH_2O$	H_2O (30)	air	100	32	11
6	$Cu(TFA)_2{\cdot}xH_2O$[c]	H_2O (30)	argon	100	0	0
7	–	H_2O (30)	O_2	100	trace	trace
8	CuI	H_2O (30)	O_2	100	trace	trace
9	$CuCl_2$	H_2O (30)	O_2	100	43	51
10	$Cu(NO_3)_2{\cdot}3H_2O$	H_2O (30)	O_2	100	58	26
11	**$Cu(NO_3)_2{\cdot}3H_2O$**	**H_2O (30), TEMPO (2)**	**O_2**	**100**	**71**	**trace**

[a] Reaction conditions: aniline (**2a**; 0.25 mmol), phenylacetaldehyde (**3a**; 1 mmol, 4 equiv), copper catalyst (0.05 mmol, 20 mol%), additive, DMF (3 mL), under O_2, air, or argon (1 atm), 12 hours.
[b] Isolated yield after column chromatography (silica gel).
[c] The loading of the copper catalyst was 1.0 equiv.

sired 2-aroylquinolines selectively. Environment-benign O_2 was demonstrated to serve as the oxygen donor for the keto moiety in the products. Further investigation on the mechanism of this chemistry, as well as the applications of this protocol, are ongoing in our group.

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Supporting Information

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(15) **Phenyl(3-phenylquinolin-2-yl)methanone** (**9a**)**; Typical Procedure**

To a reaction tube charged with $CuNO_3$·3 H_2O (12.1 mg, 0.05 mmol, 20 mol%) and TEMPO (78.1 mg, 0.5 mmol, 2 equiv) under O_2 (1 atm) was added a solution of aniline (**2a**, 0.25 mmol, 1 equiv), phenylacetaldehyde (**3a**, 1 mmol, 4 equiv), and H_2O (135 µL, 7.5 mmol, 30 equiv) in DMF (3 mL). The mixture was stirred at 100 °C for 12 h then cooled to r.t. The mixture was diluted with EtOAc, washed with sat. aq $NaHCO_3$, water, and brine, dried (Na_2SO_4), and concentrated in vacuo to give dark residue that was purified by flash chromatography [silica gel, PE–EtOAc (50:1 to 30:1)] to give an off-white oil; yield: 55 mg (71%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.28 (s, 1 H), 8.19 (d, *J* = 8.4 Hz, 1 H), 7.86–7.94 (m, 3 H), 7.76–7.80 (m, 1 H), 7.64–7.68 (m, 1 H), 7.52–7.56 (m, 1 H), 7.38–7.41 (m, 4 H), 7.30–7.33 (m, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.1, 156.3, 146.1, 137.7, 137.2, 136.2, 134.1, 133.5, 130.5, 130.1, 129.7, 129.0, 128.6, 128.4, 128.1, 128.0, 127.9, 127.8. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{16}NO$: 310.1232; found: 310.1226.