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Aerobic Synthesis of Substituted Quinoline from Aldehyde and Aniline: Copper-Catalyzed Intermolecular C–H Active and C–C Formative Cyclization

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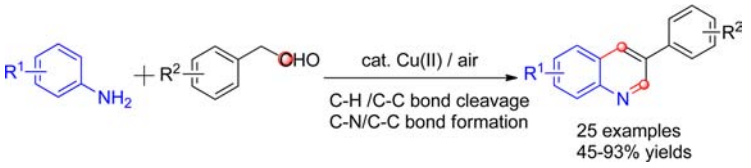
ABSTRACT



An efficient method for the direct synthesis of substituted quinolines from anilines and aldehydes through C–H functionalization, C–C/C–N bond formation, and C–C bond cleavage has been developed. The method is simple and practical and employs air as an oxidant.

During the past several years, C–H functionalization and C–C/C–N bond formation provide many powerful strategies for the synthesis of various heterocyclic compounds.[1] Among them, some great achievements have been accomplished using Rh, Pt, Pd, Cu, and Fe to catalyze C–N/C–C bond formation in the synthesis of heterocyclic compounds.[2] For example, the group of Buchwald,[3] Glorius,[4] and Jiao[5] have reported a series of leading work to construct heterocyclic compounds in this area. Particularly, air has emerged as an ideal oxidant for the synthesis of heterocyclic compounds in a step and atom-economical fashion for its abundance, environment-friendly, and numerous advantages in industry.[6] However, there are very few general methods that convert commercially available or readily accessible materials with sp^2 C–H activation and C–C bond formation and cleavage in a one-pot

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reaction under air. Thus, it is still a great challenge to use molecular oxygen and simple starting materials in heterocyclic compound synthesis.

As the most prevalent heterocyclic compounds, quinolines not only have been widely found in natural products with biological activity[7] but also have been broadly used in medical chemistry, drug synthesis,[8] and functional compound materials as building blocks.[9] Generally quinoline derivatives are synthesized by typical methods including the Skraup reaction, Combes reaction, Friedländer reaction, and Conrad−Limpach−Knorr reaction.[10] Recently, new approaches based on multicomponent coupling and tandem reactions catalyzed by transition metals have been developed and have drawn more attention.[11] So far, there is no ideal method which provides a simple and easily operable protocol for the preparation of substituted quinolines from readily available materials. With the development of C−H functionalization and C−C/C−N bond formation in organic chemistry, it would be attractive to synthesize substituted quinolines by direct C−H functionalization and C−C/C−N bond formation under mild reaction conditions.

Aldehydes and anilines, as commercially available and useful substrates, have drawn more attention and have been widely used in the synthesis of heterocyclic compounds.

Scheme 1. Aldehydes and Anilines in the Synthesis of Heterocycles

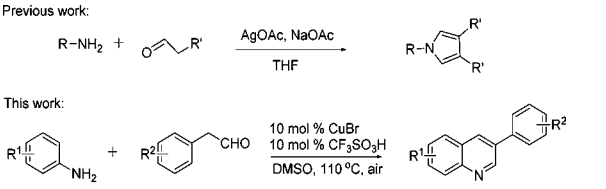
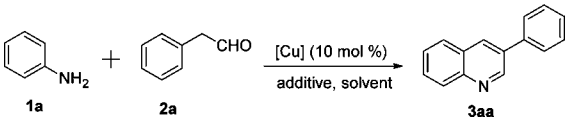


Table 1. Optimization of Reaction Condition[a]



entry	[Cu]	additive	solvent	temp (°C)	yield (%)[b]
1	CuI	CF_3COOH	DMF	130	48
2	CuI	CH_3COOH	DMF	130	trace
3	CuI	CF_3SO_3H	DMF	130	80
4	CuI	TSOH	DMF	130	74
5	CuBr	CF_3SO_3H	DMF	130	68
6	$Cu(OAc)_2$	CF_3SO_3H	DMF	130	58
7	$Cu(OTf)_2$	CF_3SO_3H	DMF	130	62
8	CuOTf	CF_3SO_3H	DMF	130	63
9	CuCl	CF_3SO_3H	DMF	130	45
10	CuI	CF_3SO_3H	DMSO	130	82
11	CuBr	CF_3SO_3H	DMA	130	15
12	CuBr	CF_3SO_3H	DMSO	130	86
13	CuBr	CF_3SO_3H	NMP	130	63
14	**CuBr**	**CF_3SO_3H**	**DMSO**	**110**	**90**
15[c]	CuBr	CF_3SO_3H	DMSO	110	84
16	CuBr	CF_3SO_3H	DMSO	80	75
17		CF_3SO_3H	DMSO	110	–
18	CuBr		DMSO	110	36

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.3 mmol), copper salt (0.03 mmol), additive (0.03 mmol), solvent (2 mL). [b] Yields of isolated products. [c] The reaction was carried out under O_2 (1 atm). Entry in bold highlights optimized reaction conditions, and the reaction time was monitored by TLC. DMSO = dimethyl sulfoxide, DMF = *N*,*N*-Dimethylformamide, NMP = *N*-methyl-2-pyrrolidone.

In 2010, the group of Jia reported the one-pot AgOAc-mediated synthesis of polysubstituted pyrroles from aldehydes and anilines (Scheme 1).[12] Inspired by recent studies in synthesizing heterocyclic compounds with molecular oxygen and simple starting materials,[13] we made an unexpected finding: the use of 2-phenylacetaldehyde and anilines via a copper-catalyzed reaction resulted in substituted quinolines with C−N/C−C bond formation and C−H/C−C bond cleavage reaction in one step under air.

Initially, the reaction of aniline (**1a**) and 2- phenylacetaldehyde (**2a**) was chosen as a model reaction to optimize the reaction. By treating the substrate **1a** and **2a** with 10% CuI, 10% CF_3COOH in DMF at 130 °C, to our delight, an unexpected product 3-phenylquinoline (**3aa**) was obtained

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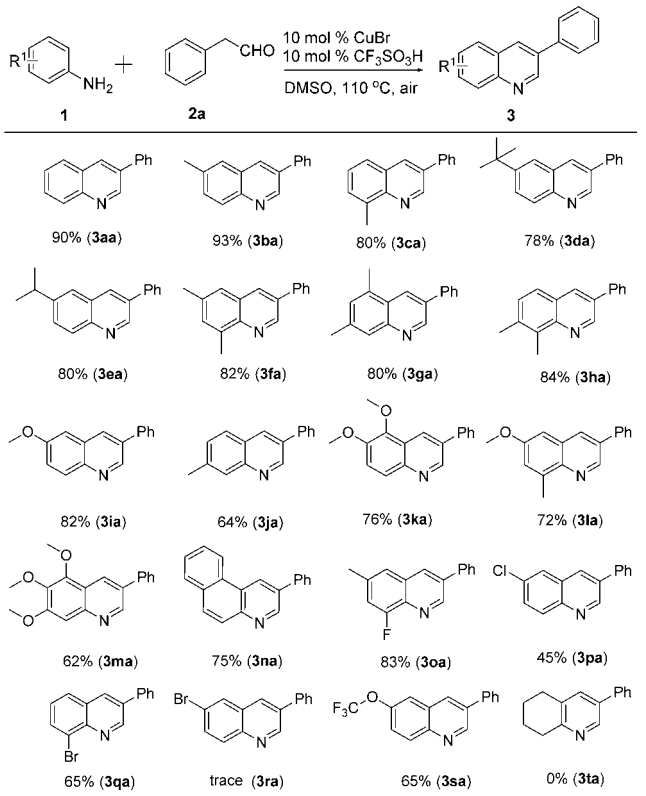
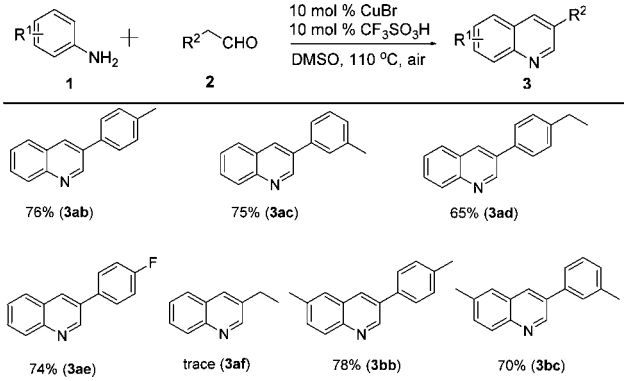
Scheme 2. Scope of Anilines



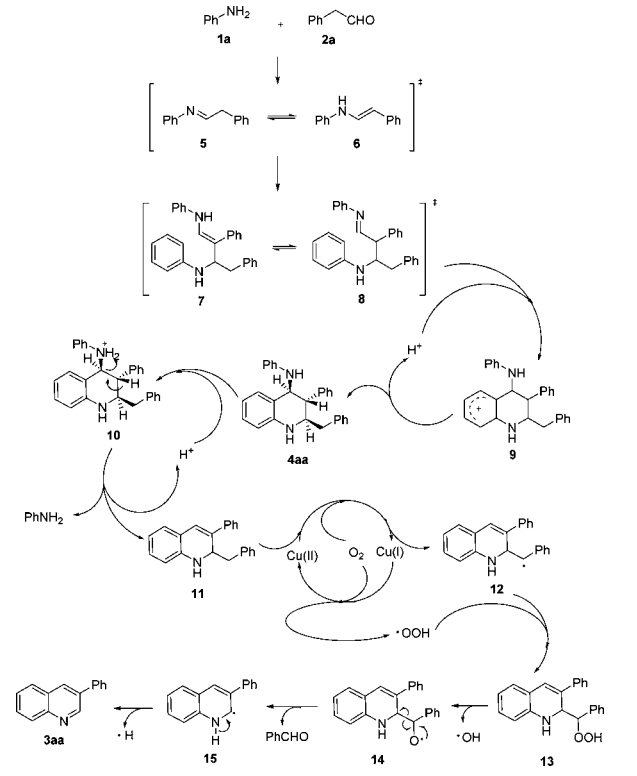
in 48% yield, and we confirmed the structure of (**3bb**) unambiguously through an X-ray crystal analysis. Among the acids we examined, CF_3SO_3H showed the highest activity for this reaction (Table 1, entries 1−4). Further studies showed that CuBr was the most efficient catalyst for the reaction when DMSO was used as solvent. Gratifyingly, simply lowering the reaction temperature to 110 °C led to an improvement and gave **3aa** in 90% yield. Significantly, air performed better and gave a higher yield than molecular oxygen. In addition, without metal salts as a catalyst, no desired product was obtained (Table 1, entry 17). Nevertheless, without acid as an additive, the reaction also could be performed but result in a lower yield.

With the optimized reaction conditions in hand (Table 1, entry 14), we then extended the scope of this reaction, and the results are illustrated in Schemes 2 and 3. As shown in Scheme 2, the reaction of substituted anilines **1** and phenylacetaldehyde **2a** proceeded well, and the desired products were obtained with high yields (**3aa**−**3oa**). Remarkably, the substituents on the aniline drastically affect the yields of this reaction. The substrates with electron-donating groups gave higher yields than the substrates with electron-withdrawing groups on the aniline. For example, the reaction of **1b** with **2a** afforded **3ba** in 93% yield, whereas **1p** was converted to **3pa** only in 45% yield. These results implied that the electronic effect is critical for the transformation. The naphthyl-substituted amine was also tolerated in this transformation, producing

Scheme 3. Scope of Aldehydes



Scheme 4. Proposed Mechanism

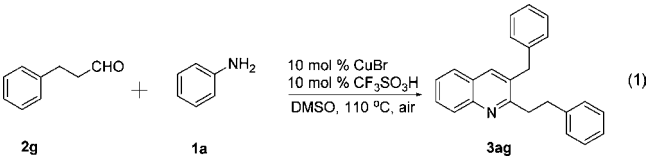


2-phenylbenzo[*f*]quinoline in 75% yield (**3na**). Futhermore, steric hindrance may affect the efficiency of the reaction (**3ma**). Unfortunately, when 4-bromoaniline was employed in this reaction, only trace product was detected (**3ra**). Cyclohexanamine also did not work in this reaction (**3ta**).

The aerobic oxidative annulation was further expanded to a range of substituted aldehydes **2** (Scheme 3). Gratifyingly, different functionalized aldehydes successfully coupled with aniline. For example, methyl (**3ab**, **3ac**), ethyl (**3ad**), and fluoro (**3ae**) substituents on the phenyl ring of the aldehydes survivied, and the desired products

were obtained in good yields. To our delight, different substituents did not significantly affect the efficiency of the reaction under the optimized conditions, and the scope was further expanded (**3bb**, **3bc**). Notably, when butyraldehyde was subjected to the transformation, we could not obtain the desired product (**3af**).

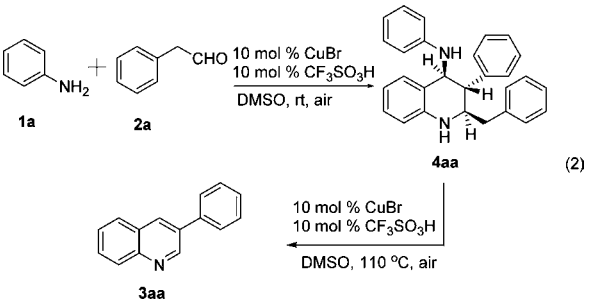
It is worth mentioning that when 3-phenylpropanal **2g** and aniline **1a** were subjected to the optimized conditions, an unexpected product, 3-benzyl-2-phenethylquinoline **3ag**, was isolated in 72% yield [eq 1].



(1)

To probe the mechanism further, some control experiments were investigated. When the annulation of **1a** and **2a** was carried out under standard conditions at room temperature, fortunately, a compound, (2*R**,3*R**,4*S**)-2-benzyl-*N*,3-diphenyl-1,2,3,4-tetrahydroquinolin-4-amine **4aa**, was isolated in 68% yield.[14] The desired product **3aa** could also be successfully obtained at 110 °C. This indicates that the compound **4aa** is an the intermediate of the transformation. Meanwhile, a small amount of benzaldehyde was detected by GC-MS in the reaction system [eq 2].

A plausible mechanism is proposed in Scheme 4 on the basis of the results described above. The reaction of amine **1a** with aldehyde **2a** produces imine **5** quickly, which equilibrates to enamine **6**. Subsequently, the reaction involved a coupling of **5** and **6** to produce the Michael addition intermediate **7**, which also can equilibrate to generate the intermediate **8**. Intramolecular cyclization of **8** gives rise to **9** with acid, which is then



(2)

further aromatized to produce **4aa**. Then aniline is eliminated from **4aa** to afford dihydroquinoline **11**. Furthermore, the hydroperoxide **13** is provided by the combination of the radical intermediate **12** and hydroperoxyl radical (•OOH), which are initially generated from **11** and oxygen in the presence of copper. Moreover, the radical **14** and hydroxide radical (•OH) are generated by decomposition of the hydroperoxide **13**. The single electron transfer of **14** forms the radical **15** and benzyl aldehyde with C−C cleavage. Finally, the quinoline **3aa** is afforded by the hydride elimination of **15**.

In summary, we have developed a simple, novel, and efficient method for the synthesis of polysubstituted quinolines in a one-pot manner. The synthesis of quinolines undergoes a copper-catalyzed aerobic oxidative dehydrogenative annulation of aniline and aldehydes by C−H functionalization, C−C formation, and cleavage. Air was used in this procedure as the oxidant, which makes the transformation very practical and economical.

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Supporting Information Available. Experimental procedures, spectral data of all compounds and X-ray data for **3bb** (CIF). This material is available free of charge via the Internetat http://pubs.acs.org.

The authors declare no competing financial interest.

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