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Copper-Catalyzed Formal [3 + 3] Annulations of Arylketoximes and *o*-Fluorobenzaldehydes: An Entry to Quinoline Compounds

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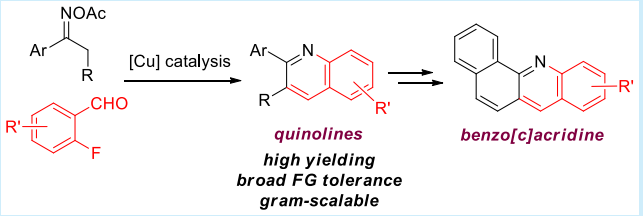
ABSTRACT: A copper-based catalytic system has been developed to enable efficient cyclization of ketoxime acetates with *o*-fluorobenzaldehydes. This protocol offers an efficient method for the synthesis of substituted quinoline derivatives with a broad range of compatible functionalities. The present system also provides a rapid access to synthetically and pharmaceutically useful quinoline-fused polycycles such as benzo[*c*]acridines.



Quinoline and its derivatives are a class of compounds with nitrogen-containing heterocyclic structure constituting a number of medicines, dyes, pesticides, and a variety of chemical additives, etc.,[1] featuring important biological activities and application values.[2] With the in-depth research on heterocyclic drugs, many quinoline compounds are pharmaceutical intermediates, and in recent years, a variety of new drugs containing quinoline rings have been approved,[3] including plant anticancer drug camptothecin,[4] TLR agonist imiquimod,[5] and antimalarial drug chloroquine,[6] etc. Considering the pharmaceutical and synthetic importance of quinoline, there is a great need to develop convenient and practical methods for constructing functionalized quinoline-containing ring structures.

On the other hand, ketoximes have been established to be readily available and highly effective raw materials in molecule synthesis.[7] Consequently, they have attracted considerable attention among organic chemists for the formation of nitrogen-containing heterocyclic compounds.[8] For instance, intramolecular aza-Heck annulations of alkyne-attached ketoximes give a useful access to functionalized pyridines (Figure 1, a).[9] In the past decade, intermolecular annulation reactions via directing C−H activation of ketoximes have proved to be a robust synthetic platform for pyridine and quinoline formation transition metal catalysis with Ru,[10] Rh,[11] Co,[12] and Pd,[13] among others[14] (Figure 1, b). Ketoximes also provide a N−C−C fragment for pyridine formation via homocouplings and cyclizations.[15,16] They were exploited to couple with a range of unsaturated compounds such as enals,[16a,b] enones,[16c−e] cyclopropanols,[16f] allyl alcohol,[16g] and isatins,[16h,i] leading to practical production of diverse pyridine and quinoline derivatives (Figure 1, c−e). Very recently, Wei et al. designed alkynylketoximes that could efficiently couple with maleimide under novel iron catalysis to enable formation of fused pyridines.[17] As part of our continuous interest in N-heterocycle construction from *O*-acyl ketoximes, herein, we

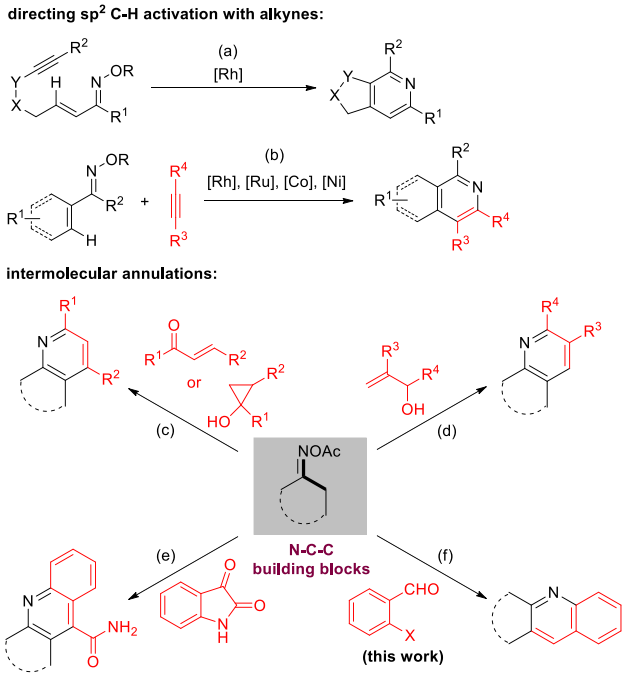


Figure 1. *O*-Acyl oximes as building blocks for the synthesis of pyridine and quinoline derivatives.

report copper-catalyzed formal [3 + 3] annulations of ketone oximes and *ortho*-halogenated aromatic aldehydes, which give a

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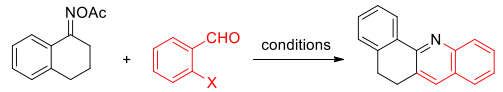
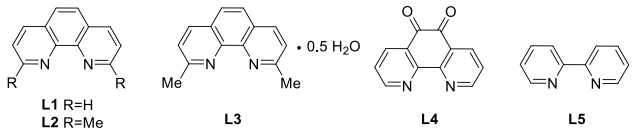
Table 1. Optimization of Reaction Conditions[a]



entry	2 (X)	catalyst	solvent	additive	ligand	yield[b] (%)
1	Br	CuBr	DCE	–	**L1**	51
2	Cl	CuBr	DCE	–	**L1**	trace
3	F	CuBr	DCE	–	**L1**	62
4	NO_2	CuBr	DCE	–	**L1**	46
5	OCH_3	CuBr	DCE	–	**L1**	41
6	F	CuCl	DCE	–	**L1**	58
7	F	CuI	DCE	–	**L1**	51
8	F	$CuBr_2$	DCE	–	**L1**	48
9	F	$Cu(OAc)_2$	DCE	–	**L1**	40
10	F	–	DCE	–	**L1**	ND
11	F	CuBr	1,4-dioxane	–	**L1**	50
12	F	CuBr	DMF	–	**L1**	42
13	F	CuBr	toluene	–	**L1**	23
14	F	CuBr	DMSO	–	**L1**	36
15	F	CuBr	CH_3CN	–	**L1**	trace
16	F	CuBr	DCE	$NaHSO_3$	**L1**	69
17	F	CuBr	DCE	$Na_2S_2O_4$	**L1**	64
18	F	CuBr	DCE	$NaHSO_3$	–	31
19	F	CuBr	DCE	$NaHSO_3$	**L2**	72
20	F	CuBr	DCE	$NaHSO_3$	**L3**	92 (80)[e]
21	F	CuBr	DCE	$NaHSO_3$	**L4**	65
22	F	CuBr	DCE	$NaHSO_3$	**L5**	59
23[c]	F	CuBr	DCE	$NaHSO_3$	**L3**	85
24[d]	F	CuBr	DCE	$NaHSO_3$	**L3**	76
25[f]	F	CuBr	DCE	$NaHSO_3$	**L3**	66
26[g]	F	CuBr	DCE	$NaHSO_3$	**L3**	90 (78)
27[h]	F	CuBr	DCE	$NaHSO_3$	**L3**	78

[a]Reaction conditions: **1a** (0.3 mmol), **2** (0.2 mmol), catalyst (15 mol %), additive (1.0 equiv), ligand (15 mol %), solvent (1.0 mL), 130 °C, 12 h, under Air. [b]Yield was determined by GC analysis with dodecane as the internal standard. [c]Under N_2. [d]Under O_2. [e]Isolated yield was given in parentheses. [f]**1a** (0.2 mmol). [g]**1a** (0.2 mmol), **2a** (0.3 mmol). [h](*E*)-3,4-Dihydronaphthalen-1(2*H*)-one *O*-benzoylated oxime instead of **1a**.



unique entry to valuable quinoline and acridine compounds (Figure 1, f).

On the basis of our previous couplings of ketoximes with aldehydes,[8o,p] we selected (*E*)-3,4-dihydronaphthalen-1(2*H*)-one *O*-acetyl oxime (**1a**) as the model substrate to react with *o*-halo-substituted benzaldehydes **2** to optimize the reaction conditions (Table 1). At the outset, when the reaction was performed in the presence of CuBr in DCE at 130 °C using 1,10-phenanthroline (**L1**) as the ligand with *o*-bromobenzaldehyde, the desired product 5,6-dihydrobenzo[*c*]acridine (**3a**) was obtained in 51% yield (Table 1, entry 1). Unexpectedly, while the desired product **3a** was obtained in only trace yield when *o*-chlorobenzaldehyde was used, *o*-fluorobenzaldehyde resulted in 62% yield (Table 1, entries 2−3). We thus speculate that the carbon-halo bond cleavage proceeds through aromatic nucleophilic substitution in this reaction. To further verify this result, we used benzaldehydes bearing nitro and methoxy in the ortho position, and all of them could afford the target product **3a** in moderate yield (Table 1, entries 4−5). With the best productivity of *o*-fluorobenzaldehyde, other parameters possibly affecting the reaction were screened. First, we screened several copper catalysts, including CuCl, CuI, $CuBr_2$, $Cu(OAc)_2$ (Table 1, entries 6−9). All of them were found to be inferior to CuBr. A control experiment in the absence of copper salts revealed that the copper catalyst was essential for the reaction (Table 1, entry 10). Other solvents including 1,4-dioxane, DMF, toluene, and DMSO were effective, while CH_3CN almost completely quenched the reaction (Table 1, entries 11−15). High conversion was observed when $NaHSO_3$ or $Na_2S_2O_4$ was employed as the additive (Table 1, entries 16−17), which may serve as a reducing reagent to activate oximes. We found the yield of **3a** dropped significantly in the absence of ligand (Table 1, entry 18). Then, a variety of ligands were investigated (Table 1, entries 19−22). We were delighted to find that the reaction with 2,9-dimethyl-1,10-phenanthroline hemihydrate (**L3**) afforded **3a** in 92% yield. In order to further increase the reaction yield, we tried to conduct the experiment in a different

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atmosphere. But disappointingly, the model reaction failed to deliver higher yields either under N_2 or O_2 (Table 1, entries 23 and 24). Notably, an excessive amount of one of the substrates is required, where an equimolar ratio of **1a** gave **3a** in 66% yield (Table 1, entries 25−26). We also used (*E*)-3,4-dihydronaphthalen-1(2*H*)-one *O*-benzoylated oxime instead of **1a**, which reduced the yield of **3a** to 78% (entry 27).

With the optimized conditions in hand, we exploited the substrate scope and generality of the defluorinated annulation reaction using various *o*-fluorobenzaldehydes (Figure 2). As

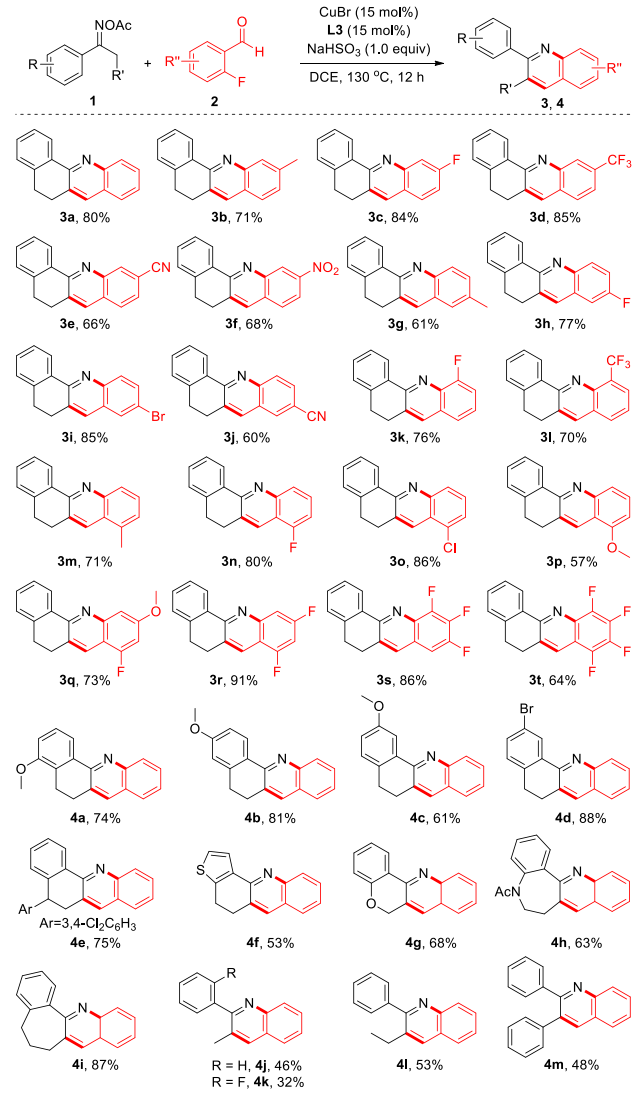

Figure 2. Substrate scope.

expected, substituted *o*-fluorobenzaldehydes smoothly participated in the reaction with **1a**, affording the desired dihydrobenzo[*c*]acridines **3a**−**3p** in moderate to high yields (57−86%). A broad range of functional groups such as methyl, methoxy, synthetically useful halogen (F, Cl, Br), and strong electron-withdrawing groups including trifluoromethyl, cyano, and nitro were all smoothly tolerated. The substrates with a 3-F group and 3-CF_3 group of the *o*-fluorobenzaldehyde were efficiently transformed into the corresponding benzo[*c*]-acridines **3k** (76%) and **3l** (70%), respectively. Similarly, the desired products **3m**−**3p** were obtained in moderate to high yields from the *o*-fluorobenzaldehydes with such substituents at C6 as methyl, fluoro, chloro, and methoxy. The results showed that the electronic properties and the steric hindrance of the substituents on the aromatic rings had no significant effect on the reaction yields. Compared with 2,6-difluorobenzaldehyde, 2,6-difluoro-4-methoxybenzaldehyde generated the corresponding product **3q** in 73% yield, and almost quantitative yield was achieved when 2,4,6-trifluorobenzaldehyde was employed (**3r**, 91% yield). Regarding multiple substitutions, we used tetrafluoro- and pentafluoro benzaldehydes, which were smoothly participated in the reaction to afford the corresponding products (**3s** and **3t**) in moderate to good yields.

Subsequently, we examined the reactions of various oximes, using **2a** as the reaction partner. The substrates (**1b**−**1d**) with a methoxy group at the 5-, 6-, or 7-position of the 1-tetralone oximes were efficiently transformed into the corresponding dihydrobenzo[*c*]acridines **4a**−**4c** in moderate to high yields. The bromo functional group attached to benzene ring gave the target product **4d** in 88% yield. Heteroaryl-fused cyclohexenone oxime acetates were compatible with the reaction system, leading to a unique access to the corresponding heteroaryl-fused dihydroacridine products in moderate yields (53−68%, **4f**−**4h**). Furthermore, benzo[6,7]cyclohepta[1,2-*b*]quinoline **4i** was efficiently generated in good yield (87%) when benzoheptanone oxime was used. Finally, arylalkylketoximes derived from phenylacetone, phenylbutanone, and 2-phenylacetophenone smoothly took part in the reactions with **2a** under the optimized conditions, affording the 2,3-disubstituted quinoline **4j**−**4m** in moderate yields. Notably, the present copper system was not suitable for acetophenone *O*-acetyl oxime, which resulted in the major pyridine product.[15a]

Given the productivity of the copper-catalyzed [3 + 3] formal annulation, next we were attracted to reveal its action model. Hence, some control experiments were carried out. First, we noted that the addition of radical scavengers including 2,2,6,6-tetramethylpiperidinooxy (TEMPO) and 2,6-di-*tert*-butyl-4-hydroxytoluene (BHT) to the reaction system had a slight effect on the cyclization yield (Figure 3, a). This finding suggests that a radical pathway may not be involved. Besides, the product **3a** was obtained in a trace amount and **1a** was

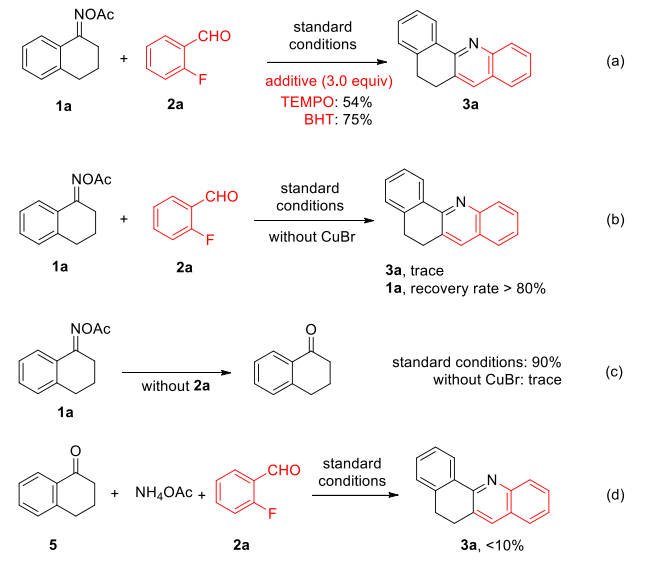

Figure 3. Control experiments.

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mostly recovered in the absence of CuBr (Figure 3, b), which suggests that the condensation process does not occur in the initial step. Next, **1a** decomposed to ketone with the assistance of the copper catalyst in the absence of *o*-fluorobenzaldehydes, while it did not work in the absence of copper salts (Figure 3, c). These results show that the copper catalyst activates the oxime ester in the initial step. Finally, the three-component reaction of 1-tetralone, *o*-fluorobenzaldehydes, and ammonium acetate could also work to furnish 5,6-dihydrobenzo[*c*]acridine **3a**, albeit in low yield (Figure 3, d), revealing the imine formation to be the initial step in the reaction procedure.

On the basis of experimental results and literature,[7a,b] a tentative reaction mechanism was proposed (Figure 4).

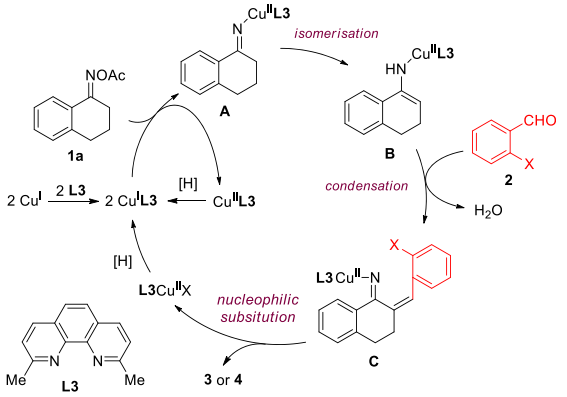

Figure 4. Possible reaction mechanism.

Initially, a [Cu^{I}**L3**] complex is formed in situ in the presence of a ligand. Then, the reduction of the N−O bond of oxime moiety by copper(I) salts furnishes the imino copper(II) species **A**, with tautomerization to afford the enamino copper complex **B**. Subsequently, the condensation of complex **B** with aldehyde **2** gives intermediate **C**. The intramolecular nucleophilic substitution forms the C−N bond of the product **3** or **4**, along with the liberation of the **L3**Cu^{II}X complex. Finally, the catalytically active Cu^{I} is regenerated by $NaHSO_3$ reduction of the released Cu^{II} species.

To demonstrate the practical synthetic utility of this reaction, a 6.0 mmol scale synthesis of 2-bromo-5,6-dihydrobenzo[*c*]acridine (**4d**) was carried out under optimal conditions, giving the product in 79% yield (Figure 5, a). Then, we used the bromo-substituted product **4d** for late-stage derivatization.[18] The oxidative aromatization of **4d** afforded a benzo[*c*]acridine compound **5a** in 70% yield (Figure 5, b). Moreover, the Pd/Cu-catalyzed Sonogashira coupling of **4d** with terminal alkynes afforded alkynylation products **5b** and **5c** in good yields (Figure 5, c). Interestingly, the resultant alkyne **5b** could transform to the pentacyclic 2-phenyl-6,7-dihydrothieno[2′,3′:3,4]benzo[1,2-*c*]acridine (**5c**) through thienannulation with elemental sulfur (Figure 5, d).[18a] The resultant 2-arylquinolines bear a quinoline moiety that can be used as a directing group for further manipulation. Hence, the corresponding acylation[18b] (**5e**, Figure 5, e) and ethoxycarbonylation[18c] products (**5f**, Figure 5, f) were successfully obtained when we subjected **3a** to palladium-catalytic systems using benzil and diethyl azodicarboxyate (DEAD), respectively.

In summary, a facile Cu-catalyzed annulation reaction of arylketoxime acetates with ortho-halogenated aromatic aldehydes has been developed that enables efficient synthesis of

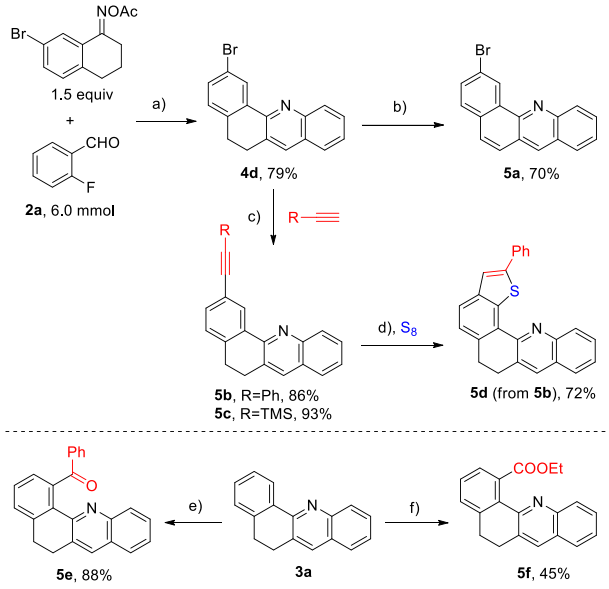

Figure 5. Application of the protocol. Detailed reaction conditions see Supporting Information.

2,3-disubstituted quinoline derivatives. While *ortho*-fluorobenzaldehydes feature high reactivity, other ortho-functionalized benzaldehydes including *o*-bromobenzaldehyde, *o*-nitrobenzaldehyde, and *o*-methoxybenzaldehyde also give promising results in the [3 + 3] formal annulations. The present copper-catalytic system tolerates a wide range of substrates with useful functionalities and, more importantly, it also provides a viable entry to structurally significant benzo[*c*]acridine compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c04138.

Experimental procedures, characterization data, and ^{1}H NMR and ^{13}C NMR spectra for all new products (PDF)

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Notes

The authors declare no competing financial interest.

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