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Copper-Catalyzed Aerobic Oxidative Carbocyclization–Ketonization Cascade: Selective Synthesis of Quinolinones

Peng Xie,[a,b] Zhi-Qiang Wang,[a] Guo-Bo Deng,[a] Ren-Jie Song,[a] Jia-Dong Xia,[a,b] Ming Hu,[a] and Jin-Heng Li[a,*]

[a] State Key Laboratory of Chemo/Biosensing and Chemometrics, College of Chemistry and Chemical Engineering, Hunan University, Changsha 410082, People's Republic of China
Fax: (+86)-731-8871-3642, phone: (+86)-731-8871-3642; e-mail: jhli@hnu.edu.cn
[b] Key Laboratory of Chemical Biology & Traditional Chinese Medicine Research, Hunan Normal University, Changsha 410081, People's Republic of China

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Abstract: A new thematic extension method is described for the carbocyclization of α-C(sp^3)–H bonds of amides with alkynes followed by ketonization of the alkynes that utilizes the inexpensive copper(II) acetoacetonate [$Cu(acac)_2$] as catalyst under an oxygen atmosphere to synthesize quinolinones. It is noteworthy that the oxygen atom of the newly formed carbonyl group is from atmospheric molecular oxygen.

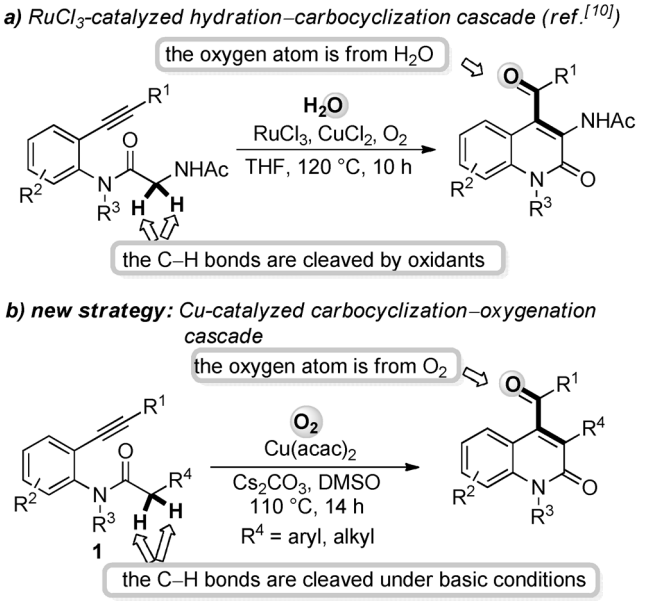
Keywords: carbocyclization; copper; C(sp^3)–H functionalization; ketonization; quinolinones

Introduction

Quinolinones are important structural motifs in a great number of bioactive natural products, pharmaceuticals, and organic functional materials.[1] For these reasons, great interest has been directed to the direct construction of the quinolinone skeleton.[2–4] To date, the cyclization approaches have been the major focus of study in this area,[3–5] such as classic base-catalyzed Friedländer reaction,[3] acid-catalyzed Knorr reaction,[4] the Baylis–Hillman reaction,[5] and recent transition metal-catalyzed cyclization of acyclic precursors.[6] However, the transition metal-catalyzed approaches are much less abundant, and many are focused on the "prefunctionalization" strategy that restricts it to the use of expensive substrates (often aryl halides) and catalytic systems (often Pd combined with a ligand). A fascinating strategy for quinolinone synthesis is metal-catalyzed C–H functionalization–cyclization cascade, but unfortunately, the reported step- and atom-economic methods have been typically achieved by rare and noble transition metal catalysts (e.g. Pd, Pt, Ru, and Au), and are limited to the sp^2 C–H bond functionalization, including (i) arylation of *N*-arylpropiolamides[7] or *N*-(2-haloaryl)-benzamides[8] and (ii) amidation of 3-arylacrylamides.[9]

We recently reported the first example of an $RuCl_3$-catalyzed carbocyclization–hydration cascade for quinolinone synthesis using $CuCl_2$ combined with O_2 as the terminal oxidants: without Ru catalysts the reaction could not take place even in the presence of $CuCl_2$ and O_2, and the oxygen atom in the newly formed carbonyl group of quinolinones is from water by hydration (Scheme 1).[10] However, the chemical disadvantages of this protocol center around using Ru catalysts as well as special α-C(sp^3)–H bonds of amides adjacent to a nitrogen atom. An alternative catalytic system for the α-C(sp^3)–H bonds in common amides with more sustainable perspectives is therefore highly appealing. Herein we report a novel $Cu(acac)_2$-catalyzed aerobic oxidative carbocyclization and oxygenation of an alkyne with two α-C(sp^3)–H bonds in a common amide with the aid of a base (Scheme 1). Notably, this work represents a different thematic extension of the metal-catalyzed oxidative C(sp^3)–H functionalization–carbocyclization–ketonization cascade for quinolinone synthesis, and the oxygen atom of the newly formed carbonyl group is incorporated from atmospheric molecular oxygen.

Generally, activation of the α-positioned carbon of a carbonyl system requires a base to deprotonate it leading to a carbon nucleophile or an enol intermediate followed by complexation of a metal and addition to an electrophile (aryl halide and pseudohalide)[11a,b] or a carbon-carbon multiple bond.[11c] Although the Cu-catalyzed cyclization of an alkyne with an α-



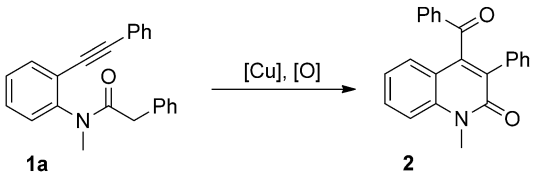
Scheme 1. Synthesis of quinolinones through C(sp^3)–H bond functionalization.

carbon of a carbonyl system has been illustrated, the *in-situ* generated carbon nucleophile **A** in this cyclization process required another electron-withdrawing group to stabilize it and the vinyl-Cu(II) intermediate **B** is readily protonated (Scheme 2).[11c] Therefore, the development of a new strategy to trap the vinyl-Cu(II) intermediate for valuable synthetic utilization is highly desirable. To the best of our knowledge, however, trapping of the vinyl-Cu(II) intermediate with atmospheric molecular oxygen through the sp^3-carbon cyclization with alkynes has not been established.[12]

Results and Discussion

Our study began to examine the feasibility of the proposed carbocyclization–oxygenation cascade using *N*-methyl-2-phenyl-*N*-[2-(phenylethynyl)phenyl]acetamide (**1a**), O_2, a series of copper catalysts and bases (Table 1). Gratifyingly, the amide **1a** was successfully reacted with O_2, $CuCl_2$ and Cs_2CO_3 in DMF at 110 °C, affording the desired product **2** in 65% yield

Table 1. Screening for optimal conditions.[a]

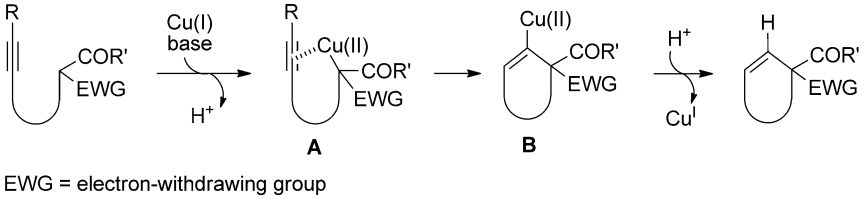


1a 2

Entry	[Cu]	Base	Solvent	Temp. [°C]	Yield [%][b]
1	$CuCl_2$ (2)	Cs_2CO_3	DMF	110	65
2	$CuCl_2$ (5)	Cs_2CO_3	DMF	110	59
3[c]	$CuCl_2$ (1)	Cs_2CO_3	DMF	110	61
4[d]	–	Cs_2CO_3	DMF	110	20
5[e]	–	Cs_2CO_3	DMF	110	< 5%
6	–	Et_3N	DMF	110	0
7	–	DABCO	DMF	110	0
8	–	P_4-*t*-Bu	DMF	110	0
9	CuCl (2)	Cs_2CO_3	DMF	110	58
10	$CuBr_2$ (2)	Cs_2CO_3	DMF	110	53
11	$Cu(OTf)_2$ (2)	Cs_2CO_3	DMF	110	64
12	$Cu(acac)_2$ (2)	Cs_2CO_3	DMF	110	68
13	$Cu(acac)_2$ (2)	K_2CO_3	DMF	110	41
14	$Cu(acac)_2$ (2)	CsOH	DMF	110	54
15	$Cu(acac)_2$ (2)	*t*-BuONa	DMF	110	67
16	$Cu(acac)_2$ (2)	Et_3N	DMF	110	16
17	*$Cu(acac)_2$ (2)*	*Cs_2CO_3*	*DMSO*	*110*	*73*
18	$Cu(acac)_2$ (2)	Cs_2CO_3	toluene	110	9
19	$Cu(acac)_2$ (2)	Cs_2CO_3	DMSO	95	70
20	$Cu(acac)_2$ (2)	Cs_2CO_3	DMSO	125	61
21[f]	$Cu(acac)_2$ (2)	Cs_2CO_3	DMSO	110	19

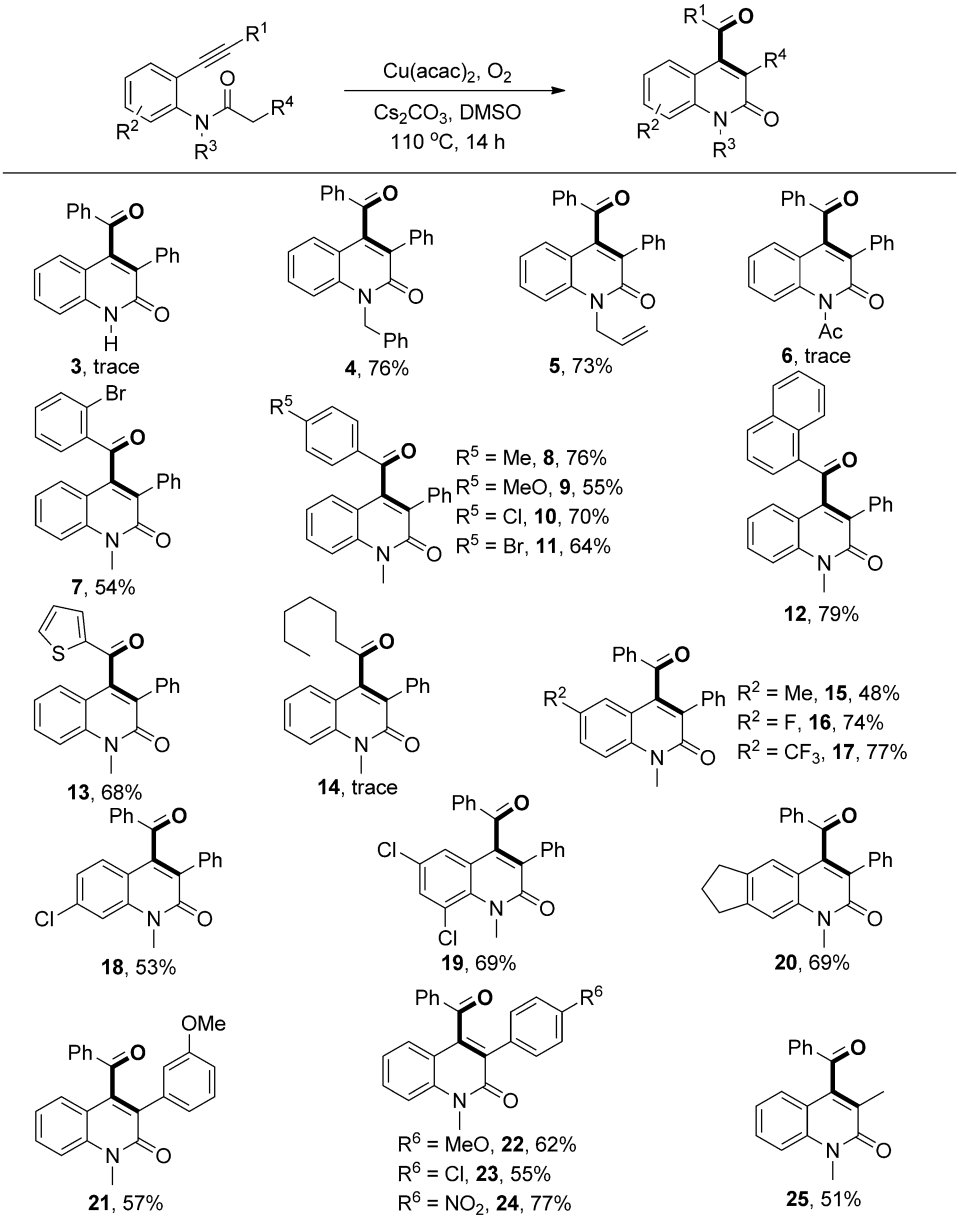
[a] *Reaction conditions:* **1a** (0.3 mmol), [Cu], O_2 (1 atm), base (2 equiv.) and solvent (2 mL) for 14 h. P_4-*t*-Bu is phosphazene base solution and the purity of Cs_2CO_3 is about 99% w/w.
[b] Isolated yield.
[c] For 24 h.
[d] Some unidentified products together with traces of 4-benzyl-1-methyl-3-phenylquinolin-2(1H)-one (**3a**) were observed by GC-MS analysis. There are about 0.005% w/w of Cu in Cs_2CO_3 (purity: 99% w/w) by ICP-MS analysis: 0.05 mol% Cu (2 equiv. Cs_2CO_3) *vs.* substrate **1a**.
[e] 99.999% w/w Cs_2CO_3 (2 equiv.) was used.
[f] Under an air atmosphere.

(entry 1). This finding prompted us to examine the amount of $CuCl_2$: identical results were achieved at a loading of either 5 mol% or 1 mol% $CuCl_2$, but the latter (1 mol% $CuCl_2$) required a prolonged reaction



Scheme 2. Cu-catalyzed carbocyclization–protonation cascade.

Table 2. Cu-catalyzed oxidative cyclization of *N*-(2-*e*thynylaryl)acetamides (**1**).[a]



[a] *Reaction conditions:* **1** (0.3 mmol), $Cu(acac)_2$ (2 mol%), O_2 (1 atm), Cs_2CO_3 (2 equiv.) and DMSO (2 mL) at 110 °C for 14 h.

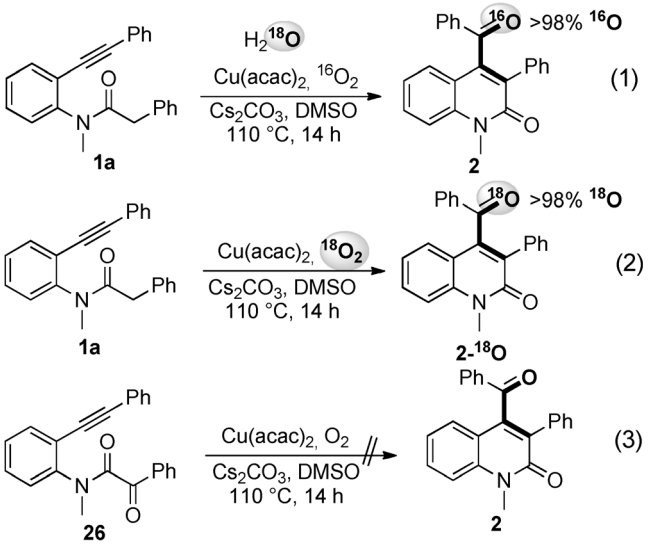
time (entries 2 and 3). To our surprise, in the absence of Cu catalyst product **2** could form in the presence of 99% purity Cs_2CO_3, albeit with a low yield (entry 4). We deduced that Cs_2CO_3 might contain some copper to realize the reaction, which was supported by the ICP-MS analysis results. To verify it, both 99.999% purity Cs_2CO_3 and organic bases were inversigated without Cu catalysts (entries 5–8): the yield of **2** was lowered to $<5\%$ with 99.999% purity Cs_2CO_3, and the use of organic bases, such as Et_3N, DABCO or P_4-*t*-Bu, resulted in no detectable formation of product **2**. In the light of these results, a number of other Cu catalysts, CuCl, $CuBr_2$, $Cu(OTf)_2$ and $Cu(acac)_2$ was tested (entries 9–12): all displayed high reactivity for the reaction, and $Cu(acac)_2$ was superior. Therefore, $Cu(acac)_2$ was employed to evaluate the effect of bases and solvents (entries 13–18). Screening revealed that the reaction using Cs_2CO_3 as base in DMSO medium gave the best results (entry 17). It is noteworthy that $Cu(acac)_2$ conbined with Et_3N can furnish the desired product **2** in 16% yield (entry 16). Among the reaction temperatures examined, the reaction at 95 °C offered an identical result to that at 110 °C (entry 19), but a higher temperature (125 °C) had a negative

effect (entry 20). However, substrate **1a** displayed a rather low reactivity under an air atmosphere (entry 21).

We next turned our attention to the scope of *N*-[2-(ethynyl)aryl]acetamides **1** for the carbocyclization–ketonization cascade under the optimal reaction conditions, and the results are summarized in Table 2. While 2-phenyl-*N*-[2-(phenylethynyl)phenyl]acetamide was not viable for this reaction (product **3**), when the N-H group was replaced by benzyl or allyl groups the respective substrates were found to furnish the corresponding products **4** and **5** in good yields, while replacement by an acetyl group resulted in a trace of the desired product **6**. Subsequently, substituents at the terminal alkyne were examined in the presence of O_2, $Cu(acac)_2$ and Cs_2CO_3: a variety of aryl groups, such as 2-BrC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, naphthalen-1-yl and even thiophen-2-yl groups, at the terminal alkyne were well-tolerated (products **7**–**13**), but an aliphatic group displayed less reactivity (product **14**). Importantly, in these cases some halo functional groups, Br and Cl, on the aromatic ring were compatible with the optimal conditions, thereby facilitating additional modifications at the halogenated positions (products **7**, **10** and **11**).

Gratifyingly, substrates with several substituents, like alkyl, F, CF_3 and Cl, on the aryl ring of the *N*-[2-(ethynyl)aryl]acetamide moiety displayed sufficient reactivity for the carbocyclization–oxygenation cascade in the presence of O_2, $Cu(acac)_2$ and Cs_2CO_3 (products **15**–**20**). For example, the CF_3-substitued amide offered the desired quinolinone **17** in 77% yield. Using a di-Cl-substitued amide, a good yield was still achieved (product **19**). It was noted that hetreo- or carbocyclic rings were consisitent with the optimal conditions, making this methodology more useful in organic synthesis (products **13** and **20**). Fianlly, a number of substrates with α-carbon in the amides were tested, and the results disclosed that the α-carbon atom joined to either an aryl group or an aliphatic group was also highly effective in the reaction (products **21**–**25**).

The results in Table 1 disclosed that the yield was lowered sharply when using air instead of O_2 (entries 17 *vs.* 21, Table 1), suggesting that the source of the oxygen atom in the newly formed carbonyl group is from atmospheric molecular oxygen. To understand of the mechanism of the carbocyclization–oxygenation cascade, some control experiments were carried out. As shown in Scheme 3, in the presence of $H_2{}^{18}O$ treatment of amide **1a** with $^{16}O_2$, $Cu(acac)_2$ and Cs_2CO_3 only afforded the ^{16}O-labelled product **2**. In contrast, the presence of $^{18}O_2$ resulted in highly ^{18}O-labelled product **2-^{18}O** as determined by GC-MS, HMRS and NMR analysis (see the Supporting Information). These results confirmed that the oxygen atom was really incorporated from atmospheric molecular oxygen, and the reaction includes a Cu-peroxo species-forming process. Notably, cyclization of substrate **26** was not observed [Eq. (3)], which ruled out the mechanism including the ketone intermediate **26** from the first oxidation of the α-C(sp^3)–H bonds.

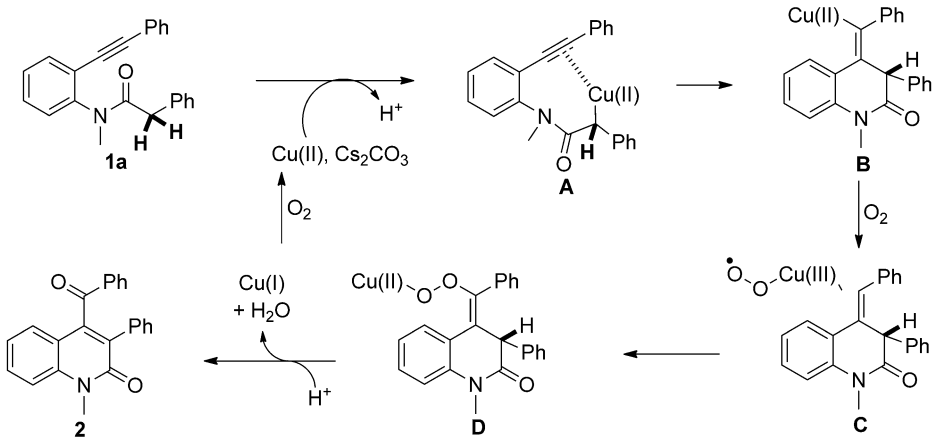


Scheme 3. Control experiments.

As outlined in Scheme 4, a possible mechanism is proposed on the basis of the results described above. Initially, complexation of Cu(II) with an α-carbon nucleophile, which is generated by deprotonation of the α-C(sp^3)–H bond in amide **1** by Cs_2CO_3, yields intermediate **A**.[11] Nucleophilic cyclization with alkyne in intermediate **A** takes place to afford intermediate **B**, followed by oxidation of intermediate **B** with O_2 which forms a Cu(III) peroxo species **C**.[12,13] Reductive elimination of intermediate **C** furnishes a peroxide intermediate **D**.[12] Finally, The peroxide intermediate **D** undergoes sequentially the O–O bond cleavage, reductive elimination and isomerization to construct quinolinone **2** and the Cu(I) species.

Conclusions

In summary, we have illustrated a new thematic extension route to quinolinone synthesis by the Cu-catalyzed oxidative C(sp^3)–H functionalization–carbocyclization–ketonization cascade. Most importantly, this present protocol provides an alternative to implant an oxygen atom from molecular oxygen into the quinolinone framework, establishing a new synthetic utility for both copper catalysts and molecular oxygen. Applications of this Cu-catalyzed oxidative carbocyclization–ketonization transformation in organic synthesis are currently under study in our laboratory.



Scheme 4. Possible mechanism.

Experimental Section

Typical Experimental Procedure for the Cu-Catalyzed carbocyclization-ketonization Reaction

To a Schlenk tube were added amide **1** (0.3 mmol), Cu(acac)$_2$ (2 mol%), Cs_2CO_3 (2 equiv.) and DMSO (2 mL). Then the tube was charged with O_2 (1 atm), and the mixture was stirred at 110 °C overnight until complete consumption of starting material as monitored by TLC analysis. After the reaction had finished, the reaction mixture was washed with brine. The aqueous phase was re-extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4, concentrated in vacuum, and the resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate) to afford the desired product.

4-Benzoyl-1-methyl-3-phenylquinolin-2(1*H*)-one (2): White solid; mp 193.1–194.9 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.63$ (d, $J = 8.0$ Hz, 2H), 7.52 (t, $J = 8.0$ Hz, 1H), 7.40–7. 36 (m, 2H), 7.30 (d, $J = 8.0$ Hz, 1H), 7.23–7.18 (m, 4H), 7.12–7.07 (m, 4H), 3.78 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 195.6$, 161.1, 145.2, 139.6, 136.0, 133.9, 130.8, 130.1, 129.8, 129.2, 128.5, 128.0, 127.7, 126.9, 122.5, 118.2, 114.5, 30.2; IR (KBr): $\nu = 1695$, 1621 cm^{-1}; LR-MS (EI 70 eV): m/z (%) = 339 (M^+, 76), 310 (100), 262 (56), 105 (56), 77 (79); HR-MS (ESI): $m/z = 340.1339$, calcd. for $C_{23}H_{18}NO_2$ $[M+H]^+$: 340.1338.

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