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Divergent Synthesis of Quinolones and Dihydroepindolidiones via Cu(I)-Catalyzed Cyclization of Anilines with Alkynes

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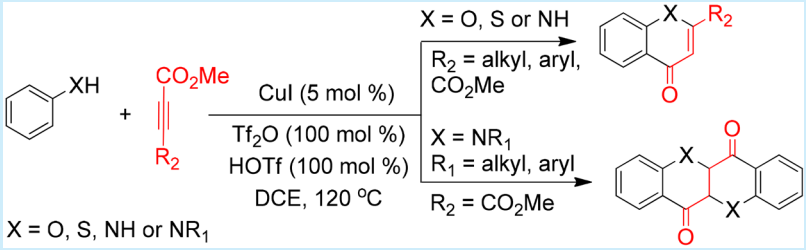
Supporting Information



ABSTRACT: A unique and efficient method for one-pot synthesis of diverse 4-quinolones from simple and readily available primary anilines and alkynes via Cu(I)-catalyzed direct cyclization has been developed. The (thio)phenols were also found to visible substrates for this reaction. Moreover, an unprecedented synthesis of dihydroepindolidiones has been demonstrated by using secondary anilines as the versatile substrates.

4-Quinolones represent a ubiquitous structural motif that is found in a broad range of biologically active compounds and pharmaceuticals.[1] Given the importance of 4-quinolones, the development of efficient methods for direct and highly efficient construction of 4-quinolone derivatives has attracted considerable attention. In the past several decades, a number of classical cyclocondensation reactions have been reported, such as Niementowski reaction,[2] Conrad−Limpach reaction,[3] Camps cyclizations,[4] etc.[5] However, most of them often suffer from harsh conditions, corrosive reagents, and a limited substrate scope. Therefore, the development of the mild, efficient and general protocols for direct assembly of this key structural motif is highly desired.

However, recently hot transition-metal (TM)-catalyzed direct functionalization has emerged as one of the most popular and powerful tools for the step- and atom-economical construction of diverse *N*-heterocycles. As a result, many TM-catalyzed protocols for the synthesis of quinolones has been extensively explored thus far, which has provided a streamlined method for building the desired quinolone products with an improved substrate/functional group scope.[6−8] For example, by using *ortho*-haloaryl acetylenic ketones/amines or *ortho*-alkynylbenzamides/aldehydes as the substrates, the TM-catalyzed reactions for building 4-quinolones have been well-established by several groups (Scheme 1a,b).[7] However, special starting materials and/or preactivated substrates are generally required for finishing the above transformations. To overcome the limitation, recently Lei and co-workers have disclosed an elegant Pd-catalyzed oxidative carbonylation of ketones, amines, and carbon monoxide for straightforward synthesis of 4-quinolones (Scheme 1c, right).[8e] Despite this compelling progress, it would be ideal to take advantage of alternative and readily available starting materials as versatile substrates for building 4-quinolone scaffolds in the absence of relatively toxic CO gas. In this regard, it is appealing to develop a more cost-effective and mild catalytic system for the direct synthesis of 4-quinolones.

Very recently, we have revealed a Cu(II)-catalyzed cyclization for one-pot construction of the 4-quinolone core by using *N*-alkyl and *N*-aryl substituted secondary anilines and alkynes as the substrates (Scheme 1d),[9] whereas the primary aniline was incompatible with the developed catalytic system. To expand this approach and improve the substrate scope further, we herein would like to report a novel and more general Cu(I)-catalyzed direct cyclization of primary/secondary anilines or (thio)phenols with alkynoates. Of note, the type and nature of anilines played a crucial role in controlling the chemoselectivity, thus leading to efficient and divergent synthesis of 4-quinolones and dihydroepindolidiones (Scheme 1e). Considering the importance of both of the resulting products in natural product chemistry and medicinal chemistry, the two-step-/atom-economical transformations should have broad synthetic utility.

We commenced our investigation with the reaction of aniline (**1a**) and dimethyl butynedioate (**2a**) in the presence of CuI (5 mol %) and HOTf (1.0 equiv) in DCE at 120 °C (Table 1). To our delight, the desired product **3a** was observed in a 24%

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Scheme 1. Transition Metal-Catalyzed Reactions for Quinolone Synthesis

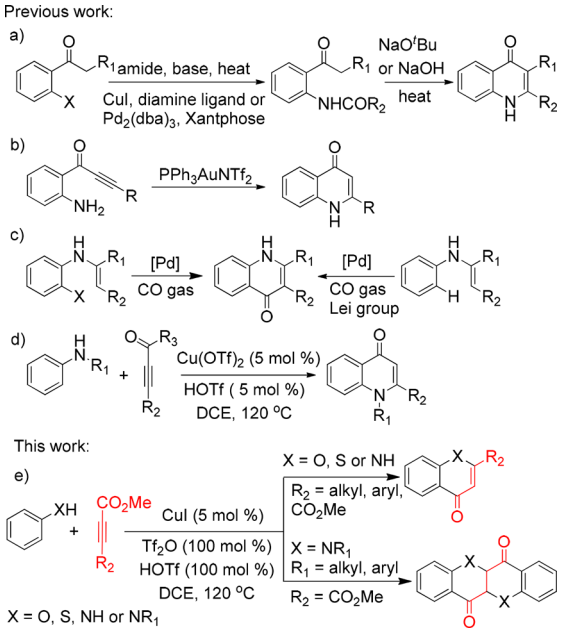
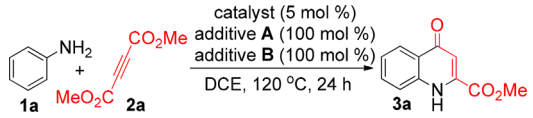


Table 1. Optimization of Reaction Conditions[a,b]



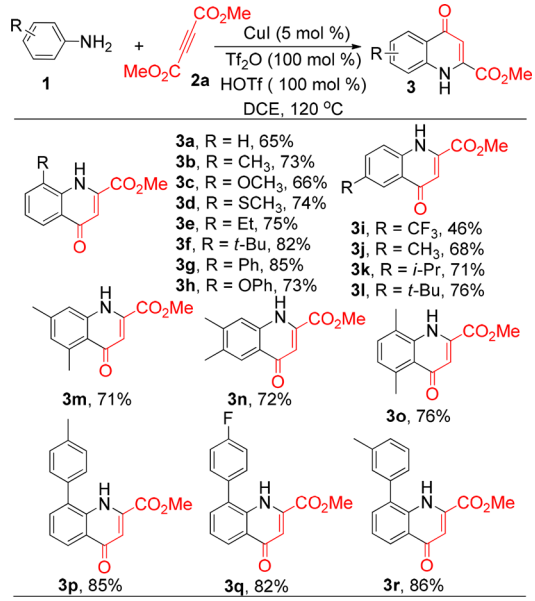
entry	catalyst	additive A	additive B	solvent	yield (%)[b]
1	CuI	HOTf		DCE	24
2	CuI		Tf_2O	DCE	42
3	CuI	HOTf	Tf_2O	DCE	65
4	CuI			DCE	0
5	CuI	TFA	Tf_2O	DCE	6
6	CuI	HOAc	Tf_2O	DCE	0
7	CuI	HOTf	Ac_2O	DCE	0
8		HOTf	Tf_2O	DCE	0
9	CuI	HOTf	Tf_2O	PhMe	0
10	CuI	HOTf	Tf_2O	DMF	0
11	CuI	HOTf	Tf_2O	DMSO	27
12	CuI	HOTf	Tf_2O	MeOH	24
13	CuI	HOTf	Tf_2O	Diox	14
14	CuI	HOTf	Tf_2O	THF	11
15	CuI	HOTf	Tf_2O	CH_3CN	0
16	CuCl	HOTf	Tf_2O	DCE	37
17	CuBr	HOTf	Tf_2O	DCE	25
18	CuOTf	HOTf	Tf_2O	DCE	42
19	$Cu(OTf)_2$	HOTf	Tf_2O	DCE	5
20	$Pd(OAc)_2$	HOTf	Tf_2O	DCE	0
21	$Cp^*Co(CO)I_2$	HOTf	Tf_2O	DCE	0

[a]Reaction conditions: aniline **1a** (0.5 mmol), dimethyl butynedioate **2a** (0.6 mmol), CuI (0.025 mmol), HOTf (0.5 mmol), and Tf_2O (0.5 mmol), in solvent (2 mL), 24 h. [b]Yields of isolated products are given.

isolated yield (entry 1). Moreover, 42% of **3a** was achieved when Tf_2O (1.0 equiv) was employed as the additive (entry 2). Gratefully, with the use of both HOTf (1.0 equiv) and Tf_2O (1.0 equiv) as coadditives, the target product **3a** led to an improved yield of 65% (entry 3). Further investigation showed that no desired product was found in the absence of both HOTf and Tf_2O (entry 4), suggesting that the introduction of them is essential for the reaction outcome and also hinting that the proper and strong acidic conditions are more favorable for improving the electrophilicity of the catalyst.[9] Inspired by these findings, a variety of additives was examined, and the coadditives of HOTf (1.0 equiv) and Tf_2O (1.0 equiv) were found to be the best choice (entries 5–7). The control experiment revealed that the CuI catalyst was indispensable for this reaction (Table 1, entry 8). The switching of solvent from DCE to various other reaction media obviously inhibited the process (entries 9–15), revealing that DCE was the optimal choice. Finally, changing CuI to other well-known copper species and TM catalysts, such as CuCl, CuBr, CuOTf, $Cu(OTf)_2$, $Pd(OAc)_2$, and $Cp^*Co(CO)I_2$ gave inferior results (entries 16–21).

Having the optimal reaction conditions in hand (Table 1, entry 3), the scope of the reaction with respect to various free-NH anilines and dimethyl butynedioate was then evaluated. As shown in Scheme 2, the results revealed that the electronic and steric

Scheme 2. Variation of Aryl Amines[a,b]



[a]Reaction conditions: aniline **1** (0.5 mmol), dimethyl butynedioate **2a** (0.6 mmol), CuI (0.025 mmol), HOTf (0.5 mmol), and Tf_2O (0.5 mmol), in solvent (2 mL), 24 h. [b]Yields of isolated products are given.

effects of the substituents on the aniline substrate had little influence on the efficiency of the reaction. First, free-NH anilines bearing the electron-donating (Me, OMe, SMe, Et, *t*-Bu, Ph, OPh) substituents at the *ortho*-position showed good compatibility, and the corresponding products **3b–h** were obtained in 66–85% yields. Similarly, *para*-substituted anilines were also successful in affording the corresponding quinoline products **3i–3l** in good yields. It was worth emphasizing that, for 3,5-dimethylaniline, 3,4-dimethylaniline, and 2,5-dimethylaniline, the sole regioisomer was detected, in which the cyclization exclusively occurred at the less-hindered *ortho*-position. Notably, sterically hindered aniline, including those bearing a *o*-tolyl (**3p**), *o*-(*p*-fluorophenyl) (**3q**), or *p*-tolyl (**3r**) group, also demonstrated excellent reactivity under the optimized conditions.

The scope of alkynes was next examined (Scheme 3). A methyl butynoate and dimethyl butynedioate substrate could be

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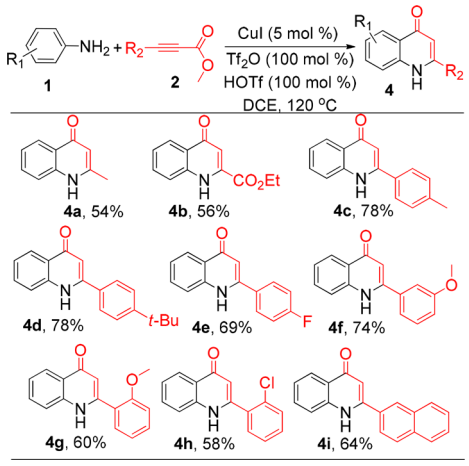
Scheme 3. Variation of Alkynes[a,b]

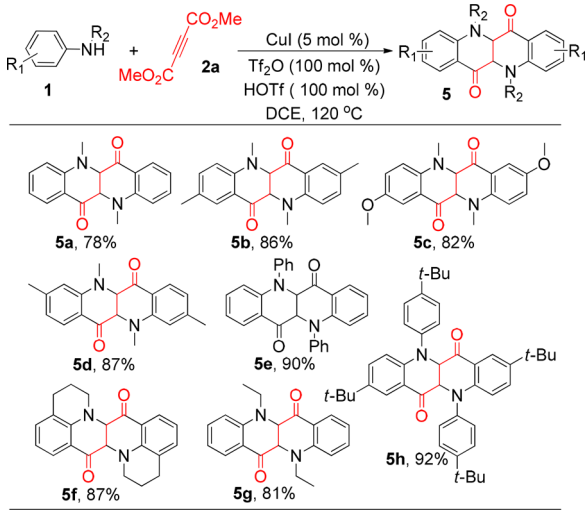


[a]Reaction conditions: **1** (0.5 mmol), **2** (0.6 mmol), CuI (0.025 mmol), HOTf (0.5 mmol), and Tf_2O (0.5 mmol), in solvent (2 mL), 24 h. [b]Yields of isolated products are given.

accommodated in the catalytic system, giving their corresponding products **4a**–**4b** in moderate yields. A wide variety of functionalized aryl alkynoates bearing the substituents at the *ortho*-, *meta*-, or *para*-position on the aryl ring all gave the corresponding products in moderate to good yields (58–78%) (**4c**–**4h**). Both electron-donating (Me, OMe, *t*-Bu) and -withdrawing (F, Cl) groups that attached at the aryl ring part of alkynes were also well tolerated. Interestingly, the alkynes can also be extended to the naphthalene (**1i**) substrate in the catalytic system, giving the desired product **4i** in moderate yield.

It is worth noting that differently *N*-substituted anilines **1** furnished the unexpected dihydroepindolidione products **5a**–**5h** (Scheme 4) in moderate to good yields when the dimethyl butynedioate **2a** was explored as the coupling partner. Various substituents, such as Me (**5a**–**5d**), Et (**5g**), and Ar (**5e**, **5h**) groups were fully tolerated. It should be emphasized that 1,2,3,4-tetrahydroquinoline was also a visible substrate since this

Scheme 4. Variation of *N*-Substituted Anilines[a,b]

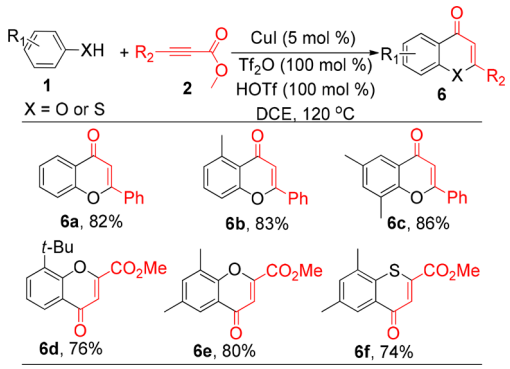


[a]Reaction conditions: **1** (1.0 mmol), **2a** (0.6 mmol), CuI (0.025 mmol), HOTf (0.5 mmol), and Tf_2O (0.5 mmol), in solvent (2 mL), 24 h. [b]Yields of isolated products are given.

transformation proceeded smoothly to give the desired **5f** in good yields.

To extend the applicability of our reaction, we next turned our attention to thiophenol or phenol derivatives as substrates. Under the standard reaction conditions, the reactions of various thiophenol or phenol derivatives **1** also proceeded well with alkyne **2** to afford the desired chromenes (**6a**–**6e**) or thiochromene **6f** in decent isolated yield (Scheme 5).

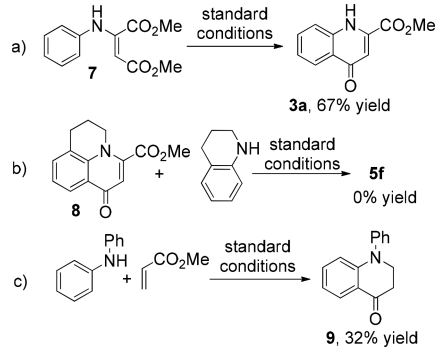
Scheme 5. Variation of Thiophenols or Phenols[a,b]



[a]Reaction conditions: **1** (0.5 mmol), **2** (0.6 mmol), CuI (0.025 mmol), HOTf (0.5 mmol), and Tf_2O (0.5 mmol), in solvent (2 mL), 24 h. [b]Yields of isolated products are given.

Considering the remarkably broad substrate scope and the switchable reactivity displayed by the Cu(I) catalysis, we performed a series of control experiments to gain more insight into the reaction mechanism (Scheme 6). First, when the

Scheme 6. Mechanistic Studies



enamine substrate **7** was subjected to the optimized conditions, the quinolone product was obtained in 67% yield, which suggested that the enamine might be used as a key intermediate for the Cu(I)-catalyzed synthesis of 4-quinolones.[10] Furthermore, to probe the divergent access to dihydroepindolidiones, if taking advantage of the quinoline form as the corresponding intermediate, quinoline-3-carboxylic acid methyl ester **8** was prepared and then coupled with 1,2,3,4-tetrahydroquinoline under the standard reaction conditions. The results show that no desired dione product **5f** was detected (Scheme 6b). In addition, the treatment of the diphenylamine with methyl acrylate under the standard reaction conditions gave the expected **9** in 32% yield (Scheme 6c). Taken together, the results revealed that the reaction might undergo an aza-Michael addition before the reaction of electrophilic addition/cyclization of carbonyl group to afford the dihydroepindolidione product.[11]

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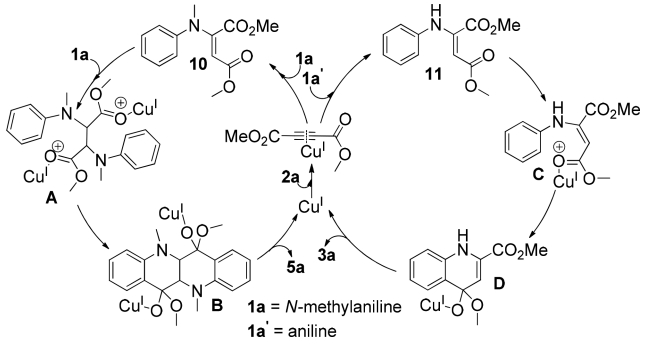
On the basis of these results and the literature precedents, a plausible catalytic cycle is depicted in Scheme 7. Alkyne **2a** is

Scheme 7. Mechanistic Studies



initially activated by Cu(I), which acts as a Lewis acid,[12] followed by the hydroamination to give enamine **10** or **11**.[13] Then, the Cu(I) is coordinated by the carbamoyl group of the enamine **11** and directly protodemetalation delivers the quinolone **3a** and regenerates the catalyst.[9] Alternatively, a Cu-catalyzed aza-Michael addition of **1a** with enamine **10** may be involved in the reaction when *N*-substituted secondary anilines as the substrates. To this end, the Cu(I) is coordinated with the carbamoyl group of **A** to deliver the intermediate **B**, which undergoes directly protodemetalation to generate the dihydroepindolidione **5a** and regenerate the catalyst.

In conclusion, we have developed a unique, direct, and more general Cu(I)-catalyzed cyclization for constructing 4-quinolines or dihydroepindolidiones from simple and readily available substrates in a one-pot and chemoselective manner by switching the type and nature of anilines. The (thio)phenols could be used as visible substrates for the Cu(I)-catalyzed system to replace the primary aniline substrates. In consideration of these impressive features, including tunable chemoselectivity, excellent substrate/functional group tolerance, good yield, and highly valuable chemical structures of the obtained products, we believe that the present protocol should have the potential for broad synthetic utility.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00436.

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

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Notes

The authors declare no competing financial interest.

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