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Transition-Metal-Free Aminoacylation of Ynones with Amides: Synthesis of 3-Carbonyl-4-quinolinones or Functionalized Enaminones

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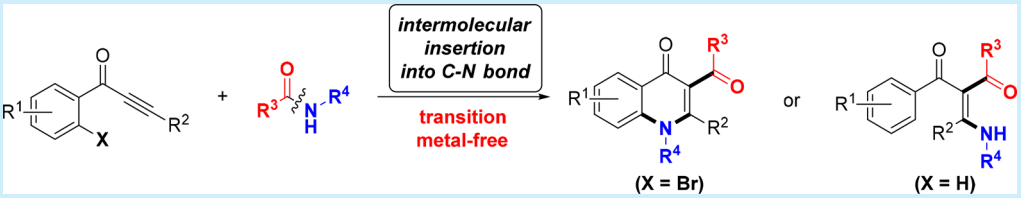
Supporting Information

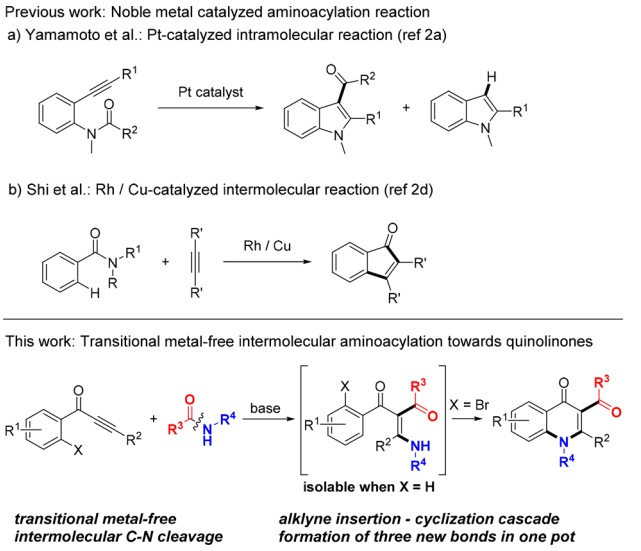


ABSTRACT: A transition-metal-free tandem process for the synthesis of substituted quinolin-4(1*H*)-ones or enaminones is presented. A base-promoted insertion of ynones into the C−N σ-bond of amides is the key step in this process, which provides the corresponding aminoacylation products in good to high yields. Quinolin-4(1*H*)-ones are selectively formed via the subsequent N-cyclization pathway in the cases of ynones bearing an *ortho*-bromo-substituted aryl ring. Easily accessible starting materials and high atom economy make this procedure attractive.

The direct addition of a C−N bond to alkynes is one of the most atom-economical transformations toward difunctionalized alkenes, with both C−C and C−N bonds being constructed simultaneously. In the last two decades, there were few procedures concerning transition-metal-catalyzed or -mediated aminoacylation of alkynes with amides for the functionalization of C−C triple bonds.[1,2] However, these reports are very rare due to lack of reactivity, and most of the reactions took place in an intramolecular fashion.[1,2a−c] The pioneering work reported by Yamamoto realized the Pt-catalyzed intramolecular aminoacylation of alkynes (Scheme 1a).[2a] Li developed the Ru-catalyzed annulation of alkynes with amides.[2b] Liu disclosed Pd-catalyzed difunctionalization of alkynes via C−N bond cleavage.[2c] Only one example of Rh/Cu-catalyzed intermolecular aminoacylation of alkynes with amides was reported by Shi's group (Scheme 1b).[2d] Despite this remarkable progress, most protocols are still confined to noble metals or *in situ* generated arynes.[3] Therefore, the development of novel procedures providing general access to aminoacylation from readily available starting materials, especially in a transition-metal-free manner, is highly desirable.

The 4-quinolinone ring is a common crucial structure in numerous naturally occurring products,[4] and it also serves as a vital substructure in hundreds of drugs, including antibiotics,[5] antivirals,[6] and anticancer agents.[7] Particularly, carbonyl substituents at the 3-position in 4-quinolinone derivatives are essential for biochemical functions such as gyrase binding and bacterial transport.[6] A recent report showed that 2-substituted 3-aroylquinolin-4(1*H*)-ones could inhibit the hedgehog signaling pathway, in which two carbonyls in the quinolinone compound provided the crucial H-bond interactions.[8] Classic methods for

Scheme 1. Recent Progress on Aminoacylation of Alkynes with Amides



the syntheses of 4-quinolinones such as Lappin cyclization[9] and Grohe−Heitzer synthesis[10] usually require a multistep procedure to build enaminone precursors[11] and high temperature[6a,b,11a−d] for cyclization. Other methods for the synthesis of 4-quinolinones used transition metal catalysts for cyclizatio-

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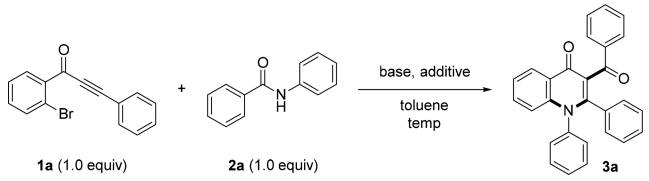
n,[8,11e,f,12] and high pressure or toxic carbon monoxide were sometimes involved. These limitations make it an intriguing goal to synthesize highly functionalized quinolinones in one pot with easily accessible substrates. During the course of our continuing work of activating inert C−X bonds (X= C, N, etc.),[13] we found that the aminoacylation of alkynes with amides was efficiently achieved in the presence of Cs_2CO_3, and 4-quinolinones could be obtained in high yields via sequential cyclization. To the best of our knowledge, this is the first example of transition-metal-free intermolecular aminoacylation of isolated alkynes with amides.

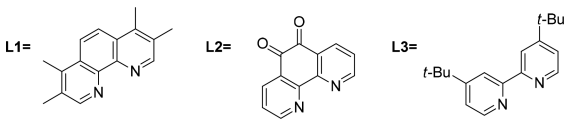
We started the investigation using *N*-phenylbenzamide **2a** as a model substrate. When the reaction of ynone **1a** with amide **2a** was carried out in the presence of Cs_2CO_3 (3.0 equiv) in toluene at room temperature, no reaction occurred. By increasing the reaction temperature to 100 °C, the desired quinolinone **3a** could be detected only in a trace amount. At 130 °C, to our delight, **3a** was obtained with a yield of 44% (Table 1, entry 1).

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



entry[a]	base (equiv)	additive (mol %)	temp (°C)	time (h)	yield (%)[b]
1	Cs_2CO_3 (3.0)	/	130	72	44
2	Cs_2CO_3 (3.0)	/	150	15.5	64
3	Cs_2CO_3 (3.0)	Phen·H_2O (20)	150	12	72
4	**Cs_2CO_3 (3.0)**	**Phen·H_2O (50)**	**150**	**8**	**78**
5	Cs_2CO_3 (3.0)	Phen·H_2O (50)	150	12	76
6	Cs_2CO_3 (3.0)	Phen·H_2O (100)	150	6	64
7	Cs_2CO_3 (3.0)	Phen·H_2O (200)	150	6	70
8	Cs_2CO_3 (3.0)	2,2′-biPy (50)	150	14	66
9	Cs_2CO_3 (3.0)	L_1 (50)	150	6	53
10	Cs_2CO_3 (3.0)	L_2 (50)	150	21	58
11	Cs_2CO_3 (3.0)	L_3 (50)	150	20	61
12	Cs_2CO_3 (3.0)	DBU (50)	150	12	/
13	Cs_2CO_3 (3.0)	DABCO (50)	150	30	66
14	tBuONa (3.0)	Phen·H_2O (50)	150	20	/
15	NaOH (3.0)	Phen·H_2O (50)	150	20	n.r.
16	Cs_2CO_3 (2.0)	Phen·H_2O (50)	150	12	55
17	Cs_2CO_3 (4.0)	Phen·H_2O (50)	150	12	76
18	/	Phen·H_2O (50)	150	24	trace

[a]Reactions were conducted on 0.2 mmol scale under air. [b]Isolated yields.



Further increasing the reaction temperature to 150 °C accelerated this reaction with a better yield of 64% (entry 2). The structure of **3a** was confirmed by X-ray crystallography. In order to achieve a better reaction outcome, several additives were screened, and it was interesting to find that 1,10-phenanthroline hydrate afforded higher yields with shorter reaction time (entries 3−7). 50 mol % of 1,10-phenanthroline hydrate gave the best yield of 78% within 8 h. A longer reaction time of 12 h did not improve the yield (entry 5). Other substituted phenanthrolines and bipyridines were tested as well; however, no better results were achieved (entries 8−11). Organic bases such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 1,4-diazabicyclo[2.2.2]octane (DABCO) were also examined, which did not generate satisfactory results (entries 12 and 13). Based on the experimental results above, we presumed that 1,10-phenanthroline hydrate could act as a metal ion chelator,[14] and thus increased the basicity of cesium carbonate and increased the reaction speed. Other bases such as $NaOBu^t$ and NaOH were subsequently screened, and no better results were observed (entries 14 and 15). A decrease of Cs_2CO_3 to 2.0 equiv led to a lower yield of **3a** (entry 16). Increase of Cs_2CO_3 to 4.0 equiv did not significantly affect the yield (entry 17). The reaction could not occur in the absence of the Cs_2CO_3 (entry 18), indicating a base condition is mandated.

With the optimal reaction conditions in hand (Table 1, entry 3), the scope of this reaction was subsequently investigated (Figure 1). First, substituent effects of R^1 on the aryl ring were studied (Figure 1, **3a**−**3e**). Substrates with electron-withdrawing groups (4-F, 5-F) and electron-donating groups (4,5-dimethoxy) were suitable for this reaction, giving the corresponding products **3a**−**3c** and **3e** with yields ranging between 70% and 80%. A heterocycle was also compatible, affording pyridine-fused product **3d** in 72% yield. Next, R^2 substituents on the triple bond were screened. A naphthyl-

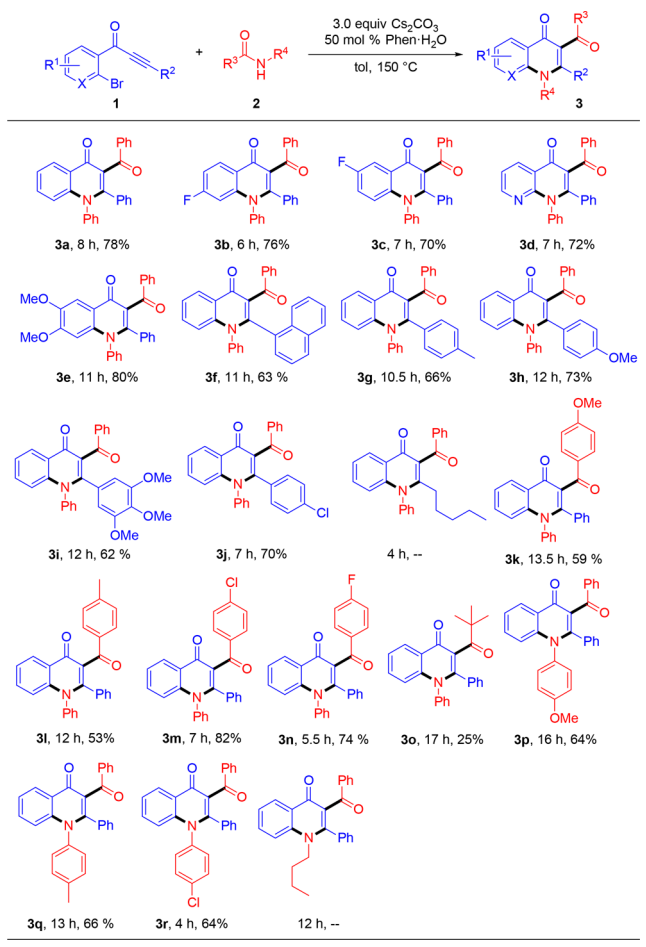


Figure 1. Scope of the synthesis of substituted quinolinone **3**. The reactions were all carried out under air on a 0.2 mmol scale with the ratio of **1**:**2** = 1:1.

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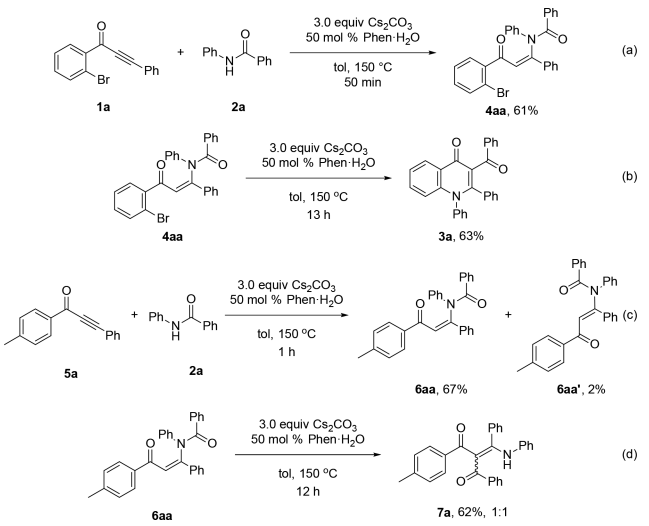
substituted ynone afforded **3f** in 63% yield. R^2 with electron-donating aryl groups (4-Me, 4-OMe, and 3,4,5-$(OMe)_3$) gave the corresponding products **3g**−**3i** with 66%, 73%, and 62% yields, respectively. The electron-withdrawing aryl group (4-Cl) also afforded the desired **3j** with 58% yield. However, alkyl-substituted (C_5H_{11}) ynone failed to give the desired product.

The substituent effects of amides were subsequently investigated. For the R^3 groups attached to the carbonyl, it was clear that both electron-donating (R^3 = 4-MeC_6H_4, 4-$OMeC_6H_4$) and electron-withdrawing groups (R^3 = 4-ClC_6H_4, 4-FC_6H_4) on the aryl ring were suitable for this reaction, offering the desired quinolinones **3k**−**3n** with moderate to high yields. It should be noted that electron-withdrawing amides provided the desired quinolinones (**3m**, **3n**) with higher yields in shorter reaction times. *tert*-Butyl-substituted R^3 also resulted in the formation of quinolinone **3o**, albeit in a low yield, possibly due to steric hindrance. A methyl substituent did not give the desired product, presumably due to the existence of acidic α-H. Substituent effects of R^4 on the amides were subsequently explored (Figure 1, **3p**−**3r**). Substrates with electron-donating groups (R^4 = 4-MeC_6H_4, 4-$OMeC_6H_4$) required longer reaction times than those of electron-withdrawing groups (R^4 = 4-ClC_6H_4) to furnish the desired products (**3p**−**3r**). However, the alkyl substituent (C_4H_9) of R^4 was unable to give the desired product.

To clarify the reaction mechanism, several control experiments were performed (Scheme 2). When ynone **1a** reacted

Scheme 2. Control Experiments



with amide **2a** under the standard reaction conditions in 50 min, a Michael addition product **4aa** was obtained in 61% yield (Scheme 2, a). Product **4aa** could be converted to quinolinone **3a** in 13 h under the optimized conditions (Scheme 2, b). However, no C−N bond cleavage intermediate could be detected, even under a lower temperature or shorter reaction time. It indicated that the ring closure reaction might be much faster than the C−N bond cleavage reaction. In order to observe the C−N bond cleavage intermediate, we envisioned that ynones without an *ortho*-bromo substituent would be suitable candidates to react with amides. When ynone **5a** reacted with **2a** under the optimal reaction conditions, **6aa** and **6aa′** were obtained in 67% and 2% yields, respectively (Scheme 2, c). The structure of **6aa** was confirmed by X-ray diffraction analysis. To our delight, **6aa** could be converted to enaminone **7a** under the optimized conditions (Scheme 2, d). This implied that an insertion of C−N σ-bond of amide occurred after the Michael addition step.

These results offered an atom-economy protocol involving direct C−N bond activation for the synthesis of highly functionalized enaminones, which are useful building blocks toward heterocycles in organic chemistry.[15] Thus, we further explored this protocol for the synthesis of functionalized enaminones in a one-pot manner. A variety of ynones and amides containing electron-withdrawing or election-donating groups on the aryl ring were employed, resulting in good to high yields of the desired products (Figure 2). It should be noted that

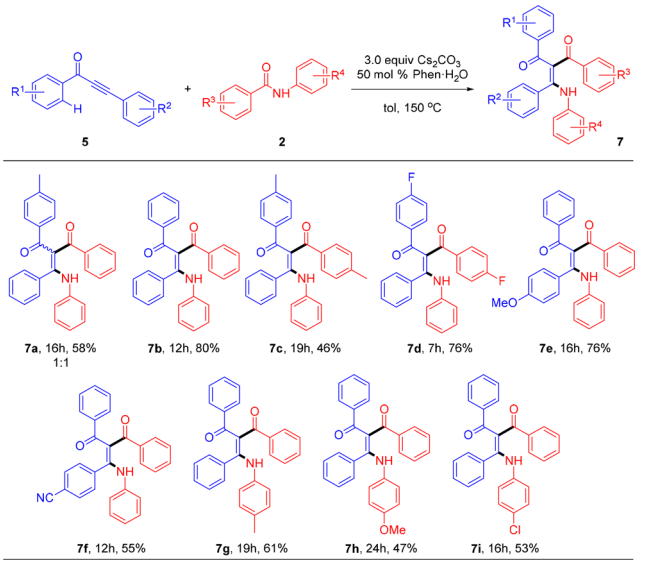
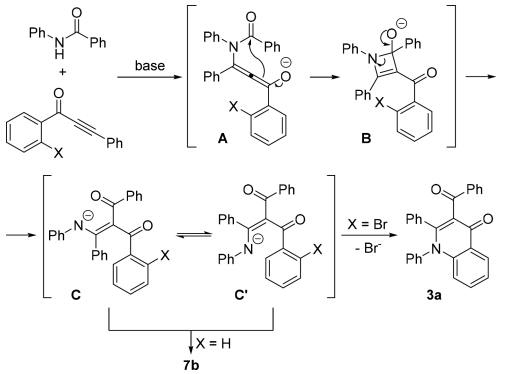


Figure 2. Synthesis of enaminone **7**. The reactions were all carried out under air on a 0.2 mmol scale with the ratio of **5**:**2** = 1:1.

enaminone **7a** was obtained with 58% yield as a pair of 1:1 *E*/*Z* isomers of a C=C double bond of the enamine, the isomerism possibly due to the imine−enamine tautomerization under basic conditions.

Based on our experimental results, and the previously reported works,[13] a plausible reaction mechanism has been proposed (Scheme 3). First, an amide undergoes a Michael-type addition with ynone under basic conditions to give an allenol intermediate **A**. An intramolecular nucleophilic addition subsequently occurred to form a highly reactive cyclobutenol

Scheme 3. Possible Mechanism



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B, which undergoes ring opening to offer a formal alkyne insertion intermediate **C**. Imine−enamine tautomerization of **C**, followed by a nucleophilic aromatic substitution (S_NAr) process, leads to quinolinone **3a**.

In summary, we have developed an efficient base-promoted C−N bond cleavage procedure for the synthesis of quinolinones and enaminones. Insertion of ynones into the C−N σ-bond of amides was the key for this process, and functionalized quinolinones were selectively formed via a N-cylization pathway. With advantages such as readily available materials and simple operations, it has the potential to be widely used in synthetic and medicinal chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01492.

Experimental details and spectroscopic characterization of all new compounds (PDF)

Accession Codes

CCDC 1562831 and 1835528 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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