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## Base-Promoted Amide Synthesis from Aliphatic Amines and Ynones as Acylation Agents through C–C Bond Cleavage

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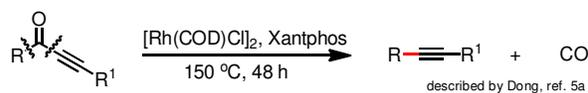
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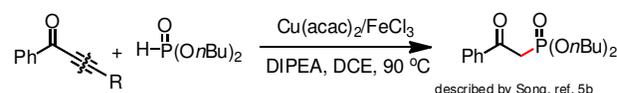
**A new protocol for the synthesis of amides via base-promoted cleavage of the C(sp)–C(CO) bond of ynones with aliphatic primary and secondary amines under transition-metal-, ligand-, and oxidant-free conditions has been developed. This method exhibits a wide substrate scope, high functional group tolerance and exclusive chemoselectivity, as well as mild reaction conditions.**

The selective cleavage of C–C bonds has attracted great attentions owing to its potential utility in organic synthesis and fundamental scientific interest.<sup>1</sup> In recent times, transition-metal (TM)-catalyzed C–C bond cleavage has been studied extensively using strained molecules bearing three- or four-membered rings<sup>2</sup> and molecules with an auxiliary directing group.<sup>3</sup> Compared with TM-catalyzed C–C bond cleavage reactions, the selective cleavage of C–C bonds in TM-free reactions represents a fascinating topic in organic synthesis for significant potential environmental and economic benefits.<sup>4</sup> However, the cleavage of unstrained C–C bonds under TM-free conditions still remains a major challenge due to its inherent inert nature and uncontrollable selectivity. Ynones are abundant structural motifs in a wide range of natural products, and can be used as versatile building blocks for rapid construction of sophisticated synthetic targets.<sup>5</sup> In 2015, Dong disclosed a Rh-catalyzed disubstituted alkynes synthesis through cleavage of the C(sp)–C(CO) bond of ynones (Scheme 1a).<sup>6</sup> Later on, a Cu/Fe-catalyzed oxidative C–C triple bond cleavage of ynones with *H*-phosphonates, followed by the formation of a new C–P bond was developed by Song's group (Scheme 1b).<sup>7</sup> Recently, our group uncovered a TM-free C–C triple bond cleavage reaction of ynones with 2-aminobenzamides for the synthesis of 4(3*H*)-quinazolinones (Scheme 1c).<sup>4c</sup> Despite the significant progress offered by the abovementioned reactions, there are still certain limitations

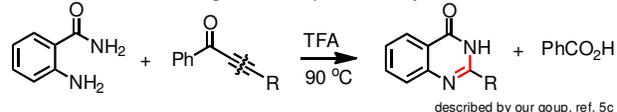
a, Rh-catalyzed cleavage of C(sp)–C(CO) bond of ynones



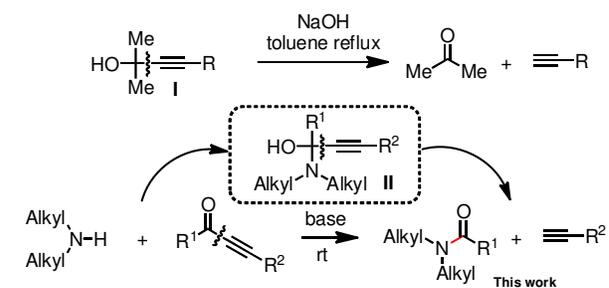
b, Cu/Fe-catalyzed cleavage of C–C triple bond of ynones



c, Acid-mediated cleavage of C–C triple bond of ynones



d, base-promoted cleavage of C(sp)–C(CO) bond of ynones



Scheme 1 Cleavage of C–C bond of ynones.

including long reaction time and elevated temperatures. Thus, it continues to be an area of intense interest to improve upon the harsh reaction conditions and develop a TM-free synthetic method for the selective cleavage of C–C bond of ynones. Driven by the ability of 2-(2-hydroxypropyl)-alkynes **I** to generate acetone and terminal alkynes at basic conditions (Scheme 1d, top),<sup>8</sup> we questioned whether the tertiary alcohol intermediate **II** could be formed from 1,2-addition of amines to ynones, thus generating amides and terminal alkynes via C(sp)–C(CO) bond cleavage (Scheme 1d, bottom). As our

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ongoing interest in ynones chemistry,<sup>9</sup> we report herein an unprecedented base-promoted chemoselective cleavage of

(0.2 mmol), **2a** (1.2 equiv), LiOtBu (1.2 equiv), DCM (1 mL), at room temperature, under air atmosphere.

With the optimized conditions in hand, we examined the substrate scope for the C–C bond cleavage reaction of ynones

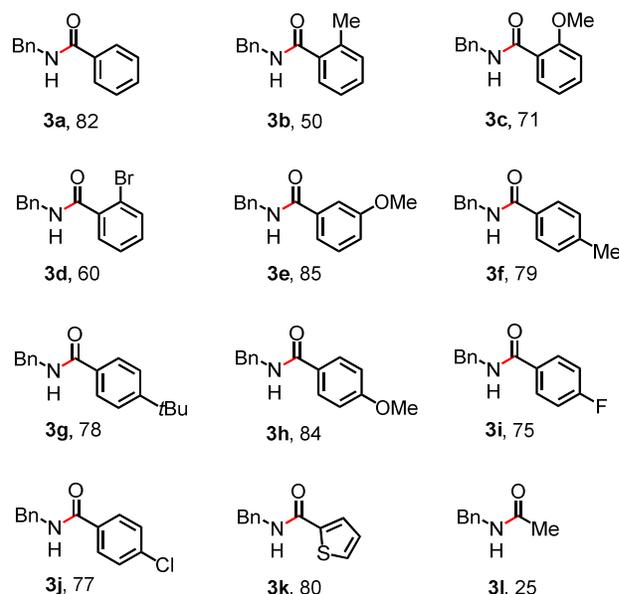
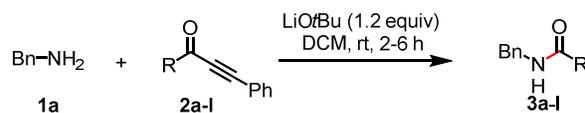
Table 1. Screen of the Reaction Conditions.<sup>a</sup>

Entry	R	Base	Solvent	Yield <sup>b</sup>
1	Ph	NaOH	toluene	<5%
2	Ph	KOtBu	toluene	9%
3	Ph	NaOtBu	toluene	16%
4	Ph	LiOtBu	toluene	45%
5	Ph	Li <sub>2</sub> CO <sub>3</sub>	toluene	0%
6	Ph	Et <sub>3</sub> N	toluene	0%
7	Ph	DBU	toluene	0%
8	Ph	LiOtBu	DCM	83%
9	Ph	LiOtBu	CH <sub>3</sub> CN	7%
10	Ph	LiOtBu	THF	0%
11	Ph	LiOtBu	DMF	0%
12 <sup>c</sup>	Ph	LiOtBu	DCM	82%
13 <sup>d</sup>	Ph	LiOtBu	DCM	65%
14 <sup>c</sup>	MeOC <sub>6</sub> H <sub>4</sub>	LiOtBu	DCM	79%
15 <sup>c</sup>	4-FC <sub>6</sub> H <sub>4</sub>	LiOtBu	DCM	72%
16 <sup>c</sup>	<i>n</i> Bu	LiOtBu	DCM	0%
17 <sup>c</sup>	<i>t</i> Bu	LiOtBu	DCM	14%
18 <sup>e</sup>	Ph	LiOtBu	DCM	83%

<sup>a</sup> Reaction conditions: **1a** (0.2 mmol), **2** (0.24 mmol), base (2.0 equiv), solvent (1 mL), room temperature for 12 h. <sup>b</sup> Isolated yield based on **1a**. <sup>c</sup> 1.2 equiv of LiOtBu was used. <sup>d</sup> 1.0 equiv of LiOtBu was used. <sup>e</sup> Under N<sub>2</sub>, DMF = *N,N*-dimethylformamide.

C(*sp*)–C(CO) single bond of ynones with alkyl amines, and subsequent formation of a new C–N bond at room temperature.<sup>10,11</sup>

We began our study to examine the model reaction of benzylamine **1a** with 1,3-diphenylprop-2-yn-1-one **2a** in the presence of 2.0 equiv of NaOH as the base in toluene at room temperature (Table 1). Gratifyingly, we observed the desired product, albeit in low yield (entry 1). Excitedly, we obtained a moderated result (45% isolated yield, entry 4) after screening of a series of bases (entries 1–7). In our subsequent screening of other solvents, we discovered that DCM was a highly effective solvent to promote the desired reaction, affording product **3a** in a satisfying 83% yield (entry 8). Then, the base equivalency was reevaluated, and we found that a little excess of base is required for good yields (entries 12 and 13). We then examined the influence that the substituents exert on the reactivity of ynones. Notably, 3-aryl-substituted ynones furnished the expected product **3a** in relatively good yields (entries 14 and 15) whereas 3-alkyl-substituted ynones proved to be essentially unreactive under identical conditions (entries 16 and 17). 83% yield was obtained when the reaction was performed under N<sub>2</sub> atmosphere, which indicated that O<sub>2</sub> may not be involved in this reaction process (entry 18). Finally, the optimized reaction conditions were identified as follows: **1a**

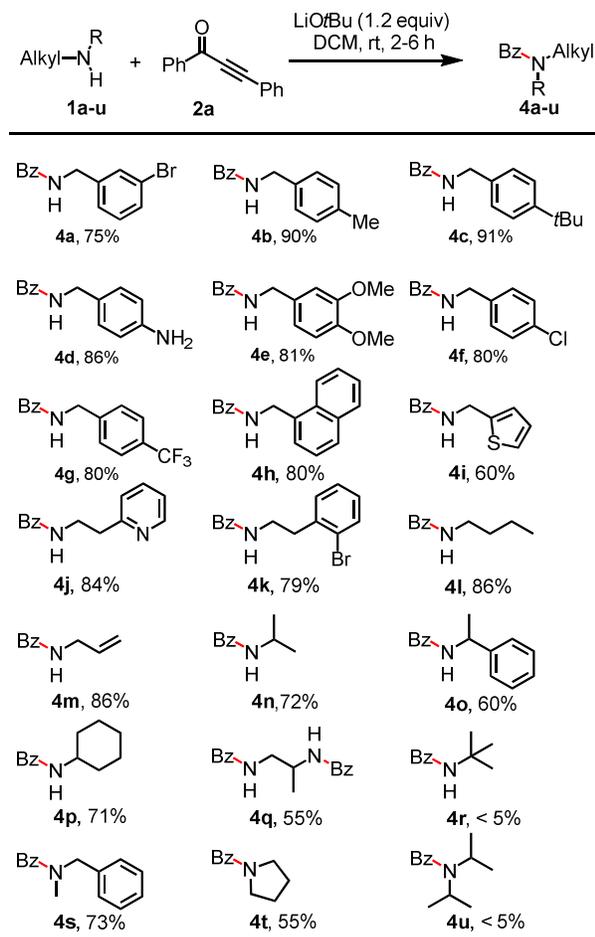
Scheme 2 Reactions of various ynones **2a–l** with benzylamine **1a**.<sup>a</sup>

**2a–l** with benzylamine **1a** (scheme 2). In general, the base-promoted reaction occurred relatively smoothly with various aryl-substituted ynones bearing either electron-donating moieties **2e–h** or electron-withdrawing moieties **2i** and **2j**, furnishing the desired amides (**3e–j**) in good yields. When the *ortho*-substituted ynones were examined, the yields were only modest (**3b–d**). Other ynone bearing a hetero aromatic substituent was also suitable substrate for the C–C bond cleavage reaction (**3k**). However, the use of 1-alkyl-substituted ynone led to a low yield (**3l**).

Furthermore, we explored the scope of amines (Scheme 3). Both electron-rich and electron-deficient benzylamines could be applied in this reaction, giving the corresponding amides in good yields (**4a–g**). It is especially noteworthy that the aniline NH<sub>2</sub> were well tolerated, and delivering the desired product **4d** in good yield, showing good chemoselectivity of aliphatic NH<sub>2</sub> over aniline NH<sub>2</sub>. Other primary amines with 1-naphthyl (**4h**), heteroaryl (**4i**, **4j**), as well as allyl substituents (**4m**) were proved to be well tolerated under the standard reaction conditions. Notably, secondary amines were also compatible substrates, affording the corresponding products in moderated yields (**4s**, **4t**). However, the reactions were not compatible

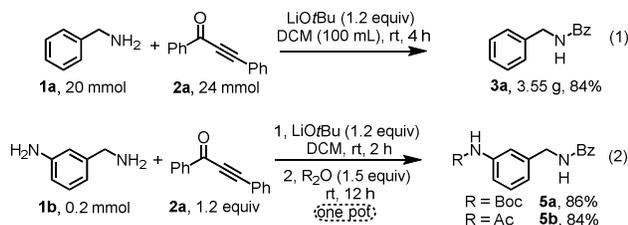
with the use of sterically hindered primary amine (**4r**) and secondary amine (**4u**).

The synthetic versatility of this chemistry was demonstrated through a large-scale reaction. The reaction of **1a** with **2a** on a 20 mmol scale completed within 4 h, producing 3.55 g of the corresponding product **3a** in 84% yield (eq. 1). As aniline NH<sub>2</sub> could be tolerated in this reaction system, we then employed a

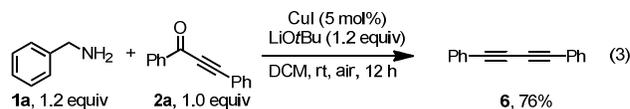


Scheme 3 Reactions of various amines with 3-diphenylprop-2-yn-1-one **2a**<sup>3</sup>

straightforward one-pot strategy to synthesize the di-amide **5** directly from the di-amines substrate **1b** and ynone **2a**, without isolating the mono-amide intermediate (eq. 2). To our delight, the di-amide **5a** and **5b** containing one benzamide and one Boc-amide or Ac-amine scaffold could be generated from **1b** and **2a** in 86% and 84% yields, respectively.



To further understand the reaction mechanism, catalytic amount of CuI was introduced in the reaction system, 1,3-diyne **6** could be isolated in 76% yield, suggesting that the putative phenylacetylene cleaved from ynone **2a** was further involved in the Glaser–Hay coupling reaction (eq.3).<sup>12</sup> On the basis of the above result, we proposed that the reaction would proceed as discussed in the introduction (Scheme 1d). Namely, the tertiary alcohol intermediate **II** was formed via 1,2-addition of amines to ynones, followed by base-promoted C(sp)–C(CO) bond cleavage, thus generating the desired amides and terminal alkynes.



In conclusion, we have developed a base-promoted highly chemoselective C(sp)–C(CO) bond cleavage of ynones with aliphatic amines for the synthesis of valuable amide derivatives. Free arylamines, alkenes, as well as halogens were tolerated, suggesting a promising substrate scope. This novel and fundamental reactivity disclosed in this work is expected to open a door to new avenues for developing transition-metal-free unstrained C–C bonds cleavage reactions.

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## Conflicts of interest

There are no conflicts to declare.

## Notes and references

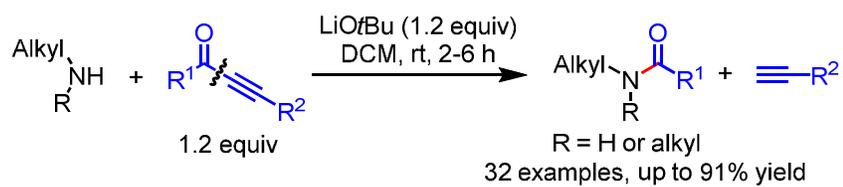
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The synthesis of amides via base-promoted cleavage of the C(*sp*)-C(CO) bond of ynones with aliphatic primary and secondary amines is reported.