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Copper-Catalyzed Annulation Cascades of Alkyne-Tethered α-Bromocarbonyls with Alkynes: An Access to Heteropolycycles

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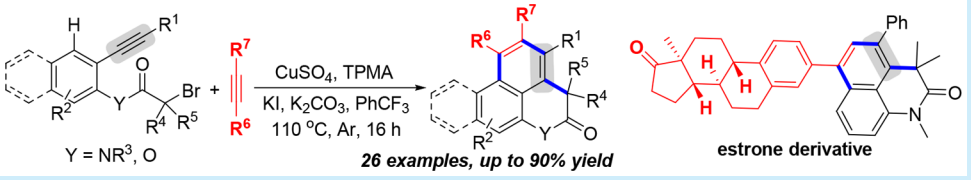
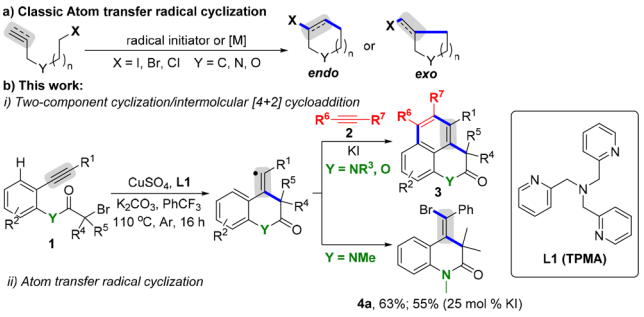
Supporting Information



ABSTRACT: We here describe a new Cu-catalyzed annulation cascade of alkyne-tethered α-bromocarbonyls with common alkynes for the synthesis of various heteropolycycle frameworks, including 1*H*-benzo[*de*]quinolin-2(3*H*)-ones, 4*H*-dibenzo[*de*,*g*]quinolin-5(6*H*)-one, and benzo[*de*]chromen-2(3*H*)-one, which were constructed with high selectivity. This was achieved by two-component annulation cascades, rather than atom-transfer radical cyclization (ATRC), with alkyne-tethered α-bromocarbonyls for one-step accessing heteropolycycles via C−Br bond split, intramolecular cyclization, intermolecular [4 + 2] annulation, and aryl C(sp^2)−H functionalization cascades.

The tandem annulation strategy has emerged as an ideal one-step platform to build various complex cyclic systems, particularly heteropolycycles, in chemical synthesis.[1−3] In this field, attractive methods include the annulation cascades reaction of haloalkanes, particularly α-halocarbonyls, with unsaturated hydrocarbons, which has proven to be an importantly straightforward alternative to access diverse cyclic compounds by means of either radical initiators[2] or transition metal redox catalysis.[2j,3] However, this technology for the synthesis of structurally diversified polycycles remains a formidable challenge, probably because such events mainly rely on the atom transfer radical cyclization (ATRC) process which includes termination by halogen atoms to inhibit the incorporation of other functional groups, thereby often leading to the construction of monocyclic compounds.[2−5] Furthermore, reports using alkynes reacted with haloalkanes and functional groups that tender polycycles via the annulation cascades rather than ATRC (Scheme 1a) remain scarce.[4a−c] These successful protocols strongly relied on the use of special functionalized haloalkanes and/or alkynes to achieve the desired reactivity, thus resulting in a great limitation in product structure variety. To date, such versions to build heteropolycycle skeletons are limited to only one report by Stephenson and Tucker, which uses terminal alkyne-tethered β-aryl-substituted α-bromoamides allowing the formation of tricyclic pyrrolidinones via visible-light-promoted Ir-catalyzed tandem radical cyclization and sigmatropic rearrangement.[4a] However, this method was achieved by employing the inherent aryl C(sp^2)−H bonds as the terminated functional groups, thereby

Scheme 1. Annulation of α-Bromoacetamides with Alkynes



allowing the resulting product variety to only be dependent on the nature of the starting materials. In order to address this deficiency, a multicomponent technique that allows annulation cascades of alkynes with α-bromocarbonyls and other functional reagents would be highly desirable to offer the opportunity for diversified construction of *N*-heteropolycyclic skeletons, while use of the external functional reagents terminated this event.

Recently, intermolecular [4 + 2] cycloaddition of alkynes involving aryl C(sp^2)−H bond functionalization has attracted increased attention for building diverse cyclic backbones due to their atom and step economy without prefunctionalizing starting materials.[6] On this basis, we reasoned that by

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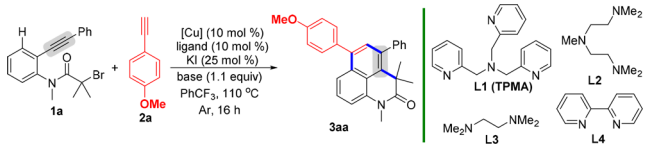
Org. Lett. XXXX, XXX, XXX−XXX

simultaneously combining alkyne-tethered α-bromoamide radical annulation cascades and an intermolecular [4 + 2] cycloaddition of an external alkyne, a one-pot, two-component annulation cascade technique that makes *N*-heteropolycyclic skeleton diversified construction would be established. Herein, we report a new Cu-catalyzed annulation cascade of 2-bromo-*N*-(2-ethynylaryl)acetamides with alkynes toward diverse heteropolycycles, namely, 1*H*-benzo[*de*]quinolin-2(3*H*)-ones, 4*H*-dibenzo[*de*,*g*]quinolin-5(6*H*)-one, and benzo[*de*]chromen-2(3*H*)-one, which are an important class of structural skeletons commonly found in numerous natural products, pharmaceuticals, functional materials, and organocatalysts (Scheme 1b).[7,8] Using the $CuSO_4$ catalyst and tris(pyridin-2-yl-methyl)amine (TPMA) ligand enables the formation of three new C−C bonds in a single reaction via a sequence of C−Br bond splitting, intramolecular cyclization by radical addition across the C≡C bond, and [4 + 2] annulation with the external alkynes and internal aryl C(sp^2)−H bonds.

We initially investigated the annulation cascades of 2-bromo-*N*,2-dimethyl-*N*-(2-(phenylethynyl)phenyl)propanamide (**1a**) with 4-ethynylanisole (**2a**) (Table 1 and Table S1 in Supporting Information (SI)). We found that a catalytic amount of KI could improve the reaction. While in the absence of KI the reaction of substrate **1a** with alkyne **2a**, $CuSO_4$, **L1** and K_2CO_3 afforded the desired 1*H*-benzo[*de*]quinolin-2(3*H*)-one **3aa** in a 61% yield (entry 1), the addition of 25 mol % KI enhanced the yield to 81% (entry 2). Notably, both Cu catalysts and ligands were necessary for the reaction to proceed (entries 3 and 8). The amount of $CuSO_4$ affected the reaction, and 10 mol % $CuSO_4$ proved to be optimal (entries 2, 4, and 5). Other alternative Cu catalysts, including $Cu(OTf)_2$ and $Cu(MeCN)_4PF_6$, showed lower catalytic activity than $CuSO_4$ (entries 6 and 7). Although three other ligands **L2**−**L4** exhibited activity, they were all inferior to **L1** (entries 9−11). The reaction could occur without a base, albeit with a lower yield (entry 12). Further survey of the base effect found K_2CO_3 to be optimal (entries 2, 13, and 14).

Table 1. Screening of Optimal Reaction Conditions[a]



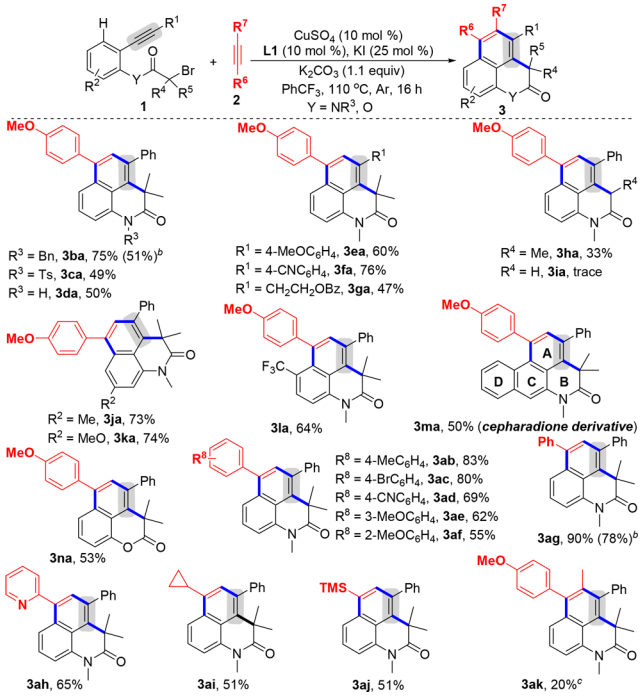
entry	[Cu] (mol %)	ligand (**L**)	base	yield (%)
1[b]	$CuSO_4$ (10)	**L1**	K_2CO_3	61
2	$CuSO_4$ (10)	**L1**	K_2CO_3	81 (72)[c]
3	–	**L1**	K_2CO_3	0
4	$CuSO_4$ (5)	**L1**	K_2CO_3	76
5	$CuSO_4$ (20)	**L1**	K_2CO_3	74
6	$Cu(OTf)_2$ (10)	**L1**	K_2CO_3	76
7	$Cu(MeCN)_4PF_6$ (10)	**L1**	K_2CO_3	72
8	$CuSO_4$ (10)	–	K_2CO_3	trace
9	$CuSO_4$ (10)	**L2**	K_2CO_3	73
10	$CuSO_4$ (10)	**L3**	K_2CO_3	13
11	$CuSO_4$ (10)	**L4**	K_2CO_3	24
12	$CuSO_4$ (10)	**L1**	—	7
13	$CuSO_4$ (10)	**L1**	K_3PO_4	74
14	$CuSO_4$ (10)	**L1**	*i*-Pr_2NH	77

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (1 mmol), [Cu] (10 mol %), **L** (10 mol %), KI (25 mol %), base (0.22 mmol), $PhCF_3$ (3 mL), argon, 110 °C, and 16 h. [b]Without KI. [c]**1a** (1 mmol).

After optimizing the reaction conditions, the scope of this annulation cascade protocol with respect to 2-bromo-*N*-(2-ethynylaryl)acetamides **1** was first investigated (Scheme 2). In the presence of 4-ethynylanisole **2a**, $CuSO_4$, **L1**, and K_2CO_3, substrates **1b**−**d** possessing a N-Bn group, a N-Ts group, or a free N−H group were all viable to produce **3ba**−**da** in 49%−75% yields. Both electron-rich and -withdrawing aryl groups at the terminal alkyne were well accommodated and gave **3ea**−**fa** in good yields. Aliphatic alkyne **1g** was also compatible with the optimal conditions (**3ga**), in which the ester group was tolerated. Secondary alkyl bromide **1h** was smoothly converted into **3ha**, albeit diminishing the yield. Unfortunately, primary alkyl bromide **1i** exhibited no reactivity (**3ia**). Substrates **1j**−**k** bearing an electron-donating group (Me or MeO) in the 5-position of the *N*-aryl moiety was highly reactive and afforded **3ja**−**ka** in good yields. Substrate **1l** bearing an electron-withdrawing CF_3 group also showed high reactivity (**3la**; 64% yield). Notably, substrate **1m** could be efficiently annulated, accessing **3ma**, a cepharadione derivative.[7,8] Gratifyingly, this reaction was applicable to construct benzo[*de*]chromen-2(3*H*)-one **3na**, a valuable oxygen-containing heteropolycycle.

Next, we tested the feasibility of this Cu-catalyzed annulation cascade protocol with a wide range of alkynes **2b**−**m**. This technology had the ability to engage various arylalkynes **2b**−**g** and high substituent compatibility (e.g., Me, Br, CN, and MeO) (**3ab**−**ag**) (CCDC 1584061 (**3ag**)). While electron-rich alkyne **2b** delivered **3ab** in 83% yield, electron-deficient alkyne **2d** tendered **3ad** with a decreased yield (69%). Alkyne **2e** bearing a

Scheme 2. Variations of the 2-Bromo-*N*-(2-ethynylaryl)acetamides (1) and Alkynes (2)[a]



[a]Reaction conditions: **1** (0.2 mmol), **2** (1 mmol), $CuSO_4{\cdot}5H_2O$ (10 mol %), **L1** (10 mol %), KI (25 mol %), K_2CO_3 (0.22 mmol), $PhCF_3$ (3 mL), argon, 110 °C, and 16 h. [b]**1** (1 mmol) and 48 h. [c]130 °C and 36 h.

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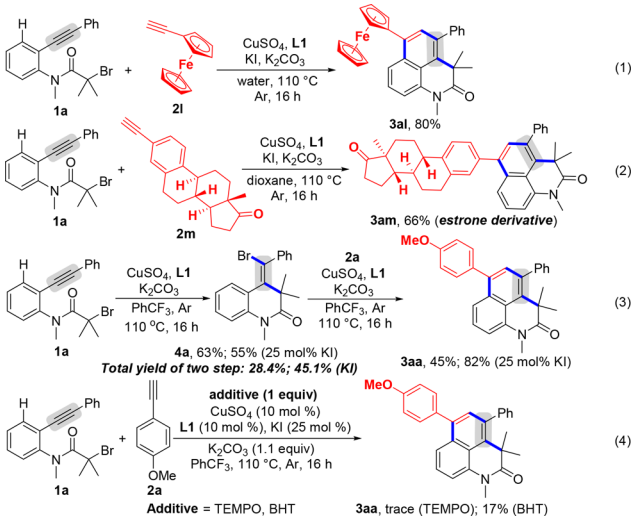
meta-MeO group was more reactive than alkyne **2f** having an *ortho*-MeO group (**3ae**−**af**). 2-Ethynylpyridine **2h** was competent to access **3ah**. Using ethynylcyclopropane **2i** and ethynyltrimethylsilane **2j** succeeded in the formation **3ai**−**aj**, and cyclopropyl and trimethylsilane groups remain intact. Prop-1-yn-1-ylbenzene **2k**, an internal alkyne, was a suitable substrate, albeit giving **3ak** in a lower yield.

To highlight the applicability of this protocol, we attempted to clarify annulation cascades of functional and/or bioactive alkynes (Scheme 3). Ethynylferrocene (**2l**), in which the

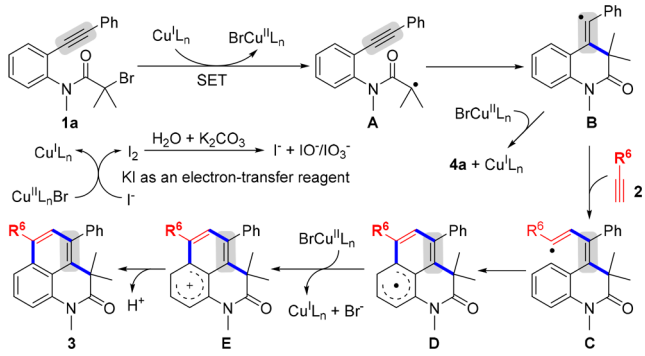
Scheme 3. Other Alkynes and Control Experiments



ferrocene moiety is a ligand, pharmaceutical, and material scaffold, was annulated, giving **3al** in 80% yield (eq 1). Substrate **2m**, an estrone analogue, was successfully converted into complex product **3am** that comprises both estrone and *N*-heteropolycycle groups (eq 2). Control experiments in eq 3 showed that KI could improve the formation of **3aa**, but disfavored ATRC. Substrate **1a** underwent the ATRC to afford **4a** in the absence of alkynes **2**. However, using 25 mol % of KI suppressed the ATRC, as the yield of **4a** decreased to 55%. It is noteworthy that **4a** can react with alkyne **2a** to access **3aa**, and KI also affects the reaction (eq 3). Without KI, only a 45% yield of **3aa** was obtained together with recovery of 43% **4a**; using 25 mol % of KI enhanced the yield to 82%. These results suggested that product **4a** is not the key intermediate in the current protocol, and KI may act as a bromo replacement reagent for the *in situ* generation of alkyl iodides and as an electron-transfer reagent to improve this annulation cascade.[9] The reaction of substrate **1a** with alkyne **2a** was completely inhibited by TEMPO, a radical inhibitor (eq 4). Using 2,6-di-*tert*-butyl-4-methylphenol (BHT) led to a sharply diminished yield. These results support a radical process.

Consequently, the possible mechanism for the current annulation cascades protocol is proposed (Scheme 4).[2−5,9] Splitting of the C−Br bond in **1** by the active $Cu^{I}L_n$ species and a base occurs via single-electron transfer (SET) to form the alkyl radical intermediate **A** and the $Cu^{II}L_n$ species,[4,5,9] followed by intramolecular addition across the C≡C bond in the intermediate **A** affording the vinyl radical intermediate **B**. In the presence of alkyne **2** intermolecular radical addition of the intermediate **B** across the C≡C bond in **2** gives the other vinyl intermediate **C**, whereas in the absence of alkyne **2** the ATRC

Scheme 4. Possible Mechanism



of the intermediate **B** occurs to deliver **4a**. Radical addition to the aryl ring in the intermediate **C** affords the aryl radical intermediate **D**, which sequentially undergoes single-electron oxidation by the $Cu^{II}L_n$ species to access the aryl cation intermediate **E**. Finally, deprotonation of the intermediate **E** offers **3**.

In summary, we have developed a novel Cu-catalyzed annulation cascade of 2-bromo-*N*-(2-ethynylaryl)acetamides with alkynes for building heteropolycyclic skeletons, including 1*H*-benzo[*de*]quinolin-2(3*H*)-ones, 4*H*-dibenzo[*de*,*g*]quinolin-5(6*H*)-one, and benzo[*de*]chromen-2(3*H*)-one. This protocol employs readily available reagents, including alkyne-tethered α-bromocarbonyls and common alkynes, to construct diverse heteropolycyclic frameworks in a single reaction with a broad substrate scope and high functional group tolerance. Importantly, this reaction provides a straightforward access to the tricyclic ABC and tetracyclic ABCD rings found in the cepharadione family and other useful molecules. The synthetic utility of this protocol is further demonstrated in the incorporation of some functional and/or bioactive units into the resulting 1*H*-benzo[*de*]quinolin-2(3*H*)-one architectures.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00236.

Descriptions of experimental procedures for compounds; analytical characterization (PDF)

Accession Codes

CCDC 1584061 contains 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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Org. Lett. XXXX, XXX, XXX−XXX

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