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Copper-Mediated Cascade C−H/N−H Annulation of Indolocarboxamides with Arynes: Construction of Tetracyclic Indoloquinoline Alkaloids

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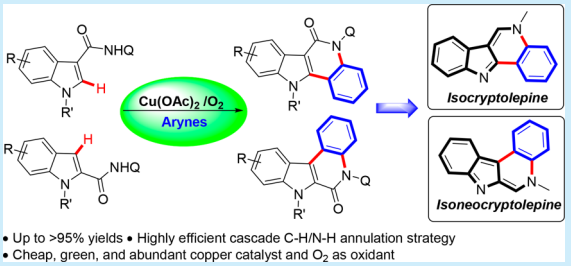
Supporting Information

ABSTRACT: An efficient and environmentally benign Cu-mediated method was developed for direct cascade C−H/N−H annulation to construct polyheterocyclic indoloquinoline scaffolds. This method highlights an emerging strategy for transforming inert C−H bonds into versatile functional groups in organic synthesis and provides a new versatile approach for the efficient synthesis of indolo[3,2-*c*] and [2,3-*c*]quinoline alkaloids.



Malaria is a tropical parasitic disease that is caused by protozoa of the genus *Plasmodium*, and significant efforts to control and treat malaria resulted in some success,[1] including in plant-derived drugs, e.g., quinine,[2a] qinghaosu[2b] (Prof. Tu, 2015 Nobel Prize in Physiology or Medicine), and in new potent antimalarial compound NITD609[2c] (IC_{50}: 1 nM, *P. falciparum*) (Figure 1). However, this devastating disease still affects more

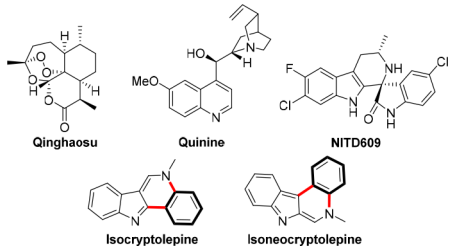


Figure 1. Antimalarial agents.

than 500 million people around the world every year. In 2015, 429000 deaths were caused by malaria.[1b] To date, the search for effective and safer antimalarial remedies remains at the forefront of scientific research.

Indoloquinoline alkaloids,[3] such as isocryptolepine[4a,b] (indolo[3,2-*c*]quinoline), isolated from the west African climbing shrub *Cryptolepis sanguinolenta* (Lindl), are used in Central and West Africa as traditional medicine for the treatment of malaria. Its synthetic analogue isoneocryptolepine[4c] (indolo[2,3-*c*]-quinoline) exhibits excellent antiplasmodial activity in the nanomolar range on L6 cells as well as antitumor activity. The activity and unique structure of the tetracyclic indoloquinoline-fused rings inspired us to devise a highly efficient synthetic protocol. Some classical transformations have been established to form isocryptolepine (e.g., Heck-type reaction,[5a,d,e] photoreaction,[5b] Pd-catalyzed oxidative C−N bond or tandem C−C/C−N formation,[5f,g] CDC reaction,[5h,i] Beckmann rearrangement,[5j] and electrochemical synthesis[5k]) or isoneocryptolepine skeletons (e.g., Suzuki reaction,[6a] Heck reaction,[6b] photocyclization,[6c,d] oxidative C−N bond[6e]). Synthetic access to certain important polycyclic indoloquinoline skeletons remains limited. An ideal and notable synthetic method should include a versatile synthetic strategy to form indolo[2,3-*c*] and [3,2-*c*]quinolones, with a synthesis protocol that avoids the use of noble metal catalysts and oxidants due to potential pharmaceutical chemical studies, and is highly efficient, economical, and environmentally benign. Development of more efficient and novel indoloquinoline formation methods continues to be extensively investigated in synthetic chemistry.

Transition-metal-catalyzed direct selective conversion of unactivated C−H bonds has emerged as an attractive and arguably ideal strategy to synthesize heterocyclic molecules.[7] Previously, we focused on the development of efficient and selective unactivated C−H functionalizations and application to the synthesis of natural biological products.[8] We are focused on developing cheap and environmentally friendly Cu-catalyzed[9] cascade annulation to rapidly access structurally diverse polyheterocyclic alkaloids.[10] Benzynes,[11] which are classical

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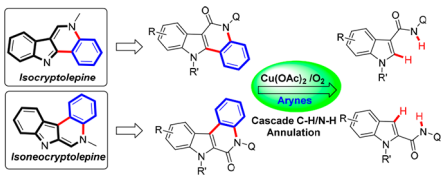
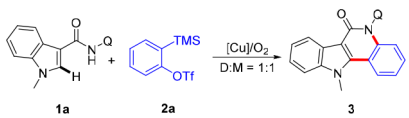
highly electrophilic reactive intermediates, have attracted much interest. Herein, we report our latest developments on Cu-mediated selective cascade C−H/N−H annulation directed by the *N,N*-bidentate directing group[12] to synthesize tetracyclic indolo[3,2-*c*] and [2,3-*c*]quinoline cores with benzynes under mild conditions (Scheme 1). This method offers a practical and arguably ideal strategy for rapid synthesis of polyheterocyclic indoloquinolines from simple starting materials.

Scheme 1. Strategies for Construction of Indoloquinolines via Cu-Mediated Cascade C−H/N−H Annulation



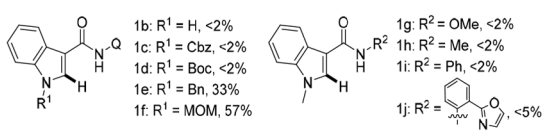
Our initial attempt was focused on intermolecular annulation of a model substrate (i.e., *N*-quinolyl 1-methylindole-3-carboxamide (**1a**) with a Kobayashi benzyne precursor **2a**[13] (Table 1). After initial screening of various Cu catalysts and solvents, the results demonstrated the feasibility of this reaction.[14] Despite low yield, the desired tetracyclic indoloquinolinone **3** was obtained using catalytic amounts of $Cu(OAc)_2$ (0.35 equiv), CsF (1.2 equiv), and TBAI (0.5 equiv) at 80 °C in a 1:1 DMF/MeCN mixture under O_2 as an oxidant for 12 h (Table 1, entry 1). To promote the conversion of **1a**, further studies surveyed a series of

Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3

entry	reagents (equiv)	yield[b] (%)
1	$Cu(OAc)_2$ (0.35), CsF (1.2), TBAI (0.5), O_2, 80 °C	21
2	$Cu(OAc)_2$ (0.35), **NaF (1.2)**, TBAI (0.5), O_2, 80 °C	<2
3	$Cu(OAc)_2$ (0.35), **KF (1.2)**, TBAI (0.5), O_2, 80 °C	18
4	$Cu(OAc)_2$ (0.35), CsF (1.2), **TBAB (0.5)**, O_2, 80 °C	20
5	$Cu(OAc)_2$ (0.35), **CsF (2.4)**, TBAI (0.5), O_2, 80 °C	23
6	$Cu(OAc)_2$ (0.35), CsF (1.2), **TBAI (1.0)**, O_2, 80 °C	31
7	**$Cu(OAc)_2$ (0.5)**, CsF (1.2), TBAI (0.5), O_2, 80 °C	43
8	**$Cu(OAc)_2$ (1.0)**, CsF (1.2), TBAI (0.5), O_2, 80 °C	12
9	**$Cu(OAc)_2$ (0.5)**, CsF (1.2), **TBAI (1.0)**, O_2, 80 °C	87(83)[c]
10	$Cu(OAc)_2$ (0.5), CsF (1.2), TBAI (1.0), **Ar**, 80 °C	17



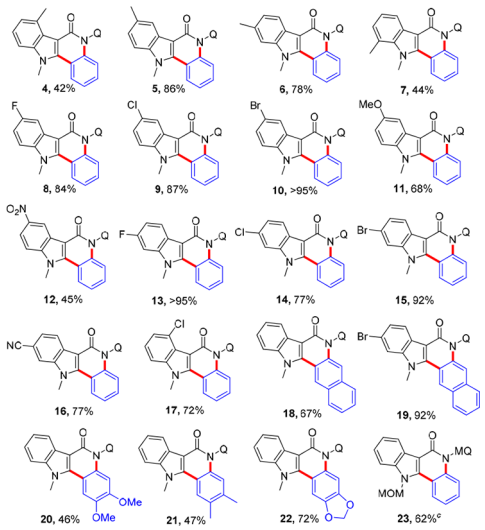
[a]All screening reactions were carried out in a 10 mL glass vial with a PTFE-lined cap at 0.2 mmol scale. [b]Yields based on ^1H NMR analysis. [c]Isolated yield in parentheses. See Supporting Information for more conditions.

fluoride sources and additives (entries 2−9). Addition of more TBAI, which is typically believed to further increase the benzyne generation rates from the Kobayashi benzyne precursor,[15] improved the yield of the reaction to 31% (entry 6). We obtained an 83% isolated yield for **3** under optimized reaction conditions (50 mol % $Cu(OAc)_2$, 1.2 equiv CsF, and 1.0 equiv TBAI, 80 °C in 1:1 DMF/MeCN under O_2 for 12 h) (entry 9). O_2, which is an ideal oxidant because it is clean, green, and inexpensive, appeared to significantly improve the Cu catalysis cycle (entry 10).[16]

The N-protecting groups (R^1) of indole were very important in these cascade C−H/N−H activation and annulation reactions. Replacing *N*-methyl (**1a**) with *N*-H (**1b**) or other electron-withdrawing N-protected groups, i.e., *N*-Cbz (**1c**) and *N*-Boc (**1d**), were not afforded under standard conditions. Installation of electron-donating protective groups (i.e., *N*-Bn (**1e**) and *N*-MOM (**1f**)) did give the desired annulation products in 33 and 57% isolated yield. Next, we examined the effect of directing groups (R^2). The desired reaction was inhibited when OMe (**1g**), Me (**1h**), or Ph (**1i**) was used in place of **1a**. The 2-oxazolinyl (**1j**) directing group only yielded trace amounts of annulation product. These results indicate that the *N,N*-bidentate directing group (i.e., 8-aminoquinoline) plays a critical role in this Cu-mediated cascade C−H/N−H activation and annulation reaction.

With an optimized set of conditions in hand, we probed the substrate scope of **1a** to survey the general reactions. Indole-3-carboxamides that were substituted with a variety of functional groups, such as alkyl, halogens, OMe, NO_2, and CN, were well tolerated in this Cu-catalyzed system and afforded tetracyclic indolo[3,2-*c*]quinoline derivative C−H/N−H annulation products **4**−**23** in good to excellent yields (Scheme 2). The 4-, 5-, 6-, or 7-methyl-substituted indole-3-carboxamides **4a**−**7a** were employed to examine remote steric effects. The lower steric hindrance of 5- or 6-methyl-substituted *N*-quinolyl 1-methyl-1*H*-indole-3-carboxamides (**5a** and **6a**) resulted in the best yield. X-ray crystallographic analysis of annulation product **4** effectively

Scheme 2. Scope of Functionalized Indolo[3,2-*c*]quinolone[a,b]



[a]Reaction conditions: benzamide (0.2 mmol), **2a** (0.4 mmol), $Cu(OAc)_2$ (0.5 equiv), CsF (0.24 mmol), and TBAI (0.2 mmol) in 1:1 DMF/MeCN (2 mL) at 80 °C under O_2 for 12 h. [b]Isolated yield after purification. [c]Benzamide (0.2 mmol), **2a** (0.4 mmol), $Cu(OAc)_2$ (0.75 equiv), CsF (0.24 mmol), and TBAI (0.3 mmol) in 1:1 DMF/MeCN (2 mL) at 100 °C under O_2 for 2 h.

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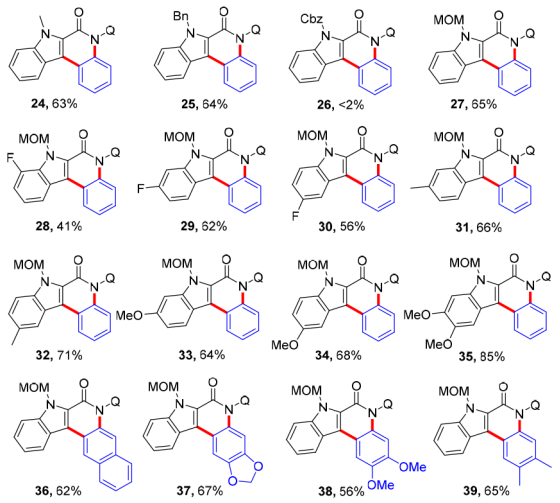
explains the remote steric effects of substituted indoles. The scope of the functionalized aryne precursors as general annulation partners for this reaction was investigated. Various substituted indole-3-carboxamide substrates were reacted with various aryne precursors **2b**–**2e** to afford good to excellent annulation yields (**18**–**23**).

Next, we examined the scope of the different N-protected groups of indole-2-carboxamides **24**–**27**. Substrates with electron-donating groups, such as *N*-methyl (**24a**), *N*-Bn (**25a**), and MOM (**27a**), afforded the desired tetracyclic **24**, **25**, and **27** in 63, 64, and 65% isolated yield, respectively (Scheme 3). Electron-withdrawing N-protected group (*N*-Cbz (**26a**)) did not result in a reaction under standard conditions. Based on these results, the *N*-quinolyl 1-MOM-indole-2-carboxamides substituted with a variety of functional groups were reacted with various aryne precursors. These precursors were well-tolerated under the $Cu(OAc)_2/O_2$ system and smoothly afforded the desired indolo[2,3-*c*]quinoline derivative C–H/N–H annulation products **28**–**39** in good to excellent yields. These results demonstrate that our approach has potential for use in the synthesis of functionalized tetracyclic indolo[3,2-*c*] and indolo[2,3-*c*]-quinoline cores.

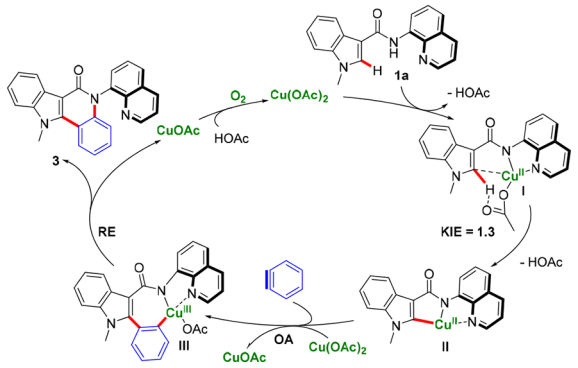
Scheme 3. Scope of Functionalized indolo[2,3-*c*]quinolone[a]



[a]Reaction conditions were the same as those of Scheme 2. See Supporting Information for more reaction conditions. X-ray determined the structure of **28**.

To gain insight into the mechanism, we conducted a primary intermolecular kinetic isotope effect experiment, and a value of 1.3 was observed (see the Supporting Information). Next, a radical trapping experiment was performed. The reaction was not inhibited by addition of 2 equiv of a radical scavenger (TEMPO), and **1a** still afforded **3** in a 76% isolated yield. These experiments suggested that a SET mechanism was most likely not involved in this reaction.[17] Based on these experiments and previous studies,[8,16,17] a plausible organometallic C–H activation mechanism via a Cu(III) intermediate[18] was proposed for this cascade C–H/N-H annulation. As shown in Scheme 4, coordination of **1a** was followed by reaction with $Cu(OAc)_2$-generated anionic complex **I** ligated by a *N*,*N*-bidentate directing group. Complex **I** underwent an acetate-assisted intramolecular C–H concerted metalation/deprotonation to yield five-membered complex **II**, which underwent carbocupration with the aryne generated from **2** to afford intermediate **III**. Finally,

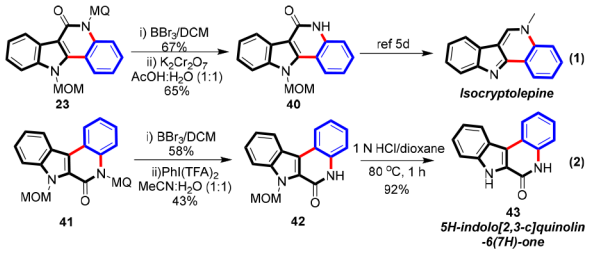
Scheme 4. Proposed Reaction Pathway



reductive elimination of **III** yielded the desired annulation production (**3**), and the Cu catalyst was regenerated by oxygen for the next cycle.

To demonstrate the application of our non-noble metal Cu-mediated cascade C–H/N–H annulation method as an efficient and versatile synthetic strategy to form indolo[3,2-*c*] and [2,3-*c*]quinolones, tetracyclic indoloquinolines **40** and **43** were synthesized under these mild conditions (Scheme 5). A previous study reported that 8-amino-5-methoxyquinoline (MQ) can be used rather than 8-aminoquinoline for easy extraction.[19] The MQ auxiliary of indolo[3,2-*c*]quinoline **23** can be readily removed by a two-step sequence to afford **40**, and the alkaloid *isocryptolepine*, a natural antimalarial, can be synthesized from **40** under the simple conditions reported.[5d] Removal of the MQ auxiliary of **41** affords **42**, which can be used to obtain various isoneocryptolepine-type indolo[2,3-*c*]quinolones. For example, 5*H*-indolo[2,3-*c*]-quinolin-6(7*H*)-one **43** (Scheme 5, eq 2), which is a potent tubulin polymerization inhibitor that inhibits the growth of human breast cancer cells,[20] was successfully synthesized from **42** in 92% yield under simple conditions.

Scheme 5. Synthetic Applicability and Removal of Auxiliary



In summary, we developed a highly efficient Cu-mediated intermolecular cascade C–H/N–H annulation of indole carboxamides with arynes. These reactions are operationally simple and robust, and the $Cu(OAc)_2/O_2$ system avoids the use of sensitive and expensive noble metals and oxidants. The reaction produced broad and structurally diverse polyheterocyclic indolo-[3,2-*c*] and [2,3,-c]quinoline products. The directing group can be easily removed under simple conditions, which results in an efficient and straightforward strategy for the synthesis of indoloquinoline alkaloids and activated motifs. Furthermore, the application of this cascade C–H/N–H annulation method to the synthesis of broader natural alkaloids is currently under investigation.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03580.

Experimental procedures, NMR spectra, X-ray and analytical data for all new compounds (PDF)

Accession Codes

CCDC 1586298−1586299 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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