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Cu(OTf)$_2$-Catalyzed Intramolecular Radical Cascade Reactions for the Diversity-Oriented Synthesis of Quinoline-Annulated Polyheterocyclic Frameworks

Shuo Yuan, Jingya Zhang, Danqing Zhang, Donghui Wei, Jiahui Zuo, Jian Song, Bin Yu,* and Hong-Min Liu*

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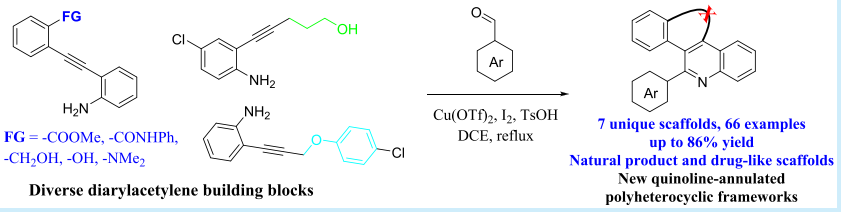

ABSTRACT: Compound libraries with high levels of structural diversity and novelty could cover underexploited chemical space and thus have been highly pursued in drug discovery. Herein, we report the first Cu(OTf)$_2$-catalyzed intramolecular radical cascade reactions that enable the diversity-oriented synthesis of quinoline-annulated polyheterocyclic compounds (7 unique scaffolds, 66 examples) in an efficient manner. This work demonstrates an alternative route to access the natural product- and druglike compound collection with high levels of structural diversity and novelty.

The privileged polyheterocyclic compounds containing a quinoline fragment are widely present in numerous natural products and bioactive molecules, and such compounds have proven to possess a wide variety of pharmacological properties, such as anticancer, antiviral, and antiangiogenic activity (Figure 1).[1−3] Representative quinoline-containing natural products are trisphaeridine (an alkaloid isolated from amaryllidaceae species with potential antitumor activity),[4] camptothecin (a topoisomerase inhibitor isolated from camptotheca acuminate with remarkable anticancer activity),[5] fagaronine (a benzophenanthridine alkaloid found in zanthoxylum zanthoxyloides with potential antimalarial activity),[6] and distomadine A (a tetracyclic alkaloid isolated from *Pseudodistoma aureum* with antifungal activity)[7] (Figure 1A). In addition, quinoline-containing polyheterocyclic fragments are also prevalent in bioactive molecules, such as torin 1 (a potent and selective mTOR inhibitor),[8] topovale (a Top1 targeting antitumor drug),[9] KuFal194 (a highly potent and selective DYRK1A inhibitor),[10] and QL47 (a potent, selective and irreversible BTK inhibitor)[11] (Figure 1B). Because of the unique structural features and interesting biological profiles of quinoline-containing polyheterocyclic scaffolds, several synthetic strategies have been developed for the construction of these structurally complex and biologically important scaffolds in recent decades; two main strategies include (a) transition-metal-catalyzed cyclization reactions of quinoline bearing substrates[12−14] and (b) transition-metal-catalyzed domino cascade reactions forming the quinoline ring system.[15−17]

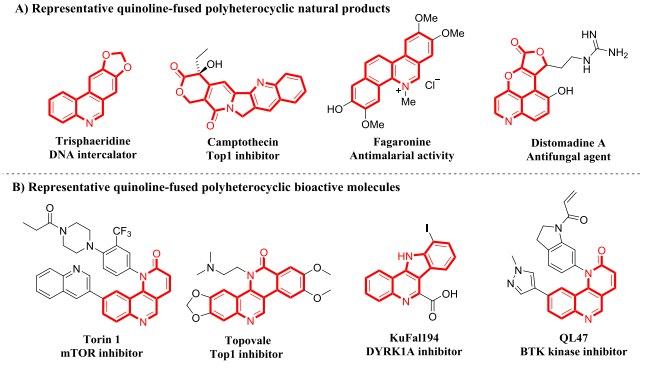

Figure 1. Selected quinoline-fused polyheterocyclic natural products and bioactive molecules.

Alkynes have been extensively used in organic synthesis, particularly for cyclization reactions.[18−21] In 2012, Zhu and coworkers successfully obtained indolo[3,2-*c*]isoquinolinones through Pd-catalyzed intramolecular cascade reactions of alkynes, in which amination, *N*-demethylation, and amidation

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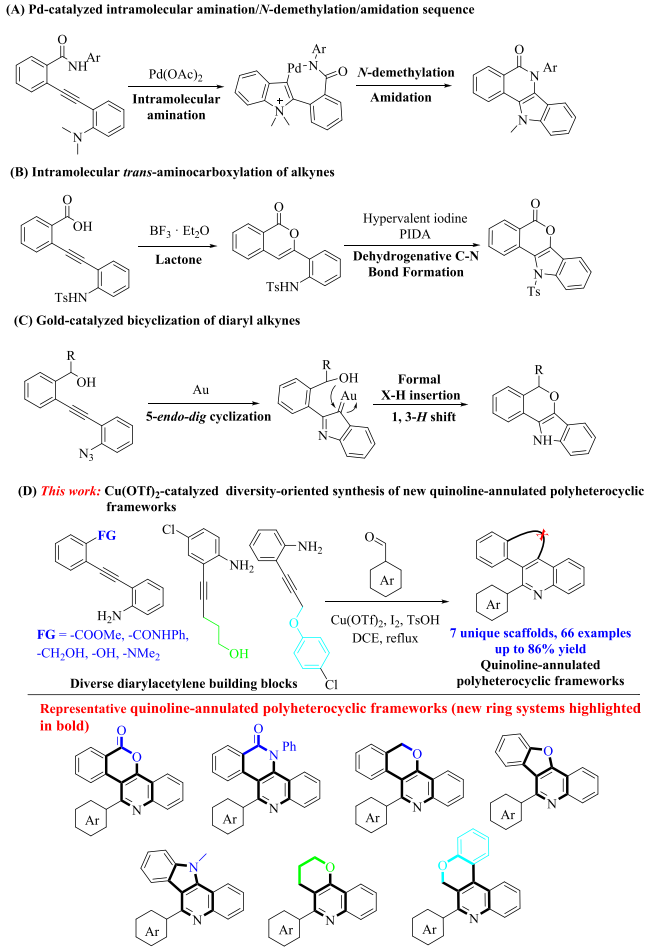
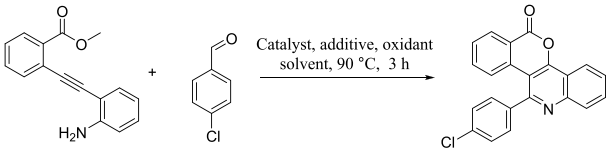
were involved (Scheme 1A).[22] In 2016, Du et al. successfully achieved stepwise synthesis of indolo[3,2-*c*]isocoumarins through intramolecular *trans*-aminocarboxylation of alkynes (Scheme 1B).[23] In 2018, Xu et al. reported a gold-catalyzed bicyclization of diarylacetylenes for the synthesis of indole annulated tetracyclic compounds (Scheme 1C).[24] These examples have demonstrated that trapping alkynes by neighboring nucleophilic groups is a viable strategy that enables rapid access to pharmacologically relevant polyheterocyclic scaffolds through cascade reactions.[25,26] To date, although several protocols about the efficient synthesis of polyheterocyclic scaffolds through alkyne-based cascade reactions have been disclosed, the versatile one-pot synthetic strategy for the construction of diverse quinoline-containing polyheterocyclic scaffolds is still rare. Moreover, achieving high levels of structural novelty and diversity in an efficient manner is challenging and highly desirable, such compound library covers underexplored chemical space and thus is a key to success in new drug discovery campaign. In continuation with our previous work on the synthesis of biologically important heterocycles,[27−33] we herein report the $Cu(OTf)_2$-catalyzed domino 6-*endo*-*dig* cyclization/C−C coupling reaction sequence that enables the efficient synthesis of architecturally diverse and novel quinoline-annulated polyheterocyclic scaffolds (7 unique scaffolds, 66 examples, up to 86% yield) from diarylacetylenes and aromatic aldehydes using I_2 as an oxidant (Scheme 1D). Of note, the structural diversity depends on the neighboring functional groups and thus is controllable. This feature could be used to generate diverse compound collection, which may have potential applications in drug discovery.

Scheme 1. Intramolecular Cascade Reactions of Alkynes Enabling the Construction of Diverse Polyheterocyclic Scaffolds



Initially, methyl 2-((2-aminophenyl)ethynyl)benzoate **1a** and 4-chlorobenzaldehyde **2a** were chosen as model substrates to optimize the reaction conditions (Table 1). Upon treatment with 20 mol % $Pd(OAc)_2$ and 0.5 equiv of TsOH in DCE (2 mL) at 90 °C for 3 h, the desired quinoline-annulated tetracyclic compound **3a** was obtained in 16% yield (Table 1, entry 1). We next screened other metal catalysts (Table 1, entries 2−5), showing that $Cu(OTf)_2$ was the optimal catalyst, giving **3a** in 37% yield (Table 1, entry 3). When AcOH and TfOH were used as acidic additives, compound **3a** was obtained in 18% and 25% yield, respectively (Table 1, entries 6 and 7). We also found that the solvent effect was remarkable: replacing DCE with toluene, DMF, MeCN, THF, and MeOH led to significantly diminished yields (Table 1, entries 8−12). To our satisfaction, addition of I_2 significantly improved the reactivity, giving **3a** in 85% yield (Table 1, entry 13), while other hypervalent iodine reagents such as iodosobenzene (PhIO), (diacetoxyiodo)benzene (PIDA), and phenyliodine bis(trifluoroacetate) (PIFA) were found to be less efficient, giving **3a** in <10% yields (Table 1, entries 13−16). It should be noted that in the absence of $Cu(OTf)_2$, compound **3a** was

Table 1. Optimization of the Reaction Conditions[a]



1a **2a** **3a**

entry	catalyst	solvent	additive	oxidant	**3a**[b] (%)
1	$Pd(OAc)_2$	DCE	TsOH		16
2	CF_3COOAg	DCE	TsOH		12
3	$Cu(OTf)_2$	DCE	TsOH		37
4	CuI	DCE	TsOH		4
5	Ni_2SO_4	DCE	TsOH		5
6	$Cu(OTf)_2$	DCE	AcOH		18
7	$Cu(OTf)_2$	DCE	TfOH		25
8	$Cu(OTf)_2$	toluene	TsOH		20
9	$Cu(OTf)_2$	DMF	TsOH		5
10	$Cu(OTf)_2$	MeCN	TsOH		6
11	$Cu(OTf)_2$	THF	TsOH		ND[c]
12	$Cu(OTf)_2$	MeOH	TsOH		5
13	$Cu(OTf)_2$	DCE	TsOH	I_2	85 (79)[d]
14	$Cu(OTf)_2$	DCE	TsOH	PhIO	6
15	$Cu(OTf)_2$	DCE	TsOH	PIDA	4
16	$Cu(OTf)_2$	DCE	TsOH	PIFA	9
17		DCE	TsOH	I_2	32
18	$Cu(OAc)_2$	DCE	TsOH	I_2	40
19	$Cu(acac)_2$	DCE	TsOH	I_2	58
20	$Cu(OTf)_2$	DCE	TsOH	I_2	75[e]
21	$Cu(OTf)_2$	DCE	TsOH	I_2	55[f]

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (1 mmol), catalyst (20 mol %), solvent (2 mL), additive (0.25 mmol), oxidant (0.5 mmol), 90 °C, 3 h. [b]NMR yields determined by ^{1}H NMR using triphenylmethane as an internal standard. [c]ND = not detected. [d]Isolated yield. [e]10 mol % of catalyst was used. [f]5 mol % of catalyst was used.

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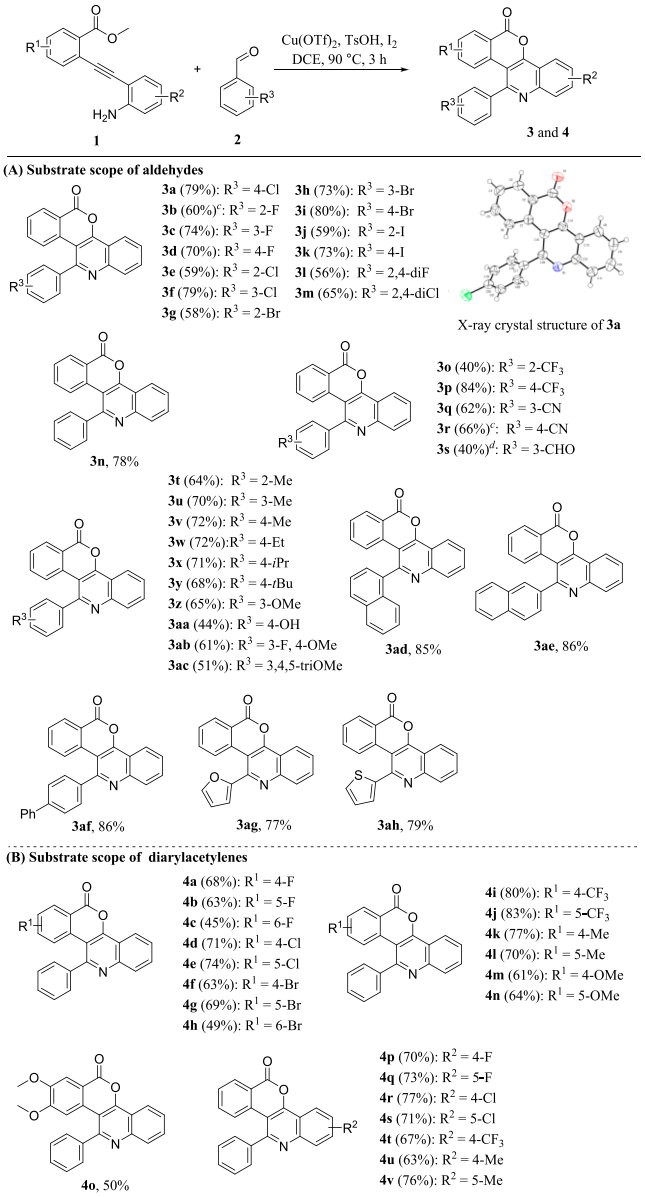
obtained in 32% yield (Table 1, entry 17). Replacement of $Cu(OTf)_2$ with $Cu(OAc)_2$ or $Cu(acac)_2$ caused significantly decreased yields, compound **3a** was generated in 40% and 58% yields, respectively (Table 1, entries 18 and 19). A lower catalyst loading of 10 and 5 mol % furnished **3a** in 75% and 55% yield, respectively (Table 1, entries 20 and 21). According to the above optimizations, the optimal reaction conditions were methyl 2-((2-aminophenyl)ethynyl)benzoate **1a** (0.5 mmol), 4-chlorobenzaldehyde **2a** (1.0 mmol), $Cu(OTf)_2$ (20 mol %), TsOH (0.25 mmol), I_2 (0.5 mmol), DCE (2 mL), 90 °C, 3 h (Table 1, entry 13).

With the optimal reaction conditions in hand, we next examined the scope of 2-((2-aminophenyl)ethynyl)benzoates and aromatic aldehydes. As shown in Scheme 2A, the quinoline-annulated polyheterocyclic compounds were obtained in moderate to good yields (40−86%). For halogen-substituted aromatic aldehydes, the corresponding products **3a**−**3m** were provided in good yields (56−80%). The halogen atoms were well tolerated and could be used for further functionalization. Mostly due to the steric hindrance, the compounds (e.g., **3b**, **3e**, **3g**, **3j**) bearing an *ortho* substituent were obtained in relatively lower yields. In general, both electron-deficient (−CF_3, −CN, −CHO) and electron-rich (−Me, −Et, −*i*Pr, −*t*Bu, −OMe, −OH) aromatic aldehydes proceeded smoothly under the optimized reaction conditions and furnished the desired compounds **3o**−**3ac** in moderate to good yield (40−84%). Compounds **3s** and **3aa** bearing the oxidizable formaldehyde and phenolic OH groups were generated in relatively lower yields. In addition, the naphthyl aldehydes, 4-phenylbenzaldehyde, and heteroaromatic aldehydes were also compatible with our protocol and delivered the corresponding polyheterocyclic compounds **3ad**−**3ah** in good yield (77−86%). To showcase the synthetic practicality, the reactions for the synthesis of compounds **3b** and **3r** were performed on a 1.0 mmol scale, providing the desired products in 60% and 66% yields, respectively. The crystal structure of **3a** was also determined by the X-ray crystallographic analysis (CCDC: 1921863). We here demonstrate that diverse functional groups such as amine, ester, and aldehyde in substrates are well tolerated under the optimized reaction conditions and could be integrated in an efficient manner to form quinoline-annulated tetracyclic scaffolds. Besides, the scope of diarylacetylenes was also explored to showcase the generality of our protocol. As shown in Scheme 2B, various substituents on both phenyl rings of diarylacetylenes were well tolerated, giving the desired products **4a**−**4v** in moderate to good yields (45−83%) under the optimal reaction conditions.

As shown in Scheme 2, the core scaffold depends on the functional ester group. Encouraged by the preceding results, it can be speculated that replacement of ester with other nucleophilic functional groups may afford novel polyheterocyclic scaffolds. As shown in Scheme 3A, diarylacetylenes bearing different functional groups (e.g., −CONHPh, $-CH_2OH$, phenolic OH, and amine) gave the corresponding products with high levels of structural diversity and novelty under the optimal conditions. Specifically, the quinoline-fused isoquinolinone scaffolds (**5a**,**b**) synthesized from 2-((2-aminophenyl)ethynyl)-*N*-phenylbenzamide widely exist in topoisomerase inhibitors and other bioactive molecules (Figure 1).[34−36] For diarylacetylenes with the hydroxyl methyl and phenolic OH groups, the quinoline-fused isochrones **5c**,**d** and quinoline-fused benzofurans **5e**,**f** were obtained in moderate to good yields through an intramolecular *O*-attack

Scheme 2. Substrate Scope of Aldehydes and Diarylacetylenes for the Synthesis of Quinoline-Annulated Tetracyclic Scaffolds[a,b]



[a]Conditions: **1a** (0.5 mmol), **2** (1.0 mmol), $Cu(OTf)_2$ (20 mol %), TsOH (0.25 mol), I_2 (0.5 mmol), DCE (2 mL), 90 °C, 3 h. [b]Isolated yields. [c]Conditions: **1a** (1 mmol), **2** (2.0 mmol), $Cu(OTf)_2$ (20 mol %), TsOH (0.5 mol), I_2 (1 mmol), DCE (5 mL), 90 °C, 3 h. [d]0.5 mmol of **2** was used.

pathway. Besides, we also found that *N*,*N*-dimethylamine could be employed as a nucleophile to produce the quinoline-annulated indoles **5g**,**h** through the *N*-attack pathway. The pyridine-fused indole scaffold, also known as γ-carboline, is an interesting structural motif existed in natural products and bioactive molecules with diverse pharmacological activities.[37−39] To further increase the scaffold diversity, the diarylacetylene **1b** bearing a terminal alcohol group was used, giving the desired tetrahydropyran-fused quinoline **6a** in 80% yield under the optimal conditions (Scheme 3B). The tricyclic heterofused quinoline **6a** is a key intermediate for the synthesis of druglike compound **A** with multitrypanosomatid

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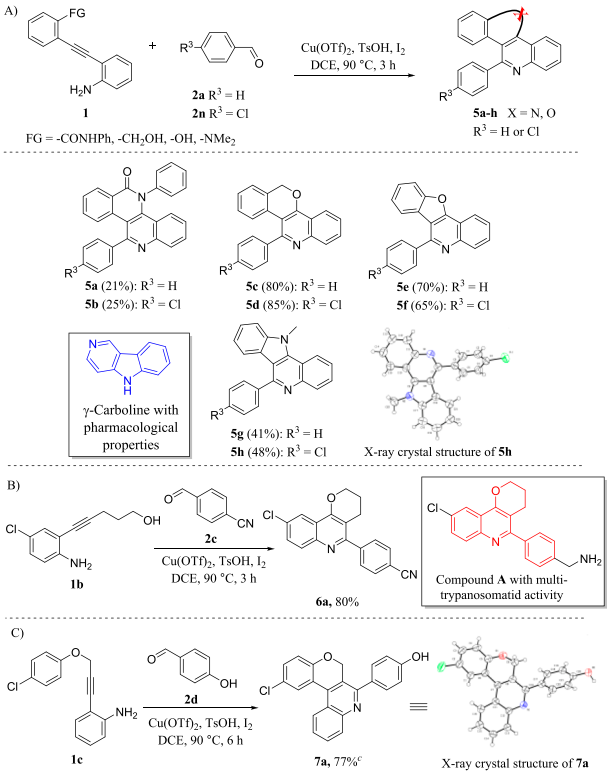
Scheme 3. Diversity-Oriented Synthesis of New Quinoline-Annulated Polyheterocyclic Scaffolds[a,b]

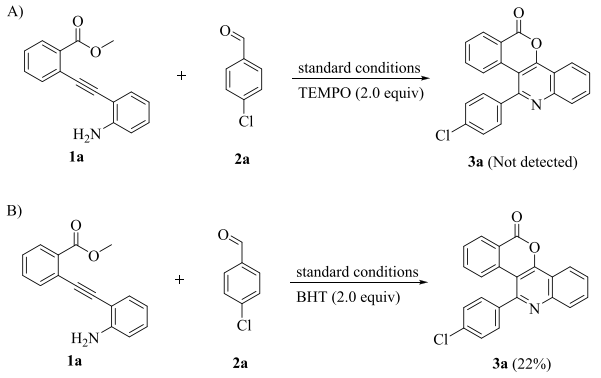


[a]Conditions: **1** (0.5 mmol), **2** (1.0 mmol), $Cu(OTf)_2$ (20 mol %), TsOH (0.25 mol), I_2 (0.5 mmol), DCE (2 mL), 90 °C, 3 h. [b]Isolated yields. [c]Conditions: **1** (0.5 mmol), **2** (1.0 mmol), $Cu(OTf)_2$ (20 mol %), TsOH (0.5 mol), I_2 (0.05 mmol), DCE (2 mL), 90 °C, 6 h.

activity.[40] This protocol provides an alternative method to synthesize compound **A** and analogues for biological testing. Similarly, compound **1c** reacted with 4-hydroxylbenzaldehyde **2d** smoothly, affording **7a** in 77% yield (Scheme 3C). Of note, the electron-rich phenyl ring served as an intramolecular nucleophile for the cascade reactions, and only 10 mol % of I_2 was used. Further investigation on using electron-rich arenes as nucleophiles for intramolecular cascade reactions is undergoing in our lab and will be reported in due course. The crystal structures of **5h** and **7a** were further confirmed by the X-ray analysis (**5h**, CCDC: 1964272; **7a**, CCDC: 1964273). Collectively, we envisioned that the copper catalysis developed herein achieved the diversity-oriented synthesis of new quinoline-fused polyheterocyclic frameworks present in natural products and bioactive molecules, and the structural diversity and novelty depended on the types of functional groups. It is anticipated that more novel scaffolds could be generated by installing other nucleophilic groups on the phenyl rings.

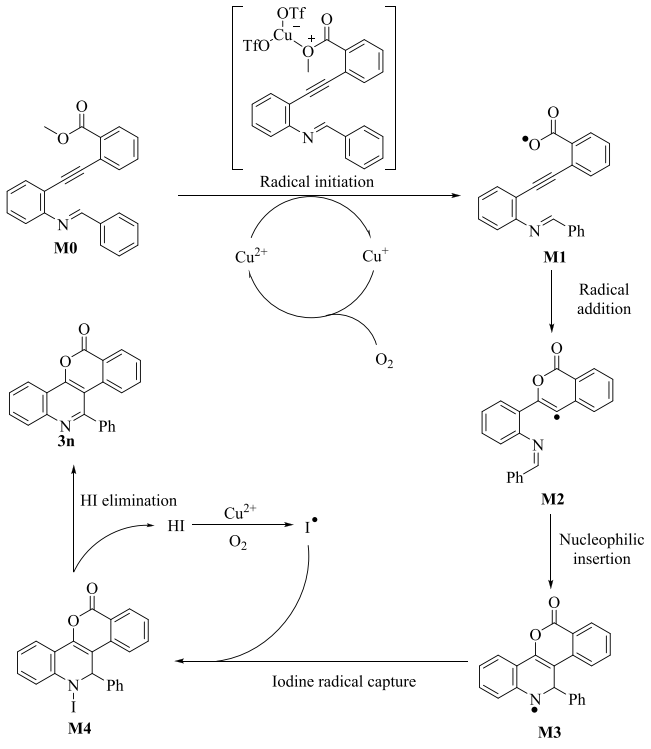
The control experiments were conducted to gain mechanistic insight into this cascade reaction. As shown in Scheme 4, the radical inhibitor 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) completely suppressed the reaction, while butylhydroxytoluene (BHT) also inhibited the reaction, giving the desired product **3a** in only 22% yield (detected by ^1H NMR using triphenylmethane as an internal standard), significantly lower than that under the optimal conditions. The data suggest that the Cu-catalyzed intramolecular cascade reactions involve a radical process.

Scheme 4. Control Experiments



Based on our observations and previous reports,[41−44] the proposed mechanism for the synthesis of quinoline-annulated polyheterocyclic scaffolds is shown in Scheme 5. Initially, the

Scheme 5. Plausible Reaction Mechanism



intermediate **M0** is generated in situ from methyl 2-((2-aminophenyl)ethynyl)benzoate (**1a**) and benzaldehyde (**2n**) through TsOH-promoted condensation. Then the intermediate **M0** undergoes a cooper salt promoted one-electron oxidation to form a radical cation **M1**. Subsequent intramolecular radical addition into the C≡C bond of **M1** affords a radical **M2**, which then adds onto intramolecular imine through nucleophilic insertion to give a cyclized radical **M3**. The nitrogen radical would be trapped by iodine radical generated from the oxidation of iodide, generating the complex **M4**. Finally, a hydrogen iodide elimination step furnishes the alkenylation product **3n**. Through the Cu-catalyzed cascade reactions, the diverse quinoline-annulated polyheterocyclic frameworks are efficiently constructed, in which one C−X (X = C, N, or O) bond, one C═N bond, one C−C bond, and two new ring systems are formed simultaneously.

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In conclusion, we have developed the first $Cu(OTf)_2$-catalyzed intramolecular radical domino reactions that enable the efficient construction of structurally novel and diverse quinoline-annulated polyheterocyclic scaffolds from readily available diarylacetylenes and aromatic aldehydes. These polyheterocyclic scaffolds show high levels of structural diversity and novelty and have been found in numerous highly valuable natural products and bioactive molecules. Of note, the scaffold diversity, a central element in diversity-oriented synthesis, solely depends on the neighboring functional groups and thus is controllable. The compound library may have potential applications in new drug discovery.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00129.

Experimental procedures, characterization data, and ^1H NMR, ^{13}C NMR spectra for new compounds (PDF)

Accession Codes

CCDC 1921863 and 1964272−1964273 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.

■ AUTHOR INFORMATION

Corresponding Authors

Bin Yu − *School of Pharmaceutical Sciences, Zhengzhou University, Zhengzhou 450001, China;* orcid.org/0000-0002-7207-643X; Email: yubin@zzu.edu.cn

Hong-Min Liu − *School of Pharmaceutical Sciences, Zhengzhou University, Zhengzhou 450001, China;* orcid.org/0000-0001-6771-9421; Email: liuhm@zzu.edu.cn

Authors

Shuo Yuan − *School of Pharmaceutical Sciences, Zhengzhou University, Zhengzhou 450001, China;* orcid.org/0000-0002-4273-5625

Jingya Zhang − *School of Pharmaceutical Sciences, Zhengzhou University, Zhengzhou 450001, China*

Danqing Zhang − *School of Pharmaceutical Sciences, Zhengzhou University, Zhengzhou 450001, China*

Donghui Wei − *College of Chemistry, and Institute of Green Catalysis, Zhengzhou University, Zhengzhou 450001, China;* orcid.org/0000-0003-2820-282X

Jiahui Zuo − *School of Pharmaceutical Sciences, Zhengzhou University, Zhengzhou 450001, China*

Jian Song − *School of Pharmaceutical Sciences, Zhengzhou University, Zhengzhou 450001, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c00129

Notes

The authors declare no competing financial interest.

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