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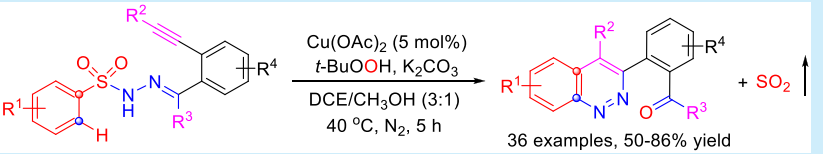
Copper-Catalyzed Cascade Cyclization of Arylsulfonylhydrazones Derived from *ortho*-Alkynyl Arylketones: Regioselective Synthesis of Functionalized Cinnolines

Biao Yao,[†] Tao Miao,*[,†] Wei Wei,[†] Pinhua Li,[†] and Lei Wang*[,†,‡]

[†]Department of Chemistry, Huaibei Normal University, Huaibei, Anhui 235000, P. R. China

[‡]State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Shanghai 200032, P. R. China

Supporting Information

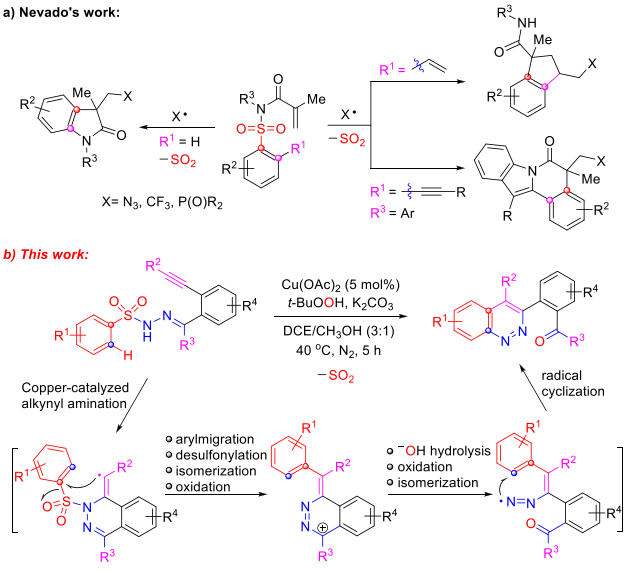


ABSTRACT: A novel copper-catalyzed cascade reaction of arylsulfonylhydrazones derived from *ortho*-alkynyl arylketones was accomplished. This reaction provides concise access to diversified cinnolines in good yields. The mechanistic investigations have disclosed involvement of the key alkynyl amination, 1,4-aryl migration, desulfonylation, and diazo radical cyclization cascade in the transformation.

Radical cascade cyclization is a powerful tool for rapidly building intricate molecular architectures in a chemoselective and atom-economical manner.[1] Over the past few decades, several efforts were focused on the radical addition−cyclization cascades, where free radical species adds to the double or triple bond followed by intramolecular cyclization to form cyclic molecules.[2] Recently, radical cascade cyclization involving aryl migration has become a highly attractive strategy for the synthesis of valuable compounds in an efficient way, which are otherwise not available through conventional methods.[3] Nevado and co-workers have developed a novel method for the synthesis of functionalized oxindoles from a variety of radicals and *N*-(arylsulfonyl)acrylamides through radical addition of double bond/aryl migration/desulfonylation cascade cyclization.[4] The Nevado group furthermore documented other elegant examples of the multistep radical cascade reaction of well-designed *ortho*-vinyl- or *ortho*-alkynyl-substituted *N*-(arylsulfonyl)arylamides and generated functionalized indanes and indolo[2,1-*a*]isoquinolines in high stereoselectivity by unconventional bond cleavage and construction reactions (Scheme 1a).[5] However, this radical cascade cyclization involving aryl migration is rare and is still an unsolved challenge largely because of the unavailability of appropriate reagents and the difficulty of identifying suitable reaction systems that would work nicely in each step of the reaction while maintaining control of the reaction selectivity. Herein, we report a copper-catalyzed cascade cyclization of readily available arylsulfonylhydrazones derived from *ortho*-alkynyl arylketones under mild condition. The reaction provides an effective and practical avenue to functionalized cinnolines in a regioselective fashion (Scheme 1b).

Cinnolines are important heterocycles comprising challenging framework and unique biological activities, including anticancer, antibacterial, antifungal, antihypertensive, and antiulcer activities,[6] as well as electrochemical and luminescent properties.[7] Accordingly, much attention from both synthetic and medicinal chemists has been paid to the chemistry of cinnolines, and a number of studies including classical Widman−Stoermer route were reported for their preparation.[8] Although great achievements have been made, the develop-

Scheme 1. Design of Radical Aryl Migration−Cyclization Cascade Reactions



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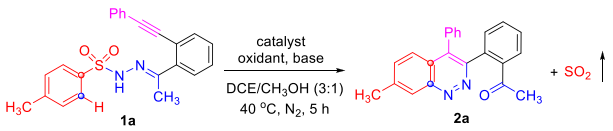
ment of a novel atom/step-economical and efficient protocol from readily available starting materials to access the cinnoline framework with a diverse substitution pattern is highly desirable.

Initially, *N*-tosylhydrazone derived from *ortho*-alkynyl acetophenone was chosen as the reaction substrate to optimize the reaction conditions (Table 1). When the reaction of **1a** was

Table 1. Optimization of the Reaction Conditions[a]



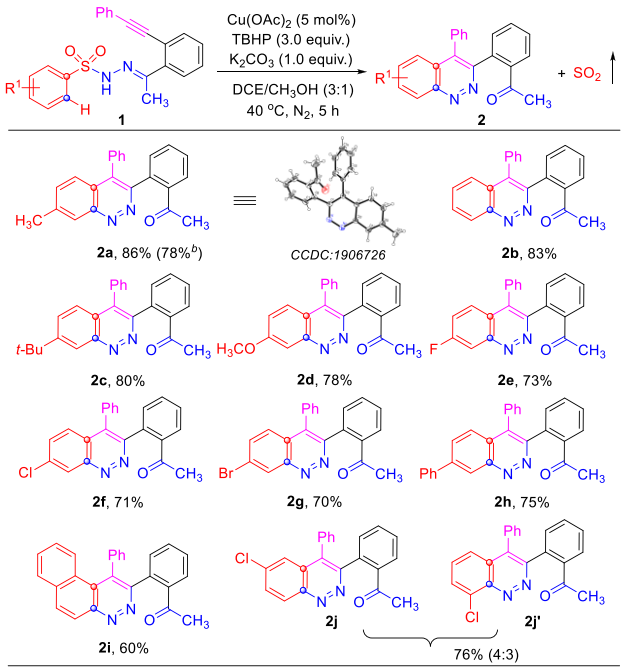
entry	catalyst	oxidant	base	yield (%)[b]
1	$CuCl_2$	TBHP	K_2CO_3	63
2	$CuBr_2$	TBHP	K_2CO_3	68
3	**$Cu(OAc)_2$**	**TBHP**	**K_2CO_3**	**86**
4	CuI	TBHP	K_2CO_3	0
5	$Cu(OAc)_2$	CHP	K_2CO_3	40
6	$Cu(OAc)_2$	TBPB	K_2CO_3	0
7	$Cu(OAc)_2$	DTBP	K_2CO_3	0
8	$Cu(OAc)_2$	DCP	K_2CO_3	0
9	$Cu(OAc)_2$	H_2O_2	K_2CO_3	0
10	$Cu(OAc)_2$	O_2	K_2CO_3	0
11	$Cu(OAc)_2$	$Na_2S_2O_8$	K_2CO_3	0
12	$Cu(OAc)_2$	TBHP	Na_2CO_3	75
13	$Cu(OAc)_2$	TBHP	Cs_2CO_3	80
14	$Cu(OAc)_2$	TBHP	*t*-BuOK	57
15	$Cu(OAc)_2$	TBHP	Et_3N	50
16	$Cu(OAc)_2$	TBHP	pyridine	38
17[c]	$Cu(OAc)_2$	TBHP	K_2CO_3	0
18[d]	$Cu(OAc)_2$	TBHP	K_2CO_3	0
19[e]	$Cu(OAc)_2$	TBHP	K_2CO_3	29
20[f]	$Cu(OAc)_2$	TBHP	K_2CO_3	67
21[g]	$Cu(OAc)_2$	TBHP	K_2CO_3	61
22[h]	$Cu(OAc)_2$	TBHP	K_2CO_3	60
23[i]	$Cu(OAc)_2$	TBHP	K_2CO_3	84
24[j]	$Cu(OAc)_2$	TBHP	K_2CO_3	81

[a]Reaction conditions: **1a** (0.25 mmol), catalyst (5 mol %), oxidant (3 equiv), base (1 equiv), DCE/CH_3OH (3:1, 4 mL), N_2, 40 °C, 5 h. TBHP = *tert*-butyl hydrogenperoxide (70% in water), CHP = cumyl hydroperoxide, TBPB = *tert*-butyl peroxybenzoate, DTBP = di-*tert*-butyl peroxide, DCP = dicumyl peroxide. [b]Yield of isolated product. [c]Without catalyst. [d]Without oxidant. [e]Without base. [f]2.0 equiv of TBHP was used. [g]0.5 equiv of K_2CO_3 was used. [h]40 °C for 3 h. [i]40 °C for 8 h. [j]60 °C for 5 h.

carried out in the presence of 5 mol % $CuCl_2$, three equivalents of *tert*-butyl hydrogenperoxide (TBHP, 70% in water) and one equivalent of K_2CO_3 in a mixed-solvent of 1,2-dichloroethane (DCE) and CH_3OH (3:1) at 40 °C for 5 h, the formation of cinnoline **2a** was obtained in 63% yield (Table 1, entry1). The structure of **2a** was confirmed by X-ray crystal analysis. Reaction in the presence of $CuBr_2$ was also examined, and a comparable result was obtained (Table 1, entry 2). To our delight, the addition of $Cu(OAc)_2$ instead of $CuCl_2$ dramatically improved the yield of **2a** up to 86% (Table 1, entry 3). However, CuI was not a suitable catalyst, and no reaction was observed (Table 1, entry 4). Several other oxidants, such as CHP (cumyl hydroperoxide), TBPB (*tert*-butyl peroxybenzoate), DTBP (di-*tert*-butyl peroxide), DCP (dicumyl peroxide), H_2O_2, O_2, and $Na_2S_2O_8$ were subsequently investigated, and they were found to be less effective than TBHP for this reaction (Table 1, entries 5−11). Different bases were also screened. Na_2CO_3 and Cs_2CO_3 were found to be efficient, while *t*-BuOK, Et_3N, and pyridine diminished the efficiency (Table 1, entries 12−16). It is worth noting that the Cu catalyst, TBHP, and K_2CO_3 are indispensable for this tandem process (Table 1, entries 17−19). Furthermore, when the amount of oxidant, base, or the reaction time was reduced, the yield of **2a** was also decreased (Table 1, entries 20−22). When the reaction was carried out for a prolonged time or at elevated temperature, product **2a** was obtained with 84% and 81% yield, respectively (Table 1, entries 23−24).

Having optimized the reaction conditions, we explored the scope of this transformation. First, arylsulfonyl substrates with an electron-donating or electron-withdrawing group at the *para*-position of the aromatic ring that is directly bound to the two nitrogen atoms produced the corresponding cinnolines **2a−2h** in 70−86% yields (Scheme 2). Notably, this reaction

Scheme 2. Scope of Arylsulfonyl Substrates[a]



[a]Reaction conditions: **1** (0.25 mmol), $Cu(OAc)_2$ (5 mol %), TBHP (3 equiv), K_2CO_3 (1 equiv), DCE/CH_3OH (3:1, 4 mL), N_2, 40 °C, 5 h; isolated yield based on **1**. [b]Gram-scale reaction (4.0 mmol **1a**) was performed.

shows complete regioselectivity, as 1,4-aryl migration takes place exclusively through the carbon atom bound to the SO_2 group in the reaction substrates. The bulkier 2-naphthyl-arylsulfonyl group was also well tolerated in this transformation, and cinnoline derivative **2i** was observed with good yield. When the substituent was placed at the *meta*-position of the sulfonyl group, the reaction led to a mixture of regioisomers (4:3 ratio of **2j**:**2j′**) because of the second C−N bond formation occurring at both the *para*- and *ortho*-positions of the chlorine group. Further, the reaction was scaled up to 4.0 mmol for the practical application, giving **2a** in 78% yield (1.06 g).

The influence of the substituted group (R^2) at the alkyne moiety was also explored, and the results are summarized in

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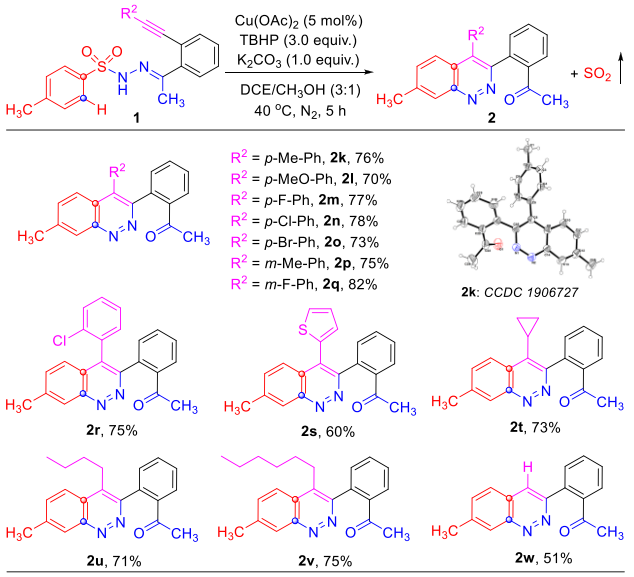
Scheme 3. Aromatic alkynes containing substituents, such as Me, OCH_3, F, Cl, and Br at the *para-*, *meta-*, or *ortho*-position

Scheme 3. Scope of 1 with Substituents at Alkyne Moiety[a]



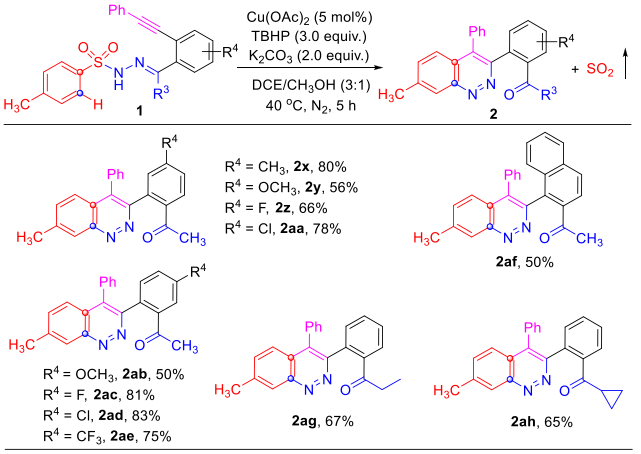
[a]Reaction conditions: **1** (0.25 mmol), $Cu(OAc)_2$ (5 mol %), TBHP (3.0 equiv), K_2CO_3 (1.0 equiv), DCE/CH_3OH (3:1, 4 mL), N_2, 40 °C, 5 h; isolated yield based on **1**.

of the phenyl ring underwent the reaction efficiently to provide the desired cinnoline derivatives (**2k**−**2r**) in 70−82% yields. It should be noted that the Cl and Br substituents on the phenyl ring were well tolerated, which can facilitate further modifications at the halogenated positions. Furthermore, heterocyclic alkynes that are usually sensitive to oxidative conditions, such as 2-thiophene alkyne, was also well tolerated in this protocol and gave cinnoline **2s** in 60% yield. Particularly, cyclopropyl alkyne could also be used in this transformation under the optimized conditions, providing the functionalized product **2t** in 73% yield. Other aliphatic alkynes including *n*-hexyl and *n*-heptyl groups worked well in this domino reaction, affording products **2u** and **2v** in 71% and 75% yield, respectively. However, when a trimethylsilyl substituted alkyne was used as the substrate under the present conditions, the trimethylsilyl group was removed by hydrolysis and gave the product **2w** with 51% yield.

To further investigate the scope of the reaction, the reactivity of different *N*-tosylhydrazones derived from aromatic ketones were explored, as described in Scheme 4. Substituted acetophenones with substituents including Me, OCH_3, F, Cl, and CF_3 could tolerate the catalytic conditions well, generating the corresponding products **2x**−**2ae** in moderate to good yields. Importantly, the method was shown to be useful in the construction of substituted cinnolines containing biologically relevant moieties such as F and CF_3, as in the case of **2z**, **2ac**, and **2ae**.[9] Furthermore, *N*-tosylhydrazone derived from acetylnaphthalene successfully engaged in this radical cyclization cascade, generating the product **2af** in 50% yield. In addition, when R^3 was either an ethyl or cyclopropyl group, the desired cinnolines **2ag** and **2ah** were obtained in 67% yield and 65% yield, respectively.

Finally, to demonstrate the synthetic potential of the procedure, we briefly explored the application of the oxidative

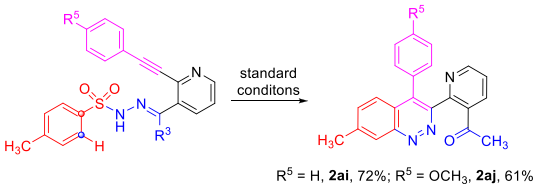
Scheme 4. Scope of 1 with Substituents at Aromatic Ketone Moiety[a]



[a]Reaction conditions: **1** (0.25 mmol), $Cu(OAc)_2$ (5 mol %), TBHP (3 equiv), K_2CO_3 (1 equiv), DCE/CH_3OH (3:1, 4 mL), N_2, 40 °C, 5 h; isolated yield based on **1**.

annulation reaction. It is well-known that cinnolines containing the pyridine motifs are found in the core structures of many bioactive molecules.[6] We thus investigated the synthesis of these compounds by using *N*-tosylhydrazones derived from 3-acetylpyridine as substrates. To our delight, the reactions led to the formation of products **2ai** and **2aj** in 72% and 61% yield, respectively (Scheme 5).

Scheme 5. Synthesis of the Analogues of Bioactive Cinnolines



For understanding the mechanism of tandem reaction, several control experiments were conducted (Scheme 6). First, an isotope labeling experiment was carried out by using TBHP (in decane) and $H_2{}^{18}O$. To our surprise, the ^{16}O-labeled product **2a** was obtained in 80% yield. However, when 2.0 equiv of $Na^{18}OH$ was added, **2a** was isolated in 21% yield, and ^{18}O-labeled **2a** was the major product. These isotopic labeling experiments supported that the oxygen in the products comes from −OH, which was generated from TBHP via a redox reaction (Scheme 6a). Subsequently, a kinetic isotope effect (KIE = 1.2) was observed in the competing intermolecular reaction of **1b** and [D_5]-**1b**. This isotopic effect confirmed that the cleavage of the C(sp^2)−H on the arylsulfonyl group should not be involved in the rate-determining step (Scheme 6b). Furthermore, when **1a** was subjected to the reaction with the addition of 2 equiv of a common free-radical trapping reagent, TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) or BHT (butylhydroxytoluene), the reaction was significantly inhibited, implying that a radical process was involved. In the former reaction, the TEMPO radical adducts (**I** and **IV**), carbocation **II**, and intermediate **III** were detected by HPLC-HRMS analysis (Scheme 6c), suggesting that the reaction might occur

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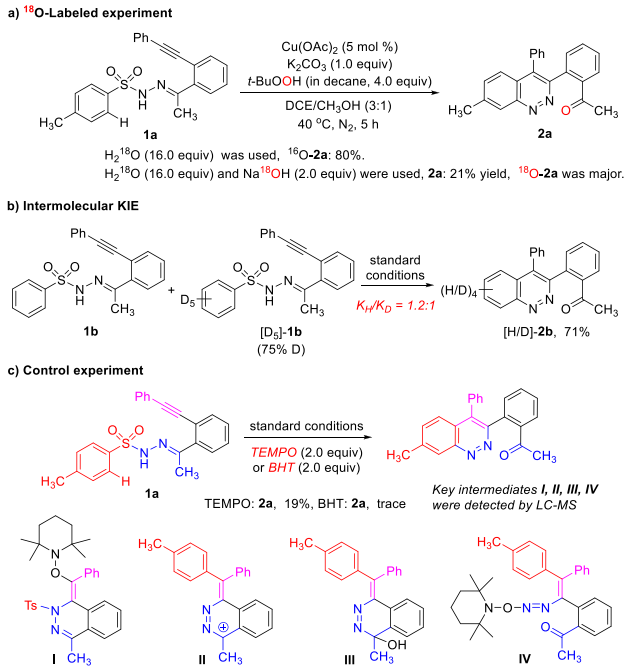
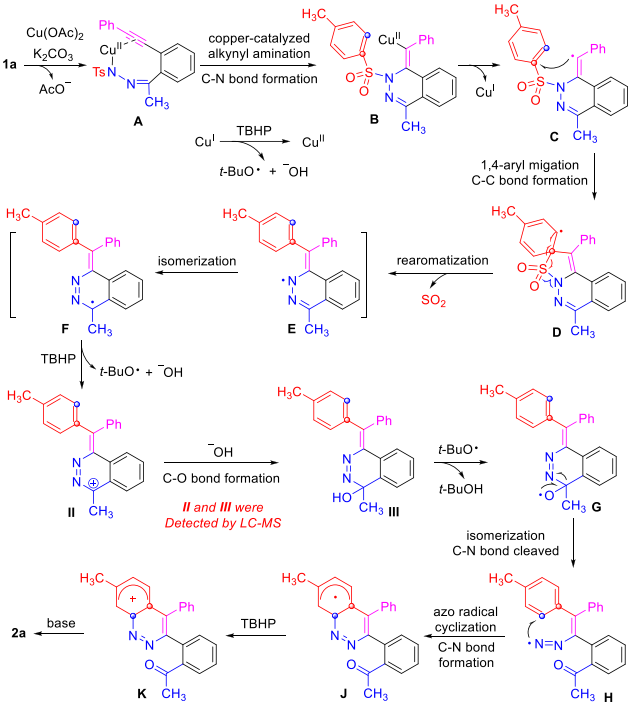
Scheme 6. Mechanistic Studies



through the formation of vinyl and diazo radicals and a carbocation *in situ*. The above results implied that a cascade radical/carbocation cyclization process triggered by the copper-catalyzed alkynyl amination was involved in this transformation.

Based on the control experiments and previous literature,[4,10] a plausible pathway was proposed (Scheme 7). First, the intramolecular aminocupration of **1a** occurred upon alkyne activation by a copper(II) intermediate **A**, which originated from copper catalyst via removal of acetic acid anion, to form

Scheme 7. Proposed Mechanistic Pathway



vinyl-copper complex **B**. Subsequently, the homolysis of complex **B** afforded vinyl radical **C** and copper(I), which could be oxidized to regenerate copper(II) for the next catalytic cycle in the presence of TBHP. A 5-*ipso* cyclization then took place on the sulfonyl aromatic ring, delivering spirocyclic intermediate **D**, which underwent a rapid rearomatization with concomitant desulfonylation to produce the key aminyl radical **E**, constructing the new C−C bond. The generated aminyl nitrogen-centered radical **E** could resonate with *C*-centered radical species **F**, which was oxidized by TBHP to form the benzylic cation **II**. Hydrolysis of cation **II** led to intermediate **III** in the presence of −OH. Subsequently, the oxidation of intermediate **III** by *t*-BuO$^{\bullet}$ onto the OH group afforded *O*-centered radical **G**, and successive N−C bond homolysis furnished diazo radical **H** with a carbonyl group, followed by an intramolecular cyclization with the aromatic ring, delivering aryl radical **J**. Then, **J** was oxidized to generate cationic intermediate **K**, which yielded the final product cinnoline **2a** by the base-assisted deprotonation.

In conclusion, we have developed a highly efficient cascade cyclization reaction of easily available arylsulfonylhydrazones derived from *ortho*-alkynyl arylketones to afford synthetically and medicinally important cinnolines in good yields. In this transformation, a new C(sp^2)−C(sp^2) bond, two C(sp^2)−N bonds, and a new ring are formed in one pot through a copper-catalyzed cascade alkynyl amination/1,4-aryl migration/desulfonylation/cyclization under mild conditions. Mechanistic studies suggest that the key intermediates, including vinyl and diazo radicals, and a carbocation were involved during the reaction. Furthermore, this powerful strategy has been successfully applied to construct analogs of bioactive cinnolines.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03134.

Full experimental details and characterization data for all products (PDF)

Accession Codes

CCDC 1906726−1906727 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

*E-mail: taomiao@chnu.edu.cn
*E-mail: leiwang88@hotmail.com

ORCID

Pinhua Li: 0000-0002-8528-8087
Lei Wang: 0000-0001-6580-7671

Notes

The authors declare no competing financial interest.

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