Organic Letters
Letter
Cite This: *Org. Lett.* XXXX, XXX, XXX−XXX
pubs.acs.org/OrgLett

Synthesis of Amino-Substituted α- and δ-Carbolines via Metal-Free [2 + 2 + 2] Cycloaddition of Functionalized Alkyne-Nitriles with Ynamides

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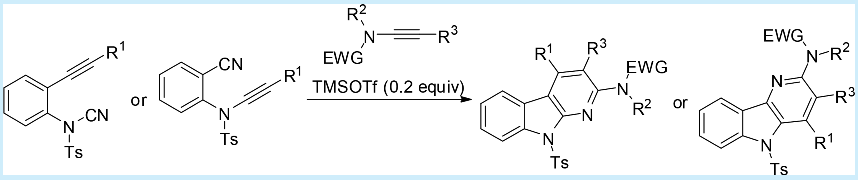
Supporting Information

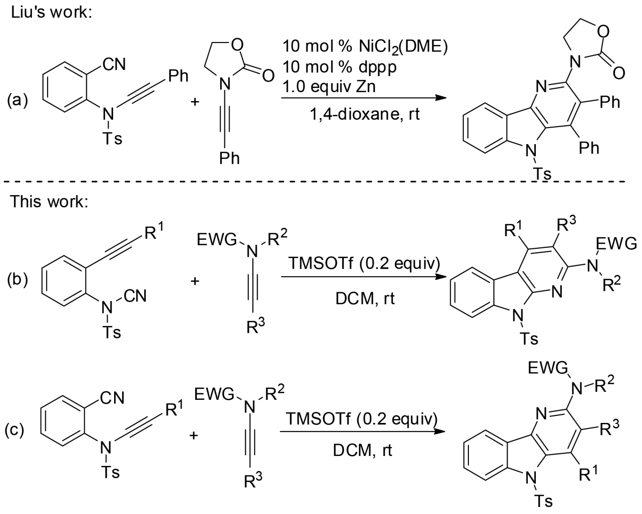


ABSTRACT: A metal-free [2 + 2 + 2] cycloaddition of alkyne-cyanamides or ynamide-nitriles with ynamides is described for the efficient synthesis of amino-substituted α- and δ-carbolines. This novel methodology is environmentally friendly and allows for highly regioselective access to carboline derivatives in good to excellent yields with wide functional group tolerance.

α- and δ-Carbolines (pyridoindoles) are key structural motifs in a diverse array of natural products and pharmaceuticals,[1] and this two-ring system has proven to be a privileged pharmacophore for application in the design of compounds with wide ranging pharmacological properties such as antibacterial, antitumor, anti-inflammatory, anxiolytic, kinase inhibitory, and central nervous system stimulating properties.[2] As important carboline derivatives, amino-substituted α- and δ-carbolines are of particular utility. For instance, amino-substituted α-carbolines have potent cyclin-dependent kinase (CDK) inhibitory and antiproliferative activities;[1a,3] amino-substituted δ-carbolines have been documented to induce and stabilize the G-quadruplex, and consequently inhibit c-MYC promoter and telomerase activity.[4] Although several approaches such as Graebe−Ullmann reaction, Fischer reaction, photochemical cyclization, metal-complex catalyzed annulation or intramolecular cyclization, and intramolecular Diels−Alder reaction have been established for the construction of α- and δ-carbolines,[5,6] and relatively few methods are available for the synthesis of amino-substituted α- and δ-carbolines,[4b,7] these methods usually suffer from serious drawbacks such as harsh reaction conditions, tedious procedures, and low yields. Therefore, exploring efficient methods to synthesize α- and δ-carbolines especially the amino-substituted α- and δ-carbolines is of significant importance.

Although recently rapid development in transition-metal-catalyzed [2 + 2 + 2] cycloaddition offers an attractive approach for the preparation of fused pyridines,[8] the synthetic approaches to α- and δ-carbolines have met with limited success. In 2017, Liu et al. disclosed the first example of Ni(II) phosphine complex-catalyzed [2 + 2 + 2] cycloaddition of alkynes with functionalized alkyne-nitriles to provide α- and δ-carbolines.[9] Among this work, only one amino-substituted δ-carboline was synthesized but with low regioselectivity (Scheme 1a). And for the synthesis of amino-substituted α-carbolines from ynamides, there has been no report about it up to now. Recently, metal-free reactions have attracted attention as environmentally friendly and we have successively

Scheme 1. Synthesis of Amino-Substituted α- and δ-Carbolines by [2 + 2 + 2] Cycloaddition

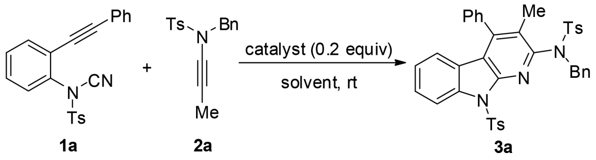


Received: January 3, 2019

developed metal-free strategies to synthesize 2,4-diaminopyridines and 2-aminonaphthalenes via the cycloadditions of ynamides.[10−12] Herein, we present the first example of constructing amino-substituted α-carbolines via TMSOTf-catalyzed [2 + 2 + 2] cycloaddition of alkyne-cyanamides with ynamides (Scheme 1b). Meanwhile, ynamide-nitriles undergo this efficient cycloaddition providing amino-substituted δ-carbolines with high regioselectivities (Scheme 1c).

Our initial investigation was in optimizing the cycloaddition of alkyne-cyanamide **1a** and ynamide **2a** (Table 1).

Table 1. Condition Optimization of the Cycloaddition

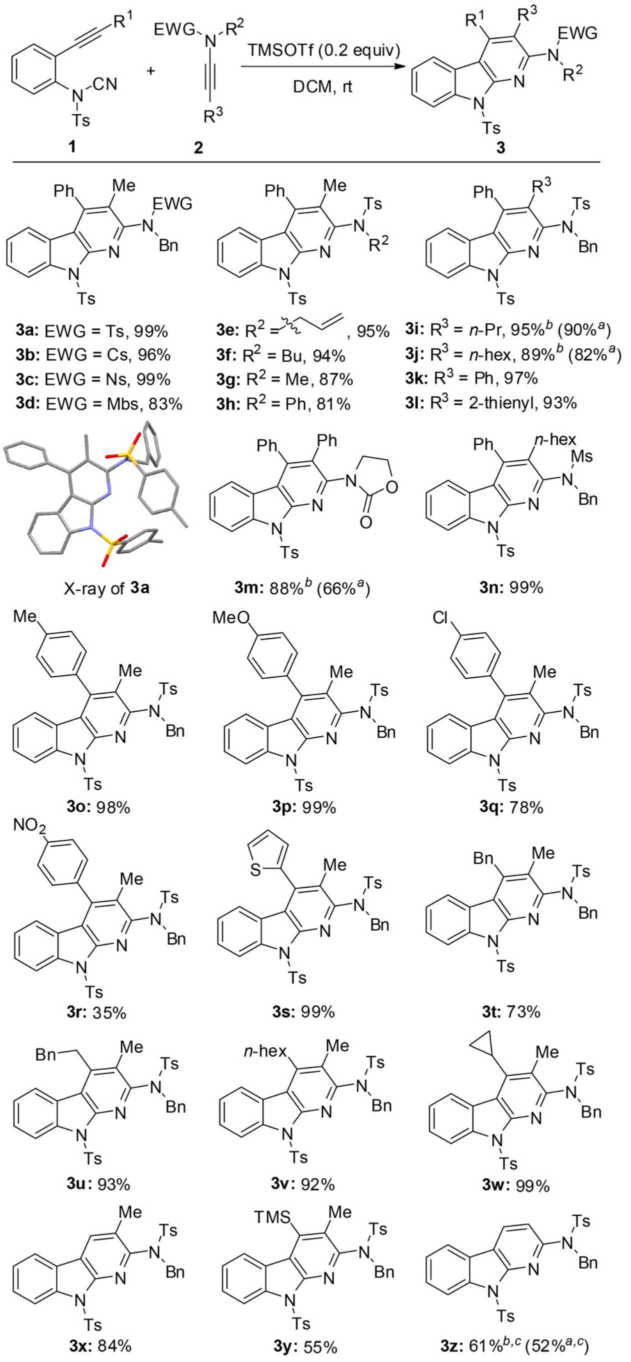


entry[a]	catalyst	solvent	time (h)	yield (%)[b]
1	$BF_3 \cdot Et_2O$	DCM	2.0	86
2	$AlCl_3$	DCM	1.0	88
3	ZnI_2	DCM	24.0	0
4	Tf_2O	DCM	1.0	61
5	TfOMe	DCM	24.0	77
6	TMSOTf	DCM	0.2	99
7	TfOH	DCM	0.2	81
8	TFA	DCM	24.0	0
9	CSA	DCM	24.0	0
10	TMSOTf	DCE	0.2	99
11	TMSOTf	toluene	0.2	38
12	TMSOTf	THF	24.0	0
13	TMSOTf	Et_2O	24.0	12
14[c]	TMSOTf	DCM	0.2	99

[a]Unless otherwise specified, reactions were performed using **1a** (0.20 mmol), **2a** (0.22 mmol), and catalyst (0.04 mmol) in solvent (1.0 mL) at rt. [b]Isolated yields. [c]**1a** (1.00 mmol) and **2a** (1.10 mmol) were added.

Fortunately, we isolated 2-amino-α-carboline **3a** in high yield under the catalysis of $BF_3 \cdot Et_2O$ or $AlCl_3$ (entries 1 and 2). However, bidentate Lewis acid ZnI_2 was a poor promoter appearing to impede the cycloaddition (entry 3). Then nonmetallic Tf_2O, TfOMe, TMSOTf, TfOH, TFA, and CSA were tested. Excitingly, Tf_2O, TfOMe, TMSOTf, and TfOH could also catalyze the reaction to provide cycloadduct **3a**, with TMSOTf leading to the highest yield (entries 4−9). With the optimized catalyst, solvent screening revealed that DCE resulted in a quantitative yield just the same as DCM (entry 10), and other solvents such as toluene, THF, and Et_2O led to decreased yields (entries 11−13).

Scheme 2. Synthesis of 2-Amino-α-carbolines[a]



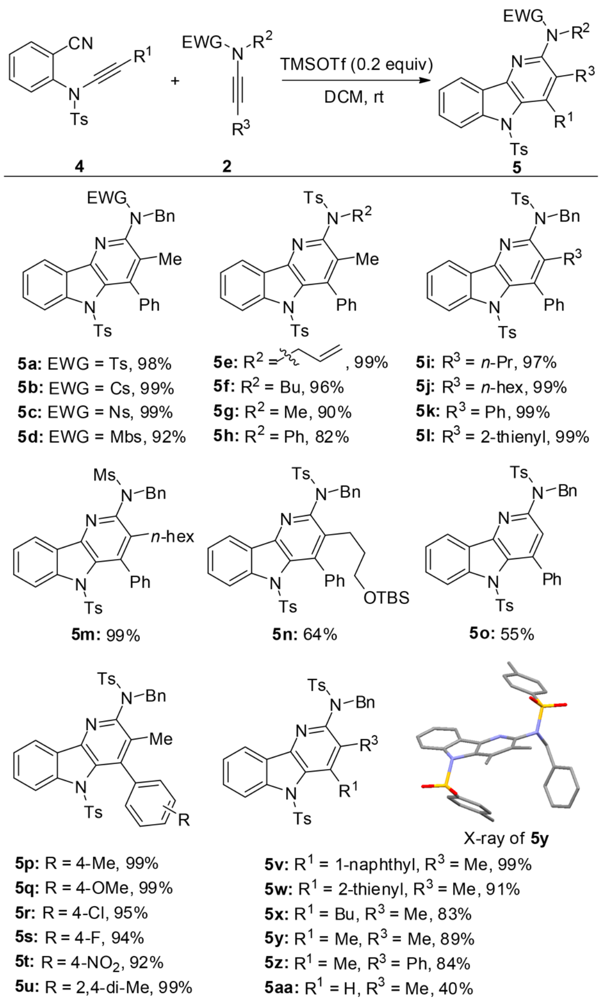
[a]Unless otherwise specified, reactions were performed using **1** (0.20 mmol) and **2** (0.22 mmol) with TMSOTf (0.04 mmol) in DCM (1.0 mL) at rt. [b]Reactions were performed in DCE (1.0 mL) at 100 °C. [c]1.3 equiv of ynamide was used.

With suitable conditions in hand, the scope of this cycloaddition was assessed in Scheme 2. Various ynamides **2a−n** were initially surveyed. For ynamides bearing electron-withdrawing and -donating sulfonyl systems, the reaction proceeded smoothly and furnished the desired 2-amino-α-carbolines **3a−c** with excellent yields. And a slightly lower yield of **3d** was obtained, most likely due to the high chemical reactivity of *N*-Mbs-substituted ynamide **2d** leading to some byproduct from hydrolysis reaction. Next, other *N*-alkenyl-, alkyl-, and aryl-substituted ynamides were perfectly compatible with the reaction conditions giving 2-amino-α-carbolines **3e−h** with high yields, even for the bulkier *N*-phenyl-substituted ynamide. For other alkyl-, aryl-, and thienyl-terminated ynamides, the desired cycloaddition products **3i−l** were obtained in excellent yields. Meanwhile, we found an interesting temperature effect: the alkyl-terminal ynamides **2i** and **2j** resulted in lower yields at room temperauture compared with 100 °C. This loss of yield is caused by the higher temperature improving the reactivity of cycloaddition, thereby suppressing the hydrolysis of ynamides. A similar phenomenon was also observed for the construction of **3m**. We were also excited to find that the highly reactive *N*-Ms-substituted ynamide **2n** underwent highly efficient cycloaddition giving 2-

amino-α-carboline **3n** in almost quantitative yield. Next, various aryl-, alkyl-, and H-terminated alkyne-cyanamides **1** were surveyed, and their reactions with ynamide **2a** generated these corresponding cycloadducts **3o**−**x** with high to excellent yields except **3q**, **3r**, and **3t**. These examples revealed that the lower the reactivity the aryl-terminated alkyne-cyanamides exhibit, the less desirable the cycloadducts become (**3q, r** vs **3o, p**). And for the benzyl-terminated alkyne-cyanamide giving a 73% yield of **3t**, this loss of yield is likely due to the benzyl-terminated alkyne-cyanamide partly transformed into allene. Moreover, TMS-substituted alkyne-cyanamide and terminally unsubstituted ynamide were also amenable to the conditions, giving **3y** and **3z** in moderate yields, respectively. The relative stereochemistry of the 2-amino-α-carbolines was verified by the single-crystal X-ray structure of **3a**.

Next, we turned our attention to extend the above method for the construction of amino-substituted δ-carbolines using ynamide-nitriles **4** (Scheme 3). Although there has been only one example reported about the construction of amino-substituted δ-carboline via [2 + 2 + 2] cycloaddition of ynamide-nitrile with ynamide catalyzed by nickel, it suffers from poor regioselectivity.[9] To our delight, under the above optimal conditions of synthesizing 2-amino-α-carbolines **3**, most of the desired 3-amino-δ-carbolines **5** were formed in high to excellent yields. Variations of the substituents on the nitrogen atom or on the terminal of the starting ynamides **2** were initially investigated, the cycloaddition proceeded smoothly leading to the desired products **5a**−**5m** in high to excellent yields. And even more surprisingly, this cycloaddition was amenable to the formations of 3-amino-δ-carbolines **5n** and **5o** using ynamide bearing a terminal TBS ether moiety and terminally unsubstituted ynamide, respectively. Subsequently, various ynamide-nitriles **4** with aryl or alkyl substituents were tested and proceeded smoothly with ynamides **2**, providing high to excellent yields of 3-amino-δ-carbolines **5p**−**5z**. Remarkably, compared with alkyl-terminated ynamide-nitriles, aryl-terminated ynamide-nitriles afforded 3-amino-δ-carbolines with higher yields. To our delight, the terminally unsubstituted ynamide-nitrile was also compatible with the reaction conditions delivering 3-amino-δ-carboline **5aa** in 40% yield. And we were also excited to find that, in the absence of ynamide **2**, the [2 + 2 + 2] cycloaddition of two discrete ynamide-nitriles **4** could also afford the corresponding 3-amino-δ-carbolines **5cc** and **5dd** with moderate yields, respectively (Scheme 4). The structure of 3-amino-δ-carbolines was confirmed by the X-ray crystallographic analysis of **5y**.

Scheme 3. Synthesis of 3-Amino-δ-carbolines[a]



5a: EWG = Ts, 98%
5b: EWG = Cs, 99%
5c: EWG = Ns, 99%
5d: EWG = Mbs, 92%

5e: R^2 = (allyl), 99%
5f: R^2 = Bu, 96%
5g: R^2 = Me, 90%
5h: R^2 = Ph, 82%

5i: R^3 = *n*-Pr, 97%
5j: R^3 = *n*-hex, 99%
5k: R^3 = Ph, 99%
5l: R^3 = 2-thienyl, 99%

5m: 99%

5n: 64%

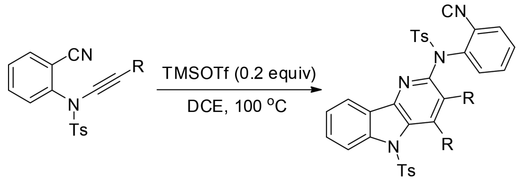
5o: 55%

5p: R = 4-Me, 99%
5q: R = 4-OMe, 99%
5r: R = 4-Cl, 95%
5s: R = 4-F, 94%
5t: R = 4-NO_2, 92%
5u: R = 2,4-di-Me, 99%

5v: R^1 = 1-naphthyl, R^3 = Me, 99%
5w: R^1 = 2-thienyl, R^3 = Me, 91%
5x: R^1 = Bu, R^3 = Me, 83%
5y: R^1 = Me, R^3 = Me, 89%
5z: R^1 = Me, R^3 = Ph, 84%
5aa: R^1 = H, R^3 = Me, 40%

[a] Unless otherwise specified, reactions were performed using **4** (0.20 mmol), and **2** (0.22 mmol), and TMSOTf (0.04 mmol) in DCM (1.0 mL) at rt, Mbs = *para*-methoxy-benzene-sulfonyl; Cs = *para*-chloro-benzene-sulfonyl; Ns = *para*-nitro-benzene-sulfonyl.

Scheme 4. [2 + 2 + 2] Cycloaddition of Two Discrete Ynamide-Nitriles



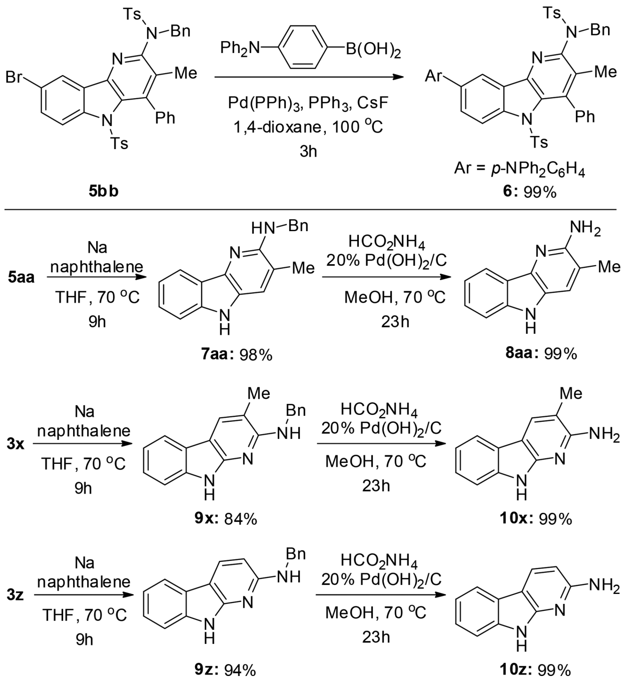
4k: R = Me
4j: R = Bu

5cc: 62%
5dd: 56%

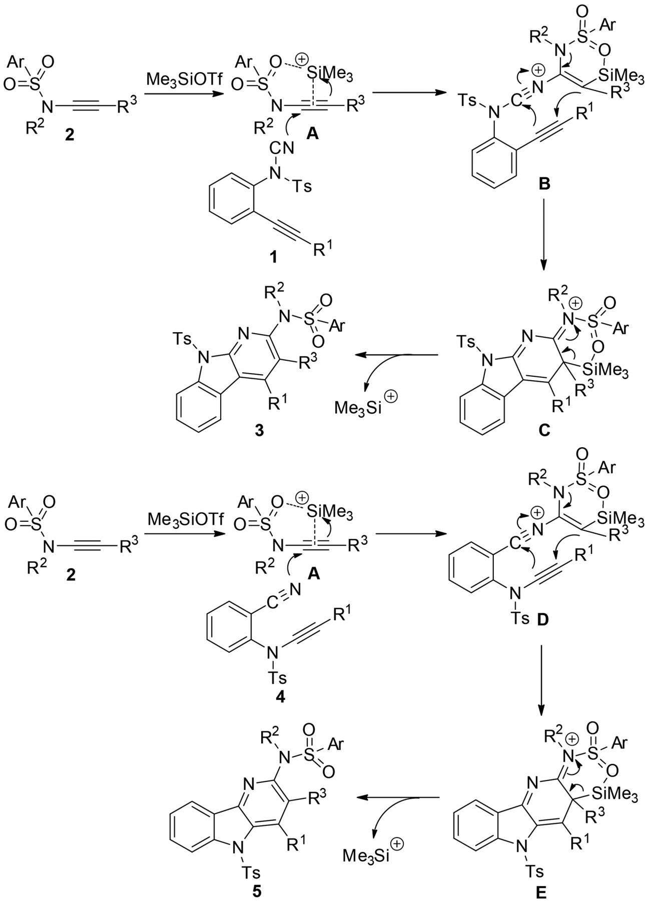
Further transformations of the as-synthesized amino-substituted carbolines were explored (Scheme 5). For example, 6-bromo-δ-carboline **5bb**, which was afforded in 94% yield from the bromo-substituted ynamide-nitrile, was subsequently modified via palladium-catalyzed Suzuki−Miyaura coupling reaction to provide more complex 3-amino-δ-carboline **6** in quantitative yield.[13] In addition, deprotection of **5aa**, **3x**, and **3z** could respectively afford benzylamino-δ-carboline **7aa** and benzylamino-α-carbolines **9x** and **9z**,[14] which have potent cyclin-dependent kinase inhibitory activities. Then **7aa**, **9x**, and **9z** could be respectively transformed into their corresponding free amines **8aa**, AαC **10x**, and MeAαC **10z**,[15] which were isolated from pyrolysates of protein and tryptophan as a result of extensive research on environmental mutagens and carcinogens.[16]

Having uncovered these novel cycloadditions, we were intrigued by their mechanisms. Based on our previous work,[10a] postulated mechanisms leading to the formations of 2-amino-α-carboline **3** and 3-amino-δ-carboline **5** are proposed as shown in Scheme 6.[17] The cycloaddition would be initiated by the coordination of TMSOTf to ynamide **2** to generate silicon π-alkyne species **A**. And then the nucleophilic addition of the species **A** with the nitrile moiety on **1** or **4** gives nitrilium species **B** or **D**. Subsequently, an intramolecular cyclization of

Scheme 5. Chemical Transformations of 2-Amino-α-carbolines and 3-Amino-δ-carbolines



Scheme 6. Proposed Mechanisms for the Cycloadditions



B via the intermediate C affords 2-amino-α-carboline **3**. Similarly, intermediate **D** undergoes the intramolecular cyclization via the intermediate **E** to furnish the desired 3-amino-δ-carboline **5**.

In conclusion, we have presented here a novel and highly efficient TMSOTf-catalyzed [2 + 2 + 2] cycloaddition of alkyne-cyanamides or ynamide-nitriles with ynamides. This strategy provides a straightforward way to furnish 2-amino-α-carbolines and 3-amino-δ-carbolines in high to excellent yields with wide diversity and functional group tolerance. More importantly, this method first realized the synthesis of 2-amino-α-carbolines via cycloaddition of alkyne-cyanamides with ynamides and enables the preparation of 3-amino-δ-carbolines with excellent selectivities. Plausible mechanisms of the cycloaddition have been proposed. Further applications of this newly developed metal-free strategy are under current study in our group.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00021.

Detailed experimental procedures and characterization data for the new compounds (PDF)
^{1}H and ^{13}C NMR spectra (PDF)

Accession Codes

CCDC 1877117–1877119 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.

■ ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (Nos. 81803406 and U1804283), the China Postdoctoral Science Foundation (Nos. 2016T90672 and 2015M570631), the Foundation of Henan Educational Committee (19A150009), and the Outstanding Young Talent Research Fund of Zhengzhou University (No. 1621331003) for financial support.

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DOI: 10.1021/acs.orglett.9b00021
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