OL | Organic Letters

Letter

Cite This: Org. Lett. XXXX, XXX, XXX–XXX

pubs.acs.org/OrgLett

Palladium-Catalyzed Cascade Reaction of *o*-Cyanobiaryls with Arylboronic Acids: Synthesis of 5-Arylidene-7-aryl-5*H*-dibenzo[*c*,*e*]azepines

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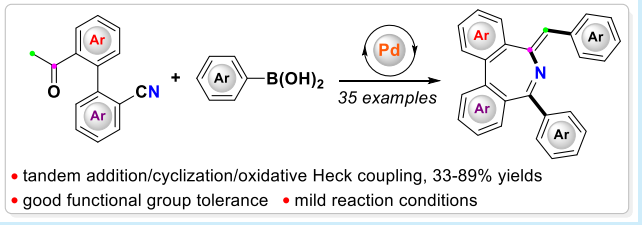
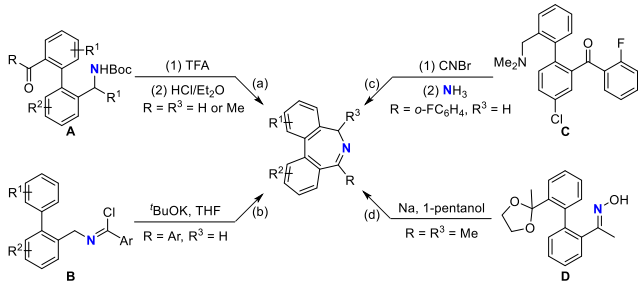
Supporting Information

ABSTRACT: A palladium-catalyzed cascade reaction of 2′-acetyl-[1,1′-biphenyl]-2-carbonitriles with arylboronic acids is developed. This reaction affords a new class of seven-membered 5-arylidene-7-aryl-5*H*-dibenzo[*c*,*e*]azepines with good functional group compatibility and selectivity. Reaction mechanistic study suggests that this transformation involves carbopalladation of nitrile and subsequent intramolecular cyclization followed by oxidative Heck coupling.



Dibenz[*c*,*e*]azepines are among the most important seven-membered N-heterocycles with a biphenyl skeleton and have received great attention because of their pharmacological properties[1] and promising applications in organic synthesis.[2] As shown in Scheme 1, Turner[3] and Zhang[4] independently described intramolecular cyclization of Boc-protected aryl-bridged aminoketones **A** to afford dibenz[*c*,*e*]azepines (Scheme 1a). Sharp[5] reported that dibenz[*c*,*e*]azepines were generated from aryl-bridged imidoyl chlorides **B** via intramolecular cyclization of nitrile ylides (Scheme 1b). Gschwend and Boyer reported the synthesis of 9-chloro-7-(*o*-fluorophenyl)-5*H*-dibenz[*c*,*e*]azepine by treatment of the substrate **C** with a volatile and highly toxic CNBr and subsequent cyclization in the presence of ethanolic ammonia (Scheme 1c).[6] Blum reported tandem reduction/intramolecular cyclization of the substrate D with sodium in the boiling solution of 1-pentanol.[7] In 2014, Maestri and Malacria developed a palladium-/norbornene-catalyzed three-component reaction of aryl iodide and bromobenzylamine with olefin to provide a new strategy for the synthesis of dibenzo[*c*,*e*]azepines.[8]

Scheme 1. Synthesis of Dibenzo[*c*,*e*]azepine Derivatives



The formation of a seven-membered dibenz[*c*,*e*]azepine framework has been rarely reported to date, possibly due to its unfavorable transannular interactions.[9] Thus, the development of a novel transformation for the synthesis of substituted dibenz[*c*,*e*]azepines has been one of the prime targets in organic synthesis.

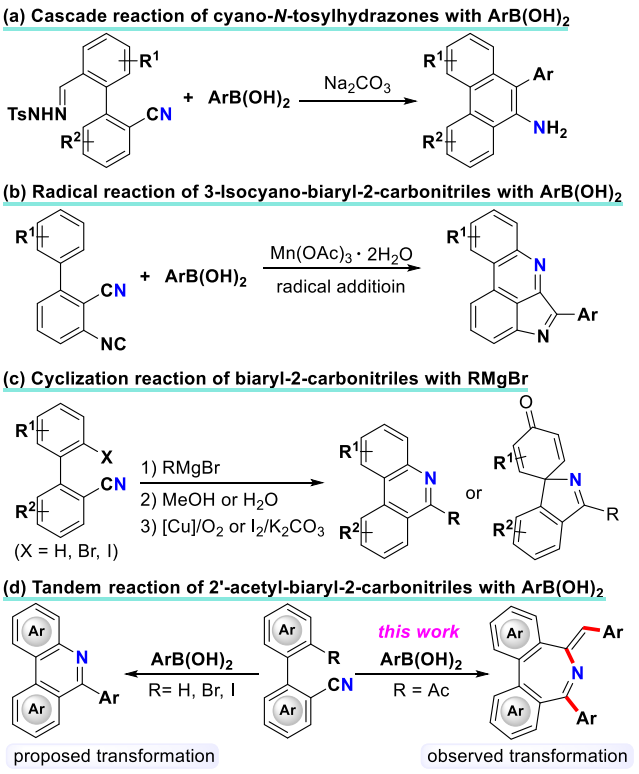
Recently, treatment of *o*-cyanobiaryl derivatives with arylboronic acids (or Grignard reagents/organic lithiums) has received much attention. The Liu group reported reaction of 2′-cyano-biaryl-2-aldehyde derivatives with arylboronic acids for the preparation of functionalized 9-amino-10-arylphenanthrenes (Scheme 2a).[10] Ji and Wang developed manganese-mediated cascade cyclization of isocyano-substituted *o*-cyanobiaryl derivatives with arylboronic acids via a radical pathway for the synthesis of pyrrolopyridines (Scheme 2b).[11] As shown in Scheme 3c,[12] reaction of biaryl-2-carbonitriles with Grignard reagents under different reaction conditions afforded phenanthridine derivatives and azaspirocyclohexadienone derivatives.

Inspired by the above-mentioned results and our studies of transformation of nitriles,[13] we envisioned that Pd-catalyzed addition of arylboronic acids to [1,1′-biphenyl]-2-carbonitriles and sequential intramolecular cyclization would provide a new method for the tandem synthesis of phenanthridines (Scheme 1d, proposed transformation). To our surprise, this reaction failed to give the anticipated six-membered N-heterocycle phenanthridines. Instead, we observed unexpected seven-membered ring products dibenzo[*c*,*e*]azepines (Scheme 1d, observed transformation). Despite the remarkable success of five- and six-membered N-heterocycles by transition-metal-catalyzed reaction of organoborons with nitriles, the construction of seven-membered N-heterocycles remains underdeveloped. Herein, we report the unexpected discovery of this novel procedure that combines three sequential nucleophilic additions, intramolecular cyclization, and oxidative Heck coupling in one pot to afford a new class of diverse

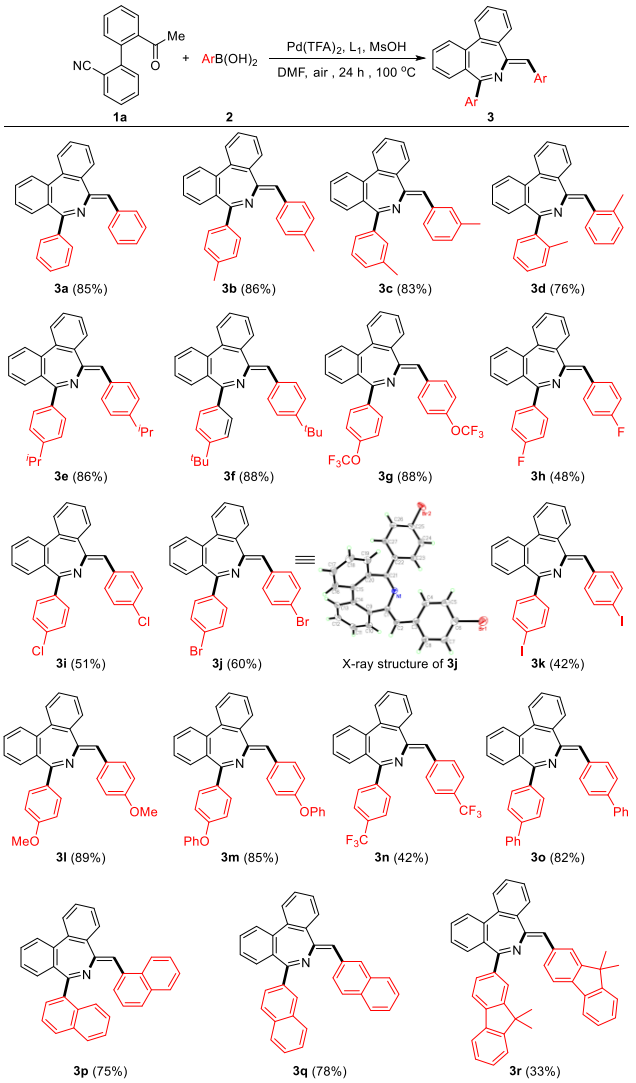
Received: July 8, 2019

DOI: 10.1021/acs.orglett.9b02351
Org. Lett. XXXX, XXX, XXX–XXX

Scheme 2. Reactions of *o*-Cyanobiaryls with $ArB(OH)_2$ or RMgBr/RLi



Scheme 3. Substrate Scope for Arylboronic Acids[a]



[a]Conditions: **1a** (0.2 mmol), **2** (0.6 mmol), $Pd(TFA)_2$ (6 mol %), L_1 (12 mol %), MsOH (2 mmol), DMF (2 mL), air, 100 °C, 24 h. Isolated yield.

seven-membered 5-benzylidene dibenzo[*c*,*e*]azepines that were often difficult to access by classical routes. DFT calculations were also conducted to explain the experimentally observed transformation.

We begin our investigation with readily available 2′-acetyl-[1,1′-biphenyl]-2-carbonitrile (**1a**) and phenylboronic acid (**2a**) for the optimization of reaction conditions (Table 1). Initially, various solvents including 2-methyltetrahydrofuran (2-MeTHF), toluene, DMSO, dioxane, THF, and DMF were examined (entries 1−6). We found that a trace amount of unexpected seven-membered product (*Z*)-5-benzylidene-7-phenyl-5*H*-dibenzo[*c*,*e*]azepine (**3a**) was detected by GC-MS analysis accompanied by a trace quantity of addition/hydrolysis byproduct 1-(2′-benzoyl-[1,1′-biphenyl]-2-yl)-ethan-1-one (**3aa**) in 2-MeTHF (entry 1). In the presence of $Pd(CF_3CO_2)_2$, 2,2′-bipyridine (L_1), and trifluoroacetic acid, the reaction afforded **3a** in 42% yield in DMF (entry 6). Other palladium catalysts, such as $Pd(OAc)_2$, $Pd(acac)_2$, and $Pd_2(dba)_3$, gave **3a** in 28%, 26%, and 38% yields, respectively (entries 7−9). $Pd(PPh_3)_4$ as a representative Pd(0) catalyst failed to afford any products (entry 10). An examination of various bidentate N-donor ligands revealed that 4,4′-di-*tert*-butyl-2,2′-bipyridine (L_2) and 1,10-phenanthroline (L_3) efficiently provided **3a** in 39−40% yields (entries 11 and 12). However, ligands including 6,6′-dimethyl-2,2′-bipyridine (L_4), 2,9-dimethyl-1,10-phenanthroline (L_5), and 2,2′-biquinoline (L_6) resulted in a trace amount of **3a**, presumably due to the enhanced steric hindrance (entries 13−15). A variety of additives including acetic acid, *p*-toluene sulfonic acid (TsOH), *p*-nitrobenzenesulfonic acid (PNSA), trifluoromethanesulfonic acid (TfOH), D-camphorsulfonic acid (CSA), and methanesulfonic acid (MsOH) were evaluated, and MsOH was found to be the best one, affording **3a** in 61% yield. In addition, slightly increasing the temperature to 100 °C improved the yield to 78% (entry 21). The reaction failed to give **3a** when HCl was used as an additive (entry 22). Increasing the amount of **2a** to 3 equiv, the yield of **3a** could be improved to 85% yield (entry 23).

We next examined the substrate scope for arylboronic acids (Scheme 3). Treatment of **1a** with *p*- and *m*-tolylboronic acid delivered **3b** and **3c** in 86% and 83% yields, respectively, while *o*-tolylboronic acid gave the corresponding **3d** in 76% yield. Moderately electron-rich substituents, such as ^{i}Pr (**3e**), ^{t}Bu (**3f**), and OCF_3 (**3g**), were well-tolerated, achieving 86−88% yields. Moderately electron-deficient halogens, such as F (**3h**), Cl (**3i**), Br (**3j**), and I (**3k**), were also compatible with this protocol, although slightly lower yields were observed. Of note, the halogens in the products (**3h**−**3k**) could be amenable to further synthetic transformations. The structure of **3j** was identified by X-ray diffraction. The strongly electron-donating groups (e.g., OMe and OPh) at the *para* position do not retard the reaction to give **3l** and **3m** in 89% and 85% yields, respectively, while the substrate with the *p*-trifluoromethyl

DOI: 10.1021/acs.orglett.9b02351
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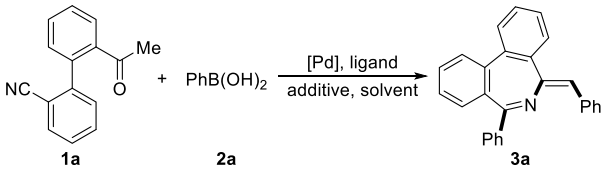
Table 1. Optimization of Reaction Conditions[a]



1a 2a 3a

entry	Pd catalyst	ligand	solvent	additive	yield[b] (%)
1	$Pd(CF_3CO_2)_2$	L_1	2-MeTHF	CF_3CO_2H	trace
2	$Pd(CF_3CO_2)_2$	L_1	toluene	CF_3CO_2H	11
3	$Pd(CF_3CO_2)_2$	L_1	DMSO	CF_3CO_2H	13
4	$Pd(CF_3CO_2)_2$	L_1	dioxane	CF_3CO_2H	21
5	$Pd(CF_3CO_2)_2$	L_1	THE	CF_3CO_2H	27
6	$Pd(CF_3CO_2)_2$	L_1	DMF	CF_3CO_2H	42
7	$Pd(OAc)_2$	L_1	DMF	CF_3CO_2H	28
8	$Pd(acac)_2$	L_1	DMF	CF_3CO_2H	26
9	$Pd_2(dba)_3$	L_1	DMF	CF_3CO_2H	38
10	$Pd(PPh_3)_4$	L_1	DMF	CF_3CO_2H	0
11	$Pd(CF_3CO_2)_2$	L_2	DMF	CF_3CO_2H	39
12	$Pd(CF_3CO_2)_2$	L_3	DMF	CF_3CO_2H	40
13	$Pd(CF_3CO_2)_2$	L_4	DMF	CF_3CO_2H	trace
14	$Pd(CF_3CO_2)_2$	L_5	DMF	CF_3CO_2H	trace
15	$Pd(CF_3CO_2)_2$	L_6	DMF	CF_3CO_2H	trace
16	$Pd(CF_3CO_2)_2$	L_1	DMF	CH_3CO_2H	15
17	$Pd(CF_3CO_2)_2$	L_1	DMF	TsOH H_2O	39
18	$Pd(CF_3CO_2)_2$	L_1	DMF	PNSA	32
19	$Pd(CF_3CO_2)_2$	L_1	DMF	TfOH	51
20	$Pd(CF_3CO_2)_2$	L_1	DMF	CSA	49
21	$Pd(CF_3CO_2)_2$	L_1	DMF	MsOH	61 (78[c])
22[c]	$Pd(CF_3CO_2)_2$	L_1	DMF	HCl	0
23[c]	$Pd(CF_3CO_2)_2$	L_1	DMF	MsOH	85[d]

[a]Conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), Pd catalyst (6 mol %), ligand (12 mol %), additive (2 mmol), solvent (2 mL), 80 °C, 24 h, air. [b]Isolated yield. [c]At 100 °C. [d]**2a** (0.6 mmol).

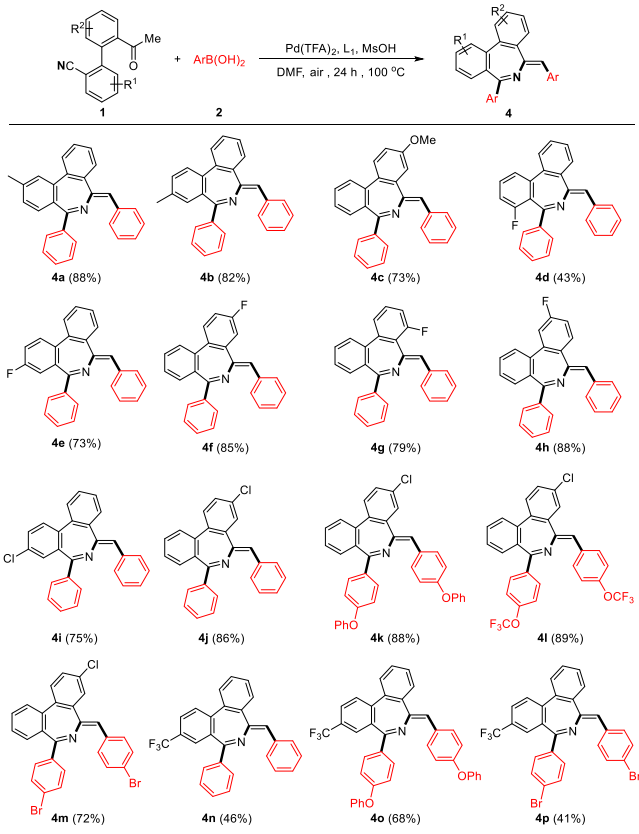
group decreased the yield to 42% (**3n**). These transformations were efficient with polycyclic substrates (e.g., biphenyl and naphthyl), providing the desired products **3o**−**3q** in 75−82% yields. Notably, the substrate (9,9-dimethyl-9*H*-fluoren-2-yl)boronic acid was also successfully reacted, albeit in slightly lower yields (**3r**).

As shown in Scheme 4, a variety of *o*-cyanobiaryl substrates are compatible with this transformation. Electron-rich groups (e.g., Me, OMe) and electron-deficient groups (e.g., F, Cl, CF_3) were all tolerated in this transformation. It is also practically important that the phenyl nitrile moiety with an *ortho*-substituent and the desired product **4d** were obtained in 43% yield, which indicates that the steric hindrance around the cyano group prevents nucleophilic addition. Pleasingly, treatment of 2-(2-acetylthiophen-3-yl)benzonitrile, a representative thienyl-containing substrate, with *o*-tolylboronic acid delivered **4q** in 83% yield (Scheme 5).

To showcase the potential synthetic applications of the as-synthesized 5-arylidene-7-aryl-5*H*-dibenzo[*c*,*e*]azepines, we performed Heck coupling reaction of **3a** with bromobenzene to deliver the corresponding product **5a** in 61% yield (Scheme 6a). In the presence of 3-chloroperoxybenzoic acid (*m*-CPBA), **3a** was oxidized to give 7-phenyl-5*H*-dibenzo[*c*,*e*]azepin-5-one (**6a**) in 94% yield (Scheme 6b).

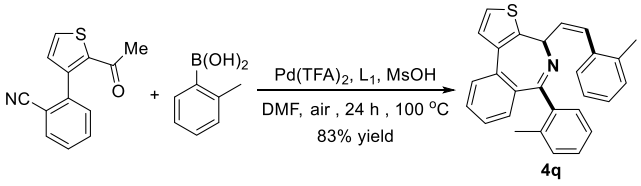
In addition, several control experiments were examined under the standard conditions (Scheme 7). The reaction of phenylboronic acid with styrenes (e.g., styrene, 1-chloro-4-

Scheme 4. Substrate Scope for *o*-Cyanobiaryls[a]

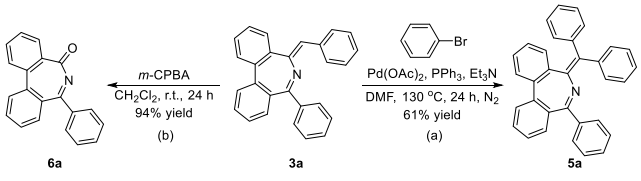


[a]Conditions: **1** (0.2 mmol), **2** (0.6 mmol), $Pd(TFA)_2$ (6 mol %), L_1 (12 mol %), MsOH (2 mmol), and DMF (2 mL), air, 100 °C, 24 h. Isolated yield.

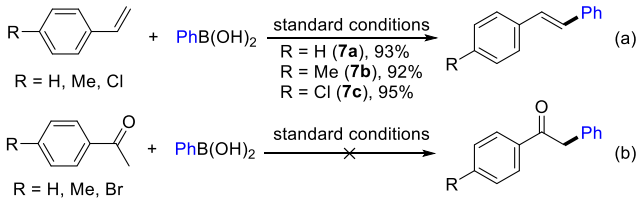
Scheme 5. Synthesis of 6-Aryl-4-styryl-4*H*-benzo[*c*]thieno[3,2-*e*]azepines



Scheme 6. Synthetic Applications



Scheme 7. Control Experiments



DOI: 10.1021/acs.orglett.9b02351
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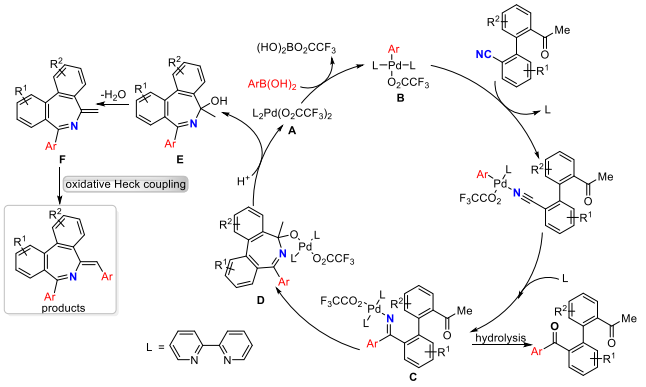
vinylbenzene, 1-methyl-4-vinylbenzene) was conducted to deliver oxidative Heck coupling products in good yield (Scheme 7a). Our initial attempts to treat acetophenones (e.g., acetophenone, 1-(4-chlorophenyl)ethan-1-one, 1-(4-methylphenyl)ethan-1-one) with phenylboronic acid did not work (Scheme 7b).

A possible mechanism for the formation of 5-arylidene-7-aryl-5*H*-dibenzo[*c*,*e*]azepines via Pd-catalyzed tandem addition/cyclization/oxidative Heck coupling reaction is shown in Scheme 8. It involves the following key steps: (i) trans-

Scheme 8. Proposed Mechanistic Pathway



metalation between Pd(II) catalyst **A** and $ArB(OH)_2$, which affords arylpalladium species **B**; (ii) coordination of 2′-acetyl-[1,1′-biphenyl]-2-carbonitriles to the Pd; (iii) carbopalladation of the cyano group to give the imine−Pd intermediate **C**; (iv) intramolecular cyclization of **C** to deliver palladium complex **D**; and (v) protonation of **D** in the presence of MsOH, which generates 5-methyl-7-aryl-5*H*-dibenzo[*c*,*e*]azepin-5-ol (**E**) and regenerates the palladium catalyst. Dehydration of **E** leads to the 5-methylene-7-aryl-5*H*-dibenzo[*c*,*e*]azepine, which was followed by oxidative Heck coupling reaction to give the corresponding 5-arylidene-7-aryl-5*H*-dibenzo[*c*,*e*]azepines as the products. The proposed mechanistic rationale for this tandem process is supported by theoretical calculations (Figure S1, see SI for details).

In summary, we have developed palladium-catalyzed tandem addition/cyclization/oxidative Heck coupling of 2′-acetyl-[1,1′-biphenyl]-2-carbonitriles with arylboronic acids, which affords a new class of seven-membered 5-arylidene-7-aryl-5*H*-dibenzo[*c*,*e*]azepines that were often difficult to prepare using existing methods.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02351.

Experimental procedures, characterization data, NMR spectra, and X-ray data for product **3j** (PDF)

Accession Codes

CCDC 1888668 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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†X.Y. and Y.S. contributed equally to this work

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (No. 21572162) and the Natural Science Foundation of Zhejiang Province (Nos. LY16B020012 and LQ18B020006) for financial support.

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DOI: 10.1021/acs.orglett.9b02351
Org. Lett. XXXX, XXX, XXX−XXX