OL | Organic Letters

Letter

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

pubs.acs.org/OrgLett

Palladium-Catalyzed Cascade Reactions of 2-(Cyanomethoxy)chalcones with Arylboronic Acids: Selective Synthesis of Emissive Benzofuro[2,3-*c*]pyridines

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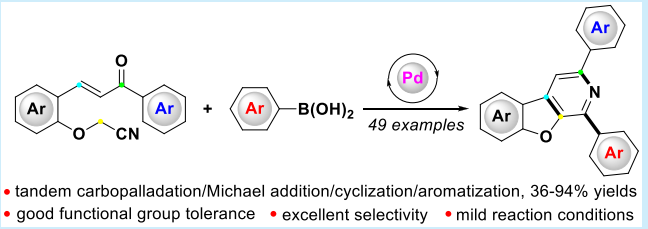
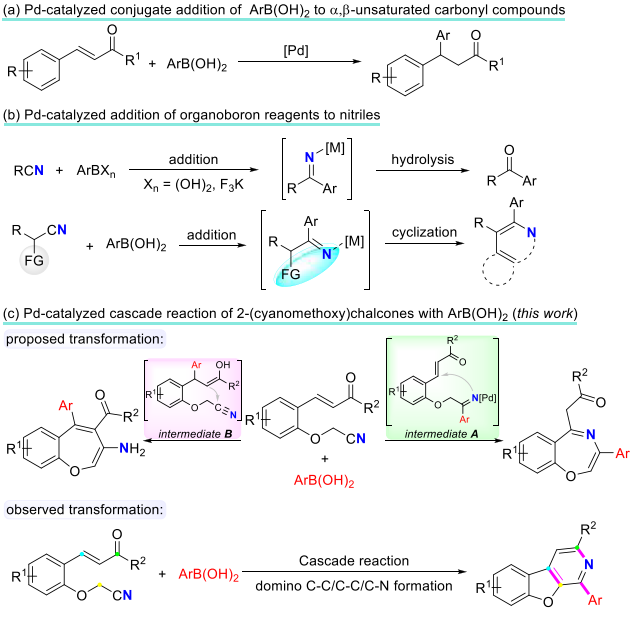
Supporting Information

ABSTRACT: The Pd(II)-catalyzed cascade reactions of 2-(cyanomethoxy)chalcones with arylboronic acids were demonstrated, allowing the rapid construction of benzofuro[2,3-*c*]pyridine skeletons with excellent selectivity. These transformations involve the domino-style formation of C−C/C−C/C−N bonds through nitrile carbopalladation, intramolecular Michael addition, cyclization, and aromatization. This chemistry allows for the reactions of 2-(cyanomethoxy)-chalcones with thiophen-3-ylboronic acid, providing 3-aryl-1-(thiophen-3-yl)benzofuro[2,3-*c*]pyridines in moderate to good yields. In addition, the resulting products represent a new class of emissive fluorophores.



The development of new transformations to generate high value-added synthetic or medicinal products from readily available starting materials via selective, one-pot domino-style bond formations is a significant research goal.[1] The transition-metal-catalyzed conjugate addition of arylboronic acids to *α,β*-unsaturated carbonyl compounds is emerging as a very powerful means of accessing a large family of *β*-aryl substituted carbonyl molecules.[2] Among the reported methods, the well-established palladium-catalyzed conjugate addition of arylboronic acids to *α,β*-unsaturated carbonyl compounds (Scheme 1a)[3] and the associated mechanism[4] have attracted significant attention over the past several decades. In addition, there has recently been remarkable progress in the palladium-catalyzed addition of arylboronic acids to nitriles for the synthesis of hydrolyzed ketones or further cyclization products.[5] This has evoked a new series of explorations concerning the carbopalladation of nitriles, with the potential to synthesize structurally diverse five- or six-membered *N*-heterocycles, as demonstrated by our own group[6] and others[7] (Scheme 1b). Very recently, our group reported the palladium-catalyzed cascade reactions of 2′-acetyl-[1,1′-biphenyl]-2-carbonitriles with arylboronic acids for the synthesis of seven-membered 5*H*-dibenzo[*c,e*]azepines.[8] However, the selective reaction of cyano-substituted chalcones with arylboronic acids is still a significant challenge, because the carbopalladation of nitriles competes with the conjugate addition of arylboronic acids to *α,β*-unsaturated carbonyl compounds. We envisioned that it might be possible to obtain seven-membered benzo[*f*][1,4]-oxazepines[9] via intermediate **A** (Scheme 1c, right) or benzo[*b*]oxepin-3-amines[10] through intermediate **B** (Scheme 1c, left), on the basis of two possible reaction pathways.

Scheme 1. Reactions Associated with this Study



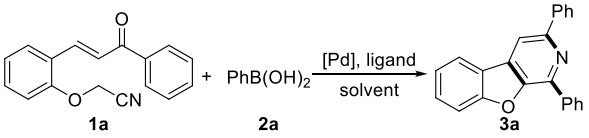
Received: November 22, 2019

DOI: 10.1021/acs.orglett.9b04185
Org. Lett. XXXX, XXX, XXX−XXX

Surprisingly, fused tricyclic benzofuro[2,3-*c*]pyridines were obtained from this process. Herein, we report the discovery of this novel transformation, involving the sequential carbopalladation reaction of the nitrile, an intramolecular Michael addition, cyclization, and aromatization. This mechanism proceeds via the one-pot domino-style formation of C−C/C−C/C−N bonds with excellent selectivity to provide benzofuro[2,3-*c*]pyridines that are often difficult to prepare by traditional routes.[11]

We began by screening the reaction conditions using the readily available reagents 2-(cyanomethoxy)chalcone (**1a**) and phenylboronic acid (**2a**) to determine optimal conditions (Table 1). The desired product **3a** was isolated in 12% yield in

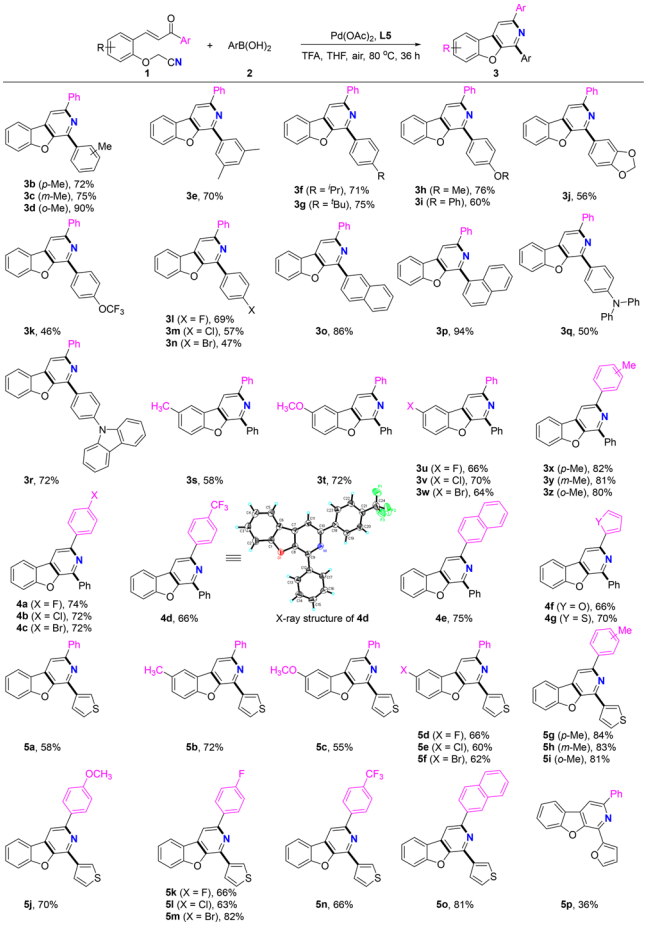
Table 1. Reaction Optimization[a]



entry	Pd catalyst	ligand	solvent	yield (%)[b]
1	$Pd(TFA)_2$	**L1**	2-MeTHF	12
2	$Pd(acac)_2$	**L1**	2-MeTHF	21
3	$Pd(OAc)_2$	**L1**	2-MeTHF	29
4	$Pd(OAc)_2$	**L2**	2-MeTHF	24
5	$Pd(OAc)_2$	**L3**	2-MeTHF	21
6	$Pd(OAc)_2$	**L4**	2-MeTHF	25
7	$Pd(OAc)_2$	**L5**	2-MeTHF	47
8	$Pd(OAc)_2$	**L5**	DMA	21
9	$Pd(OAc)_2$	**L5**	dioxane	37
10	$Pd(OAc)_2$	**L5**	THF	68
11	$Pd(OAc)_2$	**L5**	THF	81[c]
12	$Pd(OAc)_2$	–	THF	0
13	–	**L5**	THF	0

[a]Conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), Pd catalyst (5 mol %), ligand (10 mol %), TFA (0.4 mmol), solvent (1 mL), 80 °C, 24 h, air. [b]Isolated yield. [c]For 36 h.

Scheme 2. Synthesis of 1,3-Diarylbenzofuro[2,3-*c*]pyridines[a]



[a]Conditions: **1a** (0.2 mmol), **2** (0.4 mmol), $Pd(OAc)_2$ (5 mol %), **L5** (10 mol %), TFA (0.4 mmol), THF (1 mL), air, 80 °C, 36 h. Isolated yield.

the presence of $Pd(TFA)_2$ and 2,2′-bipyridine using trifluoroacetic acid (TFA) in 2-methyltetrahydrofuran (2-MeTHF) at 80 °C for 24 h under ambient air (entry 1). The **3a** yields were improved to 21% and 29% by using $Pd(acac)_2$ and $Pd(OAc)_2$ as the catalyst, respectively (entries 2−3). A variety of bidentate *N*-donor ligands, including 5,5′-dimethyl-2,2′-bipyridine (**L2**), 6,6′-dimethyl-2,2′-bipyridine (**L3**), 1,10-phenanthroline (**L4**), and 2,9-dimethyl-1,10-phenanthroline (**L5**), were examined (entries 4−7), and **L5** was found to give the best results, providing **3a** in 47% yield (entry 7). After a brief screening of solvents, THF was determined to be optimal, as it afforded **3a** in 68% yield (entries 8−10). The yield of **3a** was further improved to 82% by increasing the reaction time to 36 h (entry 11). It is worth noting that both the Pd catalyst and the ligand are necessary for this reaction to take place (entries 12−13).

We next explored the scope of arylboronic acids that could be employed, using **1a** as the substrate under the optimized reaction conditions (Scheme 2, **3b**−**3r**). Initially, the reactions of **1a** with tolylboronic acid at the *para*-, *meta*-, and *ortho*-positions were surveyed, affording the corresponding desired **3b**, **3c**, and **3d** products in 72%, 75%, and 90% yields, respectively. Dimethyl-, isopropyl-, and *tert*-butyl-substituted compounds were also well tolerated, and the corresponding products were obtained in 70−75% yields (**3e**−**3g**). Both electron-rich substituents, such as methoxy (**3h**), phenoxy (**3l**), and [1,3]dioxolo (**3j**) groups, and electron-deficient substituents, such as trifluoromethoxy (**3k**), fluoro (**3l**), chloro (**3m**), and bromo (**3n**) groups, were also compatible, giving the desired products with moderate to good yields. We also found that the reactions of 2-naphthylboronic acid and 1-naphthylboronic acid proceeded smoothly to afford the corresponding products **3o** and **3p** in 86% and 94% yields, respectively. Substrates bearing diphenylamino and *N*-carbazolyl moieties were well tolerated, providing the corresponding products **3q** and **3r** in 50% and 72% yields, respectively. Subsequently the range of 2-(cyanomethoxy)-chalcones that could be applied was assessed (Scheme 2, **3s**−**4g**). A variety of functional groups (R) could be attached to the chalcone, including electron-donating groups, such as methyl (**3s**) and methoxy (**3t**) moieties, and electron-withdrawing groups, such as fluoro (**3u**), chloro (**3v**), and bromo (**3w**) moieties. The effect of the ring position of a single substituent on the aryl ring (Ar) was evaluated, and the results indicated that the steric effects of substituents had no obvious influence on the yield. As an example, substrates with *para*-, *meta*-, and *ortho*-methyl substituents delivered **3x**, **3y**, and **3z** in 82%, 81%, and 80% yields, respectively. Moderately electron-

DOI: 10.1021/acs.orglett.9b04185
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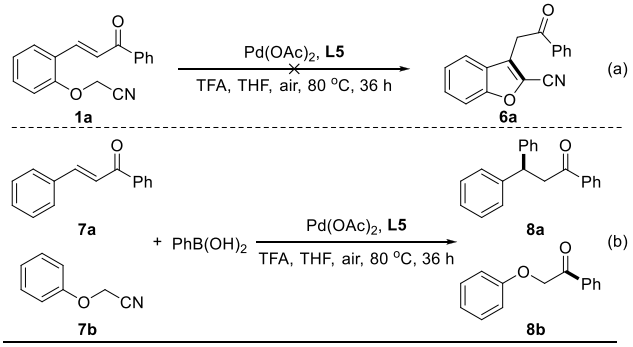
deficient halogens, such as fluoro (**4a**), chloro (**4b**), and bromo (**4c**) groups, were well tolerated, giving 86−88% yields. Highly electron-withdrawing groups (e.g., CF_3) could also be inserted at the *para* position, although the desired product **4d** was obtained in a slightly lower yield. The structure of **4d** was identified by X-ray diffraction. These transformations were also efficient when using naphthyl, furyl, and thienyl groups, affording the desired products **4e**, **4f**, and **4g** in 66−75% yields.

Although the strongly coordinating sulfur atom in the thiophene ring is known to poison Pd(II) catalysts, we determined that the reaction with thiophen-3-ylboronic acid proceeded smoothly to give various 3-aryl-1-(thiophen-3-yl)benzofuro[2,3-*c*]pyridines (Scheme 2, **5a**−**5o**). Functional groups (R) such as methyl (**5b**), methoxy (**5c**), fluoro (**5d**), chloro (**5e**), and bromo moieties, could also be applied to obtain yields ranging from 55% to 72%. In addition, a variety of substituents (e.g., Me, OMe, F, Cl, Br, CF_3, and naphthyl groups) on the aryl ring of the 2-(cyanomethoxy)chalcone moiety were well tolerated, affording the desired products **5f**−**5o** in 66−84% yields. The moderate to good yields obtained with thiophen-3-ylboronic acid provide further evidence that our catalytic system can withstand severe sulfur atom poisoning. Interestingly, furan-2-ylboronic acid was also compatible with the reaction system, albeit with a lower 36% yield of the desired 1-(furan-2-yl)-3-phenylbenzofuro[2,3-*c*]pyridine (Scheme 2, **5p**).

We next turned our attention to mechanistic investigations, and several control experiments were performed under the standard conditions (Scheme 3). First, the reaction was

Scheme 3. Control Experiments

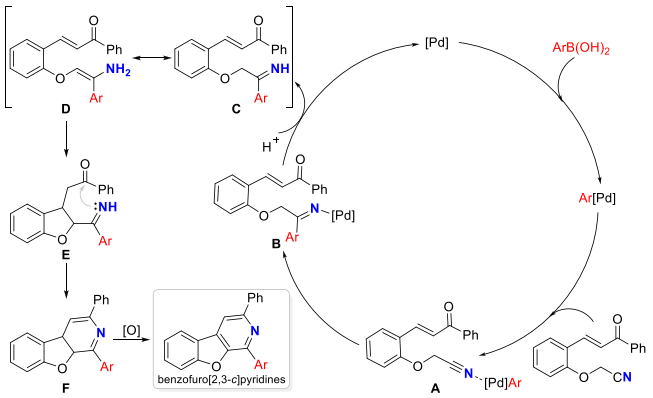


entry	**7a** (mmol)	**7b** (mmol)	**2a** (mmol)	yield of **8a** (%)	yield of **8b** (%)
1	0.2	0	0.4	82	-
2	0	0.2	0.4	-	91
3	0.2	0.2	0.4	30	63
4	0.2	0.2	0.2	13	51

attempted in the absence of phenyboronic acid, but 3-(2-oxo-2-phenylethyl)benzofuran-2-carbonitrile (**6a**) was not obtained. This result indicates that the tandem transformation is initiated by the carbopalladation of the nitrile (Scheme 3a). In addition, an intermolecular competition experiment was performed under standard conditions (Scheme 3b). Individual reactions involving chalcone (**7a**) and 2-phenoxyacetonitrile (**7b**) delivered 1,3,3-triphenylpropan-1-one (**8a**) and 2-phenoxy-1-phenylethan-1-one (**8b**) in 82% and 91% yields, respectively (entries 1−2). A competition reaction incorporating equimolar amounts of **7a** and **7b** with phenyboronic acid showed that the transformation occurred more readily with **7b** (entries 3−4). This observation suggests that the reactivity of the C≡N bond is greater than that of the C═C bond of the chalcone in our Pd-catalyzed addition reaction.

On the basis of the above experimental results, we propose a possible mechanism for the synthesis of benzofuro[2,3-*c*]pyridines (Scheme 4). The reaction begins with trans-

Scheme 4. Proposed Mechanism



metalation of the palladium catalyst and aryboronic acids followed by coordination of a cyano group to the Pd to form intermediate **A**. Next, carbopalladation of the cyano group affords the imine−Pd intermediate **B**. The protonation of **B** in the presence of TFA produces imine intermediate **C** (or tautomerization of imine to enamine intermediate **D**) and regenerates the palladium catalyst. Intramolecular Michael-type[12] addition of the intermediate **C** or **D** gives intermediate **E**, followed by cyclization to generate intermediate **F**. Finally, the intermediate **F** could be easily oxidized to a stable π-conjugated benzofuro[2,3-*c*]pyridine skeleton.

Organic luminescent materials have extremely important applications in probes, biological imaging, therapeutics, and optoelectronic devices.[13] Traditional fluorophores have relatively flat, rigid structures that enhance the conjugation within the molecule.[14] However, this planar configuration can also result in aggregation of the molecules as a result of relatively strong $\pi-\pi$ interactions. This in turn can cause quenching of the fluorescence (representing so-called aggregation caused quenching or ACQ). Therefore, the application of such materials is limited to the solution state. However, in 2001, Tang discovered a compound that only exhibits strong fluorescence in the aggregate state (aggregation induced emission: AIE). AIE materials have a distorted molecular configuration and larger spatial structure that prevent strong interactions between molecules in the aggregated state.[15] As might be expected, the applications of AIE materials are limited to aggregated states. Thus, fluorophores showing strong emission in both the solid and solution states have attracted significant interest. These materials have the advantages of both ACQ and AIE compounds and show highly efficient luminescence in both states, thus widening the range of potential applications.[16]

Despite significant research effort, materials which can exhibit emission in both solution and solid state are still very rare. Various experimental studies and theoretical calculations have shown that such compounds should have a configuration that is both rigid and twisted. In this work, the synthesized benzofuro[2,3-*c*]pyridine skeleton is a good candidate which has strong fluorescence in solution and solid state. This structure exhibits a level of planarity that ensures the intrinsic

DOI: 10.1021/acs.orglett.9b04185
Org. Lett. XXXX, XXX, XXX−XXX

luminescence of the compound. Moreover, the aromatic groups attached to the 1 and 3 positions of the pyridine ring distort the spatial configuration of the molecule to produce strong fluorescence in the solid state. To verify the properties of benzofuro[2,3-*c*]pyridine derivatives, we selected nine compounds and examined their luminescence. As shown in Figure 1a, these derivatives exhibited strong blue fluorescence

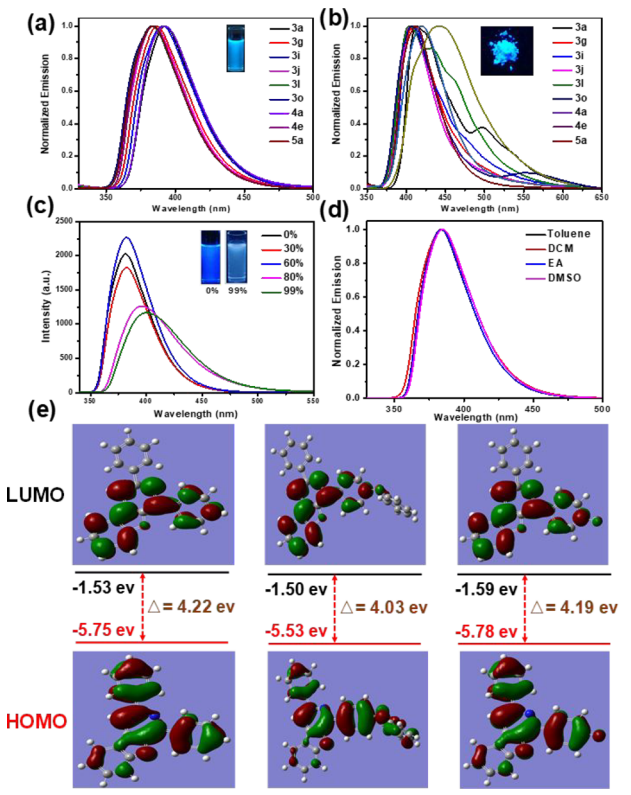


Figure 1. (a) Fluorescence spectra of compounds in the solution state (THF as solvent, concentration: 1.0×10^{-4} mol/L). (b) Fluorescence spectra of compounds in the solid state. (c) Fluorescence spectra of **3a** in THF/H2O with varying H_2O percentages (inset: fluorescent photographs of the compound at 0% and 99% water content in the mixed solvent; concentration: 1.0×10^{-4} mol/L). (d) Emission spectra of **3a** in different solvents. (e) LUMOs and HOMOs of **3a**, **3i**, and **3l**.

emissions in solution, with wavelengths in the range 484 to 492 nm and absolute quantum yields from 33% to 70% (Table S1). The fluorescence wavelengths in the solid state were in the range 405 to 440 nm, and the fluorescence quantum yields were from 20% to 40% (Figure 1b, Table S1). These results confirm that the benzofuro[2,3-*c*]pyridine derivatives can emit fluorescence in solution and solid state. Compared to the solution state, the wavelengths of the solid materials are red-shifted and the fluorescence intensity is decreased. These effects can possibly be attributed to weak intermolecular interactions between molecules in the aggregated state.[12a,14b] The luminescence properties of compounds **3a**, **3i**, and **3l** in different THF/H_2O mixtures were also investigated. In pure THF solutions, these materials showed intense fluorescence emissions. However, the compounds changed from monomolecular to an aggregated state when the proportion of the poor solvent (water) was increased to 80%. Despite the red shift of wavelengths and change in fluorescence intensity, the compounds in both the solution state and the aggregate state produced strong fluorescence emissions (Figures 1c, S1 and S2). These results provide further evidence that these derivatives have strong emission in solution and solid state. The effects of solvent polarity were examined by assessing the fluorescence emissions of the above-mentioned three compounds in toluene, dichloromethane (DCM), ethyl acetate (EA), and DMSO. The emission wavelengths of benzofuro[2,3-*c*]pyridine with either an electron-donating group (e.g., **3i**) or an electron-withdrawing group (e.g., **3l**) in different solvents were almost constant, indicating that the fluorescence of these materials is relatively unaffected by the polarity of the solvent (Figures 1d, S3 and S4). Density functional theory calculations were performed to obtain additional information regarding the optical properties of these compounds at the molecular level, using a suite of the Gaussian 09 program. The highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) energy levels of the derivatives were calculated using the B3LYP/6-31+G* method. Because pyridine is electron-withdrawing, the LUMO of each compound was primarily distributed on the benzofuro[2,3-*c*]pyridine skeleton, while the HOMO was distributed over almost the entire molecule (Figure 1e).

In summary, we successfully demonstrated the Pd(II)-catalyzed cascade reactions of (cyanomethoxy)chalcones with arylboronic acids, providing a new strategy for the synthesis of a diverse array of valuable benzofuro[2,3-*c*]pyridines that are often difficult to prepare by traditional routes. This chemistry can also be applied to the synthesis of 1-(thiophen-3-yl)benzofuro[2,3-*c*]pyridines by using thiophen-3-ylboronic acid as the coupling partner. Benzofuro[2,3-*c*]pyridines have great practical significance in terms of expanding the types and applications of fluorescent materials.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04185.

Experimental procedures, characterization data, NMR spectra, and X-ray data for product **4d** (PDF)

Accession Codes

CCDC 1971013 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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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

DOI: 10.1021/acs.orglett.9b04185
Org. Lett. XXXX, XXX, XXX−XXX

Zhejiang Province (Nos. LY20B020015 and LQ18B020006) for financial support.

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DOI: 10.1021/acs.orglett.9b04185
Org. Lett. XXXX, XXX, XXX−XXX