OL | Organic Letters

Letter

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

pubs.acs.org/OrgLett

Direct Assembly of Polysubstituted Propiolamidinates via Palladium-Catalyzed Multicomponent Reaction of Isocyanides

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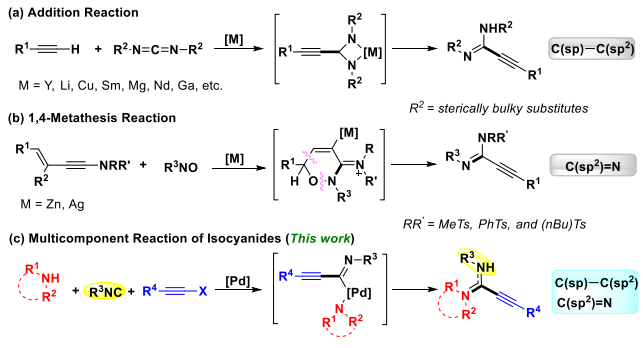
Supporting Information

- Novel access to propiolamidinates
- Formation of C-C & C=N bonds in one pot
- Involvement of alkynyl-palladium species
- 42 examples, up to 90% yield

ABSTRACT: A straightforward approach for the assembly of different polysubstituted propiolamidnates via palladium-catalyzed multicomponent reaction of isocyanides, haloalkynes, and amines has been reported in which the C(sp)−C(sp^2) and C(sp^2)=N bonds were constructed in one pot. This reaction featured in high efficiency, excellent chemoselectivity, and good functional group compatibility. The synthetic utility of this method was also demonstrated.

Amidinates and their derivatives, as ubiquitous skeletons occurring in agricultural chemicals, drug molecules, and catalysts, have received considerable attention over the past decades.[1] Among them, propiolamidines are extraordinarily attractive owing to their special chemical and structural characteristics as well as their extensive applications in synthetic chemistry.[2] However, few methods have been developed to provide propiolamidines, largely restricting their further development.[3] Traditionally, these compounds were acquired through the addition reactions between terminal alkynes and sterically bulky carbodiimides (Scheme 1a)[4] or the 1,4-metathesis reaction of nitrosoarenes with 3-en-1-ynamides bearing different sulfonamides (Scheme 1b).[5] Despite these significant advances, the synthesis of propiolamidines contains several challenging issues: (i) due to the present limitation of substrate scope, the diversity of products and compatibility with various functional groups needs to be improved; (ii) in view of the employment of prefunctionalized precursors, the direct assembly of propiolamidines from simple and available starting materials is in great demand. Therefore, the development of novel and convenient strategies for the efficient construction of propiolamidines is highly desirable.

Scheme 1. Synthesis of Polysubstituted Propiolimidines



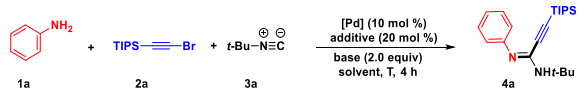
On the other hand, isocyanides, as versatile synthons in transition-metal-catalyzed transformations, have been widely investigated in recent years, affording numerous valuable nitrogen-containing compounds.[6] However, in contrast to a large amount of transformations focusing on the insertion of isocyanides into the aryl-[7] or alkenylpalladium[8] intermediates, few reports are related to the combination of isocyanides with alkynylpalladium species.[9] This might be ascribed to the limited approaches to alkynylpalladium species as well as the competitive homocoupling reactions of alkyne complexes.[10] Thus, the exploration of novel cross-coupling reactions between isocyanides and the alkynylpalladium complex remains interesting and meaningful. Based on our continuing interest in palladium-catalyzed isocyanide transformations,[11] herein we disclose a concise and convenient synthesis of various polysubstituted propiolamidinates via a palladium-catalyzed multicomponent reaction of isocyanides, haloalkynes, and amines under mild conditions (Scheme 1c). In this chemistry, the C(sp)−C(sp^2) and C(sp^2)=N bonds were constructed with high stereoselectivity and step economy in one step. The key process of this transformation was the migration insertion of isocyanides into the newly formed alkynylpalladium intermediates.

Received: September 9, 2019

DOI: 10.1021/acs.orglett.9b03201
Org. Lett. XXXX, XXX, XXX−XXX

To evaluate the optimal conditions, we initially selected aniline (**1a**), (bromoethynyl)triisopropylsilane (**2a**), and *tert*-butyl isocyanide (**3a**) as the model substrates (Table 1).

Table 1. Optimization of Reaction Conditions[a,b]



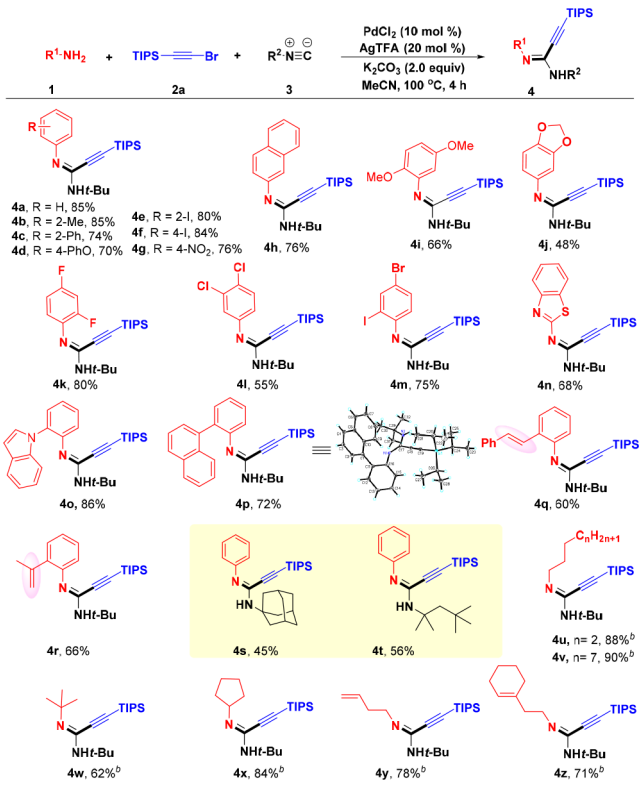
entry	catalyst	base	additive	solvent	yield[b] (%)
1	$PdCl_2$	K_2CO_3		DMF	15
2	$PdCl_2$	K_2CO_3		DMSO	20
3	$PdCl_2$	K_2CO_3		MeCN	82
4	$PdCl_2$	K_2CO_3		Toluene	50
5	$PdCl_2$	DBU		MeCN	49
6	$PdCl_2$	Et_3N		MeCN	69
7	$PdCl_2$	CH_3ONa		MeCN	60
8	$PdCl_2$	*t*-BuOK		MeCN	10
9	$PdCl_2$	Cs_2CO_3		MeCN	65
10	**$PdCl_2$**	**K_2CO_3**	**AgTFA**	**MeCN**	**92 (85)**
11	$PdCl_2$	K_2CO_3	Ag_2CO_3	MeCN	74
12	$PdCl_2$	K_2CO_3	AgOAc	MeCN	90
13	$Pd(OAc)_2$	K_2CO_3	AgTFA	MeCN	78
14[c]	$PdCl_2$	K_2CO_3	AgTFA	MeCN	76
15[d]	$PdCl_2$	K_2CO_3	AgTFA	MeCN	69

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), **3a** (0.125 mmol), catalyst (10 mol %), base (2.0 equiv), additive (20 mol %), solvent (1.0 mL), at 100 °C for 4 h in air. nd = not detected. [b]Yield of **4a** was determined by ^1H NMR using CH_2Br_2 as an internal standard. The isolated yield is shown in parentheses. [c]Under N_2 atmosphere. [d]80 °C.

Delightfully, the desired product (*E*)-*N*-(*tert*-butyl)-*N*′-phenyl-3(triisopropylsilyl)propiolimidamide (**4a**) was detected in 15% NMR yield in the presence of $PdCl_2$ (10 mol %) and K_2CO_3 (2.0 equiv) in DMF (1.0 mL) at 100 °C for 4 h (Table 1, entry 1). Subsequent screening of various solvents showed that MeCN was the best choice, which might be ascribed to its good coordinative ability to stabilize the reaction intermediates (Table 1, entries 2−4).[12] Next, different bases, such as DBU, Et_3N, CH_3ONa, *t*-BuOK, and Cs_2CO_3, were tested. However, no preferred results were observed (Table 1, entries 5−9). To further promote this reaction, different kinds of silver salts were examined (Table 1, entries 10−12). Pleasingly, AgTFA was found to be effective and increased the yield of **4a** from 82% to 92%. A lower yield was obtained when $PdCl_2$ was replaced with $Pd(OAc)_2$ (Table 1, entry 13). Furthermore, a slightly decreased yield was observed when the reaction proceeded under an N_2 atmosphere or at a lower temperature (Table 1, entries 14 and 15). Meanwhile, ligands were demonstrated to be not necessary in this reaction (see the Supporting Information for details).

With the optimized reaction conditions established, the generality and limitations of this strategy were explored (Scheme 2). A variety of anilines and their derivatives were found to be suitable for this transformation, converting to the corresponding products in moderate to good yields. All of the tested monosubstituted anilines with either electron-donating or electron-withdrawing substituents at the *para*- or *ortho*-positions of the benzene rings proceeded smoothly in this reaction to afford the desired propiolamidinates **4a**−**4h** in 74−85% yields. Despite relatively low reactivity, polysubstituted anilines also exhibited good compatibility for this chemical

Scheme 2. Substrate Scope of Primary Amines and Isocyanides[a,b]



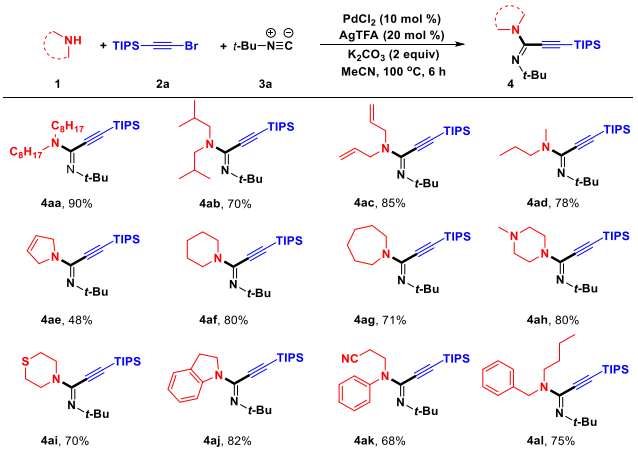
[a]Reaction conditions: **1a**−**1t** (0.10 mmol), **2a** (0.15 mmol), **3** (0.125 mmol), $PdCl_2$ (10 mol %), AgTFA (20 mol %), K_2CO_3 (2.0 equiv), MeCN (1.0 mL), 100 °C, 4 h. Yield is isolated yield. [b]Reaction conditions: **1u**−**1z** (0.3 mmol), **2a** (0.10 mmol), **3a** (0.125 mmol), $PdCl_2$ (10 mol %), AgTFA (20 mol %), K_2CO_3 (2.0 equiv), MeCN (1.0 mL), 100 °C, 6 h. Yield is isolated yield.

process (**4i**−**4m**). It should be noted that benzo[*d*]thiazol-2-amine was well adopted in this protocol and transformed to the desired product **4n** in 68% yield. Furthermore, for aromatic amines with an indolyl or naphthyl group at the *ortho*-position of the aryl ring, the corresponding products **4o** and **4p** were obtained in 78% and 86% yields, respectively. The structure of **4p** was verified unambiguously by X-ray diffraction (CCDC 1916418). Additionally, when substrates with a styrene moiety were applied in this transformation, the target products **4q** and **4r** were formed in moderate yields, providing potentials for further elaborations. The examination of different isocyanides revealed that sterically hindered 1-admantyl isocyanide and 1,1,3,3-tetramethylbutyl isocyanide were compatible with this catalytic system, while other aliphatic isocyanides or aromatic isocyanides only gave unfruitful results. Pleasingly, aliphatic primary amines bearing long or bulky alkyl substituents such as *n*-decyl, *tert*-butyl, and cyclopentyl groups worked well in this reaction, converting to the expected products **4u**−**4x** in moderate to excellent yields.[13] Similarly, homoallylic amines were tolerated in this system, and the desired propiolamidines **4y** and **4z** could be obtained in 78% and 71% yields.

To further expand the substrate scope, various secondary amines were then examined (Scheme 3). Under the standard conditions, the transformations of symmetrical and unsymmetrical linear amines proceeded well to give the corresponding products **4aa**−**4ad** in good to excellent yields. Moreover, different saturated and unsaturated cyclic amines, including

DOI: 10.1021/acs.orglett.9b03201
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 3. Substrate Scope of Secondary Amines[a]

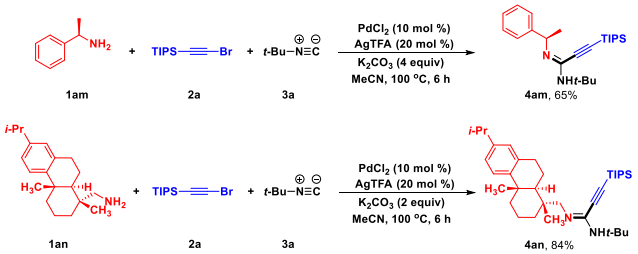


[a]Reaction conditions: **1** (0.30 mmol), **2a** (0.10 mmol), **3a** (0.125 mmol), $PdCl_2$ (10 mol %), AgTFA (20 mol %), K_2CO_3 (2.0 equiv), MeCN (1.0 mL), 100 °C, 6 h. Yield is isolated yield.

2,5-dihydro-1*H*-pyrrole, 1-methylpiperazine, thiomorpholine, and indoline, were successfully converted to the propiolamidine products **4ae**−**4aj** in 48−80% yields. The configuration of the product **4aj** was determined by X-ray crystallography analysis (CCDC 1916428). Additionally, the transformations of secondary amines with a cyano or benzyl group provided the target products **4ak** and **4al** in 68% and 75% yields, respectively.

Besides serving as versatile catalysts and ligands in organic synthesis, it is well-known that amines are common and important starting materials for many industrial products. Thus, the late-stage functionalization of amines is of great significance (Scheme 4). α-Methylbenzylamine (**1am**) was

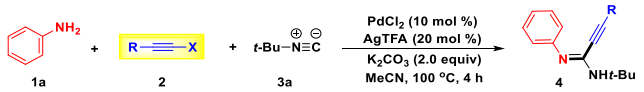
Scheme 4. Late-Stage Functionalization of Multifunctional Amines



initially tested in this reaction, and the desired product **4am** was isolated in 65% yield. Notably, when the dehydroabietic amine **1an**, a multifunctional amine widely used in the rubber industry, food manufacturing, and exploration of chiral reagents,[14] was subjected to this transformation, the functionalization product **4an** could be obtained in 84% yield, suggesting the potential applications in modification of complex molecular skeletons.

The effect of various haloalkynes on this transformation was next investigated. Initially, when the halogen atom was changed from bromine to chlorine or iodine, the propiolamidine product **4a** was isolated in 78% and 53% yields, respectively (Table 2, entries 1−3). Subsequent studies of bromoalkynes with different silyl groups afforded quite interesting results. The bromoalkynes bearing a triethylsilyl

Table 2. Effects of Various Haloalkynes[a]



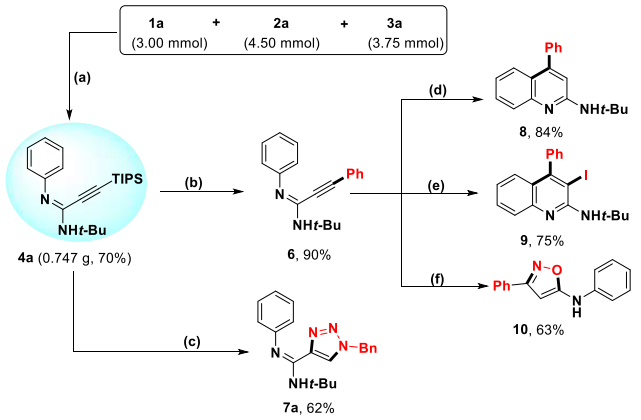
entry	substrate **2**	product **4**	yield (%)
1	**2aa**, X = Cl	**4a**	78
2	**2a**, X = Br	**4a**	85
3	**2ac**, X = I	**4a**	53
4	**2ao**, R = TMS	**4ao**	nd
5	**2ap**, R = TES	**4ap**	50
6	**2aq**, R = $SiMe_2{}^tBu$	**4aq**	55
7	**2ar**, R = $SiPh_3$	**4ar**	nd
8	**2as**, R = Ph	**4as**	trace

[a]Reaction conditions: **1a** (0.10 mmol), **2** (0.15 mmol), **3a** (0.125 mmol), $PdCl_2$ (10 mol %), AgTFA (20 mol %), K_2CO_3 (2.0 equiv), MeCN (1.0 mL), 100 °C, 4 h. Yield is isolated yield. nd = not detected.

group (**2ap**) and a (*tert*-butyl)dimethylsilyl group (**2aq**) were found to be suitable substrates, converting to the target products **4ap** and **4aq** in moderate yields. However, neither (bromoethynyl)trimethylsilane (**2ao**) nor (bromoethynyl)-triphenylsilane (**2ar**) could be applied to this system, indicating that this transformation might be more sensitive to the steric hindrance of the haloalkyne substrates. In addition, only a trace amount of the desired product was detected by GC−MS when (bromoethynyl)benzene (**2as**) was tested.

To further evaluate the practicality and synthetic utility of this reaction, a gram-scale experiment was carried out. Gratifyingly, the desired propiolamidine was isolated in 70% yield (Scheme 5a). Then a series of conversions of **4a** were performed, and different valuable structures could be constructed. For example, the diphenylpropiolimidamide **6** was easily obtained via hydrolysis and Sonogashira coupling

Scheme 5. Derivatizations of Propiolamidine 4a[a]



[a]Reaction conditions: (a) $PdCl_2$ (5 mol %), AgTFA (10 mol %), K_2CO_3 (1.5 equiv), MeCN (20 mL), 100 °C, 6 h; (b) (i) TBAF (1 M in THF, 1.0 equiv), THF (2.0 mL), rt, 5 min, (ii) $PdCl_2(PPh_3)_2$ (4 mol %), CuI (15 mol %), PhI (0.25 mmol), Et_3N (2.0 mL), rt, 24 h; (c) (i) TBAF (1 M in THF, 1.0 equiv), THF (1.0 mL), rt, 5 min, (ii) CuI (10 mol %), benzylazide (1.2 equiv), MeCN (1.5 mL), 90 °C, 3 h; (d) AgOTf (5 mol %), HOTf (10 mol %), toluene (1.0 mL), 110 °C, 10 min; (e) NIS (1.5 equiv), CuI (10 mol %), MeCN (1.0 mL), 80 °C, 15 min; (f) $NH_2OH{\cdot}HCl$ (1.5 equiv), EtOH (1.0 mL), 100 °C, 30 min.

DOI: 10.1021/acs.orglett.9b03201
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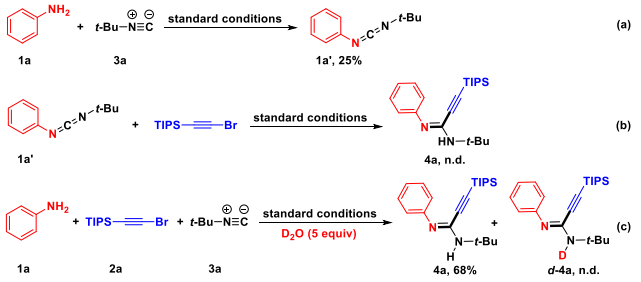
reaction of propiolamidine with iodobenzene (Scheme 5b). Additionally, the click reaction of **4a** gave a functionalized triazole skeleton **7a** in 62% yield (Scheme 5c). Furthermore, the cyclization reaction of **6** catalyzed by AgOTf afforded 2-aminoquinoline product **8** in good yield (Scheme 5d). More interestingly, another important class of 2-aminoquinoline derivative, 3-iodo-2-aminoquinoline **9**, was produced in 75% yield via electrophilic cyclization of **4a** using *N*-iodosuccinimides as electrophiles (Scheme 5e). Finally, *N*,3-diphenylisoxazol-5-amine (**10**) was synthesized in acceptable yield in the presence of a slight excess of $NH_2OH{\cdot}HCl$ (Scheme 5f).

In order to better clarify the reaction mechanism, several control experiments were conducted. First, a 25% yield of phenylmethanediimine (**1a′**) was isoalated when aniline **1a** and isocyanide **3a** were employed as substrates. Considering that the carbodiimide might be the intermediate, **1a′** was prepared and reacted under the optimal conditions. However, the reaction afforded no desired product **4a**, which could exclude that the carbodiimide was the intermediate for this transformation (Scheme 6a,b). Moreover, a deuterium-labeling

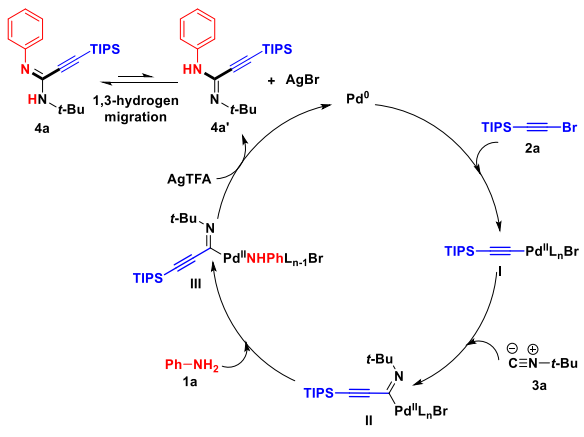
Scheme 6. Control Experiments



experiment illustrated that the free hydrogen atom in the propiolamidine product originated from aniline rather than H_2O in this system (Scheme 6c).

On the basis of these experiments and previous studies,[7,8,15] a possible catalytic cycle for this reaction was proposed in Scheme 7. Initially, oxidative addition of bromoalkyne **2a** to the Pd(0) species affords the acetylpalladium species **I**.[16] Subsequent migration insertion of *tert*-butyl isocyanide (**3a**) generates the imidoyl Pd(II) intermediate **II**, which would be trapped by aniline (**1a**) to produce the key palladium complex **III**. Finally, reductive elimination provides the unstable product **4a′** and releases the active Pd(0) species. Simultaneously, 1,3-hydrogen migration of **4a′** results in the formation of the desired product **4a**. Alternatively, although the oxidative addition of a simple Pd(II) species to an alkynyl bromide has rarely been investigated, the generation of an alkynylpalladium(IV) complex with haloalkyne derivatives as oxidative reagents has been well documented, generally in the presence of a stoichiometric amount of strong oxidant and a stable cyclopalladium intermediate.[17] Thus, another mechanism involving a Pd(II)/Pd(IV) catalytic cycle could not be fully excluded (see the Supporting Information for details).

Scheme 7. Possible Mechanism



In conclusion, we have developed a convenient approach for different propiolamidines via palladium-catalyzed multicomponent reaction of isocyanides, haloalkynes, and amines. This transformation featured in the concomitant construction of C(sp)−C(sp^2) and C(sp^2)=N bonds with broad substrate scope. More importantly, the practicability of this method was demonstrated by the synthesis of diverse useful skeletons, such as aminoquinolines, isoxazoles, and functionalized triazoles. Further exploration of the reaction mechanism and synthetic applications is ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03201.

Experimental procedures, condition screening table, characterization data, and copies of NMR spectra for all products (PDF)

Accession Codes

CCDC 1916418, 1916428, and 1920494 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

The authors thank the National Key Research and Development Program of China (2016YFA0602900), the National Natural Science Foundation of China (21672072 and 21472051), and the Guangdong Natural Science Foundation (2018B030308007) for financial support.

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DOI: 10.1021/acs.orglett.9b03201
Org. Lett. XXXX, XXX, XXX−XXX