Organic LETTERS

Letter

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

pubs.acs.org/OrgLett

Regiodivergent Ring-Opening Cross-Coupling of Vinyl Aziridines with Phosphorus Nucleophiles: Access to Phosphorus-Containing Amino Acid Derivatives

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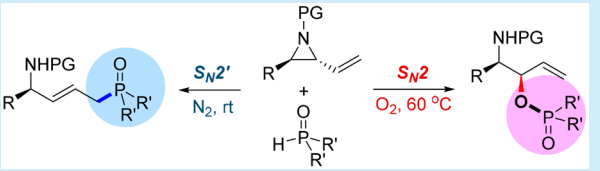
Supporting Information

ABSTRACT: Catalytic ring-opening phosphonation and phosphatation of vinyl aziridines have been developed in a regiodivergent fashion, giving linear and branched products. Generation of P-centered radicals enables S_N2'-type ring-opening reactions of vinyl aziridines to afford δ-amino alkylphosphorus products at room temperature. On the other hand, in situ generated phosphate anions via the Ag-catalyzed aerobic oxidation of phosphonyl reactants underwent S_N2 reaction to provide branched phosphorus-containing amine products. Furthermore, this divergent methodology serves as a powerful tool for the stereospecific synthesis of phosphorus-containing amino acid derivatives.

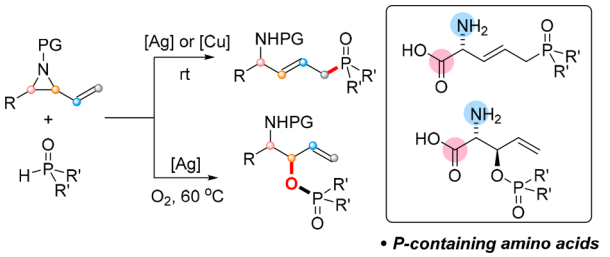


Organophosphorus motifs are frequently used in a wide range of applications in organic chemistry,[1] medicinal chemistry,[2] and the materials industries.[3] In particular, compounds containing amino phosphonate or amino phosphatate units have attracted attention because they exhibit intriguing biological activities.[4] Among them, phosphorus-containing chiral amino acids are an important class of biologically active scaffolds,[4a,b,5] and (2*R*)-amino-5-phosphonovaleric acid (AP-5) is a selective NMDA receptor antagonist.[4d,5f] Although tremendous efforts have been directed toward the development of efficient phosphonation[6] and phosphatation[7] reactions, a divergent and stereoselective synthesis of enantioenriched phosphorus functionalized amino acid derivatives remains unknown.

Aziridines serve as versatile building blocks in organic synthesis.[8] In particular, vinyl aziridines[9,10] possess multiple reactive sites and are prone to various ring opening reactions that can be exploited for the construction of a wide range of valuable β-amino-functionalized motifs.[8,10] In general, the reactions proceed via transition-metal-catalyzed C−N bond cleavage[11] or direct nucleophilic attack of the activated aziridines at the more substituted carbon.[8b] The cleavage of an allylic C−N bond and direct displacement of the C−N bond of the aziridine are the major competing pathways that result in the formation of linear-type and branched-type products. Consequently, much effort has been devoted toward achieving high discrimination among the reactive sites of the vinyl aziridines.[12] Despite recent progress, site-selective catalytic ring-opening reactions of vinyl aziridines by phosphorus nucleophiles remain a challenging synthetic problem. In this regard, predictable and controllable divergent synthetic tools applicable to common vinyl aziridine starting materials would be highly valuable.

As outlined in Scheme 1, we speculated the possibility of controlling the reaction pathways (S_N2 or S_N2'-type) by the features of the nucleophile source, which can differentiate and amplify site-discriminating interactions with the vinyl aziridines. We discovered that the ring-opening phosphonation of vinyl aziridines occurred via the cleavage of an allylic C−N bond under Cu or Ag catalysts to give δ-amino alkylphosphorus derivatives. Notably, by tuning the reaction conditions under an O_2 atmosphere at 60 °C, we observed that branched products were generated with the incorporation of phosphates. Our mechanistic studies revealed that the formation of branched products likely occurs via in situ-generated phosphate anions derived from the Ag-catalyzed oxidation of phosphonyl reactants, followed by the addition of phosphate to the vinyl aziridines. Herein, we describe our efforts toward developing catalyst-controlled ring-opening cross-coupling reactions of vinyl aziridines, which enable the divergent

Scheme 1. Regioselective and Divergent Catalytic Ring-Opening Reactions of Vinyl Aziridines



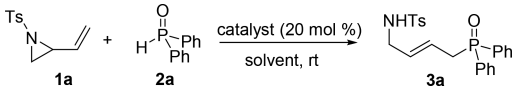
Received: October 16, 2018

DOI: 10.1021/acs.orglett.8b03309
Org. Lett. XXXX, XXX, XXX−XXX

synthesis of linear- or branched-type amino-functionalized molecules from common versatile starting materials. Furthermore, we achieved the stereospecific synthesis of two types of optically active phosphorus-containing unnatural amino acid derivatives with the retention of the chiral information.

To corroborate this scenario, our investigation began with the reaction of vinyl aziridine **1a** and diphenylphosphine oxide (**2a**) under different conditions, and selected data are listed in Table 1. After evaluating different reaction conditions, vinyl

Table 1. Reaction Optimization for the S_N2' Phosphonation[a]



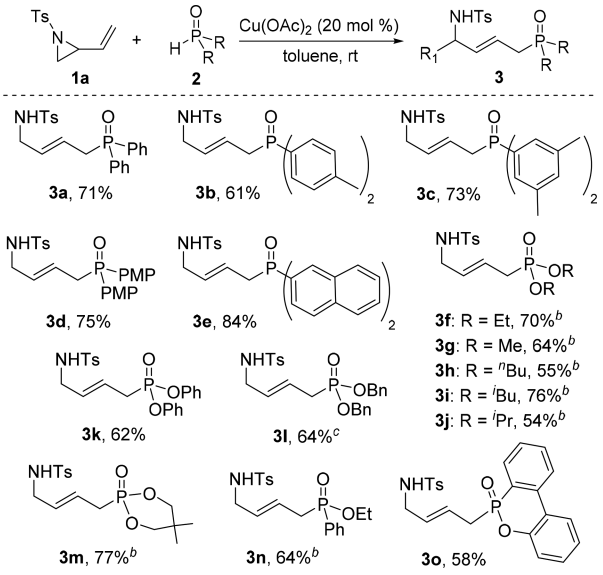
entry	catalyst	solvent	time (h)	yield[b] (%)
1[c]	$AgNO_3$	MeCN	17	52
2[c]	Cu_2O	MeCN	24	63
3[c]	$Cu(OAc)_2$	MeCN	12	66
4[c]	$Cu(OAc)_2$	toluene	2	71
5	$Cu(OAc)_2$	DCE	4	51
6	$Cu(OAc)_2$	MeCN	4	21
7	$Cu(OAc)_2$	toluene	1	72
8		toluene	1	NR
9[d]	$Cu(OAc)_2$	toluene	1	trace

[a]Conditions: **1a** (1.0 equiv), **2a** (2.0 equiv), catalyst (20 mol %) in solvent (0.1 M) at rt under air atmosphere. [b]^{1}H NMR yields of products. [c]Under N_2 atmosphere. [d]TEMPO (2.0 equiv) was added. DCE = 1,2-dichloroethane.

aziridine **1a** was found to undergo an S_N2'-type phosphonation using either Cu or Ag as the catalyst to afford linear-type product **3a**. The structure of **3a** was unambiguously confirmed by X-ray crystallographic analysis. Among the solvents screened, toluene was most efficient for this reaction, and the desired product was obtained in 71% yield (entry 4). Of the various catalysts tested, $Cu(OAc)_2$ displayed an outstanding performance for this transformation. Control experiments confirmed the essential role of the Cu catalyst in this reaction (entry 8). The inhibition of the reaction by the addition of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) (entry 9) supports a radical process being active. Through systematic screening of the reaction conditions, a stirred solution of **1a**, phosphine oxide **2a**, and $Cu(OAc)_2$ (20 mol %) in toluene at rt for 1 h afforded **3a** exclusively in 72% yield.

With the optimal conditions in hand, we next set out to determine the substrate scope with respect to phosphine oxides to demonstrate the utility and generality of this method as summarized in Scheme 2. A series of diphenylphosphine oxides bearing various substituents were employed in the present Cu-catalyzed reaction and were successfully converted to the corresponding coupled products in moderate to good yields (**3a**–**d**). In addition, reactions of di(naphthalen-2-yl)phosphine oxide smoothly afforded phosphonated product **3e** in 84% yield. Expanding the scope from phosphine oxides to H-phosphite reactants was possible, leading to the formation of corresponding products **3f**–**o**. In the case of H-phosphite reactants, the use of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was required to ensure the high reactivity.[13] With slightly modified reaction conditions, the Cu-catalyzed phosphonation reactions were successfully conducted with a variety of H-phosphites. For example, alkyl H-phosphinates

Scheme 2. Substrate Scope of S_N2' Phosphonation[a]



[a]Conditions: **1a** (1.0 equiv), **2** (2.0 equiv), and $Cu(OAc)_2$ (20 mol %) in toluene (0.2 M) at rt under air atmosphere. Yields of isolated products. [b]**2** (3.0 equiv) and DBU (1.5 equiv) were used. PMP = *p*-methoxybenzene.

(**2f**–**k**) and diphenyl and dibenzyl phosphites (**2k** and **2l**) all reacted well to provide the desired products. In addition, ethyl phenylphosphinate readily participated in the reaction and provided desired product **3n**. We subsequently assessed the applicability of our method to cyclic phosphorus reactants, such as cyclic phosphonate and cyclic oxaphosphine oxide, which worked well and provided desired products **3m** and **3o**, proving that the present reaction protocol is suitable for various types of phosphorus reagents, including H-phosphine oxides, H-phosphonates, and H-phosphinates.

We next conducted a series of experiments to investigate the scope of the vinyl aziridine substrates. As shown in Scheme 3, we observed that substrates with a variety of substitution patterns were successfully converted to the desired products. Aziridine substrates bearing nosyl and *N*-phthalimide groups worked well to afford the desired products **3p** and **3q**. Dimethyl-substituted vinyl aziridine **1d** was well tolerated, and the coupled product was isolated in 74% yield. Further exploration demonstrated that cyclohexene cores containing both amino and phosphorus groups can be accessed under the reaction conditions (**3s**). The utility of the present method was further broadened by the reaction with vinyl aziridine substrates possessing benzyl and isobutyl groups, which afforded products **3t** and **3u**, respectively. Next, the importance of phosphorus-containing amino acids in natural products and biologically active molecules prompted us to establish a general protocol to access these molecular scaffolds. To understand the stereochemical fate of the stereogenic center, enantiopure vinyl aziridine esters **1h**–**k**[9b,14] were subjected to the reactions with phosphine oxides. Our optimization studies revealed that the Ag catalyst was more effective than Cu with this type of substrate. To our delight, optically active chiral aziridine (*R*)-**1h** with 92% ee was converted into chiral phosphonated amino acid derivative **3v** in 72% yield. Notably, chiral HPLC analysis of **3v** revealed that the stereochemistry was completely retained in the reaction (92% ee, *S*). The structure and absolute configuration of **3v** was unambiguously confirmed by

DOI: 10.1021/acs.orglett.8b03309
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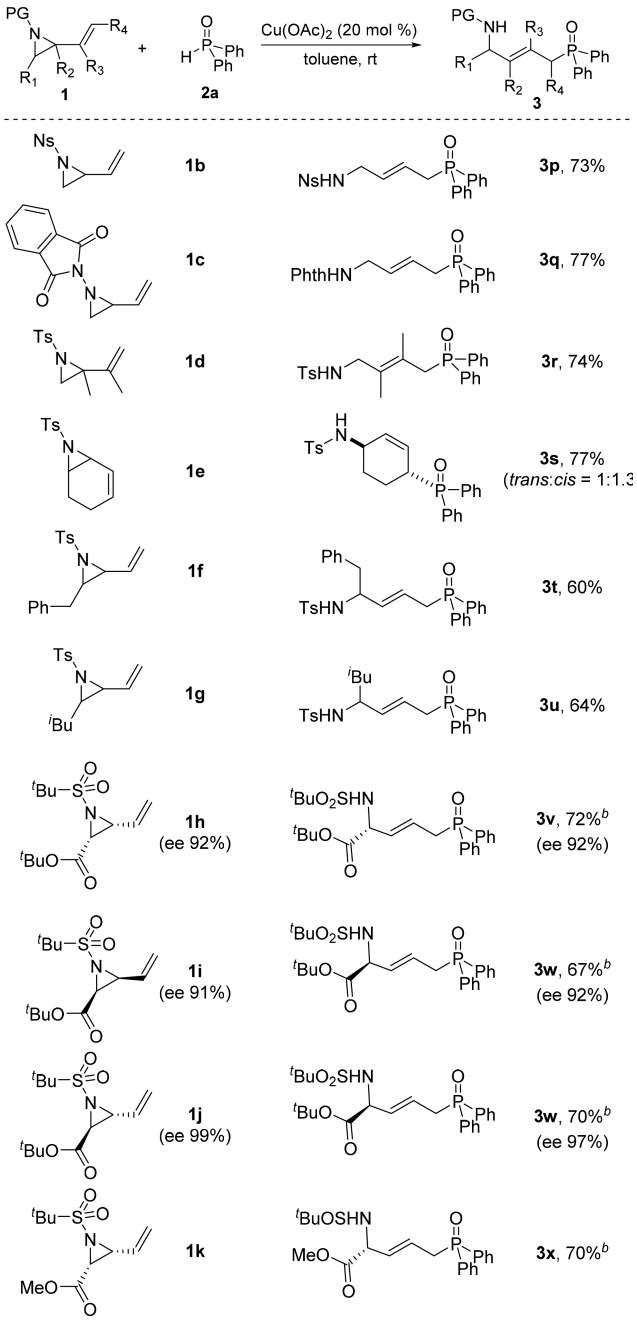
Scheme 3. Substrate Scope of Various Vinyl Aziridines[a]

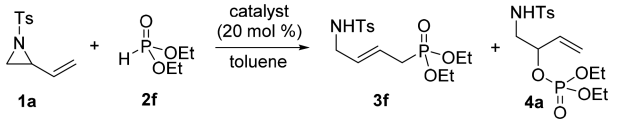


[a]Conditions: **1** (1.0 equiv), **2a** (2.0 equiv), and $Cu(OAc)_2$ (20 mol %) in toluene (0.2 M) at rt under air atmosphere. Yields of isolated products. [b]Instead of $Cu(OAc)_2$, $AgNO_3$ (20 mol %) was used in MeCN (0.1 M) for 4 h.

single-crystal X-ray diffraction analysis (see the Supporting Information (SI) for details).[15] Similarly, chiral phosphonated amino acid derivatives **3w** and **3x** were formed in a selective manner. These results indicate that the current catalytic system is stereospecific and operates with retention of stereochemical information.

During these investigations, we discovered that branched phosphate product **4a** was formed as a major product in a site-selective manner when an Ag catalyst was employed under an O_2 atmosphere at 60 °C (Table 2). We speculated that these results might offer a unique opportunity to develop divergent

Table 2. Reaction Optimization for S_N2 Phosphatation[a]



					yield[b] (%)	
entry	catalyst	atm	temp (°C)	time (h)	**3f**	**4a**
1	$AgNO_3$	N_2	rt	12	NR	
2	$Cu(OAc)_2$	air	rt	12	NR	
3[c]	$Cu(OAc)_2$	air	rt	1	65	
4	$Cu(OAc)_2$	air	60	15	24	38
5	$Cu(OAc)_2$	N_2	60	12	58	
6	$AgNO_3$	air	60	15		69
7	$AgNO_3$	O_2	40	5		44
8	$AgNO_3$	O_2	60	5		69
8	$AgNO_3$	O_2	60	9		77
9	$AgNO_3$	N_2	60	12	NR	
10[d]	$AgNO_3$	O_2	60	12	NR	

[a]Conditions: **1a** (1.0 equiv), **2f** (2.0 equiv), catalyst (20 mol %) in solvent (0.1 M). [b]^{1}H NMR yields of products. [c]DBU (1.5 equiv) was added. [d]TEMPO (2.0 equiv) was added. NR = no reaction.

approaches to produce either linear product **3f** or branched product **4a** as the dominant product. Intrigued by this interesting transformation, we screened reaction media and catalysts to optimize the reaction outcome. We reasoned that the molecular oxygen is necessary as it oxidizes the phosphonyl reactant. The best result was obtained when toluene was used as the solvent. Next, we studied the influence of temperature on the reaction outcomes, and the desired product was produced in 44 and 69% yields when the reaction mixture was heated at 40 and 60 °C, respectively (entries 7 and 8). Mechanistically, it can be postulated that phosphate anions generated in situ via the oxidation of the phosphonyl functional groups by the Ag catalysts subsequently engage in an addition to vinyl aziridine **1a** in an S_N2 ring-opening reaction through the direct displacement of the $C(sp^3)$–N bond.

With a divergent strategy for accessing branched-type products, we explored the substrate scope of the reaction. As summarized in Scheme 4, a wide range of phosphonates underwent the desired cross-coupling reaction to yield the corresponding products (**4b**–**f**). In addition, the catalytic system was applicable to di-*p*-tolylphosphine oxide, which afforded desired product **4g**. Next, we sought to demonstrate the utility of this methodology by further exploring its practical applicability in stereospecific synthesis of phosphorus-containing amino acid derivatives that are synthetically and biologically important. Notably, the respective chiral *trans*-vinyl aziridine esters could be subjected to these reaction conditions and effectively converted to phosphate-containing chiral amino acid products **4h**, **4i**, and **4j**, and the formation of only a single stereoisomer was ensured by chiral HPLC analysis of **4h** (>99% ee, see the SI for details).

To elucidate the reaction mechanisms of these two divergent synthetic transformations, several control experiments were conducted as shown in Scheme 5. To determine the possibility of a radical pathway in the phosphonation, diene **5** was subjected to the standard reaction conditions. Indeed, **5** underwent a cascade reaction under the optimized conditions and gave cyclized product **6** by capturing the radical species (Scheme 5a). Next, we evaluated our hypothesis that the use of

DOI: 10.1021/acs.orglett.8b03309
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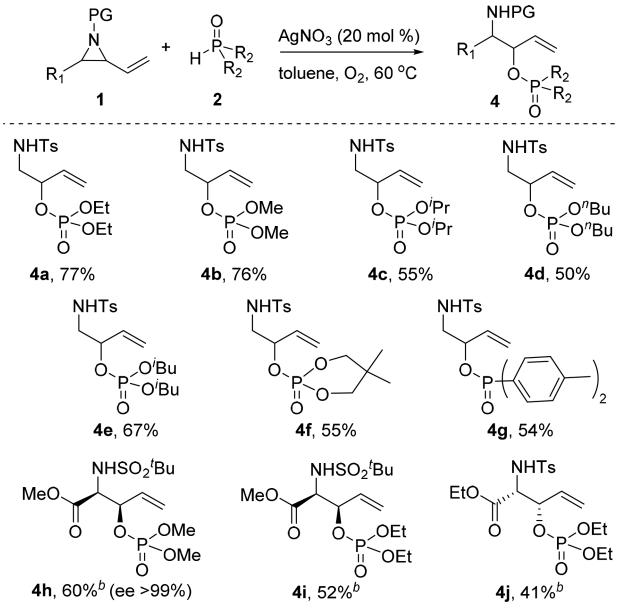
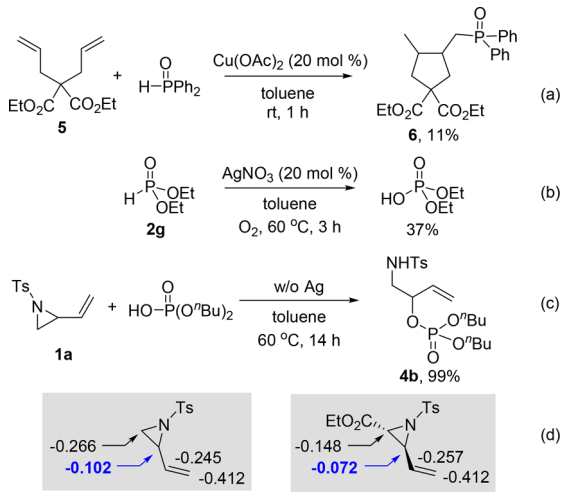
Scheme 4. Substrate Scope of S_N2 Phosphatation[a]



[a]Conditions: **1** (0.1 equiv), **2** (2.0 equiv), and $AgNO_3$ (20 mol %) in toluene (0.1 M) at 60 °C under O_2 atmosphere for 11−17 h. Yields of isolated products. [b]$AgNO_3$ (30 mol %) and **2** (3.0 equiv) were used.

Scheme 5. Control Experiments and NBO Charge Analysis of Vinyl Aziridines



the $AgNO_3$ catalyst promotes the formation of phosphate anions from phosphonyl reactants and investigated the proposed two-step sequence: (1) the generation of phosphate anions and (2) the addition of the resulting phosphate anions to vinyl aziridine. Indeed, phosphate anions were detected under the optimized conditions in the absence of a vinyl aziridine substrate. In addition, we observed the formation of branched product **4a** when H-phosphonate **2g** was used in the presence or absence of the Ag catalyst (Scheme 5c). Based on the analysis of NBO charges of vinyl aziridines, in which the C3 position is notably positive, we suggest that the regioselectivity of ring opening of the vinyl aziridines could be rationalized by the electronic properties of the vinyl aziridine and the incoming nucleophile (Scheme 5d).[12]

On the basis of the above experimental results, a plausible mechanism is proposed in Figure 1. Coordination of the

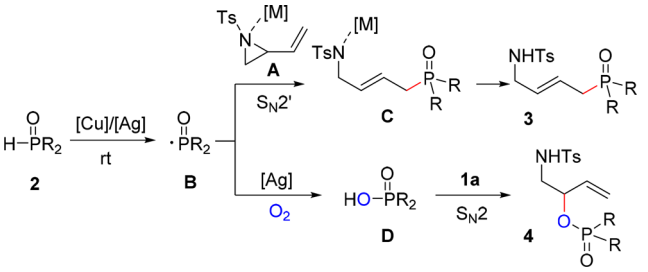


Figure 1. Plausible mechanism of divergent ring-opening of vinyl aziridine.

aziridine nitrogen to the Cu or Ag catalyst provides complex **A**. Subsequent regioselective addition of phosphinoyl radical **B** to vinylaziridine complex **A** delivers linear product **3**. In the oxidative catalytic cycle, the phosphate anion is generated via the Ag-catalyzed oxidation of the phosphonyl group, and the subsequent aziridine ring-opening takes place at the most electrophilic carbon in an S_N2 fashion to afford phosphated branched-type product **4**.

In summary, we have developed a product-switchable catalytic ring-opening cross-coupling of vinyl aziridines and phosphorus reactants to access valuable phosphorus-containing amino compounds. Importantly, the regioselective divergency is controlled by the choice of reaction atmosphere (O_2 vs N_2) and temperature. This divergent strategy offers a convenient and powerful synthetic tool for accessing optically active phosphorus-containing amino acid derivatives with potential applications in the construction of focused chemical libraries of medicinally relevant compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03309.

Experimental procedures and characterization of new compounds (^1H, ^{13}C, and ^{31}P NMR spectra) (PDF)

Accession Codes

CCDC 1872730, 1872732, 1872880, 1872886−1872887, and 1873505 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

This research was supported financially by the Institute for Basic Science (IBS-R010-G1). We thank Dr. Dongwook Kim (IBS) for XRD analysis.

DOI: 10.1021/acs.orglett.8b03309
Org. Lett. XXXX, XXX, XXX−XXX

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DOI: 10.1021/acs.orglett.8b03309
Org. Lett. XXXX, XXX, XXX−XXX