OL | Organic Letters

Letter

Cite This: Org. Lett. 2019, 21, 9753–9758

pubs.acs.org/OrgLett

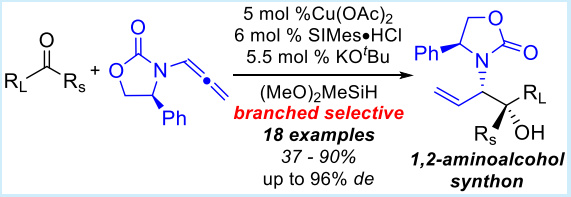
Access to a Catalytically Generated Umpolung Reagent through the Use of Cu-Catalyzed Reductive Coupling of Ketones and Allenes for the Synthesis of Chiral Vicinal Aminoalcohol Synthons

Samantha L. Gargaro,[†] Raphael K. Klake,[†] Kevin L. Burns, Sharon O. Elele, Skyler L. Gentry, and Joshua D. Sieber*

Department of Chemistry, Virginia Commonwealth University, 1001 West Main Street, Richmond, Virginia 23284-3028, United States

Supporting Information

ABSTRACT: We report the development of a stereoselective method for the allylation of ketones utilizing N-substituted allyl equivalents generated from a chiral allenamide. By employing N-heterocyclic carbenes as ligands for the Cu catalyst, good branched selectivity can be obtained with high diastereocontrol. This methodology allows access to a catalytically generated, polarity-reversed (umpolung) allyl nucleophile to enable the preparation of chiral 1,2-aminoalcohol synthons containing a dissonant functional group relationship.



Chiral 1,2-aminoalcohols [**1** (Figure 1)] make up an important class of biologically active compounds prevalent in nature and the pharmaceutical industry.[1] A recent publication[2] states that there are currently >300000 compounds, >2000 natural products, and >80 Food and Drug Administration-approved drugs bearing this motif. As a result, the development of asymmetric methods for preparing 1,2-aminoalcohols is an important endeavor in organic chemistry.[1b−d,3] However, the 1,2-dipolar substitution present in **1** can be challenging to access using typical two-electron processes (i.e., electrophile + nucleophile) because the 1,2-relationship between the hydroxyl and amino groups creates a dissonant pattern about the carbon skeleton.[4] As a result, polarity-reversed (umpolung[4a]) methods for accessing anion equivalents of type **3** or **4** are a possible strategy for enabling this challenging bond formation. For example, the Henry reaction[5] between a nitroalkane nucleophile and a carbonyl electrophile is a powerful technique for accessing vicinal aminoalcohols after reduction of the nitro group to the desired amine. Alternatively, **4** can be prepared by direct α-lithiation of alkylamines,[6,7] but these methods require cryogenic conditions, the use of stoichiometric amounts of sparteine to control stereochemistry, and the use of a strong base (alkyllithiums). To circumvent these limitations, it would be desirable to develop methodologies that enable generation of the polarity-reversed anion **3** or **4** in a catalytic fashion under ambient conditions.[8]

Recently, Malcolmson[8a] developed an elegant umpolung-based approach for the stereoselective synthesis of 1,2-aminoalcohols (**8**) by an asymmetric Cu-catalyzed reductive coupling of enamines and ketones (Figure 1 B). The process presumably is enabled by the catalytic generation of α-aminoanion equivalent **9** by hydrocupration of enamine **7** by a chiral Cu−H catalyst. Addition of **9** to a ketone ultimately generates silylated product **10** after turnover of the catalyst with silane. Additionally, we recently developed a Cu-catalyzed reductive coupling of ketones and allenamide **11** for the diastereoselective synthesis of linear product *l*-**12** that represents a masked γ-hydroxyaldehyde equivalent (Figure 1C).[9] By tuning of the ligand in this reaction, high linear selectivity could be obtained when using phosphoramidite $(PhO)_2PNMe_2$ (**14**) for this process. This methodology is currently proposed to proceed through the catalytically generated α,γ-aminoanion **13**. Initial results imply that linear selectivity occurs through addition of **13** to ketone **6** at the γ-position of the anion due to the directing effect of the oxazolidinone by coordination with Cu. Inspired by the work of Malcolmson,[8a,b] we envisioned that if the ligand could be modified to destabilize the coordinating ability of the oxazolidinone, the α-site of nucleophile **13** may become more reactive, enabling a branched selective process to provide *b*-**12** as an 1,2-aminoalcohol surrogate. Such a process would represent a catalytic stereoselective aminoallylation reaction that is only recently beginning to emerge.[2,10,11] The results of our study to enable a diastereoselective synthesis of 1,2-aminoalcohol synthon *b*-**12** by use of an N-heterocyclic carbene (NHC)-derived Cu catalyst are disclosed herein.

Investigation of the ligand effect in the reaction of acetophenone with allenamide **11** was initially studied in an effort to develop a branched selective reductive coupling for the formation of product *b*-**12a** (Table 1). Allenamide **11** bearing the phenethanol-derived oxazolidinone chiral auxiliary

Received: November 4, 2019
Published: November 26, 2019

DOI: 10.1021/acs.orglett.9b03937
Org. Lett. 2019, 21, 9753–9758

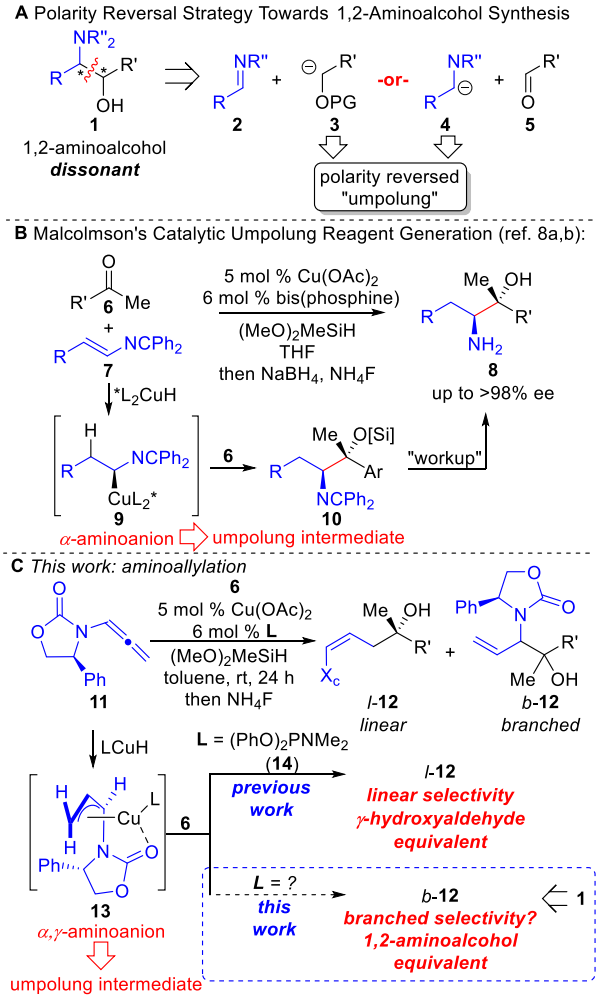
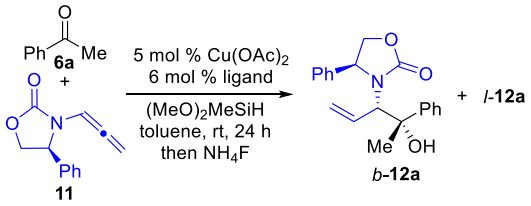


Figure 1. Catalytic umpolung reagent generation.

was specifically examined because the benzylic N-substitution allows for additional options for subsequent deprotection of the amino group within *b*-**12a** (e.g., hydrogenolysis). Previous work toward developing the linear selective version of this reaction identified that when using monodentate phosphine ligands, a decreasing linear selectivity was obtained as the electron-donating ability of the phosphine improved (entries 1−4).

Because coordination of the oxazolidinone moiety to Cu is believed to be important for improving linear selectivity, increasing branched selectivity with increasing ligand electron-donating ability can be rationalized by inhibition of oxazolidinone binding to Cu as the catalyst becomes more electron-rich. On the basis of this concept, we hypothesized that reaction conditions that would inhibit oxazolidinone coordination should enable improved branched selectivity (e.g., bidentate ligands, coordinating solvents, and strongly electron-donating ligands[12]). Therefore, we initially investigated some electron-rich bidentate phosphine ligands (entries 5−10). Use of dcpe, a common ligand employed in Cu-catalyzed reductive coupling reactions,[13] afforded branched selectivity albeit with poor diastereocontrol (entry 5). Use of more strongly coordinating solvents was not beneficial (entries 6 and 7), and changing the bite angle of the ligand (entry 8) or the size of the phosphorus substituent (entries 9 and 10) did not offer any additional improvements. Finally, we investigated

Table 1. Copper-Catalyzed Reductive Coupling[a]



entry	ligand	TEP[b]	yield *b*-**12a**[c] (%)	dr[c]	*b*:*l*[c]
1	$P(OPh)_3$	2085	<2	–	1:99
2	$(PhO)_2PNMe_2$	–	2	–	3:97
3	$P(NMe_2)_3$	2062	16	88:12	17:83
4	PCy_3	2056	17	93:7	20:80
5	dcpe	–	47	53:47	77:23
6[d]	dcpe	–	28	59:41	65:35
7[e]	dcpe	–	24	60:40	53:47
8	dcpm[f]	–	25	92:8	39:61
9	dcyppe[g]	–	32	54:46	66:34
10	depe[h]	–	27	57:43	50:50
11	IPr	2052	70	87:13	87:13
12	SIPr	2052	15	82:18	99:1
13	IMes	2051	76	93:7	83:17
14	SIMes	2052	78	92:8	89:11

[a]**6a** (0.25 mmol) and **11** (0.30 mmol) in 0.5 mL of toluene. See the Supporting Information for details. [b]Tolman electronic parameter from refs 12 and 14a. [c]Determined by ^{1}HNMR spectroscopy on the unpurified reaction mixture using dimethylfumarate as a standard. [d]Reaction in DME. [e]Reaction in THF. [f]Dicyclohexylphosphinomethane. [g]Dicyclopentylphosphinoethane. [h]Diethylphosphinoethane.

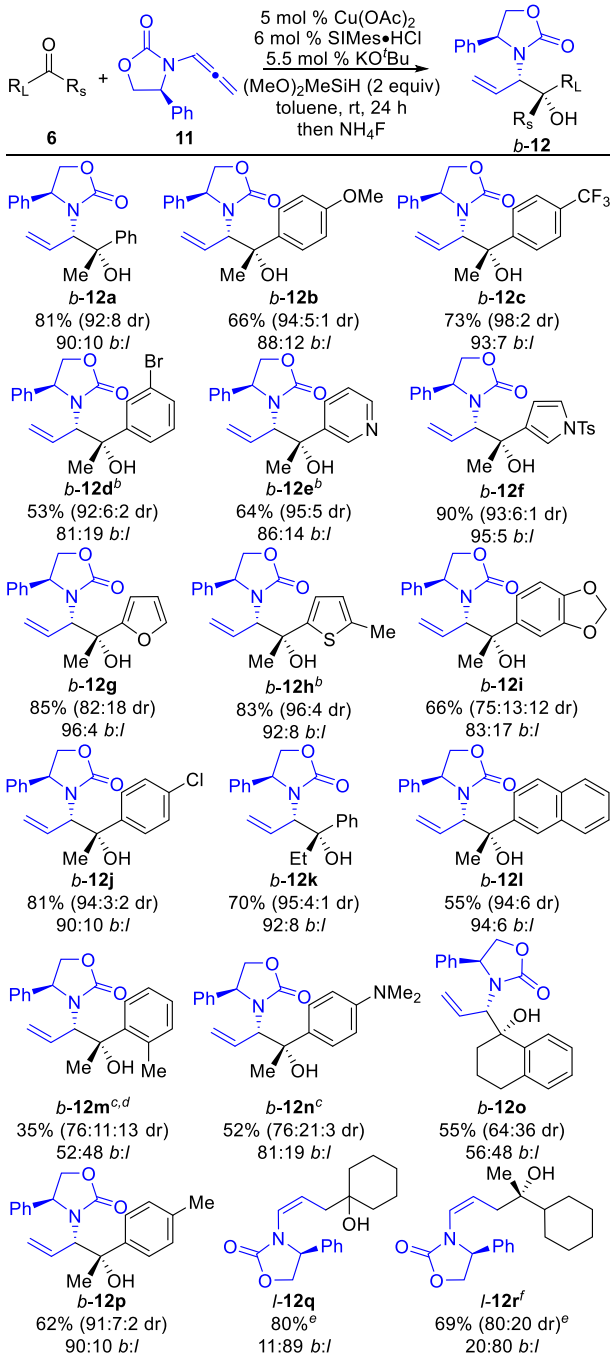
NHC ligands due to their strong electron-donating ability (entries 11−14).[14] Gratifyingly, use of SIMes enabled good branched selectivity with good yield and acceptable diastereoselectivity (entry 14).

After identifying a catalyst for selective generation of the branched product (Table 1, entry 14), we next investigated the scope of this reductive coupling reaction (Scheme 1). Both electron-rich (*b*-**12b**) and electron-poor (*b*-**12c** and *b*-**12j**) ketones performed similarly in the reaction, affording slightly improved diastereoselectivities. Aryl halides (*b*-**12d** and *b*-**12j**) and heterocyclic ketones (*b*-**12e−h**) were well tolerated in the reaction, and a ketone with a free amino group (*b*-**12n**) could also be employed. Overall, the reaction was very sensitive to steric effects. For example, *meta* substitution (*b*-**12d** and *b*-**12i**) afforded reduced branched selectivity, resulting in a lower overall yield. Similarly, *ortho* substitution (*b*-**12m**) was not well tolerated, leading to a low yield of a branched product due to the formation of increased amounts of the linear product. Cyclic ketones (*b*-**12o** and *l*-**12q**) also afforded reduced branched selectivity. Furthermore, an aliphatic ketone also generated preferentially the linear reaction product (*l*-**12r**).

A rationale for the observed stereochemical outcome and the branched selectivity obtained when using NHC ligands in the reaction is given in Scheme 2. Previous work demonstrated that the use of phosphine ligands in the reaction results in selective formation of linear product *l*-**12a** through proposed γ-addition of complex *π*-**15** or *b*-*σ*-**15** to ketones through a closed chairlike transition state.[9] Initial hydrocupration of **11** is proposed to occur *trans* to the large oxazolidinone group to give rise initially to the *Z* geometry of (*σ*-allyl)Cu complex *l*-*Z*-**15**.[9,16] The preferred linear selectivity is believed to occur by a preference for complexes *π*-**15** and/or *b*-*σ*-**15** due to the A^{1,3}-

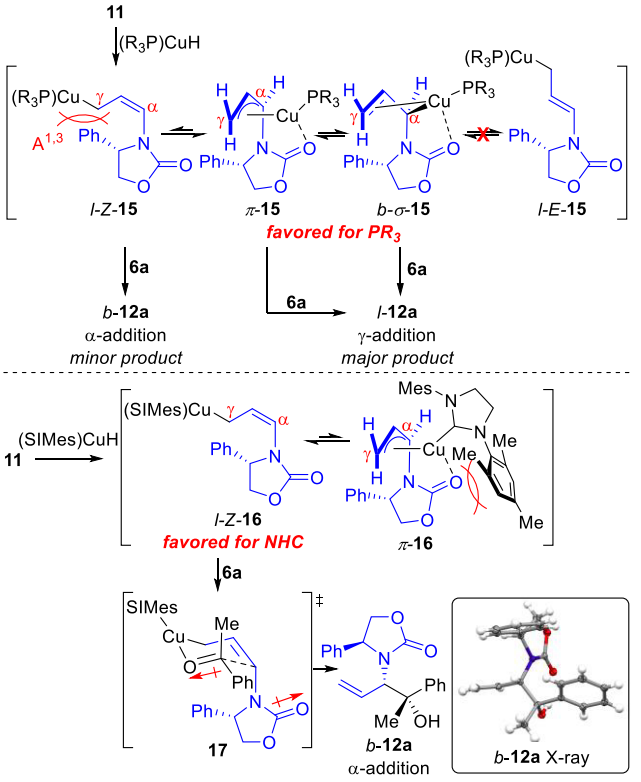
DOI: 10.1021/acs.orglett.9b03937
Org. Lett. 2019, 21, 9753−9758

Scheme 1. Branched Selective Copper(NHC)-Catalyzed Reductive Coupling of Ketones and Allenamide 11[a]



[a]Isolated yields are of the branched product as a mixture of detectable diastereomers (ref 15) as an average of two experiments performed on a 0.5 mmol scale of **6** using 1.2 equiv of **11**. Diastereomerically pure material can be obtained by crystallization (see the Supporting Information for details). Diastereomeric ratios (dr's) and branched:-linear ratios (*b*:*l*) were determined by ^{1}H NMR spectroscopy on the unpurified reaction mixture. [b]IMes·HCl was used. [c]Reaction performed at 40 °C. [d]Double the catalyst loading used. [e]Isolated yield and dr of the linear isomer. [f]Reaction performed at 60 °C.

Scheme 2. Stereo- and Regiochemical Model



strain present in *l*-*Z*-**15** and the directing effect of the oxazolidinone carbonyl[9,17] that distorts π-**15** so that Cu is biased toward the α-site.[18] The A^{1,3}-strain present in *l*-*Z*-**15** appears to be the main interaction that leads to linear product formation using phosphine ligands because both electron-rich (Table 1, entry 4) and electron-deficient (Table 1, entry 1) phosphines provide linear selectivity. However, ligand electronics still play an important role as weakening the electron-donating ability of the phosphine allows for an increase in the linear selectivity, presumably due to enhancement of the coordinating ability of the oxazolidinone moiety as Cu becomes more electrophilic (Table 1, entries 1−4).[9] Finally, because the A^{1,3}-strain appears to play a critical role in regioselectivity, full isomerization of **15** to *l*-*E*-**15** likely is not occurring, which suggests that the alkene moiety of *b*-σ-**15** is still bound to Cu.[9,18]

On the basis of the preceding analysis, the branched product would be expected to arise from reaction of ketone **6a** with *l*-*Z*-**15** or *l*-*Z*-**16**. When NHC ligands are employed (i.e., *l*-*Z*-**16** and π-**16**), reaction of the linear (σ-allyl)Cu complex *l*-*Z*-**16** with ketone **6a** through dipole-minimized[19] chairlike[20] transition structure **17** correctly predicts the observed major diastereomer formed in the reaction (determined by X-ray crystollagraphic analysis of *b*-**12a**).[15] The preference for *l*-*Z*-**16** over π-**16** for NHC ligands can be rationalized by the strong electron-donating ability of these ligands[14] that can disfavor oxazolidinone coordination and because the large mesitylene group may sterically shield the Cu atom from carbonyl coordination. Evidence for this steric shielding effect by the NHC is supported by the improved branched selectivity that was obtained when utilizing IPr or SIPr in place of IMes or SIMes, respectively (Table 1, entries 11 and 12 vs entries 13 and 14). For example, SIPr and SIMes are electronically similar, yet the more sterically demanding SIPr ligand provided improved branched selectivity over SIMes albeit with reduced diastereocontrol. Presumably, these effects introduced by the NHC ligand are stronger than those of the A^{1,3}-strain present

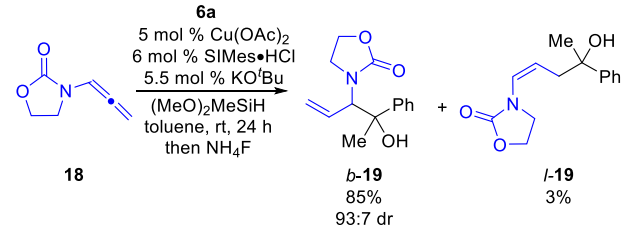
DOI: 10.1021/acs.orglett.9b03937
Org. Lett. 2019, 21, 9753−9758

in *l-Z*-**16**, resulting in selective formation of the branched product.

Overall, there appears to be a delicate balance between the stability of *l-Z*-**16** versus π-**16**, and the resulting transition states leading to branched versus linear product formation in this (NHC)Cu-catalyzed reductive coupling reaction as *ortho*-substituted (**12m** and **12o**), cyclic (**12o** and **12q**), and dialkyl (**12r**) ketones all resulted in reduced branched selectivity. The cause of this decreased regioselectivity for these ketones requires further investigation but may arise due to enhanced steric interactions present with these ketones in transition structure **17** due to the presence of *ortho* substitution (**12m** and **12o**) or nonplanar substituents (**12q** and **12r**) on the ketone electrophile.

On the basis of the model given in Scheme 2, allenamide **18** lacking branching on the oxazolidinone was examined in the reaction (Scheme 3). If steric and electronic effects of the

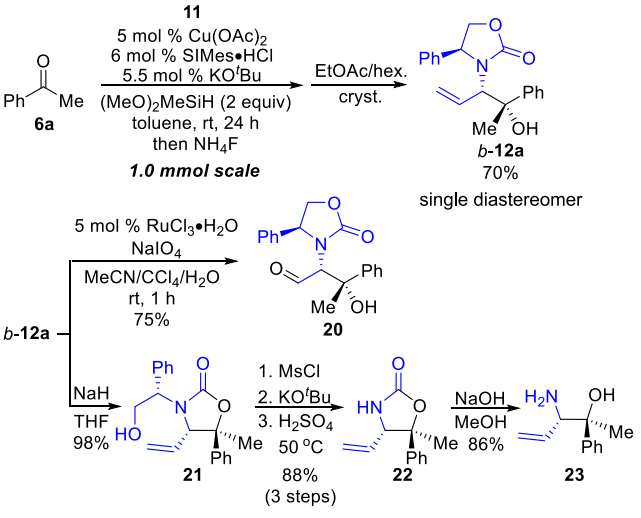
Scheme 3. Effect of Oxazolidinone Structure on Reaction Regioselectivity



NHC ligand in π-**16** are more pronounced than the $A^{1,3}$-strain present in *l-Z*-**16**, one would predict that alleviating $A^{1,3}$-strain in *l-Z*-**16** would lead to increased branched selectivity. Consistent with this proposal, use of unsubstituted allenamide **18** having a smaller oxazolidinone group relative to allenamide **11** in the reaction afforded improved branched selectivity (96:4 *b*:*l*), further supporting the importance of oxazolidinone size on the magnitude of the $A^{1,3}$ interaction present in the linear (σ-allyl)Cu complexes (*l-Z*-**15** and *l-Z*-**16**) as a tuning element for reaction regioselectivity.

Synthetic applications of the products produced in the branched selective Cu-catalyzed reductive coupling reaction are given in Scheme 4. The reaction could be carried out on a

Scheme 4. Synthetic Applications



1.0 mmol scale, and diastereomerically pure product could be isolated after crystallization from hexanes/EtOAc in good overall yield. Oxidative cleavage of the olefin functionality of *b*-**12a** was achieved to enable the synthesis of chiral α-amido-β-hydroxyaldehyde **20**. Finally, to remove the chiral oxazolidinone group to unmask the 1,2-aminoalcohol, treatment of *b*-**12a** with NaH led to clean carbamate migration affording **21**. The phenethanol group of **21** was then cleaved to carbamate protected aminoalcohol **22** through mesylation/elimination followed by acidic hydrolysis of the enamide in good overall yield for the three-step sequence.[21] Basic hydrolysis of **22** then provided 1,2-aminoalcohol **23**.

In conclusion, we have disclosed a strategy for the stereoselective reductive coupling of ketones and a chiral allenamide to selectively afford branched products providing dissonant 1,2-aminoalcohol patterns. This method employs simple starting materials and a readily available catalyst system for furnishing chiral products with increased complexity in an efficient manner. Further development of this reaction to enable stereocontrol by a chiral catalyst is currently being pursued and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b03937.

Experimental procedures, characterization data for all compounds, and NMR spectra (PDF)

Accession Codes

CCDC 1936234 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.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jdsieber@vcu.edu.

ORCID

Samantha L. Gargaro: 0000-0001-7518-3591
Raphael K. Klake: 0000-0002-7135-0505
Joshua D. Sieber: 0000-0001-6607-5097

Author Contributions

†S.L.G. and R.K.K. contributed equally to this work.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Start-up funding from Virginia Commonwealth University (VCU) and the Bill and Melinda Gates Foundation (The Medicines for All Institute, Grant OPP#1176590) is gratefully acknowledged. The authors thank Dr. Faik Musayev (VCU) for X-ray crystallographic analysis that was partially supported by Structural Biology resources provided by National Institutes of Health Shared Instrumentation Grant S10-OD021756 (MKS) and Virginia General Assembly Higher Education Equipment Trust Fund (HEETF) to VCU. The authors thank

DOI: 10.1021/acs.orglett.9b03937
Org. Lett. 2019, 21, 9753−9758

Dr. Joseph Turner (VCU) for assistance in collecting HRMS data.

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DOI: 10.1021/acs.orglett.9b03937
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