Organic LETTERS

Letter

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

pubs.acs.org/OrgLett

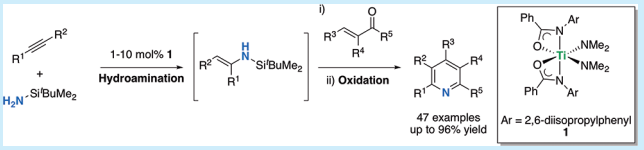
# N-Silylenamines as Reactive Intermediates: Hydroamination for the Modular Synthesis of Selectively Substituted Pyridines

Erica K. J. Lui, Daniel Hergesell, and Laurel L. Schafer*

Department of Chemistry, University of British Columbia, 2036 Main Mall, Vancouver, British Columbia, Canada V6T 1Z1

Supporting Information

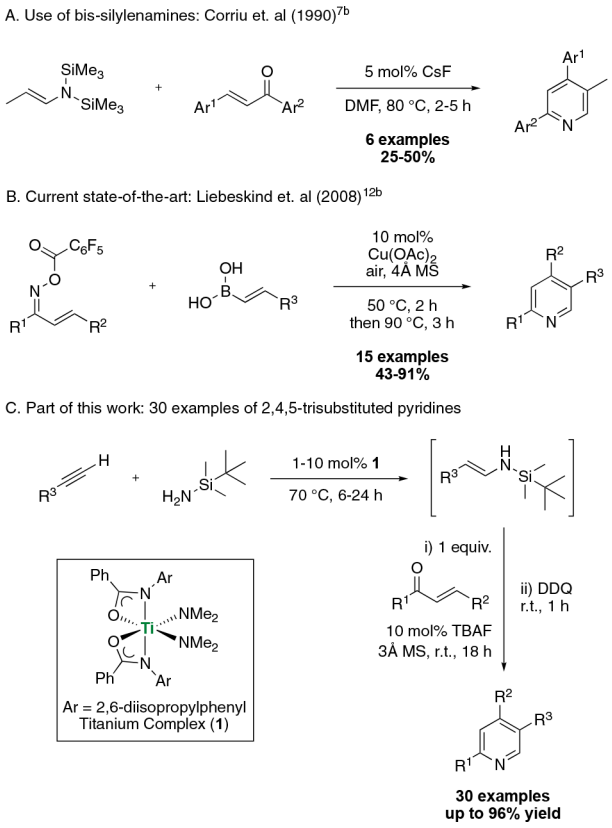
**ABSTRACT:** A modular and selective synthesis of mono-, di-, tri-, tetra-, and pentasubstituted pyridines is reported. Hydroamination of alkynes with *N*-silylamine using a bis(amidate)-bis(amido)titanium(IV) precatalyst furnishes the regioselective formation of *N*-silylenamines. Addition of α,β-unsaturated carbonyls to the crude mixtures followed by oxidation affords 47 examples of pyridines in yields of up to 96%. This synthetic route allows for the synthesis of diverse pyridines containing variable substitution patterns, including pharmaceutically relevant 2,4,5-trisubstituted pyridines, using this one-pot protocol.




A wide variety of pyridines can be found in natural products[1] and pharmaceutical agents,[2] thus, significant effort has been employed toward their efficient preparation. In order to access pyridines with selected substitution patterns, two approaches are commonly employed: stepwise functionalization of the pyridine core[3] or formation of the six-membered aromatic ring through condensation, cycloisomerization, or cycloaddition.[4] Selective functionalization of the pyridine core is a useful approach, although in the cases of multisubstituted pyridines, it can be material and labor intensive. On the other hand, combining two or more simple molecules via thermal or metal-catalyzed reactions can readily assemble variously substituted pyridines.[4b−d] Established condensation methods using 1,3- or 1,5-dicarbonyl derivatives are easy to use but offer restricted substitution patterns. For example, the Hantzsch pyridine synthesis reacts 1,3-dicarbonyls, an aldehyde, and an ammonia source in one pot to typically form substituted pyridines with specifically electron-withdrawing substituents in the 3- and/or 5-positions.[5] The Kröhnke synthesis, on the other hand, starts with a pyridinium salt and an α,β-unsaturated carbonyl to form a 1,5-dicarbonyl intermediate, which can then react with ammonium acetate to deliver 2,4,6-trisubstituted pyridines selectively.[6] However, yields can be problematic as dicarbonyls are prone to side reactions, such as intra- or intermolecular condensations, especially in cases where aldehydes are required to make pyridines without ortho-substituents. Thus, a flexible and selective approach for the rapid assembly of a library of pyridines with diverse substitution patterns would allow for the modular assembly of important substituted pyridine products and building blocks.

*N*-Silylated enamines have been used to construct select substituted pyridines (Scheme 1A),[7] although few preliminary results were disclosed due to the difficult preparation and handling of moisture-sensitive *N*-silylenamines using traditional stoichiometric approaches. However, our recently reported regioselective catalytic alkyne hydroamination reaction to give *N*-silylamines enables reliable and efficient access to a wide range of monosilylated enamines.[8] Such masked primary enamines are reactive nucleophilic synthons that allow for subsequent reactivity. Here, we show how the in situ generation of silylenamines by the anti-Markovnikov regioselective hydroamination of alkynes followed by six-membered ring formation

**Scheme 1. Synthesis of 2,4,5-Trisubstituted Pyridines**




**Received:** August 23, 2018






DOI: 10.1021/acs.orglett.8b02703
Org. Lett. XXXX, XXX, XXX−XXX

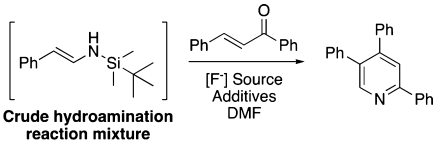
via addition to an α,β-unsaturated aldehyde or ketone and subsequent oxidation affords a range of selectively substituted pyridines, including 3-mono-, 2,5-di-, 3,4-di-, 2,3,5-tri-, 2,4,5-tri-, 2,3,4,5-tetra-, 2,3,4,6-tetra-, and even 2,3,4,5,6-pentasubstituted pyridines. In three sequential steps, 47 examples of substituted pyridines were synthesized, including 30 examples of 2,4,5-trisubstituted pyridines. This specific substitution pattern was important for the development of a new class of $NK_1$ receptor antagonists,[9] the preparation of radiolabels for PET imaging,[10] and the synthesis of alkaloids, such as flavocarpine and dihydrovincarpine.[11] Notably, there are few general syntheses of 2,4,5-trisubstituted pyridines,[7b,12] and it is rare to find an approach where the 5-position is something other than methyl (Scheme 1B).[12a−d,f]

Furthermore, the alkyne and α,β-unsaturated carbonyl starting materials are both commercially available. Commercially available *N*-triphenylsilylamine can also be used (vide infra). The intermolecular synthesis of pyridines using unactivated alkynes is commonly performed using late transition metals with coupling partners such as nitriles,[12d,f,13] haloviny-limines,[14] enamides,[15] α,β-unsaturated imines,[16] and α,β-unsaturated ketoximes,[17] which are typically presynthesized. Although α,β-unsaturated carbonyls are readily available, they have been most typically applied toward the synthesis of 2,4,6-trisubstituted pyridines[18] or pyridines containing electron-withdrawing groups (amide, cyano, ester, and ketone groups) at the 3-position,[19] with few examples that reach beyond these limitations.[7a,b,12e,20] Here, we show how alkynes and α,β-unsaturated carbonyls can be used to access a variety of selectively substituted pyridines in moderate to excellent yields, in particular, 2,4,5-substituted pyridines (Scheme 1C).

Preliminary studies on the feasibility of synthesizing substituted pyridines using this approach were performed using ethynylbenzene and (*N*-*tert*-butyldimethylsilyl)amine to generate the reactive *N*-silylenamine synthon in situ. Subsequently *trans*-chalcone was added for the development of optimized conditions for the second step of the reaction (Table 1).[21] Whereas the reaction does occur in the absence of additives at 100 °C, the 11% yield is unsatisfactory. The addition of catalytic amounts of a fluoride source helped activate the N−Si bond. For example, by adding 0.05 equiv of CsF, the yield of the desired product was increased to 43%. By changing the fluoride source to TBAF, the yield was not improved; however, a 1 M solution of TBAF in THF is procedurally easier to handle.[22] The addition of 3 Å molecular sieves further increased the yield to 62% (entry 4). Finally, addition of DDQ as an oxidant allowed for the isolation of the desired product in 78% yield (entry 5).[23] A slight improvement in the yield was obtained using DMSO as the solvent (entry 6). Furthermore, a 5 mmol scale of the reaction was performed to give more than a gram of the desired pyridine (entry 6, yield in parentheses). To demonstrate that the titanium and amidate ligand present no deleterious effect upon this one-pot reaction, intermediate *N*-silylenamine was purified by vacuum distillation prior to ring closure and oxidation. This resulted in a comparable yield (entry 7). The reaction was also successful using commercially available *N*-triphenylsilylamine with a somewhat diminished yield (65%, entry 8).

With optimized conditions in hand, the scope of the sequential procedure was investigated (Scheme 2). We first examined the reaction of ethynylbenzene, with a variety of α,β-unsaturated aldehydes and ketones, which were commercially available or easily synthesized through aldol condensation.[24] By

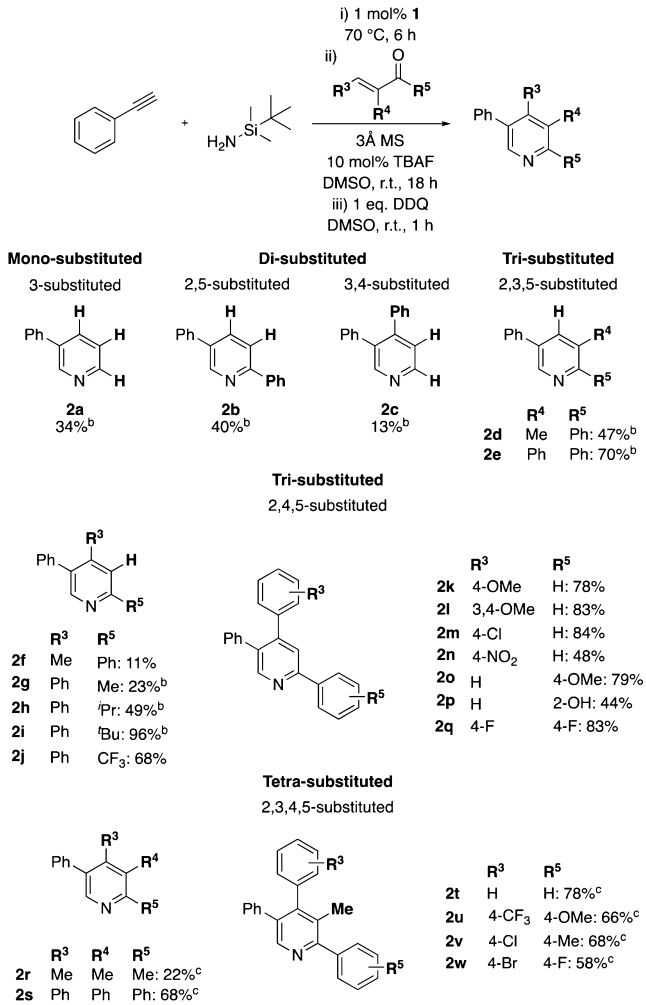
**Table 1. Optimization of Conditions for the Pyridine Formation**




| entry | fluoride source | additive | yield (%)[a] |
|---|---|---|---|
| 1 | | | 11[b] |
| 2 | 0.05 equiv of CsF | | 43[c] |
| 3 | 0.1 equiv of TBAF | | 43 |
| 4 | 0.1 equiv of TBAF | 3 Å MS | 62 |
| 5 | 0.1 equiv of TBAF | 3 Å MS; 1 equiv of DDQ | 78 |
| 6 | 0.1 equiv of TBAF | 3 Å MS; 1 equiv of DDQ | 85[d] (74)[e] |
| 7 | 0.1 equiv of TBAF | 3 Å MS; 1 equiv of DDQ | 83[f] |
| 8 | 0.1 equiv of TBAF | 3 Å MS; 1 equiv of DDQ | 65[g] |

[a]Isolated yields. [b]Heated to 100 °C. [c]Heated to 50 °C. [d]DMSO as solvent. [e]5 mmol scale. [f]Using isolated *N*-silylenamine. [g]Commercially available $Ph_3SiNH_2$.

**Scheme 2. Various α,β-Unsaturated Carbonyl Substrates can be Incorporated[a]**




[a]Isolated yields. [b]One-pot reaction: hydroamination reaction performed under neat conditions followed by addition of α,β-unsaturated carbonyl. [c]Second step performed at 80 °C.



DOI: 10.1021/acs.orglett.8b02703
Org. Lett. XXXX, XXX, XXX−XXX

reacting the hydroamination product mixture with prop-2-enal, an example of a monosubstituted pyridine was obtained in 34% yield (**2a**). By using a monosubstituted $\alpha,\beta$-unsaturated carbonyl substrate, disubstituted pyridines, with 2,5- or 3,4-substitution patterns, were obtained in 40 and 13% yields, respectively (**2b** and **2c**). Reduced yields observed for the reactions using aldehydes are likely due to ill-defined side reactions of these substrates in the presence of the Lewis acidic titanium catalyst. The flexibility of this approach is highlighted by the fact that 2,5-diphenylpyridine is commonly prepared via a double Suzuki coupling.[25] However, synthesis of 2,5-disubstituted pyridines with different substituents demands sequential and chemospecific reaction conditions to distinguish between (pseuso)halogens. For 3,4-diphenylpyridine, only six procedures have been disclosed, all of which require multistep protocols.[26] Meanwhile, our approach is completely regioselective and features a common reaction protocol in all cases.

Disubstituted $\alpha,\beta$-unsaturated ketones can be used to access trisubstituted pyridines with excellent regioselectivity for either 2,3,5- or 2,4,5-positions. These variably substituted products were synthesized in a variety of yields ranging from 11 to 96% (**2d**−**q**). In medicinal chemistry, a trifluoromethyl group can drastically change the physical and biological properties of heterocycles.[27] Thus, a noteworthy example is pyridine **2j**, which contains a trifluoromethyl group at the 2-position. This desirable motif was synthesized in 68% yield from 1,1,1-trifluoro-4-phenylbut-3-en-2-one.[28] The regioselectivity of pyridine formation was confirmed by X-ray diffraction of crystalline product **2m** (Figure 1). Finally, the synthesis of 2,3,4,5-tetrasubstituted

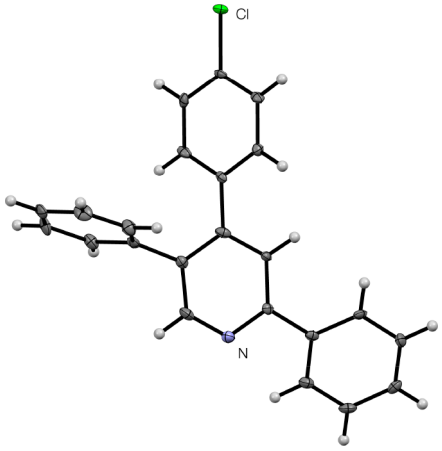
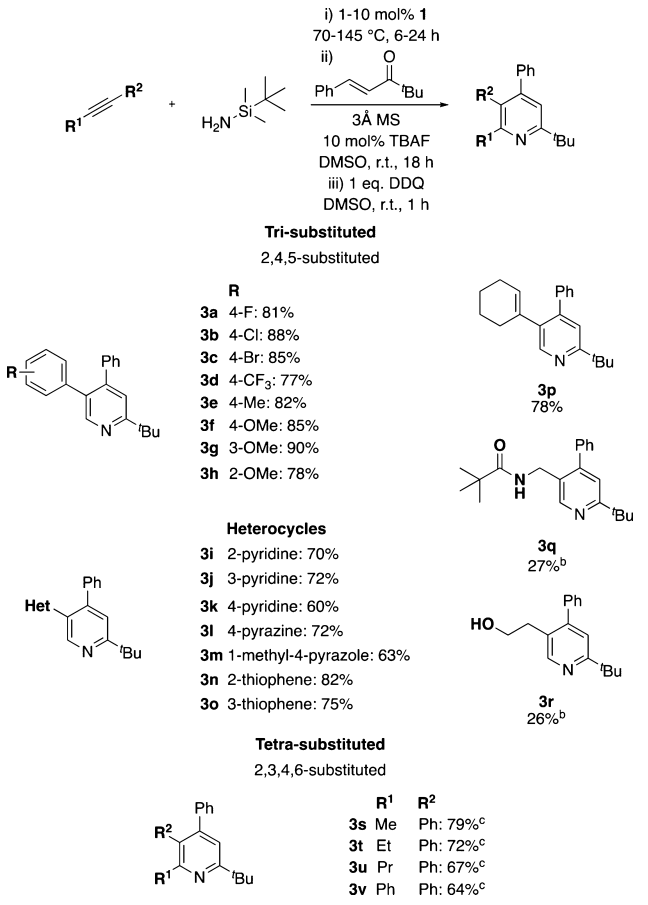



**Figure 1.** X-ray crystallographic structure of pyridine **2m**.

pyridines could also be achieved using trisubstituted $\alpha,\beta$-unsaturated ketones. Notably, this transformation features symmetrical and unsymmetrical $\alpha,\beta$-unsaturated ketones in yields of up to 78% (**2r**−**w**). In particular, 4 of the 5 examples of 2,3,4,5-tetrasubstituted pyridines reported here are new compounds, which suggests that routine methods for accessing these more highly substituted pyridines are underdeveloped.[29]

Next, the effect of different alkyne substituents on the sequential reaction was examined using 4,4-dimethyl-1-phenylpent-1-en-3-one as a consistent $\alpha,\beta$-unsaturated carbonyl substrate (Scheme 3). In all cases, full consumption of starting materials in the hydroamination step is observed, and the $^1$H NMR yields for the synthesized *N*-silylenamines vary between 69 and 99%.[8] Halogenated *para*-substituted ethynylbenzenes (**3a**−**c**) were successfully employed in 81−88% yields. The

**Scheme 3. Effect of Alkyne Substituents on Sequential Reaction for Pyridine Synthesis**[a]




[a]Isolated yields. [b]Second step performed at 50 °C. [c]Second step performed at 80 °C.

presence of chloro and bromo substituents could allow for further cross-coupling transformations to be performed. Other *para*-substituted ethynylbenzenes bearing electron-donating and electron-withdrawing substituents were used to give products (**3d**−**f**) in great yields. The *meta*- (**3g**) and *ortho*-substituted (**3h**) ethynylbenzenes were also tolerated with no notable decrease in pyridine yield.

The synthesis of pyridines containing other heterocycles on the 3- or 5-positions is important, as seen in current commercial drugs such as Crizotinib, Etoricoxib, and Imatinib. Using our developed methodology, alkynes containing various nitrogen or sulfur heterocycles (**3i**−**o**) were also compatible with these reaction conditions, and the resultant pyridines could be synthesized and isolated in good yields (60−82%).

Importantly, our reaction conditions are not limited to arylalkyne substrates, as shown with an enyne precursor (**3p**), as well as the use of an alkylamide to give product (**3q**) and silylether to furnish pyridine (**3r**). Although these different derivatives were tolerated, the latter two were noted to be lower yielding. Synthetic routes to access such alkylated pyridines are rarely reported.[30]

Finally, internal alkynes could be used in combination with disubstituted $\alpha,\beta$-unsaturated ketones to give 2,3,4,6-tetrasubstituted pyridines in 64−79% yields (**3s**−**v**). In the case of unsymmetrical aryl−alkyl internal alkynes, the regioselective hydroamination reaction allowed for the selective synthesis of

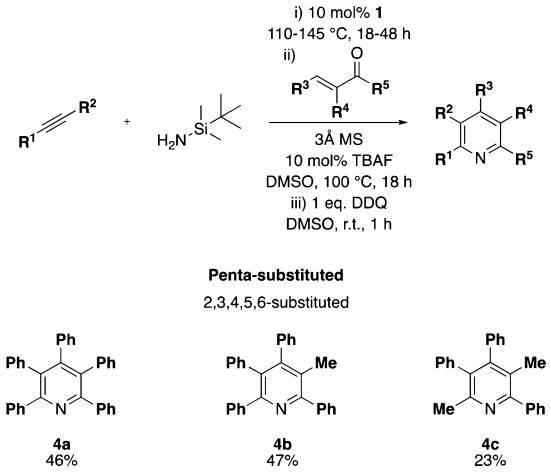


DOI: 10.1021/acs.orglett.8b02703
*Org. Lett.* XXXX, XXX, XXX−XXX

tetrasubstituted pyridines containing an alkyl group at the 2-position and an aryl group on the 3-position (**3s–u**). None of these examples has been reported previously.

The synthesis of pentasubstituted pyridines is a synthetic challenge, particularly in cases where the pyridine core contains five-carbon substitutents.[12c,16,17,31] However, using the developed sequential methodology, pentasubstituted pyridines can be readily assembled in yields of 23–47% (**4a–c**) using the same three-step sequential protocol (Scheme 4).

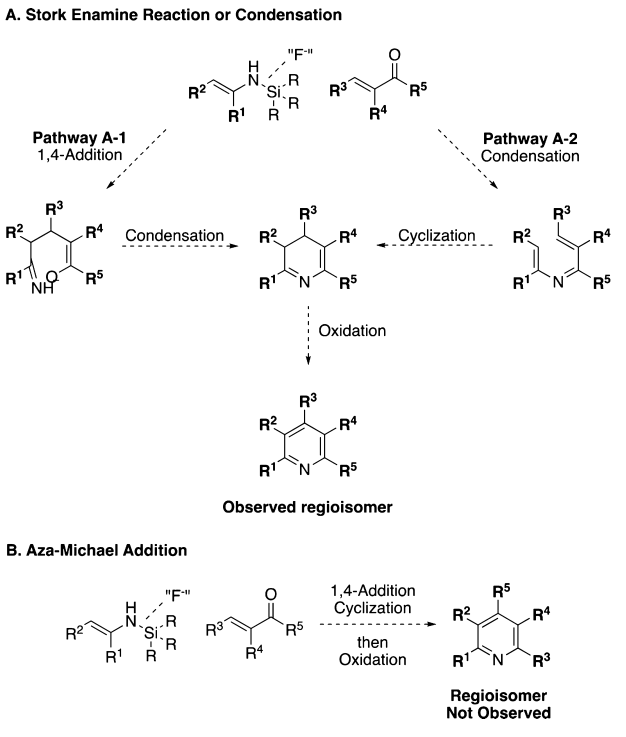
**Scheme 4. Synthesis of Pentasubstituted Pyridines**[a]




[a]Isolated yields.

Analysis of the substitution patterns obtained, as confirmed by crystallographic analysis of product **2m**, provides insight into the mechanistic path for the cycloaddition step of pyridine formation (Scheme 5). As observed, $R^3$ is located in the 4-position, which is consistent with two different mechanistic pathways, a Stork enamine reaction, where the $\beta$-carbon of the enamine attacks the $\alpha,\beta$-unsaturated carbonyl in a 1,4-addition followed by a condensation event (Scheme 5A, pathway A-1), or a condensation followed by a cylization event (Scheme 5A, pathway A-2). After oxidation, the correct pyridine regioisomer would be obtained in both pathways. An alternative pathway could have been an aza-Michael addition, where the nitrogen of the enamine nucleophilically attacks the $\beta$-position of the $\alpha,\beta$-unsaturated carbonyl (Scheme 5B). However, the product resulting from this mechanism would not furnish the observed regioisomer. Carbon-based enamines are known to preferentially react through the $\beta$-carbon of the enamine moiety. However, as shown from our previous study on *N*-silylenamines,[8] which were notably resistant to tautomerization, in contrast to their carbon-substituted variants, the reactivity of enamines containing silicon-based substituents can be different from enamines containing carbon-based substituents. Thus, further investigation on the nucleophilicity of monosilylated enamines is necessary to confirm the mechanistic pathway of this reaction.

**Scheme 5. Potential Pathways for the Formation of Pyridines**




In conclusion, one simple, modular method to prepare mono-, di-, tri-, tetra-, and pentasubstituted pyridines has been disclosed. The one-pot method we have developed employs a sequential regioselective hydroamination of alkynes with *N*-silylamine followed by the addition of an $\alpha,\beta$-unsaturated carbonyl substrate to give a six-membered nitrogen-containing ring intermediate that can undergo oxidation to afford pyridines. A broad range of targeted products could be isolated in typically good yields. The generality of the transformation is demonstrated by using a wide scope of both $\alpha,\beta$-unsaturated carbonyl and alkyne substrates. Notably, both of these starting materials are commercially available and/or easily synthesized. The ring formation is proposed to proceed by a Stork enamine 1,4-addition to furnish the observed selectively substituted pyridine products. Mechanistic investigations and applications in the synthesis of selectively substituted pharmaceutically relevant pyridine compounds are ongoing.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02703.

Full experimental procedures and spectroscopic data (PDF)

### Accession Codes

CCDC 1864356 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: schafer@chem.ubc.ca.

### ORCID

Erica K. J. Lui: 0000-0001-9916-9700
Laurel L. Schafer: 0000-0003-0354-2377

### Notes

The authors declare no competing financial interest.



DOI: 10.1021/acs.orglett.8b02703
*Org. Lett.* XXXX, XXX, XXX–XXX

## ■ ACKNOWLEDGMENTS

The authors thank NSERC for financial support of this work. D.H. thanks the PROMOS scholarship from DAAD.

## ■ REFERENCES

(1) Kiuru, P.; Yli-Kauhaluoma, J. Pyridine and Its Derivatives. In *Heterocycles in Natural Product Synthesis*; Majumdar, K. C., Chattopadhyay, S. K., Eds.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2011.

(2) (a) Baumann, M.; Baxendale, I. R. *Beilstein J. Org. Chem.* **2013**, *9*, 2265. (b) Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 10257.

(3) (a) Nakao, Y. *Synthesis* **2011**, *2011*, 3209. (b) Bull, J. A.; Mousseau, J. J.; Pelletier, G.; Charette, A. B. *Chem. Rev.* **2012**, *112*, 2642. (c) Murakami, K.; Yamada, S.; Kaneda, T.; Itami, K. *Chem. Rev.* **2017**, *117*, 9302.

(4) (a) Varela, J. A.; Saa, C. *Synlett* **2008**, *2008*, 2571. (b) Hill, M. D. *Chem. - Eur. J.* **2010**, *16*, 12052. (c) Gulevich, A. V.; Dudnik, A. S.; Chernyak, N.; Gevorgyan, V. *Chem. Rev.* **2013**, *113*, 3084. (d) Allais, C.; Grassot, J. M.; Rodriguez, J.; Constantieux, T. *Chem. Rev.* **2014**, *114*, 10829.

(5) Henry, G. D. *Tetrahedron* **2004**, *60*, 6043.

(6) (a) Krohnke, F. *Synthesis* **1976**, *1976*, 1. (b) Sasaki, I. *Synthesis* **2016**, *48*, 1974.

(7) (a) Corriu, R. J. P.; Huynh, V.; Moreau, J. J. E.; Pataudsat, M. *Tetrahedron Lett.* **1982**, *23*, 3257. (b) Corriu, R. J. P.; Moreau, J. J. E.; Pataudsat, M. *J. Org. Chem.* **1990**, *55*, 2878. (c) Hojahmat, M.; Konakahara, T.; Tamura, S. *Heterocycles* **2000**, *53*, 629.

(8) Lui, E. K. J.; Brandt, J. W.; Schafer, L. L. *J. Am. Chem. Soc.* **2018**, *140*, 4973.

(9) Harrington, P. J.; Johnston, D.; Moorlag, H.; Wong, J. W.; Hodges, L. M.; Harris, L.; McEwen, G. K.; Smallwood, B. *Org. Process Res. Dev.* **2006**, *10*, 1157.

(10) Damont, A.; Lemee, F.; Raggiri, G.; Dolle, F. *J. Heterocycl. Chem.* **2014**, *51*, 404.

(11) Hirose, Y.; Tsuchikawa, H.; Kobayashi, T.; Katsumura, S. *Heterocycles* **2015**, *90*, 150.

(12) (a) Katritzky, A. R.; Mazurkiewicz, R.; Stevens, C. V.; Gordeev, M. F. *J. Org. Chem.* **1994**, *59*, 2740. (b) Liu, S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2008**, *130*, 6918. (c) Yu, N.; Wang, C.; Zhao, F.; Liu, L.; Zhang, W. X.; Xi, Z. *Chem. - Eur. J.* **2008**, *14*, 5670. (d) Ohashi, M.; Takeda, I.; Ikawa, M.; Ogoshi, S. *J. Am. Chem. Soc.* **2011**, *133*, 18018. (e) Wei, H.; Li, Y.; Xiao, K.; Cheng, B.; Wang, H.; Hu, L.; Zhai, H. *Org. Lett.* **2015**, *17*, 5974. (f) Sheng, J. Y.; Wang, Y.; Su, X.; He, R.; Chen, C. *Angew. Chem., Int. Ed.* **2017**, *56*, 4824.

(13) (a) Wakatsuki, Y.; Yamazaki, H. *J. Chem. Soc., Chem. Commun.* **1973**, 280a. (b) Suzuki, D.; Tanaka, R.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **2002**, *124*, 3518. (c) Takahashi, T.; Tsai, F. Y.; Li, Y.; Wang, H.; Kondo, Y.; Yamanaka, M.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc.* **2002**, *124*, 5059. (d) Satoh, Y.; Obora, Y. *J. Org. Chem.* **2013**, *78*, 7771. (e) Wang, K.; Meng, L. G.; Wang, L. *Org. Lett.* **2017**, *19*, 1958.

(14) (a) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 5306. (b) Roesch, K. R.; Zhang, H.; Larock, R. C. *J. Org. Chem.* **2001**, *66*, 8042.

(15) (a) Movassaghi, M.; Hill, M. D.; Ahmad, O. K. *J. Am. Chem. Soc.* **2007**, *129*, 10096. (b) Yamamoto, S.; Okamoto, K.; Murakoso, M.; Kuninobu, Y.; Takai, K. *Org. Lett.* **2012**, *14*, 3182. (c) Wu, J. C.; Xu, W. B.; Yu, Z. X.; Wang, J. *J. Am. Chem. Soc.* **2015**, *137*, 9489.

(16) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 3645.

(17) (a) Parthasarathy, K.; Jeganmohan, M.; Cheng, C. H. *Org. Lett.* **2008**, *10*, 325. (b) Cheng, C.-H.; Parthasarathy, K. *Synthesis* **2009**, *2009*, 1400. (c) Chiba, S.; Li, X.; Too, P.; Noji, T.; Lim, Y. *Synlett* **2011**, *2011*, 2789. (d) Hyster, T. K.; Rovis, T. *Chem. Commun.* **2011**, *47*, 11846. (e) Martin, R. M.; Bergman, R. G.; Ellman, J. A. *J. Org. Chem.* **2012**, *77*, 2501.

(18) (a) Krohnke, F.; Zecher, W. *Angew. Chem., Int. Ed. Engl.* **1962**, *74*, 626. (b) Del Carmen, M.; Barrio, G.; Barrio, J. R.; Walker, G.; Novelli, A.; Leonard, N. J. *J. Am. Chem. Soc.* **1973**, *95*, 4891. (c) Katritzky, A. R.; Belyakov, S. A.; Sorochinsky, A. E.; Henderson, S. A. *J. Org. Chem.* **1997**, *62*, 6210. (d) Katritzky, A. R.; Abdel-Fattah, A. A. A.; Tymoshenko, D. O.; Essawy, S. A. *Synthesis* **1999**, *1999*, 2114. (e) Boruah, R.; Borthakur, M.; Dutta, M.; Gogoi, S. *Synlett* **2008**, *2008*, 3125.

(19) (a) Sakurai, A.; Midorikawa, H. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 430. (b) Palacios, F.; Herran, E.; Alonso, C.; Rubiales, G.; Lecea, B.; Ayerbe, M.; Cossio, F. P. *J. Org. Chem.* **2006**, *71*, 6020. (c) Lieby-Muller, F.; Allais, C.; Constantieux, T.; Rodriguez, J. *Chem. Commun.* **2008**, 4207. (d) Allais, C.; Constantieux, T.; Rodriguez, J. *Chem. - Eur. J.* **2009**, *15*, 12945. (e) Tenti, G.; Ramos, M. T.; Menendez, J. C. *ACS Comb. Sci.* **2012**, *14*, 551. (f) Xia, Y. J.; Cai, J. H.; Huang, H. W.; Deng, G. J. *Org. Biomol. Chem.* **2018**, *16*, 124.

(20) (a) Donohoe, T. J.; Basutto, J. A.; Bower, J. F.; Rathi, A. *Org. Lett.* **2011**, *13*, 1036. (b) Wei, Y.; Yoshikai, N. *J. Am. Chem. Soc.* **2013**, *135*, 3756. (c) Hardegger, L. A.; Habegger, J.; Donohoe, T. J. *Org. Lett.* **2015**, *17*, 3222. (d) Rieckhoff, S.; Hellmuth, T.; Peters, R. *J. Org. Chem.* **2015**, *80*, 6822. (e) Huang, H.; Cai, J.; Tang, L.; Wang, Z.; Li, F.; Deng, G. J. *J. Org. Chem.* **2016**, *81*, 1499.

(21) Further optimization conditions can be found in the Supporting Information, Tables S1−S3.

(22) Other fluoride sources were also attempted, but no improvement in the yield was obtained (Supporting Information, Table S2).

(23) Further screening of stoichiometric and catalytic oxidant sources were attempted to no avail (Supporting Information, Table S3).

(24) (a) Harrison, C. R. *Tetrahedron Lett.* **1987**, *28*, 4135. (b) Peach, P.; Cross, D. J.; Kenny, J. A.; Mann, I.; Houson, I.; Campbell, L.; Walsgrove, T.; Wills, M. *Tetrahedron* **2006**, *62*, 1864. (c) Smith, C. D.; Rosocha, G.; Mui, L.; Batey, R. A. *J. Org. Chem.* **2010**, *75*, 4716.

(25) (a) Berthiol, F.; Kondolff, I.; Doucet, H.; Santelli, M. *J. Organomet. Chem.* **2004**, *689*, 2786. (b) Pierrat, P.; Gros, P. C.; Fort, Y. *J. Comb. Chem.* **2005**, *7*, 879. (c) El Kadib, A.; McEleney, K.; Seki, T.; Wood, T. K.; Crudden, C. M. *ChemCatChem* **2011**, *3*, 1281. (d) Quan, Z.-J.; Jing, F.-Q.; Zhang, Z.; Da, Y.-X.; Wang, X.-C. *Eur. J. Org. Chem.* **2013**, *2013*, 7175. (e) Shen, Y.; Chen, J.; Liu, M.; Ding, J.; Gao, W.; Huang, X.; Wu, H. *Chem. Commun.* **2014**, *50*, 4292. (f) Zhang, E.; Tang, J.; Li, S.; Wu, P.; Moses, J. E.; Sharpless, K. B. *Chem. - Eur. J.* **2016**, *22*, 5692. (g) Lamei, K.; Eshghi, H.; Bakavoli, M.; Rounaghi, S. A.; Esmaeili, E. *Catal. Commun.* **2017**, *92*, 40.

(26) (a) Yamamoto, K.; Yamazaki, S.; Murata, I.; Fukazawa, Y. *J. Org. Chem.* **1987**, *52*, 5239. (b) Chang, M. Y.; Lin, C. Y.; Hung, C. Y. *Tetrahedron* **2007**, *63*, 3312. (c) Chiba, S.; Xu, Y. J.; Wang, Y. F. *J. Am. Chem. Soc.* **2009**, *131*, 12886. (d) Chang, M. Y.; Lin, C. H.; Chen, Y. L. *Tetrahedron Lett.* **2010**, *51*, 1430. (e) Gati, W.; Rammah, M. M.; Rammah, M. B.; Couty, F.; Evano, G. *J. Am. Chem. Soc.* **2012**, *134*, 9078. (f) Gati, W.; Rammah, M. M.; Rammah, M. B.; Evano, G. *Beilstein J. Org. Chem.* **2012**, *8*, 2214.

(27) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320.

(28) Wang, Y.; Han, J.; Chen, J.; Cao, W. *Tetrahedron* **2015**, *71*, 8256.

(29) Compound **2s** has been recently synthesized by Chen and co-workers. In their synthesis, an alkenylation of nitriles with presynthesized vinyliodonium salts is performed. Refer to reference 12f.

(30) Palacios, F.; Vicario, J.; Aparicio, D. *Tetrahedron Lett.* **2007**, *48*, 6747.

(31) (a) Chibiryaev, A. M.; De Kimpe, N.; Tkachev, A. V. *Tetrahedron Lett.* **2000**, *41*, 8011. (b) Doebelin, C.; Wagner, P.; Bihel, F.; Humbert, N.; Kenfack, C. A.; Mely, Y.; Bourguignon, J. J.; Schmitt, M. *J. Org. Chem.* **2014**, *79*, 908. (c) Reimann, S.; Ehlers, P.; Petrosyan, A.; Kohse, S.; Spannenberg, A.; Surkus, A. E.; Ghochikyan, T. V.; Saghyan, A. S.; Lochbrunner, S.; Kuhn, O.; Ludwig, R.; Langer, P. *Adv. Synth. Catal.* **2014**, *356*, 1987. (d) Tan, W. W.; Ong, Y. J.; Yoshikai, N. *Angew. Chem., Int. Ed.* **2017**, *56*, 8240.



DOI: 10.1021/acs.orglett.8b02703
*Org. Lett.* XXXX, XXX, XXX−XXX