Organic LETTERS

Letter

pubs.acs.org/OrgLett

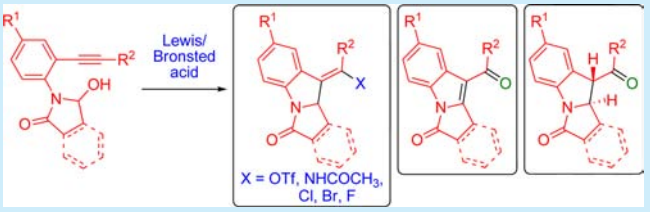
Counter-Ion-Dependent Alkyne Iminium Ion Cyclization for Divergent Synthesis of *N*-Fused Indolylidine, Indole, and Indoline Derivatives Promoted by the Lewis/Bronsted Acid

Santosh J. Gharpure,* Yogesh G. Shelke, and Dasari Praveen Kumar

Department of Chemistry, Indian Institute of Technology Bombay, Powai, Mumbai 400076, India

Supporting Information

ABSTRACT: Divergent synthesis of *N*-fused indolylidine, indole, and indoline derivatives using alkyne iminium ion cyclization is described. Trapping of vinyl cation intermediate generated after alkyne iminium ion cyclization was found to be dependent on the Lewis/Bronsted acid and solvent used. *N*-Fused indolylidine triflate could be used in the divergent synthesis of *N*-fused indole derivatives.



The indole framework is a "privileged" structure and is a constituent of many pharmaceuticals and natural products.[1] *N*-Fused indoles in general and pyrrolo[1,2-*a*]indoles in particular are primary targets as they are found to be important pharmacophores (Figure 1). Mitomycin C (**1**) and mitomycins

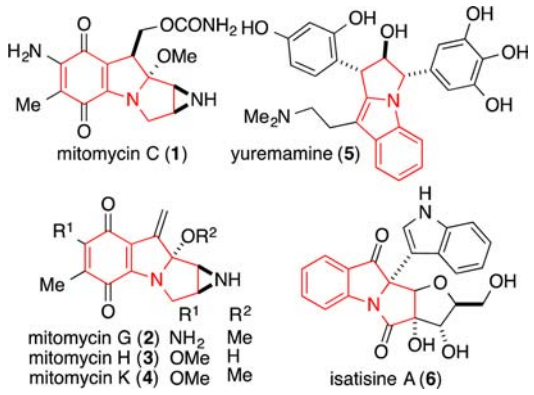
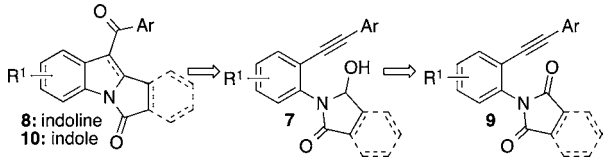


Figure 1. Natural products bearing the pyrrolo[1,2-*a*]indole core.

G, H, and K (**2**–**4**) are some of the most prominent members of this class of natural products, which exhibit a strong ability to bind DNA and show antitumor activity.[2] Yuremamine (**5**), which is isolated from the stem bark of *Mimosa hostilis*, shows hallucinogenic and psychoactive effects, whereas isatisine A (**6**) is an antiviral agent.[3,4] Biological activity of many of these *N*-fused indole derivatives coupled with structural diversity has attracted considerable attention from synthetic chemists, and many strategies for their synthesis have been reported.[5] Iminium ion cyclization is one of the most powerful methods for construction of nitrogen-containing heterocycles. The use of *N*-acyliminium ions in these cyclizations is particularly preferred, as they are more electrophilic (and hence more reactive toward various range of nucleophiles) and can be easily generated.[6] However, to the best of our knowledge, *a divergent synthesis of pyrroloindoles and pyrroloindolines starting from a common intermediate using alkyne-N-acyliminium ion cyclization is not reported in the literature*. In continuation of our interest in stereoselective synthesis of fused indole derivatives, we disclose herein a divergent approach for the construction of pyrrolo[1,2-*a*]indole derivatives using alkyne *N*-acyliminium ion cyclization.[7]

Recently, we developed a novel and efficient protocol for the stereoselective synthesis of dihydrobenzofurans by using alkynyl Prins reaction on vinylogous carbonates.[8] Based on this approach, we envisioned that intramolecular trapping of the *N*-acyliminium ion intermediate generated from the γ-hydroxy lactam **7** with alkyne, which is a π-nucleophile, could assemble the pyrroloindoline derivative **8** (Scheme 1). The γ-hydroxy

Scheme 1. Retrosynthetic Analysis for *N*-Fused Indole Derivatives Using Alkyne Iminium Ion Cyclization



lactam **7** can be readily prepared from the imide **9** by reduction. We also anticipated that pyrroloindole **10** could be obtained by the oxidation of pyrroloindoline moiety **8**. Further, there was a possibility that intermediate vinyl cation generated by attack of the alkyne on the iminium ion may get trapped by the counteranion of the Lewis/Bronsted acid used for its generation.[9]

Our studies began with the synthesis of the requisite substrate γ-hydroxy lactam **7a**. Thus, the known iodide **11** was subjected to Sonogashira coupling reaction with phenyl acetylene (**12**) to

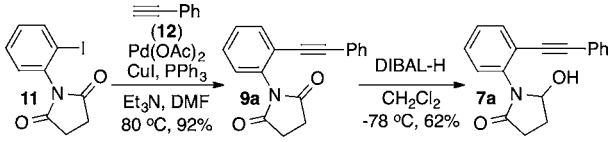
Received: February 28, 2015
Published: March 27, 2015

ACS Publications © 2015 American Chemical Society

DOI: 10.1021/acs.orglett.5b00615
Org. Lett. 2015, 17, 1926–1929

furnish the imide **9a** in excellent yield.[10] Selective reduction of the imide **9a** using DIBAL-H gave the requisite γ-hydroxy lactam **7a** in 62% yield (Scheme 2).

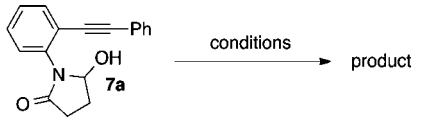
Scheme 2. Synthesis of the γ-Hydroxy Lactam 7a

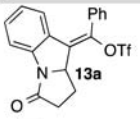
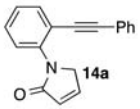
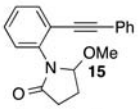
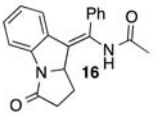
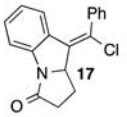
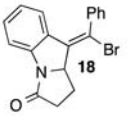
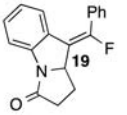
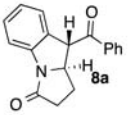
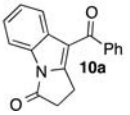


Having the γ-hydroxy lactam **7a** in hand, attention was turned toward using it in the synthesis of *N*-fused indole derivatives under various reaction conditions. The results are summarized in Table 1. When γ-hydroxy lactam **7a** was treated with 1 equiv of TMSOTf in CH_2Cl_2 at 0 °C, *N*-fused indolylidine triflate **13a** was obtained in 65% yield as a mixture of geometrical isomers by the trapping of intermediate vinyl cation with counteranion of the Lewis acid, and none of indoline **8a** or indole **10a** was formed. After some optimization, it was found that when 2 equiv of TMSOTf was used the reaction time was reduced significantly (to 1.5 h vs 8 h) with an increase in yield (75%) and selectivity (Table 1, entry 1). In order to study the effect of solvent, the reaction was carried out in diethyl ether. However, rather than the cyclization, the intermediate acyl iminium ion underwent loss of proton followed by isomerization to yield the lactam **14a** (Table 1, entry 2). Similarly, in MeOH, the reaction led to aminal **15** in excellent yield, and none of alkyne iminium ion cyclization was observed. Interestingly, when CH_3CN was used as a solvent, cascade *N*-acyliminum cyclization/Ritter reaction ensued and *N*-fused indolylidine amide derivative **16** was obtained in good yield (Table 1, entry 4). *It is pertinent to mention here that this type of Ritter reaction involving vinyl cation is very uncommon.*[11] As expected, the product **16** was found to be unstable, and elimination of all possible sources of acid during purification was essential. In order to test whether counteranions other than triflate could trap the vinyl cation, the reaction was carried out with other Lewis acids. Thus, when $TiCl_4$ was used as the Lewis acid, the vinyl chloride derivative **17** was obtained in good yield, and bromide **18** was the product when $BiBr_3$ was used (Table 1, entries 5 and 6). Fluorinated compounds are the least abundant organohalides and have been widely utilized in pharmaceutical drugs and agrochemicals. Synthesis of vinyl fluorides in general is particularly challenging.[12] Keeping this in mind, we attempted reaction of γ-hydroxy lactam **7a** with $BF_3{\cdot}OEt_2$. Gratifyingly, *N*-fused indolylidine fluoride **19** was indeed obtained in good yield and selectivity (Table 1, entry 7). Again, *the synthesis of vinyl fluorides under metal free conditions using a simple, inexpensive Lewis acid is very rarely encountered.*[13] When a Bronsted acid like triflic acid was used, triflate **13a** was obtained in moderate yield. When a milder acid like BINOL-phosphoric acid was used, only starting material was recovered. On the other hand, H_2SO_4 in acetone gave the *N*-fused indoline derivative **8a** as the sole product (Table 1, entry 8). Interestingly, when formic acid was used to effect the cyclization, pyrrolo[1,2-*a*]indole derivative **10a** was obtained in 88% yield (Table 1, entry 9). Given the stability of the triflate derivatives **13**, the possibility of using triflates in further transformations and, keeping in mind importance of indoline scaffold, these reactions were explored further to study the substrate scope.[14]

The scope of the alkyne iminium ion cyclization using TMSOTf as the Lewis acid was studied with a variety of

Table 1. Synthesis of *N*-Fused Indole Derivatives



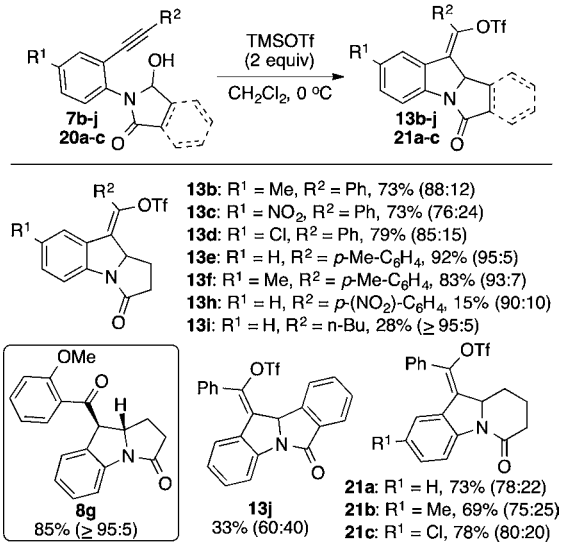
entry	conditions	yield %[a,b]	product
1.	TMSOTf (2 equiv), CH_2Cl_2, 0 °C, 1.5 h	75[c] (85:15)	
2.	TMSOTf (2 equiv), Et_2O, 0 °C, 1.5 h	82	
3.	TMSOTf (2 equiv), MeOH, 0 °C, 1 h	85	
4.	TMSOTf (2 equiv), CH_3CN, rt, 8 h	73 (95:5)	
5.	$TiCl_4$ (2 equiv) CH_2Cl_2, rt, 5 h	89[d] (89:11)	
6.	$BiBr_3$ (2 equiv) CH_2Cl_2, rt, 3 h	85 (95:5)	
7.	$BF_3{\cdot}OEt_2$ (2 equiv) CH_2Cl_2, rt, 3 h	62 (78:22)	
8.	10 M H_2SO_4, acetone, 40 °C, 3 h	52 (82:18)	
9.	HCO_2H, rt, 24 h	88	

[a]Isolated yield of *Z*-isomer unless otherwise noted. [b]The numbers in parentheses refer to *Z*/*E* ratio or dr. [c]52% (*Z*/*E* = 82:18) with TfOH as the catalyst. [d]Isolated yield of mixture of isomer.

substituted γ-hydroxy lactams **7b–j** (Scheme 3). Initially, the effect of substitution, which is in conjugation with the nitrogen atom on the iminium ion, was studied. The reactions were found to be generally efficient with the electron-releasing as well as electron-withdrawing group working efficiently, and the corresponding triflates **13b–d** were obtained in good yield with moderate *Z*/*E* selectivities. On the other hand, changing the aryl groups bearing a mildly electron-releasing methyl group on the alkyne part worked more efficiently and furnished the indolylidine triflates **13e,f** in excellent yield and diastereoselectivity. When a stronger electron-releasing methoxy group was used as the substituent, formation of the corresponding triflate **13g** was observed in the crude sample along with indoline **8g** (ca. 1:1). However, the triflate **13g** was found to be rather labile and underwent complete hydrolysis during silica gel column chromatography to furnish exclusively the indoline **8g**.

DOI: 10.1021/acs.orglett.5b00615
Org. Lett. 2015, 17, 1926–1929

Scheme 3. Scope of Synthesis of *N*-Fused Indolylidine Triflate Derivatives[a,b]



[a]Isolated yields of major isomer, [b]Numbers in parentheses refer to *Z*/*E* ratio or dr.

Interestingly, in the nitro group substituted γ-hydroxy lactam **7h**, the indolylidine triflate **13h** was formed in poor yield. The major product was lactam **14b** formed by elimination of water (similar to **14a**, cf. Table 1, entry 2). Alkyl group substituted alkynes were found to react sluggishly, and the corresponding product **13i** was obtained in poor yields albeit with excellent diastereoselectivity. Indolylidine triflate derivative **13j** having a tetracyclic core was also synthesized in moderate yield and diastereoselectivity from γ-hydroxy lactam **7j**. To further expand the scope of the reaction, we also investigated the synthesis of pyrido[1,2-*a*]indolylidine triflate derivatives. When δ-hydroxylactams **20a−c** were subjected to optimized reaction conditions, the corresponding pyrido[1,2-*a*]indolylidine triflate derivatives **21a−c** were obtained in excellent yield with good diastereoselectivities. The geometry of the double bond was assigned as *Z* on the basis of NOE experiments. These were further confirmed by single-crystal X-ray diffraction studies on the triflate derivatives **13a**, **13c**, **21a−c**, and indoline **8g**.[15]

Formation of the *Z*-isomer can be explained as a result of an attack of triflate counterion from Lewis acid on vinyl cation **22** generated from the *N*-acyliminium ion **23** during the course of reaction. Since the vinyl cation intermediate **22** is planar, there are two possible paths for attack as shown in Figure 2. Transition-state structure **A** formed during attack by path "a" is more favorable than transition-state structure **B** as it is comparatively free from steric interaction between the aromatic ring and hydrogen present in the pyrrolo[1,2-*a*]indolylidine framework. Thus, the *Z*-isomer formed through transition-state structure **A** is the major product.

During this study, we attempted this alkyne iminium ion cyclization reaction on the γ-hydroxy lactams **7k−p** bearing an olefin. To our surprise, rather than the expected triflates **13k−p**, this reaction furnished exclusively the indolyl ketone derivatives **10a−f** in excellent yield (Scheme 4). This reaction was found to be quite general, and a variety of substrates bearing different aryl substituents furnished the indole derivatives **10a−e** in excellent yields. However, the reaction with alkyl-substituted alkyne **7p** was sluggish, and the reaction proceeded only at reflux furnishing

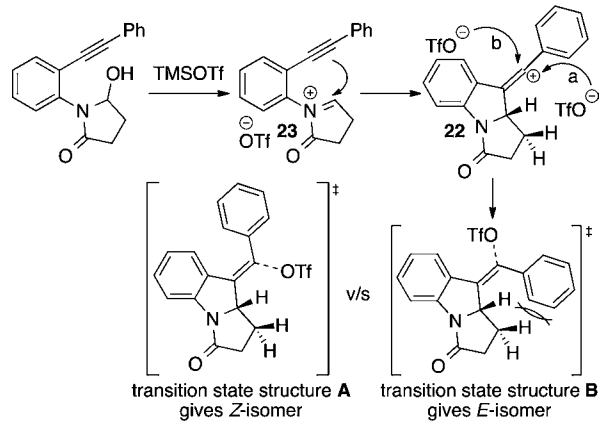
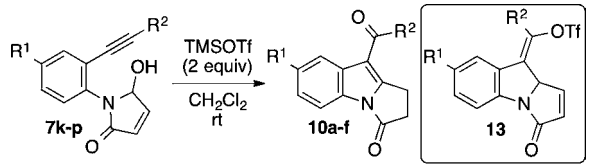


Figure 2. Proposed mechanism and explanation for stereochemical outcome.

Scheme 4. Scope of Synthesis of *N*-Fused Indole Derivatives

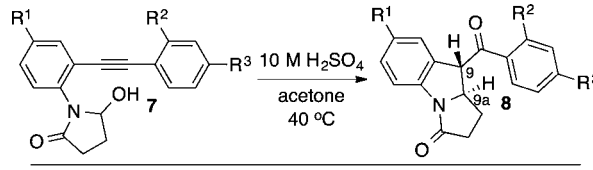


10a: R1 = H, R2 = Ph, 87%
10b: R1 = CN, R2 = Ph, 81%
10c: R1 = Cl, R2 = Ph, 94%
10d: R1 = Me, R2 = Ph, 80%
10e: R1 = NO2, R2 = Ph, 62%
10f: R1 = H, R2 = CH2OAc, 22%

the indole derivative **10f** in 22% yield. The structures of the indoles **10a−f** were confirmed based on the spectroscopic data as well as single-crystal X-ray diffraction studies on the indole derivative **10a**.[15] Further efforts are underway to probe this reaction mechanistically.

Attention was next turned toward exploring the generality of the indoline derivatives using Bronsted acidic conditions. Thus, γ-hydroxy lactam derivatives **7** were subjected to reaction with 10 M H_2SO_4 in acetone at 40 °C to furnish *N*-fused indoline derivatives **8** in good yield and selectivity (Scheme 5). The

Scheme 5. Scope of Stereoselective Synthesis of *N*-Fused Indoline Derivatives 8.[a,b]



8b: R1 = Me, R2 = H, R3 = H, 68%[a] (76:24)
8d: R1 = Cl, R2 = H, R3 = H, 80%[a] (86:14)
8f: R1 = Me, R2 = H, R3 = Me, 88%[b] (78:22)
8g: R1 = H, R2 = OMe, R3 = H, 69%[a] (70:30)

[a]Isolated yield of *trans*-isomer. [b]Isolated yield of the mixture of isomers.

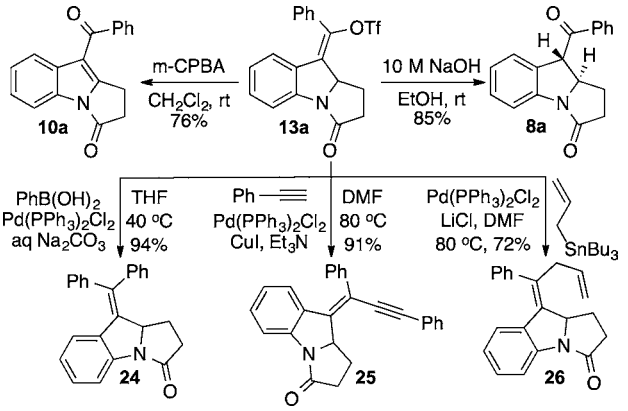
substrates **7b,d,f,g** bearing electron-releasing as well as mildly electron-withdrawing groups were found to work efficiently furnishing the indolines **8b,d,f,g**, respectively, in excellent yield albeit with moderate diastereoselectivity. In all the cases, the *trans* isomer was the major isomer, which was unambiguously confirmed by single-crystal X-ray diffraction studies on indolines **8f,g**.[15] Formation of *trans* isomer as the major product can be

DOI: 10.1021/acs.orglett.5b00615
Org. Lett. 2015, 17, 1926−1929

explained on the basis of trapping of the vinyl cation with water resulting in enol, which upon tautomerization gives the ketone. During tautomerization, the substituents on C9 and C9a prefer to be *trans* to each other to minimize steric interaction.

We decided to exploit the potential of *N*-fused indolylidine triflates to generate various *N*-fused pyrroloindole derivatives (Scheme 6). Thus, indolylidine triflate **13a** could be converted

Scheme 6. Reactions of *N*-Fused Indolylidine Triflate Derivative 13a



into the pyrrolo[1,2-*a*]indole derivative **10a** by subjecting it to oxidation with *m*-CPBA. On the other hand, hydrolysis of indolylidine triflate **13a** under basic conditions provided *N*-fused indoline derivative **8a**. The triflate **13a** also proved to be an excellent partner in Suzuki, Sonogashira, and Stille coupling reactions, giving access to *N*-fused indole derivatives **24**, **25**, and **26**, respectively. These reactions clearly show the potential of indolylidine triflates in the synthesis of diversely substituted *N*-fused indole derivatives.

In conclusion, we have studied the alkyne iminium ion cyclization reaction for the synthesis of *N*-fused indole derivatives. The reaction gives diversely substituted indolylidine derivatives depending on the counterion of the Lewis/Bronsted acid. The indolylidine triflates and indolines could be synthesized in good yield and diastereoselectivity. Reaction of γ-hydroxy lactam bearing olefin led to indole derivatives. We have also shown that the indolylidine triflates are versatile synthons, which can be elaborated into substituted *N*-fused indole derivatives.

■ ASSOCIATED CONTENT

Supporting Information

Synthetic procedures, spectroscopic data of products, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: sjgharpure@iitb.ac.in.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank BRNS, Mumbai, and the Council of Scientific and Industrial Research (CSIR), New Delhi, for financial support. We are grateful to CSIR, New Delhi, for the award of a research fellowships to Y.G.S. We thank Mr. Darshan Mhatre, Department of Chemistry, IIT Bombay, for collecting single-crystal X-ray diffraction data.

■ REFERENCES

(1) (a) Sundberg, R. J. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. *4*, p 313. (b) Toyota, M.; Ihara, M. *Nat. Prod. Rep.* **1998**, *15*, 327.

(2) Wolkenberg, S. E.; Boger, D. L. *Chem. Rev.* **2002**, *102*, 2477.

(3) Vepsalainen, J. J.; Auriola, S.; Tukiainen, M.; Ropponen, N.; Callaway, J. C. *Planta Med.* **2005**, *71*, 1053.

(4) Liu, J.-F.; Jiang, Z.-Y.; Wang, R.-R.; Zheng, Y.-T.; Chen, J.-J.; Zhang, X.-M.; Ma, Y.-B. *Org. Lett.* **2007**, *9*, 4127.

(5) For selected recent syntheses of pyrrolo[1,2-*a*]indoles, see: (a) Gogoi, A.; Modi, A.; Guin, S.; Rout, S. K.; Das, D.; Patel, B. K. *Chem. Commun.* **2014**, *50*, 10445. (b) Kern, N.; Hoffmann, M.; Blanc, A.; Weibel, J.-M.; Pale, P. *Org. Lett.* **2013**, *15*, 836. (c) Dethe, D. H.; Boda, R.; Das, S. *Chem. Commun.* **2013**, *49*, 3260. (d) Zhao, L.; Li, Z.; Chang, L.; Xu, J.; Yao, H.; Wu, X. *Org. Lett.* **2012**, *14*, 2066. (e) Mahoney, S. J.; Fillion, E. *Chem.—Eur. J.* **2012**, *18*, 68. (f) Chen, K.; Zhang, Z.; Wei, Y.; Shi, M. *Chem. Commun.* **2012**, *48*, 7696. (g) Patil, D. V.; Cavitt, M. A.; France, S. *Org. Lett.* **2011**, *13*, 5820. (h) Li, L.; Du, D.; Ren, J.; Wang, Z. *Eur. J. Org. Chem.* **2011**, 614. (i) Hong, L.; Sun, W.; Liu, C.; Wang, L.; Wang, R. *Chem.—Eur. J.* **2010**, *16*, 440. (j) Johansen, M. B.; Kerr, M. A. *Org. Lett.* **2008**, *10*, 3497.

(6) Selected reviews: (a) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817. (b) Martínez-Estibalez, U.; Gómez-SanJuan, A.; García-Calvo, O.; Aranzamendi, E.; Lete, E.; Sotomayor, N. *Eur. J. Org. Chem.* **2011**, 3610. (c) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431. (d) Yazici, A.; Pyne, S. G. *Synthesis* **2009**, 339. (e) Yazici, A.; Pyne, S. G. *Synthesis* **2009**, 513.

(7) (a) Gharpure, S. J.; Sathiyanarayanan, A. M. *Chem. Commun.* **2011**, *47*, 3625. (b) Gharpure, S. J.; Prasath, V. *Org. Biomol. Chem.* **2014**, *12*, 7397.

(8) Gharpure, S. J.; Prasath, V. *J. Chem. Sci.* **2011**, *123*, 943.

(9) (a) Gesson, J. P.; Jacquesy, J. C.; Rambaud, D. *Tetrahedron Lett.* **1992**, *33*, 3633. (b) Miranda, P. O.; Carballo, R. M.; Ramirez, M. A.; Martin, V. S.; Padrón, J. I. *ARKIVOC* **2007**, 331. (c) Yeh, M.-C. P.; Liang, C.-J.; Fan, C.-W.; Chiu, W.-H.; Lo, J.-Y. *J. Org. Chem.* **2012**, *77*, 9707. (d) Metais, E.; Overman, L. E.; Rodriguez, M. I.; Stearns, B. A. *J. Org. Chem.* **1997**, *62*, 9210. (e) Xu, T.; Yu, Z.; Wang, L. *Org. Lett.* **2009**, *11*, 2113. (f) Lolkema, L. D. M.; Hiemstra, H.; Semeyn, C.; Speckamp, W. N. *Tetrahedron* **1994**, *50*, 7115. (g) Chavre, S. N.; Choo, H.; Lee, J. K.; Pae, A. N.; Kim, Y.; Cho, Y. S. *J. Org. Chem.* **2008**, *73*, 7467.

(10) Takayama, C.; Fujinami, A. *Pestic. Biochem. Physiol.* **1979**, *12*, 163.

(11) Kitamura, T.; Kobayashi, S.; Taniguchi, H. *Chem. Lett.* **1984**, 1351.

(12) (a) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (b) Campbell, N. H.; Smith, D. L.; Reszka, A. P.; Neidle, S.; O'Hagan, D. *Org. Biomol. Chem.* **2011**, *9*, 1328. (c) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470. (d) Grushin, V. V. *Acc. Chem. Res.* **2010**, *43*, 160.

(13) Yeh, M.-C. P.; Liang, C.-J.; Huang, T.-L.; Hsu, H.-J.; Tsau, Y.-S. *J. Org. Chem.* **2013**, *78*, 5521.

(14) Chassaing, S.; Specklin, S.; Weibel, J.-M.; Pale, P. *Tetrahedron* **2012**, *68*, 7245.

(15) CCDC 1049514−1049522, 1050948 (**8a**,**f**,**g**, **10a**, ***Z*-13a**, ***E*-13a**, **13c**, **21a**−**c**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

DOI: 10.1021/acs.orglett.5b00615
Org. Lett. 2015, 17, 1926−1929