Organic LETTERS

Letter

pubs.acs.org/OrgLett

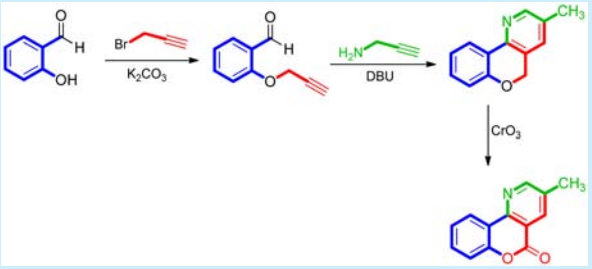
Intramolecular Heterocyclization of *O*-Propargylated Aromatic Hydroxyaldehydes as an Expedient Route to Substituted Chromenopyridines under Metal-Free Conditions

Selbi Keskin and Metin Balci*

Department of Chemistry, Middle East Technical University, 06800 Ankara, Turkey

Supporting Information

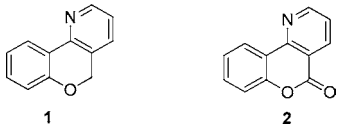
ABSTRACT: A concise and regioselective approach to the synthesis of chromenopyridine and chromenopyridinone derivatives was developed. The synthetic strategy relies on the *O*-propargylation of aromatic hydroxyaldehydes followed by reaction with propargylamine. The intramolecular cycloaddition reaction between the alkyne and azadiene, which is formed as an intermediate, furnished the desired skeletons.



Nitrogen-containing heterocyclic compounds are extremely important because of their abundance in various natural products as well as in synthetic organic compounds. Accordingly, the construction of the C−N bond is of significant importance as it opens up avenues for the introduction of nitrogen into organic molecules.

Coumarins[1] are an important group of heterocyclic compound due to their significant functions in nature and their pharmacological applications.[2] In this regard, they are ubiquitous in numerous natural products, dyes, pharmaceuticals, and agrochemicals and in materials science.

Chromenopyridine **1** and chromenopyridinone **2**, with a 2*H*-chromene ring and a 2*H*-chromen-2-one ring fused to a pyridine ring (Figure 1), are well-known for their pharmacological

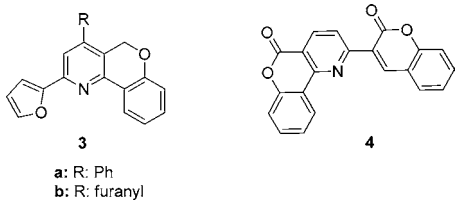


1 **2**

Figure 1. Structures of 5*H*-chromeno[4,3-*b*]pyridine (**1**) and 5*H*-chromeno[4,3-*b*]pyridin-5-one (**2**).

properties, such as antimicrobial,[3,4] antiinflammotory,[3] antibacterial,[5,6] antifungal,[6] and anticancer[7] activities including as an estrogen receptor βselective ligand[8] in TNFα inhibition,[9] and in anti-inflammatory processes.[10] Furthermore, chromeno[4,3-*b*]quinoline and chromene derivatives have been found to have other activities, such as fluorescent pH sensors.[11]

An efficient and straightforward method for the synthesis of chromenopyridines via the catalyst-free, three-component condensation of 3-formylchromones, amines, and dialkyl acetylenedicarboxylate was reported by Bazgir and co-workers.[12] Lee and co-workers synthesized chromenopyridine derivative **3a** and determined that this compound shows moderate cytotoxicity against some cancer cell lines.[13] Compounds that contain 2-(2-oxo-2*H*-chromen-3-yl)-5*H*-chromeno[4,3-*b*]pyridin-5-one (**4**) skeletons have antibacterial and antimicrobial activity (Figure 2).[14]



3 **4**

a: R: Ph
b: R: furanyl

Figure 2. Structures of 5*H*-chromeno[4,3-*b*]pyridine (**3**) and 5*H*-chromeno[4,3-*b*]pyridin-5-one (**4**).

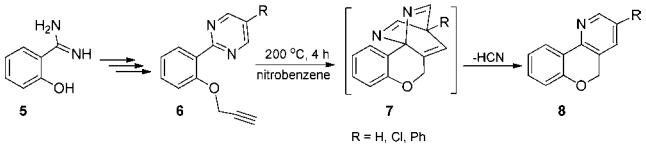
The intramolecular [4 + 2] Diels−Alder cycloaddition reactions play a very important role in the design of heterocyclic scaffolds. It requires efficient linking of the two reacting moieties prior to the reaction. Upon heating, the compounds **6**, which were synthesized starting from *o*-hydroxybenzamidine **5** in a few steps, undergo an intramolecular Diels−Alder reaction and a subsequent retro-Diels−Alder reaction to yield the chromenopyridines **8** (Scheme 1).[15]

Palacios et al.[16] reported the synthesis of a variety of tricyclic and tetracyclic condensed chromenopyridines using an aza-Wittig reaction of N-vinylic phosphazenes with functionalized aldehydes. More recently, a new [3 + 2 + 1] cycloaddition strategy was demonstrated using an aldehyde, an aldimine of a glycine ester, and a terminal triple bond with $AuCl_3$ catalyst to generate novel fused-tricyclic heterocycles such as 5*H*-chromeno[4,3-*c*]pyridines.[17] Recently, Singh et al.[18] attempted

Received: January 8, 2015
Published: February 5, 2015

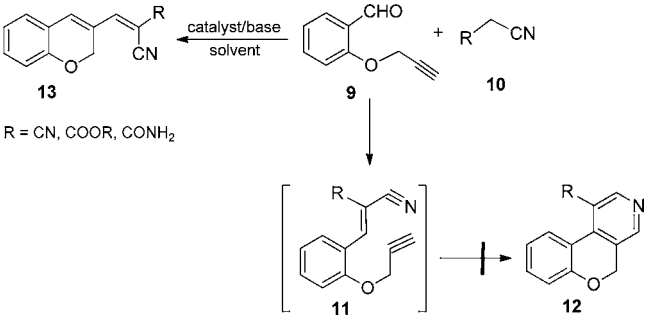
DOI: 10.1021/acs.orglett.5b00067
Org. Lett. 2015, 17, 964−967

Scheme 1. Synthesis of Chromenopyridine Derivatives 8 via an Intramolecular [4 + 2] Cycloaddition Reaction



to prepare 5*H*-chromeno[3,4-*c*]pyridine derivatives **12** by adopting an established strategy related to the domino Knoevenagel/Diels–Alder reaction, involving *O*-propargyl salicylaldehyde (**9**) and malononitrile or ethyl cyanoacetate or cyanoacetamide (Scheme 2). Unfortunately, instead of formation of the expected product **12**, the product **13** was formed.

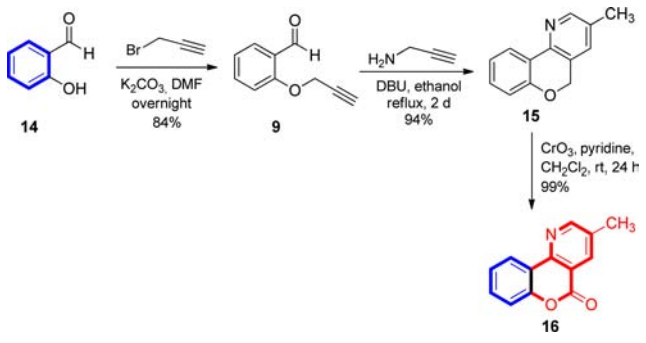
Scheme 2. Attempted Synthesis of Chromenopyridine 12



Therefore, an efficient synthetic methodology for the preparation of chromenopyridine derivatives substituted at the pyridine ring as well as at the benzene ring would be of interest.[19] Herein, we report a new, concise methodology for the synthesis of the chromenopyridine scaffold in just two steps, where alkyne cyclization is used as the major reaction without metals to promote the process.

For the construction of the chromenopyridine skeleton, first we synthesized 2-(prop-2-yn-1-yloxy)benzaldehyde (**9**) starting from salicylaldehyde (**14**). Treatment of salicylaldehyde (**14**) with propargyl bromide in the presence of potassium carbonate afforded compound **9** in 84% yield (Scheme 3).[20] For the incorporation of the second propargyl group, the appropriate compounds were reacted with the propargylamine in the presence of DBU to form the corresponding condensation product **17**. To our delight, the cyclization proceeded, and **15** was isolated in 94% yield. The structure was determined by 1D and 2D (DEPT, COSY, HSQC, and HMBC) NMR spectral data.

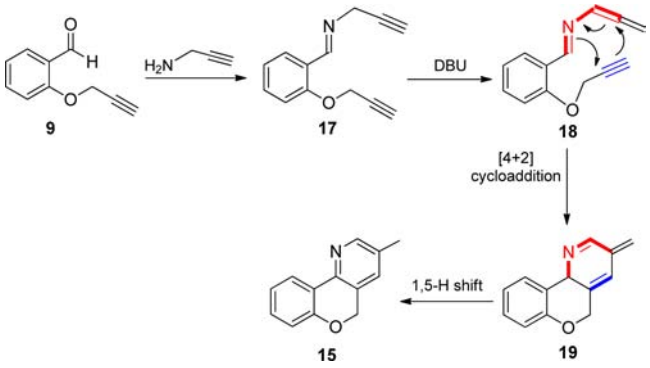
Scheme 3. Synthesis of Chromenopyridine 15 and Chromenopyridinone 16



For the synthesis of 5*H*-chromeno[4,3-*b*]pyridin-5-one derivative **16**, the product **15** was oxidized with CrO_3 in pyridine/methylene chloride to yield the desired product **16** in almost quantitative yield.

A tentative mechanism for the formation of **15** is outlined in Scheme 4. It is proposed that the first step is formation of the

Scheme 4. Mechanism for the Formation of Chromenopyridine Derivative 15



condensation product, imine **17**. With this step, two alkyne functionalities were now incorporated into the starter molecule. The terminal alkyne connected to the imine group can undergo base-catalyzed isomerization to form an allene structure **18**, which is conjugated with the imine double bond. Recently, we demonstrated that alkynes having similar structures can easily undergo isomerization into the corresponding allenes upon treatment with bases.[21] Then, the intramolecular [2 + 4] heterocycloaddition reaction between the alkyne and the diene system (formed with the imine and allene double bond) afforded, after a 1,5-H shift, the tricyclic product **15**.

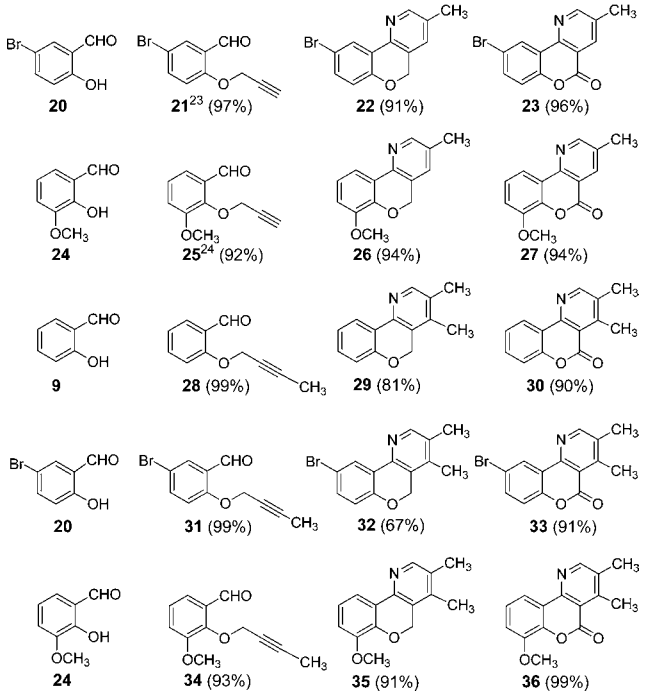
With these encouraging results in hand, we embarked on the evaluation of the substrate scope for this useful transformation. First, two aromatic alkynes with substituents at the *meta*-position (referred to the aldehyde functionality), **21** and **25**, were tested. We were able to show that these compounds were also suitable substrates for the synthesis of chromenopyridine derivatives **23** and **27** (Scheme 5). Next, we tested alkynes **28**, **31**, and **34** substituted with methyl groups. Generally, disubstituted alkynes are usually less reactive than terminal alkynes. For the synthesis of the starting materials, we used 1-bromobut-2-yne as a reagent instead of propargyl bromide. The desired heterocyclization products **29**, **32**, and **35** were also formed in high yields (Scheme 5).

Next, the effect of substituents conjugated with alkyne functionality was tested. The Sonogashira cross-coupling reaction[22] was used for the synthesis of the desired starting materials **37** and **38**. For the Sonogashira coupling reaction, we used a palladium catalyst and a copper(I) cocatalyst. To our delight, *N*-alkynes substituted with aromatic groups **37** and **38** underwent a facile cyclization reaction upon treatment with propargylamine at elevated temperature followed by cyclization to give access to substituted chromenopyridine derivatives **39** and **40** (Scheme 6). Oxidation of the methylene groups with CrO_3 furnished the chromenopyridinone derivatives **41** and **42** in high yields.

Finally, to explore the scope of this reaction, three isomeric hydroxynapthaldehydes **43**–**45** were also evaluated. First, the *O*-propargylated naphthaldehydes **46**–**48** were prepared from the corresponding hydroxynaphthaldehydes with good to excellent

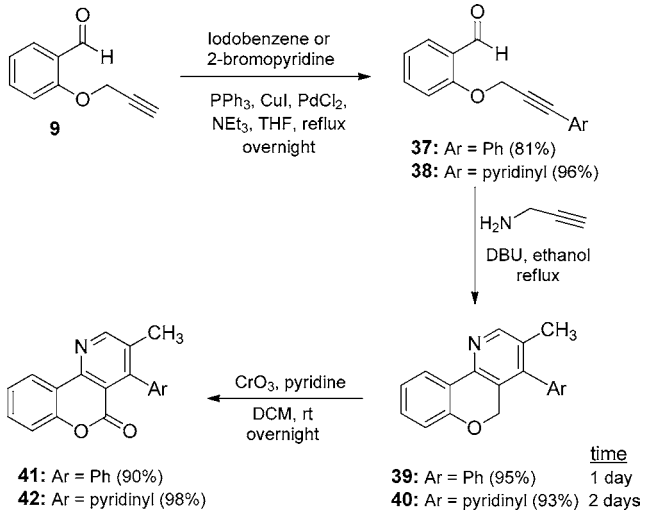
DOI: 10.1021/acs.orglett.5b00067
Org. Lett. 2015, 17, 964–967

Scheme 5. Structures of Chromenone Derivatives 23, 27, 30, 33, and 36 and Their Precursors[a]



[a]Yields are given in parentheses.

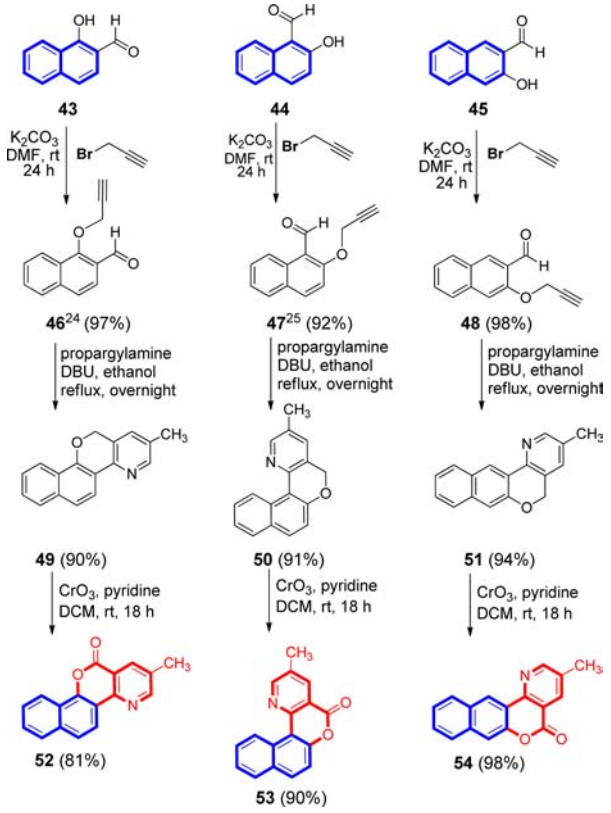
Scheme 6. Synthesis of Chromenopyridine Derivatives Substituted with Aromatic Groups



yields as described above (Scheme 7). Using the optimized conditions, naphthaldehydes **46**–**48** were treated with propargylamine and DBU under the reflux temperature of ethanol. The isomeric benzochromenopyridine derivatives **49**–**51** were formed in high yields. Oxidation of those compounds with CrO_3 in methylene dichloride resulted in the formation of the corresponding benzochromenopyridinone derivatives **52**–**54** (Scheme 7).

In conclusion, we describe a concise synthetic methodology for obtaining (benzo)chromenopyridine and (benzo)-chromenopyridinone derivatives. The key features of our method include (i) the synthesis of *O*-propargylated benz- and naphthaldehydes; (ii) the introduction of substituents into the

Scheme 7. Structures of Benzochromenopyridinone Derivatives 52–54 and Their Precursors[a]



[a]Yields are given in parentheses.

alkyne functionality by Sonogashira cross-coupling; (iii) alkyne cyclization via heterocycloaddition to form the chromenopyridine scaffold; and (iv) CrO_3 pyran oxidation reaction. This synthetic strategy also represents a reasonable methodology, that will allow us to introduce various substituents into all positions of the target compounds.

■ ASSOCIATED CONTENT

Supporting Information

Experimental conditions and spectroscopic data (1D and 2D NMR spectra) of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: mbalci@metu.edu.tr.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the Scientific and Technological Research Council of Turkey (TUBITAK, Grant No. TBAG-112 T360 and TBAG 113Z901), the Turkish Academy of Sciences (TUBA), and Middle East Technical University (METU) is gratefully acknowledged.

■ REFERENCES

(1) (a) Vekariya, R. H.; Patel, H. D. *Synth. Commun.* **2014**, *44*, 2756. (b) Sandhu, S.; Bansal, Y.; Silakari, O.; Bansal, G. *Bioorg. Med. Chem.*

DOI: 10.1021/acs.orglett.5b00067
Org. Lett. 2015, 17, 964–967

2014, *22*, 3806. (c) Spevak, A.; Hrobonova, K. *Chem. Listy* **2014**, *108*, 251. (d) Peng, X.-M.; Damu, G. L. V.; Zhou, C.-H. *Curr. Pharm. Des.* **2013**, *19*, 3884. (e) Bubols, G. B.; Vianna, D. R.; Medina-Remon, A.; von Poser, G.; Lamuela-Raventos, R. M.; Eifler-Lima, V. L.; Garcia, S. *Med. Chem.* **2013**, *13*, 318. (f) Bansal, Y.; Sethi, P.; Bansal, G. *Med. Chem. Res.* **2013**, *22*, 3049. (g) Song, Y.; Chen, Z.; Li, H. *Curr. Org. Chem.* **2012**, *16*, 2690. (h) Fedorov, A. Y.; Nyuchev, A. V.; Beletskaya, I. P. *Chem. Heterocycl. Compd.* **2012**, *48*, 166. (i) Musa, M. A.; Cooperwood, J. S.; Khan, M. O. F. *Curr. Med. Chem.* **2008**, *15*, 2664.

(2) (a) Riveiro, M. E.; De Kimpe, N.; Moglioni, A.; Vazquez, R.; Monczor, F.; Shayo, C.; Davio, C. *Curr. Med. Chem.* **2010**, *17*, 1325. (b) Raboin, J. C.; Beley, M.; Kirsch, G. *Tetrahedron Lett.* **2000**, *41*, 1175. (c) Nunez-Vergara, L. J.; Pardo-Jimenez, V.; Barrientos, C.; Olea-Azar, C. A.; Navarrete-Encina, P. A.; Squella, J. A. *Electrochim. Acta* **2012**, *85*, 336. (d) Brun, M.-P.; Bischoff, L.; Garbay, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 3432. (e) Bochkov, A. Y.; Akchurin, I. O.; Dyachenko, O. A.; Traven, V. F. *Chem. Commun.* **2013**, *49*, 11653. (f) Khan, I. A.; Kulkarni, M. V.; Gopal, M.; Shahabuddin, M. S.; Sun, C. M. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3584. (g) Zhu, S.; Lin, W.; Yuan, L. *Dyes Pigm.* **2013**, *99*, 465. (h) Cervi, A.; Aillard, P.; Hazeri, N.; Petit, L.; Chai, C. L. L.; Willis, A. C.; Banwell, M. G. *J. Org. Chem.* **2013**, *78*, 9876. (i) Dugrand, A.; Olry, A.; Duval, T.; Hehn, A.; Froelicher, Y.; Bourgaud, F. *J. Agric. Food Chem.* **2013**, *61*, 10677.

(3) Khan, I. A.; Kulkarni, M. V.; Gopal, M.; Shahabuddin, M. S.; Sun, C. M. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3584.

(4) El-Essawy, F. A.; El-Etrawy, A. S. *J. Heterocycl. Chem.* **2014**, *51*, 191.

(5) Frolova, L. V.; Malik, I.; Uglinskii, P. V.; Rogelj, S.; Kornienko, A.; Magedov, I. V. *Tetrahedron Lett.* **2011**, *52*, 6643.

(6) Ramalingam, P.; Ganapaty, S.; Rao, C. B.; Ravi, T. K. *Indian J. Heterocycl. Chem.* **2006**, *15*, 359.

(7) Al-Said, M. S.; Ghorab, M. M.; Nissan, Y. M. *Chem. Cent. J.* **2012**, *64*, 1.

(8) Vu, A. T.; Campbell, A. N.; Harris, H. A.; Unwalla, R. J.; Manas, E. S.; Mewshaw, R. E. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4053.

(9) Cheng, J. F.; Ishikawa, A.; Ono, Y.; Arrhenius, T.; Nadzan, A. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3647.

(10) Gebhardt, P.; Dornberger, K.; Gollmick, F. A.; Grafe, U.; Hartl, A.; Schlegel, B.; Hertweck, C. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2558.

(11) Huang, W.; Lin, W.; Guan, X. *Tetrahedron Lett.* **2014**, *55*, 116.

(12) Dolatkhah, Z.; Nasiri-Aghdam, M.; Bazgir, A. *Tetrahedron Lett.* **2013**, *54*, 1960.

(13) Thapa, U.; Thapa, P.; Karki, R.; Yun, M.; Choi, J. H.; Jahng, Y.; Lee, E.; Jeon, K. H.; Na, Y.; Ha, E.; Cho, W.; Kwon, Y.; Lee, E. *Eur. J. Med. Chem.* **2011**, *46*, 3201.

(14) Patel, A. A.; Lad, H. B.; Pandya, K. R.; Patel, C. V.; Brahmbhatt, D. I. *Med. Chem. Res.* **2013**, *22*, 4745.

(15) Stolle, W. A. W.; Frissen, A. E.; Marcelis, A. T. M.; van der Plas, H. C. *J. Org. Chem.* **1992**, *57*, 3000.

(16) (a) Palacios, F.; Alonso, C.; Amezua, P.; Rubiales, G. *J. Org. Chem.* **2002**, *67*, 1941. (b) Palacios, F.; Alonso, C.; Rubiales, G. *J. Org. Chem.* **1997**, *62*, 1146.

(17) Gayen, K. S.; Maiti, D. K. *RSC Adv.* **2014**, *4*, 10204.

(18) Kumari, K.; Raghuvanshi, D. S.; Singh, K. N. *Tetrahedron* **2013**, *69*, 82.

(19) For selected recent literature, see: (a) Hamama, W. S.; Ibrahim, M. E.; Metwalli, A. E.; Zoorob, H. H. *Med. Chem. Res.* **2014**, *23*, 2615. (b) Thapa, P.; Lee, E.-S. *Bull. Korean Chem. Soc.* **2012**, *33*, 3103. (c) Chen, J.; Liu, W.; Ma, J.; Xu, H.; Wu, J.; Tang, X.; Fan, Z.; Wang, P. *J. Org. Chem.* **2012**, *77*, 3475. (d) Patel, M. A.; Bhila, V. G.; Patel, N. H.; Patel, A. K.; Brahmbhatt, D. I. *Med. Chem. Res.* **2012**, *21*, 4381. (e) Kudale, A. A.; Miller, D. O.; Dawea, L. N.; Bodwell, G. J. *Org. Biomol. Chem.* **2011**, *9*, 7196. (f) Xiang, H.; Chen, J.; Miao, Z.; Yang, C. *RSC Adv.* **2014**, *4*, 16132. (g) Ramesh, S.; Nagarajan, R. *Tetrahedron Lett.* **2011**, *52*, 4857. (h) Iaroshenko, V. O.; Ali, S.; Babar, T. M.; Dudkin, S.; Mkrtchyan, S.; Rama, N. H.; Villinger, A.; Langer, P. *Tetrahedron Lett.* **2011**, *52*, 373. (i) Ramesh, S.; Gaddam, V.; Nagarajan, R. *Synlett* **2010**, *5*, 757. (j) Navarrete-Encina, P. A.; Salazar, R.; Vega-Retter, C.; Perez, K.; Squella, J. A.; Nunez-Vergara, L. J. *J. Braz. Chem. Soc.* **2010**, *21*, 413. (k) Sosnovskikh, V. Y.; Irgashev, R. A.; Kodess, M. I. *Tetrahedron.* **2008**, *64*, 2997. (l) An, H.; Eum, S.−J.; Koh, M.; Lee, S. K.; Par, S. B. *J. Org. Chem.* **2008**, *73*, 1752. (m) Vu, A. T.; Campbell, A. N.; Harris, H. A.; Unwalla, R. J.; Manas, E. S.; Mewshaw, R. E. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4053. (n) Beccalli, E. M.; Contini, A.; Trimarco, P. *Tetrahedron Lett.* **2004**, *45*, 3447.

(20) (a) Khoshkholgh, M. J.; Balalaie, S.; Gleiter, R.; Rominger, F. *Tetrahedron* **2008**, *64*, 10924. (b) Rohlmann, R.; Daniliuc, C.-G.; Mancheno, O. G. *Chem. Commun.* **2013**, *49*, 11665. (c) Bashiardes, G.; Safir, I.; Barbot, F.; Laduranty, J. *Tetrahedron Lett.* **2004**, *45*, 1567.

(21) (a) Menges, N.; Sari, O.; Abdullayev, Y.; Erdem, S. S.; Balci, M. *J. Org. Chem.* **2013**, *78*, 5184−5195. (b) Cetinkaya, Y.; Balci, M. *Tetrahedron Lett.* **2014**, *55*, 6698.

(22) (a) Chinchilla, R.; Najera, C. *Chem. Rev.* **2007**, *107*, 874. (b) Douchet, H.; Hierso, J.-C. *Angew. Chem., Int. Ed.* **2007**, *46*, 834. (c) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467. (d) Kost, A. N.; Grandberg, I. I. *Adv. Heterocycl. Chem.* **1966**, *6*, 347. (e) Caporale, A.; Tartaggia, S.; Castellin, A.; de Lucchi, O. *Beilstein J. Org. Chem.* **2014**, *10*, 384.

(23) Khoshkholgh, M. J.; Balalaie, S.; Bijanzadeh, H. R.; Gross, J. H. *ARKIVOC* **2008**, *9*, 114.

(24) Sze, E. M. L.; Rao, W.; Koh, M. J.; Chan, P. W. H. *Chem.—Eur. J.* **2011**, *17*, 1437.

(25) Vedachalam, S.; Wong, Q.; Maji, B.; Zeng, J.; Ma, J.; Liu, X. *Adv. Synth. Catal.* **2011**, *353*, 219.

DOI: 10.1021/acs.orglett.5b00067
Org. Lett. 2015, 17, 964−967