Organic LETTERS

Letter

pubs.acs.org/OrgLett

Access to Thiophene and 1*H*-Pyrrole via Amine-Initiated (3 + 2) Annulation and Aromatization Cascade Reaction of β′-Acetoxy Allenoate and 1,2-Bisnucleophile

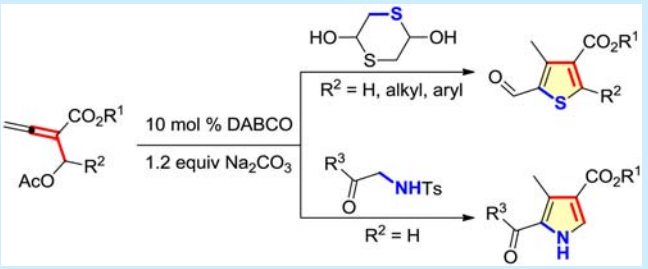
Chunjie Ni,[†] MingLi Wang,[†] and Xiaofeng Tong*[,†,‡]

[†]College of Chemistry and Molecular Engineering, East China University of Science and Technology, 130 Meilong Road, Shanghai 200237, China

[‡]Jiangsu Key Laboratory of Advanced Catalytic Materials & Technology, School of Petrochemical Engineering, Changzhou University, 1 Gehu Road, Changzhou 213164, China

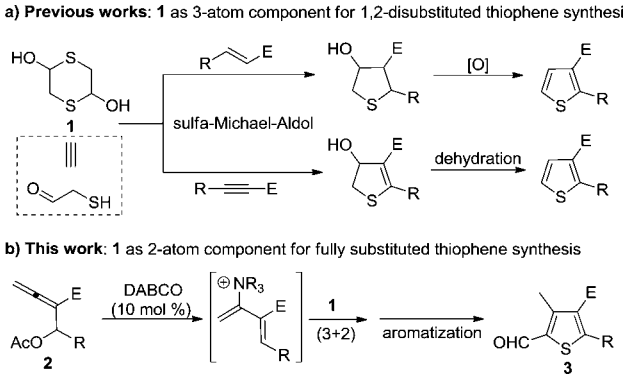
Supporting Information

ABSTRACT: The amine-catalyzed cascade (3 + 2) annulation and aromatization sequence between β′-acetoxy allenoates and 1,2-bisnucleophiles has been developed. When 1,4-dithane-2,5-diol is used as the bisnucleophile partner, the corresponding reaction affords fully substituted thiophene-2-carbaldehyde, which might proceed via the amine-catalyzed (3 + 2) annulation and subsequent oxidative aromatization. The reaction protocol is also applicable to a 2-tosylamino-carbonyl bisnucleophile, wherein the (3 + 2) annulation is followed by 1,2-elimination of a tosyl group and isomerization to give a 1*H*-pyrrole product.



The thiophene structure is a privileged five-membered hetreocycle, which presents as a subunit in numerous natural products and pharmaceuticals.[1] In addition, due to their unique structural rigidity and electronic properties, thiophene derivatives are also highly attractive in the field of organic materials.[2] Thiophene derivatives also serve as versatile intermediates in organic synthesis.[3] Therefore, it is unsurprising that a wide range of processes have been developed for the synthesis of thiophene structures with diverse substitution patterns.[4] Among these established methods, the strategy using commercially available 1,4-dithane-2,5-diol **1** as a three-atom component has received extensive attention (Scheme 1a). In this manner, compound **1** serves as mercaptoacetaldehyde synthon, which contains both a sulfydryl nucleophile and an aldehyde electrophile. This unique feature eventually facilitates the sulfa-Michael−aldol cascade reaction with an electron-poor alkene, leading to the tetrahydrothiophen-3-ol intermediacy.[5] Upon treatment with an oxidant, 1,2-disubstituted thiophene is finally obtained (Scheme 1a). The more convenient way to 1,2-disubstituted thiophene is to alternatively use an electron-poor alkyne as the other reactant, in which the similar sulfa-Michael−aldol sequence is followed by the facile dehydration step (Scheme 1a).[6] Despite these achievements, the employment of 1,4-dithane-2,5-diol **1** as a two-atom component in the thiophene synthesis, to the best of our knowledge, is rare.[7] Herein, we report a tertiary amine-catalyzed (3 + 2) annulation between 1,4-dithane-2,5-diol **1** and β′-acetoxy allenoate **2**, which unexpectedly results in the formation of thiophene **3**. In this way, compound **1** serves as a two-atom component while allenoate **2** is a three-atom component (Scheme 1b).

Scheme 1. Applications of 1,4-Dithiane-2,5-diol 1 in Thiophene Synthesis (E = Electron-Withdrawing Group)



Recently, our group has realized several Lewis base catalyzed annulations of readily available β′-acetoxy allenoates **2**, which features the involvement of either 1,3-diene-2-phosphonium or 1,3-diene-2-aminium intermediate via 1,4-addition of a catalyst and subsequent 1,2-elimination of an acetate group (Scheme 1b).[8,9] These inherently bis-electrophilic intermediates have been proven to exhibit excellent reactivity with various bis-nucleophiles to furnish annulation

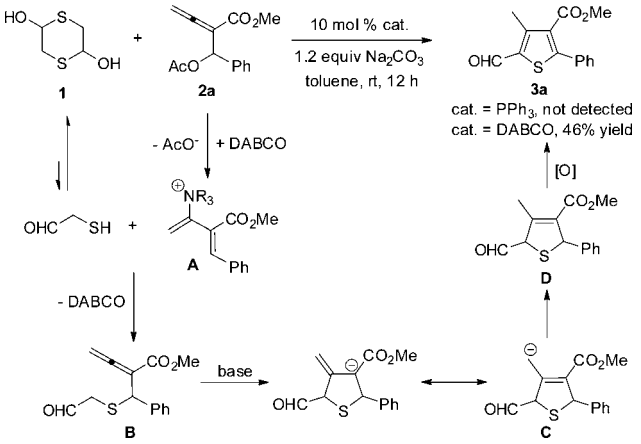
Received: March 25, 2016
Published: April 26, 2016

DOI: 10.1021/acs.orglett.6b00874
Org. Lett. 2016, 18, 2240−2243

reactions. As an extension of our study on the Lewis base catalyzed annulations of allenoates **2**, we were particularly interested in 1,4-dithane-2,5-diol **1** due to its two apparent nucleophilic sites, sulfhydryl group, and α-carbon of aldehyde. Herein, we report the amine-catalyzed reactions of allenoates **2** and compound **1**, which provide a facile and straightforward access to fully substituted thiophene-2-carbaldehyde (Scheme 1b).

To validate the feasibility of the reaction between allenoate **2a** and compound **1**, we commenced our study with the screening of the Lewis base catalyst (for details, see the Supporting Information). To our disappointment, no reaction was observed when PPh_3 (10 mol %) was used as the catalyst with the assistance of Na_2CO_3 (1.2 equiv) in toluene (Scheme 2). However, tertiary amine DABCO (10 mol %) was found

Scheme 2. Preliminary Results and Plausible Mechanism for the Formation of 3a



to trigger the reaction of **2a** and **1**, delivering product **3a** in 46% yield (Scheme 2). The structure of **3a** was determined on the basis of X-ray analysis (Figure 1).[10]

On the basis of our previous findings and the structure of **3a**, a plausible mechanism for the DABCO-catalyzed (3 + 2) annulation between **1** and **2a** was depicted in Scheme 2. The reaction is triggered by the 1,4-addition of DABCO to allenoate **2a** followed by 1,2-elimination of acetate, resulting

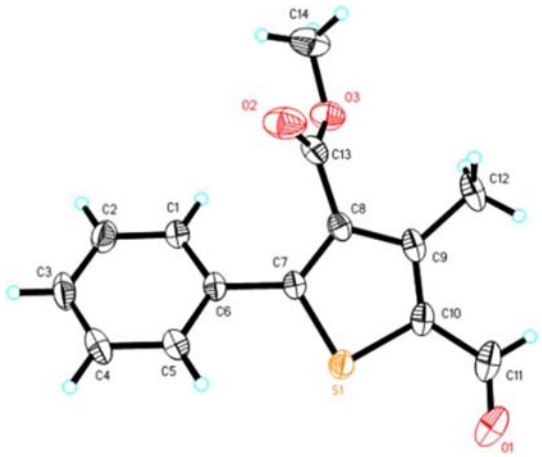
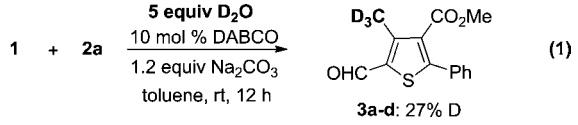


Figure 1. X-ray structure of **3a** (thermal ellipsoids are shown at the 50% probability level, T = 100 K).

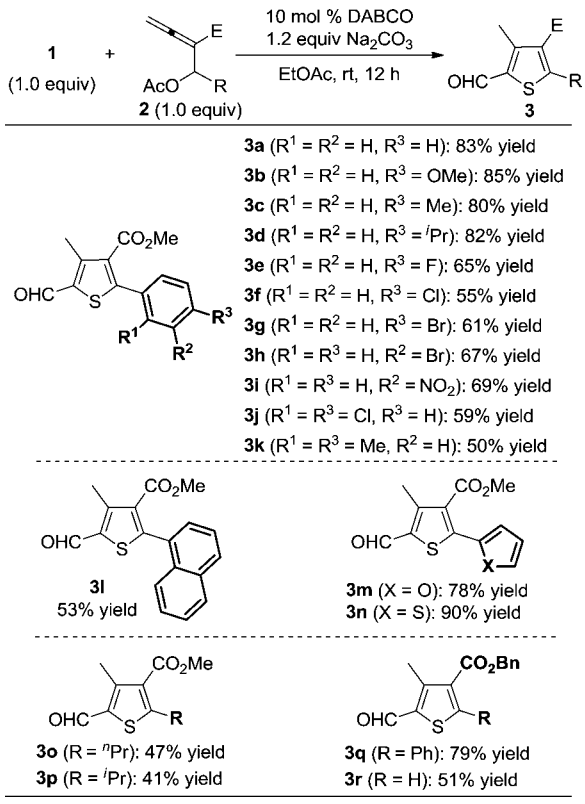
in the formation of 1,3-diene-2-aminium intermediate **A**. On the other hand, 1,4-dithane-2,5-diol **1** releases mercaptoacetaldehyde under basic conditions. Then, an S_N2'-type reaction between mercaptoacetaldehyde and intermediate **A** occurs to produce intermediate **B** and regenerate the DABCO catalyst.[11] According to the Baldwin rules,[12] intermediate **B** is able to undergo the intramolecular Michael addition in a 5-endo-dig manner, which is followed by resonance to give intermediate **C**.[13] When the reaction of **1** and **2a** was conducted in the presence of D_2O (5 equiv), **3a–d** were isolated with the incorporation of deuterium (27%) into the 3-methyl group (eq 1). This result was in line with the



formation of carboanion intermediate **C**. After abstraction of a proton, **C** is converted into 2,5-dihydrothiophene **D**, which underwent oxidative aromatization to give thiophene **3a** via the process shown in Scheme 2.

Further evaluation of reaction parameters rapidly disclosed that the use of EtOAc as the solvent was optimal, improving the yield of product **3a** to 83% (see the Supporting Information). Under the optimal reaction conditions, the reaction scope of allenoate **2** was investigated and the results are shown in Scheme 3. Allenoates **2a–2k** with a substituted phenyl group at the β'-position are proven to be suitable substrates for (3 + 2) annulations with compound **1**, delivering the corresponding products **3a–3k** in moderate to good yields. The reaction efficiency is strongly affected by both the electronic and steric nature of the phenyl group. For

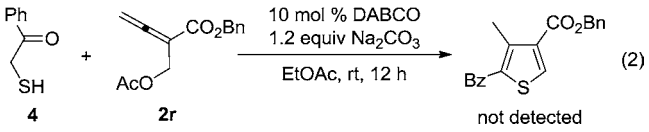
Scheme 3. Scope of (3 + 2) Annulations of 1 and 2



DOI: 10.1021/acs.orglett.6b00874
Org. Lett. 2016, 18, 2240–2243

instance, allenoates **2b**–**2d** with an electron-rich phenyl group give the corresponding products in ~85% yields while **2e**–**2i** with an electron-poor phenyl group afford relatively lower yields. Likely due to the steric hindrance, the reactions of allenoates **2j** and **2k** bearing a 2,4-disubstituted phenyl ring offer the corresponding products only in moderate yields. Moreover, heteroatom aromatic rings, such as furan and thiophene, are well tolerated, affording products **3m** and **3n** in 78% and 90% yields, respectively. Although allenoates **2o** and **2p** with an alkyl group at he β'-position also smoothly react with **1**, their yields are somewhat lower. Benzyl allenoate **2q** exhibits similar reactivity to that of **2a**, giving product **3q** in 79% yield. Additionally, the reaction of allenoate **2r** with **1** produces tertiary-substituted thiophene **3r** in 51% yield.

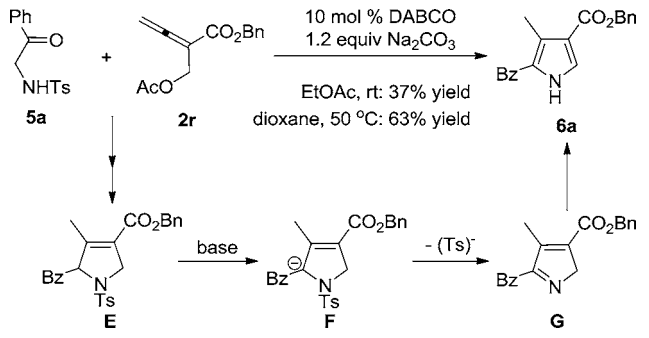
Then, we attempted to explore the use of 2-mercapto-1-phenylethanone **4** as the 1*S*,2*C*-bisnucleophile partner. However, the reaction of compound **4** with **2r** was found to be very complicated and no desired thiophene product was observed (eq 2). This result clearly indicated the advanta-



geous reactivity of compound **1**, which might slowly release mercaptoacetaldehyde. Likely due to the strong nucleophilicity of the sulfydryl group, a low concentration of mercaptoacetaldehyde was supposed to be beneficial for the reaction with allenoate **2** under the standard conditions.

In contrast to 2-mercapto-phenylethanone **4**, 2-tosylamino-phenylethanone **5a** was found to be the suitable 1,2-bisnucleophile partner for the (3 + 2) annulation (Scheme 4). Indeed, the reaction of **5a** with **2r** smoothly occurred to

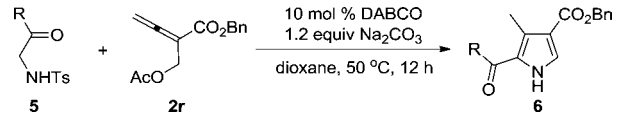
Scheme 4. Reaction of 5a and 2r



give 1*H*-pyrrole product **6a** albeit only in 37% yield. The yield of **6a** could be improved to 63% when dioxane was instead used as the solvent at an elevated temperature (50 °C). Following a similar reaction pathway as that depicted in Scheme 2, intermediate **E** would be produced. With the assistance of Na_2CO_3, **E** is capable of undergoing 1,2-elimination of the Ts^- group to form intermediate **G**,[14] which is followed by the isomerization process to give pyrrole derivative **6a** (Scheme 4).

As shown in Table 1, a wide range of 2-tosylamino-ketones **5** could serve as 1*N*,2*C*-bisnucleophile partners for the reaction with allenoate **2r**. However, the reaction efficiency was somewhat lower, affording pyrrole products **6** only in moderate yields, which might arise from the relatively lower

Table 1. Scope of (3 + 2) Annulation of 2r and 5[a]



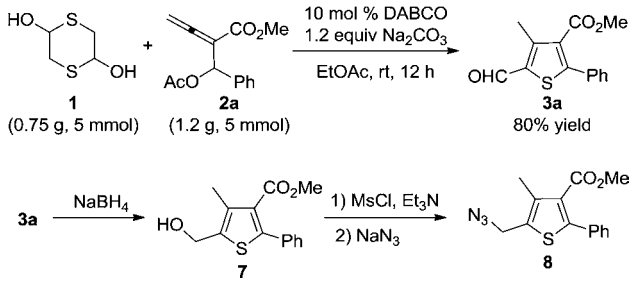
entry	5 (R)	6/yield (%)[b]
1	**5a** (R = C_6H_5)	**6a**/63
2	**5b** (R = 4-F-C_6H_4)	**6b**/53
3	**5c** (R = 4-Cl-C_6H_4)	**6c**/47
4	**5d** (R = 4-Br-C_6H_4)	**6d**/51
5	**5e** (R = 4-CF_3-C_6H_4)	**6e**/44
6	**5f** (R = 3-NO_2-C_6H_4)	**6f**/52
7	**5g** (R = 4-Me-C_6H_4)	**6g**/68
8	**5h** (R = 4-MeO-C_6H_4)	**6h**/75
9	**5i** (R = 2,4-$(Me)_2$-C_6H_4)	**6i**/67
10	**5j** (R = 2-furan)	**6j**/71
11	**5k** (R = 2-thiophene)	**6k**/69
12	**5l** (R = Me)	**6l**/37
13	**5m** (R = cyclopropane)	**6m**/43

[a]Reaction conditions: **5** (0.2 mmol), **2r** (0.2 mmol), DABCO (0.02 mmol), Na_2CO_3 (0.24 mmol), dioxane (2 mL), 50 °C. [b]Isolated yield.

nucleophilicity of compounds **5**. In line with these results, no reaction of **5a** and **2a** was observed.

To showcase the scalability of this process, a gram-scale reaction of allenoate **2a** and **1** was conducted. Gratifyingly, **3a** could be still obtained in 80% yield under the identical conditions (Scheme 4). Upon the treatment of $NaBH_4$, **3a** was reduced to give thiophen-2-ylmethanol **7** in 92% yield, which could be further converted into 2-(azidomethyl)-thiophene **8** (Scheme 5).

Scheme 5. Scale Up and Synthetic Transformations



In summary, we have developed the DABCO-initiated (3 + 2) annulation and aromatization cascade sequence between β'-acetoxyl allenaotes **2** and 1,2-bisnucleophiles. The tetrasubstituted thiophene-2-carbaldehydes **3** are readily obtained when 1,4-dithane-2,5-diol **1** is used as the 1*S*,2*C*-bisnucleophile partner, which proceed via the (3 + 2) annulation and subsequent aerobic oxidation. On the other hand, 2-aminoketone derivatives **5** are able to serve as the 1*N*,2*C*-bisnucleophile partner for the reaction with allenoate **2r**, providing facile access to tertiary substituted 1*H*-pyrroles **6**, in which the aromatization process consists of 1,2-elimination of a tosyl group and isomerization. Both of the reactions feature mild reaction conditions and readily available starting materials.[14]

DOI: 10.1021/acs.orglett.6b00874
Org. Lett. 2016, 18, 2240–2243

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00874.

Experimental procedures, characterization data and copies of NMR for compounds **3** and **6**−**8** (PDF)
Crystallographic data for compound **3a** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: txf@cczu.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work is supported by NSFC/China (Nos. 21272066 and 21472042). We are grateful to Changzhou University for experimental assistance and financial support.

■ REFERENCES

(1) (a) Heyde, C.; Zug, I.; Hartmann, H. *Eur. J. Org. Chem.* **2000**, *2000*, 3273. (b) Nandi, G. C.; Samai, S.; Singh, M. S. *J. Org. Chem.* **2011**, *76*, 8009. (c) Liao, Q.; You, W.; Lou, Z.-B.; Wen, L.-R.; Xi, C. *Tetrahedron Lett.* **2013**, *54*, 1475. (d) You, W.; Yan, X.; Liao, Q.; Xi, C. *Org. Lett.* **2010**, *12*, 3930. (e) Lamb, E. *Pharm. Times* **2008**, No. May, 20. (f) Eicher, T.; Hauptmann, S.; Speicher, A. *The Chemistry of Heterocycles*; Wiley-VCH: New York, 2003; Chapter 5, Section 5.6. (g) Gronowitz, S.; Hornfeldt, A. B. *Thiophenes*; Elsevier: Oxford, U.K., 2004.

(2) (a) Perepichka, I. F.; Perepichka, D. F.; Meng, H.; Wudl, F. *Adv. Mater.* **2005**, *17*, 2281. (b) McCullough, R. D. *Adv. Mater.* **1998**, *10*, 93. (c) Nalwa, H. S. *Adv. Mater.* **1993**, *5*, 341. (d) Wang, C.; Dong, H.; Hu, W.; Liu, Y.; Zhu, D. *Chem. Rev.* **2012**, *112*, 2208. (e) Lin, Y.; Li, Y.; Zhan, X. *Chem. Soc. Rev.* **2012**, *41*, 4245. (f) Li, C.; Liu, M.; Pschirer, N. G.; Baumgarten, M.; Müllen, K. *Chem. Rev.* **2010**, *110*, 6817.

(3) (a) Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795. (b) Rassu, G.; Zanardi, F.; Battistini, L.; Casiraghi, G. *Chem. Soc. Rev.* **2000**, *29*, 109. (c) Rajappa, S.; Deshmunkh, A. R. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Eds.; Elsevier Ltd.: Oxford, 2008; Vol. 3, pp 741−841.

(4) For a review, see: (a) *The Chemistry of Heterocyclic Compounds: Thiophene and Its Derivatives*; Gronowitz, S., Ed.; Wiley: New York, 1991; Vol. *44*. For selected examples, see: (b) Lin, M.-H.; Huang, Y.-C.; Kuo, C.-K.; Tsai, C.-H.; Li, Y.-S.; Hu, T.-C.; Chuang, T.-H. *J. Org. Chem.* **2014**, *79*, 2751. (c) Sathishkannan, G.; Srinivasan, K. *Chem. Commun.* **2014**, *50*, 4062. (d) Kutty, S. K.; Bhadbhade, M. M.; Iskander, G.; Black, D. S.; Kumar, N. *Tetrahedron Lett.* **2014**, *55*, 3916. (e) Hirotaki, K.; Hanamoto, T. *Org. Lett.* **2013**, *15*, 1226. (f) Mishra, P.; Maurya, H. K.; Kumar, B.; Tandon, V. K.; Ram, V. J. *Tetrahedron Lett.* **2012**, *53*, 1056. (g) Fang, G.; Li, J.; Wang, Y.; Gou, M.; Liu, Q.; Li, X.; Bi, X. *Org. Lett.* **2013**, *15*, 4126. (h) Yin, G.; Wang, Z.; Chen, A.; Gao, M.; Wu, A.; Pan, Y. *J. Org. Chem.* **2008**, *73*, 3377. (i) Guilarte, V.; Fernandez-Rodriguez, M. A.; Garcia-Garcia, P.; Hernando, E.; Sanz, R. *Org. Lett.* **2011**, *13*, 5100. (j) Jiang, H.; Zeng, W.; Li, Y.; Wu, W.; Huang, L.; Fu, W. *J. Org. Chem.* **2012**, *77*, 5179. (k) Gabriele, B.; Mancuso, R.; Salerno, G.; Larock, R. C. *J. Org. Chem.* **2012**, *77*, 7640. (l) Reddy, C. R.; Valleti, R. R.; Reddy, M. D. *J. Org. Chem.* **2013**, *78*, 6495. (m) Ransborg, L. K.; Albrecht, L.; Weise, C. F.; Bak, J. R.; Jorgensen, K. A. *Org. Lett.* **2012**, *14*, 724. (n) Jullien, H.; Quiclet-Sire, B.; Tétart, T.; Zard, S. Z. *Org. Lett.* **2014**, *16*, 302.

(5) (a) McNabola, N.; O'Connor, C. J.; Roydhouse, M. D.; Wall, M. D.; Southern, J. M. *Tetrahedron* **2015**, *71*, 4598. (b) Zhong, Y.; Ma, S.; Li, B.; Jiang, X.; Wang, R. *J. Org. Chem.* **2015**, *80*, 6870. (c) Ling, J.-B.; Su, Y.; Zhu, H.-L.; Wang, G.-Y.; Xu, P.-F. *Org. Lett.* **2012**, *14*, 1090. (d) Shi, W.; Sun, S.; Hu, Y.; Gao, T.; Peng, Y.; Wu, M.; Guo, H.; Wang, J. *Tetrahedron Lett.* **2015**, *56*, 3861. (e) Huckabee, B. K.; Stuk, T. L. *Synth. Commun.* **2001**, *31*, 1527.

(6) (a) Vatansever, E. C.; Kılıç, K.; Özer, M. S.; Koza, G.; Menges, N.; Balci, M. *Tetrahedron Lett.* **2015**, *56*, 5386. (b) Shi, W.; Wan, L.; Hu, Y.; Sun, S.; Li, W.; Peng, Y.; Wu, M.; Guo, H.; Wang, J. *Tetrahedron Lett.* **2015**, *56*, 2083. (c) Chen, B.; Ni, H.; Guo, X.; Zhang, G.; Yu, Y. *RSC Adv.* **2014**, *4*, 44462.

(7) (a) Sathishkannan, G.; Srinivasan, K. *Chem. Commun.* **2014**, *50*, 4062. (b) Bharathiraja, G.; Sathishkannan, G.; Punniyamurthy, T. *J. Org. Chem.* **2016**, *81*, 2670.

(8) For examples of a phosphine catalyst: (a) Zhang, Q.; Yang, L.; Tong, X. *J. Am. Chem. Soc.* **2010**, *132*, 2550. (b) Gu, Y.; Hu, P.; Ni, C.; Tong, X. *J. Am. Chem. Soc.* **2015**, *137*, 6400. (c) Han, X.; Yao, W.; Wang, T.; Tan, Y. R.; Yan, Z.; Kwiatkowski, J.; Lu, Y. *Angew. Chem., Int. Ed.* **2014**, *53*, 5643. (d) Ziegler, D. T.; Riesgo, L.; Ikeda, T.; Fujiwara, Y.; Fu, G. C. *Angew. Chem., Int. Ed.* **2014**, *53*, 13183. (e) Kramer, S.; Fu, G. C. *J. Am. Chem. Soc.* **2015**, *137*, 3803.

(9) For examples of an amine catalyst: (a) Li, C.; Zhang, Q.; Tong, X. *Chem. Commun.* **2010**, *46*, 7828. (b) Li, K.; Hu, J.; Liu, H.; Tong, X. *Chem. Commun.* **2012**, *48*, 2900.

(10) The crystallographic coordinates of **3a** have been deposited with the deposition number CCDC 1470577. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre, at deposit@ccdc.cam.ac.uk.

(11) Hu, J.; Tian, B.; Wu, X.; Tong, X. *Org. Lett.* **2012**, *14*, 5074.

(12) (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734. (b) Johnson, C. D. *Acc. Chem. Res.* **1993**, *26*, 476.

(13) For selected examples, see: (a) Zheng, C.; Wang, Y.; Fan, R. *Org. Lett.* **2015**, *17*, 916. (b) Miura, T.; Tanaka, T.; Matsumoto, K.; Murakami, M. *Chem. - Eur. J.* **2014**, *20*, 16078. (c) Boominathan, S. S. K.; Hu, W.-P.; Senadi, G. C.; Wang, J.-J. *Adv. Synth. Catal.* **2013**, *355*, 3570. (d) Li, L.; Zhang, J. *Org. Lett.* **2011**, *13*, 5940.

(14) Allenoates **2** are readily prepared from 3-(methoxycarbonyl) propargyl bromide and the corresponding aldehydes with the assistance of NaI and $SnCl_2$ according to the literature report: Deng, Y.; Jin, X.; Ma, S. *J. Org. Chem.* **2007**, *72*, 5901.

DOI: 10.1021/acs.orglett.6b00874
Org. Lett. 2016, 18, 2240−2243