Organic LETTERS

Letter

pubs.acs.org/OrgLett

Synthetic Progress toward Azadirachtins. 2. Enantio- and Diastereoselective Synthesis of the Right-Wing Fragment of 11-*epi*-Azadirachtin I

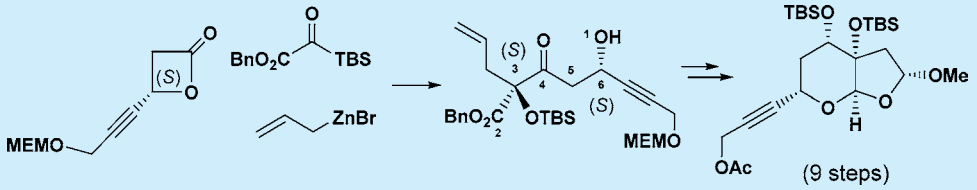
Ceheng Tan,[†] Wei Chen,[†] Xinpeng Mu,[†] Qi Chen,[†] Jianxian Gong,*[,†] Tuoping Luo,*[,‡] and Zhen Yang*[,†,‡,§]

[†]Laboratory of Chemical Genomics, School of Chemical Biology and Biotechnology, Peking University Shenzhen Graduate School, Shenzhen 518055, China

[‡]Key Laboratory of Bioorganic Chemistry and Molecular Engineering, Ministry of Education and Beijing National Laboratory for Molecular Science (BNLMS) and Peking-Tsinghua Center for Life Sciences, Peking University, Beijing 100871, China

[§]Key Laboratory of Marine Drugs, Chinese Ministry of Education, School of Medicine and Pharmacy, Ocean University of China, 5 Yushan Road, Qingdao 266003, China

Supporting Information

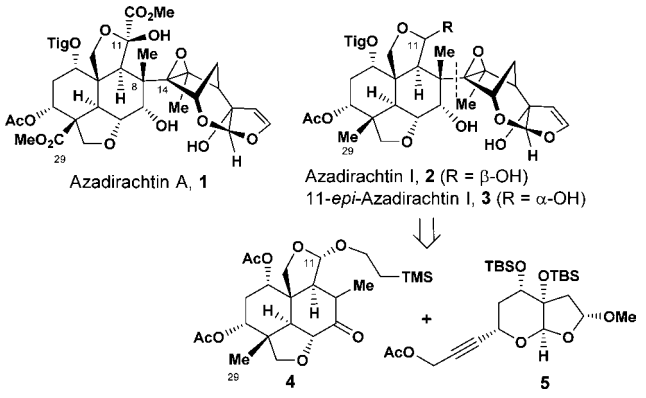


ABSTRACT: A stereoselective three-component coupling reaction of allylzinc bromide, silyl glyoxylate, and a *β*-lactone has been developed. This has been successfully applied to the enantio- and diastereoselective synthesis of the fully functionalized furopyran moiety of azadirachtins.

Azadirachtins **1**−**3** are complex natural products isolated from the Indian neem tree (Scheme 1).[1] They are potent insect antifeedants and growth inhibitors. Their interesting biological activity, together with their complex structures, has generated great interest in their chemical synthesis.

In a previous paper,[1] we described the analysis for total syntheses of azadirachtin I (**2**) and 11-*epi*-azadirachtin I (**3**), and a novel gold-catalyzed tandem reaction of a 1,7-diyne for the enantio- and diastereoselective synthesis of fully functionalized *trans*-decalin (**4**) (Scheme 1). We are also interested in developing a novel approach for the synthesis of furopyran moiety **5**.

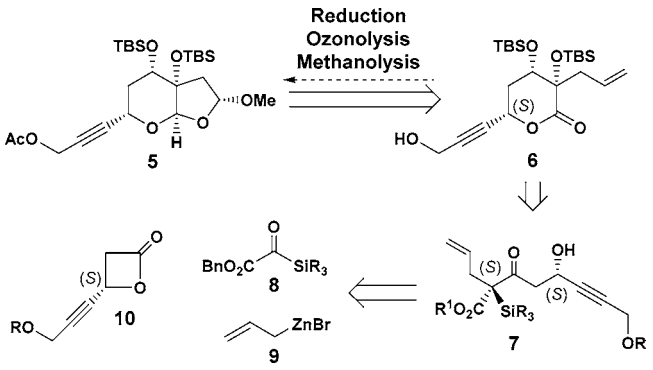
Scheme 1. Azadirachtins and Retrosynthetic Analysis



Synthetically, there are many methods for the synthesis of furo[2,3*b*]furans.[2] In contrast, there are relatively few reports for furo[2,3*b*]pyrans.[3] Our aim was to develop a flexible and relatively short route to the bioactive portion of the most potent azadirachtins.

Our retrosynthetic analysis for the synthesis of furopyran **5** is illustrated in Scheme 2. This could be generated from lactone **6**

Scheme 2. Retrosynthetic Analysis



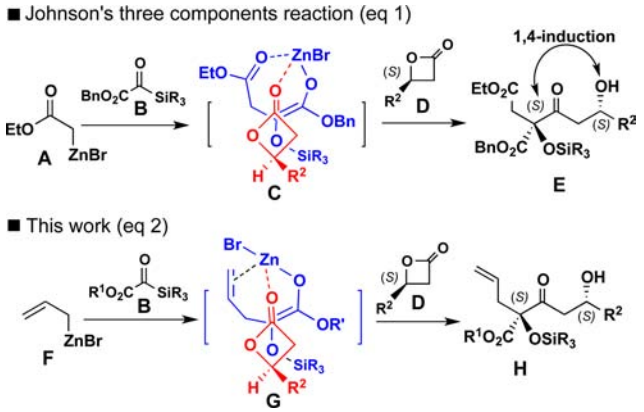
Received: March 20, 2015
Published: April 28, 2015

DOI: 10.1021/acs.orglett.5b00831
Org. Lett. 2015, 17, 2338−2341

via the methodology reported by Ley and co-workers,[3] featuring a reduction/ozonolysis/methanolysis sequence. Lactone **6** could be made via the chemo- and stereoselective reduction of ketone **7**, followed by intramolecular lactonization. Key intermediate **7**, with a quaternary center, could be constructed using a modified diastereoselective three-component coupling[3] of silyl glyoxylate **8**, allylzinc bromide **9**, and β-lactone **10**. To the best of our knowledge, there are no reports on the use of allylzinc bromide as a nucleophile to initiate the silyl glyoxylate-mediated diastereoselective cascade reaction.

Silyl glyoxylates have recently emerged as a reliable class of reagents for the union of nucleophilic and electrophilic partners.[4,5] The reaction of substituted β-lactone **D** with intermediate **C** derived from the addition of Reformatsky's agent **A** to a silyl glyoxylate **B**, followed by the [1,2]-Brook rearrangement[6] of the resultant zinc aldolate, was developed by Johnson and co-workers.[7] This reaction is thought to proceed through transition state **C** formed by stronger chelation with the pendant ethyl ester.[4h] This allows the resultant nucleophile to access β-lactone **D** via its less hinder convex side to give **E** in a highly diastereoselective manner (1,4-induction) (Scheme 3, eq 1).

Scheme 3. Three-Component Coupling Reactions

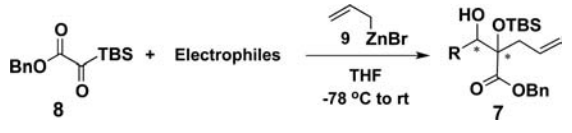


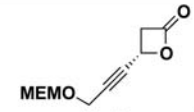
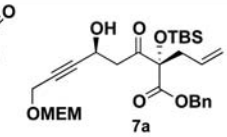
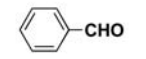
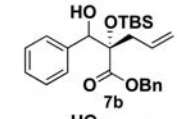
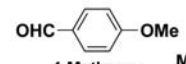
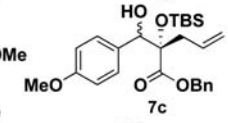
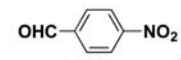
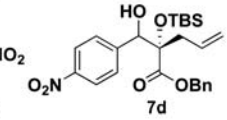
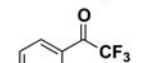
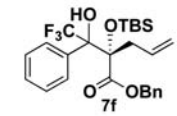
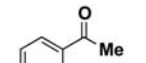
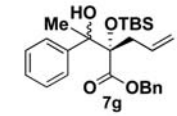
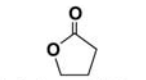
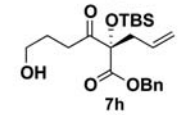
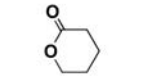
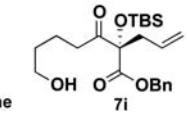
In consideration of the fact that cationic zinc can form a complex with olefins,[8] we therefore would like to explore the feasibility of using allylzinc bromide to initiate our three-component reaction. We envisioned that nucleophilic addition of allylzinc bromide **F** to silyl glyoxylate **B** might form a transition state **G**, which could approach β-lactone **D** from its less hindered side; as a result, product **H** with the desired stereochemistry at C3 and C4 could be obtained (Scheme 3, eq 2). We envisaged that given the lower basicity of allylzinc bromide, this chemistry could be used to synthesize structurally more diverse compounds and provide access to lactone **6** (Scheme 2).

Our research began with the identification of the conditions for the proposed three-component reaction. In the event, the easily prepared allylzinc bromide **9** (2.0 equiv) was added to a solution of *tert*-butyl dimethylsilylglyoxylate **8** (2.0 equiv) in THF at −78 °C, and the resultant mixture was then mixed with a solution of β-lactone **10** (1.0 equiv, see the Supporting Information) in THF at −78 °C, followed by reaction at room temperature for 10 min to give the expected coupling product **7a** in 83% yield with a diastereomeric ratio up to 20:1. This indicates an excellent stereochemical induction that transmitted the β-lactone stereochemistry to the newly formed stereocenter. It is worth mentioning that this excellent diastereoselective result is opposite that of the previous results with other viable terminal electrophiles.[9] The structure of **7a** was initially confirmed by NMR study and later was confirmed by its X-ray crystallographic analysis[10] (Scheme 5). Thus, by application of allylzinc bromide as a nucleophile, we achieved a concise synthetic pathway for synthesis of the key intermediate **5** in a highly diastereoselective manner.

To extend the scope of this three-component coupling reaction, alternative electrophiles, such as other medium-sized lactones, aldehydes, and ketones, were employed, and the results are shown in Table 1. The following observations can be made: (1) Coupling product **7b** was obtained in relatively low yield but with high diastereoselectivity when benzaldehyde was

Table 1. Substrate Scope of the Allylzinc Bromide Initiated Three-Component Coupling Reaction[a]



entry	electrophiles	product	yield[b] (dr)[c]
1	 (-)-10	 7a	83% (> 20:1)
2	 Benzaldehyde	 7b	53% (> 20:1)
3	 4-Methoxy-benzaldehyde	 7c	81% (1:2)
4	 4-Nitro-benzaldehyde	 7d	79% (> 20:1)
5	 2,2,2-Trifluoro-1-phenylethanone	 7f	67% (> 20:1)
6	 Acetophenone	 7g	62% (1:1)
7	 Dihydrofuran-2(3*H*)-one	 7h	0%
8	 Tetrahydro-2*H*-pyran-2-one	 7i	0%

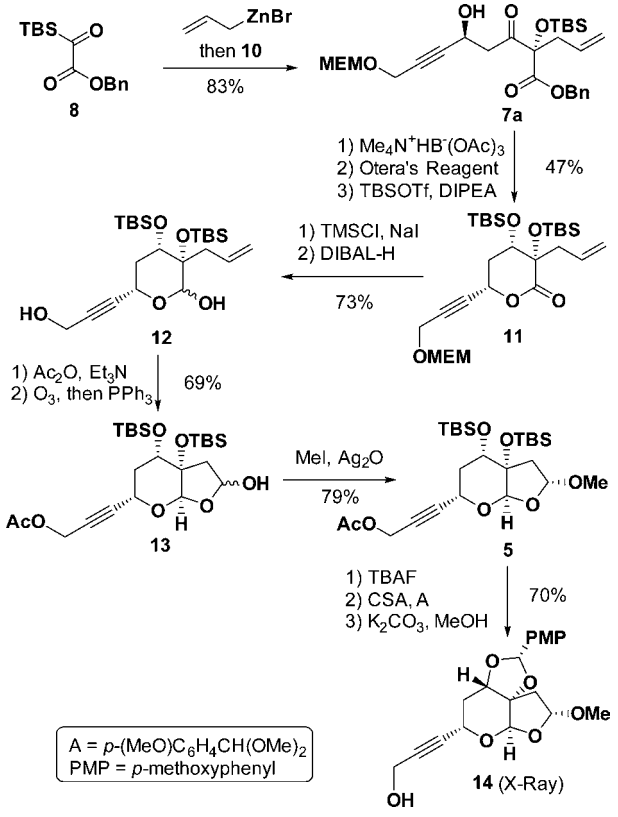
[a]Reaction conditions: benzyl 2-(*tert*-butyldimethylsilyl)-2-oxoacetate (**8**) (1.8−2.0 equiv), allyl zinc bromide (**9**) (1.8−2.0 equiv) THF, −78 °C, then electrophile (1.0 equiv) at −78 °C then 0 °C to ambient temperature. All reactions were run at 0.05 M. [b]Isolated yields. [c]The dr values were determined by ^{1}H NMR spectroscopy.

DOI: 10.1021/acs.orglett.5b00831
Org. Lett. 2015, 17, 2338−2341

used. Coupling product **7c** was formed in 81% yield with a lower diastereoselectivity of 2:1 when 4-methoxybenzaldehyde (Table 1, entry 3) was used. In contrast, when 4-nitrobenzaldehyde (Table 1, entry 4) was used, the coupling product was formed in 79% yield as a single product. This indicates that the electron-deficient substrate could favor this zinc coordination. (2) 2,2,2-Trifluoro-1-phenylethanone and acetophenone (Table 1, entries 5 and 6) undergo the three-component reaction to afford products **7e** and **7f** in 67% and 62% yield, respectively. However, the electron-deficient substrate 2,2,2-trifluoro-1-phenylethanone gave 20:1 diastereoselectivity, while acetophenone gave only 1:1. (3) The five- and six-membered ring-based lactones gave no coupling products (Table 1, entries 7 and 8), indicating that ring strain is the driving force.

Synthesis of the right-wing fragment began with the preparation of enantioenriched β-lactone **10** (82% ee) using an organocatalytic reaction (see the Supporting Information for details).[11] Thus, silyl glyoxylate **8**, allylzinc bromide, and **10** were then assembled using the optimized conditions to afford **7a** in 83% yield as a single diastereomer (Scheme 4).

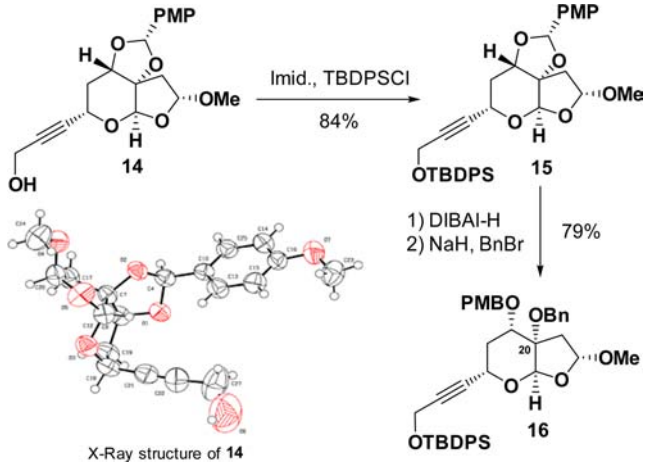
Scheme 4. Synthesis of Right-Wing Fragment 5



Stereoselective reduction of the ketone in **7a**, followed by lactonization[12] and alcohol protection, afforded lactone **11** in 47% yield over three steps. The stereochemistry of **11** was assigned using extensive 2D-NMR experiments (see the Supporting Information).

Removal of the MEM protecting group and DIBAL-H reduction provided hemiacetal **12** as a pair of inseparable epimers (1:5). Acetylation of the primary alcohol and ozonolysis of the olefin furnished bicyclic hemiacetal **13** in 69% yield over two steps, again as a pair of inseparable epimers (1.8:1). Intriguingly, reaction of **13** with iodomethane in the presence of silver(I) oxide resulted in only one stereoisomer **5**.[3d] To confirm the stereochemistry, **5** was first treated with TBAF, and the resultant diol was protected as its benzylidene acetal, followed by deacetylation to give alcohol **14**. The structure of **14** was confirmed by X-ray crystallography[10] (Scheme 5).

Scheme 5. Synthesis of Furo[2,3*b*]pyrans 16



The core structure of **5** with different protecting groups might be required for the total syntheses of azadirachtins **1**−**3**. Thus, substrate **16** (Scheme 5) with more stable protecting groups (PMB/Bn vs TBS/TBS) was selected as an alternative because this compound had been successfully used as a key intermediate in the total synthesis of azadirachtin A (**1**) by Ley and co-workers.[3h]

To this end, the primary hydroxyl group in **15** was protected as its *tert*-butyldiphenylsilyl ether (TBDPS) by reaction with TBDPSCl in the presence of imidazole to give **15** in 84% yield. Regioselective ring opening of the benzylidene acetal protecting group by DIBAL-H and protection of the resultant C20 hydroxyl group as the corresponding benzyl ether gave rise to **16** in 79% yield in two steps. The spectroscopic data of **16** (^{1}H and ^{13}C NMR spectra, HRMS analysis) are in good agreement with those reported by Ley's group.[3f]

In summary, we have synthesized the right-wing fragments of azadirachtin-type limonoids. The synthesis of **5** from chiral β-lactone **10** constitutes a novel and efficient approach to access this highly substituted framework, and the highly diastereoselective tandem allylation/quaternary Claisen condensation of the silyl glyoxylate and β-lactone can be applied to a structurally diverse range of substrates. The work reported herein serves as a milestone in our program toward understanding and synthesizing azadirachtin-type limonoids as environmentally friendly insecticides. Further studies will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectral data, and other characterization data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b00831.

DOI: 10.1021/acs.orglett.5b00831
Org. Lett. 2015, 17, 2338−2341

AUTHOR INFORMATION

Corresponding Authors

*E-mail: gongjx@pku.edu.cn.
*E-mail: tuopingluo@pku.edu.cn.
*E-mail: zyang@pku.edu.cn.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was supported by the NSF of China (Grant Nos. 21372016 and 21402002), 863 Program (Grant No. 2013AA092903), 973 Program (Grant No. 2012CB722602), NSFC-Shandong Joint Fund for Marine Science Research Centers (U1406402), and Shenzhen Basic Research Program (Grant Nos. JCYJ20130329180217059 and ZDSYS20140509094114168).

REFERENCES

(1) Shi, H.; Tan, C.-H.; Zhang, W. B.; Zhang, Z. C.; Long, R.; Luo, T. P.; Yang, Z. *Org. Lett.* **2015**, DOI: 10.1021/acs.orglett.5b00831.

(2) For selected examples of synthesis of furo[2,3*b*]furan moiety: (a) Hatakeyama, S.; Kawamura, M.; Takano, S. *J. Am. Chem. Soc.* **1994**, *116*, 4081. (b) Zhou, G.; Corey, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 11958. (c) Shishido, K.; Bando, T. *J. Mol. Catal. B: Enzym.* **1998**, *5*, 183. (d) Roggenbuck, R.; Schmidt, A.; Elibracht, P. *Org. Lett.* **2002**, *4*, 289. (e) Stromgaard, K.; Suehiro, M.; Nakanishi, K. *Bioorg. Med. Chem. Lett.* **2004**, *12*, 5673. (f) Ghosh, A. K.; Leshchenko, S.; Noetzel, M. *J. Org. Chem.* **2004**, *69*, 7822. (g) Gopalakrisnan, S.; Stone, M. P.; Harris, T. M. *J. Am. Chem. Soc.* **1989**, *111*, 7232. (h) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 3090. (i) Dzyuba, S. V.; Bolshaov, S.; Nakanishi, K. *Tetrahedron Lett.* **2005**, *46*, 7797. (j) Ghosh, A. K.; Martyr, C. D.; Steffey, M.; Wang, Y.; Agniswamy, J.; Amano, M.; Weber, I. T.; Mitsuya, H. *ACS Med. Chem. Lett.* **2011**, *2*, 298. (k) Kulkarni, M. G.; Shaih, Y. B.; Borhade, A. S.; Dhondge, A. P.; Chavhan, S. W.; Desai, M. P.; Birhade, D. R.; Dhatrak, N. R.; Gannimani, R. *Tetrahedron: Asymmetry* **2010**, *21*, 2394. (l) Canoy, W. L.; Cooley, B. E.; Corona, J. A.; Lovelace, T. C.; Millar, A.; Weber, A. M.; Xie, S.; Zhang, Y. *Org. Lett.* **2008**, *10*, 1103. (m) Quaedflieg, P. J. L. M.; Kesteleyn, B. R. R.; Wigerinck, P. B. T. P.; Goyvaerts, N. M. F.; Vijn, R. J.; Liebregts, C. S. M.; Kooistra, J. H. M. H.; Cusan, C. *Org. Lett.* **2005**, *7*, 5917.

(3) (a) Nishikimi, Y.; Iimori, T.; Sodeoka, M.; Shibasaki, M. *J. Org. Chem.* **1989**, *54*, 3354. (b) Anderson, J. C.; Ley, S. V.; Santafianos, D.; Sheppard, R. N. *Tetrahedron* **1991**, *47*, 6813. (c) Henry, K. J., Jr.; Fraser-Reid, B. *J. Org. Chem.* **1994**, *59*, 5128. (d) Watanabe, H.; Watanabe, T.; Moil, K. *Tetrahedron* **1996**, *52*, 13939. (e) Ishihara, J.; Fukuzaki, T.; Murai, A. *Tetrahedron Lett.* **1999**, *40*, 1907. (f) Boyer, A.; Veitch, G. E.; Beckmann, E.; Ley, S. V. *Angew. Chem., Int. Ed.* **2009**, *48*, 1317. (g) Bhanu Prasad, S. R. B. A.; Singh, V. K. *ARKIVOC* **2003**, 16. (h) Veitch, G. E.; Beckmann, E.; Burke, B. J.; Boyer, A.; Maslen, S. L.; Ley, S. V. *Angew. Chem., Int. Ed.* **2007**, *46*, 7629.

(4) (a) Nicewicz, D. A.; Johnson, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 6170. (b) Linghu, X.; Satterfield, A. D.; Johnson, J. S. *J. Am. Chem. Soc.* **2006**, *128*, 9302. (c) Nicewicz, D. A.; Satterfield, A. D.; Schmitt, D. S.; Johnson, J. S. *J. Am. Chem. Soc.* **2008**, *130*, 17281. (d) Nicewicz, D. A.; Breteche, G.; Johnson, J. S. *Org. Synth.* **2008**, *85*, 278. (e) Greszler, S. N.; Johnson, J. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 3689. (f) Greszler, S. N.; Johnson, J. S. *Org. Lett.* **2009**, *11*, 827. (g) Greszler, S. N.; Johnson, J. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 3689. (h) Greszler, S. N.; Malinowski, J. T.; Johnson, J. S. *J. Am. Chem. Soc.* **2010**, *132*, 17393. (i) Boyce, G. R.; Johnson, J. S. *Angew. Chem., Int. Ed.* **2010**, *49*, 8930. (j) Schmitt, D. C.; Johnson, J. S. *Org. Lett.* **2010**, *12*, 944. (k) Schmitt, D. C.; Lam, L.; Johnson, J. S. *Org. Lett.* **2011**, *13*, 5136. (l) Slade, M. C.; Johnson, J. S. *Beilstein J. Org. Chem.* **2013**, *9*, 166.

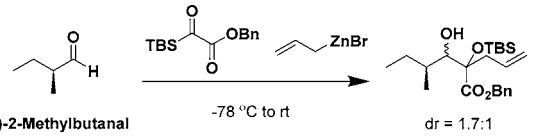
(5) The synthetic applications of silyl glyoxylates are growing in prominence. For related examples see: (a) Lettan, R. B.; Woodward, C. C.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 2294. (b) Lettan, R. B.; Galliford, C. V.; Woodward, C. C.; Scheidt, K. A. *J. Am. Chem. Soc.* **2010**, *132*, 8805. (c) Yao, M.; Lu, C.-D. *Org. Lett.* **2011**, *13*, 2782. (d) Jiang, J.-L.; Yao, M.; Lu, C.-D. *Org. Lett.* **2014**, *16*, 318.

(6) Brook, A. G. *Acc. Chem. Res.* **1974**, *7*, 77.

(7) (a) Boyce, G. R.; Greszler, S. N.; Johnson, J. S.; Xin, L.; Malinowski, J. T.; Nicewicz, D. A.; Satterfield, A. D.; Schmitt, D. C.; Steward, K. M. *J. Org. Chem.* **2012**, *77*, 4503. (b) Xin, L.; Bausch, C. C.; Johnson, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 1833.

(8) Zn−olefin complex: (a) Fernandez, R.; Resa, I.; delRıo, D.; Carmona, E. *Organometallics* **2003**, *22*, 381. (b) Gabrienko, A. A.; Arzumanov, S. S.; Freude, D.; Stepanov, A. G. *J. Phys. Chem. C* **2010**, *114*, 12681. (c) Gabrienko, A. A.; Stepanov, A. G. *J. Phys. Chem. C* **2012**, *116*, 11096. (d) Gao, H.; Ke, Z.; DeYonker, N. J.; Wang, J.; Xu, H.; Mao, Z.; Phillips, D. L.; Zhao, C. *J. Am. Chem. Soc.* **2011**, *133*, 2904. (e) Jacobsen, F. E.; Lewis, J. A.; Cohen, S. M. *J. Am. Chem. Soc.* **2006**, *128*, 3156. (f) Fabbrini, G.; Menna, E.; Maggini, M.; Canazza, A.; Marcolongo, G.; Meneghetti, M. *J. Am. Chem. Soc.* **2004**, *126*, 6238. (g) Vallet, V.; Wahlgren, U.; Grenthe, I. *J. Am. Chem. Soc.* **2003**, *125*, 14941. (h) Kaminskaia, N.; Spingler, B.; Lippard, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 6555.

(9) Slade, M. C.; Johnson, J. S. *Beilstein J. Org. Chem.* **2013**, *9*, 166. In this report, Johnson and Slade developed a three-component coupling with allylzinc bromide, silyl glyoxylate, and an aldehyde to give a poor diastereoselective result.



(10) CCDC1031567 **14** contains 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.

(11) (a) Nelson, S. G.; Peelen, T. J.; Wan, Z. *J. Am. Chem. Soc.* **1999**, *121*, 9742. (b) Zhu, C.; Shen, X.; Nelson, S. G. *J. Am. Chem. Soc.* **2004**, *126*, 5352. (c) Nelson, S. G.; Wan, Z.; Peelen, T. J.; Spencer, K. L. *Tetrahedron Lett.* **1999**, *40*, 6535. (d) Nelson, S. G.; Peelen, T. J.; Wan, Z. *Tetrahedron Lett.* **1999**, *40*, 6541. (e) Wan, Z.; Nelson, S. G. *J. Am. Chem. Soc.* **2000**, *122*, 10470.

(12) Otera, J.; Dan-oh, N.; Nozaki, H. *J. Org. Chem.* **1991**, *56*, 5307.

DOI: 10.1021/acs.orglett.5b00831
Org. Lett. 2015, 17, 2338−2341