Organic LETTERS

Letter

pubs.acs.org/OrgLett

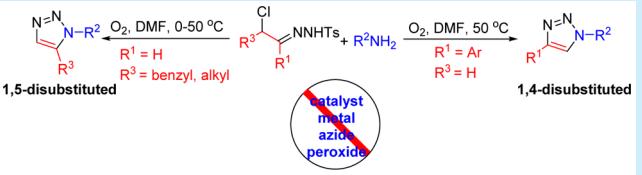
Aerobic Oxidative Cycloaddition of α-Chlorotosylhydrazones with Arylamines: General Chemoselective Construction of 1,4-Disubstituted and 1,5-Disubstituted 1,2,3-Triazoles under Metal-Free and Azide-Free Conditions

Hui-Wen Bai, Zhong-Jian Cai, Shun-Yi Wang,* and Shun-Jun Ji*

Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry, Chemical Engineering and Materials Science & Collaborative Innovation Center of Suzhou Nano Science and Technology, Soochow University, Suzhou, 215123, P. R. China

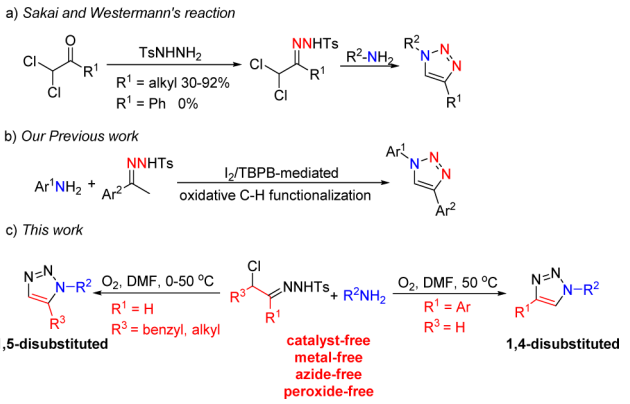
Supporting Information

ABSTRACT: A novel synthetic approach toward 1,4-disubstituted 1,2,3-triazoles and 1,5-disubstituted 1,2,3-triazoles by aerobic oxidative cycloaddition of α-chlorotosylhydrazone with primary aryl amine has been developed. Significantly, the reaction proceeds smoothly to afford 1,4-disubstituted 1,2,3-triazoles and 1,5-disubstituted 1,2,3-triazoles under catalyst-free, metal-free, azide-free, and peroxide-free conditions.



1,2,3-Triazoles are significant five-membered ring heterocyclic compounds, and they have been widely utilized in synthetic intermediates, bioactive products, and pharmaceutical drugs.[1] It is well-known that the mixture of both regioisomers could be obtained by Huisgen's 1,3-dipolar cycloaddition of alkynes with organic azides.[2] The Cu(I)-catalyzed azide−alkyne cycloaddition has been exploited as a vigorous strategy for 1,4-disubstituted triazoles with high regioselectivity indepently developed by the groups of Sharpless and Meldal.[3,4] The CuAAC reaction has huge implications in organic synthesis according to Sharpless' concept of "Click Chemistry".[5] Subsequently, the 1,5-disubstituted triazole isomers were achieved by the RuAAC reaction.[6] Several other methods including the IrAAC reaction, Pd-catalyzed alkenyl bromide−azide cycloaddition, and Ce-catalyzed nitroolefin−azide [3 + 2] cycloaddition have been developed for the regioselective synthesis of triazoles.[7−9] Nevertheless, all these reactions could not avoid employing heavy metals, which restricted their application in biological and life sciences. Metal-free strategies containing an organocatalytic enamine-mediated 1,2,3-triazole synthesis, an enaminone-azide multicomponent cascade reaction, and a TsOH-catalyzed nitroolefin−azide cycloaddition have been reported for the preparation of specific 1,2,3-triazoles.[10−12] However, all of these transformations are in need of sodium azides or organic azides, which are explosive and toxic. To the best of our knowledge, no literature reports chemoselective construction of 1,4-disubstituted and 1,5-disubstituted triazoles using the same strategy. Zhang and coworkers provided a copper-mediated method to achieve the desired 1,4-disubstituted 1,2,3-triazoles without the use of azides.[13] Westermann improved Sakai's reaction and reported the synthesis of 1,4-disubstituted 1,2,3-triazoles though the condensation of α,α-dichlorotosylhydrazones and primary amines under metal-free conditions (Scheme 1a).[14,15] Recently,

Scheme 1. A Proposed Route to 1,2,3-Triazoles under Metal-Free and Azide-Free Conditions



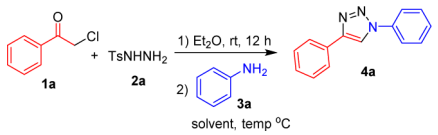
Ramasastry summarized the synthetic methods for 1,2,3-triazoles.[16] There are rare methods to construct 1,2,3-triazoles, especially the 1,5-disubstituted 1,2,3-triazoles under metal-free and azide-free conditions. More recently, we reported a I_2/TBPB mediated oxidative reaction of *N*-tosylhydrazones with arylamines, which provided a simple and general approach for the establishment of 1,4-disubstituted triazoles (Scheme 1b).[17] However, only 1,4-disubstituted isomers were obtained. On the basis of our previous work, herein, we demonstrate a novel synthetic approach toward 1,4-disubstituted and 1,5-disubstituted triazoles by the cycloaddition of α-chlorotosylhydrazones with arylamines under metal-free and azide-free conditions (Scheme 1c).

Received: April 7, 2015

DOI: 10.1021/acs.orglett.5b01000
Org. Lett. XXXX, XXX, XXX−XXX

We initiated our study by α-chlorotosylhydrazone and aniline **3a** in the conditions of DMSO (1 mL), 50 °C for 3 h. As the α-chlorotosylhydrazone could be easily generated from the addition of α-chloroacetophenone **1a** and *p*-toluenesulfonhydrazide **2a** in the solvent Et_2O (1 mL), we adopted a one-pot method without isolating the intermediate. To our delight, 1,4-diphenyl-1,2,3-triazole **4a** was detected in 38% LC-yield. With the aim to improve the yield of **4a**, we examined the influences of solvents, temperature, ratio of substrates, and so on. Among the different solvents, it was found that DMF was the suitable solvent for this reaction (Table 1, entries 1−10).

Table 1. Optimization of the Reaction Conditions[a]



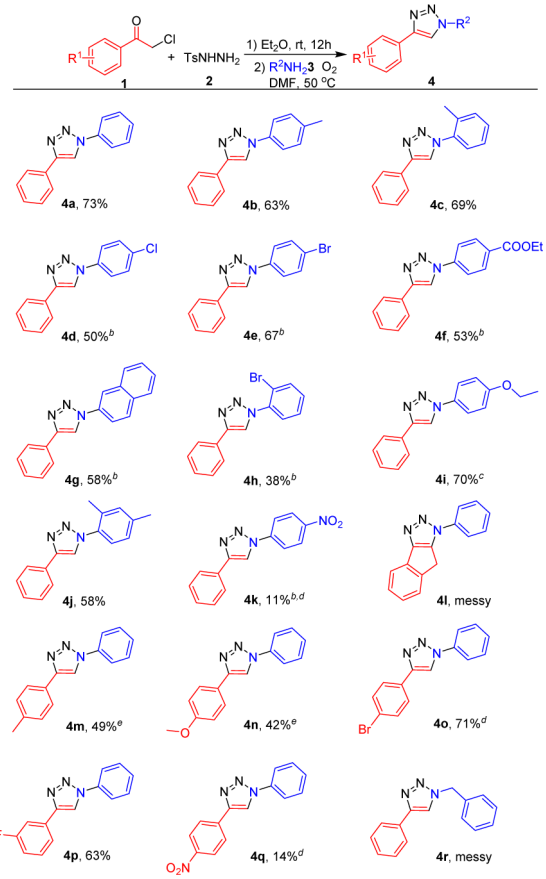
entry	atmosphere	temp (°C)	solvent	yield (LC)[b]
1	air	50	THF	57
2	air	50	toluene	33
3	air	50	MeCN	40
4	air	50	CH_2Cl_2	5
5	air	50	DMF	64
6	air	50	DMSO	38
7	air	50	1,4-dioxane	36
8	air	50	EA	21
9	air	50	MeOH	41
10	air	50	$CHCl_3$	17
11	air	40	DMF	57
12	air	60	DMF	41
13	air	70	DMF	37
14	air	80	DMF	28
15	air	50	DMF	37[c]
16	air	50	DMF	51[d]
17	O_2	50	DMF	75
18	Ar	50	DMF	8

[a]Reaction conditions: **1a** (0.3 mmol) and **2a** (0.3 mmol) were performed in Et_2O (1 mL) at room temperature for 12 h. Then after removal of the solvent, solvent (1 mL) and **3a** (0.6 mmol) were added at room temperature. The mixture was stirred at 50 °C for 3 h. [b]Yields were determined by LC analysis using biphenyl as the internal standard. [c]**2a**:**3a** = 1:1.5. [d]**2a**:**3a** = 1:2.5

Increasing or decreasing the temperature did not have a beneficial effect on the reaction (Table 1, entries 11−14). Changing the amount of aniline **3a** led to lower yields (Table 1, entries 15−16). A higher yield was obtained in an atmosphere of O_2, while, in the Ar atmosphere, a trace of product **4a** was detected (Table 1, entries 17−18). Consequently, the optimized conditions were obtained: **1a** (0.3 mmol), **2a** (0.3 mmol), Et_2O (1 mL), 12 h, **3a** (0.6 mmol), DMF (1 mL), 50 °C, 3 h.

Under our optimized experimental conditions, different arylamines and α-chloroketones were tested. As listed in Scheme 2, various arylamines were tested in the reaction of α-chlorotosylhydrazones which could be in situ observed by the condensation of α-chloroketones with *p*-$TsNHNH_2$ and directly used for the next step reaction without further purification. It was found that a range of arylamines could be transformed into the corresponding 1,4-disubstituted-1,2,3-triazoles in moderate to good yields. Arylamines bearing electron-donating substituents (−CH_3, −OCH_2CH_3) or

Scheme 2. Substrate Scope of Reaction[a]



[a]Reaction conditions (unless otherwise noted): **1a** (0.3 mmol) and **2a** (0.3 mmol) were performed in Et_2O (1 mL) at room temperature for 12 h. Then removing the solvent, DMF (1 mL) and **3** (0.6 mmol) were added at room temperature. The mixture was stirred at 50 °C for 3 h. Isolated yield. [b]**3** (0.3 mmol) was used. [c]The reaction was performed for 6 h. [d]The reaction was performed for 20 h. [e]The reaction was performed for 8 h.

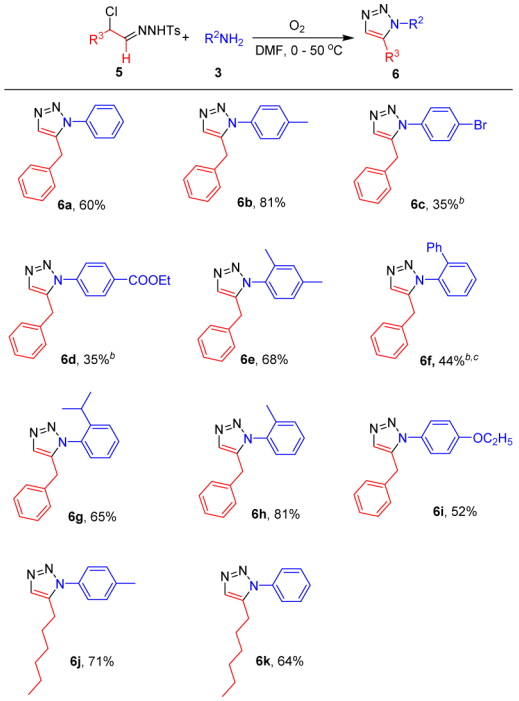
electron-withdrawing substituents (−Cl, −Br, −COOEt) proceeded smoothly with good yields (**4b**, **4i**, **4d**−**4f**). Similarly, when β-CH_3 substituted arylamines were participating in the reactions, the desired products **4c** and **4j** were obtained in 69% and 58% yields, respectively. Nevertheless, when 2-bromoaniline with a sterically demanding substituent group was used, the triazole **4h** could also be observed in 38% yield. 2-Naphthylamine also exhibited good reactivity to give the product **4g**. Unfortunately, 4-nitroaniline resulted in the corresponding product **4k** in 11% yield. These results indicated that the electronic effect of the substituents of arylamines influenced the yields. Subsequently, different in situ prepared α-chlorotosylhydrazones were applied to the reaction with aniline **3**. A longer reaction time was required when the benzene ring of α-chloroketones was bearing a substituent group. In the case of aromatic rings containing electron-donating groups (−CH_3, −OCH_2CH_3), the yields of the reaction decreased slightly. The reactions were compatible with the substituents of 3-F and 4-Br, giving the compounds **4o** and **4p** in good yields, respectively. The reaction of 2-chloro-1-(4-nitropheyl)ethan-1-one could also work. However, the yield of **4q** was only 14%. Unfortunately, the reaction of alkyl amine such as benzylamine

DOI: 10.1021/acs.orglett.5b01000
Org. Lett. XXXX, XXX, XXX−XXX

failed to give the desired products under the identical conditions.

Since 1,4-disubstituted 1,2,3-triazoles could be obtained by the cyclization of α-chloroketones derived tosylhydrazones with arylamines under mild conditions, we reasoned that 1,5-disubstituted triazoles could also be obtained utilizing the same strategy by the reaction of α-chloroaldehyde derived tosylhydrazones and arylamines. Considering that α-chloroaldehydes were easily oxidized, the required α-chlorotosylhydrazones **5** were synthesized separately in Et_2O in good yields. Fortunately, this idea worked well. The reaction of 2-chloro-3-phenypropanal derived tosylhydrazone **5a** and aniline **4a** proceeded smoothly to give the desired 5-benzyl-1-phenyl-1,2,3-triazole **6a** in 60% isolated yield (Scheme 3). With this promising result

Scheme 3. Substrate Scope of Reaction[a]

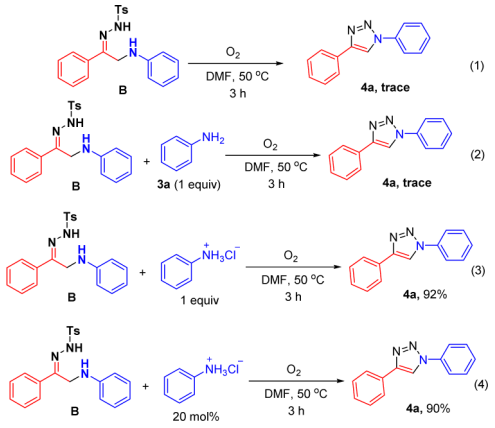


[a]Reaction conditions (unless otherwise noted): **3** (0.6 mmol) was added to a stirred ice-cooled (0 °C) solution of **5** (0.3 mmol) in DMF (1 mL). The mixture was stirred for at 0 °C for 1 h and then warmed to 50 °C for 4 h. Isolated yield. [b]**3** (0.3 mmol) was used. [c]The reaction was performed for 8 h.

in hand, we next explored a range of arylamines with **5a**. The 4-substituted anilines with electron-donating groups ($-CH_3$, $-OCH_2CH_3$) provided the product **6b** and **6i** in good yields, respectively. The substrates of 4-bromoaniline and ethyl 4-aminobenzoate could also be converted to the desired products in lower yields for their poor nucleophilicity. Moreover, the transformation was not influenced by the position of the substituent groups, even the steric hindrance at the β-position on benzene rings (**6e**, **6f**, **6g**, **6h**). 2-Chlorooctanal derived tosylhydrazone **5b** could also take part in the reactions to give the 1,5-disubstituted 1,2,3-trazoles **6j** and **6k** smoothly in good yields, respectively.

To further understand the reaction mechanism, the control experiments of **B** have been carried out as shown in Scheme 4. It was found that the intermediate **B** failed to result in the triazole **4a** under the standard conditions (Scheme 4, eq 1).

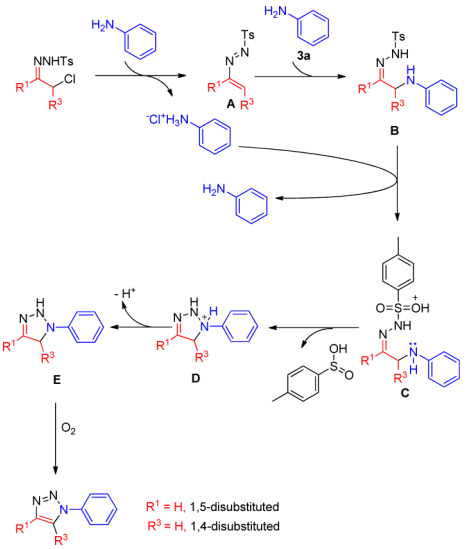
Scheme 4. Control Experiments



Meanwhile, the intermediate **B** also could not lead to **4a** in the presence of anline (Scheme 4, eq 2). To our surprise, the reaction of intermediate **B** with aniline hydrochloride (1 equiv or 20 mol %) gave **4a** in 92% and 90% yields, respectively (Scheme 4, eqs 3 and 4). These results indicated that a proton has a significant role in the reactions.

Based on the results at hand and the literature reports, a plausible reaction pathway is proposed in Scheme 5. α-

Scheme 5. Mechanism Studies



Chlorotosylhydrazone easily converts to the azoalkene **A** and leaves aniline hydrochloride by the reaction with anline. The 1,4-addition of **A** with amine gives **B**.[18] **B** (Ts functional group of **B**) is protonated by benzenaminium to give the activated intermediate **C**. After intramolecular cyclization of **C** with the leaving of 4-methylbenzenesulfinic acid, **D** is formed. **D** loses H^+ to give the neutral intermediate **E**. Following subsequent further oxidation by O_2, **E** converts to the desired 1,2,3-triazole.

In summary, we have developed a new methodology for the synthesis of 1,4-disubstituted and 1,5-disubstituted 1,2,3-triazoles from arylamines with α-chloroketone derived tosylhydrazones and α-chloroaldehyde derived tosylhydrazones. Significantly, this transformation provides selective synthesis of both regioisomers of 1,2,3-triazoles under metal-free and azide-free conditions. Further investigations to establish other heterocylic compounds by α-chlorotosylhydrazones under mild

DOI: 10.1021/acs.orglett.5b01000
Org. Lett. XXXX, XXX, XXX−XXX

conditions are ongoing in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and characterization data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01000.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: shunyi@suda.edu.cn.
*E-mail: shunjun@suda.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge the Natural Science Foundation of China (21172162, 21372174), the Young National Natural Science Foundation of China (No. 21202111), the Ph.D. Programs Foundation of Ministry of Education of China (2013201130004), the Young Natural Science Foundation of Jiangsu Province (BK2012174), PAPD, Key Laboratory of Organic Synthesis of Jiangsu Province (KJS1211), and Soochow University for financial support.

■ REFERENCES

(1) (a) Wamhoff, H. In *Comprehensive Heterocyclic Chemistry*, Vol. *5*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; p 669. (b) Abu-Orabi, S. T.; Atfah, M. A.; Jibril, I.; Mari'I, F. M.; Ali, A. A. *J. Heterocycl. Chem.* **1989**, *26*, 1461−1468. (c) Fan, W.-Q.; Katritzky, A. R. In *Comprehensive Heterocyclic Chemistry II*, Vol. *4*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Elsevier Science: Oxford, 1996; p 1−126. (d) Alvarez, R.; Velazquez, S.; San, F.; Aquaro, S.; De, C.; Perno, C. F.; Karlsson, A.; Balzarini, J.; Camarasa, M. J. *J. Med. Chem.* **1994**, *37*, 4185−4181. (e) Baures, P. W. *Org. Lett.* **1999**, *1*, 249−252. (f) Palmer, L. M.; Janson, C. A.; Smith, W. W. *PCT Int. Appl.* 2005; p 347. CODEN: PIXXD2 WO 2005016237 A2 20050224, CAN: 142:256748 (patent written in English).

(2) (a) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 565−598. (b) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 633−645. (c) Huisgen, R.; Knorr, R.; Möbius, L.; Szeimies, G. *Chem. Ber.* **1965**, *98*, 4014−4021.

(3) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem.* **2002**, *114*, 2708−2711; *Angew. Chem., Int. Ed.* **2002**, *41*, 2596−2599.

(4) Tornøe, C. W.; C. Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057−3064.

(5) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004−2021.

(6) (a) Zhang, L.; Chen, X. G.; Xue, P.; Sun, H. H. Y.; Williams, I. D.; Sharpless, K. B.; Fokin, V. V.; Jia, G. *J. Am. Chem. Soc.* **2005**, *127*, 15998−15999. (b) Rasmussen, L. K.; Boren, B. C.; Fokin, V. V. *Org. Lett.* **2007**, *9*, 5337−5339. (c) Boren, B. C.; Narayan, S.; Rasmussen, L. K.; Zhang, L.; Zhao, H.; Lin, Z.; Jia, G.; Fokin, V. V. *J. Am. Chem. Soc.* **2008**, *130*, 8923−8930. (d) Johansson, J. R.; Lincoln, P.; Norden, B.; Kann, N. *J. Org. Chem.* **2011**, *76*, 2355−2359. (e) For Sm(III)-catalyzed azide−alkyne cycloaddition, see: Hong, L.; Lin, W.; Zhang, F.; Liu, R.; Zhou, X. *Chem. Commun.* **2013**, *49*, 5589−5591.

(7) Ding, S.; Jia, G.; Sun, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 1877−1880.

(8) Barluenga, J.; Valdés, C.; Beltrán, G.; Escribano, M.; Aznar, F. *Angew. Chem., Int. Ed.* **2006**, *45*, 6893−6896.

(9) Wang, Y. C.; Xie, Y. Y.; Qu, H. E.; Wang, H. S.; Pan, Y. M.; Huang, F. P. *J. Org. Chem.* **2014**, *79*, 4463−4469.

(10) (a) Brunner, M.; Maas, G.; Klarner, F.-G. *Helv. Chim. Acta* **2005**, *88*, 1813−1825. (b) Belkheira, M.; El Abed, D.; Pons, J.-M.; Bressy, C. *Chem.—Eur. J.* **2011**, *17*, 12917−12921. (c) Danence, L. J. T.; Gao, Y.; Li, M.; Huang, Y.; Wang, J. *Chem.—Eur. J.* **2011**, *17*, 3584−3587. (d) Seus, N.; Goncalves, L. C.; Deobald, A. M.; Savegnago, L.; Alves, D.; Paixao, M. W. *Tetrahedron.* **2012**, *68*, 10456−10463. (e) Wang, L.; Peng, S.; Danence, L. J. T.; Gao, Y.; Wang, J. *Chem.—Eur. J.* **2012**, *18*, 6088−6093. (f) Li, W.; Jia, Q.; Du, Z.; Wang, J. *Chem. Commun.* **2013**, *49*, 10187−10189.

(11) Cheng, G.; Zeng, X.; Shen, J.; Wang, X.; Cui, X. *Angew. Chem., Int. Ed.* **2013**, *52*, 13265−13268.

(12) (a) Thomas, J.; John, J.; Parekh, N.; Dehaen, W. *Angew. Chem., Int. Ed.* **2013**, *53*, 10155−10159. (b) Quan, X.-J.; Ren, Z.-H.; Wang, Y.-Y.; Guan, Z.-H. *Org. Lett.* **2014**, *16*, 5728−5731.

(13) (a) Chen, Z. K.; Yan, Q. Q.; Liu, Z. X.; Xu, Y. M.; Zhang, Y. H. *Angew. Chem., Int. Ed.* **2013**, *52*, 13324−13328. (b) Chen, Z.; Yan, Q.; Yi, H.; Liu, Z.; Lei, A.; Zhang, Y. *Chem.—Eur. J.* **2014**, *20*, 13692−13697.

(14) van Berkel, S. S.; Brauch, S.; Gabriel, L.; Henze, M.; Stark, S.; Vasilev, D.; Wessjohann, L. A.; Abbas, M.; Westermann, B. *Angew. Chem., Int. Ed.* **2012**, *51*, 5343−5346.

(15) Sakai, K.; Hida, N.; Kondo, K. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 179−183.

(16) Ramasastry, S. S. V. *Angew. Chem., Int. Ed.* **2014**, *53*, 14310−14312.

(17) Cai, Z.-J.; Lu, X.-M.; Zi, Y.; Yang, C.; Shen, L.-J.; Li, J.; Wang, S.-Y.; Ji, S.-J. *Org. Lett.* **2014**, *16*, 5108−5111.

(18) (a) Attanasi, O. A.; De Crescentini, L.; Favi, G.; Filippone, P.; Mantellini, F.; Perrulli, F. R.; Santeusanio, S. *Eur. J. Org. Chem.* **2009**, 3109−3112. (b) Rossi, E.; Arcadi, A.; Abbiati, G.; Attanasi, O. A.; Crescentini, L. D. *Angew. Chem., Int. Ed.* **2002**, *41*, 1400−1402. (c) Attanasi, O. A.; Favi, G.; Filippone, P.; Giorgi, G.; Mantellini, F.; Moscatelli, G.; Spinelli, D. *Org. Lett.* **2008**, *10*, 1983−1986. (d) Attanasi, O. A.; Favi, G.; Filippone, P.; Mantellini, F.; Moscatelli, D.; Perrulli, F. R. *Org. Lett.* **2010**, *12*, 468−471. (e) Attanasi, O. A.; Favi, G.; Mantellini, F.; Moscatelli, G.; Santeusanio, S. *Adv. Synth. Catal.* **2011**, *353*, 1519−1524. (f) Chen, J.-R.; Dong, W.-R.; Candy, M.; Pan, F.-F.; Jörres, M.; Bolm, C. *J. Am. Chem. Soc.* **2012**, *134*, 6924−6927. (g) Hatcher, J. M.; Coltart, D. M. *J. Am. Chem. Soc.* **2010**, *132*, 4546−4547. (h) Tong, M.-C.; Chen, X.; Li, J.; Huang, R.; Tao, H.; Wang, C.-J. *Angew. Chem., Int. Ed.* **2014**, *53*, 4680−4684.

DOI: 10.1021/acs.orglett.5b01000
Org. Lett. XXXX, XXX, XXX−XXX