Organic LETTERS

Letter

pubs.acs.org/OrgLett

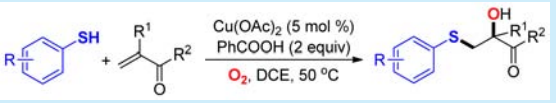
Hydroxysulfenylation of Electron-Deficient Alkenes through an Aerobic Copper Catalysis

Hui Xi, Bicheng Deng, Zhenzhen Zong, Shenglin Lu, and Zhiping Li*

Department of Chemistry, Renmin University of China, Beijing 100872, China

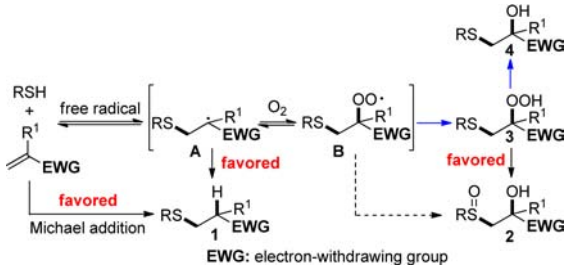
Supporting Information

ABSTRACT: A copper-catalyzed hydroxysulfenylation of α,β-unsaturated esters/amides is reported. The method presents a selective and efficient synthesis of β-hydroxysulfides bearing electron-withdrawing groups. The synthetic utility of this method is demonstrated by the concise synthesis of the anticancer drug bicalutamide.



The addition of organosulfurs to C−C unsaturated bonds is one of the powerful synthetic tools toward sulfur-containing compounds.[1,2] Hydroxysulfenylation (thiol−oxygen co-oxidation) of alkenes with thiols provides an excellent route to introduce vicinal heteroatomic substituents, affording β-hydroxysulfides in one step. Although the strategy is well-suited for electron-rich alkenes,[3] hydroxysulfenylation of electron-deficient alkenes has remained largely underdeveloped for a long time. It is not surprising that the greatest difficulty is attributed to the selectivity of the reaction (Scheme 1).[4] The formation of the

Scheme 1. Outline for Hydroxysulfenylation of Electron-Deficient Alkenes

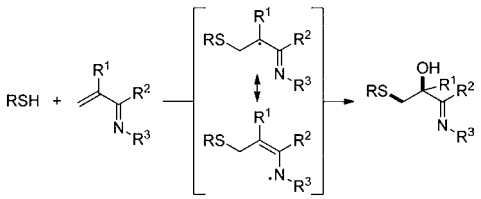


hydrothiolation product **1** is favored for the alkene with an electron-withdrawing group in both radical and nucleophilic mechanisms.[1] In addition, the hydroxyl sulfoxide **2** is also feasibly generated via an intramolecular oxygen transfer of **3** (or **B**).[5] We anticipate that the desired β-hydroxysulfide product **4** can be favored by pushing the radical equilibrium to generate the hydroperoxide **3** and reducing the peroxyl bond simultaneously (blue arrows in Scheme 1).

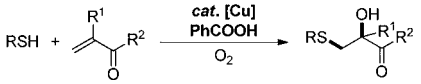
In 2008, Naito and co-workers creatively applied α,β-unsaturated imines as the thiyl radical acceptors by enhancing the stability of the intermediate radical **A** and reducing the ability of the Michael acceptor (Scheme 2a).[6] Despite the success of this method, the selective hydroxysulfenylation of simple α,β-unsaturated esters/amides still remained an important challenge. Herein, we present a practical hydroxysulfenylation of electron-deficient alkenes based on an aerobic copper catalysis that

Scheme 2. Strategies for Hydroxysulfenylation of Electron-Deficient Alkenes

a) Naito's work: **the α-imino radical**



b) This work: **an aerobic copper catalysis**



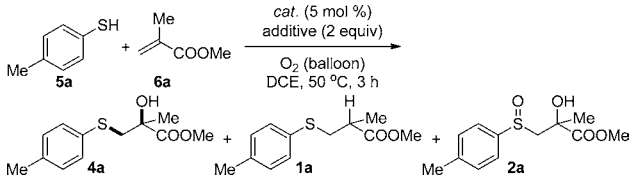
effectively overcomes the selective issue of the reactions of α,β-unsaturated esters/amides with thiols (Scheme 2b).

The reaction of *p*-toluenethiol **5a** and methyl methacrylate **6a** under oxygen atmosphere was chosen as a model to investigate the reaction conditions (Table 1). The desired β-hydroxysulfide **4a** was obtained in 30% yield, while the hydroxyl sulfoxide **2a** was formed as a major product along with trace amounts of the hydrothiolation product **1a** without catalyst (entry 1). To our delight, metal catalysts greatly prevented the formation of **2a**. Accordingly, we performed an extensive survey of a variety of metal salts (entries 2−10). It turned out that the copper catalysts were beneficial to the formation of **4a** in the terms of efficiency and selectivity (entries 7−10). Importantly, although benzoic acid as an additive showed no obvious influence (entries 11−13), a 98% yield of **4a** was achieved by using $Cu(OAc)_2$ as catalyst (entry 14). These results indicated that the efficiency of hydroxysulfenylation heavily depends on both the copper anion and the extra proton source. Further studies showed that the acidity of carboxylic acid slightly affected the efficiency and selectivity of the reaction (entries 15 and 16). Significantly, **4a** could be obtained in an excellent yield without benzoic acid by prolonging the reaction time (entry 17). On the basis of the

Received: January 13, 2015
Published: February 13, 2015

DOI: 10.1021/acs.orglett.5b00112
Org. Lett. 2015, 17, 1180−1183

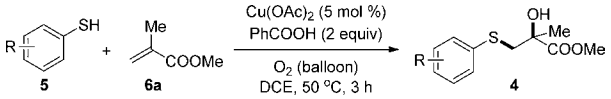
Table 1. Optimization of Reaction Conditions[a]

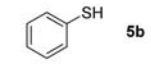
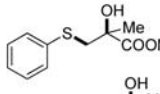
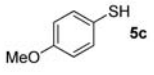
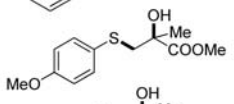
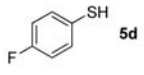
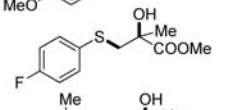
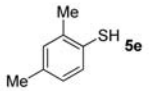
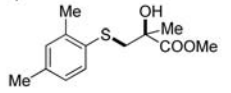
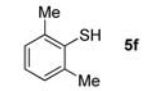
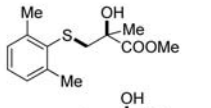
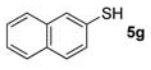
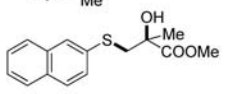
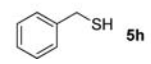
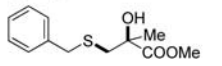


entry	cat.	additive	NMR yield (%)[b] 4a	1a	2a
1			30	4	66
2	$FeCl_2$		36	10	3
3	$FeCl_3$		34	6	6
4	$Fe(OAc)_2$		25	15	15
5	$CoCl_2$		40	5	5
6	$Mn(OAc)_2$		30	3	3
7	CuCl		64	13	3
8	CuBr		74	4	6
9	$CuCl_2$		46	3	5
10	$Cu(OAc)_2$		20	1	1
11	CuCl	PhCOOH	70	15	5
12	CuBr	PhCOOH	40	15	3
13	$CuCl_2$	PhCOOH	49	9	2
14	$Cu(OAc)_2$	PhCOOH	98	1	1
15	$Cu(OAc)_2$	4-NO_2-PhCOOH	67	3	3
16	$Cu(OAc)_2$	4-MeO-PhCOOH	90	5	5
17[c]	$Cu(OAc)_2$		97	1	1

[a]Reaction conditions: **5a** (2.0 mmol), **6a** (0.5 mmol), cat. (0.025 mmol), additive (1.0 mmol), DCE (5.0 mL), 50 °C, 3 h, unless otherwise noted. [b]NMR yields were based on **6a**. [c]12 h.

Table 2. Scope of Substrates 5[a]



entry	5	4	yield (%)[b]
1			**4b**, 93(85)
2			**4c**, 88(77)
3			**4d**, 98(93)
4			**4e**, 74(66)
5			**4f**, 70(68)
6			**4g**, 85(75)
7			**4h**, 0

[a]Reaction conditions: **5** (2.0 mmol), **6a** (0.5 mmol), $Cu(OAc)_2$ (0.025 mmol), PhCOOH (1.0 mmol), DCE (5.0 mL), 50 °C, 3 h. [b]NMR yields; isolated yields are given in parentheses.

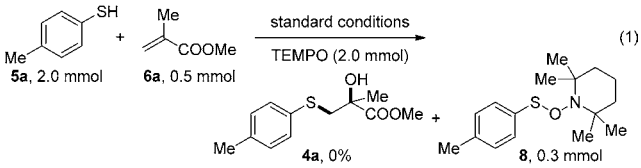
results, we rationalized that (1) copper catalysis could be an easy to accomplish approach for hydroxysulfenylation of electron-deficient alkenes, which was one of the unsettled problems in synthetic chemistry, and (2) Brønsted acid greatly accelerated the process.

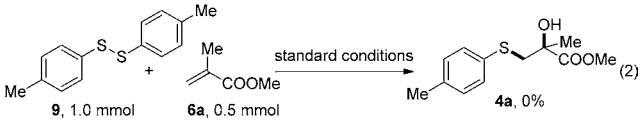
The applicability of the method was subsequently explored by using the conditions of entry 14 in Table 1 as the standard reaction conditions. First, the scope of thiols was investigated (Table 2). Thiophenol and its derivatives **5b**−**5f** were applied, and the corresponding *β*-hydroxysulfides **4b**−**4f** were obtained in good to excellent yields (entries 1−5). The results indicated that the electronic effect of thiophenols shows no obvious influence on the efficiency of the desired transformation, while the steric hindrance reduced the yields of **4** (entries 4 and 5). Thionaphthol **5g** also reacted smoothly with **6a** to afford **4g** in 85% yield (entry 6). However, aliphatic thiols, for an example of benzyl mercaptan **5h**, could not be used under the standard reaction conditions, indicating that the stable thiyl radicals generated by the oxidation of thiols were required for the present transformation.

Next, the scope of alkenes **6** was surveyed by the use of **5a** as a test substrate (Figure 1). To our satisfaction, a broad range of alkenes was applied smoothly for the hydroxysulfenylation under the standard conditions, including *α*,*β*-unsaturated esters, amides and ketone, styrenes, and the conjugated diene. More importantly, a variety of functional groups of alkenes were well-tolerated, such as allyl **4j**, hydroxy **4k**, and free amino **4q**. It should be noted that the internal alkene also led to the desired product **4y** under the standard reaction conditions, albeit in a low yield due to the steric hindrance, which could be improved by prolonging the reaction time. These results demonstrated that this copper catalysis presents a general method for hydroxysulfenylation of alkenes, overcoming limitations of the previous reports.

The utility of this catalytic system was demonstrated by the synthesis of bicalutamide,[7] which is the leading nonsteroidal androgen receptor inhibitor used for the treatment of prostate cancer. We successfully completed the synthesis of bicalutamide through a two-step strategy, hydroxysulfenylation and oxidation (Scheme 3). Although the efficiency of the hydroxysulfenylation step is unsatisfactory, this synthetic route is attractive because the starting materials are easily available and both reactions are feasible.[8]

To rationalize the possible mechanism of this hydroxysulfenylation reaction, the controlled experiments were carried out. First, a radical inhibition test was examined. The formation of **4a** was completely suppressed, and the TEMPO adduct **8** was obtained by reaction of **5a** and **6a** in the presence of TEMPO under the standard conditions (eq 1). The result supports that





the hydroxysulfenylation is initiated by a thiyl radical. Second, the reaction of 1,2-di-*p*-tolyldisulfane **9** and **6a** did not generate the desired product **4a** (eq 2). The result excluded one of the

DOI: 10.1021/acs.orglett.5b00112
Org. Lett. 2015, 17, 1180−1183

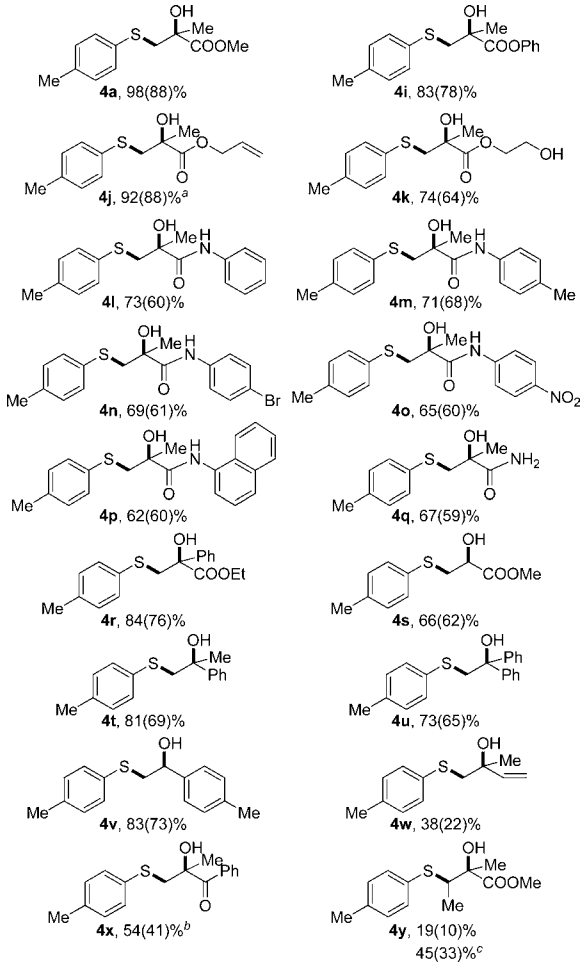
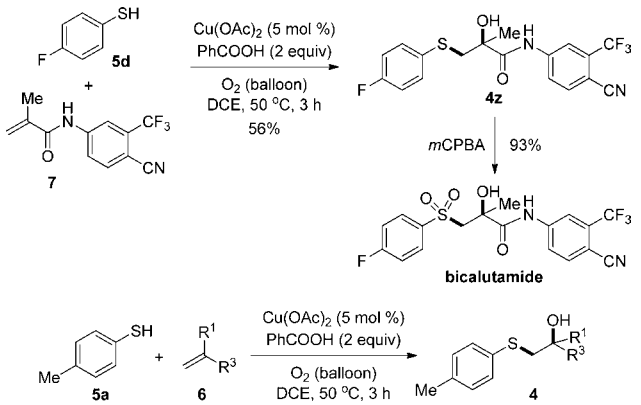


Figure 1. Scope of the substrates **6**: **5a** (2.0 mmol), **6** (0.5 mmol), $Cu(OAc)_2$ (0.025 mmol), PhCOOH (1.0 mmol), DCE (5.0 mL), 50 °C, 3 h. NMR yields; isolated yields are given in parentheses. [a]4-MeO-PhCOOH instead of PhCOOH. [b]The debenzoylation product **4x′** was obtained in 45% yield (see SI). [c]24 h.

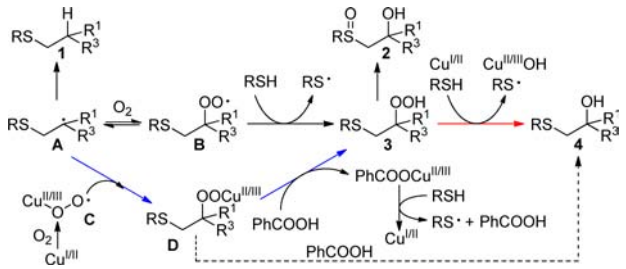
Scheme 3. Two-Step Synthesis of Bicalutamide



possible pathways for the reported reactions, in which the thiols **5** were oxidized to the disulfides and then reacted with the alkenes **6** to give the final product **4**.[9]

On the basis of the results and previous reports, a plausible scenario of the Cu-catalyzed hydroxysulfenylation is described in Scheme 4. Compared with a metal-free pathway (**A** → **B** → **3**), the generation of the key hydroperoxide intermediate **3** is more feasible via the $Cu^{II/III}OOR'$ species **D** (blue arrows). Although

Scheme 4. Cu-Catalyzed Hydroxysulfenylation



the valence of copper is unclear, a sulfur-containing ligand[10] to the copper catalyst might assist the activation of O_2 and generate a peroxy-copper species **C**.[11,12] Finally, the reduction of **3** by the copper catalyst leads to the desired product **4** (red arrow).[13] Overall, the Cu-mediated pathway (**A** → **D** → **3** → **4**) favors the generation of both **3** and **4** and avoids the formation of the other products **1** and **2** accordingly. However, the possibility of the direct conversion of **D** into **4** could not be fully excluded in the present copper catalysis (dotted arrow).[14]

In conclusion, we have developed a general and practical method for hydroxysulfenylation of alkenes through an aerobic copper catalysis. A great feature of the methodology is to realize the hydroxysulfenylation of simple α,β-unsaturated esters/amides for the first time. The developed method was successfully applied for the selective and concise synthesis of bicalutamide. Efforts to understand the reaction mechanism and apply this catalytic system to other substrates are underway and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: zhipingli@ruc.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support was from the National Science Foundation of China (21272267), State Key Laboratory of Heavy Oil Processing (SKLOP201401001), the Fundamental Research Funds for the Central Universities, the Research Funds of Renmin University of China (10XNL017), and Beijing National Laboratory for Molecular Sciences (BNLMS).

■ REFERENCES

(1) (a) Denes, F.; Pichowicz, M.; Povie, G.; Renaud, P. *Chem. Rev.* **2014**, *114*, 2587. (b) Yin, C.; Huo, F.; Zhang, J.; Martinez-Manez, R.; Yang, Y.; Lv, H.; Li, S. *Chem. Soc. Rev.* **2013**, *42*, 6032. (c) Beletskaya, I. P.; Ananikov, V. P. *Chem. Rev.* **2011**, *111*, 1596. (d) Kondo, T.; Mitsudo, T.-a. *Chem. Rev.* **2000**, *100*, 3205.

(2) (a) Tamai, T.; Ogawa, A. *J. Org. Chem.* **2014**, *79*, 5028. (b) Lu, Q.; Zhang, J.; Zhao, G.; Qi, Y.; Wang, H.; Lei, A. *J. Am. Chem. Soc.* **2013**, *135*, 11481. (c) Lu, Q.; Zhang, J.; Wei, F.; Qi, Y.; Wang, H.; Liu, Z.; Lei, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 7156. (d) Wei, W.; Liu, C.; Yang, D.; Wen, J.; You, J.; Suo, Y.; Wang, H. *Chem. Commun.* **2013**, *49*, 10239. (e) Liu, K.; Jia, F.; Xi, H.; Li, Y.; Zheng, X.; Guo, Q.; Shen, B.; Li, Z. *Org.*

DOI: 10.1021/acs.orglett.5b00112
Org. Lett. 2015, 17, 1180–1183

Lett. **2013**, *15*, 2026. (f) Sabarre, A.; Love, J. *Org. Lett.* **2008**, *10*, 3941. (g) Cao, C.; Fraser, L. R.; Love, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 17614.
(3) (a) Rahaman, H.; Ueda, M.; Miyata, O.; Naito, T. *Org. Lett.* **2009**, *11*, 2651. (b) Kamal, A.; Reddy, D. R.; Rajendar. *J. Mol. Catal. A: Chem.* **2007**, *272*, 26. (c) Surendra, K.; Krishnaveni, N. S.; Sridhar, R.; Rao, K. R. *J. Org. Chem.* **2006**, *71*, 5819. (d) O'Neill, P. M.; Mukhtar, A.; Ward, S. A.; Bickley, J. F.; Davies, J.; Bachi, M. D.; Stocks, P. A. *Org. Lett.* **2004**, *6*, 3035.
(4) (a) Hoyle, C. E.; Bowman, C. N. *Angew. Chem., Int. Ed.* **2010**, *49*, 1540. (b) Beckwith, A. L. J.; Wagner, R. D. *J. Org. Chem.* **1981**, *46*, 3638. (c) Griesbaum, K. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 273.
(5) (a) Bagiyan, G. A.; Koroleva, I. K.; Soroka, N. V.; Ufimtsev, A. V. *Russ. Chem. Bull.* **2003**, *52*, 1135. (b) Szmant, H. H.; Mata, A. J.; Namis, A. J.; Panthananickal, A. M. *Tetrahedron* **1976**, *32*, 2665. (c) Iriuchijima, S.; Maniwa, K.; Sakakibara, T.; Tsuchihashi, G.-i. *J. Org. Chem.* **1974**, *39*, 1170. (d) Oswald, A. A. *J. Org. Chem.* **1961**, *26*, 842. (e) Kharasch, M. S.; Nudenberg, W.; Mantell, G. J. *J. Org. Chem.* **1951**, *16*, 524.
(6) Ueda, M.; Miyabe, H.; Shimizu, H.; Sugino, H.; Miyata, O.; Naito, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 5600.
(7) (a) Bhise, N. B.; Sathe, D. G.; Radhakrishanan, T.; Deore, R. *Synth. Commun.* **2009**, *39*, 1516. (b) Parent, E. E.; Dence, C. S.; Jenks, C.; Sharp, T. L.; Welch, M. J.; Katzenellenbogen, J. A. *J. Med. Chem.* **2007**, *50*, 1028. (c) Chen, B.-C.; Zhao, R.; Gove, S.; Wang, B.; Sundeen, J. E.; Salvati, M. E.; Barrish, J. C. *J. Org. Chem.* **2003**, *68*, 10181. (d) James, K. D.; Ekwuribe, N. N. *Tetrahedron* **2002**, *58*, 5905.
(8) Khatik, G. L.; Kaur, J.; Kumar, V.; Tikoo, K.; Nair, V. A. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 1912.
(9) (a) Movassagh, B.; Navidi, M. *Tetrahedron Lett.* **2008**, *49*, 6712. (b) Taniguchi, N. *J. Org. Chem.* **2006**, *71*, 7874.
(10) (a) Solomon, E. I.; Heppner, D. E.; Johnston, E. M.; Ginsbach, J. W.; Cirera, J.; Qayyum, M.; Kieber-Emmons, M. T.; Kjaergaard, C. H.; Hadt, R. G.; Tian, L. *Chem. Rev.* **2014**, *114*, 3659. (b) Varela-Alvarez, A.; Liebeskind, L. S.; Musaev, D. G. *Organometallics* **2012**, *31*, 7958.
(11) (a) Allen, S. E.; Walvoord, R. R.; Padilla-Salinas, R.; Kozlowski, M. C. *Chem. Rev.* **2013**, *113*, 6234. (b) Shi, Z.; Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3381. (c) Rolff, M.; Tuczek, F. *Angew. Chem., Int. Ed.* **2008**, *47*, 2344. (d) Cramer, C. J.; Tolman, W. B. *Acc. Chem. Res.* **2007**, *40*, 601. (e) Punniyamurthy, T.; Velusamy, S.; Iqbal, J. *Chem. Rev.* **2005**, *105*, 2329. (f) Gamez, P.; Aubel, P. G.; Driessen, W. L.; Reedijk, J. *Chem. Soc. Rev.* **2001**, *30*, 376.
(12) (a) Toh, K. K.; Wang, Y.-F.; Ng, E. P. J.; Chiba, S. *J. Am. Chem. Soc.* **2011**, *133*, 13942. (b) Wang, H.; Wang, Y.; Liang, D.; Liu, L.; Zhang, J.; Zhu, Q. *Angew. Chem., Int. Ed.* **2011**, *50*, 5678. (c) Donoghue, P. J.; Gupta, A. K.; Boyce, D. W.; Cramer, C. J.; Tolman, W. B. *J. Am. Chem. Soc.* **2010**, *132*, 15869. (d) Chiba, S.; Zhang, L.; Lee, J.-Y. *J. Am. Chem. Soc.* **2010**, *132*, 7266. (e) Poater, A.; Cavallo, L. *Inorg. Chem.* **2009**, *48*, 4062.
(13) (a) Hiatt, R.; Irwin, K. C.; Gould, C. W. *J. Org. Chem.* **1968**, *33*, 1430. (b) Richardson, W. H. *J. Am. Chem. Soc.* **1966**, *88*, 975. (c) Richardson, W. H. *J. Am. Chem. Soc.* **1965**, *87*, 1096. (d) Kharasch, M. S.; Fono, A. *J. Org. Chem.* **1959**, *24*, 72. (e) Kharasch, M. S.; Fono, A. *J. Org. Chem.* **1958**, *23*, 324.
(14) (a) Su, Y.; Sun, X.; Wu, G.; Jiao, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 9808. (b) Lucas, H. R.; Li, L.; Sarjeant, A. A. N.; Vance, M. A.; Solomon, E. I.; Karlin, K. D. *J. Am. Chem. Soc.* **2009**, *131*, 3230.

DOI: 10.1021/acs.orglett.5b00112
Org. Lett. 2015, 17, 1180−1183