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Reaction of Arynes with Sulfoxides

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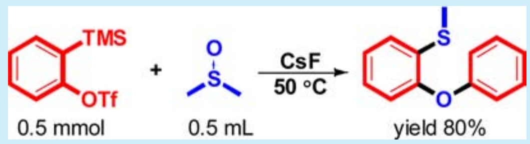
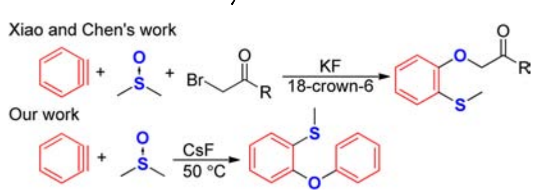
Supporting Information

ABSTRACT: A S−O bond insertion reaction of sulfoxides with arynes is reported. This reaction represents a rare instance of semipolar single bond insertion in aryne chemistry. The study of mechanism indicates that a sulfur ylide triggered by aryne is the key intermediate, which further transfers its methylene group to carbonyl compounds to give epoxides and thioethers through a sequential process.



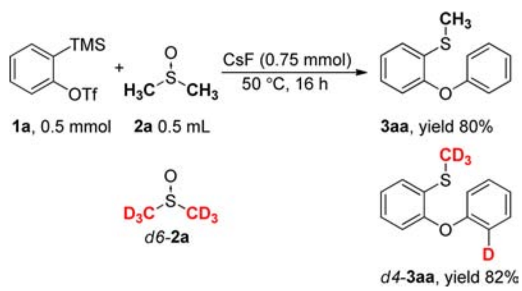
The highly reactive arynes are valuable species in various carbon−carbon and carbon−heteroatom bond-forming reactions.[1] Among these reactions, the insertion of arynes into σ and π bonds has been extensively studied over the past seven decades.[1g,2] Many kinds of bonds, such as C−C,[3] C−N,[4] C−O,[5] C−S,[6] carbon−metal,[7] heteroatom−heteroatom,[8] heteroatom−metal,[9] metal−metal,[10] and carbon (formyl)−hydrogen bonds,[11] have been utilized in aryne insertions. These reactions provide versatile strategies to synthesize complex *ortho*-disubstituted arenes. Surprisingly, the insertion of arynes into S−O bond is rare.[12] Although the bonding nature of S−O linkage in sulfoxides is still a matter of controversy, this bond is generally believed to be a semipolar single bond, rather than a double bond.[13] We questioned whether *ortho*-oxygen substituted aryl sulfides might be created via an insertion of arynes into the S−O bond of sulfoxides. Very recently, the Xiao and Chen group reported elegant work on a three-component coupling reaction of arynes, DMSO, and α-bromo carbonyl compounds (Scheme 1)[12a] Herein we describe an interesting insertion reaction of sulfoxides and arynes under very mild conditions. The mechanism investigation disclosed that a sulfur ylide is formed after insertion, which will make the reaction especially attractive for generating sulfur ylide free from bases (Scheme 1).

Scheme 1. Insertion of Aryne into S−O Bond



We initiated our investigation with Kobayashi aryne precursor **1a**[14] and DMSO **2a** as the model substrates to identify the optimum reaction conditions.[15] After exploring various fluorides, temperatures, and reaction times, we observed that 0.5 mmol of the 2-(trimethylsilyl)phenyl triflate **1a** and 0.75 mmol of CsF in 0.5 mL of DMSO at 50 °C afforded methyl(2-phenoxyphenyl)sulfane **3aa** in 80% yield after 16 h (Scheme 2). Interestingly, two molecules of benzyne and one molecule of DMSO participated in assembling **3aa**, accompanying the demethylation of DMSO. The structure of **3aa** was confirmed unambiguously by single crystal X-ray diffraction.[16] To probe mechanistic information on this novel reaction, *d6*-DMSO was subjected to the current conditions (Scheme 2). Surprisingly, a tetradeuterated analogue *d4*-**3aa** was isolated in 82% yield.[15] The result indicated that one *d3*-methyl group of DMSO remained intact during the reaction, and the phenoxyl group of **3aa** was labeled with a deuterium atom in its *ortho*-position. We reasoned that the deuterium atom on the phenoxyl group might be generated from another *d3*-methyl group, which was removed in the conversion. This suggested to us that a deprotonation reaction between the released methyl group and benzyne might occur to produce a highly reactive sulfur ylide, which could readily transfer its methylene unit to electrophiles in the reaction mixture, leading to the demethylation of DMSO. In further mechanistic studies and to verify the above-mentioned idea, a sulfur ylide trapping experiment using *N*-methyl isatin **4** was performed (Scheme 3).

Scheme 2. Reaction of Benzyne with DMSO



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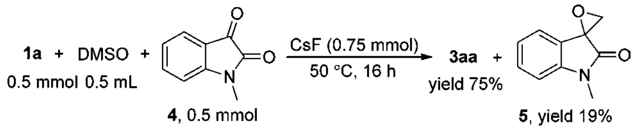
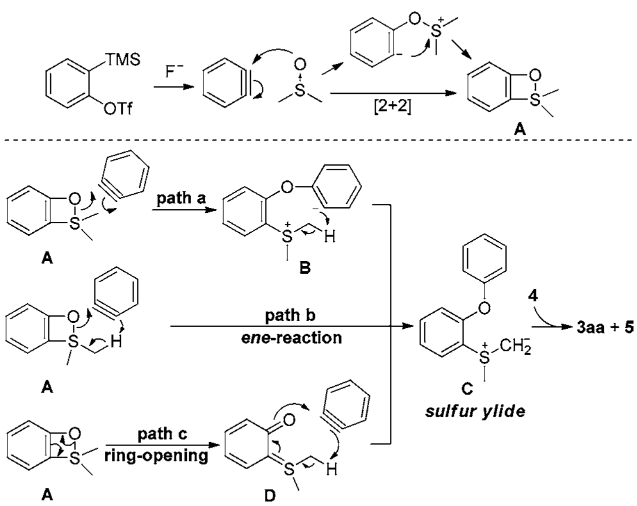
Scheme 3. Ylide Trapping Experiment with Isatin



Gratifyingly, the reaction did afford epoxide **5** in 19% yield in addition to **3aa**. The results indicated that a phenylmethylsulfoxoniummethylide was involved in the transformation. Generally, sulfur ylides are prepared by deprotonation of the corresponding sulfonium salts in the presence of bases.[17] To the best of our knowledge, this novel strategy for the preparation of sulfur ylide utilizing arynes and sulfoxides has been very rare.[12a] Based on our preliminary results, a plausible mechanism of the transformation is shown in Scheme 4. A

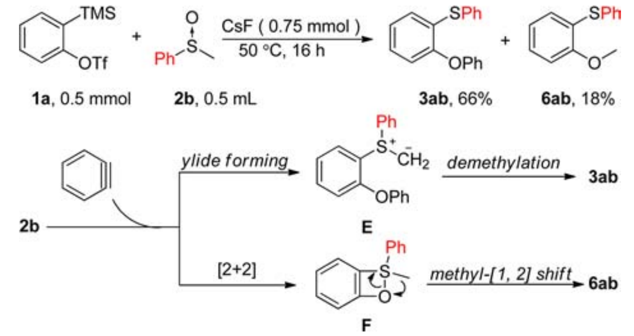
Scheme 4. Possible Mechanism



benzannulated four-membered ring intermediate **A** is first formed through a [2 + 2] cycloaddition or a stepwise pathway involving a 1,4-zwitterionic adduct. We think that the following reaction of instable intermediate **A** may take three possible pathways, leading to the formation of sulfur ylide **C**. Upon nucleophilic reaction with another equivalent of benzyne, the intermediate **A** undergoes a ring-opening process to give zwitterion **B**, and then an intramolecular proton transfer occurs to afford the sulfur ylide **C** (**path a**). Recently, arynes have been utilized as powerful enophiles in *ene* reactions due to their low-lying LUMO level.[18] In this case, an *ene* reaction may also take place in a concerted manner, so the *ene*-type mechanism involving intermediate **A** and benzyne has also been possible (**path b**).[19] In the third pathway, the ring strain of intermediate **A** allows for a ready, spontaneous opening process to afford an *ortho*-quinone intermediate **D**, which is frequently proposed in aryne insertion reactions.[4f,5a−d,20] After nucleophilic attack and deprotonation, sulfur ylide **C** could be produced from intermediate **D** and benzyne (**path c**). Finally, the resulting sulfur ylide **C** reacts with *N*-methyl isatin **4** to yield **3aa** and epoxide **5** via a typical addition−cyclization pathway.[21]

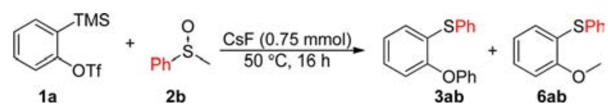
On the basis of the success of DMSO, we further explored unsymmetrical sulfoxides. Methyl phenyl sulfoxide **2b** was subsequently utilized to examine the reaction (Scheme 5). Surprisingly, the major product was 2-phenoxyphenyl phenyl sulfane **3ab**, which was formed in 66% yield through insertion

Scheme 5. Reaction of Benzyne with Methyl 4-Methylphenyl Sulfoxide



and demethylation under solvent-free conditions, and a 1:1 insertion reaction between **1a** and **2b** occurred simultaneously to give a minor product 2-methoxyphenyl phenyl sulfane **6ab** in 18% yield. In this case, besides the ylide forming/demethylation pathway described in Scheme 4, a small amount of benzannulated four-membered ring intermediate **F** also underwent a methyl-[1,2] shift with the concomitant ring opening to give the minor product **6ab** (Scheme 5). Clearly, the transformation leading to sulfur ylide **E** will be desirable in view of synthesis application. Thus, the stoichiometry ratios of benzyne and sulfoxide as well as various solvents were surveyed to improve the reaction selectivity. As summarized in Table 1,

Table 1. Optimization of the Reaction Conditions[a]



entry	solvent	ratio (**1a**:**2b**)	**3ab** (%)	**6ab** (%)
1	THF	1:2	trace	0
2	1,4-dioxane	1:2	trace	0
3	CH_3CN	1:2	69	10
4	DME	1:2	71	8
5	DME	1:3	71	8
6	DME	2:3	72	8
7	DME	1:1	69	7
8	DME	3:1	68	7
9	DME	5:1	trace	trace

[a]Reaction conditions: **1a** (0.5 mmol) in 0.5 mL of solvent under air; isolated yield.

the use of THF and 1,4-dioxane as solvent gave very low yields when the **1a**/**2b** ratio was 2:1 (Table 1, entries 1, 2). In sharp contrast, CH_3CN and DME offered good results with the ratio 1:2 of **1a** and **2b** (Table 1, entries 3, 4). We then screened the ratio of **1a**/**2b** ranging from 1:3 (0.3 equiv) to 5:1 (20 equiv) using DME as the solvent. There was no clear improvement of product selectivity with **1a**/**2b** decreasing from 1:2 to 1:3 (Table 1 entries 4, 5) or increasing to 3:1 (Table 1, entries 6−8). Using the ratio 5:1 of **1a**/**2b**, the reaction gave a very poor yield (Table 1, entry 9). Although the present optimized procedure could not make the reaction give a single product **3ab**, to our delight, the side product **6ab** was completely suppressed in the sulfur ylide trapping reaction with isatin (Scheme 6S in the Supporting Information).[15] The epoxide **5** was obtained in a good yield of 91%, and the result further

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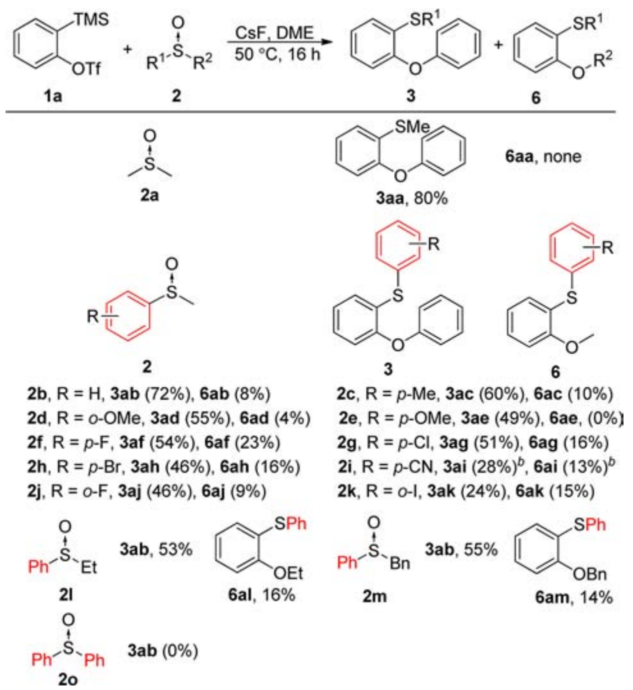
supports our conclusion that a sulfur ylide is generated from benzyne and sulfoxide.

We then turned our attention to the sulfoxide substrate scope using benzyne **1a** as the reaction partner under the conditions described in Table 1, entry 6. As shown in Scheme 6, DMSO **2a** could also react smoothly to give product **3aa** in a high yield when using DME as the solvent (Scheme 6, **3aa**). A variety of substituted groups on the aromatic ring of the sulfoxide was next investigated. Electron-donating groups such as *p*-methyl, *o*-methoxy, and *p*-methoxy group were compatible, and the reaction of **2d** gave slightly better selectivity than that of **2b**. In the case of methyl 4-methoxyphenyl sulfoxide **2e**, the methyl-shift and ring-opening product **6ae** was not observed. The aromatic ring with electron-withdrawing groups such as a halogen and cyano group also allowed the formation of **3** and **6** in low to good total yields (Scheme 6, **2f**–**2k**). Moreover, this novel transformation is not limited to only methyl aryl sulfoxides. Ethyl phenyl sulfoxide **2l** and benzyl phenyl sulfoxide **2m** also furnished good yields of the desired compounds. It is noted that diphenyl sulfoxide **2o** does not react with benzyne **1a** under those conditions (Scheme 6, **2o**).

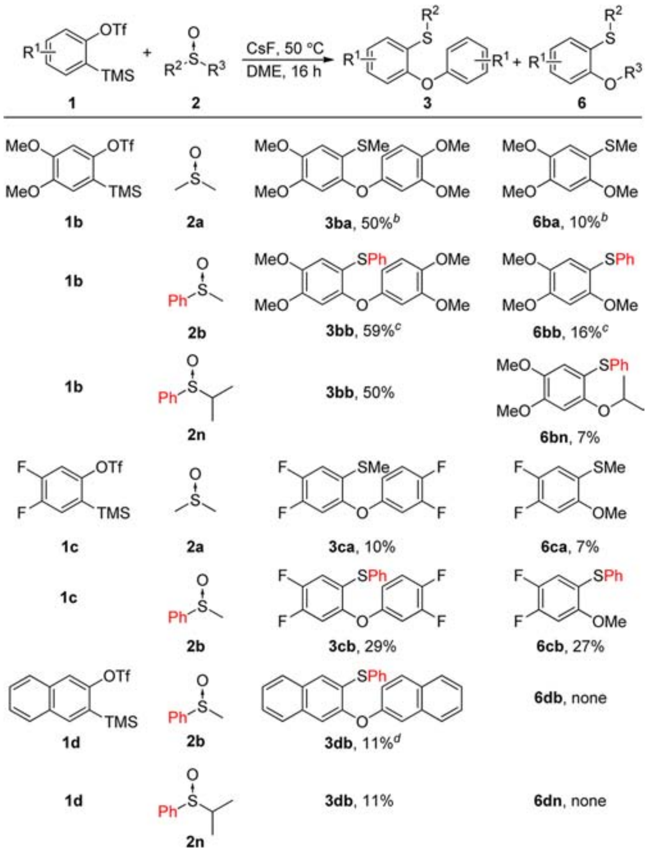
Scheme 6. Substrate Scope of Various Sulfoxides[a]



[a]Reaction conditions: **1a** (0.5 mmol), **2** (0.75 mmol), CsF (0.75 mmol) in DME (0.5 mL); isolated yield. [b]25 °C, 2 h.

The insertion reaction is also applicable to a variety of Kobayashi aryne precursors and sulfoxides. As shown in Scheme 7, the benzyne precursor bearing two electron-donating methoxy groups could react with DMSO **2a**, methyl phenyl sulfoxide **2b**, and isopropyl phenyl sulfoxide **2n** in moderate yields and with the product **3** bias (Scheme 7, **1b**). However, the reactions using benzyne precursors with two fluoro groups on the phenyl ring gave a mixture of the 1:1 products in low yields (Scheme 7, **1c**). Noteworthy, the reaction of 2,3-naphthalyne **1d** with **2b** or **2n** produced exclusively the ylide forming/dealkylation pathway product **3db**, albeit in very low yields (Scheme 7, **1d**). Besides the substrates described in Schemes 6 and 7, the cyclic sulfoxides and unsymmetrical 3-methoxybenzyne were also examined in the reaction. However, low efficiency was observed (Schemes 7S, 8S).[15]

Scheme 7. Substrate Scopes of Various Aryne Precursors[a]



[a]Reaction conditions: **1** (0.5 mmol), **2** (0.75 mmol), CsF (0.75 mmol) in DME (0.5 mL); isolated yields. [b]DMSO (0.5 mL) as the solvent. [c]60 °C. [d]25 °C.

In summary, we have developed a novel and mild reaction of sulfoxides and arynes. The reaction proceeds through a unique insertion of arynes into the S−O bond and subsequent sulfur ylide formation to offer thioethers and epoxides. The generation of sulfur ylides without the use of bases is expected to be a useful methodology for organic synthesis. Further work on the applications and extension of the scope of the protocol, as well as a comprehensive theoretical study on the mechanistic details, is currently under investigation in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Procedures and full characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For selected reviews of aryne chemistry, see: (a) Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, *59*, 701. (b) Wenk, H. H.; Winkler, M.; Sander, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 502. (c) Tadross, P. M.; Stoltz, B. M. *Chem. Rev.* **2012**, *112*, 3550. (d) Yoshida, H.; Ohshita, J.; Kunai, A. *Bull. Chem. Soc. Jpn.* **2010**, *83*, 199. (e) Kitamura, T. *Aust. J. Chem.* **2010**, *63*, 987. (f) Bhunia, A.; Yetra, S. R.; Biju, A. T. *Chem. Soc. Rev.* **2012**, *41*, 3140. (g) Bhojgude, S. S.; Biju, A. T. *Angew. Chem., Int. Ed.* **2012**, *51*, 1520. (h) Gampe, C. M.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 3766. (i) Wu, C.; Shi, F. *Asian J. Org. Chem.* **2013**, *2*, 116. (j) Dubrovskiy, A. V.; Markina, N. A.; Larock, R. C. *Org. Biomol. Chem.* **2013**, *11*, 191.

(2) For the aryne insertion reviews, see: (a) Peña, D.; Pérez, D.; Guitián, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 3579. (b) Okuma, K. *Heterocycles* **2012**, *85*, 515. (c) Yoshida, H.; Takaki, K. *Synlett* **2012**, *23*, 1725.

(3) (a) Li, R.; Wang, X.; Wei, Z.; Wu, C.; Shi, F. *Org. Lett.* **2013**, *15*, 4366. (b) Kaicharla, T.; Bhojgude, S. S.; Biju, A. T. *Org. Lett.* **2012**, *14*, 6238. (c) Huang, X.; Xue, J. *J. Org. Chem.* **2007**, *72*, 3965. (d) Liu, Y.-L.; Liang, Y.; Pi, S.-F.; Li, J.-H. *J. Org. Chem.* **2009**, *74*, 5691. (e) Ni, C.; Zhang, L.; Hu, J. *J. Org. Chem.* **2008**, *73*, 5699. (f) Tambar, U. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 5340.

(4) (a) Yoshida, H.; Shirakawa, E.; Honda, Y.; Hiyama, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 3247. (b) Liu, Z.; Larock, R. C. *J. Am. Chem. Soc.* **2005**, *127*, 13112. (c) Dong, Y.; Liu, B.; Chen, P.; Liu, Q.; Wang, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 3442. (d) Rao, B.; Zeng, X. *Org. Lett.* **2013**, *16*, 314. (e) Fang, Y.; Rogness, D. C.; Larock, R. C.; Shi, F. *J. Org. Chem.* **2012**, *77*, 6262. (f) Li, R.; Tang, H.; Fu, H.; Ren, H.; Wang, X.; Wu, C.; Wu, C.; Shi, F. *J. Org. Chem.* **2014**, *79*, 1344. (g) Xie, C.; Zhang, Y.; Huang, Z.; Xu, P. *J. Org. Chem.* **2007**, *72*, 5431.

(5) (a) Yoshioka, E.; Miyabe, H. *Tetrahedron* **2012**, *68*, 179. (b) Yoshioka, E.; Tanaka, H.; Kohtani, S.; Miyabe, H. *Org. Lett.* **2013**, *15*, 3938. (c) Yoshioka, E.; Kohtani, S.; Miyabe, H. *Org. Lett.* **2010**, *12*, 1956. (d) Yoshida, H.; Watanabe, M.; Fukushima, H.; Ohshita, J.; Kunai, A. *Org. Lett.* **2004**, *6*, 4049. (e) Łączkowski, K. Z.; García, D.; Peña, D.; Cobas, A. n.; Pérez, D.; Guitián, E. *Org. Lett.* **2011**, *13*, 960. (f) Dubrovskiy, A. V.; Larock, R. C. *Org. Lett.* **2010**, *12*, 3117. (g) Yoshioka, E.; Kohtani, S.; Miyabe, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 6638. (h) Yoshida, H.; Ito, Y.; Ohshita, J. *Chem. Commun.* **2011**, *47*, 8512. (i) Zhang, T.; Huang, X.; Wu, L. *Eur. J. Org. Chem.* **2012**, 3507. (j) Zhou, C.; Wang, J.; Jin, J.; Lu, P.; Wang, Y. *Eur. J. Org. Chem.* **2014**, *2014*, 1832. (k) Kivrak, A.; Larock, R. C. *J. Org. Chem.* **2010**, *75*, 7381.

(6) Biswas, K.; Greaney, M. F. *Org. Lett.* **2011**, *13*, 4946.

(7) (a) Yoshida, H.; Morishita, T.; Nakata, H.; Ohshita, J. *Org. Lett.* **2008**, *11*, 373. (b) Liu, Z.; Larock, R. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 2535. (c) Lu, C.; Dubrovskiy, A. V.; Larock, R. C. *J. Org. Chem.* **2012**, *77*, 8648. (d) Liu, Z.; Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2005**, *127*, 15716. (e) Zeng, Y.; Zhang, L.; Zhao, Y.; Ni, C.; Zhao, J.; Hu, J. *J. Am. Chem. Soc.* **2013**, *135*, 2955.

(8) (a) Chakrabarty, S.; Chatterjee, I.; Tebben, L.; Studer, A. *Angew. Chem., Int. Ed.* **2013**, 2968. (b) Yoshida, H.; Ikadai, J.; Shudo, M.; Ohshita, J.; Kunai, A. *J. Am. Chem. Soc.* **2003**, *125*, 6638. (c) Alajarin, M.; Lopez-Leonardo, C.; Raja, R.; Orenes, R.-A. *Org. Lett.* **2011**, *13*, 5668. (d) Yoshida, H.; Ikadai, J.; Shudo, M.; Ohshita, J.; Kunai, A. *Organometallics* **2004**, *24*, 156.

(9) Gerfaud, T.; Neuville, L.; Zhu, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 572.

(10) Yoshida, H.; Tanino, K.; Ohshita, J.; Kunai, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5052.

(11) Biju, A. T.; Glorius, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 9761.

(12) (a) Liu, F.-L.; Chen, J.-R.; Zou, Y.-Q.; Wei, Q.; Xiao, W.-J. *Org. Lett.* **2014**, *16*, 3768. (b) Cram, D. J.; Day, A. C. *J. Org. Chem.* **1966**, *31*, 1227.

(13) Oae, S.; Doi, J. *Organic Sulfur Chemistry*; CRC Press: 1991; Vol. *1*.

(14) Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, *12*, 1211.

(15) For more details, see the Supporting Information.

(16) The information for the crystal structure of **3aa** (CCDC 928175) can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(17) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.

(18) (a) Jayanth, T. T.; Jeganmohan, M.; Cheng, M.-J.; Chu, S.-Y.; Cheng, C.-H. *J. Am. Chem. Soc.* **2006**, *128*, 2232. (b) Candito, D. A.; Panteleev, J.; Lautens, M. *J. Am. Chem. Soc.* **2011**, *133*, 14200. (c) Jayanth, T. T.; Jeganmohan, M.; Cheng, M.-J.; Chu, S.-Y.; Cheng, C.-H. *J. Am. Chem. Soc.* **2006**, *128*, 2232. (d) Karmakar, R.; Mamidipalli, P.; Yun, S. Y.; Lee, D. *Org. Lett.* **2013**, *15*, 1938.

(19) Pirali, T.; Zhang, F.; Miller, A. H.; Head, J. L.; McAusland, D.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2012**, *51*, 1006.

(20) Yoshioka, E.; Tamenaga, H.; Miyabe, H. *Tetrahedron Lett.* **2014**, *55*, 1402.

(21) Xu, H.-D.; Cai, M.-Q.; He, W.-J.; Hu, W.-H.; Shen, M.-H. *RSC Adv.* **2014**, *4*, 7623.

DOI: 10.1021/ol5036326
Org. Lett. 2015, 17, 1098−1101