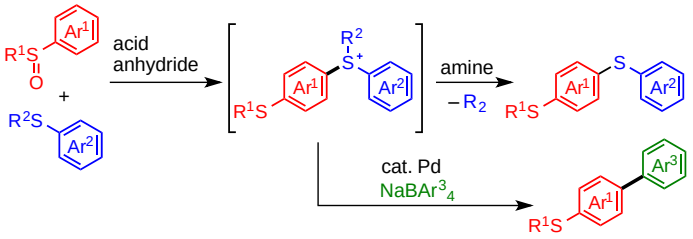
Regioselective C–H Sulfanylation of Aryl Sulfoxides by Means of Pummerer-Type Activation

Hitomi Kawashima,[†] Tomoyuki Yanagi,[†] Chien-Chi Wu,[†,‡] Keisuke Nogi,[†] and Hideki Yorimitsu*[,†]

[†]Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo-ku, Kyoto 606-8502, Japan

[‡]Institute of Organic and Polymeric Materials, National Taipei University of Technology, 1, Sec. 3, Chung-Hsiao E. Road, Taipei 106, Taiwan

Supporting Information Placeholder

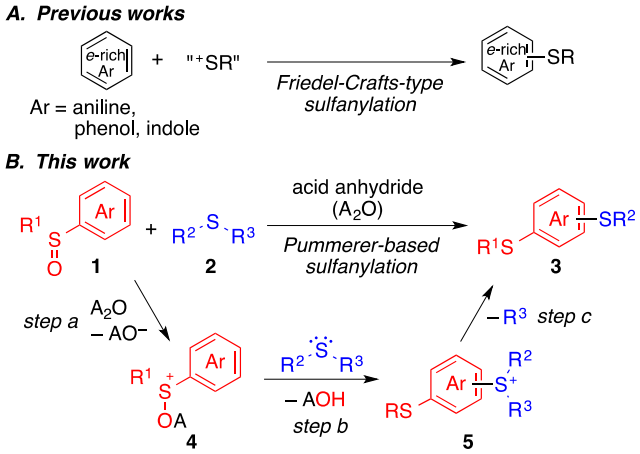


ABSTRACT: A regioselective C–H sulfanylation of aryl sulfoxides with alkyl aryl sulfides in the presence of acid anhydride was developed, which resulted in the formation of 1,4-disulfanylarenes after dealkylation of initially formed sulfonium salts. The reaction began with Pummerer-type activation of aryl sulfoxides followed by nucleophilic attack of alkyl aryl sulfides. The nucleophilic attack occurred exclusively at the *para* positions, or at specific positions in case the *para* position was not available, under perfect control by the dominating sulfoxide directors regardless of any other substituents. The initially formed aryl sulfonium salts were isolable and usefully served as aryl halide surrogates for palladium-catalyzed arylation with sodium tetraarylborates.

Aryl sulfides are valuable structural motifs, and C(sp^2)–S bond-forming reactions are fundamental and important transformations in organic synthesis.[1] Construction of C(sp^2)–S bonds usually depends on halogen-based transformations, in which aryl halides reacted with thiols via S_NAr or transition-metal-catalyzed reactions.[2] However, these halogen-based strategies often suffer from narrow substrate scope, or heavy metal contaminations of products. To avoid such problems, significant efforts have been devoted to invent C–H sulfanylation of arenes under metal-free conditions.[2e,3] However, previous methods entirely focused on Friedel-Crafts-type reactions of arenes with electrophilic sulfur reagents or their precursors, i.e., *N*-sulfanylsuccinimides,[4] disulfides,[5] thiols,[6] and so on.[7] Consequently, harsh reaction conditions and/or highly electron-rich arenes such as anilines, phenols, and indoles have been required (Scheme 1A). In addition, the Friedel-Crafts-type sulfanylation essentially faces poor regioselectivity as well as overreactions providing multi-sulfanylated products.

To exploit an alternative methodology to consummate metal-free C–H sulfanylation, we have now focused on Pummerer-type activation of aryl sulfoxides **1**. Because the activated sulfinyl moiety works as a mild internal oxidant, the Pummerer-based strategy is now regarded as a powerful tool to achieve intramolecularly redox-neutral C–H functionalization of aryl sulfoxides.[8,9] Our reaction design for C–H sulfanylation is shown in Scheme 1B. It is well known that the sulfinyl moiety of **1** is activated by acid anhydrides (A_2O) (*step a*). We expected that the resulting aryl sulfonium **4** is highly electron-deficient to allow the sulfur atom of aryl sulfides **2** to attack the activated arene unit of **4** in an additive Pummerer fashion (*step b*).[9] When R^3 is an alkyl moiety, dealkylation of the resulting aryl sulfonium species **5** with a Lewis base would furnish desired disulfanylarenes **3** (*step c*).

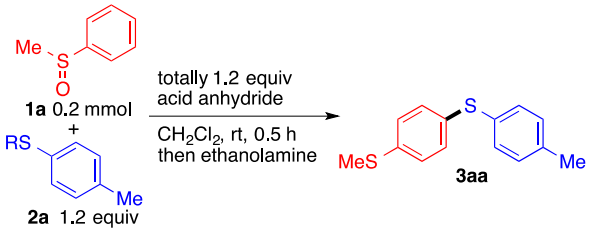
Scheme 1. Metal-Free C–H Sulfanylation of Arenes



Here we report regioselective C–H sulfanylation of aryl sulfoxides with alkyl aryl sulfides through Pummerer-type activation. This methodology is totally different from the previous Friedel-Crafts-type C–H sulfanylation, and enables us to access precisely regiocontrolled 1,4-disulfanylarenes.[10]

As a model reaction, we attempted the anhydride-induced reaction of methyl phenyl sulfoxide (**1a**) with methyl *p*-tolyl sulfide (**2a**) (Table 1). Fortunately, in the presence of trifluoromethanesulfonic anhydride (Tf_2O), C–H bond sulfanylation of **1a** proceeded. To our delight, the reaction took place at the *para* position of **1a** exclusively; 1,4-disulfanylbenzene **3aa** was obtained as a sole product in 78% yield after demethylation with ethanolamine (entry 1). Owing to its lower reactivity than Tf_2O, trifluoroacetic anhydride ($(CF_3CO)_2O$) did not give **3aa** (entry 2). Intriguingly, when a 1:1 mixture of Tf_2O and $(CF_3CO)_2O$ was used as an activator, the yield of **3aa** increased (entry 3). Eventually, a 1:2 mixture of Tf_2O and $(CF_3CO)_2O$ was found to be optimal to afford **3aa** in 96% NMR yield, and in 93% isolated yield (entry 4). As the reaction proceeds, strongly acidic TfOH is formed. We infer that TfOH would degrade the substrates and/or products, and that $(CF_3CO)_2O$ would spontaneously consume TfOH through the formation of less acidic CF_3CO_2H. The methylsulfanyl moiety of **2a** was crucial for smooth sulfanylation. Benzenethiol (**2a'**) did not give the product (entry 6). The reactions with ethyl *p*-tolyl sulfide (**2a''**) and isopropyl *p*-tolyl sulfide (**2a'''**) gave **3aa** in lower yields with ca. 50% recovery of **2a''** and **2a'''** probably due to the steric hindrance around the sulfur atom for nucleophilic attack (entries 7 and 8).

Table 1. Condition Screening

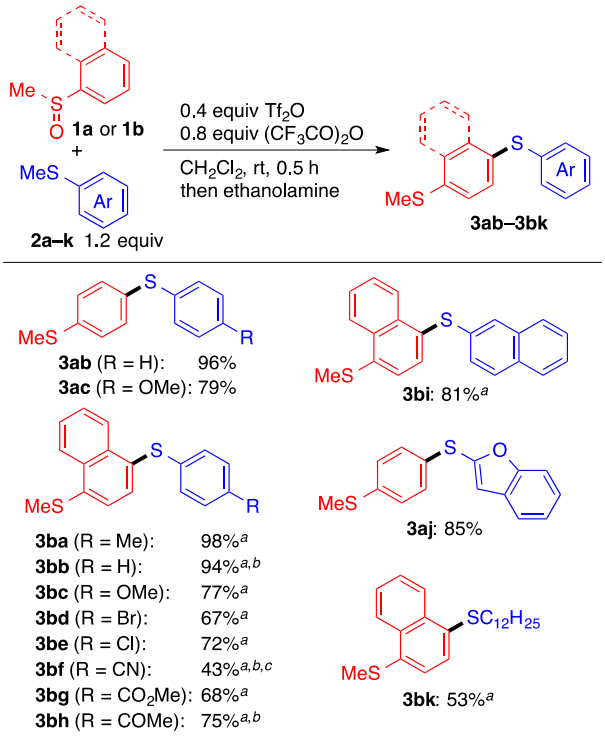


entry	activator	R	NMR yield (%)
1	Tf_2O	Me (**2a**)	78
2	$(CF_3CO)_2O$	Me	<1
3	Tf_2O /$(CF_3CO)_2O$ = 1/1	Me	95
4	Tf_2O /$(CF_3CO)_2O$ = 1/2	Me	96 (93),[a] (80)[a,b]
5	Tf_2O /$(CF_3CO)_2O$ = 1/3	Me	70
6	Tf_2O /$(CF_3CO)_2O$ = 1/2	H (**2a'**)	<1
7	Tf_2O /$(CF_3CO)_2O$ = 1/2	Et (**2a''**)	51
8	Tf_2O /$(CF_3CO)_2O$ = 1/2	*i*Pr (**2a'''**)	18

[a]Isolated yield. [b]1.5 mmol scale.

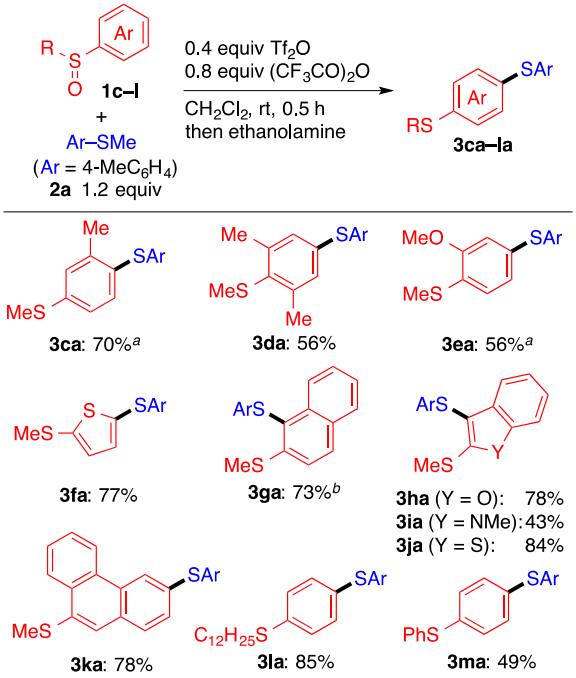
With the optimal reaction conditions, scope of aryl sulfides **2** was investigated (Scheme 2). Both thioanisole (**2b**) and *p*-methoxyphenyl methyl sulfide (**2c**) smoothly reacted with **1a**. Various aryl sulfides **2** coupled with methyl 1-naphthyl sulfoxide (**1b**) affording 1,4-disulfanylnaphthalenes **3ba**–**3bi** with exclusive regioselectivity. In these cases, the products were obtained with only Tf_2O without deterioration of the yield. For simple manipulation, we used Tf_2O as the sole activator for the reactions of **1b**. Due to difficulty in separation from remaining **2**, sulfanylated products **3bb**, **3bf**, and **3bh** were isolated as the corresponding bissulfones after oxidation with an excess amount of *m*CPBA. Bromo, chloro, and carbonyl moieties were compatible with the reaction conditions. Although a strongly electron-withdrawing *p*-cyano substituent retarded the reaction, use of an excess of **2f** increased the yield satisfactorily. 2-Benzofuryl sulfide **2j** also reacted with **1a** to give **3aj** in 85% yield. In place of aryl sulfides, dodecyl methyl sulfide (**2k**) underwent the C–S bond formation. It is noteworthy that the methyl moiety on the sulfur atom was selectively removed by ethanolamine to furnished dodecylsulfanyl-substituted **3bk**.

Scheme 2. Scope of Aryl Sulfide



[a]1.2 equiv of Tf_2O. [b]Isolated as bissulfone after oxidation with *m*CPBA. [c]2.5 equiv of **2f**.

Scheme 3. Scope of Aryl Sulfoxide

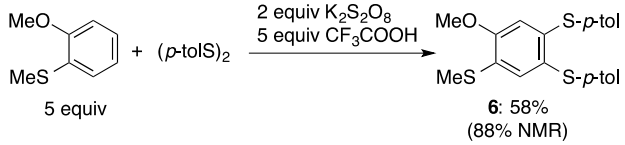


[a]Isolated as bissulfone after oxidation with *m*CPBA. [b]1.2 equiv of Tf_2O.

We then conducted the C–H sulfanylation of other aryl sulfoxides **1c**–**m** with **2a** (Scheme 3). It is worth noting that 2-methoxyphenyl methyl sulfoxide (**1e**) also gave 1,4-disulfanylarene **3ea** selectively. As an alternative protocol for

C-H sulfanylation to obtain **3ea**, electrophilic sulfanylation of 2-methoxythioanisole might be conceivable. However, the sulfanylation of 2-methoxythioanisole with the combination of di-*p*-tolyl disulfide and $K_2S_2O_8$[5d] failed to afford **3ea**, and disulfanylated product **6** was obtained instead (Scheme 4). Our Pummerer-based system relies on the selective activation of the sulfoxide unit, which naturally suppressed undesired multi-sulfanylation to yield monosulfanylated **3ea** exclusively. These results clearly demonstrate the complementarity of our system to the Friedel-Crafts-type C–H sulfanylation (Scheme 1).

Scheme 4. Uncontrollable Electrophilic Sulfanylation

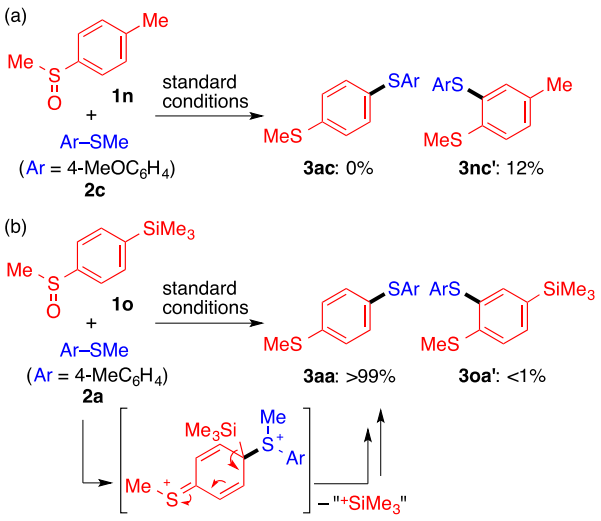


Thienyl sulfoxide **1f** underwent the regioselective C–H bond sulfanylation to provide **3fa** (Scheme 3). Naturally, methyl 2-naphthyl sulfoxide (**1g**) with no reactive *para* position afforded 1,2-disulfanylnaphthalene **3ga**. Benzoheteroaryl sulfoxides **1h**–**j** were also arylated at the vicinal positions to afford 2,3-disulfanylarenes **3ha**–**3ja**. Surprisingly, methyl 9-phenanthryl sulfoxide (**1k**) underwent the C–H sulfanylation at its 3 position exclusively, affording 3,9-disulfanylphenanthrene **3ka**.[11] In general, the 10 position of phenanthrene is considered to be the most reactive site. Our C–H sulfanylation will be a powerful tool to access 3-substituted phenanthrenes. Dodecyl phenyl sulfoxide (**1l**) could be involved in the reaction to provide **3la** in 85% yield. Diphenyl sulfoxide (**1m**) also furnished the monosulfanylated product **3ma** in moderate yield. We assume that Tf_2O-activated diphenyl sulfonium **4m** would be more stable than other aryl methyl sulfoniums **4** and might be reluctant to undergo subsequent reaction. Electron-deficient methyl 2-trifluoromethylphenyl sulfoxide did not react with **2a**, and the reduced compound, methyl 2-trifluoromethylphenyl sulfide, was mainly obtained in 63% yield.

We next became interested in the C–H sulfanylation of *para*-substituted aryl sulfoxides (Scheme 5). Although we anticipated that C–H sulfanylation of methyl *p*-tolyl sulfoxide (**1n**) would take place cleanly at the vicinal position of the sulfinyl moiety to yield **3nc'**, a complex mixture containing only 12% yield of **3nc'** was obtained (Scheme 5a). In contrast, *para*-trimethylsilyl-substituted aryl sulfoxide **1o** underwent desilylative sulfanylation to provide **3aa** quantitatively (Scheme 5b). Presumably, *para*-selective nucleophilic attack of **2** would smoothly proceed in spite of the *para*-substituents. Triflate anion would attack the proton or the trimethylsilyl moiety to recover the original aromaticity (Scheme 5b, bottom). However, in the reaction of **1n**, elimination of the methyl moiety would not occur with TfO^- and departure of **2c** would take place reversibly.

The reasons for the low reactivity of the *ortho* positions of aryl sulfoxides are not clear at this stage. We speculate the reasons as follows: Nucleophilic attack onto activated aryl sulfonium **4** with loss of its aromaticity should occur by developing positive charge on both of the sulfur atoms originally in **1** and **2**. Conceivable nucleophilic attack at an *ortho* or vicinal position would develop positive charge in closer proximity and be thus disfavored compared with that at a *para* position. A steric factor would be additionally important. On the other hand, less aromatic 2-heteroaryl and 2-naphthyl sulfoxides would be more reactive to allow the nucleophilic attack at their vicinal positions.

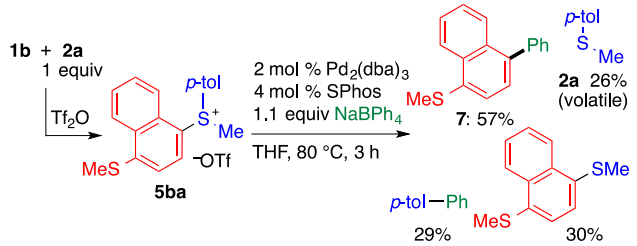
Scheme 5. Reactions of *para*-Substituted Aryl Sulfoxides



To explore further synthetic utility of our *para*-selective C–H functionalization, we focused on aryl sulfonium salts **5** as surrogates for aryl halides in cross-coupling reactions. Following the seminal work by Liebeskind,[12] we[13] and others[14] developed cross-coupling reactions of aryl sulfonium salts with organometallic reagents. We thus applied our palladium-catalyzed base-free arylation with sodium tetraarylborates[13] to the sulfonium products **5**.

Isolation of **5** was facile. For instance, after the C–S bond formation between **1b** and **2a**, the corresponding aryl sulfonium salt **5ba** precipitated upon addition of Et_2O to the reaction mixture. Simple filtration of the precipitates yielded **5ba** with sufficient purity for cross-coupling. The attempted cross-coupling of **5ba** with sodium tetraphenylborate[13b] indeed afforded desired coupling product **7** in 57% NMR yield along with **2a** as the leaving group (Scheme 6). However, undesirable cleavage of the C(*p*-tolyl)–S bond was inevitable to occur, forming 4-methylbiphenyl as a by-product along with 1,4-di(methylsulfanyl)naphthalene as the leaving group (29% and 30% NMR yields, respectively).

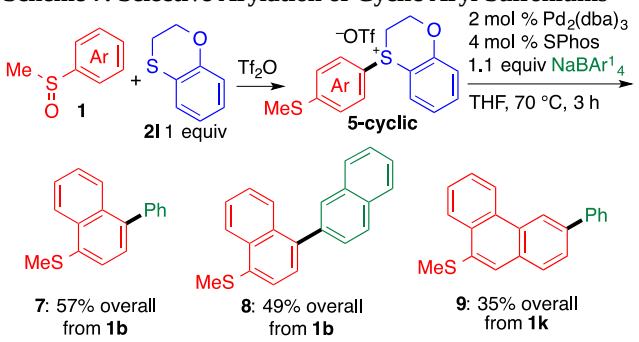
Scheme 6. Attempted Arylation of 5ba



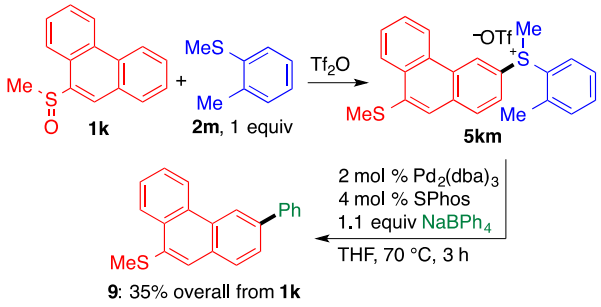
To avoid such undesired cleavage, we envisioned utilizing sulfonium salt **5-cyclic** generated from cyclic aryl sulfide **2l**, wherein the exocyclic C–S bond would be preferentially cleaved (Scheme 7). As expected, desired products **7**–**9** were selectively obtained in overall yields of 57%, 49%, and 35%, respectively.[15] In addition to the control by the cyclic leaving skeleton, steric hindrance is an alternative to control C–S bond cleavage. Aryl sulfonium salt **5km** derived from **1k** and 2-methylthioanisole (**2m**) showed similar reactivity (Scheme 8).

In summary, we have developed regioselective C–H sulfanylation of aryl sulfoxides with aryl sulfides via Pummerer-type activation. The initially formed sulfonium salts were demethylated to yield disulfanylarenes or used as electrophiles in cross-coupling to afford *para*-arylated aryl sulfides.

Scheme 7. Selective Arylation of Cyclic Aryl Sulfoniums



Scheme 8. Sterically Controlled Arylation of 5km



ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: XXXXX.

Detailed experimental procedures, full spectroscopic data for all new compounds, and crystallographic data (PDF)

AUTHOR INFORMATION

Corresponding Author

*yori@kuchem.kyoto-u.ac.jp

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

This work was supported by JSPS KAKENHI Grant Numbers JP25107002, JP15K21722, JP16H01149, as well as JST ACT-C Grant Number JPMJCR12ZE, Japan.

REFERENCES

(1) (a) Cremlyn, R. J.; *An Introduction to Organosulfur Chemistry*; Wiley: New York, 1996. (b) *Organosulfur Chemistry I*; Page, P. C. B., Ed.; Springer: Heidelberg, 1999. (c) *Organosulfur Chemistry II*, Page, P. C. B., Ed.; Springer: Heidelberg, 1999. (d) Rayner, C. M.; *Advances in Sulfur Chemistry*, *Vol. 2*; JAI Press: Greenwich, 2000. (f) *Sulfur Compounds: Advances in Research and Application*, Acton, A. Q., Ed.; Scholarly Editions: Atlanta, GA, 2012.

(2) (a) Kondo, T.; Mitsudo, T.-a. *Chem. Rev.* **2000**, *100*, 3205. (b) Beletskaya, I. P.; Ananikov, V. P. *Chem. Rev.* **2011**, *111*, 1596. (c) Lee, C.-F.; Liu, Y.-C.; Badsara, S. S. *Chem. Asian J.* **2014**, *9*, 706. (d) Shen, C.; Zhang, P.; Sun, Q.; Bai, S.; Hor, T. S. A.; Liu, X. *Chem. Soc. Rev.* **2015**, *44*, 291.

(3) Aida, F.; Oyaizu, K. *Chem. Lett.* **2016**, *45*, 102.

(4) (a) Tudge, M.; Tamiya, M.; Savarin, C.; Humphrey, G. R. *Org. Lett.* **2006**, *8*, 565. (b) Tian, H.; Yang, H.; Zhu, C.; Fu, H. *Adv. Synth. Catal.* **2015**, *357*, 481. (c) Hostier, T.; Ferey, V.; Ricci, G.; Pardo, D. G.; Cossy, J. *Org. Lett.* **2015**, *17*, 3898. (d) Hostier, T.; Ferey, V.; Ricci, G.; Pardo, D. G.; Cossy, J. *Chem. Commun.* **2015**, *51*, 13898.

(5) (a) Ravi, C.; Mohan, D. C.; Adimurthy, S. *Org. Lett.* **2014**, *16*, 2978. (b) Parumala, S. K. R.; Peddinti, R. K. *Green Chem.* **2015**, *17*, 4068. (c) Huang, Z.; Zhang, D.; Qi, X.; Yan, Z.; Wang, M.; Yan, H.; Lei, A. *Org. Lett.* **2016**, *18*, 2351.

(6) (a) Ge, W.; Wei, Y. *Green Chem.* **2012**, *14*, 2066. (b) Huang, D.; Chen, J.; Dan, W.; Ding, J.; Liu, M.; Wu, H. *Adv. Synth. Catal.* **2012**, *354*, 2123. (c) Zou, L.-H.; Reball, J.; Mottweiler, J.; Bolm, C. *Chem. Commun.* **2012**, *48*, 11307. (d) Prasad, C. D.; Balkrishna, S. J.; Kumar, A.; Bhakuni, B. S.; Shrimali, K.; Biswas, S.; Kumar, S. *J. Org. Chem.* **2013**, *78*, 1434.

(7) (a) Wu, Q.; Zhao, D.; Qin, X.; Lan, J.; You, J. *Chem. Commun.* **2011**, *47*, 9188. (b) Yang, F.-L.; Tian, S.-K. *Angew. Chem., Int. Ed.* **2013**, *52*, 4929. (c) Kang, X.; Yan, R.; Yu, G.; Pang, X.; Liu, X.; Li, X.; Xiang, L.; Huang, G. *J. Org. Chem.* **2014**, *79*, 10605. (d) Xiao, F.; Xie, H.; Liu, S.; Deng, G.-J. *Adv. Synth. Catal.* **2014**, *356*, 364. (e) Miao, T.; Li, P.; Zhang, Y.; Wang, L. *Org. Lett.* **2015**, *17*, 832. (f) Xiao, F.; Chen, S.; Tian, J.; Huang, H.; Liu, Y.; Deng, G.-J. *Green Chem.* **2016**, *18*, 1538. (g) Qi, H.; Zhang, T.; Wan, K.; Luo, M. *J. Org. Chem.* **2016**, *81*, 4262. (h) Fernández-Salas, J. A.; Pulis, A. P.; Procter, D. J. *Chem. Commun.* **2016**, *52*, 12364.

(8) Recent reviews of Pummerer-based transformations of aryl sulfoxides: (a) Feldman, K. S. *Tetrahedron* **2006**, *62*, 5003. (b) Smith, L. H. S.; Coote, S. C.; Sneddon, H. F.; Procter, D. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 5832. (c) Huang, X.; Klimczyk, S.; Maulide, N. *Synthesis* **2012**, *44*, 175. (d) Pulis, A. P.; Procter, D. J. *Angew. Chem., Int. Ed.* **2016**, *55*, 9842. (e) Shafir, A. *Tetrahedron Lett.* **2016**, *57*, 2673. (f) Yorimitsu, H. *Chem. Rec.* **2017**, in press, DOI: 10.1002/tcr.201700017.

(9) For selected recent examples: (a) Akai, S.; Morita, N.; Iio, K.; Nakamura, Y.; Kita, Y. *Org. Lett.* **2000**, *2*, 2279. (b) Akai, S.; Kawashita, N.; Satoh, H.; Wada, Y.; Kakiguchi, K.; Kuriwaki, I.; Kita, Y. *Org. Lett.* **2004**, *6*, 3793. (c) Huang, X.; Maulide, N. *J. Am. Chem. Soc.* **2011**, *133*, 8510. (d) Eberhart, A. J.; Imbriglio, J. E.; Procter, D. J. *Org. Lett.* **2011**, *13*, 5882. (e) Huang, X.; Patil, M.; Farès, C.; Thiel, W.; Maulide, N. *J. Am. Chem. Soc.* **2013**, *135*, 7312. (f) Eberhart, A. J.; Cicoira, C.; Procter, D. J. *Org. Lett.* **2013**, *15*, 3994. (g) Eberhart, A. J.; Procter, D. J. *Angew. Chem., Int. Ed.* **2013**, *52*, 4008. (h) Eberhart, A. J.; Shrives, H. J.; Álvarez, E.; Carrër, A.; Zhang, Y.; Procter, D. J. *Chem. Eur. J.* **2015**, *21*, 7428. (i) Fernández-Salas, J. A.; Eberhart, A. J.; Procter, D. J. *J. Am. Chem. Soc.* **2016**, *138*, 790. (j) Eberhart, A. J.; Shrives, H.; Zhang, Y.; Carrër, A.; Parry, A. V. S.; Tate, D. J.; Turner, M. L.; Procter, D. J. *Chem. Sci.* **2016**, *7*, 1281. (k) Yanagi, T.; Otsuka, S.; Kasuga, Y.; Fujimoto, K.; Murakami, K.; Nogi, K.; Yorimitsu, H.; Osuka, A. *J. Am. Chem. Soc.* **2016**, *138*, 14582. (l) Shrives, H. J.; Fernández-Salas, J.; Hedtke, C.; Pulis, A. P.; Procter, D. J. *Nat. Commun.* **2017**, *8*, 14801. (m) Shang, L.; Chang, Y.; Luo, F.; He, J.-N.; Huang, X.; Zhang, L.; Kong, L.; Li, K.; Peng, B. *J. Am. Chem. Soc.* **2017**, *139*, 4211.

(10) Similar TfOH-mediated C–S bond formations were reported. However, the mechanisms of these reactions are unclear, and the scope as well as synthetic utility of the reactions were not fully investigated. (a) Yamamoto, K.; Shouji, E.; Nishide, H.; Tsuchida, E. *J. Am. Chem. Soc.* **1993**, *115*, 5819. (b) Reddy, P. G.; Pal, S. P.; Kumar, P.; Pradeep, C. P.; Ghosh, S.; Sharma, S. K.; Gonsalves, K. E. *ACS Appl. Mater. Interfaces* **2017**, *9*, 17.

(11) The structure of **3ka** was unambiguously determined by single-crystal X-ray diffraction as well as ^{1}H and ^{13}C NMR analysis.

(12) (a) Srogl, J.; Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1997**, *119*, 12376. (b) Zhang, S.; Marshall, D.; Liebeskind, L. S. *J. Org. Chem.* **1999**, *64*, 2796.

(13) (a) Vasu, D.; Yorimitsu, H.; Osuka, A. *Angew. Chem., Int. Ed.* **2015**, *54*, 7162. (b) Vasu, D.; Yorimitsu, H.; Osuka, A. *Synthesis* **2015**, *47*, 3286.

(14) (a) Lin, H.; Dong, X.; Li, Y.; Shen, Q.; Lu, L. *Eur. J. Org. Chem.* **2012**, 4675. (b) Cowper, P.; Jin, Y.; Turton, M. D.; Kociok-Köhe, G.; Lewis, S. E. *Angew. Chem., Int. Ed.* **2016**, *55*, 2564.

(15) We attempted the coupling with diaryl sulfonium derived from methyl phenyl sulfoxide. However, the sulfonium was difficult to isolate because of some impurity and the subsequent coupling suffered from lack of reproducibility. Further optimization of the procedure should be necessary.