ChemComm

ROYAL SOCIETY OF CHEMISTRY

COMMUNICATION

View Article Online
View Journal

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Cite this: DOI: 10.1039/d6cc01087c

Received 20th February 2026,
Accepted 17th April 2026

DOI: 10.1039/d6cc01087c

rsc.li/chemcomm

Thiosulfonate synthesis *via* halothiolation of aryne intermediates followed by oxidative *S*-sulfonylation

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An efficient method for preparing aryl thiosulfonates through aryne intermediates is disclosed. Following aryne halothiolation with potassium xanthate, the resulting aryl xanthates were transformed into thiosulfonates using iodine and sodium sulfinates. The versatility of thiosulfonates together with divergent aryne precursors enabled the access to a wide range of highly functionalized organosulfur compounds.

Thiosulfonates are promising bench-stable sulfur surrogates owing to their good electrophilicity, which enables the synthesis of a wide range of sulfides in an odorless manner (Fig. 1A).[1,2] For example, carbanions readily react with thiosulfonates to afford various sulfides with liberation of water-soluble sulfinate anions.[2a,2b,2l] We have developed efficient methods for the preparation of sulfides from thiosulfonates and aryl- and alkenylborons catalyzed by copper[2d,2g,2k] or rhodium.[2e] In addition, alkynyl sulfides were also synthesized from thiosulfonates and terminal alkynes with copper catalysis.[2i]

In view of the versatility of thiosulfonates, their limited availability should be addressed to improve access to diverse organosulfur compounds.[3] In particular, conventional thiol-based syntheses are limited in the scope of accessible thiosulfonates owing to the instability of thiols under air, their incompatibility with electrophilic functionalities, and their unpleasant odor (Fig. 1B). We herein disclose an efficient method for the synthesis of a wide variety of aromatic thiosulfonates from *o*-silylaryl triflates *via* halothiolation of aryne intermediates followed by oxidative *S*-sulfonylation.

Our recent studies on organosulfur chemistry involving transformations of aryne intermediates have enabled the efficient synthesis of aryl xanthates bearing a masked thiol functionality from *o*-silylaryl triflates, potassium xanthates, and electrophiles such as pentafluorophenyl bromide (Fig. 1C).[4,5] Building on this novel transformation, we envisioned a stepwise thiosulfonate synthesis from *o*-silylaryl triflates involving aryne halothiolation followed by oxidative *S*-sulfonylation of the resulting aryl xanthates, thereby enabling umpolung of the masked thiol functionality to an electrophilic sulfur surrogate (Fig. 1D). In light of our previous study on the direct oxidative transformation of thioesters into sulfinate esters, we hypothesized that oxidation of aryl xanthates followed by addition of metal sulfinates would promote thiosulfonate formation owing to the electron-rich nature of the xanthate moiety (Fig. 1E).[6] Compared with the previous hydrolysis–oxidation approach,[4] the present strategy offers a significant advantage by avoiding thiols, which often exhibit poor functional-group compatibility due to their high nucleophilicity.

We first examined the oxidation of aryl xanthate **2a** with an equimolar amount of iodine in dichloromethane at room temperature, followed by the addition of sodium sulfinate (Table 1, entry 1). Under these conditions, **3a** was obtained in moderate yield. Subsequent optimization of the reaction conditions enabled more efficient thiosulfonate formation. Increasing the amount of iodine slightly improved the yield of **3a** (entry 2). The use of other oxidants including *N*-iodo-, *N*-bromo-, and *N*-chlorosuccinimide decreased the yields of **3a** (entries 3–5). While thiosulfonate synthesis in ethanol or THF resulted in lower efficiencies (entries 6 and 7), we succeeded in the preparation of **3a** in good yield when using acetonitrile (entry 8). Finally, treatment of **2a** with iodine in acetonitrile at 80 °C followed by the addition of sodium *p*-toluenesulfinate at room temperature provided thiosulfonate **3a** in high yield (entry 9).

With the optimized conditions in hand, we synthesized a wide variety of thiosulfonates **3** from aryl xanthates **2** prepared by our previously reported aryne chemistry (Fig. 2). For example, **3b** was obtained from *O*-ethyl *S*-phenyl xanthate (**2b**) in good yield. In the case of electron-deficient 3,4-difluorophenyl-substituted xanthate **2c**, we achieved the synthesis of **3c** in moderate yield. Also, oxidation–*S*-sulfonylation of electron-rich aromatic xanthates also proceeded smoothly, affording **3d**–**3f** in high yields. Notably, we accomplished the synthesis of **3g** in good yield without oxidation of the 4-methoxyphenylthio group.

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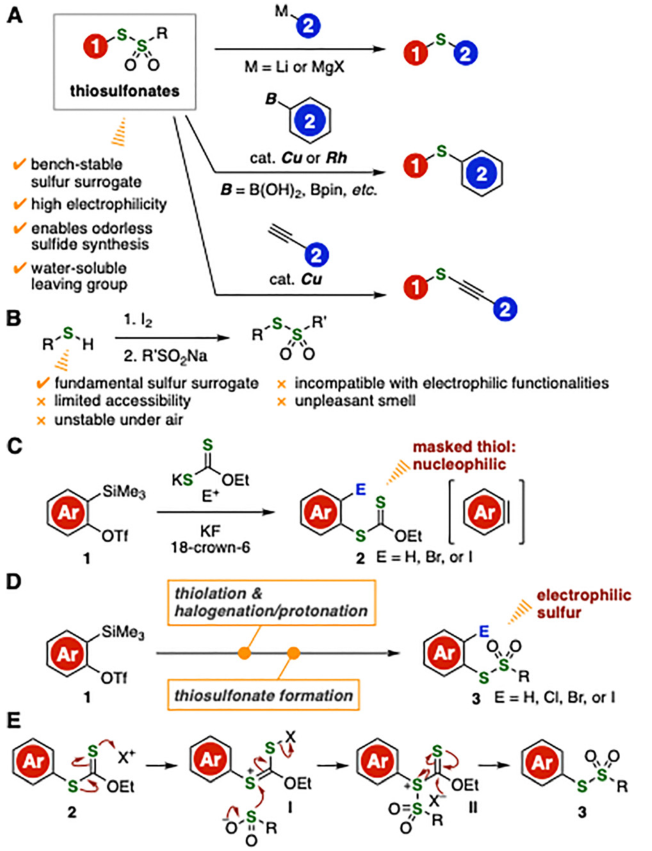


Fig. 1 (A) Transformations of thiosulfonates. (B) Synthesis of thiosulfonates from thiols. (C) Our previous study. (D) This work. (E) Working hypothesis.

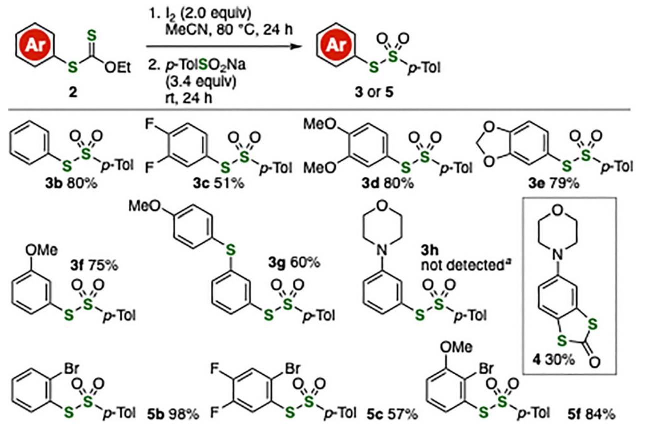
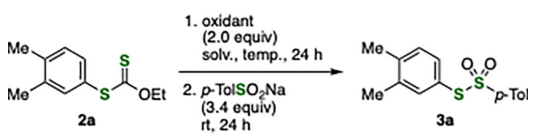


Fig. 2 Synthesis of various thiosulfonates from aryl xanthates **2**. [a] I_2 (4.0 equiv) was employed and 2nd step was conducted at 80 °C. See the SI for details.

Table 1 Optimization of the reaction conditions



Entry	Oxidant	Solv.	Temp.	Yield[a] (%)
1[b]	I_2	CH_2Cl_2	rt	57
2	I_2	CH_2Cl_2	rt	63
3	NIS	CH_2Cl_2	rt	30
4	NBS	CH_2Cl_2	rt	54
5	NCS	CH_2Cl_2	rt	25
6	I_2	EtOH	rt	50
7	I_2	THF	rt	18
8	I_2	MeCN	rt	72
9	I_2	MeCN	80 °C	87[c]

[a] ^{1}H NMR yields. [b] I_2 (1.0 equiv) was employed. [c] Isolated yield.

This result demonstrates that hydrothiolation of 3-sulfanylbenzyne followed by oxidative conversion enabled the selective synthesis of 3-sulfanylphenyl-substituted thiosulfonates.[7] Unfortunately, attempts to synthesize **3h** from *O*-ethyl *S*-(3-morpholinophenyl) xanthate, prepared from 3-morpholinobenzyne precursor,[8] were unsuccessful, and cyclized product **4** was obtained instead. It is also worth noting that the oxidation–*S*-sulfonylation took place efficiently with *o*-bromo-substituted aryl xanthates without affecting the *ortho* substituents, to afford thiosulfonates **5b**, **5c**, and **5f.**

Then, efficient preparation of *S*-aryl thiosulfonates **3**, **5**, **9**, and **10** was achieved from *o*-silylaryl triflates **1** as aryne precursors (Fig. 3). For instance, a mixture of thiosulfonates **3i** and **3i′** (= **3f**) was synthesized by hydrothiolation of 4-methoxybenzyne (step A) followed by oxidation–*S*-sulfonylation (step B).[9] Of note, the synthesis of thiosulfonate **3j** bearing an ester moiety was realized by hydrothiolation of the corresponding aryne intermediate

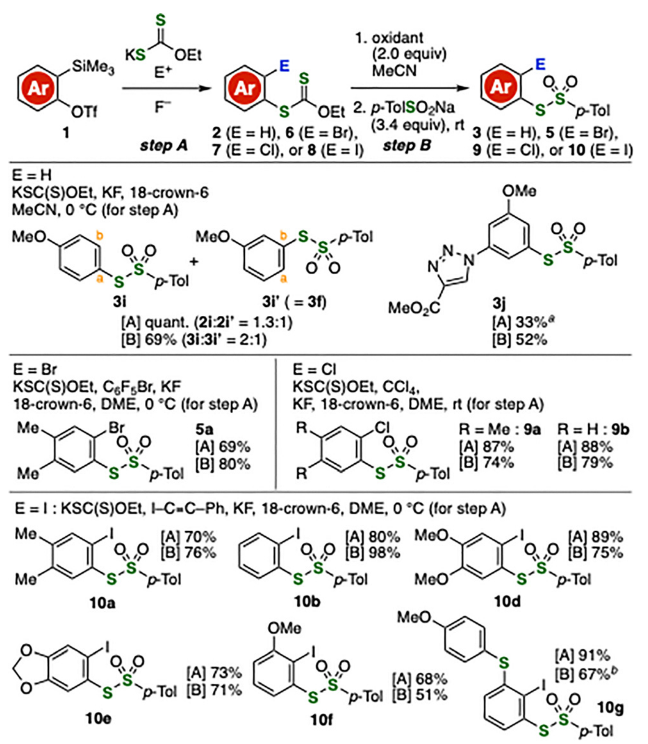


Fig. 3 Synthesis of various thiosulfonates from *o*-silylaryl triflates **1**. DME = 1,2-dimethoxyethane. See the SI for details. [a] ^{1}H NMR yield. [b] Step B was performed at 80 °C.

followed by oxidative *S*-sulfonylation. Because ester functionalities are often susceptible to hydrolysis under basic conditions, this result supports the advantage of the present thiol-free protocol for the preparation of thiosulfonates bearing electrophilic functional groups such as esters. We accomplished the synthesis of **5a** through bromothiolation of 3,4-dimethylbenzyne followed by oxidation–*S*-sulfonylation developed in this study. Furthermore, chlorothiolation of aryne intermediates was achieved using tetrachloromethane as an electrophilic chlorine source. Subsequent conversion of the resulting xanthates afforded **9a** and **9b** in good yields. Preparation of **10a**, **10b**, and **10d**–**10g** was accomplished by iodothiolation of arynes using 1-iodo-2-phenylacetylene, followed by oxidation with iodine and subsequent addition of sodium sulfinate. These results clearly demonstrate that a wide range of *o*-halogen-substituted aryl thiosulfonates can be synthesized through aryne intermediates, benefiting from the recent great achievements in readily accessible aryne precursors.[10,11]

To clarify the reaction mechanism of thiosulfonate formation, we conducted a series of control experiments (Fig. 4A–D). Treatment of aryl xanthate **2a** with iodine in acetonitrile-d_3 at 80 °C furnished disulfide **11a** and iodoethane, as identified by ^{1}H and ^{13}C NMR analysis of the crude reaction mixture (Fig. 4A). The formation of iodoethane was further supported by an experiment in which 2-naphthalenethiol (**12**) was added, affording sulfide **13** (Fig. 4B). While **3a** was not observed when sodium *p*-toluenesulfinate was added to disulfide **11a** in acetonitrile (Fig. 4C, upper), treatment of **11a** with sodium sulfinate in the presence of iodine afforded **3a** in high yield (Fig. 4C, lower), consistent with the report by Fujiki and coworkers.[3b] These control experiments indicate that residual iodine plays a crucial role in the *S*-sulfonylation.

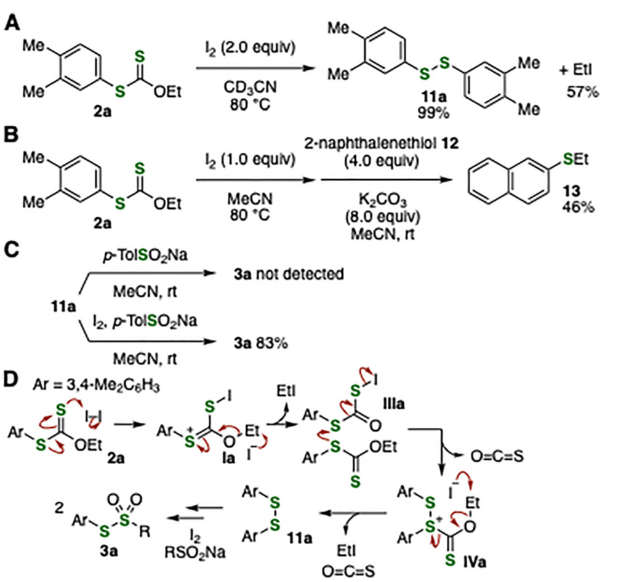


Fig. 4 (A) NMR analysis of crude products from **2a**. (B) Trap of iodoethane generated *in situ*. (C) Reaction of disulfide **11a** with sodium *p*-toluenesulfinate in the absence and presence of iodine. (D) Plausible reaction mechanism. See the SI for details.

Control experiments shown in Fig. 4A–C support the following plausible mechanism for thiosulfonate formation from **2a** (Fig. 4D). First, oxidation of **2a** with iodine generates disulfide **11a**, presumably *via* **Ia**, which undergoes deethylation promoted by iodide. This novel oxidation of xanthates realized an umpolung transformation of masked thiols into electrophilic sulfur surrogates. In the synthesis of **3h**, which bears a strong electron-donating morpholino group, competing intramolecular electrophilic aromatic substitution of **Ia** may result in the formation of side-product **4**. Second, thiosulfonate formation proceeded from **11a** with sodium *p*-toluenesulfinate and an additional equivalent of iodine, according to the previous report by Fujiki.[3b] Thus, we have established not only a practical and efficient method for the synthesis of thiosulfonates from aryne precursors, but also a novel iodine-mediated oxidative transformation of aryl xanthates **2**. In contrast to previous oxidative transformations of xanthates leading to *S*-oxidation or thiocarbonate formation,[12] the present finding enables thiosulfonate synthesis by *S*-sulfonylation of disulfides.

The good versatility of thiosulfonates was demonstrated by odorless sulfide synthesis (Fig. 5A). Treatment of **3a** with 4-methoxyphenylmagnesium bromide provided **15a** in high yield (Fig. 5A, upper).[2b] Preparation of **15b** bearing an ester moiety was achieved by copper-catalyzed *S*-arylation with **16a** under mild conditions (Fig. 5A, middle), following our recently developed protocol.[2d] In addition, alkynyl sulfide **15c** was efficiently synthesized from **3a** and terminal alkyne **17** in the presence of a catalytic amount of copper iodide and Xantphos (Fig. 5A, lower).[2i] These results clearly demonstrate that a broad range of sulfides can be accessed from *o*-silylaryl triflates *via* thiolation of arynes, oxidative conversion to thiosulfonates, and subsequent *S*-arylation with diverse reaction partners, including organomagnesium reagents, organoborons, and terminal alkynes.

Thiosulfonate synthesis *via* aryne halothiolation followed by oxidation–*S*-sulfonylation enabled access to highly functionalized *o*-arylamino-substituted diaryl sulfides **20** in combination with our aryne-based organosulfur chemistry (Fig. 5B–E). Specifically, we accomplished the preparation of **18** through copper-catalyzed *S*-arylation of **5** followed by *S*-imidation and subsequent hydrolysis. Sulfilimines then served as aminothiolation reagents for aryne intermediates generated from **19** under carbanion-free conditions using triethylsilane and cesium fluoride, affording sulfides **20a**–**20d** while retaining fluoro, bromo, methyl, benzyloxy, methoxy, and dibenzofuran moieties (Fig. 5B and D).[13,14] For example, following the synthesis of *S*-(2-bromophenyl)-*S*-(4-tolyl)sulfilimine (**18a**) from **5b** and arylboronic acid **16b**, we succeeded in preparing **21a**–**21c** by migrative aminothiolation of arynes generated from **19a**–**19c** in moderate to good yields. It is worth noting that sulfide **20d** possessing fluoro, bromo, and methoxy substituents was synthesized *via* bromothiolation of 4,5-difluorobenzyne from 4,5-difluoro-2-silylphenyl triflate, where methoxy group was selectively introduced during the hydrolysis in sulfilimine synthesis under basic conditions.[15] Moreover, we achieved the synthesis of **21a**–**21c** by *t*-BuOK-facilitated migrative *N*-arylation from arylthio group followed by ring-closing *S*-arylation

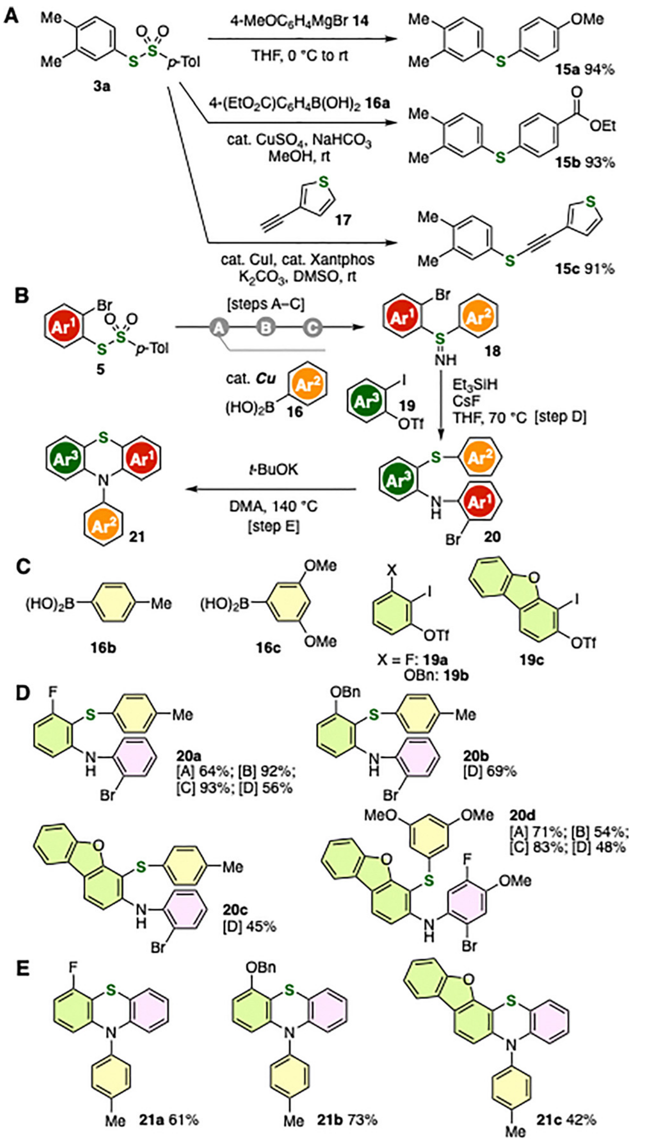


Fig. 5 (A) Synthesis of **15**. (B) Transformations of **5**. [step A: **16**, cat. $CuSO_4$, $NaHCO_3$, MeOH, rt; step B: $CF_3C(O)NH_2$, cat. $Rh_2(OAc)_4$, $PhI(OAc)_2$, MgO, CH_2Cl_2, rt; step C: K_2CO_3, MeOH, rt] (C) Substrates. (D) Sulfides **20**. (E) Phenothiazines **21**. See the SI for details.

through C–Br cleavage (Fig. 5B and E).[16] Notably, a pentacyclic scaffold was constructed in **21c** from **19c** through aryne aminothiolation, *t*-BuOK-promoted migrative *N*-arylation, and subsequent ring closure.

In conclusion, we have established an efficient method for synthesizing aryl thiosulfonates from *o*-silylaryl triflates. A key finding is an umpolung transformation in which aryl xanthates are readily oxidized with iodine to afford the corresponding thiosulfonates *via* disulfide intermediates. The versatility of thiosulfonates, together with our divergent aryne-based toolbox, enables access to highly functionalized sulfides involving phenothiazine derivatives. Further studies in our group are underway, including detailed mechanistic investigations supported by theoretical calculations and applications to the synthesis of bioactive organosulfur compounds.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information: experimental procedures, characterization for new compounds including NMR spectra. See DOI: https://doi.org/10.1039/d6cc01087c.

Acknowledgements

The authors thank Central Glass Co., Ltd. for providing Tf_2O. This work was supported by JSPS KAKENHI Grant Number JP22H02086 (S. Y.); and Tokuyama Science Foundation (S. Y.).

References

1 For reviews of thiosulfonate chemistry, see: (*a*) P. Mampuys, C. R. McElroy, J. H. Clark, R. V. A. Orru and B. U. W. Maes, *Adv. Synth. Catal.*, 2020, **362**, 3; (*b*) S. Yu, Z. Chen, Q. Chen, S. Lin, J. He, G. Tao and Z. Wang, *Chin. J. Org. Chem.*, 2022, **42**, 2322; (*c*) D. Ge, J.-W. Chen, P. Xu, J. Pan and X.-Q. Chu, *Chin. Chem. Lett.*, 2022, **33**, 4732.

2 (*a*) M. Balasubramanian and V. Baliah, *J. Chem. Soc.*, 1954, 1844; (*b*) S. H. Wunderlich and P. Knochel, *Angew. Chem., Int. Ed.*, 2007, **46**, 7685; (*c*) P. Saravanan and P. Anbarasan, *Org. Lett.*, 2014, **16**, 848; (*d*) S. Yoshida, Y. Sugimura, Y. Hazama, Y. Nishiyama, T. Yano, S. Shimizu and T. Hosoya, *Chem. Commun.*, 2015, **51**, 16613; (*e*) K. Kanemoto, Y. Sugimura, S. Shimizu, S. Yoshida and T. Hosoya, *Chem. Commun.*, 2017, **53**, 10640; (*f*) Y. Fang, T. Rogge, L. Ackermann, S.-Y. Wang and S.-J. Ji, *Nat. Commun.*, 2018, **9**, 2240; (*g*) K. Kanemoto, S. Yoshida and T. Hosoya, *Chem. Lett.*, 2018, **47**, 85; (*h*) S. Huang, N. Thirupathi, C.-H. Tung and Z. Xu, *J. Org. Chem.*, 2018, **83**, 9449; (*i*) K. Kanemoto, S. Yoshida and T. Hosoya, *Org. Lett.*, 2019, **21**, 3172; (*j*) K. Kanemoto, Y. Sakata, T. Hosoya and S. Yoshida, *Chem. Lett.*, 2020, **49**, 593; (*k*) K. Mutsuura, Y. Sakata, K. Uchida, T. Hosoya and S. Yoshida, *Chem. Lett.*, 2020, **49**, 753; (*l*) A. Kobayashi, T. Matsuzawa, T. Hosoya and S. Yoshida, *Chem. Lett.*, 2021, **50**, 1624; (*m*) K. Gadde, P. Mampuys, A. Guidetti, H. Y. V. Ching, W. A. Herrebout, S. Van Doorslaer, K. A. Tehrani and B. U. W. Maes, *ACS Catal.*, 2020, **10**, 8765; (*n*) J. Luo, M. Lin, D. Xia, G. Du, Z. Cai, B. Dai and L. He, *Org. Chem. Front.*, 2023, **10**, 1224; (*o*) J. Mindner, S. Rombach and D. B. Werz, *Org. Lett.*, 2024, **26**, 2124.

3 (*a*) F. Freeman and C. N. Angeletakis, *J. Org. Chem.*, 1985, **50**, 793; (*b*) K. Fujiki, N. Tanifuji, Y. Sasaki and T. Yokoyama, *Synthesis*, 2002, 343; (*c*) K. Bahrami, M. M. Khodaei and D. Khaledian, *Tetrahedron Lett.*, 2012, **53**, 354; (*d*) H. T. Pham, N.-L. T. Nguyen, F. Duus and T. X. T. Luu, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2015, **190**, 1934; (*e*) P. Natarajan, *Tetrahedron Lett.*, 2015, **56**, 4131; (*f*) Y. Zheng, F.-L. Qing, Y. Huang and X.-H. Xu, *Adv. Synth. Catal.*, 2016, **358**, 3477; (*g*) L. Liu, B. Luo and C. Wang, *Eur. J. Org. Chem.*, 2021, 5880; (*h*) J. Strehl and G. Hilt, *Eur. J. Org. Chem.*, 2022, 35; (*i*) L. Sancineto, J. K. Kibambe, C. Scimmi and C. Santi, *ARKIVOC*, 2023, 135.

4 S. Tabata and S. Yoshida, *Org. Lett.*, 2024, **26**, 3816.

5 For selected papers of functionalization of arynes with sulfur functional groups, see: (*a*) M. Pawliczek, L. K. B. Garve and D. B. Werz, *Chem. Commun.*, 2015, **51**, 9165; (*b*) H.-Y. Li, L.-J. Xing, M.-M. Lou, H. Wang, R.-H. Liu and B. Wang, *Org. Lett.*, 2015, **17**(5), 1098; (*c*) X. Wu, M. Chen, F.-S. He and J. Wu, *Org. Lett.*, 2023, **25**, 5157; (*d*) Y. Guo, Z. Zhuang, X. Feng, Q. Ma, N. Li, C. Jin, H. Yoshida and J. Tan, *Org. Lett.*, 2023, **25**, 7192.

6 K. Nakamura, Y. Kumagai, A. Kobayashi and S. Yoshida, *Org. Biomol. Chem.*, 2023, **21**, 6886.

7 Y. Nakamura, Y. Miyata, K. Uchida, S. Yoshida and T. Hosoya, *Org. Lett.*, 2019, **21**, 5252.
8 (*a*) S. Yoshida, Y. Nakamura, K. Uchida, Y. Hazama and T. Hosoya, *Org. Lett.*, 2016, **18**, 6212; (*b*) Y. Nakamura, S. Ozawa, S. Yoshida and T. Hosoya, *Chem. Lett.*, 2019, **48**, 1296.
9 We attempted a one-pot synthesis of thiosulfonate **3d** from 4,5-di(methoxy)-2-(trimethylsilyl)phenyl triflate by aryne hydrothiolation with potassium xanthate in acetonitrile followed by oxidative S-sulfonylation. However, the desired product 3d was not obtained under these conditions.
10 *Modern Aryne Chemistry*, ed. A. T. Biju, Wiley-VCH, Weinheim, 2021.
11 For selected reviews of aryne chemistry, see: (*a*) P. M. Tadross and B. M. Stoltz, *Chem. Rev.*, 2012, **112**, 3550; (*b*) A. E. Goetz, T. K. Shah and N. K. Garg, *Chem. Commun.*, 2015, **51**, 34; (*c*) J.-A. García-López and M. F. Greaney, *Chem. Soc. Rev.*, 2016, **45**, 6766; (*d*) F. I. M. Idiris and C. R. Jones, *Org. Biomol. Chem.*, 2017, **15**, 9044; (*e*) H. Takikawa, A. Nishii, T. Sakai and K. Suzuki, *Chem. Soc. Rev.*, 2018, **47**, 8030; (*f*) T. Roy and A. T. Biju, *Chem. Commun.*, 2018, **54**, 2580; (*g*) D. B. Werz and A. T. Biju, *Angew. Chem., Int. Ed.*, 2020, **59**, 3385; (*h*) J. Shi, L. Li and Y. Li, *Chem. Rev.*, 2021, **121**, 3892; (*i*) H. Hazarika and P. Gogoi, *Org. Biomol. Chem.*, 2021, **19**, 8466; (*j*) R. Zhang, X. Peng and J. Tan, *Synthesis*, 2022, 5064; (*k*) N. Kim, M. Choi, S.-E. Suh and D. M. Chenoweth, *Chem. Rev.*, 2024, **124**, 11435; (*l*) S. Tabata and S. Yoshida, *Tetrahedron Chem.*, 2025, **14**, 100136.
12 (*a*) B. G. Cox and R. Natarajan, *J. Chem. Soc., Perkin Trans. 2*, 1977, 113; (*b*) E. Silvester, D. Truccolo and F. P. Hao, *J. Chem. Soc., Perkin Trans. 2*, 2002, 1562.
13 (*a*) S. Yoshida, T. Yano, Y. Misawa, Y. Sugimura, K. Igawa, S. Shimizu, K. Tomooka and T. Hosoya, *J. Am. Chem. Soc.*, 2015, **137**, 14071; (*b*) S. Yoshida, T. Kuribara, T. Morita, T. Matsuzawa, K. Morimoto, T. Kobayashi and T. Hosoya, *RSC Adv.*, 2018, **8**, 21754; (*c*) T. Matsuzawa, K. Uchida, S. Yoshida and T. Hosoya, *Chem. Lett.*, 2018, **47**, 825.
14 M. Minoshima, K. Uchida, Y. Nakamura, T. Hosoya and S. Yoshida, *Org. Lett.*, 2021, **23**, 1868.
15 J. R. Rodriguez, J. Agejas and A. B. Bueno, *Tetrahedron Lett.*, 2006, **47**, 5661.
16 T. Matsuzawa, T. Hosoya and S. Yoshida, *Org. Lett.*, 2021, **23**, 2347.