


 Cite this: *Chem. Commun.*, 2024, 60, 1611

 Received 21st November 2023,
 Accepted 9th January 2024

DOI: 10.1039/d3cc05703h

rsc.li/chemcomm

Facile synthesis of dibenzothiophene *S*-oxides from sulfinato esters†

 Yukiko Kumagai,^a Akihiro Kobayashi,^{ab} Keisuke Nakamura^a and Suguru Yoshida^{ib}*^a

An efficient method to prepare dibenzothiophene *S*-oxides is disclosed. Suzuki–Miyaura cross-coupling of 2-bromoaryl sulfinato esters with arylboronic acids selectively at the bromo group followed by electrophilic cyclization of the resulting sulfinato ester moiety provides diverse dibenzothiophene *S*-oxides. Further transformations including Pummerer-type C–H propargylation and aryne reactions realize to synthesize highly functionalized dibenzothiophene derivatives.

Dibenzothiophenes and their derivatives having *S*-oxide or *S,S*-dioxide moieties are of great significance in broad research fields such as pharmaceutical sciences, materials chemistry, and chemical biology (Fig. 1A).^{1–3} Particularly, dibenzothiophene *S*-oxides are gaining attention as precursors to generate atomic oxygen triggered by UV irradiation, which can facilitate DNA cleavage, oxidation of adenosine-*S'*-phosphosulfate kinase, and so on.¹ In addition, recent advances in synthetic methods through the activation of S–O bond have allowed us to prepare diverse functionalized dibenzothiophenes from dibenzothiophene *S*-oxides (Fig. 1B).⁴ Despite the importance of dibenzothiophene *S*-oxides, it is not always easy to synthesize highly functionalized dibenzothiophene *S*-oxides in a conventional manner, which involves thiophene ring formation of biaryls using S₈ and subsequent *S*-oxidation with oxidants such as *m*CPBA (Fig. 1C).^{5,6} Herein, we disclose a novel method to prepare dibenzothiophene *S*-oxides from 2-bromoaryl-substituted sulfinato esters by Br-selective Suzuki–Miyaura coupling followed by intramolecular electrophilic sulfonylation (Fig. 1D). Since we recently found that sulfinato esters can be activated easily by triflic anhydride (Tf₂O)

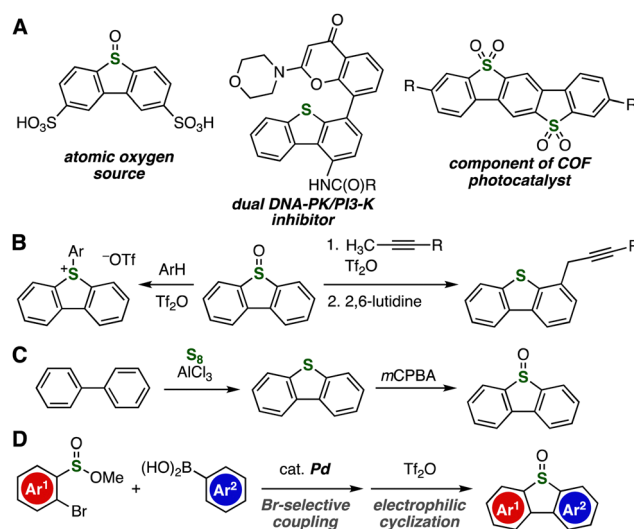


Fig. 1 (A) Significant dibenzothiophene derivatives. (B) Transformations of dibenzothiophene *S*-oxide. (C) Representative synthesis of dibenzothiophene *S*-oxide. (D) This work.

realizing *S*-allylation with allylsilanes, we conceived the synthesis of dibenzothiophene *S*-oxides from 2-biarylyl sulfinato ester through the electrophilic activation.^{7,8}

We succeeded in the synthesis of dibenzothiophene *S*-oxide **4a** through Br-selective coupling and subsequent cyclization by electrophilic activation (Table 1). Treatment of 2-bromobenzenesulfinic acid methyl ester (**1a**)⁹ with 4-tolylboronic acid (**2a**) in the presence of potassium phosphate and a catalytic amount of (amphos)₂PdCl₂ afforded 2-(4-tolyl)benzenesulfinic acid methyl ester (**3a**) in an excellent yield. Of note, the coupling proceeded selectively at the bromo group, where palladium-catalyzed sulfoxide formation was not observed.¹⁰ Then, reaction conditions were screened for the cyclization of methyl 2-(4-tolyl)benzenesulfinate (**3a**) by electrophilic activation using acid anhydrides. As a result, we successfully synthesized dibenzothiophene *S*-oxide **4a** in high yield from **3a** with Tf₂O. Indeed, treatment of **3a** with Tf₂O in dichloromethane at room temperature followed by the addition of aqueous sodium

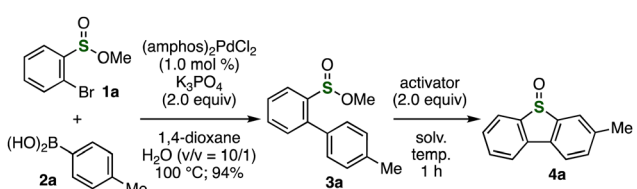
^a Department of Biological Science and Technology, Faculty of Advanced Engineering, Tokyo University of Science, 6-3-1 Niijuku, Katsushika-ku, Tokyo 125-8585, Japan. E-mail: s-yoshida@rs.tus.ac.jp

^b Laboratory of Chemical Bioscience, Institute of Biomaterials and Bioengineering, Tokyo Medical and Dental University (TMDU), 2-3-10 Kanda-Surugadai, Chiyoda-ku, Tokyo 101-0062, Japan

† Electronic supplementary information (ESI) available: Experimental procedures, characterization for new compounds including NMR spectra. See DOI: <https://doi.org/10.1039/d3cc05703h>



Table 1 Optimization of the reaction conditions



Entry	Activator	Solv.	Temp.	Yield (%) ^a
1	Tf ₂ O	CH ₂ Cl ₂	rt	90
2	Tf ₂ O	CH ₂ Cl ₂	rt	88
3	2,6-(<i>t</i> -Bu) ₂ py ^b	CH ₂ Cl ₂	rt	0
4	(CF ₃ CO) ₂ O	CH ₂ Cl ₂	rt	0
5	(CH ₃ CO) ₂ O	CH ₂ Cl ₂	rt	0
6	TfOH	CH ₂ Cl ₂	rt	51
7 ^c	Tf ₂ O	CH ₂ Cl ₂	0 °C	97
8	Tf ₂ O	CH ₂ Cl ₂	0 °C	83
9	Tf ₂ O	CH ₂ Cl ₂	-40 °C	0
10	Tf ₂ O	Toluene	rt	3
11	Tf ₂ O	CH ₃ CN	rt	0
12	Tf ₂ O	CH ₃ NO ₂	rt	0
13	Tf ₂ O	Et ₂ O	rt	97
14	Tf ₂ O	Et ₂ O	0 °C	Quant.
	2,6-(<i>t</i> -Bu) ₂ py ^b	Et ₂ O	0 °C	88

^a Isolated yields. ^b The reaction was conducted using 2,6-di(*tert*-butyl)pyridine (4.0 equiv.) with Tf₂O (2.0 equiv.). ^c Gram-scale synthesis. See details in the ESI.

bicarbonate provided the desired dibenzothiophene *S*-oxide **4a** in high yield, where side-products from further Pummerer-type reactions were not observed (entry 1). The reaction also took place smoothly when using Tf₂O with 2,6-di(*tert*-butyl)pyridine as a base (entry 2). In contrast, trifluoroacetic anhydride (TFAA) or acetic anhydride did not activate sulfinate ester **3a** (entries 3 and 4). Dibenzothiophene *S*-oxide **4a** was also obtained in moderate yield using triflic acid (TfOH) (entry 5). The yield was slightly improved when the reaction was conducted at 0 °C to realize the synthesis of dibenzothiophene *S*-oxide **4a** in an excellent yield (entry 6). We accomplished the gram-scale synthesis of **4a** in good yield (entry 7). No reaction took place at -40 °C (entry 8). While the efficient synthesis of cyclized product **4a** failed when the reaction was conducted in toluene, acetonitrile, or nitromethane (entries 9–11), we also succeeded in the facile synthesis of dibenzothiophene *S*-oxide in diethyl ether at room temperature or 0 °C (entries 12 and 13). The synthesis of **4a** in the presence of 2,6-di(*tert*-butyl)pyridine was achieved also in diethyl ether (entry 14). We also prepared dibenzothiophene *S*-oxide **4a** from **1a** in high yield through a single silica-gel column chromatography, obviously indicating good practicality of the benzothiophene *S*-oxide synthesis from sulfinate esters (Fig. 2A).

A wide range of dibenzothiophene *S*-oxides having diverse functional groups were prepared from sulfinate ester **1a** and various arylboronic acids **2** (Fig. 2B and C). Due to the good solubility of dichloromethane for broad aromatic compounds, we chose the conditions using dichloromethane for synthesizing various dibenzothiophene *S*-oxides. For example, we succeeded in the synthesis of dibenzothiophene *S*-oxides **4b** and **4c** in good yields by the 2-step protocol without damaging fluoro and chloro groups. In the case of synthesis of dibenzothiophene *S*-oxide **4d** from **1a**

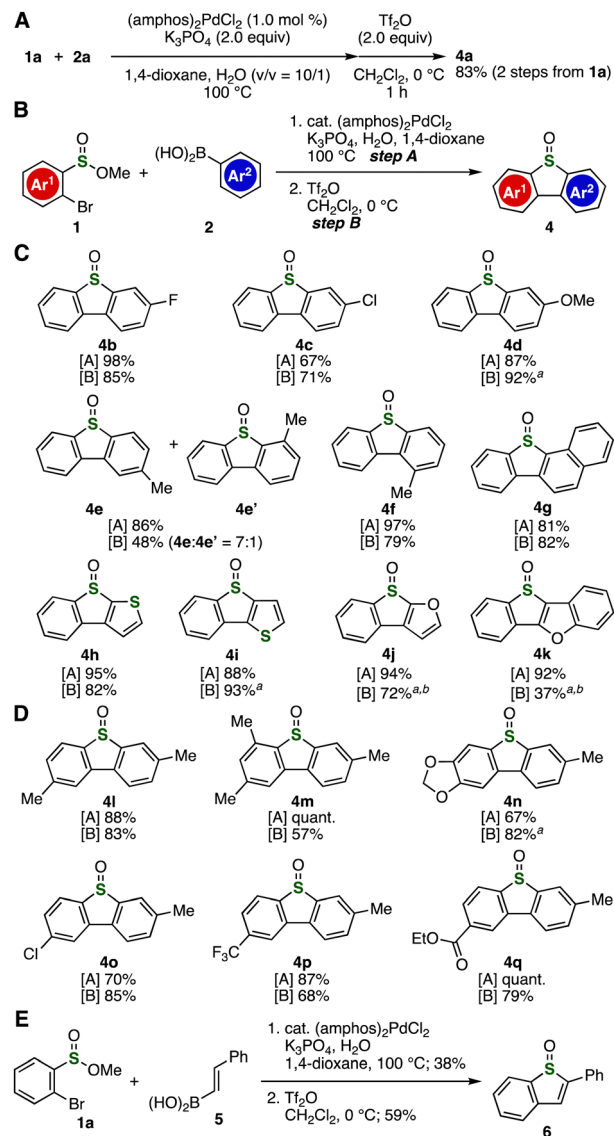


Fig. 2 (A) Synthesis of **4a** with a single silica-gel column chromatography purification. (B) General scheme for synthesizing various dibenzothiophene *S*-oxides. (C) Results using various arylboronic acids **2** with **1a**. (D) Results using various sulfinate esters **1** with **2a**. (E) Synthesis of benzothiophene *S*-oxide **6**. ^a Et₂O was used as a solvent instead of CH₂Cl₂. ^b The reaction was conducted in the presence of 2,6-di(*tert*-butyl)pyridine (4.0 equiv.). See details in the ESI. † amphos = di(*tert*-butyl)(4-(dimethylamino)phenyl)phosphine.

and 4-methoxyphenylboronic acid, the electrophilic cyclization of methyl 2-(4-methoxyphenyl)benzenesulfinate bearing an electron-rich aryl group took place efficiently when using diethyl ether as a solvent.¹¹ We succeeded in the preparation of 2-methyl-dibenzothiophene *S*-oxide (**4e**) along with minor isomer **4e'** from 3-methylboronic acid by efficient Suzuki–Miyaura coupling and following intramolecular arylation, in which cyclization at sterically unhindered site predominantly proceeded. The 2-step protocol using sulfinate ester **1a** and bulky 2-methylphenyl boronic acid allowed us to synthesize dibenzothiophene *S*-oxide **4f** in high yields. We successfully synthesized π -extended dibenzothiophene *S*-oxide **4g**, which was reported as a promising dibenzothiophene



S-oxide derivative having an extended chromophore to red-shift the absorption spectra for atomic oxygen precursors,¹² from 2-naphthylboronic acid through regioselective cyclization, where the regioisomer was not detected. It is worth noting that a variety of heteroarylboronic acids participated in the coupling-cyclization protocol to furnish heteroaromatic ring-fused dibenzothiophene S-oxides **4h–4k**. When using 3-thienyl- or 3-furylboronic acid, intramolecular S-arylation proceeded at 2-position selectively to afford dibenzothiophene S-oxide analog **4h** or **4j**, respectively. The synthesis of furan- or benzo[*b*]furan-fused benzo[*b*]thiophene **4j** or **4k** was realized by the addition of 2,6-di(*tert*-butyl)pyridine as a base. We also succeeded in the preparation of benzo[*b*]thiophene S-oxide **6** from sulfinate ester **1a** and 2-styrylboronic acid (**5**) through the intramolecular S-alkenylation (Fig. 2E).

Various sulfinate esters served in synthesizing dibenzothiophene S-oxides having various electron-donating or electron-withdrawing functional groups (Fig. 2B and D). Indeed, 2,7-dimethyl- and 2,4,7-trimethyl-substituted unsymmetric dibenzothiophene S-oxides **4l** and **4m** were prepared efficiently from 4-methyl- and 4,6-dimethyl-substituted 2-bromobenzenesulfinic acid esters, respectively. The synthesis of dibenzothiophene S-oxide **4n** bearing a methylenedioxy moiety was achieved efficiently through cross-coupling and cyclization in diethyl ether. We also accomplished the preparation of dibenzothiophene S-oxides **4o–4q** leaving electron-withdrawing chloro, trifluoromethyl, and ethoxycarbonyl groups untouched. These results obviously indicated that Br-selective coupling and following cyclization were not affected by a broad range of electron-donating or -withdrawing functional groups.

To gain insight into the reaction mechanism of the electrophilic cyclization of sulfinate esters, we then isolated sulfuran intermediate **7** by changing the protocol (Fig. 3A). Indeed, after treatment of sulfinate ester **3a** with Tf₂O, the resulting mixture was quenched with solid sodium bicarbonate instead of aqueous sodium bicarbonate. Then, filtrating the mixture to remove

sodium bicarbonate and washing the resulting filtrate with *n*-hexane furnished sulfuran **7** quantitatively. We achieved the synthesis of dibenzothiophene S-oxide **4a** with the hydrolysis of sulfuran **7** with aqueous sodium bicarbonate. Based on this result, we proposed a plausible reaction mechanism for the dibenzothiophene S-oxide synthesis (Fig. 3B). First, Tf₂O activates S=O moiety to form sulfuran intermediate **I**. Second, electrophilic aromatic substitution at the electrophilic sulfur provides sulfuran **7**. Finally, hydrolysis of sulfuran **7** with aqueous sodium bicarbonate furnishes dibenzothiophene S-oxide **4a** via the nucleophilic attack of water or bicarbonate anion to the sulfur atom. When sulfoxide **8** was treated with Tf₂O followed by the addition of sodium bicarbonate, dibenzothiophene **9a** was obtained in good yield through the demethylative hydrolysis of sulfonium intermediate **III**, where sulfoxide **4a** was not obtained (Fig. 3C).¹³ This result shows that the difference between sulfinate esters and sulfoxides in the electrophilic cyclization lies in the reaction sites in the hydrolysis.

Good transformability of dibenzothiophene S-oxide enabled us to synthesize a wide variety of dibenzothiophene derivatives (Fig. 4A). For instance, S-oxidation of **4a** with *m*CPBA afforded dibenzothiophene S,S-dioxide **10a** in high yield.¹⁴ Rhodium-catalyzed imidation of **4a** with trifluoroacetamide took place efficiently in the presence of iodobenzene diacetate and magnesium oxide to provide sulfoximine **11**.¹⁵ Reduction of sulfoxide **4a** with TFAA and sodium iodide proceeded smoothly to furnish dibenzothiophene **9a** in high yield.¹⁶ We also accomplished the preparation of thiophene- and furan-fused benzothiophenes **9b** and **9c** by the reduction of sulfoxides **4i** and **4j**. To our surprise, we found that the decomposition of furan-fused benzothiophene **9c** took place gradually in CDCl₃ at room temperature.¹⁷

We clarified that it is not easy to achieve the efficient synthesis of sulfoxides **4i** and **4j** by the conventional oxidation with *m*CPBA (Fig. 4B and C).⁵ Indeed, the oxidation of thienobenzothiophene **9b** with *m*CPBA (0.7 or 1.4 equiv.) afforded a

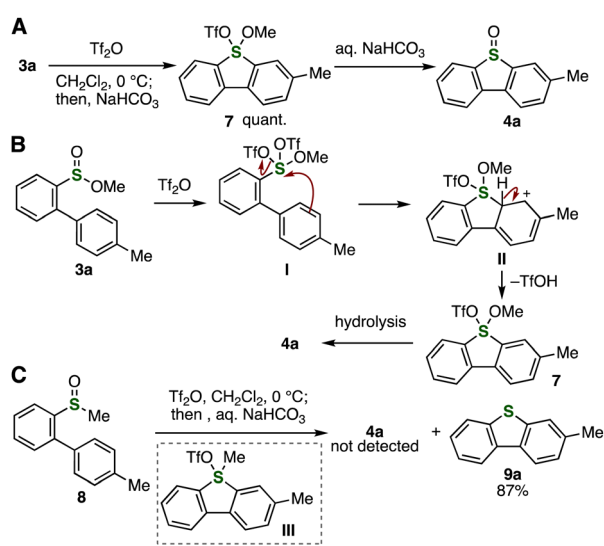


Fig. 3 (A) Stepwise synthesis of **4a** via isolation of **7**. (B) Plausible mechanism for the synthesis of **4a** from **3a**. (C) Electrophilic cyclization of sulfoxide **8**.

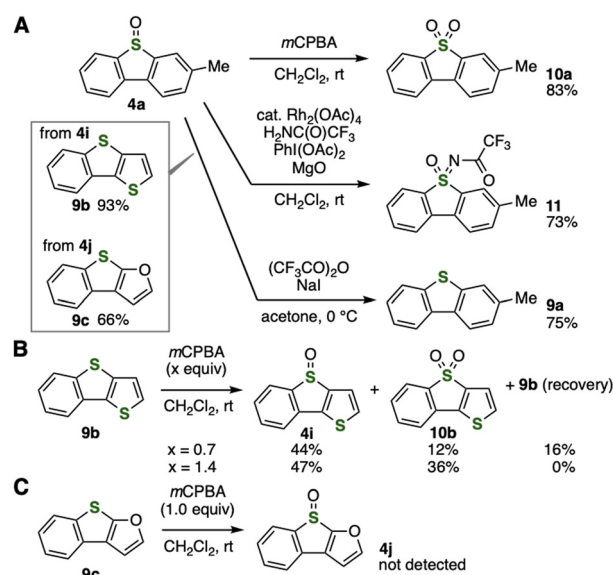


Fig. 4 (A) Transformations of **4a**, **4i**, and **4j**. (B) Oxidation of **9b**. (C) Oxidation of **9c**.



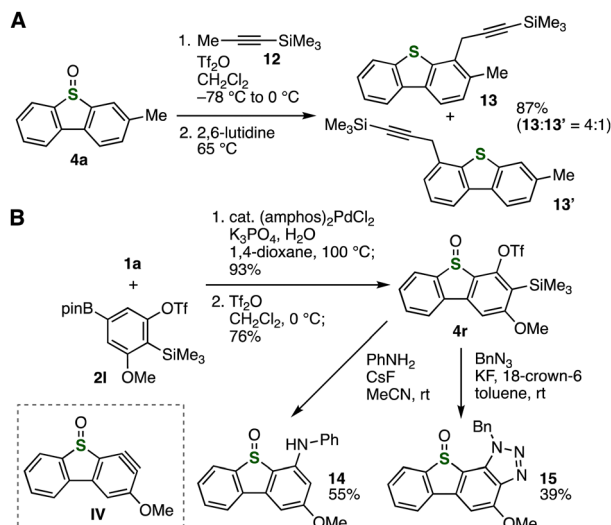


Fig. 5 (A) C–H propargylation using **4a**. (B) Synthesis and transformations of *o*-silylaryl triflate **4r**.

mixture of sulfoxide **4i** and sulfone **10b**, clearly showing the problematic reactivity of sulfoxides under the oxidation conditions leading to sulfones (Fig. 4B). Furthermore, *m*CPBA oxidation of furanobenzothiophene **4j** provided a complex mixture of products (Fig. 4C). These results obviously indicate an advantage of the newly developed method to synthesize dibenzothiophene *S*-oxides.

Further transformations of dibenzothiophene *S*-oxides realized a wide variety of highly functionalized dibenzothiophene derivatives (Fig. 5). An extended Pummerer-type propargylation of dibenzothiophene *S*-oxide **4a** with silane **12** took place efficiently to provide **13** and **13'** in high combined yield, where C–C formation at the electron-rich but bulky site occurred smoothly to furnish **13** as a major product (Fig. 5A).^{4a} It is worth noting that the good functional group tolerance allowed us to prepare *o*-silylaryl triflate **4r** efficiently by the coupling–cyclization approach without damaging reactive silyl and triflyloxy groups (Fig. 5B). This result shows a clear advantage over other dibenzothiophene *S*-oxide synthesis with nucleophilic carbanions or heating under basic conditions.⁶ Then, regioselective *N*-arylation of aniline with aryne **IV** took place smoothly to afford adduct **14** in moderate yield without forming the regioisomer, in which the sulfoxide moiety remained unreacted.^{18–20} Moreover, we accomplished the synthesis of triazole-fused dibenzothiophene *S*-oxide **15** by regioselective cycloaddition of aryne **IV** with benzyl azide. Since *o*-silylaryl triflate moiety serves to synthesize highly substituted arenes through aryne intermediates by a wide variety of transformations, a broad range of dibenzothiophene derivatives will be prepared by diverse aryne reactions.

In summary, we have developed an efficient method to prepare dibenzothiophene *S*-oxides from 2-bromoaryl sulfinates and arylboronic acids in 2 steps. Diverse dibenzothiophene *S*-oxides having various functionalities were synthesized by Br-selective cross-coupling and subsequent cyclization with Tf₂O without side reactions through the activation of sulfoxides. The good transformability

of dibenzothiophene *S*-oxides allowed us to access novel heterocyclic molecules such as highly ring-fused thiophenes. Further studies including applications for the construction of new organo-sulfur skeletons by transformations of dibenzothiophene *S*-oxides are ongoing in our laboratory.

The authors thank Central Glass Co., Ltd. for providing Tf₂O. This work was supported by JSPS KAKENHI Grant Number JP22H02086 (S. Y.); The Uehara Memorial Foundation (S. Y.); Tokuyama Science Foundation (S. Y.); The Ube Foundation (S. Y.); and Inamori Research Grants (S. Y.).

Conflicts of interest

There are no conflicts to declare.

Notes and references

- M. Zhang, G. E. Ravilious, L. M. Hicks, J. M. Jez and R. D. McCulla, *J. Am. Chem. Soc.*, 2012, **134**, 16979.
- G. C. M. Smith, A. J. Slade, C. J. Richardson and B. W. Durkacz, WO2006/126010 A2, 2006.
- H. Wang, H. Wang, Z. Wang, L. Tang, G. Zeng, P. Xu, M. Chen, T. Xiong, C. Zhou, X. Li, D. Huang, Y. Zhu, Z. Wang and J. Tang, *Chem. Soc. Rev.*, 2020, **49**, 4135.
- (a) J. A. Fernández-Salas, A. J. Eberhart and D. J. Procter, *J. Am. Chem. Soc.*, 2016, **138**, 790; (b) X. Wang, X. Xun, H. Song, Y. Liu and Q. Wang, *Org. Lett.*, 2022, **24**, 4580; (c) X. Li, C. Golz and M. Alcarazo, *Angew. Chem., Int. Ed.*, 2021, **60**, 6943.
- (a) D. Villemain and X. Vlieghe, *Sulfur Lett.*, 1998, **21**, 199; (b) M. H. Aukland, M. Šiaučiuolis, A. West, G. J. P. Perry and D. J. Procter, *Nat. Catal.*, 2020, **3**, 163.
- For other dibenzothiophene *S*-oxide synthesis, see: (a) T. Wesch, A. Berthelot-Bréhier, F. R. Leroux and F. Colobert, *Org. Lett.*, 2013, **15**, 2490; (b) R. Wada, S. Kaga, Y. Kawai, K. Futamura, T. Murai and F. Shibahara, *Tetrahedron*, 2021, **83**, 131978.
- (a) A. Kobayashi, T. Matsuzawa, T. Hosoya and S. Yoshida, *Chem. Commun.*, 2020, **56**, 5429; (b) A. Kobayashi, T. Matsuzawa, T. Hosoya and S. Yoshida, *Chem. Lett.*, 2020, **49**, 813.
- For arylation of sulfinate esters using AlCl₃, see: F. Yuste, A. H. Linares, V. M. Mastranzo, B. Ortiz, R. Sánchez-Obregón, A. Fraile and J. L. G. Ruano, *J. Org. Chem.*, 2011, **76**, 4635. In this report, it is not easy to perform *ortho*-sulfinylation of arenes.
- K. Nakamura, Y. Kumagai, A. Kobayashi and S. Yoshida, *Org. Biomol. Chem.*, 2023, **21**, 6886.
- M. Suzuki, K. Kanemoto, Y. Nakamura, T. Hosoya and S. Yoshida, *Org. Lett.*, 2021, **23**, 3793.
- When the reactions were performed in CH₂Cl₂ at 0 °C, dibenzothiophene *S*-oxides **4d**, **4i**, **4j**, **4k**, and **4n** were obtained in 28, 76, 25, 0, and 0% yield, respectively.
- A. Isor, B. V. Chartier, M. Abo, E. R. Currens, E. Weerapana and R. D. McCulla, *RSC Chem. Biol.*, 2021, **2**, 577.
- D. Vasu, J. N. Hausmann, H. Saito, T. Yanagi, H. Yorimitsu and A. Osuka, *Asian J. Org. Chem.*, 2017, **6**, 1390.
- H. Hussain, A. Al-Harrasi, V. R. Green, I. Ahmed, G. Abbas and N. U. Rehman, *RSC Adv.*, 2014, **4**, 12882.
- H. Okamura and C. Bolm, *Org. Lett.*, 2004, **6**, 1305.
- M. de Greef and S. Z. Zard, *Tetrahedron*, 2004, **60**, 7781.
- When a time-course monitoring experiment of furan-fused benzothiophene **9c** in CDCl₃ at room temperature was conducted, 85% of **9c** was decomposed after 7 days.
- Y. Nakamura, Y. Miyata, K. Uchida, S. Yoshida and T. Hosoya, *Org. Lett.*, 2019, **21**, 5252.
- (a) T. Matsuzawa, K. Uchida, S. Yoshida and T. Hosoya, *Org. Lett.*, 2017, **19**, 5521; (b) S. Yoshida, H. Nakajima, K. Uchida, T. Yano, M. Kondo, T. Matsushita and T. Hosoya, *Chem. Lett.*, 2017, **46**, 77.
- S. Yoshida, T. Kuribara, T. Morita, T. Matsuzawa, K. Morimoto, T. Kobayashi and T. Hosoya, *RSC Adv.*, 2018, **8**, 21754.

