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

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An efficient method to prepare dibenzothiophene *S*-oxides is disclosed. Suzuki–Miyaura cross-coupling of 2-bromoaryl sulfinate esters with arylboronic acids selectively at the bromo group followed by electrophilic cyclization of the resulting sulfinate 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-5′-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 S_8 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 sulfinate esters by Br-selective Suzuki–Miyaura coupling followed by intramolecular electrophilic sulfinylation (Fig. 1D). Since we recently found that sulfinate esters can be activated easily by triflic anhydride (Tf_2O) realizing *S*-allylation with allylsilanes, we conceived the synthesis of dibenzothiophene *S*-oxides from 2-biarylyl sulfinate ester through the electrophilic activation.[7,8]

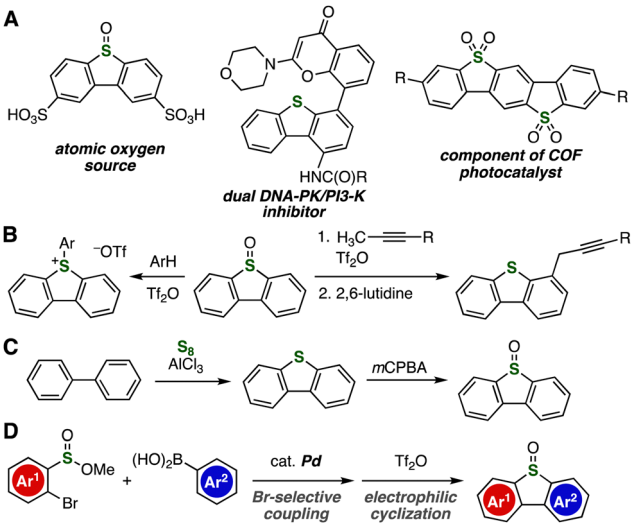

Fig. 1 (A) Significant dibenzothiophene derivatives. (B) Transformations of dibenzothiophene *S*-oxide. (C) Representative synthesis of dibenzothiophene *S*-oxide. (D) This work.

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 $(amphos)_2PdCl_2$ 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 Tf_2O. Indeed, treatment of **3a** with Tf_2O in dichloromethane at room temperature followed by the addition of aqueous sodium

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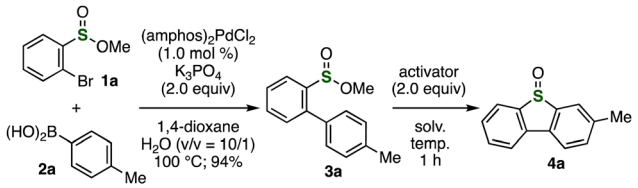
Table 1 Optimization of the reaction conditions



Entry	Activator	Solv.	Temp.	Yield (%)[a]
1	Tf_2O	CH_2Cl_2	rt	90
2	Tf_2O 2,6-(*t*-Bu)$_2$py[b]	CH_2Cl_2	rt	88
3	$(CF_3CO)_2O$	CH_2Cl_2	rt	0
4	$(CH_3CO)_2O$	CH_2Cl_2	rt	0
5	TfOH	CH_2Cl_2	rt	51
6	Tf_2O	CH_2Cl_2	0 °C	97
7[c]	Tf_2O	CH_2Cl_2	0 °C	83
8	Tf_2O	CH_2Cl_2	−40 °C	0
9	Tf_2O	Toluene	rt	3
10	Tf_2O	CH_3CN	rt	0
11	Tf_2O	CH_3NO_2	rt	0
12	Tf_2O	Et_2O	rt	97
13	Tf_2O	Et_2O	0 °C	Quant.
14	Tf_2O 2,6-(*t*-Bu)$_2$py[b]	Et_2O	0 °C	88

[a] Isolated yields. [b] The reaction was conducted using 2,6-di(*tert*-butyl)-pyridine (4.0 equiv.) with Tf_2O (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 Tf_2O with 2,6-di(*t*-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(*t*-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 dibenzothiphene *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**

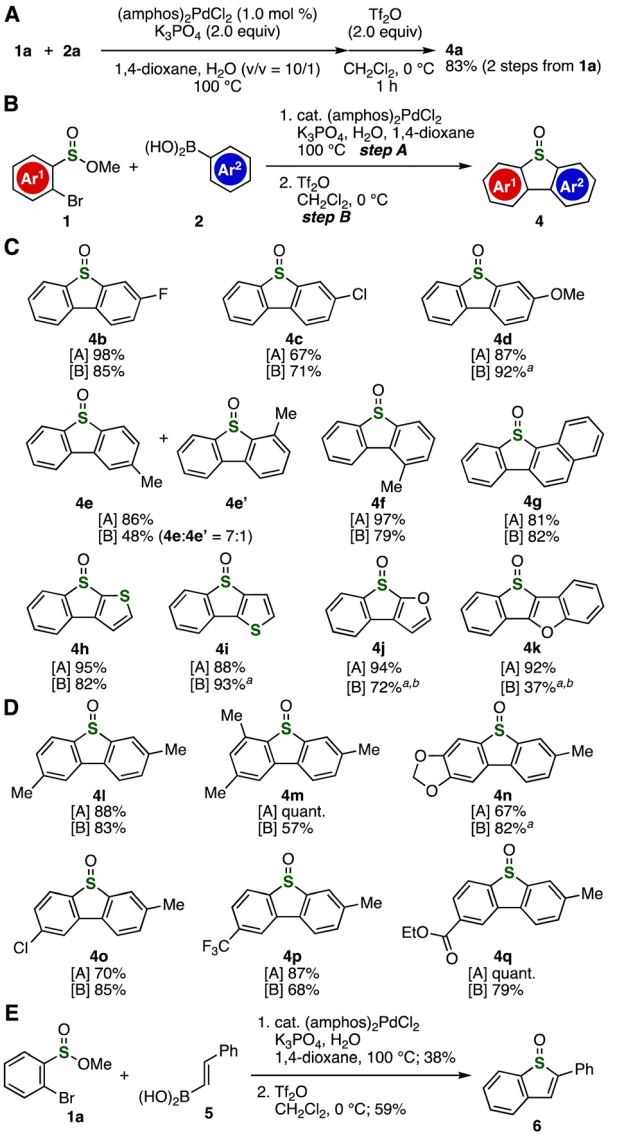


Fig. 2 (A) Synthesis of **4a** with a single silica-gel column chromatography purification. (B) General scheme for synthesizing various dibenzothiophene *S*-oxides. (C) Results using various arylboronic acids **2** with **1a**. (D) Results using various sulfinate esters **1** with **2a**. (E) Synthesis of benzothiophene *S*-oxide **6**. [a] Et_2O was used as a solvent instead of CH_2Cl_2. [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-methyldibenzothiophene *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 Tf_2O, 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, Tf_2O 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 Tf_2O 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 $CDCl_3$ 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

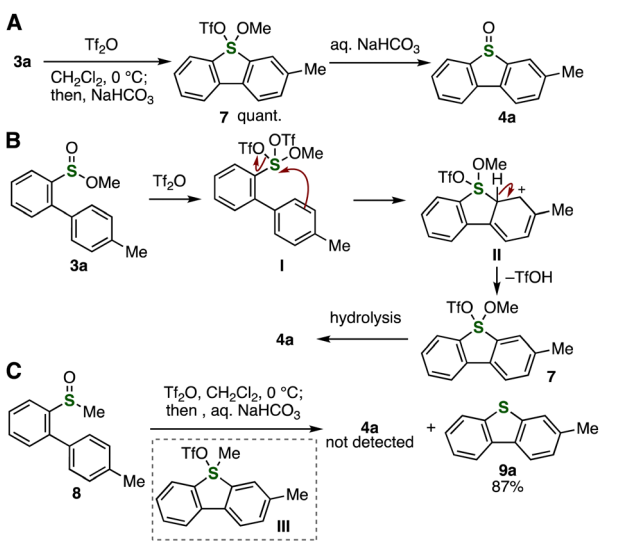


Fig. 3 (A) Stepwise synthesis of **4a** *via* isolation of **7**. (B) Plausible mechanism for the synthesis of **4a** from **3a**. (C) Electrophilic cyclization of sulfoxide **8**.

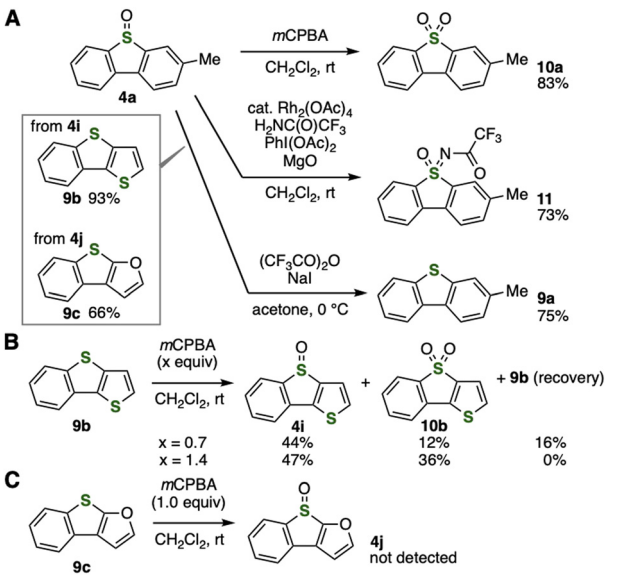


Fig. 4 (A) Transformations of **4a**, **4i**, and **4j**. (B) Oxidation of **9b**. (C) Oxidation of **9c**.

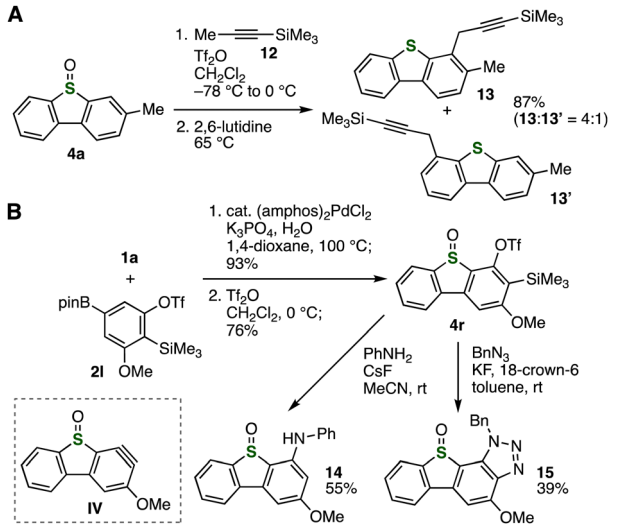


Fig. 5 (A) C–H propargylation using **4a**. (B) Synthesis and transformations of *o*-silylaryl triflate **4r**.

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 sulfinate esters and arylboronic acids in 2 steps. Diverse dibenzothiophene *S*-oxides having various functionalities were synthesized by Br-selective cross-coupling and subsequent cyclization with Tf_2O 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 organosulfur skeletons by transformations of dibenzothiophene *S*-oxides are ongoing in our laboratory.

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Conflicts of interest

There are no conflicts to declare.

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