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Sulfoxide synthesis from sulfinate esters under Pummerer-like conditions†

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A facile synthetic method for the preparation of allyl sulfoxides by *S*-allylation of sulfinate esters proceeds through sulfonium intermediates without [3,3]-sigmatropic rearrangement and further Pummerer-type reactions of the resulting allyl sulfoxides. On the basis of the plausible reaction mechanism involving sulfonium salt intermediates, *S*-alkynylation and *S*-arylation were also accomplished.

Organosulfur compounds have gained attention in a broad range of research fields such as pharmaceutical sciences, agrochemistry, and materials science.^{1,2} The recent remarkable successes of synthetic chemistry using sulfoxides have enhanced the accessibility of highly functionalized compounds by virtue of the significant transformability of sulfoxides.^{3–8} For example, the preparations of diverse compounds 2–5 were achieved by a variety of transformations of allyl aryl sulfoxides **1** through C–S bond cleavage (Fig. 1A).^{6,7,8h,j} In particular, multisubstituted aromatic sulfides **4** and **5** were synthesized from sulfoxides **1** by a reaction with aryne intermediate **I** in the presence of electrophiles and the [3,3]-sigmatropic rearrangement of allyl sulfonium intermediate **II**, respectively.^{6,7} Similar interrupted Pummerer reactions of sulfoxides **6** and **8** with trifluoromethanesulfonic anhydride (Tf₂O) in the presence of allyltrimethylsilane were also accomplished through the [3,3]-sigmatropic rearrangement, showing the notable reactivity of allyl sulfonium intermediates **III** and **IV** (Fig. 1B and C).^{4b,d,e,n} Herein, we describe an efficient synthesis of various allyl sulfoxides by allylation of sulfinate esters⁹ using allyltrimethylsilane under the Pummerer-like conditions⁴ through sulfonium intermediate **V** having a methoxy group, enabling to avoid the [3,3]-sigmatropic rearrangement and further Pummerer-type reactions of the resulting allyl sulfoxides (Fig. 1D).

Sulfinate esters hitherto have served in the sulfoxide synthesis with Grignard reagents.^{9a} Recently, Lewis acid-mediated

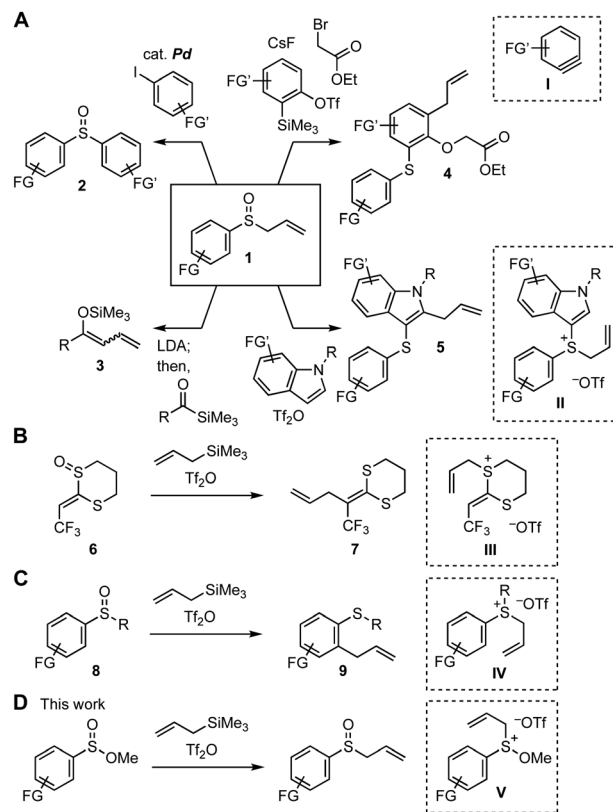


Fig. 1 Transformations through the Pummerer-type activation of sulfoxides and sulfinate esters. (A) Versatile transformations using allyl sulfoxides **1**. (B) Interrupted Pummerer reaction of ketenedithioacetal monoxide **6**. (C) Interrupted Pummerer reaction of aromatic sulfoxide **8**. (D) This work.

Friedel–Crafts-type sulfonylation of electron-rich arenes using sulfinate esters was developed.^{9b} Taking the sulfinate ester chemistry into account, we envisioned that the Pummerer-type activation of sulfinate esters **10** in the presence of allylsilanes **11** and stability of methoxy sulfonium intermediates¹⁰ would allow for the facile synthesis of allyl sulfoxides **12**, considering that the hydrolysis of methoxy sulfonium intermediates **V'** can

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afford sulfoxides (Fig. 2A). As a result of screening the reaction conditions, we found that treatment of methyl benzenesulfinate (**10a**) with TiF_2O in the presence of allyltrimethylsilane (**11a**) followed by addition of aqueous sodium bicarbonate provided allyl phenyl sulfoxide (**12a**) in high yield (Fig. 2A and 2B). Examinations using a variety of acid anhydrides or Lewis acids showed the remarkable reactivity of TiF_2O in the *S*-allylation of sulfinate ester **10a**.^{11,12} A wide range of allyl sulfoxides **12b–12j** were prepared by the *S*-allylation under the Pummerer-like conditions, where *C*-allylation products through the [3,3]-sigmatropic rearrangement were not obtained. Indeed, not only electron-rich aromatic sulfinate esters bearing methyl and methoxy groups but also electron-deficient substrates with chloro and nitro groups were efficiently allylated to furnish sulfoxides **12b–12e**. Sulfoxides **12f** and **12g** were obtained uneventfully by the reactions of bulky 2-bromo- and 2,6-dimethyl-substituted benzenesulfinate esters. Furthermore, *S*-allylations of 2-naphthyl-, benzyl-, and *n*-pentyl-substituted sulfinate esters also took place smoothly to provide sulfoxides **12h–12j**.

Various functionalized allylsilanes **11** participated in the *S*-allylation of sulfinate ester **10a** (Fig. 2A and C).¹³ Sulfoxides **12k** and **12l** were efficiently synthesized by 2-methyl- and 2-phenyl-allylation, respectively. It is worth noting that the C–S bond formation enabled to prepare allyl chloride **12m**, allyl acetate

12n, ester **12o**, and bromoalkene **12p** leaving highly electrophilic functional groups untouched, while it is not easy to synthesize sulfoxides having electrophilic moieties by the conventional allyl sulfoxide synthesis *via* allylation of thiols and subsequent oxidation. Moreover, transformable sulfoxides **12q** and **12r** possessing a silyl and boryl groups were obtained in moderate to good yields without damaging these reactive functional groups.

To gain insight into the reaction mechanism of the *S*-allylation of sulfinate esters under the Pummerer-like conditions, we then examined control experiments (Fig. 3). Firstly, the reaction using $[\text{18O}]\text{H}_2\text{O}$ in the hydrolysis using aqueous sodium bicarbonate was conducted to clarify the origin of the oxygen atom of sulfoxide **12a** (Fig. 3A). The result showed that ^{18}O -incorporated **12a'** was obtained selectively, indicating that the sulfoxide oxygen was derived from water in the hydrolysis. We then attempted to isolate sulfonium intermediate **13** (Fig. 3B). As a result, after sulfinate ester **10a** was treated with TiF_2O in the presence of allylsilane **11a**, an addition of solid sodium bicarbonate, filtration of the resulting mixture, removal of the solvent of the filtrate, and washing with diethyl ether afforded sulfonium salt **13** quantitatively. Hydrolysis of sulfonium salt **13** with aqueous sodium bicarbonate underwent uneventfully to give sulfoxide **12a**. In addition, reduction of sulfonium salt **13** with sodium borohydride successfully provided allyl phenyl sulfide (**14**) in good yield.^{10c} On the basis of these results, we proposed a reaction mechanism of the *S*-allylation (Fig. 3C). The Pummerer-type activation of sulfinate ester by virtue of the remarkable reactivity of TiF_2O ,¹⁴ and following *S*-allylation of the resulting sulfonium intermediate **VI** would furnish sulfonium intermediate **13** along with trimethylsilyl triflate. Then, hydrolysis of sulfonium salt **13** with aqueous sodium bicarbonate involving the nucleophilic attack of external water to the sulfur atom leads

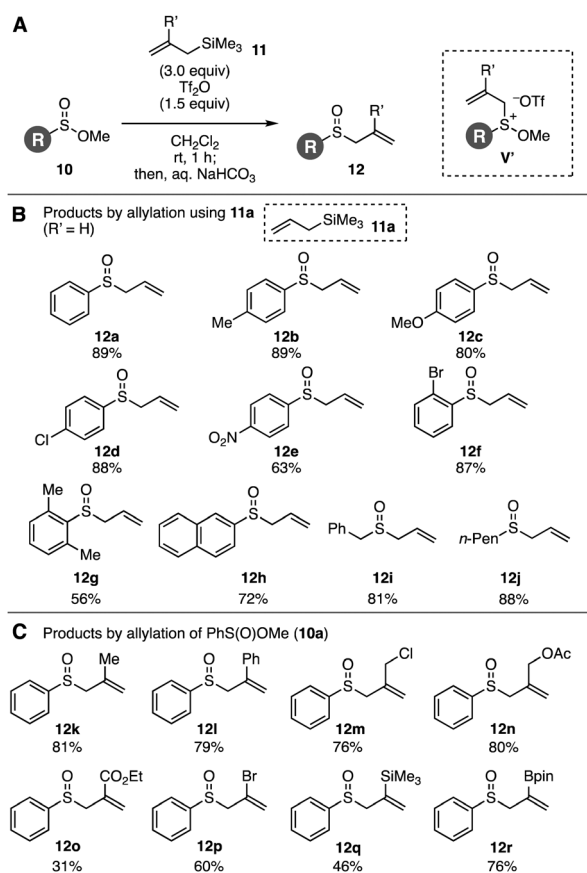


Fig. 2 Allyl sulfoxide synthesis from sulfinate esters **10** and allylsilanes **11**. (A) General scheme. (B) Results using various sulfinate esters **10** with **11a**. (C) Results using allylsilanes **11** with **10a**.

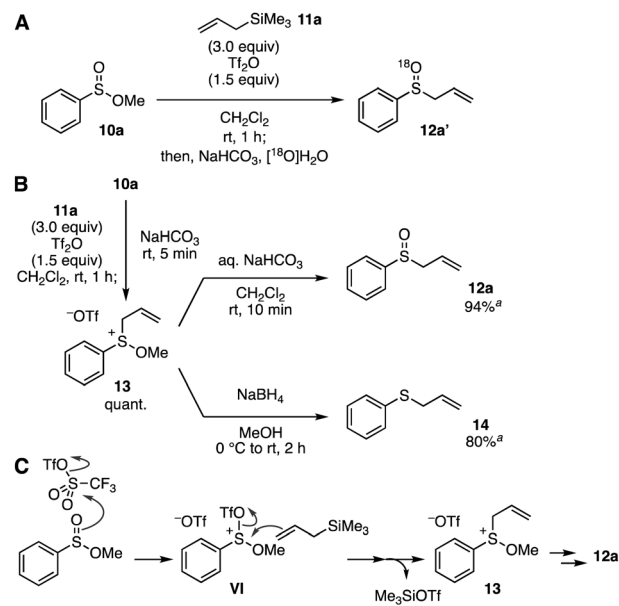


Fig. 3 Control experiments. (A) Reaction using $[\text{18O}]\text{H}_2\text{O}$. (B) Isolation of sulfonium salt **13**, hydrolysis of **13**, and reduction of **13**. (C) Plausible reaction mechanism. ^a ^1H NMR yield.



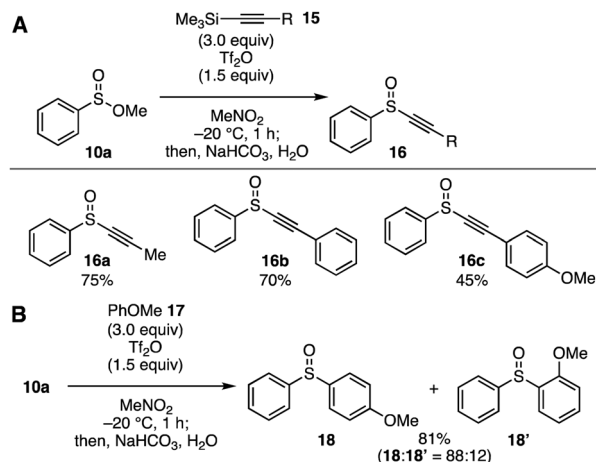


Fig. 4 Alkynylation and arylation of sulfinate ester **10a**. (A) Alkynylation with alkynylsilanes **15**. (B) Arylation with anisole (**17**).

to sulfoxide **12a**. Although the role of methoxy group is still unclear, the stability of sulfonium salt **13** would achieve the sulfoxide synthesis without [3,3]-sigmatropic rearrangement or the Pummerer-type reactions of allyl sulfoxide **12a** and further Pummerer-type reactions of the resulting allyl sulfoxides.¹⁵

Our attention then directed toward novel transformations through the cationic intermediates generated by the Pummerer-type activation of sulfinate esters with TiF_2O (Fig. 4). In this context, we have developed a facile synthetic method of alkynyl sulfoxides **16** using alkynyl silanes **15** (Fig. 4A). Indeed, treatment of sulfinate ester **10a** dissolved in nitromethane with TiF_2O in the presence of ethynylsilanes **15** at -20°C furnished alkynyl sulfoxides **16** in moderate to high yields. This novel transformation enabled the preparation of alkynyl sulfoxides **16a–16c** having a methyl, phenyl, and 4-anisyl group. Since alkynyl sulfoxides serve in a variety of reactions including carbometallation, [2+2] cycloaddition, and cyclopropanation, the alkynyl sulfoxide synthesis developed in this study would allow for the preparation of a range of organo-sulfur compounds.^{4k,16} In addition, Friedel–Crafts-type arylation of sulfinate ester **10a** also took place smoothly to afford a regioisomeric mixture of diaryl sulfoxides **18** and **18'** in good yield (Fig. 4B).^{9b}

Wide transformability of allyl aryl sulfoxides synthesized from sulfinate esters was showcased by the syntheses of multi-substituted aromatic compounds (Fig. 5). Modifying the conditions for the trifunctionalization of aryne intermediates reported by Li and coworkers⁶ (Fig. 1A, **1** to **4**), we found that 2,3,6-trisubstituted phenol **20a** was obtained in moderate yield with avoiding further arylation between phenol **20a** and 3-methoxybenzyne when the aryne trifunctionalization was performed in hot 1,4-dioxane in the absence of electrophiles such as ethyl bromoacetate (Fig. 5A). Iodine-mediated cyclization of the resulting phenol **20a** and subsequent elimination with a base successfully furnished benzofuran **21**.¹⁷ Methallylation of sulfinate ester **10d** followed by the aryne trifunctionalization led to the synthesis of highly functionalized phenol **20b** (Fig. 5B). Furthermore, tetra-substituted indole **23** was prepared through 2-bromoallylation

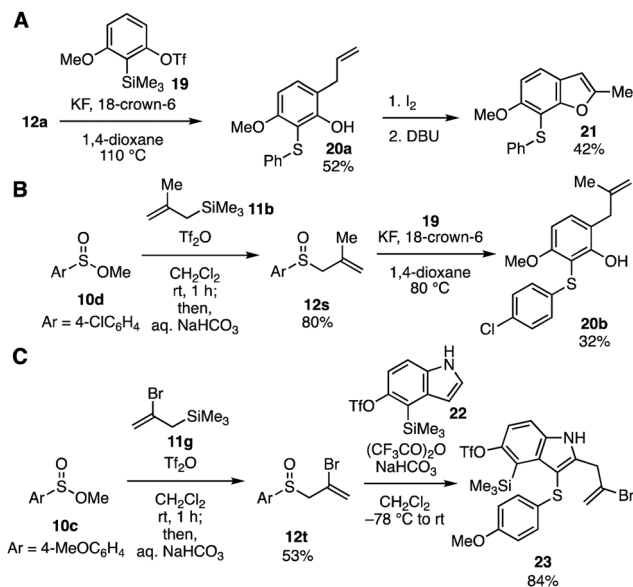


Fig. 5 Transformations of allyl sulfoxides. (A) Benzofuran synthesis. (B) Trisubstituted phenol synthesis. (C) Multisubstituted indole synthesis.

of sulfinate ester **10c** and following 2,3-difunctionalization of indole **22** according to the reports by Procter and coworkers⁷ (Fig. 5C). Functionalized allyl aryl sulfoxide **12t** and indole **22** bearing *o*-silylaryl triflate moiety¹⁸ for the aryne generation participated in the 2,3-disubstituted indole synthesis leaving the reactive functional groups intact. Thus, a wide variety of indoles would be synthesized by *S*-allylation of sulfinate esters, 2,3-difunctionalization of indoles, and further transformations through indolyne intermediates with a number of arynophiles.^{18,19}

In summary, we have developed a facile synthetic method of allyl sulfoxides by *S*-allylation of sulfinate esters through sulfonium intermediates without [3,3]-sigmatropic rearrangement and further Pummerer-type reactions of the resulting allyl sulfoxides. On the basis of the plausible reaction mechanism, *S*-alkynylation and *S*-arylation were also accomplished. Further studies to expand the scope of these transformations using sulfinate esters under the Pummerer-like conditions, chiral sulfoxide synthesis, and the applications to the synthesis of bioactive compounds are now in progress.

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Conflicts of interest

There are no conflicts to declare.



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