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## Introduction

Dearomatization is a powerful strategy that enables the direct conversion of readily available 2-D arenes to value-added 3-D alicyclic architectures in a step-economical manner.<sup>1</sup> The dearomatization protocol has constantly received intensive research interest due to its great potential in the synthesis of natural products and bioactive compounds.<sup>2</sup> Despite considerable advances in this context, the discovery of methods for dearomatizing a new class of arenes is still a useful endeavor.

In the past few decades, *ortho*-C–H functionalization of aryl sulfoxides with certain nucleophiles *via* [3,3]-rearrangement has been validated and significantly progressed (Fig. 1a).<sup>3,4</sup> Until now, an array of nucleophiles including allyl/propargyl silanes,<sup>5,6</sup> carbonyl compounds,<sup>7</sup> phenols,<sup>8</sup> alkyl nitriles<sup>9</sup> and cyclopropanols<sup>10</sup> have been found to be suitable for this process. A noteworthy feature of these reactions is the unique [3,3]-rearrangement that allows for the transient formation of a dearomatization intermediate, which conventionally undergoes a rearomatization to yield rearomatized *ortho*-functionalized aryl sulfide. Based on this reaction pattern, we wondered if blocking the rearomatization of transiently formed dearomatized species could lead to dearomatization products. Interestingly, the dearomatization pathway we envisioned has been previously observed by Proctor and co-workers who showcased an elegant dearomatization of benzothiophene S-

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† Electronic supplementary information (ESI) available: Experimental details and characterization of all new compounds and details of DFT calculations. CCDC compound 5 (1973270) and compound 4s (1973271). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0sc00244e

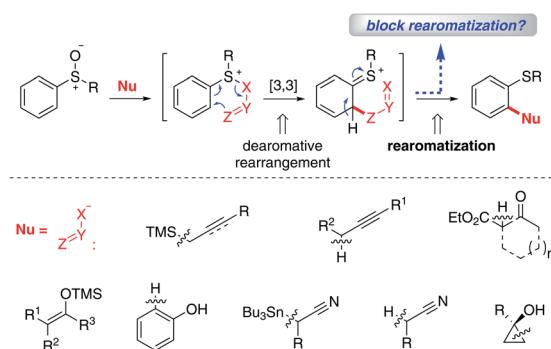
‡ These authors contributed equally to this work.

## Dearomatization of aryl sulfoxides: a switch between mono- and dual-difluoroalkylation†

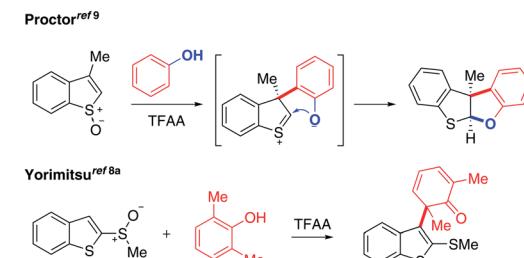
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Herein we describe the dearomatization of aryl sulfoxides with difluoroenol silyl ether (DFESE) using a rearrangement/addition protocol. The selection of the sulfoxide activator determines whether one or two difluoroalkyl groups are incorporated into dearomatized products. Using TFAA can deliberately halt the reaction at the mono-difluoroalkylated dearomatized intermediate formed via a [3,3]-rearrangement, which can be further trapped by external nucleophiles to give mono-difluoroalkylated alicycles. In contrast, switching to  $\text{TiF}_2\text{O}$  enhances the electrophilicity of dearomatized intermediates, thus allowing for the adoption of a second DFESE to produce dual-difluoroalkylated alicycles.

### a) Well developed [3,3]-rearrangement of aryl sulfoxides and our hypothesis



### b) Dearomatization of benzothiophene S-oxides and phenols



### c) This work: a switchable dearomatization of aryl sulfoxides

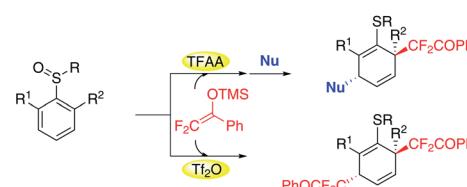


Fig. 1 (a) Well developed [3,3]-rearrangement of aryl sulfoxides and our hypothesis, (b) dearomatization of benzothiophene S-oxides and phenols and (c) this work.



oxides with phenols, in which a methyl group instead of hydrogen was introduced into the  $\beta$ -position for impeding the rearomatization process.<sup>11</sup> As a result, the phenolic oxygen acting intramolecularly as a nucleophile trapped the dearomatized intermediate providing dearomatization products (Fig. 1b). In contrast, Yorimitsu and co-workers demonstrated the possibility of dearomatizing a nucleophilic counterpart such as 2,6-dimethyl- and 2,6-difluoro-phenols with the S(iv)-rearrangement protocol (Fig. 1b).<sup>8a,c</sup> However, to the best of our knowledge, there have been no examples of dearomatization of aryl sulfoxides, which is probably due to the relatively higher resonance energy of arenes than of heteroarenes.<sup>12</sup> Herein we describe the dearomatization of aryl sulfoxides with difluoroenol silyl ether (DFESE) which has been identified as a highly effective rearrangement partner with aryl iodanes owing to the unique effect of fluorine in our recent studies.<sup>13</sup> This protocol allows for the on-demand incorporation of one or two difluoroalkyl groups into dearomatized products by switching electrophilic activators (TFAA vs.  $\text{Tf}_2\text{O}$ ) (Fig. 1c). It is worth noting that the difluoroalkyl group plays critical roles in drug discovery since it can serve as a more-lipophilic isostere of carbinol, thiol, hydroxamic acid, or amide groups.<sup>14,15</sup>

We investigated the model reaction of *ortho*, *ortho*'-dimethyl phenyl sulfoxide **1a** with DFESE **2a** using  $\text{Et}_3\text{SiH}$  as a reductive quencher (Table 1). Gratifyingly, the initial use of TFAA as the activator and MeCN as the solvent afforded mono-difluoroalkylated dearomatization product **3a** in a modest

yield (57%) (entry 1). It is worth mentioning that, in our recent studies, *ortho*, *ortho*'-dimethyl phenyl iodine(III) diacetate was also found to be suitable for a related dearomative rearrangement process.<sup>16</sup> To our surprise, aside from the expected **3a**, the reaction also produced a small amount of dual-difluoroalkylated product **4a** (15%) which showed sufficient nucleophilicity of DFESE not only for the rearrangement with sulfoxide but also for the capture of the in situ-formed dearomatized intermediate. Notably, the reaction is unusually sensitive to the polarity of the solvent since slightly tuning the ratio of the combined solvents could exert a significant influence on the reaction outcome (entries 2–5). Switching to a nonpolar solvent (DCM) could completely inhibit the reaction (entry 2). The use of a 9/1 ratio of MeCN/DCM led to the best yield of **3a** (65%) and showed the highest selectivity for **3a** formation (entry 4). In contrast, slightly tuning the solvent ratio (10/1 and 8/1) dramatically decreased the efficiency of the reaction (entries 3 and 5). Further screening of different activators revealed that the use of  $\text{Tf}_2\text{O}$  as an activator could exclusively afford the dual-difluoroalkylated product **4a** albeit in rather poor yield (17%) (entry 7). To our delight, further optimization of the solvent and reaction temperature led to identification of the best conditions ( $\text{Tf}_2\text{O}$ , DCM,  $-100\text{ }^\circ\text{C}$ , 24 h) for dual-difluoroalkylation (entry 12). To the best of our knowledge, methods for dual-difluoroalkylation have not yet been reported.

With the best conditions in hand, we were curious about the intriguing dearomatized intermediate formed after rearrangement and prior to being trapped by the second nucleophile. Therefore, we attempted to identify the intermediate using *in situ* NMR at low temperature ( $-50\text{ }^\circ\text{C}$ ). To our surprise, the reaction of **1b** with **2a** using TFAA as the activator produced a bicyclic dearomatized intermediate **IM1** with concurrent formation of C–C and C–O bonds (Fig. 2). Interestingly, **IM1** could not only be reduced to the expected dearomatization product **3b**, but could also be hydrolyzed to bicyclic hemiacetal **5**, the structure of which was confirmed by single crystal X-ray structure analysis. It should be noted that we failed to attain the dearomatized intermediate using  $\text{Tf}_2\text{O}$  as the activator. It is likely that the use of such a strong activator could facilitate the further trapping of the dearomatized intermediate, thus directly leading to the dual-difluoroalkylated product.

Table 1 Optimization of reaction conditions<sup>a</sup>

Entry	Activator	Solvent	Temp.	Yield <sup>b</sup> of <b>3a</b> : <b>4a</b>
1	TFAA	MeCN	$-50\text{ }^\circ\text{C}$	57% : 15%
2	TFAA	DCM	$-50\text{ }^\circ\text{C}$	0% : 0%
3	TFAA	MeCN/DCM (10/1)	$-50\text{ }^\circ\text{C}$	50% : 20%
4	TFAA	MeCN/DCM (9/1)	$-50\text{ }^\circ\text{C}$	65% : 5%
5	TFAA	MeCN/DCM (8/1)	$-50\text{ }^\circ\text{C}$	27% : 29%
6	$\text{Ts}_2\text{O}$	MeCN/DCM (9/1)	$-50\text{ }^\circ\text{C}$	0% : trace
7	$\text{Tf}_2\text{O}$	MeCN/DCM (9/1)	$-50\text{ }^\circ\text{C}$	0% : 17%
8	$(\text{ClF}_2\text{CO})_2\text{O}$	MeCN/DCM (9/1)	$-50\text{ }^\circ\text{C}$	61% : 8%
9	$\text{Tf}_2\text{O}$	DCM	$-78\text{ }^\circ\text{C}$	0% : 48% <sup>b</sup>
10	$\text{Tf}_2\text{O}$	MeCN	$-50\text{ }^\circ\text{C}$	0% : 19% <sup>b</sup>
11	$\text{Tf}_2\text{O}$	DCM	$-50\text{ }^\circ\text{C}$	0% : 35% <sup>b</sup>
12	$\text{Tf}_2\text{O}$	DCM	$-100\text{ }^\circ\text{C}$	0% : 73% <sup>b</sup>

<sup>a</sup> Unless otherwise noted, the reaction was performed with **1a** (0.3 mmol), **2a** (1.5 equiv.), activator (1.5 equiv.) and  $\text{Et}_3\text{SiH}$  (3.0 equiv.).

<sup>b</sup> The reaction of **1a** and **2a** (3.0 equiv.) was performed with  $\text{Tf}_2\text{O}$  (1.5 equiv.) at the indicated temperature for 24 h and  $\text{Et}_3\text{SiH}$  was not used herein. For the investigation of other reaction parameters, see the ESI.

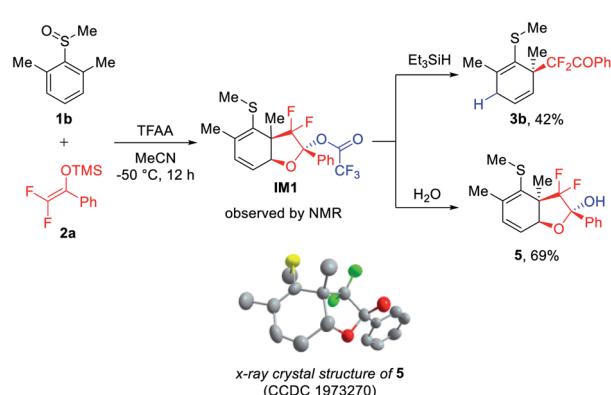


Fig. 2 Identification of dearomatized key intermediate **IM1**.



Table 2 Mono- and dual-difluoroalkylative dearomatization of aryl sulfoxides 1<sup>a</sup>

<sup>a</sup> Unless otherwise noted, the reaction was performed under the optimum conditions (condition A: Table 1, entry 5; condition B: Table 1, entry 13). The relative configurations of 4 were deduced from the X-ray structure of 4s. <sup>b</sup> After Et<sub>3</sub>SiH was added, the reaction mixture was slowly warmed to 0 °C for 1i, 1j, 1q, 1r, and 1s or 20 °C for 1k. <sup>c</sup> After warming to room temperature, 1k and 1u decomposed into complex mixtures.



Next, we examined the generality of both methods under optimum conditions A and B (Table 2). Regardless of the length of alkyl chains on sulfur, both reactions proceeded smoothly to afford mono-difluoroalkylated products **3a–c** and dual-difluoroalkylated products **4a–c** in good yields (entry 1 to 3). Both electron-donating and -withdrawing groups (**1d–l**) at the *para*-position were generally well-tolerated in both reactions except the dual difluoroalkylation of *para*-alkynyl sulfoxide **1k** (entry 7). This unsuccessful case was probably due to the instability of **1k** with the alkynyl group which was found to deteriorate upon the addition of  $\text{Tf}_2\text{O}$ . To our delight, both mono- and dual-difluoroalkylation reactions exhibited excellent functional group compatibility. Functional groups including alkyl/aromatic halides (**1f**, **1l**, **1q**, and **1s**), ethers (**1g** and **1p**), esters (**1h**, **1i**, and **1q–s**), and nitriles (**1j**) proved to be suitable for both reactions. Such functionalities provide a versatile platform for further asymmetric functionalization of the products. Remarkably, highly electrophilic benzyl chloride (**1f**) and  $\alpha,\beta$ -unsaturated esters (**1h** and **1r**) that can be problematic functional groups for conventional cross-coupling reactions were also tolerated herein (entries 3, 4 and 14). Except for **1n** the reaction demonstrated an excellent regioselectivity when using aryl sulfoxides **1o–s** (entries, 10–15). When using stereo-hindered substrate **1o**, mono-difluoroalkylation proceeded smoothly to produce **3o** in a good yield (74%) (entry 11). In contrast, the dual-difluoroalkylation of **1o** merely furnished the expected **4o** in a modest yield (43%). This is likely due to the relatively smaller size of  $\text{Et}_3\text{SiH}$  than of DFESE, which allows the second nucleophile to easily approach the stereo-hindered dearomatization intermediate. In the case of sulfoxide **1t** bearing chloro and methyl groups at the *ortho* positions, the use of different activators was found to be crucial to the regioselectivity of the rearrangement step (entry 16). Using TFAA as the activator exclusively afforded mono-difluoroalkylated product **3t**, whereas the use of  $\text{Tf}_2\text{O}$  resulted in poor regioselectivity yielding a mixture of regioisomers including dearomatized product **4t** and dechlorinated, rearomatization product **4t'**. In addition to aryl sulfoxides, furan sulfoxide **1u** was also suitable for the dual-difluoroalkylation process. However, in the presence of TFAA, **1u** could not afford any desired mono-difluoroalkylated product **3u**. This was probably due to the less electrophilic nature of the relatively electron-rich furan moiety that inhibited the interaction of activated sulfoxide with nucleophiles.

Encouraged by the obtained results in Table 2, we further studied the generality of second nucleophiles for trapping the dearomatized intermediate (Table 3). Gratifyingly, an array of carbon and heteroatom nucleophiles such as allyl silanes, ZnEt<sub>2</sub>, enol silyl ethers, thiophenes, indoles, naphthols, thiophenols, and Ts-NH<sub>2</sub> were suitable for the reaction. As a result, a diverse set of densely functionalized alicyclic compounds **6a-h** were obtained from simple aryl sulfoxide **1a** which can be a challenging synthetic target using known methods. Interestingly, in contrast to aryl sulfoxides, naphthyl sulfoxide **1v** and indole sulfoxide **1w** could be converted to the desulfurated carbonyls **7a** and **7b** through electrophilic rearrangement and simple hydrolysis although they were not suitable for the aforementioned mono- and dual-difluoroalkylative dearomatization reactions (below the dashed line).<sup>17</sup> It is likely that the

Table 3 Mono-difluoroalkylative dearomatization of aryl sulfoxide **1**<sup>a</sup>

		TFAA	Nu	
Nu	product		Nu	product
<chem>CC=C[Si](C)(C)C</chem>			<chem>ZnEt2</chem>	
<chem>CC(=O)[Si](C)(C)OEt</chem>			<chem>MeOc1ccsc1</chem>	
<chem>c1cc2cc[nH]c2[nH]1</chem>			<chem>c1ccccc1O</chem>	
<chem>Clc1ccc(cc1)S</chem>			<chem>TSNH2</chem>	
<chem>O=S(nBu)c1ccccc2c1ccc2c1ccccc1</chem>		<chem>H2O</chem>	<chem>O=S(nBu)c1ccccc2c1ccc2c1ccccc1</chem>	
<chem>O=S(nBu)c1ccccc2c1ccc2c1ccccc1</chem>		<chem>H2O</chem>		

<sup>a</sup> Only one diastereoisomer was obtained in all cases. The relative configurations of **6** were deduced from the X-ray structure of **4s**.

“S(IV)=C” bonds of these dearomatization intermediates formed *via* [3,3]-rearrangement were inert to the aforementioned nucleophiles ( $\text{Et}_3\text{SiH}$  and DFESE) but could be quenched by  $\text{H}_2\text{O}$ . This result also demonstrated the possibility of applying the current protocol for the synthesis of difluoroalkylated cyclohexenones. Unfortunately, the protocol of desulfurizing ketone formation could not be applicable to model sulfoxide **1a**.

Based on the obtained results, a plausible mechanism is shown in Fig. 3. Both TFAA and  $\text{Tf}_2\text{O}$  can activate aryl sulfoxide (**1a** as a representative substrate) to yield highly electrophilic S(iv) species, which can be trapped by DFESE **2a** to provide sulfonium enolates. Subsequent [3,3]-rearrangement of the “S(iv)–O<sup>TMS</sup>” linked enolates affords *ortho*-difluoroalkylated

dearomatization S(n) intermediates that readily undergo intramolecular addition to form bicyclic intermediates **IM1** and **IM2**. The different leaving groups such as  $\text{OCOCF}_3$  and  $\text{OTf}$  anchored on **IM1** and **IM2** provide these intermediates with different electrophilicity. As a result, **IM1** could be halted and characterized by NMR analysis and be trapped by different types of nucleophiles as demonstrated in Table 3. In contrast, due to its relatively high electrophilicity, **IM2** is easily captured by the second DFESE **2a** to furnish dual difluoroalkylated product **4a**. As depicted in Fig. 3, the regioselectivity for introducing the second nucleophile into the 5-positions could be attributable to the stereo hindrance of the *ortho*-quaternary carbon of **IM1** and **IM2**. The stereoselective formation of *trans*-cyclohexadiene products is probably due to the furan moieties of **IM1** and **IM2** that block one face of these intermediates. The outcome of this stereochemistry may also be understood *via* analysis of the X-ray crystal structure of **5** given in Fig. 2.

Encouraged by the success of DFESE **2a**, we also examined other DFESEs by replacing the Ph group of **2a** with *n*-Bu, OEt, and  $\text{CF}_3$  (Fig. 3, below the dashed line). Unfortunately, all these DFESEs (**2b**–**2d**) were found to be unsuitable for the two dearomatization processes.

To our delight, both dearomatization reactions on the gram-scale could produce the desired products in good yields which demonstrated the practicality of these protocols (Fig. 4). Inspired by the progress of sulfoxide mediated rearrangements,<sup>3</sup> we attempted to apply the rearrangement protocol for further elaboration of the dearomatization product **3a**. As illustrated in Fig. 4, after oxidation by *m*-CPBA, **3a** could undergo a second rearrangement with nucleophiles such as DFESE and  $\alpha$ -stannyl nitrile to produce highly substituted cyclohexenones **8a** and **8b** after desulfurization hydrolysis.<sup>17</sup> Notably, the relative configuration of **8b** was assigned according to NOE studies (for details, see the ESI<sup>†</sup>).

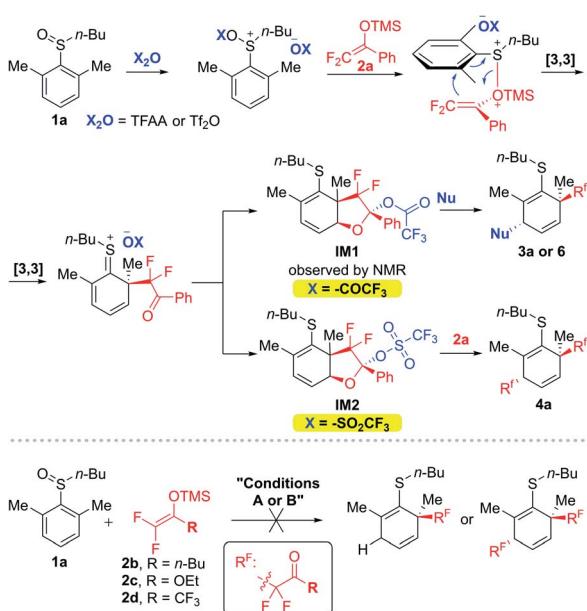


Fig. 3 Proposed mechanism and examination of difluoroenol silyl ethers **2b**–**2d**.

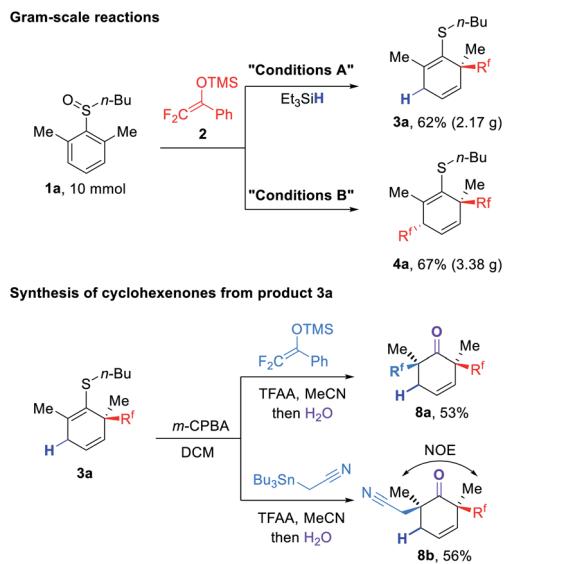


Fig. 4 Gram-scale reactions and conversion of **3a** to highly substituted difluoroalkylated cyclohexenones.

## Conclusions

In summary, we have developed the dearomatic difluoroalkylation of aryl sulfoxides. Through the choice of appropriate sulfoxide activators ( $\text{Tf}_2\text{O}$  or TFAA), one or two difluoroalkyl groups according to the demand could be incorporated into the dearomatized products. The use of TFAA as the activator allowed determination of the structure of the key dearomatized intermediate **IM1**, which was elucidated to be a bicyclic dearomatized sulfide. Remarkably, both the mono- and dual-difluoroalkylation processes exhibited excellent functional group compatibility and excellent regioselectivity for asymmetric aryl sulfoxides. In addition to  $\text{Et}_3\text{SiH}$  and DFESE, other carbon and heteroatom nucleophiles were also suitable for capturing the dearomatized difluoroalkylated intermediate. In brief, this study showcases the possibility of conducting the dearomatic rearrangement in a very controlled manner which allows for the on-demand synthesis of a diverse array of valuable highly substituted alicycles from readily available aryl sulfoxides.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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