

# Organocatalytic synthesis of $\delta$ -sultone-fused benzofurans by the tandem reaction of $\beta$ -arylethenesulfonyl fluorides

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**Abstract:** An organocatalytic annulative sulfur(VI)-fluoride exchange (SuFEx) reaction of  $\beta$ -arylethenesulfonyl fluorides has been reported. Under the catalysis of 10 mmol% BTMG and molecular sieves 4Å,  $\beta$ -arylethenesulfonyl fluorides undergo Michael addition-intramolecular SuFEx click reaction with benzofuran-3(2*H*)-ones to give  $\delta$ -sultone-fused benzofurans in 76-99% yield. Using 10 mmol% DBU and molecular sieves 4Å,  $\beta$ -arylethenesulfonyl fluorides coupled with oxindoles to produce  $\delta$ -sultone-fused indoles in 81-85% yield. In these reactions, molecular sieves 4Å act as efficient HF scavenger, which avoid the using of stoichiometric silicon additives and bases. Importantly, density functional theory (DFT) calculations reveal that Michael addition is a decisive speed step for the reaction.

## Introduction:

Benzofurans and  $\delta$ -sultones are two important class of structural motifs present in many natural products, biologically active compounds,

pharmaceutical molecules and functional materials.<sup>1</sup> Due to the remarkable significance of these heterocycles, their synthetic methods have been attracted substantial attention. In the past decade, transition-metal catalyzed intramolecular cyclization of *o*-alkynyl phenols<sup>2</sup> have been extensively studied for the synthesis of benzofurans and their derivatives. In addition, photoinduced cyclization reactions,<sup>3</sup> C-H bond activation<sup>4</sup> and other methods<sup>5</sup> have also been developed for the construction of benzofurans derivatives.

On the other hand, different protocols for the synthesis of sultones have been established.<sup>6</sup> However, to the best of our knowledge, no catalytic method for the assembly of  $\delta$ -sultone-fused benzofurans has been reported<sup>7</sup>. Giving the pharmacological importance of both benzofurans and  $\delta$ -sultones, the development of efficient method for the construction of the  $\delta$ -sultone fused benzofurans will be highly interesting to drug discovery and medicinal chemistry.

Sulfur(VI) fluorides exchange (SuFEx) click chemistry<sup>8</sup> that developed by Sharpless and coworkers has been established as a powerful and robust strategy for modular assembly of different sulfonyl-containing molecules. Interestingly, as one important type of SuFExable hub,  $\beta$ -arylethenesulfonyl fluorides can be used as dienophiles to undergo annulative SuFEx reactions. Lupton and coworkers reported<sup>9</sup> an *N*-heterocyclic carbene catalyzed [3+3] annulation of  $\beta$ -arylethenesulfonyl

fluorides with trimethylsilyl enol ethers of 1,3-dicarbonyl compounds, which provided a novel organocatalytic method for the synthesis of  $\delta$ -sultones. Later, Mayr and coworkers reported<sup>10</sup> that using excess of triethylamine,  $\beta$ -arylethenesulfonyl fluorides can react with dimedone to produce  $\delta$ -sultone-fused cyclic enones. Recently, Qin and coworkers documented<sup>11</sup> an interesting DBU-catalyzed annulative SuFEx reaction of  $\beta$ -arylethenesulfonyl fluorides and pyrazolones for the synthesis of  $\delta$ -sultone fused pyrazoles. These fused heterocycles showed very interesting cholinesterase inhibitory activity and several products can be used as effective BuchE inhibitors.<sup>12</sup> Using the similar strategy, the same group also reported a novel method for the synthesis of  $\delta$ -sultone functionalized pyridines.<sup>13</sup> Despite the progress made in this research field, the study of catalytic synthesis of  $\delta$ -sultone fused heterocycles is still very limited. Very recently, we found that the combination of catalytic amount of organic superbase and molecular sieves 4Å can efficiently catalyze SuFEx reactions of different SuFExable hubs.<sup>14</sup>

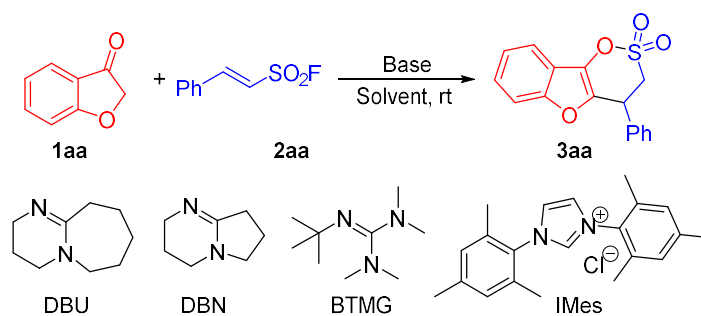
We also found that this catalytic method can be used for the synthesis of functionalized  $\delta$ -sultones and  $\delta$ -sultone-fused heterocycles.<sup>14</sup> In these reactions, molecular sieves 4Å was used as efficient HF scavenger instead of stoichiometric silicon additives and excess of bases. In line with our continuous study on SuFEx reactions, we proposed that  $\beta$ -arylethenesulfonyl fluorides could undergo annulative SuFEx reaction

with benzofuran-3(2*H*)-ones to form  $\delta$ -sultone-fused benzofurans. Herein, we wish to report our results.

We began our study with the readily available benzofuran-3(2*H*)-ones **1a** and  $\beta$ -phenylethenesulfonyl fluorides **2a** as the model substrates (**Table 1**). To our delight, in the presence of 0.5 equivalent of Cs<sub>2</sub>CO<sub>3</sub>, the annulation reaction proceeded smoothly in acetonitrile at room temperature to afford the desired  $\delta$ -sultone fused benzofuran **3a** in 81% yield (**Table 1**, entry 1). Increasing the loading of Cs<sub>2</sub>CO<sub>3</sub> to 1.0 equivalent, the yield of **3a** was increased to 92% yield (**Table 1**, entry 2). Further increasing the amount of Cs<sub>2</sub>CO<sub>3</sub> cannot give a better yield (**Table 1**, entries 3 and 4). The strong basic sodium hydroxide mediated the reaction in 80% yield (**Table 1**, entry 5). Owing to the lowered basicity, Na<sub>2</sub>CO<sub>3</sub> mediated the reaction in low yield (**Table 1**, entry 6). Organic bases such as triethylamine, DBU (1,8-Diazabicyclo[5.4.0]undec-7-ene), DBN (1,5-Diazabicyclo[4.3.0]non-5-ene) and KO<sup>t</sup>Bu mediated the tandem reaction in moderate yields (**Table 1**, entries 7 to 10). The brief evaluation of reaction media showed that THF and DMSO gave the desired product in high yield (**Table 1**, entries 11 and 12), while dichloromethane, toluene, 1,4-dioxane and ethyl acetate showed slightly decreased efficiency (**Table 1**, entries 13 to 16). When the reaction was performed in methanol, only 25% yield of **3a** was obtained (**Table 1**, entry 17). Increasing the amount of **2a** to 1.5 equivalent, **3a** was formed in quantitative yield (**Table 1**, entry 18). Pleasingly, when the combination of

20 mol% DBU and molecular sieves 4Å was used instead of stoichiometric base, the desired  $\delta$ -sultone fused benzofuran can also be obtained in 87% yield (**Table 1**, entry 19). Encouraged by this success, other bases were than screened for the reaction. Triethylamine catalyzed the reaction in moderate yield (**Table 1**, entry 20). The strong organic superbase BTMG (2-tert-butyl-1,1,3,3-tetramethyl-guanidine) catalyzed the reaction in 95% yield (**Table 1**, entry 21). *N*-heterocyclic carbene, which showed high reactivity in SuFEx reactions, catalyzed the tandem cyclization in 85% yield (**Table 1**, entry 22). Interestingly, the combination of 10 mol% Cs<sub>2</sub>CO<sub>3</sub> and molecular sieves 4Å can also catalyzed the reaction in 78% yield (**Table 1**, entry 23).

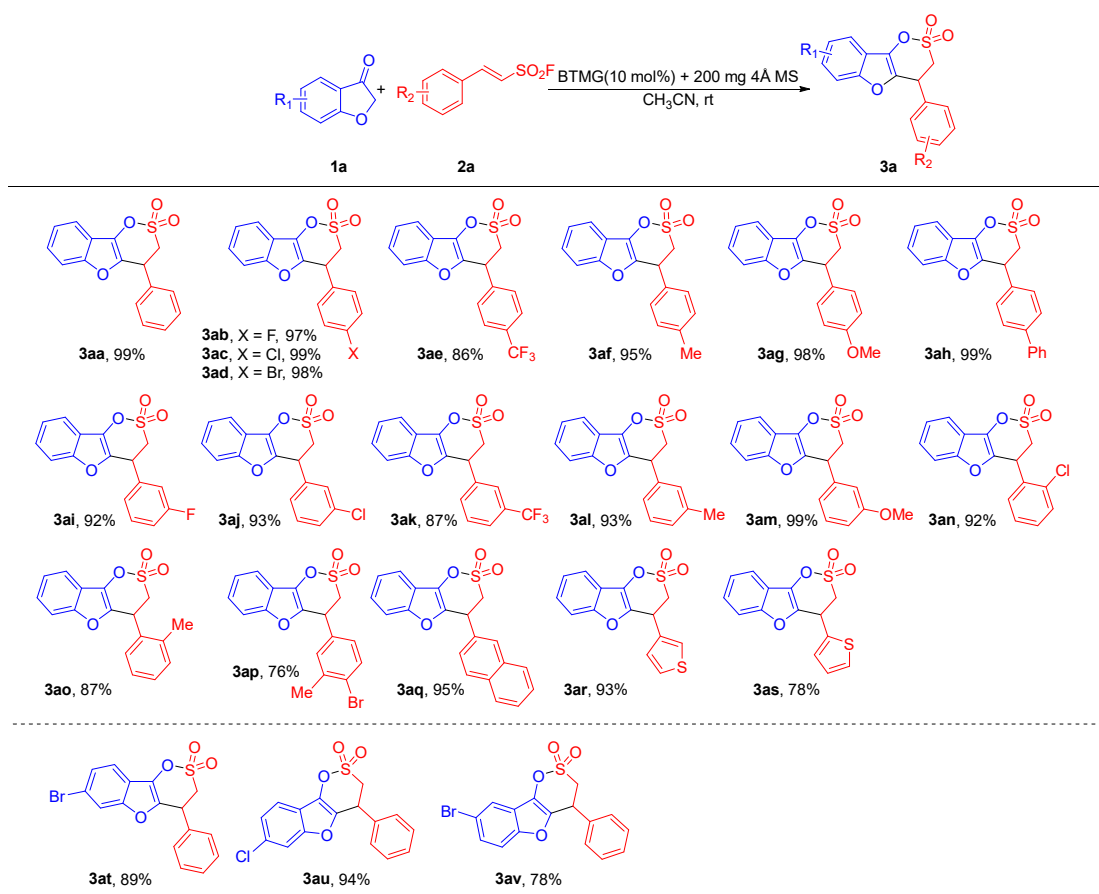
With the optimized reaction conditions in hand, we next studied the substrates scope. As shown in **Table 2**, both electron-withdrawing and -donating substituents substituted  $\beta$ -arylethenesulfonyl fluorides reacted with benzofuran-3(2*H*)-one **1a** smoothly to furnish the corresponding  $\delta$ -sultone fused benzofurans in high yields (**3aa-3ah**). Different positions of the substituents have no apparent impact on the reaction yields (**3ai-3ap**).  $\alpha$ -Naphthyl substituted ethenesulfonyl fluorides participated in the tandem reaction to produce the corresponding products in excellent yields **3aq**. Heteroaryl substituted ethenesulfonyl fluorides performed well to afford **3ar** and **3as** in 93% and 78% yield, respectively. On the other hand, different substituted benzofuran-3(2*H*)-ones were proved to be suitable

**Table 1 Optimization of Reaction Conditions <sup>a</sup>**

entry	base	<b>1a</b> : <b>2a</b>	solvent	<b>3a</b> yield <sup>b</sup> (%)
1	Cs <sub>2</sub> CO <sub>3</sub> (0.5 eq)	1:1	MeCN	81
2	Cs <sub>2</sub> CO <sub>3</sub> (1.0 eq)	1:1	MeCN	92
3	Cs <sub>2</sub> CO <sub>3</sub> (1.5 eq)	1:1	MeCN	88
4	Cs <sub>2</sub> CO <sub>3</sub> (2.0 eq)	1:1	MeCN	70
5	NaOH(1.0 eq)	1:1	MeCN	80
6	Na <sub>2</sub> CO <sub>3</sub> (1.0 eq)	1:1	MeCN	32
7	Et <sub>3</sub> N(1.0 eq)	1:1	MeCN	57
8	DBU(1.0 eq)	1:1	MeCN	46
9	DBN(1.0 eq)	1:1	MeCN	63
10	KO <sup>t</sup> Bu(1.0 eq)	1:1	MeCN	60
11	Cs <sub>2</sub> CO <sub>3</sub> (1.0 eq)	1:1	THF	87
12	Cs <sub>2</sub> CO <sub>3</sub> (1.0 eq)	1:1	DMSO	87
13	Cs <sub>2</sub> CO <sub>3</sub> (1.0 eq)	1:1	DCM	65
14	Cs <sub>2</sub> CO <sub>3</sub> (1.0 eq)	1:1	Toluene	62
15	Cs <sub>2</sub> CO <sub>3</sub> (1.0 eq)	1:1	1,4-Dioxane	69
16	Cs <sub>2</sub> CO <sub>3</sub> (1.0 eq)	1:1	EA	77
17	Cs <sub>2</sub> CO <sub>3</sub> (1.0 eq)	1:1	MeOH	25
18	Cs <sub>2</sub> CO <sub>3</sub> (1.0 eq)	1:1.5	MeCN	99
19 <sup>c</sup>	DBU(0.2 eq) + 4Å MS	1:1.5	MeCN	87
20 <sup>c</sup>	Et <sub>3</sub> N(0.2 eq) + 4Å MS	1:1.5	MeCN	42
21 <sup>c</sup>	BTMG(0.1 eq) + 4Å MS	1:1.5	MeCN	95
22 <sup>c</sup>	IMeS(0.1 eq) + 4Å MS	1:1.5	MeCN	85
23 <sup>c</sup>	Cs <sub>2</sub> CO <sub>3</sub> (0.1 eq) + 4Å MS	1:1.5	MeCN	78

<sup>a</sup> Reaction conditions: **1a** (0.20 mmol), **2a** (0.30 mmol), solvent 2.0 mL, rt, under air, 6 hours. <sup>b</sup> Isolated yields. <sup>c</sup> 200 mg 4Å MS was used.

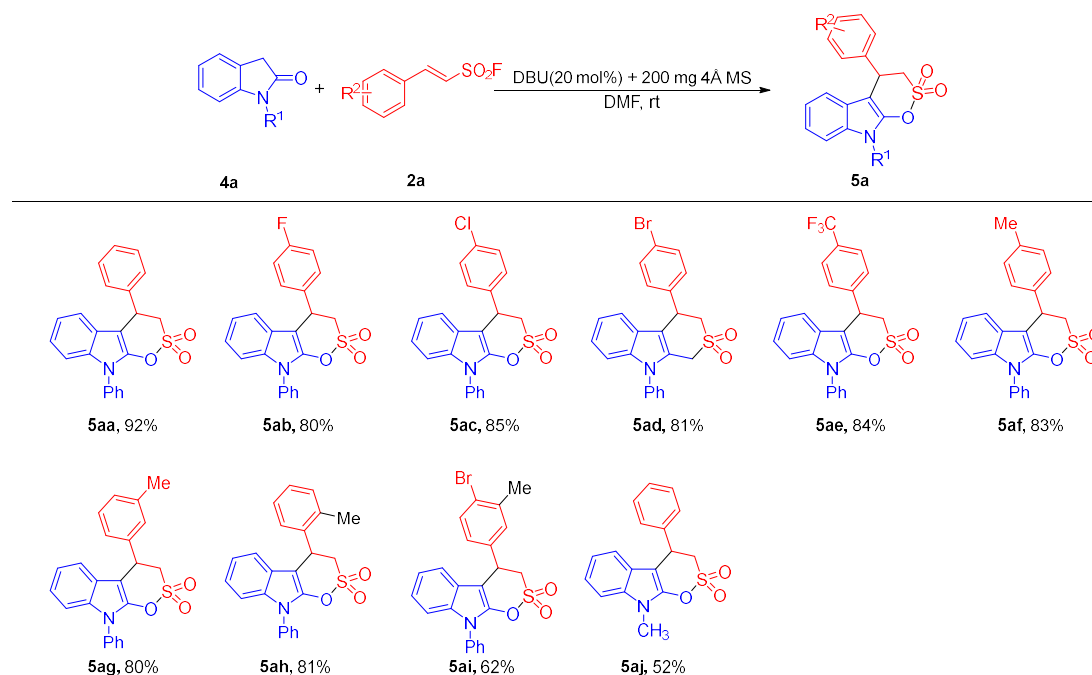
reactants for the reaction, giving the corresponding products in high yields (**3at-3av**).

**Table 2 Evaluation of substrate scope**<sup>a</sup>

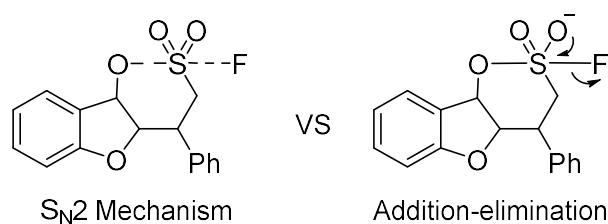
To further demonstrate the application of this catalytic method, the analogous tandem cyclization of oxindoles and  $\beta$ -arylethenesulfonyl fluorides was next examined. Interestingly, under standard reaction conditions,  $\delta$ -sultone fused indole **5a** was formed in 66% yield. Switching the solvent to DMF, the yield was improved to 92%. Under this modified reaction conditions, we then investigated the substrate scope of this tandem annulation reaction. As shown in Table 4. Oxindole **4a** reacted with different substituted  $\beta$ -arylethenesulfonyl fluorides to provide the corresponding  $\delta$ -sultone fused indoles in high yield (**5aa-5ai**). *N*-methyl

substituted oxindole **4j** reacted with **2a** to afford **5aj** in 52% yield.

**Table 3 Evaluation of substruct scope <sup>a</sup>**



The SuFEx reaction mechanism proceeds via an  $S_N2$  or addition-elimination mechanism<sup>15</sup>. To further distinguish concerted  $S_N2$  and addition-elimination reaction paths, we computed the potential energy surfaces (PES) for the tandem reaction between benzofuran-3(2*H*)-ones **1a** and  $\beta$ -phenylethanesulfonyl fluorides **2a** (Scheme 1).

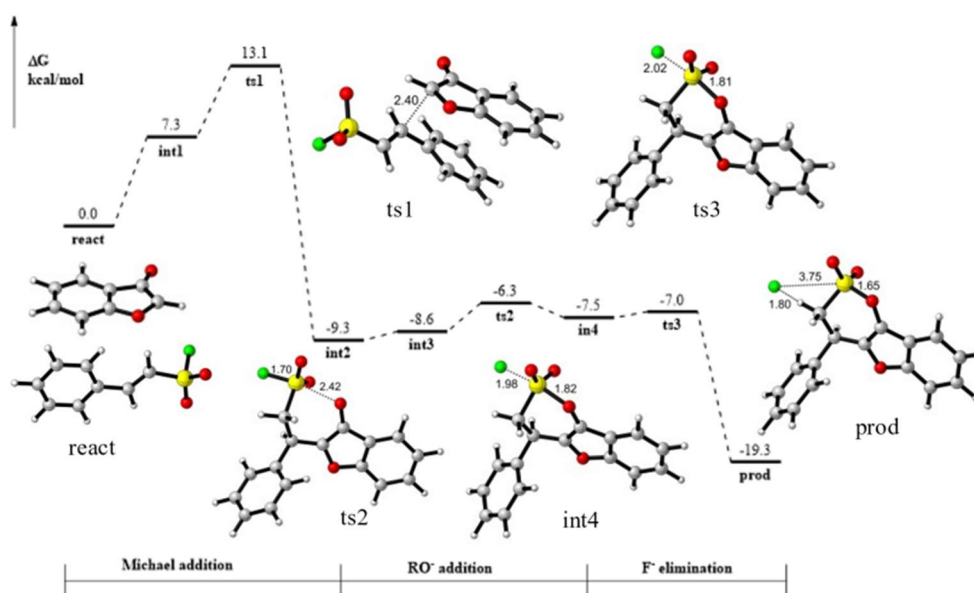


**Figure 1** The  $S_N2$  or addition-elimination mechanism

Firstly, benzofuran-3(2*H*)-ones **1aa** are stripped of proton by base to generate **I**, the tautomerization of **I** will give enolate intermediate **I'**. Substrate **2aa** undergoes nucleophilic attack by 2,3-dihydrobenzofuran-3-



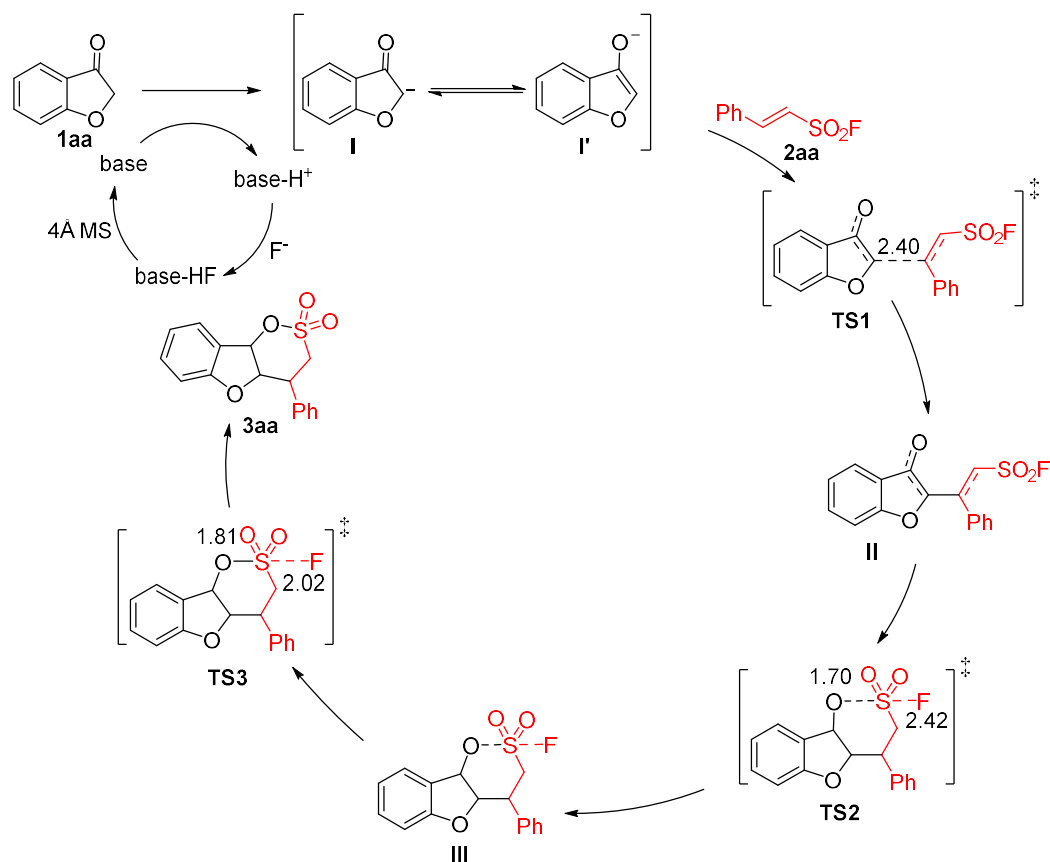
olate **I'** via **TS1**, with a rate-limiting Gibbs free barrier of 13.1 kcal • mol<sup>-1</sup>. The **int2** undergoes hydrogen transfer and conformation transformation to generate **int3** with a barrier of 0.7 kcal • mol<sup>-1</sup>. The **int3** undergoes nucleophilic attack by oxyanion via **TS2**, with a rate-limiting enthalpic barrier of 2.3 kcal • mol<sup>-1</sup>. In **TS2** the S-F bond was still largely unchanged (length increase from 1.65 to 1.70). However, the next stationary point was not the set of product, but a five-coordinated sulfur intermediate **int4**, which was found to be lower in energy than the reactant pair. This intermediate readily loses F<sup>-</sup> via **TS3**, this step Gibbs free barrier is only 0.5 kcal • mol<sup>-1</sup> to give the product. In summary, these DFT calculations suggest that these SuFEx reactions proceed via an addition-elimination mechanism.



**Scheme 1.** Potential energy surface for tandem reaction.

Based on our previous studies and literature report, a plausible

mechanism of the reaction is depicted in **Figure 2**. Base attacks the acidic proton of benzofuran-3(2*H*)-one to form species **I**, which undergoes Michael addition with  $\beta$ -arylethanesulfonyl fluorides to produce intermediate **II**. Base catalyzed enolization of intermediate **II** generates intermediate **III**, which undergoes intramolecular SuFEx click reaction to produce  $\delta$ -sultone-fused benzofuran.



**Figure 2** Mechanistic proposal.

In conclusion, we developed a method to construct sulfonate esters through a tandem reaction of Michael addition-click reaction and studied the reaction pathways. DFT calculations show that Michael addition is the rate-determining step of the reaction.

## Methods

### 1. Experimental methods

#### 1.1 General procedure for the synthesis of $\delta$ -sultone (**3aa**).

A 10 mL reaction tube equipped with a stir bar was charged with benzofuran-3(2H)-ones **1aa** (0.20 mmol), 2-phenylethene-1-sulfonyl fluoride **2aa** (0.30 mmol), BTMG (0.02 mmol) and molecular sieves 4Å (200 mg), MeCN (2 mL) were added in turn to the reaction tube. The reaction mixture was stirred at room temperature for 6 h. When the reaction was finished (monitored by TLC), the crude products were purified by column chromatography (Petroleum ether / ethyl acetate = 30 : 1 (v / v) ) on silica gel to give the desired product **3aa** (White solid, 99%, 59.4 mg).

#### 1.2 General procedure for the synthesis of $\delta$ -sultone (**5aa**).

A 10 mL reaction tube equipped with a stir bar was charged with 1-phenylindolin-2-one **4aa** (0.20 mmol), 2-phenylethene-1-sulfonyl fluoride **2aa** (0.30 mmol), DBU (0.04 mmol) and molecular sieves 4Å (200 mg), DMF (2 mL) were added in turn to the reaction tube. The reaction mixture was stirred at room temperature for 2 h. When the reaction was finished (monitored by TLC), the reaction mixture was poured into water (30 mL), extracted with ethyl acetate (3 × 25 mL). The combined organic layers were then washed with water (3 × 25 mL) and dried over anhydrous sodium sulfate. The crude products were purified by column chromatography (Petroleum ether / ethyl acetate = 30 : 1 (v / v) ) on silica gel to give the

desired product **5aa** (White solid, 92%, 69.0 mg).

## 2. Computational details

All theoretical calculations were performed with Gaussian 16<sup>16</sup>. All structures were completely optimized by using the M062X-D3<sup>17</sup> method and the 6-311+G(d, p) basis set in solvent of MeCN, which employs the integral equation formalism polarizable continuum model (SMD)<sup>18</sup>. Frequency calculations were carried out at the same level to confirm all the optimized structures as minima (no imaginary frequency) or transition states (only one imaginary frequency), and provided the thermal relative Gibbs free energy correction. The single-point energies (SPE) by using a higher computational level of the M062X-D3 method and the ma-def2-TZVPP basis set in solvent of MeCN. All thermodynamic data were corrected by Shermo<sup>19</sup> software at 298.15 K, 1.0 atm. Images of the 3D structures of molecules were generated using CYLview<sup>20</sup>.

## Conflicts of interest

The authors declare no competing financial interest.

## Acknowledgements

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## Graphical abstract

