Synthesis of γ-alkenylated δ-sultones via Brønsted base-catalyzed Michael addition-SuFEx click reaction of allyl ketones and ethenesulfonyl fluorides

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Abstract: A tandem annulation reaction of allyl ketones and ethenesulfonyl fluoride has been described. Under the catalysis of Brønsted base, vinyl ketones reacted with ethenesulfonyl fluoride through a cascade intermolecular Michael addition-intramolecular SuFEx process to afford γ-alkenylated δ-sultones in good to excellent reaction yields. In this reaction, no additional base was needed, and 4 Å Molecular sieves was used as efficient HF scavenger to restrict the neutralization and deactivation of the Brønsted base catalyst.

Introduction:

As the sulfur analogous of lactones, sultones are an important class of sulfur heterocycles that used widely in the synthesis of natural products, pharmaceuticals, biologically active molecules and advanced functional

materials[1]. Due to the remarkable synthesis importance, considerable efforts have been exerted to develop efficient methods for the synthesis of these valuable building blocks. Over the past decade, transition-metal catalyzed C-H insertion reactions[2], cycloaddition reactions[3], radical reactions[4] and metathesis reactions[5] have been developed for the construction of sultones. Recently, Lupton[6] and Qin[7] developed a tandem annulation reaction of easily tautomerizable ketones (or their TMS enol ethers) and ethenesulfonyl fluorides, which provide a novel protocol for the synthesis of δ-sultones. Despite these important progress, development of efficient and mild method for the construction of different functionalized δ-sultones is still highly significant.

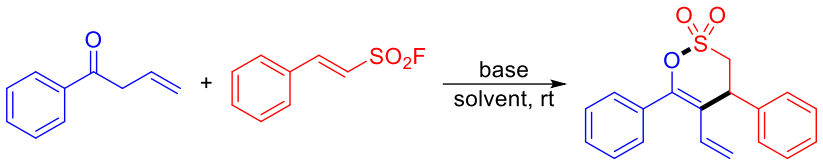
On the other hand, allyl ketones are another type of synthetically valuable reagents that used widely in organic synthesis. Owing to the steric effect, these deconjugated carbonyls usually serve as vinylogous nucleophiles to undergo aldol reactions or Michael additions at γ-position selectively[8]. In addition, the terminal carbon-carbon double bond of allyl ketones can also participate in Diels-Alder cyclization to form heterocycles[9]. During our research on SuFEx click reactions[10], we found that allyl ketones do not undergo the anticipated γ-selective Michael addition with the active ethenesulfonyl fluoride. Interestingly, an unexpected α-selective Michael addition-SuFEx cyclization reaction performed to produce γ-alkenylated δ-sultones efficiently. Herein, we

would like to report this result.

Results and Discussion：

Initially, the reaction of phenyl allyl ketone **1a** and β-phenyl-substituted ethenesulfonyl fluoride **2a** was examined. In the presence of 20 mol% DBU, γ-ethenylated δ-sultone **3a** was obtained in 48% yield in DMSO at room temperature (Table 1, entry 1). We concluded HF generated in the reaction neutralized DBU and thus quenched the reaction. Increasing the amount of DBU to 1.0 equivalent, the yield of **3a** was improved to 60% (Table 1, entry 2). However, triethylamine and DIPEA promoted the reaction in low efficiently (Table 1, entries 3 and 4). Pleasingly, Inorganic bases such as Na_2CO_3, K_2CO_3, Cs_2CO_3 and $NaHCO_3$ mediated the reaction in high yields (Table 1, entries 5-8). Further study showed that the combination of catalytic amount of DBU and stoichiometric amount of inorganic base can promote the reaction to afford the desired product in excellent yield (Table 1, entries 9 and 10). Interestingly, when 4 Å Molecular sieves was used instead of inorganic bases, DBU can also catalyze the tandem reaction in 96% yield (Table 1, entries 11-13). A brief screening of the reaction solvent showed that high polar solvents such as DMSO, DMF and acetonitrile give the desired product in high yield (Table 1, entries 12, 14 and 15), while DCM, THF, ethyl acetate showed low efficiency (Table 1, entries 16-18). Finally, control experiment showed that in the absence of DBU, no desired product was formed (Table 1, entry 19).

Table 1 Optimization of Reaction Conditions [a]



1a 2a 3a

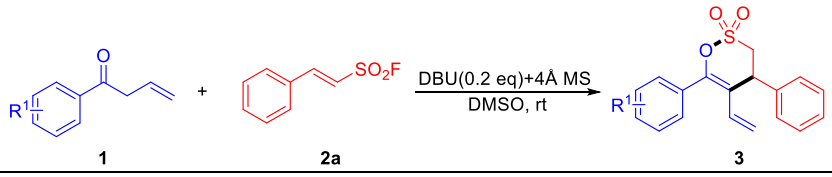
entry	base	solvent	yield (%) [b]
1	DBU (0.2 eq)	DMSO	48
2	DBU (1.0 eq)	DMSO	60
3	Et_3N (1.0 eq)	DMSO	18
4	DIPEA (1.0 eq)	DMSO	31
5	Na_2CO_3 (1.0 eq)	DMSO	82
6	K_2CO_3 (1.0 eq)	DMSO	80
7	Cs_2CO_3 (1.0 eq)	DMSO	83
8	$NaHCO_3$ (1.0 eq)	DMSO	85
9	DBU (0.2 eq) + $NaHCO_3$ (1.0 eq)	DMSO	99
10	DBU (0.2 eq) + Na_2CO_3 (1.0 eq)	DMSO	98
11 [c]	DBU (0.2 eq) + 4 Å MS	DMSO	85
12 [d]	DBU (0.2 eq) + 4 Å MS	DMSO	96
13 [e]	DBU (0.2 eq) + 4 Å MS	DMSO	90
14 [d]	DBU (0.2 eq) + 4 Å MS	DMF	89
15 [d]	DBU (0.2 eq) + 4 Å MS	CH_3CN	77
16 [d]	DBU (0.2 eq) + 4 Å MS	DCM	44
17 [d]	DBU (0.2 eq) + 4 Å MS	THF	19
18 [d]	DBU (0.2 eq) + 4 Å MS	EtOAc	< 10
19	none	DMSO	< 10

[a] Reaction conditions: **1a** (0.20 mmol), **2a** (0.20 mmol), solvent 2.0 mL, rt, under air, 2 hours. [b] Isolated yields. [c] 100 mg 4 Å MS was used. [d] 200 mg 4 Å MS was used. [e] 300 mg 4 Å MS was used.

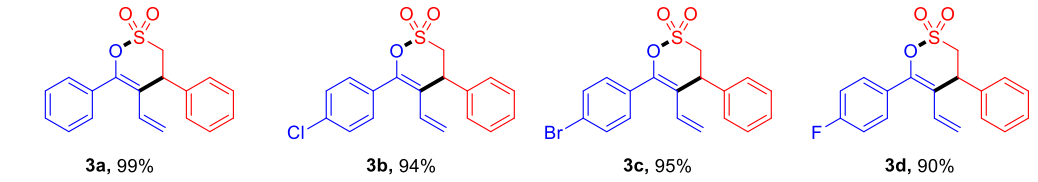
Having evaluated the optimal reaction conditions, we then investigated the substrate scope of this tandem annulation reaction. As shown in Table 2, both electron-withdrawing and electron-donating substituents substituted aryl allyl ketones participated in the reaction efficiently, producing the corresponding δ-sultones in high yields (**3a**-**3f**). However, very strong electron-withdrawing cyanide group substituted allyl ketone

only gave the desired product in moderate yield (**3g**). Different positions of the substituents have no obvious effect on the reaction yield (**3h-3k**). Bulkyl naphthyl substituted allyl ketones underwent the reaction to produce the corresponding δ-sultones in high yield (**3l** and **3m**). Heteroaryl substituted allyl ketones coupled with **2a** to furnish the desired ethenylated δ-sultones in good yields (**3a-3o**). β-Alkyl substituted vinyl ketones were also proved to be competent reactants for the reaction, providing the corresponding δ-sultones **3p** and **3q** in 63% and 87% yield, respectively.

Table 2 Scope of phenyl allyl ketones [a]



1 **2a** **3**

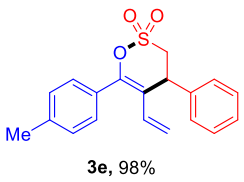


3a, 99%

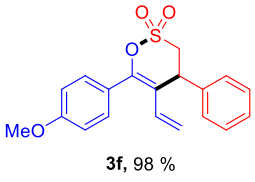
3b, 94%

3c, 95%

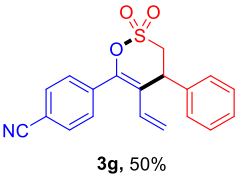
3d, 90%



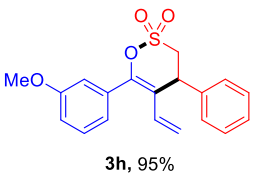
3e, 98%



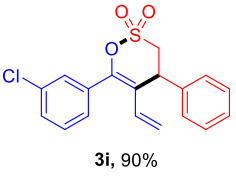
3f, 98 %



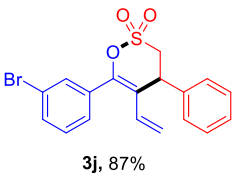
3g, 50%



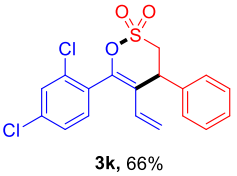
3h, 95%



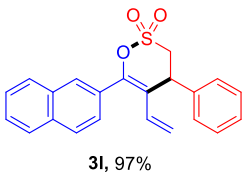
3i, 90%



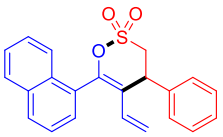
3j, 87%



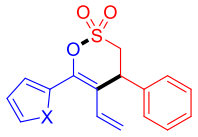
3k, 66%



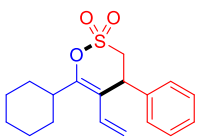
3l, 97%



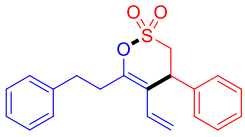
3m, 72%



X = S, **3n**, 62%
X = O, **3o**, 55%



3p, 63%



3q, 87%

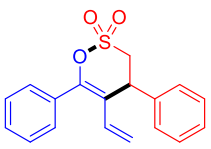
[a] Reaction conditions: **1** (0.20 mmol), **2a** (0.20 mmol), DBU (0.2 eq), 4

Å MS (200 mg), DMSO 2.0 mL, rt, under air, 2 hours; isolated yield.

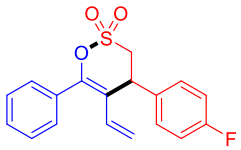
We next explored the scope of ethenesulfonyl fluorides and the results are summarized in Table 3. A variety of electron-withdrawing, -neutral and -donating substituents substituted β-aryl ethenesulfonyl fluorides smoothly underwent the tandem reaction to produce the corresponding products in high yields (**3r**-**3ab**). In addition, varied positions of the substituents can be well tolerated for the reaction (**3ac**-**3an**). However, when phenolic hydroxy group substituted ethenesulfonyl fluoride was used to react with allyl ketone **1a**, the reaction was complex and no desired product was obtained (**3ao**). We assumed that the phenolic hydroxy group can undergo SuFEx click reaction or other side reactions, which restricted the desired tandem annulation reaction. In contrast, when the phenolic hydroxy group was protected with -SO_2F group, the desired product was obtained in 84% yield (**3aa**). Naphthyl-substituted ethenesulfonyl fluorides were suitable reactants for the reaction, affording the corresponding sultones in excellent yields (**3ap** and **3aq**). Heteroaryl substituted ethenesulfonyl fluorides can also undergo this reaction, albeit with relatively low yields (**3ar**-**3at**). The reaction involving ESF only gives 38% yield (**3au**). The structure of **3ab** and **3au** were determined via X-Ray crystallographic analysis.[11]

Table 3 Scope of β-phenyl-substituted ethenesulfonyl fluorides [a]

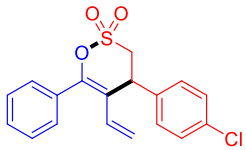
1 2 3



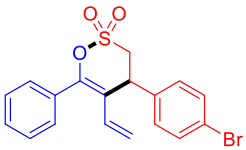
3a, 99%



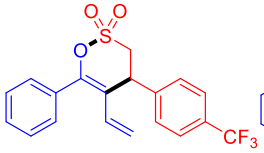
3r, 92%



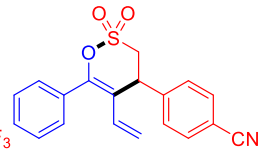
3s, 99%



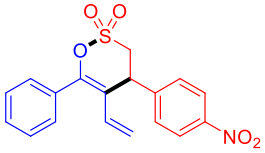
3t, 90%



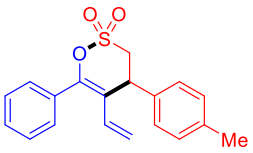
3u, 82%



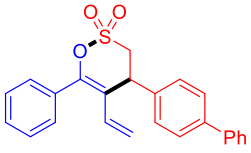
3v, 83%



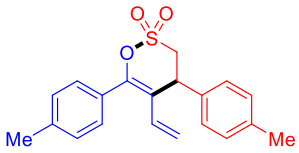
3w, 58%



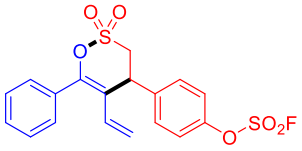
3x, 94%



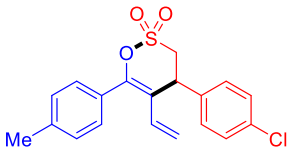
3y, 93%



3z, 95%

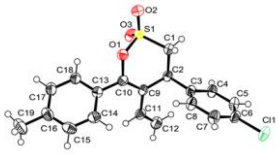


3aa, 84%



3ab, 98%

≡



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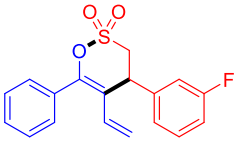
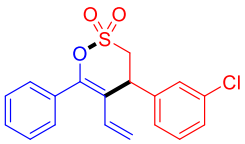
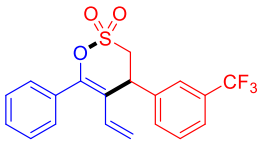


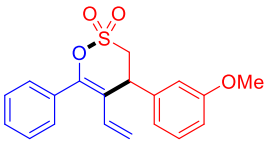
3ac, 95%



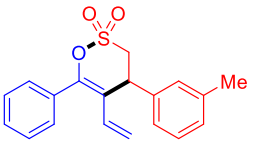
3ad, 94%



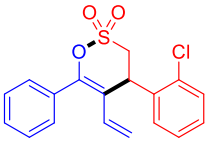
3ae, 85%



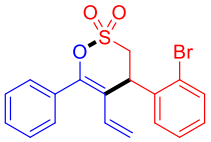
3af, 90%



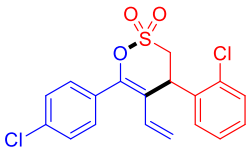
3ag, 99%



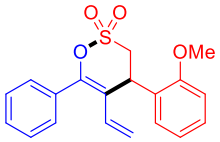
3ah, 83%



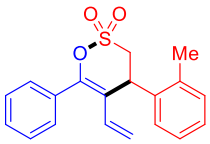
3ai, 75%



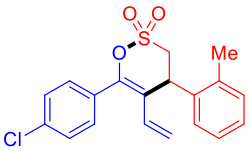
3aj, 95%



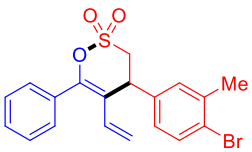
3ak, 89%



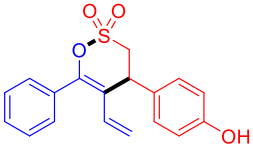
3al, 78%



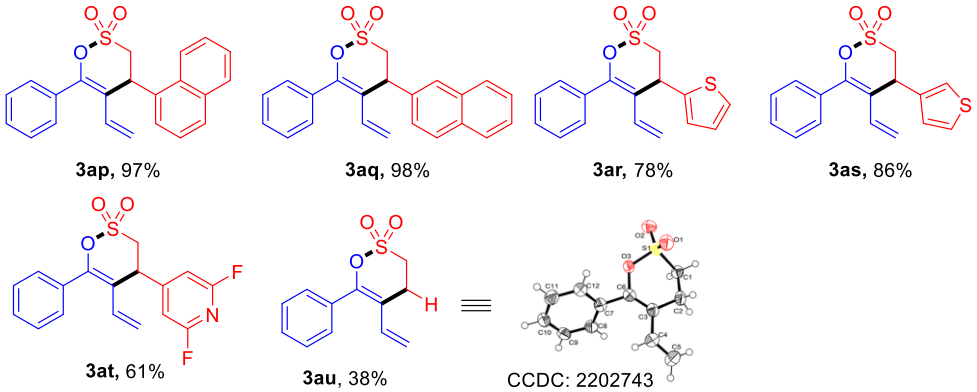
3am, 83%



3an, 85%



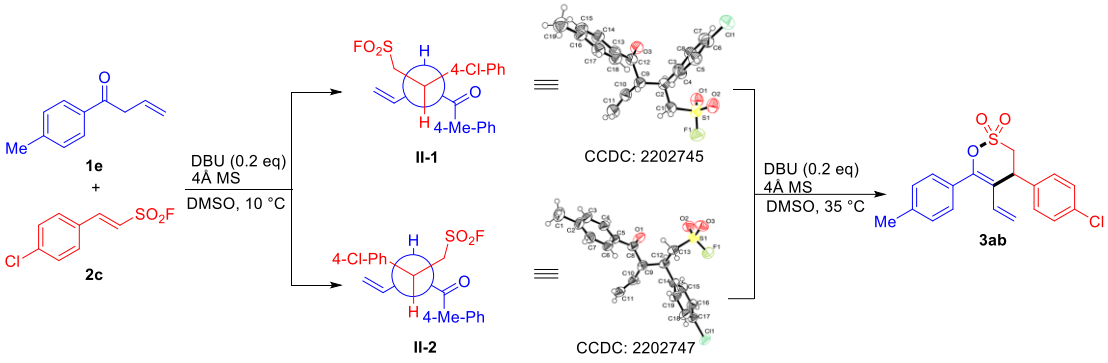
3ao, complicated



[a] Reaction conditions: **1** (0.20 mmol), **2** (0.20 mmol), DBU (0.2 eq), 4 Å MS (200 mg), DMSO 2.0 mL, rt, under air, 2 hours; isolated yield.

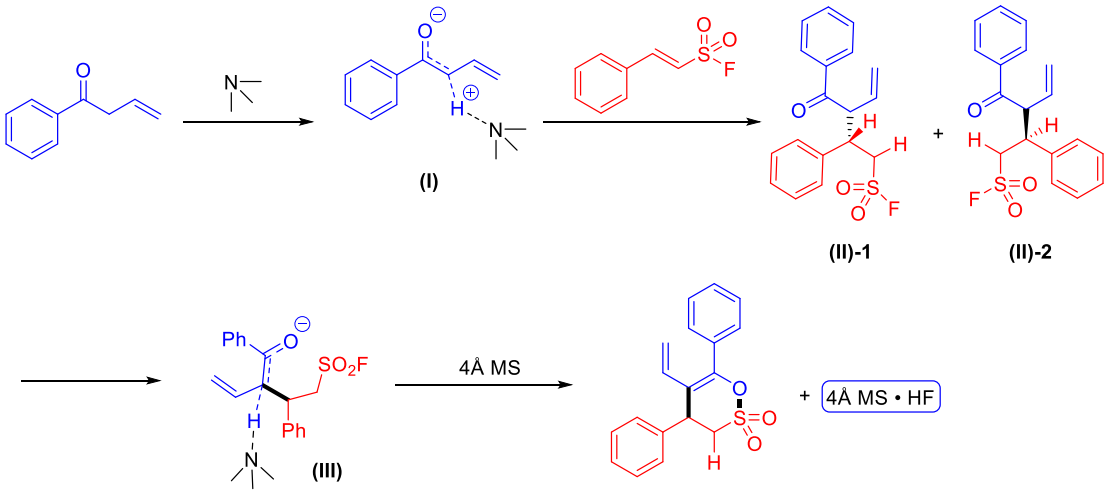
To gain insight into the reaction mechanism, the control experiment of allyl ketone **1** and ethenesulfonyl fluoride **2** were conducted (Scheme 1). Fortunately, the Michael addition intermediates were successfully obtained at relatively low reaction temperature. The Michael adduct has two stable conformational isomers and their structures were confirmed unambiguously by single crystal X-Ray analysis.[11] When reaction was raised to 35 °C, both of the two isomers can be transformed to δ-sultones **3ab** smoothly. These results indicated that allyl ketone and ethenesulfonyl fluoride undergo kinetically controlled Michael addition firstly, then the adducts undergo thermodynamically controlled intramolecular SuFEx reaction to give δ-sultone product.

Scheme 1 control experiment



Based on the aforementioned result and literature report,[6,7] a plausible mechanism was proposed as depicted on Scheme 2. DBU attacks the acidic α-proton of allyl ketone to generate intermediate **I**, which might trigger the intermolecular Michael addition with ethenesulfonyl fluoride to form the stable conformational isomers **II-1** and **II-2**. Under the catalysis of DBU, the tautomerization of **II-1** and **II-2** will generate intermediate **III**, which subsequently undergo intramolecular SuFEx reaction to produce the final ethenylated δ-sultone product.

Scheme 2 Tentative Mechanism



Conclusions:

In summary, we have demonstrated a tandem annulation reaction of allyl ketones and ethenesulfonyl fluorides. The mild and transition-metal free conditions. Simple procedure, generally high reaction yield and broad substrate scope provide a new method for the synthesis of γ-ethenylated δ-sultones. Further study of the applications of this method are ongoing in our laboratory.

Conflicts of interest

The authors declare no competing financial interest.

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11. CCDC 2202743 (**3au**), 2202745 (**II-1**), 2202746 (**3ab**) and 2202747 (**II-2**) contain the supplementary crystallographic data for this paper. These data are available free of charge from The Cambridge Crystallographic Centre via www.ccdc.cam.ac.uk/data_request/cif.