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N-Heterocyclic Carbene Catalyzed Synthesis of δ-Sultones via α,β-Unsaturated Sulfonyl Azolium Intermediates

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Abstract: *A limited array of reactive intermediates have enabled a wealth of discoveries in N-heterocyclic carbene organocatalysis. In this study, the viability of α,β-unsaturated sulfonyl azoliums as double electrophiles in new reactions is examined. Specifically, the (3+3) annulation of such species with the trimethylsilyl enol ethers of various 1,3-dicarbonyl compounds has been developed. This reaction provides access to a range of novel unsaturated δ-sultones (18 examples) in good yields (40–88 %) under mild reaction conditions. Mechanistic studies and the development of an enantioselective variant (55 % yield, 73:27 e.r.) support the intermediacy of an α,β-unsaturated sulfonyl azolium species.*

Catalysis with α,β-unsaturated carbonyl compounds and N-heterocyclic carbenes (NHCs) has delivered a range of important chemical reactions.[1] Central to many[2] are homoenolate (**1**)[3] or α,β-unsaturated acyl azolium (**2**) intermediates (Figure 1).[4] These intermediates enable bond-forming cascade processes that are characterized by reactions at multiple electrophilic and nucleophilic sites. For example, homoenolate intermediates (**1**) allow electrophiles to be introduced at the β-carbon atom, which is then followed by the addition of a nucleophile at the acyl carbon atom. In contrast, α,β-unsaturated acyl azolium intermediates (**2**) enable bond formation with nucleophiles at the β-carbon atom, followed by electrophiles (often protons) at the α-position, and finally a second nucleophile at the acyl position. Although homoenolate (**1**) and α,β-unsaturated acyl azolium (**2**) intermediates are now integral to NHC catalysis, non-carbonyl analogues are yet to be reported, despite their potential to deliver new transformations (see below). To address this deficiency, we recently investigated nucleophilic catalysis with α,β-unsaturated sulfonyl fluorides (**3**; Figure 2).

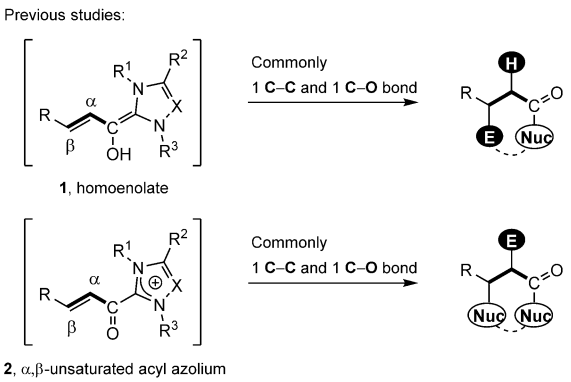

Figure 1. Homoenolates and α,δ-unsaturated acyl azoliums as intermediates in NHC catalysis.

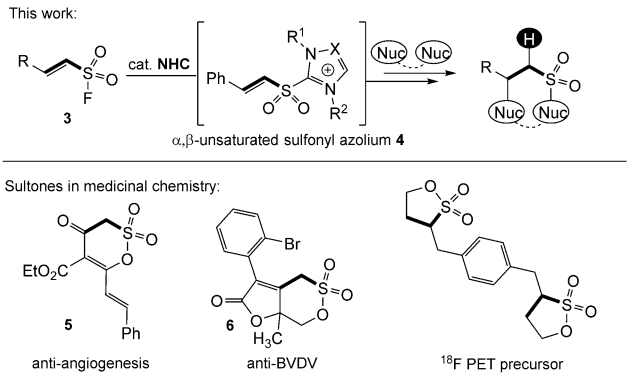

Figure 2. Working hypothesis and sultones of importance in medicinal chemistry. BVDV = bovine viral diarrhea virus, PET = positron emission tomography.

It was envisaged that with such substrates, the chemistry of "non-carbonyl" analogues of α,β-unsaturated acyl azoliums, such as α,β-unsaturated sulfonyl azoliums **4**, could be investigated, and that their reaction with enolates should deliver δ-sultone heterocycles.[5] Herein, we report the NHC-catalyzed synthesis of an array of δ-sultones, a somewhat overlooked heterocycle in medicinal chemistry (two bioactive examples are compounds **5** and **6**),[6] exploiting unsaturated sulfonyl azoliums (**4**) as new doubly electrophilic intermediates for organocatalysis. Mechanistic studies in support of the intermediacy of unsaturated sulfonyl azolium **4** and proof of principle for an enantioselective variant (73:27 e.r.) are also reported.

The chemistry of unsaturated sulfonyl(V) fluorides (e.g., **3**) was first studied in 1954 by Truce and Hoerger who reported the Diels–Alder reaction of 2-*para*-nitrophenylethylene sulfonyl fluoride (**3a**, R = *p*-$NO_2C_6H_4$) with cyclopentadiene.[7] Twenty-five years later, Krutak, Hyatt, and coworkers thoroughly investigated the use of ethylene sulfonyl fluoride (ESF, **3b**, R = H) as a Michael acceptor.[8] Although both reports have received little attention, the application of ESF (**3b**) in click chemistry has recently been studied.[9] We postulated that exposure of unsaturated sulfonyl(V) fluorides **3** to NHC catalysts should provide access to sulfonyl azoliums

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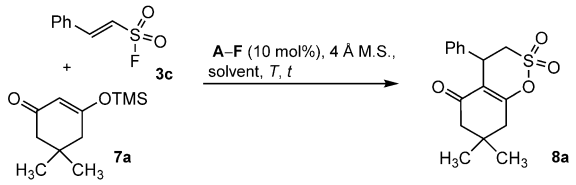
4, which are potentially well-suited to cascade processes that involve bond formation at the β-carbon atom and the sulfonyl group, analogous to the reactivity of unsaturated acyl azoliums.[10–12]

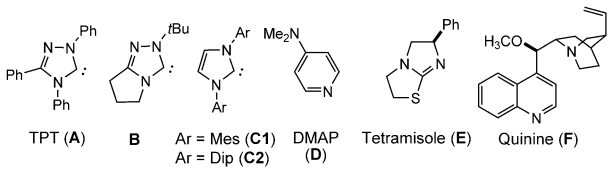
Our investigations commenced with an examination of the NHC-catalyzed annulation of trimethylsilyl (TMS) enol ether **7a** with 2-phenyl-substituted ESF (**3c**, R = Ph).[13] Pleasingly, when exposed to the Enders TPT catalyst (**A**; TPT = 1,3,4-triphenyl-4,5-dihydro-1*H*-1,2,4-triazol-5-ylidene), the expected δ-sultone product **8a** was formed in 13% yield (Table 1, entry 1). The yield could not be improved by

Table 1: Optimization of the reaction conditions for the synthesis of δ-sultone **8a**.



Entry	Cat.[a] (mol%)	Solvent	T[b] [°C]	t [h]	Yield[c] [%]
1	**A** (10)	THF	RT	16	13
2	**A** (10)	THF	66	16	15
3	**B** (10)	THF	66	16	7
4	**C1 (10)**	**THF**	**66**	**6**	**88**
5	**C1** (10)	toluene	110	6	60
6	**C2** (10)	THF	66	6	10
7	**D** (10)	THF	66	6	–[d]
8	**E** (10)[e]	THF	66	6	–[d]
9	**F** (10)	THF	66	6	–[d]
10	DABCO (10)	THF	66	6	–[d]
11	DBU (10)	THF	66	6	trace
12	DBU (120)	THF	66	6	30
13	**C1** (5)	THF	66	6	45
14	–	THF	66	6	–

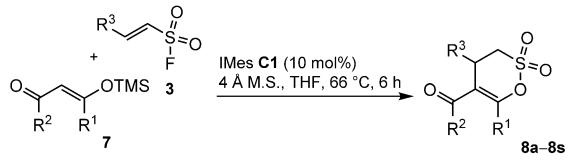
[a] The free NHCs were generated using KHMDS. [b] All reaction mixtures were prepared at 0°C and then heated to the indicated temperature. [c] Yield of isolated product after flash column chromatography. [d] No conversion according to ^{1}H NMR analysis. [e] Generated from the HCl salt with DIPEA. DABCO = 1,4-diazabicyclo-[2.2.2]octane, DBU = 1,8-diazabicycloundec-7-ene, Dip = 2,6-diisopropylphenyl, Mes = mesityl, M.S. = molecular sieves.

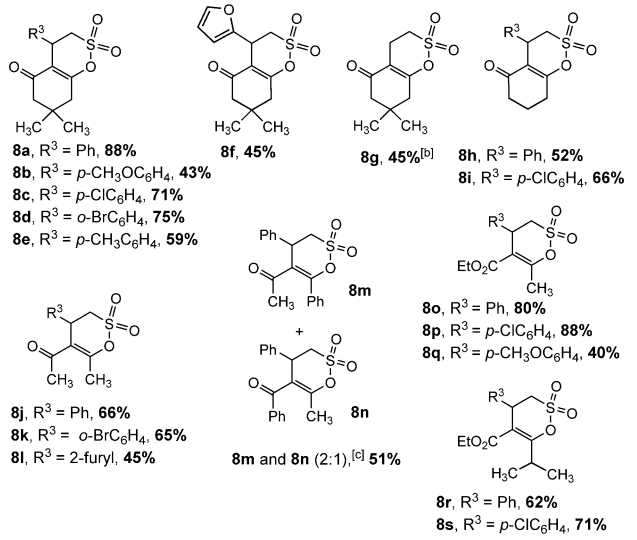


raising the reaction temperature (entry 2) nor by using the *tert*-butyl-substituted triazolylidene catalyst **B** (entry 3). In contrast, the use of the more nucleophilic and Lewis basic NHC IMes (**C1**) gave the expected δ-sultone in an improved yield of 88% (entry 4). The reaction could be conducted in toluene at reflux (entry 5), whereas the use of the more hindered imidazolylidene catalyst IDip (**C2**; IDip = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) resulted in significantly decreased yield (entry 6). The reaction was sensitive to the nature of the catalyst, as no reactions were observed using other common Lewis basic catalysts, such as DMAP (**D**), isothiourea **E**, quinine (**F**), or DABCO (entries 7–10). In contrast, 10 mol% of DBU provided traces of **8a**, and when 120 mol% was used, the desired product was isolated in 30% yield (entries 11 and 12). The sensitivity of the reaction to the nature of the Lewis base and the partial viability with DBU are consistent with observations by the groups of Gembus[11] and Sharpless and Fokin[9b] regarding organocatalysis with aliphatic sulfonyl fluorides and sulfuryl fluorides, respectively. Returning to IMes catalyst **C1**, we found that decreasing the catalyst loading led to a decrease in yield (entry 13), whereas its absence caused the reaction to fail (entry 14).

The generality of this reaction was examined with a number of TMS enol ethers and α,β-unsaturated sulfonyl fluorides. Thus, novel β-aromatic α,β-unsaturated sulfonyl fluorides bearing electron-rich or electron-poor aromatic substituents were prepared[13] and coupled with various TMS enol ethers **7** (Table 2). Using the TMS enol ether derived from dimedone (**7a**), we found that the reaction was moderately sensitive to the electronic character of the substrates; for example, electron-rich sulfonyl fluorides afforded the corresponding sultones in modest yield (**8b** and **8e**), whereas electron-poor sulfonyl fluorides were converted more efficiently (**8c** and **8d**). 2-Furyl-substituted sultone **8f** and ESF-derived sultone **8g** were formed in modest yield, the latter proving to be unstable during characterization. The TMS enol ether derived from 1,3-cyclohexadione and the acyclic TMS enol ether of acetylace-

Table 2: δ-Sultone substrate scope.[a]



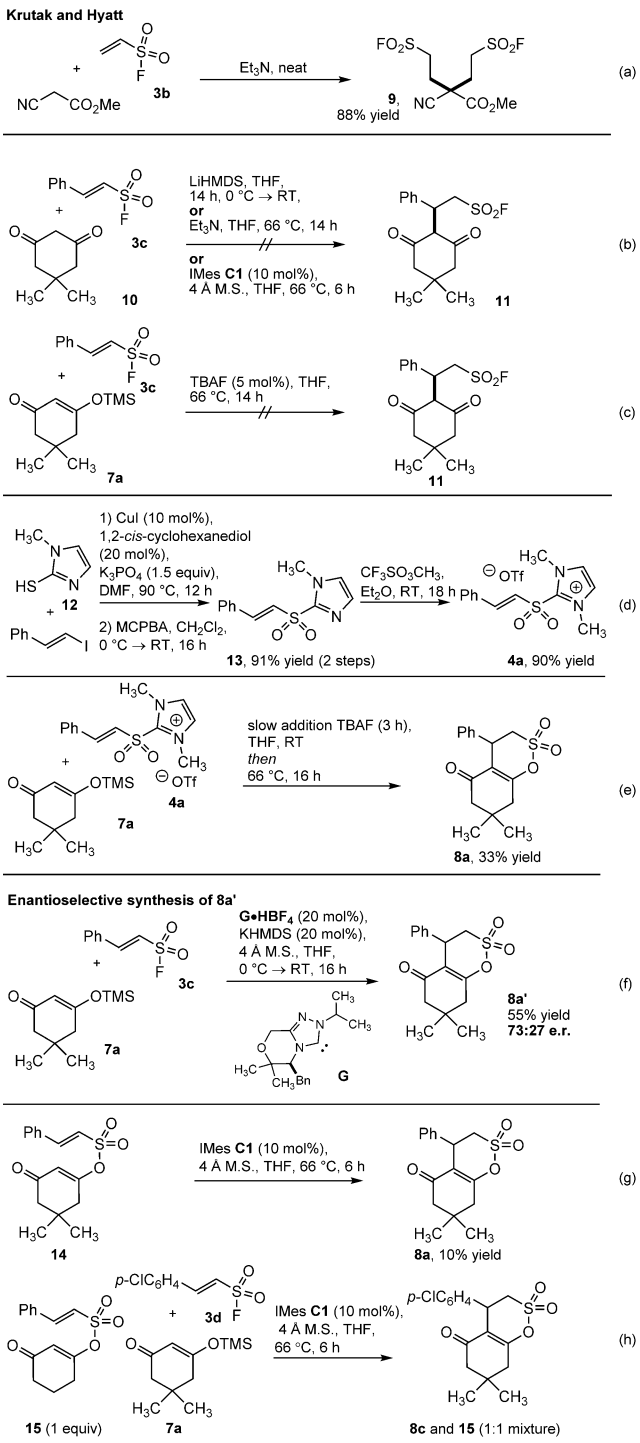


[a] Yield of isolated product after flash column chromatography. [b] Reaction run at RT for 16 h; **8g** was isolated in >90% purity as an unstable material. [c] Regioisomeric ratio determined by ^{1}H NMR analysis.

tone gave the δ-sultones **8h** and **8i** and **8j**–**8l**, respectively, in acceptable yields. TMS enol ethers derived from unsymmetric diketones gave the expected δ-sultones in good yield; however, modest regioselectivities were observed, with **8m** and **8n** formed as 2:1 isomeric mixtures. In contrast, TMS enol ethers derived from β-ketoesters gave the methyl-substituted δ-sultones **8o**–**8q** and the isopropyl sultones **8r** and **8s** in good yields, without formation of the ketene acetal isomers.

Our mechanistic studies focused on 1) clarifying the role of the NHC catalyst and gaining evidence for the intermediacy of sulfonyl azolium **4**, and 2) examining the preference of the ambident enolate nucleophile for attack through the O versus C atom (Scheme 1). With regard to the first point, whereas unsubstituted ESF (**3b**) is a potent Michael acceptor (for example, it reacts rapidly with methyl 2-cyanoacetate to form sulfonyl fluoride **9**, see Scheme 1 a),[8] the ability of β-substituted ESF derivatives such as **3c** to undergo conjugate addition is unknown. To address whether a related reaction that potentially competes with the postulated pathway via the sulfonyl azolium intermediate was occurring, β-phenyl-substituted ESF (**3c**) was exposed to dimedone (**10**) in the presence of Et_3N or LiHMDS or under the standard reaction conditions (Table 1, entry 4). In all cases, the reaction failed to provide sulfonyl fluoride **11** (or sultone **8a**), as did the transformation of TMS enol ether **7a** with **3c** in the presence of 5 mol% TBAF (Scheme 1 b, c). These observations indicate that phenyl-substituted ESF is a weaker Michael acceptor than unsubstituted ESF. The impact of a β-phenyl substituent on the electrophilicity of various Michael acceptors has been examined by Mayr and co-workers, who found an approximately 1000 fold decrease in reactivity.[14] To demonstrate the viability of unsaturated sulfonyl azolium **4a** as an intermediate towards δ-sultones, it was independently synthesized.[15] Therefore, sulfonyl azolium **4a** was prepared by S vinylation of imidazole **12**,[16a] oxidation of the resultant thioether to sulfone **13**,[16b] and N methylation using modified procedures of Mück-Lichtenfeld, Mayr, Studer, and co-workers.[16c] Having prepared sulfonyl azolium **4a**, it was found to react with the dimedone anion generated from TMS enol ether **7a** with TBAF, providing **8a** in 33% yield. The modest yield may be due to the limited solubility of **4a** in THF.[17] Further support for the intermediacy of unsaturated sulfonyl azolium **4** in the reaction was derived from studies on an enantioselective variant. Specifically, we found that *N*-isopropyl morpholinone NHC **G**[10f] catalyzed the synthesis of enantioenriched **8a′** with 73:27 e.r. and moderate yield (Scheme 1 f). This result implicates the chiral catalyst in the enantiodetermining step of the reaction, which is consistent with the formation of the sulfonyl azolium. Taken together, these studies support the mechanistically significant formation of an unsaturated sulfonyl azolium intermediate (**4**), which displays enhanced electrophilicity in comparison to the starting sulfonyl fluoride.

After formation of the α,β-unsaturated sulfonyl azolium intermediate, it can presumably react with the nucleophile either through the O or the C atom of the enolate. To examine the viability of the former pathway, sulfonate ester **14** was prepared and subjected to the reaction conditions, potentially

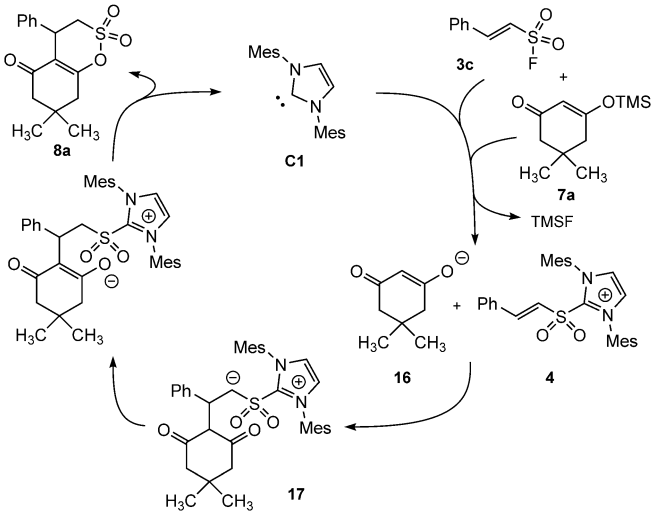


Scheme 1. Mechanistic experiments. MCPBA = *meta*-chloroperbenzoic acid, TBAF = tetrabutylammonium fluoride, Tf = trifluoromethanesulfonyl.

triggering an NHC-catalyzed Claisen-type[18] rearrangement (Scheme 1 g). Although the expected product **8a** was indeed observed, it was isolated in reduced yield indicating that this pathway is unlikely to be operating. To examine whether a vinyl sulfonate ester such as **14** might be involved as an intermediate that undergoes conjugate addition with a second enolate molecule, a scenario not probed in Scheme 1 g,

a cross-over study was performed. A mixture of dimedone TMS enol ether **7a** and sulfonyl fluoride **3d**, containing also one equivalent of sulfonate **15**, was subjected to the standard conditions. None of the cross-over products (**8a**, **8h**, or **8i**) were observed, which would be expected to form if enolate addition to a vinyl sulfonate intermediate **15** occurred (Scheme 1g).

Based on these mechanistic experiments (Scheme 1), a catalytic cycle was postulated (Scheme 2). Thus, the reaction



Scheme 2. Proposed reaction mechanism.

commences with addition of the NHC to unsaturated sulfonyl fluoride **3c** with concomitant loss of fluoride and desilylation of TMS enol ether **7a**, which provides dimedone anion **16** and sulfonyl azolium **4**. Intermediate **4** then undergoes conjugate addition with the dimedone anion to provide sulfonyl azolium enolate **17**, which, after proton transfer and loss of the NHC, affords δ-sultone **8a**.

In conclusion, we have introduced a new double electrophile for nucleophilic catalysis, namely α,β-unsaturated sulfonyl azoliums. In this study, they were combined with enolates for the synthesis of unsaturated δ-sultones. Preliminary studies on an enantioselective variant of this reaction demonstrate its viability (55% yield, 73:27 e.r.), while providing mechanistic insight. The studies reported herein raise questions related to the chemistry of sulfonyl Lewis base intermediates, some of which we continue to investigate.

Keywords: N-heterocyclic carbenes · nucleophilic catalysis · organocatalysis · sulfonyl azolium intermediates · sulfonyl fluorides

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[18] For related reactions of unsaturated esters, see Refs. [4] and [10a].

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