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Solvent-Controlled, Tunable Hydrosulfonylation of 3-Cyclopropylideneprop-2-en-1-ones

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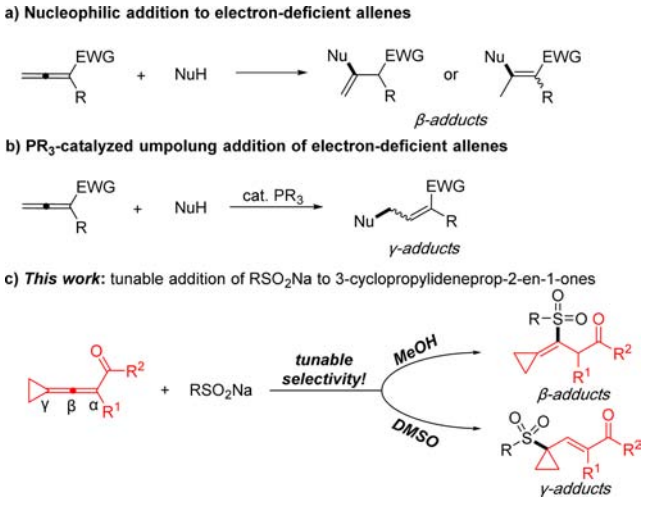
Supporting Information

ABSTRACT: An interesting and tunable hydrosulfonylation of 3-cyclopropylideneprop-2-en-1-ones with sodium sulfinates and acetic acid is described. The corresponding β- or γ-addition products can be produced in good to excellent yields with high selectivities, respectively. A rationale for these transformations is proposed base on the controlled experiments.

The functionalization of a carbon−carbon multiple bond constitutes highly synthetically versatile processes.[1] Particularly, the nucleophilic additions to functionalized allenes continue to attract the attention of chemists because they could provide an efficient way to form a new C−C or C−heteroatom bond in an inter- or intramolecular fashion with enormous potential.[2] Generally, the nucleophilic addition to acceptor substituted allenes usually takes place at the β-position yielding either the nonconjugated (*kinetic control*) or the conjugated (*thermodynamic control*) products (Scheme 1a).[3] However, a troublesome feature of the reaction is the potential migration of the C=C bond that may lead to formation of a synthetically useless mixture.[4] The phosphine-catalyzed additions of nucleophiles to electron-deficient allenes provide additional selectivity, which enables the nucleophiles to add to the γ-position to give allyl products (Scheme 1b).[5] Nevertheless, the formation of geometric isomers is often observed.[6] Thus, complete control of the regio- and stereoselective addition remains a grand challenge and is still highly pursued.

Scheme 1. Additions of Nucleophiles to Electron-Deficient Allenes



On the other hand, the 3-cyclopropylideneprop-2-en-1-ones, which contain the highly strained cyclopropyl ring and carbonyl group adjacent to the two ends of cumulated double bonds, are a class of thermally stable, yet activated allenic derivatives.[7] The versatile and unique reactivity makes these compounds highly attractive synthetic building blocks in organic synthesis. Due to interest in exploring the synthetic potential of these derivatives, we have comprehensively studied the transition-metal-catalyzed cycloisomerization of 3-cyclopropylideneprop-2-en-1-ones to provide a facile synthesis of functionalized 2-alkylidenecyclobutanones, benzofuran-7(3a*H*)-ones, and furans.[8] Moreover, we have also reported a hydroxyphosphinylation of 3-cyclopropylideneprop-2-en-1-ones, introducing the hydroxyl and phosphonyl group simultaneously to afford highly functionalized vinylcyclopropanol units in high yields.[9] Recently, the incorporation of a sulfonyl group into organic molecules has emerged as a significant research field of current interest in organic chemistry as sulfones are commonly encountered in agrochemicals,[10] pharmaceuticals,[11] and organic materials.[12] We thus envisioned that the hydrosulfonylation of 3-cyclopropylideneprop-2-en-1-ones would give valuable sulfonylated entities, proceeding in a highly regio- and stereoselective manner. As a result, herein we report the solvent-controlled[13] switchable addition reactions of sodium sulfinates to 3-cyclopropylideneprop-2-en-1-ones, which could give either the β- or γ-sulfonylation products with high selectivities (Scheme 1c). To our knowledge, such a facile and tunable catalyst-free nucleophilic addition of activated allenes to give both β- and γ-addition products of high selectivity has not been observed before.

We initially studied the hydrosulfonylation reaction by reacting 3-cyclopropylidene-1,2-diphenylprop-2-en-1-one (**1a**) with $PhSO_2Na$ (**2a**) in acetone at room temperature employing

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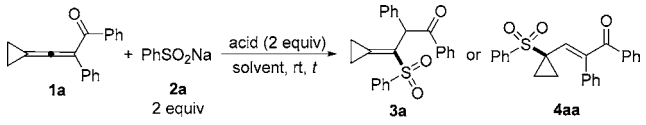
acetic acid as the proton source. The nonconjugated β-addition product **3a** was produced with high selectivity in 85% yield as expected (Table 1, entry 1). The use of strong organic acids as

Table 1. Examinations on Reaction Conditions[a]



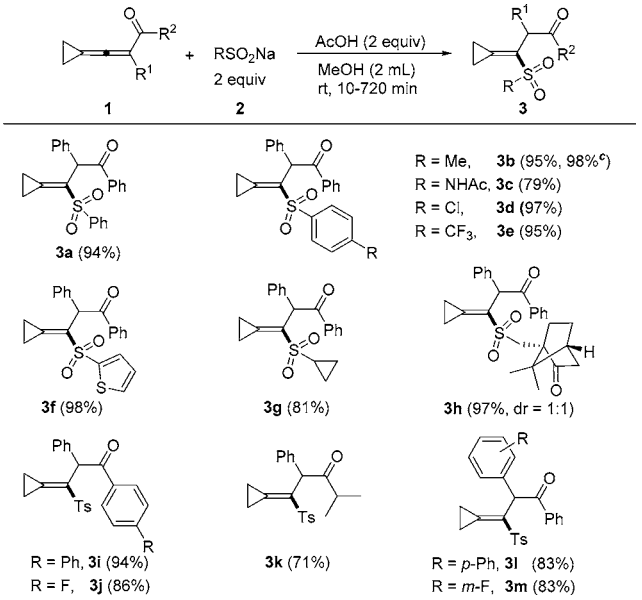
entry	acid	solvent	t (h)	yield[b] of **3a** (%)	yield[b] of **4aa** (%)
1	AcOH	acetone	3	85	–
2	TsOH·H_2O	acetone	3	28	–
3	TfOH	acetone	0.5	trace	–
4	$PhCO_2H$	acetone	1.5	84	–
5	AcOH	MeCN	7	84	–
6	AcOH	THF	7	86	trace
7[c]	**AcOH**	**MeOH**	**0.1**	**94**	–
8	AcOH	EtOH	0.1	91	trace
9	AcOH	toluene	12	76	–
10	AcOH	cyclohexane	10	84	trace
11	AcOH	DCM	12	89	–
12	AcOH	dioxane	12	71	–
13	**AcOH**	**DMSO**	**8**	–	**98**
14	AcOH	DMF	24	trace	95
15	AcOH	HMPA	24	–	64

[a]Conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), AcOH (0.2 mmol) at rt in open air. [b]Isolated yield. [c]The reaction generated a complex product mixture when $PhSO_2H$ was directly used instead of $PhSO_2Na$ and AcOH.

the proton source gave terrible results (entries 2 and 3). In contrast, the reaction of the weak acid $PhCO_2H$ also gave **3a** in high yield (entry 4). Reaction in other solvents such as MeCN, THF, MeOH, EtOH, toluene, cyclohexane, DCM, and dioxane favorably produced the β-addition product **3a** with high efficiency (entries 5−12), and MeOH gave the best performance (entry 7). When the reaction was examined by using $PhSO_2H$ instead of $PhSO_2Na$ and AcOH in MeOH, it generated a complex product mixture. Surprisingly, the regioselectivity was reversed when DMSO was employed as solvent for 8 h, offering the γ-addition product **4aa** in 98% yield with good geometric selectivity (entry 13). In addition, selective production of **4aa** was also obtained in the case of polar aprotic solvent DMF or HMPA; nevertheless, a long reaction time and slightly low yield was observed (entries 14 and 15).

Upon the identification of a set of reaction conditions, we next explored the scope of the reactions. Scheme 2 lists some typical results of the selective nucleophilic addition of 3-cyclopropylideneprop-2-en-1-ones to afford β-adducts. A series of sodium sulfinates bearing substituted phenyl rings could be used to react with **1a** affording the corresponding products **3a**−**3e** in good to excellent yields. A heterocyclic substrate i.e., sodium thiophene-2-sulfinate, also reacted smoothly with **1a** to give the adduct **3f** in 98% yield. The reaction could also be performed with sodium sulfinates bearing alkyl substituents. For example, the reaction of sodium cyclopropanesulfinate and (1*S*)-10-camphorsulfinate with **1a** gave **3g** and **3h** in 81% and 97% yield, respectively. With respect to 3-cyclopropylideneprop-2-en-1-ones, typical substrates bearing substituted phenyls at the 1- or 2-position were examined, which all delivered the

Scheme 2. Scope of β-Adducts[a,b]



[a]Conditions: **1** (0.2 mmol), **2** (0.4 mmol), AcOH (0.4 mmol) in 2 mL of MeOH at rt in open air. [b]Isolated yield. [c]Large-scale reaction: **1a** (5 mmol, 1.232 g), **2b** (2 equiv), AcOH (2 equiv) to afford **3b** (1.975 g).

products in high yield. In addition, a substrate bearing an alkyl substituent at the 1-position, i.e., 1-cyclopropylidene-4-methyl-2-phenylpent-1-en-3-one, also successfully gave the desired product **3k** cleanly, albeit in a somewhat low yield.

The selective addition of sodium sulfinates to 3-cyclopropylideneprop-2-en-1-ones to produce γ-adducts is particularly interesting, and our subsequent examination on the scope of the reaction reveals that this transformation is quite general. As shown in Scheme 3, a variety of sodium sulfinates are applicable to produce the γ-adducts with excellent regioselectivity and good to high geometric selectivity. Except in the case of the sodium 4-acetamidobenzenesulfinate and sodium thiophene-2-sulfinate, which gave the products **4af** and **4am** in modest yields, the reactions of other sodium sulfinates with **1a** all gave the desired products in high yields (81−98%). Particularly, a sodium sulfinate bearing an isoxazol unit also proved to be a good substrate to deliver the product **4an** in 97% yield. Furthermore, the reaction could also be performed with sodium alkylsulfinates, as exemplified by the successful production of **4ao** and **4ap** from sodium methanesulfinate and sodium cyclopropanesulfinate. Moreover, the generality of the reaction with various 3-cyclopropylideneprop-2-en-1-ones **1** was also investigated. Substrates **1** bearing aryl groups at the 1-position (R^1 = aryl) gave the products in 64−97% yields. Nevertheless, a low yield (43%) was observed in the case of the isopropyl substituted substrate. The reaction of a vinyl substrate (R^1 = 2-methylpropenyl) afforded the desired product **4lb** in high yield. The substituent effect regarding R^2 in **1** was also briefly examined. As can be seen, substrates with both electron-donating and -withdrawing aromatic groups are all good substrates to afford the corresponding products **4mb**−**4rb** in good yields. Here it is worth noting that the reactions all proceed with high geometric selectivity, giving the products with an overwhelming *E*-selectivity referring to the double bonds in the products.

To obtain some information on the mechanism of the selective γ-addition, several controlled experiments were

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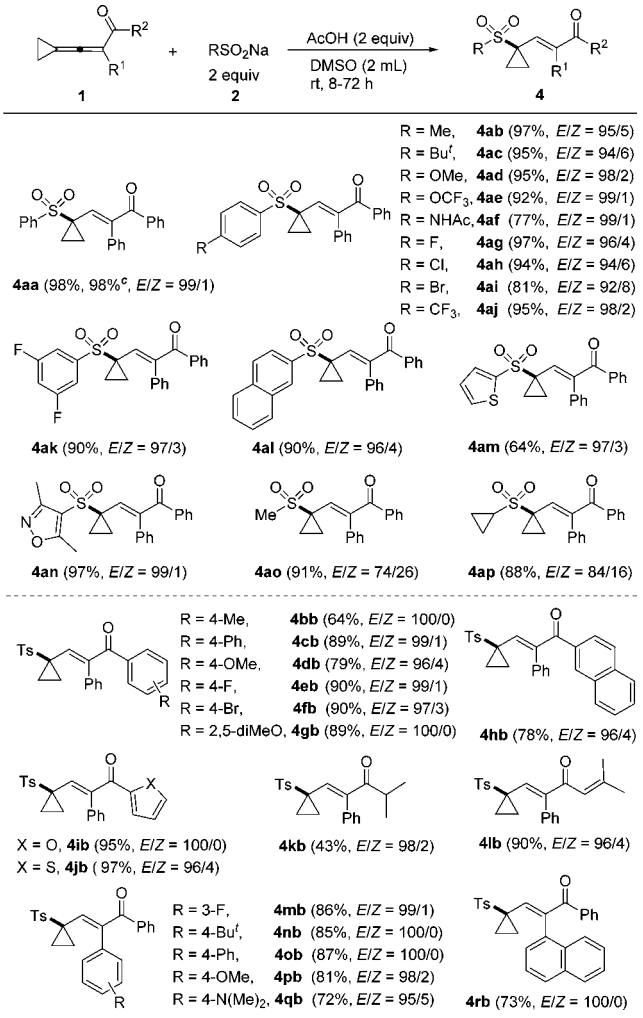
Scheme 3. Scope of γ-Adducts[a,b]



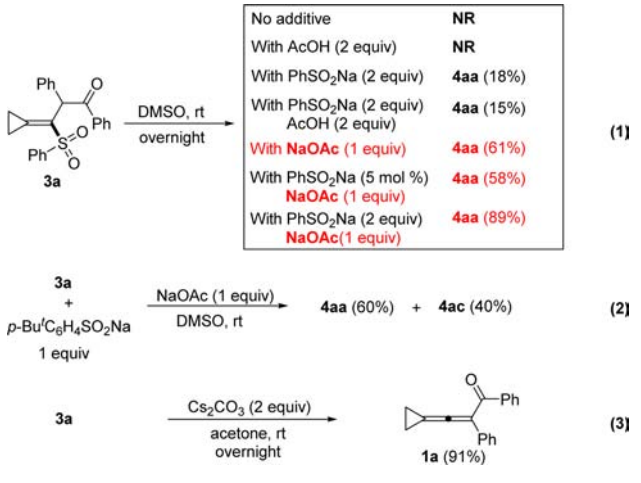
[a]Conditions: **1a** (0.2 mmol), **2** (0.4 mmol), AcOH (0.4 mmol) in 2 mL of DMSO at rt in open air. [b]Isolated yield. [c]Large-scale reaction: **1a** (5 mmol, 1.240 g), **2a** (2 equiv), AcOH (2 equiv) to afford **4aa** (1.956 g).

performed (Scheme 4). While the conversion of the product **3a** into **4aa** was observed as monitored by TLC during the optimization study, we noted that the transformation was bad even adding both $PhSO_2Na$ and AcOH (standard condition). In contranst, the efficiency of the transformation improved when the additive NaOAc was used, indicating that a basic condition is crucial for the reaction. Furthermore, the yield of **4aa** could be increased up to 89% when the additional $PhSO_2Na$ was introduced to the reaction system (eq 1). The involvement of the sodium sulfinate in the transformation of the β-adduct to γ-adduct was further evident, as the reaction of **3a** with *p*-Bu^{t}C$_6$H$_4$SO$_2$Na in the presence of NaOAc gave a mixture of **4aa** and **4ac** with a ratio of 6/4 (eq 2). Finally, **3a** could be converted to the starting material **1a** by using strong base Cs_2CO_3 in acetone via an elimination reaction (eq 3).

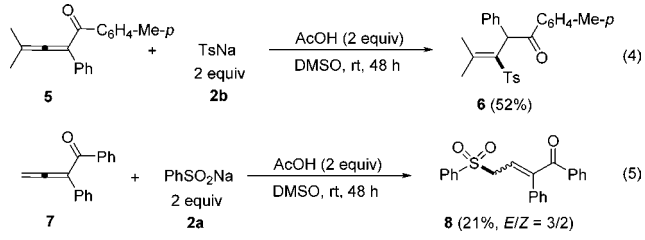
Furthermore, it should be noted that the cyclopropyl group in substrate **1** is quite critical for the current transformation of a highly selective regio- and stereo-γ-addition (Scheme 5). As a matter of fact, when a dimethyl substituted allenyl ketone **5** was subjected to the optimal conditions for 48 h, only the Micheal addition-type product (β-adduct) was isolated. Although the reaction of a simple allenyl ketone **7** also afforded the γ-adduct, nevertheless an *E*/*Z* mixture with a 3/2 ratio was obtained. It is reasonable that the release of the strain from the MCP unit of the β-adducts should contribute to the tendency to form the γ-adducts.

Based on the above results, a plausible mechanism is proposed in Scheme 6. The nucleophilic addition of TsNa to the α,β double bonds of **1** first takes place to give the β-adducts **3**. The second nucleophilic addition of Ts^- to the electron-deficient double bond occurs to afford the double-addition

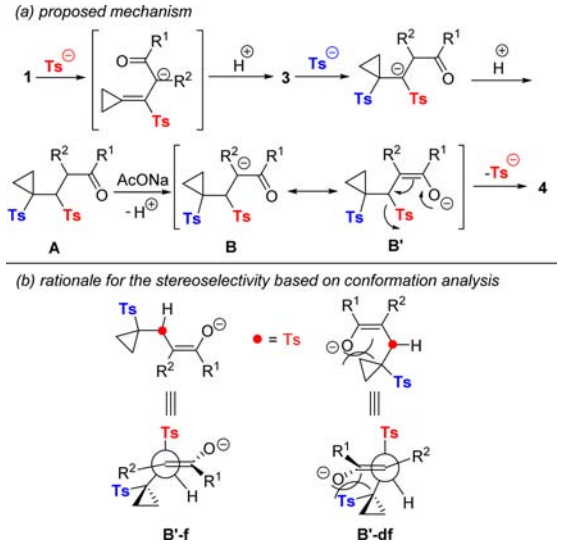
Scheme 4. Controlled Experiments



Scheme 5. Hydrosulfonylation of Allenyl Ketones



Scheme 6. A Plausible Mechanism



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intermediate[14] **A** when DMSO is used as a solvent. In the presence of NaOAc which serves as a suitable base, **A** may lose a proton to form two resonance structures, carbanion form **B** and enolate **B′** (note: it is reasonable that when R^1 = alkyl substituents, the reactions gave low yields due to the relatively low stability of the corresponding intermediates like **B′**). Loss of the Ts^- from **B′** by adopting a preferential conformer such as **B′-f** finally gives the product **4** stereoselectively. The steric repulsive effect between the sulfonylated cyclopropyl group and enolate group may elevate the energy of the conformer **B′-df**.

In summary, we have reported a solvent-dependent hydrosulfonylation of 3-cyclopropylideneprop-2-en-1-ones with sodium sulfinates. The β-adducts could be obtained in high yields in MeOH with high efficiency. Particularly interesting is that the reaction could also produce the γ-sulfonylation product in DMSO with high geometric selectivity. Further investigation into the reaction is underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02047.

Experimental procedures and copies of ^1H and ^{13}C NMR spectra for all new compounds (PDF)

Crystallographic information file for compound **3d** (CIF)

Crystallographic information file for compound **4aa** (CIF)

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Notes

The authors declare no competing financial interest.

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