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Hydrogen Bonding Cluster-Enabled Addition of Sulfonic Acids to Haloalkynes: Access to Both (*E*)- and (*Z*)-Alkenyl Sulfonates

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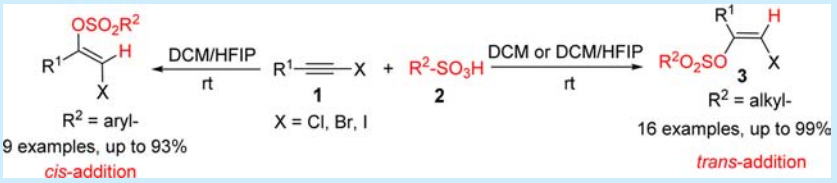
Supporting Information

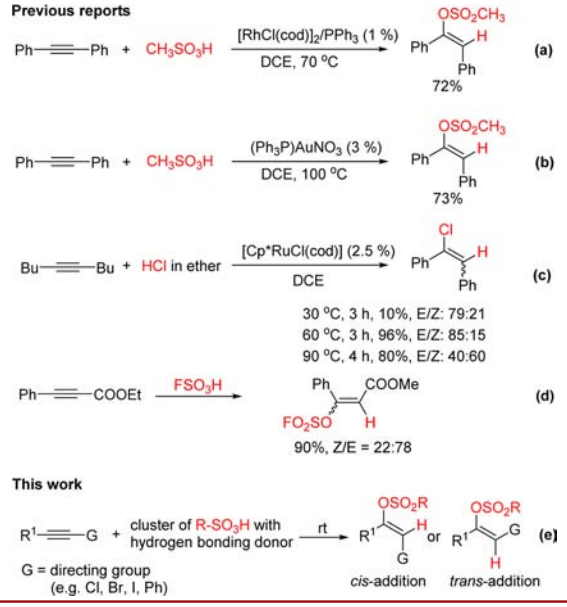


ABSTRACT: We developed an efficient synthesis of alkenyl sulfonates via hydrogen bonding cluster-enabled addition of sulfonic acids to haloalkynes. The reactivity of sulfonic acids could be significantly enhanced in the presence of strong hydrogen bonding donors. This metal-free method results in good chemical yields for a wide range of haloalkyne substrates and demonstrates good functional group tolerance. What is more, we can control the stereoselectivity of addition (*cis* vs *trans*) by varying the steric bulk of the sulfonic acid.

Although so-called alkynophilic metal (e.g., Pd, Pt, Au, Rh)-catalyzed nucleophilic addition to alkynes is extremely common in synthesis,[1] the Brønsted acid-catalyzed counterpart is underutilized. Compared with alkynophilic metals, Brønsted acids are generally believed to have less affinity toward alkyne substrates than heteroatoms (e.g., O, N) in nucleophiles or solvents, so they are not alkynophilic. Therefore, they are considered to be unsuitable for electrophilic activation of functionalized alkynes. This is especially true for nucleophilic addition to internal alkynes, which are generally less reactive than terminal alkynes. To the best of our knowledge, the stereo outcome (*cis* addition vs *trans* addition) of Brønsted acid-catalyzed nucleophilic alkyne addition is still not clear.

More specifically, the nucleophilic addition of sulfonic acids to alkynes gives alkenyl sulfonates, which are important building blocks in organic synthesis, especially in cross-coupling reactions[2] such as the Suzuki reaction,[2a] the Heck reaction,[2b] and Buchwald−Hartwig amination.[2c] Alkynophilic metals such as Rh (Scheme 1a)[3] and Au (Scheme 1b)[4] have been used to catalyze this process. A Rh-based system gave the *cis* addition product (Scheme 1a),[3] and a Au-based system also gave the *cis* addition product (Scheme 1b),[4] which was uncommon in gold catalysis.[5] Recently, Dérien and co-workers reported the Ru-catalyzed addition of HCl (which has similar acidity as sulfonic acids) to alkynes (Scheme 1c).[6] This reaction gave a mixture of *cis* and *trans* addition products, and the *cis* addition product appeared to be kinetically favored. These reactions need expensive transition metals and also need harsh reaction conditions like high temperature. For metal-free systems, only the reaction of superacids like FSO_3H and CF_3SO_3H with electron-deficient alkynes has been reported, and the stereoselectivity was not ideal (Scheme 1d).[7] Herein we are glad to report a metal-free hydrogen bonding cluster-enabled addition of sulfonic acids to haloalkynes at room temperature. What is more, we can control the stereoselectivity of addition (*cis* vs *trans*) by varying the steric bulk of the sulfonic acid (Scheme 1e).

Scheme 1. Literature Reports on the Addition of Strong Acids to Alkynes



The concept of combined acid catalysis has been proposed by Yamamoto and co-workers.[8] The acidity of a Brønsted acid can be enhanced by complexation with another Brønsted acid or Lewis acid (Scheme 2a). In a relatively nonpolar solvent (e.g., DCM), the interaction between two Brønsted acids should involve hydrogen bonding (Scheme 2b). It has been found that the hydrogen bonding energy of a chain of H-bonds would be greater than the total energies of the individual links in hydrogen

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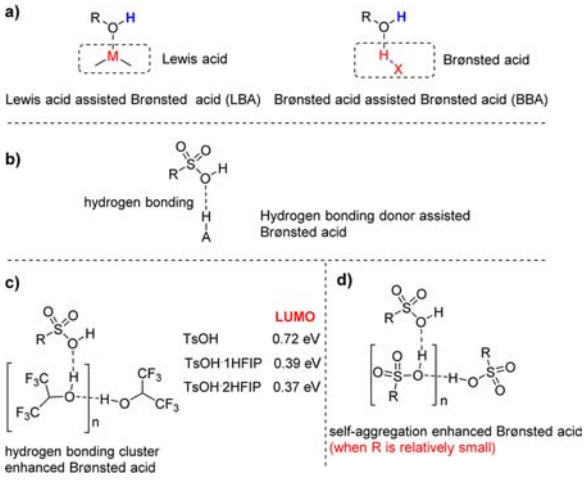
Scheme 2. Hydrogen Bonding Cluster-Enhanced Brønsted Acid Catalysis (LUMO Energies Calculated at the B3LYP/6-311+G(2df,2p) Level)

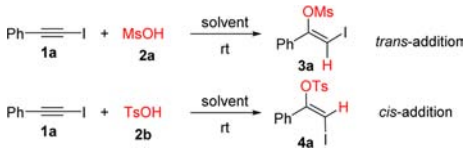


bonding networks of various water and carbohydrate systems; this effect is called σ-cooperativity or nonadditivity.[9] As a result of nonadditivity, hydrogen bonding interactions are not limited to two molecules, and a hydrogen bonding aggregate or H-bond network will form preferentially. This hydrogen bonding aggregation may further enhance the reactivity of Brønsted acids.

More specifically, as weak hydrogen bonding acceptors, sulfonic acids can form hydrogen bonding clusters with strong hydrogen bonding donors such as hexafluoro-2-propanol (HFIP) (Scheme 2c). DFT calculations indicate that when TsOH is bonded with an increased number of HFIP molecules via hydrogen bonding, the LUMO energy decreased, leading to increased reactivity (acidity) (Scheme 2c). Also, if the R group in a sulfonic acid is relatively small, it may form a cluster by self-aggregation (Scheme 2d). Thus, a hydrogen bonding network or cluster may enable chemistry possible only via transition metal or superacid catalysis. A hydrogen bonding network or cluster has the advantages of being environmentally friendly (vs transition metal) and exhibiting good functional group tolerance (vs superacids). Indeed, hydrogen bonding donor solvents like HFIP have been shown to provide significant rate enhancements for many reactions,[10] and kinetic data suggest that higher-order hydrogen bonding solvent aggregates play an important role.[11]

Haloalkynes have emerged as powerful and versatile building blocks in a variety of synthetic transformations.[12] First we used the addition of TsOH to haloalkyne **1a** as our model system (Table 1). As expected, no reaction took place in donor solvents such as CH_3CN, 1,4-dioxane, MeOH, DMF, and acetone (Table 1, entries 1−5). There was also no reaction in the weakly coordinating solvent DCM (Table 1, entry 6). But in a mixed solvent of DCM with the strong hydrogen bonding donor solvent HFIP (Table 1, entry 7), a good yield of the addition product **4a** was obtained. With the less bulky sulfonic acid MsOH, the DCM/HFIP system appeared to be too reactive, and there was no clean transformation (Table 1, entry 8). However, the reaction proceeded very well in the weakly coordinating solvent DCM alone without additional hydrogen bonding donors (Table 1, entry 9). Because MsOH (pK_a = −2.6) is a slightly weaker Brønsted acid than TsOH (pK_a = −2.8), the much higher reactivity of MsOH may due to self-aggregation (Scheme 2d). For TsOH, self-aggregation is not efficient because of its poorer solubility and bulkier aromatic

Table 1. Optimization of the Reaction Conditions[a]



entry	RSO_3H	solvent	yield (%)
1	TsOH	CH_3CN	NR
2	TsOH	1,4-dioxane	NR
3	TsOH	MeOH	NR
4	TsOH	DMF	NR
5	TsOH	acetone	NR
6	TsOH	DCM	NR
7	TsOH	DCM/HFIP (1:4)	95[b] (62[c])
8	MsOH	DCM/HFIP (1:4)	complex
9	MsOH	DCM	98[b] (90[c])
10	MsOH	DCE	95[b]
11	MsOH	PhF	25[b]
12	MsOH	$CHCl_3$	54[b]

[a]Conditions: **1a** (0.2 mmol), sulfonic acid **2** (0.28 mmol), solvent (0.5 mL), rt, 8 h. Only one isomer was detected for both **3a** (*Z*) and **4a** (*E*). [b]Determined by GC. [c]Isolated yield.

substitution. We also tested other weakly coordinating solvents (DCE, PhF, and $CHCl_3$), and DCM appeared to be the best solvent (Table 1, entries 10−12). It should be noted that the reaction of MsOH exclusively gave the *trans* product **3a** and the reaction of TsOH exclusively gave the *cis* product **4a**.

With the optimized conditions in hand, we first explored the scope and functional group tolerance of *trans* addition with MsOH (Table 2). 1-Iodoalkyne **1a**, 1-bromoalkyne **1b**, and 1-chloroalkyne **1c** all worked very well with exclusive regio- and stereoselectivity (Table 2, entries 1−3). Unlike traditional superacid-mediated reactions, this method has very good functional group tolerance, as almost all substitutions on the aromatic ring (halogen, alkyl, ketone, ester, methyl ether) had little influence on the reactivity (Table 2, entries 4−10). To our delight, even highly electron-rich phenol and nonbasic amine groups (TsMeN−) were also well-tolerated (Table 2, entries 11 and 12). The steric bulk of the substituents also had little effect, as sterically hindered *ortho*-substituted 1-iodo-2-arylalkynes **1m** and **1n** both worked well (Table 2, entries 13 and 14). It should be noted that in all of the MsOH additions, only one regio- and stereoisomer (the *trans* addition product) was isolated. In general, we used two conditions for different substrates. Conditions A (using HFIP as a cosolvent) exhibited better reactivity than conditions B (DCM as the solvent). Thus, for reactive substrates, conditions B were used (Table 2, entries 1−6), while for less reactive substrates, conditions A were used (Table 2, entries 7−14). We also tested another alkylsulfonic acid, $EtSO_3H$, and slightly lower yields were observed (Table 2, entries 15 and 16).

Because the *cis* addition product was obtained exclusively when a bulkier aromatic sulfonic acid (TsOH) was used, we also explored the substrate scope for *cis* addition (Table 3). All of the tested aromatic sulfonic acids worked very well under conditions A (Table 3, entries 1−9), and in all cases only one regio- and stereoisomer (the *cis* addition product) was isolated. The assignments of double-bond configurations were confirmed by NOESY and by comparison of spectroscopic data with literature reports (see the Supporting Information).[13]

We also tested alkynes other than 1-halo-2-arylalkynes. The reaction of diphenylacetylene (**1o**) with MsOH gave *cis* product

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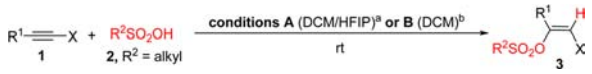
Table 2. Scope of Addition of MsOH to Haloalkynes (*Trans* Addition)

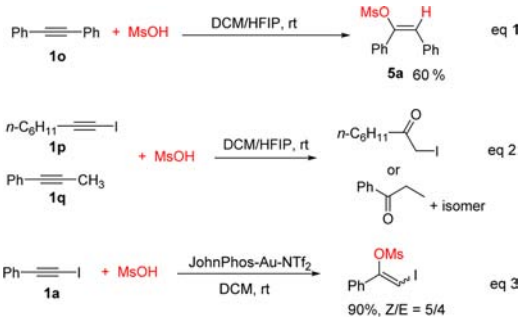


entry	1	3	yield (%)[c]	entry	1	3	yield (%)[c]
1	1a	3a	90[d] *Z*/*E*> 30:1	9	1i	3i	86[e] *Z*/*E*> 30:1
2	1b	3b	92[d] *Z*/*E*> 30:1	10	1j	3j	55[e] *Z*/*E*> 30:1
3	1c	3c	94[d] *Z*/*E*> 30:1	11	1k	3k	80[e] *Z*/*E*> 30:1
4	1d	3d	93[d] *Z*/*E*> 30:1	12	1l	3l	80[e] *Z*/*E*> 30:1
5	1e	3e	91[d] *Z*/*E*> 30:1	13	1m	3m	72[e] *Z*/*E*> 30:1
6	1f	3f	88[d] *Z*/*E*> 30:1	14	1n	3n	65[e] *Z*/*E*> 30:1
7	1g	3g	57[e] *Z*/*E*> 30:1	15	1a	3o	46[d] *Z*/*E* = 30:1
8	1h	3h	85[e] *Z*/*E*> 30:1	16	1b	3p	54[d] *Z*/*E* > 30:1

[a]Conditions A: alkyne **1** (0.2 mmol), sulfonic acid **2** (0.28 mmol, 1.4 equiv), DCM (0.1 mL), HFIP (0.4 mL), rt, 0.5−8 h. [b]Conditions B: alkyne **1** (0.2 mmol), sulfonic acid **2** (0.28 mmol, 1.4 equiv), DCM (0.5 mL), rt, 0.5−8 h. [c]Isolated yields. [d]Conditions B were used. [e]Conditions A were used.

5a under standard conditions A (eq 1), which is different compared with the reaction of MsOH with 1-halo-2-arylalkynes (*trans* addition; Table 2). We tested alkynes **1p** and **1q**, but the major products were the hydration ketone products (eq 2); the source of water could be trace water present in the reaction mixture or water generated from self-condensation of the sulfonic acid. This easy hydration process is consistent with Li and co-workers' alkyne hydration using the HFIP/TfOH system.[10a] We also investigated the addition of MsOH to **1a** using a cationic gold catalyst (eq 3). Interestingly, a mixture of *Z* and *E* isomers was obtained, which indicated that two mechanisms (acid catalysis and gold catalysis) operated at the same time.

The proposed mechanism is shown in Scheme 3. The hydrogen bonding cluster results in an increase in acidity, facilitating the rate-determining proton transfer step (Scheme 3a). The proton transfer gives the key intermediate, a vinyl carbocation.[14] This vinyl cation will have a linear geometry, with the upper face being sterically hindered by the phenyl group (**A1**) or the iodine atom (**A2**), thus favoring the approach of the nucleophile (sulfonic acid) *syn* to the H atom, leading to the formation of the *cis* addition product.[15] Thus, if steric hindrance plays a major role, the *cis* addition product will be the dominant product. This could explain why nucleophilic attack of MsOH on **A1** leads to



the *cis* product **5a** (Scheme 3b). However, for vinyl cation **A2**, the smaller steric hindrance of the iodine atom may reduce the *cis* selectivity, and the electronegative iodine atom may also act as a directing group.[15] The nucleophile (sulfonic acid) could form a competitive hydrogen bond with the iodine atom in **A2**, and the iodine atom would then direct the nucleophilic attack to approach **A2** *trans* to the H atom (Scheme 3c), leading to the formation of the *trans* addition product **3a**. For bulkier TsOH, however, the steric hindrance outweighs the directing effect of iodine, so still the *cis* product **4a** is obtained (Scheme 3c).

In summary, we have developed a metal-free hydrogen bonding cluster-enabled addition of sulfonic acids to alkynes at room

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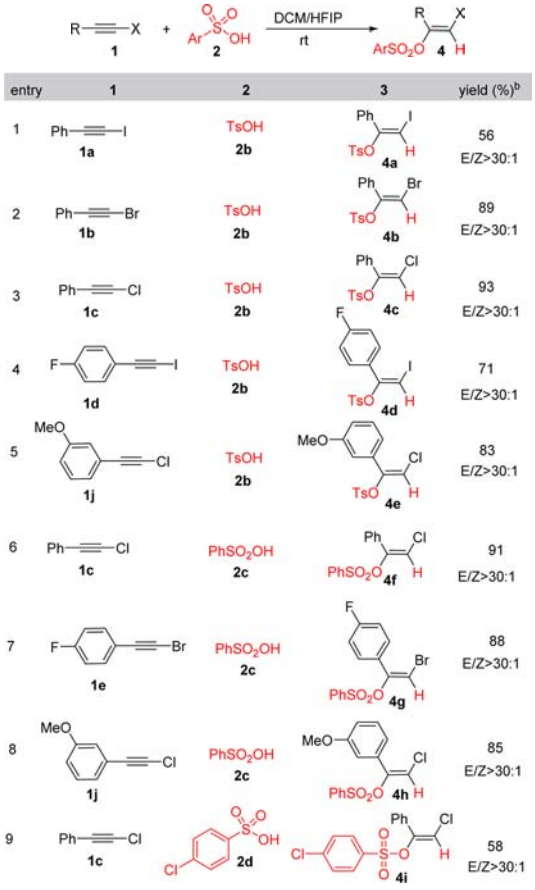
Table 3. Scope of Addition of Aromatic Sulfonic Acids to Haloalkynes (*Cis* Addition)[a]



[a]Conditions: alkyne **1** (0.2 mmol), sulfonic acid **2** (0.28 mmol, 1.4 equiv), DCM (0.1 mL), HFIP (0.4 mL), rt, 0.5−8 h. [b]Isolated yields.

temperature. The stereochemistry (*cis* addition vs *trans* addition) can be switched by varying the bulkiness of the sulfonic acid.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02061.

Experimental details and copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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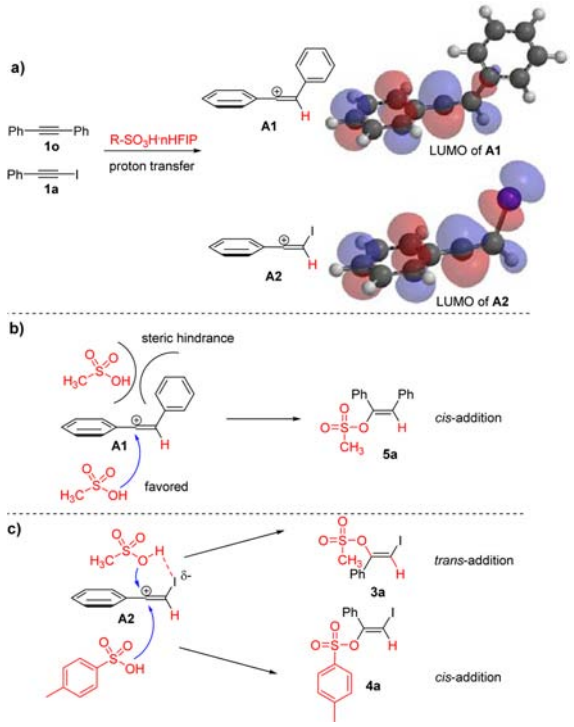
Scheme 3. Proposed Mechanism (Vinyl Cation LUMOs Calculated at the B3LYP/6-311+G(2df,2p) Level)



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