Hydrogen-bonding catalysis of sulfonium salts

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Although quaternary ammonium and phosphonium salts are known as important catalysts in phase-transfer catalysis, the catalytic ability of tertiary sulfonium salts has not yet been well demonstrated. Herein, we demonstrate the catalytic ability of trialkylsulfonium salts as hydrogen-bonding catalysts on the basis of the characteristic properties of the acidic α hydrogen atoms on alkylsulfonium salts.

The importance of onium salt compounds has been established in the field of organic chemistry.¹ Alkyl-ammonium, phosphonium, and sulfonium salts are some of the most important and reliable onium salt reagents in organic synthesis (Fig. 1). These compounds are often utilized as very useful reagents in the construction of organic building blocks, and the reactions using these reagents appear in textbooks of organic chemistry as important, named reactions.^{2,3} Furthermore, quaternary ammonium and phosphonium salts are also known as reliable catalysts, which are used to promote a wide variety of organic transformations as phase-transfer and/or base catalysts.⁴ Despite the wide synthetic utility of onium salt compounds as reagents and catalysts, the catalytic ability of tertiary sulfonium salts has not yet been demonstrated well in organic synthesis.⁵ The limitation of sulfonium salt catalysts has been attributed mainly to the high reactivity and instability of the compounds with acidic α hydrogen atoms. To create new possibilities for sulfonium salts as catalysts, we focused on the hydrogen-bonding abilities of α hydrogen atoms on alkylsulfonium salts when we reported the use of type 1 tetraalkylammonium salts as hydrogen-bonding catalysts on the basis of the characteristic properties of the α hydrogen

atoms (Fig. 2).^{6,7} Herein, we demonstrate the catalytic ability of trialkylsulfonium salts in hydrogen-bonding catalysis.⁸

	$R_4N^+ X^-$ ammonium salt	$R_4P^+ X^-$ phosphonium salt	$R_3S^+ X^-$ sulfonium salt
reagents	Hofmann elimination	Wittig reaction	Corey-Chaykovsky reaction
catalysts	phase-transfer catalyst Brønsted and Lewis base catalysts		lack of examples (this work)

Fig. 1 Onium salts in organic synthesis.

Based on the design of type 1 tetraalkylammonium salts as effective hydrogen-bonding catalysts,⁶ we focused on simple type 2 trialkylsulfonium salts (Fig. 2). The structures of the α hydrogen atoms that binded to the iodide anion compared favorably to the X-ray crystal structures of ammonium iodide 1a and sulfonium iodide 2a.^{9,10} Furthermore, we expected the acidity of the α hydrogen atoms of 2a to approximate the acidity of 1a, based on the reported pK_a values.¹¹

Fig. 2 Comparison between ammonium iodide 1a and sulfonium iodide 2a.

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With important structural information of the sulfonium salts of type **2** in hand, the catalytic ability of **2** as a hydrogen-bonding catalysts was investigated in a Mannich-type reaction of *N*-acylisoquinoline **5a**, which was generated *in situ* from 2,2,2-trichloroethyl chloroformate (TrocCl) and isoquinoline, as a benchmark reaction (Table 1).¹² As previously reported,^{6a} the reaction of **5a** with ketene silyl acetal **6a** proceeded slowly in the absence of a catalyst at $-78\text{ }^{\circ}\text{C}$ for 3 h (7% yield; entry 1). The reaction with ammonium iodide catalyst **1a** was promoted to a moderate extent (38% yield; entry 2). Sulfonium iodide **2a** was then examined as a catalyst, and a moderate acceleration of the reaction was also observed (30% yield; entry 3). It should be noted that simple ammonium iodide catalyst **3a** showed almost no acceleration of the reaction (9% yield; entry 4). These results clearly demonstrated the importance of the acidity of α hydrogen atoms on a sulfonium salt **2a** to promote the reaction. The exchange of the counteranion in **2a** to tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (BArF^-) as a non-coordinating counteranion (**2b**) improved the results (47% yield, entry 5). The reaction with benzylium sulfonium barfate **4** further improved the results, and the catalyst **4** exhibited a somewhat higher reactivity than that of ammonium barfate **1b** (67 and 61% yields, respectively; entries 6 vs. 7).

Table 1. Effect of catalysts in the Mannich-type reaction of *N*-acylisoquinoline **5a**^a

Entry	Catalyst	Yield ^b (%)
1	none ^c	7
2	1a	38
3	2a	30
4	3a	9
5	2b	47
6	4	67
7	1b	61

^aReaction conditions: **5a** (0.20 mmol), **6a** (0.30 mmol), catalyst (0.020 mmol, 10 mol %), THF (4.0 mL), $-78\text{ }^{\circ}\text{C}$, 3 h.

^bYield of the isolated product **7a**. ^cThe reaction was performed without a catalyst.

To further investigate the hydrogen-bonding interaction between the α hydrogen atoms of sulfonium salts and the

chloride substrates of type **5**, we performed NMR titration studies of benzylium sulfonium salt **4** with chlorodiphenylmethane **8** as a relatively stable chloride compound (Fig. 3). As a result of the titration of **8**, the clear upfield chemical shifts (0.065–0.073 ppm after adding 20 equiv of **8**) of the α hydrogen atoms of **4** were observed in ^1H NMR measurements (0.010 M in CDCl_3). This result strongly supported the proposition that sulfonium salts could activate chloride substrates of type **5** via hydrogen bonding to promote the Mannich-type reaction. A titration experiment with ammonium salt **1b** was also performed with the same concentration (0.010 M in CDCl_3), and the degrees of chemical shifts (0.041–0.048 ppm after adding 20 equiv of **8**) were smaller than those for the titration with **4** (Fig. S2 in Supplementary Information).

Fig. 3 ^1H NMR titration study of **4**.

Benzylium sulfonium salt catalyst **4** could accelerate the reaction of *N*-acylisoquinoline **5a** with ketone-derived silyl enol ether **6b** to give the corresponding product **7b** in a moderate yield (Scheme 1). The reaction with 3-methylisoquinoline derivative **5b** with **6a** was also accelerated by catalyst **4** to obtain product **7c** in a moderate yield. We also examined sulfonium salt-catalyzed regioselective reactions with quinolines **9**.¹³ The reaction of quinoline **9a** was efficiently promoted by catalyst **4** to give product **10a** in a good yield and regioselectivity (**10a/11a** 6:1). Furthermore, the reaction with 6-chloroquinoline **9b** gave product **10b** in a good yield with an almost perfect level of regioselectivity (**10b/11b** >30:1).

To expand the utility of sulfonium salt catalysts, we were next interested in the activation of imines **12**. An aza Diels-Alder reaction of *N*-phenylbenzaldimine **12a** and Danishefsky diene **13** was employed as a model reaction to evaluate the ability of sulfonium salt catalysts for the activation of imines (Scheme 2).^{14,15} In this reaction, sulfonium iodide **2a** showed higher reactivity than ammonium iodides **1a** and **3a**. Also, sulfonium barfate **2b** was a more effective catalyst than

ammonium barfates **1b** and **3b**, and the reaction with catalyst **2b** gave the highest yield of product **14a** (98% yield). It should be noted that the more sterically hindered benzylation barfate **4** showed reactivity that was inferior to that of **2b**. These results completely agree with our previous observations that sterically less-hindered catalysts are more effective in activating imines **12**.^{6b}

The substrate generality for the aza Diels-Alder reaction of imines **12** was examined with catalyst **2b** (Scheme 3). Not only substituted aromatics but also heteroaromatic and alkyl group-

introduced imines could be employed for the reaction to obtain products **14b–14f** in moderate to high yields (54–99% yields). It should be noted that the addition of catalyst **2b** produced clear accelerations of each reaction.

Scheme 3 Scope of the aza Diels-Alder reaction.

Furthermore, sulfonium barfate **2b** efficiently promoted the reduction of imines **12** with Hantzsch ester **15** (Scheme 4).¹⁶ The reactions with catalyst **2b** gave secondary amine products **16a–16c** in good yields (67–81% yields).¹⁷

Scheme 4 Reduction of imines **12** with Hantzsch ester **15**.

In summary, we have successfully demonstrated that trialkylsulfonium salts can function as hydrogen-bonding catalysts. The structure and binding abilities of sulfonium salts were discussed in this study based on the X-ray crystal structures and ¹H NMR titration studies. The catalytic ability of trialkylsulfonium salts was superior to that of the related tetraalkylammonium salts in both the Mannich-type reaction as well as in the aza Diels-Alder reaction. This report revealed a new dimension of sulfonium salt chemistry in organic synthesis on the basis of the characteristic properties of the acidic α hydrogen atoms on alkylsulfonium salts. Further applications of sulfonium salts as catalysts are currently underway in our group.

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