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## 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  $\alpha$  hydrogen atoms on alkylsulfonium salts.

The importance of onium salt compounds has been established in the field of organic chemistry.<sup>1</sup> 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.<sup>2,3</sup> 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.<sup>4</sup> 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.<sup>5</sup> The limitation of sulfonium salt catalysts has been attributed mainly to the high reactivity and instability of the compounds with acidic  $\alpha$  hydrogen atoms. To create new possibilities for sulfonium salts as catalysts, we focused on the hydrogen-bonding abilities of  $\alpha$  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  $\boldsymbol{\alpha}$  hydrogen

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atoms (Fig. 2).<sup>6,7</sup> Herein, we demonstrate the catalytic ability of trialkylsulfonium salts in hydrogen-bonding catalysis.<sup>8</sup>

R₄N⁺ X⁻	R₄ <b>P</b> <sup>+</sup> X <sup>–</sup>	R <sub>3</sub> S⁺ X⁻			
ammonium salt	phosphonium salt	sulfonium salt			
<i>reagents</i> Hofmann elimination	Wittig reaction	Corey-Chaykovsky reaction			
catalysts phase-tran	lack of examples				
Brønsted and Le	(this work)				

#### Fig. 1 Onium salts in organic synthesis.

Based on the design of type **1** tetraalkylammonium salts as effective hydrogen-bonding catalysts,<sup>6</sup> we focused on simple type **2** trialkylsulfonium salts (Fig. 2). The structures of the  $\alpha$  hydrogen atoms that binded to the iodide anion compared favorably to the X-ray crystal structures of ammonium iodide **1a** and sulfonium iodide **2a**.<sup>9,10</sup> Furthermore, we expected the acidity of the  $\alpha$  hydrogen atoms of **2a** to approximate the acidity of **1a**, based on the reported pK<sub>a</sub> values.<sup>11</sup>





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#### COMMUNICATION

With important structural information of the sulfonium salts of type 2 in hand, the catalytic ability of 2 as a hydrogenbonding 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).<sup>12</sup> As previously reported,<sup>6a</sup> the reaction of 5a with ketene silyl acetal 6a proceeded slowly in the absence of a catalyst at -78 °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  $\alpha$  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<sup>-</sup>) as a non-coordinating counteranion (2b) improved the results (47% yield, entry 5). The reaction with benzylsulfonium 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  $5a^{a}$ 

		OSiMe <sub>3</sub>	catalyst (10 mol %) ────►		
	5a Cl	6a	THF –78 °C, 3 h	7aCO <sub>2</sub> Me	5
		MeO <sub>2</sub> C <sup>\\\'</sup>	↔ X <sup>⊖</sup>	Me S	
	$X^{\bigcirc} \xrightarrow{\delta^{+}} H \xrightarrow{CI^{\delta^{-}}} H \xrightarrow{\delta^{+}} H$	1a : 1b :	$X^{-} = I^{-}$ $X^{-} = BArF^{-}$ $I^{\bigcirc}$ $N$ $3a$	2a : $X^- = I^-$ 2b : $X^- = BArF^-$ $\bigcirc \\ & \bigcirc \\ & \bigcirc \\ & & \bigcirc \\ & & & \\ & & & \\ & & & \\ & & & &$	
	$-\frac{\delta^{+}H}{H\delta^{+}}$	BA	rF <sup>−</sup> = [3,5-(CF	<sub>3</sub> )₂-C <sub>6</sub> H <sub>3</sub> ]₄B <sup>⊝</sup>	
En	try C	atalyst		Yield <sup>b</sup> (%)	
1	n	one <sup>c</sup>		7	
2	1	1a		38	
3	2	а		30	
4	3	a		9	
5	2	b		47	
0 7	4	h		0/ 61	
1	1	U		01	

<sup>*a*</sup>Reaction conditions: **5a** (0.20 mmol), **6a** (0.30 mmol), catalyst (0.020 mmol, 10 mol %), THF (4.0 mL), -78 °C, 3 h. <sup>*b*</sup>Yield of the isolated product **7a**. <sup>*c*</sup>The reaction was performed without a catalyst.

To further investigate the hydrogen-bonding interaction between the  $\alpha$  hydrogen atoms of sulfonium salts and the

#### chloride substrates of type **5**, we performed NMRAtitation studies of benzylsulfonium salt **4** with chlorideliphenylmethane **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 $\alpha$ hydrogen atoms of **4** were observed in <sup>1</sup>H NMR measurements (0.010 M in CDCl<sub>3</sub>). 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<sub>3</sub>), 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** <sup>1</sup>H NMR titration study of **4**.

Benzylsulfonium 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**.<sup>13</sup> 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).<sup>14,15</sup> 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

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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 benzylsulfonium 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**.<sup>6b</sup>



**Scheme 1** Benzylsulfonium barfate-catalyzed Mannich-type reactions.



**Scheme 2** Effect of catalysts in the aza Diels-Alder reaction of imine **12a**.

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 introduced imines could be employed for the introducts obtain products 14b-14f in moderate to High 1978/05/054899% 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).<sup>16</sup> The reactions with catalyst **2b** gave secondary amine products **16a–16c** in good yields (67–81% yields).<sup>17</sup>



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 <sup>1</sup>H 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  $\alpha$  hydrogen atoms on alkylsulfonium salts. Further applications of sulfonium salts as catalysts are currently underway in our group.

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