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Remarkable Enhancement of Reactivity by Brønsted Acids in Aldol Reactions Mediated by Lewis Acid–Surfactant-Combined Catalysts in Water

Kei Manabe and Shū Kobayashi*

Graduate School of Pharmaceutical Sciences, The University of Tokyo, CREST, Japan Science and Technology Corporation (JST), Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

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Abstract: *Remarkable enhancement of reactivity by a Brønsted acid such as HCl was observed in aldol reactions of aldehydes with silyl enolates in the presence of a Lewis acid–surfactant-combined catalyst, scandium tris(dodecyl sulfate) or scandium trisdodecanesulfonate, in water.*

Recently, much attention has been focused on Lewis acid-catalyzed carbon–carbon bond-forming reactions due to their unique reactivity and selectivity.[1] While diverse of Lewis acid-promoted reactions have been developed, these reactions must be generally carried out under strictly anhydrous conditions because most Lewis acids are decomposed by water. On the other hand, in the course of our investigations to develop new synthetic methods, we have found that rare earth metal triflates ($Sc(OTf)_3$, $Yb(OTf)_3$, etc.)[2–5] and some other metal salts[6,7] are water-stable Lewis acids, and catalyze several organic reactions even in aqueous solvents such as H_2O–THF. Moreover, $Sc(OTf)_3$-catalyzed aldol reactions of aldehydes with silyl enol ethers (Mukaiyama aldol reaction) in pure water have been achieved with the aid of a small amount of a surfactant such as sodium dodecyl sulfate.[8] Quite recently, we have reported that Lewis acid–surfactant-combined catalysts (LASCs), scandium tris(dodecyl sulfate) (STDS, **1**) and scandium trisdodecanesulfonate (**2**), form stable dispersion systems with organic substrates in water and efficiently catalyze aldol reactions of aldehydes with silyl enol ethers.[9]

$Sc(O_3SOC_{12}H_{25})_3$	$Sc(O_3SC_{12}H_{25})_3$
1	**2**

During our investigations on the effect of additives in the reactions mediated by LASCs, we have found that addition of a small amount of a Brønsted acid dramatically increases the reactivity of the aldol reaction. Here we describe a cooperative catalysis of the LASCs (**1**, **2**) and Brønsted acids, especially hydrogen chloride (HCl), in Mukaiyama aldol reactions in water.

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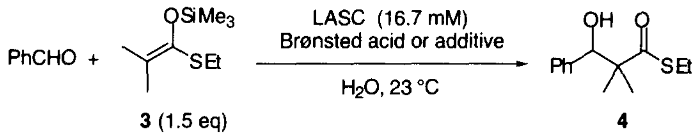
Table 1. Aldol Reactions under Various Conditions in Water



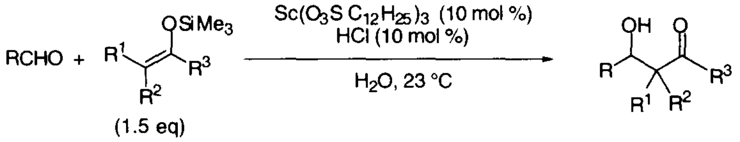
Entry	LASC (mol %)	Brønsted acid or additive (mol %)	Time (min)	Yield (%)
1	**1** (10)	-	5	16
2	**1** (10)	TsOH (10)	5	52
3	**1** (10)	TfOH (10)	5	51
4	**1** (10)	HCl (10)	5	67
5	**1** (10)	HCl (10)	15	88
6	-	TsOH (10)	5	0
7	-	HCl (10)	5	0
8	**2** (10)	-	5	10
9	**2** (10)	HCl (10)	5	67
10	**2** (10)	HCl (10)	15	89
11	**2** (10)	HCl (5)	5	52
12	**2** (10)	HCl (100)	5	41
13	$Co(O_3SC_{12}H_{25})_2$ (**5**) (10)	HCl (10)	5	0
14	$Mn(O_3SC_{12}H_{25})_2$ (**6**) (10)	HCl (10)	5	0
15	$NaO_3SOC_{12}H_{25}$ (**7**) (10)	HCl (10)	5	9
16	$Cu(O_3SOC_{12}H_{25})_2$ (**8**) (10)	HCl (10)	5	32
17	**2** (10)	$ScCl_3$ (10)	5	14
18	**2** (100)	-	2	9
19	**2** (100)	HCl (100)	2	73

The aldol reaction of benzaldehyde with thioketene silyl acetal **3** is known to be catalyzed by **1** or **2**, affording aldol adduct **4** in >90% yield in 1.5 h. As shown in Table 1, however, the reaction time of 5 min is insufficient to complete the reaction, giving **4** in only 16% yield (entry 1). To our surprise, addition of a small amount of a strong Brønsted acid accelerated the aldol reaction without decreasing the yield of the product by hydrolysis of the thioketene silyl acetal (entries 2–5). Among the Brønsted acids tested, HCl (10 mol %) gave the best results (entries 4 and 5).[10] Note that, without the LASC, the Brønsted acids alone did not catalyze the aldol reactions at all under these conditions (entries 6 and 7).[11] These results indicate that *both* the LASC (**1**) and the Brønsted acids are indispensable for the rate acceleration of the reaction. This type of Brønsted acid accelaration was also observed in the reaction mediated by another scandium LASC **2** (entry 8 vs 9), with 89% of the product after 15 min (entry 10). Decreasing the amount of HCl to 5 mol % reduced the yield (entry 11), while increasing to 100 mol % resulted in a lower yield because of the rapid hydrolysis of **3** (entry 9 vs 12). On the other hand, when other LASCs (**5**–**8**)[9] were used in the presence of 10 mol % of HCl, remarkable rate enhancement by Brønsted acids was not observed: the Co and Mn salts (**5**, **6**) did not catalyze the aldol reaction (entries 13 and

14), and the Na salt (**7**) afforded the product in a very low yield (entry 15). In the case of the Cu salt (**8**, entry 16), not only the aldol reaction but also the hydrolysis of **3** was accelerated, resulting in a lower yield than in the case using Sc salts **1** and **2**. Addition of $ScCl_3$ (instead of HCl), which is known as an effective catalyst for Mukaiyama aldol reactions in aqueous THF,[7] did not significantly affect the rate of the aldol reaction (entry 17). Finally, we carried out the reactions using a stoichiometric amount of the Sc salt. Under these conditions, HCl was also found to accelerate the reaction (entry 18 vs 19), suggesting that the key step accelerated by HCl is *not* the catalyst turnover step.[12–14] All the results stated above would suggest that the scandium cation and proton cooperatively act as a combined catalyst in the step of nucleophilic addition of **3** to benzaldehyde.[15,16]

The Brønsted acid acceleration was also observed for other substrates. As shown in Table 2, the reaction of benzaldehyde with the silyl enol ether derived from propiophenone was cooperatively catalyzed by the Sc salt and HCl (entry 1). Not only the aromatic aldehyde but α,β-unsaturated and aliphatic aldehydes afforded the products in higher yields than in the reactions without HCl (entries 2 and 3). For the reaction with a silyl enolate derived from an α-monosubstituted thioester, the Brønsted acid also accelerated the aldol reaction, although the yield was modest because of the accelerated hydrolysis of the thioketene silyl acetal (entry 4). Unfortunately, in the case of a ketene silyl acetal as a nucleophile, the hydrolysis of the acetal by HCl became the predominant pathway, giving the aldol adduct in a low yield (entry 5).

Table 2. Aldol Reactions of Various Substrates



Entry	R	R¹	R²	R³	Time (min)	Yield (%)	Yield (%) without HCl
1	Ph	Me	H	Ph	180	82[a]	35[b]
2	PhCH=CH	Me	H	Ph	300	82[c]	38[d]
3	$PhCH_2CH_2$	Me	H	Ph	300	76[c]	37[e]
4[f]	Ph	H	Me	SEt	15	56[g]	13[h]
5[f]	Ph	Me	Me	OMe	15	18	48

[a] *Syn/anti* = 57/43. [b] *Syn/anti* = 55/45. [c] *Syn/anti* = 45/55. [d] *Syn/anti* = 44/56. [e] *Syn/anti* = 47/53. [f] The Sc salt (20 mol %), silyl enolate (3 eq). [g] *Syn/anti* = 64/36. [h] *Syn/anti* = 53/47.

In summary, Brønsted acids dramatically accelerated the Mukaiyama aldol reactions mediated by LASCs in water. In particular, the combination of HCl and scandium tris(dodecyl sulfate) or scandium trisdodecanesulfonate exhibited high catalytic activity for the reactions of various substrates. This system is the first example of cooperative catalysis by a catalytic amount of a Lewis acid and a Brønsted acid in aldol reactions of silyl enolates in water. Although, from a mechanistic point of view, little is known about the real catalytic function of scandium and proton, this cooperative effect of a Lewis acid and a Brønsted acid will provide a new methodology for efficient catalytic systems in synthetic chemistry. Further investigations for improvement of the present system and its application to various reactions are now in progress.

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(10) A general experimental procedure is as follows: To a mixture of benzaldehyde (0.25 mmol, 1 eq), a Brønsted acid (10 mol %), and water (1.5 mL) was added a LASC (10 mol %). After stirring at 23 ℃ for 10 min, thioketene silyl acetal **3** (1.5 eq) was added during 30 sec, and the mixture was vigorously stirred at 23 ℃. The reaction was quenched with a mixture of satd. $NaHCO_3$ aq. (5 mL) and brine (5 mL). The product was extracted with Et_2O, dried over Na_2SO_4, concentrated, and purified by silica gel chromatography.

(11) Brønsted acids have been used as catalysts for aldol reactions of aldehydes with silyl enolates in organic solvents. For example: Kawai, M.; Onaka, M.; Izumi, Y. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1237.

(12) A precise kinetic study is currently under way.

(13) Greeves *et al.* reported benzoic acid acceleration in $Yb(OTf)_3$-catalyzed allylation of aldehydes in acetonitrile, and proposed the mechanism in which benzoic acid accelerated the catalyst regeneration step. Aspinall, H. C.; Greeves, N.; McIver, E. G. *Tetrahedron Lett.* **1998**, *39*, 9283.

(14) In their chiral Lewis acid-catalyzed Mukaiyama aldol reaction under anhydrous conditions, Evans *et al.* reported that addition of TMSOTf accelerated the rate-limiting catalyst turnover step. Evans, D. A.; Kozlowski, M. C.; Burgey, C. S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **1997**, *119*, 7893.

(15) For acetic acid acceleration in $Yb(fod)_3$-catalyzed ene reaction of aldehydes with alkyl vinyl ethers, see: Deaton, M. V.; Ciufolini, M. A. *Tetrahedron Lett.* **1993**, *34*, 2409.

(16) Yamamoto *et al.* reported Brønsted acid-assisted chiral Lewis acids and Lewis acid-assisted Brønsted acids which were used for catalytic asymmetric Diels–Alder reactions and protonations and stoichiometric asymmetric aza Diels–Alder reactions, aldol-type reactions of imines, and an aldol reaction. (a) Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 1561. (b) Ishihara, K.; Kurihara, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 3049. (c) Ishihara, K.; Nakamura, S.; Kaneeda, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 12854. (d) Ishihara, K.; Miyata, M.; Hattori, K.; Tada, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 10520. (e) Ishihara, K.; Kurihara, H.; Matsumoto, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1998**, *120*, 6920. See also: (f) Aggarwal, V. K.; Anderson, E.; Giles, R.; Zaparucha, A. *Tetrahedron: Asymmetry* **1995**, *6*, 1301.