

Development of Novel Lewis Acid Catalysts for Selective Organic Reactions in Aqueous Media

SHŪ KOBAYASHI* AND KEI MANABE

Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

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ABSTRACT

New types of Lewis acids as water-compatible catalysts have been developed. Various metal salts were found to work as Lewis acid catalysts in aqueous media, and catalytic asymmetric aldol reactions in such media have been attained. Furthermore, Lewis acid–surfactant combined catalysts, which can be used for reactions in water without using any organic cosolvents, have been also developed. These investigations will contribute to reducing the use of harmful organic solvents and to develop efficient catalytic systems which cannot be realized in conventional organic solvents.

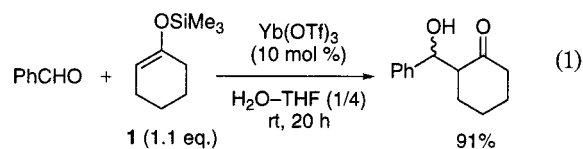
Introduction

Lewis acid catalysis has attracted much attention in organic synthesis.¹ Although various kinds of Lewis acids have been developed and many have been applied in industry, these Lewis acids generally must be used under strictly anhydrous conditions. The presence of even a small amount of water stops the reactions, because most Lewis acids immediately react with water rather than substrates. In addition, recovery and reuse of the conventional Lewis acids are formidable tasks. These disadvantages have restricted the use of Lewis acids in organic synthesis.

On the other hand, in the course of our investigations on developing new synthetic methods, we have found that rare earth metal triflates ($\text{Sc}(\text{OTf})_3$, $\text{Yb}(\text{OTf})_3$, etc.) can be used as Lewis acid catalysts in water-containing solvents (water-compatible Lewis acids).² For example, the Mukaiyama aldol reaction of benzaldehyde with silyl enol ether **1** was catalyzed by $\text{Yb}(\text{OTf})_3$ in water–THF (1/4) to give the corresponding aldol adduct in high yield (eq 1).³

Shū Kobayashi was born in Tokyo in 1959. He received his Ph.D. in 1988 under the direction of Professor T. Mukaiyama (The University of Tokyo). After spending 11 years at Science University of Tokyo, he moved to Graduate School of Pharmaceutical Sciences, The University of Tokyo, in 1998. His research interests include development of new synthetic methods and novel catalysts, organic reactions in water, solid-phase synthesis, total synthesis of biologically interesting compounds, and organometallic chemistry. He received the Springer Award in Organometallic Chemistry (1997) and IBM Science awards (2001).

Kei Manabe was born in Fujisawa, Kanagawa, Japan, in 1965. He received his Ph.D. in 1993 from The University of Tokyo under the direction of Professor K. Koga. He was then appointed as Assistant of Pharmaceutical Sciences at the University of Tokyo, and promoted to be Lecturer in 2000. From 1993 to 1995, he worked as a postdoctoral fellow with Professor G. Stork at Columbia University. His current research interest centers around the development of new catalytic systems for environmentally friendly organic synthesis.



When this reaction was carried out in dry THF (without-water), the yield of the aldol adduct was very low (ca. 10%). Thus, this catalyst is not only compatible with water but also activated by water, probably due to dissociation of the counteranions from the Lewis acidic metal. Furthermore, these catalysts can be easily recovered and reused.

These findings prompted us to investigate Lewis acid catalysis in aqueous media in further detail, because reactions in such media have the following advantages compared with reactions under anhydrous conditions. (1) It is not necessary to dry solvents and substrates for the reactions in aqueous media. This means that aqueous solutions of substrates or hydrated substrates can be directly used without further drying. (2) From the viewpoint of recent environmental consciousness, it is desirable to use water instead of organic solvents as a reaction solvent, since water is a safe, harmless, and environmentally benign solvent. Therefore, development of organic reactions in water will contribute to the progress of green chemistry.⁴ (3) Water has unique physical and chemical properties such as high dielectric constant and high cohesive energy density compared with most organic solvents. This unique nature of water is also essential for most enzymatic reactions in living systems. Many enzymes catalyze desired reactions with high efficiency and excellent stereoselectivity under mild conditions in water, and this effectiveness is often regarded as a goal for synthetic chemists. Although many researchers have developed synthetic mimics of active sites of enzymes to realize enzymatic activity, we have focused our attention on the medium of enzymatic reactions, water, which plays major roles in the reactions. By utilizing the unique nature of water, it should be possible to develop reaction systems which cannot be attained in dry organic solvents. In fact, many research groups have paid attention to organic reactions in water, which has beneficial effects (mainly hydrophobic effect and hydrogen bonding) on the reactions.⁵ In this Account, we present our recent investigations on Lewis acid-catalyzed reactions in aqueous media.

Criteria for Water-Compatible Lewis Acids

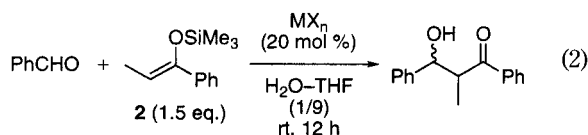
As mentioned above, $\text{Sc}(\text{OTf})_3$, $\text{Y}(\text{OTf})_3$, and lanthanide triflates ($\text{Ln}(\text{OTf})_3$) such as $\text{Yb}(\text{OTf})_3$ were found to act as Lewis acids in water-containing solvents. Although these catalytic systems need organic cosolvents such as THF to dissolve organic substrates, the systems still have the advantages of simple reaction operation and easy catalyst recovery. Therefore, we first began to study these aqueous organic solvent systems in further detail.

Table 1. Hydrolysis Constants and Exchange Rate Constants for Substitution of Inner-Sphere Water Ligands

Li ⁺¹		Be		M ⁺ⁿ												B ⁺³	C	N
13.64		—		pK _h ^a												—	—	—
4.7 × 10 ⁷		—		WERC ^b												—	—	—
Na ⁺¹		Mg ⁺²		Sc ⁺³	Ti ⁺⁴	V ⁺³	Cr ⁺³	Mn ⁺²	Fe ⁺²	Co ⁺²	Ni ⁺²	Cu ⁺²	Zn ⁺²	Ga ⁺³	Ge ⁺⁴	As		
14.18		11.44		4.3	≤ 2.3	2.26	4.0	10.59	9.5	9.65	9.86	7.53	8.96	2.6	—	—		
1.9 × 10 ⁸		5.3 × 10 ⁵		4.8 × 10 ⁷	—	1 × 10 ³	5.8 × 10 ⁻⁷	3.1 × 10 ⁷	3.2 × 10 ⁶	2 × 10 ⁵	2.7 × 10 ⁴	2 × 10 ⁸	5 × 10 ⁸	7.6 × 10 ²	—	—		
Rb	Sr	Y ⁺³	Zr ⁺⁴	Nb ⁺⁵	Mo ⁺⁵	Tc	Ru ⁺³	Rh ⁺³	Pd ⁺²	Ag ⁺¹	Cd ⁺²	In ⁺³	Sn ⁺⁴	Sb ⁺⁵				
—	—	7.7	0.22	(0.6)	—	—	—	3.4	2.3	12	10.08	4.00	—	—				
—	—	1.3 × 10 ⁷	—	—	—	—	—	3 × 10 ⁻⁸	—	> 5 × 10 ⁶	> 1 × 10 ⁸	4.0 × 10 ⁴	—	—				
Cs	Ba ⁺²	Ln ⁺³	Hf ⁺⁴	Ta ⁺⁵	W ⁺⁶	Re ⁺⁵	Os ⁺³	Ir ⁺³	Pt ⁺²	Au ⁺¹	Hg ⁺²	Tl ⁺³	Pb ⁺²	Bi ⁺³				
—	13.47	7.6-8.5	0.25	(-1)	—	—	—	—	4.8	—	3.40	0.62	7.71	1.09				
—	> 6 × 10 ⁷	10 ⁶ -10 ⁸	—	—	—	—	—	—	—	—	2 × 10 ⁹	7 × 10 ⁵	7.5 × 10 ⁹	—				
La ⁺³	Ce ⁺³	Pr ⁺³	Nd ⁺³	Pm	Sm ⁺³	Eu ⁺³	Gd ⁺³	Tb ⁺³	Dy ⁺³	Ho ⁺³	Er ⁺³	Tm ⁺³	Yb ⁺³	Lu ⁺³				
8.5	8.3	8.1	8.0	—	7.9	7.8	8.0	7.9	8.0	8.0	7.9	7.7	7.7	7.6				
2.1 × 10 ⁸	2.7 × 10 ⁸	3.1 × 10 ⁸	3.9 × 10 ⁸	—	5.9 × 10 ⁸	6.5 × 10 ⁸	6.3 × 10 ⁷	7.8 × 10 ⁷	6.3 × 10 ⁷	6.1 × 10 ⁷	1.4 × 10 ⁸	6.4 × 10 ⁶	8 × 10 ⁷	6 × 10 ⁷				

^a pK_h = -log K_h. Reference 7a,b. ^b Exchange rate constants for substitution of inner-sphere water ligands. Reference 7c.

To find other Lewis acids which can be used in aqueous solvents and to find criteria for water-compatible Lewis acids, we screened group 1–15 metal chlorides, perchlorates, and triflates in the aldol reaction of benzaldehyde with silyl enol ether **2** in water–THF (1/9) (eq 2).⁶ This



screening revealed that not only Sc(III), Y(III), and Ln(III) but also Fe(II), Cu(II), Zn(II), Cd(II), and Pb(II) worked as Lewis acids in this medium to afford the desired aldol adduct in high yields.

From these results, we noticed a correlation between the catalytic activity of the metal cations and two kinds of constants for the metal cations: hydrolysis constants (K_h) and exchange rate constants for substitution of inner-sphere water ligands (water exchange rate constants (WERC)).⁷ Table 1 shows these constants for each metal cation, and metals which exhibited good catalytic activity in the screening are surrounded by red squares. These active metal compounds were found to have pK_h values in the range from about 4 (4.3 for Sc(III)) to 10 (10.08 for Cd(II)) and WERC values greater than $3.2 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$. Cations are generally difficult to hydrolyze when their pK_h values are large. In the case that pK_h values are less than 4, cations are easily hydrolyzed to produce certain amounts of protons. Under these conditions, the silyl enol ether decomposes rapidly. On the other hand, in the case that pK_h values are more than 10, the Lewis acidities of the cations are too low to catalyze the aldol reaction. Large WERC values may be necessary to secure fast exchange between hydrating water molecules and an aldehyde which must coordinate to the metal cation to be activated. “Borderline” elements such as Mn(II), Ag(I), and In(III), whose pK_h and WERC values are close to the criteria limits,

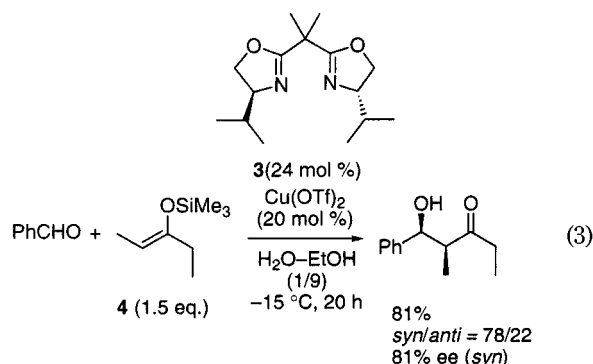
gave the aldol adduct in modest yields. Although the precise activity as Lewis acids in aqueous media cannot be quantitatively predicted by pK_h and WERC values, these results have shown the possibility of using several promising metal compounds such as Cu(II) and Pb(II) salts as water-compatible Lewis acid catalysts.

Recently, Fringuelli and co-workers reported the use of Al(III), Ti(IV), and Sn(IV) as Lewis acids for epoxide-opening reactions in acidic water, the pH of which is adjusted by adding H₂SO₄.⁸ Although this system cannot be applied to acid-sensitive substrates such as silyl enol ethers, it expands the scope of Lewis acid catalysis in aqueous media.

Catalytic Asymmetric Aldol Reactions in Aqueous Media

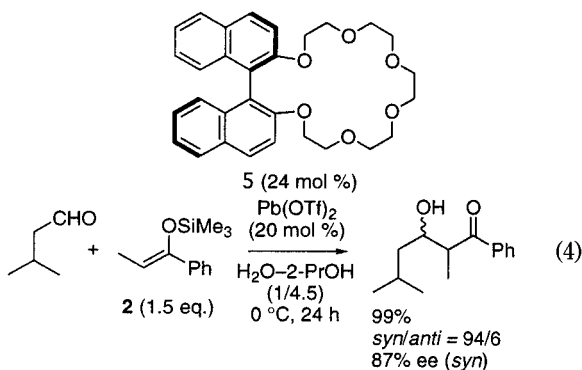
Catalytic asymmetric aldol reactions have emerged as one of the most powerful types of carbon–carbon bond-forming processes affording synthetically useful, optically active β-hydroxy carbonyl compounds.⁹ Among these reactions, chiral Lewis acid-catalyzed reactions of aldehydes with silyl enol ethers are one of the most promising methods. Although several successful examples have been developed since 1990,¹⁰ most of the reactions have to be conducted at low reaction temperatures (e.g., -78 °C) in aprotic anhydrous solvents such as dry dichloromethane, toluene, and propionitrile.

To develop new catalytic asymmetric reactions in aqueous media, we focused on several elements whose salts behave as water-compatible Lewis acids. We first chose Cu(II) and found, after several trials, that a combination of Cu(OTf)₂ and bis(oxazoline) ligand **3** was effective for aldol reactions in aqueous ethanol (eq 3).¹¹ It is surprising that simple aldehydes such as benzaldehyde gave the aldol products with good enantioselectivity, because the combination of Cu(OTf)₂ and **3** in dry organic solvents was reported to be effective only for bidentate-



type aldehydes.¹² Indeed, the reaction of benzaldehyde with silyl enol ether **4** in dry ethanol or dichloromethane in the presence of a chiral catalyst resulted in a much lower yield and selectivity (10% yield, *syn/anti* = 70/30, 41% ee (*syn*) in ethanol; 11% yield, *syn/anti* = 68/32, 20% ee (*syn*) in dichloromethane). These results indicate that water molecules not only accelerate the reaction but also play an essential role in the good enantioselectivity. Although the precise mechanism of the water effects is unclear, the following factors may operate in the present reaction. (1) Coordination of water molecules to the metal will dissociate the counteranions and lead to a change of the catalyst structure and reactivity compared with the case in dry organic solvents. (2) In water, regeneration of the active catalyst from the corresponding metal aldolate, which is an intermediate in the aldol reaction, will be very fast, because metal alkoxides are rapidly hydrolyzed in water. As a result, catalyst turnover will be faster than that in dry solvents. (3) Silyl cation equivalents, which are produced from silyl enol ethers during aldol reactions, are often responsible for the decrease of enantioselectivity in asymmetric aldol reactions to give racemic products. On the other hand, these silyl cation equivalents will be rapidly hydrolyzed in aqueous solvents; as a result, the undesired reaction pathway should be avoided.

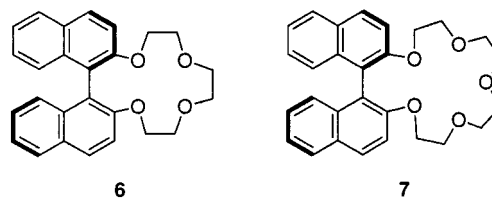
We have also developed another example of catalytic asymmetric aldol reactions in water-containing solvents using a combination of $\text{Pb}(\text{OTf})_2$ and chiral crown ether **5**¹³ (eq 4).¹⁴ In this case, a good fit in sizes between the



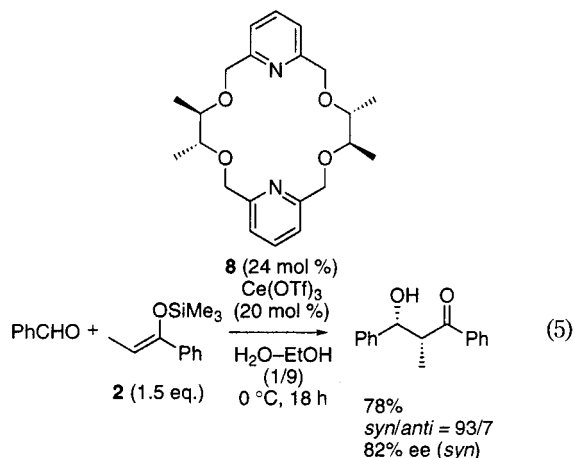
$\text{Pb}(\text{II})$ cation and the crown ring may be an important factor for the good stereoselectivity, and only the combination of $\text{Pb}(\text{II})$ and **5** exhibited substantial enantioselectivity, as shown in Table 2.

Table 2. Effect of Metal–Ligand Combinations on Asymmetric Aldol Reaction

MX_n	ligand ^a	yield (%)	<i>syn/anti</i>	ee (%), (<i>syn</i>)
$\text{Zn}(\text{OTf})_2$	6	88	69/31	2
$\text{Cu}(\text{OTf})_2$	6	86	87/13	0
$\text{Sc}(\text{OTf})_3$	7	75	52/48	1
$\text{Yb}(\text{OTf})_3$	7	74	63/37	1
AgOTf	5	61	75/25	5
$\text{Pb}(\text{OTf})_2$	5	62	90/10	55
$\text{Pb}(\text{OTf})_2$	6	78	89/11	0
$\text{Pb}(\text{OTf})_2$	7	92	89/11	0



While $\text{Ln}(\text{OTf})_3$ are the first metal salts which were found to catalyze Mukaiyama aldol reactions efficiently in aqueous media, it has been difficult to realize asymmetric versions of $\text{Ln}(\text{OTf})_3$ -catalyzed reactions in such media. Recently, we have developed the first example of this type of reaction using chiral bis-pyridino-18-crown-6 **8**¹⁵ (eq 5).¹⁶ In the reaction of benzaldehyde with **2** in



water–ethanol (1/9), the cation size of rare earth metal triflates including $\text{Ln}(\text{OTf})_3$ strongly affected the diastereo- and enantioselectivities of the aldol adduct, as shown in Figure 1. For the larger cations such as La, Ce, Pr, and Nd, both diastereo- and enantioselectivities were high, while the smaller cations such as Sc and Yb showed no enantioselection.

A study on the reaction profiles of the asymmetric aldol reactions catalyzed by $\text{Pb}(\text{OTf})_2$ with **5** or $\text{Pr}(\text{OTf})_3$ with **8** revealed that these crown ether-type chiral ligands did not significantly reduce the activity of the metal triflates.

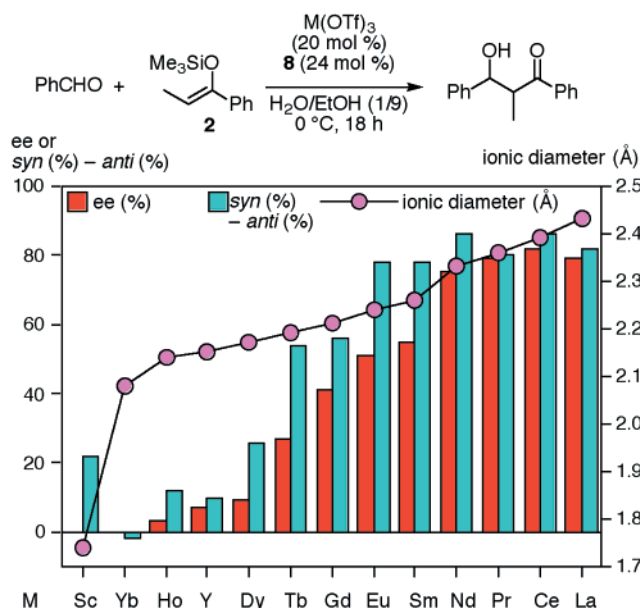


FIGURE 1. Enantio- and diastereoselectivities in the aldol reaction using rare earth metal triflates and ionic diameters (eight-coordination for Sc, nine-coordination for other metals) of the metal cations (M^{3+}). Ee: ((2*R*,3*R*)%–(2*S*,3*S*)%). Yields: 49–95%.

This retention of the activity even in the presence of the crown ethers containing oxygen and nitrogen atoms is a key to realize the asymmetric induction in these asymmetric aldol reactions in aqueous media. The X-ray structures of $Pb(OTf)_2 \cdot 5 \cdot H_2O$ and $[Pr(NO_3)_2 \cdot 8]_3 [Pr(NO_3)_6]$ show that Pb(II) and Pr(III) cations are located in the centers of the crown rings (Figure 2). We think that use of chiral multidentate ligands such as the crown ethers is a versatile concept for catalytic asymmetric reactions in aqueous media.

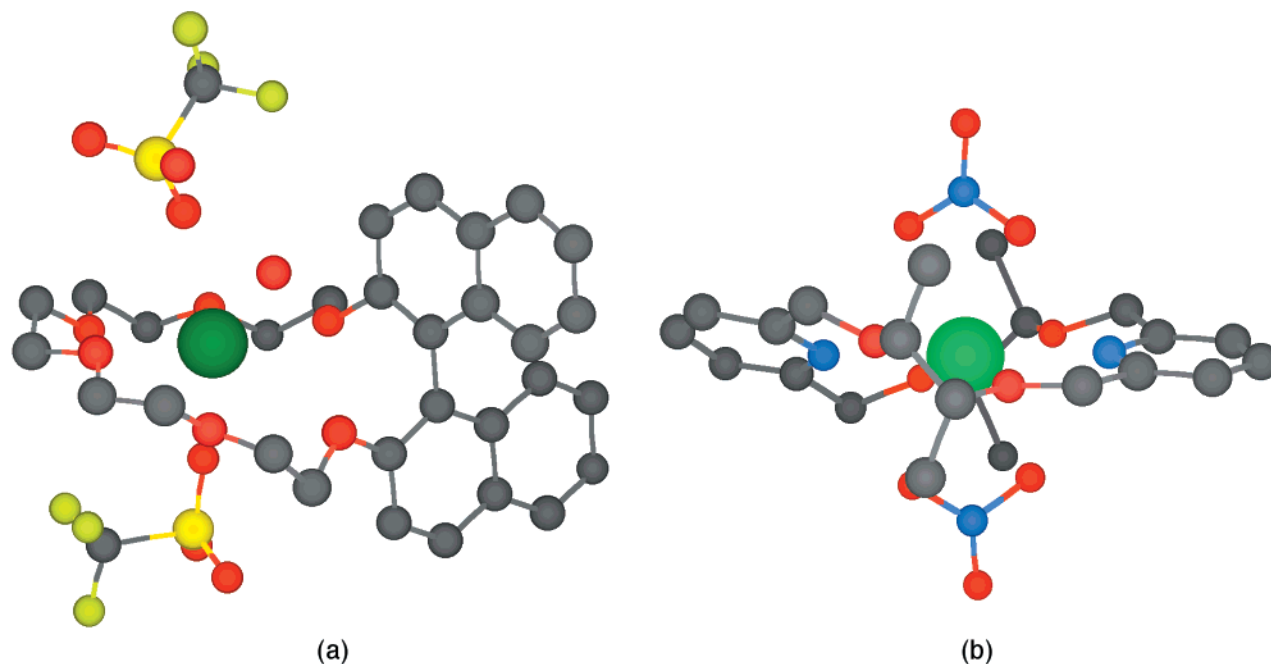


FIGURE 2. (a) X-ray structure of $Pb(OTf)_2 \cdot 5 \cdot H_2O$. (b) X-ray structure of $Pr(NO_3)_2 \cdot 8$ moiety of $[Pr(NO_3)_2 \cdot 8]_3 [Pr(NO_3)_6]$.

Surfactant-Type Lewis Acids for Reactions in Water

While the Lewis acid-catalyzed aldol reactions in water-containing solvents described above were catalyzed by several metal salts, a certain amount of organic solvents such as THF and ethanol still had to be combined with water to dissolve organic substrates and promote the reactions efficiently. From the viewpoint of today's environmental consciousness, however, it is desirable to avoid the use of harmful organic solvents. Therefore, we next initiated investigations to develop a new system for Lewis acid-catalyzed reactions in water without using organic solvents.

The main drawback in the use of water (low solubility of most organic substances in water) could be overcome by using surfactants, which solubilize organic materials or form emulsions with them in water. In fact, surfactants have occasionally been used in organic synthesis.¹⁷ However, large quantities of surfactant molecules compared with the reaction substrates are needed for many cases. To address this solubility issue, therefore, we planned to use surfactants—hopefully small amounts of them—for the Lewis acid-catalyzed reactions in water.

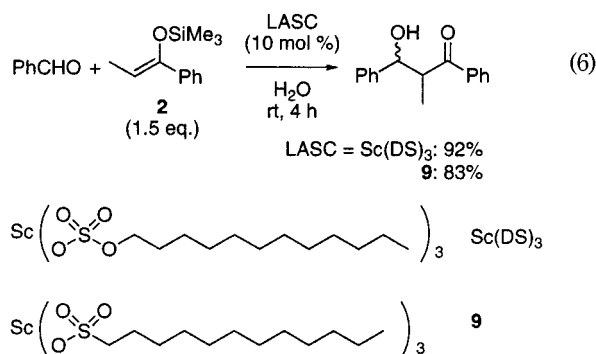
The surfactant-aided Lewis acid catalysis was first demonstrated in the model reaction shown in Table 3.¹⁸ While the reaction proceeded sluggishly in the presence of 10 mol % $Sc(OTf)_3$ in water, a remarkable enhancement of the reactivity was observed when the reaction was carried out in the presence of 10 mol % $Sc(OTf)_3$ in an aqueous solution of sodium dodecyl sulfate (SDS, 20 mol %, 35 mM), and the corresponding aldol adduct was obtained in high yield. It was found that the type of surfactant influenced the yield, and that Triton X-100, a nonionic surfactant, was effective in the aldol reaction (but required longer reaction time), while only a trace amount

Table 3. Effect of Surfactants on Aldol Reaction in Water

surfactant	time (h)	yield (%)
–	4	3
SDS	4	88
Triton X-100	60	89
CTAB	4	trace

of the adduct was detected when using a representative cationic surfactant, cetyltrimethylammonium bromide (CTAB). The effectiveness of the anionic surfactant is attributed to a high local concentration of scandium cation on the surfaces of dispersed organic phases, which are surrounded by the surfactant molecules.

The results mentioned above prompted us to synthesize a more simplified catalyst, scandium tris(dodecyl sulfate) ($\text{Sc}(\text{DS})_3$).¹⁹ This new type of catalyst, “Lewis acid–surfactant combined catalyst (LASC)”, was expected to act *both* as a Lewis acid to activate the substrate molecules *and* as a surfactant to form emulsions in water. Engberts and co-workers also reported a surfactant-type Lewis acid, copper bis(dodecyl sulfate) ($\text{Cu}(\text{DS})_2$).²⁰ Although they studied detailed mechanistic aspects of Diels–Alder reactions in water, the reaction needs an excess of the catalyst compared with the reaction substrates and has severe substrate limitations. On the other hand, catalytic amounts of $\text{Sc}(\text{DS})_3$ and another LASC, **9**, efficiently promoted the aldol reaction of benzaldehyde with silyl enol ether **2** in water (eq 6). While $\text{Sc}(\text{DS})_3$ and **9** are only slightly soluble

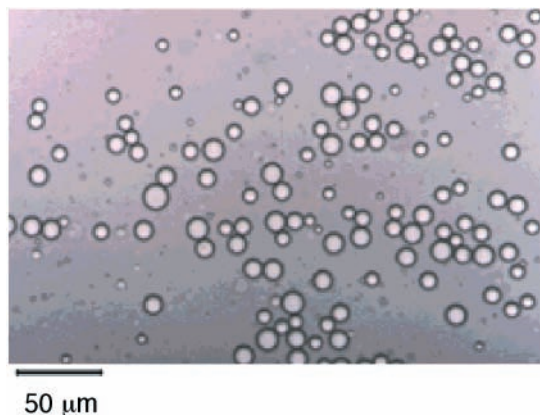


in water, stable emulsions were formed upon addition of the aldehyde with stirring or vigorous mixing. Addition of **2**, followed by stirring at room temperature for 4 h, afforded the desired aldol product in high yields. It should be noted that hydrolysis of the silyl enol ether is not a severe problem under the reaction conditions despite the water-labile nature of silyl enol ethers under acidic conditions.

We also found that $\text{Sc}(\text{DS})_3$ worked well only in water rather than in organic solvents (Table 4). A kinetic study on the initial rate of the aldol reaction revealed that the reaction in water was about 100 times faster than that in

Table 4. Effect of Solvents on LASC-Catalyzed Aldol Reaction

solvent	yield (%)	solvent	yield (%)
H_2O	92	THF	trace
MeOH	4	Et_2O	trace
DMF	14	toluene	trace
DMSO	9	hexane	4
MeCN	3	– (neat)	31
CH_2Cl_2	3		


FIGURE 3. Optical micrograph of a mixture of **9** and benzaldehyde in water (**9**:PhCHO = 1:20).

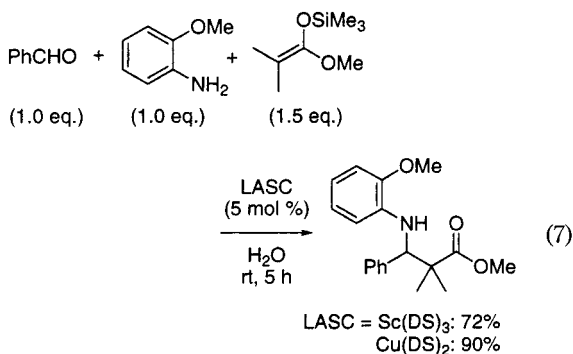
dichloromethane. In addition, the reaction under neat conditions was slower than that in water and resulted in a lower yield (31%), showing the advantage of the use of water in this reaction. This advantageous effect of water is attributed to the following factors: (1) hydrophobic interactions in water to concentrate the catalyst and the substrates; (2) aggregation of the substrates through hydrophobic interactions, which squeeze water molecules out of the organic substrate phase, leading to reducing the rate of hydrolysis of the silyl enol ethers; (3) hydration of Sc(III) ion and the counteranion by water molecules to form highly Lewis acidic species such as $[\text{Sc}(\text{H}_2\text{O})_n]^{3+}$; (4) rapid hydrolysis of the initially formed scandium aldolate to secure fast catalytic turnover.

Various substrates have been successfully used in the present LASC-catalyzed aldol reaction. Aromatic as well as aliphatic, α,β -unsaturated, and heterocyclic aldehydes worked well. As for silyl enolates, silyl enol ethers derived from ketones as well as ketene silyl acetals derived from a thioester and an ester reacted well to give the corresponding adducts in high yields. Highly water-sensitive ketene silyl acetals reacted smoothly in water under these conditions.

In the LASC-catalyzed reactions, the formation of stable emulsions seemed to be essential for efficient catalysis. We thus undertook the observation of the emulsions by means of several tools. Optical microscopic observations of the emulsions revealed the formation of spherical emulsion droplets in water (Figure 3). The average size of

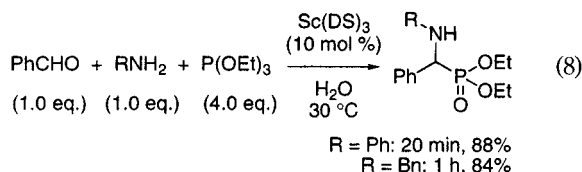
the droplets formed from **9** in the presence of benzaldehyde in water was measured by dynamic light scattering and proved to be ca. 1.1 μm in diameter. The shape and size of the emulsion droplets were also confirmed by transmission electron microscopy and atomic force microscopy.

LASCs were also found to be applicable to other Lewis acid-catalyzed reactions in water. For example, three-component Mannich-type reactions of aldehydes, amines, and silyl enolates in water were catalyzed by $\text{Sc}(\text{DS})_3$ (eq 7).^{19b} In this case, $\text{Cu}(\text{DS})_2$,^{20,21} another LASC, gave the



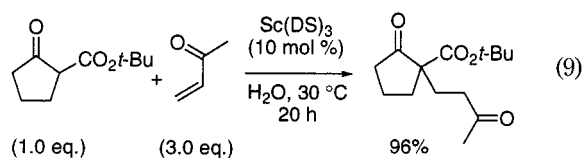
product in slightly higher yield. This reaction system will provide a useful method for the synthesis of β -amino carbonyl compounds, which constitute various pharmaceuticals, natural products, and versatile synthetic intermediates.

Use of a phosphite ester as a nucleophilic component enables $\text{Sc}(\text{DS})_3$ -catalyzed three-component α -amino phosphonate synthesis in water (eq 8).²² A characteristic point



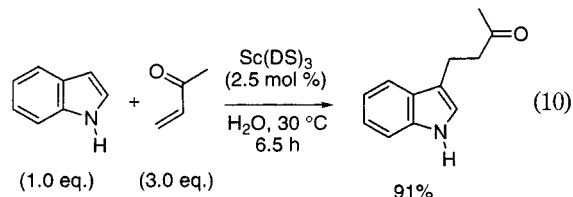
of these reactions is the extremely short reaction time. In the case of aniline-type amines such as aniline and *o*-anisidine, the reaction proceeded rapidly, and greater than 80% yields of the products were attained in 20–30 min. Thus, the turnover frequencies (TOFs) for these reactions are 17–26 h^{-1} , in contrast to reported procedures in organic solvents, in which the TOFs are less than 1 h^{-1} .²³

Michael reactions are one of the most useful types of carbon–carbon bond-forming reactions in organic synthesis, and Lewis acid-catalyzed versions have been developed to solve problems which are often observed in traditional, base-catalyzed Michael reactions. $\text{Sc}(\text{DS})_3$ can be also applied to Michael reactions in water, as shown in eq 9.²⁴ Compared with $\text{Yb}(\text{OTf})_3$ -catalyzed Michael



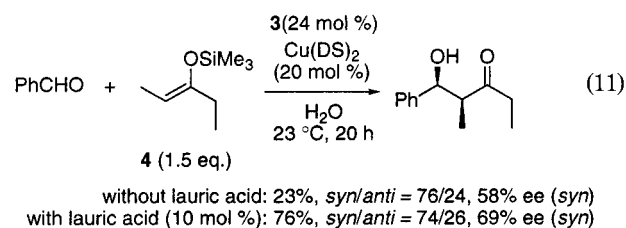
reactions in water,²⁵ the $\text{Sc}(\text{DS})_3$ -catalyzed reaction was found to be very fast.

Similarly, reactions of indoles with electron-deficient olefins were catalyzed by $\text{Sc}(\text{DS})_3$ (eq 10).²⁶ As for electron-



deficient olefins, not only enones but also β -nitrostyrene were successfully used. It is noteworthy that solid substrates such as indole and β -nitrostyrene as well as liquid ones reacted smoothly. This is the first example of Lewis acid-catalyzed Friedel–Crafts-type reactions of aromatic compounds in water.

Catalytic asymmetric aldol reactions in water have been attained by a combination of $\text{Cu}(\text{DS})_2$ and chiral bis-(oxazoline) ligand **3**.²⁷ In this case, addition of a Brønsted acid, especially a carboxylic acid such as lauric acid, is essential for good yield and enantioselectivity (eq 11). This



is the first example of Lewis acid-catalyzed asymmetric aldol reactions in water without using organic solvents. Although the yield and the selectivities have not yet been optimized, it is noted that this enantioselectivity has been achieved at ambient temperature in water.

The concept of surfactant-type catalysts described above was also found to be applicable to catalytic systems other than Lewis acid-catalyzed reactions. For example, we have developed Brønsted acid-catalyzed Mannich-type^{28,29} and esterification reactions³⁰ using a surfactant-type acid, dodecylbenzenesulfonic acid (DBSA), and palladium-catalyzed allylic substitution reactions using a combination of $\text{Pd}(\text{PPh}_3)_4$ and a nonionic surfactant, Triton X-100.³¹

Quite recently, we have developed a new catalytic system for aldol reactions in water. The reaction of benzaldehyde with silyl enol ether **2** was catalyzed by a combination of diphenylborinic acid (Ph_2BOH), benzoic acid, and SDS in water to give the aldol adduct in high yield with a high *syn/anti* ratio (eq 12).³² All of the three

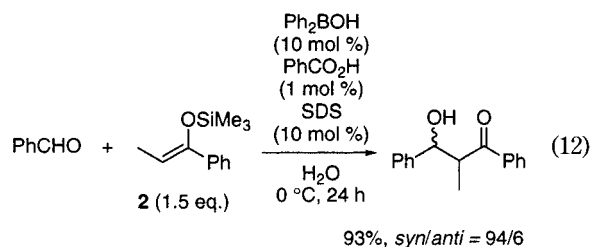
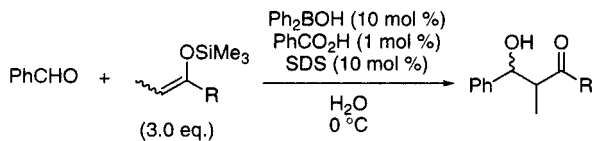
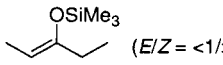
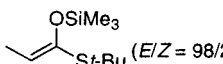
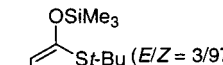
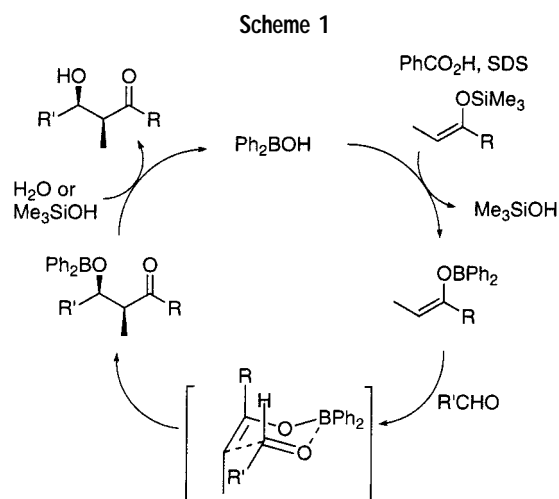


Table 5. Diastereoselective Aldol Reactions in Water


Silyl enolate	Time (h)	Yield (%)	syn/anti
 (E/Z = <1/>99)	8 ^a	60	96/4
 (E/Z = 98/2)	18	62	96/4
 (E/Z = 3/97)	72	84	39/61

^a At 30 °C.

components in the catalyst combination were indispensable for the high yield and selectivity. This high diastereoselectivity was unexpected for us, because lower diastereoselectivity had been obtained in previous Lewis acid-catalyzed aldol reactions in water (in the case of Sc(DS)₃, syn/anti = ca. 1/1). Furthermore, the diastereoselectivity was found to depend on the olefin geometry of the silyl enol ethers used, as shown in Table 5.

A kinetic study of the Ph₂BOH-catalyzed reactions of several aldehydes with **2** revealed that the rate of the disappearance of **2** followed first-order kinetics and was independent of the reactivity of the aldehydes used. Taking into account this result, we have proposed a reaction mechanism in which a silyl enol ether is transformed to the corresponding diphenylboryl enolate before the aldol addition step takes place (Scheme 1). The high diastereoselectivity is consistent with the mechanism, in which the aldol step proceeds via a chairlike six-membered transition state. The opposite diastereoselectivity in the reaction with the geometric isomers of the thioketene silyl acetal shown in Table 5 also supports the mechanism via the boron enolate, because this trend was also observed in the classical boron enolate-mediated reactions in dry organic solvents.³³ Although we have not yet

observed the boron enolates directly under the reaction conditions, this mechanism can explain all of the experimental data obtained and is considered to be the most reasonable one. As far as we know, this is the first example of the formation of boron enolates using a catalytic amount of a boron source. In addition, it is noted that these catalytic boron–enolate reactions have been attained in water, in which boron enolates had been believed to be too water-sensitive to use as substrates for aqueous reactions. These results are expected to open a new field for development of aqueous systems for water-sensitive compounds.

Conclusion

In this Account, we have described our recent investigations on Lewis acid-catalyzed reactions, most of which are carbon–carbon bond-forming reactions, in aqueous media. Various metal cations can function as useful Lewis acid catalysts in aqueous solution. Asymmetric aldol reactions have also been developed. Furthermore, surfactant-type Lewis acids, LASCs, promoted reactions in water without organic cosolvents. In addition, the concept of surfactant-type catalytic systems has been extended to include types of catalysis other than Lewis acids. The Lewis acids described in this Account are expected to be new types of catalysts providing certain solutions for environmental problems associated with use of harmful organic solvents. Since our discovery of the Yb(OTf)₃-catalyzed aldol reactions in aqueous media,^{2d} some Lewis acid-catalyzed reactions, mainly Diels–Alder reactions, in water have been developed.^{8,20,25,34} The field of Lewis acid catalysis in aqueous media is expanding and will lead to efficient catalytic systems which cannot be realized in conventional organic solvents.

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