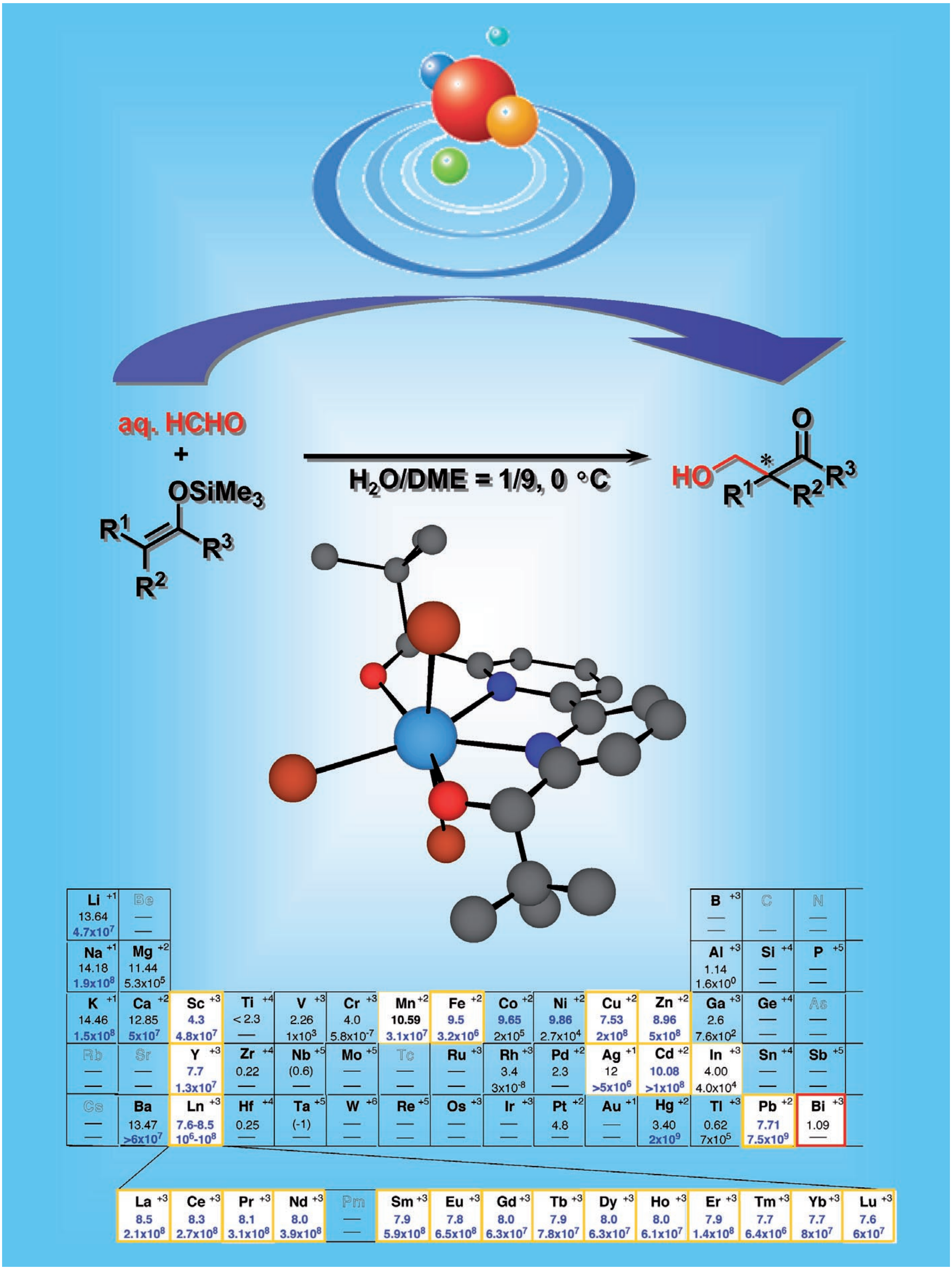

Li $^{+1}$ 13.64 4.7×10^{7}	Be — —											B $^{+3}$ — —	C —	N — —
Na $^{+1}$ 14.18 1.9×10^{8}	Mg $^{+2}$ 11.44 5.3×10^{5}											Al $^{+3}$ 1.14 1.6×10^{0}	Si $^{+4}$ — —	P $^{+5}$ — —
K $^{+1}$ 14.46 1.5×10^{8}	Ca $^{+2}$ 12.85 5×10^{7}	Sc $^{+3}$ 4.3 4.8×10^{7}	Ti $^{+4}$ < 2.3 —	V $^{+3}$ 2.26 1×10^{3}	Cr $^{+3}$ 4.0 5.8×10^{-7}	Mn $^{+2}$ 10.59 3.1×10^{7}	Fe $^{+2}$ 9.5 3.2×10^{6}	Co $^{+2}$ 9.65 2×10^{5}	Ni $^{+2}$ 9.86 2.7×10^{4}	Cu $^{+2}$ 7.53 2×10^{8}	Zn $^{+2}$ 8.96 5×10^{8}	Ga $^{+3}$ 2.6 7.6×10^{2}	Ge $^{+4}$ — —	As — —
Rb — —	Sr — —	Y $^{+3}$ 7.7 1.3×10^{7}	Zr $^{+4}$ 0.22 —	Nb $^{+5}$ (0.6) —	Mo $^{+5}$ — —	Tc — —	Ru $^{+3}$ — —	Rh $^{+3}$ 3.4 3×10^{-8}	Pd $^{+2}$ 2.3 —	Ag $^{+1}$ 12 $>5\times10^{6}$	Cd $^{+2}$ 10.08 $>1\times10^{8}$	In $^{+3}$ 4.00 4.0×10^{4}	Sn $^{+4}$ — —	Sb $^{+5}$ — —
Cs — —	Ba 13.47 $>6\times10^{7}$	Ln $^{+3}$ 7.6-8.5 10^{6}-10^{8}	Hf $^{+4}$ 0.25 —	Ta $^{+5}$ (-1) —	W $^{+6}$ — —	Re $^{+5}$ — —	Os $^{+3}$ — —	Ir $^{+3}$ — —	Pt $^{+2}$ 4.8 —	Au $^{+1}$ — —	Hg $^{+2}$ 3.40 2×10^{9}	Tl $^{+3}$ 0.62 7×10^{5}	Pb $^{+2}$ 7.71 7.5×10^{9}	Bi $^{+3}$ 1.09 —

La $^{+3}$ 8.5 2.1×10^{8}	Ce $^{+3}$ 8.3 2.7×10^{8}	Pr $^{+3}$ 8.1 3.1×10^{8}	Nd $^{+3}$ 8.0 3.9×10^{8}	Pm — —	Sm $^{+3}$ 7.9 5.9×10^{8}	Eu $^{+3}$ 7.8 6.5×10^{8}	Gd $^{+3}$ 8.0 6.3×10^{7}	Tb $^{+3}$ 7.9 7.8×10^{7}	Dy $^{+3}$ 8.0 6.3×10^{7}	Ho $^{+3}$ 8.0 6.1×10^{7}	Er $^{+3}$ 7.9 1.4×10^{8}	Tm $^{+3}$ 7.7 6.4×10^{6}	Yb $^{+3}$ 7.7 8×10^{7}	Lu $^{+3}$ 7.6 6×10^{7}

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New Entries to Water-Compatible Lewis Acids

Shu Kobayashi* and Chikako Ogawa[a]

Abstract: Lewis acid catalysis has attracted much attention in organic synthesis as it often affords access to unique reactivity and selectivity under mild conditions. Although various kinds of Lewis acids have been developed and applied in industry, these Lewis acids must be generally used under strictly anhydrous conditions, as the presence of even a small amount of water interferes with the reactions due to preferential reaction of the Lewis acids with water rather than the substrates. In contrast to this, rare earth and other metal complexes have been found to be water-compatible. Furthermore, $Bi(OTf)_3$- and $Ga(OTf)_3$-basic ligand complexes have also been found to be stable in water, and have been used as water-compatible Lewis acids. This application is particularly significant, as $Bi(OTf)_3$ and $Ga(OTf)_3$ themselves are unstable in the presence of water, but are stabilized by the basic ligands. This observation has led to the development of a new approach to Lewis acid catalysis in which Lewis acids that are generally unstable in the presence of water are rendered amenable to aqueous systems when combined with basic ligands. In particular, the use of chiral basic ligands leading to new types of water-compatible chiral Lewis acids may enable a wide range of asymmetric catalysis in aqueous media.

Keywords: asymmetric catalysis • C−C bond formation • Lewis acids • rare earth metals • water chemistry

Introduction

Organic reactions in aqueous media are of current interest due to the key roles played by water as a solvent for green chemistry.[1] Indeed, water is a safe, harmless, and environmentally benign solvent. In addition, from practical and synthetic standpoints, a benefit of using water is immediately evident as it is not necessary to dry solvents and substrates for the reactions in aqueous media, and aqueous solutions of substrates or hydrated substrates can be directly used without further drying. Moreover, water has unique physical and chemical properties, such as high dielectric constant and high cohesive energy density relative to most organic solvents. By utilizing these properties, highly efficient and selective enzymatic reactions are conducted in living systems under mild conditions. Notably, the medium of enzymatic reactions is water, which plays major roles in the reactions. If the unique nature of water could be utilized in vitro as it is in vivo, it would be possible to develop interesting reactions with unique reactivity and selectivity that cannot be attained in organic solvents.

On the other hand, Lewis acid catalysis has attracted much attention in organic synthesis.[2] Unique reactivity and selectivity are often observed under mild conditions in Lewis acid catalyzed reactions. Although various kinds of Lewis acids have been developed and many have been applied in industry, these Lewis acids must be generally 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 conventional Lewis acids are difficult, and these disadvantages have restricted the use of Lewis acids in organic synthesis.

Water-Compatible Lewis Acids

While most Lewis acids decompose in water, it was found that rare earth triflates ($Sc(OTf)_3$, $Yb(OTf)_3$, etc.) can be used as Lewis acid catalysts in water or water-containing solvents (water-compatible Lewis acids).[3] For example, the

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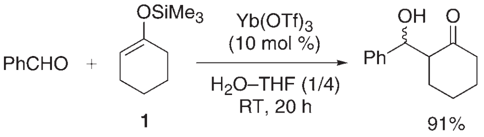
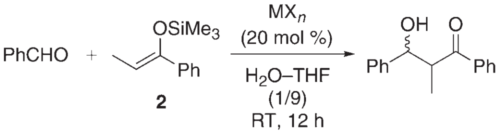
Mukaiyama aldol reaction of benzaldehyde with silyl enol ether **1** was catalyzed by $Yb(OTf)_3$ in water/THF (1:4) to give the corresponding aldol adduct in high yield [Eq. (1)].[4] Interestingly, when this reaction was carried out in dry THF (without water), the yield of the aldol adduct was very low (ca. 10%). Thus, this catalyst is not only compatible with water, but is also activated by water, probably due to dissociation of the counterions from the Lewis acidic metal. Furthermore, in this example, the catalyst can be easily recovered and reused.



(1)

Metal salts other than those derived from rare earth elements were also found to be water-compatible Lewis acids. To find other Lewis acids that can be used in aqueous solvents and to find criteria for water-compatible Lewis acids, Group 1–15 metal chlorides, perchlorates, and triflates were screened in the aldol reaction of benzaldehyde with silyl enol ether **2** in water/THF (1:9) [Eq. (2)].[5] 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.

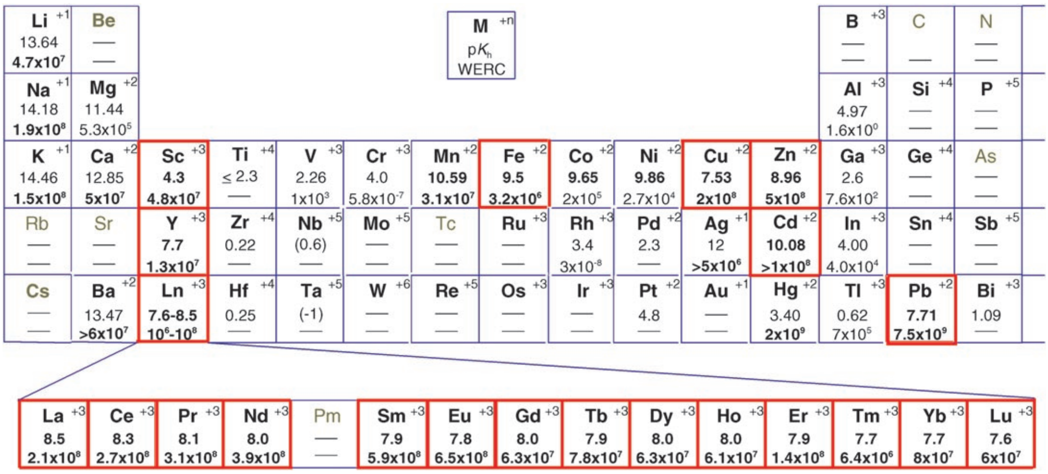


(2)

From these results, a correlation between the catalytic activity of the metal cations and their hydrolysis constants (K_h) and exchange rate constants for substitution of inner-sphere water ligands (water exchange rate constants (WERC)) was revealed.[6] Figure 1 shows these constants for each metal cation; metals which exhibited good catalytic activity in the screening (>50% yield) 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 $3.2\times10^6\,\text{M}^{-1}\,\text{s}^{-1}$. Cations with large pK_h values do not generally undergo efficient hydrolysis. In cases in which the pK_h values are less than 4, cations are readily hydrolyzed to produce protons in sufficient number to cause rapid decomposition of the silyl enol ether. On the other hand, if the pK_h values higher than 10, the Lewis acidities of the cations concerned are too low to catalyze the aldol reaction. Large WERC values may be necessary to have sufficiently fast exchange between the water molecules coordinated to the metal and the aldehyde substrate, and so to act as efficient catalyst. "Borderline" species, such as Mn^{II}, Ag^{I}, and In^{III}, the pK_h and WERC values of which are close to the criteria limits, gave the aldol adduct in moderate yields. Whereas the precise activity of Lewis acids in aqueous media cannot be quantitatively predicted by pK_h and WERC values, the use of this technique has led to the identification of promising metal compounds as water-compatible Lewis acid catalysts,[7] and also provide mechanistic insights into Lewis acid catalysis in aqueous media.

Lewis Acids Stabilized by Ligands in Water: The Cases of Bi^{III} and Ga^{III}

Discovery of water-compatible Lewis acids has greatly expanded the use of Lewis acids in organic synthesis in aqueous media. However, conventional Lewis acids such as Al^{III}, Ti^{IV}, Sn^{IV}, and so forth still cannot be used in aqueous media under standard conditions. This restriction has been partially removed by recent work.



Li +1 13.64 4.7×10^{7}	Be — —					M +n pK_h WERC						B +3 — —	C — —	N — —
Na +1 14.18 1.9×10^{8}	Mg +2 11.44 5.3×10^{5}											Al +3 4.97 1.6×10^{0}	Si +4 — —	P +5 — —
K +1 14.46 1.5×10^{8}	Ca +2 12.85 5×10^{7}	Sc +3 4.3 4.8×10^{7}	Ti +4 ≤ 2.3 —	V +3 2.26 1×10^{3}	Cr +3 4.0 5.8×10^{-7}	Mn +2 10.59 3.1×10^{7}	Fe +2 9.5 3.2×10^{6}	Co +2 9.65 2×10^{5}	Ni +2 9.86 2.7×10^{4}	Cu +2 7.53 2×10^{8}	Zn +2 8.96 5×10^{8}	Ga +3 2.6 7.6×10^{2}	Ge +4 — —	As — —
Rb — —	Sr — —	Y +3 7.7 1.3×10^{7}	Zr +4 0.22 —	Nb +5 (0.6) —	Mo +5 — —	Tc — —	Ru +3 — —	Rh +3 3.4 3×10^{-8}	Pd +2 2.3 —	Ag +1 12 $>5\times10^{6}$	Cd +2 10.08 $>1\times10^{8}$	In +3 4.00 4.0×10^{4}	Sn +4 — —	Sb +5 — —
Cs — —	Ba +2 13.47 $>6\times10^{7}$	Ln +3 7.6-8.5 10^{6}-10^{8}	Hf +4 0.25 —	Ta +5 (-1) —	W +6 — —	Re +5 — —	Os +3 — —	Ir +3 — —	Pt +2 4.8 —	Au +1 — —	Hg +2 3.40 2×10^{9}	Tl +3 0.62 7×10^{5}	Pb +2 7.71 7.5×10^{9}	Bi +3 1.09 —
La +3 8.5 2.1×10^{8}	Ce +3 8.3 2.7×10^{8}	Pr +3 8.1 3.1×10^{8}	Nd +3 8.0 3.9×10^{8}	Pm — —	Sm +3 7.9 5.9×10^{8}	Eu +3 7.8 6.5×10^{8}	Gd +3 8.0 6.3×10^{7}	Tb +3 7.9 7.8×10^{7}	Dy +3 8.0 6.3×10^{7}	Ho +3 8.0 6.1×10^{7}	Er +3 7.9 1.4×10^{8}	Tm +3 7.7 6.4×10^{6}	Yb +3 7.7 8×10^{7}	Lu +3 7.6 6×10^{7}

Figure 1. Hydrolysis ($pK_h = -\log K_h$.[7a,b]; upper value) and exchange-rate constants (WERC; lower value)[7c] for the substitution of inner-sphere water ligands.

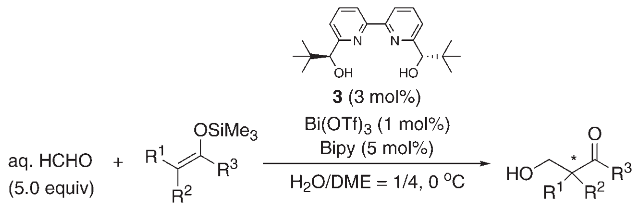
Due to increasing demands for optically active compounds, many catalytic asymmetric reactions have been investigated over the last ten years. However, asymmetric catalysis in water or water/organic solvent systems is difficult because many chiral catalysts are not stable in the presence of water.[8] In particular, chiral Lewis acid catalysis in aqueous media is extremely difficult because most of them decompose rapidly in the presence of water.[9] To address this issue, catalytic asymmetric reactions with water-compatible Lewis acids with chiral ligands have been developed.[10] During this work, we encountered the phenomenum that Lewis acids that are decomposed in the presence of water might be stabilized by combining with chiral basic ligands in water.

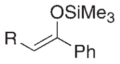
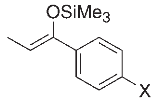
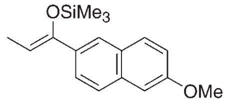
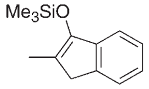
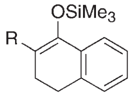
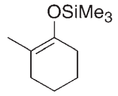
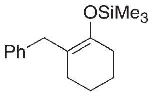
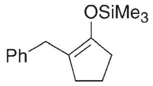
Formaldehyde is one of the most important C1 electrophiles in organic synthesis. Whereas hydroxymethylation of enolate components with formaldehyde provides an efficient method to introduce a C1 functional group at the α-position of carbonyl groups, few successful examples of catalytic asymmetric hydroxymethylation have been reported.[11,12]

Recently highly enantioselective, catalytic hydroxymethylation reactions of silicon enolates with an aqueous formaldehyde solution have been developed by using a novel scandium complex prepared from $Sc(OTf)_3$ and chiral bipyridine **3**.[13] Indeed, Lewis acid catalyzed hydroxymethylation of silicon enolates[14] is promising, and the reactions are expected to proceed regioselectively with excellent substrate generality and synthetic efficiency. As for the formaldehyde source, use of a commercial aqueous solution of formaldehyde is the most convenient, because it avoids tedious and harmful procedures to generate formaldehyde monomer from formaldehyde oligomers such as paraformaldehyde and trioxane.[15] It should be noted that a novel chiral scandium complex has realized highly enantioselective, catalytic hydroxymethylation of silicon enolates with a formaldehyde aqueous solution.

As an extension of this work, other metal salts (10 mol %) and chiral bipyridine **3**[16] (12 mol %) in the reaction of silicon enolate **2** with an aqueous formaldehyde solution were tested, and remarkably it was found that $Bi(OTf)_3$[17] gave promising results. In addition to the big difference in the ionic diameters between bismuth (2.34 Å for eight-coordinate) and scandium (1.74 Å for eight-coordinate), this result was unexpected, because $Bi(OTf)_3$ is known to be hydrolyzed in the presence of water.[18] Only a trace amount of the hydroxymethylated adduct was obtained when $Bi(OTf)_3$ was used in the absence of the chiral bipyridine,[19] since it is known that silicon enolates such as **2** are rapidly decomposed by TfOH, which was easily generated from $Bi(OTf)_3$ in water. On the other hand, decomposition of silicon enolate **2** was slow and the desired hydroxymethylation proceeded in the presence of $Bi(OTf)_3$ and **3**. These results indicate that $Bi(OTf)_3$ was stabilized by chiral bipyridine **3** in water. As a chiral bismuth catalyst, it was revealed that the desired product was obtained in 94 % yield with 91 % *ee* by using 1 mol % $Bi(OTf)_3$ and 3 mol % **3** in the coexistence of 5 mol % of 2,2′-bipyridine. Several other substrates were applicable to this catalyst system (Table 1).[20] The hydroxymethylation proceeded smoothly by using an aqueous formaldehyde solution to afford the desired adducts in high yields with high enantioselectivities. It is worth noting that asymmetric quaternary carbon atoms were constructed with high selectivities.

Table 1. Bi-catalyzed hydroxymethylation.



Entry	Enolate	Time [h]	Yield[a] [%]	*ee*[b] [%]
1	 R = Me (**2**)	21	93	91
2	R = Et	70	79	92
3	 X = MeO	30	80	88
4	X = Cl	34	87	89
5		22	59	92
6		9	89	88
7	 R = Me	22	81	95
8	R = C_4H_9	22	68	93
9		20	66	77
10		48	79	92
11		20	82	79

[a] Isolated yield. [b] Determined by chiral HPLC analysis.

From several experiments, it was revealed that the active catalyst was formed from an equimolar mixture of $Bi(OTf)_3$ and **3**. X-ray crystal structure of the $BiBr_3$-**3** complex is shown in Figure 2. The complex adopts a pentagonal bipyramidal structure in which the tetradentate ligand occupies four of the equatorial sites. The structure of the $Bi^{III}Br_3$ complex of **3** is closely related to that of the corresponding $Sc^{III}Br_3$ complex.[21] NMR analysis of formation of $Bi(OTf)_3$–**3** complexes with different ratios of $Bi(OTf)_3$ and **3** was conducted (Figure 3). When $Bi(OTf)_3$ and **3** were combined in the ratio of 1:0.5, the signal at $\delta = 5.49$ ppm was dominant. Increasing the ligand/$Bi(OTf)_3$ ratio resulted in the appearance of another signal at $\delta = 4.72$ ppm and the

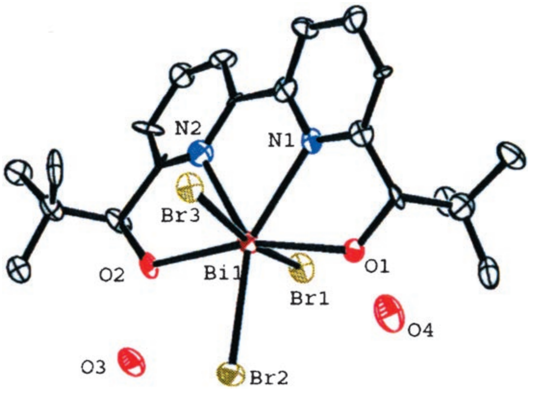


Figure 2. Ortep drawing of the X-ray crystal structure of $[BiBr_3.\mathbf{1}]\cdot 2H_2O\cdot DME$. DME is omitted for clarity.

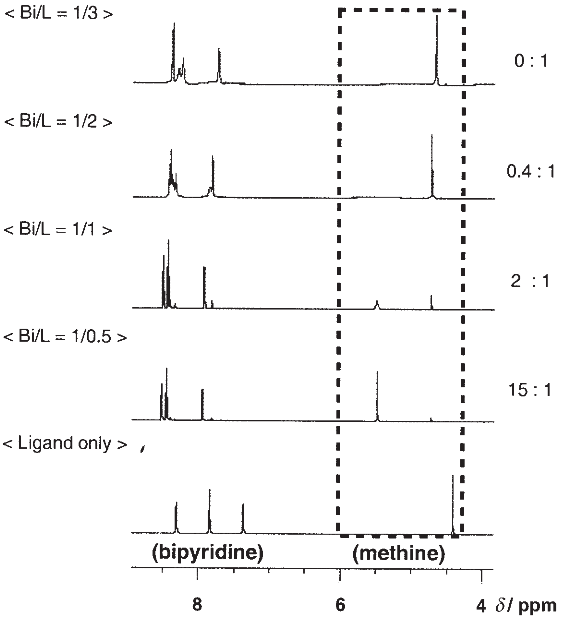


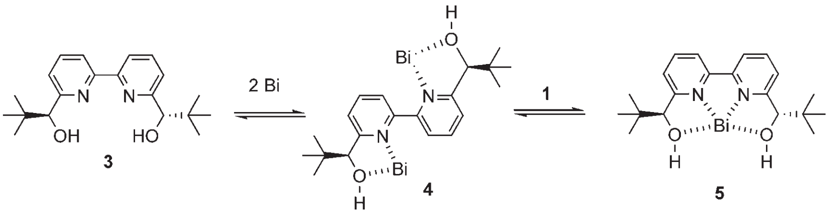
Figure 3. ^1H NMR analysis of the Bi catalyst structure.

concomitant decrease in intensity of the peak at $\delta = 5.49$ ppm until, at a ligand/$Bi(OTf)_3$ ratio of 3:1, it disappeared completely. These results indicate that two equivalents of $Bi(OTf)_3$ and one equivalent of **1** formed complex **4**, and that complex **5**, consisting of one equivalent of $Bi(OTf)_3$ and one equivalent of **3**, was generated when an excess amount of **3** was added (Scheme 1). The stability of complex **5** even in the presence of 2,2′-bipyridine was confirmed by the following experiments. When $Bi(OTf)_3$ (1 mol %) and **3** (3 mol %) were combined in DME at room temperature for 30 min and then 2,2′-bipyridine was added at 0 °C, the hydroxymethylation of **2** proceeded at 0 °C in 21 h to afford the desired adduct in 93 % yield with 91 % *ee*. On the other hand, the yield and the enantioselectivity decreased (73 % yield, 85 % *ee*) when $Bi(OTf)_3$ and 2,2′-bipyridine were combined at room temperature for 30 min and then **3** was added and the mixture was stirred at room temperature for 30 min. However, when the mixture was stirred at room temperature for 1 h, the enantioselectivity was improved (81 % yield, 91 % *ee*). It is noted that complex **5** is stable even in the presence of 2,2′-bipyridine, and that **5** is readily formed from $Bi(OTf)_3$-2,2′-bipyridine complex and **3**.[22]

Similar ligand stabilization was recently observed in gallium-catalyzed asymmetric aldol reactions[23] of silicon enolates with aldehydes in aqueous media.[24] In the presence of a chiral Ga complex prepared from $Ga(OTf)_3$ and chiral ligand **6**, silicon enolates reacted with aldehydes in water–ethanol to afford the desired aldol adducts in moderate to high yields and diastereoselectivities (Table 2). In general, combinations of silicon enolates derived from aromatic ketones and aromatic aldehydes gave high diastereo- and enantioselectivities, while use of either silicon enolates derived from aliphatic ketones or aliphatic aldehydes resulted in lower yields and selectivities. Interestingly, silyl ketene acetal **7** reacted with aromatic aldehydes to give the corresponding aldol adducts in good yields with high stereoselectivities.

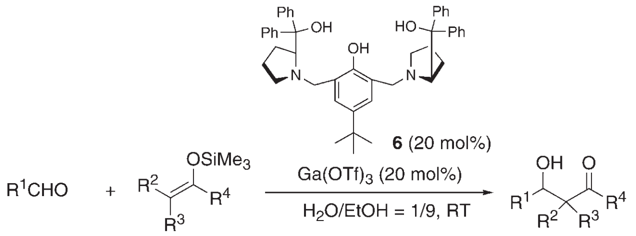
It has been noted that $Ga(OTf)_3$ is known to decompose rapidly in the presence of water to generate protons. Indeed, when $Ga(OTf)_3$ was used alone without the chiral ligand, no aldol adduct was obtained due to rapid decomposition of the silicon enolate. The hydrolyzed product, propiophenone, was obtained in 95 % yield. On the other hand, when a chiral Ga complex prepared from $Ga(OTf)_3$ and chiral ligand **6** was employed, the desired aldol adduct was obtained in high yield with high diastereo- and enantioselectivities in aqueous media. This result indicates that ligand **6** stabilized $Ga(OTf)_3$ in the presence of water to prevent decomposition of $Ga(OTf)_3$.

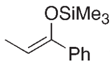
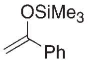
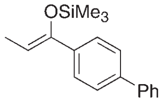
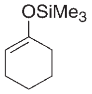
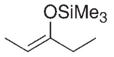
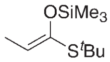
The structure of a chiral Ga complex was proved by UV/Vis titration and electrospray mass spectrometer analysis. These analyses indicate the formation of a 1:1 complex ($Ga(OTf)_3$ and **6**). They also suggested that an O–Ga bond was formed with removal of TfOH by the reaction of the phenolic OH of **6** with $Ga(OTf)_3$, and that a dynamic equilibrium between the active catalyst complex, $Ga(OTf)_3$ and the ligand (**6**) in aqueous media. Further investigations aimed at determining unequivocally the structure of the complex are now in progress.



Scheme 1. Formation of chiral Bi^{3+} catalysts.

Table 2. Ga-catalyzed asymmetric aldol reactions in aqueous media.



Entry	R^1	Enolate	Yield[a]/[%]	*syn/anti*[b]	*ee*[c] [%]
1	Ph	 **2**	89	89/11	87
2[d]	Ph	**2**	85	85/15	85
3[d]	PhCH=CH	**2**	90	90/10	86
4[d]	$CH_3(CH_2)_3$	**2**	78	82/18	30
5	Ph		30	–	66
6	Ph		92	91/9	94
7	Ph		66	90/10	73
8	Ph		64	84/16	71
9	Ph	 **7**	67	91/9	84
10	1-naphthyl	**7**	72	99/1	93

[a] Isolated yield. [b] Determined by ^{1}H NMR analysis. [c] Determined by chiral HPLC analysis. [d] H_2O/EtOH = 9/1, 0–5 °C.

Perspective

For a long time, Lewis acids were believed to hydrolyze rapidly in the presence of water. Contrary to this, we found that rare earth and other metal complexes were water-compatible. Furthermore, $Bi(OTf)_3$–**3** and $Ga(OTf)_3$–**6** complexes have been added as water-compatible Lewis acids. $Bi(OTf)_3$ and $Ga(OTf)_3$ are unstable in the presence of water, but are stabilized by the basic ligand. Whereas it is known that some ligands stabilize metal complexes, this is the first example to be demonstrated that basic ligands stabilize Lewis acids in water. There are many strong Lewis acids that are unstable in water, and as a result they have not been used in aqueous media. However, these Lewis acids may be available in water when combined with basic ligands. In particular, the use of chiral basic ligands leading to new types of water-compatible chiral Lewis acids may enable a wide range of asymmetric catalysis in aqueous media and open the door to new applications of Lewis acid in synthesis.

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