# Asymmetric catalysis in aqueous media*

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*Abstract*: Lewis acid catalysis has attracted much attention in organic synthesis because of unique reactivity and selectivity attained 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. The presence of even a small amount of water handles the reactions owing to preferential reactions of the Lewis acids with water rather than the substrates. In contrast, rare earth and other metal complexes have been found to be water-compatible. Several catalytic asymmetric reactions in aqueous media, including hydroxy-methylation of silicon enolates with an aqueous solution of formaldehyde in the presence of $Sc(OTf)_3$–chiral bipyridine ligand or $Bi(OTf)_3$–chiral bipyridine ligand, Sc- or Bi-catalyzed asymmetric *meso*-epoxide ring-opening reactions with amines, and asymmetric Mannich-type reactions of silicon enolates with *N*-acylhydrazones in the presence of a chiral Zn catalyst have been developed. Water plays key roles in these asymmetric reactions.

*Keywords*: reactions in aqueous media; Lewis acids; catalytic asymmetric reactions; hydroxymethylation of silicon enolates; $Sc(OTf)_3$–chiral bipyridine ligand.

## INTRODUCTION

Organic reactions in aqueous media are of current interest owing to the key role 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 obvious 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 compared with 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

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water rather than with 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 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 (Scheme 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 owing to dissociation of the counteranions from the Lewis acidic metal. Furthermore, in this example, the catalyst can be easily recovered and reused.
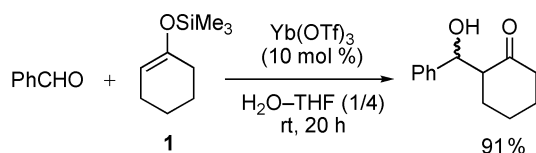


**Scheme 1**

Metal salts other than those derived from rare earth elements were also found to be water-compatible Lewis acids. In order to find other Lewis acids which 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) (Scheme 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.
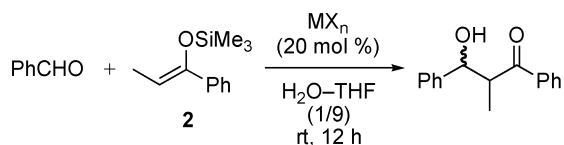


**Scheme 2**

From these results, 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, WERCs) was revealed [6]. Table 1 shows these constants for each metal cation, and metals that exhibited good catalytic activity in the screening (>50 % yield) are surrounded by red squares. These active metal compounds were found to have p$K_h$ values in the range from about 4 [4.3 for Sc(III)] to 10 [10.08 for Cd(II)] and WERC values greater than $3.2 \times 10^6$ M$^{-1}$ s$^{-1}$. Cations having large p$K_h$ values do not generally undergo efficient hydrolysis. In the case of p$K_h$ values being 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, in the case of p$K_h$ 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, to act as efficient catalyst.

"Borderline" species 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 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.

**Table 1**

Legend box: **M** $^{+n}$, $pK_h^a$, WERC$^b$

| Gp 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Li** +1 13.64 $4.7\times10^7$ | **Be** — — | | | | | | | | | | | **B** +3 — — | **C** — | **N** — |
| **Na** +1 14.18 $1.9\times10^8$ | **Mg** +2 11.44 $5.3\times10^5$ | | | | | | | | | | | **Al** +3 4.97 $1.6\times10^0$ | **Si** +4 — | **P** +5 — |
| **K** +1 14.46 $1.5\times10^8$ | **Ca** +2 12.85 $5\times10^7$ | **Sc** +3 4.3 $4.8\times10^7$ | **Ti** +4 ≤2.3 — | **V** +3 2.26 $1\times10^3$ | **Cr** +3 4.0 $5.8\times10^{-7}$ | **Mn** +2 10.59 $3.1\times10^7$ | **Fe** +2 9.5 $3.2\times10^6$ | **Co** +2 9.65 $2\times10^5$ | **Ni** +2 9.86 $2.7\times10^4$ | **Cu** +2 7.53 $2\times10^8$ | **Zn** +2 8.96 $5\times10^8$ | **Ga** +3 2.6 $7.6\times10^2$ | **Ge** +4 — | As |
| Rb — — | Sr — — | **Y** +3 7.7 $1.3\times10^7$ | **Zr** +4 0.22 — | **Nb** +5 (0.6) — | **Mo** +5 — | Tc | **Ru** +3 — | **Rh** +3 3.4 $3\times10^{-8}$ | **Pd** +2 2.3 — | **Ag** +1 12 $>5\times10^6$ | **Cd** +2 10.08 $>1\times10^8$ | **In** +3 4.00 $4.0\times10^4$ | **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 $2\times10^9$ | **Tl** +3 0.62 $7\times10^5$ | **Pb** +2 7.71 $7.5\times10^9$ | **Bi** +3 1.09 — |

| **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 |
| $2.1\times10^8$ | $2.7\times10^8$ | $3.1\times10^8$ | $3.9\times10^8$ | — | $5.9\times10^8$ | $6.5\times10^8$ | $6.3\times10^7$ | $7.8\times10^7$ | $6.3\times10^7$ | $6.1\times10^7$ | $1.4\times10^8$ | $6.4\times10^6$ | $8\times10^7$ | $6\times10^7$ |

$^a$$pK_h = -\log K_h$. Reference 6a,b.  $^b$Exchange rate constants for substitution of inner-sphere water ligands. Reference 6c.

## ASYMMETRIC CATALYSIS IN AQUEOUS MEDIA

### Hydroxymethylation

Increasing demands for optically active compounds have stimulated the investigation of many catalytic asymmetric reactions during the past decade. 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 chiral Lewis acids decompose rapidly in the presence of water [9]. To address this issue, catalytic asymmetric reactions using water-compatible Lewis acids with chiral ligands have been developed (Scheme 3) [10].

Pb(OTf)$_2$     Ln(OTf)$_3$
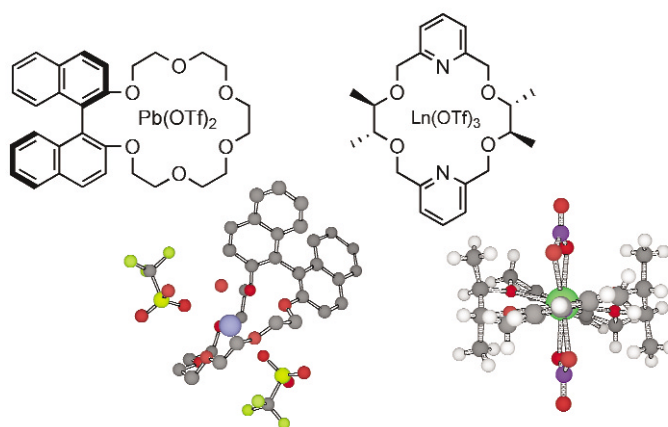
**Scheme 3**

Formaldehyde is one of the most important $C_1$ electrophiles in organic synthesis. Although hydroxymethylation of enolates with formaldehyde provides an efficient method to introduce a $C_1$ functional group at the α-position of carbonyl groups, there have been few successful examples of catalytic asymmetric hydroxymethylation, which satisfies synthetic utility in terms of both yield and selectivity for a wide range of substrates [11]. To achieve such reactions, Lewis acid-catalyzed hydroxymethylation of silicon enolates [12] is promising. The reactions proceed regioselectively, and excellent substrate generality and synthetic efficiency can be expected [13]. As for the source of formaldehyde, use of a commercial aqueous solution of formaldehyde is the most convenient, because tedious and harmful procedures to generate formaldehyde monomer from formaldehyde oligomers such as paraformaldehyde and trioxane can be avoided [14]. Although we have previously reported the use of an aqueous solution of formaldehyde for hydroxymethylation of silicon enolates [15], it is still difficult to realize catalytic asymmetric versions of this reaction. Quite recently, the catalytic asymmetric hydroxymethylation of silicon enolates in aqueous solvents was first achieved by our group [16] and by Yamamoto et al. [17]. However, in both cases, the enantioselectivities were moderate, and several issues still remained to be resolved. In order to achieve a higher level of yields and selectivity in this reaction, development of a new catalytic system is required.

We have achieved catalytic asymmetric hydroxymethylation of silicon enolates using a $Sc(OTf)_3$·**3** complex as the catalyst. In this reaction, a commercial aqueous solution of formaldehyde can be used, and as a result, this process can be conducted very easily and safely. This new catalytic system will provide not only a useful method to synthesize optically active β-hydroxymethylated carbonyl compounds but also a guide to various kinds of catalytic asymmetric C–C bond-forming reactions in aqueous media.

Single crystals that were suitable for the X-ray analysis were obtained from a $ScBr_3$·**3** complex (Fig. 1) [18]. The complex adopts a pentagonal bipyramidal structure [19] in which the hydroxy groups of **3** coordinate to $Sc^{3+}$ in a tetradentate manner. Formation of this type of structure may be a key for obtaining high enantioselectivity. In addition, on considering the absolute configurations of some of the hydroxymethylated products [16,20], it is clear that formaldehyde tends to react with the same face of the silicon enolates in no relation to the substituents on the α-position. Therefore, we assume that the reactions proceed not via extended, acyclic transition states, but via transition states where the oxygen of a silicon enolate interacts with the chiral complex, although the details are still unclear.
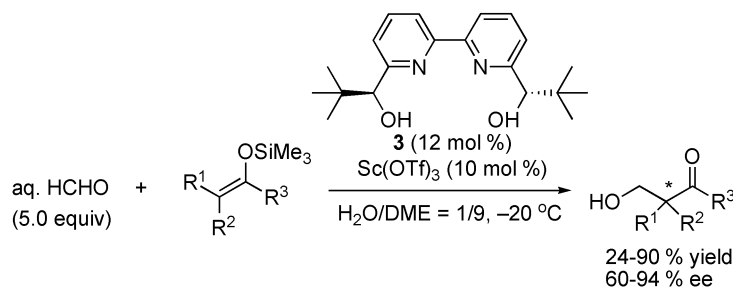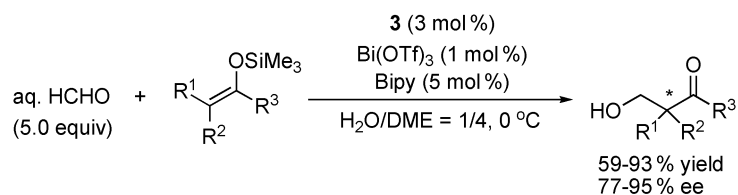


**Scheme 4**
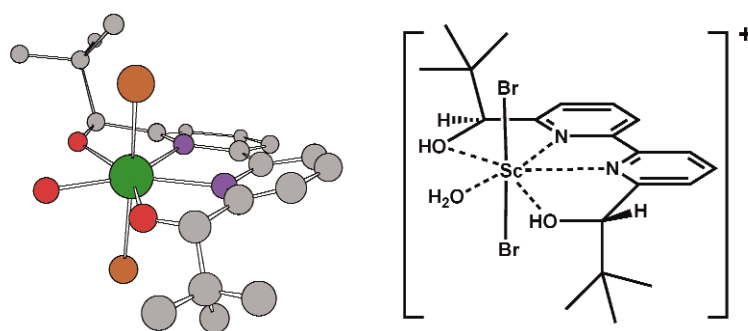
**Fig. 1** [3·ScBr$_2$·H$_2$O]$^+$ moiety in the X-ray structure of [3·ScBr$_2$·H$_2$O]·Br·H$_2$O. Hydrogen atoms are omitted for clarity.

As an extension of this work, other metal salts (10 mol %) and chiral bipyridine **3** (12 mol %) were tested in the reaction of silicon enolate **2** with an aqueous formaldehyde solution, and remarkably it was found that Bi(OTf)$_3$ [21] gave promising results. In addition to the big difference in the ionic diameters between bismuth (2.34 Å for 8-coordination) and scandium (1.74 Å for 8-coordination), this result was unexpected because Bi(OTf)$_3$ is known to be hydrolyzed in the presence of water [22]. Indeed, only a trace amount of the hydroxymethylated adduct was obtained using Bi(OTf)$_3$ in the absence of the chiral bipyridine [23], since it is known that silicon enolates such as **2** are rapidly decomposed by trifluoromethanesulfonic acid (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 using 1 mol % Bi(OTf)$_3$ and 3 mol % **3** in the presence of 5 mol % of 2,2'-bipyridine. Several other substrates were applicable to this catalyst system [24]. The hydroxymethylation proceeded smoothly using an aqueous formaldehyde solution to afford the desired adducts in high yields with high enantioselectivities. It is noteworthy that asymmetric quaternary carbons were constructed with high selectivities.



**Scheme 5**

From several experiments, it was revealed that the active catalyst was formed from an equimolar mixture of Bi(OTf)$_3$ and **3**. The X-ray crystal structure of the BiBr$_3$-**3** complex is shown in Fig. 2. The complex adopts a pentagonal bipyramidal structure in which the tetradentate ligand occupies four of the equatorial sites. The structure of the BiBr$_3$ complex of **3** is closely related to that of the corresponding ScBr$_3$ complex [25]. NMR analysis indicates that an active complex consisting of one equivalent of Bi(OTf)$_3$ and one equivalent of **3** was generated when an excess amount of **3** was added.
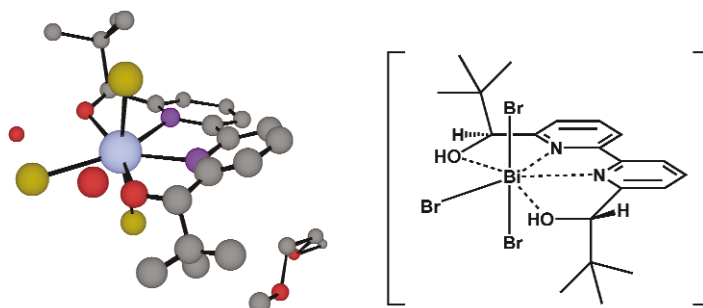
**Fig. 2** The X-ray crystal structure of [BiBr$_3$·1]·(H$_2$O)$_2$·DME. DME is omitted for clarity.

This work provides a new entry to "water-compatible Lewis acids". For a long time, Lewis acids were believed to decompose in the presence of water. Contrary to this, we found that rare earth and other metal complexes are water-compatible. In addition, we have added Bi(OTf)$_3$-**3** complex as a water-compatible Lewis acid. It is noteworthy that Bi(OTf)$_3$ is unstable in the presence of water but is stabilized by the basic ligand. Although discovery of water-compatible Lewis acids has greatly expanded the use of Lewis acids in organic synthesis in aqueous media, conventional Lewis acids based on species such as Al(III), Ti(IV), Sn(IV), etc. still cannot be used in aqueous media under standard conditions. This restriction has been partially removed by recent works.

## Epoxide ring-opening

Chiral β-amino alcohol units are found in many biologically active compounds and chiral auxiliaries/ligands used in asymmetric reactions [26]. Catalytic enantioselective synthesis of these chiral building blocks mainly relies on asymmetric ring-opening of *meso*-epoxides. Indeed, several examples using a chiral catalyst (typically a chiral Lewis acid) are reported in literature [27]; however, all these reactions proceeded in organic solvents. Probably, epoxides are readily decomposed under acidic conditions in water. As a part of our ongoing program to develop new asymmetric reactions in aqueous media, we have found Sc(OTf)$_3$·**3** complex as a chiral Lewis acid shown in the previous chapter. To extend the use of this novel chiral scandium complex to other reactions in water, we decided to investigate the asymmetric ring-opening of *cis*-stilbene oxide with aniline in water. Quite recently, Schneider et al. reported the same ring-opening reaction using Sc(OTf)$_3$ and **3** in dichloromethane [27d]. Independently, we were pleased to find that the reaction proceeded smoothly in high yield with high enantioselectivity using 1 mol % of scandium tris(dodecylsulfate) ["Sc(DS)$_3$"] as a Lewis acid–surfactant-combined catalyst (LASC), a concept previously introduced by our group [28], and 1.2 mol % of **3** in water (Scheme 6) [10h]. It is noted that the ring-opening reaction proceeded smoothly in water, and that no diol formation was observed. In general, even a trace amount of water exerts a detrimental effect on yield and enantioselectivity and only few examples of enantioselective Lewis acid-catalyzed reactions in pure water have been reported [29]. To the best of our knowledge, this is the first example to date of an asymmetric epoxide ring-opening in pure water [30].
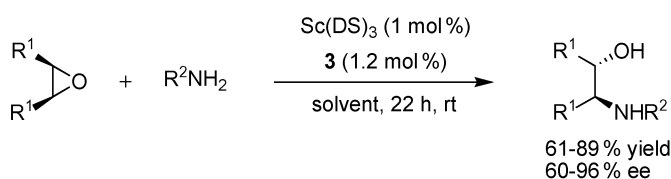


**Scheme 6**

Catalytic asymmetric ring-opening reactions of *meso*-epoxides with aromatic amines also proceeded in the presence of a catalytic amount of bismuth triflate [Bi(OTf)$_3$], chiral bipyridine ligand (**3**), and sodium dodecylbenzene sulfonate (SDBS) in pure water to give the corresponding β-amino alcohols in good yields with high enantioselectivities [31a].

## Mannich-type reactions

Asymmetric Mannich reactions provide useful routes for the synthesis of optically active β-amino ketones and esters, which are versatile chiral building blocks for the preparation of many nitrogen-containing biologically important compounds [32]. In the past few years, various enantioselective Mannich reactions have been developed. Among them, catalytic enantioselective additions of silicon enolates to imines have been elaborated into one of the most powerful and efficient asymmetric Mannich-type reactions, not least because silicon enolates can be prepared regio- and stereoselectively from various carbonyl compounds [33].

We and others have recently reported several examples of catalytic asymmetric C–C bond-forming reactions catalyzed by water-compatible Lewis acids in aqueous media. However, it has been difficult to realize catalytic asymmetric Mannich-type reactions in aqueous media, and no examples had been reported before our first report [34]. In 2002, we reported the first catalytic asymmetric Mannich-type reactions of an α-hydrazono ester with silicon enolates in H$_2$O–THF by using a combination of a stoichiometric amount of zinc fluoride and a catalytic amount of a chiral diamine and TfOH [35]. Furthermore, we also found that, in water without any organic cosolvents, the above Mannich-type reactions proceeded in high yields with high stereoselectivities by using ZnF$_2$, a cationic surfactant, and a chiral diamine having the MeO groups on its aromatic rings [36].

Imines are usually used as electrophiles in Mannich reactions [37]. Although some imines are easily prepared from the corresponding carbonyl compounds and amines, most of them necessitate dehydrative preparation by azeotropic distillation or with dehydrating agents. In addition, imines are generally difficult to purify by distillation or column chromatography and unstable when stored for long periods. In contrast, *N*-acylhydrazones [38] are readily prepared from aldehydes and *N*-acylhydrazines, and often isolated as much more stable crystals than the corresponding imines. Recently, we found that such electrophiles reacted smoothly with several nucleophiles in the presence of a catalytic amount of a Lewis acid [39,40]. It should be noted that hydrazines such as the products of the Mannich reaction or allylation are interesting compounds, not only because hydrazines themselves can be used as unique building blocks [41], but also because N–N bond cleavage would lead to amine products. Furthermore, *N*-acylhydrazones have been successfully used in Sc(OTf)$_3$-catalyzed allylation in aqueous THF [42], indicating that they can be regarded as imine surrogates stable even in aqueous media. Therefore, we decided to examine the catalytic asymmetric Mannich-type reactions of *N*-acylhydrazones with silicon enolates in aqueous media.

Diastereo- and enantioselective Mannich-type reactions of α-hydrazono ester **4** with silicon enolates in aqueous media have been achieved with a ZnF$_2$–chiral diamine complex (Scheme 7). This reaction seems to proceed with double activation where Zn$^{2+}$ acts as a Lewis acid to activate **4** and fluoride anion acts as a Lewis base to activate silicon enolates. Indeed, both Zn$^{2+}$ and fluoride anion were needed to obtain high yields and high enantioselectivities. The effect of the diamines **5a** having MeO groups on their aromatic rings is noteworthy, and the advantageous points of using these diamines are as follows: (i) the reactions in aqueous THF were remarkably accelerated; (ii) the reactions with some silicon enolates proceeded in high yields even in the absence of TfOH or NaOTf, which was needed in the reactions using **5b**; (iii) the ZnF$_2$ loading could be reduced to 10–20 mol % without loss of yield and enantioselectivity, whereas more than 50 mol % of ZnF$_2$ was required in the reactions using **1a**; (iv) the reactions in water without any organic cosolvents proceeded smoothly to give high yields and high stereoselectivities. It is also noted that, in contrast to most asymmetric Mannich-type reactions, either
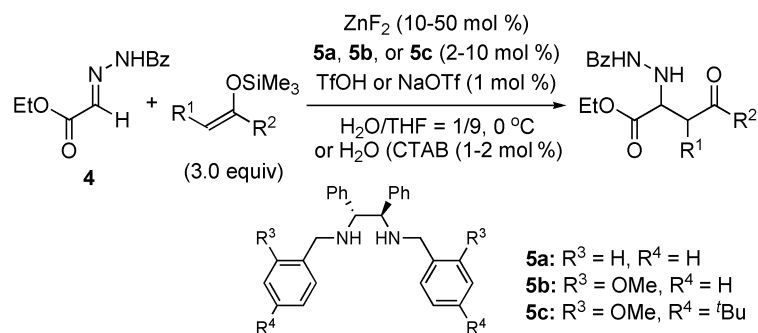
**Scheme 7**

*syn*- or *anti*-adducts were stereospecifically obtained from (*E*)- or (*Z*)-silicon enolates in the present re-action.

As for the reaction mechanism, some experimental evidence suggests that $ZnF_2$–chiral diamine complex is the real catalytically active species, and is regenerated from $Me_3SiF$, formed during the course of the reaction (Scheme 8, fluoride-catalyzed mechanism).
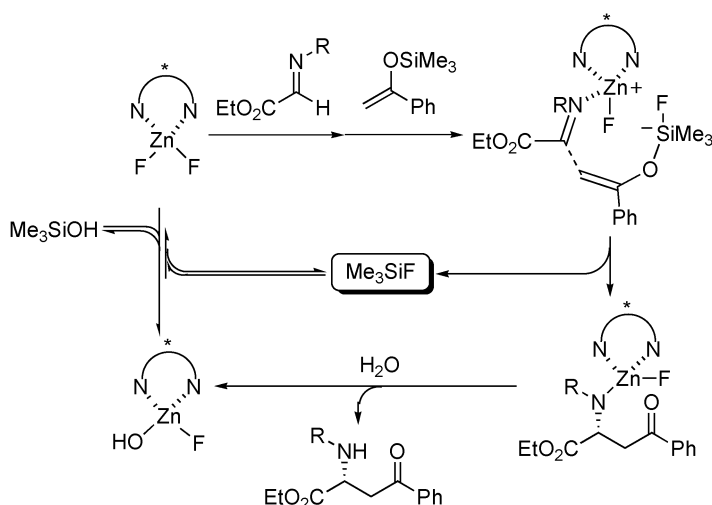


**Scheme 8**

Finally, it was found that the present reaction proceeded smoothly only in water without using any organic solvents, in the presence or absence of a small amount of a cationic surfactant, cetyltrimethyl-ammonium bromide (CTAB) [10g].

## CONCLUSION

The use of water as a solvent in organic synthesis is destined to play a key role in progress toward green chemistry. On the other hand, in spite of importance of Lewis acid-catalyzed reactions in laboratories as well as industry, such reactions have not been carried out in aqueous media, because Lewis acids were believed to hydrolyze rapidly in the presence of water. Contrary to this, we have found that rare earth and other metal complexes are water-compatible. Moreover, chiral Lewis acid catalysis in aqueous media, which is known to present a very difficult challenge owing to instability not only of Lewis

acids but also chiral Lewis acids even in the presence of a small amount of water, has been attained. Hydroxymethylation of silicon enolates with an aqueous solution of formaldehyde in the presence of Sc(OTf)$_3$–chiral bipyridine ligand or Bi(OTf)$_3$–chiral bipyridine ligand, Sc- or Bi-catalyzed asymmetric *meso*-epoxide ring-opening reactions with amines, and asymmetric Mannich-type reactions of silicon enolates with *N*-acylhydrazones in the presence of a chiral Zn catalyst have been developed. In all cases, water plays key roles in these asymmetric reactions. In addition to synthetic utility of these enantioselective reactions, the studies will provide a useful guide to the development of catalytic asymmetric C–C bond-forming reactions in water.

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