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Catalytic Asymmetric Mannich-Type Reactions Activated by ZnF_2 Chiral Diamine in Aqueous Media

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Abstract: Catalytic asymmetric Mannich-type reactions of an α-hydrazono ester with silicon enolates in aqueous media have been developed by using ZnF_2 and chiral diamines as catalysts. In these reactions, both Zn^{2+} and a fluoride anion were necessary to achieve high yields and enantioselectivities, suggesting a double activation mechanism, in which Zn^{2+} activates the α-hydrazono ester and the fluoride anion simultaneously activates the silicon enolate. When chiral diamine ligands bearing methoxy-substituted aromatic rings were employed, the reactions in aqueous THF were markedly accelerated. Furthermore, the use of these diamines facilitated the asymmetric Mannich-type reactions in water without any organic cosolvents. It is noteworthy that either *syn* or *anti* adducts were stereospecifically obtained from (*E*)- or (*Z*)-silicon enolates, respectively. Interestingly, these reactions proceeded smoothly only in the presence of water. On the basis of several experimental results, it can be concluded that the reaction mechanism is likely to be a fluoride-catalyzed one, in which the ZnF_2 chiral diamine complex is regenerated from the Me_3SiF formed during the reaction.

Keywords: aqueous media · asymmetric catalysis · Lewis acids · Mannich reaction · water chemistry

Introduction

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.[1] 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.[2]

In recent years, organic reactions in aqueous media have attracted a great deal of attention.[3] Water is no doubt cheap, safe, and environmentally friendly when compared with organic solvents, and unique reactivity and selectivity, which cannot be obtained in organic solvents, are often observed in aqueous reactions. Moreover, from a synthetic viewpoint, these reactions have several advantages compared with reactions under anhydrous conditions, which are required in many conventional synthetic procedures. For example, while it is necessary to dry solvents and substrates vigorously before use for many reactions in dry organic solvents, such drying is unnecessary for reactions in aqueous media. We and others have recently reported several examples of catalytic asymmetric carbon–carbon bond-forming reactions catalyzed by water-compatible Lewis acids[4] in aqueous media.[5] However, it has been difficult to achieve catalytic asymmetric Mannich-type reactions in aqueous media, and no examples had been reported before our first report.[6] In 2002, we reported the first catalytic asymmetric Mannich-type reactions of an α-hydrazono ester with silicon enolates in H_2O/THF by using a combination of a stoichiometric amount of zinc fluoride and a catalytic amount of a chiral diamine and trifluoromethanesulfonic acid (TfOH).[7] Furthermore, we also found that by using ZnF_2, a cationic surfactant, and a chiral diamine, containing MeO groups on its aromatic rings, in water without any organic cosolvents, the above Mannich-type reactions proceeded to give high yields and stereoselectivities.[8] Herein we describe the full details of our studies on these Mannich-type reactions.

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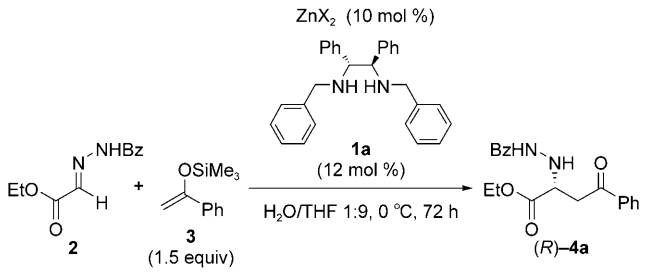
Results and Discussion

Imines are usually used as electrophiles in Mannich reactions.[9] 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 are unstable when stored for long periods. In contrast, *N*-acylhydrazones[10] are readily prepared from aldehydes and *N*-acylhydrazines, and are 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.[11,12] 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,[13] but also because N–N bond cleavage would lead to amine products. Furthermore, N-acylhydrazones have been successfully used for $Sc(OTf)_3$-catalyzed allylation reactions in aqueous THF,[14] 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*-acylhydrazone with silicon enolates in aqueous media.

An important feature in the design of a chiral ligand for Lewis acid mediated asymmetric reactions in aqueous media is its binding affinity to metal cations. We noted the strong binding ability of ethylenediamine to Zn^{2+} ion,[15] and decided to test various chiral analogues of ethylenediamine for use in catalytic asymmetric Mannich-type reactions in aqueous media. After many trials, we found that the combination of chiral diamine **1a**[16] and $Zn(OTf)_2$ gave a low but significant enantiomeric excess (*ee*, 24%) in the reaction of α-hydrazono ester **2** with silyl enol ether **3** in H_2O/THF 1:9 (Table 1, entry 1). The effect of the counteranions of Zn^{2+} was then examined, and it was found that the same level of enantioselectivity was obtained when $Zn(ClO_4)_2$ was used (entry 2). While the reaction hardly proceeded when $ZnBr_2$ or $ZnCl_2$ were employed (entries 3 and 4), it was remarkable to find that high enantioselectivity was obtained when ZnF_2 was used (entry 5).[17] Although the yield was low, this high *ee* prompted us to investigate the ZnF_2-mediated reaction further.

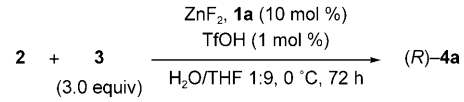
Table 1. Effect of counterions.



Entry	ZnX_2	Yield [%]	*ee* [%]
1	$Zn(OTf)_2$	21	24
2	$Zn(ClO_4)_2 \cdot 6H_2O$	25	26
3	$ZnBr_2$	trace	–
4	$ZnCl_2$	0	–
5	ZnF_2	7	86

Several reaction conditions were examined in order to improve the yield (Table 2). Interestingly, a stoichiometric amount of ZnF_2 led to a low yield, due to rapid hydrolysis of **3**, and high enantioselectivity was maintained in spite of the use of a large excess of ZnF_2, relative to the chiral diamine (entry 1). Next, we examined the effect of additives. It was exciting to find that 1 mol% of TfOH (Tf = triflate) significantly suppressed the hydrolysis of **3**, increasing the yield dramatically (entry 2 versus 1). The same level of enantioselectivity was obtained when the amount of ZnF_2 was lowered to 50 mol% (entry 3), although the yield was decreased when the amount of ZnF_2 was reduced further (entries 4 and 5). It should be noted that the presence of **1a** significantly improved the yield (entry 2 versus 6), and that this ligand effect is key to the success of the present catalytic system.[18]

Table 2. Several reaction conditions.



Entry	ZnF_2 [mol%]	Yield [%]	*ee* [%]
1[a]	100	19	90
2	100	93	92
3	50	89	92
4	30	34	89
5[b]	10	17	85
6[c]	100	34	–

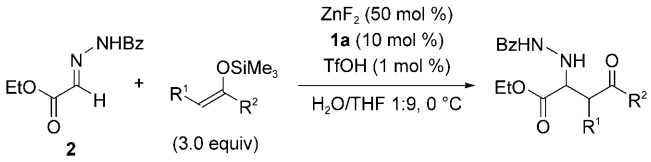
[a] Without TfOH. [b] 143 h. [c] Without **1a**.

For the catalytic asymmetric Mannich-type reaction of **2** in aqueous THF with ZnF_2, **1a**, and TfOH, other silyl enol ethers were tested (Table 3). Silyl enol ethers derived from aromatic ketones gave the desired products, mostly, in high yields and with high enantioselectivities (entries 1–4). When using an aliphatic ketone (entry 5), high selectivity was also obtained, but the yield of the reaction was low. Furthermore, in entries 4 and 5, the *syn* adducts were obtained with high diastereo- and enantioselectivities.

While the first catalytic, diastereo- and enantioselective Mannich-type reactions in aqueous media had been developed, there were several problems that remained to be solved. These were as follows: 1) TfOH is essential to obtain high yields, 2) the reaction time is long, and 3) more than 50 mol% of ZnF_2 is necessary to complete the reaction. Accordingly, it was clear that this Mannich-type reaction left much room for improvement; therefore, we decided to investigate this reaction further.

Effect of additives: As mentioned above, addition of TfOH was essential for obtaining high yields in the reaction. We

Table 3. Catalytic asymmetric Mannich-type reactions.

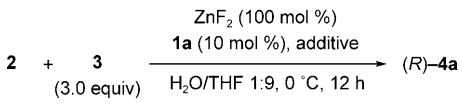


Entry	R^1	R^2	*t* [h]	Product	Yield [%]	*syn*/*anti*	*ee* [%]
1	H	4-Me-C_6H_4	120	**4b**	82	–	91
2	H	4-MeO-C_6H_4	72	**4c**	63	–	91
3[a]	H	4-Cl-C_6H_4	96	**4d**	88	–	89
4[a,b]	Me	Ph	72	**6a**	91	96:4	88
5[a,c]	Me	*i*Pr	420	**6b**	30	90:10	91

[a] 100 mol% of ZnF_2 and 20 mol% of **1a** were used. [b] *E*/*Z* <2:>98. [c] *E*/*Z* 4:96.

searched for effective additives other than TfOH in the reaction of **2** with **3** in aqueous THF. First, we tested several acids; however, no marked effect was observed. Interestingly, the reactions utilizing metal triflates as additives produced better yields than the reaction conducted without any additives (Table 4, entries 3–6 versus 1). In particular, alkali

Table 4. Effect of metal triflates.

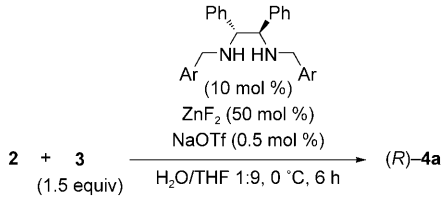


Entry	Additive (mol%)	Yield [%]	*ee* [%]
1	–	21	90
2	TfOH (1)	57	90
3	LiOTf (1)	69	90
4	NaOTf (1)	73	92
5	KOTf (1)	68	91
6	$Zn(OTf)_2$ (0.5)	48	89

metal triflates produced higher yields than TfOH, and the best yield was obtained when NaOTf was employed (entry 4). These results indicate that TfOH acts not as a protic acid, but as a triflate anion source. It is likely that one fluoride anion of ZnF_2 is replaced with a triflate anion, thus generating ZnF(OTf) in the reaction system. It is noted that ZnF(OTf) must be more Lewis acidic than ZnF_2.

Effect of chiral diamines: Next, we examined the effect of chiral diamines on the rate of the Mannich-type reaction. Indeed, various chiral diamines derived from (1*R*,2*R*)-1,2-diphenylethylenediamine were tested in the reaction of **2** with **3** (1.5 equiv) under the conditions shown in Table 5. It was exciting to find that diamine **1c**, which contains *ortho*-MeO groups on its aromatic rings, afforded a much higher yield than **1a** (entry 3), although the corresponding *ortho*-tolyl ligand **1b** gave a comparable yield to **1a** (entry 2). To our further delight, **1c** produced greater enantioselectivity than **1a**. Moreover, it was found that the use of **1e** resulted in both a high yield and *ee* (entry 5), whereas **1f** gave a comparable yield and *ee* to **1a** (entry 6). The above results demonstrate that the MeO groups located at the *ortho* position on

Table 5. Effect of chiral diamines **1**.



Entry	Ar (diamine)	Yield [%]	*ee* [%]
1	Ph (**1a**)	25	86
2	2-Me-C_6H_4 (**1b**)	23	57
3	2-MeO-C_6H_4 (**1c**)	83	93
4	2-EtO-C_6H_4 (**1d**)	35	94
5	2,5-$(MeO)_2$-C_6H_3 (**1e**)	84	93
6	3,5-$(MeO)_2$-C_6H_3 (**1f**)	19	86
7	3-MeO-2-naphthyl (**1g**)	43	91
8	2-MeO-4-*t*Bu-C_6H_3 (**1h**)	53	92
9	2-MeO-5-*t*Bu-C_6H_3 (**1i**)	72	96
10[a]	2-MeO-5-*t*Bu-C_6H_3 (**1i**)	81	96

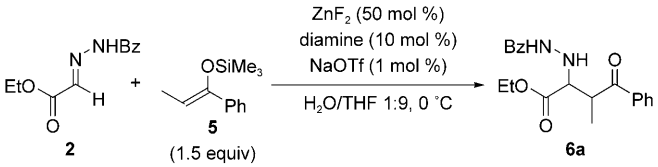
[a] Without NaOTf.

the aromatic rings of chiral diamine ligands plays an essential role in producing the high yields and selectivities observed in these reactions.[19] When **1i** was employed, Mannich adduct (*R*)-**4a** was obtained in a satisfactory yield, and with the greatest enantioselectivity observed for the diamines examined in Table 5 (entry 9). Furthermore, it is worth noting that the reaction with **1i** proceeded to produce a high yield, even in the absence of NaOTf (entry 10).

One of the interesting features of the present Mannich-type reactions is that high enantioselectivity can be obtained in spite of the use of a large excess of ZnF_2 with respect to the chiral diamine. Thus, we investigated the use of reduced amounts of diamine **1i** in the reaction of **2** with **3** (3.0 equiv) and ZnF_2 (100 mol%). It was found that **1i** could be reduced to only 2 mol% without significant loss of enantioselectivity (87% yield, 94% *ee*, 20 h).

We also examined the effect of the diamines in the reaction with propiophenone-derived silyl enol ether **5** (Table 6). As with the reaction using **3**, both diamines **1c** and **1i** were found to be effective in accelerating the reaction. In contrast to when **3** was employed, however, **1c** produced greater enantioselectivity than **1i** (entry 1 versus 2). It is further

Table 6. Effect of chiral diamines **2**.



Entry	Diamine	*t* [h]	Yield [%]	*syn*/*anti*	*ee*[a] [%]
1	**1i**	6	62	96:4	86
2	**1c**	16	87	95:5	92
3[b]	**1c**	20	89	91:9	94

[a] *ee* of *syn* adduct. [b] Without NaOTf.

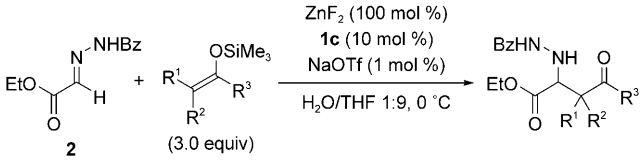
noted that the reaction using **1c** proceeded to afford **6a** in a high yield with high diastereo- and enantioselectivities in the absence of NaOTf (entry 3).

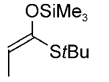
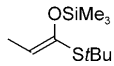
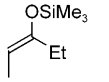
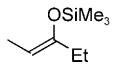
Stereospecificities: Diastereoselection in this Mannich-type reaction is of great interest not only from a synthetic point of view, but also from a mechanistic aspect. In fact, the *Z* silyl enol ethers derived from propiophenone and 2-methyl-3-pentanone afforded high *syn* selectivities, as shown in Tables 3 and 6. Thus, we took an interest in the relationship between the configurations of the silicon enolates and the relative configurations of the major products. The reaction of **2** with the (*Z*)-ketene silyl acetal (*Z*)-**7**, derived from (*S*)-*tert*-butyl thiopropionate, and **1c** afforded the corresponding adduct with high *syn* selectivity and good *ee* (Table 7, entry 1). In this reaction, the addition of NaOTf was essential for obtaining a high yield (entry 2). To our surprise, the *anti* adduct was obtained with good diastereoselectivity from the reaction with the (*E*)-**7** under the same conditions as those of entry 1 (entry 3). We then examined the reactions with the (*E*)- and (*Z*)-silyl enol ethers derived from 3-pentanone, (*E*)-**8** and (*Z*)-**8**. When (*E*)-**8** was employed, the *anti* adduct was obtained selectively with high diastereo- and enantioselectivity (entry 4). In contrast, (*Z*)-**8** afforded good *syn* selectivity (entry 5). Good stereospecificity was observed in the reactions of both **7** and **8**. It is noted that such stereospecificities are rare in catalytic asymmetric Mannich-type reactions,[20] and that both *syn* and *anti* adducts can be easily prepared by simply changing the geometry of the silicon enolates. Furthermore, **7** and **8** afforded the opposite results with regards to the relationships between the geometry of the enolates and the relative configurations of the products. We suppose that this interesting phenomenon is due to the different steric influences of the Et and S*t*Bu groups.[21]

Reduction of the ZnF_2 loading: As mentioned earlier, one of problems in the present reactions is that more than 50 mol% of ZnF_2 is required to obtain high yields. Catalytic use of the fluoride anion presents a significant challenge due to the great strength of the silicon–fluorine bond (592 kJ mol^{-1}) of Me_3SiF, which was generated by the activation of the silicon enolate with the fluoride anion of ZnF_2. However, the marked acceleration of the reaction observed when using diamine **1c** or **1i** prompted us to re-examine the reduction of the ZnF_2 loading by using these diamines.

It was exciting to find that when 20 mol% of ZnF_2 was used in the reaction of **2** with **3** and diamine **1i**, a comparable yield and enantioselectivity, compared to that found with 100 mol% of ZnF_2 were obtained (Table 8, entry 2 versus 1). The use of **1a** instead of **1i** resulted in a very low yield, due to the rapid hydrolysis of **3** (entry 3). Furthermore, when NaOTf (1 mol%) was added to this reaction,

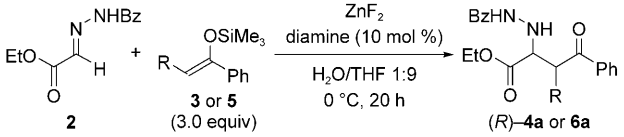
Table 7. Stereospecific, asymmetric Mannich-type reactions.



Entry	Enolate	*t* [h]	Product	Yield [%]	*syn*/*anti*	*ee* [%] (*syn*/*anti*)
1	 (*Z*)-**7**[a]	8	**6c**	80	97:3	87:27[b]
2[c]	(*Z*)-**7**[a]	8	**6c**	32	97:3	86:24[b]
3	 (*E*)-**7**[d]	20	**6c**	22	27:73	65:85[b]
4	 (*E*)-**8**[e]	72	**6d**	98	13:87	88:91
5	 (*Z*)-**8**[f]	72	**6d**	65	77:23	86:81

[a] *E*/*Z* 3:97. [b] (2*R*,3*R*):(2*R*,3*S*). [c] Without NaOTf. [d] *E*/*Z* 98:2. [e] *E*/*Z* 76:24. [f] *E*/*Z* 1:99.

Table 8. Reduction of ZnF_2 loading.



Entry	Enolate	ZnF_2 [mol%]	Diamine	Yield [%]	*syn*/*anti*	*ee* [%]
1	**3**	100	**1i**	94	–	96
2	**3**	20	**1i**	94	–	96
3	**3**	20	**1a**	13	–	87
4[a]	**3**	20	**1a**	25	–	79
5[b,c]	**3**	20	**1i**	82	–	96
6	**5**	20	**1c**	95	94:6	94[d]

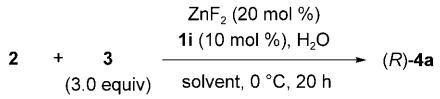
[a] NaOTf (1 mol%) was added. *t* = 72 h. [b] Enolate (1.5 equiv). [c] NaOTf (4 mol%) was added. [d] *ee* of *syn* adduct.

the yield produced was still low, despite the fact that large amounts of silicon enolate **3** remained after the reaction had been completed (entry 4). These results clearly indicate that **1i** permits catalytic turnover of the fluoride anion. In addition, 20 mol% of ZnF_2 was sufficient to obtain both a high yield and stereoselectivity in the reaction of **5** with diamine **1c** (entry 6). Therefore, diamines containing *ortho*-methoxy groups were effective not only for the acceleration of the reaction, but also for the reduction of the ZnF_2 loading. It is worth noting that the use of these diamines overcame the problems (1–3, see above) of the reaction when using **1a**.

On the other hand, it was found that NaOTf suppressed the hydrolysis of the silicon enolates for the reactions involving diamines **1i** and **1a**, and that the reaction proceeded smoothly with a reduced amount of the silicon enolate, without a significant decrease in the yield. In fact, when 1.5 equivalents of **3** were employed, satisfactory results were obtained (entry 5).

Effect of water: It was also revealed that the present Mannich-type reactions proceeded only in aqueous media. Indeed, the reaction of **2** with **3** in anhydrous THF produced only a trace amount of the product (Table 9, entry 2), and

Table 9. Effect of water.

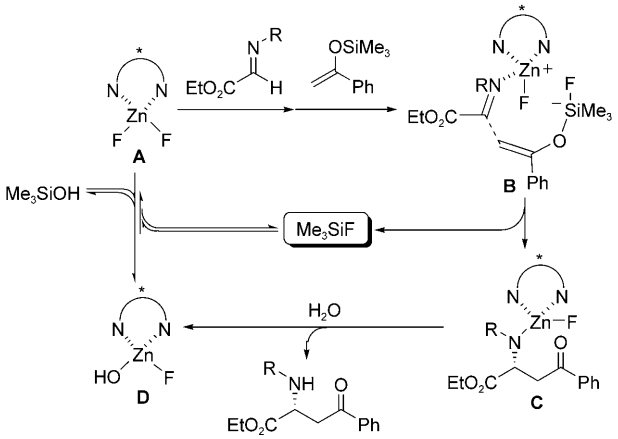


Entry	Solvent	H_2O [equiv]	Yield [%]	*ee* [%][a]
1	H_2O/THF 1:9	–	94	96
2	THF	–	trace	nd
3	THF	1	trace	nd
4	THF	5	10	95
5	MeOH/THF 1:9	–	0	–
6	DMF	–	0	–

[a] nd = not detected.

no product was obtained in anhydrous DMF (entry 6). When one or five equivalents of water were added to the reaction in THF, the yield was still very low (entries 3 and 4). These results evidently indicate that a large excess of water is required to obtain a satisfactory yield. In addition, the reaction in MeOH/THF 1:9 did not proceed at all (entry 5). Accordingly, it is not likely that water merely acts as a proton source. At this stage, we speculate that water facilitates the dissociation of the fluoride anion from Zn^{2+}, thereby enhancing the catalytic activity of the chiral ZnF_2 complex.

Reaction mechanism: A proposed catalytic cycle for this Mannich-type reaction is depicted in Scheme 1. This reaction is likely to proceed with double activation, in which Zn^{2+} acts as a Lewis acid to activate **2**, whilst at the same time, the fluoride anion acts as a Lewis base to attack the silicon atom of the silicon enolate **B**.[22–24] In other words, zinc amide **C** and Me_3SiF are formed first, and subsequent

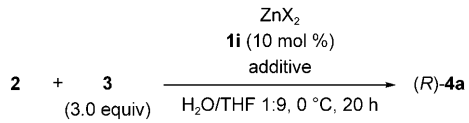


Scheme 1. Proposed catalytic cycle (fluoride-catalyzed mechanism).

hydrolysis of **C** affords the Mannich adduct and ZnF(OH)–diamine complex **D**. It is considered that a catalytic amount of the fluoride anion provides a high yield of the product for this reaction, probably because catalytic turnover of the fluoride anion occurs. This apparently means that **D** reacts with Me_3SiF, regenerating ZnF_2 diamine complex **A** for the next catalytic cycle (fluoride-catalyzed mechanism[25,26]).

The double activation mechanism was partly supported by the following experiments. The reaction of **2** with **3** by using $Zn(OTf)_2$ (10 mol%) and **1i** (12 mol%) gave a much lower *ee* than the reaction with ZnF_2 and **1i** (Table 10, entry 3 versus 2). When tetrabutylammonium fluoride (TBAF) was employed as a catalyst, no product was obtained due to the rapid hydrolysis of **3** (entry 4). These results indicate that both Zn^{2+} and the fluoride anion are required to gain high yields and enantioselectivity.

Table 10. Investigations into the proposed double activation mechanism and catalyst turnover step.



Entry	ZnX_2 (mol%)	Additive (mol%)	Yield [%]	*ee* [%]
1	ZnF_2(100)	–	94	96
2	ZnF_2 (20)	–	94	96
3[a]	$Zn(OTf)_2$ (10)	–	16	20
4[b]	–	TBAF (20)	0	–
5	ZnF(OH) (100)	–	7	94
6	ZnF(OH) (100)	Me_3SiF (100)	90	96

[a] **1i** (12 mol%). [b] Without **1i**.

To confirm the catalytic turnover step (from **D** to **A** in Scheme 1), we investigated the ability of Me_3SiF to regenerate ZnF_2 from ZnF(OH). First, it was confirmed that the reaction of **2** with **3** proceeded very sluggishly in the presence of ZnF(OH)[27] (100 mol%) and **1i** (10 mol%, entry 5). When Me_3SiF (100 mol%) was added, however, the reaction proceeded well, and (*R*)-**4a** was obtained with a similar

yield and selectivity to that obtained for the reaction with ZnF_2 (entry 6 versus 1). These results indicate that the exchange of the fluoride anion between ZnF(OH) and Me_3SiF regenerates ZnF_2, which is a requirement for effective catalysis of this reaction.

Next, we investigated the stability of the Si–F bond of Me_3SiF in aqueous THF. The hydrolysis of Me_3SiF in D_2O/[D_8]THF 1:9 was followed by ^{1}H NMR spectroscopy. The hydrolysis of Me_3SiF proceeded[28] to afford Me_3SiOD, after 25 h, in a quite low but significant yield (2.5%) that did not change even after 69 h (Table 11). Moreover, when

Table 11. Hydrolysis of Me_3SiF.[a]

$Me_3SiF \xrightarrow{D_2O/[D_8]THF\ 1:9,\ 0\ ^\circ C} Me_3SiOD$

Entry	t [h]	Me_3SiOD[b] [%]	Me_3SiF[b] [%]
1	0.5	0.6	93
2	25	2.5	91
3	69	2.5	89

[a] A small amount of $(Me_3Si)_2O$ was observed in all cases (approximately 0.2% yield). [b] Determined by ^{1}H NMR spectroscopy (internal standard = benzotrifluoride or 4-fluorotoluene).

Me_3SiOH was treated with ZnF_2 (100 mol%) and chiral diamine **1i** (10 mol%), Me_3SiF was obtained in 60% yield [Eq. (1)], indicating the existence of the reverse reaction (from **A** to **D** in Scheme 1).

$$Me_3SiOH \xrightarrow[\textbf{1i}\ (10\ mol\ \%)]{ZnF_2\ (1.0\ equiv)} Me_3SiF \quad (1)$$
$$D_2O/[D_8]THF\ (1{:}9),\ 0\ ^\circ C,\ 20\ h\ (60\%)$$

These results show that the thermodynamically stable Si–F bond is kinetically labile in aqueous THF on the timescale of the Mannich-type reaction, and that the catalytic turnover of the fluoride anion can occur. The results shown in Table 11 and Equation (1) suggest that the equilibrium of the catalytic turnover step (**D** to **A**) lies in favor of **D**. However, the strong Si–F interaction, resulting in the formation of **B** (Scheme 1), could be the driving force that facilitates the catalytic turnover, and indeed, the presence of a catalytic amount of the fluoride anion afforded the Mannich adduct in high yield.

We next turned our attention to the structure of the chiral catalyst to clarify the origin of the unique stereoselectivities. Although crystals of the [ZnF_2-**1c**] complex, suitable for XRD analysis, could not be prepared due to its low solubility, a complex suitable for X-ray analysis was obtained from $ZnCl_2$ and **1c** (Figure 1). In this X-ray structure, as expected, the complex exhibits a tetrahedral geometry, and the asymmetric information carried by the two asymmetric carbon atoms on the ligand backbone is transferred to the two benzyl moieties on the nitrogen atoms upon coordination to the metal; this would play a key role in the production of high stereoselectivity in catalysis. In addition, interactions

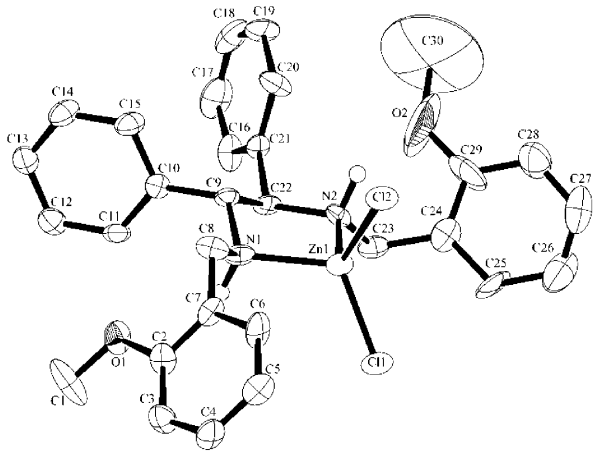


Figure 1. ORTEP drawing of the [$ZnCl_2$-**1c**] moiety in the X-ray crystal structure of [$ZnCl_2$-**1c**]·CH_2Cl_2 (all hydrogen atoms, except the NH proton and those in solvent of crystallization have been omitted for clarity).

between the MeO groups of **1c** and Zn^{2+} were not observed, a finding contrary to our initial expectation. Instead, the MeO groups proved to be located near the amino groups, suggesting hydrogen bonding between the MeO oxygen atom and the amino proton (N1···O1 = 3.028 Å; N2···O2 = 3.141 Å). On the basis of this X-ray crystal structure, and that **1a** and **1c** produced similar enantioselectivities (Table 5), it is proposed that the MeO groups of the diamine do not coordinate to Zn^{2+}, even in the transition states for the asymmetric reactions.[29]

To gain an insight into the structure of the catalyst in a reaction solution, we examined the influence of the optical purity of the chiral diamine on the enantioselectivity of the product in the reaction of **2** with **3**. When the enantiomeric excesses of Mannich adduct (*R*)-**4a** were monitored as a function of the *ee* of (*R*,*R*)-**1i**, a linear correlation was observed (Figure 2). This result implies that the active catalyst

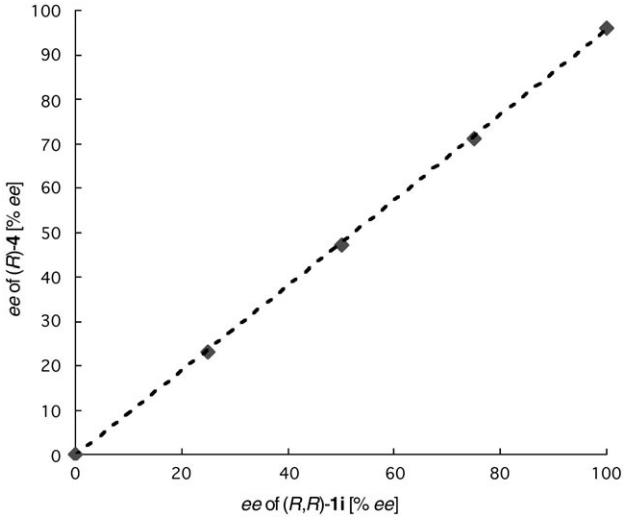


Figure 2. Plot of % *ee* for product (*R*)-**4** versus % *ee* for diamine (*R*,*R*)-**1i**.

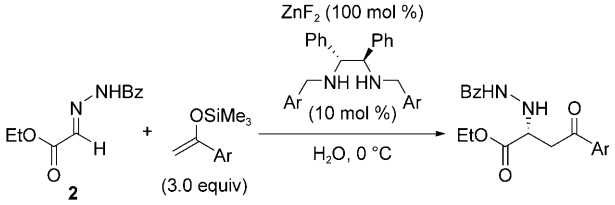
is the monomeric [ZnF_2-**1i**] complex, which has a similar structure to the $ZnCl_2$ complex shown in Figure 1.

As mentioned above, marked acceleration of the reaction was observed when using diamine **1c** or **1i**. The origin of this acceleration was assumed to be explained by the following: The intramolecular hydrogen-bonding effect (see above) or the electron-donating effect of the MeO groups seems to increase the basicity of the amino nitrogen atoms[30] that coordinate to Zn^{2+}. Therefore, the use of these diamines could facilitate the dissociation of the fluoride anion from ZnF_2, leading to the improved catalytic activity of chiral ZnF_2 complexes.

Catalytic asymmetric Mannich-type reactions in water: While it was revealed that the Mannich-type reactions in aqueous THF produce high yields and stereoselectivities in the presence of catalytic amounts of ZnF_2 and a chiral diamine, it is more desirable to use only water as a solvent. However, catalytic asymmetric carbon–carbon bond-forming reactions in water without any organic cosolvents, are difficult to achieve due to the low solubility of most catalysts and substrates in water, although some examples have been reported recently.[5] Therefore, we decided to apply the present Mannich-type reaction in aqueous THF to the reaction in water.

It was surprising to find that the reaction of **2** with **3** in water (direct application of the catalytic system that was most effective in H_2O/THF 1:9) produced satisfactory results. Indeed, when ZnF_2 (100 mol%) and **1i** (10 mol%) were employed, Mannich adduct **4a** was obtained in 91% yield with 95% *ee* (Table 12, entry 1). In contrast, diamine

Table 12. Catalytic asymmetric Mannich-type reactions of the silyl enol ethers, derived from acetophenone analogues, in water.



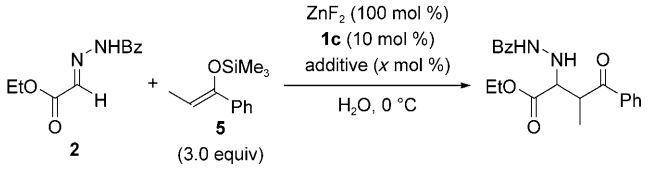
Entry	Ar	Diamine	*t* [h]	Product	Yield [%]	*ee* [%]
1	Ph, **3**	**1i**	20	**4a**	91	95
2[a]	Ph, **3**	**1a**	72	**4a**	44	95
3[b]	Ph, **3**	**1i**	20	**4a**	35	96
4	4-Me-C_6H_4	**1i**	20	**4b**	91	95
5	4-MeO-C_6H_4	**1i**	20	**4c**	93	91
6	4-Cl-C_6H_4	**1i**	36	**4d**	94	95

[a] NaOTf (1 mol%) was added. [b] ZnF_2 (10 mol%).

1a produced a moderate yield, even after 72 h and despite the addition of NaOTf (entry 2). Significantly, from these results, it is apparent that the reaction of **2** with **3** in water has reached a practical level by using diamine **1i**. We then tested other silyl enol ethers under the same reaction conditions. For 4′-substituted acetophenone-derived silyl enol ethers, the corresponding adducts were obtained in high yields with excellent enantioselectivities (entries 4–6). To our disappointment, however, reduction of the ZnF_2 loading resulted in a low yield, because the hydrolysis of **3** became predominant over the desired Mannich-type reaction (entry 3).

We next turned our attention to the enantio- and diastereoselective reactions of the silyl enol ethers derived from α-monosubstituted carbonyl compounds. Unexpectedly, the reactions of **5** proceeded sluggishly, in spite of the fact that a large amount of **5** remained after the reaction had been completed (Table 13, entries 1 and 2). In an attempt to accelerate the reaction, the addition of surfactants was then in-

Table 13. Catalytic asymmetric Mannich-type reactions of **5** in water.



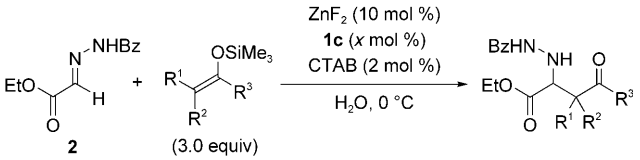
Entry	Additive (mol%)	*t* [h]	Yield [%]	*syn*/*anti*	*ee* [%, *syn*]
1	–	20	6	91:9	94
2	NaOTf (1)	20	8	87:13	92
3	SDS (5)	20	9	91:9	78
4	Triton X-405 (5)	20	10	91:9	93
5	CTAB(5)	20	94	94:6	97
6	CTAB(2)	20	93	94:6	96
7	CTAB(5)	5	60	94:6	96
8[a]	CTAB(5)	5	32	95:5	95
9	TBAB(5)	5	<2	89:11	92
10[b]	TBAB(5)	20	24	89:11	92

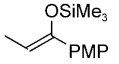
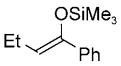
[a] Neat conditions. [b] The solvent system H_2O/CH_2Cl_2 (1:1) was used.

vestigated.[31] While sodium dodecyl sulfate (SDS) or Triton X-405 was not effective (entries 3 and 4), it was remarkable that cetyltrimethylammonium bromide (CTAB) produced an excellent yield, and that it also improved the enantiomeric excess slightly (entry 5). It is worth noting that a cationic surfactant is effective in this reaction,[32,33] while an anionic surfactant has been reported to work well in Lewis acid catalyzed aldol reactions.[34] Moreover, 2 mol% of CTAB was sufficient for producing high yields and enantioselectivities (entry 6). The reaction under neat conditions gave a lower yield than that in water, suggesting the importance of water (entry 7 versus 8).[35] It was also noted that tetrabutylammonium bromide (TBAB) was ineffective not only in water, but also under biphasic conditions, which are often used for phase-transfer catalysis[36] (entries 9 and 10).

Finally, we reduced the amount of ZnF_2 to 10 mol% for several reactions of silyl enol ethers derived from α-monosubstituted carbonyl compounds, although unsatisfactory results were obtained in the case of **3**. To our delight, the reaction with **5** proceeded to give the desired adduct **6** in high yield with high stereoselectivity, even when the amount of **1c** was reduced to 5 mol% (Table 14, entry 1). However, a further decrease in the ZnF_2 loading resulted in a moderate yield (entry 2). When the silyl enol ethers derived from 4′-methoxypropiophenone and butyrophenone were employed, high yields and high diastereo- and enantioselectivities were

Table 14. Catalytic asymmetric Mannich-type reactions in water.



Entry	Enolate[b]	**1c** [mol %]	*t* [h]	Product	Yield [%]	*syn*/*anti*	*ee* [%][a]
1	**5**	5	40	**6a**	87	93:7	96
2[c]	**5**	5	40	**6a**	60	93:7	96
3[d]		10	40	**6e**	76	96:4	96
4[d]		10	40	**6f**	74	96:4	96
5	(*E*)-**8**	10	155	**6d**	75	13:87	92
6	(*Z*)-**8**	10	144	**6d**	63	90:10	98

[a] *ee* of the major diastereomer. [b] PMP = *p*-Methoxyphenyl. [c] $E/Z < 2:>98$. [d] ZnF_2 (5 mol %).

obtained (entries 3 and 4). Furthermore, stereospecific, enantio- and diastereoselective reactions were achieved in water by using only 10 mol % of ZnF_2 and **1c**. In fact, the reactions with (*E*)-**8** and (*Z*)-**8** proceeded to afford *anti* and *syn* adducts in good yields with high diastereo- and enantioselectivities, respectively, although a longer reaction time was required (entries 5 and 6). It is noted that the products obtained in the present Mannich-type reactions were often highly crystalline, and one recrystallization afforded almost diastereomerically and enantiomerically pure materials (entries 1, 3, 4 and 6).

Summary

Diastereo- and enantioselective Mannich-type reactions of α-hydrazono ester **2** with silicon enolates in aqueous media have been achieved with a ZnF_2 chiral diamine complex. This reaction seems to proceed with double activation, in which Zn^{2+} acts as a Lewis acid to activate **2**, and a fluoride anion acts as a Lewis base to activate the silicon enolates. Indeed, both Zn^{2+} and a fluoride anion were needed to obtain high yields and enantioselectivities. The effect of the diamines, which contain MeO groups on their aromatic rings, is worth noting, and the advantages of using these diamines are as follows:

1) The reactions in aqueous THF were remarkably accelerated.
2) The reactions with the silicon enolates **3** or **5** proceeded in high yield, even in the absence of TfOH or NaOTf, which was needed in the reactions involving **1a**.
3) 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 involving **1a**.
4) The reactions in water, without any organic cosolvents, proceeded smoothly to give high yields and stereoselectivities.

It is also noted that, in contrast to most asymmetric Mannich-type reactions, either *syn*- or *anti*-adducts were stereospecifically obtained from (*E*)- or (*Z*)-silicon enolates. As for the reaction mechanism, some experimental evidence suggests that the ZnF_2 chiral diamine complex is the real catalytically active species, and that it is regenerated from the Me_3SiF formed during the reaction (fluoride-catalyzed mechanism). Finally, it should be noted that the present reaction proceeds smoothly only in the presence of water, although the exact role of water in this reaction is as yet unclear. The studies in this article will provide a useful guide for the development of catalytic asymmetric carbon–carbon bond-forming reactions in water.

Experimental Section

General: Melting points are uncorrected. $CDCl_3$ was used as a solvent for ^1H and ^{13}C NMR spectra unless otherwise noted. TMS served as an internal standard ($\delta = 0$ ppm) for ^1H NMR spectra and $CDCl_3$ as an internal standard ($\delta = 77.0$ ppm) for ^{13}C NMR spectra. For spectroscopic analysis conducted in $[D_6]$DMSO, the methyl peak of the DMSO served as the internal standard (2.49 ppm for ^1H NMR spectra and 39.5 ppm for ^{13}C NMR spectra). Preparative TLC was carried out by using Wakogel B-5F. ZnF_2 was purchased from Soekawa Rikagaku or Aldrich. (1*R*,2*R*)-(+)-1,2-Diphenyl-1,2-ethanediamine was purchased from Kanto Kagaku.

Silicon enolate: All the silicon enolates (**3**, **5**,[37a] (*E*)-**7**,[37b,c] (*Z*)-**7**,[37b,c] (*E*)-**8**,[37b,d] (*Z*)-**8**,[37d] (*Z*)-(1-isopropyl-propenyloxy)-trimethylsilane, (*Z*)-[1-(4-methoxy-phenyl)-propenyloxy]-trimethylsilane,[37a] and (*Z*)-trimethyl-(1-phenyl-but-1-enyloxy)-silane[37a]) were prepared from the corresponding carbonyl compounds by using known methods.[2]

Preparation of ethyl benzoylhydrazono-acetate (2):[38] Benzoylhydrazine (42.3 mmol) was added to a solution of ethyl glyoxylate (45–50 % in toluene, 10.04 g) in EtOH (50 mL). After stirring at 80 °C for 15 min, the reaction mixture was gradually allowed to cool to RT. The precipitated hydrazone **2** was then filtered with suction and washed successively with EtOH (30 mL), toluene (300 mL), and hexane (500 mL). Yield: 62 %; m.p. 140–141 °C; ^1H NMR ($[D_6]$DMSO, 80 °C): $\delta = 1.28$ (t, $J = 7.1$ Hz, 3H), 4.26 (q, $J = 7.1$ Hz, 2H), 7.48–7.55 (m, 2H), 7.57–7.64 (m, 1H), 7.83 (s, 1H), 7.86–7.92 (m, 2H), 12.07 ppm (s, 1H); ^{13}C NMR ($[D_6]$DMSO, 80 °C): $\delta = 13.6$, 60.3, 127.6, 128.0, 131.7, 132.4, 137.1, 162.6, 164.3 ppm; IR (KBr): $\tilde{\nu} = 3195$, 3043, 1739, 1665, 1558, 1347, 1216, 1137, 1088 cm^{-1}; HRMS (ESI-TOF): calcd for $C_{11}H_{13}N_2O_3$: 221.0926 $[M+H]^+$; found: 221.0914; elemental analysis calcd for $C_{11}H_{12}N_2O_3$: C 59.99, H 5.49, N 12.72; found: C 59.95, H 5.49, N 12.73.

A typical experimental procedure for the Mannich-type reactions in aqueous THF (Table 2, entry 2): A solution of **1a** (0.0419 mmol) in H_2O/THF (1:9, 0.83 mL), a solution of trifluoromethanesulfonic acid in H_2O/THF (1:9, 0.079 M, 53 μL, 4.2 μmol), and **2** (0.419 mmol) were added to a solution of ZnF_2 (0.419 mmol) in H_2O/THF (1:9, 0.27 mL). A solution of **3** (1.26 mmol) in H_2O/THF (1:9, 1.19 mL) was then added, and the mixture was stirred at 0 °C. After 72 h at this temperature, the reaction was quenched with saturated aqueous $NaHCO_3$. The resultant mixture was then extracted with dichloromethane (×3), and the combined organic

layers were dried over anhydrous Na_2SO_4. Finally, the solvents were evaporated, and the residue was purified by preparative TLC (silica gel, $CHCl_3$/MeOH 39:1) to give (*R*)-**4** (93% yield). The enantiomeric excess of the product was determined by HPLC analysis (92% *ee*).

Ethyl 2-(*N'*-benzoylhydrazino)-4-oxo-4-phenylbutyrate (4a):[7] $[\alpha]_D^{22}=+4.42$ ($c=5.07$ in $CHCl_3$, 96% *ee*); ^{1}H NMR ($CDCl_3$): $\delta=1.23$ (t, $J=7.1$ Hz, 3H), 3.51 (dd, $J=17.9$, 6.5 Hz, 1H), 3.60 (dd, $J=17.9$, 4.9 Hz, 1H), 4.06–4.35 (m, 3H), 5.51 (brs, 1H), 7.31–7.64 (m, 6H), 7.74 (d, $J=7.6$ Hz, 2H), 7.93 (d, $J=7.6$ Hz, 2H), 8.50 ppm (brd, $J=4.4$ Hz, 1H); ^{13}C NMR ($CDCl_3$): $\delta=14.0$, 39.4, 59.0, 61.4, 126.9, 128.0, 128.5, 128.5, 131.7, 132.6, 133.4, 136.1, 166.9, 172.5, 197.1 ppm; IR (neat): $\tilde{\nu}=3289$, 1735, 1681, 1536, 1216, 689 cm^{-1}; MS: *m/z*: 340 $[M]^+$; HRMS: calcd for $C_{19}H_{20}N_2O_4$: 340.1423; found: 340.1379; HPLC (Daicel Chiralcel OD, hexane/*i*PrOH 4:1, flow rate = 1.0 mL min^{-1}): $t_R=11.9$ min (*R*), $t_R=17.7$ min (*S*).

Ethyl 2-(*N'*-benzoylhydrazino)-4-oxo-4-*p*-tolylbutyrate (4b):[7] ^{1}H NMR ($CDCl_3$): $\delta=1.25$ (t, $J=7.1$ Hz, 3H), 2.40 (s, 3H), 3.51 (dd, $J=17.8$, 6.3 Hz, 1H), 3.59 (dd, $J=17.8$, 4.6 Hz, 1H), 4.06–4.37 (m, 3H), 5.40–5.52 (brs, 1H), 7.16–7.56 (m, 5H), 7.73 (d, $J=7.3$ Hz, 2H), 7.84 (d, $J=8.3$ Hz, 2H), 8.27 ppm (brd, $J=5.1$ Hz, 1H); ^{13}C NMR ($CDCl_3$): $\delta=14.1$, 21.6, 39.4, 59.2, 61.5, 126.9, 128.2, 128.6, 129.3, 131.8, 132.7, 133.7, 144.4, 166.8, 172.7, 196.8 ppm; IR (neat): $\tilde{\nu}=3295$, 2924, 1735, 1680, 1606, 1181 cm^{-1}; HRMS: calcd for $C_{20}H_{22}N_2O_4$: 354.1580; found: 354.1548; HPLC (Daicel Chiralcel OD, hexane/*i*PrOH 4:1, flow rate = 1.0 mL min^{-1}): $t_R=12.0$ min (*R*), $t_R=17.0$ min (*S*).

Ethyl 2-(*N'*-benzoylhydrazino)-4-(4-methoxyphenyl)-4-oxobutyrate (4c):[7] ^{1}H NMR ($CDCl_3$): $\delta=1.25$ (t, $J=7.2$ Hz, 3H), 3.49 (dd, $J=17.6$, 6.3 Hz, 1H), 3.57 (dd, $J=17.6$, 4.4 Hz, 1H), 3.87 (s, 3H), 4.10–4.33 (m, 3H), 5.29–5.60 (m, 1H), 6.92 (d, $J=8.8$ Hz, 2H), 7.36–7.46 (m, 2H), 7.50 (t, $J=7.3$ Hz, 1H), 7.73 (d, $J=7.3$ Hz, 2H), 7.93 (d, $J=8.8$ Hz, 2H), 8.26 ppm (brs, 1H); ^{13}C NMR ($CDCl_3$): $\delta=14.1$, 39.2, 55.5, 59.2, 61.5, 113.8, 126.9, 128.6, 129.3, 130.5, 131.8, 132.7, 163.8, 166.8, 172.8, 195.7 ppm; IR (neat): $\tilde{\nu}=3257$, 1740, 1686, 1627, 1600, 1453, 1262, 1222, 1192, 1169 cm^{-1}; MS: *m/z*: 370 $[M]^+$; HPLC (Daicel Chiralcel OD, hexane/*i*PrOH 4:1, flow rate = 1.0 mL min^{-1}): $t_R=19.6$ min (*R*), $t_R=28.2$ min (*S*).

Ethyl 2-(*N'*-benzoylhydrazino)-4-(4-chlorophenyl)-4-oxobutyrate (4d):[7] ^{1}H NMR ($CDCl_3$): $\delta=1.22$ (t, $J=7.1$ Hz, 3H), 3.46 (dd, $J=17.9$, 6.2 Hz, 1H), 3.56 (dd, $J=17.9$, 5.0 Hz, 1H), 4.10–4.34 (m, 3H), 5.52 (brs, 1H), 7.32–7.55 (m, 5H), 7.69–7.79 (m, 2H), 7.85 (d, $J=8.6$ Hz, 2H), 8.55 ppm (brd, $J=5.0$ Hz, 1H); ^{13}C NMR ($CDCl_3$): $\delta=14.1$, 39.4, 59.1, 61.6, 127.0, 128.6, 129.0, 129.5, 131.9, 132.5, 134.5, 140.0, 167.0, 172.3, 196.0 ppm; IR (neat): $\tilde{\nu}=3293$, 1733, 1683, 1590, 1535, 1215, 693 cm^{-1}; MS: *m/z*: 374 $[M]^+$; HPLC (Daicel Chiralcel OD, hexane/*i*PrOH 4:1, flow rate = 1.0 mL min^{-1}): $t_R=14.0$ min (*R*), $t_R=19.7$ min (*S*).

Ethyl 2-(*N'*-benzoylhydrazino)-3-methyl-4-oxo-4-phenylbutyrate (6a):[7] M.p. 120–122 °C; $[\alpha]_D^{23}=+24.5$ ($c=0.40$ in $CHCl_3$, *syn*/*anti* 99.7:0.3, >99.5% *ee* (*syn*)); ^{1}H NMR ($CDCl_3$); *syn*: $\delta=1.23$ (t, $J=7.1$ Hz, 3H), 1.28 (d, $J=7.1$ Hz, 3H), 3.88–4.37 (m, 4H), 4.83 (brs), 7.30–7.61 (m, 6H), 7.71 (d, $J=7.3$ Hz, 2H), 7.94 (d, $J=7.1$ Hz, 2H), 8.29 ppm (brs, 1H); detectable peak of *anti* isomer: 8.14 ppm (brs, 1H); ^{13}C NMR ($CDCl_3$); *syn*: $\delta=13.9$, 14.2, 42.5, 61.2, 65.9, 126.9, 128.3, 128.4, 128.6, 131.6, 132.5, 133.1, 136.0, 166.8, 172.1, 201.5 ppm; IR (KBr): $\tilde{\nu}=3269$, 1732, 1682, 1628, 1551, 1194, 706 cm^{-1}; MS: *m/z*: 354 $[M]^+$; elemental analysis calcd for $C_{20}H_{22}N_2O_4$: C 67.78, H 6.26, N 7.90; found: C 67.84, H 6.47, N 7.93; HPLC (Daicel Chiralcel OD, hexane/*i*PrOH 19:1, flow rate = 1.0 mL min^{-1}); *syn*: $t_R=23.5$ min (major), $t_R=28.2$ min (minor); *anti*: $t_R=31.4$ min (major), $t_R=32.9$ min (minor).

Ethyl 2-(*N'*-benzoylhydrazino)-3,5-dimethyl-4-oxohexanoate (6b):[7] ^{1}H NMR ($CDCl_3$); *syn*: $\delta=1.11$ (d, $J=6.8$ Hz, 3H), 1.12 (d, $J=6.8$ Hz, 3H), 1.23 (d, $J=7.2$ Hz, 3H), 1.26 (t, $J=7.1$ Hz, 3H), 2.73–2.91 (m, 1H), 3.24 (quin, $J=7.2$ Hz, 1H), 3.81 (d, $J=7.2$ Hz, 1H), 4.21 (dq, $J=7.1$, 3.2 Hz, 1H), 7.38–7.56 (m, 3H), 7.69–7.78 (m, 2H), 8.08 ppm (brs, 1H); detectable peak of the *anti* isomer: 3.93 ppm (d, $J=4.8$ Hz, 1H); ^{13}C NMR ($CDCl_3$); *syn*: $\delta=13.7$, 14.1, 18.1, 18.3, 39.6, 45.7, 61.4, 65.8, 126.9, 128.6, 131.8, 132.6, 166.7, 172.4, 215.7 ppm; IR (KBr): $\tilde{\nu}=3253$, 3228, 1731, 1707, 1625, 1204, 696 cm^{-1}; MS: *m/z*: 320 $[M]^+$; elemental analysis calcd for $C_{17}H_{24}N_2O_4$: C 63.73, H 7.55, N 8.74; found: C 63.70, H 7.78; N 8.44; HPLC (Daicel Chiralcel OD, hexane/*i*PrOH 19:1, flow rate = 1.0 mL min^{-1}); *syn*: $t_R=14.2$ min (major), $t_R=17.2$ min (minor); *anti*: $t_R=22.2$ min (major), $t_R=27.0$ min (minor).

A typical experimental procedure for the Mannich-type reactions with acetophenone-derived silyl enol ether 3 in water (Table 12, entry 1): Compound **2** (0.421 mmol) and **3** (1.26 mmol) were added to a mixture of **1i** (0.0421 mmol) and ZnF_2 (0.421 mmol) in H_2O (2.35 mL), and the mixture was stirred vigorously (~1400 rpm) at 0 °C. After 20 h, the reaction was quenched with saturated aqueous $NaHCO_3$. The resultant mixture was then extracted with dichloromethane (×3), and the combined organic layers were dried over anhydrous Na_2SO_4. Finally, the solvent was evaporated, and the residue was purified by preparative TLC (silica gel, chloroform/MeOH 39:1 and then hexane/ethyl acetate 3:2) to give Mannich adduct (*R*)-**4** (91% yield, 95% *ee*).

A typical experimental procedure for the Mannich-type reactions of propiophenone-derived silyl enol ether 5 in water (Table 13, entry 5): A solution of CTAB (0.0716 M, 0.0200 mmol) in H_2O, **2** (0.400 mmol), and **5** (1.20 mmol) were added to a mixture of ZnF_2 (0.400 mmol) and **1c** (0.0400 mmol) in H_2O (1.95 mL), and the mixture was stirred vigorously (~1400 rpm) at 0 °C. After 20 h, the reaction was quenched with saturated aqueous $NaHCO_3$. The resultant mixture was then extracted with dichloromethane (×3), and the combined organic layers were dried over anhydrous Na_2SO_4. Finally, the solvent was evaporated, and the residue was purified by preparative TLC (silica gel, hexane/ethyl acetate 2:1, ×2) to give Mannich adduct **6** (94% yield, *syn*/*anti* 94:6, 97% *ee* (*syn*)).

Ethyl 2-(*N'*-benzoylhydrazino)-4-*tert*-butylthio-3-methyl-4-oxobutanoate (6c):[8] ^{1}H NMR ($CDCl_3$); *syn*: $\delta=1.28$ (t, $J=7.2$ Hz, 3H), 1.31 (d, $J=7.1$ Hz, 3H), 1.44 (s, 9H), 3.12 (dq, $J=4.3$, 7.1 Hz, 1H), 4.00 (dd, $J=3.7$, 4.3 Hz, 1H), 4.15–4.29 (m, 2H), 5.50 (dd, $J=3.7$, 6.3 Hz, 1H), 7.38–7.44 (m, 2H), 7.46–7.52 (m, 1H), 7.71–7.77 (m, 2H), 8.08 ppm (brd, $J=6.3$ Hz, 1H); ^{13}C NMR ($CDCl_3$); *syn*: $\delta=13.2$, 14.0, 29.6, 48.3, 49.5, 61.4, 64.5, 126.9, 128.5, 131.7, 132.5, 166.7, 171.1, 201.8 ppm; ^{1}H NMR ($CDCl_3$); *anti*: $\delta=1.27$ (t, $J=7.1$ Hz, 3H), 1.29 (d, $J=7.1$ Hz, 3H), 1.47 (s, 9H), 3.10 (dq, $J=6.8$, 7.1 Hz, 1H), 3.85 (dd, $J=6.2$, 6.8 Hz, 1H), 4.09–4.35 (m, 2H), 5.32 (dd, $J=5.4$, 6.2 Hz, 1H), 7.39–7.56 (m, 3H), 7.70–7.79 (m, 2H), 7.94 ppm (brd, $J=5.4$ Hz, 1H); ^{13}C NMR ($CDCl_3$); *anti*: $\delta=14.1$, 14.5, 29.7, 48.4, 49.4, 61.4, 65.9, 126.9, 128.6, 131.8, 132.6, 166.9, 171.4, 201.4 ppm; IR (neat, *syn*/*anti* 8:92): $\tilde{\nu}=3292$, 2966, 1738, 1680, 1456, 1211, 964, 696 cm^{-1}; HRMS (FAB): calcd for $C_{18}H_{27}N_2O_4S$: 367.1692 $[M+H]^+$; found: 367.1671; HPLC (Daicel Chiralpak AD-H (double), hexane/*i*PrOH 4:1, flow rate = 0.50 mL min^{-1}); *syn*: $t_R=34.8$ min (2*S*,3*S*), $t_R=41.4$ min (2*R*,3*R*). *anti*: $t_R=28.8$ min (2*S*,3*R*), $t_R=33.1$ min (2*R*,3*S*).

Ethyl 2-(*N'*-benzoylhydrazino)-3-methyl-4-oxohexanoate (6d):[8] *syn* (*syn*/*anti* 98.5:1.5, >99.5% *ee* (*syn*)): m.p. 117–119 °C; $[\alpha]_D^{25}=+8.3$ ($c=0.25$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta=1.06$ (t, $J=7.2$ Hz, 3H), 1.23 (d, $J=7.2$ Hz, 3H), 1.26 (t, $J=7.2$ Hz, 3H), 2.43–2.66 (m, 2H), 3.08 (dq, $J=7.2$, 7.2 Hz, 1H), 3.87 (d, $J=7.2$ Hz, 1H), 4.12–4.30 (m, 2H), 4.84 (brs, 1H), 7.37–7.56 (m, 3H), 7.70–7.79 (m, 2H), 8.08 ppm (s, 1H); ^{13}C NMR ($CDCl_3$): $\delta=7.6$, 13.5, 14.1, 34.7, 47.1, 61.3, 65.5, 126.9, 128.6, 131.8, 132.6, 166.7, 172.0, 212.2 ppm; IR (KBr): $\tilde{\nu}=3251$, 1730, 1711, 1626, 1556, 1452, 1205, 694 cm^{-1}; HRMS (ESI-TOF): calcd for $C_{16}H_{22}N_2O_4Na$: 329.1477 $[M+Na]^+$; found: 329.1460; *anti*: ^{1}H NMR ($CDCl_3$): $\delta=1.04$ (t, $J=7.2$ Hz, 3H), 1.25 (d, $J=7.2$ Hz, 3H), 1.26 (t, $J=7.2$ Hz, 3H), 2.48–2.70 (m, 2H), 3.11 (dq, $J=4.9$, 7.2 Hz, 1H), 3.98 (dd, $J=4.5$, 4.9 Hz, 1H), 4.10–4.29 (m, 2H), 5.35 (dd, $J=4.5$, 5.5 Hz, 1H), 7.36–7.54 (m, 3H), 7.70–7.78 (m, 2H), 8.18 ppm (brd, $J=5.5$ Hz, 1H); ^{13}C NMR ($CDCl_3$): $\delta=7.5$, 12.4, 14.0, 34.3, 46.9, 61.3, 64.0, 126.8, 128.5, 131.7, 132.4, 166.9, 171.7, 212.3 ppm; HPLC (Daicel Chiralpak AD-H, hexane/*i*PrOH 9:1, flow rate = 0.80 mL min^{-1}); *syn*: $t_R=23.9$ min (minor), $t_R=33.7$ min (major); *anti*: $t_R=26.7$ min (minor), $t_R=44.3$ min (major).

Ethyl 2-(*N'*-benzoylhydrazino)-3-methyl-4-(4-methoxyphenyl)-4-oxobutyrate (6e): *syn*: m.p. 117–118 °C; $[\alpha]_D^{25}=+12.5$ ($c=0.51$ in $CHCl_3$); ^{1}H NMR (C_6D_6): $\delta=0.97$ (t, $J=7.1$ Hz, 3H), 1.27 (d, $J=6.9$ Hz, 3H), 3.20 (s, 3H), 3.92–4.12 (m, 3H), 4.42 (dd, $J=7.6$, 7.6 Hz, 1H), 5.90 (dd, $J=7.6$, 6.0 Hz, 1H), 6.65 (d, $J=8.7$ Hz, 2H), 6.95–7.10 (m, 3H), 7.69 (d, $J=8.2$ Hz, 2H), 7.97 (d, $J=8.7$ Hz, 2H), 8.36 ppm (d, $J=6.0$ Hz, 1H); ^{13}C NMR ($CDCl_3$): $\delta=14.1$, 14.8, 42.1, 55.5, 61.3, 66.2, 113.9, 126.9, 128.5,

128.9, 130.8, 131.7, 132.6, 163.7, 166.7, 172.4, 200.0 ppm; IR (KBr): $\tilde{\nu}$ = 3267, 1728, 1665, 1620, 1601, 1176 cm^{-1}; HRMS (ESI-TOF): calcd for $C_{21}H_{25}N_2O_5$: 385.1763 $[M+H]^+$; found: 385.1751; *anti*: ^1H NMR (C_6D_6); detectable peaks of the *anti* isomer: δ = 0.92 (t, J = 7.1 Hz, 3H), 1.46 (d, J = 6.9 Hz, 3H), 3.19 (s, 3H), 4.32 (d, J = 6.0 Hz, 1H), 6.61 (d, J = 9.2 Hz, 2H), 7.75–7.82 (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 13.8, 14.0, 41.8, 55.3, 61.4, 64.8, 113.8, 126.8, 128.3, 128.4, 130.7, 131.7, 132.4, 163.6, 166.7, 171.7, 200.3 ppm; HPLC (Daicel Chiralcel OJ-H (double), hexane/*i*PrOH 4:1, flow rate = 1.0 mL min^{-1}); *syn*: t_R = 33.9 min (minor), t_R = 38.0 min (major); *anti*: t_R = 46.2 min (minor), t_R = 54.1 min (major).

Ethyl 2-(*N'*-benzoylhydrazino)-3-ethyl-4-oxo-4-phenylbutyrate (6f):[8] *syn* (*syn*/*anti* 99:1, >99.5% *ee* (*syn*)): m.p. 88–91 °C; $[\alpha]_D^{27}$ = +13.2 (c = 2.72 in $CHCl_3$); ^1H NMR ($CDCl_3$): δ = 0.97 (t, J = 7.3 Hz, 3H), 1.20 (t, J = 7.1 Hz, 3H), 1.75–1.90 (m, 2H), 3.93 (ddd, J = 6.9, 6.9, 7.6 Hz, 1H), 4.04 (d, J = 7.6 Hz, 1H), 4.08–4.23 (m, 2H), 5.09 (br s, 1H), 7.35–7.51 (m, 5H), 7.53–7.59 (m, 1H), 7.71 (d, J = 7.3 Hz, 2H), 7.96 (d, J = 7.6 Hz, 2H), 8.20 ppm (s, 1H); ^{13}C NMR ($CDCl_3$): δ = 11.6, 14.0, 22.7, 48.9, 61.4, 64.8, 126.9, 128.3, 128.5, 128.7, 131.7, 132.6, 133.3, 137.2, 166.6, 172.5, 202.1 ppm; IR (KBr): $\tilde{\nu}$ = 3269, 1732, 1682, 1628, 1551, 1194, 706 cm^{-1}; HRMS (FAB): calcd for $C_{21}H_{25}N_2O_4$: 369.1814 $[M+H]^+$; found: 369.1834; *anti*: ^1H NMR ($CDCl_3$): δ = 0.93 (t, J = 7.3 Hz, 3H), 1.25 (t, J = 7.1 Hz, 3H), 1.78–1.92 (m, 1H), 2.01–2.16 (m, 1H), 3.99 (ddd, J = 5.0, 5.1, 7.8 Hz, 1H), 4.07 (d, J = 5.0 Hz, 1H), 4.17–4.28 (m, 2H), 4.96 (br s, 1H), 7.35–7.57 (m, 6H), 7.62–7.68 (m, 2H), 7.93–8.01 ppm (m, 3H); ^{13}C NMR ($CDCl_3$): δ = 11.9, 14.0, 21.7, 48.7, 61.5, 63.5, 126.8, 128.4, 128.5, 128.7, 131.8, 132.4, 133.3, 136.5, 166.8, 171.8, 201.7 ppm; HPLC (Daicel Chiralpak AD-H, hexane/*i*PrOH 4:1, flow rate = 0.70 mL min^{-1}); *syn*: t_R = 18.3 min (major), t_R = 29.4 min (minor); *anti*: t_R = 20.2 min (minor), t_R = 25.2 min (major).

The absolute configurations of Mannich adduct **4a** and the adduct obtained in the reaction with **7** were determined to be 2*R*.[7,8] By analogy the absolute configurations of all the other adducts were assumed to be 2*R*.

The relative configurations of the Mannich adducts obtained in the reactions of both (*Z*)-**7** and (*Z*)-**8** were determined to be *syn*.[8] The relative configurations of the adducts obtained in the reactions of **5**, (*Z*)-(1-isopropylpropenyloxy)trimethylsilane, (*Z*)-[1-(4-methoxyphenyl)propenyloxy]-trimethylsilane, and (*Z*)-trimethyl(1-phenylbut-1-enyloxy)silane were assumed to be *syn* by analogy with (*Z*)-**8**.

Reaction mechanism:

ZnF(OH): This material was prepared by a known method.[27] IR (KBr): $\tilde{\nu}$ = 3558, 3367, 1024, 908, 787, 465 cm^{-1}.

Me_3SiF: This material was purchased from Aldrich and purified by distillation (through K_2CO_3) just before use. All the experiments using Me_3SiF were conducted in a low temperature room (4 °C).

Mannich-type reactions with ZnF(OH) and Me_3SiF (Table 10, entry 6): A solution of **1i** (0.0466 mmol) in H_2O/THF (1:9, 0.95 mL) and **2** (0.466 mmol) were added to a solution of ZnF(OH) (0.466 mmol) in H_2O/THF (1:9, 0.28 mL). Compound **3** (1.40 mmol) in H_2O/THF (1:9, 1.35 mL) and Me_3SiF (54 μL, 0.466 mmol) were then added to this mixture, and the mixture was stirred at 0 °C. After 20 h, the reaction was quenched with saturated aqueous $NaHCO_3$, and the resultant mixture was extracted with dichloromethane (×4). The combined organic layers were then dried over anhydrous Na_2SO_4, and the solvents were evaporated. The resulting residue was purified by preparative TLC (silica gel, $CHCl_3$/MeOH (39:1) and then hexane/ethyl acetate 3:2) to give (*R*)-**4a** (90% yield, 96% *ee*).

Me_3SiOH: This compound was prepared by a known method.[39] ^1H NMR ($CDCl_3$): δ = 0.14 ppm (s, 9H); ^{13}C NMR ($CDCl_3$): δ = 1.3 ppm.

Hydrolysis of Me_3SiF (Table 11): Me_3SiF (41 μL, 0.35 mmol) and D_2O/[D_8]THF (1:9, 0.70 mL) were added at 0 °C to a solution of benzotrifluoride (internal standard, 0.183 mmol) in a NMR tube. The resulting solution was then stored at 0 °C. After 0.5 h, 25 h, and 69 h, ^1H NMR spectra were recorded (600.17 MHz, D_2O/[D_8]THF 1:9, 0 °C) to measure the amounts of Me_3SiOD, $(Me_3Si)_2O$, and Me_3SiF present in the reaction mixture.

Me_3SiOD: ^1H NMR (D_2O/[D_8]THF 1:9, 0 °C): δ = 0.03 ppm (s, 9H).

$(Me_3Si)_2O$: ^1H NMR (D_2O/[D_8]THF 1:9, 0 °C): δ = 0.04 (s, 18H).

Me_3SiF: ^1H NMR (D_2O/[D_8]THF 1:9, 0 °C): δ = 0.18 (d, J = 6.9 Hz, 9H).

Reaction of Me_3SiOH with ZnF_2 [Eq. (1)]: Me_3SiOH (0.499 mmol) was added to a solution of ZnF_2 (0.492 mmol), **1i** (0.0492 mmol), and 4-fluorotoluene (internal standard, 0.232 mmol) in D_2O/[D_8]THF (1:9, 0.97 mL) at 0 °C. The reaction vessel was then capped and stirred at 0 °C. After 20 h, the stirring was stopped, and the mixture was allowed to stand for 15 min. The supernatant liquid (~0.70 mL) was transferred to a NMR tube with a gas-tight syringe. A ^1H NMR spectrum was then recorded (600.17 MHz, D_2O/[D_8]THF 1:9, 0 °C) to measure the amounts of Me_3SiOD, $(Me_3Si)_2O$, and Me_3SiF present in the reaction mixture.

Crystallization of [$ZnCl_2$-1c]·CH_2Cl_2 complexes[8] (Figure 1): Crystallization of [$ZnCl_2$–**1c**]·CH_2Cl_2 was carried out as follows: A solution of **1c** (0.032 mmol) in CH_2Cl_2 (0.81 mL) was added to a suspension of $ZnCl_2$ (0.039 mmol) in CH_2Cl_2 (0.81 mL), and the mixture was stirred for 16 h at RT. The resulting clear solution was filtered, and slow vapor diffusion of hexane into this solution at 5 °C produced the product as colorless crystals. CCDC-244175 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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