#### Lewis acid catalysts have been developed.<sup>[1]</sup> Among them, enantioselective addition of allylmetal reagents to imino compounds<sup>[2]</sup> provides a useful route to optically active homoallylic amines, which are important building blocks in organic synthesis as the $\gamma$ , $\delta$ -double bonds of homoallylic amines can be readily converted into many different functional groups. In spite of the synthetic utility of optically active homoallylic amines, however, examples of catalytic asymmetric allylation of imino compounds are limited.

Recently, we reported catalytic asymmetric Mannich-type reactions of acylhydrazono esters in H<sub>2</sub>O/THF by using a combination of a stoichiometric amount of zinc fluoride and a catalytic amount of a chiral diamine and TfOH (TfOH = Trifluoromethanesulfonic acid).<sup>[3]</sup> Acylhydrazones are imine surrogates more stable than imines even in aqueous media.<sup>[4]</sup> Furthermore, hydrazines, such as the products in the Mannich reaction or allylation are interesting compounds, not only because hydrazines themselves can be used as unique building blocks.<sup>[5]</sup> but also because, if the N–N bond can be cleaved. amines are obtained. Accordingly, asymmetric allylation of hydrazones is considered to be a versatile methodology, although there are no examples of a catalytic version.<sup>[6]</sup> Herein, we describe the first catalytic asymmetric allylation of acylhydrazones, especially acylhydrazono esters. The reactions proceeded smoothly by using a chiral Zn catalyst in aqueous media.

We focused on allyltrimethoxysilane as an allylating agent,<sup>[7,8]</sup> because it can form a pentacoordinate silicate easily,<sup>[9]</sup> and is a preferable reagent compared with allyltin compounds from the standpoint of toxicity. As a chiral catalyst system, we initially used the combination of  $ZnF_2^{[10]}$ (100 mol%), diamine 1 (10 mol%), and TfOH (1 mol%), which was effective for the previous Mannich-type reaction. The reaction of hydrazono ester 2 with allyltrimethoxysilane was conducted in H<sub>2</sub>O/THF (1:9), to afford the corresponding allylated product 3 in moderate yield with a relatively high ee value (Table 1, entry 1). Interestingly, it was found that TfOH, which was essential in the Mannich-type reaction, was not needed in the allylation reaction (Table 1, entry 2). Moreover, even when only 20 mol% of ZnF<sub>2</sub> was used, the allylation proceeded with a good yield (Table 1, entry 3), although more than 50 mol % of ZnF2 was necessary to achieve high yields in the Mannich-type reaction. These results indicate that a catalytic amount of the fluoride anion is sufficient for the allylation, while a stoichiometric amount of the fluoride anion is needed in the Mannich-type reaction. The fluoride anion is considered to be a key in this reaction, as  $Zn(OTf)_2$  gave no product (Table 1, entry 5). Furthermore, it was found that 1 accelerated the reaction significantly<sup>[11]</sup> (Table 1, compare entries 2 and 6). From these results, it is concluded that the reaction mechanism including the catalytic cycle of the present asymmetric allylation may be different from that of the previous Mannich-type reaction.

We speculate that this reaction proceeds with double activation<sup>[12,13]</sup> in which  $Zn^{2+}$  acts as a Lewis acid to activate **2** and, at the same time, the fluoride anion acts as a Lewis base to attack the silicon atom of allyltrimethoxysilane. In other words, the zinc amide and (MeO)<sub>3</sub>SiF are formed first, and subsequent hydrolysis of the amide affords allylated product **3** 

### Asymmetric Allylation

Catalytic Asymmetric Allylation of Hydrazono Esters in Aqueous Media by Using ZnF<sub>2</sub>-Chiral Diamine\*\*

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Over the past several years, highly efficient methods for enantioselective addition to C=N double bonds by chiral

- [\*\*] This work was partially supported by CREST and SORST, Japan Science and Technology Corporation (JST), and a Grant-in-Aid for Scientific Research from Japan Society of the Promotion of Science. T.H. thanks the JSPS fellowship for Japanese Junior Scientists.
- Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

Angew. Chem. Int. Ed. 2003, 42, 3927-3930

DOI: 10.1002/anie.200351778

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# Communications

Table 1: Investigation of catalyst system.



[a] The absolute configuration is assumed to be R (see [5])



Scheme 1. Proposed reaction mechanism.

and Zn(OH)F (Scheme 1). It is considered that a catalytic amount of the fluoride anion gives a good yield in this reaction probably because catalytic turnover of the fluoride anion occurs. This apparently means that the Si-F bond of (MeO)<sub>3</sub>SiF is hydrolyzed by Zn(OH)F, regenerating ZnF<sub>2</sub>. To elucidate this mechanism, we investigated the ability of  $(MeO)_3SiF$  to regenerate  $ZnF_2$ from Zn(OH)F. In fact, the reaction of 2 with allyltriethoxysilane did not proceed in the presence of  $Zn(OH)F^{[14]}$  (100 mol%) and **1** (10 mol%) in  $H_2O/THF = 1:9$  at 0°C for 20 h. When (EtO)<sub>3</sub>SiF (100

Table 2: Effect of chiral diamines.

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ίΗ ΗŇ 4-MeO(C<sub>6</sub>H<sub>4</sub>) MeO(C<sub>6</sub>H<sub>4</sub>) (10 mol %) NH ZnF2 (20 mol %) Si(OMe) FtO  $H_{2}O/THF = 1:9$ ö (3.0 equiv) 0°C, 55 h 5 Entry Ar Yield [%] ee [%] 2-MeO-C<sub>6</sub>H<sub>4</sub> (1) 84 81  $C_6H_5$  (6) 29 48 2-Me-C<sub>6</sub>H<sub>4</sub> (7) 26 83 2,5-(MeO)<sub>2</sub>-C<sub>6</sub>H<sub>3</sub> (8) 81 76 3,5-(MeO)<sub>2</sub>-C<sub>6</sub>H<sub>3</sub> (9) 27 31 2-MeO-5-tBu-C<sub>6</sub>H<sub>3</sub> (10) 99 64 1-MeO-2-naphthyl (11) 19 70 8-MeO-2-naphthyl (12) 59 84

mol%) was added, however, the reaction proceeded, and 3 was obtained in similar yield and selectivity to that of the reaction with  $ZnF_2$  (33% yield, 76% *ee*, compare with Table 1, entry 2). These results indicate that the exchange of the fluoride anion between Zn(OH)F and (EtO)<sub>3</sub>SiF regenerates ZnF<sub>2</sub>, which is active to catalyze the reaction.

Next, we examined the effect of chiral diamines on the enantioselectivity in the reaction of 4-**4**.<sup>[15]</sup> methoxybenzoylhydrazone Diamine  $\mathbf{6}^{[16]}$  without the methoxy group on the aromatic ring of 1 gave lower yield and ee (Table 2, entry 2). When 7 was employed, the yield was low, while the same ee value was obtained as that in the

reaction with 1 (Table 2, entry 3). Diamine 8 afforded comparable yield and ee value to 1, although 9 gave a disappointing result (Table 2, entries 4 and 5). The above results indicate that the MeO group in the chiral diamine ligand plays an essential role for attaining high yields and selectivities. Among the diamines examined in Table 2, 12 gave the highest ee value (Table 2, entry 8).

Several examples of the allylation reactions are shown in Table 3. The reactions were conducted in the presence of  $ZnF_2$  (20 mol%) and a chiral diamine (10 mol%) in H<sub>2</sub>O/ THF (1:9) at 0°C. When 4-methoxybenzoylhydrazone derived from methyl glyoxylate was used as a substrate, the ee value was slightly improved (Table 3, entries 1 and 2). An improvement in the yield was observed when the reaction of 4-ethoxybenzoylhydrazone derived from ethyl glyoxylate was performed (Table 3, entries 3 and 4). The reactions of 2substituted allylsilanes gave the desired products with moderate to good yields and selectivities (Table 3, entries 5 and 6).

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Table 3: Catalytic asymmetric allylation.

$ \begin{array}{c} H \\ N^{-N} \stackrel{4-R^{2}O(C_{6}H_{4})}{\qquad} R^{3} \\ R^{1}O \stackrel{H}{\swarrow} 0 \qquad + \stackrel{Si(C_{6}H_{4})}{\swarrow} Si(C_{6}H_{4}) \end{array} $			∠Si(OMe) <sub>3</sub>	Diamine (10 mol %) ZnF <sub>2</sub> (20 mol %)	$\begin{array}{ccc} 4 R^2 O(C_6 H_4) & H \\ & & & N \\ O & & N \\ & & & R^1 O \\ \end{array}$	
U O		(3.	0 equiv)	H <sub>2</sub> O/THF = 1:9 0 °C, 55 h	0	$\checkmark$ $\approx$
Entry	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Diamine	Yield [%]	ee [%]
1	Me	Me	н	1	61	83
2 <sup>[a]</sup>	Me	Me	н	12	60	86
3	Et	Et	н	1	92	81
4	Et	Et	н	12	81	85
5	Et	Et	Me	1	88	65
6 <sup>[b]</sup>	Et	Et	Ph	1	62	78

[a] 96 h. [b] 162 h.

To highlight the importance of the allylated products obtained in this reaction, **5** (84% *ee*) was converted into synthetically important *N*-Boc (Boc = 1,1-dimethylethoxycarbonyl)  $\alpha$ -amino acid **13** [Eq. (1)]; DMAP = 4-dimethylamino pyridine. N-Boc protection of **5** afforded *N*-Boc hydrazine<sup>[17]</sup>



in 82 % yield, and the N–N bond of the hydrazine was cleaved with  $\text{SmI}_2^{[18]}$  to afford **13** in 91 % yield without significant loss of the enantiomeric purity.<sup>[19]</sup> Thus, this allylation reaction has been shown to be a versatile method to obtain not only the optically active  $\alpha$ -amino ester hydrazine analogues but also *N*-protected  $\alpha$ -amino esters.

(DMAP = N, N-dimethyl 1, 3-propanediamine). Another important aspect of the present catalytic asymmetric allylation is that the reactions proceed smoothly in aqueous media. Recently, organic reactions in aqueous media have attracted a great deal of attention,<sup>[20]</sup> because water is a clean and safe solvent. In addition, the drying of substrates and solvents by dehydration is not required, and unique reactivities and selectivities are often observed by using water as a solvent. However, catalytic asymmetric carbon-carbon bond-forming reactions in aqueous media are extremely difficult to attain, because most chiral catalysts are not stable in the presence of even a small amount of water.<sup>[21]</sup> However, water plays a key role to obtain the product in the present allylation. Namely, it was shown that the reaction of 2 with allyltrimethoxysilane did not proceed at all in THF without water or MeOH/THF (1:9) in the presence of  $ZnF_2$  (100 mol%) and **1** (10 mol%) at 0°C for 20 h.

In summary, the asymmetric allylation of acylhydrazono esters in aqueous media has been achieved by using a catalytic amount of  $ZnF_2$  and a chiral diamine ligand. This reaction is the first example of catalytic asymmetric allylation of hydrazones. Furthermore, it should be noted that the catalytic

asymmetric allylation to the C=N bond in aqueous media is unprecedented. Further investigations involving elucidation of the detailed reaction mechanism are currently in progress.

Received: April 30, 2003 [Z51778]

**Keywords:** allylation · asymmetric synthesis · fluorides · zinc

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