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Highly Enantioselective Allylation of α-Ketoesters Catalyzed by *N*,*N*′-Dioxide−In(III) Complexes

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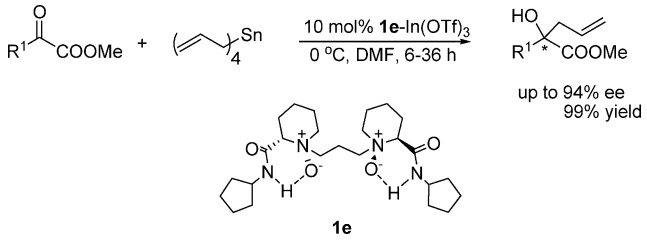

An efficient asymmetric allylation of α-ketoesters was catalyzed by the *N*,*N*′-dioxide−In(III) complex in excellent yields (up to 99%) and high enantioselectivities (up to 94% ee) for a variety of substrates under mild reaction conditions. On the basis of experimental results, a possible catalytic cycle including a transition state has been proposed to explain the origin of the reactivity and asymmetric inductivity, and a bifunctional catalysis was described with Lewis base *N*-oxide activating tetraallylstannane and Lewis acid indium activating α-ketoester.

Introduction

Optically active α-hydroxy acids and their derivatives are very important structural motifs in numerous biologically interesting compounds[1] and are often utilized as resolving agent.[2] α-Ketoesters, as a new type of prochiral substrate, can be readily transformed to a series of α-hydroxyesters by alkylation,[3] alkynylation,[4] and nitroaldol[5] reaction. Accordingly, considerable effort has been devoted to their preparation via catalytic asymmetric reactions. Kozlowski et al. reported the addition of Et_2Zn to α-ketoesters catalyzed by chiral Ti complexes.[3b,c] Snapper and Hoveyda et al. have developed a related method of Al-catalyzed asymmetric additions of dialkylzinc.[3a] Asymmetric nitroaldol reaction of α-ketoesters catalyzed by cinchona alkaloids was reported by Deng and co-workers.[5d] Jiang and co-workers have employed chiral amino alcohol as ligands in Zn-catalyzed enantioselective alkynylations of aromatic α-ketoesters.[4] However, the asymmetric allylation of α-ketoesters

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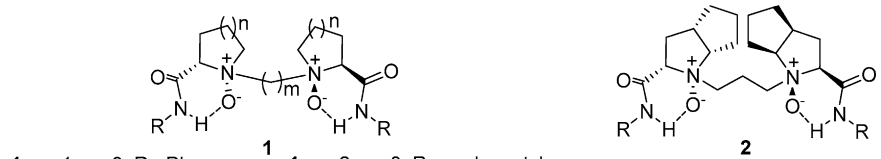
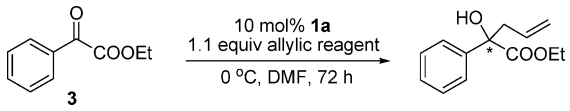


1a n=1, m=3. R= Ph
1b n=2, m=3. R= Ph
1c n=2, m=3. R= *o*-CH_3-Ph
1d n=2, m=3. R= *t*-Bu
1e n=2, m=3. R= cyclopentyl
1f n=2, m=3. R= 1-adamantyl
1g n=2, m=2. R= cyclopentyl
1h n=2, m=5. R= cyclopentyl

2a R= cyclopentyl
2b R= cyclohexyl

FIGURE 1. Ligands employed for asymmetric allylation.

TABLE 1. Effect of Allylic Reagents in Enantioselective Allylation of α-Ketoester 3[a]

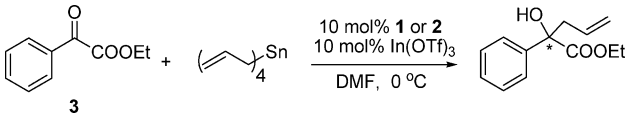


3

entry	allylic reagent	yield (%)[b]	ee (%)[c]
1	allyltrichlorosilane	ND[d]	
2	allyltrimethylsilane	ND[d]	
3	allyltrimethoxysilane	ND[d]	
4	allyltributylstannane	ND[d]	
5	tetraallylstannane	15	0

[a] Conditions: All reactions were performed with α-ketoester **3** (0.1 mmol) and allylic reagent (1.1 equiv) in DMF (1.0 mL) at 0 °C for 72 h. [b] Isolated yield. [c] Determined by HPLC on a Chiralcel OJ-H column. [d] Not detected.

TABLE 2. Allylation of α-Ketoester 3 Catalyzed by In(III) Complexes[a]



3

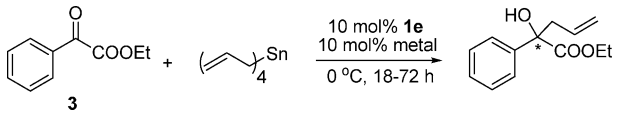
entry	*N*,*N*′-dioxide	time (h)	yield (%)[b]	ee (%)[c]
1	**1a**	48	80	27
2	**1b**	48	78	60
3	**1c**	48	87	71
4	**1d**	10	93	80
5	**1e**	18	99	86
6	**1f**	12	95	80
7	**2a**	12	85	84
8	**2b**	10	99	83
9	**1g**	12	95	77
10	**1h**	24	67	10

[a] Conditions: All reactions were performed with α-ketoester **3** (0.1 mmol) and tetraallylstannane (1.1 equiv) in DMF (1.0 mL) at 0 °C for 10 to 48 h. Catalyst was composed of a 1:1 molar ratio of ligand to In(OTf)$_3$. [b] Isolated yield. [c] Determined by HPLC on a Chiralcel OJ-H column.

was rarely described[6g] although the resultant α-allyl-α-hydroxyesters are useful starting components for the synthesis of pharmaceutical agents and natural products.[1,6]

As a versatile catalyst, chiral *N*-oxides play a significant role in many asymmetric procedures.[7] A series of C_2-symmetric chiral *N*,*N*′-dioxides as highly efficient organocatalysts have been successfully used in the cyanation of aldehydes,[8] aldimines,[9] ketones,[10] and ketoimines.[11] Recently, the chiral *N*,*N*′-dioxide metal complexes also showed good results in the cyanation[12] and allylation[13] of carbonyl compounds. Herein, we wish to report the asymmetric allylation of α-ketoesters catalyzed by *N*,*N*′-dioxide−In(III) complex in excellent yields with high enantioselectivities.

TABLE 3. Effect of Metal Reagents and Solvent on the Asymmetric Allylation of α-Ketoester 3[a]



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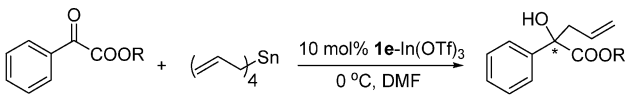
entry	metal	solvent	time (h)	yield (%)[b]	ee (%)[c]
1	$InBr_3$	DMF	24	90	73
2	In(OTf)$_3$	DMF	18	99	86
3	Sc(OTf)$_3$	DMF	72	ND[d]	
4	Ti(O^{i}Pr)$_4$	DMF	72	ND[d]	
5	Cu(OTf)$_2$	DMF	72	ND[d]	
6	In(OTf)$_3$	Et_2O	48	60	10
7	In(OTf)$_3$	THF	48	46	22
8	In(OTf)$_3$	toluene	48	15	5
9	In(OTf)$_3$	CH_2Cl_2	48	21	12
10	In(OTf)$_3$	CH_3CN	36	82	15

[a] Conditions: All reactions were performed with α-ketoester **3** (0.1 mmol) and tetraallylstannane (1.1 equiv) in solvent (1.0 mL) at 0 °C for 18 to 72 h. Catalyst was composed of a 1:1 molar ratio of **1e** to metal. [b] Isolated yield. [c] Determined by HPLC on a Chiralcel OJ-H column. [d] Not detected.

TABLE 4. Effect of Ester Group on the Asymmetric Allylation of α-Ketoesters[a]



3 R=Et **7** R=*i*-Pr
4a R=Me **8** R=*t*-Bu

entry	α-ketoesters	time (h)	yield (%)[b]	ee (%)[c]
1	**3**	18	99	86
2	**4a**	6	99	93
3	7	12	92	89
4	**8**	12	85	87

[a] Conditions: All reactions were performed with α-ketoesters (0.1 mmol) and tetraallylstannane (1.1 equiv) in DMF (1.0 mL) at 0 °C for 6 to 18 h. Catalyst was composed of a 1:1 molar ratio of **1e** to In(OTf)$_3$. [b] Isolated yield. [c] Determined by HPLC on a Chiralcel OJ-H column.

Results and Discussion

It has been demonstrated in the asymmetric cyanation[8,9] and allylation[13] that the *N*,*N*′-dioxide acted as Lewis base to activate the silicon atom and tin atom. So the *N*,*N*′-dioxide **1a** derived from L-proline (Figure 1) was employed as an organocatalyst for the enantioselective allylation of α-ketoester **3** with different

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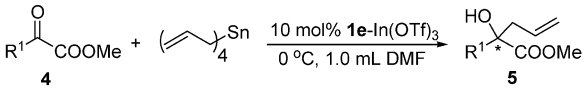
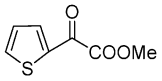
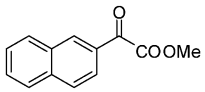
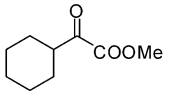
TABLE 5. Scope of the Enantioselective Allylation of α-Ketoesters[a]



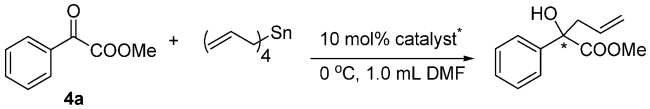
entry	substrate	product	time (h)	yield (%)[b]	ee (%)[c]
1	**4a** R= H	**5a**	6	>99	93(*R*)[d]
2	**4b** R= *o*-CH_3	**5b**	36	87	77(*R*)[e]
3	**4c** R= *m*-CH_3	**5c**	14	>99	90(*R*)[e]
4	**4d** R= *p*-CH_3	**5d**	6	>99	91(*R*)[e]
5	**4e** R= *m*-F	**5e**	14	>99	89(*R*)[e]
6	**4f** R= *p*-F	**5f**	6	>99	92(*R*)[e]
7	**4g** R= *o*-CH_3O	**5g**	24	97	83
8	**4h** R= *p*-CH_3O	**5h**	6	89	94(*R*)[e]
9		**4i**	**5i**	6	98	89
10		**4j**	**5j**	6	80	91
11		**4k**	**5k**	10	90	69

[a] Conditions: All reactions were performed with α-ketoesters (0.1 mmol) and tetraallylstannane (1.1 equiv) in DMF (1.0 mL) at 0 °C for 6 to 36 h. Catalyst was composed of a 1:1 molar ratio of **1e** to $In(OTf)_3$. [b] Isolated yield. [c] Determined by chiral HPLC or GC analysis as described in the Supporting Information. [d] The absolute configuration of the product **5a** was determined by comparison with the reported value[16] of optical rotation (see the Supporting Information). [e] The absolute configurations were assigned by comparing the Cotton effect of the CD spectra with that of **5a**.

allylic reagent (Table 1). Unfortunately, only tetraallylstannane gave a racemate product in low yield (Table 1, entry 5).

We speculated that the *N*,*N*′-dioxide coordinated with a suitable metal reagent might increase the chiral induction. So In(III), which had been effective in allylation of the carbonyl compounds,[13−15] was selected as a promising candidate. Fortunately, $In(OTf)_3$ combined with *N*,*N*′-dioxide **1a** could successfully catalyze the reaction with 27% ee and 80% yield (Table 2, entry 1). Encouraged by this result, a series of *N*-oxides **1** and **2** were prepared and evaluated in the asymmetric allylation of α-ketoester **3** (Table 2, entries 2−9). Excitingly, the enantiomeric excess was improved to 60% and 71% when the L-proline-derived *N*,*N*′-dioxide **1a** was replaced by (*S*)-pipecolic acid-derived *N*,*N*′-dioxides **1b** and **1c** (Table 2, entries 2 and 3). The enantioselectivity was further increased by changing the R group of the ligand's amide moiety from the aromatic group to the aliphatic group (Table 2, entries 4−6). The enantiomeric excess was increased to 86% with the cyclopen-

TABLE 6. Control Experiments[a]



entry	ligand (mol %)	$In(OTf)_3$ (mol %)	tetraallylstannane (equiv)	yield (%)[b]	ee (%)[c]
1	**6** (10)		1.1	ND[d]	
2	**6** (10)	10	1.1	67	0
3	**1e** (10)		1.1	18	0
4	**9** (10)	10	1.1	53	8
5	**1e** (10)	10	1.1	99	93
6	**1e** (10)	10	0.5	83	92
7	**1e** (10)	10	0.25	42	81

[a] Conditions: All reactions were performed with α-ketoester **4a** (0.1 mmol) and tetraallylstannane in DMF (1.0 mL) at 0 °C for 36 h. [b] Isolated yield. [c] Determined by HPLC on a OJ-H column. [d] Not detected.

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tanylamine-base *N*,*N*′-dioxide **1e** (Table 2, entry 5). However, no better results were obtained by using aliphatic amine based *N*,*N*′-dioxides (**2a**, **2b**) with ramipril acid backbone (Table 2, entries 7 and 8). Moreover, the linker length of the catalyst was also screened and the results indicated that the three-carbon linkage was the best (Table 2, entries 5 vs 9, 10).

Following these results, different metal reagents were investigated to improve the enantioselectivity. As shown in Table 3, only $InBr_3$ or $In(OTf)_3$ coordinated with ligand **1e** could produce the product with a high enantioselectivity of 73% ee and 86% ee, respectively (Table 3, entries 1 and 2); other metal reagents coordinated with ligand **1e** could not catalyze the enantioselective allylation of α-ketoester **3** (Table 3, entries 3−5).

Subsequently, we examined the effect of solvents under the condition of 10 mol % of **1e**−$In(OTf)_3$ (1:1) complex as catalyst and 1.1 equiv of tetraallylstannane. As shown in Table 3, the enantioselectivity and reactivity were deeply dependent on the solvents (Table 3, entries 2 and 6−10). DMF was chosen as the optimal solvent, in which 99% yield and 86% ee were obtained (Table 3, entry 2).

Under the conditions of 10 mol % of **1e** and 10 mol % of $In(OTf)_3$ in DMF, further improvement was achieved by changing the ester group of the α-ketoester. When the ester group was changed from ethyl to methyl, the ee value was increased to 93% (Table 4, entry 2). However, the ee value was not increased when the ester group was changed to larger groups such as *i*-Pr and *t*-Bu (Table 4, entries 3 and 4). These results showed that the smaller ester group was suitable for this catalytic system.

Next, the concentration of α-ketoester, molar ratios of metal to ligand, temperature, and catalyst loading were investigated, but the reactivity and enantioselectivity could not be improved (see the Supporting Information). Moreover, this allylation could be conducted under air without any decrease in yield and enantiomeric excess. Hence, the optimal condition was 10 mol % of **1e**−$In(OTf)_3$ and 0.1 M concentration of α-ketoester with 1.1 equiv of tetraallylstannane in DMF at 0 °C.

Encouraged by the results obtained from α-ketoester **4a** under the optimized conditions, a variety of α-ketoesters were investigated. As summarized in Table 5, aromatic α-ketoesters as well as heterocyclic α-ketoester afforded α-allyl-α-hydroxyesters **5** in excellent yields (up to 99%) with high enantiomeric excess (up to 94% ee). Comparison of the experimental results (Table 5, entries 2−8) revealed the negative effect of ortho-substitution on aromatic α-ketoesters for the enantioselectivity. The *o*-methyl- and *o*-methoxylphenyl α-ketoesters (**4b** and **4g**) afforded the products with 77% ee and 83% ee, respectively (Table 5, entries 2 and 7), which were lower than those obtained from *m*- or *p*-substituted-phenyl α-ketoesters (89−94% ee, Table 5, entries 3−6 and 8). In particular, α-ketoester **4h** gave the best ee value (94% ee, Table 5, entry 8). However, the aliphatic α-ketoester **4k** only gave a moderate enantioselectivity (69% ee, Table 5, entry 11).

The absolute configuration of **5a** was determined as *R* by comparison with literature data.[16] To determine the absolute configurations of the other products, the CD (circular dichroism) spectra of the products **5a**−**f**,**h** were measured in ethanol. These compounds exhibited a similar (−) Cotton effect in their CD spectra (see the Supporting Information). It could be deduced that these compounds possess the same configuration (*R*) as **5a**.

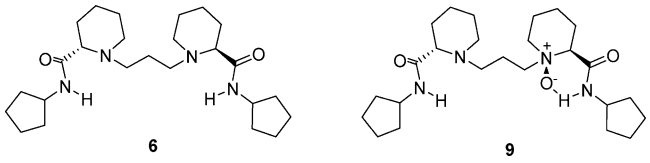

FIGURE 2. Precursor of the chiral *N*,*N*′-dioxide **1e** and chiral *N*-oxide **9**.

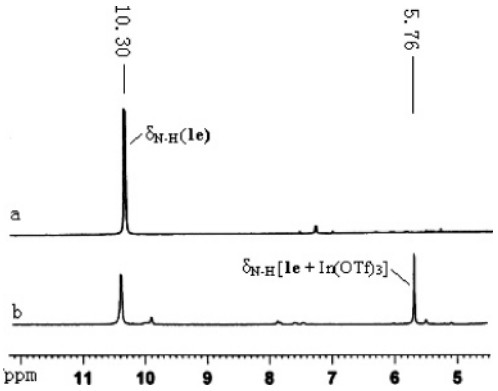

FIGURE 3. ^1H NMR spectra of the NH group of *N*,*N*′-dioxide **1e** in diverse reaction stage: (a) **1e** in $CDCl_3$ and (b) **1e** and $In(OTf)_3$ (ratio 1/1) in DMSO-d_6.

Mechanism Studies. Control experiments were performed to provide insight into the mechanism. As shown in Table 6, no corresponding α-hydroxyester was obtained with amide **6** (Figure 2) as catalyst (Table 6, entry 1), which suggested that the reaction could not occur with only chiral amide **6** activating tetraallylstannane. The $In(OTf)_3$ coordinated with amide **6** as the catalyst could catalyze the allylation of α-ketoesters with 67% yield, but no enantiomeric excess was observed (Table 6, entry 2). The result demonstrates that the *N*-oxide played a key role in the reaction. To compare with *N*,*N*′-dioxide **1e**, *N*-oxide **9** with one dipolar group was prepared and evaluated in the reaction (Table 6, entry 4). However, only 8% ee and 53% yield were observed in the allylation of α-ketoester. This important piece of evidence suggested that tetraallylstannane was simultaneously activated by the two oxygen atoms of *N*,*N*′-dioxide **1e**. In addition, by decreasing the amount of tetraallylstannane to 0.5 and 0.25 equiv, the reaction proceeded smoothly with 81% yield and 92% ee and 42% yield and 81% ee, respectively (Table 6, entries 6 and 7). This result showed that one molecular tetraallylstannane could provide more than one allyl group.

To determine the status of the coordination between $In(OTf)_3$ and *N*,*N*′-dioxide **1e**, the ^1H NMR and ESI-HRMS studies have been carried out (Figure 3). The NH proton showed a deshielding effect at 10.30 ppm due to the characteristic strong intramolecular hydrogen bond between *N*-oxide and the NH proton (Figure 3a). However, upon combination of $In(OTf)_3$ and *N*,*N*′-dioxide **1e** in a ratio of 1:1, a new upfield shift was observed at 5.76 ppm (Figure 3b). Furthermore, the catalyst compositions and molecular weight studies by the positive mode ESI-HRMS spectrum showed that the major peak corresponded to the 1:1 complex of In(III) and *N*,*N*′-dioxide **1e** (727.0610, calcd for [*N*,*N*′-dioxide **1e** + In(OTf) − H]$^+$ = 727.1843), which might be the major active species (Figure 4).

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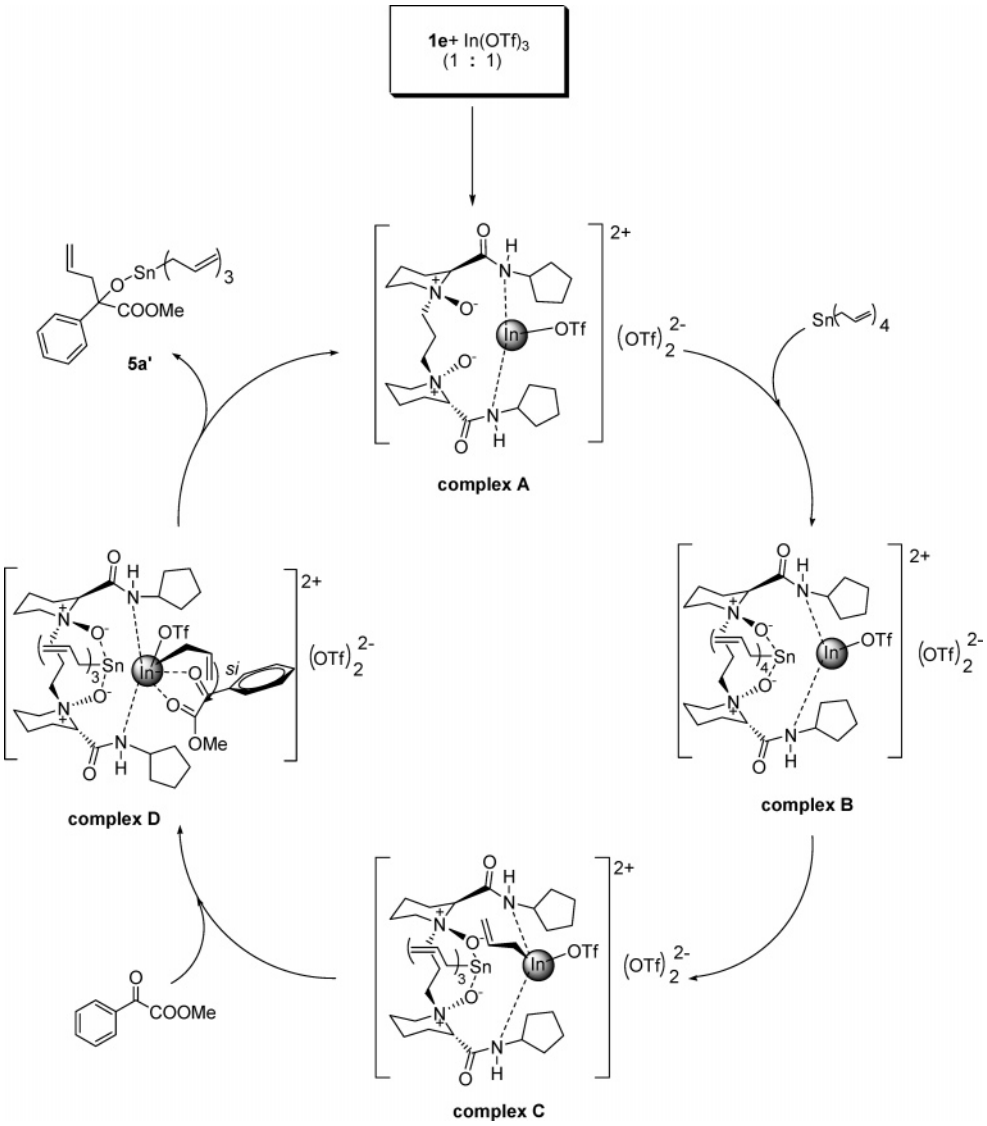

FIGURE 4. The proposed catalytic cycle.

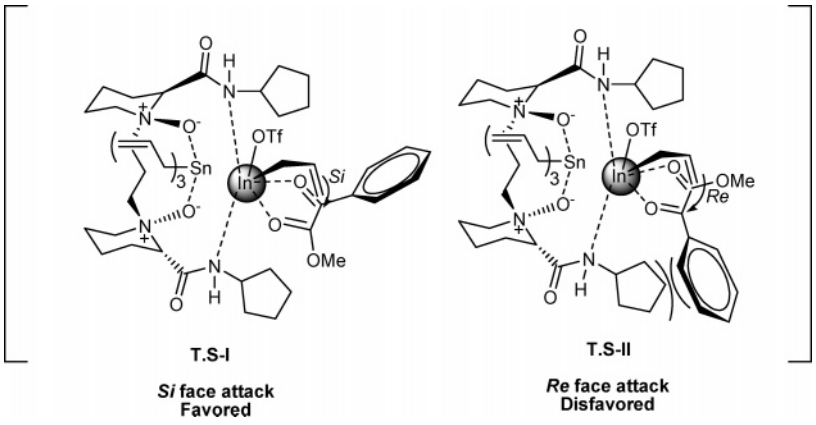

FIGURE 5. Plausible transition state.

On the basis of the experimental results, the possible catalytic cycle was proposed in Figure 4. We speculated the *N*,*N*′-dioxide **1e** coordinated with $In(OTf)_3$ to form complex **A**.[17] Then the *N*-oxide as the Lewis base actived the tin atom by formation of a possible hypervalent tin species (complex **B**) and enhanced the nucleophilicity of the allylic reagent.[18] One of the activated allyl groups might be transferred from the tin atom to the indium atom so as to form an allylic indium complex (complex **C**).[13,19]

As a Lewis acid, the indium activated the α-ketoester to form the possible complex **D**.[3a,5a] The allylic group in indium preferred to attack the activated α-ketoester to afford the product **5a′**. The triallylstannane was eliminated from complex **D** as **5a′**, and another tetraallylstannane was coordinated by the *N*-oxide to regenerate complex **B**.

On the basis of the observed absolute configuration of **5a**,[16] we proposed a possible transition state **I**. In transition state **I**, the allylic group was much more accessible to attack the *Si*-face of the carbonyl of α-ketoester **4a** than the *Re*-face, since the *Re*-face attack was likely to increase the steric repulsion between the phenyl group of α-ketoester **4a** and the cyclopentyl subunit of the catalyst in proposed transition state **II** (Figure 5).

Conclusions

In summary, we have developed the first enantioselective allylation of α-ketoesters by chiral *N*,*N*′-dioxide−In(III) complex. Under the optimized conditions, excellent yields (up to 99%) and high enantioselectivities (up to 94% ee) were obtained for a range of α-ketoesters. Attractive features of the current method included the catalyst preparation with readily available material, mild reaction conditions, and convenient procedure with the tolerance of moisture and air. On the basis of the experimental results, a possible catalytic cycle and favorable transition state have been proposed. Future efforts will be devoted to search for effective catalyst systems that tolerate a range of α-ketoesters with higher yield and enantioselectivity.

Experimental Section

Typical Experimental Procedure for the Enantioselective Allylation of α-Ketoesters. The (*S*)-pipecolic acid-based *N*,*N*′-dioxide **1e** (4.7 mg, 10 mol %) and $In(OTf)_3$ (5.6 mg, 10 mol %) in anhydrous DMF (1.0 mL) was stirred at ambient temperature for 10 min, then α-ketoester **4a** (16.4 mg, 0.1 mmol) was added to the mixture. The tetraallylstannane (25 μL, 0.11 mmol) was added at 0 °C. After being stirred for 6 h, the reaction mixture was directly purified by column chromatography on silica gel eluted ether/petroleum ether (1/10) to give (*R*)-methyl 2-hydroxy-2-phenylpent-4-enoate **5a** in 99% isolated yield with 93% ee, $[\alpha]^{28}_D$ −36.8 (*c* 0.38, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58−7.60 (m, 2H), 7.27−7.37 (m, 3H), 5.74−5.85 (m, 1H), 5.12−5.19 (m, 2H), 3.76 (s, 4H), 2.98 (dd, J = 14.0, 7.6 Hz, 1H), 2.77 (dd, J = 14.0, 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 140.2, 131.3, 127.3, 126.8, 124.5, 118.4, 77.1, 52.2, 43.1; ESI-HRMS calcd for ($C_{12}H_{14}O_3$ + Na^+) 229.0835, found 229.0841. HPLC (DAICEL CHIRALCEL OJ-H, hexane/2-propanol 80/20, 1.0 mL/min) t_R(minor) = 6.77 min, t_R(major) = 13.36 min.

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Supporting Information Available: Experimental precedures and characterization of products for catalysts and racemates, CD spectra, ^{1}H NMR and ^{13}C NMR spectra, HRMS and HPLC conditions, etc. This material is available free of charge via the Internet at http://pubs.acs.org.

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