JOC Article

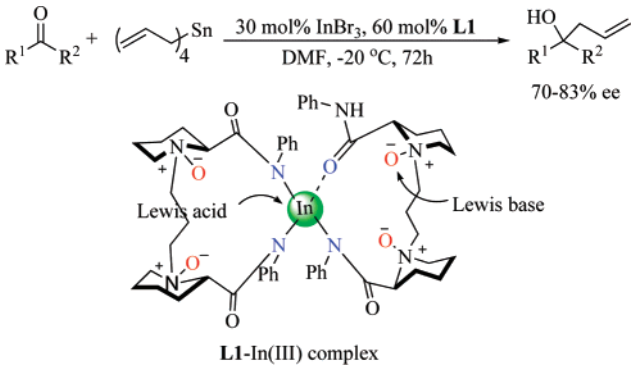
Enantioselective Allylation of Ketones Catalyzed by *N*,*N*′-Dioxide and Indium(III) Complex

Xin Zhang,[†] Donghui Chen,[†] Xiaohua Liu,[†] and Xiaoming Feng*[,†,‡]

Key Laboratory of Green Chemistry & Technology (Sichuan University), Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, China, and State Key Laboratory of Applied Organic Chemistry, Lanzhou 730000, China

xmfeng@scu.edu.cn

Received March 27, 2007



Complexes of (*S*)-pipecolic acid-, L-proline-, and other amino acid-derived *N*,*N*′-dioxides coordinated with different metal ions have been investigated in the enantioselective allylation of ketones. A variety of aromatic ketones were found to be suitable substrates in the presence of the **L1**-In(III) complex, and afforded the corresponding homoallylic alcohols with good enantioselectivites (up to 83% ee) and moderate to high yields (up to 94%). On the basis of the 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 catalyst was described with Lewis base *N*-oxide activating tetraallyltin and Lewis acid indium activating ketone.

Introduction

The enantioselective allylation of carbonyl compouds is one of the most valuable methods to furnish chiral homoallylic alcohols, which are widely used in the syntheses of many natural products and biologically active compounds.[1,2] The development of efficient synthetic methods for the preparation of chiral homoallylic alcohols has attracted considerable attention. In recent years, several new procedures with either metal complexes[2] or organocatalysts[3] have been developed for the allylation of aldehydes. However, allylation of ketones is still challenging, due to their reduced reactivities and lower binding

[†] Sichuan University.
[‡] State Key Laboratory of Applied Organic Chemistry.

(1) For reviews, see: (a) Marshall, J. A. *Chem. Rev.* **1996**, *96*, 31−48. (b) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207−2293. For representative examples, see: (c) Felpin, F. X.; Lebreton, J. *J. Org. Chem.* **2002**, *67*, 9192−9199. (d) Nicolaou, K. C.; Kim, D. W.; Baati, R. *Angew. Chem.* **2002**, *114*, 3853−3856; *Angew. Chem., Int. Ed.* **2002**, *41*, 3701−3704. (e) Hoveyda, A. H.; Morken, J. P. *Angew. Chem.* **1996**, *108*, 1378−1401; *Angew. Chem., Int. Ed.* **1996**, *35*, 1262−1284. (f) Leighton, J. L.; Hornberger, K. R.; Hamblett, C. L. *J. Am. Chem. Soc.* **2000**, *122*, 12894−12895.

(2) For reviews, see: Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763−2794.

(3) For representative examples, see: (a) Denmark, S. E.; Coe, D. M.; Pratt, N. E.; Griedel, B. D. *J. Org. Chem.* **1994**, *59*, 6161−6163. (b) Denmark, S. E; Fu, J. *J. Am. Chem. Soc.* **2000**, *122*, 12021−12022. (c) Denmark, S. E.; Fu, J.; Coe, D. M.; Su, X.; Pratt, N. E.; Griedel, B. D. *J. Org. Chem.* **2006**, *71*, 1513−1522. (d) Denmark, S. E.; Fu, J.; Lawler, M. J. *J. Org. Chem.* **2006**, *71*, 1523−1536. (e) Nakajima, M.; Saito, M.; Shiro, M.; Hashimoto, S. *J. Am. Chem. Soc.* **1998**, *120*, 6419−6420. (f) Malkov, A. V.; Orsini, M.; Pernazza, D.; Muir, K. W.; Langer, V.; Meghani, P.; Kočovský, P. *Org. Lett.* **2002**, *4*, 1047−1049. (g) Malkov, A. V.; Bell, M.; Castelluzzo, F.; Kočovský, P. *Org. Lett.* **2005**, *7*, 3219−3222. (h) Shimada, T.; Kina, A.; Ikeda, S.; Hayashi, T. *Org. Lett.* **2002**, *4*, 2799−2801. (i) Kina, A.; Shimada, T.; Hayashi, T. *Adv. Synth. Catal.* **2004**, *346*, 1169−1174. (j) Pignataro, L.; Benaglia, M.; Annunziata, R.; Cinquini, M.; Cozzi, F. *J. Org. Chem.* **2006**, *71*, 1458−1463. (k) Traverse, J. F.; Zhao, Y.; Hoveyda, A. H.; Snapper, M. L. *Org. Lett.* **2005**, *7*, 3151−3154. (l) Rabbat, P. M. A.; Valdez, S. C.; Leighton, J. L. *Org. Lett.* **2006**, *8*, 6119−6121. (m) Teo, Y. C.; Tan, K. T.; Loh, T. P. *Chem. Commun.* **2005**, 1318−1320.

10.1021/jo0706325 CCC: $37.00
Published on Web 06/09/2007

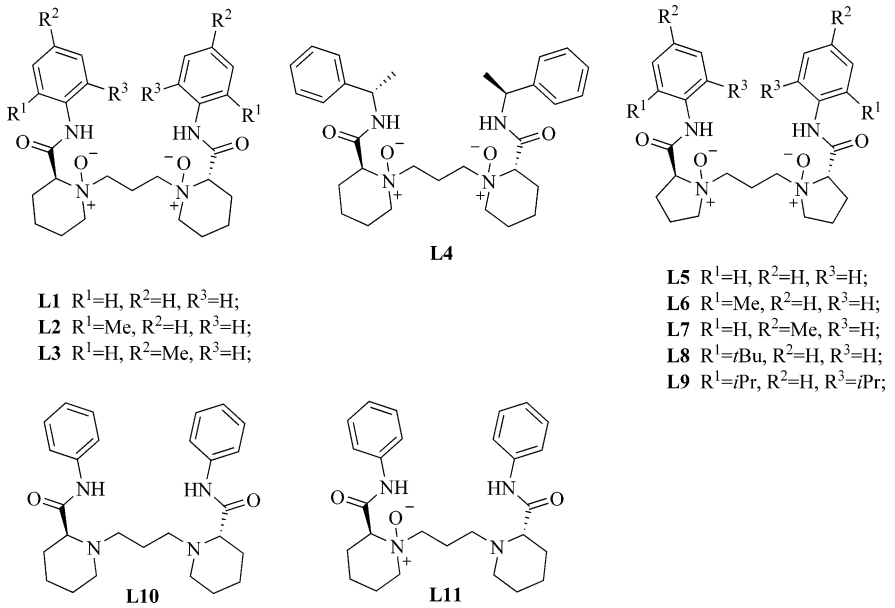


FIGURE 1. Ligands evaluated in this study.

affinity to metals.[4] Over the past decade, many efforts have been devoted in this area.[5−11] Typically, Yamamoto et al. reported the Ag-catalyzed asymmetric Sakurai−Hosomi allylation of ketones in which the (*R*)-DIFLUORPHOS was used as the chiral ligand.[6] Loh and co-workers developed two novel In-complex catalysts in which the BINOL or PYBOX and $InBr_3$ promoted the asymmetric addition of allyltributylstannane to aromatic and aliphatic ketones.[7−8] Tagliavini et al. and Walsh et al. outlined a method for the addition of allylic group to ketones using BINOL and Ti(O*i*-Pr)$_4$,[9] in which 2-propanol played a key role in the catalytic system. Shibasaki and co-workers reported the new approaches to asymmetric allylation of ketones and other broad rangesof substrates by Cu(I)-tol-BINAP[10] and Cu(II)-(*R*,*R*)-*i*Pr-DUPHOS[11] catalysts. Despite the progress achieved, the development of new approaches for the enantioselective allylation of ketones is still highly desirable.

N-Oxides, a series of strong electron donors, have long been recognized as suitable entities for ligand design.[12] As a coin, the application of chiral *N*-oxides has two sides. One is metal-free catalytic transformations, and the other is as ligands in transition metal catalysts.[12b] In our previous studies, continuing attention has been paid to the synthesis and application of the achiral and chiral *N*-oxide library.[13] Very recently, *N*,*N*′-dioxides as a highly efficient organocatalyst have been successfully used in the cyanosilylation of aldehydes,[14] aldimines,[15] ketones,[16] and ketoimines.[17] However, use of *N*-oxides in metal-mediated asymmetric synthesis has been limited. We reported successful attempts in the cyanosilylation of ketones dually catalyzed by proline-based *N*,*N*′-dioxides and Ti(O*i*-Pr)$_4$ complexes,[18,19] in which *N*-oxide as the Lewis base activated the TMSCN. Herein, we wish to report the enantioselective allylation of ketones catalyzed by (*S*)-pipecolic acid-derived *N*,*N*′-dioxides and indium(III) bromide complexes, which delivered good yields and enantioselectivities.

Results and Discussion

In the preliminary study, (*S*)-pipecolic acid-derived *N*,*N*′-dioxide **L1** (Figure 1) was employed as an organocatalyst for the enantioselective allylation of acetophenone with tetraallyltin. Unfortunately, no homoallylic alcohol was obtained

(4) Walsh, P. J.; Kim, J. G.; Camp, E. H. *Org. Lett.* **2006**, *8*, 4413−4416.

(5) For representative examples of enantioselective allylation of ketones, see: (a) Leighton, J. L.; Burns, N. Z.; Hackman, B. M.; Ng, P. Y.; Powelson, I. A. *Angew. Chem.* **2006**, *118*, 3895−3897; *Angew. Chem., Int. Ed.* **2006**, *45*, 3811−3813. (b) Schaus, S. E.; Lou, S.; Moquist, P. N. *J. Am. Chem. Soc.* **2006**, *128*, 12660−12661. (c) Soderquist, J. A.; Canales, E.; Prasad, K. G. *J. Am. Chem. Soc.* **2005**, *127*, 11572−11573. (d) Soderquist, J. A.; Burgos, C. H.; Canales, E.; Matos, K. *J. Am. Chem. Soc.* **2005**, *127*, 8044−8049. (e) Chong, J. M.; Wu, T. R.; Shen, L. *Org. Lett.* **2004**, *6*, 2701−2704. (f) Woodward, S.; Cunningham, A. *Synlett* **2002**, 43−44. (g) Woodward, S.; Prieto, O. *J. Organomet. Chem.* **2006**, *691*, 1515−1519. (h) Woodward, S.; Cunningham, A.; Mokalparekh, V.; Wilson, C. *Org. Biomol. Chem.* **2004**, *2*, 741−748. (i) Tietze, L. F.; Kinzel, T.; Schmatz, S. *J. Am. Chem. Soc.* **2006**, *128*, 11483−11495. (j) Tietze, L. F.; Völkel, L.; Wulff, C.; Weigand, B.; Bittner, C.; McGrath, P.; Johnson, K.; Schäfer, M. *Chem. Eur. J.* **2001**, *7*, 1304−1308. (k) Tietze, L. F.; Weigand, B.; Völkel, L.; Wulff, C.; Bittner, C. *Chem. Eur. J.* **2001**, *7*, 161−168. (l) Tietze, L. F.; Schiemann, K.; Wegner, C.; Wulff, C. *Chem. Eur. J.* **1998**, *4*, 1862−1869. (m) Tietze, L. F.; Wegner, C.; Wulff, C. *Eur. J. Org. Chem.* **1998**, 1639−1644. (n) Tietze, L. F.; Wegner, C.; Wulff, C. *Synlett* **1996**, 471−472. (o) Baba, A.; Yasuda, M.; Kitahara, N.; Fujibayashi, T. *Chem. Lett.* **1998**, *8*, 743−744. (p) Miller, J. J.; Sigman, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 2752−2753.

(6) Wadamoto, M.; Yamamoto, H. *J. Am. Chem. Soc.* **2005**, *127*, 14556−14557.

(7) Loh, T. P.; Lu, J.; Hong, M. L.; Ji, S. J.; Teo, Y. C. *Chem. Commun.* **2005**, 4217−4218.

(8) Loh, T. P.; Teo, Y. C.; Goh, J. D. *Org. Lett.* **2005**, *7*, 2743−2745.

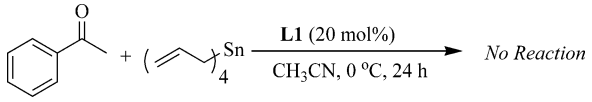
(9) For representative examples, see: (a) Wooten, A. J.; Kim, J. G.; Walsh, P. J. *Org. Lett.* **2007**, *9*, 381−384. (b) Walsh, P. J.; Kim, J. G.; Waltz, K. M.; Garcia, L. F.; Kwiatkowski, D. *J. Am. Chem. Soc.* **2004**, *126*, 12580−12585. (c) Walsh, P. J.; Waltz, K. M.; Gavenonis, J. *Angew. Chem.* **2002**, *114*, 3849−3852; *Angew. Chem., Int. Ed.* **2002**, *41*, 3697−3699. (d) Tagliavini, E.; Casolari, S.; D'Addario, D. *Org. Lett.* **1999**, *1*, 1061−1063. (e) Maruoka, K.; Kii, S. *Chirality* **2003**, *15*, 68−70. (f) Maruoka, K.; Hanawa, H.; Kii, S. *Adv. Synth. Catal.* **2001**, *343*, 57−60.

(10) Shibasaki, M.; Yamasaki, S.; Fujii, K.; Wada, R.; Kanai, M. *J. Am. Chem. Soc.* **2002**, *124*, 6536−6537.

(11) Shibasaki, M.; Wada, R.; Oisak, K.; Kanai, M. *J. Am. Chem. Soc.* **2004**, *126*, 8910−8911.

(12) For review, see: (a) Chelucci, G.; Murineddu, G.; Pinna, A. G. *Tetrahedron*: *Asymmetry* **2004**, *15*, 1373−1389. (b) Kočovský, P.; Malkov, A. *Eur. J. Org. Chem.* **2007**, 29−36.

SCHEME 1. Allylation of Acetophenone with Tetraallyltin Promoted by L1



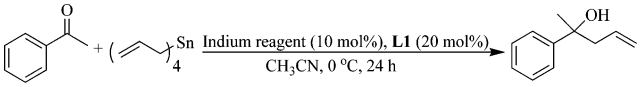
(Scheme 1), which showed that only *N*-oxide activating the tetraallyltin could not overcome the activation energy barrier of the reaction.

Following the concept of bifunctional catalysis, and to compensate for the low reactivity of ketones, several indium(III) reagents were screened, which had proved to be efficient in allylation of the carbonyl compounds[3m,7,8] as Lewis acids to activate acetophenone (Table 1). The results indicated that $InBr_3$ coordinated with **L1** in the ratio of 1:2 as the catalyst could catalyze the enantioselective allylation of acetophenone with 74% enantiomeric excess and 8% yield (Table 1, entry 1). $In(OTf)_3$ produced the homoallylic alcohol with 21% ee and 25% yield (Table 1, entry 2). When $InCl_3$ and $In(OCOCH_3)_3$ were examined, no allylic product was detected (Table 1, entries 3 and 4). Therefore, we chose $InBr_3$ combined with **L1** as a catalyst to optimize other parameters.

The enantioselectivity and reactivity were largely dependent on solvent. As shown in Table 2, in hexane, THF, or toluene, the desired products were not detected (Table 2, entries 1−3). The desired product was obtained in CH_2Cl_2 with 44% ee and 18% yield (Table 2, entry 4). To improve the yield and the enantioselectivity, we investigated other solvents with greater polarity, such as CH_3CN (Table 2, entry 5). Fortunately, the homoallylic alcohol was isolated in 25% yield and 75% ee in DMF (Table 2, entry 6). In HMPA, the enantioselectivity of product was 23% ee with 18% yield (Table 2, entry 7). In terms of enantioselectivity, DMF was a better choice over the other solvents for exploring the other conditions.

These results prompted us to screen other *N*,*N*′-dioxides (Figure 1). Other (*S*)-pipecolic acid-derived *N*,*N*′-dioxides and L-proline-based *N*,*N*′-dioxides were prepared and evaluated, with the results listed in Table 3. When the R^1 group of the (*S*)-pipecolic acid-derived *N*,*N*′-dioxides (**L2**) was a methyl group, the ee value was lower, which was probably due to the steric effect (Table 3, entry 2). When the R^2 group was a methyl group (**L3**), the yield of the homoallylic alcohol was dramatically decreased to 13% with the enantioselectivity slightly increased to 76% ee (Table 3, entry 3). No better result was provided when the phenyl group (**L1**) was replaced by the (*S*)-1-phenylethanamine-based aliphatic group (**L4**) (Table 3, entry 4). When the amide portion of the *N*,*N*′-dioxides was the same

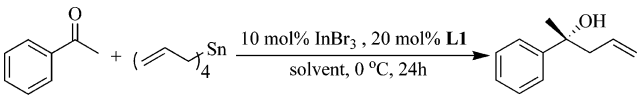
TABLE 1. Effect of Indium Reagents in Enantioselective Allylation of Acetophenone with L1[a]



entry	indium reagent[b]	yield (%)[c]	ee (%)[d]
1	$InBr_3$	8	74[e]
2	$In(OTf)_3$	25	21[e]
3	$InCl_3$	nd[f]	
4	$In(OCOCH_3)_3$	nd[f]	

[a] All reactions were carried out under nitrogen at 0 °C, 0.2 mmol of ketone, 1.1 equiv of tetraallyltin, and **L1**-indium reagent complex (2:1, 10 mol %) in CH_3CN for 24 h. [b] The catalyst loading was calculated according to the center metal. [c] Isolated yield. [d] Determined by chiral HPLC on a Chiralcel OJ-H column. [e] The absolute configuration of the major product was *R*, which was determined by comparison with the reported value of optical rotation, see ref 7. [f] Not detected.

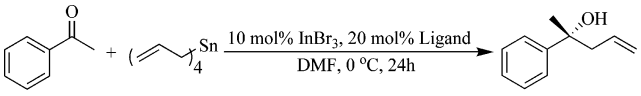
TABLE 2. Solvent Effect in the Enantioselective Allylation of Acetophenone with $InBr_3$ and L1[a]



entry	solvent	yield (%)[b]	ee (%)[c]
1	hexane	nd.[d]	
2	toluene	nd[d]	
3	THF	nd[d]	
4	CH_2Cl_2	18	44[e]
5	CH_3CN	8	74[e]
6	DMF	25	75[e]
7	HMPA	18	23[e]

[a] All reactions were carried out under nitrogen at 0 °C, 0.2 mmol of ketone, 1.1 equiv of tetraallyltin for 24 h. [b] Isolated yield. [c] Determined by chiral HPLC on a Chiralcel OJ-H column. [d] Not detected. [e] The absolute configuration of the major product was *R*, which was determined by comparison with the reported value of optical rotation, see ref 7.

TABLE 3. The Enantioselective Allylation of Acetophenone Catalyzed by $InBr_3$ and Different *N*,*N*′-Dioxide Complexes[a]



entry	*N*,*N*′-dioxides	yield (%)[b]	ee (%)[c,d]
1	**L1**	25	75 (*R*)
2	**L2**	14	16 (*R*)
3	**L3**	13	76 (*R*)
4	**L4**	22	9 (*S*)
5	**L5**	20	16 (*S*)
6	**L6**	18	15 (*S*)
7	**L7**	25	13 (*S*)
8	**L8**	17	8 (*R*)
9	**L9**	11	5 (*S*)
10	**L10**	trace	0
11	**L11**	21	72 (*R*)

[a] All reactions were carried out under nitrogen at 0 °C, 0.2 mmol of ketone, 1.1 equiv of tetraallyltin in DMF for 24 h. [b] Isolated yield. [c] Determined by chiral HPLC on a Chiralcel OJ-H column. [d] The absolute configuration of the major product was determined by comparison with the reported value of optical rotation, see ref 7.

(13) For achiral and chiral *N*-oxides acting as Lewis base or organocatalysts catalytic systems. See: (a) He, B.; Chen, F. X.; Feng, X. M.; Zhang, G. L. *Tetrahedron Lett.* **2004**, *45*, 5465−5467. (b) Li, Y.; He, B.; Feng, X. M.; Zhang, G. L. *Synlett* **2004**, 1598−1600. (c) Zhou, H.; Chen, F. X.; Qin, B.; Feng, X. M.; Zhang, G. L. *Synlett* **2004**, 1077−1079. (d) Chen, F. X.; Feng, X. M.; Qin, B.; Zhang, G. L.; Jiang, Y. Z. *Org. Lett.* **2003**, *5*, 949−952. (e) Shen, Y. C.; Feng, X. M.; Zhang, G. L.; Jiang, Y. Z. *Synlett* **2002**, 1353−1355. (f) Liu, B.; Feng, X. M.; Chen, F. X.; Zhang, G. L.; Cui, X.; Jiang, Y. Z. *Synlett* **2001**, 1551−1554.

(14) Wen, Y. H.; Huang, X.; Huang, J. L.; Xiong, Y.; Qin, B.; Feng, X. M. *Synlett* **2005**, 2445−2448.

(15) Jiao, Z. G.; Feng, X. M.; Liu, B.; Chen, F. X.; Zhang, G. L.; Jiang, Y. Z. *Eur. J. Org. Chem.* **2003**, 3818−3826.

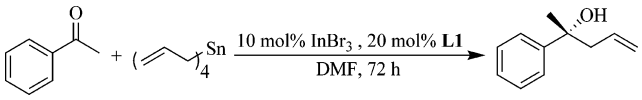
(16) (a) Huang, J. L.; Liu, X. H.; Wen, Y. H.; Qin, B.; Feng, X. M. *J. Org. Chem.* **2007**, *72*, 204−208. (b) Huang, X.; Huang, J. L.; Wen, Y. H.; Feng, X. M. *Adv. Synth. Catal.* **2006**, *348*, 2579−2584.

(17) Qin, B.; Liu, X. H.; Shi, J.; Zheng, K.; Zhao, H. T.; Feng, X. M. *J. Org. Chem.* **2007**, *72*, 2374−2378.

(18) Li, Q. H.; Chang, L.; Liu, X. H.; Feng, X. M. *Synlett* **2006**, 1675−1678.

(19) (a) Li, Q. H.; Liu, X. H; Wang, J.; Shen, K.; Feng, X. M. *Tetrahedron Lett.* **2006**, *47*, 4011−4014. (b) Shen, Y. C.; Feng, X. M.; Li, Y.; Zhang, G. L.; Jiang, Y. Z. *Eur. J. Org. Chem.* **2004**, 129−137.

TABLE 4. Effect of Temperature for the Enantioselective Allylation of Acetophenone Catalyzed by L1-In(III) Complex[a]



entry	temp (°C)	yield (%)[b]	ee (%)[c,d]
1	23	72	70
2	0	66	77
3	−20	48	80
4[e]	−45	nd	

[a] All reactions were carried out under nitrogen, 0.2 mmol of ketone, 1.1 equiv of tetraallyltin in DMF for 72 h. [b] Isolated yield. [c] Determined by chiral HPLC on a Chiralcel OJ-H column. [d] The absolute configuration of the major product was *R*, which was determined by comparison with the reported value of optical rotation, see ref 7. [e] Reacted for 120 h.

TABLE 5. Effect of the Molar Ratios between $InBr_3$ and L1[a]

entry	ratio ($InBr_3$:**L1**)	yield (%)[b]	ee (%)[c,d]
1	2:1	44	47
2	1:1	43	70
3	1:1.5	46	76
4	1:2	48	80
5	1:3	44	80

[a] All reactions were carried out under nitrogen at −20 °C, 0.2 mmol of ketone, 1.1 equiv of tetraallyltin in DMF for 72 h. [b] Isolated yield. [c] Determined by chiral HPLC on a Chiralcel OJ-H column. [d] The absolute configuration of the major product was *R*, which was determined by comparison with the reported value of optical rotation, see ref 7.

TABLE 6. Effect of the Concentration of Acetophenone for the Enantioselective Allylation Catalyzed by L1-In(III) Complex[a]

entry	concn of acetophenone (M)	yield (%)[b]	ee (%)[c,d]
1	0.1	37	82
2	0.2	48	80
3	0.5	56	79
4	1.0	55	77

[a] All reactions were carried out under nitrogen at −20 °C, 0.2 mmol of ketone, 1.1 equiv of tetraallyltin, 10 mol % of $InBr_3$, and 20 mol % of **L1** in DMF for 72 h. [b] Isolated yield. [c] Determined by chiral HPLC on a Chiralcel OJ-H column. [d] The absolute configuration of the major product was *R*, which dwas etermined by comparison with the reported value of optical rotation, see ref 7.

phenyl group as **L1**, L-proline-derived *N*,*N*′-dioxide (**L5)** (Table 3, entry 5) only gave 16% ee and 20% yield. No more than 15% ee was afforded when substituted phenyl groups in the amide portion of the L-proline-derived *N*,*N*′-dioxides (**L6**−**L9**) were investigated (Table 3, entries 6−9). It was notable that when the piperidinamide (**L10)** was studied as a ligand, trace racemic product was obtained (Table 3, entry 10), which proved that the *N*-oxide was essential to activate the allylic tin reagent. Interestingly, the (*S*)-pipecolic acid-derived single *N*-oxide (**L11)** also gave 72% ee (Table 3, entry 11). The (*S*)-pipecolic acid-derived *N*,*N*′-dioxide **L1** was found be a more efficient ligand to possess good enantioselectivity for the enantioselective allylation of ketones.

An examination of the temperature effect revealed that the temperature affected both the yield and the enantioselectivity (Table 4). A higher ee value was achieved at lower temperature but the yield decreased significantly. When the reaction was carried out at −20 °C, allylic product was obtained with 80% ee (Table 4, entry 3). Unfortunately, if the reaction temperature was decreased to −45 °C, no product was detected for 120 h

TABLE 7. Effect of Different Catalyst Loading for the Enantioselective Allylation of Acetophenone Catalyzed by L1-In(III) Complex[a]

entry	catalyst loading (mol %)	yield (%)[b]	ee (%)[c,d]
1	5	17	85
2	10	48	80
3	20	49	79
4	30	60	76

[a] All reactions were carried out under nitrogen at −20 °C, 0.2 mmol of ketone, 1.1 equiv of tetraallyltin in DMF for 72 h. [b] Isolated yield. [c] Determined by chiral HPLC on a Chiralcel OJ-H column. [d] The absolute configuration of the major product was *R*, which was determined by comparison with the reported value of optical rotation, see ref 7.

TABLE 8. Effect of the Amount of Tetraallyltin for the Enantioselective Allylation of Acetophenone Catalyzed by Chiral L1-In(III) Complex[a]

entry	amount of tetraallyltin (equiv)	yield (%)[b]	ee (%)[c,d]
1	1.1	60	76
2	2	63	76
3	3	72	80

[a] All reactions were carried out under nitrogen at −20 °C, 0.2 mmol of ketone, 30 mol % of $InBr_3$, and 60 mol % of **L1** in DMF for 72 h. [b] Isolated yield. [c] Determined by chiral HPLC on a Chiralcel OJ-H column. [d] The absolute configuration of the major product was ***R,*** which was determined by comparison with the reported value of optical rotation, see ref 7.

(Table 4, entry 4). To provide good levels of enantioselectivity, the appropriate reaction temperature was −20 °C.

The molar ratio of $InBr_3$ to **L1** was found to be another important factor for the enantioselectivity. When the ratio ($InBr_3$/**L1**) was 2:1, low enantioselectivity (47% ee) and yield (44%) was obtained (Table 5, entry 1). Decreasing the molar ratio ($InBr_3$/**L1**) from 2:1 to 1:2, enantiomeric excesss increased to 80% ee (Table 5, entries 1−4). However, when the molar ratio was decreased to 1:3, a similar enantioselectivity was maintained (Table 5, entry 5). The molar ratio of $InBr_3$ to **L1** was seen to be most efficient at 1:2.

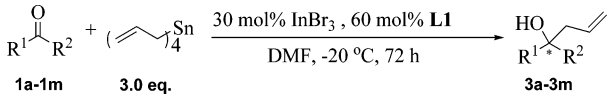
The effect of the concentration of substrate was also investigated (Table 6). A moderate result was observed when the reaction was carried out at 0.5 M (Table 6, entry 3). When the concentration of acetophenone was diminished from 0.5 to 0.1 M, the reactivity was decreased remarkably (Table 6, entries 1 and 2). When the concentration of acetophenone was increased to 1.0 M, both the reactivity and the enantioselectivity were decreased (Table 6, entry 4).

To improve the reactivity, the effect of the catalyst loading was examined (Table 7). By increasing of the catalyst loading from 5 mol % to 30 mol %, the yield was sharply enhanced from 17% to 60% with the ee value slightly dropped from 85% to 76%. To hold the moderate yield, 30 mol % catalyst loading had to be employed (Table 7, entry 4).

The amount of tetraallyltin was also studied (Table 8). There was a tendency that the higher amount of tetraallyltin resulted in higher yields. When the amount of tetraallyltin was increased from 1.1 to 2.0 equiv, the reactivity increased slightly (yield from 60% to 63%) and enantioselectivity was maintained (Table 8, entries 1 and 2). When 3.0 equiv of tetraallyltin was used, the reaction led to an increase in both yield and enantioselectivity (Table 8, entry 3).

With the optimal conditions, the scope of the catalytic enantioselective allylation of ketones was investigated by

TABLE 9. The Scope of Ketones for the Enantioselective Allylation Catalyzed by L1-In(III) Complex[a]



entry	ketone	product	yield (%)[b]	ee (%)
1	acetophenone (**1a**)	**3a**	72	80 (*R*)[c,e]
2	2-methoxyacetophenone (**1b**)	**3b**	69	83[d]
3	4-methoxyacetophenone (**1c**)	**3c**	48	80 (*R*)[d,e]
4	3-methoxyacetophenone (**1d**)	**3d**	85	74[d]
5	4-methylacetophenone (**1e**)	**3e**	70	81 (*R*)[c,f]
6	4-fluoroacetophenone (**1f**)	**3f**	61	81[c]
7	4-chloroacetophenone (**1g**)	**3g**	86	80[c]
8	4-bromoacetophenone (**1h**)	**3h**	94	79[d]
9	3-chloroacetophenone (**1i**)	**3i**	77	70[d]
10	2-acetonaphthone (**1j**)	**3j**	89	73 (*R*)[d,f]
11	3,4-dihydronaphthalen-1(2*H*)-one (**1k**)	**3k**	36	75 (*R*)[d,e]
12	2,2,2-trifluoroacetophenone (**1*l***)	**3*l***	70	73[d]
13	4-phenylbutan-2-one (**1m**)	**3m**	49	53 (*S*)[d,g]

[a] All reactions were carried out under nitrogen at −20 °C, 0.2 mmol of ketone, and 0.6 mmol of tetraallyltin in DMF (0.4 mL) for 72 h. [b] Isolated yield. [c] Determined by chiral HPLC on a Chiralcel OJ-H column. [d] Determined by chiral HPLC on a Chiralcel OD-H column. [e] The absolute configuration of the major product was determined by comparison with the reported value of optical rotation, see ref 6. [f] The absolute configuration of the major product was determined by comparison with the reported value of optical rotation, see ref 7. [g] The absolute configuration of the major product was determined by comparison with the reported value of optical rotation, see ref 8.

treatment of a series of ketones. The results were listed in Table 9. Substituents on the aromatic ring had a slight influence on the enantioselectivity. For example, 2-methoxyacetophenone gave the allylic product with highest ee value (83% ee) (Table 9, entry 2), the homoallylic alcohol from 4−methoxyacetophenone obtained with 48% yield and 80% ee (Table 9, entry 3), and 3-methoxyacetophenone only gave 74% ee with the 85% yield (Table 9, entry 4). 4-Methylacetophenone also produced good yield (70%) and enantioselectivity (81% ee) (Table 9, entry 5). The halogen-substituted aromatic ketones afforded the corresponding homoallylic alcohols in moderate to high yields and good enantioselectivities (Table 9, entries 6−9). The allylation of 2-acetonaphthone under the influence of the chiral indium catalyst furnished the homoallylic alcohol with 89% yield and 73% ee (Table 9, entry 10). Both cyclic ketone (3,4-dihydronaphthalen-1(2*H*)-one) and 2,2,2-trifluoroacetophenone underwent the allylation to afford the products in 75% ee (Table 9, entry 11) and 73% ee (Table 9, entry 12). Inspired by the results from aromatic ketones, aliphatic ketones were surveyed. However, moderate enantioselectivity (53% ee) was obtained with 4-phenylbutan-2-one (Table 9, entry 13) under the current system as well as other aliphatic ketones.

Mechanisic Consideration

To obtain the information on the mechanism of the allylation of ketones with the *N*,*N*′-dioxide In(III) complex, the relationship between the enantiopurity of the ligand **L1** and the enantiopurity of the product **3a** was studied (Figure 2). The result indicated a positive nonlinear effect for the reaction. We considered the ML_2 model fit to experimental data described by Kagan and co-workers.[20]

On the basis of the experimental investigation and previous reports,[21−23] we considered here that indium activated the ketone as a Lewis acid and the *N*-oxide activated tetraallyltin as a Lewis base. A plausible catalytic cycle of the enantioselective allylation of aromatic ketones was illustrated in Figure 3. We speculated that two molecules of *N*,*N*′-dioxide **L1** were tetradentate coordinated with $InBr_3$ (complex **A**).[21] The ^{1}H NMR date (combination of $InBr_3$ and **L1** in ratio of 1:2 in d_6-DMSO) indicate that in the generation of the In(III)-**L1** complex **A**, three molecules HBr were removed (see the Supporting Information for details). The *N*-oxide coordinated to the tin atom as a Lewis base in the presence of tetraallyltin to form a possible hypervalent tin species (complex **B**).[22] One of the activated allylic groups might be transferred from the tin atom to the indium atom to form an allylic indium complex (complex **C**).[23] It was notable that the solvent played a key role for the formation of the allylic indium complex in this step. DMF made this procedure more effective.[23a] As a Lewis acid, the indium activated the ketone. So the allylic group in indium preferred to attack the activated ketone to afford **2a**, and the product was

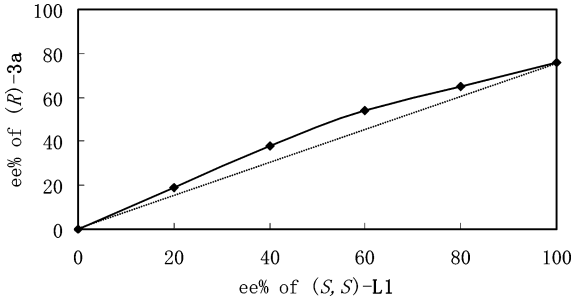


FIGURE 2. NLE in enanotioselective allylation of acetophenone with tetraallyltin catalyzed by *N*,*N*′-dioxide **L1**-In(III) complex.

(20) Guillaneux, D.; Zhao, S. H.; Samuel, O.; Rainford, D.; Kagan, H. B. *J. Am. Chem. Soc.* **1994**, *116*, 9430−9439.

(21) Delpech, F.; Guzei, I. A.; Jordan, R. F. *Organometallics* **2005**, *21*, 1167−1176.

(22) Denmark, S. E.; Fu, J. *J. Am. Chem. Soc.* **2003**, *125*, 2208−2216.

(23) (a) Yasuda, M.; Miyai, T.; Shibata, I.; Baba, A. *Tetrahedron Lett.* **1995**, *36*, 9497−9500. (b) Shibata, I.; Kato, H.; Ishida, T.; Yasuda, M.; Baba, A. *Angew. Chem.* **2004**, *116*, 729−732; *Angew. Chem., Int. Ed.* **2004**, *43*, 711−714. (c) Takita, R.; Fukuta, Y.; Tsuji, R.; Ohshima, T.; Shibasaki. M. *Org. Lett.* **2005**, *7*, 1363−1366.

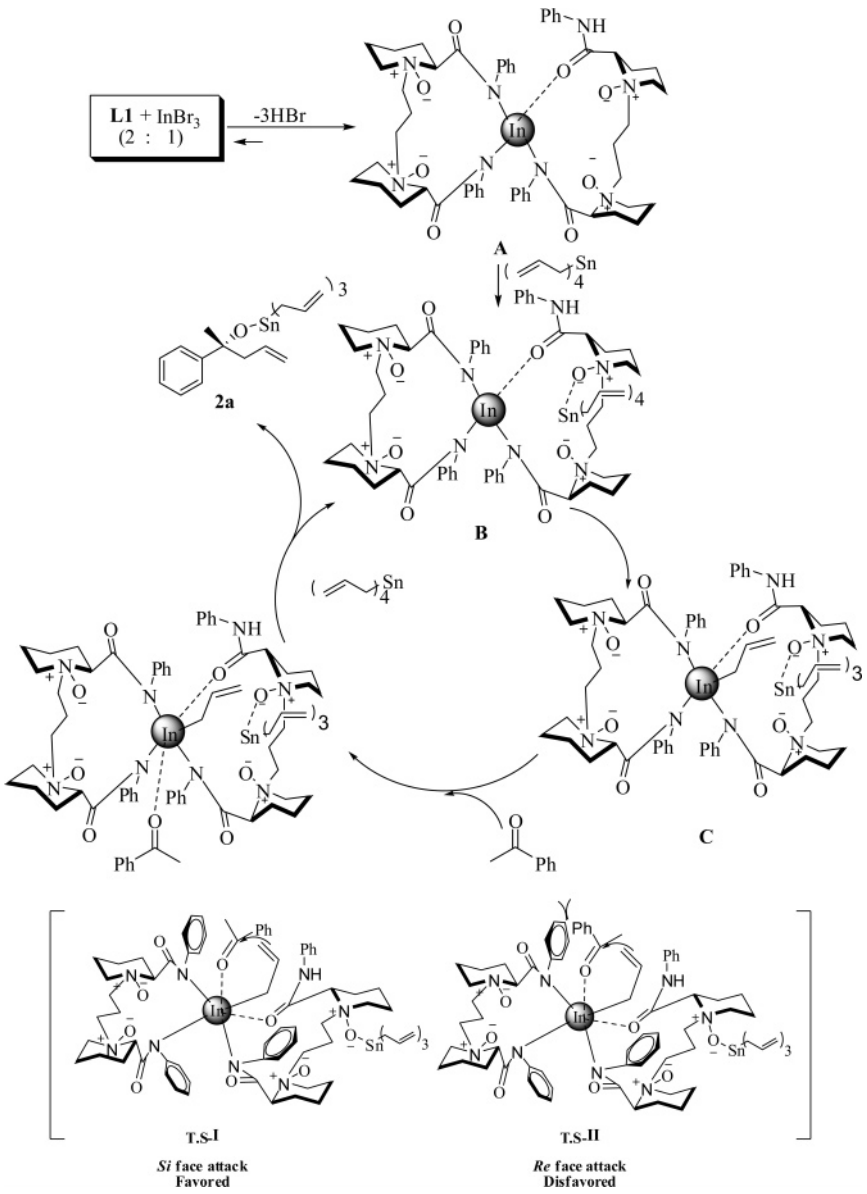


FIGURE 3. Plausible catalytic cycle and transition state.

obtained after general workup. When another tetraallyltin was coordinated by *N*-oxides, complex **B** was regenerated.

On the basis of the observed absolute configuration of **3a**,[6] 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 acetophenone than the *Re*-face, since the *Re*-face attack was likely to increase the steric repulsion between the phenyl group of acetophenone and the phenyl subunit of the catalyst in proposed transition state **II**.

Conclusion

We have developed a novel chiral indium complex prepared from indium(III) bromide and (*S*)-pipecolic acid-derived *N*,*N*′-dioxides for the enantioselective allylation of ketones. Under the optimized conditions, good enantioselectivities (up to 83% ee) and moderate to high yields were observed for a range of aromatic ketones. The experimental results showed that it was feasible for the **L1**-$InBr_3$ complex to be an efficient catalyst for the allylation of ketones with good enantioselectivity. A possible catalytic cycle including a transition state has been proposed. Future efforts will be focused on the possibility of reducing the catalyst loading to obtain maximum levels of enantioselectivity and yield and examine other silicon allyl reagents for the enantioselective allylation of ketones.

Experimental Section

Typical Experimental Procedure for the Enantioselective Allylation of Ketones. To an oven dried tube equipped with a magnetic stirring bar were added $InBr_3$ (21.3 mg, 0.06 mmol) and **L1** (57.6 mg, 0.12 mmol) in anhydrous DMF (0.4 mL), and the solution was allowed to stir at ambient temperature for 2 h under N_2 atmosphere. The tetraallyltin (144 μL, 0.6 mmol) was added at −20 °C, then acetophenone **1a** (24 μL, 0.2 mmol). The reaction mixture was stirred at −20 °C for 72 h and directly purified by column chromatography on silica gel eluted with diethyl ether/petroleum ether (1:10 v/v) to afford product **3a** as a colorless oil in 72% isolated yield with 80% ee [determined with chiral HPLC, DAICEL CHIRALCEL OJ-H, isopropanol:hexane 2:98, 1.0 mL/min, λ = 254 nm, t_R(major) = 12.019 min, t_R(minor) = 15.512

min]; $[\alpha]^{25}_D$ +42.6 (*c* 0.108, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.43−7.46 (m, 2H), 7.33−7.37 (m, 2H), 7.24−7.26 (m, 1H), 5.58−5.63 (m, 1H), 5.11−5.17 (m, 2H), 2.69(dd, J = 13.6, 6.4 Hz, 1H), 2.50 (dd, J = 13.6, 8.4 Hz , 1H), 2.05 (s, 1H), 1.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.6, 132.6, 127.2, 125.6, 123.7, 118.5, 72.6, 47.4, 28.9 ppm.

Acknowledgment. This work was financially supported by the National Nature Science Foundation of China (Nos. 20390055, 20372050, and 20602025). We also thank Sichuan University Analytival and Testing Center for ^1H NMR and ^{13}C NMR spectra analysis.

Supporting Information Available: Experimental procedures and structural proofs for catalysts and racemates, ^1H NMR, and ^{13}C NMR spectra, and HPLC. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0706325