J|A|C|S
ARTICLES
Published on Web 02/04/2003

Direct Catalytic Asymmetric Michael Reaction of Hydroxyketones: Asymmetric Zn Catalysis with a Et_2Zn/Linked-BINOL Complex

Shinji Harada, Naoya Kumagai, Tomofumi Kinoshita, Shigeki Matsunaga, and Masakatsu Shibasaki*

Contribution from the Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

Received October 14, 2002; E-mail: mshibasa@mol.f.u-tokyo.ac.jp

Abstract: Full details of our direct Michael addition of unmodified ketones using new asymmetric zinc catalysis are described. Et_2Zn/(*S*,*S*)-linked-BINOL complexes were successfully applied to direct 1,4-addition reactions of hydroxyketones. The first generation Et_2Zn/(*S*,*S*)-linked-BINOL **1** = 2/1 system was effective for 1,4-addition of 2-hydroxy-2′-methoxyacetophenone (**3**). Using 1 mol % of (*S*,*S*)-linked-BINOL **1** and 2 mol % of Et_2Zn, we found that a 1,4-addition reaction of β-unsubstituted enone proceeded smoothly at 4 °C to afford products in high yield (up to 90%) and enantiomeric excess (up to 95%). In the case of β-substituted enones, however, the first generation Et_2Zn/(*S*,*S*)-linked-BINOL **1** = 2/1 system was not at all effective. The second generation Et_2Zn/(*S*,*S*)-linked-BINOL **1** = 4/1 with MS 3A system was developed and was effective for various β-substituted enones to afford products in good dr, yield (up to 99%), and high enantiomeric excess (up to 99% ee). With the Et_2Zn/**1** = 4/1 systems, catalyst loading for β-unsubstituted enone was reduced to as little as 0.01 mol % (substrate/chiral ligand = 10 000). The new system was also effective for 1,4-addition reactions of 2-hydroxy-2′-methoxypropiophenone (**9**) to afford chiral *tert*-alcohol in high enantiomeric excess (up to 96% ee). Mechanistic investigations as well as transformations of the Michael adducts into synthetically versatile intermediates are also described.

Introduction

The catalytic asymmetric carbon−carbon bond formation is a major focus of modern synthetic organic chemistry.[1] The increasing demand for efficient and environmentally benign processes requires the development of atom-economic asymmetric catalysis[2] in which enantiomerically enriched compounds are produced using unmodified substrates. Toward this end, we and others successfully demonstrated direct catalytic asymmetric aldol reactions[3−5]and direct catalytic asymmetric Mannich reactions[6,7] that utilize unmodified ketones and/or aldehydes as donors. In contrast to these promising results[8] with aldol reactions and Mannich reactions, direct catalytic asymmetric 1,4-addition reactions of unmodified ketones are very rare despite their importance in synthetic organic chemistry for providing 1,5-dicarbonyl chiral building blocks.[9] Many excellent catalytic asymmetric 1,4-addition reactions have been developed over the past decade. Almost all of them utilize either active methylene compounds, such as malonates[10] and β-ketoesters,[11] or reactive nucleophiles prepared by using no less than

(1) (a) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999. (b) *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley: New York, 2000.
(2) (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) Trost, B. M. *Angew. Chem., Int. Ed. Engl*. **1995**, *34*, 259.
(3) Reviews: (a) Palomo, C.; Oiarbide, M.; García, J. M. *Chem.-Eur. J.* **2002**, *8*, 37. (b) Alcaide, B.; Almendros, P. *Eur. J. Org. Chem.* **2002**, 1595. (c) List, B. *Tetrahedron* **2002**, *58*, 5573. (d) Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, *102*, 2187 and references therein.
(4) Unmodified ketones as donors: (a) Yamada, Y. M. A.; Yoshikawa, N.; Sasai, H.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1871. (b) Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 4168. (c) Yamada, Y. M. A.; Shibasaki, M. *Tetrahedron Lett.* **1998**, *39*, 5561. (d) Yoshikawa, N.; Shibasaki, M. *Tetrahedron* **2001**, *57*, 2569. (e) Suzuki, T.; Yamagiwa, N.; Matsuo, Y.; Sakamoto, S.; Yamaguchi, K.; Shibasaki, M.; Noyori, R. *Tetrahedron Lett.* **2001**, *42*, 4669. Unmodified α-hydroxyketones as donors: (f) Yoshikawa, N.; Kumagai, N.; Matsunaga, S.; Moll, G.; Ohshima, T.; Suzuki, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 2466. (g) Kumagai, N.; Matsunaga, S.; Yoshikawa, N.; Ohshima, T.; Shibasaki, M. *Org. Lett.* **2001**, *3*, 1539. (h) Yoshikawa, N.; Suzuki, T.; Shibasaki, M. *J. Org. Chem.* **2002**, *67*, 2556.
(5) Unmodified ketones as donors: (a) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395. (b) Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003. (c) List, B.; Pojarliev, P.; Castello, C. *Org. Lett.* **2001**, *3*, 573. (d) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2001**, *123*, 5260. (e) Trost, B. M.; Silcoff, E. R.; Ito, H. *Org. Lett.* **2001**, *3*, 2497. (f) Saito, S.; Nakadai, M.; Yamamoto, H. *Synlett* **2001**, 1245. (g) Mahrwald, R.; Ziemer, B. *Tetrahedron Lett.* **2002**, *43*, 4459. For a partially successful attempt, see: (h) Nakagawa, M.; Nakao, H.; Watanabe, K.-I. *Chem. Lett.* **1985**, 391. Unmodified α-hydroxyketones as donors: (i) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386. (j) Trost, B. M.; Ito, H.; Silcoff, E. R. *J. Am. Chem. Soc.* **2001**, *123*, 3367. See also ref 4d. Unmodified aldehydes as donors: (k) Córdova, A.; Notz, W.; Barbas, C. F., III. *J. Org. Chem.* **2002**, *67*, 301. (l) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798. (m) Bøgevig, A.; Kumaragurubaran, N.; Jørgensen, K. A. *Chem. Commun.* **2002**, 620. For highly selective direct aldol reaction using chiral auxiliary: (n) Evans, D. A.; Tedrow, J. S.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2002**, *124*, 392.
(6) (a) Yamasaki, S.; Iida, T.; Shibasaki, M. *Tetrahedron Lett.* **1999**, *40*, 307. (b) Yamasaki, S.; Iida, T.; Shibasaki, M. *Tetrahedron* **1999**, *55*, 8857.
(7) (a) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336. (b) Notz, W.; Sakthivel, K.; Bui, T.; Zhong, G.; Barbas, C. F., III. *Tetrahedron Lett.* **2001**, *42*, 199. (c) Juhl, K.; Gathergood, N.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 2995. (d) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827. (e) Córdova, A.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1842. (f) Córdova, A.; Watanabe, S.; Tanaka, F.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1866.

10.1021/ja028928+ CCC: $25.00

stoichiometric amounts of reagents, such as enol silyl ethers and organometallic reagents.[12]Quite recently direct catalytic asymmetric Michael reactions of unmodified ketones and aldehydes were realized by using a phase transfer catalyst,[13] proline,[14] and chiral diamine.[14] There remains room for improvement, however, in terms of substrate scope, catalyst loading, enantioselectivity, and chemical yield. Thus, the development of direct catalytic asymmetric 1,4-addition of unmodified ketones, which have high reactivity and selectivity, is in high demand. We recently communicated an efficient direct catalytic asymmetric 1,4-addition of a hydroxyketone, which afforded 1,4-adducts in good yield and high enantiomeric excess.[15] The reaction proceeded with a catalytic amount of base (Et_2Zn, 2 mol %) and chiral ligand (linked-BINOL **1**, 1 mol %, Figure 1).[16,17] The system was applicable to only β-unsubstituted enones (vinyl ketones) and indenones, however, leaving room for improvement in terms of substrate scope. Herein we report the full details of our asymmetric zinc catalysis in direct catalytic asymmetric 1,4-addition reactions of hydroxyketones: (1) The first generation Et_2Zn/(*S*,*S*)-linked-BINOL **1** = 2/1 complex was applied to a 1,4-addition of β-unsubstituted enones and indenones with 2-hydroxy-2′-methoxyacetophenone (**3**). (2) The second generation Et_2Zn/(*S*,*S*)-linked-BINOL **1** = 4/1 with MS 3A system was then developed to widen the substrate scope and was effective for various β-substituted enones to afford products in high yield (up to 99%) and high enantiomeric excess (up to 99%). With the Et_2Zn/**1** = 4/1 system, catalyst loading for β-unsubstituted enone was reduced to as little as 0.01 mol % (substrate/chiral ligand = 10 000). (3) A 1,4-addition of 2-hydroxy-2′-methoxypropiophenone (**9**) was examined. (4) Finally, mechanistic investigations and transformations of 1,4-adducts are also discussed.

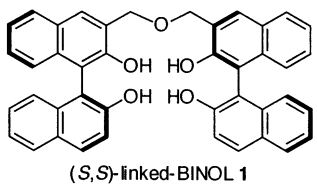


Figure 1. (*S*,*S*)-Linked-BINOL **1**.

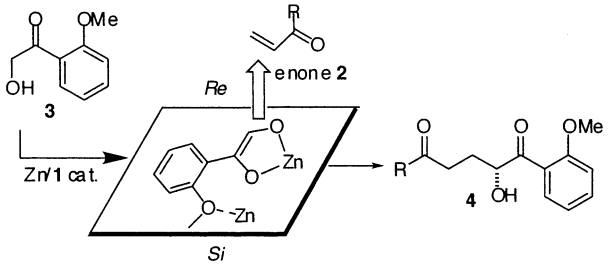


Figure 2. Concept for direct catalytic asymmetric Michael reaction using hydroxyketone **3**.

Results and Discussion

(A) First Generation Et_2Zn/(*S*,*S*)-Linked-BINOL 1 = 2/1 System. In our continuing investigation of direct catalytic asymmetric aldol reactions, a Et_2Zn/(*S*,*S*)-linked-BINOL **1** complex was determined to be very effective for shielding one enantioface of an enolate generated from 2-hydroxy-2′-methoxyacetophenone (**3**), affording a practical method to provide *syn*-1,2-dihydroxyketones through the aldol reaction of **3** with various aldehydes.[18] We anticipated that the efficient enantioface selection would also be applicable to asymmetric 1,4-addition reactions to afford optically active 2-hydroxy-1,5-dicarbonyl compounds **4** as shown in Figure 2. Thus, we investigated the catalytic asymmetric 1,4-addition reaction using vinyl ketone **2a** as a substrate. As shown in Table 1, 5 mol % of **1** and 10 mol % of Et_2Zn efficiently promoted the 1,4-addition of **3** to **2a** at −20 °C to afford **4a** in 90% yield and 94% ee after 8 h (Table 1, entry 1). These promising results led us to further examine the effects of catalyst loading, changes in the reaction temperature, and various ketone equivalents (Table 1). By reducing the amount of ketone **3** from 2.0 to 1.1 equiv (entry 2), we found that the reaction rate and chemical yield decreased (14 h, 72% yield), while high enantiomeric excess was maintained (97% ee). The reaction temperature greatly affected the reaction rate. By decreasing the reaction temperature to −30 °C (entry 3), we obtained a higher enantiomeric excess (98%

(8) For other promising atom economic asymmetric catalysis for carbon−carbon bond-forming reaction, see alkynylation: (a) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687. For other selected examples of atom economic asymmetric catalysis, see β-lactam synthesis: (b) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Drury, W. J., III; Lectka, T. *J. Am. Chem. Soc.* **2000**, *122*, 7831. (c) Hodous, B. L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 1578. α-amination: (d) Kumaragurubaran, N.; Juhl, K.; Zhuang, W.; Bøgevig, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 6254 and references therein. (e) List, B. *J. Am. Chem. Soc.* **2002**, *124*, 5656.

(9) For recent reviews on the catalytic asymmetric 1,4-addition reactions, see: (a) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171. (b) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Chapter 31.

(10) For recent leading references, see: Yamaguchi, M.; Shiraishi, T.; Hirama, M. *J. Org. Chem.* **1996**, *61*, 3520. See also ref 17a.

(11) For recent leading references, see: (a) Ji, J.; Barnes, D. M.; Zhang, J.; King, S. A.; Wittenberger, S. J.; Morton, H. E. *J. Am. Chem. Soc.* **1999**, *121*, 10215. (b) Hamashima, Y.; Hotta, D.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 11240 and references therein. See also: (c) Sawamura, M.; Hamashima, H.; Ito, Y. *Tetrahedron* **1994**, *50*, 4439 for α-cyano esters.

(12) Excellent catalytic asymmetric 1,4-addition reactions with latent enolates, such as enol silyl ether, are established (>90% ee), although those reactions require stoichiometric amounts of reagents to prepare latent enolates. For recent representative examples, see: (a) Kobayashi, S.; Suda, S.; Yamada, M.; Mukaiyama, T. *Chem Lett.* **1994**, *97*. (b) Kitajima, H.; Ito, K.; Katsuki, T. *Tetrahedron* **1997**, *53*, 17015. (c) Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Downey, W.; Tedrow, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 9134. (d) Zhang, F.-Y.; Corey, E. J. *Org. Lett.* **2001**, *3*, 639. (e) Evans, D. A.; Scheidt, K. A.; Johnston, J. N.; Willis, M. C. *J. Am. Chem. Soc.* **2001**, *123*, 4480 and references therein. For leading references on catalytic asymmetric 1,4-addition reactions of other carbon nucleophiles, see Zn reagents: (f) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346. B reagents: (g) Hayashi, T. *Synlett* **2001**, 879. Ti reagents: (h) Hayashi, T.; Tokunaga, N.; Yoshida, K.; Han, J.-W. *J. Am. Chem. Soc.* **2002**, *124*, 12102.

(13) Zhang, F.-Y.; Corey, E. J. *Org. Lett.* **2000**, *2*, 1097.

(14) (a) Betancort, J. M.; Sakthivel, K.; Thayumanavan, R.; Barbas, C. F., III. *Tetrahedron Lett.* **2001**, *42*, 4441. (b) List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423. Unmodified aldehydes as donors: (c) Betancort, J. M.; Barbas, C. F., III. *Org. Lett.* **2001**, *3*, 3737. (d) Enders, D.; Seki, A. *Synlett* **2002**, 26. (e) Alexakis, A.; Andrey, O. *Org. Lett.* **2002**, *4*, 3611.

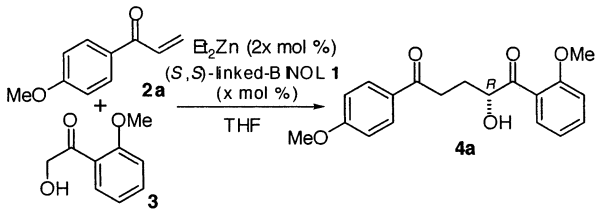
(15) Kumagai, N.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2001**, *3*, 4251.

(16) For the synthesis and application of linked-BINOL, see: (a) Matsunaga, S.; Das, J.; Roels, J.; Vogl, E. M.; Yamamoto, N.; Iida, T.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 2252. (b) Matsunaga, S.; Ohshima, T.; Shibasaki, M. *Adv. Synth. Catal.* **2002**, *344*, 4. Linked-BINOL is also commercially available from Wako Pure Chemical Industries, Ltd. Catalog No. 152-02431 for (*S*,*S*)-ligand, No. 155-02421 for (*R*,*R*)-ligand. Fax +1-804-271-7791 (USA), +81-6-6201-5964 (Japan), +81-3-5201-6590 (Japan).

(17) For other examples of catalytic asymmetric syntheses using linked-BINOL as a chiral ligand, see: (a) Kim, Y. S.; Matsunaga, S.; Das, J.; Sekine, A.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 6506. (b) Matsunaga, S.; Ohshima, T.; Shibasaki, M. *Tetrahedron Lett.* **2000**, *41*, 8473. (c) Takita, R.; Ohshima, T.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 4661. See also refs 4f and 4g. For related compounds: (d) Vogl, E. M.; Matsunaga, S.; Kanai, M.; Iida, T.; Shibasaki, M. *Tetrahedron Lett.* **1998**, *39*, 7917. (e) Ishitani, H.; Kitazawa, T.; Kobayashi, S. *Tetrahedron Lett.* **1999**, *40*, 2161 and references therein.

(18) *J. Am. Chem. Soc.* **2003**, *125*, 2169−2178 Direct Catalytic Asymmetric Aldol Reaction of Hydroxyketones: Asymmetric Zinc Catalysis with a Et_2-Zn/linked-BINOL Complex (1) by Kumagai, N.; Matsunaga, S.; Kinoshita, T.; Harada, S.; Okada, S.; Sakamoto, S.; Yamaguchi, K.; Shibasaki, M., See, also refs 4f and 4g.

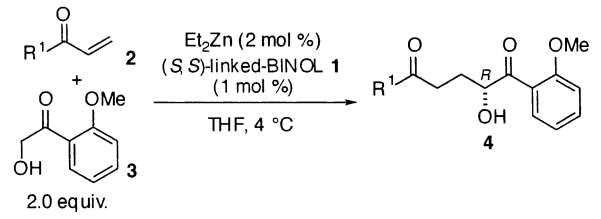
Table 1. Optimization of 1,4-Addition Reaction of Vinyl Ketone **2a** with **3**



entry	ketone **3** (equiv)	catalyst (mol %)	temp (°C)	time (h)	yield[a]	ee (%)
1	2	5	−20	8	90	94
2	1.1	5	−20	14	72	97
3	2	5	−30	14	87	98
4	2	5	4	3	87	91
5	2	3	−20	14	90	96
6	2	1	−20	30	84	97
7	2	1	4	8	83	95

[a] Isolated yield.

Table 2. 1,4-Addition Reaction of Various Vinyl Ketones **2**[a]



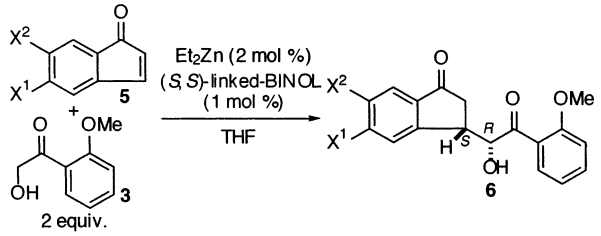
entry	R^1	vinyl ketone	product	time (h)	yield[b]	ee (%)
1	*p*-$MeOC_6H_4$	**2a**	**4a**	8	83	95
2	C_6H_5	**2b**	**4b**	4	86[c]	93
3	*o*-$MeOC_6H_4$	**2c**	**4c**	12	90	94
4	*p*-ClC_6H_4	**2d**	**4d**	12	84[c]	92
5	CH_3	**2e**	**4e**	4	86	93
6	CH_3CH_2	**2f**	**4f**	4	82	91

[a] Reactions were run on a 1.0 mmol scale at 0.4 M in **2**. [b] Isolated yield unless otherwise noted. [c] Determined by ^{1}H NMR analysis with hexamethyldisiloxane as an internal standard.

ee), but a prolonged reaction time was necessary. At a higher temperature (entry 4: 4 °C), there was a drastic improvement in the reaction rate. The reaction reached completion after 3 h (entry 4) while maintaining a high enantiomeric excess (91% ee). Good yield and excellent enantiomeric excess were obtained even when the ligand loading was decreased from 5 to either 3 or 1 mol % (entries 5 and 6, respectively). The reaction rate dropped significantly, however, at −20 °C. Finally, as shown in entry 7, the reaction was completed within 8 h to afford **4a** in 83% yield and 95% ee with 1 mol % of (*S*,*S*)-linked-BINOL **1** and 2 mol % of Et_2Zn at 4 °C.

The optimized reaction conditions were applicable to various vinyl ketones **2**, which usually tend to polymerize under harsh reaction conditions (Table 2). The mild basicity of the Et_2Zn/(*S*,*S*)-linked-BINOL complex allowed for 1,4-addition of **3** to proceed smoothly with only a small amount of polymerization. Aryl vinyl ketones with and without substituents on the aromatic ring were successfully converted to the corresponding 1,4-adducts in good chemical yield (83−90%) and enantiomeric excess (92−95% ee; entries 1−4). Alkyl vinyl ketones **2e** and **2f** also afforded the desired 1,4-adducts in good yield and enantiomeric excess (entries 5 and 6).

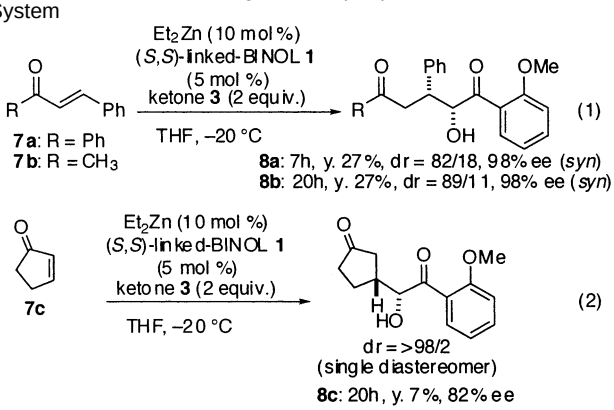
Table 3. 1,4-Addition Reaction of Indenones **5**[a]



entry	X^1	X^2	enone	product	catalyst (mol %)	temp (°C)	time (h)	yield[b] (%)	dr[c]	ee (%)
1	H	H	**5a**	**6a**	1	4	1.5	68	95/5	97
2	H	H	**5a**	**6a**	1	−20	4	74	98/2	99
3	H	H	**5a**	**6a**	3	−20	3	80	98/2	99
4	Br	H	**5b**	**6b**	1	4	2	76	86/14	99
5	Br	H	**5b**	**6b**	1	−20	4	74	98/2	99
6	H	MeO	**5c**	**6c**	1	−20	4	65	97/3	97

[a] Reactions were run on a 1 mmol scale (entries 1−3, 6) or on a 0.5 mmol scale (entries 4, 5) at 0.25 M (entries 2, 3, 4, 6) or at 0.4 M (entries 1, 4) in **5**. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis of crude mixture.

Scheme 1. Unsuccessful Trials of 1,4-Addition Reactions with β-Substituted Enones Using a Et_2Zn/(*S*,*S*)-Linked-BINOL **1** = 2/1 System

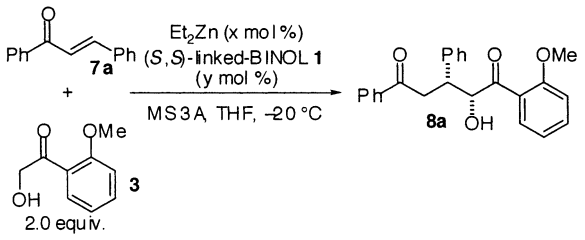


With indenone **5a**, good diastereomeric ratio and excellent enantiomeric excess were observed at 4 °C (Table 3, entry 1: 97% ee, dr = 95/5), although the chemical yield was modest due to polymerization. An excellent diastereomeric ratio was achieved when the reaction was run at −20 °C (entry 2: dr 98/2, 99% ee). With 3 mol % ligand loading, the chemical yield was slightly improved (entry 3: 80% yield). The relative configuration of **6a** was determined by X-ray crystallography.[19] Indenones **5b** and **5c** also gave 1,4-adducts in excellent stereoselectivity at −20 °C (entry 5, dr = 98/2, 99% ee; entry 6, dr = 97/3, 97% ee).

(B) Second Generation Et_2Zn/(*S*,*S*)-Linked-BINOL 1 = 4/1 System. In contrast to the successful results with vinyl ketones and indenones, 1,4-addition reactions with other Michael acceptors, such as β-substituted enones, were a formidable task. As shown in Scheme 1, using Et_2Zn (5 mol %) and (*S*,*S*)-linked-BINOL **1** (10 mol %), we found that 1,4-addition reactions with acyclic (eq 1) and cyclic enones (eq 2) afforded products in poor yield (**8a**, 27%; **8b**, 27%; and **8c**, 7%), although the enantioselectivity was excellent (82−98% ee). The results

(19) The relative configurations of **6a**, **8g**, and **8o** were determined by X-ray analysis, see Supporting Information. The absolute configurations of the carbinolic stereocenters on **4c**, **6a**, and **8i** were determined by Mosher's method. (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

Table 4. Optimization of 1,4-Addition Reaction of β-Substituted Enone **7a**



entry	Et_2Zn (mol %)	ligand **1** (mol %)	additive (mg/mmol of **7a**)	additive (mg/mmol of **7a**)	time (h)	yield[a] (%)	dr[b] (syn/anti)	ee (%) (syn/anti)
1	10	5	none		7	27	82/18	98/nd
2	15	5	none		7	44	84/16	98/nd
3	20	5	none		7	68	83/17	97/nd
4	20	10	none		48	51	84/16	98/nd
5	20	5	MS 13X	150	3	90	73/27	95/91
6	20	5	MS 5A	150	3	91	77/23	95/87
7	20	5	MS 4A	150	3	87	76/24	95/93
8	20	5	MS 3A	150	3	93	78/22	95/93

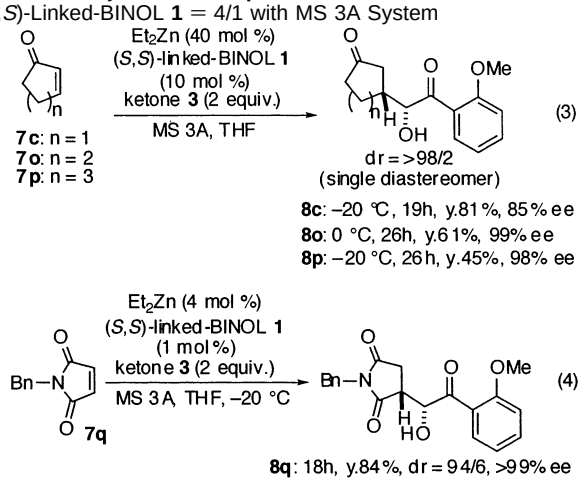
[a] Isolated yield. [b] Determined by ^{1}H NMR analysis of crude mixture.

suggested that the catalyst turnover step would be problematic using the Et_2Zn/(*S*,*S*)-linked-BINOL **1** = 2/1 complex.

On the basis of our investigations of the structure of the Et_2Zn/(*S*,*S*)-linked-BINOL **1** complex with and without hydroxyketone **3**, a small excess amount of Et_2Zn with respect to (*S*,*S*)-linked-BINOL **1** was expected to be effective for efficient catalyst turnover.[18] As summarized in Table 4, entries 1−3, the chemical yield increased significantly by changing the ratio of Et_2Zn/(*S*,*S*)-linked-BINOL **1**, and the best chemical yield was obtained with an Et_2Zn/**1** = 4/1 ratio (entry 1, 27%; entry 2, 44%; entry 3, 68%). Enantiomeric excess was similar when the ratio of Et_2Zn/**1** = 2/1, 3/1, or 4/1 (98, 98, and 97%, respectively). With 20 mol % of Et_2Zn, less chiral ligand afforded better chemical yield (entry 3, 5 mol % of **1**, 68%; entry 4, 10 mol % of **1**, 51%), indicating the effectiveness of the new Et_2Zn/**1** = 4/1 ratio. Examination of various achiral additives indicated that activated molecular sieves were effective for further improving reactivity. Among various types of molecular sieves (MS; entries 5−8), the best reactivity (yield 93%), diastereoselectivity (syn/anti = 78/22), and enantioselectivity (95% ee for syn, 93% ee for anti) were achieved with MS 3A (entry 8). Molecular sieves were used after activation at 160 °C under reduced pressure (ca. 0.7 kPa) for 3 h prior to use.

With the optimized Et_2Zn/ **1** = 4/1 with MS 3A system at −20 °C, 1,4-addition reactions of various β-substituted enones with ketone **3** were examined. The results with acyclic enones are summarized in Table 5. **7a** and its derivatives **7d**−**7g**, with either electron-donating or -withdrawing substituents on the aromatic ring, afforded products syn-selectively in good yield (entries 1−5, 93−99%) and high enantiomeric excess (entries 1−5, syn: 95−97% ee). The relative configuration of **8g** was determined by X-ray crystallography.[19] α-Enolizable enones such as **7b** (entry 6) and **7h** (entry 7) were also suitable substrates, and products were obtained in good dr (entry 6, 86/14; entry 7, 86/14) and ee (entry 6, syn 99% ee; entry 7, syn 87% ee). With sterically hindered enone **7i**, the dr was high (syn/anti = 93/7), but the chemical yield and ee were modest (yield 58%, syn: 74% ee). β-Alkyl-substituted enones (entries 10−12) were also appropriate substrates even in the presence of oxygen functional groups (entry 11, TBDPS-ether, and entry 12, BOM-ether). Dialkyl substituted enone **7n** afforded product **8n** in high enantiomeric excess (syn: 93% ee), although the reactivity was low (yield 39% after 24 h).

Scheme 2. 1,4-Addition Reaction of β-Substituted Cyclic Enones **7** and *N*-Benzylmaleimide **7q** with the Second Generation Et_2Zn/(*S*,*S*)-Linked-BINOL **1** = 4/1 with MS 3A System

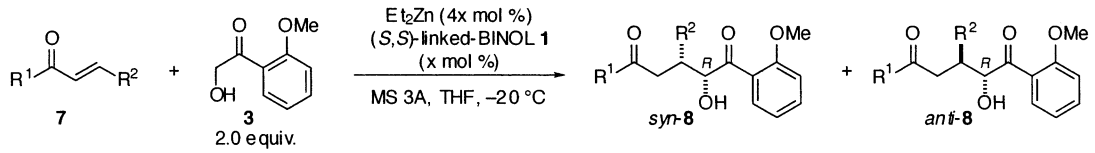


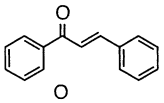
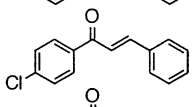
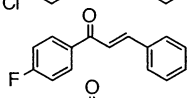
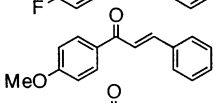
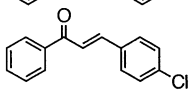
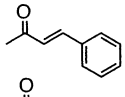
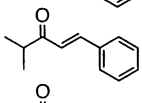
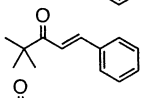
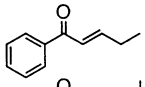
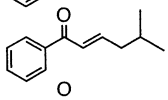
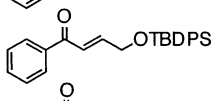
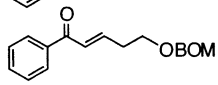
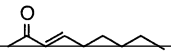
The results with cyclic enones and related compounds are shown in Scheme 2. In case of cyclic enones (eq 3), 1,4-addition reactions proceeded with excellent diastereoselectivity to give **8c**, **8o**, and **8p** as single diastereomers. Diastereoisomer was not observed in any case (dr > 98/2). Good to high ee was also achieved (**8c**, 85% ee; **8o**, 99% ee; **8p**, 98% ee), although the chemical yield remained moderate (**8c**, 81%; **8o**, 61%; **8p**, 45%). In the case of *N*-benzylmaleimide (**7q**, eq 4), the reactivity was much higher than that of cyclic enones, and the reaction proceeded smoothly with 1 mol % of **1** and 4 mol % of Et_2Zn to afford **8q** in 84% yield, >99% ee, and in high dr (94/6). The relative configuration of **8o** was determined by X-ray crystallography.[19]

The successful results obtained using the Et_2Zn/**1** = 4/1 with MS 3A system in less reactive β-substituted enones **7** led us to apply the new system to vinyl ketone **2e** to compare the effectiveness of the new system with the prior Et_2Zn/**1** = 2/1 system. Reaction profiles using four different conditions, (A) 2 mol % of Et_2Zn in the absence of (*S*,*S*)-linked-BINOL **1**, (B) 2 mol % of Et_2Zn, 1 mol % of (*S*,*S*)-**1**, (C) 2 mol % of Et_2Zn, 0.5 mol % of (*S*,*S*)-**1**, and (D) 2 mol % of Et_2Zn, 0.5 mol % of (*S*,*S*)-**1** with MS 3A, are summarized in Figure 3. The 1,4-addition reactions were performed using 2 mol equiv of ketone **3** at 0 °C. Ligand acceleration was observed in (B) and (C) as compared to (A). With conditions (C), in which only one-half the amount of chiral ligand was used as compared to conditions (B), the reaction proceeded at a rate similar to (B). Because the enantiomeric excesses in conditions (B) and (C) were similarly high (B, 93% ee; C, 93% ee), the results suggest that no racemic pathway with ligand-free Et_2Zn was involved and that a small excess of Et_2Zn interacts with Zn/**1**/ketone **3** complex and accelerates the reaction rate.[20] It is noteworthy that a similar reaction rate and ee were achieved with only one-half the amount

(20) For the beneficial effects of additional achiral base to enhance the reaction rate of bifunctional asymmetric catalysis: (a) Arai, T.; Yamada, Y. M. A.; Yamamoto, N.; Sasai, H.; Shibasaki, M. *Chem.-Eur. J.* **1996**, *2*, 1368. (b) Tian, J.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3636.

Table 5. 1,4-Addition Reaction of β-Substituted Acyclic Enones with the Second Generation Et_2Zn/(*S*,*S*)-Linked-BINOL **1** = 4/1 with MS 3A System



entry	enone		product	cat. (mol %)	time (h)	yield[a] (%)	dr[b] (*syn*/*anti*)	ee (*syn*/*anti*)
1		**7a**	**8a**	5	3	93	78/22	95/93
2		**7d**	**8d**	5	3	95	79/21	97/83
3		**7e**	**8e**	5	3	96	81/19	97/80
4		**7f**	**8f**	5	6	99	85/15	97/52
5		**7g**	**8g**	5	5	96	76/24	95/71
6		**7b**	**8b**	10	16	82	86/14	99/7
7		**7h**	**8h**	10	17	73	86/14	87/—
8		**7i**	**8i**	10	24	58	93/7	74/—
9		**7j**	**8j**	10	7	85	81/19	97/79
10		**7k**	**8k**	5	7	95	69/31	97/65
11		**7l**	**8l**	10	24	93	61/39	81/52
12		**7m**	**8m**	10	24	72	77/23	80/—
13		**7n**	**8n**	10	24	39	68/32	93/86

[a] Isolated yield. [b] Determined by ^{1}H NMR analysis of crude mixture.

of chiral ligand **1**. In the presence of MS 3A (D), the reaction rate increased dramatically, strongly supporting the effectiveness of the optimized conditions for β-substituted enones.

As shown in Table 6, in the case of the first Et_2Zn/**1** = 2/1 without MS 3A system, addition of 2 mol equiv of ketone **3** was essential to achieve satisfactory chemical yield (entry 1, 86% with 2 equiv of **3**; entry 2, 53% with 1.1 equiv of **3**), probably due to problems in the catalyst turnover step. With the new Et_2Zn/**1** = 4/1 with MS 3A system, however, there was no difficulty in catalyst turnover with only 1.1 equiv of ketone **3**. With 0.5 mol % of (*S*,*S*)-linked-BINOL **1**, 2 mol % of Et_2Zn, and 1.1 equiv of **3**, the reaction reached completion within 3 h to give product **4e** in better yield and ee (entry 3: yield 90%, 96% ee). With reduced catalyst loading (entry 4, 0.25 mol %; entry 5, 0.1 mol %), the reaction proceeded efficiently to afford **4e** in good yield and high ee after 5 h (entry 5, yield 86%, 96% ee; entry 6, yield 83%, 96% ee). With 0.05 mol % (entry 6) and 0.02 mol % (entry 7), the reaction rate and chemical yield decreased at 4 °C. At room temperature, the reaction proceeded smoothly even with 0.02 mol % of (*S*,*S*)-linked-BINOL **1** (substrate/chiral ligand = 5000) to afford **4e** in good yield (entry 8: 90%) after 13 h, maintaining high enantiomeric excess (entry 8: 91% ee). With 0.01 mol % loading (substrate/chiral ligand = 10 000), **4e** was obtained in moderate yield (78%) and good ee (89%). It is noteworthy that the substrate/chiral ligand ratio improved by 2 orders of magnitude from substrate/chiral ligand = 100 with the prior Zn/**1** = 2/1 ratio system to 5000−10 000 with the new Zn/**1** = 4/1 ratio and MS 3A system even with reduced amounts of ketone **3**. The results in entries 8 and 9 indicate that the new system is exceptionally efficient in terms of catalyst loading among reported catalytic asymmetric carbon−carbon bond-forming reactions. Using as little as 1.5 mg of (*S*,*S*)-linked-BINOL **1** and 10 μL of commercially available Et_2Zn solution

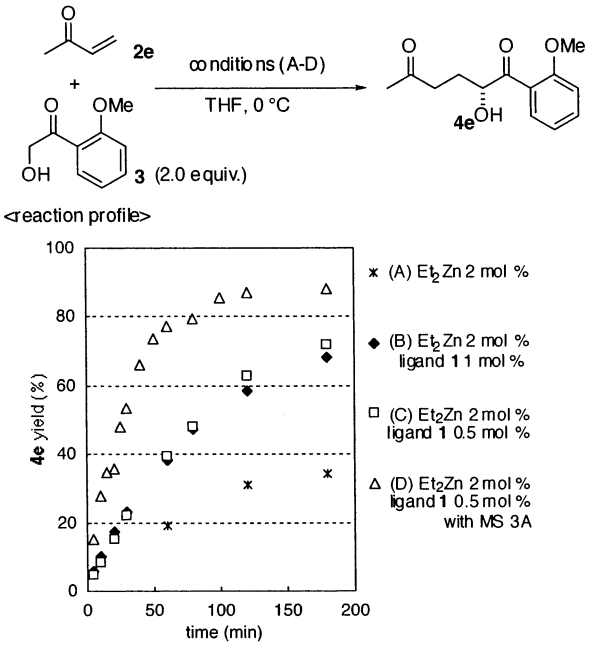
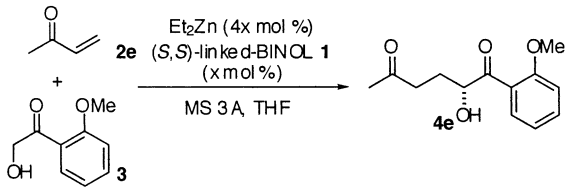


Figure 3. Reaction profiles of 1,4-addition reaction using Et_2Zn alone, Et_2Zn/(*S*,*S*)-linked-BINOL **1** = 2/1, 4/1 without MS 3A, and 4/1 with MS 3A systems.

Table 6. Optimization of 1,4-Addition Reaction of Vinyl Ketone **2e** with the Second Generation Et_2Zn/(*S*,*S*)-Linked-BINOL **1** = 4/1 with MS 3A System



entry	ketone (equiv)	ligand (mol %)	Et_2Zn (mol %)	temp (°C)	time (h)	yield[a] (%)	ee (%)
1[b]	2	1	2	4	4	86	93
2[b]	1.1	1	2	4	4	53	97
3	1.1	0.5	2	4	3	90	96
4	1.1	0.25	1	4	5	86	96
5	1.1	0.1	0.4	4	5	83	96
6	1.1	0.05	0.2	4	16	72	95
7	1.1	0.02	0.08	4	30	74	88
8	1.1	0.02	0.08	rt	13	90	91
9	1.1	0.01	0.04	rt	28	78	89

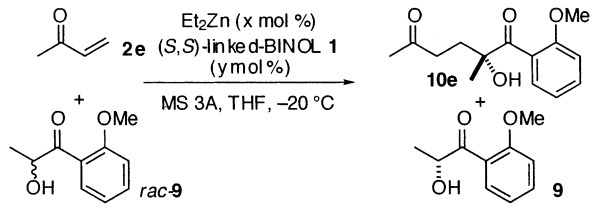
[a] Isolated yield. [b] In the absence of MS 3A.

in hexanes (1.0 M, 0.01 mmol), we obtained 4.63 g of product **4e** (entry 9).

(C) Construction of Chiral Tetrasubstituted Carbon Stereocenter. Catalytic asymmetric construction of a chiral tetrasubstituted carbon stereocenter,[21] which is not accessible via asymmetric hydrogenation reactions,[22] is one of the most important topics in recent synthetic organic chemistry. We envisioned that the present asymmetric zinc catalysis would also differentiate the enantioface of tetrasubstituted enolate derived from 2-hydroxy-2′-methoxypropiophenone (**9**). The 1,4-adduct would then be chiral *tert*-alcohol. As shown in Table 7, the

(21) Review: Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388.
(22) For excellent achievements in catalytic asymmetric hydrogenation of ketones, see review: Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40 and references therein.

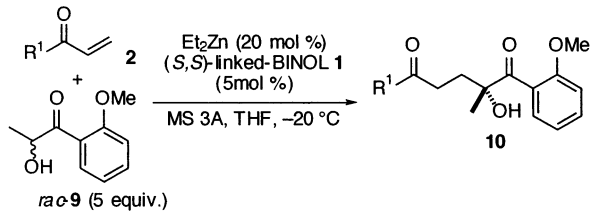
Table 7. Optimization of 1,4-Addition Reaction of Vinyl Ketone **2e** with *rac*-2-Hydroxy-2′-methoxypropiophenone (*rac*-**9**)



entry	Et_2Zn (mol %)	ligand **1** (mol %)	ketone **9** (equiv)	additive	time (h)	yield[a] (%)	ee (%) **10e**	ee (%) **9**
1	10	5	2.2	none	16	15	93	8
2	10	5	2.2	MS 3A	16	35	96	22
3	20	5	2.2	MS 3A	16	51	96	35
4	20	5	5	MS 3A	16	88	96	33

[a] Isolated yield.

Table 8. 1,4-Addition Reaction of Various Vinyl Ketones **2** with Racemic Ketone **9**



entry	R^1	vinyl ketone	product	time (h)	yield[a] (%)	ee (%)
1	*p*-$MeOC_6H_4$	**2a**	**10a**	12	95	90
2	C_6H_6	**2b**	**10b**	24	82	93
3	*o*-$MeOC_6H_4$	**2c**	**10c**	24	78	91
4	*p*-BrC_6H_4	**2g**	**10g**	24	82	93
5	CH_3	**2e**	**10e**	16	88	96
6	CH_3CH_2	**2f**	**10f**	24	86	90

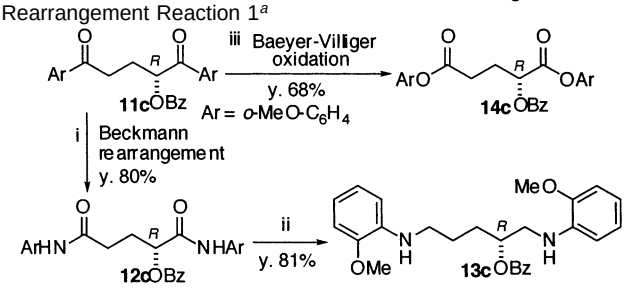
[a] Isolated yield.

ratio of Et_2Zn/(*S*,*S*)-linked-BINOL **1** and the addition of MS 3A were again important to achieve high yield. With 2.2 mol equiv of racemic ketone **9** and the Et_2Zn/(*S*,*S*)-linked-BINOL **1** = 2/1 complex, **10e** was obtained in 15% yield in the absence of MS 3A (entry 1) and 35% yield in the presence of MS 3A (entry 2). With a 4/1 ratio, chemical yield improved to 51%, maintaining high ee (96% ee, entry 3). By increasing the amount of *rac*-**9**, chemical yield was improved to 88% (entry 4, 96% ee). Interestingly, the recovered ketone **9** was optically active in all cases (entries 1−4).

Under the optimized conditions, the 1,4-addition reaction of ketone **9** to various vinyl ketones proceeded smoothly as shown in Table 8 (entries 1−6). The present reaction provides a new methodology of synthesizing optically active chiral *tert*-alcohol in a catalytic asymmetric manner. Good yield (78−95%) and high ee (90%-96%) were achieved with vinyl ketones; however, the reaction did not proceed with other acceptors such as **7a**, probably due to steric hindrance.

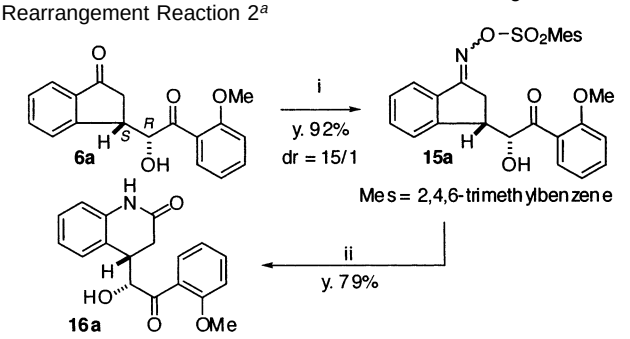
(D) Transformation of 1,4-Adducts. The usefulness of the Michael adduct becomes much higher by assuming that the 2-methoxyphenyl moiety is a placeholder for further conversions. To demonstrate the utility of the 1,4-adducts as chiral building blocks, several transformations were performed via regioselective rearrangements. As shown in Scheme 3, the Beckmann rearrangement of benzoate **11c** with *O*-mesitylene-

Scheme 3. Transformation of Michael Adduct via Regioselective Rearrangement Reaction 1[a]



[a] (i) *O*-Mesitylenesulfonylhydroxylamine, CH_2Cl_2, room temperature, 24 h; (ii) DIBAL, CH_2Cl_2, −78 °C to room temperature, 2 h; (iii) *m*CPBA, NaH_2PO_4, $ClCH_2CH_2Cl$, 50 °C, 24 h.

Scheme 4. Transformation of Michael Adduct via Regioselective Rearrangement Reaction 2[a]



[a] (i) *O*-Mesitylenesulfonylhydroxylamine, CH_3CN, room temperature, 1 h; (ii) $AlCl_3$, CH_2Cl_2, room temperature, 30 min.

sulfonylhydroxylamine (MSH)[23] gave 1,5-diamide **12c** in 80% yield. The subsequent DIBAL reduction of **12c** afforded **13c** in 81% yield. The *o*-methoxyphenyl group in **13c** acts as a protecting group for amine, which is removable by oxidative cleavage.[24] On the other hand, Baeyer−Villiger oxidation of benzoate **11c** with *m*CPBA regioselectively gave 1,5-diester **14c** in 68% yield with the aid of electron-donating groups on the aromatic rings. As shown in Scheme 4, treatment of **6a** with MSH gave oxime mesitylenesulfonate **15a** in 92% yield as a 15/1 diastereomixture. **15a** was unusually stable, and treatment of **15a** either with basic alumina or with silica gel resulted only in recovery of **15a** even at an elevated temperature. Rearrangement of **15a** proceeded smoothly in the presence of $AlCl_3$[25] to give lactam **16a** in 79% yield. The optically active lactam **16a** should be useful for synthesizing various biologically interesting compounds.

(E) Mechanistic Studies and Discussion. Because the chirality in the 1,4-adducts from vinyl ketones **2** is induced in the hydroxyketone part (Tables 2, 6, and 8), it is clear that the catalyst system differentiates the enantioface of enolate derived from hydroxyketones. In all cases with β-unsubstituted and β-substituted enones, the absolute configurations of the 1,4-adducts were the same as those of the α-position in aldol adducts (2*R*).[18] We believe that the active species for the present Michael reaction would be the same as that for the direct catalytic asymmetric aldol reaction with the Zn/(*S*,*S*)-linked-BINOL **1** system.[18] To clarify the mechanism and catalytic cycle of the present reaction, several mechanistic studies were performed.

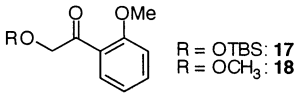


Figure 4. Protected ketone **17** and **18**.

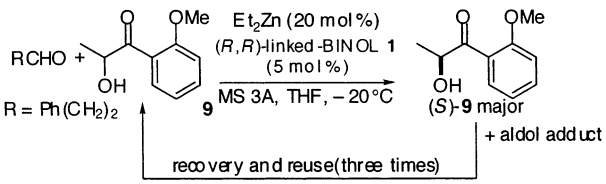
Reactions using protected ketones such as **17** and **18** (Figure 4) gave either no 1,4-adduct (**17**) or only trace amounts of 1,4-adduct (**18**: 6% at 4 °C after 12 h) in low enantiomeric excess (<9% ee) using 5 mol % of **1** and 20 mol % of Et_2Zn with MS 3A, suggesting the importance of the OH-group in ketones to promote the reaction. The tendency was the same as that observed in the direct catalytic asymmetric aldol reaction with the Zn/**1** system.[18]

The fact that recovered ketone **9** was optically active with the (*R*)-configuration (8−35% ee; Table 7) provided a clue to the mechanism of the present asymmetric zinc catalysis. To obtain more precise results, reaction profiles using optically active (*S*)-**9** (>99% ee, 2.5 equiv)[26] with (a) Et_2Zn/(*S*,*S*)-linked-BINOL **1** and (b) Et_2Zn/(*R*,*R*)-linked-BINOL were examined. The results are shown in Figure 5. With (b) (*R*,*R*)-linked-BINOL, only a trace amount of **10e** was obtained (yield < 2% determined by ^1H NMR), and the ee of recovered ketone **9** was still 99% ee, suggesting that trace, if any, enolization occurred under the reaction conditions. On the other hand, with (a) (*S*,*S*)-linked-BINOL **1**, the reaction proceeded smoothly to afford product **10e** in 97% ee, and the ee of the recovered ketone was lower (97% ee) than that of starting ketone **9** (>99% ee). These results indicate that the Et_2Zn/linked-BINOL complex recognizes the absolute configuration of α-hydroxyketone very well. In addition, the 1,4-addition reaction proceeded smoothly even when the racemic-**9** was used, and the ee of the product was similarly high as summarized in Table 8 (**10e**, 96% ee, Table 8, entry 5). Thus, it seemed that one enantiomer, (*S*)-**9**, was involved in the reaction pathway using (*S*,*S*)-linked-BINOL **1**, while the other enantiomer, (*R*)-**9**, would not interact with the Zn/(*S*,*S*)-linked-BINOL complex at all. The (*R*)-**9** enantiomer had no adverse effects on the reaction with (*S*,*S*)-linked-BINOL **1**. The results are also consistent with the exceptionally low catalyst loading for the 1,4-addition reaction of **2e** with ketone **3** (Table 6, 0.01 mol %, substrate/chiral ligand = up to 10 000). The absolute configuration of the 1,4-adduct **4e** was *R*, which should not interact well with the Zn/(*S*,*S*)-linked-BINOL/ketone **3** complex. Thus, product inhibition was not problematic in the case of the present 1,4-addition reaction, unlike many other common asymmetric catalyses by chiral Lewis acids.[27]

To gain more insight into the catalytic cycle, initial rate kinetics were investigated using enone **2e** and ketone **3**. Under

(23) Tamura, Y.; Fujiwara, H.; Sumoto, K.; Ikeda, M.; Kita, Y. *Synthesis* **1973**, 215.
(24) (a) Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. C. *J. Am. Chem. Soc.* **2001**, *123*, 10409. (b) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 8180 and references therein.
(25) Tanga, M. J.; Reist, E. J. *J. Heterocycl. Chem.* **1986**, *23*, 747.

(26) Optically active ketone **9** (99% ee) was prepared as shown in the scheme below. Starting from the racemic ketone **9**, the aldol reaction with (*R*,*R*)-linked-BINOL was repeated by using recovered ketone **9** each time. After four direct aldol reaction and recovery processes, ketone **9** was recovered in high ee (>99% ee).



(27) In the direct aldol reaction of **3** with Zn/linked-BINOL complex, the maximum substrate/chiral ligand ratio was 1000, probably due to the product (dihydroxyketone) inhibition.

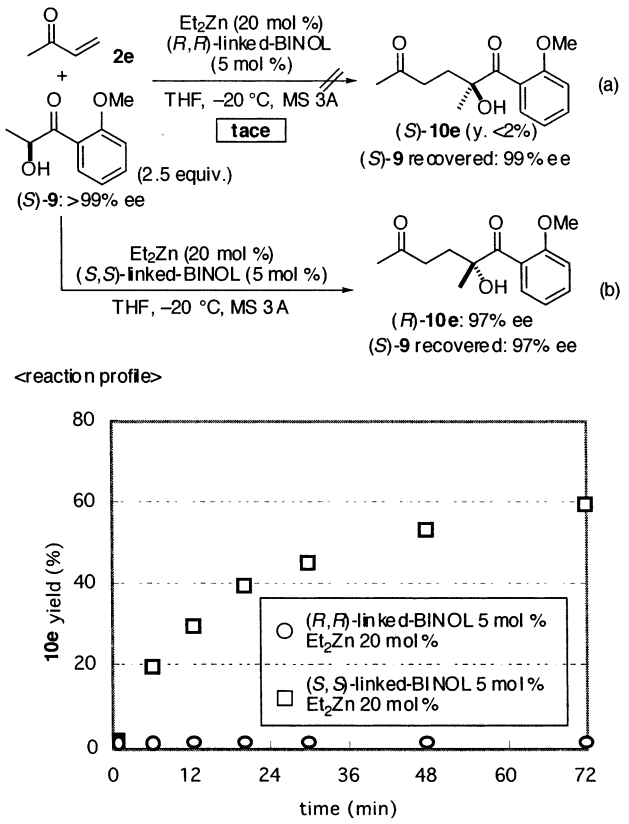
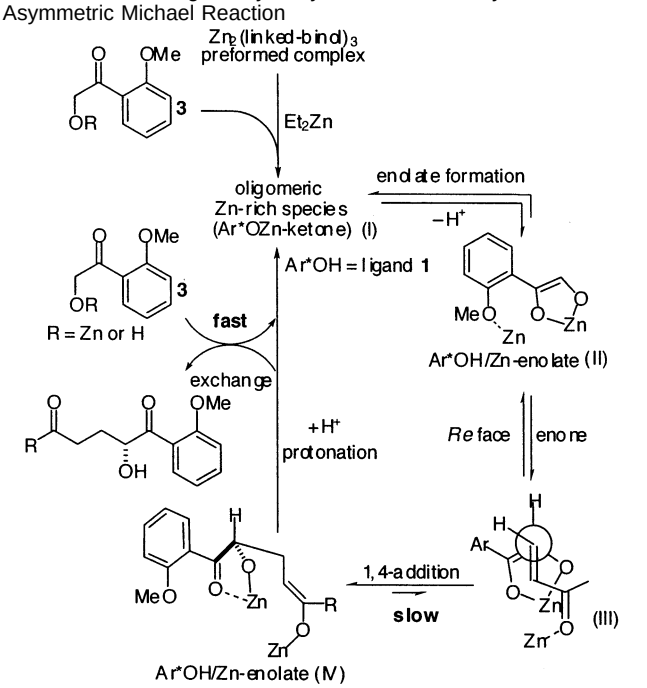


Figure 5. Reaction profiles of 1,4-addition reaction with optically active ketone (*S*)-**9** (99% ee) catalyzed by (a) Et_2Zn/(*R*,*R*)-linked-BINOL and (b) Et_2Zn/(*S*,*S*)-linked-BINOL.

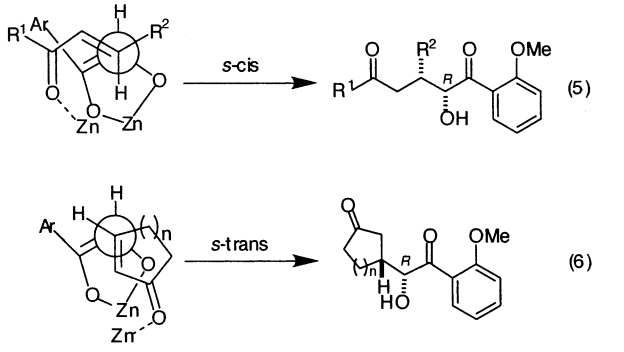
conditions (1) first generation Zn/(*S*,*S*)-linked-BINOL **1** = 2/1 without MS 3A, the reaction was around 0.8-order on enone **2e**, 0.7-order on Zn/**1** complex, and 0.8-order on ketone **3**,[28] suggesting that the 1,4-addition step and product dissociation step would be equally slow. In contrast, under (2) the Et_2Zn/(*S*,*S*)-linked-BINOL **1** = 4/1 with MS 3A system, the reaction was first-order on enone **2e**, first-order on Zn/**1** complex, and zero-order on ketone **3**.[28] These results clearly indicate that the rate-determining step in the catalytic cycle is the 1,4-addition step. Thus, the effectiveness of the Zn/**1** = 4/1 with MS 3A system on acceleration of the catalyst dissociation step was clear.[29] The rate-determining step was completely different from the case of the direct aldol reaction, where kinetics suggested that 1,2-addition was fast and the rate-determining step would be the catalyst turnover step.[30] The difference can be rationalized by considering the above-mentioned results in Figure 5 with optically active ketone **9**. Interaction of (2*R*)-1,4-adducts with Zn/**1** should be weaker than that of aldol adducts (dihydroxyketones). Thus, the rates for the product dissociation step would be different from each other.

The postulated catalytic cycle is shown in Scheme 5. We believe that the same Zn/ligand **1**/ketone **3** oligomeric complex (I) as involved in direct aldol reaction would be the putative actual active species.[18] Although the exact structure of actual active oligomeric species has not yet been clarified, the reaction

Scheme 5. Working Catalytic Cycle of Direct Catalytic Asymmetric Michael Reaction



Scheme 6. Postulated Transition State Models for Acyclic Enones (eq 5) and Cyclic Enones (eq 6)



via a bifunctional mechanism utilizing two or more zinc centers seems reasonable on the basis of related examples of achiral zinc catalysis.[31] Zn-binaphthoxide (Ar*O-Zn, Zn-**1** in Scheme 5) would function as a Brønsted base to deprotonate the α-proton in **3** to form (II). Enones come from the Re-face of the enolate selectively to be activated by the Lewis acidic zinc center. Initial rate kinetics suggested that the 1,4-addition to form (IV) is the rate-limiting step. Protonation with phenolic proton of **1** (Ar*OH) followed by ligand exchange with **3** would regenerate (I). The product dissociation step via exchange with ketone **3** (IV) proceeded smoothly with the Et_2Zn/(*S*,*S*)-linked-BINOL **1** = 4/1 and MS 3A system. Considering the relative configurations of 1,4-adducts from acyclic and cyclic enones, we proposed the working transition state models for acyclic enones (Scheme 6, eq 5) and cyclic enones (Scheme 6, eq 6). In the case of

(28) See Supporting Information for detailed results, including numerical data.
(29) For precedent examples where activated molecular sieves had a key role to accelerate the product dissociation step in the catalytic cycle, see: Iida, T.; Yamamoto, N.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1997**, *119*, 4783 and references therein.
(30) In the case of the direct aldol reaction, the reaction was first-order on ketone **3**, first-order on Zn/**1** complex, and zero-order on aldehyde **3**.[18]
(31) Bifunctional mechanism was proposed for the reaction by achiral dinuclear Zn complexes as zinc metalloenzyme models. For selected recent examples, see: (a) Chapman, W. H., Jr.; Breslow, R. *J. Am. Chem. Soc.* **1995**, *117*, 5462. (b) Yashiro, M.; Ishikubo, A.; Komiyama, M. *J. Chem. Soc., Chem. Commun.* **1995**, 1793. (c) Koike, T.; Inoue, M.; Kimura, E.; Shiro, M. *J. Am. Chem. Soc.* **1996**, *118*, 3091. (d) Molenveld, P.; Kapsabeils, S.; Engbersen, J. F. J.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1997**, *119*, 2948. (e) Kaminskaia, N. V.; Spingler, B.; Lippard, S. J. *J. Am. Chem. Soc.* **2000**, *122*, 6411. (f) Abe, K.; Izumi, J.; Ohba, M.; Yokoyama, T.; Okawa, H. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 85 and references therein.

acyclic enones, the reaction would proceed through the s-cis conformation, and relatively lower diastereoselectivity (Table 5, 61/39−93/7) as compared to that of cyclic enones was attributed to the conformational flexibility between s-cis and s-trans forms. The conformation of cyclic enone is fixed to s-trans, thus leading to high diastereoselectivity (86/14−98/2, Table 3, and single diastereomer, Scheme 2).

Summary

We successfully developed new highly enantioselective 1,4-addition reactions of hydroxyketones. The first generation Et_2-Zn/linked-BINOL = 2/1 complex was effective for 1,4-addition of β-unsubstituted enones and indenones with 2-hydroxy-2′-methoxyacetophenone. The second generation Et_2Zn/(*S*,*S*)-linked-BINOL **1** = 4/1 with MS 3A system was developed to widen the substrate scope and was effective for various β-substituted enones to afford products in up to 99% yield and up to 99% ee. With the new 4/1 system, ligand loading for the β-unsubstituted enone was reduced to as little as 0.01 mol % (substrate/chiral ligand = 10 000). Mechanistic studies using optically active ketone **9** afforded a clue to the reason for the exceptionally low catalyst loading for β-unsubstituted enone. Kinetic studies revealed that the rate-determining step is the 1,4-addition step, which is different from the direct aldol reaction. Application of the present efficient asymmetric zinc catalysis to other asymmetric reactions such as direct aldol and Michael reactions of unmodified esters is currently underway in our group.

Acknowledgment. We thank financial support by RFTF and Grant-in-Aid for Encouragements for Young Scientists (B) (for S.M.). We thank Prof. S. Kobayashi and Mr. T. Hamada at the University of Tokyo for generous support in X-ray analysis.

Supporting Information Available: Experimental procedures, characterization of the products, X-ray data (CIF), and detailed data for kinetic studies (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA028928+