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

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Abstract: Full details of our newly developed catalyses with asymmetric zinc complexes as mimics of class II zinc-containing aldolase are described. A Et_2Zn/(*S*,*S*)-linked-BINOL complex was developed and successfully applied to direct catalytic asymmetric aldol reactions of hydroxyketones. A Et_2Zn/(*S*,*S*)-linked-BINOL **1** = 2/1 system was initially developed, which efficiently promoted the direct aldol reaction of 2-hydroxy-2′-methoxyacetophenone (**7d**). Using 1 mol % of (*S*,*S*)-linked-BINOL **1** and 2 mol % of Et_2Zn, we obtained 1,2-dihydroxyketones syn-selectively in high yield (up to 95%), good diastereomeric ratio (up to 97/3), and excellent enantiomeric excess (up to 99%). Mechanistic investigation of Et_2Zn/(*S*,*S*)-linked-BINOL **1**, including X-ray analysis, NMR analysis, cold spray ionization mass spectrometry (CSI-MS) analysis, and kinetic studies, provided new insight into the active oligomeric Zn/(*S*,*S*)-linked-BINOL **1**/ketone **7d** active species. On the basis of mechanistic investigations, a modified second generation Et_2Zn/(*S*,*S*)-linked-BINOL **1** = 4/1 with molecular sieves 3A (MS 3A) system was developed as a much more effective catalyst system for the direct aldol reaction. As little as 0.1 mol % of (*S*,*S*)-linked-BINOL **1** and 0.4 mol % of Et_2Zn promoted the direct aldol reaction smoothly, using only 1.1 equiv of **7d** as a donor (substrate/ligand = 1000). This is the most efficient, in terms of catalyst loading, asymmetric catalyst for the direct catalytic asymmetric aldol reaction. Moreover, the Et_2Zn/(*S*,*S*)-linked-BINOL **1** = 4/1 system was effective in the direct catalytic asymmetric aldol reaction of 2-hydroxy-2′-methoxypropiophenone (**12**), which afforded a chiral tetrasubstituted carbon center (*tert*-alcohol) in good yield (up to 97%) and ee (up to 97%), albeit in modest syn-selectivity. Newly developed (*S*,*S*)-sulfur-linked-BINOL **2** was also effective in the direct aldol reaction of **12**. The Et_2Zn/(*S*,*S*)-sulfur-linked-BINOL **2** = 4/1 system gave aldol adducts anti-selectively in good ee (up to 93%). Transformations of the aldol adducts into synthetically versatile intermediates were also described.

Introduction

The aldol reaction is generally regarded as one of the most powerful and efficient carbon−carbon bond-forming reactions. Many efforts have been devoted to the development of catalytic and asymmetric aldol reactions,[1] but almost all of these reactions require a preconversion of the ketone or ester moiety into a more reactive species, such as an enol silyl ether or a ketene silyl acetal, using no less than stoichiometric amounts of reagents. On the other hand, living organisms utilize aldolases, which directly catalyze aldol reactions of unmodified ketones under mild conditions. The feature of bifunctional aldolases, classified as class I (peptide base) and class II (zinc metalloenzyme), has attracted chemists very much as a potentially advantageous strategy to develop efficient and atom-economic[2] artificial asymmetric catalysis.[3,4] Since our success in performing direct catalytic asymmetric aldol reactions with unmodified ketones using the heterobimetallic multifunctional $LaLi_3$tris(binaphthoxide) (LLB) complex,[5a] several groups, including ours, have reported various methodologies for direct catalytic asymmetric aldol reactions over the past 5 years. Our group,

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(1) For a general review on the catalytic enantioselective aldol reaction, see: (a) Palomo, C.; Oiarbide, M.; García, J. M. *Chem.-Eur. J.* **2002**, *8*, 37. (b) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325. (c) Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, *9*, 357. (d) Gröger, H.; Vogl, E. M.; Shibasaki, M. *Chem.-Eur. J.* **1998**, *4*, 1137. (e) Carreira, E. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Heidelberg, 1999; Vol. 3, Chapter 29.1.

(2) (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259.

(3) Recent reviews for bifunctional asymmetric catalysis: (a) Shibasaki, M.; Kanai, M.; Funabashi, K. *Chem. Commun.* **2002**, 1989. (b) Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, *102*, 2187. (c) Gröger, H. *Chem.-Eur. J.* **2001**, *7*, 5246. (d) Rowlands, G. J. *Tetrahedron* **2001**, *57*, 1865. (e) Shibasaki, M.; Kanai, M. *Chem. Pharm. Bull.* **2001**, *49*, 511. (f) Shibasaki, M. *Chemtracts-Org. Chem.* **1999**, *12*, 979. (g) Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1236. (h) Sawamura, M.; Ito, Y. *Chem. Rev.* **1992**, *92*, 857.

(4) Reviews for direct catalytic asymmetric aldol reactions: (a) Alcaide, B.; Almendros, P. *Eur. J. Org. Chem.* **2002**, 1595. (b) List, B. *Tetrahedron* **2002**, *58*, 5573. See also refs 3a, 3b, and 15b.

Trost et al., and others reported chiral La,[5b,d] Ba,[5c] Zn,[6] Ca,[7] and Ti[8] catalysts, respectively, as class II aldolase mimics. List et al.,[9] Barbas et al.,[9] and others[10] reported direct aldol reactions with L-proline and its derivatives as class I aldolase mimics. Recently, several groups reported enantio- and diastereoselective direct aldol reactions using biological-type catalysts and/or small molecular catalysts, which considerably widened the scope of the direct aldol reaction.[11,12] In particular, the direct aldol reaction of hydroxyketones afforded a new method to effectively synthesize either *syn*- or *anti*-1,2-diols.[13] In many cases, however, more than 5 mol % catalyst loading was required to ensure the completion of the aldol reactions, leaving room for improvement in terms of catalyst loading and reactivity. Moreover, mechanistic studies to clarify the structure of the active species are still lacking in many direct catalytic asymmetric aldol reactions, despite the fact that knowledge of the active species structure would aid in logically designing studies to further improve the catalytic activity, selectivity, and substrate scope. In this article, we report full details of our new approach.[14] Asymmetric zinc catalysis as a mimic of class II zinc metalloenzymes was developed and successfully applied to the direct catalytic enantio- and diastereoselective aldol reaction of hydroxyketones, giving a new efficient and atom-economic method for the synthesis of optically active 1,2-diols. Development of the first generation Et_2Zn/linked-BINOL **1** = 2/1 system for the direct aldol reaction of 2-hydroxy-2′-methoxyacetophenone (**7d**), mechanistic investigations, including revision of the structure of Zn/linked-BINOL complex, and modification into the second generation Et_2Zn/linked-BINOL **1** = 4/1 system based on those mechanistic studies are discussed. In the best system, as little as 0.1 mol % chiral ligand (substrate/chiral ligand = 1000) efficiently promoted the aldol reaction in excellent enantioselectivity. The direct aldol reaction of 2-hydroxy-2′-methoxypropiophenone (**12**) using either linked-BINOL (Figure 1, **1**)[15,16] or a newly developed sulfur-linked-BINOL (Figure 1, **2**), which afforded aldol adducts with a *tert*-OH group, is also described.

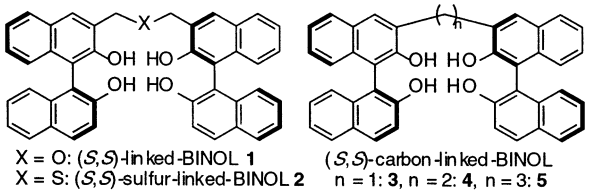


Figure 1. (*S*,*S*)-Linked-BINOL **1** and its derivatives **2**−**5**.

Results and Discussion

(A) First Generation Et_2Zn/Linked-BINOL = 2/1 System. Considering (1) the effectiveness of class II aldolase, in which the Zn moiety has a crucial role in promoting the direct aldol reaction of hydroxyketone, and (2) the effectiveness of the previously reported La/Zn/linked-BINOL complex in asymmetric catalysis,[16b] we initiated screening of the catalyst system using various metals including Zn and lanthanides, linked-BINOL **1**, and its derivatives (Figure 1, **3**−**5**)[16e,f] as chiral ligands, 2-hydroxyacetophenone (**7a**), and aldehyde **6a**. Initial screening revealed that a complex prepared from 20 mol % of Et_2Zn and 10 mol % of linked-BINOL **1** in THF was most promising.[17] As shown in Table 1, entry 1, the Et_2Zn/(*S*,*S*)-linked-BINOL **1** complex promoted an aldol reaction of **6a** and **7a** in THF at −20 °C to give **8** in 66% yield and 70% ee. At −40 °C with prolonged reaction time, **8** was obtained in good yield and in moderate dr and ee (entry 2, yield 81%, syn/anti = 67/33, syn: 78% ee). Neither BINOL itself (entry 3) nor other bridged BINOL ligands with carbon linkers (Figure 1, **3**−**5**; Table 1, entries 4−6) were effective, suggesting the importance of a heteroatom in the linker to construct proper asymmetric space.

Our previous results[5b] suggested that substituents on the aromatic ring of acetophenones would affect both the diastereoselectivity and the enantioselectivity. To improve the present direct catalytic asymmetric aldol reaction, we chose methoxy-substituted acetophenones, considering the following background: from a synthetic point of view, the use of aryl ketones is potentially advantageous over the use of dialkyl ketones such as acetone and hydroxyacetone,[18] because the aromatic ring functions as a placeholder for further conversions via regio-

(5) (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.

(6) (a) Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003. (b) Trost, B. M.; Silcoff, E. R.; Ito, H. *Org. Lett.* **2001**, *3*, 2497. For a partially successful attempt, see: (c) Nakagawa, M.; Nakao, H.; Watanabe, K.-I. *Chem. Lett.* **1985**, 391.

(7) Suzuki, T.; Yamagiwa, N.; Matsuo, Y.; Sakamoto, S.; Yamaguchi, K.; Shibasaki, M.; Noyori, R. *Tetrahedron Lett.* **2001**, *42*, 4669.

(8) Mahrwald, R.; Ziemer, B. *Tetrahedron Lett.* **2002**, *43*, 4459.

(9) (a) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395. (b) List, B.; Pojarliev, P.; Castello, C. *Org. Lett.* **2001**, *3*, 573. (c) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2001**, *123*, 5260. Unmodified aldehydes as donors: (d) Córdova, A.; Notz, W.; Barbas, C. F., III. *J. Org. Chem.* **2002**, *67*, 301.

(10) (a) Saito, S.; Nakadai, M.; Yamamoto, H. *Synlett* **2001**, 1245. Unmodified aldehydes as donors: (b) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798. (c) Bøgevig, A.; Kumaragurubaran, N.; Jørgensen, K. A. *Chem. Commun.* **2002**, 620.

(11) For impressive direct catalytic asymmetric cross-aldol reaction of unmodified aldehydes by MacMillan et al., see ref 10b. Excellent direct catalytic diastereoselective aldol reaction using chiral auxiliary was reported by Evans et al., see: (a) Evans, D. A.; Tedrow, J. S.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2002**, *124*, 392. (b) Evans, D. A.; Downey, C. W.; Shaw, J. T.; Tedrow, J. S. *Org. Lett.* **2002**, *4*, 1127.

(12) Review for biological and chemical methods: (a) Machajewski, T. D.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352. For the use of catalytic antibodies, see: (b) Turner, J. M.; Bui, T.; Lerner, R. A.; Barbas, C. F., III; List, B. *Chem.-Eur. J.* **2000**, *6*, 2772 and references therein.

(13) The use of hydroxyketones as a donor was pioneered by List et al. *anti*-1,2-diol: (a) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386. (b) Yoshikawa, N.; Suzuki, T.; Shibasaki, M. *J. Org. Chem.* **2002**, *67*, 2556. See also refs 9c and 13d. *syn*-1,2-diol: (c) Trost, B. M.; Ito, H.; Silcoff, E. R. *J. Am. Chem. Soc.* **2001**, *123*, 3367. (d) Yoshikawa, N.; Kumagai, N.; Matsunaga, S.; Moll, G.; Ohshima, T.; Suzuki, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 2466. (e) Kumagai, N.; Matsunaga, S.; Yoshikawa, N.; Ohshima, T.; Shibasaki, M. *Org. Lett.* **2001**, *3*, 1539.

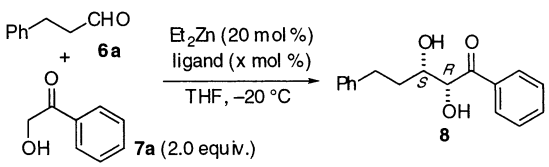
(14) For the preliminary communication on this topic concerning the development of the first generation Et_2Zn/(*S*,*S*)-linked-BINOL **1** = 2/1 complex, see refs 13d and 13e.

(15) 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).

(16) 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) Kumagai, N.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2001**, *3*, 4251. (d) Takita, R.; Ohshima, T.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 4661. For related compounds, see: (e) Vogl, E. M.; Matsunaga, S.; Kanai, M.; Iida, T.; Shibasaki, M. *Tetrahedron Lett.* **1998**, *39*, 7917. (f) Ishitani, H.; Kitazawa, T.; Kobayashi, S. *Tetrahedron Lett.* **1999**, *40*, 2161 and references therein.

(17) Other metal complexes, such as La-linked-BINOL[16a] and La-Zn-linked-BINOL,[16b] gave less satisfactory results. Other solvents, such as Et_2O, DME, toluene, and CH_2Cl_2, gave less satisfactory results.

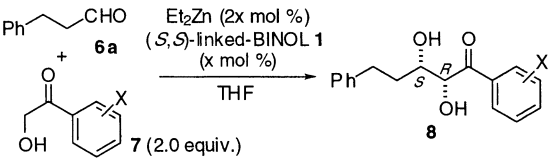
Table 1. Direct Aldol Reaction of **6a** and **7** Using Various BINOL Derivatives



entry	ligand	(x mol %)	temp (°C)	time (h)	yield (%)	dr[a] (syn/anti)	ee (syn/anti)
1	(*S*,*S*)-linked-BINOL **1**	10	−20	12	66	67/33	70/60
2	(*S*,*S*)-linked-BINOL **1**	10	−40	48	81	67/33	78/76
3	(*S*)-BINOL	20	−20	24	84	56/44	32/47[b]
4	**3**	10	−20	24	trace		
5	**4**	10	−20	24	91	60/40	5/19
6	**5**	10	−20	24	trace		

[a] Determined by ^{1}H NMR of crude mixture. [b] The syn (2*S*,3*R*) enantiomer was obtained in major.

Table 2. Direct Aldol Reaction of **6a** with Methoxy-substituted 2-Hydroxyacetophenones **7**[a]



entry	X		catalyst (x mol %)	temp (°C)	time (h)	yield[b] (%)	dr[c] (syn/anti)	ee[d] (syn/anti)
1	H	**7a**	10	−40	48	81	67/33	78/76
2	4′-MeO	**7b**	10	−20	24	73	60/40	86/86
3	3′-MeO	**7c**	10	−30	12	85	70/30	77/77
4	2′-MeO	**7d**	10	−30	3	93	89/11	86/88
5	2′-MeO	**7d**	3	−30	4	94	90/10	90/89
6	2′-MeO	**7d**	1	−30	20	94	89/11	92/89
7	2′-MeO	**7d**	1	−30	16	94	87/13	93/91

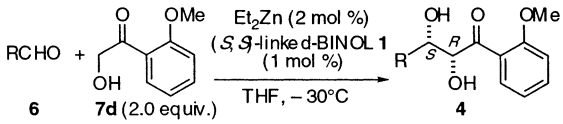
[a] Reactions were run on a 0.30 mmol scale (entries 1−4), 0.67 mmol scale (entry 5), 1.0 mmol scale (entry 6), and 8.0 mmol scale (1.05 g of **8**, entry 7) at 0.2 M in aldehyde. [b] Isolated yield after conversion to acetonides. [c] Determined by ^{1}H NMR of crude mixture. [d] Determined by chiral HPLC analysis of diols.

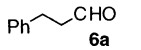
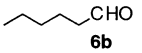
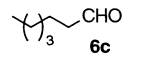
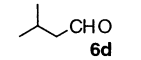
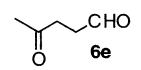
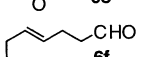
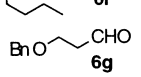
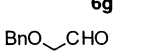
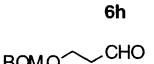
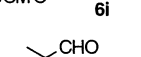
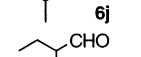
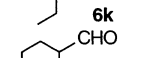
selective rearrangements.[19] By using electron-rich methoxy substituted acetophenones, conversions such as a Baeyer−Villiger oxidation would become facile. We investigated the direct aldol reaction of aldehyde **6a** using methoxy substituted 2-hydroxyacetophenones **7b**−**7d** (Table 2). In the case of 2-hydroxy-4′-methoxyacetophenone (**7b**), the reaction was run at −20 °C due to the poor solubility of **7b**. Although a slightly higher ee was obtained, dr and yield were lower than in the case of **7a** (entry 2). In the case of 2-hydroxy-3′-methoxyacetophenone (**7c**), the reaction was run at −30 °C. Yield, dr, and ee were comparable with those of **7a**, and the reaction rate increased (entry 3). Gratifyingly, the reaction rate, yield, dr, and ee all improved when using 2-hydroxy-2′-methoxyacetophenone (**7d**; entry 4). It is noteworthy that the aldol reaction of **7d** still proceeded smoothly even when the catalyst amount was reduced. The reaction was completed within 4 h

(18) No reaction proceeded with hydroxyacetone as a donor using Zn/linked-BINOL = 2/1 complex. L-Proline afforded excellent results with hydroxyacetone. See refs 9c and 13a.

(19) Utility of 2′-hydroxy-2-acetylfuran for further conversion via oxidative cleavage was demonstrated by Trost et al. Trost, B. M.; Vince, Y. S. C. *Org. Lett.* **2002**, *4*, 3513.

Table 3. Direct Aldol Reaction of Various Aldehydes with 2-Hydroxy-2′-methoxyacetophenone (**7d**)[a]



entry	aldehyde	product	time (h)	yield[b] (%)	dr[c] (*syn*/*anti*)	ee[d] (*syn*/*anti*)
1		**8a**	20	94	89/11	92/89
2		**8b**	18	88	88/12	95/91
3		**8c**	18	84	87/13	96/87
4		**8d**	18	84	84/16	93/87
5		**8e**	12	91	93/7	95/—
6		**8f**	24	94	86/14	87/92
7		**8g**	18	81	86/14	95/90
8		**8h**	16	84	72/28	96/93
9		**8i**	14	93	84/16	90/84
10		**8j**	24	83	97/3	98/—
11		**8k**	16	92	96/4	99/—
12		**8l**	18	95	97/3	98/—

[a] All reactions were run on a 1.0 mmol scale at 0.2 M in aldehyde. [b] Isolated yield after conversion to acetonides. [c] Determined by ^{1}H NMR of crude mixture. [d] Determined by chiral HPLC analysis.

with 3 mol % of ligand **1** (entry 5). Moreover, satisfactory yield (94%), dr (syn/anti = 89/11), and ee (syn = 92%, anti = 89%) were achieved after 20 h with as little as 1 mol % of **1** (entry 6), and the reaction proceeded smoothly without any problem on a gram scale (entry 7).

The optimized reaction conditions were also applicable to various α-unsubstituted and α-monosubstituted aldehydes (Table 3). In all cases, 1 mol % of **1** was sufficient to complete the reaction within 24 h. Both normal (entries 1−3) and branched (entry 4) α-unsubstituted aldehydes afforded good results (entries 1−4; yield, 84−94%; dr, syn/anti = 84/16 to 89/11; ee, syn = 92−96%, anti = 87−91%). It should be mentioned that α-unsubstituted aldehydes gave the corresponding aldol adducts in good to excellent yield and ee without forming any self-condensation products. Remarkably, aldehyde **6e** (entry 5) with a methyl ketone unit also afforded the desired aldol adduct **8e** with excellent chemoselectivity (yield of **8e**: 91%), diastereomeric ratio (syn/anti = 93/7), and ee (95%). The results indicate the high chemoselectivity of the present asymmetric zinc catalysis. In the case of aldehyde **6f** (entry 6), synthesis of the corresponding diol **8f** via Sharpless asymmetric dihydroxylation (AD)[20] might be difficult due to the chemoselectivity issue. Aldehydes with oxygen functionalities such as **6g**, **6h**, **6i**, which lead to useful intermediates for the synthesis of

polyoxygenated compounds, were also converted into diols in excellent ee (syn: 95% in entry 7, 96% in entry 8, and 90% in entry 9). α-Monosubstituted aldehydes (entries 10−12) showed good yield (83−95%) and excellent dr (syn/anti = 96/4 to 97/3) and ee (98−99%).

(B) Mechanistic Studies. What is the mechanism of the direct aldol reaction? What is the structure of the catalyst? As mentioned in the Introduction, many asymmetric catalysts for the direct catalytic asymmetric aldol reaction were recently developed. Detailed mechanistic investigations, however, especially trials to characterize the active species *in the presence of a ketone donor*, were absent in those studies. Even a little information about the structure of the active species would help to further improve the asymmetric catalysis. Thus, we attempted to clarify the mechanism and structure of the Et_2Zn/(*S*,*S*)-linked-BINOL **1** = 2/1 complex with and without ketone **7d** in detail.

Initially, we postulated that the complex prepared from 2 equiv of Et_2Zn and 1 equiv of (*S*,*S*)-linked-BINOL **1** would be a bimetallic monomer[13d,e] on the basis of the related X-ray structure of a Ga-Li-linked-BINOL complex[15a] and Zn bimetallic complexes.[21] Unexpectedly, however, X-ray analysis of a crystal obtained from the Et_2Zn/(*S*,*S*)-linked-BINOL **1** = 2/1 solution in THF revealed that the complex consisted of Zn and **1** in a ratio of 3:2 [trinuclear Zn_3(linked-binol)$_2$thf$_3$] with C_2-symmetry.[22] The revised structure of the Zn/linked-BINOL preformed complex **9** is shown in Figure 2. Three Zn atoms were aligned in almost a straight line (Zn(2)−Zn(1)−Zn(3) angle = 6.6°), and each Zn center was pentacoordinated.

The existence of the trinuclear **9** in Et_2Zn/**1** = 2/1 solution was confirmed by NMR and cold spray ionization mass spectrometry (CSI-MS) analyses,[23] and by measuring ethane gas emission. ^{1}H NMR spectra of (a) free (*S*,*S*)-linked-BINOL **1** and (b) the Zn/**1** = 2/1 mixture in THF-d_8 are shown in Figure 3. The ^{1}H NMR spectrum of (b) the Zn/**1** = 2/1 mixture had four different ArC*H* signals, suggesting a non-C_2-symmetric environment around each of the two linked-BINOL **1** units in **9**. ^{1}H NMR spectrum of crystal **9** in THF-d_8 was the same as that of Zn/**1** = 2/1 solution. Free ligand **1** and **9** were mainly observed in NMR spectra of the Zn/**1** = 1/1 mixture, indicating that formation of **9** is thermodynamically preferred. The presence of **9** in major and additional minor free linked-BINOL **1** was observed in the NMR spectrum of the Zn/**1** = 1.5/1 mixture, even when freshly titrated Et_2Zn (1.0 M in hexanes) was used.[24] The necessity of a slight excess of Et_2Zn (≥2 equiv against **1**) to form a trinuclear Zn/**1** = 3/2 complex was confirmed by NMR and ethane gas emission experiments. The presence of additional Et_2Zn (0.5 mol equiv with respect to ligand **1**) in the Zn/**1** = 2/1 solution was checked by measuring ethane gas emission.[25] With CSI-MS, a Zn/**1** = 3/2 complex (*m*/*z* = 1418.9)[26] was observed as a prominent peak in both the Zn/**1** = 1.5/1 and 2/1 solutions.[24]

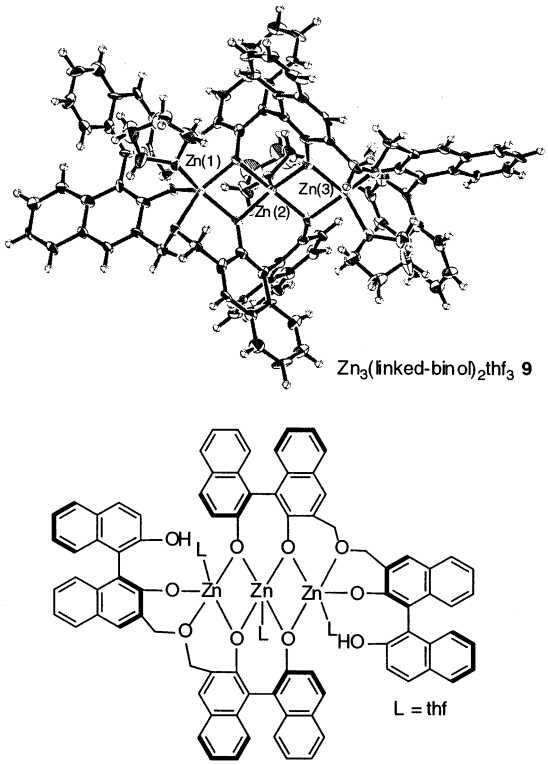


Figure 2. X-ray structure of the preformed complex Zn_3(linked-binol)$_2$-thf$_3$ **9**.

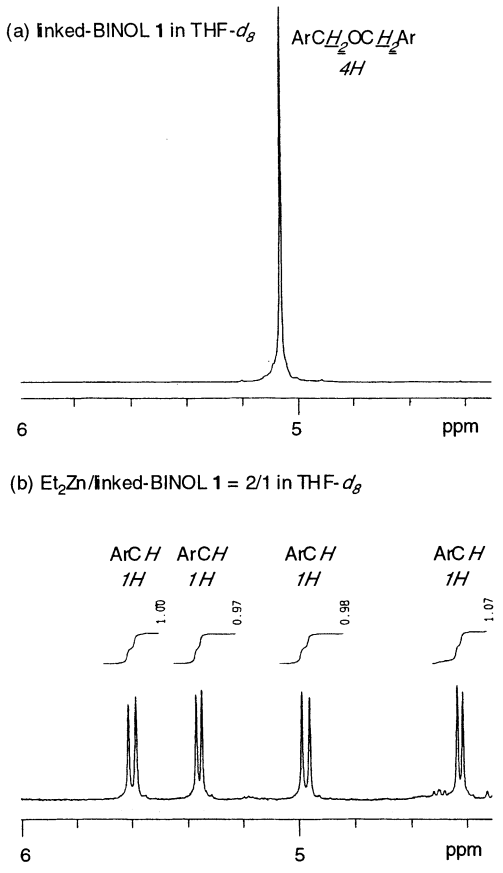


Figure 3. ^{1}H NMR spectra of (a) (*S*,*S*)-linked-BINOL **1** and (b) Et_2Zn/(*S*,*S*)-linked-BINOL **1** = 2/1 in THF-d_8.

(20) Review: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
(21) For selected examples of X-ray structures of bimetallic achiral zinc complexes, see: (a) Kaminskaia, N. V.; Spingler, B.; Lippard, S. J. *J. Am. Chem. Soc.* **2000**, *122*, 6411. (b) Koike, T.; Inoue, M.; Kimura, E.; Shiro, M. *J. Am. Chem. Soc.* **1996**, *118*, 3091. (c) Abe, K.; Izumi, J.; Ohba, M.; Yokoyama, T.; Okawa, H. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 85 and references therein.
(22) CIF file of crystal **9** was deposited to CCDC (CCDC 186559). See also Supporting Information.
(23) The coldspray ionization mass spectrometry (CSI-MS) method enables the direct observation of labile species in solution phase: Sakamoto, S.; Fujita, M.; Kim, K.; Yamaguchi, K. *Tetrahedron* **2000**, *56*, 955 and references therein.
(24) For full details of all of the ^{1}H NMR and CSI-MS charts mentioned in text, see Supporting Information.

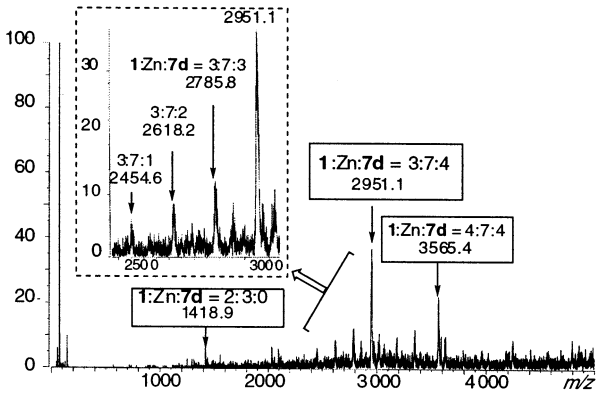


Figure 4. CSI-MS spectrum of a ligand **1**/Et_2Zn/ketone **7d** = 1/2/10 solution.

With isolated crystal **9**, the direct aldol reaction of aldehyde **6l** did proceed to afford product **8l** in 87% yield and 95% ee; however, the reaction rate was unexpectedly slower (−30 °C, 5 h, with 5 mol % of **9**) than that under standard conditions. The reaction rate with 5 mol % of crystal **9** (which contained 10 mol % of ligand **1**) was $v_{crystal} = 2.92 \times 10^{-5}$ M s^{-1}, while the rate with in situ prepared Zn/**1** = 2/1 catalyst (which contained 10 mol % of ligand **1)** was $v_{in\ situ} = 4.47 \times 10^{-5}$ M s^{-1}. Because the ee of the products was similar in both cases (95% ee with crystal **9**, 98% ee with in situ prepared Zn/**1** = 2/1 catalyst), the effects of a background racemic reaction with ligand-free Et_2Zn should be negligible. A small excess of Et_2Zn would have some interaction with the preformed complex **9** in the presence of ketone **7d**, enhancing the reaction rate.[27]

To clarify the role of a small excess of Et_2Zn, we then turned our attention to observe the formation of a Zn-ketone active species directly using CSI-MS analysis. When 1 mol equiv of ketone **7d** (against ligand **1**) was added to Zn/**1** = 2/1 solution, peaks derived from **1**:Zn:**7d** = 2:3:1 (*m*/*z* = 1585.8) and 2:3:2 (*m*/*z* = 1750.9) appeared.[24,26] The addition of 1 mol equiv of aldehyde **6a** to the mixture, however, did not afford any aldol product **8a**, which clearly indicates that neither the crystal **9** nor the **1**:Zn:**7d** = 2:3:1 complex is a real catalyst but only a preformed complex. As the amount of ketone **7d** increased from 1 to 5 and 10 mol equiv, there was a drastic change in the CSI-MS spectra. With 5 mol equiv of ketone **7d**, the peak corresponding to **9** diminished, and a peak derived from a novel heptanuclear Zn complex **10** (**1**:Zn:**7d** = 3:7:4, *m*/*z* = 2951.1) and **11** (**1**:Zn:**7d** = 4:7:4, *m*/*z* = 3565.4)[26] appeared as a major peak. The peak increased by increasing ketone **7d** from 5 to 10 mol equiv. In addition, fragment peaks assigned as **1**:Zn:**7d** = 3:7:3 (*m*/*z* = 2785.8), 3:7:2 (*m*/*z* = 2618.2), and 3:7:1 (*m*/*z* = 2454.6) were also observed.[26] The CSI-MS chart of Zn/**1**/**7d** = 2/1/10 is shown in Figure 4. Other charts are shown in the Supporting Information. The formation of the heptanuclear complex **10** and **11** should be more favorable under the reaction conditions (Table 3), because as much as 200 mol equiv of ketone **7d** exists against ligand **1**. More than 100 mol equiv of **7d** remained even at the final stage of the reaction under the conditions listed in Table 3. As expected, the addition of 1 mol equiv of aldehyde **6a** to Zn/**1**/**7d** = 2/1/10 solution led to the formation of aldol adduct **8a**, suggesting that a complicated oligomeric Zn-rich complex, such as **10** or **11**, may be a putative actual active species.[28] All of the trials to elucidate the exact structure of oligomeric Zn-rich active species, however, failed. For example, NMR analysis trials only afforded complex charts, suggesting the existence of several species in equilibrium in the presence of excess ketone **7d**.

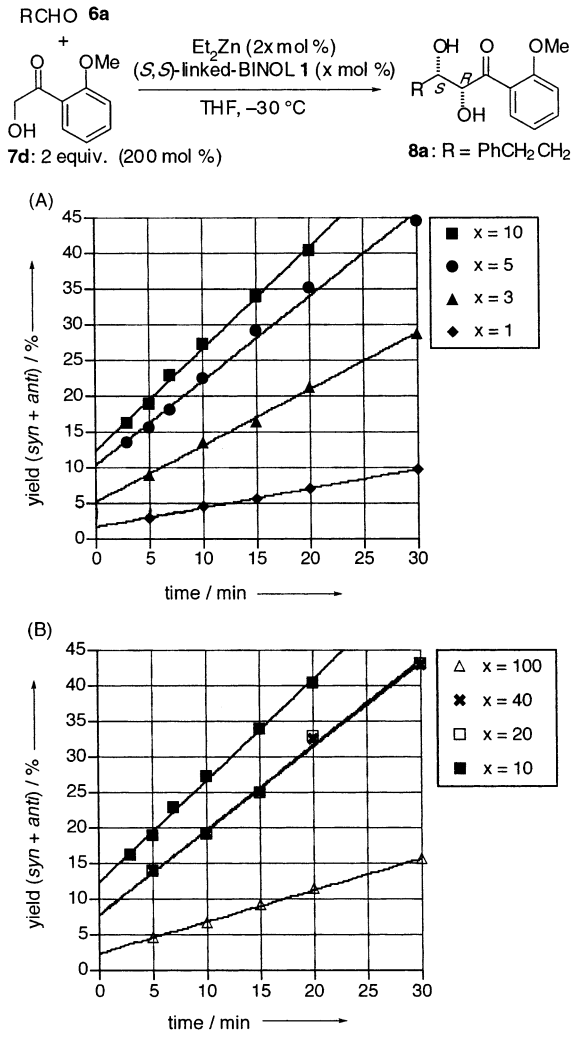


Figure 5. Reaction profile with various catalyst loading.

To support the CSI-MS observations, we performed kinetic experiments as follows. (1) The beneficial effects of excess ketone **7d** were confirmed by measuring the initial rate of the aldol reaction using 1 mol equiv (100 mol %) of **6a**, 2 mol equiv (200 mol %) of **7d**, and varied amounts of ligand **1** and Et_2Zn (Zn/**1** = 2/1). The reaction rate increased as usual when the catalyst loading (based on ligand) increased from $x = 1$ and 3 to 5 mol % (Figure 5A). In contrast, the rate gradually decreased by increasing the catalyst loading (based on ligand)

(25) Three mol equivalents of ethane gas emitted after addition of 2 mol equivalents of Et_2Zn to 1 mol equivalent of ligand **1**. When concentrated H_2SO_4 was added to the mixture, an additional 1 mol equivalent of ethane gas was detected, suggesting that 0.5 mol equivalent of Et_2Zn remained in Et_2Zn/**1** = 2/1 solution.

(26) The theoretical ion distribution pattern derived from Zn isotopes matched nicely with the observed peaks.

(27) 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.

(28) In general, it is true that the observed major species is not always an active species. However, it seems at least sure that some Zn-rich complex should be an actual active species as supported by kinetics in the following paragraph.

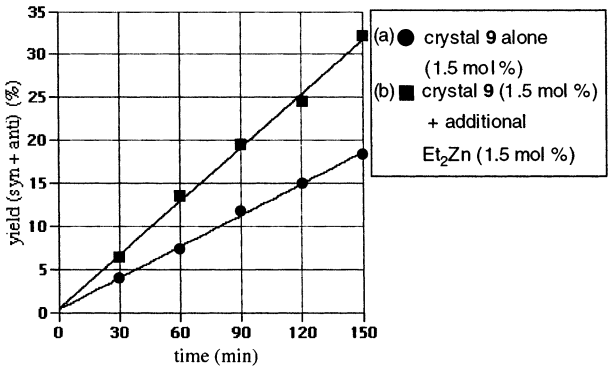


Figure 6. Reaction profile with (a) crystal **9** alone (1.5 mol %) and (b) crystal **9** (1.5 mol %) + additional Et_2Zn (1.5 mol %).

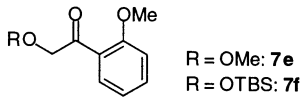


Figure 7. Protected ketone **7e** and **7f**.

from $x = 10$, 20, 40 to 100 mol % (Figure 5B). With too much catalyst loading ($x = 40$ and 100), there was not enough ketone **7d** (200 mol %) to smoothly form the putative active heptanuclear complex. (2) Kinetic profiles of the reaction (a) with only crystal **9** (1.5 mol %) and (b) with **9** (1.5 mol %) and additional Et_2Zn (1.5 mol %) also supported the CSI-MS observations. The aldol reaction of **7d** and **6a** proceeded 1.7 times faster with the additional Et_2Zn (Figure 6, (a) $v_a = 4.06 \times 10^{-6}$ M s^{-1}, (b) $v_b = 6.95 \times 10^{-6}$ M s^{-1}). The results support the idea that Zn-rich species, like heptanuclear complex **10** or **11**, would be the actual active species. Additional Et_2Zn could react with hydroxyketone **7d** to form Zn-alkoxide (Zn-**7d**), and then react smoothly with the preformed trinuclear Zn_3(linked-binol)$_2$ complex **9** to form oligomeric Zn-rich species, increasing the total amount of putative Zn-rich active species. We also hypothesized that Zn-alkoxide (Zn-**7d**) generated from small excess Et_2Zn would accelerate the catalyst turn over step, in which aldol adducts dissociate from catalyst via ligand exchange with ketone **7d** or with the Zn-alkoxide (Zn-**7d**) (details are discussed in Scheme 1, vide infra). In fact, with 2-methoxy-2′-methoxyacetophenone (Figure 7, **7e**) and 2-(*tert*-butyldimethylsilyloxy)-2′-methoxyacetophenone (Figure 7, **7f**), no reaction proceeded after 25 h at −20 °C, and 12 h at 0 °C using 3 mol % of **1** and 6 mol % of Et_2Zn, respectively. The results support our assumption that Zn-alkoxide (Zn-**7d**) has a crucial role to enhance the reaction rate.

The absolute and relative configuration of aldol adducts also provided useful information regarding the mechanism of the present aldol reaction. Identical absolute configuration (*R*) was expressed at the α-position of both the syn- and the anti-aldol products (Figure 8A, *syn*-(2*R*,3*S*), *anti*-(2*R*,3*R*)). Both syn- and anti-isomers were obtained in similarly high ee (>84% ee, see Table 3), suggesting that the present catalyst differentiates the enantioface of the enolate very well and aldehydes come from the Re-face of the zinc enolate (Figure 8A). Syn-selectivity can be explained by assuming the transition state shown in Figure 8B. On the basis of the mechanisms of related bifunctional asymmetric catalysis[3] and related achiral bimetallic zinc catalysts,[21] it seems reasonable to assume a synergistic function of two or more zinc centers in an oligomeric Zn-rich complex. The extreme positive effects of the *ortho*-MeO-group on the ee

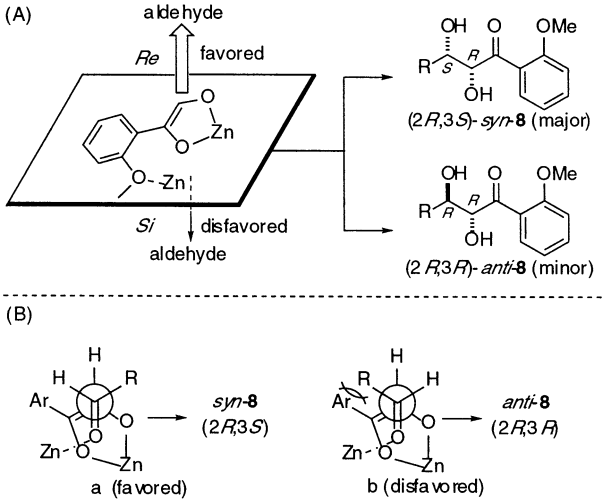
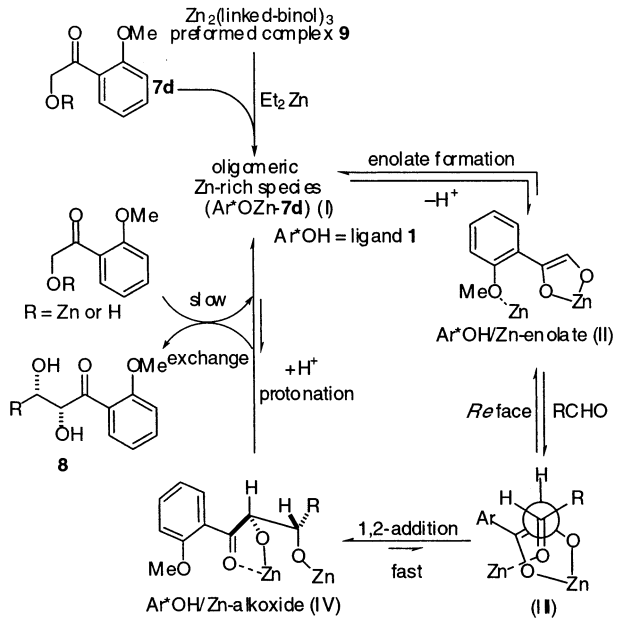


Figure 8. Stereochemical course of the direct aldol reaction of hydroxyketone **7d**.

Scheme 1. Postulated Catalytic Cycle for the Direct Aldol Reaction

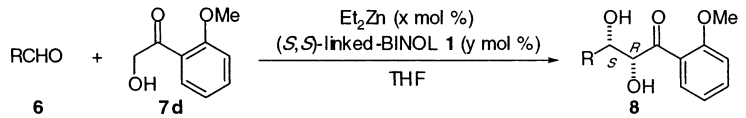


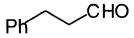
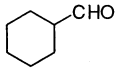
and dr can be rationalized as follows. The MeO-group would coordinate to one of the Zn centers in the oligomeric complex (Figure 8A), increasing the preference of one chelate complex (shielding Si-face) over the other (shielding Re-face). Thus, the shielding Si-face would become more effective, resulting in the higher ee of both the syn- and the anti-products. Enhanced syn-selectivity is explained by the steric hindrance of the aromatic ring in the enolate against aldehydes.

To gain insight into the catalytic cycle of the aldol reaction, initial rate kinetics were surveyed. The reaction was first-order on ketone, first-order on the Et_2Zn/linked-BINOL **1** complex, and, importantly, zero-order on aldehyde.[29] Thus, the possible rate-determining step would be the product dissociation step to regenerate the Zn/linked-BINOL **1**/ketone **7d** oligomeric putative active species.[30] The postulated catalytic cycle for the direct aldol reaction is shown in Scheme 1. In the presence of ketone **7d**, the oligomeric Zn-rich putative active complex (I) would

(29) See Supporting Information for detailed results, including numerical data.

Table 4. Optimization of Direct Aldol Reaction of **7d** with the Second Generation Zn/**1** = 4/1 System



entry	aldehyde R		product		ketone (equiv.)	additive	Et_2Zn (x mol %)	ligand (y mol %)	temp. (°C)	time (h)	yield (%)	dr (*syn*/*anti*)	ee (%) (*syn*)
1			**6a**	**8a**	2	none	2	1	–20	18	92	90/10	93
2			**6a**	**8a**	1.1	none	2	1	–20	18	77	90/10	93
3			**6a**	**8a**	1.1	none	2	0.5	–20	18	78	90/10	93
4			**6a**	**8a**	1.1	MS3A	2	0.5	–20	18	93	89/11	94
5			**6a**	**8a**	1.1	MS3A	1	0.25	–20	18	90	89/11	96
6			**6a**	**8a**	1.1	MS3A	0.4	0.1	–20	36	84	89/11	92
7			**6l**	**8l**	1.1	MS3A	1	0.25	–20	17	92	98/2	96
8[a]			**6l**	**8l**	1.1	MS3A	1	0.25	–20	12	96	98/2	94

[a] Reaction was run on a 200 mmol scale (53.7 g of **8l** was obtained).

be generated, as observed by CSI-MS analysis (I). Zn-binaphthoxide (Ar*O-Zn, Zn-**1** in Scheme 1) would function as a Brønsted base to deprotonate the α-proton in **7d** to form (II). Aldehyde comes from the Re-face of the enolate selectively to be activated by the Lewis acidic zinc center. Initial rate kinetics suggest that the 1,2-addition step proceeds quickly to form (IV). Protonation with the phenolic proton of **1** (Ar*OH) followed by ligand exchange with **7d** would regenerate (I). The catalyst turn over step would be the rate-limiting step. This is consistent with the rate acceleration effects due to small excess Et_2Zn. The Zn-alkoxide (Zn-**7d** complex) should react more smoothly with (IV) through transmetalation than does ketone **7d** itself.[27]

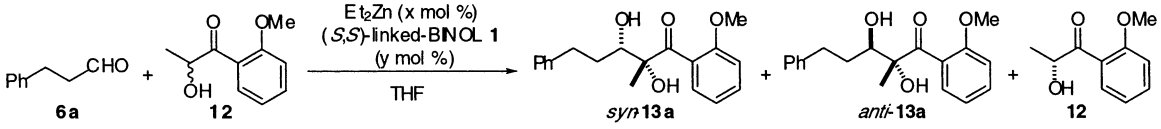
(C) Second Generation Et_2Zn/Linked-BINOL 1 = 4/1 System. Although the exact structure of putative active oligomeric species was not completely clarified, important information to improve the present asymmetric zinc catalysis was obtained through mechanistic studies in section B: (1) The rate-determining step of the present direct aldol reaction was speculated to be the product dissociation step. (2) NMR, CSI-MS, and ethane gas emission analysis revealed that small excess Et_2Zn remained in the Et_2Zn/**1** = 2/1 solution. (3) Kinetic profiles using preformed trinuclear Zn complex **9** with and without additional Et_2Zn suggested that a small excess of Et_2Zn accelerates the reaction rate. Thus, we hypothesized that the addition of more Et_2Zn would lead to better reactivity, maintaining high selectivity. In addition, other additives to accelerate the ligand exchange were also expected to improve the reaction rate and catalyst loading.

With the first generation Zn/**1** = 2/1 system, the aldol reaction proceeded smoothly in the presence of 2 equiv of ketone **7d**; however, the chemical yield decreased to 77% with 1.1 equiv of **7d** (Table 4, entry 1 vs entry 2). We assumed that the amount of ketone loading could be reduced by enhancing the catalyst turn over step. As the first trial, the reaction with a reduced amount of ligand **1** (0.5 mol %) was examined to increase the Zn/**1** ratio (entry 3, Zn/**1** = 4/1, vs entry 2, Zn/**1** = 2/1). As expected, the reaction proceeded to afford product **8a** with the same ee (93%) as in that entry 2, suggesting that no racemic pathway with ligand-free Et_2Zn was involved in entry 3. Considering the efficiency, we found that it is important that the same results (93% ee, yield 78% in entry 3) were obtained with only one-half the amount of chiral ligand; however, the chemical yield with 1.1 equiv of ketone **7d** was still unsatisfactory. To further improve the turn over step, we surveyed various achiral additives to find activated MS 3A as the best additive.[31] MS 3A was used after activation at 160 °C under reduced pressure (ca. 0.7 kPa) for 3 h prior to use. In the presence of MS 3A, the Zn/**1** = 4/1 system promoted the direct aldol reaction of **2a** smoothly using 0.5 mol % (entry 4) or 0.25 mol % (entry 5) of ligand **1** to give **8a** in high yield (entry 4, 93%; entry 5, 90%), good dr (syn/anti = 89/11), and high ee (entry 4, 94%; entry 5, 96%) after 18 h. The reaction also proceeded smoothly with 0.1 mol % ligand loading to afford **8a** in high ee (92% ee), although the reaction time became longer (36 h, 84% yield; entry 6). The optimized conditions were applicable to α-substituted aldehyde **6l** to afford **8l** in high yield, dr, and ee (entry 7, yield 92%, dr = 98/2, 96% ee). To demonstrate the practical utility of the present reaction, a direct aldol reaction was performed on a 200 mmol scale with aldehyde **6l** (entry 8). Using 0.25 mol % of **1** (0.5 mmol, 307 mg), 1 mol % of Et_2Zn (2 mL, 2 mmol, 1.0 M in hexanes), and 1.1 equiv of ketone **7d**, we found that the reaction proceeded smoothly and 53.7 g of **8l** (yield 96%) was obtained in high dr (syn/anti = 98/2) and ee (94% ee) after 12 h. By using the second generation Et_2Zn/(*S*,*S*)-linked-BINOL **1** = 4/1 with MS 3A system, we successfully improved the substrate/chiral ligand ratio from 100 (1 mol % with prior 2/1 system) to 400 to 1000 (0.25−0.1 mol %). This is the most efficient, in terms of catalyst loading, asymmetric catalyst for the direct catalytic asymmetric aldol reaction. Considering that the standard catalyst loading for the direct catalytic asymmetric aldol reaction is 5 to 20 mol %,[4−10] we find that the exceptionally low catalyst loading in the present asymmetric zinc catalysis is remarkable.

(30) Judging from initial rate kinetic data alone, we cannot completely rule out the possibility that the enolization step would be the rate-determining step. Considering the drastic additive effects of MS 3A to accelerate the reaction (see section C: Second Generation System with MS 3A), we believe it more reasonable to assume that the rate-limiting step would be the product dissociation step.

(31) For precedent examples where activated molecular sieves had a key role to accelerate the catalyst turn over step (the product dissociation step), see: Iida, T.; Yamamoto, N.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1997**, *119*, 4783 and references therein.

Table 5. Optimization of Direct Aldol Reaction of 2-Hydroxy-2′-methoxypropiophenone (**12**)



entry	Et_2Zn (x mol %)	ligand **1** (y mol %)	ketone **12** (equiv)	additive	temp (°C)	time (h)	yield (%)	dr (syn/anti)	ee (%) syn	ee (%) anti	ee (%) ketone **12** recovered
1	10	5	2.2	none	−10	24	39	62/38	88	92	26
2	15	5	2.2	none	−10	24	51	62/38	88	93	36
3	20	5	2.2	none	−10	24	65	64/36	84	93	61
4	30	5	2.2	none	−10	24	64	65/35	76	87	60
5	20	10	2.2	none	−10	24	52	67/33	88	92	41
6	20	5	5	none	−10	24	78	64/36	85	91	25
7	20	5	5	MS 3A	−10	6	94	67/33	75	85	31
8	20	5	5	MS 3A	−20	16	97	62/38	87	95	27

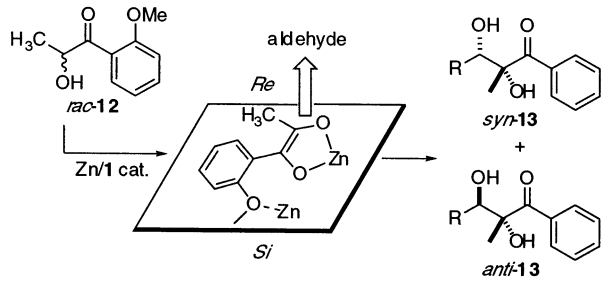
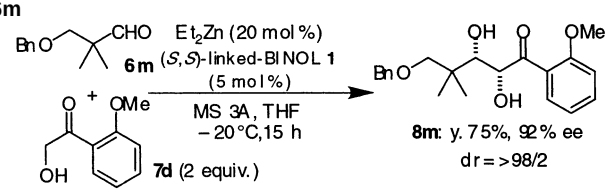


Figure 9. Concept for the construction of a tetrasubstituted carbon stereocenter via direct aldol reaction of hydroxyketone **12**.

Scheme 2. Direct Aldol Reaction of α,α-Disubstituted Aldehyde **6m**



With the new 4/1 with the MS 3A system, aldol adduct **8m** from the sterically hindered α,α-disubstituted aldehyde **6m** was also obtained in excellent dr (>98/2) and high ee (92% ee, Scheme 2). In the case of **6m**, 5 mol % of ligand **1** and 2 equiv of ketone **7d** were necessary to achieve **8m** in moderate chemical yield (75%). Because **8m** was unstable, the aldol adduct was isolated after conversion into acetonide.

(D) Construction of Chiral Tetrasubstituted Carbon Stereocenter. Catalytic asymmetric construction of a chiral tetrasubstituted carbon stereocenter,[32] which is not accessible via asymmetric hydrogenation reactions,[33] 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 (Figure 9, **12**). The aldol reaction of **12** would then afford products with a chiral tetrasubstituted carbon stereocenter (Figure 9).[34] As shown in Table 5, the ratio of Et_2Zn/(*S*,*S*)-linked-BINOL **1** and the addition of MS 3A were important to achieve high yield. With 2.2 equiv of **12**, the aldol reaction of aldehyde **6a** was examined using Et_2Zn/(*S*,*S*)-linked-BINOL **1** = 2/1, 3/1, 4/1, and 6/1 ratio (entries 1−4). The chemical yield increased by increasing the ratio from 2/1 (entry 1, 39%) to 4/1 (entry 3, 65%) to afford **13a** in high ee (entry 3, syn 84% ee, anti 93% ee), albeit with modest diastereoselectivity. With a 6/1 ratio (entry 4), the enantiomeric excess decreased (syn 76% ee, anti 87% ee), probably due to the racemic pathway being promoted by too much excess Et_2Zn. Interestingly, with the same amount of Et_2Zn (20 mol %), less (*S*,*S*)-linked-BINOL **1** afforded a better chemical yield (entry 3, 5 mol % of **1**, yield 65%; entry 5, 10 mol % of **1**, yield 52%), suggesting the effectiveness of the new 4/1 ratio to improve the reactivity. With the optimized Et_2Zn/(*S*,*S*)-linked-BINOL **1** = 4/1 ratio, the chemical yield was improved by using 5 equiv of ketone **12** to afford **13** in 78% yield (entry 6). The addition of activated MS 3A (entries 7−8) further improved reactivity, and the product was obtained in excellent yield (entry 8, 97%) and high ee (entry 8, syn 87% ee, anti 95% ee) at −20 °C.

The optimized reaction conditions, Et_2Zn 20 mol %, (*S*,*S*)-linked-BINOL **1** 5 mol %, and MS 3A, were applied to various α-unsubstituted aldehydes. As shown in Table 6, both linear (entries 1−3) and branched (entry 4) α-unsubstituted aldehydes afforded products in moderate to high yield (72−97%) and in moderate to excellent ee (68−96% ee). Aldehydes with oxygen functionality were also applicable substrates (entries 5−7), and products were obtained in good yield (80−92%) and high ee (85−97% ee). In all cases, diastereoselectivity was moderate (syn/anti = 59/41−71/29). With α-substituted aldehyde **6l**, no reaction proceeded, probably because the aldol adduct **13l** was thermodynamically unfavorable under the reaction conditions.

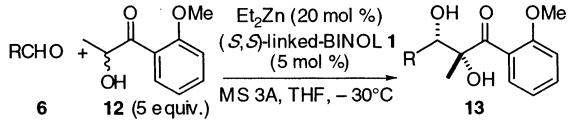
Our investigation to improve diastereoselectivity of the direct aldol reaction of **12** revealed that the heteroatom in the linker part of linked-BINOL affected the diastereoselectivity. With a new (*S*,*S*)-sulfur-linked-BINOL **2**, the aldol reaction of **12** proceeded anti-selectively (Table 7). The synthetic scheme for the new ligand **2** is shown in Scheme 3. Reactivity with **2** was

(32) For a review of catalytic enantioselective synthesis of chiral quaternary centers, see: Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388.

(33) For excellent achievements in catalytic asymmetric hydrogenation of ketones, see review: Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40.

(34) For the construction of a chiral *tert*-OH group at the α-position to the carbonyl group via the diastereoselective aldol reaction using chiral auxiliary, see: (a) Kamino, T.; Murata, Y.; Kawai, N.; Hosokawa, S.; Kobayashi, S. *Tetrahedron Lett.* **2001**, *42*, 5249. For the construction of a chiral *tert*-OH group at the *β*-position to the carbonyl group via kinetic resolution (enantioselective retroaldol reaction) using catalytic antibody, see: (b) List, B.; Shabat, D.; Zhong, G.; Turner, J. M.; Li, A.; Bui, T.; Anderson, J.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **1999**, *121*, 7283.

Table 6. Direct Aldol Reaction of Various Aldehydes with 2-Hydroxy-2′-methoxypropiophenone (**12**)

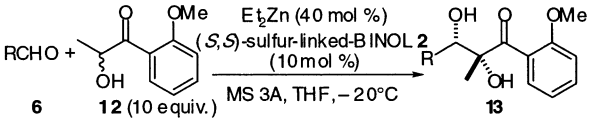


6 12 (5 equiv.) 13

entry	R	product	time (h)	yield[a] (%)	dr[b] (*syn*/*anti*)	ee (*syn*/*anti*)
1	Ph–CHO (6a)	**13a**	16	97	62/38	87/96
2	Ph–CHO (6o)	**13o**	19	72	64/36	78/90
3	CHO (6p)	**13p**	12	88	71/29	68/86
4	CHO (6d)	**13d**	10	80	68/32	72/87
5	PMBO–CHO (6q)	**13q**	13	89	59/41	86/95
6	BOMO–CHO (6i)	**13i**	10	92	69/31	87/97
7	BnO–CHO (6h)	**13h**	18	80	65/35	85/92
8	CHO (6l)	**13l**	24	0	—	—

[a] Isolated yield. [b] Determined by ^{1}H NMR of mixture (entries 1−3, 5−7), determined after isolation (entry 4).

Table 7. Direct Aldol Reaction with 2-Hydroxy-2′-methoxypropiophenone (**12**) Using (*S*,*S*)-Sulfur-linked-BINOL **2**



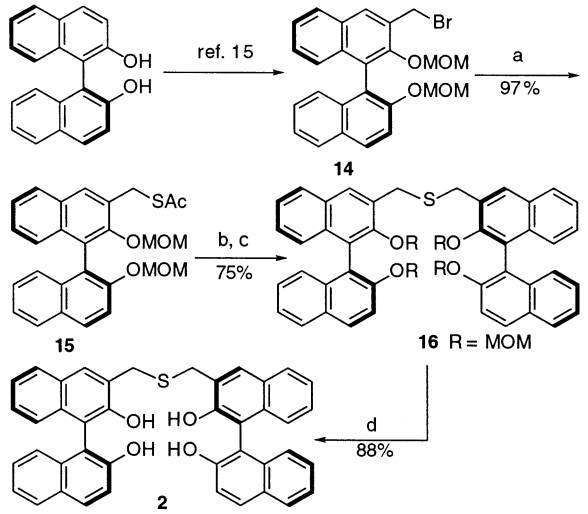
6 12 (10 equiv.) 13

entry	R	product	time (h)	yield[a] (%)	dr[b] (*syn*/*anti*)	ee (*syn*/*anti*)
1	Ph–CHO (6a)	**13a**	45	82	35/65	60/92
2	Ph–CHO (6o)	**13o**	24	63	41/59	45/86
3	CHO (6p)	**13p**	24	56	41/59	48/87
4	PMBO–CHO (6q)	**13q**	24	73	41/59	58/93
5	BOMO–CHO (6i)	**13i**	24	72	39/61	52/81

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

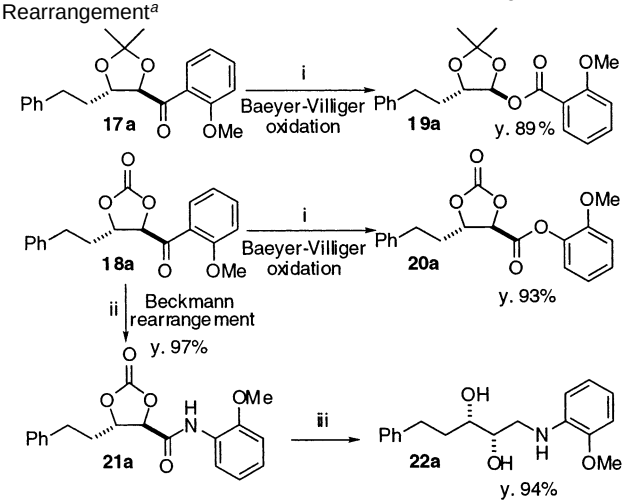
somewhat lower than that with **1**, and aldol adducts were obtained in moderate to good yield (56−82%) by using 10 equiv of **12**. Major anti-isomers were obtained in high ee (81−93% ee), although the ee of minor syn-isomers was rather low (48−60% ee). We believe that heteroatoms in the linker would coordinate to the Zn atom, affecting the structure of the putative active oligomeric complex. It is difficult to explain precisely the effect of heteroatoms in the linker, however, because the exact structure of the putative oligomeric active species is not clarified yet.

Scheme 3. Synthesis of a New (*S*,*S*)-Sulfur-linked-BINOL **2**[a]



[a] (a) AcSK, DMF, 0 °C, 10 min, 97%; (b) NaOMe, MeOH, THF 0 °C, 5 min; (c) **14**, NaH, THF, 0 °C, 30 min, 75% (two steps); (d) TsOH·H_2O, CH_2Cl_2, MeOH, 40 °C, 12 h, 88%.

Scheme 4. Transformations of Aldol Adducts via Regioselective Rearrangement[a]



[a] (i) *m*CPBA, NaH_2PO_4, $ClCH_2CH_2Cl$, 50 °C, 2 h; (ii) *O*-mesitylenesulfonylhydroxylamime, CH_2Cl_2, room temperature, 4 h; (iii) DIBAL, −78 °C to room temperature, 2 h.

(E) Transformation of Aldol Adducts. As mentioned previously, the usefulness of the aldol adducts becomes much higher by assuming the 2-methoxyphenyl moiety as a placeholder for further conversions. As shown in Scheme 4, the Baeyer−Villiger oxidation proceeded smoothly by treating the ketones **17a** and **18a** with *m*CPBA, probably with the aid of neighboring oxygen atoms. Interestingly, benzoate **19a** was obtained in 89% yield when acetonide **17a** was used. On the other hand, phenyl ester **20a** was obtained in 93% yield when carbonate analogue **18a** was subjected to the same conditions. In both cases, no regioisomer was observed. Furthermore, **18a** afforded amide **21a** exclusively in 97% yield in one step via Beckmann rearrangement with *O*-mesitylenesulfonylhydroxylamine (MSH).[35] The amide **21a** was readily transformed into **22a** by reduction with DIBAL. The *ortho*-MeO-phenyl group of **22a** can be regarded as an oxidatively removable protecting group of amine.[36]

(35) Tamura, Y.; Fujiwara, H.; Sumoto, K.; Ikeda, M.; Kita, Y. *Synthesis* **1973**, 215.

Summary

We successfully developed new highly efficient direct catalytic asymmetric aldol reactions of hydroxyketones by catalysis with asymmetric zinc complexes as mimics of zinc metalloenzymes (class II aldolases). The first generation Et_2-Zn/linked-BINOL **1** = 2/1 system was initially developed, which promoted the direct aldol reaction of 2-hydroxy-2′-methoxy-acetophenone (**7d**) with 1 mol % ligand loading. Through mechanistic studies using X-ray, NMR, CSI-MS, and kinetic experiments, the role of a small excess of Et_2Zn to accelerate the catalyst turn over step was revealed. On the basis of mechanistic studies, the second generation Et_2Zn/linked-BINOL **1** = 4/1 with MS 3A was developed as a much more efficient system. With the new system, as little as 0.1 mol % of ligand and 0.4 mol % of Et_2Zn efficiently promoted the aldol reaction in the presence of only 1.1 equiv of ketone **7d**. This is the most efficient, in terms of catalyst loading, asymmetric catalyst for direct catalytic asymmetric aldol reactions (substrate/chiral ligand = 1000). The new system was also applicable to the direct aldol reaction of 2-hydroxy-2′-methoxypropiophenone (**12**) to afford products with a tetrasubstituted carbon stereocenter in good yield (up to 97%) and ee (up to 97% ee), although diastereoselectivity was still unsatisfactory. The reaction provided a new method to synthesize chiral *tert*-alcohol with a small molecular chiral catalyst. Application of the present efficient asymmetric zinc catalysis to other asymmetric reactions such as direct aldol and Mannich reactions of unmodified esters is currently underway in our group.

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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.

JA028926P

(36) (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.