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Enantioselective 1,4-Addition of Unmodified Ketone Catalyzed by a Bimetallic Zn–Zn-Linked–BINOL Complex

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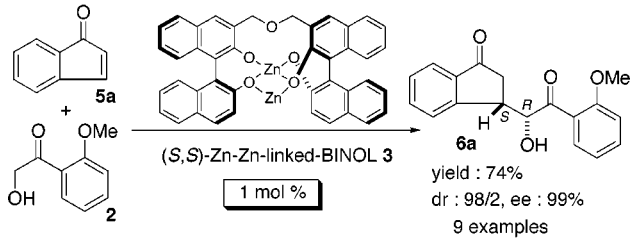
ABSTRACT



1,4-Addition (Michael addition) of 2-hydroxy-2′-methoxyacetophenone (2) to various α,β-unsaturated ketones was efficiently promoted by a bimetallic Zn–Zn-linked–BINOL complex 3 with good yield (up to 90%) and excellent enantiomeric excess (up to 99% ee). The resulting 2-hydroxy-1,5-diketones were successfully converted to synthetically more versatile esters and amides.

The catalytic asymmetric carbon−carbon bond formation is a major focus of modern synthetic organic chemistry.[1] Moreover, the increasing demand for efficient and environmentally benign processes requires the development of atom economic[2] asymmetric catalysis in which enantiomerically enriched compounds are produced using unmodified substrates. Toward this end, we[3] and others[4,5] successfully demonstrated *direct* catalytic asymmetric aldol reactions that utilize unmodified ketones as donors. In contrast to these promising results[6] with aldol reactions, however, *direct* catalytic asymmetric 1,4-addition reactions of unmodified ketones are very rare[7] despite their importance in synthetic organic chemistry in providing 1,5-dicarbonyl chiral building blocks.[8,9] Thus, development of the direct catalytic asym-

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

(3) 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.

(4) 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. For a partially successful attempt, see: (g) Nakagawa, M.; Nakao, H.; Watanabe, K.-I. *Chem. Lett.* **1985**, 391. Unmodified α-hydroxyketones as donors: (h) The use of α-hydroxyketones with chemical catalysts has been pioneered by List et al.: Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386. (i) Trost, B. M.; Ito, H.; Silcoff, E. R. *J. Am. Chem. Soc.* **2001**, *123*, 3367. See, also ref 4d.

(5) 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.

(6) For other promising atom economic asymmetric catalysis, see: Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc*. **2001**, *123*, 9687.

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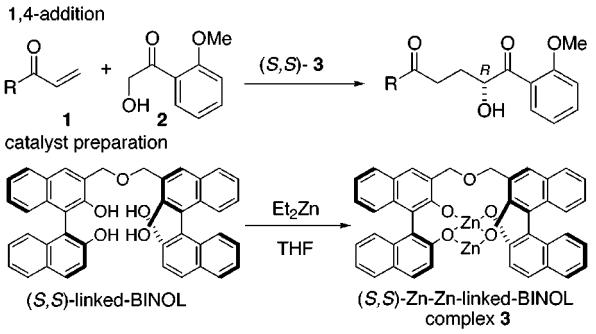
metric 1,4-addition reaction of unmodified ketones, which has high reactivity and selectivity, is in high demand. Herein, we report the enantioselective 1,4-addition of unmodified hydroxyketone **2** catalyzed by a bimetallic Zn−Zn-linked−BINOL complex **3** (Scheme 1).[3f,3g,10,11] The reaction provides

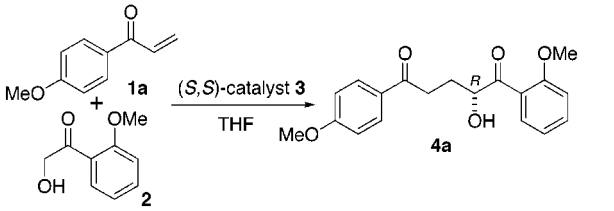
Scheme 1. 1,4-Addition of Unmodified Hydroxyketone **2** to Enones Catalyzed by (*S*,*S*)-Zn−Zn-linked-BINOL Complex **1**



direct access to optically active 2-hydroxy-1,5-diketones in a highly enantioselective manner (91−99% ee). The usefulness of the products was further exemplified by facile transformations into synthetically versatile esters and amides by regioselective rearrangements.

In our continuing investigations of the direct catalytic asymmetric aldol reaction, the dinuclear Zn−Zn-linked−BINOL complex **3** was determined to be very effective for shielding one enantioface of enolate generated from 2-hydroxy-2′-methoxyacetophenone (**2**),[12] affording a practical method to provide *syn*-1,2-dihydroxyketones through the aldol reaction of **2** with various aldehydes. Thus, we investigated the catalytic asymmetric 1,4-addition reaction using **3** as a catalyst and **2** as a donor. As shown in Table 1,

Table 1. 1,4-Addition of 2′-Hydroxy-2-methoxyacetophenone (**2**) to *p*-Methoxyphenyl Vinyl Ketone (**1a**)



entry	ketone **2** (equiv)	catalyst (mol %)	temp. (°C)	time (h)	yield[a] (%)	ee[b] (%)
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	5	rt	1	86	91
6	2	3	−20	14	90	96
7	2	1	−20	30	84	97
8	2	1	4	8	83	95

[a] Isolated yield. [b]Determined by chiral HPLC analysis.

5 mol % of **3** efficiently promoted the 1,4-addition of **2** to *p*-methoxyphenyl vinyl ketone **1a** 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 **2** from 2.0 equiv to 1.1 equiv (entry 2), the reaction rate and chemical yield decreased somewhat (14 h, 72% yield), while high enantiomeric excess was maintained (97% ee). Reaction temperature greatly affected the reaction rate. By decreasing the reaction temperature to −30 °C (entry 3), higher enantiomeric excess was obtained (98% ee), but a prolonged reaction time was necessary. At a higher temperature (entry 4: 4 °C and entry 5: rt), a drastic improvement in the reaction rate was observed. The reaction reached completion after 3 h (entry 4) and 1 h (entry 5), respectively, while maintaining a high enantiomeric excess (91% ee). Good yield and excellent enantiomeric excess were obtained even when the catalyst loading was decreased from 5 mol % to either 3 or 1 mol % (entries 6 and 7, respectively) The reaction rate dropped significantly, however, at −20 °C. Finally, as shown in entry 8, the reaction was completed within 8 h to afford **4a** in 83% yield and 95% ee with as little as 1 mol % catalyst at 4 °C.

(7) (a) Zhang, F.-Y.; Corey, E. J. *Org. Lett.* **2000**, *2*, 1097. (b) Betancort, J. M.; Sakthivel, K.; Thayumanavan, R.; Barbas, C. F., III. *Tetrahedron Lett.* **2001**, *42*, 4441. (c) List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423. Unmodified aldehyde as a donor: (d) Betancort, J. M.; Barbas, C. F., III. *Org. Lett.* **2001**, *3*, 3737.

(8) 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.

(9) 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 malonates: (f) Yamaguchi, M.; Shiraishi, T.; Hirama, M. *J. Org. Chem.* **1996**, *61*, 3520. *β*-Keto esters: (g) Ji, J.; Barnes, D. M.; Zhang, J.; King, S. A.; Wittenberger, S. J.; Morton, H. E. *J. Am. Chem. Soc.* **1999**, *121*, 10215. α-Cyano esters: (h) Sawamura, M.; Hamashima, H.; Ito, Y. *Tetrahedron* **1994**, *50*, 4439. Zn reagents: (i) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346. B reagents: (j) Hayashi, T. *Synlett* **2001**, 879. See also, ref 8, 10b and references therein.

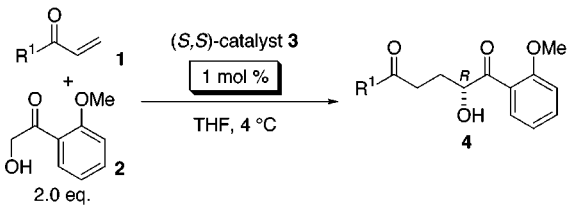
(10) For catalytic asymmetric syntheses using linked−BINOL as a chiral ligand, see: (a) Matsunaga, S.; Das, J.; Roels, J.; Vogl, E. M.; Yamamoto, N.; Iida, T.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 2252. (b) Kim, Y. S.; Matsunaga, S.; Das, J.; Sekine, A.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 6506. (c) Matsunaga, S.; Ohshima, T.; Shibasaki, M. *Tetrahedron Lett.* **2000**, *41*, 8473. (d) Matsunaga, S.; Ohshima, T.; Shibasaki, M. *Adv. Synth. Catal.*, in press, and references therein. See also refs 3f and 3g.

(11) For other chiral bimetallic Zn catalysts, see refs 4b, 4e, 4i and references therein.

(12) **2** was prepared from commercially available 2′-methoxyacetophenone via α-hydroxylation with $C_6H_5I(OAc)_2$ and NaOH in CH_3OH. (a) Moriarty, R. M.; Hu, H.; Gupta, S. C. *Tetrahedron Lett.* **1981**, *22*, 1283. (b) Togo, H.; Abe, S.; Nogami, G.; Yokoyama, M. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2351.

The optimized reaction conditions were applicable to various vinyl ketones **1**,[13] which usually tend to polymerize under harsh reaction conditions (Table 2). Because of the

Table 2. 1,4-Addition of 2-Hydroxy-2′-methoxyacetophenone (**2**) to Various Vinyl Ketones **1**[a]



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

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

mild basicity of Zn−Zn-linked−BINOL complex **3**, 1,4-addition of **2** proceeded smoothly with only a small amount of polymerization. Aryl vinyl ketones with and without substituents on the aromatic ring were successfully converted to corresponding 1,4-adducts in good chemical yield (83−90%) and enantiomeric excess[14] (92−95% ee) (entries 2−4). Alkyl vinyl ketones **1e** and **1f** also afforded the desired 1,4-adducts in good yield and enantiomeric excess (entries 5, 6).

With indenone **5a**,[15] good diastereomeric ratio (dr) and excellent enantiomeric excess were observed at 4 °C (Table 3, entry 1: 98% 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 % catalyst loading, the chemical yield was slightly improved (entry 3: 80% yield). The relative configuration of **6a** was determined by X-ray crystallography.[16] 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).

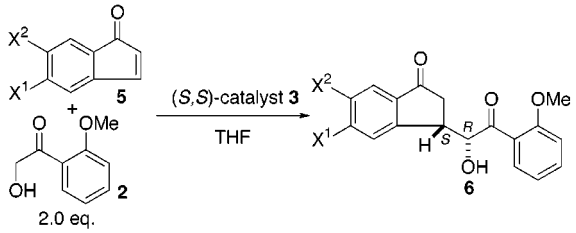
(13) Beracierta, A. P.; Whiting, D. A. *J. C. S. Perkin Trans. 1* **1978**, 1257.

(14) **General procedure**: To a stirred solution of (*S*,*S*)-linked−BINOL (0.01 mmol) in THF (0.3 mL) at −78 °C was added Et_2Zn (20 μL, 0.02 mmol, 1.0 M in hexanes). The resulting mixture was stirred for 30 min at −20 °C, and a solution of **2** (2.0 mmol) in THF (2.0 mL) was added. After the mixture was warmed to 4 °C, **1a** (1.0 mmol) was added and the reaction mixture was stirred for 8 h at 4 °C, followed by addition of saturated aqueous NH_4Cl. The mixture was extracted with ethyl acetate (× 3), and the combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash silica gel column chromatography (hexane/acetone 6/1) to afford **4a** (272.5 mg, 0.829 mmol, 83%).

(15) Hauser, F. M.; Zhou, M.; Sun, Y. *Synth. Commun.* **2001**, *31*, 77.

(16) See Supporting Information.

Table 3. 1,4-Addition of 2-Hydroxy-2′-methoxyacetophenone (**2**) to Indenones **5**[a]



entry	X^1	X^2	enone	product	catalyst (mol %)	temp (°C)	time (h)	yield[b] (%)	dr[c]	ee[d] (%)
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 1 mmol scale (entry 1−3, 6) or on 0.5 mmol scale (entry 4, 5) at 0.25 M (entry 2, 3, 4, 6) or at 0.4 M (entry 1, 4) in **5**. [b]Isolated yield. [c]Determined by ^1H NMR analysis of crude mixture. [d]Determined by chiral HPLC analysis.

The relative and absolute configurations of the 1,4-adducts[17] can be explained in a similar manner as those of the previous direct aldol reaction with **3**.[3f,3g] The bimetallic Zn complex **3** functions as Brønsted base to generate a Zn-enolate from 2-hydroxy-2′-methoxyacetophenone (**2**). The formation of a chelate complex between the (*S*,*S*)-catalyst **3** and the enolate, including the participation of the 2′-methoxy group in a chelate formation (Figure 1),[18] would result in an

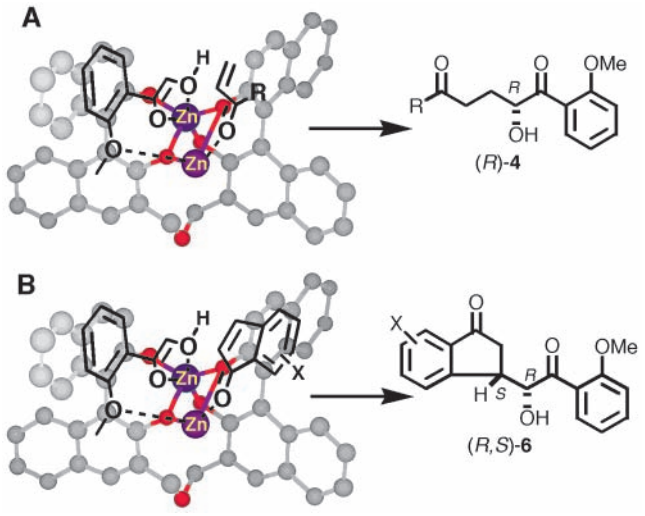


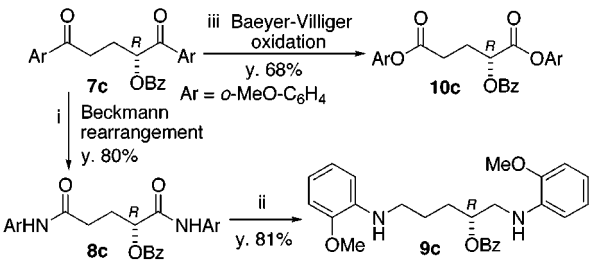
Figure 1. Working model for transition state.

efficient shielding of the *Si*-face of the enolate. Considering the steric repulsion between the enolate and enones, the enones **1** and **5** seem to coordinate to the other Zn metal as

in manner A and B, affording (*R*)-**4** and (*R,S*)-**6** respectively (Figure 1).

To demonstrate the utility of the 1,4-adducts as chiral building blocks, several transformations were performed via regioselective rearrangements. As shown in Scheme 2, the

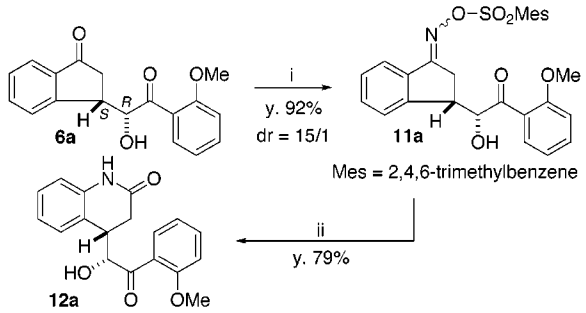
Scheme 2. Transformation of 1,4-Adduct via Regioselective Rearrangement[a]



[a] (i) *O*-mesitylenesulfonylhydroxylamine, CH_2Cl_2, rt, 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.

Beckmann rearrangement of benzoate **7c**[19] with *O*-mesitylenesulfonylhydroxylamine (MSH)[20] gave 1,5-diamide **8c** in 80% yield. The subsequent DIBAL reduction of **8c** afforded **9c** in 81% yield. The *o*-methoxyphenyl group in **9c** acts as a protecting group for amine, which is removable by oxidative cleavage.[21] On the other hand, Baeyer−Villiger oxidation of benzoate **7c** with *m*CPBA regioselectively gave 1,5-diester **10c** in 68% yield with the aid of electron-donating groups on the aromatic rings. As shown in Scheme 3, treatment of **6a** with MSH gave oxime mesitylenesulfonate **11a** in 92% yield as a 15/1 diastereomixture.[22] **11a** was

Scheme 3. Transformation of **6a** into Lactam **12a**[a]



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

unusually stable and treatment of **11a** either with basic alumina or with silica gel resulted only in recovery of **11a** even at an elevated temperature. Rearrangement of **11a** proceeded smoothly in the presence of $AlCl_3$[23] to give lactam **12a** in 79% yield. The optically active lactam **12a** should be useful for synthesizing various biologically interesting compounds.

In conclusion, we achieved a highly enantioselective 1,4-addition reaction of unmodified hydroxyketone **2** to enones, which leads to optically active 2-hydroxy-1,5-diketones. It is noteworthy that the reaction was efficiently catalyzed by as little as 1 mol % of Zn−Zn-linked−BINOL complex **3**, affording the 1,4-adducts in good yield (up to 90%), excellent enantiomeric excess, and diastereomeric ratio (up to 99% ee, dr = 98/2). The 1,4-adducts were successfully converted to the synthetically more versatile ester and amide. Further investigation on the substrate scope, reaction mechanism, and catalyst structure is currently in progress.

Acknowledgment. We thank Prof. S. Kobayashi, Mr. R. Akiyama, and Mr. H. Usuda at the University of Tokyo for their generous support in X-ray crystallographic analysis of **6a**. We thank RFTF for financial support.

Supporting Information Available: Experimental procedures, characterization data for products **4**, **6**−**10**, **12** and the CIF file for **6a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) The absolute configurations of **4c** and **6a** were determined by Mosher's method. Those of others were temporarily determined by analogy. (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

(18) The chelate complex formation through the coordination of 2′-methoxy group was essential to achieve high ee in the direct aldol reaction of **2** and aldehydes. See ref 3h.

(19) The benzoate **7c** was prepared by treating **4c** with benzoyl chloride. See Supporting Information.

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

(21) (a) Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. C. *J. Am. Chem. Soc.* **2001**, *123*, 10409. (b) Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. C. *J. Am. Chem. Soc.* **2001**, *123*, 984. (c) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 8180 and references therein.

(22) Determined by ^{1}H NMR analysis of isolated product.

(23) Tanga, M. J.; Reist, E. J. *J. Heterocycl. Chem.* **1986**, *23*, 747.