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Direct Catalytic Enantio- and Diastereoselective Aldol Reaction Using a Zn–Zn-Linked-BINOL Complex: A Practical Synthesis of *syn*-1,2-Diols

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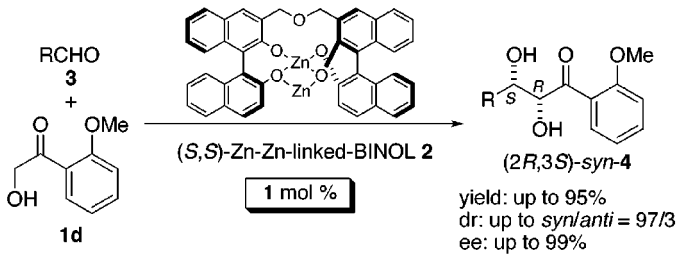
ABSTRACT



The direct catalytic enantio- and diastereoselective aldol reaction with 2-hydroxy-2′-methoxyacetophenone proceeded smoothly using as little as 1 mol % of a dinuclear zinc catalyst, Zn–Zn-linked-BINOL complex 2, to afford α,β-dihydroxy ketones in a highly *syn*-selective manner (up to *syn*/*anti* 97/3) and in excellent yields (up to 95%) and ees (up to 99%). Efficient transformations of the α,β-dihydroxy ketone into an α,β-dihydroxy ester and an α,β-dihydroxy amide via regioselective rearrangements are also described.

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 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 by using no less than stoichiometric amounts of reagents. Since our success in carrying out direct catalytic asymmetric aldol reactions with unmodified ketones,[2] this potentially advantageous strategy has attracted much interest in terms of atom economy.[3] List et al.[4] and Trost et al.[5] reported direct asymmetric aldol reactions using L-proline or a chiral semi-crown Zn complex as catalysts. Moreover, recently several groups reported enantio- and diastereoselective direct aldol reactions using biological-type catalysts[6] or small molecular catalysts,[7,8] which considerably widened the scope of this field. We also reported an enantio- and diastereoselective direct aldol reaction with 2-hydroxyacetophenone (**1a**), which provided

(1) For a general review on the catalytic enantioselective aldol reaction, see: (a) Carreira, E. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Heidelberg, 1999; Vol. 3, Chapter 29.1. (b) Machajewski, T. D.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352. (c) Gröger, H.; Vogl, E. M.; Shibasaki, M. *Chem. Eur. J.* **1998**, *4*, 1137. (d) Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, *9*, 357. See also: (e) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325.

(2) (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. For a partially successful attempt, see: (e) Nakagawa, M.; Nakao, H.; Watanabe, K.-I. *Chem. Lett.* **1985**, 391.

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

(4) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395.

(5) Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003.

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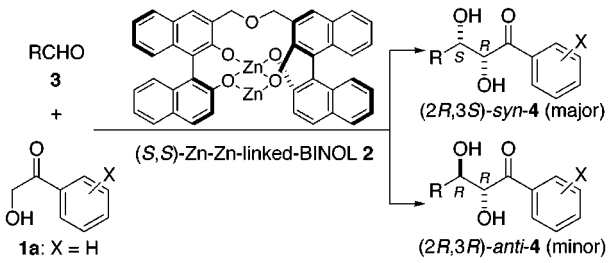
either the *anti*- or the *syn*-α,β-dihydroxy ketones when using two different catalysts, a $LaLi_3$tris(binaphthoxide)·KOH (LLB·KOH) complex (*anti* selective) or Zn−Zn-linked-BINOL complex **2** (Scheme 1, *syn* selective).[9] In the case

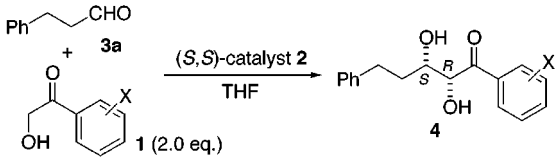
Scheme 1. *syn*-Selective Direct Catalytic Asymmetric Aldol Reaction Using (*S*,*S*)-Zn−Zn-Linked-BINOL Complex **2**



of the aldol reaction catalyzed by **2**, however, there remained much room to be improved in respect to catalyst amount (10 mol %), diastereomeric ratio (*syn*/*anti* = 2/1 to 7/1), enantiomeric excess (77−86% for *syn* isomer), reaction rate, and yield. Herein, we now report the great improvement of the *syn*-selective direct catalytic asymmetric aldol reaction in all aspects mentioned above by modifying the donor substrate. In addition, efficient further transformations of the aldol adduct into an ester and an amide via regioselective rearrangements, enhancing the utility of the present reaction, are also reported.

On the basis of our previous results,[10] we supposed that substituents on the aromatic ring of acetophenones should affect both diastereoselectivity and enantioselectivity. 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,[11] because the aromatic ring functions as a placeholder for further conversions via regioselective rearrangements. By using electron-rich methoxy-substituted acetophenones, conversions such as a Baeyer−Villiger oxidation would become facile. We first investigated the direct aldol reaction of 3-phenylpropanal (**3a**) using methoxy-substituted 2-hydroxyacetophenones **1b**−**1d** (Table 1). The aldol adducts were

Table 1. Direct Aldol Reaction of **3a** with Methoxy-Substituted 2-Hydroxyacetophenone **1** Catalyzed by (*S*,*S*)-Zn−Zn-Linked-BINOL **2**[a]



entry	X		catalyst (mol %)	temp (°C)	time (h)	yield[b] (%)	dr[c] (*syn*/*anti*)	ee[d] (*syn*/*anti*)
1	H	**1a**	10	−40	48	81	67/33	78/76
2	4′-MeO	**1b**	10	−20	24	73	60/40	86/86
3	3′-MeO	**1c**	10	−30	12	85	70/30	77/77
4	2′-MeO	**1d**	10	−30	3	93	89/11	86/88
5[e]	2′-MeO	**1d**	10	−30	3	93	86/14	86/77
6	2′-MeO	**1d**	3	−30	4	94	90/10	90/89
7	2′-MeO	**1d**	1	−30	20	94	89/11	92/89
8	2′-MeO	**1d**	1	−30	16	94	87/13	93/91

[a] Reactions were run on a 0.30 mmol scale (entry1−5), a 0.67 mmol scale (entry 6), a 1.0 mmol scale (entry 7), and an 8.0 mmol scale (1.05 g of **3a**, entry 8) 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. [e] In the presence of $Ph_3P(O)$ (20 mol %).

isolated after their conversion into the corresponding acetonides.[12] In the case of 2-hydroxy-4′-methoxyacetophenone (**1b**), the reaction was run at −20 °C due to the poor solubility of **1b**. Although a slightly higher ee was obtained, dr and yield were lower than those in the case of **1a** (entry 2). In the case of 2-hydroxy-3′-methoxyacetophenone (**1c**), the reaction was run at −30 °C. Yield, dr, and ee were comparable with those of **1a** and the reaction rate increased (entry 3). Gratifyingly, the reaction rate, yield, dr, and ee all were improved when using 2-hydroxy-2′-methoxyacetophenone (**1d**) (entry 4). In contrast to the case of **1a**,[13] $Ph_3P(O)$ as an additive had no positive effects (entry 5). It is noteworthy that the aldol reaction of **1d** still proceeded smoothly even when the catalyst amount was reduced. The reaction was completed within 4 h with 3 mol % of catalyst **2** (entry 6). 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 **2** (entry 7), and the reaction proceeded smoothly without any problem on a gram scale (entry 8). To the best of our knowledge, in terms of catalyst loading, this is the most effective small molecular catalyst for direct asymmetric aldol reactions. In combination with the successful gram scale experiment, the simple protocol proves the present reaction to be practically useful. The catalyst was prepared by just mixing commercially available Et_2Zn in hexanes and easily available linked-BINOL[14] in THF without any other additives, followed by the addition of ketone **1d** and the aldehyde.[15]

(6) For the synthesis of *syn*- or *anti*-1,2-diols by aldolases or catalytic antibodies, see: (a) Bednarski, M. D.; Simon, E. S.; Bischofberger, N.; Fessner, W.-D.; Kim, M.-J.; Lees, W.; Saito, T.; Waldmann, H.; Whitesides, G. M. *J. Am. Chem. Soc.* **1989**, *111*, 627. (b) Fessner, W.-D.; Sinerius, G.; Schneider, A.; Dreyer, M.; Schulz, G. E.; Badia, J.; Aguilar, J. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 555. (c) List, B.; Shabat, D.; Barbas, C. F., III.; Lerner, R. A. *Chem. Eur. J.* **1998**, *4*, 881. (d) Hoffmann, T.; Zhong, G.; List, B.; Shabat, D.; Anderson, J.; Gramatikova, S.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **1998**, *120*, 2768.

(7) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386.

(8) Trost, B. M.; Ito, H.; Silcoff, E. R. *J. Am. Chem. Soc.* **2001**, *123*, 3367.

(9) Yoshikawa, N.; Kumagai, N.; Matsunaga, S.; Moll, G.; Ohshima, T.; Suzuki, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 2466.

(10) For the direct catalytic asymmetric aldol reaction of acetophenones promoted by the LLB·KOH complex, the use of 3′-nitroacetophenone was effective in some cases. See ref 2b.

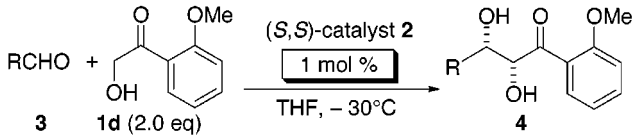
(11) The use of hydroxyacetone gave unasatisfactory results with Zn−Zn-linked-BINOL **2**. Further studies are currently under investigation.

(12) No change of ee and dr was observed. For detailed procedures, see Supporting Information. Isolation of diols was also possible.

(13) When **1a** was used as the donor, $Ph_3P(O)$ had positive effects. The result in the presence of $Ph_3P(O)$ (20 mol %): −40 °C, 48 h, yield 89%, *syn*/*anti* = 72/28, *syn* = 81% ee, *anti* = 81% ee. See ref 9.

Zn−Zn-linked-BINOL **2** was also applicable to various primary (α-unsubstituted) and secondary (α-monosubstituted) aldehydes (Table 2). In all cases, 1 mol % of catalyst **2** was

Table 2. Direct Aldol Reaction of Various Aldehydes with 2-Hydroxy-2′-methoxyacetophenone (**1d**)[a]



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

sufficient to complete the reaction within 24 h.[16] Both normal (entry 1−3 and 5−7) and branched (entry 4) primary aldehydes afforded good results (yield, 81−94%, dr, *syn*/*anti* = 72/28 to 88/12; ee, *syn* = 87−96%, *anti* = 87−93%). It should be mentioned that primary (α-unsubstituted) aldehydes gave the corresponding aldol adducts in good to excellent yields and ees without forming any self-condensation products. The results indicate the high chemoselectivity of the present catalysis. In the case of *trans*-4-decenal (**3e**, entry 5), the synthesis of the corresponding diol **4e** via Sharpless asymmetric dihydroxylation (AD)[17] may be difficult due to the chemoselectivity issue. Aldehydes with oxygen functionalities such as **3f** (entry 6) and **3g** (entry 7), which lead to useful intermediates for the synthesis of polyoxygenated compounds, were also converted into diols in excellent ee (*syn*: 95% in entry 6 and 96% in entry 7). Remarkably, secondary (α-monosubstituted) aldehydes (entry 8−10) showed good yield (83−95%) and excellent dr (*syn*/*anti* = 96/4 to 97/3) and ee (98−99%).

The relative and absolute configurations of the *syn*-aldol adducts **4** ((2*R*,3*S*) from (*S*,*S*)-catalyst **2**, Scheme 1) were determined by comparison with authentic samples prepared by Sharpless AD. The absolute configurations of the *anti*-aldol adducts **4** ((2*R*,3*R*) from (*S*,*S*)-catalyst **2**, Scheme 1) were analyzed after epimerization of the acetonides.[18] The observed stereoselectivity obtained with ketone **1d** is well explained by assuming the following reaction mechanism. The formation of a chelate complex between the (*S*,*S*)-catalyst **2** and the enolate generated from **1d** would result in an efficient shielding of the *Si*-face of the enolate (Figure 1), so that both *syn*- and *anti*-aldol adducts were obtained

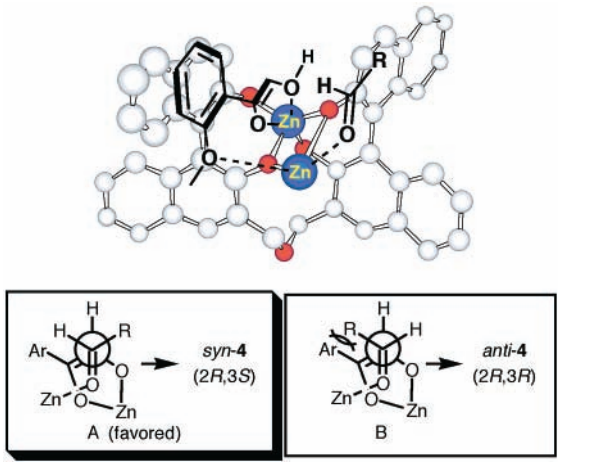


Figure 1. Working model for transition state.

with an identical configuration at the α-position (2*R*) after the attack toward the aldehyde. Moreover, the electron-donating substituent (methoxy group) on the aromatic ring should increase the preference of one chelate complex (shielding *Si*-face) to the other (shielding *Re*-face) through

(14) For catalytic asymmetric syntheses using linked-BINOL as ligand, see: ref 9 and the following: (a) Matsunaga, S.; Das, J.; Roels, J.; Vogl, E. M.; Yamamoto, N.; Iida, T.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 2252−2260. (b) Kim, Y. S.; Matsunaga, S.; Das, J.; Sekine, A.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 6506−6507. (c) Matsunaga, S.; Ohshima, T.; Shibasaki, M. *Tetrahedron Lett.* **2000**, *41*, 8473−8478 and references therein.

(15) **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 **1d** (2.0 mmol) in THF (4.7 mL) was added. After the mixture was cooled to −30 °C, **3a** (1.0 mmol) was added and the reaction mixture was stirred for 20 h, followed by addition of 1 M HCl. The mixture was extracted with ethyl acetate, and the combined organic layers were washed with brine and dried over Na_2SO_4. Evaporation of solvent gave a crude mixture of the aldol products.

(16) In all cases, the reaction was quenched after an appropriate time (<24 h). A prolonged reaction time resulted in a lower ee of *syn*-**4**, probably due to the epimerization of *anti*-**4** under the reaction conditions.

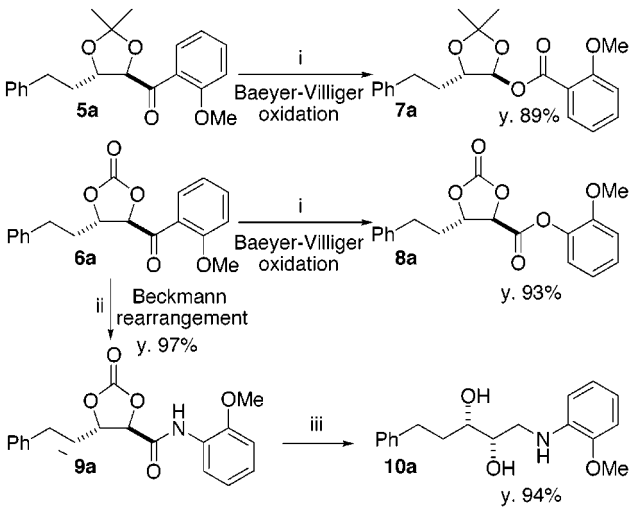
(17) Review: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

(18) See Supporting Information for detailed synthetic procedures.

participation of the 2′-methoxy group in chelate formation (Figure 1). Thus, the *Si*-face shielding would become more effective, resulting in the higher ee of both *syn*- and *anti*-products. On the other hand, enhanced *syn*-selectivity is explained by the steric hindrance of the aromatic ring in the enolate against aldehydes. Considering the positions of the two Zn atoms in the proposed structure of **2**, it seems reasonable to assume that the enolate would coordinate to one Zn metal and the aldehyde would coordinate to the other in a manner as shown in A or B (Figure 1).[19] The transition state A, which leads to *syn*-diols, is sterically more favorable than B. By using ketone **1d** instead of nonsubstituted **1a**, the steric bias should increase, thus resulting in the higher *syn*-selection.

As mentioned in the introduction, the usefulness of the aldol adducts becomes much higher by assuming that the 2-methoxyphenyl moiety is a placeholder for further conversions. As shown in Scheme 2, the Baeyer−Villiger oxidation proceeded smoothly by treating the ketones **5a** and **6a** with *m*CPBA, probably with the aid of neighboring oxygen atoms. Interestingly, benzoate **7a** was obtained in 89% yield when acetonide **5a** was used. On the other hand, phenyl ester **8a** was obtained in 93% yield when carbonate analogue **6a**[20] was subjected to the same conditions. In both cases, no regioisomer was observed. Furthermore, **6a** afforded amide **9a** exclusively in 97% yield in one step via Beckmann rearrangement with *O*-mesitylenesulfonylhydroxylamine (MSH).[21] The amide **9a** was readily transformed into **10a** by reduction with DIBAL. **10a** can be converted into an amino-diol after oxidative removal of the 2-methoxyphenyl group.[22]

Scheme 2. 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, rt, 4 h; (iii) DIBAL, −78 °C to rt, 2 h.

In conclusion, we have achieved a highly enantio- and diastereoselective direct catalytic aldol reaction, which afforded α,*β*-dihydroxy ketones from a variety of aldehydes using as little as 1 mol % of the Zn−Zn-linked-BINOL complex **2**. The reaction was also performed on a gram scale and reached completion within 24 h. The simple reaction protocol, in combination with options for further efficient transformations of the resulting aldol adducts into synthetically interesting compounds, makes this process more useful. Detailed investigation on the reaction mechanism as well as the development of a direct catalytic asymmetric aldol reaction with an unmodified ester is currently underway in our group.

Acknowledgment. We thank CREST and RFTF for financial support. S. M. and N. Y. thank JSPS Research Fellowships for Young Scientists.

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

OL015878P

(19) Similar mechanisms are proposed for the hydrolysis of phosphates catalyzed by achiral dinuclear Zn complexes. (a) Abe, K.; Izumi, J.; Ohba, M.; Yokoyama, T.; Okawa, H. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 85 and references therein. For selected examples of recent dinuclear Zn catalysts, see refs 5 and 8 and references therein. See also: (b) Hikichi, S.; Tanaka, M.; Moro-oka, Y.; Kitajima, N. *J. Chem. Soc., Chem. Commun.* **1992**, 814. (c) Chapman, W. H., Jr.; Breslow, R. *J. Am. Chem. Soc.* **1995**, *117*, 5462. (d) Yashiro, M.; Ishikubo, A.; Komiyama, M. *J. Chem. Soc., Chem. Commun.* **1995**, 1793. (e) Koike, T.; Inoue, M.; Kimura, E.; Shiro, M. *J. Am. Chem. Soc.* **1996**, *118*, 3091. (f) Molenveld, P.; Kapsabeils, S.; Engbersen, J. F. J.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1997**, *119*, 2948. (g) Bazzicalupi, C.; Bencini, A.; Bianchi, A.; Fusi, V.; Giorgi. C.; Paoletti, P.; Valtancoli, B.; Zanchi, D. *Inorg. Chem.* **1997**, *36*, 2784. (h) Kaminskaia, N. V.; Spingler, B.; Lippard, S. J. *J. Am. Chem. Soc.* **2000**, *122*, 6411. (i) Rossi, P.; Felluga, F.; Tecilla, P.; Formaggio, F.; Crisma, M.; Toniolo, C.; Scrimin, P. *J. Am. Chem. Soc.* **1999**, *121*, 6948. (j) Kim, H.-S.; Kim, J.-J.; Lee, B.-G.; Jung, O.-S.; Jang, H.-G.; Kang, S.-O. *Angew. Chem., Int. Ed.* **2000**, *39*, 4096 and references therein.

(20) The carbonate **6a** was prepared by treating *syn*-**4a** with triphosgene (93% yield). See Supporting Information.

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

(22) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 8180 and references therein.