

# syn-Selective Kobayashi Aldol Reaction Using Acetals

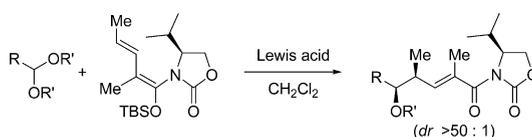
Hiroyuki Tsukada, Yuki Mukaeda, and Seiji Hosokawa\*

Department of Applied Chemistry, Faculty of Advanced Science and Engineering,  
Waseda University, 3-4-1 Ohkubo, Shinjuku-ku, Tokyo 169-8555, Japan

seiji@waseda.jp

Received December 22, 2012

## ABSTRACT



The Kobayashi aldol reaction has been used to construct *anti*-aldol products by remote stereinduction. Since the product of the Kobayashi aldol reaction has a typical polyketide structure, this reaction has been applied to the total synthesis of natural products. By varying this reaction, it was found that the reaction with acetals in the presence of Lewis acid proceeded to give *syn* adducts in high stereoselectivity. This is the first example of the stereoselective reaction of the chiral dienol ether and acetals.

The Kobayashi aldol reaction, a vinylogous Mukaiyama aldol reaction using chiral silyl dienol ethers and aldehydes, has been used to construct *anti*-aldol products by remote stereinduction (Scheme 1).<sup>1</sup> This reaction allows

construction of two stereogenic centers and introduction of the multifunctional C5 unit including  $\alpha,\beta$ -unsaturated imide. Since the product of the Kobayashi aldol reaction has a typical polyketide structure, this reaction has been applied to the total synthesis of natural products.<sup>2</sup> Some cases of this reaction have been reported to give *syn* adducts predominantly (Scheme 2). Kobayashi's group found that  $\alpha$ -heteroatom substituted aldehyde **a** provided *syn* adducts selectively by switching the facial selectivity of the aldehyde (Scheme 2, eq 1).<sup>3</sup> Chen's group reported that *syn* adducts were obtained by aldehydes capable of chelation in Kobayashi aldol reactions (eq 2).<sup>4</sup> Kalesse published that the (1*E*,3*Z*)-ketene *N,O*-acetal **4** gave *syn* adducts **5** in a highly stereoselective manner (eq 3).<sup>5</sup> Recently, we also reported a *syn*-selective Kobayashi aldol reaction using excess amount of Lewis acid (eq 4), of which the stereochemistry is different from that of Kalesse's adducts.<sup>6</sup> These efforts have realized stereoswitching by using the same chiral synthon. However, the reactions of the chiral dienol ether and acetals to prepare the protected aldol adducts have been unprecedented. Herein, we present

(1) Shirokawa, S.; Kamiyama, M.; Nakamura, T.; Okada, M.; Nakazaki, A.; Hosokawa, S.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 13604–13605.

(2) (a) Hosokawa, S.; Ogura, T.; Togashi, H.; Tatsuta, K. *Tetrahedron Lett.* **2005**, *46*, 333–337. (b) Tatsuta, K.; Hosokawa, S. *Chem. Rev.* **2005**, *105*, 4707–4729. (c) Hosokawa, S.; Yokota, K.; Imamura, K.; Suzuki, Y.; Kawarasaki, M.; Tatsuta, K. *Tetrahedron Lett.* **2006**, *47*, 5415–5418. (d) Hosokawa, S.; Kuroda, S.; Imamura, K.; Tatsuta, K. *Tetrahedron Lett.* **2006**, *47*, 6183–6186. (e) Nakamura, T.; Shirokawa, S.; Hosokawa, S.; Nakazaki, A.; Kobayashi, S. *Org. Lett.* **2006**, *8*, 677–679. (f) Shirokawa, S.; Shinoyama, M.; Ooi, I.; Hosokawa, S.; Nakazaki, A.; Kobayashi, S. *Org. Lett.* **2007**, *9*, 849–852. (g) Hosokawa, S.; Yokota, K.; Imamura, K.; Suzuki, Y.; Kawarasaki, M.; Tatsuta, K. *Chem. Asian J.* **2008**, *3*, 1415–1421. (h) Hosokawa, S.; Tatsuta, K. *Mini-Rev. Org. Chem.* **2008**, *5*, 1–18. (i) Schmauder, A.; Müller, S.; Maier, M. E. *Tetrahedron* **2008**, *64*, 6263–6269. (j) Hosokawa, S. *J. Synth. Org. Chem., Jpn* **2009**, *67*, 24–37. (k) Lipshutz, B.; Amorelli, B. *J. Am. Chem. Soc.* **2009**, *131*, 1396–1397. (l) Yamaoka, M.; Fukatsu, Y.; Nakazaki, A.; Kobayashi, S. *Tetrahedron Lett.* **2009**, *50*, 3849–3852. (m) Hosokawa, S.; Mukaeda, Y.; Kawahara, R.; Tatsuta, K. *Tetrahedron Lett.* **2009**, *50*, 6701–6704. (n) Yamaoka, M.; Nakazaki, A.; Kobayashi, S. *Tetrahedron Lett.* **2009**, *50*, 6764–6768. (o) Yamaoka, M.; Nakazaki, A.; Kobayashi, S. *Tetrahedron Lett.* **2010**, *51*, 287–289. (p) Schmauder, A.; Sibley, L.; Maier, M. E. *Chem.—Eur. J.* **2010**, *16*, 4328–4336. (q) Paterson, I.; Kan, S. B. J.; Gibson, J. *Org. Lett.* **2010**, *12*, 3724–3727. (r) Hosokawa, S.; Matsushita, K.; Tokimatsu, S.; Toriumi, T.; Suzuki, Y.; Tatsuta, K. *Tetrahedron Lett.* **2010**, *51*, 5532–5536. (s) Matsui, R.; Seto, K.; Sato, Y.; Suzuki, T.; Nakazaki, A.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 680–683. (t) Iwasaki, Y.; Matsui, R.; Suzuki, T.; Nakazaki, A.; Kobayashi, S. *Chem. Pharm. Bull.* **2011**, *59*, 522–524. (u) Fujita, K.; Matsui, R.; Suzuki, T.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 7271–7274. (v) Höfle, G.; Gerth, H.; Reichenbach, H.; Kunze, B.; Sasse, F.; Forche, E.; Prusov, E. *Chem.—Eur. J.* **2012**, *8*, 11362–11370.

(3) Shinoyama, M.; Shirokawa, S.; Nakazaki, A.; Kobayashi, S. *Org. Lett.* **2009**, *11*, 1277–1280.

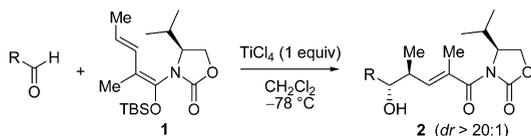
(4) (a) Wang, L.; Gong, J.; Deng, L.; Xiang, Z.; Chen, Z.; Wang, Y.; Chen, J.; Yang, Z. *Org. Lett.* **2009**, *11*, 1809–1812. (b) Wang, L.; Xi, Y.; Yang, S.; Zhu, R.; Liang, Y.; Chen, J.; Yang, Z. *Org. Lett.* **2011**, *13*, 74–77.

(5) Symkenberg, G.; Kalesse, M. *Org. Lett.* **2012**, *14*, 1608–1611.

(6) Mukaeda, Y.; Kato, T.; Hosokawa, S. *Org. Lett.* **2012**, *14*, 5298–5301.

a *syn*-selective Kobayashi aldol reaction with acetals in the presence of 1 equiv of Lewis acid to produce the protected aldol adducts (eq 5).

### Scheme 1. Kobayashi Aldol Reaction



There are some natural products possessing a *syn* relation between the vicinal methyl and methoxy group.<sup>7</sup> Therefore, aldol reactions with acetals have been developed and used in natural product synthesis.<sup>8</sup> Since development of the Kobayashi aldol reaction has led to fruitful success in the total syntheses of natural products, establishment of the Kobayashi reaction with acetals would become a powerful tool for natural product synthesis. Herein, we present the Kobayashi reaction with acetals to give *syn* adducts in high stereoselectivity.

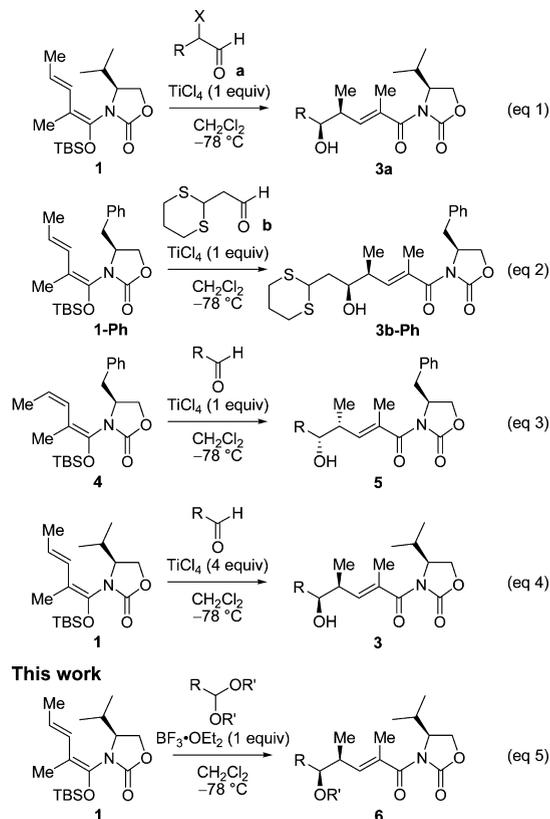
At first, the reaction using the chiral dienol ether **1** and 4-bromobenzaldehyde dimethyl acetal **c** was examined with Lewis acids including  $\text{TiCl}_4$ ,  $\text{SnCl}_4$ ,  $\text{BF}_3 \cdot \text{OEt}_2$ , TMSOTf, and  $\text{Et}_2\text{AlCl}$  (Table 1). With  $\text{TiCl}_4$ , the reaction proceeded to give *syn* adduct **6c** in good selectivity, but another *syn* adduct **7c** was produced significantly (Table 1, entries 1 and 2). When  $\text{SnCl}_4$  was employed as Lewis acid, stereoselectivity became higher, but the yield was not so high (Table 1, entries 3 and 4). On the other hand, both  $\text{BF}_3 \cdot \text{OEt}_2$  and TMSOTf gave *syn* adduct **6c** in high yield with high selectivity (Table 1, entries 5 and 6). In the case using  $\text{Et}_2\text{AlCl}$ , the reaction proceeded to give multiple spots on TLC, and the yield was decreased to 44% (Table 1, entry 7). All cases showed three diastereomers, and another diastereomer **9c** was not observed.

The configurations of the products **6c**, **7c**, and **8c** were determined by derivatization of known compounds as shown in Scheme 3. The known *syn* adduct **3c**<sup>6</sup> possessing an unprotected alcohol was converted into methyl ether **6c**, of which the <sup>1</sup>H NMR spectrum data were identical with those of the major product of the reaction in Table 1. Methyl ether *anti*-**6c** was further transformed to **7c** by hydrolysis of the imine moiety and following attachment of the oxazolidine derived from D-valine. The <sup>1</sup>H NMR spectrum data of **7c** were identical with one of the minor adducts. On the other hand, the known *anti* adduct **2c**<sup>2a</sup>

(7) (a) Furusaki, A.; Matsumoto, T.; Nakagawa, A.; Omura, S. *J. Antibiot.* **1980**, *33*, 781–782. (b) Muroi, M.; Haibara, K.; Asai, M.; Kamiya, K.; Kishi, T. *Tetrahedron* **1981**, *37*, 1123–1130. (c) Raju, R.; Piggott, A. M.; Khalil, Z.; Bernhardt, P. V.; Capon, R. J. *Tetrahedron Lett.* **2012**, *53*, 1063–1065.

(8) (a) Mukaiyama, T.; Hayashi, M. *Chem. Lett.* **1974**, 15–16. (b) Johnson, W. S.; Edington, C.; Elliott, J. D.; Silverman, I. R. *J. Am. Chem. Soc.* **1984**, *106*, 7588–7591. (c) Smith, A. B., III; Lupo, A. T.; Ohba, M.; Chen, K. *J. Am. Chem. Soc.* **1989**, *111*, 6648–6656. (d) Smith, T. E.; Kuo, W.-H.; Balskus, E. P.; Bock, V. D.; Roizen, J. L.; Theberge, A. B.; Carroll, K. A.; Kurihara, T.; Wessler, J. D. *J. Org. Chem.* **2008**, *73*, 142–150. (e) Crimmins, M. T.; Dechert, A.-M. R. *Org. Lett.* **2009**, *11*, 1635–1638. (f) Sugano, Y.; Kikuchi, F.; Toita, A.; Nakamura, S.; Hashimoto, S. *Chem.—Eur. J.* **2012**, *18*, 9682–9690.

### Scheme 2. *syn*-Selective Kobayashi Aldol Reactions

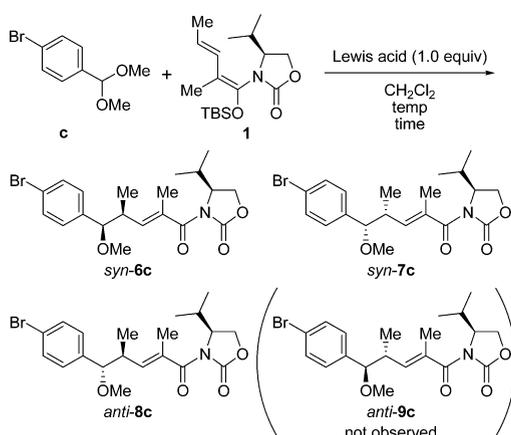


was derived to the *anti* **8c**, of which the <sup>1</sup>H NMR spectrum data were identical with those of the third products. In the case of the reaction in Table 1, the major product **6c** was easily crystallized, and its absolute configuration was confirmed by X-ray crystallography.<sup>9</sup>

Next, a variety of acetals were subjected to the reaction of the *E,E*-ketene *N,O*-acetal **1** in the presence of Lewis acid (Tables 2 and 3). The results were optimized by comparison of Lewis acids including  $\text{BF}_3 \cdot \text{OEt}_2$ , TMSOTf,  $\text{TiCl}_4$ , and  $\text{SnCl}_4$ . Table 2 summarizes the Kobayashi reaction using aromatic aldehyde-derived acetals. All reactions using aromatic aldehyde-derived acyclic acetals (Table 2, entries 1, 2, 4–7) gave the *syn* adduct in excellent yield with high stereoselectivity in the presence of  $\text{BF}_3 \cdot \text{OEt}_2$ . The *anti* adducts were observed only in a trace amount. The inductive effect of the substituent affected the reaction temperature (Table 2, entries 2, 4, and 5). In the case of 1,3-dioxane **e** (Table 2, entry 3), the best result was obtained by using  $\text{TiCl}_4$ , and both the yield and selectivity were slightly lower.

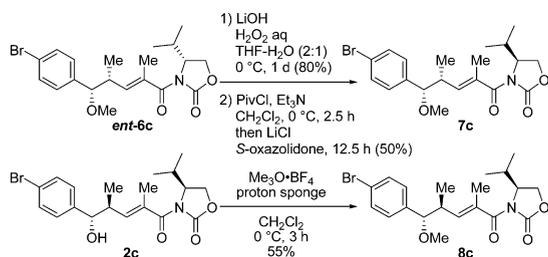
This reaction was applied to the one-pot conversion of an aldehyde to the corresponding benzyl-protected *syn* adduct (Scheme 4). Aldehyde **10** was transformed to dibenzyl acetal **i** by using BnOTMS and TMSOTf (0.2 equiv), and TMSOTf (1.0 equiv) and dienol ether **1** were added to the resulting mixture. The reaction sequence did

(9) Crystallographic data (excluding structure factors) for the structure of **6c** are given in the Supporting Information.

**Table 1.** Effects of Lewis Acids in Kobayashi Aldol Reaction with Acetal **c**

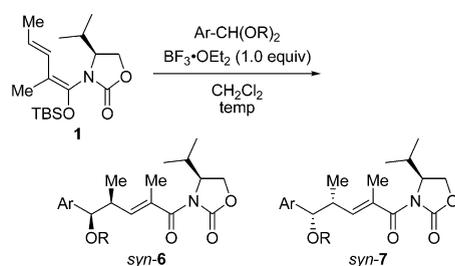
entry	Lewis acid	temp (°C)	time (h)	yield (%)	dr ( <b>6c</b> : <b>7c</b> : <b>8c</b> ) <sup>a</sup>
1	TiCl <sub>4</sub>	-78	22	61	79:19:2
2	TiCl <sub>4</sub>	-60	4.5	quant	84:10:6
3	SnCl <sub>4</sub>	-78	22	79	93:5:2
4	SnCl <sub>4</sub>	-60	4.5	71	87:7:6
5	BF <sub>3</sub> ·OEt <sub>2</sub>	-60	4.5	92	95:3:2
6	TMSOTf	-60	4.5	96	93:3:4
7	Et <sub>2</sub> AlCl	-40	18	44	90:4:6

<sup>a</sup> Determined by <sup>1</sup>H NMR.

**Scheme 3.** Determination of the Stereochemistry of the Minor Adducts

not affect the yield and selectivity, and the *syn* adduct **6i** was obtained in high yield and stereoselectivity.

The reactions with  $\alpha,\beta$ -unsaturated aldehyde-derived and saturated aldehyde-derived acetals are summarized in Table 3. In the case of  $\alpha,\beta$ -unsaturated aldehyde-derived acetals including **j**, **k**, and **l**, the reactions proceeded to give *syn* adducts in good (Table 3, entries 1 and 2) to excellent (Table 3, entry 3) selectivity. Saturated aldehyde-derived acetals also gave the *syn* adducts in good to high yield (Table 3, entries 4–8). The minor products in Table 3 were *anti* adducts **8** and the other isomers observed in a trace amount. The branched alkyl acetal **m** afforded the *syn* adduct **6m** as a single isomer in high yield (Table 3, entry 4). Although *n*-alkyl acetal **n** gave the *syn* adduct **6n** in high yield with high selectivity (Table 3, entry 5), Br-attaching **o** and the short alkyl acetals **p** and **q** afforded the

**Table 2.** Kobayashi Aldol Reactions with Acetal Derivatives of Aromatic Aldehydes

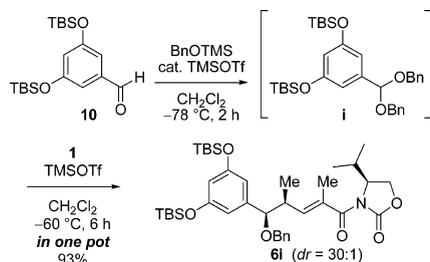
entry	Ar-CH(OR) <sub>2</sub> <sup>a</sup>	temp (°C)	yield (%)	dr ( <b>6</b> : <b>7</b> ) <sup>b</sup>
1		-78	93	25:1
2		-60	92	31:1
3 <sup>c</sup>		-40	66	10:1
4		-40	quant	31:1
5		-78	quant	9.5:1
6		-20	98	15:1
7		-40	95	30:1

<sup>a</sup> All reactions were performed in the ratio of acetal:silyl dienol ether: BF<sub>3</sub>·OEt<sub>2</sub> = 1:1:1. <sup>b</sup> The diastereo ratio was determined by 400 MHz <sup>1</sup>H NMR. <sup>c</sup> Performed with TiCl<sub>4</sub> (1.0 equiv) instead of BF<sub>3</sub>·OEt<sub>2</sub>.

corresponding *syn* adducts in good to high yield with moderate to good selectivity. (Table 3, entries 6–8). It is obvious by comparing the reaction temperature of entries 5 with 6 that the reaction was affected by the inductive effect of the substituent. These results indicate that the reaction proceeded via an oxonium cation. Additionally, judging from the results in Table 3 (entries 4, 5, and 8), the bulkiness of the alkyl group should influence the stereoselectivity.

As mentioned in Scheme 2, although the original Kobayashi aldol reaction conditions afford the *anti* adduct generally, it is known that the aldehyde having a

#### Scheme 4. One-Pot Acetalization–Kobayashi Aldol Reaction



**Table 3.** Kobayashi Aldol Reactions with Acetal Derivatives of Aliphatic Aldehydes

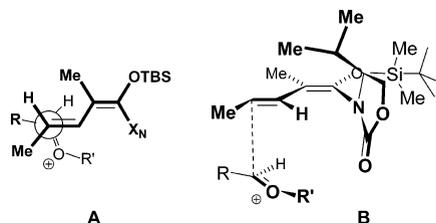
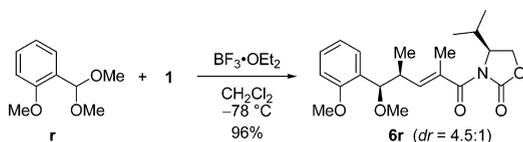
entry	R-CH(OR') <sub>2</sub> <sup>a</sup>	Lewis acid	temp (°C)	yield (%)	dr (6:8) <sup>b</sup>
1		BF <sub>3</sub> ·OEt <sub>2</sub>	-78	70	7.7:1
2 <sup>c</sup>		TiCl <sub>4</sub>	-78	68	11:1
3 <sup>c</sup>		TMSOTf	-78	69	> 50:1
4		TMSOTf	-40	84	> 50:1
5		TMSOTf	-40	94	11:1
6		BF <sub>3</sub> ·OEt <sub>2</sub>	0	75	7.7:1
7		BF <sub>3</sub> ·OEt <sub>2</sub>	-78	84	4:1
8		TMSOTf	-60	98	5.3:1

<sup>a</sup> All reactions were performed in the ratio of acetal:silyl dienol ether: Lewis acid = 1:1:1. <sup>b</sup> The diastereomeric ratio was determined by 400 MHz <sup>1</sup>H NMR. <sup>c</sup> The reaction was performed in the ratio of acetal: silyl dienol ether:Lewis acid = 1:2:1.

heteroatom at the  $\alpha$ - or  $\beta$ -position gives the *syn* adduct predominantly. Therefore, we submitted *o*-methoxybenzaldehyde dimethyl acetal under the same reaction conditions as Table 2 (Scheme 5). The reaction produced two adducts in quantitative yield, but the stereoselectivity was moderate. The major product of the reaction was *syn* adduct **6r**, and the minor one was *syn*-**7r**.

According to the results of the reactions, we propose the transition state of the *syn* selective reaction (Figure 1).

#### Scheme 5. Reaction with the Dimethyl Acetal of *o*-Methoxybenzaldehyde



**Figure 1.** Tentative transition state.

Here the oxonium intermediate contains the substituted methyl group as R' so that R' is not large. Thus, R is the largest group and should be directed outside of the dienyl chain, whereas the smallest hydrogen would face the crowded area between the  $\alpha$ -methyl group and  $\gamma$ -hydrogen of the dienyl chain to minimize the steric repulsion as shown in the transition state **A**. Considering the stereochemistry of the carbon attaching to the  $\gamma$ -methyl group, the oxonium cation would approach the diene from the bottom face. Therefore, we propose the transition state as indicated as **B**.

In conclusion, we succeeded in the *syn*-selective Kobayashi aldol reaction with acetals. This reaction directly gave the structure containing vicinal methyl and methoxy groups that some bioactive natural products have. It is also useful that aldol adducts protected with a benzyl group are obtained by using the sequential acetalization–Kobayashi aldol reaction procedure (Scheme 4). These advantages would make the natural product synthesis speedy. Application of this reaction to the total synthesis of natural products is in progress.

**Acknowledgment.** The authors are grateful for financial support of the GCOE program “Center for Practical Chemical Wisdom” and Grant-in-Aid for Challenging Exploratory Research from The Ministry of Education, Culture, Sports, Science and Technology (MEXT). This research was also supported by the Supporting Strategic Research Platform for Fusion Biotechnology based on Biology, Chemistry, and Informatics Project to Form the Strategic Research Platforms for Private University, and a Matching Fund Subsidy from MEXT, Japan.

**Supporting Information Available.** Experimental procedure and physical properties of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.