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Syn-Selective Kobayashi Aldol Reaction Using the *E,E*-Vinylketene Silyl *N,O*-Acetal

Yuki Mukaeda, Takuya Kato, and Seijiro Hosokawa*

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

seijiro@waseda.jp

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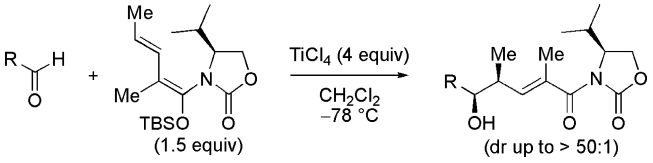
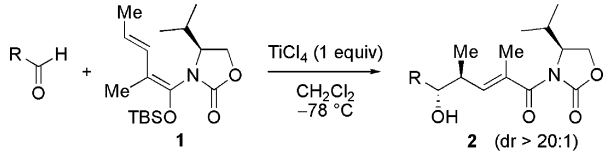
ABSTRACT



The Kobayashi aldol reaction is one of the most powerful methods to synthesize the polyketide skeleton and has been applied to the total synthesis of natural products. This methodology has been used to construct *anti*-aldol products, and only a few precedents on the *syn*-selective Kobayashi aldol reaction are known. A *syn*-selective Kobayashi aldol reaction by using the *E,E*-vinylketene silyl *N,O*-acetal and an excess amount of Lewis acid is presented.

The vinylogous Mukaiyama aldol reaction (VMAR) is one of the most useful methods to synthesize polyketide compounds.[1] Recently, the asymmetric VMARs have been developed and applied to synthesize natural products.[2] Among these methodologies, the Kobayashi aldol reaction is successful and has been widely applied to the synthesis of natural products (Scheme 1).[3] The *E,E*-vinylketene silyl *N,O*-acetal **1** reacts with aldehyde in the presence of 1 equiv of Lewis acid to give the *anti* adduct **2** in high stereoselectivity.

Scheme 1. Kobayashi Aldol Reaction



This methodology has been used to construct *anti*-aldol products, and only a few precedents on the *syn*-selective Kobayashi aldol reaction are known. Kobayashi's group found that α-heteroatom substituted aldehyde **a** provided *syn* adducts selectively by switching the facial selectivity of the aldehyde (Scheme 2, eq 1).[4] Chen's group reported that *syn* adducts were obtained by aldehydes capable of chelation in Kobayashi aldol reactions (eq 2).[5] More recently, Kalesse published that the 1-*E*, 3-*Z*-vinylketene silyl *N,O*-acetal **4** gave *syn* adducts **5** in a highly stereoselective manner (eq 3).[6] Herein, we present a *syn*-selective Kobayashi reaction with 1-*E*,3-*E*-vinylketene silyl *N,O*-acetal **1** by using an excess amount of Lewis acid (eq 4). The stereochemistry of the adduct **3** possesses stereogenic centers different from Kalesse's adduct.

The relationship between the amount of Lewis acid and the stereochemistry of the adduct is shown in Table 1. Equal equivalents of the aldehyde **c** and the *E,E*-vinylketene silyl *N,O*-acetal **1** reacted with 1 equiv of $TiCl_4$ to afford the *anti* adduct **2c** predominantly (Table 1, entry 1), while in the case of the 1:2 equiv amounts of the aldehyde and Lewis acid, the *syn* adduct was obtained as a major product while other diastereomers were observed

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unambiguously (Table 1, entry 3). Treatment with 3 equiv of $TiCl_4$ promoted the reaction to afford *syn* adduct **3c** predominantly (Table 1, entry 4). When the conditions included 1:1.5:4 equiv amounts of the aldehyde, the *E,E*-vinylketene silyl *N,O*-acetal **1**, and $TiCl_4$, excellent yield and selectivity were observed (Table 1, entry 6). More Lewis acid did not affect both yield and selectivity (Table 1, entry 7). The stereochemistry of the *syn* adduct **3c** was confirmed by esterification which afforded the ester **6** derived by the Mitsunobu reaction from the known *anti* adduct **2c**[3a] (Scheme 3).

Scheme 2. *Syn*-Selective Kobayashi Aldol Reactions

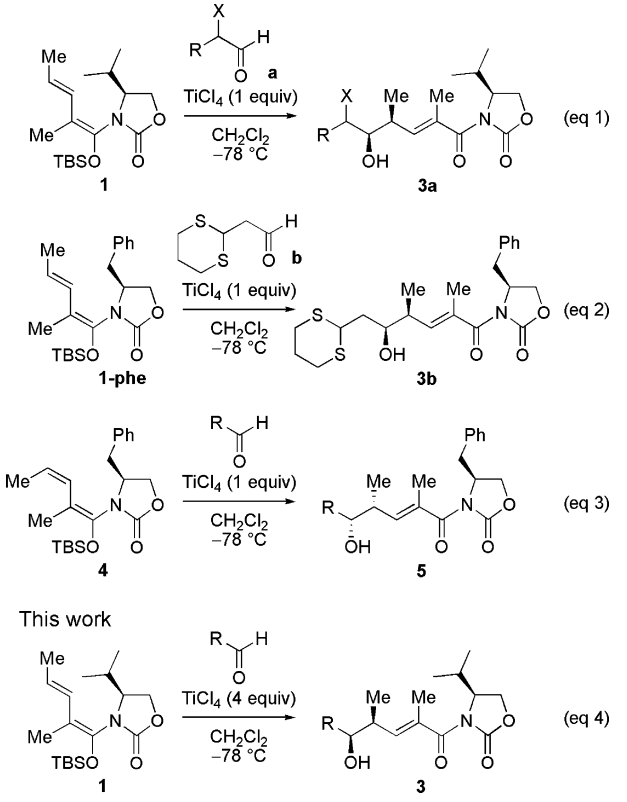
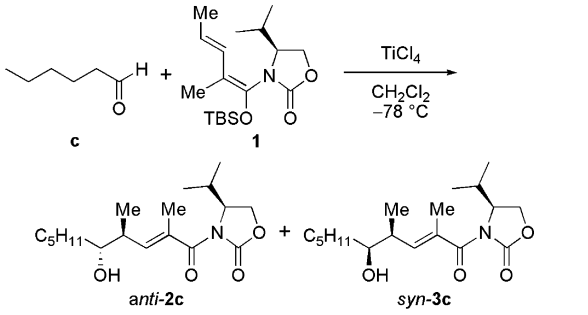


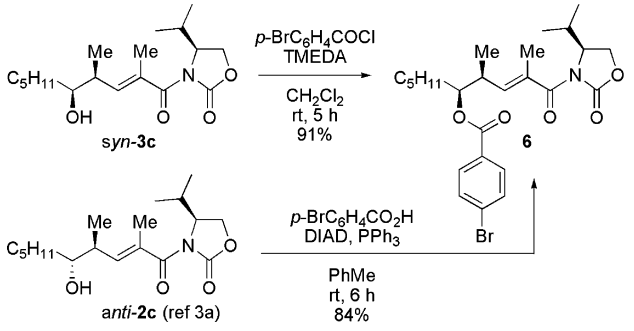
Table 1. Relationship between Amount of Reactants and the Stereochemistry of the Adduct



entry	**1** (equiv)	Lewis acid (equiv)	yield (%)[b]	**2c:3c**[a]
1[c]	1.0	1.0	72	44:1[b]
2	1.0	1.5	75	32:1[c]
3	1.0	2.0	77	1:27[d]
4	1.0	3.0	67	>1:50[c]
5	1.0	4.0	74	>1:50[c]
6	1.5	4.0	94	>1:50[c]
7	1.5	9.0	92	>1:50[c]

[a] Determined by ^{1}H NMR. [b] Reference 3a. [c] Trace amounts of diastereomers were observed. [d] Other isomers were observed in the ratio of **2**/**3**/diastereomers = 1:27:1.6:16.

Scheme 3. Determination of the Stereochemistry of the *Syn* Adduct



(3) (a) Shirokawa, S.; Kamiyama, M.; Nakamura, T.; Okada, M.; Nakazaki, A.; Hosokawa, S.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 13604–13605. (b) Hosokawa, S.; Ogura, T.; Togashi, H.; Tatsuta, K. *Tetrahedron Lett.* **2005**, *46*, 333–337. (c) Tatsuta, K.; Hosokawa, S. *Chem. Rev.* **2005**, *105*, 4707–4729. (d) Hosokawa, S.; Yokota, K.; Imamura, K.; Suzuki, Y.; Kawarasaki, M.; Tatsuta, K. *Tetrahedron Lett.* **2006**, *47*, 5415–5418. (e) Hosokawa, S.; Kuroda, S.; Imamura, K.; Tatsuta, K. *Tetrahedron Lett.* **2006**, *47*, 6183–6186. (f) Nakamura, T.; Shirokawa, S.; Hosokawa, S.; Nakazaki, A.; Kobayashi, S. *Org. Lett.* **2006**, *8*, 677–679. (g) Shirokawa, S.; Shinoyama, M.; Ooi, I.; Hosokawa, S.; Nakazaki, A.; Kobayashi, S. *Org. Lett.* **2007**, *9*, 849–852. (h) Hosokawa, S.; Yokota, K.; Imamura, K.; Suzuki, Y.; Kawarasaki, M.; Tatsuta, K. *Chem.—Asian J.* **2008**, *3*, 1415–1421. (i) Hosokawa, S.; Tatsuta, K. *Mini-Rev. Org. Chem.* **2008**, *5*, 1–18. (j) Schmauder, A.; Müller, S.; Maier, M. E. *Tetrahedron* **2008**, *64*, 6263–6269. (k) Hosokawa, S. *J. Synth. Org. Chem., Jpn* **2009**, *67*, 24–37. (l) Lipshutz, B.; Amorelli, B. *J. Am. Chem. Soc.* **2009**, *131*, 1396–1397. (m) Yamaoka, M.; Fukatsu, Y.; Nakazaki, A.; Kobayashi, S. *Tetrahedron Lett.* **2009**, *50*, 3849–3852. (n) Hosokawa, S.; Mukaeda, Y.; Kawahara, R.; Tatsuta, K. *Tetrahedron Lett.* **2009**, *50*, 6701–6704. (o) Yamaoka, M.; Nakazaki, A.; Kobayashi, S. *Tetrahedron Lett.* **2009**, *50*, 6764–6768. (p) Yamaoka, M.; Nakazaki, A.; Kobayashi, S. *Tetrahedron Lett.* **2010**, *51*, 287–289. (q) Schmauder, A.; Sibley, L.; Maier, M. E. *Chem.—Eur. J.* **2010**, *16*, 4328–4336. (r) Paterson, I.; Kan, S. B. J.; Gibson, J. *Org. Lett.* **2010**, *12*, 3724–3727. (s) Hosokawa, S.; Matsushita, K.; Tokimatsu, S.; Toriumi, T.; Suzuki, Y.; Tatsuta, K. *Tetrahedron Lett.* **2010**, *51*, 5532–5536. (t) Matsui, R.; Seto, K.; Sato, Y.; Suzuki, T.; Nakazaki., A.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 680–683. (u) Iwasaki, Y.; Matsui, R.; Suzuki, T.; Nakazaki, A.; Kobayashi, S. *Chem. Pharm. Bull.* **2011**, *59*, 522–524. (v) Fujita, K.; Matsui, R.; Suzuki, T.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 7271–7274. (w) Höfle, G.; Gerth, H.; Reichenbach, H.; Kunze, B.; Sasse, F.; Forche, E.; Prusov, E. *Chem.—Eur. J.* **2012**, *8*, 11362–11370.

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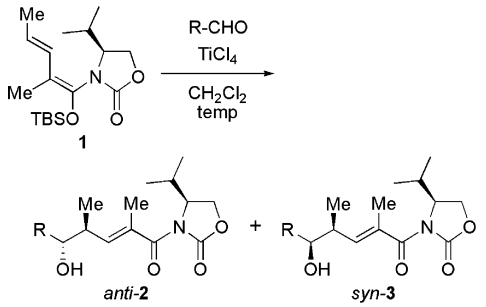
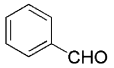
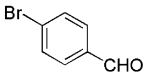
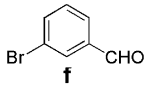
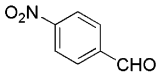
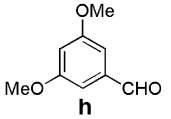
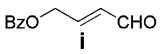
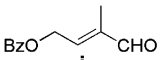
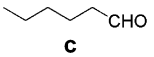
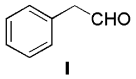
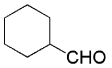
(5) (a) Wang, L.; Gong, J.; Deng, L.; Xiang, Z.; Chen, Z.; Wang, Y.; Chen, J.; Yang, Z. *Org. Lett.* **2009**, *11*, 1809–1812. (b) Wang, L.; Xi, Y.; Yang, S.; Zhu, R.; Liang, Y.; Chen, J.; Yang, Z. *Org. Lett.* **2011**, *13*, 74–77.

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

Table 2. *Syn*-Selective Kobayashi Aldol Reactions



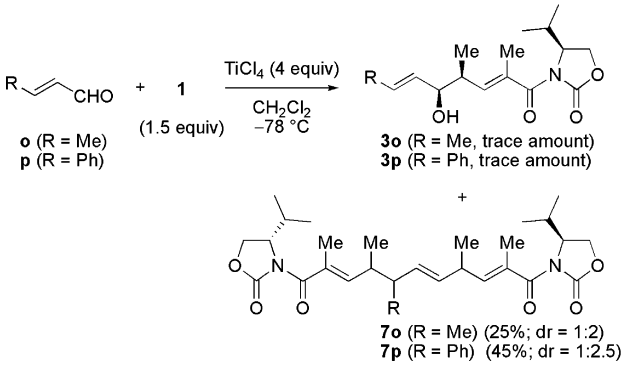
entry	R-CHO[a]	temp (°C)	yield (%)	dr (*anti*:*syn*)[b]
1	 **d**	−78 to −40	84	> 1:50
2	 **e**	−78 to −40	83	> 1:50
3	 **f**	−78 to −40	69	1:21
4	 **g**	−78 to −40	82	> 1:50
5	 **h**	−78 to −40	81	> 1:50
6[c]	 **i**	−78	92	> 1:50
7[c]	 **j**	−78	62	1:8
8	Me-CHO **k**	−78	94	1:3
9	 **c**	−78	94	> 1:50
10	 **l**	−78	89	> 1:50
11	 **m**	−78	70	> 1:50
12	 **n**	−78	74	> 1:50

[a] All reactions were performed in the ratio of aldehyde/dienol ether/$TiCl_4$ = 1:1.5:4. [b] The diastereomeric ratio was determined by 400 MHz ^1H NMR. [c] Performed in the ratio of aldehyde/dienol ether/$TiCl_4$ = 1:3:7.

According to the stereochemical divergency dependent on the amount of the Lewis acid in the reaction of the *E,E*-vinylketene silyl *N,O*-acetal **1** with hexanal **c**, we performed the Kobayashi aldol reaction with a variety of aldehydes by using 1.5 equiv of the *E,E*-ketene *N,O*-acetal **1** and 4 equiv of $TiCl_4$ in dichloromethane (Table 2). The initial color of the reaction mixture was dark blue while Kobayashi's conditions exhibited a dark red color. As the reaction proceeded, the color of the mixture became yellow. In all cases, including aromatic aldehydes and saturated aldehydes, the reactions proceeded in good to high yield with excellent stereoselectivity to give *syn* adducts.[7] In the case of γ-oxygenated aldehydes **i** and **j** (Table 2, entries 6 and 7), the reaction proceeded slowly, and the *syn* adducts were obtained as in other cases by increasing the amount of the dienol silyl ether (3 equiv) and $TiCl_4$ (7 equiv). However, in the case of crotonaldehyde **o** and cinnamaldehyde **p**, the reaction gave multiple products including 2:1 adducts of the *E,E*-ketene *N,O*-acetal and the aldehyde (Scheme 4). Since a trace amount of the 1:1 adduct was observed in each reaction, the 1:1 adduct might easily receive the second nucleophilic addition of the *N,O*-acetal or other reactions. The 2:1 adducts **7o** and **7p** were obtained as a mixture of stereoisomers in a moderate ratio, of which stereochemistry of the major isomer was not determined.

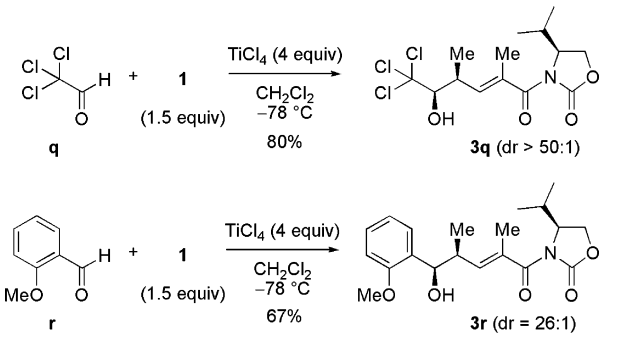
Next we examined the same reaction with chloral **q** and *o*-methoxybenzaldehyde **r** (Scheme 5). Kobayashi reported that the reaction with chloral **q** by using 1.0 equiv of $TiCl_4$ provided the *syn* adduct predominantly.[4] Treatment of chloral **q** with 1.5 equiv of the *E,E*-vinylketene *N,O*-acetal **1** and 4 equiv of $TiCl_4$ allowed the reaction to proceed and to give the *syn* adduct **3q** predominantly. On the other hand, Chen's group found that the reaction with *o*-methoxybenzaldehyde **r** under the original Kobayashi's conditions gave the *syn* adduct predominantly. Kalesse's *E,Z*-vinylketene *N,O*-acetal **4** afforded the *anti* adduct via the same transition state as in Chen's report.[6] The *E,E*-vinylketene *N,O*-acetal **1**, however, yielded the *syn* adduct **3r** as a single isomer. It is interesting that chloral **q** and *o*-methoxybenzaldehyde **r** did not turn the stereoselectivity in VMAR, and both Kobayashi's original conditions and our conditions gave the *syn* adduct in high stereoselectivity.

Scheme 4. Reactions with Crotonaldehyde and Cinnamaldehyde



Although it is clear that the stereoselectivity of the Kobayashi aldol reaction is dependent on the amount of

Scheme 5. Reactions with Chloral and *o*-Methoxybenzaldehyde



Lewis acid, the transition state of the *syn* selective reaction remains obscure. Differences in the initial reaction color from Kobayashi's *anti* aldol reaction reveal the differences in the structure of the initial titanium complexes. Studies including calculations to identify the transition state are in progress.

In conclusion, we succeeded in utilizing the *syn* selective Kobayashi aldol reaction by using an excess amount of $TiCl_4$. It is useful that the same starting materials and reactants give each stereochemistry in high selectivity.[8] Stereochemical switching is an advantage of the Kobayashi reaction in coping with polypropionate skeletons having a variety of configurations.[9] Application of this reaction to the total synthesis of natural products is in progress.

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Supporting Information Available. The experimental procedure and physical property 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.

(7) Absolute configurations of products were determined as shown in Scheme 3. Configurations of **3e** and **3g** were determined by X-ray crystallography. The Kobayashi aldol adducts **3d** and **3m** were derived into the crystalline **3d** methyl ether and **3m** 3,5-dinitrobenzoate, respectively, to perform X-ray crystallography. Crystallographic data (excluding structure factors) for the structures of **3d** methyl ether, **3e**, **3g**, and **3m** 3,5-dinitrobenzoate are shown in the Supporting Information.

(8) Danda, H.; Hansen, M. M.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 173–181.

(9) The De Brabander and Nicolaou groups have achieved the total synthesis of palmerolide A independently, in which both groups made the γ,δ-*syn* adduct by using Kobayashi aldol reaction followed by inversion of the configuration of the δ-hydroxy group: (a) Jiang, X.; Liu, B.; Lebreton, S.; De Brabander, J. K. *J. Am. Chem. Soc.* **2007**, *129*, 6386–6387. (b) Nicolaou, K. C.; Guduru, R.; Sun, Y.-P.; Banerji, B.; Chen, D. Y.-K. *Angew. Chem., Int. Ed.* **2007**, *46*, 5896–5900. (c) Nicolaou, K. C.; Sun, Y.-P.; Guduru, R.; Banerji, B.; Chen, D. Y.-K. *J. Am. Chem. Soc.* **2008**, *130*, 3633–3644.