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Syn-Selective Vinylogous Kobayashi Aldol Reaction

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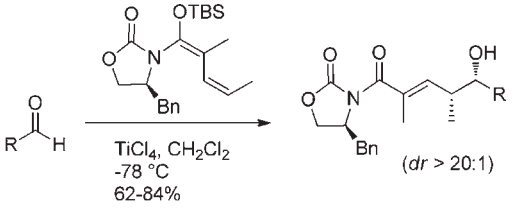
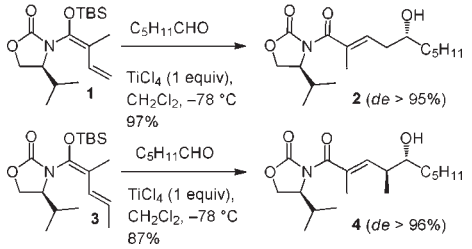
ABSTRACT



The Kobayashi aldol reaction has become a prominent transformation in polyketide syntheses. This methodology takes advantage of the directing effects of the Evans auxiliary and allows the stereoselective incorporation of a four carbon segment with two additional methyl branches establishing an *anti*-relationship between the two newly formed chiral centers. So far this transformation was restricted to *anti*-aldol products. We present here a modified protocol that provides the corresponding aldol product with high *syn*-selectivity.

Vinylogous Mukaiyama aldol reactions are among the most efficient transformations in polyketide chemistry.[1] They serve in establishing carbon–carbon bonds and chiral centers at the same time. A variety of strategies to utilize these reactions in an enantioselective fashion were put forward and exhibit chiral Lewis acids,[2] Lewis acid–base pairs, or organo catalysts[4] for activation. A very prominent and widely used example of a chiral auxiliary-based approach was put forward by Kobayashi et al. in 2004.[5] Their highly stereoselective vinylogous Mukaiyama aldol reaction using Evans' auxiliary based vinylketene silyl *N*,*O*-acetals provides an efficient and hitherto unprecedented high degree of remote (1,7- and 1,6,7-) asymmetric induction (Scheme 1). It was found that chiral vinylketene silyl *N*,*O*-acetals **1** and **2** underwent a highly regio- and diastereoselective vinylogous Mukaiyama aldol reaction. Kobayashi and co-workers could also show that the α-methyl group of these amide-derived silyl dienol ethers is important for achieving the high level of diastereoselectivity.

Scheme 1. Kobayashi's Vinylogous Mukaiyama Aldol Reaction



(1) (a) Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929. (b) Brodmann, T.; Lorenz, M.; Schäckel, R.; Simsek, S.; Kalesse, M. *Synthesis* **2009**, 174. (c) Soriente, A.; De, R. M.; Villano, R.; Scettri, A. *Curr. Org. Chem.* **2004**, *8*, 993. (d) Kalesse, M. Top. *Curr.Chem.* **2005**, *244*, 43. (e) Denmark, S. E.; Heemstra, J. R., Jr.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 4682. (f) Casiraghi, G.; Battistini, L.; Curti, C.; Rassu, G.; Zanardi, F. *Chem. Rev.* **2011**, *111*, 3076.

(2) (a) Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Campos, K. R.; Connell, B. T.; Staples, R. J. *J. Am. Chem. Soc.* **1999**, *121*, 669. (b) Singer, R. A.; Carreira, E. M. *J. Am. Chem. Soc.* **1995**, *117*, 12360. (c) Szlosek, M.; Figadère, B. *Angew. Chem., Int. Ed.* **2000**, *39*, 1799. (d) Sato, M.; Sunami, S.; Sugita, Y.; Kaneko, C. *Chem. Pharm. Bull.* **1994**, *42*, 839. (e) Gieseler, M. T.; Kalesse, M. *Org. Lett.* **2011**, *13*, 2430. (f) Simsek, S.; Horzella, M.; Kalesse, M. *Org. Lett.* **2007**, *9*, 5637. (g) Simsek, S.; Kalesse, M. *Tetrahedron Lett.* **2009**, *50*, 3485. (h) Evans, D. A.; Dunn, T. B.; Kværnø, L.; Beauchemin, A.; Raymer, B.; Olhava, E. J.; Mulder, J. A.; Juhl, M.; Kagechika, K.; Favor, D. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 4698. (i) Remy, P.; Langner, M.; Bolm, C. *Org. Lett.* **2006**, *8*, 1209. (j) Kruger, J.; Carreira, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 837. (k) Matsuoka, Y.; Irie, R.; Katsuki, T. *Chem. Lett.* **2003**, *32*, 584.

(3) (a) Denmark, S. E.; Beutner, G. L.; Wynn, T.; Eastgate, M. D. *J. Am. Chem. Soc.* **2005**, *127*, 3774. (b) Palombi, L.; Acocella, M. R.; Celenta, N.; Massa, A.; Villano, R.; Scettri, A. *Tetrahedron: Asymmetry* **2006**, *17*, 3300.

(4) (a) Singh, R. P.; Foxman, B. M.; Deng, L. *J. Am. Chem. Soc.* **2010**, *132*, 9558. (b) Nagao, H.; Yamane, Y.; Mukaiyama, T. *Chem. Lett.* **2007**, *36*, 8. (c) Zhu, N.; Ma, B. C.; Zhang, Y.; Wang, W. *Adv. Synth. Catal.* **2010**, *352*, 1291. (d) Ratjen, L.; García-García, P.; Lay, F.; Edmund Beck, M.; List, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 754.

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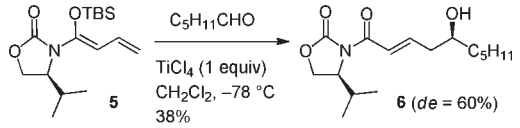
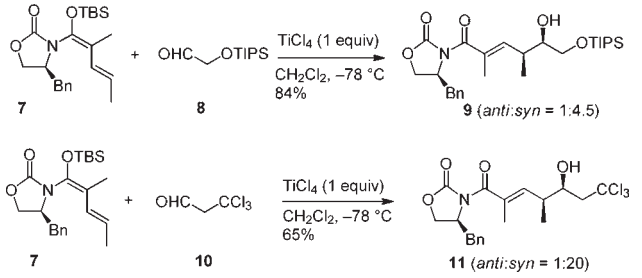
Remarkably, reagents lacking this methyl substituent not only exhibit lower selectivities but also provide the opposite chiral induction (Scheme 2).

Scheme 2. Kobayashi's Vinylogous Mukaiyama Aldol Reaction of *Unsubstituted* Vinylketene Silyl *N,O*-Acetals



This new methodology using Evans' auxiliary-derived vinylketene silyl *N,O*-acetals was further put to use in several total syntheses of complex natural products. One of its early applications is the total synthesis of palmerolide A. Nicolaou[6] and De Brabander[7] independently demonstrated the extreme viability and sustainability of this process.

Scheme 3. Kobayashi's Vinylogous Aldol Reaction with Chelating Aldehydes



However, for palmerolide A as for other natural products[8] the *syn*-aldol product was required and consequently the configuration at the newly established secondary alcohol had to be inverted later in the synthesis. Nevertheless, these examples clearly have shown the important status of this variation of Mukaiyama's aldol reaction.

Naturally, the *syn*-variation of Kobayashi's protocol would add to the impact of this reaction on natural products syntheses.

So far, only a limited number of reports on the *syn*-Kobayashi aldol reaction were reported. Kobayashi[9a] found that α-heteroatom substituted aldehydes switch the facial selectivity of this vinylogous Mukaiyama aldol reaction (Scheme 3). Yang[9] and Chen[9] reported on the *syn*-selective Kobayashi aldol reaction when aldehydes capable of chelation were employed.

The rationale for the observed selectivities in the Kobayashi aldol reaction discriminates between the favored and the unfavored transition state based on the steric interaction as indicated in Figure 1.

However, the use of 3-*Z*-vinylketene silyl *N,O*-acetal **16** would lead to steric interaction between the Lewis acid and either the terminal methyl group of the vinylketene acetal or the alkyl chain of the aldeyhde. Even with this aspect of ambiguity the generation of the *N,O*-ketene acetal of *Z*-configuration at position 3 (**16**) would be a prerequisite for the successful implementation of this transformation as a general method.

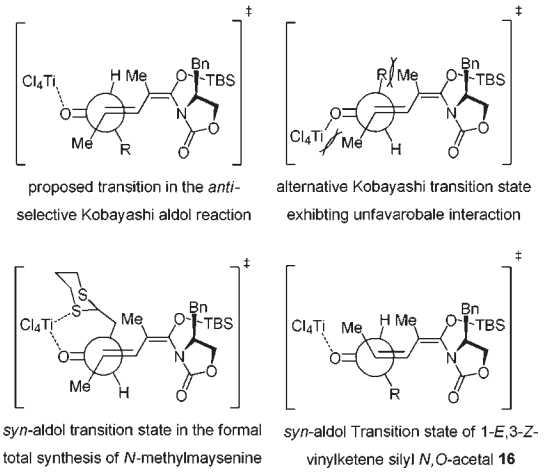
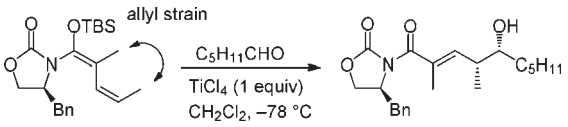


Figure 1. Proposed transition state for Kobayashi's *syn*-selective aldol reaction.

However, deprotonation of the corresponding unsaturated imide generates the ketene *N,O*-acetal with an *E*-configuration at position 3. Additionally, due to unfavorable 1,3-allylic strain interactions of the two methyl groups it was questionable if the two double bonds would be in conjugation in order to affect nucleophilicity at the γ-position (Scheme 4).

Scheme 4. *Syn*-Selective Vinylogous Aldol Reaction Using *Z*-Configured Ketene *N,O*-Acetals



Our strategy to generate the 1-*E*,3-*Z*-ketene *N,O*-acetal takes advantage of the deprotonation of unsaturated ester **12** with concomitant methylation of the so-generated

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

(6) (a) Nicolaou, K.; Guduru, R.; Sun, Y. P.; Banerji, B.; Chen, D. K. *Angew. Chem., Int. Ed.* **2007**, *46*, 5896. (b) Nicolaou, K. C.; Sun, Y. P.; Guduru, R.; Banerji, B.; Chen, D. Y. K. *J. Am. Chem. Soc.* **2008**, *130*, 3633.

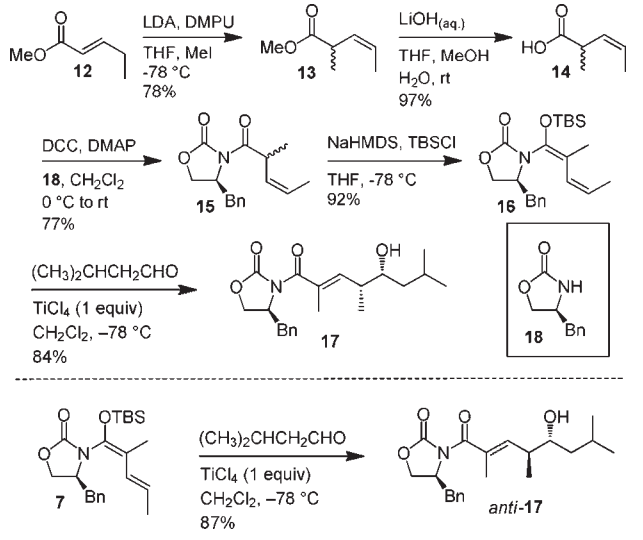
(7) Jiang, X.; Liu, B.; Lebreton, S.; De Brabander, J. K. *J. Am. Chem. Soc.* **2007**, *129*, 6386.

(8) Schmauder, A.; Müller, S.; Maier, M. E. *Tetrahedron* **2008**, *64*, 6263.

(9) (a) Shinoyama, M.; Shirokawa, S.; Nakazaki, A.; Kobayashi, S. *Org. Lett.* **2009**, *11*, 1277. (b) Wang, L.; Gong, J.; Deng, L.; Xiang, Z.; Chen, Z.; Wang, Y.; Chen, J.; Yang, Z. *Org. Lett.* **2009**, *11*, 1809. (c) Wang, L.; Xi, Y.; Yang, S.; Zhu, R.; Liang, Y.; Chen, J.; Yang, Z. *Org. Lett.* **2011**, *13*, 74.

enolate.[10] Ester **13** was subsequently hydrolyzed and transformed to the corresponding imide **15**.[11] Additional deprotonation and treatment with TBSCl provided the desired ketene *N,O*-acetal **16** for the *syn*-selective Kobayashi aldol reaction. Treatment of this acetal under Kobayashi's conditions provided the *syn*-aldol product **17** in 84% yield and with >20:1 selectivity (Scheme 5).

Scheme 5. Synthesis of *Z*-Configured Ketene *N,O*-Acetal (**16**) and Its Application in the *Syn*-Selective Aldol Reaction



The configuration was assigned with the aid of Mosher ester formation and observed identity of the reduced VMAR product **19** to known **20**.[8] Additional reassurance was obtained by comparison of the *anti*-products *anti*-**17** and **21** to their *syn*-isomers **17** and **22**[12] and by judgment of the NOE contacts and couplings constants of the corresponding acetonide **24** (Scheme 6).

In order to demonstrate the general applicability of this procedure we performed vinylogous aldol reactions on different aldehydes. Table 1 shows that aliphatic, unsaturated, and aromatic aldehydes can be converted to their corresponding *syn*-aldol products.

However, taking into consideration the proposed transition state that leads to *syn*-aldol products when conditions for the Kobayashi aldol reaction were employed (Figure 1) we hypothesized that using ketene acetals of *Z*-configurations at position 3 in combination with aldehydes that are capable of chelation would in our case lead to *anti*-aldol products instead. Indeed, the transformation of 2-methoxybenzaldehyde (**25**) with 3-*Z*-ketene *N,O*-acetal **16** leads to *anti*-aldol product **26** in 72% yield and *dr* > 20:1 (Scheme 7).

(10) (a) Johnson, W. S.; Lyle, T. A.; Daub, G. W. *J. Org. Chem.* **1982**, *47*, 163. (b) Adam, W.; Saha-Möller, C. R.; Weichold, O. *Monatsh. Chem.* **2000**, *131*, 697.

(11) Kleber, C.; Andrade, Z.; Rocha, R. O.; Vercillo, O. E.; Silva, W. A.; Matos, R. A. F. *Synlett* **2003**, *15*, 2351.

(12) For comparison of the spectra, see Supporting Information.

Scheme 6. Configurational Assignment of the *Syn*-Selective Aldol Reaction

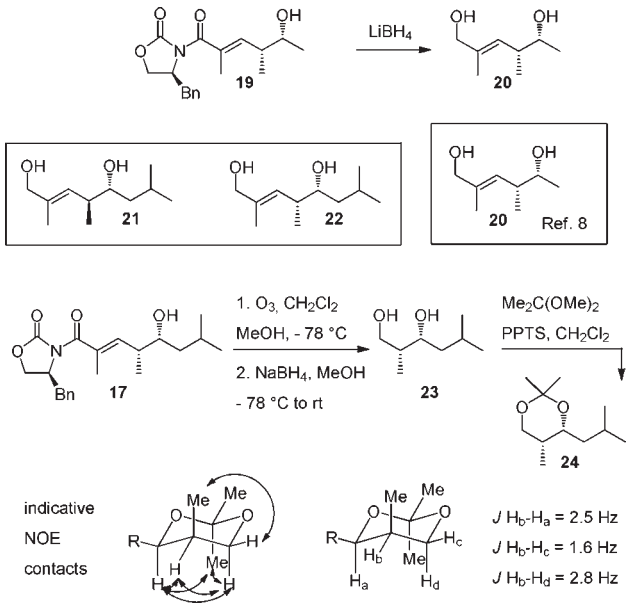
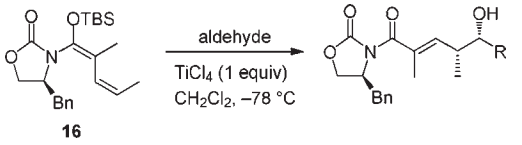


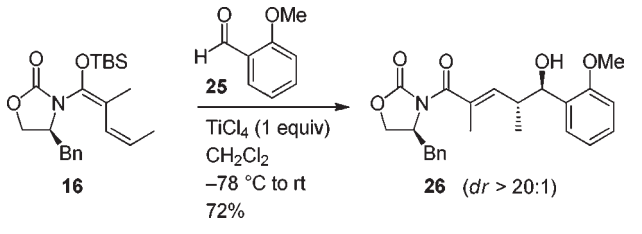
Table 1. Conversion of Aldehydes to *Syn*-Aldol Products



entry	aldehyde	yield (%)[a]	*dr*[b]
1	acetaldehyde	75	>20:1
2	isovaleraldehyde	84	>20:1
3	cyclohexanecarbaldehyde	74	>20:1
4	hexanal	73	>20:1
5	*E*-crotonaldehyde	71	>20:1
6[c]	benzaldehyde	64	>20:1

[a] Isolated yield after chromatography. [b] Determined by ^{1}H NMR. [c] –78 °C to rt.

Scheme 7. Kobayashi's Vinylogous Mukaiyama Aldol Reaction on a Chelating Aldehyde



In summary, we introduced a general applicable *syn*-selective vinylogous Kobayashi aldol reaction using 1-*E*, 3-*Z*-ketene *N,O*-acetal **16**. This protocol provides the *syn*-aldol product in yields ranging from 62 to 84% and selectivities higher than 20:1 and can be applied to aliphatic, unsaturated, and aromatic aldehydes as well. As a complement, this protocol provides the *anti*-isomers when aldehydes with substituents capable of chelation are used.

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Supporting Information Available. Spectroscopic data and experimental procedures for compounds **12**–**34**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.