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A Switch of Facial Selectivities Using α-Heteroatom-Substituted Aldehydes in the Vinylogous Mukaiyama Aldol Reaction

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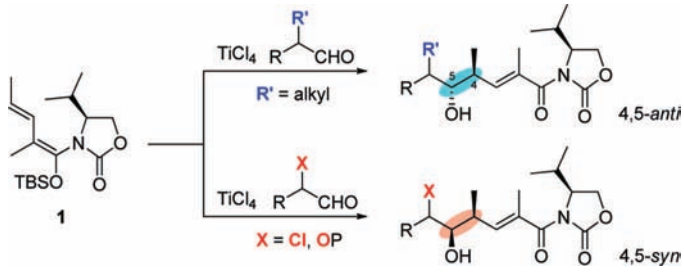
ABSTRACT

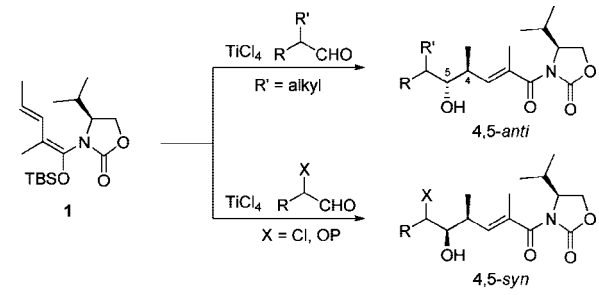


The vinylogous Mukaiyama aldol reaction (VMAR) of chiral nonracemic ketene silyl *N,O*-acetal with various aldehydes is demonstrated. VMAR with α-heteroatom-unsubstituted aldehydes proceeded with a high degree of *anti*-selectivity. In sharp contrast, moderate to high *syn*-selectivity was observed when α-heteroatom-substituted aldehydes were used.

We have developed the vinylogous Mukaiyama aldol reaction (VMAR) of chiral ketene silyl *N*,*O*-acetal **1** with a variety of aldehydes affording *anti*-aldol adducts (Scheme 1),[1,2] which have been used toward the total synthesis of naturally occurring products.[3] During the course of our investigation of the VMAR, we have observed a remarkable switch to *syn*-stereoselectivity using α-heteroatom-substituted aldehydes. Herein, we report the scope and limitation of the VMAR and the detail of a stereochemical switch when α-heteroatom-substituted aldehydes were used.

Initially, we examined VMAR of **1** (dr = >20:1) with a variety of achiral aldehydes (Table 1). Compound **1** used in this study was prepared from commercially available *trans*-2-methyl-2-pentenoic acid and Evans chiral auxiliary derived from

Scheme 1



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

(2) For reviews of the vinylogous aldol reaction, see: (a) Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929–1972. (b) Soriente, A.; De Rosa, M.; Villano, R.; Scettri, A. *Curr. Org. Chem.* **2004**, *8*, 993–1007. (c) Denmark, S. E.; Heemstra, J. R., Jr.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 4682–4698. (d) Kalesse, M. *Top. Curr. Chem.* **2005**, *244*, 43–76. (e) Brodmann, T.; Lorenz, M.; Schäckel, R.; Simsek, S.; Kalesse, M. *Synthesis* **2009**, 174–192.

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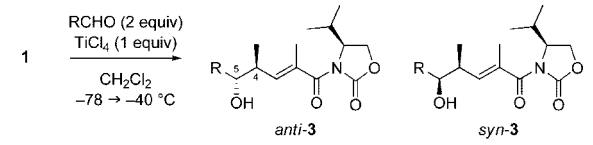
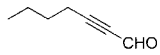
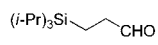
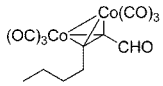
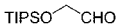
Table 1. VMAR of **1** with Achiral Aldehydes



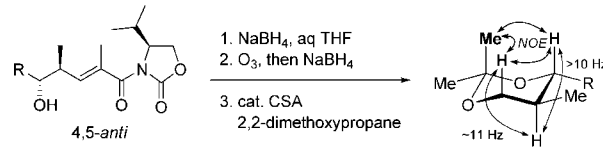
enrty	aldehyde		yield (%)	*anti*:*syn*[a]
1		**2a**	80	7.7:1
2		**2b**	97	>20:1
3		**2c**	88	>20:1
4		**2d**	83[b]	>20:1
5		**2e**	0	-
6		**2f**	84	1:4.5
7		**2g**	97	1:15
8		**2h**	65	1:>20

[a] Diastereomeric ratio was determined by ^{1}H NMR analysis. [b] Demetallated aldol adduct **3a** was obtained in 13% yield with high *anti* selectivity (dr = >20:1).

L-valine.[1] Treatment of 2 equiv of ynal **2a** with 1 equiv of $TiCl_4$ in CH_2Cl_2 at −78 °C and careful addition of chiral nonracemic ketene silyl *N*,*O*-acetal **1**, followed by warming of the reaction mixture to −40 °C, led to the aldol adduct **3a** in 80% yield, albeit with moderate 4,5-*anti*-diastereoselectivity (dr = 7.7:1, entry 1). However, the related reaction using **2b**−**d** was found to afford the corresponding adducts **3b**−**d** in good-to-excellent yield with high *anti* diastereoselectivity (entries 2−4). Demetalation of the aldol adduct **3d** was easily achieved using a conventional method (NMO) to afford **3a** in good yield without loss of stereochemical integrity. Thus, the VMAR−demetalation

(3) (a) Hosokawa, S.; Ogura, T.; Togashi, H.; Tatsuta, K. *Tetrahedron Lett.* **2005**, *46*, 333–337. (b) Nakamura, T.; Shirokawa, S.-i.; Hosokawa, S.; Nakazaki, A.; Kobayashi, S. *Org. Lett.* **2006**, *8*, 677–679. (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) Xin Jiang, X.; Liu, B.; Lebreton, S.; De Brabander, J. K. *J. Am. Chem. Soc.* **2007**, *129*, 6386–6387. (f) Nicolaou, K. C.; Guduru, R.; Sun, Y.-P.; Banerji, B.; Chen, D. Y.-K. *Angew. Chem., Int. Ed.* **2007**, *46*, 5896–5900. (g) Shirokawa, S.-i.; Shinoyama, M.; Ooi, I.; Hosokawa, S.; Nakazaki, A.; Kobayashi, S. *Org. Lett.* **2007**, *9*, 849–852. (h) Nicolaou, K. C.; Sun, Y.-P.; Guduru, R.; Banerji, B.; Chen, D. Y.-K. *J. Am. Chem. Soc.* **2008**, *130*, 3633–3644. (i) Schmauder, A.; Müller, S.; Maier, M. E. *Tetrahedron* **2008**, *64*, 6263–6269. (j) Hosokawa, S.; Yokota, K.; Imamura, K.; Suzuki, Y.; Kawarasaki, M.; Tatsuta, K. *Chem. Asian J.* **2008**, *3*, 1415–1421. For reviews, see: (k) Tatsuta, K.; Hosokawa, S. *Chem. Rev.* **2005**, *105*, 4707–4729. (l) Tatsuta, K.; Hosokawa, S. *Chem. Rec.* **2006**, *6*, 217–233. (m) Hosokawa, S.; Tatsuta, K. *Mini-Rev. Org. Chem.* **2008**, *5*, 1–18.

Scheme 2. Determination of the C4−C5 Relationships of **3a**−**c**

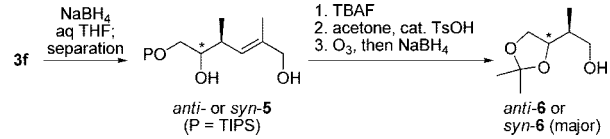


3a: R = *n*-BuC≡C-
3b: R = (*i*-Pr_3Si)$(CH_2)_2$-
3c: R = Ph_2CH-

sequence, rather than the direct VMAR with **2a**, is the most effective method of obtaining aldol adduct **3a** with high diastereoselectivity. Unfortunately, pivalaldehyde **2e**, one of the bulky aldehydes, was not a suitable substrate for the VMAR (entry 5). Stereochemical determination (vide infra) revealed that the observed facial selectivities were consistent with similar previously reported reactions.[1] Intriguingly, however, the VMAR with α-heteroatom-substituted aldehydes was found to proceed with 4,5-*syn*-diastereoselectivity (entries 6−8). Thus, similar reaction of **1** with siloxyacetaldehyde **2f** resulted in the formation of the *syn*-aldol adduct **3f** in 84% yield in a diastereomeric ratio of 1:4.5 (entry 6). In addition, the VMAR of monochlorinated aldehyde **2g** was found to afford *syn* adduct **3g** as a predominant diastereomer (entry 7). Rather hindered α-heteroatom-substituted aldehyde **2h** also underwent the VMAR with **1** to afford the aldol adduct **3h** with high *syn* selectivity, although the yield was only moderate (entry 8). Several trends became obvious: (1) The C4 chiral center of the aldol adduct **3** is controlled as an *S* configuration independent of the substituent of the aldehyde. (2) *syn* or *anti* selectivity is generally enhanced when hindered aldehydes are used. (3) Facial selectivity of the aldehyde changes depending on the substituents on the aldehydes used, although the exact origin of this stereo changeover remains obscure.

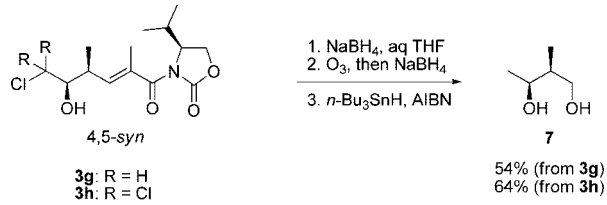
Stereochemical determinations of the aldol adducts **3** were performed as follows. The C4−C5 relationships of the aldol adducts **3a**−**c** were determined by the coupling constants of the corresponding 1,3-dioxane derivatives **4a**−**c** (Scheme 2). The absolute stereochemistry of the aldol adduct **3a** was confirmed by the modified Mosher method,[4] and the absolute configuration of **3b** and **3c** was tentatively assigned by assuming an analogous diastereoselection. The spectroscopic data of the aldol adducts **3f** and **3g**,**h** matched those of the known compounds **6**[5] and **7**,[6] respectively (Schemes 3 and 4).

Scheme 3. Determination of the Stereochemistry of **3f**



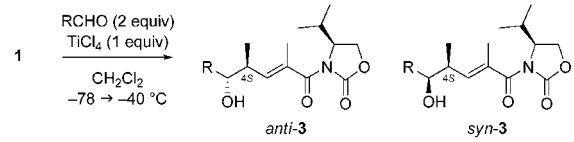
With these observations in hand, our attention was turned to the VMAR of **1** with chiral nonracemic aldehydes (Table

Scheme 4. Determination of the Stereochemistry of **3g** and **3h**



2). It is anticipated that matched or mismatched cases of **1** should be observed. However, the VMAR of **1** with each enantiomer of aldehydes provided a high level of diastereoselectivity (entries 1 vs 2 and entries 4 vs 5); thus, the VMAR of these aldehydes resulted in the exclusive formation of the corresponding 4*S*-aldol adducts independent of the configuration at the α-chiral center of aldehydes in each case. It suggested that highly reagent-controlled diastereoselective VMAR was established. The VMAR of **1** with (*S*)-aldehyde **2i**, a previously reported system toward the synthesis of khafurefungin,[3g] afforded the corresponding *anti*-adduct in excellent yield with high diastereoselectivity (entry 1). In addition, the related reaction with (*R*)-aldehyde **2j** provided the same level of yield and *anti*-selectivity (entry 2). The stereochemical changeover was observed in the VMAR with α-oxygenated aldehydes (entries 3−5). We examined the reaction with benzyl-protected lactaldehyde **2k**, which unfortunately resulted in poor stereoselectivity, but the *syn* product was predominant (entry 3).[7] The low level of diastereoselectivity using an aldehyde containing a chelatable heteroatom suggests that the highly stereocontrolled VMAR is not mediated through chelation. In contrast, high level of

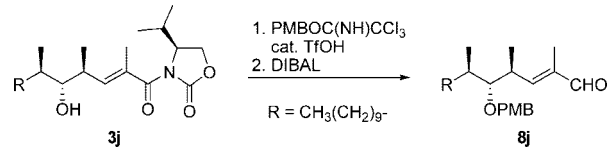
Table 2. VMAR of **1** with Chiral Nonracemic Aldehydes



enrty	aldehyde		yield (%)	*anti*:*syn*[a]
1[b]	$CH_3(CH_2)_9$CHO	**2i**	98	>20:1
2[b]	$CH_3(CH_2)_9$CHO	**2j**	95	>20:1
3	BnO CHO	**2k**	76	1:1.8
4	TIPSO CHO	**2l**	88	1:>20
5	TIPSO CHO	**2m**	92	1:>20

[a] Diastereomeric ratio was determined by ^{1}H NMR analysis. [b] Reaction was performed at −78 to −30 °C.

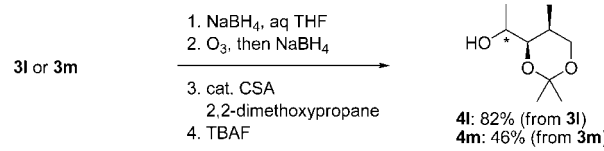
Scheme 5. Determination of the Stereochemistry of **3j**



syn-selective VMAR affording **3l** was achieved using TIPS surrogate **2l** as a hindered substrate (entry 4), and its enantiomer **2m** led us to the corresponding *syn*-aldol adducts **3m** in good yield (entry 5).

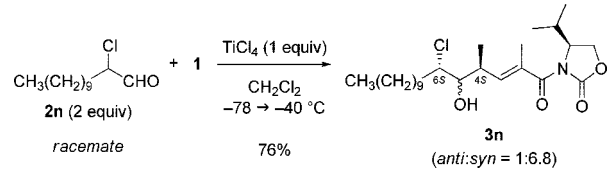
Stereochemical determination of the aldol adducts was performed by comparison of the ^{1}H NMR spectra with those of known compounds (Schemes 5 and 6).[8,9]

Scheme 6. Determination of the Stereochemistry of **3l** and **3m**



We next demonstrated the VMAR of **1** with racemic α-monochlorinated aldehyde **2n** to investigate the possibility of kinetic resolution (Scheme 7). Exposure of 2 equiv of

Scheme 7. Demonstrated VMAR of **1** with Racemic Chlorinated Aldehyde **2n**



racemic **2n** to 1 equiv of $TiCl_4$ and **1** gave the corresponding aldol adduct **3n** in 76% yield as a mixture of epimers at C5 (*anti*:*syn* = 1:6.8). Our result suggested that the *syn*-aldol adduct was mainly obtained through the VMAR, as previously observed, and that perfect kinetic resolution was achieved.

(4) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096.

(5) (a) Mori, K.; Nomi, H.; Chuman, T.; Kohno, M.; Kato, K.; Noguchi, M. *Tetrahedron* **1982**, *38*, 3705–3711. (b) Nicolaou, K. C.; Papahatjis, D. P.; Claremon, D. A.; Magolda, R. L.; Dolle, R. E. *J. Org. Chem.* **1985**, *50*, 1440–1456.

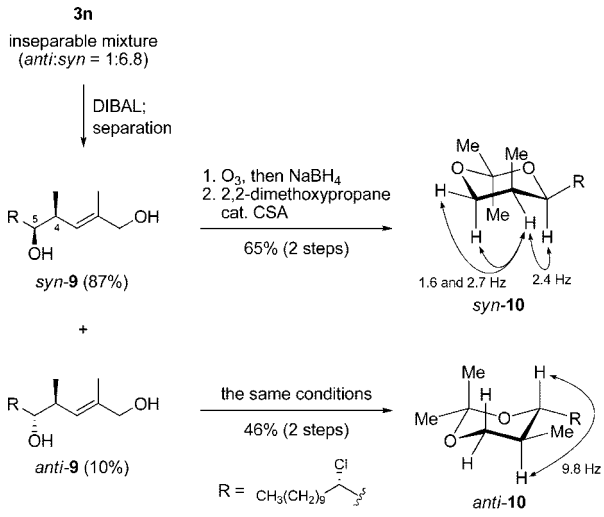
(6) Dandapani, S.; Jeske, M.; Curran, D. P. *J. Org. Chem.* **2005**, *70*, 9447–9462.

(7) The VMAR of *ent*-**1** with **2k** was found to provide the corresponding aldol adduct in 81% yield with moderate diastereoselectivity (*anti*:*syn* = 1:4.2).

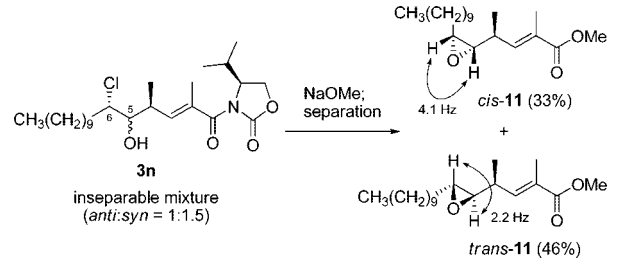
(8) Wakabayashi, T.; Mori, K.; Kobayashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 1372–1375.

(9) Terada, M. Ph.D. Thesis, Tokyo Institute of Technology, 1993.

Scheme 8. Structural Determination of the C4−C5 Relationship of the Aldol Adduct **3n**



Scheme 9. Structural Determination of the C5−C6 Relationship of the Aldol Adduct **3n**



The stereochemical assignment is shown in Schemes 8 and 9. Thus, the inseparable mixture (*anti*:*syn* = 1:6.8) was first reduced with DIBAL to obtain the *syn*-**9** and *anti*-**9** in 87% and 10% yields, respectively. The C4−C5 relationships of each isomer were established by correlating to the corresponding 1,3-dioxane derivative, *syn*-**10** or *anti*-**10** (Scheme 8). The C5−C6 relationship of **3n** was established by converting the mixture (*anti*:*syn* = 1:1.5) into the corresponding epoxides *cis*-**11** and *trans*-**11** (Scheme 9). These results imply that only (*S*)-aldehyde **2n** underwent VMAR with **1**. The relatively low level of facial selection might be attributed to the comparatively weak electronegative character of monochlorinated aldehyde **2n**.

In summary, we have demonstrated the VMAR of chiral ketene silyl *N*,*O*-acetal **1** with a variety of aldehydes. The most striking feature is a remarkable switch to *syn*-stereoselectivity using α-heteroatom-substituted aldehyde. To the best of our knowledge, there has been no precedent for this kind of stereochemical switch. Further investigation of the details of the switch as well as extension of this finding is in progress.

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Supporting Information Available: Detailed experimental procedure and characterization data for compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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