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Syn Selective Vinylogous Mukaiyama Aldol Reaction Using *Z,E*-Vinylketene *N,O*-Acetal with Acetals

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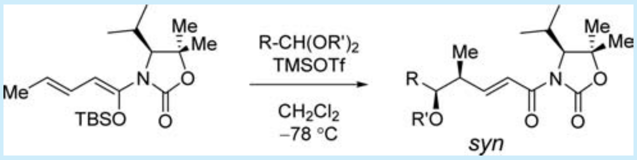
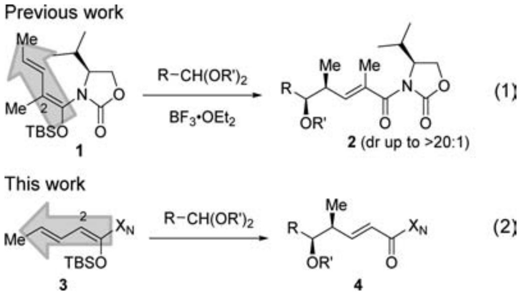
Supporting Information

ABSTRACT: Stereoselective vinylogous Mukaiyama aldol reactions using the *Z,E*-vinylketene silyl *N,O*-acetal possessing a chiral auxiliary, derived from (*E*)-3-pentenoic acid and L-valine, have been achieved. The reaction proceeded smoothly to give a *syn* adduct in high stereoselectivity. Since the products possess structures including *δ*-alkoxy-*γ*-methyl-*α*,*β*-unsaturated imide, this reaction would be applicable to synthesize polyketides in a short procedure.



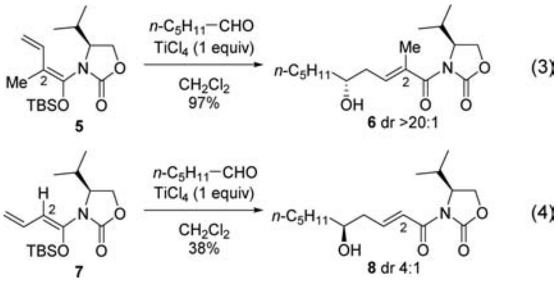
Remote asymmetric induction has been studied as a challenging problem; however, only a limited number of methodologies have been developed.[1] The stereoselective vinylogous Mukaiyama aldol reaction (VMAR) of acyclic vinylketene silyl *N,O*-acetal should be a powerful method to synthesize natural products because it would afford a polyketide skeleton.[2] In particular, the reaction with acetal would provide the protected polyketide structure, which could afford access to shorter synthetic routes to natural products. However, few precedents of the stereoselective vinylogous Mukaiyama aldol reaction affording *syn*-*δ*-hydroxy-*γ*-methyl-*α*,*β*-unsaturated carboxylate have been reported,[3] while the reaction providing *anti*-*δ*-hydroxy-*γ*-methyl-*α*,*β*-unsaturated carboxylate has a few precedents.[4] Recently, we have reported the stereoselective vinylogous Mukaiyama aldol reaction with acetal by using chiral *E,E*-vinylketene silyl *N,O*-acetal **1** (Scheme 1, eq 1).[5] The reaction proceeded to give a *syn* adduct having a polypropionate skeleton in a stereoselective manner. Herein, we present the stereoselective Mukaiyama aldol reaction using *Z,E*-vinylketene silyl *N,O*-acetal with acetal to yield a *syn* adduct (Scheme 1, eq 2).

Scheme 1. Remote Asymmetric Induction Reactions Using Vinylketene Silyl *N,O*-Acetal and Acetal



Asymmetric induction using C2-methyl-missing dienol ether **3** is more difficult than that with vinylketene silyl *N,O*-acetal **1** because the diene of **3** directs far from the chiral auxiliary. Actually, in the reaction with aldehyde (Scheme 2), *α*-methyl-missing dienol ether **7** afforded adduct **8** in low yield with moderate stereoselectivity (eq 4), while C2-methyl-possessing **5** providing **6** in excellent selectivity and yield (eq 3).[6] These results encouraged us to search for an effective vinylketene silyl *N,O*-acetal possessing the terminal methyl group and a chiral auxiliary.

Scheme 2. Previous Work on Vinylogous Mukaiyama Aldol Reactions Using Vinylketene Silyl *N,O*-Acetals



At first, a stable dienol ether attaching the TBDPS group was submitted to the vinylogous Mukaiyama aldol reaction in the presence of various Lewis acids (Table 1). Both $TiCl_4$ and $SnCl_4$ gave adducts in good yield with low stereoselectivity (entries 1 and 2). On the other hand, $BF_3{\cdot}OEt_2$ and TMSOTf provided adducts in high yield, but stereoselectivities were moderate (entries 3 and 4). When TBS-attaching dienol ether was employed, the yield of adducts was moderate due to generation of adducts at the C2 position; however, the stereoselectivity increased (entry 5). Treatment of **3b** in the presence of TMSOTf provided **4** in better yield with comparable stereoselectivity (entry 6). Therefore, TBS as the

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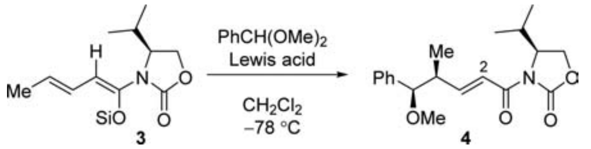
Table 1. Vinylogous Mukaiyama Aldol Reaction with Benzaldehyde Dimethyl Acetal and TBDPS or TBS Dienol Ether



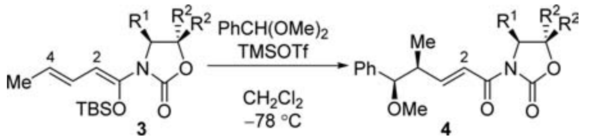
entry	Lewis acid	Si	yield (%)	dr[a] (**4**:isomers[b])
1	$TiCl_4$	TBDPS **a**	70	51:49
2	$SnCl_4$	TBDPS **a**	68	48:52
3	$BF_3{\cdot}OEt_2$	TBDPS **a**	92	72:28
4	TMSOTf	TBDPS **a**	93	69:31
5	$BF_3{\cdot}OEt_2$	TBS **b**	51	79:21
6	TMSOTf	TBS **b**	59	78:22

[a] Determined by 400 MHz ^{1}H NMR. [b] Including other three isomers.

silyl group and TMSOTf as Lewis acid were employed in further studies.

Next, various chiral auxiliaries have been examined (Table 2). Oxazolidone possessing a benzyl group and cyclohexyl group afforded adducts in comparable stereoselectivity with a reduced yield due to reaction at the C2 position (entries 2 and 3). When SuperQuat,[7] the oxazolidone possessing isopropyl group at the C4′ position and the dimethyl group at C5′ position, was employed as the chiral auxiliary, the reaction proceeded at the C4 position of the diene of **3e** and adduct **4** was obtained in high yield and high stereoselectivity (entry 4). SuperQuats possessing a diphenyl group at the C5′ position[8] and a benzyl group at the C4′ position reduced the yield and selectivity (entries 5, 6, and 7). Therefore, the best conditions were determined to include **3e** as the vinylketene silyl *N*,*O*-acetal and TMSOTf as the Lewis acid.

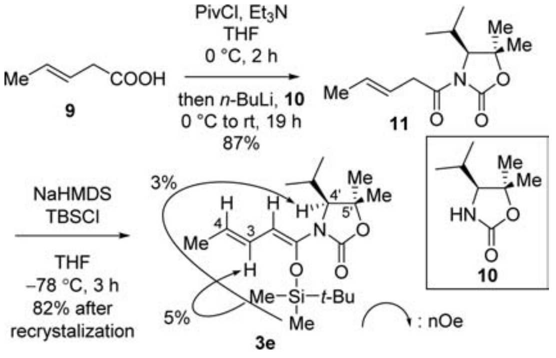
Table 2. Vinylogous Mukaiyama Aldol Reaction with Benzaldehyde Dimethyl Acetal and TBS Dienol Ether



entry	R^1	R^2	yield (%)	dr[a] (**4**:isomers[b])
1	*i*-Pr	H **b**	59	78:22
2	Bn	H **c**	27	79:21
3	Cy	H **d**	47	80:20
4	*i*-Pr	Me **e**	86	94:6[c]
5	*i*-Pr	Ph **f**	74	69:31
6	Bn	Me **g**	46	64:36
7	Bn	Ph **h**	46	69:31

[a] Determined by 400 MHz ^{1}H NMR. [b] Including other three isomers. [c] Determined by HPLC.

Scheme 3. Preparation of Vinylketene Silyl *N*,*O*-Acetal 3e



Vinylketene silyl *N*,*O*-acetal **3e** was prepared from (*E*)-3-pentenoic acid **9**[9] (Scheme 3). Carboxylic acid **9** was converted to mixed anhydride, which was reacted with lithiated oxazolidone **10** to obtain imide **11**. Treatment of imide **11** with NaHMDS in the presence of TBSCl afforded *Z*,*E*-diene **3e** in a stereoselective manner. The stereochemistry of the diene was determined by NOE correlation between H3 and a methyl group of TBS as well as the coupling constant between H3 and H4 ($J = 15.0$ Hz). Crystalline **3e** was also characterized using X-ray crystallography as shown in Figure 1. The side view of crystal **3e** shows that the chiral auxiliary lies at an angle of 40° with the diene chain (Figure 1B). The isopropyl group at the C4′ position of the oxazolidone ring directed the TBS group into the opposite side of the diene. Additionally, one of the methyl groups at the C5′ position further pushed the TBS group down. As a result of the steric repulsion, one of the methyl groups of TBS was directed below the diene chain. The NOE correlation between H4′ and one of the methyl groups of TBS as well as between H3 and another methyl group of TBS indicated that it would be possible that the conformation in the crystal would be taken in the $CDCl_3$ solution (Scheme 3).

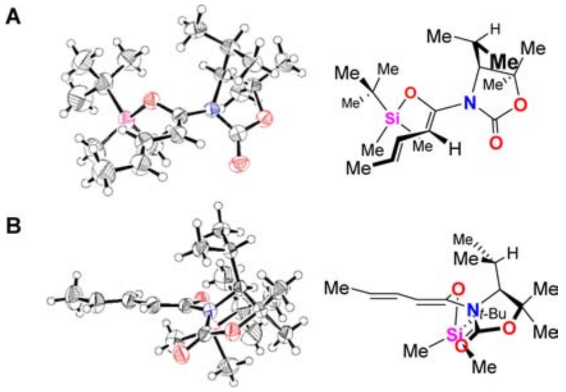
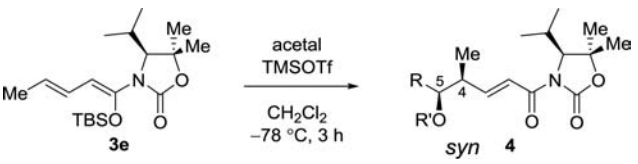


Figure 1. ORTEP drawing of **3e**. (A) Front view; (B) side view.

Next, we performed the vinylogous Mukaiyama aldol reaction using chiral vinylketene silyl *N*,*O*-acetal **3e** with various acetals (Table 3). Reactions with 4-bromobenzaldehyde dimethyl acetal and dibenzyl acetal gave **4i** and **4j** in high yield with high stereoselectivity (Table 3, entries 2 and 3). *p*- and *m*-Methoxybenzaldehyde dimethyl acetal also afforded **4k** and **4l** in high yield with good and high stereoselectivity, respectively (entries 4 and 5). However, *p*-nitrobenzaldehyde dimethyl acetal produced **4m** in low yield and moderate stereoselectivity due to slow generation of an unstabilized cation (entry 6). In the case of aliphatic acetals, reactions proceeded smoothly in the presence of molecular sieves 4A removing moisture and a proton and provided **4** in high yield and high stereoselectivity (entries 7 to 11).[10] Both a linear alkyl chain including methyl and ethyl groups and a branched alkyl group as well as both dimethyl acetal and dibenzyl acetal gave *syn* adduct **4**. Dibenzyl acetals derived from *α*,*β*-unsaturated aldehydes including a di- and trisubstituted olefin afforded protected allylic alcohols in high yield with high stereoselectivity (entries 12 and 13).

Table 3. Vinylogous Mukaiyama Aldol Reaction with 3e and Various Acetals

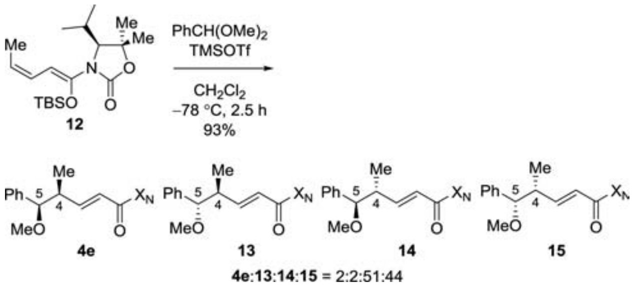


entry	acetal	yield	dr[a] (**4**:isomers[b])
1	Ph-CH(OMe)$_2$ **e**	86	94:6
2	*p*-Br-Ph-CH(OMe)$_2$ **i**	93	92:8
3	*p*-Br-Ph-CH(OBn)$_2$ **j**	89	96:4
4[c]	*p*-MeO-Ph-CH(OMe)$_2$ **k**	86	83:17
5	*m*-MeO-Ph-CH(OMe)$_2$ **l**	92	91:9
6[d]	*p*-NO$_2$-Ph-CH(OMe)$_2$ **m**	27	61:39
7[e]	Me-CH(OMe)$_2$ **n**	99	82:18
8[e]	Et-CH(OMe)$_2$ **o**	90	92:8
9[e]	Et-CH(OBn)$_2$ **p**	90	91:9
10[e]	*i*-Pr-CH(OMe)$_2$ **q**	84	93:7
11[e]	*i*-Pr-CH(OBn)$_2$ **r**	81	93:7
12[e]	(*E*)-MeCH=CHCH(OBn)$_2$ **s**	90	86:14
13[e]	(*E*)-MeCH=CMeCH(OBn)$_2$ **t**	87	97:3

[a]Determined by HPLC. [b]Including other three isomers. [c]0.05 equiv of TMSOTf was employed. [d]2.2 equiv of TMSOTf were employed. [e]MS 4 A was added.

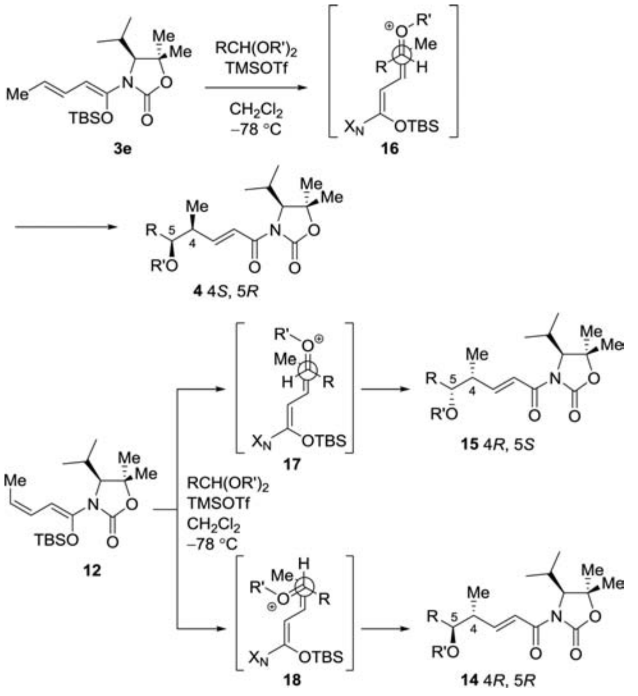
On the other hand, VMAR with *Z,Z*-diene **12**[11] gave a mixture of four diastereomers including **14** and **15** as major products in almost equal ratio (Scheme 4). These results indicated that the reaction *Z,Z*-diene **12** was converted to 4*R* isomers predominantly.

Scheme 4. Vinylogous Mukaiyama Aldol Reaction with *Z,Z*-Dienol Ether 12



Based on X-ray crystallography and NOE of **3e** (Figure 1), the stereoselective vinylogous Mukaiyama aldol reaction with **3e** (Table 3), and the reaction with **12** (Scheme 4), we propose the transition state as shown in Scheme 5. The oxonium cation derived from the acetal approached from the upper face of the diene to avoid steric repulsion of the methyl group of TBS positioned below the diene, which would make the favored transition state **16** to generate 4*S*,5*R*-isomer **4**. On the other hand, the VMAR with *Z,Z*-diene **12** proceeded via two kinds of favored transition states **17** and **18**,[12] including the approach of the electrophile from the upper face of the diene, to afford 4*R*,5*S*-isomer **15** and 4*R*,5*R*-isomer **14**, respectively. It is interesting that in these transition states the isopropyl group at the C4′ position and one methyl group at the C5′ position of the oxazolidone directed the position of the TBS group, which determined the accessible face of the diene. This unique stereocontrol system realized the remote asymmetric induction.

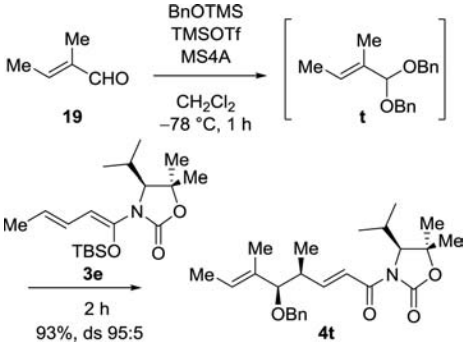
Scheme 5. Proposed Transition State



In our previous work on the reaction with **1** possessing the C2 methyl group (Scheme 1, eq 1), the electrophile came from the lower face of the diene to avoid the steric repulsion with the isopropyl group of the chiral auxiliary. However, the present reaction, employing the vinylketene silyl *N,O*-acetal missing the C2-methyl group, underwent the vinylogous Mukaiyama aldol reaction from the upper face of the diene to avoid the steric repulsion with the methyl group of TBS.

Additionally, the one-pot synthesis of **4t** from aldehyde **19** was examined (Scheme 6). After preparation of acetals by using BnOTMS and TMSOTf (0.2 equiv), **3e** was added to the resulting mixture.[5] The reaction proceeded smoothly to give **4t** in high yield with high stereoselectivity.

Scheme 6. One-Pot Transformation of Aldehyde 19 to Adduct 4t



In conclusion, the stereoselective vinylogous Mukaiyama aldol reaction using vinylketene silyl *N,O*-acetal derived from (*E*)-3-pentenoic acid has been developed. This reaction proceeded via remote asymmetric induction to give a *syn* adduct possessing δ-alkoxy-γ-methyl-α,β-unsaturated imide. SuperQuat was an effective chiral auxiliary to direct the methyl group of TBS to cover one face of the diene. It is noteworthy that the electrophile approached the C2-methyl-missing vinylketene silyl *N,O*-acetal from the face opposite to that of the C2-methyl-possessing vinylketene silyl *N,O*-acetal. Products of this reaction have a polyketide structure so that this reaction would be useful in natural product synthesis. Synthetic studies on bioactive polyketides using this reaction are in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03549.

X-ray data for compound **3e** (CIF)
X-ray data for compound **4e** (CIF)
X-ray data for compound **4n** (CIF)
Experimental procedures, spectral data of compounds, and ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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