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Remote Asymmetric Induction Using Acetate-Type Vinylketene Silyl *N,O*-Acetals

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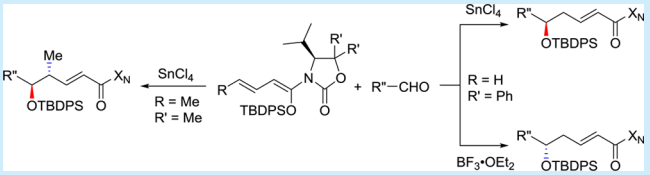
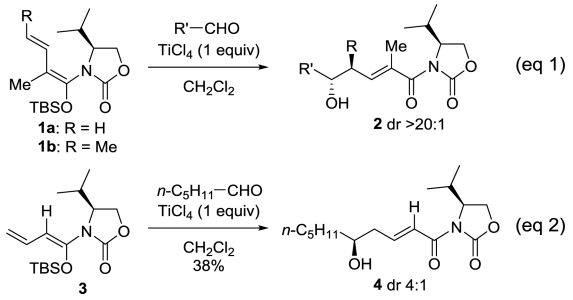
Supporting Information

ABSTRACT: Remote asymmetric induction by the vinylogous Mukaiyama aldol reaction using the acetate-type vinylketene silyl *N,O*-acetal possessing a chiral auxiliary has been achieved. The silyl *N,O*-acetal derived from crotonate and L-valine afforded the *O*-silylated 5*R*- and 5*S*-adducts selectively by treatment with $SnCl_4$ and $BF_3{\cdot}OEt_2$, respectively. The $SnCl_4$-mediated isomerization of silyl dienol ether was found, and the resulting major isomer showed high reactivity to give γ-adduct in high stereoselectivity.



Remote asymmetric induction reactions have been studied as challenging matters in organic chemistry.[1] Although a limited number of systems have been developed, they have been used as powerful tools in natural product syntheses.[2] During the course of our research on methodologies and strategies to realize the short-step synthesis of polyketides, we have developed remote asymmetric induction reactions using the vinylketene silyl *N,O*-acetals **1a** and **1b** (Scheme 1, eq 1).[3] This reaction

Scheme 1. Previous Results on Remote Asymmetric Induction Using Vinylketene Silyl *N,O*-Acetals[3a]



featured simultaneous introduction of both asymmetric centers and the multifunctionalized carbon chain, which made it possible to establish short-step synthesis of polypropionates. Easy preparation and stability of crystalline **1a** and **1b** make them to be friendly compounds. Therefore, this methodology has been used to natural product synthesis.[4] Additionally, we have developed analogous reactions using **1b** to synthesize a variety types of polypropionates.[5] In the report in 2004, we also revealed that α-methyl-missing dienolate **3** possessed the diene chain in which the reaction site directed far from the chiral auxiliary and thereby the stereoselectivity reduced to be moderate (Scheme 1, eq 2).[3a] Additionally, dienol ether **3** was found to be unstable for purification by column chromatography, and the lability of **3** made the reaction to afford products **4** in low yield. Improvement of this reaction would give a new methodology to construct the polyacetate skeleton in short step. Herein, we present improved vinylogous Mukaiyama aldol reactions using newly designed chiral dienolates.

The X-ray crystallograph of **1a** is disclosed in Figure 1. The oxazolidone ring places almost perpendicular to the diene chain

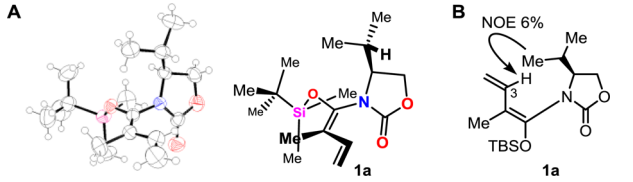


Figure 1. Conformation of **1a**: (A) ORTEP drawing of crystal **1a**; (B) NOE correlation of **1a** in $CDCl_3$.

(Figure 1A). This conformation does not allow participation of the lone-pair electron of nitrogen to the diene, which is a reason for the stability of **1a**. The oxazolidone ring looks impossible to rotate because it is sandwiched between a methyl group of TBS and the dienol side chain. One of methyl groups of the isopropyl group overlaps the tetrasubstituted olefin. A similar conformation of **1a** in $CDCl_3$ solution was observed by NOE correlation between H3 and the methyl group of the isopropyl group (Figure 1B).

On the other hand, direction of extension of the side chain of **3** (Scheme 1, eq 2) was different from that of **1a**. The terminal carbon of the diene **3**, the reaction site, should be far from isopropyl group on the oxazolidone ring. To improve the direction of the isopropyl group and stability of dienol ether, we designed new vinylketene *N,O*-acetal as **5** shown in Figure 2. When the chiral auxiliary attaches to the dienyl group, substituents at the C5′ position should direct the isopropyl

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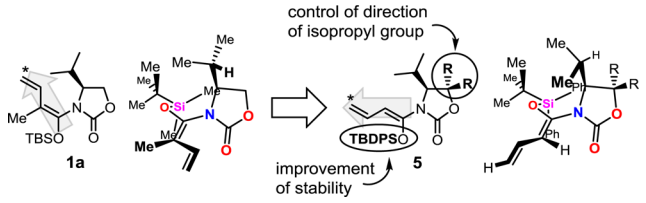
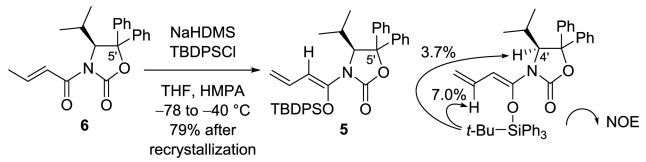


Figure 2. Design of a new vinylketene silyl *N*,*O*-acetal.

group to cover the diene. Therefore, we decided to employ the SuperQuat auxiliary having dimethyl[6] or diphenyl groups[7] at the C5′ position of the oxazolidone ring. Additionally, TBDPS instead of TBS would make the vinylketene silyl *N*,*O*-acetal more stable.[8]

A new vinylketene silyl *N*,*O*-acetal **5** possessing 5′,5′-diphenyloxazolidone and a *tert*-butyldiphenylsilyl group was obtained as a single isomer by O-silylation of imide **6**[7b] (Scheme 2). Dienol ether **5** was obtained as a crystal that allowed X-ray crystallography (Figure 3). The crystal structure of **5** revealed

Scheme 2. Preparation of Vinylketene Silyl *N*,*O*-Acetal 5



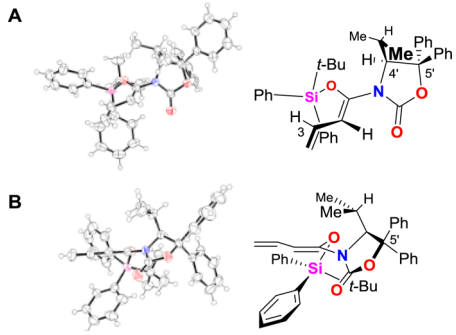
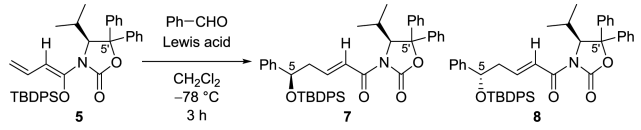


Figure 3. (A) ORTEP drawing of **5**: front view. (B) ORTEP drawing of **5**: side view.

that one of the phenyl groups on the oxazolidone ring determined the direction of the isopropyl group and another phenyl group pushed the TBDPS group down. Therefore, one of the phenyl groups of TBDPS was directed below the diene chain. The isopropyl group on oxazolidone placed far from the terminal carbon of the diene, the reaction site with an electrophile. This conformation would be possible in a solution since NOE correlation between H4′ and the *tert*-butyl group of TBDPS was observed in $CDCl_3$ (Scheme 2).

With vinylketene silyl *N*,*O*-acetal **5** in hand, the vinylogous Mukaiyama aldol reaction with benzaldehyde using various Lewis acid has been performed (Table 1). $TiCl_4$ afforded 5*S*-isomer **8** as a major product in good yield and stereoselectivity (Table 1, entry 1). Compared with dienol ether **3** (Table 1, eq 2), both yield and stereoselectivity were improved, which reflected reform of the chiral vinylketene silyl *N*,*O*-acetal. The products attached the TBDPS group; thus, protected aldol adducts were obtained in one step.[9] $BF_3{\cdot}OEt_2$ afforded the same major product

Table 1. Effect of Lewis Acid in the Vinylogous Mukaiyama Aldol Reaction Using 5



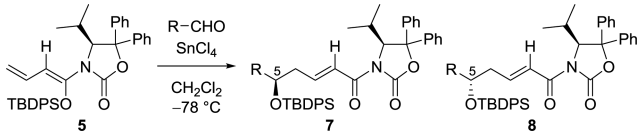
entry	Lewis acid[a]	yield (%)	dr (7:8)
1	$TiCl_4$	85	1:7
2	$BF_3{\cdot}OEt_2$	76	1:7
3	TMSOTf	27	1:8
4	$SnCl_4$	88	>20:1
5[b]	$SnCl_4$	85	10:1
6[c]	$SnCl_4$	80	10:1

[a]PhCHO (1.05 equiv) and Lewis acid (1,0 equiv) were used. [b]5′-Nonsubstituted oxazolidone derivative was used. [c]5′,5′-Dimethyloxazolidone derivative was used.

in comparable yield and selectivity (entry 2), while TMSOTf gave the product in low yield (entry 3). The best yield and stereoselectivity were obtained by using $SnCl_4$ (entry 4). In this reaction, the predominant product was 5*R*-isomer **7**, the isomer possessing the opposite configuration at C5 position to **8**. Use of the 5′-nonsubstituted derivative of **5** and 5′,5′-dimethyl derivative reduced both yield and stereoselectivity (entries 5 and 6).[8] Therefore, we employed 5′,5′-diphenyloxazolidone derivative **5** for further studies.

Next, we examined the reaction with various aldehydes in the presence of $SnCl_4$ (Table 2). *p*-Bromo- and *p*-methoxybenzalde-

Table 2. Vinylogous Mukaiyama Aldol Reaction Using 5



entry	RCHO	time (h)	yield (%)	dr (7:8)
1	PhCHO (**a**)	3	88	>20:1
2	4-BrC_6H_4CHO (**b**)	3	93	>20:1
3	4-$MeOC_6H_4CHO$ (**c**)	3	95	20:1
4	4-$NO_2C_6H_4CHO$ (**d**)	12	27	10:1
5	EtCHO (**e**)	5	66	15:1
6	*i*-PrCHO (**f**)	8	72	>20:1
7	*c*-HexCHO (**g**)	5	65	19:1
8	(*E*)-MeCH=CHCHO (**h**)	14.5	88	9:1
9	(*E*)-MeCH=CMeCHO (**i**)	20	76	5:1
10[a]	(*E*)-MeCH=CMeCHO (**i**)	4	86	1:20

[a]$BF_3{\bullet}OEt_2$ was used as Lewis acid.

hyde also gave the *O*-protected adduct in high yield with excellent selectivity (Table 2, entries 2 and 3). In the case of *p*-nitrobenzaldehyde (entry 4), the reaction proceeded slowly and afforded *O*-protected adduct in low yield but good selectivity. Products possessing free hydroxy groups were obtained as a mixture of diastereomers. Saturated alkylaldehydes including linear and branched side chains gave *O*-protected adducts in good yield with high stereoselectivity (entries 5−7). In the case of *α*,*β*-unsaturated aldehydes (entries 8 and 9), the reaction gave *O*-protected adduct in good yield with good to moderate selectivity. When a mixture of dienol ether **5** and tiglic aldehyde was treated with $BF_3{\cdot}OEt_2$, the stereoselectivity was switched and

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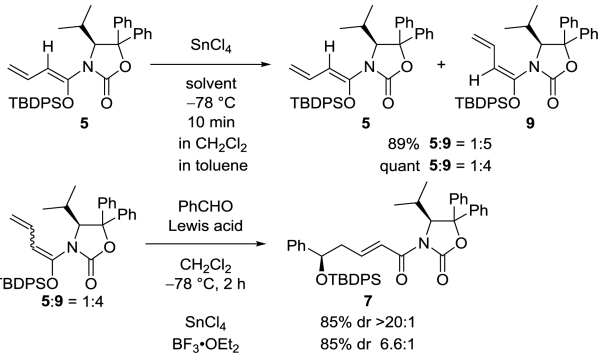
the 5*S*-isomer **8** was obtained in high yield with excellent stereoselectivity (entry 10).

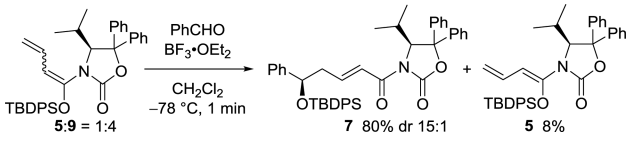
Interested in the stereoselectivity switching by using $SnCl_4$, we examined a control experiment without aldehyde. Treatment of vinylketene silyl *N*,*O*-acetal **5** with $SnCl_4$ in dichloromethane at −78 °C smoothly afforded a mixture of geometric isomers in which the *E*-isomer **9** existed as the major isomer.[10] Toluene gave the mixture in quantitative yield with comparable stereoselectivity. The resulting mixture of vinylketene silyl *N*,*O*-acetal **5** and **9** was submitted to the reaction with benzaldehyde and $SnCl_4$ under the same conditions, which gave the same results as entry 4 in Table 1. On the other hand, treatment of the mixture of **5** and **9** with benzaldehyde in the presence of $BF_3{\cdot}OEt_2$ gave **7** as a major product. Since $BF_3{\cdot}OEt_2$ did not promote isomerization of vinylketene silyl *N*,*O*-acetal **5**, the major product of the reaction was derived from *E*-isomer **9** in Scheme 3.

Scheme 3. Isomerization of 5 and the Vinylogous Mukaiyama Aldol Reaction Using the Geometric Mixture



When the reaction proceeded with $BF_3{\cdot}OEt_2$ in only 1 min, *E*-enolate **9** disappeared, while *Z*-enolate **5** remained in the reaction mixture (Scheme 4). The adduct **7** was obtained with

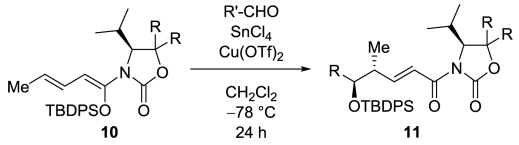
Scheme 4. Reactivity of *E*- and *Z*-Enolates



high stereoselectivity (dr 15:1), which indicated that *E*-enolate **9** was more reactive than *Z*-enolate **5** and was converted to **7** in high stereoselectivity.

Next, we examined the vinylogous Mukaiyama aldol reaction by using vinylketene silyl *N*,*O*-acetal **10** possessing the terminal methyl group (Table 3). 5′,5′-Dimethyloxazolidone derivative **10m** and 5′,5′-diphenyloxazolidone derivative **10p** were compared in yield and stereoselectivity of the reaction. Addition of Cu(II) triflate improved the reproducibility of the reaction.[11] 5′,5′-Dimethyloxazolidone derivative **10m** provided *anti* adduct **11** in good yield and excellent stereoselectivity (Table 3, entry 1). 5′,5′-Diphenyloxazolidone derivative **10p** also gave **11** in reduced yield and stereoselectivity (entry 2). The difference in these derivatives was found clearly in the reactivity for propionaldehyde (entries 3 and 4). Although **10m** retained good yield and stereoselectivity (entry 3), **10p** gave moderate yield and selectivity (entry 4). Therefore, 5′,5′-dimethyloxazolidone derivative **10m** was preferred over diphenyl derivative **10p**.

Table 3. Comparison of Oxazolidones for the Vinylogous Mukaiyama Aldol Reaction

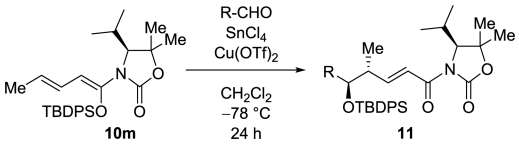


entry	R	R′	yield (%)	dr (**11**/isomers[a])
1[b]	Me (**10m**)	4-BrC_6H_4	78	19:1
2[b]	Ph (**10p**)	4-BrC_6H_4	61	15:1
3[c]	Me (**10m**)	Et	72	12:1
4[b]	Ph (**10p**)	Et	47	4:1

[a]Three diastereomers were included. [b]Determined by 400 MHz ^{1}H NMR. [c]Determined by HPLC.

The vinylogous Mukaiyama aldol reaction using **10m** was performed with various aldehydes (Table 4).[12] Aromatic

Table 4. Vinylogous Mukaiyama Aldol Reaction Using 10m



entry	RCHO	yield (%)	dr (**11**/isomers[a])
1	PhCHO (**a**)	66	16:1[b]
2	4-BrC_6H_4CHO (**b**)	78	19:1[b]
3	4-$NO_2C_6H_4$CHO (**c**)	68	14:1[b]
4	EtCHO (**d**)	71	12:1[c]
5	*i*-PrCHO (**e**)	73	6:1[c]
6	*c*-HexCHO (**f**)	62	5:1[c]
7	(*E*)-MeCH═CMeCHO (**g**)	0[d]	

[a]Three diastereomers were included. [b]Determined by 400 MHz ^{1}H NMR. [c]Determined by HPLC. [d]Michael adducts were obtained as a diastereomeric mixture.

compounds including benzaldehyde, *p*-bromobenzaldehyde, and *p*-nitrobenzaldehyde gave *O*-silylated *anti* adduct **11** in good yield with high stereoselectivity (Table 4, entries 1−3). Propionaldehyde gave TBDPS-protected adduct **11** in high selectivity, while branched saturated aldehyde including isobutyraldehyde and cyclohexanecarboxaldehyde gave *anti* adduct in good to moderate selectivity (entries 4−6). However, tiglic aldehyde, an *α*,*β*-unsaturated aldehyde, promoted the conjugate addition to give Michael adducts as a diastereomeric mixture and did not afford aldol adduct (entry 7).

These results, including X-ray crystallography of vinylketene silyl *N*,*O*-acetal **5**, Sn(IV)-mediated geometry-shuffling, and the vinylogous Mukaiyama aldol reactions, suggest reaction mechanisms shown in Scheme 5. X-ray crystallography of **5** indicated that one of the phenyl groups of TBDPS covered the lower face of the diene. Therefore, an electrophile should approach from the upper face. Additionally, aldehyde was placed to avoid steric repulsion of H2 in the preferred transition state. These factors might lead to the stereocontrol modes shown in Scheme 5. In the case of using $TiCl_4$ and $BF_3{\cdot}OEt_2$, the reaction proceeded via the transition state **12** to give adduct **8** as a major product (Scheme 5, route A). On the other hand, $SnCl_4$ isomerized **5** to more reactive diene **9**, which also allowed the electrophilic attack from the upper face. This face selectivity was proved by using methyl-attaching diene **10**, which gave

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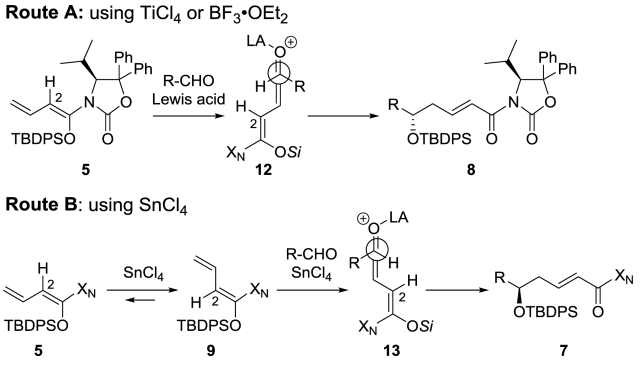
Scheme 5. Proposed Reaction Mechanisms



4*R*-adduct **11** (Tables 3 and 4). Therefore, the transition state of this reaction might be drawn as **13** (Scheme 5, route B). TBDPS migrated to prepare the stable TBDPS-O bond with an aldol adduct.

In conclusion, remote asymmetric induction reactions using crotonate-derived vinylketene silyl *N*,*O*-acetal have been developed. $SnCl_4$ was found to isomerize the geometry of the silyl dienol ether, and the resulting *E*-enolate **9** showed high reactivity to give the adduct with high stereoselectivity. Aldehydes approached from the upper face of **5** and **9**, while previous reactions in Scheme 1 proceeded from the lower face of **1a** and **1b**. These results indicated a new system of remote asymmetric induction. Vinylketene silyl *N*,*O*-acetal **10m** gave *anti* adducts in good to high stereoselectivity and indicated the face selectivity of dienolates. These reactions would be straightforward methods to synthesize polyketides.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03476.

X-ray data for compound **1a** (CIF)
X-ray data for compound **5** (CIF)
Experimental procedures, optimization of the reactions with **5** and **10m**, spectral data of compounds, and ^{1}H and ^{13}C NMR spectra (PDF)
X-ray data for compound **S5** (CIF)

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Notes

The authors declare no competing financial interest.

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