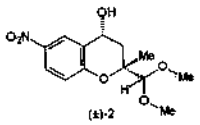
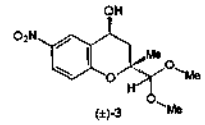
Table 1. Non-equivalent chemical shifts in a mixture of (1*S*,2*S*)-(−)-DPEDA and alcohols

Substrate	CSA (molar ratio)	Δδ (Hz)	Proton	Solvent
 (±)-2	0.5	1.8	CH(OMe)$_2$	$CDCl_3$
	0.8	1.4		
	1.0	1.5		
	1.6	2.9		
	2.0	3.7		
	3.0	4.4		
 (±)-3	1.0	2.5	Me	$CDCl_3$
	1.6	3.0		
	2.0	3.5		
	3.0	4.0		

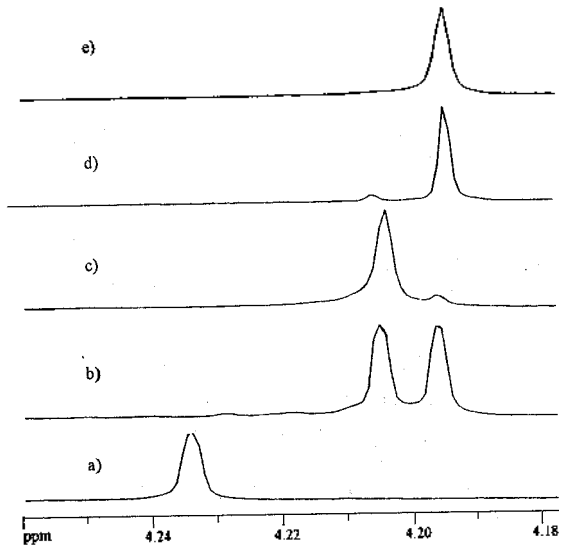


Figure 1. ^{1}H NMR resonances (500 MHz, $CDCl_3$) of CH(OMe)$_2$ acetal in; (a) free (±)-2. (b) the mixture of (±)-2 and 3 equimolar of (1*S*,2*S*)-DPEDA. (c) the mixture of (−)-2 enriched and 3 equimolar of (1*S*,2*S*)-DPEDA. (d) the mixtute of (+)-2 enriched and 3 equimolar of (2*S*,2*S*)-DPEDA. (e) the mixture of enantiomerically pure (+)-2 and 3 equimolar of (1*S*,2*S*)-DPEDA.

is completely saturated with (1*S*,2*S*)-DPEDA. Although the amount of (1*S*,2*S*)-DPEDA required to exhibit this effect depends on the interaction strength of the alcohol-amine pair, many alcohols have association constants great enough in a typical NMR amine concentration and enough non-equivalency normally observed when the chiral sovating agent and the alcohol ratio is between 2 and 3.

In conclusion, this study shows that (1*S*,2*S*)-(−)-diphenylethylenediamine is a convenient and effective chiral solvating agent for the *in situ* NMR determination of the enantiomeric purity of chiral alcohols. This agent is found be advantageous over other chiral amines such as (*R*)-(+)-α-methylbenzylamine or (*R*)-(+)-1-(1-naphthyl)ethylamine for this purpose.

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Syn-Selectivity in Titanium (IV) Mediated Aldol Condensation of the Silyl Ketene Acetal of S-2-Pyridyl Thioester with Aldehydes

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Over the past decade, a variety of Lewis acid mediated aldol condensation methods between ester or thioester silyl

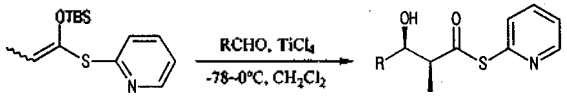
ketene acetals and aldehydes have been developed to construct α-methyl-β-hydroxy carbonyl unit, diastereo- and enantioselectively.[1] Most of the investigations in this area have been directed toward the reaction with thioester silyl ketene acetals,[2] because thioesters can be readily transformed to synthetically valuable entities.[3] Furthermore, the aldol reaction of thioester silyl ketene acetals with simple aldehyde is known to be stereoconvergent.[4] In the Lewis acid promoted condensation of a thioester silyl ketene acetal with a prochiral aldehyde, "simple stereoselectivity" can be achieved regardless of the geometry of double bond of the acetal, and thus *anti* isomer can selectively be prepared using either (*E*)- or (*Z*)-silyl ketene acetals. However, much remains to be explored for the similar stereocontrolled *syn* addition methods.[5]

During our effort to develop highly diastereoselective methods for aldol condensation, silyl ketene acetals of some activated esters, particularly *S*-2-pyridyl thioester, have drawn our attention. Because this group in aldol products can directly offer many synthetic opportunities over general reaction features of thioester.[6] In addition, pyridine nitrogen of *S*-2-pyridyl thioester can behave as a stereocontrolling group through the coordination with the Lewis acid used.[7] This fact has been utilized recently by Cinquini *et al.* in their aldol and imine condensation with titanium (IV) enolates of *S*-2-pyridyl thioesters.[8] And β-lactam synthesis through imine condensation with the silyl ketene acetal of *S*-2-pyridyl thioester was established by Hirai *et al.* as well.[9] We also have shown that the *syn* isomer could be obtained by the condensation of several *O*-silyl ketene *O,S*-acetals of *S*-2-pyridyl thioesters with benzaldehyde in the presence of titanium (IV) chloride.[10] Here we report another successful examples of *syn* selective aldol condensation with several aldehydes.

The silyl ketene acetal employed in this reaction, (*E*)-*O*-*tert*-butyldimethylsilyl ketene *O,S*-acetal **1** (*E/Z*>98/2), was easily prepared from *S*-2-pyridyl thiopropionate by internal quenching with *tert*-butyldimethylsilyl chloride according to the known procedure.[11] The silyl ketene acetal **1** prepared was then allowed to react with aldehydes in dichloromethane in the presence of titanium (IV) chloride at −78 ℃. The reaction mixture was allowed to warm up to 0 ℃ to afford aldol products **2**, after usual aqueous work up and purification by chromatography. Diastereomeric ratio was determined from ^{1}H NMR (200 MHz) spectral analysis of crude products or of their methyl esters which were generated by treating the products with mecury (II) acetate in methanol. Stereochemistry of the products was established by comparing the chemical shifts and the coupling patterns[12] of the aldol adducts with those of the reported. The results are summarized in Table 1.

As shown in Table 1, the *syn* products **2** were exclusively obtained from the (*E*)-silyl ketene acetal **1** in moderate to good yields in all cases, though, with bulky aldehydes, both the reactivity and selectivity were slightly decreased (entries, 4, 6, and 7). Moreover, the same selectivity toward *syn* isomer (entries, 2 and 5) was retained in the condensation with the (*E*)- and (*Z*)-mixture (*E/Z*=55/45) of silyl ketene acetal **1**, which was synthesized from *tert*-butyldimethylsilyl triflate and triethylamine in dichloromethane. These results contrast with our previous work[10] of boron mediated condensation

Table 1. $TiCl_4$ mediated aldol condensation of the silyl ketene acetal **1** of *S*-2-pyridyl thiopropionate with aldehydes[a]



1 **2**
syn selective
syn:anti = 95:5~100:0

Entry	**1** *E/Z*	Aldehyde	Condition[b] ℃, hr	Yield[c] %	**2** *syn/anti*[d]
1	98/2	PhCHO	−78, 0.5 to 0, 0.5	76	~100/0[e]
2	55/45	PhCHO	−78, 0.5 to 0, 0.5	74	~100/0[e]
3	98/2	C_2H_5CHO	−78, 0.5 to 0, 1.0	52	~100/0
4	98/2	C_3H_7CHO	−78, 0.5 to 0, 0.5	48	~100/0
5	55/45	C_3H_7CHO	−78, 0.5 to 0, 0.5	45	~100/0
6	98/2	Me_2CHCHO	−78, 0.5 to 0, 12	42	98/2
7	98/2	Me_3CCHO	−78, 0.5 to 0, 16	46	96/4
8	98/2	1-NpCHO[f]	−78, 0.5 to 0, 1.0	79	98/2
9	98/2	2-NpCHO	−78, 0.5 to 0, 1.0	82	97/3
10	98/2	C_3H_5CHO	−78, 0.5 to 0, 1.0	84	99/1
11	98/2	$C_6H_{11}CHO$	−78, 0.5 to 0, 1.0	56	95/5
12	98/2	$C_8H_{15}CHO$	−78, 0.5 to 0, 2.5	43	99/1
13	98/2	PhCH=CHCHO	−78, 0.5 to 0, 1.0	48	95/5
14	98/2	MeCH=CHCHO	−78, 0.5 to 0, 1.0	50	97/3

[a] See the typical procedure. [b] Not optimized. [c] Isolated yield after chromatography. [d] Determined by ^{1}H NMR (200 MHz). [e] see reference 10. [f] Np=naphthyl

with benzaldehyde, in which *anti* product was obtained as a major adduct (*anti/syn*=77/23) from both (*E*)- and (*Z*)-silyl ketene acetal **1**. From these observations in the titanium mediated aldol reaction with the silyl ketene acetal **1**, it seems that the high *syn* selectivity is independent of the geometry of double bond and thus the reaction is stereoconvergent.

About the mechanistic aspect of these results, it should be pointed out that such syn selectivity cannot be explained in terms of the reported acyclic transition state,[13,4] which has been generally accepted for Mukaiyama's aldol reaction of ester or thioester silyl ketene acetal so far. The observed *syn* preference might be explained by titanium mediated chelation mechanism of the transition states E_S and Z_S which were derived from (*E*)- and (*Z*)-silyl ketene acetals of "pinwheel" conformation,[13] respectively, as depicted in Figure 1. That is, the coordination of titanium ion with both aldehyde carbonyl and pyridine nitrogen of (*E*)-silyl ketene acetal **1** in the transition state E_S completes the formation of *cis*-octahedral complex.[14] Such coordination would reduce the conformational freedom of reaction, and the C-C bond formation would occur on the titanium metal to give *syn* isomer in a highly stereoselective way. In addition, *syn* selectivity attained from (*Z*)-**1** in the case of entries 2 and 5 could be explained through the transition states Z_S, in which oxygen of silyloxy group as well as pyridine nitrogen participated in the coordination with titanium. Analogous chelation model was shown by Gennari *et al.*[15] in titanium (IV) mediat-

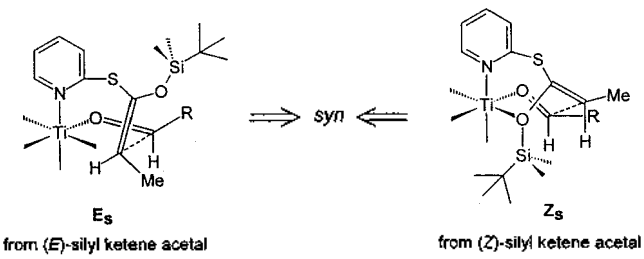


Figure 1. Titanium Mediated Chelation Transition State.

ed aldol condensation of the silyl ketene acetal derived from *N*-methyl ephedrine-*O*-propionate, in which the ephedrine nitrogen was expected to bind to titanium metal in the transition state.

In summary, we found that the silyl ketene acetal of *S*-2-pyridyl thioester condensed with several aldehydes to give highly *syn* selective aldol products irrespective of its geometry. The selectivity could be explained in terms of chelation model. The 2-mercaptopyridyl moiety of the aldol adduct is a good leaving group, thus it would be utilized in further synthetic transformation according to the conventional methods.

Experimental Section

Typical procedure for the aldol condensation. To a cooled (−78 ℃) solution of 282 mg (1.0 mmol) of the silyl ketene acetal **1** and 83 μL (1.1 mmol) of cyclopropane carboxaldehyde in 10 mL of dichloromethane was added dropwise 1.1 mL (1.1 mmol) of titanium (IV) chloride in 1.0 M dichloromethane, and the red solution was stirred for 0.5 h at −78 ℃. Warmed to 0 ℃ over 0.5 h, the mixture was further stirred for 1.0 h at 0 ℃ and then quenched with saturated sodium bicarbonate solution. The precipitate was filtered off, and the organic phase was separated, dried over magnesium sulfate, and concentrated to afford a yellow oil, which was purified by flash chromatography (hexane : ethyl ether = 1 : 1) to give 199 mg (84%) of product as a pale yellow oil.

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6. For example, 2-pyridyl thioester can be utilized in the synthesis of thioester (RSH, base), peptide (RNH_2, base), lactone (Hg^{2+}, Ag^+, Cu^+, or Cu^{2+}), lactame and so on, or the resolution by $Ti(OPr^i)_4$.
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12. In general, the *syn* isomers feature smaller *CHOH J* values. Also, *CH*OH resonates at lower field in *syn* than in *anti* isomers.
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Regioselective Synthesis of 2-Amino-3-cyanofuran Derivatives and Its Guanidine Cyclization Reaction

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It is reported that acyloins reacted with malononitrile in aqueous base to give 2-amino-3-cyanofuran derivatives.[1] The regioselective synthesis of 4- or 5-substituted-2-amino-3-cyanofuran was interested for the synthesis of pyrrolo[2,3-d] pyrimidine based anti tumor reagents.[2]

For the synthesis of 4-substituted-2-amino-3-cyanofuran, α-hydroxy ketone was reacted with malononitrile in triethyl-