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VERSATILE RELATIVE AND ABSOLUTE STEREOCONTROL IN STANNOUS TRIFLATE MEDIATED ALDOL-TYPE REACTIONS OF 3-(2-BENZYLOXYACETYL)THIAZOLIDINE-2-THIONE

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In the stannous triflate mediated aldol-type reactions of 3-(2-benzyloxyacetyl)thiazolidine-2-thione, stereochemical course of the reactions is dramatically altered by the addition of tetramethylethylenediamine as a ligand. High asymmetric induction is also achieved by the addition of chiral diamine derived from L-prolin.

Recently, aldol reaction has attracted much attention as a useful method for the stereoselective synthesis of acyclic compounds. The stereochemical aspects of this reaction have been studied in detail, and it is widely accepted that in kinetically controlled aldol reactions, the stereostructure of an enolate determines the relative configuration of its aldol product.[1] Thus, *Z*-enolate gives *syn* (*erythro*) isomer, and *E*-enolate gives *anti* (*threo*) isomer. A versatile method for the stereoselective formation of *Z*-enolate is developed recently using, for example, dialkylboryl triflate, and stereoselective synthesis of *syn* isomer is already established.[2] However, it is rather difficult to produce *anti* isomer selectively, and use of the boron enolate of *S*-*t*-butylpropanethioate[3] or use of the lithium enolate of 2,6-di-*t*-butyl-4-methylphenol ester[4] is developed recently for this purpose.

Judging from the synthetic utility of the reaction, it is desirable that both stereoisomers could be stereoselectively produced from the same starting material with minimum change in the reaction conditions.

In our continuous work on the stannous trifluoromethanesulfonate (stannous triflate) mediated aldol reaction,[5] we have found that the intermediate divalent tin enolate forms tight complex with diamine and highly enantioselective aldol reaction can be achieved in the presence of chiral diamine derived from L-prolin.[6]

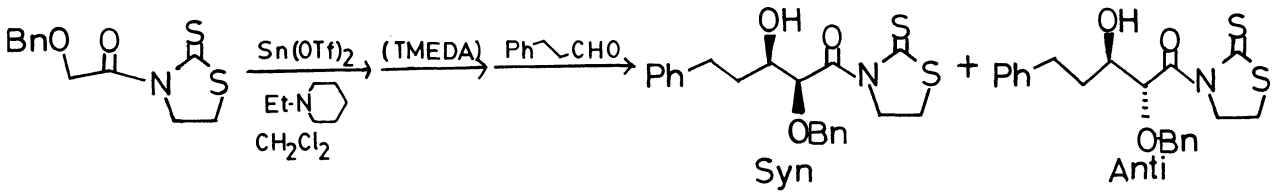
In this communication, we wish to report a new and efficient synthetic control in both relative and absolute stereochemistry in the stannous triflate mediated aldol-type reaction of 3-(2-benzyloxyacetyl)thiazolidine-2-thione.[7] The control is achieved by coordination of diamine with divalent tin enolate; that is, controlling element of stereochemistry is not covalently bonded to the reactants.

Thus, according to the previously mentioned procedure, stannous triflate was treated with 3-(2-benzyloxyacetyl)thiazolidine-2-thione in dichloromethane in the presence of N-ethylpiperidine as a base at -78 °C, and β-phenylpropanal was added to the reaction mixture. Work up of the reaction mixture afforded two

stereoisomers in the ratio of 74 : 26 in 62% yield. The stereochemistry of the major product was assigned *syn* by the derivation described in Ref.8.

We next examined the reaction in the presence of tetramethylethylenediamine (TMEDA). Thus, 1.2-equivalent of TMEDA was added to the solution of the enolate and then aldehyde was added. And in this case, the ratio of the two stereoisomers was reversed and *anti* isomer was obtained as a major isomer in the ratio of 85 : 15 in 70% yield.

In order to clarify these stereoselectivities, various reaction conditions were examined, and the results are summarized in the Table 1.



$Sn(OTf)_2$: Et-N⟨⟩ : 3-(2-Benzyloxyacetyl)thiazolidine-2-thione : Diamine : Aldehyde = 1.0 : 1.2 : 0.8 : 1.2 : 1.2.

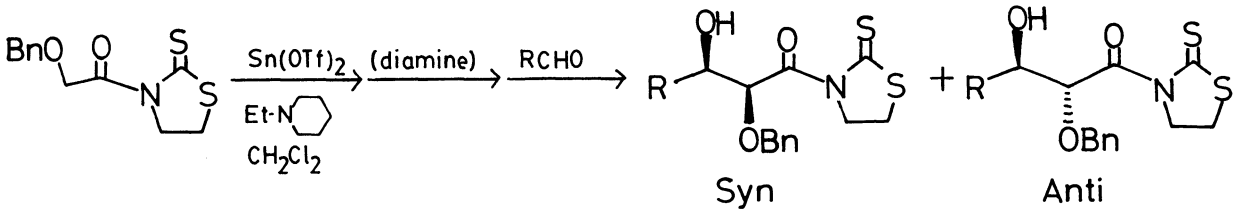
Table 1. Examination of the Reaction Conditions

Reaction conditions[a)]	Yield/%	*Syn* : *Anti*
1. In the absence of TMEDA.	62	74 : 26
2. In the presence of TMEDA.	70	15 : 85
3. In the presence of TMEDA, reaction with aldehyde was run for 10s.	30	20 : 80
4. In the absence of TMEDA, reaction with aldehyde was run at 0 °C.	67	59 : 41
5. In the presence of TMEDA, reaction with aldehyde was run at 0 °C.	79	17 : 83
6. TMEDA was added after the reaction with aldehyde was run for 1 h, and the reaction was further run for 12 h.	84	49 : 51

a) Fundamental reaction conditions are as follows; enolization, -78 °C, 30 min, addition of 1.2 equiv. of TMEDA, -78 °C, 5 min later, reaction with aldehyde, -78 °C, 1 h.

These results indicate that product equilibration is rather slow in this reaction (Entry 6), and it is assumed that the selection of stereochemistry is determined by the fact that coordination of TMEDA exchanges the coordinating pattern of divalent tin enolate (probably tetragonal to octahedral), which might cause the transformation of the favorable transition state (one possibility is the transformation of chair-type transition state to boat-type transition state).[9)] Furthermore, when (*S*)-1-methyl-2-[(piperidin-1-yl)methyl]pyrrolidine was employed as a chiral ligand instead of TMEDA, high asymmetric induction was observed and the optical purity of the major *anti* isomer reaches up to 94%.

Finally, we examined the reaction with various aldehydes, and the results are summarized in Table 2.

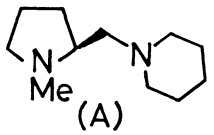


$Sn(OTf)_2$: Et-N⬡ : 3-(2-Benzyloxyacetyl)thiazolidine-2-thione : Diamine : Aldehyde = 1.0 : 1.2 : 0.8 : 1.2 : 1.2.

Table 2. Reaction with Various Aldehydes[a)]

Aldehyde	Diamine	Yield/%	*Syn* : *Anti*[c)]	Optical purity/%[f)]
Ph⟋CHO	———	62	74 : 26[d)]	——
	TMEDA	70	15 : 85	——
	Chiral Diamine[b)]	81	13 : 87	94
$n\text{-}C_5H_{11}CHO$	———	62	74 : 26[e)]	——
	TMEDA	68	12 : 88	——
	Chiral Diamine[b)]	75	17 : 83	90
⬡-CHO	———	74	56 : 44[e)]	——
	TMEDA	74	7 : 93	——
	Chiral Diamine[b)]	68	7 : 93	87
⟋⟍CHO	———	60	61 : 39[e)]	——
	TMEDA	65	9 : 91	——
	Chiral Diamine[b)]	70	9 : 91	87
PhCHO	———	95	23 : 77[d)]	——
	TMEDA	82	17 : 83	——
	Chiral Diamine[b)]	93	19 : 81	90

a) Reaction conditions are as follows; enolization, -78 °C, 30 min to 1 h, addition of diamine, -78 °C, 5 min later, reaction with aldehyde, -78 °C, 1 to 12 h.
b) (*S*)-1-Methyl-2-[(piperidin-1-yl)methyl]pyrrolidine (A) is employed.
c) The ratio is determined by separation of each isomer.
d) The stereochemistry is determined by the method described in Reference 8).
e) The stereochemistry is determined by the analogy of the NMR spectra (coupling constant of the α-proton of carbonyl group: *syn* isomer J=2-4 Hz, *anti* isomer J=6-9 Hz).
f) That of *anti* isomer. Determined by the measurement of the ^1H NMR spectrum of the corresponding methyl ester[5)] using $Eu(hfc)_3$ as a chiral shift reagent. The $-OCH_3$ signal is completely separated.



Several features of this reaction are pointed out as follows:

(1) Reversal of *syn-anti* stereoselection is observed with aliphatic aldehydes. But *anti* isomer is the major product in the cases of aromatic aldehydes either in the presence or in the absence of TMEDA.

(2) High asymmetric induction (about 90% e.e.) is achieved with every aldehyde employed using (*S*)-1-methyl-2-[(piperidin-1-yl)methyl]pyrrolidine as a ligand.

It should be noted that in the present aldol-type reaction of 3-(2-benzyloxyacetyl)thiazolidine-2-thione, both *syn-anti* stereocontrol and absolute stereocontrol could be achieved utilizing non-bonded interaction between stannous enolate and various diamines. Further investigation of the mechanistic aspects of this reaction and application to the enantioselective syntheses of natural products are now in progress in this laboratory.

References

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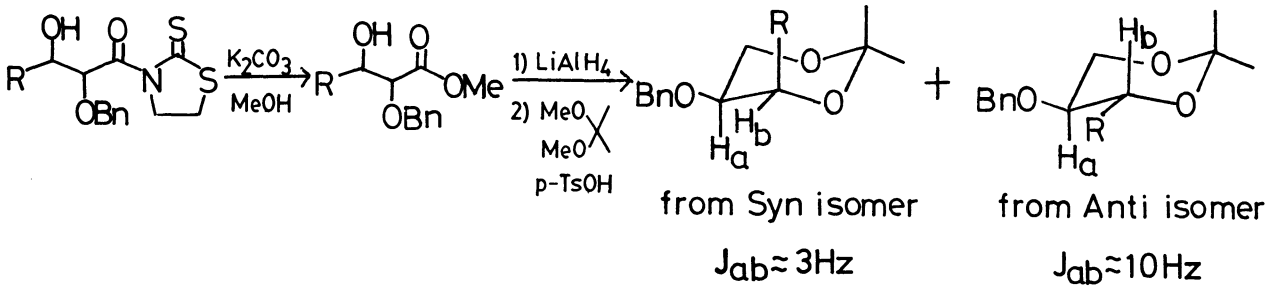
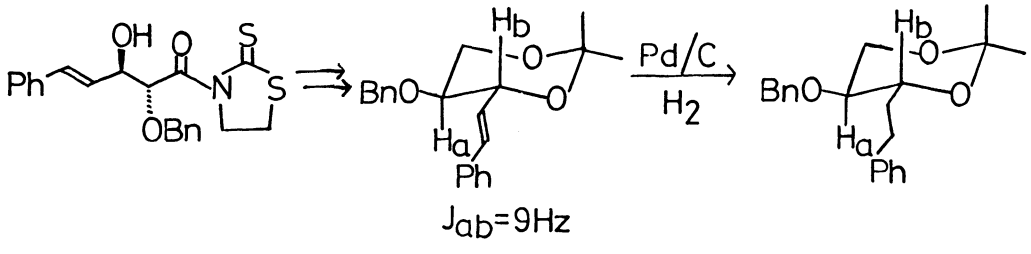
2) For example, see, D. A. Evans, J. V. Nelson, E. Vogel, and T. R. Taber, J. Am. Chem. Soc., 103, 3099 (1981).
3) M. Hirama and S. Masamune, Tetrahedron Lett., 1979, 2225.
4) C. H. Heathcock, M. C. Pirrung, S. H. Montgomery, and J. Lampe, Tetrahedron, 37, 4087 (1981).
5) For example, see, T. Mukaiyama and N. Iwasawa, Chem. Lett., 1982, 1903.
6) N. Iwasawa and T. Mukaiyama, Chem. Lett., 1982, 1441; N. Iwasawa and T. Mukaiyama, Chem. Lett., 1983, 297; R. W. Stevens and T. Mukaiyama, Chem. Lett., 1983, 1779.
7) For the aldol reaction of α-alkoxyester, see; A. M. Touzin, Tetrahedron Lett., 1975, 1477; C. H. Heathcock, J. P. Hagan, E. T. Jarri, M. C. Pirrung, and S. D. Young, J. Am. Chem. Soc., 103, 4972 (1981).
8) The stereochemistries of the aldol products are determined as follows:



In the case of the aldol-type product of β-phenylpropanal, the coupling constant between H_a and H_b is not clear from 90MHz NMR spectrum, and the stereochemistry is determined by comparison with the authentic sample prepared from the aldol-type product of cinnamaldehyde (in this case, the stereochemistry is clearly assigned).



9) No (*E*)-(*Z*) equilibration of the enolate is observed, because the same single enol ester is obtained when the enolate is trapped by acyl chloride either in the presence or in the absence of TMEDA.

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