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STEREOSELECTIVE ALDOL REACTION FOR THE PREPARATION OF β-ETHYLTHIOMETHYL ALDOLS VIA TIN(II) ENOLATE BY THE USE OF A CATALYTIC AMOUNT OF THE TIN(II) SPECIES

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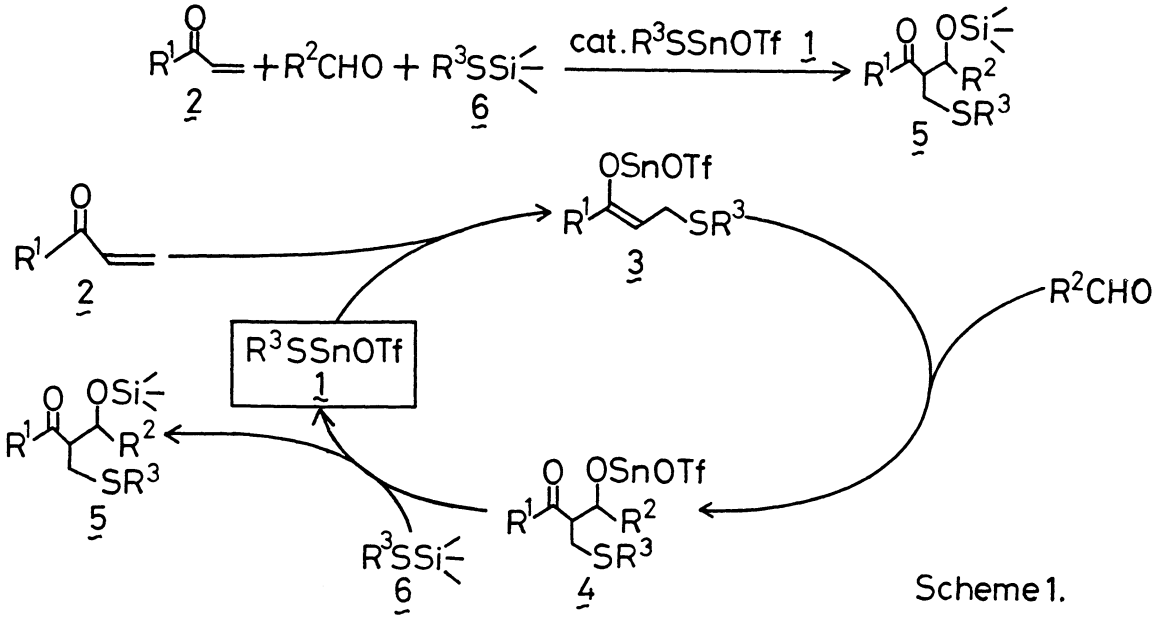
An aldol type reaction of divalent tin enolates with aldehydes is successfully achieved by the use of only a catalytic amount of the tin(II) species to afford the cross aldol products in good yields with high stereoselectivity.

The aldol reaction is one of the most fundamental carbon-carbon bond forming reactions, and in recent years extensive studies on the stereocontrol of this reaction have been carried out based on various intermediate metal enolates.[1] In most of these reactions, the starting carbonyl compound is quantitatively converted to the corresponding metal enolate prior to reaction with the second carbonyl compound and consequently a stoichiometric amount of the metal reagent is generally required. Therefore, it is strongly desired to explore efficient stereoselective aldol reactions in which the metal reagents are used in only catalytic amounts.

In a previous paper, we reported an aldol reaction via divalent tin enolates, generated in situ from ketones and stannous trifluoromethanesulfonate (stannous triflate), and it was shown that the corresponding aldol products are produced in high yields with good stereoselectivity.[2]

In continuation of our work on the chemistry of tin(II) enolates, we now wish to report, in this communication, a tin(II) enolate mediated aldol type reaction in which only a catalytic amount of the tin(II) species is employed. The catalytic cycle to generate the tin(II) enolate could be shown in Scheme 1. Namely, in the first step, the conjugate addition of the tin(II) species 1 to vinyl ketone 2 produces the tin(II) enolate 3 which in turn reacts with aldehyde to give the corresponding aldol product as its tin(II) alkoxide 4.[3] In the next step, this tin(II) alkoxide 4 reacts with alkylthiotrimethylsilane 6 to regenerate the tin(II) species along with the aldol product as its TMS ether 5. Thus, it was assumed that the aldol type reaction would proceed smoothly by employing only a catalytic amount of the tin(II) species 1.

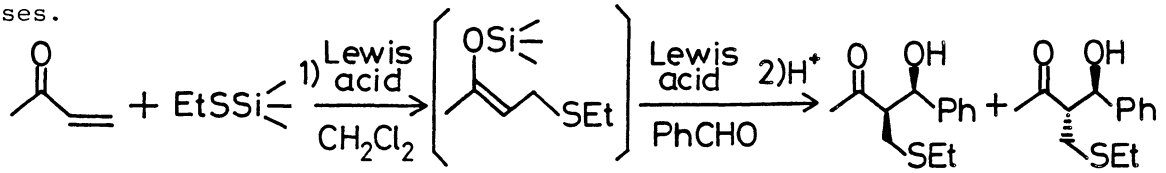
We first tried the reaction according to the following procedure. A catalytic amount (10 mol%) of tin (II) triflate sulfide 1, prepared in situ from tin(II) triflate and the lithium salt of ethanethiol, was treated with methyl vinyl ketone (MVK) in methylene chloride, followed by the addition of benzaldehyde and ethylthiotrimethylsilane. The reaction proceeded smoothly to afford the



Scheme 1.

desired aldol product in 76% yield with a diastereomer ratio of 89:11.

At this stage, we considerd an alternative possibility that the reaction would proceed via the silyl enol ether of the ketone, promoted by the tin(II) species, a Lewis acid catalysis, as shown in Scheme 2.[4] However, when a scheme mixture of MVK, benzaldehyde and ethylthiotrimethylsilane was treated with several Lewis acids such as $BF_3.OEt_2$, $SnCl_4$ and $Sn(OTf)_2$ as shown in Table 1, both the yields and stereoselectivity of the aldol products obtained were poor in all cases.



Scheme 2.

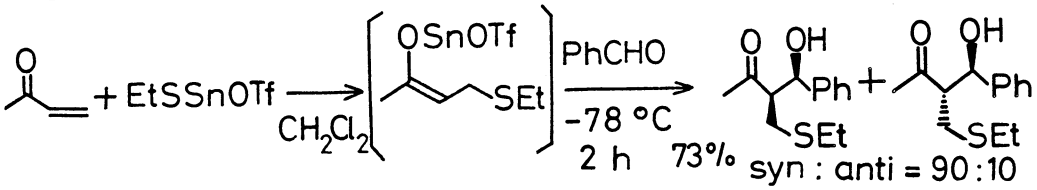
Table 1.

Lewis acid	Yield/%[a]	syn : anti[b]
$BF_3.OEt_2$[c]	36	31 : 69
$SnCl_4$[c]	24	34 : 66
$Sn(OTf)_2$[d]	36	63 : 37

a) Isolated yield.
b) Diastereomers were separated by silica gel column chromatography. The stereochemistry of the diastereomers was determined by the ^1H NMR and ^{13}C NMR spectra.[5]
c) The Lewis acid was employed in a catalytic amount (10 mol%).
d) Stoichiometric amount of $Sn(OTf)_2$ was employed.
e) Reaction temperature was raised gradually from -78 °C to 0 °C.

In contrast, when MVK was treated with an equimolar amount of tin(II)

triflate sulfide 1 followed by the addition of benzaldehyde, the reaction proceeded smoothly to afford the aldol product in 73% yield with a syn:anti ratio of 90:10. This yield and ratio are quite similar to those obtained when a catalytic amount of tin(II) triflate sulfide 1 is used. These observations strongly suggest that the present reaction is indeed proceeding via the tin(II) enolate by the use of tin(II) triflate sulfide as a catalyst.



Subsequent screening of solvents showed that tetrahydrofuran (THF) is the solvent of choice, realizing the highest diastereomer ratio (95:5) as shown in Table 2. Further, it was found that the yield was improved to 68% without loss of stereoselectivity when the reaction was carried out at -45 °C.

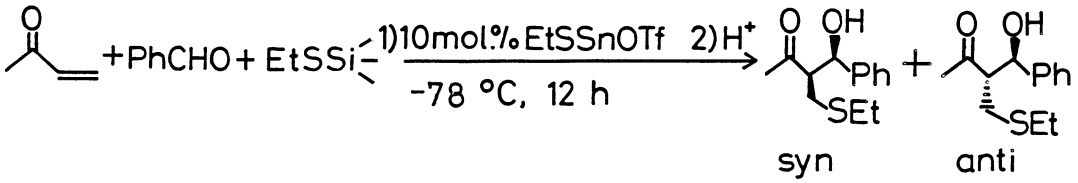


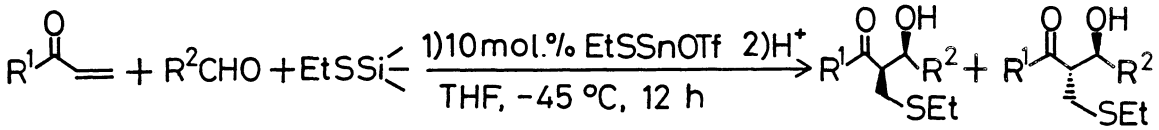
Table 2.

Solvent	Yield/%[a)]	syn : anti[b)]
CH_2Cl_2	76	89 : 11
THF	54	95 : 5
Et_2O	57	89 : 11
toluene	48	68 : 32
THF	68[d)]	95 : 5

a) Isolated yield.
b) Diastereomers were separated by silica gel column chromatography.
c) The stereochemistry of the diastereomers was determined by the ^1H NMR and ^{13}C NMR spectra.[5)]
d) The reaction was carried out at -45 °C.

Having attained the best reaction conditions, the reaction of MVK and phenyl vinyl ketone with benzaldehyde and β-phenylpropionaldehyde was tried and in all cases the corresponding aldol products were obtained in good yields with high stereoselectivity. (Table 3)

A typical procedure is described for the reaction of methyl vinyl ketone with 3-phenylpropanal; to a solution of ethanethiol (10 mg, 0.17 mmol) in 2 ml of tetrahydrofuran was added 0.11 ml of 1.54 M n-butyllithium in hexane at 0 °C under argon atmosphere. Stannous triflate (69 mg, 0.17 mmol) was added and, after 20 min, the mixture was cooled to -45 °C. Methyl vinyl ketone (118 mg. 1.68 mmol) in 1.5 ml of tetrahydrofuran and 3-phenylpropanal (350 mg, 2.61 mmol) in 1.5 ml of tetrahydrofuran were successively added to the mixture. The reaction mixture was



syn anti

Table 3.

R^1	R^2	Yield/%[a]	syn : anti[b]
CH_3	Ph	68	95 : 5
CH_3	$PhCH_2CH_2$	75	90 : 10
Ph	$PhCH_2CH_2$	73	84 : 16

a) Isolated yield. All samples gave satisfactory ^1H NMR and IR spectra.
b) Diastereomers were separated by silica gel column chromatography.
c) The stereochemistry of the diastereomers was determined by the ^1H NMR and ^{13}C NMR spectra.[5]

further stirred for 12 h, then quenched with 10% aqueous solution of citric acid, and the organic materials were extracted with methylene chloride three times. To completely hydrolyze the trimethylsilyl ether group, the crude aldol product obtained after evaporation of the solvent was dissolved in methanol and to this solution was added citric acid. After stirring for 30 min, the reaction was quenched with pH 7 phosphate buffer. The organic layer was extracted three times with methylene chloride and the combined extracts were dried over anhydrous Na_2SO_4. After evaporation of the solvent, the crude product was purified by silica gel column chromatography to afford 3-ethylthiomethyl-4-hydroxy-6-phenyl-2-hexanone (336 mg, 75% yield, syn:anti = 90:10).

Thus, a tin(II) enolate mediated aldol reaction of vinyl ketone, alkylthiosilane and aldehyde was realized by the use of only a catalytic amount of the tin(II) species. The reaction proceeds smoothly to afford the corresponding aldol products in good yields with high stereoselectivity.

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