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Reversal Phenomena of the Preferential Activation of Aldehydes to the Corresponding Acetals under Non-Basic Conditions. The Chemoselective Aldol Reaction of Aldehydes with t-Butyldimethylsilyl Enol Ethers Using TBSCl-$InCl_3$ as a Catalyst

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In the presence of a catalytic amount of t-butyldimethylsilyl chloride (TBSCl) and indium(III) chloride ($InCl_3$), aldehydes smoothly react with t-butyldimethylsilyl enol ethers to afford the corresponding aldol adducts in good yields whereas acetals do not react under the same reaction conditions.

During last few decades acetals have been widely employed not only as protective groups but also as electrophiles in various coupling reactions including carbon-carbon bond forming reactions.[1)] In general, acetals are more reactive than aldehydes under acidic conditions; for example, it was reported that in the presence of 5 mol% of trimethylsilyl triflate, benzaldehyde dimethyl acetal smoothly reacted with 1-trimethylsiloxycyclohexene (**1**) in dichloromethane at -78 °C to afford the corresponding aldol-type adducts in a high yield, while benzaldehyde reacted with **1** only at room temperature.[2)] In this communication, we would like to report a reversal phenomena of the preferential activation of aldehydes to the corresponding acetals in the above mentioned aldol-type reaction using a novel catalyst system, t-butyldimethylsilyl chloride (TBSCl) and indium(III) chloride ($InCl_3$).

In the previous paper, we have shown that a novel catalyst system, trimethylsilyl chloride (TMSCl) and $InCl_3$, effectively catalyzes the reaction of O-trimethylsilyl monothioacetals with triethylsilane to give the corresponding sulfides in good to high yields.[3)] Later, this catalyst system was found to be effective in an activation of aldehydes and one pot synthesis of sulfides from aldehydes could be attained.[4)] In these reactions, O-trimethylsilyl monothioacetals or aldehydes were activated under the quite mild conditions and reduction of these compounds smoothly proceeded without accompanying undesirable side reactions. Bearing in mind this excellent catalyst system, we next intended to employ it in carbon-carbon bond forming reactions, especially the aldol reaction of silyl enol ethers with aldehydes or acetals which is considered as one of the most fundamental and important processes in organic synthesis.

Several examples of the aldol reaction are shown in Table 1. Both aldehydes and the corresponding dimethyl acetals smoothly react with trimethylsilyl enol ethers to produce the corresponding aldol adducts in high yields using a catalytic amount of TMSCl and $InCl_3$.

Next, we examined other silyl enol ethers than trimethylsilyl enol ethers in order to examine the scope of nucleophiles employed in this reaction. While 1-t-butyldimethylsiloxy-1-ethoxyethylene (**2**) smoothly reacted with benzaldehyde to give the corresponding aldol-type adduct in a good yield, the corresponding dimethyl acetal did not react at all under the same reaction conditions. Further examination of several reaction

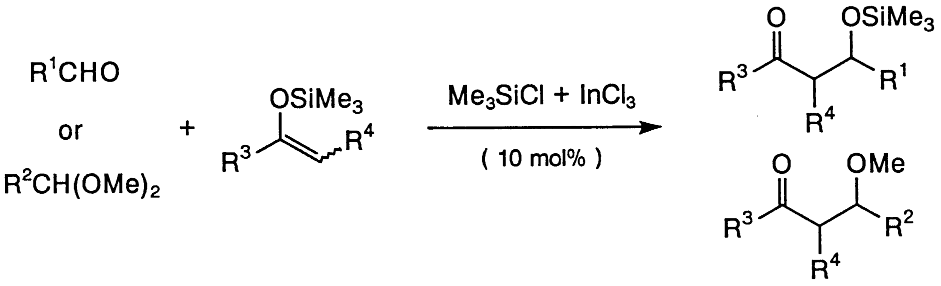


Table 1. The Aldol Reaction of Silyl Enol Ethers with Aldehydes or Acetals

R^1CHO or $R^2CH(OMe)_2$	R^3	R^4	Yield / %
PhCHO	Ph	H	70
PhCHO	OMe	Me_2	96
$Ph(CH_2)_2CHO$	Ph	H	87
$PhCH(OMe)_2$	Ph	H	91
$PhCH(OMe)_2$	OMe	Me_2	81
$Ph(CH_2)_2CH(OMe)_2$	Ph	H	58

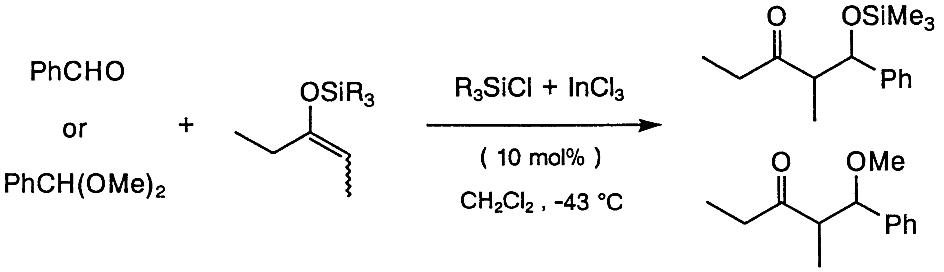


Table 2. Effect of Substituent on Silicon in the Aldol Reaction

Electrophile	R_3	Time/h	Yield/%
PhCHO	$^tBuMe_2$ a)	1.5	83 b)
$PhCH(OMe)_2$	$^tBuMe_2$	1.5	0
PhCHO	Me_3 a)	24	38 c)
$PhCH(OMe)_2$	Me_3	24	74
PhCHO	Et_3	3	73
$PhCH(OMe)_2$	Et_3	3	79
PhCHO	$PhMe_2$	7	68
$PhCH(OMe)_2$	$PhMe_2$	7	0

a) E/Z=4/1 b) syn/anti=1/3 c) syn/anti=3/1 parameters revealed that this characteristic reactivity was strongly influenced by the substituents on the silicon of the silyl enol ether. Some silyl groups were examined by taking the reaction of 3-trimethylsiloxy-2-pentene (**3**) with benzaldehyde or benzaldehyde dimethyl acetal as a model system under the influence of the corresponding silyl chloride and $InCl_3$, and the results are summarized in Table 2. Both aldehydes and acetals reacted with **3** to give the corresponding adducts in moderate to good yields in the case of using TMS or triethylsilyl (TES) group, whereas only the aldehyde reacted in the case of employing enol ether having TBS or dimethylphenylsilyl group. This preferential activation of aldehydes to acetals was generally observed in the reaction of aldehydes or acetals with TBS enol ethers in the presence of a catalytic amount of TBSCl and $InCl_3$ (see Table 3). In every case, only aldehydes smoothly reacted, while no adduct was formed by treating the corresponding acetals under the same conditions.

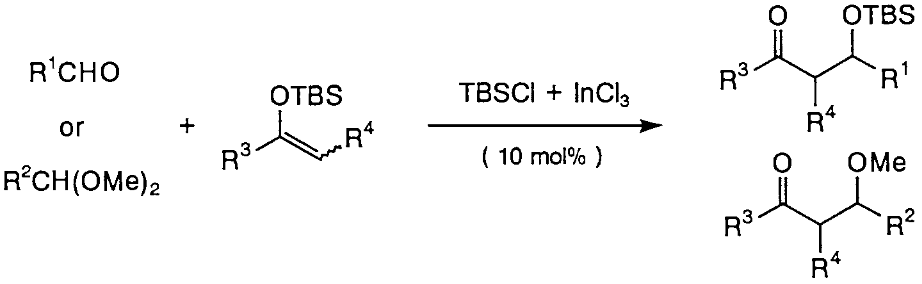
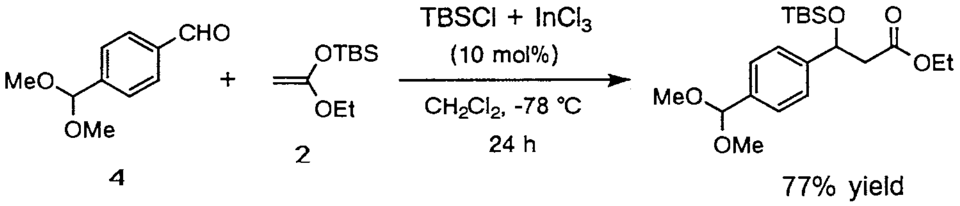


Table 3. The Chemoselective Aldol Reaction

R^1CHO or $R^2CH(OMe)_2$	R^3	R^4	Condition	Yield / %
PhCHO	Me	H	-43 °C, 1.5 h	93
$PhCH(OMe)_2$	Me	H	-43 °C, 1.5 h	0
PhCHO	EtO	H	-43 °C, 1.5 h	80
$PhCH(OMe)_2$	EtO	H	-43 °C, 1.5 h	0
PhCHO	Et	Me	-43 °C, 1.5 h	83
$PhCH(OMe)_2$	Et	Me	-43 °C, 1.5 h	0
$Ph(CH_2)_2CHO$	Ph	Me	-23 °C, 2 h	68
$Ph(CH_2)_2CH(OMe)_2$	Ph	Me	-23 °C, 2 h	0

It is noteworthy that only aldehyde part of **4** reacts with **2**, while acetal part of **4** remains intact under the above conditions.



Though the ground for this characteristic selectivity is not yet clear, TBS group involved in the nucleophiles would play an essential role. Similar tendencies were observed when TBSCl-$SnCl_2$ or TBSOTf was employed in the reaction of 3-t-butyldimethylsiloxy-2-pentene with benzaldehyde or benzaldehyde dimethyl acetal (see Table 4). It should be noted that TBSCl-$InCl_3$ catalyst system is superior over these catalysts in realizing the above mentioned chemoselectivity.

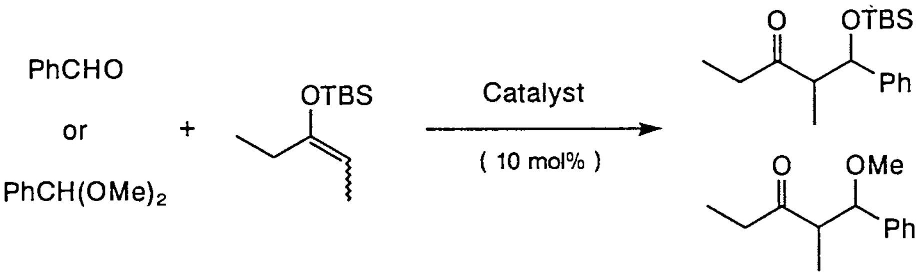


Table 4. Effect of Other Catalysts

R^1CHO or $R^2CH(OMe)_2$	Catalyst	Condition	Yield / %
PhCHO	TBSCl-$SnCl_2$	-43 °C, 1.5 h	91
$PhCH(OMe)_2$	TBSCl-$SnCl_2$	-43 °C, 1.5 h	18
PhCHO	TBSOTf	-43 °C, 1.5 h	86
$PhCH(OMe)_2$	TBSOTf	-43 °C, 1.5 h	27

Further investigations concerning the mechanism of this reaction are now in progress.

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