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AN EFFICIENT METHOD FOR THE PREPARATION OF *THREO* CROSS-ALDOLS FROM SILYL ENOL ETHERS AND ALDEHYDES USING TRITYL PERCHLORATE AS A CATALYST

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Threo cross-aldol products are predominantly formed in good yields by treating tert-butyldimethylsilyl enol ethers with aldehydes in the presence of a catalytic amount of trityl perchlorate.

Recently we have demonstrated that trityl perchlorate is an efficient catalyst in the O-[1] and C-[2]glycosylation reactions and also in the aldol-type reaction between silyl enol ethers and acetals.[3] In these reactions, trityl perchlorate effectively activates acyloxy groups of the anomeric centers or alkoxy groups of acetals. In the course of our investigations to explore useful synthetic reactions by utilizing these characteristic properties of trityl perchlorate, we have found that it is also effective to activate carbonyl groups of aldehydes in the aldol reaction with silyl enol ethers. In this communication, we wish to describe the efficient method for the preparation of *threo* aldols, which have been known rather difficult to prepare by the hitherto reported methods of the aldol reaction.[4]

In the first place, a trimethyl silyl enol ether was chosen as an enolate component and was treated with benzaldehyde in the presence of a catalytic amount of trityl perchlorate (5% mol) in dichloromethane. The aldol reaction proceeded smoothly at -78 °C to give the corresponding β-hydroxy ketones in good yields as shown in Table 1. It is noted that trityl perchlorate effectively activates carbonyl groups of free aldehydes to produce cross-aldols, though the diastereoselectivity of the reaction was low.

Next, in order to improve the diastereoselectivity, several reaction parameters such as solvent, reaction time, the amount of the catalyst, and the substituents attached to silicon, etc. were examined. It was found that, of these reaction parameters, the effect of the substituent of silicon is significant on the diastereoselectivity and that the *threo* aldol was obtained preferentially by using the tert-butyldimethyl silyl enol ether.

Several examples are illustrated in Table 2. *Threo* aldols are obtained predominantly in good yields regardless of geometry of silyl enol ethers.

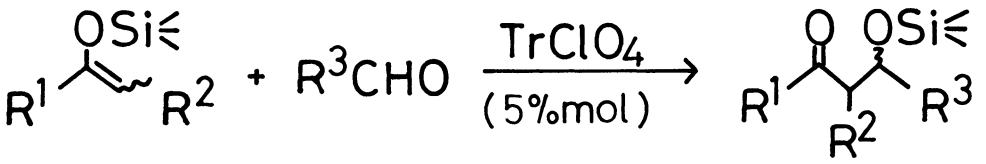
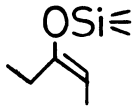
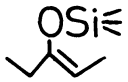
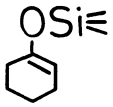
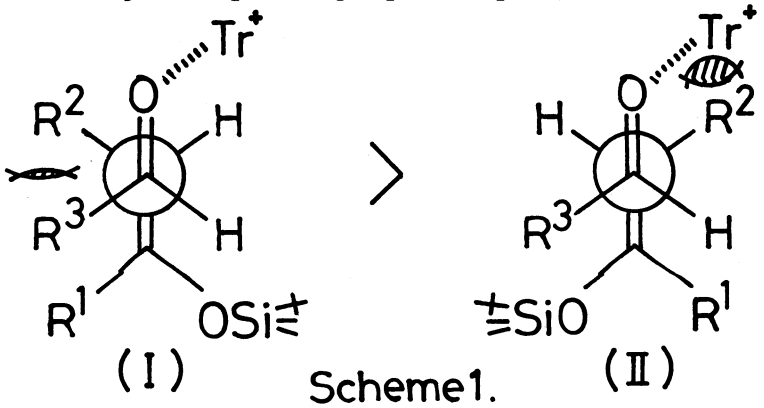


Table 1. The Reaction of Trimethyl Silyl Enol Ethers with Benzaldehyde[a)]

Silyl Enol Ethers		Aldehyde	Yield/%	Erythro:Thereo[b)]
	(E/Z=89/11)	PhCHO	74	51 : 49
	(E/Z=1/99)	PhCHO	89	58 : 42
		PhCHO	77	64 : 36

a) All products gave satisfactory NMR and IR spectra.
b) Diastereomeric ratios determined by ^{1}H NMR.

While the precise reaction mechanism is not yet known, we postulate the open transition states[5)] as shown below. Namely, trityl cation interacts with the aldehyde from the side of proton of the aldehyde.[6)] The silyl enol ether with bulky silyloxy group approaches to the aldehydes in such a way that the steric hindrance between trityl cation, sterically large group, and tert-butyldimethyl-silyloxy group can be minimized.[7)] Transition state (I) is favored over transition state (II) because Tr-R^2 interaction of transition state (II) is larger than R^3-R^2 interaction of transition state (I), leading to the *threo* aldol. On consideration of the postulated transition states, the predominant Tr-R^2 interaction compared with other steric hindrances, may explain the preferential formation of *threo* aldols regardless of the geometry of employed silyl enol ethers.



Scheme1.

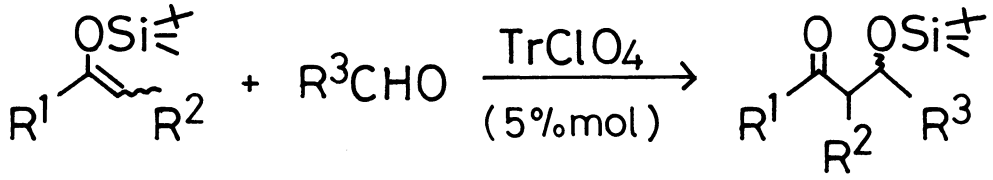
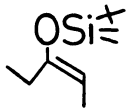
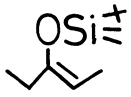
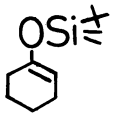
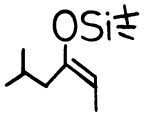


Table 2. The reaction of silyl enol ethers with aldehydes[a)]

Silyl Enol Ethers		Aldehydes	Yield/%	Erythro:Threo[b)]
	(E/Z=76/24)	PhCHO	89	16 : 84
		$Ph(CH_2)_2CHO$	79	21 : 79
	(E/Z=6/94)	PhCHO	87	27 : 73
		$Ph(CH_2)_2CHO$	80	27 : 73
		PhCHO	92	26 : 74
		$Ph(CH_2)_2CHO$	81	18 : 82[c)]
	(E/Z=82/18)	PhCHO	89	20 : 80

a) All products gave satisfactory NMR and IR spectra.
b) Diastereomeric ratios determined by ^1H NMR, ^{13}C NMR, and/or HPLC.
c) Relative configuration assignment was not made.

A typical procedure is described for the reaction of tert-butyldimethyl silyl enol ether of 3-pentanone with benzaldehyde; the mixture of tert-butyldimethyl silyl enol ether of 3-pentanone (0.55 mmol, E/Z=76/24), benzaldehyde (0.5 mmol), and trityl perchlorate (0.02 mmol) in dichloromethane (3 ml) was stirred at -78 °C for 15 min. Then, aqueous sodium hydrogen carbonate was added and the aqueous layer was extracted with dichloromethane. The organic layer was dried and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel to yield 1-tert-butyldimethylsilyloxy-1-phenyl-2-methyl-3-pentanone

(89%, erythro/threo=16/84).

Concerning the cross-aldol reaction using silyl enol ethers, synthetically potential isolable enolates, the $TiCl_4$-promoted reaction is the first example,[8] and much study has been made because of its general availabilities.[9] In these reactions, rather low diastereoselectivity was achieved or erythro aldols were obtained predominantly.

It should be noted that, according to the present method, the *threo* aldols were obtained preferentially in good yields by treating silyl enol ethers with aldehydes by using a catalytic amount of trityl perchlorate under very mild conditions.

Further studies towards clarification of mechanism as well as other synthetic reactions utilizing the unique characteristics of trityl perchlorate are currently in progress in our laboratory.

References

1) T. Mukaiyama, S. Kobayashi, and S. Shoda, Chem. Lett., 1984, 907.

2) T. Mukaiyama, S. Kobayashi, and S. Shoda, Chem. Lett., 1984, 1529.

3) T. Mukaiyama, S. Kobayashi, and M. Murakami, Chem. Lett., 1984, 1759.

4) a) (E)-Boron enolates were reported to give *threo* aldols stereoselectively. However, there remain some problems with the stereoselective generation of the enolates. S. Masamune, S. Mori, D. Van Horn, and D. W. Brooks, Tetrahedron Lett., 1979, 1665; D. A. Evans, J. V. Nelson, E. Vogel, and T. R. Taber, J. Am. Chem. Soc., 103, 3099 (1981).

b) Chan and co-workers reported that the $TiCl_4$-promoted condensation of the (E)-ketene silyl acetal of ethyl propionate with aldehydes gave the *threo* aldols preferentially. T. H. Chan, T. Aida, P. W. K. Lau, V. Gorys, and D. N. Harpp, Tetrahedron Lett., 1979, 4029.

5) J. -E. Dubois and J. -F. Fort, Tetrahedron, 28, 1665 (1972); S. Murata, M. Suzuki, and R. Noyori, J. Am. Chem. Soc., 102, 3248 (1980).

6) For examples, see S. Danishefsky, E. R. Larson, and D. Askin, J. Am. Chem. Soc., 104, 6457 (1982), and references cited therein.

7) We assumed that, in the case of the silyl enol ethers with smaller siloxy groups, the selectivity is low because the silyl enol ethers are able to approach to aldehydes by a pathway different from one shown in Scheme 1.

8) T. Mukaiyama, K. Narasaka, and K. Banno, Chem. Lett., 1973, 1011; T. Mukaiyama, K. Banno, and K. Narasaka, J. Am. Chem. Soc., 96, 7503 (1974); T. Mukaiyama, Angew. Chem., Int. Ed. Engl., 16, 817 (1977).

9) E. Nakamura, M. Shimizu, and I. Kuwajima, Tetrahedron Lett., 1976, 1699; R. Noyori, K. Yokoyama, J. Sakata, I. Kuwajima, E. Nakamura, and M. Shimizu, J. Am. Chem. Soc., 99, 1265 (1977); E. Nakamura, M. Shimizu, I. Kuwajima, J. Sakata, K. Yokoyama, and R. Noyori, J. Org. Chem., 48, 932 (1983); R. Noyori, I. Nishida, and J. Sakata, J. Am. Chem. Soc., 105, 1598 (1983); C. H. Heathcock, K. T. Hug, and L. A. Flippin, Tetrahedron Lett., 25, 5973(1984).

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