

TRITYL PERCHLORATE CATALYZED TANDEM MICHAEL-ALDOL REACTION.  
A FACILE METHOD FOR THE STEREOSELECTIVE SYNTHESSES OF  
 $\gamma$ -ACYL SUBSTITUTED  $\delta$ -HYDROXY KETONE DERIVATIVES

Shū KOBAYASHI and Teruaki MUKAIYAMA  
Department of Chemistry, Faculty of Science,  
The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113

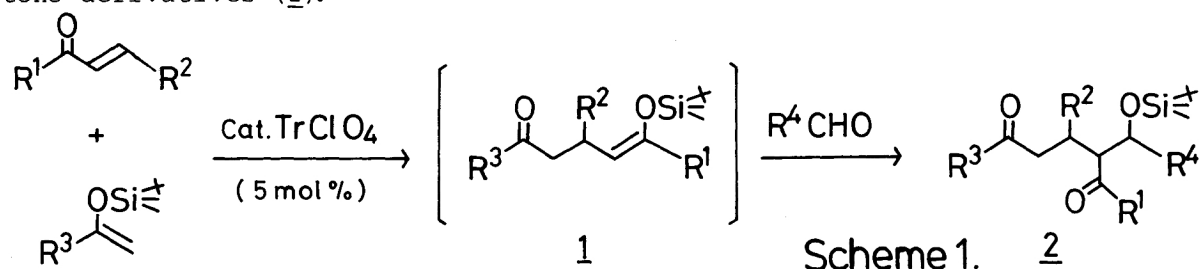
In the presence of a catalytic amount of trityl perchlorate, the intermediate adducts, produced in situ by the conjugate addition of silyl enol ethers with  $\alpha,\beta$ -unsaturated ketones, react with aldehydes to give the corresponding  $\gamma$ -acyl substituted  $\delta$ -hydroxy ketone derivatives stereoselectively in high yields. The ketones thus obtained are easily converted to tetrahydropyran derivatives.

Conjugate addition of organocuprates to  $\alpha,\beta$ -unsaturated ketones and the sequential reaction with electrophiles are very useful synthetic tools for the formation of two carbon-carbon bonds in one step, and much efforts have been made concerning organocuprates, electrophilic reagents, and various metal salts as additives.<sup>1)</sup> However, application of enolates derived from ketones to the above mentioned reaction is unprecedented, in spite of versatile use of metal enolates and potential utility of this reaction.

Recently, we have demonstrated new possibilities of various trityl salts in synthetic reactions;<sup>2)</sup> for example, it was shown that trityl perchlorate is an efficient catalyst in the Michael reaction between silyl enol ethers derived from ketones and  $\alpha,\beta$ -unsaturated ketones, and the adducts, synthetically valuable  $\delta$ -keto silyl enol ethers, are isolated in high yields.<sup>3)</sup> Another advantage of this reaction is that this silyl enol ether and trityl perchlorate coexist in the reaction mixture after the Michael reaction has completed owing to the recycle system of trityl perchlorate. Therefore, it is assumed that, if appropriate electrophiles are added to the reaction system, it is possible to obtain the products from further reactions of the intermediate silyl enol ethers with the electrophiles. In this communication, we wish to disclose our preliminary finding on the trityl perchlorate catalyzed tandem Michael-aldol reaction, and also the utilization of this reaction for the stereoselective syntheses of tetrahydropyran derivatives.

The scheme of the tandem Michael-aldol reaction is shown below (Scheme 1). In the first step (the Michael reaction), silyl enol ethers react with  $\alpha,\beta$ -unsaturated ketones to afford the intermediate silyl enol ethers (1) in the presence of a catalytic amount of trityl perchlorate (5 mol%). In the second step

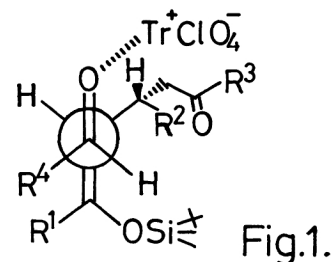
(the aldol reaction), the silyl enol ethers (1) thus produced react with aldehydes by the promotion of trityl perchlorate to afford the  $\gamma$ -acyl-substituted  $\delta$ -hydroxy ketone derivatives (2).



Several examples are shown in Table 1. In every case,  $\gamma$ -acyl-substituted  $\delta$ -hydroxy ketone derivatives are obtained in high yields. In this reaction a catalytic amount of trityl perchlorate effectively catalyzed both the Michael and the successive aldol reaction, and the formation of two carbon-carbon bonds at  $\alpha$  and  $\beta$  position of  $\alpha,\beta$ -unsaturated ketones is realized in one pot. Moreover, the products of this reaction are easily isolated as O-protected t-butyldimethyl silyl ethers, though it is well-known that  $\delta$ -hydroxy ketones are in an equilibrium with hemiacetals and the separation of both compounds is difficult.

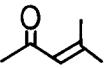
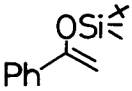
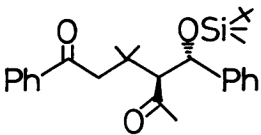
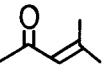
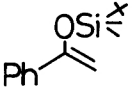
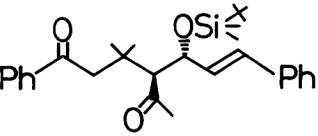
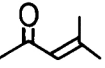
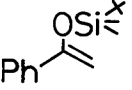
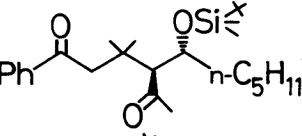

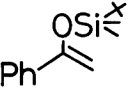
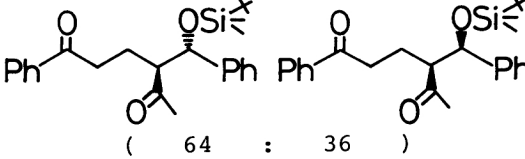
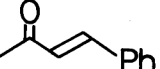
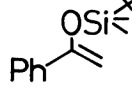
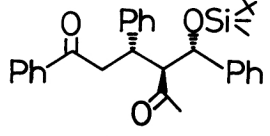
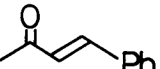
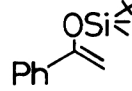
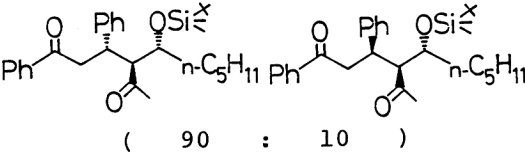
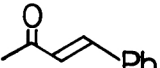
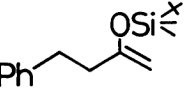
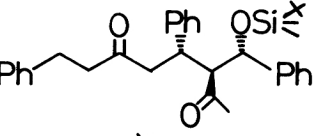
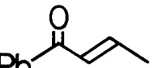
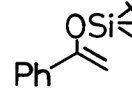
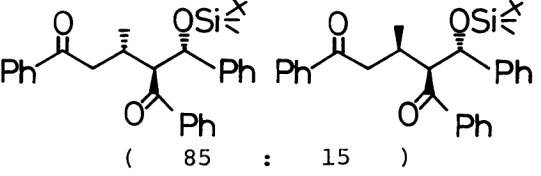
In addition, remarkable stereocontrol was achieved in the present reaction. Concerning the relative configuration of  $\gamma$  and  $\delta$  position of the  $\delta$ -hydroxy ketone derivatives, the anti products<sup>4)</sup> were obtained exclusively (except for entry 4 (Table 1)). Further, as shown in entries 5 and 7, in the cases of mono  $\beta$ -substituted  $\alpha,\beta$ -unsaturated ketones, only one of four diastereomers was obtained. In the cases of entries 6 and 8, two of four diastereomers are obtained and one of them, the anti-anti adduct<sup>4)</sup> is produced predominantly. This high stereo-selectivity is explained by assuming the transition state as shown below in Fig. 1.

A typical procedure for the preparation of  $\gamma$ -acyl-substituted  $\delta$ -hydroxy ketone derivatives is as follow; the mixture of a silyl enol ether (0.50 mmol), an  $\alpha,\beta$ -unsaturated ketone (0.53 mmol), and trityl perchlorate (0.03 mmol, 5 mol%) in dichloromethane (3 ml) was stirred at  $-78^\circ\text{C}$  for an appropriate time (15-60 min). Then an aldehyde (0.47 mmol) in dichloromethane (1 ml) was added to this pot and further stirred at  $-78^\circ\text{C}$  overnight. After the reaction was completed, 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 separated by silica gel column chromatography.



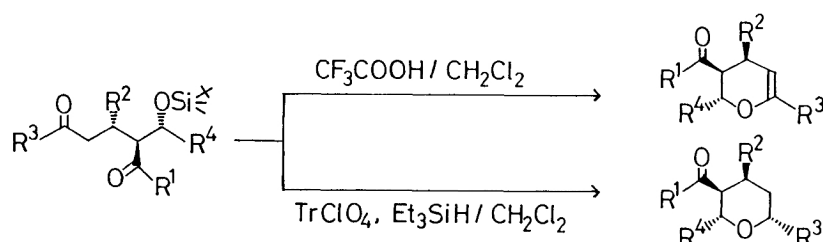
The  $\gamma$ -acyl-substituted  $\delta$ -hydroxy ketone derivatives thus obtained was easily converted to the tetrahydropyran derivatives. Namely, the treatment of the  $\delta$ -hydroxy ketones with trifluoroacetic acid in dichloromethane gave dihydropyran derivatives in excellent yields. The reduction with triethylsilane in the presence of a catalytic amount of trityl perchlorate<sup>5)</sup> yielded 3-acyl-substituted 2,4,6-tri-substituted tetrahydropyran derivatives in high yields.<sup>6)</sup>

Table 1. Stereoselective syntheses of  $\gamma$ -acyl-substituted  $\delta$ -hydroxy ketone derivatives <sup>a)</sup> (Scheme 1)

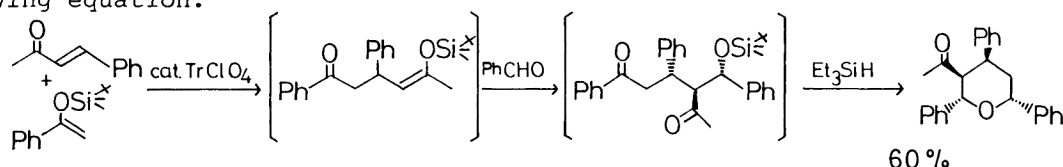
Entry	$\alpha,\beta$ -Unsaturated ketone	Silyl enol ether	Aldehyde	Product <sup>b)</sup> (Diastereomer ratio)	Yield/%
1			PhCHO		91
2			PhCH=CHCHO		93
3			<i>n</i> -C <sub>5</sub> H <sub>11</sub> CHO		83
4			PhCHO	 ( 64 : 36 )	67
5			PhCHO		93
6			<i>n</i> -C <sub>5</sub> H <sub>11</sub> CHO	 ( 90 : 10 )	98
7			PhCHO		72
8			PhCHO	 ( 85 : 15 )	85

a) All products gave satisfactory NMR and IR spectra.

b) Each compound was separated by silica gel column chromatography.



The latter compound was also prepared from a silyl enol ether, an  $\alpha,\beta$ -unsaturated ketones, and an aldehyde by one pot procedure as shown in the following equation.



It is noted that the tandem reaction of conjugate addition of silyl enol ethers to  $\alpha,\beta$ -unsaturated ketones and the sequential aldol addition with aldehydes is carried out smoothly to afford  $\gamma$ -acyl-substituted  $\delta$ -hydroxy ketone derivatives in high yields. The ketones thus obtained are easily converted to tetrahydropyran derivatives stereoselectively.

Further progress using the tandem Michael-aldol reaction leading to versatile products is now in progress.

#### References

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- 5) J. Kato, N. Iwasawa, and T. Mukaiyama, *Chem. Lett.*, **1985**, 743.
- 6) Stereoselective syntheses of 2,3,5-trisubstituted tetrahydrofurans from the corresponding aldolized  $\gamma$ -diketones using this method are now in progress in our laboratory. See T. Mukaiyama, J. Ichikawa, M. Toba, and M. Hayashi, *Chem. Lett.*, **1985**, 1539.

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