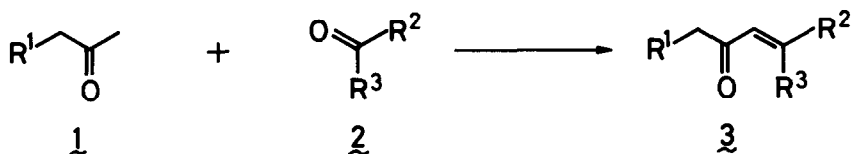


A REGIOSELECTIVE ENOLATE FORMATION OF TRIMETHYLSILYLMETHYL KETONES
APPLICATION TO THE (E)-SELECTIVE SYNTHESIS OF α,β -UNSATURATED KETONES

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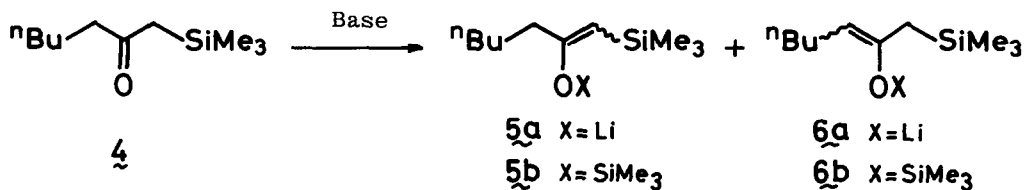
Summary: Two possible enolate anions of trimethylsilylmethyl ketones have been prepared regioselectively by the appropriate choice of base. The one directed to the silylmethyl site behaves as a highly reactive and (E)-selective condensation reagent to aldehydes.

The regiocontrolled "crossed aldol" coupling of an unsymmetrical ketone (1) and an aldehyde or another ketone (2) to form an α,β -unsaturated ketone (3) is a highly useful synthetic operation in organic synthesis. Although Horner-Emmons-Wadsworth reaction is generally applied to this type one step condensation, ¹⁾ this method needs a relatively cumbersome procedure for the preparation of phosphate carbanion and dull reaction time. ²⁾ Enhancement of reactivity may be attained by the substitution of phosphate group to silyl group because successful examples have been reported in the Peterson type olefination of α -silylcarbanion stabilized by electron withdrawing group; $R_3Si\overset{\ominus}{C}HX$ [X = CO_2R' , ³⁾ $C\equiv N$, ⁴⁾ $C(=N-Bu^t)R'$, ⁵⁾ and $C(=O)SiMe_3$ ⁶⁾]. Thus, we disclose the efficacy of trimethylsilylmethyl ketones ⁷⁾ as a new condensation reagent in carbonyl olefinations.

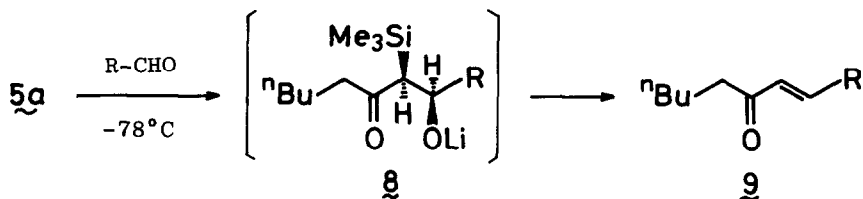


Deprotonation of α -silyl ketone 4 in tetrahydrofuran (THF) with lithium diisopropylamide and the subsequent addition of trimethylchlorosilane gave two regioisomers 5b and 6b in 93% yield (5b:6b = 83:17). ⁸⁾ Remarkable change of this ratio was not observed in the case of lithium amide reagents of secondary amine such as diethylamine (88:12), di-n-propylamine (80:20), and 2,2,6,6-tetramethylpiperidine (89:11) except hexamethyldisilazane (24:76).

On the other hand, *sec*-BuLi (96:4) and *ter*-BuLi (98:2) contributed to the preferable formation of $\tilde{5}b$ accompanying 20 to 30% of nucleophilic adducts of alkyl lithium. After all, silicon modified alkyl lithium such as 1-trimethylsilylhexyllithium ($\tilde{7}$) and 1-trimethylsilylethyllithium gave the best result in the selectivity of $\tilde{5}b$ ($\tilde{5}b:\tilde{6}b = 98:2$)⁹⁾ and yields (90–96%).

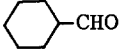
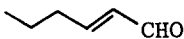


Thus, $\tilde{5}a$ derived from $\tilde{4}$ was treated with an appropriate aldehyde. Elimination of the oxygen and trimethylsilyl moieties from the resultant crossed aldol condensation product $\tilde{8}$ proceeded spontaneously at -78°C and produced (*E*)- α,β -unsaturated ketones $\tilde{9}$.¹¹⁾ The reactivity of the present reagent $\tilde{5}a$ did not depend on the type of aldehyde. The results are summarized in Table 1. A typical procedure for the preparation of $\tilde{9}a$ is as follows. To a solution of $\tilde{7}$ (6.03 mmol) prepared from *n*-BuLi and vinyltrimethylsilane in 40 ml of THF at -78°C was added a solution of $\tilde{4}$ (6.32 mmol) in 5 ml of THF. After stirring the mixture for 1h at -78°C , nonanal (5.98 mmol) in 5 ml of THF was added to the solution. The mixture was stirred for 20 min. at -78°C and quenched with 20 ml of saturated aqueous NH_4Cl . After extraction with ethyl acetate the combined organic phases were washed with brine and dried over MgSO_4 . Evaporation of the solvent and purification of the residual oil by column chromatography through silica gel using hexane/ethyl acetate (25:1) as an eluent gave $\tilde{9}a$ in 82% yield.



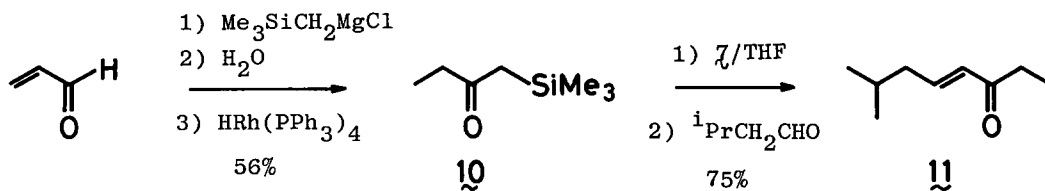
It is well documented that β -alkoxysilane undergo *syn* elimination producing the corresponding olefins.¹²⁾ Therefore, provided that the (*E*)- α,β -unsaturated ketones $\tilde{9}$ obtained in this study represent the kinetic elimination products, the crossed aldol reaction $\tilde{5}a \rightarrow \tilde{8}$ must have proceeded in a stereoselective manner explained by a conventional six-membered transition state. It was deduced from the result that only (*E*)- $\tilde{9}a$ was obtained in 49%

Table 1. Results of condensation of $5a$ with aldehydes.

Entry	Aldehyde	Product	Yield (%)
1	$n\text{-C}_8\text{H}_{17}\text{-CHO}$	$9a$	82
2		$9b$	88
3	$ter\text{-Bu-CHO}$	$9c$	75
4	Ph-CHO	$9d$	91
5		$9e$	81

yield as a sole condensation product after extremely short reaction time (about 10 seconds).

The efficacy of the present method is demonstrated by the synthesis of (*E*)-7-methyl-4-octen-3-one (11) isolated from a sponge.¹³ 1-Trimethylsilylbutan-2-one (10) prepared from acrolein and trimethylsilylmethylmagnesium chloride⁷) was deprotonated with 7 and treated with 3-methylbutanal to give 11 selectively in 75% yield.



The present route to α,β -unsaturated ketones has great potential in that it allows for considerable flexibility in the choice of disconnected components and reaction conditions. In fact the operation under acidic conditions was also realized by the intervention of silyl enol ether $5b$. For example, the reaction $5b$ with nonanal gave (*E*)- $9a$ selectively in a yield of 79 to 86% in the presence of TiCl_4 or a mixture of TiCl_4 and $\text{Ti}(\text{O}^i\text{Pr})_4$.

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