Novel Reactive Silyl Enolates. Highly Stereoselective Aldol and Michael Reactions without Catalysts

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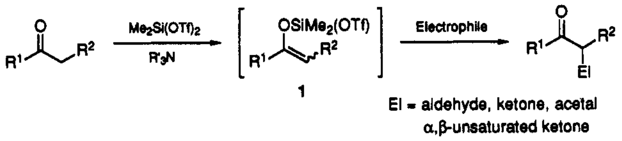
Summary: Novel silyl enolates, prepared in situ from ketones and dimethylsilyl ditriflate ($Me_2Si(OTf)_2$) in the presence of a tertiary amine, reacted smoothly with electrophiles such as aldehydes, acetals, or α,β-unsaturated ketones without catalyst at −78 °C to afford the corresponding adducts in high yields and with high selectivities.

Formation of enolates and their selective reactions are among the most important processes in organic synthesis.[1] In the last decade, fruitful results have been reported especially in the stereoselective aldol and Michael reactions with development of several metal enolates such as lithium, boron, aluminum, silicon, titanium, tin, etc. to realize high reactivities and selectivities.[2] Among them, silyl enolates are superior to other metal enolates in isolation, regioselective formation, and unique reactivities under mild conditions.[3] However, stoichiometric use of a Lewis acid such as titanium tetrachloride or a catalyst such as TMSOTf,[4] trityl salt,[5] fluoride anion,[6] transition metal complex,[7] or lanthanide chloride[8] or triflate,[9] etc.[10] is required to complete the reactions, and stereoselectivities are generally moderate except for a few examples.[11] Quite recently, Myers et al. reported the direct aldol condensation of some modified silyl enolates with aldehydes.[12] Although the silyl enolates derived from amides or esters reacted smoothly with aldehydes, higher temperature is still required in the reaction of a ketone enolate with an aldehyde.[12c]

In this paper, we report novel silyl enolates which smoothly react with not only aldehydes but also acetals or α,β-unsaturated ketones *without catalysts* under mild conditions to afford the corresponding adducts in high yields with high diastereoselectivities.



The novel silyl enolate, prepared in situ from a ketone and dimethylsilyl ditriflate ($Me_2Si(OTf)_2$)[13] in the presence of a tertiary amine,[14] reacts smoothly with aldehydes, acetals, or α,β-unsaturated ketones (see Table I). In the reactions of aldehydes, the corresponding syn aldol adducts are stereoselectively obtained in high yields, and only the 1,2-addition product is obtained from crotonaldehyde. Cyclohexanone is also an excellent acceptor. Furthermore, acetals smoothly react with 1 *in the absence of catalyst* to give the corresponding aldol-type adducts in high yields with high selectivities. In the reactions of α,β-unsaturated ketones, the enolates regioselectively react in a 1,4-addition manner to give the corresponding Michael-type adducts in high yields.[15] It should be noted that the enolates have unprecedented properties that they can react with alde-

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[14] Boron and tin(II) enolates are successfully produced from a ketone and dialkylboryl triflate or tin(II) triflate in the presence of a tertiary amine. See: (a) Mukaiyama, T.; Inoue, T. *Chem. Lett.* **1976**, 559. (b) Mukaiyama, T.; Iwasawa, N.; Stevens, R. W.; Haga, T. *Tetrahedron* **1984**, *40*, 1381.

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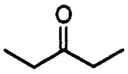
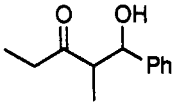
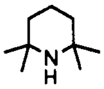
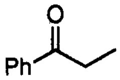
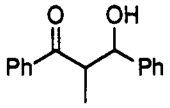
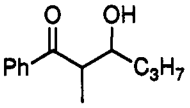
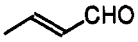
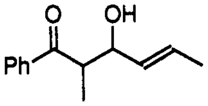
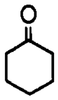
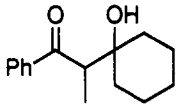
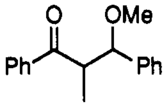
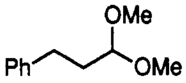
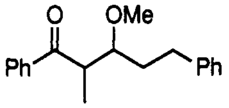
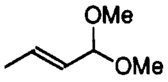
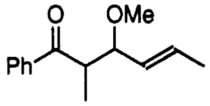
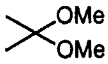
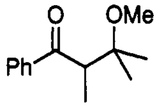
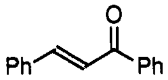
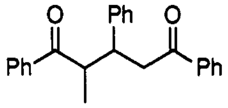
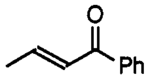
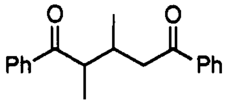
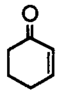
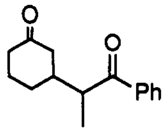
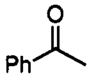
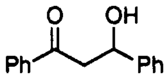
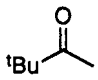
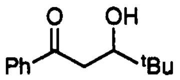
Table I. Reaction of Silyl Enolate 1 with Electrophiles

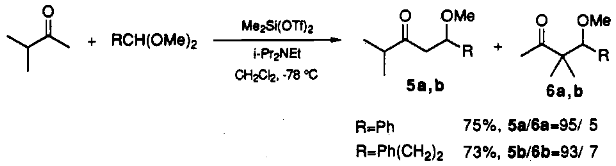
entry	ketone	electrophile	base	product	yield/%	syn/anti[a]
1		PhCHO	i-Pr$_2$NEt		71	89/11
2			Et$_3$N		78	91 / 9
3					70	80/20
4					66	90/10
5		PhCHO	i-Pr$_2$NEt		88 [b)]	91 / 9
6		C$_3$H$_7$CHO	i-Pr$_2$NEt		66	92/ 8
7			i-Pr$_2$NEt		64	92/ 8 [c)]
8			i-Pr$_2$NEt		72	—
9		PhCH(OMe)$_2$	i-Pr$_2$NEt		88	88/12
10			i-Pr$_2$NEt		90	94/ 6
11			i-Pr$_2$NEt		64	83/17
12			i-Pr$_2$NEt		59	—
13			i-Pr$_2$NEt		83	10/90
14			i-Pr$_2$NEt		66	<5 / >95
15			i-Pr$_2$NEt		64	10/90 [d)]
16		PhCHO	i-Pr$_2$NEt		65	—
17		PhCHO	i-Pr$_2$NEt		81	—

[a] Diasteromer ratio was determined by ^{1}H NMR unless otherwise noted. Relative configuration assignment was made by comparison with the literature. See refs 2b (entries 1–7), 18 (entries 9–11), and 19 (entries 13–15). [b] Lower yield was observed when Et$_3$N was used instead of i-Pr$_2$NEt. [c] Determined by HPLC analysis. [d] Determined by ^{13}C NMR.

hydes, ketones, and acetals as well as α,β-unsaturated ketones in high regio- and stereoselectivities without catalysts.[16]

A typical experimental procedure is described for the reaction of 3-pentanone with benzaldehyde: to a dichloromethane solution (0.6 mL) of $Me_2Si(OTf)_2$ (0.6 mmol) was successively added diisopropylethylamine (0.66 mmol) in dichloromethane (1 mL) and 3-pentanone (0.4 mmol) in dichloromethane (1 mL) at −78 °C. After the solution was stirred for 30 min, benzaldehyde (0.33 mmol) in dichloromethane (1 mL) was added and the mixture was further stirred for 20 h. Saturated aqueous sodium hydrogen carbonate was added to quench the reaction mixture, the organic layer was separated, and the aqueous layer was extracted with dichloromethane (three times). The combined organic layer was dried (Na_2SO_4), filtered, evaporated, and chromatographed on silica gel to afford the corresponding aldol-type adduct (71%, syn/anti = 89/11).

Regioselective formation of such enolates is attained according to the present procedure. Thus, 3-methyl-2-butanone regioselectively reacts with acetals to give the corresponding adducts in good yields.



The novel silyl enolates **1** have a trifluoromethanesulfonyl group as a substituent on silicon, different from the conventional trimethylsilyl enol ethers. Owing to the strong electron-withdrawing group on silicon, enol ethers **1** can serve as Lewis acids and high reactivities and selectivities can be attained.

Further investigations to apply this new concept to other nucleophilic reagents such as allylsilanes and vinylsilanes as well as other metal compounds are now in progress.

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Supplementary Material Available: ^1H and ^{13}C NMR spectra (23 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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[16] Although boron or tin(II) enolates react with aldehydes to give the corresponding aldol adducts in high stereoselectivities, they do not react with acetals or α,β-unsaturated ketones.[17] Even most reactive lithium enolates do not react with acetals, and mixtures of 1,2- and 1,4-addition products are obtained in the reactions with α,β-unsaturated ketones.[2c]

[17] Tin(II) enolates regioselectively react with α,β-unsaturated ketones in the presence of TMSCl as an activator. See: Yura, T.; Iwasawa, N.; Mukaiyama, T. *Chem. Lett.* **1987**, 791.

[18] Murata, S.; Suzuki, M.; Noyori, R. *Tetrahedron* **1988**, *44*, 4259.

[19] (a) Heathcock, C. H.; Norman, M. H.; Uehling, D. E. *J. Am. Chem. Soc.* **1985**, *107*, 2797. (b) Mukaiyama, T.; Tamura, M.; Kobayashi, S. *Chem. Lett.* **1986**, 1017.