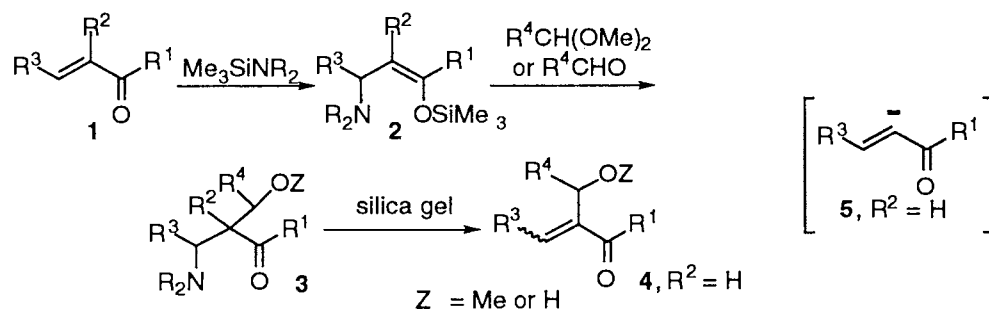


Introduction of Electrophiles to the α -Position of α,β -Unsaturated Aldehydes and Ketones by Sequential Conjugate Aminosilylation-Alkylation-Deamination¹⁾

Makoto HOJO, Masayuki NAGAYOSHI, Atsuko FUJII, Toshiharu YANAGI,
Naruyasu ISHIBASHI, Katsukiyo MIURA, and Akira HOSOMI*
Department of Chemistry, University of Tsukuba, Tsukuba, Ibaraki 305

Silylamines add to α,β -unsaturated aldehydes and ketones in 1,4-addition mode to generate amino-substituted silyl enol ethers without any catalysts. These easily isolable silyl enol ethers react with acetals and aldehydes in the presence of a Lewis acid to give α -alkoxyalkyl and α -hydroxyalkyl substituted α,β -unsaturated carbonyl compounds, respectively, after deamination by treatment with silica gel.

Tandem 1,4-addition-alkylation to α,β -unsaturated carbonyl compounds is an efficient method for the introduction of a nucleophile at the β -position and an electrophile at the α -position to the carbonyl group in one step.²⁾ According to this methodology, the addition of an amino group at the β -position of α,β -unsaturated carbonyl compounds to generate temporarily the corresponding enolates, the reaction of the enolates with electrophiles at the α -position followed by the elimination of the amino group successively make possible the introduction of electrophiles at the α -position to the parent α,β -unsaturated carbonyl compounds, and we have previously demonstrated that such transformation using titanium amides is useful.³⁾ Although these titanium reagents were effective for α,β -unsaturated esters, α,β -unsaturated ketones were not always suitable for this 1,4-aminotitanation, presumably due to strong acidity of titanium. In searching for other metalloamides that exhibit oxophilicity of a metal and nucleophilicity of an amino moiety, we have found silylamines are appropriate for such transformation using α,β -unsaturated aldehydes and ketones. Now we wish to report herein that the introduction of an electrophile at the α -position of α,β -unsaturated aldehydes and ketones using silylamines where silyl enol ethers of β -aminocarbonyl compounds can be easily isolated, although the 1,4-addition of silylamines has hitherto been unsuccessful without catalysts under mild conditions. Such a transformation is synthetically equivalent to the generation of α -carbanion **5** for α,β -unsaturated carbonyl compounds (Scheme 1).



Scheme 1.

At first we found that silylamines reacted with α,β -unsaturated carbonyl compounds **1** in 1,4-addition mode without any catalysts under mild conditions to give the corresponding amino-substituted silyl enol ethers **2** stereoselectively and that the amino group served as a nucleophile in this reaction, but not as a base. Selected results are listed in Table 1. Interestingly in all cases silyl enol ethers **2** were only (*Z*)-isomer and presumably the reaction proceeded through a cyclic transition state consisting of the *s*-cis form of **1** and silylamine.⁴⁾ These silyl enol ethers were easily isolated by distillation after evaporation of the solvent and used for further reactions.

Table 1. 1,4-Addition of Silylamine to α,β -Unsaturated Carbonyl Compounds **1**^{a)}

Entry	Silylamine NR ₂	1			Conditions	Silyl Enol Ether 2 ^{b)} (Yield/%) ^{c)}
		R ¹	R ²	R ³		
1	NEt ₂	Me	H	H	Et ₂ O, rt, 24 h	2a (94)
2	NEt ₂	Bu	H	H	Et ₂ O, rt, 15 h	2b (57)
3	NEt ₂	Me	Me	H	DME, reflux, 24 h	2c (49)
4	NEt ₂	Me	H	Me	DME, reflux, 24 h	2d (18)
5	NEt ₂	H	H	H	Et ₂ O, reflux, 18 h	2e (78)
6	NMe ₂	Me	H	H	Et ₂ O, rt, 15 h	2f (98)
7	NMe ₂	Bu	H	H	Et ₂ O, rt, 15 h	2g (84)
8	NMe ₂	Me	H	Me	DME, reflux, 15 h	2h (88)
9	NMe ₂	Ph	H	H	Et ₂ O, rt, 15 h	2i (100)

a) Reaction conditions: to a solution of α,β -unsaturated carbonyl compounds (6 mmol) in a solvent (5 ml) was added silylamine (5 mmol) under nitrogen. b) Only (*Z*)-isomer was obtained and the purity of **2** was confirmed by ¹H NMR and GC. c) Purified and Isolated yield by distillation after evaporation of the solvent under reduced pressure.

Reaction of silyl enol ethers **2** with acetals were carried out using TiCl₄ as a Lewis acid in CH₂Cl₂ at -78 °C. In all cases using aliphatic and aromatic acetals, silyl enol ethers were converted to α -alkylated aminoketones **3**.⁵⁾ These crude products were subsequently deaminated by treatment with silica gel and α -alkylated enones **4** were obtained in excellent yields. In all cases diethylamino-substituted silyl enol ethers **2** gave better yields than dimethylamino-substituted ones. The representative results are listed in Table 2. In these reactions, it was difficult to determine the diastereoselectivity with respect to an aldol moiety of **3**. However the diastereoselectivity between amino and α -substituent to the carbonyl group is presumably moderate (ca. 5/1), judging from the stereochemistry of regenerated double bond (entry 6). A typical procedure is as follows: to a solution of a silyl enol ether **2a** (2 mmol) and propionaldehyde dimethylacetal (3 mmol) in dichloromethane (10 ml) was added TiCl₄ (4 mmol) during a period of 10 min at -78 °C. After 1 h, the reaction mixture was poured into

saturated aqueous NaHCO_3 at 0°C . Extraction with Et_2O , washing with a brine, drying with Na_2SO_4 , and evaporation of the resulting mixture gave a crude adduct **3a**. Without isolation of **3a**, this oil was subjected to column chromatography on silica gel (hexane/chloroform = 3/1) and collection of the fraction ($R_f = 0.3$) gave a pure α,β -enone **4a** in quantitative yield.⁶⁾

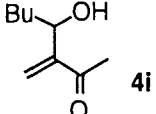
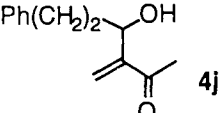
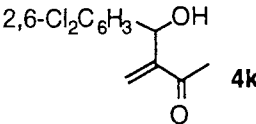
Aldol reaction with aldehydes is also attained and typical examples are listed in Table 3. A combination of titanium tetrachloride-chlorotrimethylsilane is the best choice as a promoter of this reaction.

Table 2. Reaction of Silyl Enol Ether **2** with Acetals^{a)}

$\begin{array}{c} \text{R}^3 \\ \\ \text{Et}_2\text{N}-\text{CH}=\text{CH}-\text{OSiMe}_3 \\ \text{2} \end{array} + \text{R}^4\text{CH(OMe)}_2 \xrightarrow[\text{-78}^\circ\text{C, 1 h}]{\text{TiCl}_4, \text{CH}_2\text{Cl}_2} \begin{array}{c} \text{R}^4 \\ \\ \text{R}^3-\text{CH}-\text{CH}(\text{OMe})-\text{C(=O)}-\text{R}^1 \\ \\ \text{Et}_2\text{N} \\ \text{3} \end{array} \xrightarrow{\text{silica gel}} \begin{array}{c} \text{R}^4 \\ \\ \text{R}^3-\text{CH}=\text{CH}-\text{C(=O)}-\text{R}^1 \\ \text{4} \end{array}$			
Entry	Silyl Enol Ether 2	Acetal (R^4)	Product 4 ^{b)} (Yield/%) ^{c)}
1		Et	 4a (100)
2	2a	Hex	 4b (100)
3	2a	4-MeC ₆ H ₄	 4c (82)
4	2a	Ph	 4d (100)
5		Ph	 4e (93)
6		Bu	 4f (71) ^{d)}
7		Bu	 4g (39)
8	2e	Ph	 4h (43) 6 (21) ^{e)}

a) All reactions were carried out with two equivalents of TiCl_4 as a Lewis acid in CH_2Cl_2 at -78°C . b) After treatment with silica gel by column chromatography without isolation of **3**. c) Isolated yield. d) An E/Z ratio was 82/18. e) Along with **4h**, an α,β -unsaturated aldehyde **6** was obtained by the elimination of MeOH in an E/Z ratio of 80/20.

Table 3. Reaction of Silyl Enol Ether **2** with Aldehydes^{a)}

$\text{Et}_2\text{N}-\text{CH}=\text{CH}-\text{OSiMe}_3 \quad \mathbf{2a} + \text{R}^4\text{CHO} \xrightarrow[\text{CH}_2\text{Cl}_2]{\text{TiCl}_4/\text{Me}_3\text{SiCl}} \text{Et}_2\text{N}-\text{CH}(\text{R}^4)-\text{CH}(\text{OH})-\text{C}(=\text{O})\text{CH}_3 \quad \mathbf{3} \xrightarrow{\text{silica gel}} \text{R}^4-\text{CH}(\text{OH})-\text{C}(=\text{O})\text{CH}_3 \quad \mathbf{4}$				
Entry	Aldehyde (R ⁴)	Conditions	Product 4 ^{b)}	(Yield/%) ^{c)}
1	Bu	-20 °C, 6 h	 4i	(68)
2	Ph(CH ₂) ₂	-40 °C, 11.5 h	 4j	(62)
3	2,6-Cl ₂ C ₆ H ₃	0 °C, 10 min	 4k	(36)

a) All reactions were carried out with three equivalents of TiCl₄ and 0.5 equivalent of chlorotrimethylsilane in CH₂Cl₂. b) After treatment with silica gel by column chromatography without isolation of **3**. c) Isolated yield.

In conclusion alkoxyalkylation and hydroxyalkylation at the α-position of α,β-unsaturated aldehydes and ketones can be achieved using silylamines by sequential conjugate aminosilylation-alkylation-deamination reaction. Further applications of isomerically pure silyl enol ethers are now under investigation.

Financial support for our work is provided by Grants-in-Aid for Scientific Research (No. 05554022) and Grants-in-Aid for Scientific Research on Priority Areas (No. 05236102) from the Ministry of Education, Science and Culture, Japan, and the Chemical Materials Research and Development Foundation.

References

- 1) Studies on organosilicon chemistry. No. 121. For 120, see, M. Hojo, K. Tomita, Y. Hirohara, and A. Hosomi, *Tetrahedron Lett.*, **34**, 8123-8126 (1993).
- 2) M. J. Chapdelaine and M. Hulce, *Org. Reactions*, **38**, 225 (1990); Y. Xia and A. P. Kozikowski, *J. Am. Chem. Soc.*, **111**, 4116 (1989); S. J. Danishefsky, M. P. Cabal, and K. Chow, *ibid.*, **111**, 3456 (1989) and references cited therein.
- 3) A. Hosomi, T. Yanagi, and M. Hojo, *Tetrahedron Lett.*, **32**, 2371 (1991). For a recent report using other heteronucleophiles, see, S. Kim, J. H. Park, Y. G. Kim, and J. M. Lee, *J. Chem. Soc., Chem. Commun.*, 1188 (1993), and references cited therein. For the synthesis of β-lactams using the sequential 1,4-amination-alkylation to α,β-unsaturated esters of copper amides, see, Y. Yamamoto, N. Asao, and T. Uyehara, *J. Am. Chem. Soc.*, **114**, 5427 (1992), and references cited therein.
- 4) The (Z)-stereochemistry of silyl enol ethers is confirmed by NOE experiments.
- 5) Reaction of **2c** with PhCH(OMe)₂ gave the corresponding amino ketones **3** in 58% yield, because the formation of α-alkylated α,β-enone by deamination was impossible.
- 6) Satisfactory spectral and analytical data are obtained for all products in this work.

(Received January 13, 1994)