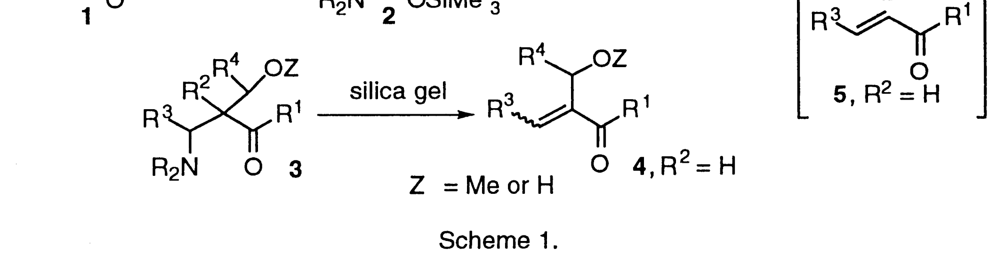
CHEMISTRY LETTERS, pp. 719-722, 1994.

Introduction of Electrophiles to the α-Position of α,β-Unsaturated Aldehydes and Ketones by Sequential Conjugate Aminosilylation-Alkylation-Deamination[1)]

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.

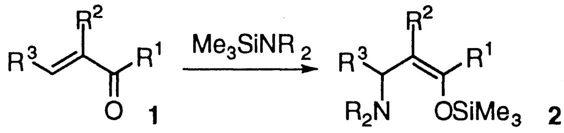
Tandem 1,4-addition-alkylation to α,β-unsaturated carbonyl compounds is an efficient method for the introduction of a nucleophile at the β-position and an electrophile at the α-position to the carbonyl group in one step.[2)] According to this methodology, the addition of an amino group at the β-position 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]



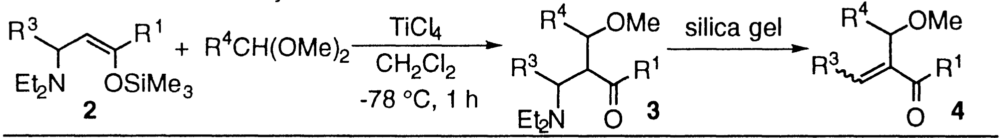
Entry	Silylamine NR_2	**1** R^1	R^2	R^3	Conditions	Silyl Enol Ether **2**[b] (Yield/%)[c]
1	NEt_2	Me	H	H	Et_2O, rt, 24 h	**2a** (94)
2	NEt_2	Bu	H	H	Et_2O, rt, 15 h	**2b** (57)
3	NEt_2	Me	Me	H	DME, reflux, 24 h	**2c** (49)
4	NEt_2	Me	H	Me	DME, reflux, 24 h	**2d** (18)
5	NEt_2	H	H	H	Et_2O, reflux, 18 h	**2e** (78)
6	NMe_2	Me	H	H	Et_2O, rt, 15 h	**2f** (98)
7	NMe_2	Bu	H	H	Et_2O, rt, 15 h	**2g** (84)
8	NMe_2	Me	H	Me	DME, reflux, 15 h	**2h** (88)
9	NMe_2	Ph	H	H	Et_2O, rt, 15 h	**2i** (100)

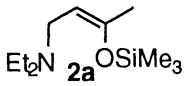
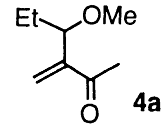
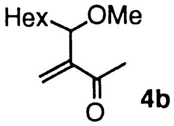
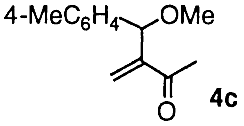
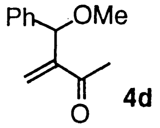
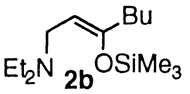
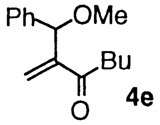
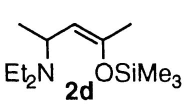
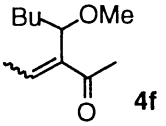
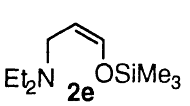
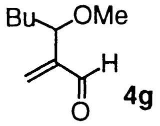
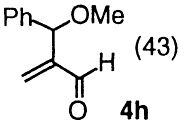
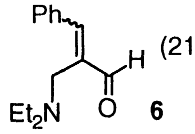
a) Reaction conditions: to a solution of α,β-unsaturated carbonyl compounds (6 mmol) in a solvent (5 ml) was added silylamine (5 mmol) under nitrogen. b) Only (*Z*)-isomer was obtained and the purity of **2** was confirmed by ^1H NMR and GC. c) Purified and Isolated yield by distillation after evaporation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

Reaction of silyl enol ethers **2** with acetals were carried out using $TiCl_4$ as a Lewis acid in CH_2Cl_2 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 $TiCl_4$ (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.

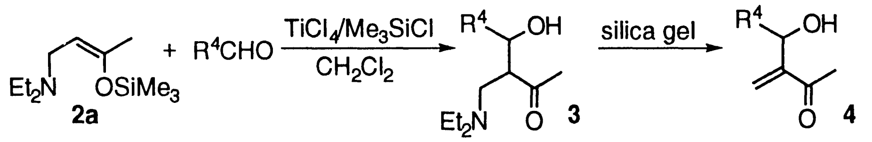
Table 2. Reaction of Silyl Enol Ether **2** with Acetals$^{a)}$

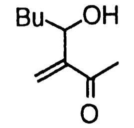
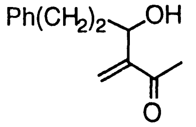
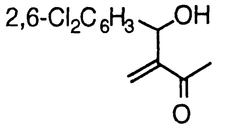


Entry	Silyl Enol Ether **2**	Aacetal (R⁴)	Product **4**$^{b)}$ (Yield/%)$^{c)}$
1		Et	 (100)
2	**2a**	Hex	 (100)
3	**2a**	4-MeC_6H_4	 (82)
4	**2a**	Ph	 (100)
5		Ph	 (93)
6		Bu	 (71)$^{d)}$
7		Bu	 (39)
8	**2e**	Ph	 (43)  (21)$^{e)}$

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)]



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-$Cl_2C_6H_3$	0 °C, 10 min	 **4k**	(36)

a) All reactions were carried out with three equivalents of $TiCl_4$ and 0.5 equivalent of chlorotrimethylsilane in CH_2Cl_2. 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)