

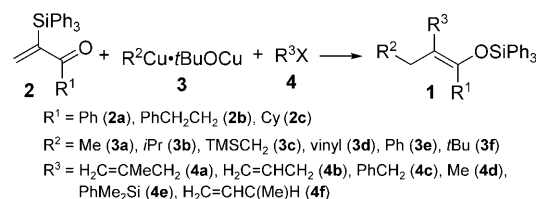
# Complete Regio- and Stereoselective Construction of Highly Substituted Silyl Enol Ethers by Three-Component Coupling\*\*

Akira Tsubouchi,\* Shouko Enatsu, Ryo Kanno, and Takeshi Takeda\*

Silyl enol ethers are important building blocks in organic synthesis.<sup>[1]</sup> The aldol reaction carried out using trisubstituted silyl enol ethers generates a quaternary carbon center next to the carbonyl group, and can potentially provide a powerful method for the stereocontrolled construction of adjacent stereogenic centers on acyclic carbon chains.<sup>[1b]</sup> It is difficult to attain the complete regio- and stereoselective formation of trisubstituted silyl enol ethers by silylation of thermodynamically or kinetically favorable enolates generated by enolization of ketones with bases. Another approach involves the regioselective formation of enolates through the conjugate addition of organocopper reagents to enones.<sup>[2]</sup> This synthetic strategy is not applicable, however, to the preparation of silyl enol ethers with a broad range of substitution patterns and geometries. Thus, much difficulty has been encountered in controlling the stereochemical integrity of trisubstituted silyl enol ethers.

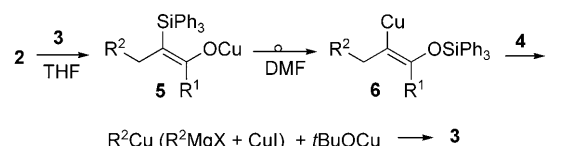
In the context of our studies aimed at the synthetic application of the silyl migration from an sp<sup>2</sup> carbon atom to an oxygen atom,<sup>[3]</sup> we have recently focused on the copper(I) *tert*-butoxide-promoted silyl migration to the oxygen atom of an enolate group<sup>[4]</sup> to develop a new strategy for the preparation of silyl enol ethers. It was found that alkenylcopper species bearing a silyl enol ether substructure were stereoselectively generated by treatment of acylsilanes<sup>[4b]</sup> and *o*-silylphenyl ketones<sup>[4c]</sup> with copper(I) *tert*-butoxide through 1,2- and 1,4-silyl migration, respectively. Also, their alkylation with organic halides produced disubstituted silyl enol ethers stereoselectively. Herein we report a strategy based on silyl migration for the highly regio- and stereoselective preparation of trisubstituted silyl enol ethers **1**. This strategy consists of a three-component coupling of  $\alpha$ -silyl  $\alpha,\beta$ -unsaturated ketones **2**, new organocopper reagents **3** [RCu-*t*BuOCu], and organic halides **4** (Scheme 1).

The process involves the following steps: 1) the formation of copper(I) enolates **5** by conjugate addition of the organocopper reagent **3** to the silyl ketones **2**, 2) the 1,3-silyl migration to the enolate oxygen atom to form the alkenyl-



**Scheme 1.** Regio- and stereoselective preparation of silyl enol ethers by three-component coupling. Cy = cyclohexyl, TMS = trimethylsilyl.

copper compounds **6**, and 3) alkylation of **6** with organic halides **4** (Scheme 2). The organocopper reagents **3** were prepared by adding a solution of copper(I) *tert*-butoxide<sup>[5]</sup> in THF to a solution of alkylcopper species<sup>[6]</sup> in THF formed from the Grignard reagents and copper(I) iodide.



**Scheme 2.** Reaction pathway. DMF = *N,N*-dimethylformamide, THF = tetrahydrofuran.

The  $\alpha$ -silyl  $\alpha,\beta$ -unsaturated ketone **2a** was treated with the organocopper reagent **3a** in THF. The copper(I) enolate **5a** thus formed was treated with DMF at 50 °C and then with methyl chloride **4a** and gave the silyl enol ether **1a** in 85 % yield with complete *Z* selectivity (Table 1, entry 1). The addition of DMF is crucial for the silyl migration;<sup>[7]</sup> when the reaction was performed without DMF, **1a** was obtained only in 4 % yield along with the formation of hydrolysis product of the enolate **5a** (the  $\alpha$ -silylketone, in 75 % yield).

Another advantage of this reaction is that various Grignard reagents can be used in the preparation of organocopper reagents **3** and hence various substituents can be conveniently introduced in the silyl enol ethers. Thus, the reaction of the  $\alpha$ -silyl  $\alpha,\beta$ -unsaturated ketone **2a** with various organocopper reagents **3** and the allylic halides **4a** and **4b** produced silyl enol ethers **1b–e** stereoselectively (Table 1, entries 2–5). The three-component coupling of **2a** proceeded also with benzyl chloride (**4c**), methyl iodide (**4d**), and chlorodimethylphenylsilane (**4e**) as well as with the allylic halides **4a** and **4b** and gave silyl enol ethers **1f–h** (Table 1, entries 6–8).

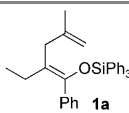
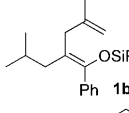
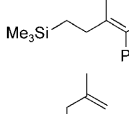
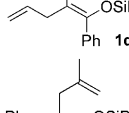
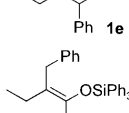
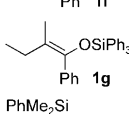
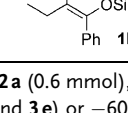
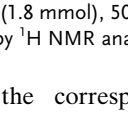
This coupling is found to be general for  $\alpha$ -silylvinyl ketones **2**; aliphatic primary and secondary ketones **2b** and **2c** can also be employed to give the silyl enol ethers **1** with good yields and perfect stereoselectivity (Table 2). The normally difficult achievement of regio- and stereoselective formation of **1l** and **1n** through thermodynamically or kinetically

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**Table 1:** Formation of trisubstituted silyl enol ethers by three-component coupling of phenyl  $\alpha$ -silylvinyl ketone **2a**, organocopper reagents **3**, and organic halides **4**.<sup>[a]</sup>

$\text{2a} \xrightarrow{1) \text{ 3; 2) DMF; 3) 4} \text{R}^2\text{-CH=C(R}^1\text{)-OSiPh}_3 \text{ 1a-h}$				
Entry	Copper reagent <b>3</b>	Organic halide <b>4</b>	Product <b>1</b>	Yield [%] <sup>[b]</sup> (Z:E) <sup>[c]</sup>
1	<b>3a</b>	<b>4a</b>		85 (100:0)
2	<b>3b</b>	<b>4a</b>		75 (100:0)
3	<b>3c</b>	<b>4b</b>		81 (100:0)
4	<b>3d</b>	<b>4a</b>		65 (97:3)
5	<b>3e</b>	<b>4a</b>		79 (0:100)
6	<b>3a</b>	<b>4c</b>		76 (100:0)
7	<b>3a</b>	<b>4d</b>		85 (13:87)
8	<b>3a</b>	<b>4e</b>		64 (93:7)

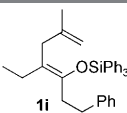
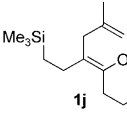
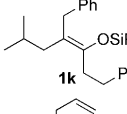
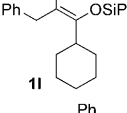
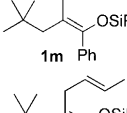
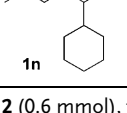
[a] Reaction conditions: 1) the ketone **2a** (0.6 mmol), the copper reagent **3** (0.72 mmol), 2 h, 0 °C (for **3a**, **3c**, and **3e**) or –60 to 0 °C (for **3b** and **3d**); 2) 50 °C, 30 min; 3) the halide **4** (1.8 mmol), 50 °C, 4 h. [b] Yield of the isolated product. [c] Determined by <sup>1</sup>H NMR analysis.

controlled deprotonation of the corresponding  $\alpha,\alpha'$ -di-branched ketones demonstrates the unique advantage of this method. The configuration of the silyl enol ethers **1** were confirmed by NOE or NOESY experiments.

Notably, the organocopper reagent **3a** was more effective than methylcopper and lithium dimethylcuprate toward the three-component coupling. The reaction of methylcopper, **2b**, and **4a** gave **1i** in 47% yield and the similar reaction using lithium dimethylcuprate gave **1i** in 31% yield. In contrast, the use of copper reagent **3a** significantly improved the yield of **1i** to 71% under similar reaction conditions (Table 2, entry 1). In the preparation of the reagent **3**, the Grignard reagents can be replaced with alkyl lithium compounds without loss of stereoselectivity and reactivity (Table 2, entries 5 and 6).

The stereoselectivity of the current reaction apparently originates from the formation of cyclic silicate species **7** (Scheme 3). Among the two potential stereoisomers of copper(I) enolates **5** and **8**, which exist in equilibrium via isomeric C-metalated enolates,<sup>[8]</sup> only the enolates **5** undergo the silyl migration via the silicates **7** to furnish the

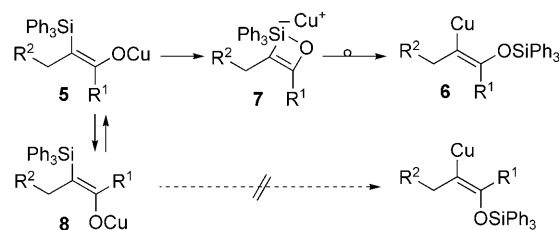
**Table 2:** Preparation of trisubstituted silyl enol ethers **1** utilizing  $\alpha$ -silylvinyl ketones **2**.<sup>[a]</sup>

$\text{2} \xrightarrow{1) \text{ 3; 2) DMF; 3) 4} \text{R}^2\text{-CH=C(R}^1\text{)-OSiPh}_3 \text{ 1i-n}$				
Entry	Silyl enone <b>2</b>	<b>3/4</b>	Product <b>1</b>	Yield [%] <sup>[b]</sup> (Z:E) <sup>[c]</sup>
1	<b>2b</b>	<b>3a/4a</b>		71 (100:0)
2	<b>2b</b>	<b>3c/4a</b>		70 (100:0)
3	<b>2b</b>	<b>3b/4c</b>		66 (100:0)
4	<b>2c</b>	<b>3e/4b</b>		80 (0:100)
5 <sup>[d]</sup>	<b>2a</b>	<b>3f/4c</b>		88 (100:0)
6 <sup>[d]</sup>	<b>2c</b>	<b>3f/4f</b>		91 (100:0)

[a] Reaction conditions: 1) the ketone **2** (0.6 mmol), the copper reagent **3** (0.72 mmol), 2 h, 0 °C (for **3a**, **3c**, and **3e**), –60 to 0 °C (for **3b**), or –78 to 0 °C (for **3f**); 2) 70 °C (for **3a–c** and **3e**) or 25 °C (for **3f**), 30 min; 3) the halide **4** (1.8 mmol), 70 °C (for **3a–c** and **3e**), or 25 °C (for **3f**), 4 h. [b] Yield of the isolated product. [c] Determined by <sup>1</sup>H NMR analysis. [d] *tert*-Butyllithium was used for the preparation of **3f**.

Z-alkenylcopper species **6** (containing a silyl enol ether substructure) stereoselectively. Subsequent alkylation of **6** with organic halides **4** with retention of the configuration of the double bond gives **1**. The formation of the stereoisomers of **1d**, **1g**, and **1h** would arise from the stereoisomerization of the primarily formed silyl enol ethers.

Application of the Brook-type rearrangement to the preparation of silyl enol ethers have been investigated.<sup>[9]</sup> Typical approaches consist of three steps: 1) generation of  $\alpha$ -silylalkoxide intermediates having a leaving group at the  $\beta$  position, 2) the 1,2 migration of the silyl group from an  $\text{sp}^3$  carbon atom to an oxygen atom and 3)  $\beta$  elimination to form

**Scheme 3.** Plausible stereochemical pathways.

the C–C double bond of the silyl enol ethers. Alternative strategies have also been reported: for examples, 1,2-addition of 1-alkenyl Grignard reagents to acylsilanes, 1,2-silyl migration of the resulting  $\alpha$ -silylallylic alkoxides, and reaction of electrophiles at the  $\gamma$  position of  $\alpha$ -siloxyallylic anions to afford silyl enol ethers.<sup>[9e,f]</sup> There have been, however, only limited examples of the preparation of trisubstituted silyl enol ethers. In contrast, the current reaction made it possible to assemble the stereochemically pure silyl enol ethers having three different substituents, each of which were originated from  $\alpha$ -silyl  $\alpha,\beta$ -unsaturated ketones, organocopper reagents, and organic halides.

In conclusion, we have developed a new method for the highly regio- and stereoselective preparation of synthetically useful trisubstituted silyl enol ethers by a silyl migration from an  $sp^2$  carbon atom to the oxygen atom of the enolate group through three-component coupling. The configuration of the silyl enol ethers is defined by the cyclic silicates. Such a strategy for controlling regio- and stereochemistry of the silyl enol ethers has not been reported until now. Study of the scope of this new method and synthetic application of the triphenylsilyl enol ethers to stereoselective carbon–carbon bond formations is currently underway.<sup>[10]</sup>

## Experimental Section

Typical procedure: Methylmagnesium bromide (0.93 M in THF, 0.77 mL, 0.72 mmol) was added to a suspension of CuI (137 mg, 0.72 mmol) in THF (1.5 mL) at 0°C under Ar and the mixture was stirred for 30 min. To this solution was added a solution of *t*BuOCu (0.72 mmol) in THF, prepared by the reaction of CuI (137 mg, 0.72 mmol) with *t*BuOLi (0.93 M in THF, 0.77 mL, 0.72 mmol) in THF (1.5 mL), through a stainless-steel canula at 0°C. After stirring for 30 min, a (1.5 mL) solution of ketone **2a** (234 mg, 0.60 mmol) in THF was added at 0°C and the mixture was stirred for 2 h. After addition of DMF (6 mL), the mixture was heated to 50°C for 30 min. A (3 mL) solution of methallyl chloride (163 mg, 1.8 mmol) in DMF was added and the mixture was stirred for 4 h. The reaction was quenched by addition of 3.5% aqueous  $NH_3$  and the product was extracted with diethyl ether. The extract was washed with  $H_2O$  and dried over  $K_2CO_3$ . The solvent was evaporated under reduced pressure and the residue was subjected to PTLC on silica gel and developed twice (*n*-hexane/EtOAc = 98:2). The silyl enol ether **1a** (235 mg, 85%) was obtained as a single isomer.

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- [1] a) S. Kobayashi, K. Manabe, H. Ishitani, J.-I. Matsuo in *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*, Vol. 4 (Ed.: I. Fleming), Thieme, Stuttgart, **2002**, pp. 317–369; b) B. Schetter, R. Mahrwald, *Aldol Reactions, in Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis* (Eds.: J. Christoffers, A. Baro), Wiley-VCH, Weinheim, **2005**, Chapter 3, pp. 51–82.
- [2] a) H. O. House, W. L. Respass, G. M. Whitesides, *J. Org. Chem.* **1966**, *31*, 3128–3141; b) S. Matsuzawa, Y. Horiguchi, E. Nakamura, I. Kuwajima, *Tetrahedron* **1989**, *45*, 349–362.

- [3] a) H. Taguchi, K. Ghoroku, M. Tadaki, A. Tsubouchi, T. Takeda, *J. Org. Chem.* **2002**, *67*, 8450–8456; b) W. H. Moser, J. Zhang, C. S. Lecher, T. L. Frazier, M. Pink, *Org. Lett.* **2002**, *4*, 1981–1984; c) H. Taguchi, A. Tsubouchi, T. Takeda, *Tetrahedron Lett.* **2003**, *44*, 5205–5207; d) H. Taguchi, K. Takami, A. Tsubouchi, T. Takeda, *Tetrahedron Lett.* **2004**, *45*, 429–432; e) A. Tsubouchi, M. Itoh, K. Onishi, T. Takeda, *Synthesis* **2004**, 1504–1508; f) N. O. Devarie-Baez, B. J. Shuhler, H. Wang, M. Xian, *Org. Lett.* **2007**, *9*, 4655–4658; g) A. B. Smith III, W. S. Kim, W. M. Wuest, *Angew. Chem.* **2008**, *120*, 7190–7194; *Angew. Chem. Int. Ed.* **2008**, *47*, 7082–7086; h) S. Akai, T. Ikawa, S. Takayanagi, Y. Morikawa, S. Mohri, M. Tsubakiyama, M. Egi, Y. Wada, Y. Kita, *Angew. Chem.* **2008**, *120*, 7787–7790; *Angew. Chem. Int. Ed.* **2008**, *47*, 7673–7676, and references therein.
- [4] a) H. Taguchi, H. Miyashita, A. Tsubouchi, T. Takeda, *Chem. Commun.* **2002**, 2218–2219; b) A. Tsubouchi, K. Onishi, T. Takeda, *J. Am. Chem. Soc.* **2006**, *128*, 14268–14269; c) A. Tsubouchi, H. Matsuda, T. Kira, T. Takeda, *Chem. Lett.* **2009**, 38, 1180–1181.
- [5] T. Tsuda, T. Hashimoto, T. Saegusa, *J. Am. Chem. Soc.* **1972**, *94*, 658–659.
- [6] Alkylcopper reagents were prepared by the reaction of copper(I) iodide with the Grignard reagents in THF according to the following procedure; K. Ruitenberg, H. Westmijze, H. Kleijn, P. Vermeer, *J. Organomet. Chem.* **1984**, *277*, 227–234.
- [7] Aprotic polar solvents accelerate the anionic silyl migration. For examples, see a) H. Shinokubo, K. Miura, K. Oshima, K. Utimiti, *Tetrahedron* **1996**, *52*, 503–514; b) A. B. Smith III, S. M. Pitram, *Org. Lett.* **1999**, *1*, 2001–2004; c) A. Tsubouchi, T. Kira, T. Takeda, *Synlett* **2006**, 2577–2580.
- [8] a) J. Berlan, J. P. Battioni, K. Koosha, *J. Organomet. Chem.* **1978**, *152*, 359–365; b) K. Oisaki, D. Zhao, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2006**, *128*, 7164–7165; c) K. Oisaki, D. Zhao, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2007**, *129*, 7439–7443.
- [9] For selected examples, see a) A. G. Brook, W. W. Limburg, D. M. MacRae, S. A. Fieldhouse, *J. Am. Chem. Soc.* **1967**, *89*, 704–706; b) A. G. Brook, S. A. Fieldhouse, *J. Organomet. Chem.* **1967**, *10*, 235–246; c) P. F. Hudrlik, R. H. Schwartz, A. K. Kulkarni, *Tetrahedron Lett.* **1979**, *20*, 2233–2236; d) P. F. Hudrlik, G. Nagendrappa, A. K. Kulkarni, A. M. Hudrlik, *Tetrahedron Lett.* **1979**, *20*, 2237–2240; e) M. Kato, A. Mori, H. Oshino, J. Enda, K. Kobayashi, I. Kuwajima, *J. Am. Chem. Soc.* **1984**, *106*, 1773–1778; f) J. Enda, I. Kuwajima, *J. Am. Chem. Soc.* **1985**, *107*, 5495–5501; g) M. Koreeda, S. Koo, *Tetrahedron Lett.* **1990**, *31*, 831–834; h) H. J. Reich, R. C. Holtan, C. Bolm, *J. Am. Chem. Soc.* **1990**, *112*, 5609–5617; i) F. Jin, B. Jiang, Y. Xu, *Tetrahedron Lett.* **1992**, *33*, 1221–1224; j) F. Jin, Y. Xu, W. Huang, *J. Chem. Soc. Perkin Trans. 1* **1993**, 795–799; k) T. Nakajima, M. Segi, F. Sugimoto, R. Hioki, S. Yokota, K. Miyashita, *Tetrahedron* **1993**, *49*, 8343–8358; l) P. Cuadrado, A. M. González-Nogal, *Tetrahedron Lett.* **1997**, *38*, 8117–8120; m) I. Fleming, R. S. Roberts, S. C. Smith, *J. Chem. Soc. Perkin Trans. 1* **1998**, 1215–1228; n) K. Takeda, A. Nakajima, M. Takeda, Y. Okamoto, T. Sato, E. Yoshii, T. Koizumi, M. Shiro, *J. Am. Chem. Soc.* **1998**, *120*, 4947–4959; o) H. Berber, T. Brigaud, O. Lefebvre, R. Plantier-Royon, C. Portella, *Chem. Eur. J.* **2001**, *7*, 903–909; p) S. C. Ngo, W. J. Chung, D. S. Lim, S. Higashiyama, J. T. Welch, *J. Fluorine Chem.* **2002**, *117*, 207–211.
- [10] Several Lewis acid promoted reactions of triphenylsilyl enol ethers with carbon electrophiles have appeared in the literature. For examples, see a) I. Fleming, J. Iqbal, *Tetrahedron Lett.* **1983**, *24*, 2913–2916; b) T. V. Lee, R. J. Boucher, K. L. Ellis, K. A. Lichardson, *Tetrahedron Lett.* **1988**, *29*, 685–688; c) W. J. Chung, S. C. Ngo, S. Higashiyama, J. T. Welch, *Tetrahedron Lett.* **2004**, *45*, 5403–5406.