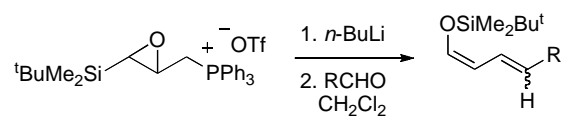


## Graphical Abstract

### Tandem Epoxysilane Rearrangement/Wittig-Type Reactions Using $\gamma$ -Phosphinoyl- and $\gamma$ -Phosphonio- $\alpha\beta$ -epoxysilane

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# Tandem Epoxysilane Rearrangement/Wittig-Type Reactions Using $\gamma$ -Phosphinoyl- and $\gamma$ -Phosphonio- $\alpha,\beta$ -epoxysilane

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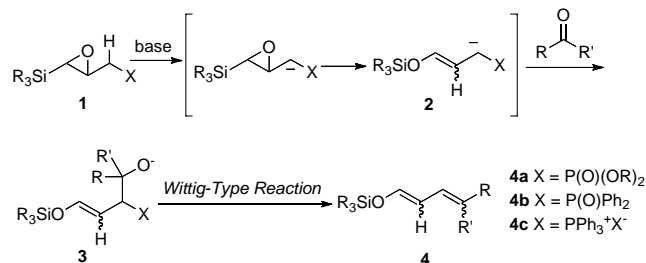
**Abstract**—Reaction of  $\gamma$ -phosphinoyl- and  $\gamma$ -phosphonio- $\alpha,\beta$ -epoxysilane with a base followed by addition of a ketone or an aldehyde afforded dienol silyl ether derivatives via a tandem process that involves base-induced ring opening of the epoxide, Brook rearrangement, and Wittig-type reaction. © 2007 Elsevier Science. All rights reserved © 2007 Elsevier Science. All rights reserved

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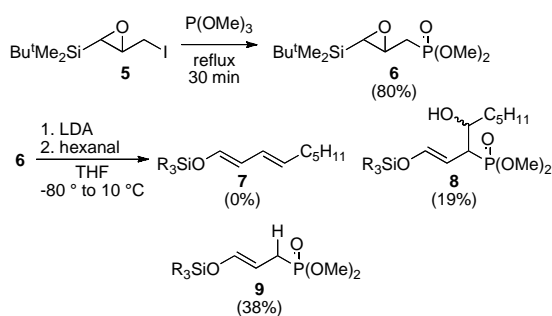
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Recently we have developed the epoxysilane rearrangement that converts  $\gamma$ -metalated  $\alpha,\beta$ -epoxysilanes into  $\beta$ -siloxyallylic carbanion derivatives, which are often difficult to generate in other ways.<sup>1</sup> During the exploration of the possibility of cascade reactions initiated by the rearrangement, we became interested in its use in Wittig-type reactions<sup>2</sup> (Scheme 1) by introduction of a heteroatom substituent such as a phosphonoyl group as an  $\alpha$ -carbanion-stabilizing group, allowing a direct access to dienol silyl ethers. Dienol silyl ethers have been used as versatile building blocks in a variety of synthetic transformations, including Diels-Alder reaction,<sup>3</sup>  $\gamma$ -selective reaction with electrophiles in dienolates,<sup>4</sup> and modular synthesis of a polyenic backbone.<sup>5</sup> Although this has led to considerable efforts toward developing methods for synthesizing such conjugated systems,<sup>6</sup> most of which use  $\alpha,\beta$ -unsaturated aldehydes as a starting material, only a few methods of synthesis have so far been reported.



Scheme 1. Epoxysilane **1** as a precursor of dienol silyl ethers

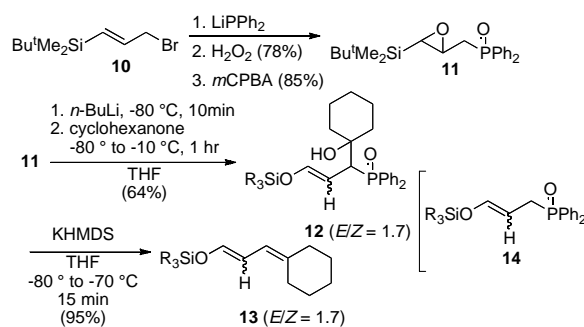
First we prepared  $\gamma$ -phosphoryl derivative **6** from the known epoxy silane **5** and examined the tandem epoxysilane rearrangement/Horner-Wadsworth-Emmons reaction. Treatment of **6** with LDA followed by addition of hexanal afforded the adduct **8** (single diastereomer) and the protonated product **9** in 19% and 38% yields, respectively, no desired product **7** being obtained.



Scheme 2. Preparation of **6** and its reaction with hexanal

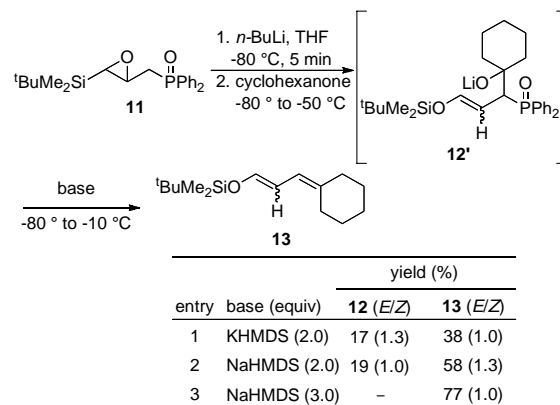
The result can be understood by considering that cycloelimination from betaine intermediates does not readily occur when electron-withdrawing groups in the phosphonate reagents are absent.<sup>2b</sup> Next we focused on a phosphine oxide-based approach, which can afford condensation products directly in the presence of potassium ion without isolation of the adducts. When phosphine oxide **11**, prepared from **10** via the reaction with lithium

diphenylphosphide followed by H<sub>2</sub>O<sub>2</sub> oxidation and then epoxidation, was treated with KHMDS followed by cyclohexanone, dienol silyl ether **13** and protonated products **14** were obtained in low yield together with decomposition products (Scheme 3). In contrast, the use of *n*-BuLi produced adducts of ketone **12** in 64% yield, which were converted into **13** by exposure to KHMDS. These results prompted us to change a counter cation from lithium to potassium or sodium in situ after the formation of lithium salt of **12**.<sup>7</sup>



Scheme 3. Preparation of **11** and its reaction with cyclohexanone

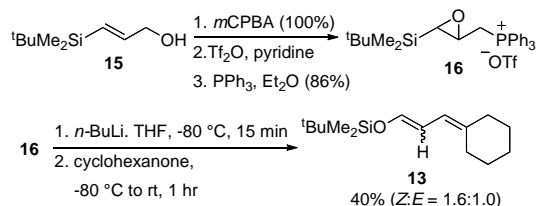
Lithium salt **12'**, generated from **11** with *n*-BuLi and cyclohexanone, was treated with KHMDS or NaHMDS in situ (Table 1). The best result was obtained by 3 equiv of NaHMDS to afford **13** (Table 1) in 77% yield. Reactions with aldehydes resulted in low yields.



Scheme 4. One-pot synthesis of **13**

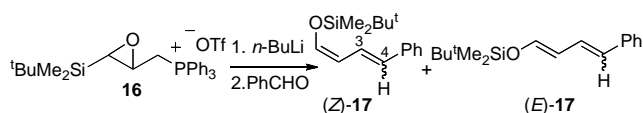
We next turned our attention to Wittig reaction using  $\gamma$ -phosphonio derivative **4c**, the synthesis of which using the corresponding halides we had attempted at the initial stage of the project but had given up on because of unavailability of isolable and purifiable material. Encouraged by the above result with the phosphine oxide, we decided to reexamine the preparation of **4c**. After extensive experimentation, we found triflate derivative **16**,<sup>8</sup> readily prepared by the sequence shown in Scheme 4, to be suitable for our purposes. When **16** was treated with *n*-BuLi at -80 °C over a period of 15 min followed by addition of cyclohexanone and then warmed to room temperature,

dienol silyl ethers **13** were obtained in 40% yield in a ratio of 1.6 (*Z/E*).



**Scheme 5.** Preparation of **16** and its reaction with cyclohexanone

The reactions with aldehydes gave somewhat better results in terms of yield and *Z/E* selectivity of the enol silyl ether moiety. Thus, when **16** was reacted with *n*-BuLi and then benzaldehyde at  $-80\text{ }^{\circ}\text{C}$ , **17** was obtained in 47% yield in a ratio of 3.4 (*Z/E*) (Table 1, entry 1). The yield was improved to 75% yield when the reaction was conducted at  $15\text{ }^{\circ}\text{C}$  (entry 2). The reactivity and selectivity of the reaction were affected by a change in the solvent from THF to  $\text{CH}_2\text{Cl}_2$ . Although the reaction in  $\text{CH}_2\text{Cl}_2$  under the same reaction conditions led to recovery of the starting material (entry 3), lowering the reaction temperature to  $-40\text{ }^{\circ}\text{C}$  gave **17** in the *Z* selectivity (entry 4).

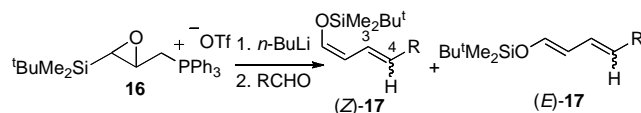


entry	conditions	solvent	yield (%)	<i>Z/E</i> <sup>a</sup>
1	1. $-80\text{ }^{\circ}\text{C}$ , 15 min 2. $-80\text{ }^{\circ}\text{C}$ , 30 min	THF	47	3.4
2	1. $15\text{ }^{\circ}\text{C}$ to $20\text{ }^{\circ}\text{C}$ , 3 min 2. $15\text{ }^{\circ}\text{C}$ to $20\text{ }^{\circ}\text{C}$ , 5 min	THF	75	3.4
3	1. $15\text{ }^{\circ}\text{C}$ to $20\text{ }^{\circ}\text{C}$ , 3 min 2. $15\text{ }^{\circ}\text{C}$ to $20\text{ }^{\circ}\text{C}$ , 10 min	$\text{CH}_2\text{Cl}_2$	0	-
4	1. $-40\text{ }^{\circ}\text{C}$ to $-35\text{ }^{\circ}\text{C}$ , 3 min 2. $-40\text{ }^{\circ}\text{C}$ to $-30\text{ }^{\circ}\text{C}$ , 25 min	$\text{CH}_2\text{Cl}_2$	65	9.4

<sup>a</sup> The ratios of 3*E*/3*Z* were almost 1.0. <sup>c</sup> 3*Z* isomer was formed exclusively.

**Table 1.** Reaction of **16** with benzaldehyde

A similar trend was observed with the reactions with other aldehydes (Table 2).



entry	R	conditions <sup>a</sup>	yield (%)	<i>Z/E</i> <sup>b</sup>
1	<i>n</i> -C <sub>5</sub> H <sub>11</sub>	A	77	4.4
2	<i>n</i> -C <sub>5</sub> H <sub>11</sub>	B	60	8.0
3	(CH <sub>3</sub> ) <sub>2</sub> CH	A	68	10.6
4	(CH <sub>3</sub> ) <sub>2</sub> CH	B	58	8.0
5	<i>c</i> -C <sub>6</sub> H <sub>11</sub>	A	69	6.6
6	<i>c</i> -C <sub>6</sub> H <sub>11</sub>	B	48	9.1
7	(CH <sub>3</sub> ) <sub>3</sub> C	A	50	<i>Z</i> only <sup>c</sup>
8	(CH <sub>3</sub> ) <sub>3</sub> C	B	42	<i>Z</i> only <sup>c</sup>

<sup>a</sup> condition A: 1.  $15\text{ }^{\circ}\text{C}$  to  $20\text{ }^{\circ}\text{C}$ , 3 min, 2.  $15\text{ }^{\circ}\text{C}$  to  $20\text{ }^{\circ}\text{C}$ , 5 min in THF; condition B:

1.  $-40\text{ }^{\circ}\text{C}$  to  $-35\text{ }^{\circ}\text{C}$ , 3 min, 2.  $-40\text{ }^{\circ}\text{C}$  to  $-30\text{ }^{\circ}\text{C}$ , 25 min in  $\text{CH}_2\text{Cl}_2$

<sup>b</sup> The ratios of 3*E*/3*Z* were almost 1.0. <sup>c</sup> 3*Z* isomer was formed exclusively.

**Table 2.** Reaction of **16** with aldehydes

In conclusion, we have demonstrated further possibilities of the epoxysilane rearrangement as an initiator in cascade reactions. A unique feature of this method is that, in addition to the tandem nature of the process, the starting phosphonium salt is a stable crystalline solid that is readily derived from propargyl alcohol and can be stored for several months without significant decomposition.

## Acknowledgments

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## References

- (a) Takeda, K.; Kawanishi, E.; Sasaki, M.; Takahashi, Y.; Yamaguchi, K. *Org. Lett.* **2002**, *4*, 1511-1514. (b) Sasaki, M.; Kawanishi, E.; Nakai, Y.; Matsumoto, T.; Yamaguchi, K.; Takeda, K. *J. Org. Chem.* **2003**, *68*, 9330-9339. (c) Okugawa, S.; Takeda, K. *Org. Lett.* **2004**, *6*, 2973-2975. (d) Matsumoto, T.; Masu, H.; Yamaguchi, K.; Takeda, K. *Org. Lett.* **2004**, *6*, 4367-4369. (e) Tanaka, K.; Takeda, K. *Tetrahedron Lett.* **2004**, *45*, 7859-7861. (f) Sasaki, M.; Takeda, K. *Org. Lett.* **2004**, *6*, 4849-4851. (g) Tanaka, K.; Masu, H.; Yamaguchi, K.; Takeda, K. *Tetrahedron Lett.* **2005**, *46*, 6429-6432. (h) Sasaki, M.; Higashi, M.; Masu, H.; Yamaguchi, K.; Takeda, K. *Org. Lett.* **2005**, *7*, 5913-5915. (i) Okugawa, S.; Masu, H.; Yamaguchi, K.; Takeda, K. *J. Org. Chem.* **2005**, *70*, 10515-10523. (j) Okamoto, N.; Sasaki, M.; Kawahata, M.; Yamaguchi, K.; Takeda, K. *Org. Lett.* **2006**, *8*, 1889-1891.
- For reviews on Wittig-type reactions, see: (a) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863-927. (b) Wadsworth, Jr., W. S. *Org. React.* **1977**, *25*, 73-253.
- (a) Petrzilka, M.; Grayson, J. I. *Synthesis* **1981**, 753-786. (b) Brownbridge, P. *Synthesis* **1983**, 85-104. (c) White, J. D.;

- Choi, Y. *Helv. Chim. Acta* **2002**, *85*, 4306-4327. (d) Trost, B. M.; Chupak, L. S.; Luibbers, T. *J. Org. Chem.* **1997**, *62*, 736-736. (e) Danishefsky, S.; Prisbylla, M. P.; Hiner, S. *J. Am. Chem. Soc.* **1978**, *100*, 2918-2920.
4. (a) Martin, S. F.; Clark, C. W.; Corbett, J. W. *J. Org. Chem.* **1996**, *60*, 3236-3242. (b) Paolobelli, A. B.; Latini, D.; Ruzziconi, R. *Tetrahedron Lett.* **1993**, *34*, 721-724.
5. Domagalska, B. W.; Syperb, L. Wilk, K. A. *Tetrahedron* **2004**, *60*, 1931-1939.
6. (a) Sodeoka, M.; Yamada, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1990**, *112*, 4906-4911. (b) Iqbal, J.; Khan, M. A. *Synth. Commun.* **1989**, *19*, 515-521. (c) Cazeau, P.; Duboudin, F.; Moulines, F.; Babet, O.; Dunogues, J. *Tetrahedron* **1987**, *43*, 2089-2092. (d) Kozikowski, A. P.; Jung, S. H. *Tetrahedron Lett.* **1986**, *27*, 3227-3230. (e) Kozikowski, A. P.; Jung, S. H. *J. Org. Chem.* **1986**, *51*, 3400-3402. (f) Fleming, I.; Goldhill, J.; Paterson, I. *Tetrahedron Lett.* **1979**, 3209-3212. (g) Suzuki, H.; Koyama, Y.; Morooka, Y.; Ikawa, T. *Tetrahedron Lett.* **1979**, 1415-1418.
7. We have reported that the exchanging cation in enolate can be realized by addition of NaHMDS to a solution of lithium enolate. Takeda, K.; Sawada, Y.; Sumi, K. *Org. Lett.* **2002**, *4*, 1031-1033.
8. We found that **16** is a stable crystalline compound (mp 126 °C) when stored at room temperature.