



## Preparation of proximal $\beta$ -hydroxy silyl enol ethers from $\alpha,\beta$ -epoxyketones using silyllithium reagents

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### ABSTRACT

A new method for the stereoselective preparation of proximal  $\beta$ -hydroxy silyl enol ethers from  $\alpha,\beta$ -epoxyketones using silyllithium reagents has been developed. The reaction is believed to proceed via Brook rearrangement assisted by opening of the adjacent epoxide. A number of  $\alpha,\beta$ -epoxyketones were reacted with methyldiphenylsilyllithium to form the corresponding proximal  $\beta$ -hydroxy silyl enol ethers in good to excellent yield and excellent stereoselectivity.

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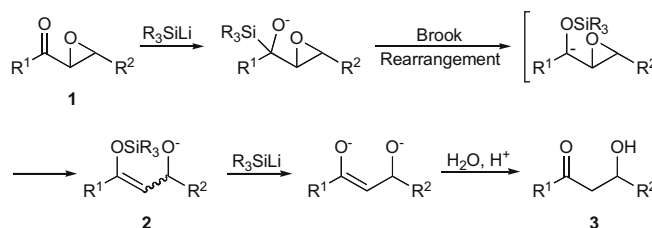
Recently, we reported a selective  $\alpha$ -reduction of  $\alpha,\beta$ -epoxyketones **1** using silyllithium reagents to form  $\beta$ -hydroxyketones (aldols) **3**.<sup>1</sup> The proposed mechanism (Scheme 1) involves initial nucleophilic attack of the silyllithium reagent on the carbonyl to form an  $\alpha$ -silylalkoxide, triggering a Brook rearrangement. Concomitant  $\pi$  bond formation and opening of the epoxide ring result in the formation of a silyl enol ether. Desilylation of the silyl enol ether by the silyllithium reagent then forms an aldolate dianion, providing the  $\beta$ -hydroxyketone upon acidic aqueous work-up.

We were intrigued by the possibility of isolating the initially formed  $\beta$ -hydroxy silyl enol ethers **2**, which would have great potential as multifunctional synthetic intermediates.  $\beta$ -hydroxy silyl enol ethers have already been shown to be valuable substrates for the stereoselective preparation of  $\alpha,\beta$ -dihydroxycarbonyls<sup>2</sup> and could find further application in the synthesis of 'asymmetrical' or proximal double aldols, for which there are few synthetic routes.<sup>3</sup>

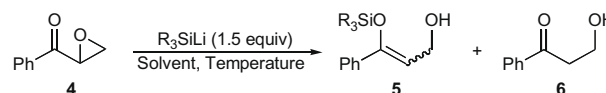
Existing methods for the preparation of proximal  $\beta$ -hydroxy silyl enol ethers are sparse and of limited utility due to narrow substrate scope, poor stereoselectivity, or the need for complex substrate functionalization.<sup>2,4</sup> The preparation of  $\beta$ -hydroxy silyl enol ethers from  $\alpha,\beta$ -epoxyketones is attractive, given the accessibility of the substrates.

Isolation of proximal  $\beta$ -hydroxy silyl enol ethers from  $\alpha,\beta$ -epoxyketones would require the suppression of the observed cleavage of the Si–O bond by the silyllithium reagent. A series of reactions using  $\alpha,\beta$ -epoxyketone **4** was performed to determine the effect of temperature, solvent, and silyllithium reagent on the relative amounts of silyl enol ether **5** and aldol **6** formed (Scheme 2). The results are summarized in Table 1.

As expected from our previous studies with acyloins,<sup>5</sup> the reaction solvent had a significant influence on product distribution.



Scheme 1.



Scheme 2.

Reactions performed in THF produced substantial amounts of the undesired aldol **6**. The use of the less polar solvents toluene and ether suppressed Si–O bond cleavage and provided significantly improved yields of **5**. Lower temperatures also generally enhanced the yield of the silyl enol ether **5**.<sup>6</sup> The reaction of **4** with methyldiphenylsilyllithium in toluene at  $-78^\circ\text{C}$  provided the highest yield of desired **5**. The use of methyldiphenylsilyllithium provided another critical advantage, as unlike dimethyldiphenylsilyl enol ethers, methyldiphenylsilyl enol ethers are known to be stable to silica gel chromatography.<sup>7</sup>

The scope of the method was demonstrated by reacting a number of  $\alpha,\beta$ -epoxyketones with methyldiphenylsilyllithium in toluene at  $-78^\circ\text{C}$ . Under these conditions, we found that a larger excess of silyllithium reagent could be used to ensure complete reaction of the  $\alpha,\beta$ -epoxyketones without formation of the undesired aldol. The results are summarized in Table 2. Good to

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**Table 1**Reaction of **4** with silyllithium reagents (1.5 equiv)

Entry	Silyllithium	Solvent	Temperature (°C)	<b>5</b> <sup>a</sup> (%)	<b>6</b> <sup>a</sup> (%)
1	Me <sub>2</sub> PhSiLi	THF	−40	35	13
2	Me <sub>2</sub> PhSiLi	Ether	−40	54	2
3	Me <sub>2</sub> PhSiLi	Toluene	−40	53	0
4	Me <sub>2</sub> PhSiLi	Toluene	−78	54	2
5	MePh <sub>2</sub> SiLi	THF	−40	2	47
6	MePh <sub>2</sub> SiLi	Ether	−40	51	13
7	MePh <sub>2</sub> SiLi	Toluene	−40	45	5
8	MePh <sub>2</sub> SiLi	Toluene	−78	72	2

Effects of silyl group, solvent, and temperature.

<sup>a</sup> Yields determined by <sup>1</sup>H NMR using hexamethylbenzene as an internal standard.


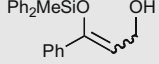
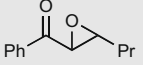
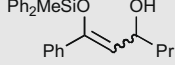
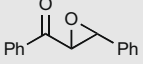
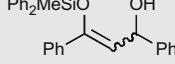
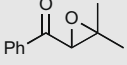
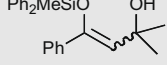
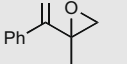
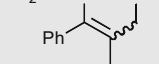
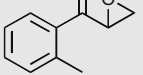
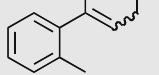
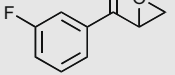
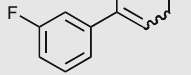
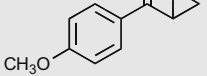
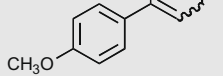
excellent yields were obtained with all aromatic ketones except the  $\alpha$ -substituted ketone (entry 5), which gave exclusively 2-methyl-3-(methyldiphenylsilyl)-1-phenyl-1-propanone. In all cases, the reaction greatly favored the *E* stereoisomer,<sup>8</sup> and in several cases was the exclusive isomer observed. Aliphatic ketones

were found to decompose under these conditions, giving predominantly the enone. It is likely that in the absence of an anion stabilizing aryl substituent, the use of an apolar solvent significantly suppresses the rate of the Brook rearrangement, allowing a competing carbon–carbon migration of the silyl group to dominate.<sup>9</sup> Subsequent Peterson elimination would then result in the enone.

In conclusion, a new method for the stereoselective preparation of proximal  $\beta$ -hydroxy silyl enol ethers from  $\alpha,\beta$ -epoxyketones using silyllithium reagents has been developed. The method was effective for aryl ketones lacking an  $\alpha$ -substituent, but was ineffective for alkyl ketones.

**Typical procedure:** 2,3-Epoxy-1-phenyl-1-propanone (**4**) (0.150 g, 1.0 mmol) was dissolved in 10 mL of dry toluene and was cooled to −78 °C under argon. A 1.0 M solution of methyldiphenylsilyllithium in THF (2.0 mL, 2.0 equiv) was added dropwise via syringe with stirring. After 15 min, the reaction was quenched at −78 °C with 10 mL of saturated NH<sub>4</sub>Cl and warmed to room temperature. The mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 15 mL) and the combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>. The dried solution was concentrated in vacuo and the residue was purified by

**Table 2**Reaction of  $\alpha,\beta$ -epoxyketones with methyldiphenylsilyllithium (1.7–2.0 equiv) in toluene at −78 °C

Entry	Substrate	Product	Yield (%)	<i>E/Z</i> <sup>a</sup>
1			81	100/0
2			71	100/0
3			66	80/20
4			91	100/0
5			0 <sup>b</sup>	—
6			74	96/4
7			66	96/4
8			83	100/0

<sup>a</sup> Determined by <sup>1</sup>H NMR.<sup>b</sup> 2-Methyl-3-(methyldiphenylsilyl)-1-phenyl-1-propanone was isolated in 55% yield.

flash chromatography (dry silica gel, 20% ethyl acetate/petroleum ether) to give 0.283 g of *E*-3-methyldiphenylsiloxy-3-phenyl-2-propen-1-ol (**5**) as a colorless oil.

### Acknowledgments

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### Supplementary data

Supplementary data (spectroscopic data for the  $\beta$ -hydroxy silyl enol ethers) associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2009.04.085](https://doi.org/10.1016/j.tetlet.2009.04.085).

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