

Selective reduction of α,β -epoxyketones to β -hydroxyketones using silyllithium reagents

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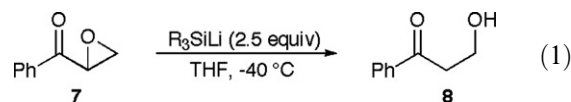
Abstract—2,3-Epoxy-1-phenyl-1-propanone was reduced to 3-hydroxy-1-phenyl-1-propanone using dimethylphenyl-, methylphenyl- or triphenylsilyllithium in THF at $-40\text{ }^{\circ}\text{C}$. The methylphenylsilyllithium reagent was superior, providing the product in 70% yield. The reaction is believed to proceed via an epoxide ring-opening assisted Brook rearrangement. A number of α,β -epoxyketones underwent reduction with methylphenylsilyllithium to form the corresponding β -hydroxyketones in moderate to good yield. © 2007 Elsevier Ltd. All rights reserved.

The regioselective α -reduction of α,β -epoxyketones is a synthetically useful transformation, providing an alternative to the aldol addition for the formation of β -hydroxyketones. Several reducing agents have been used to perform this reduction, including samarium iodide,¹ aluminum amalgam,² tributyltinhydride,³ tellurides,⁴ titanocenes,⁵ hydrogen,⁶ lithium/ammonia,⁷ sodium iodide/sodium acetate,⁸ hydrazine hydrate,⁹ organoseleniums,¹⁰ zinc/acetic acid,¹¹ chromium salts,¹² and lithium naphthalenide.¹³ Photoinduced electron transfer¹⁴ and electrochemical methods¹⁵ have also been developed.

We envisioned that the regioselective α -reduction of α,β -epoxyketones could be accomplished using silyllithium reagents via a concomitant Brook rearrangement-epoxide ring opening process (Scheme 1). Initial nucleophilic attack of the silyllithium reagent on the carbonyl would form α -silylalkoxide **2**. Brook rearrangement of **2** and

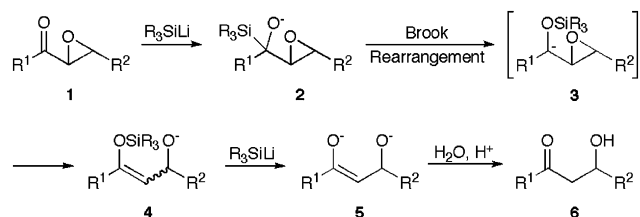
concomitant π bond formation and epoxide ring opening would then give β -oxidosilyl enol ether **4**. Desilylation of **4** by a second equivalent of silyllithium reagent¹⁶ would form dianion **5**, providing β -hydroxyketone **6** upon acidic aqueous work-up.

To investigate this hypothesis, 2,3-epoxy-1-phenyl-1-propanone (**7**) was treated with 2.5 equiv of dimethylphenylsilyllithium in THF at $-40\text{ }^{\circ}\text{C}$ (Eq. 1, $\text{R}_3 = \text{Me}_2\text{Ph}$). The reduction proceeded to form 3-hydroxy-1-phenyl-1-propanone (**8**) but with only a moderate yield of 49%.



Believing that acceleration of the Brook rearrangement of **2** would facilitate the overall desired reaction, we next attempted the reduction of **7** with the less common methylphenylsilyl- and triphenylsilyllithium reagents. Both the methylphenylsilyl and triphenylsilyl groups have been reported to undergo Brook rearrangement faster than the dimethylphenylsilyl group,¹⁷ presumably due to the enhanced stability of the negative charge that develops on silicon during migration. Treatment of **7** with methylphenylsilyllithium (Eq. 1, $\text{R}_3 = \text{MePh}_2$) and triphenylsilyllithium (Eq. 1, $\text{R}_3 = \text{Ph}_3$) in THF at $-40\text{ }^{\circ}\text{C}$ proceeded to form β -hydroxyketone **8** in 70% and 65% yields, respectively.

A number of α,β -epoxyketones underwent reduction with methylphenylsilyllithium to form the correspond-



Scheme 1.

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Table 1. Reduction of α,β -epoxyketones with methyldiphenylsilyllithium (2.5–3.0 equiv) in THF at $-40\text{ }^{\circ}\text{C}$

Entry	Substrate	Product	Yield ^a (%)
1			89
2			65
3			70
4			77
5			45
6			52
7			32
8			41

^a Yields determined by ^1H NMR using hexamethylbenzene as an internal standard.

ing β -hydroxyketones in moderate to good yield. These results are summarized in Table 1.

We were pleased to find that both aromatic and aliphatic ketones were reduced successfully under these conditions. The Brook rearrangement of α -silylalkoxides under kinetic conditions (complete and irreversible formation of the alkoxide) is usually disfavored unless an anionic stabilizing group (phenyl, vinyl, and silyl) is present on the α -carbon.¹⁸ In this case, the rearrangement of **2** is promoted by opening of the epoxide ring and transfer of the developing negative charge from carbon to the β -oxygen. It is unclear whether carbanion **3** is an intermediate in the overall reaction or if the migration of silicon and epoxide opening are concerted. The proposed mechanism is supported by the observation of the corresponding alcohol of **4** ($R_1 = \text{Ph}$, $R_2 = \text{H}$) in 29% yield when epoxyketone **7** was treated with 1.2 equiv of dimethylphenylsilyllithium in THF at $-40\text{ }^{\circ}\text{C}$.

In conclusion, a new method for the selective reduction of α,β -epoxyketones to β -hydroxyketones using silyl-

lithium reducing agents has been developed. Use of the commonly encountered dimethylphenylsilyllithium resulted in low yields, however, the less frequently employed methyldiphenylsilyllithium provided significantly higher yields.

Typical procedure: A solution of α,β -epoxyketone (1 mmol) in 5 mL of dry THF was cooled to $-40\text{ }^{\circ}\text{C}$ under argon. A solution of silyllithium reagent ($\sim 1\text{ M}$, 2.5–3.0 equiv) in THF was added dropwise with stirring. The reaction was immediately quenched with saturated aqueous ammonium chloride, extracted with dichloromethane, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give the crude β -hydroxyketone.

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