



0040-4039(94)01720-4

Stereospecific Substituted Alkene Synthesis by Organo Lithium Reductive Alkylation of Epoxides

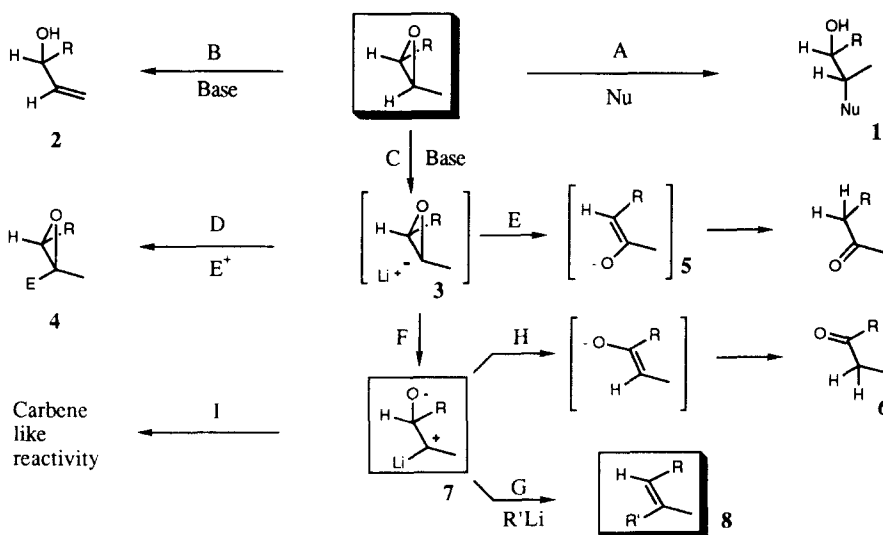
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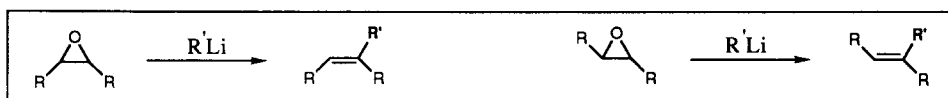
Abstract: Stereospecifically alkylated olefins were synthesized in good yields by reaction of various epoxides with organolithium reagents with concomitant introduction of the alkyl group.

Epoxides are useful intermediates in organic synthesis and have been widely used because of their chemical reactivity ¹ which can be explained by the ring strain of the small heterocycle. Their reaction with nucleophiles is a well known method for the preparation of substituted alcohols ² **1** (Path A). However, a strong organo metallic base is able to deprotonate the epoxide ³ either at the β position ⁴ (Path B), leading to an allylic alcohol **2**, or at the α position ^{3a} (Path C), furnishing a metallated oxirane ring **3** that can undergo several types of reactions depending on the reaction conditions and on the substrate structure. The anionic species **3** can be trapped by various electrophiles ⁵ (Path D) or can rearrange by β -elimination into the corresponding ketone-enolate ^{3b} **5** (Path E) or by α -elimination to an alkoxy carbenoid ^{3c} **7** (Path F).



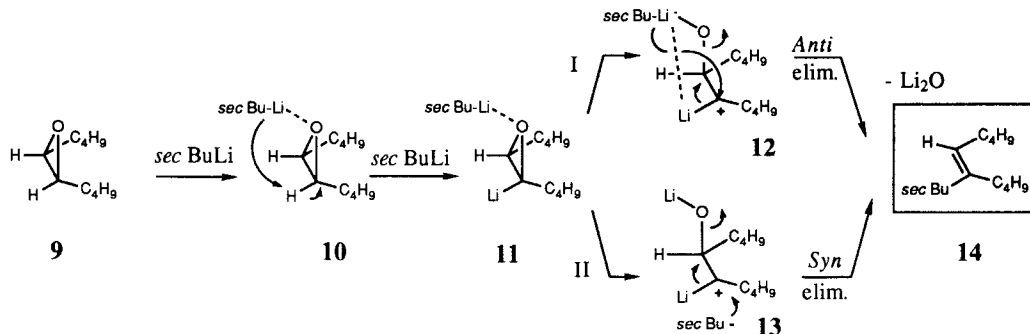
Scheme 1

This highly reactive intermediate **7** might exhibit carbene reactivity ^{3a, 6} (dimerizations, C-H or double bond insertion) (Path I) but it may also, *via* an hydrogen shift, give the isomerized ketone **6** (Path H). If the alkoxy-carbenoid is generated by an excess of organo lithium reagent, substituted alkenes **8** are obtained by a carbenoid insertion into a second R'Li carbon-lithium bond ⁷ (Path G). The reactivity of the α -lithiated oxirane **3** has only been extensively studied in the cases of epoxides bearing stabilizing groups ⁸ such as Si, SO₂, PO, Ph. Herein, we would like to report further studies about the alkoxy-carbenoid **7** reactivity in the case of non activated epoxides for which, except pioneer work of Crandall ⁷, no data to our knowledge are available in spite of the synthetical importance of C-C bond forming and double bond generation. We recently found that stereospecifically substituted olefins can be synthesized starting from either *cis* or *trans* epoxides (Scheme 2).



Scheme 2


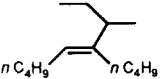

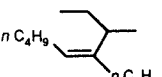
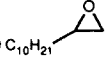
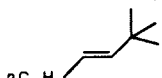
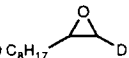
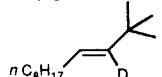
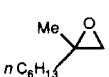
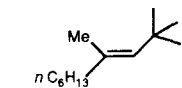
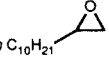
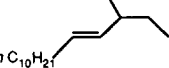
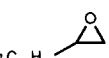
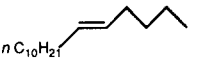
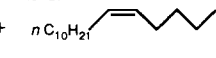
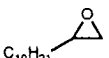
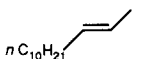
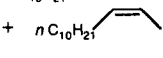
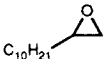
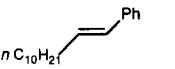

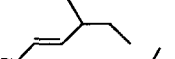
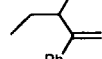

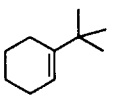
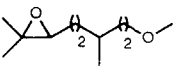
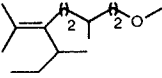
These observations are consistent with a reaction mechanism where all intermediates fully keep their stereochemical integrity. The model proposed by Soderquist *et al.* ⁹ involves a proton abstraction leading to an α -lithiated epoxide intermediate that can readily undergo ring opening via α -elimination to form an alkoxy-carbenoid. The *syn*-addition of the alkyl group followed by spontaneous lithium-oxide *anti*-elimination, explains the stereochemical feature of the reaction product (Scheme 3, Path I). An alternative model involving the *anti*-addition of the alkyl group and subsequent *syn*-elimination of Li₂O might also explain these results (Scheme 3, Path II). A proposed summarized mechanistic sequence is illustrated below in scheme 3.



Scheme 3

In the case of non activated, mono-substituted epoxides, the metallation occurs at the primary carbon atom generally from the less hindered side. This is proved by the *tert* BuLi induced generation of the *trans* olefin, starting from the *cis* deuterated epoxide (entry 4). High stereospecificity is also observed in the case of unsymmetrical α,α' -bis-substituted epoxides (entry 5). Bulky organolithium reagents lead with high selectivity to *trans* alkenes (entries 3-6), whereas less hindered reagents such as BuLi and MeLi (entries 7,8) exhibit lower stereoselectivity. This can be explained by the formation of both chelated *anti* or *syn* complexes ¹⁰ which results from weaker steric repulsion between the base and the oxirane ring substituent allowing non specific metallation. In contrast with the regio specific deprotonation of non-activated oxirane systems, epoxystyrene affords a mixture of two regio-isomers resulting from both α and β proton abstraction when treated with *sec* BuLi (entry 10).

Table: Examples of Reductive Alkylation of Epoxides.

Entry	Substrate	RLi	React.Cond.	Product ^{a,b} (ratio %)	Yield ^c (%)
1		<i>sec</i> BuLi	-70°C to r.t., 90 min.		76
2		<i>sec</i> BuLi	-70°C to r.t., 90 min.		65
3		<i>tert</i> BuLi	-70°C to r.t., 90 min.		98
4		<i>tert</i> BuLi	-70°C to r.t., 90 min.		95
5		<i>tert</i> BuLi	-70°C to r.t., overnight.		82
6		<i>sec</i> BuLi	-70°C to -50°C, 20 min.		96
7		<i>n</i> BuLi	-70°C to r.t., 180 min.	 (74) +  (26)	91
8		MeLi	-70°C to r.t., overnight.	 (66) +  (34)	48
9		PhLi	-70°C to r.t., overnight.	 (20)	20
10		<i>sec</i> BuLi	-70°C, 20 min.	 (28) +  (72)	29
11		<i>tert</i> BuLi	-70°C to r.t., overnight.		56
12		<i>sec</i> BuLi	-70°C to -10°C, 60 min.		15

a: For selected spectral data see ref.12. b: Double bond stereochemistry was determined either by coupling constant measurements between vinylic hydrogens (bis-substituted alkenes) or by nuclear Overhauser effect (tri-substituted alkenes). c: Isolated yields.

The reaction has been extended to cyclic epoxide (entry 11) with moderated yields and even to tri-substituted epoxide (entry 12), affording tetra-substituted olefin. Interestingly we noticed that the reaction of *cis* epoxide is more efficient than the reaction of the corresponding *trans* isomer. This is probably due to the easier formation of the organo lithium-epoxide complex ¹⁰ producing a more efficient metallation. Nucleophilic addition adducts are observed as side reactions in the case of mono-substituted epoxides, while, in the case of di- and tri-substituted substrates, the β -elimination pathway leading to rearranged allylic alcohols as by-products, is the major side reaction.

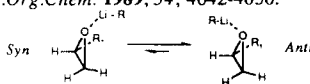
In summary, we have shown that organo lithium reagents react with epoxides at -70°C to afford substituted alkenes with high stereoselectivity and predictable stereochemistry. The reaction proceeds by α -metallation of the oxirane, the following α -elimination to an α -alkoxy-carbenoid intermediate and subsequent addition of an organo metallic compound leads to substituted olefins ¹¹ after Li_2O elimination. This reaction should have further interest in synthetic applications.

Experimental Procedure: Under argon, *sec* butyl lithium (3 ml of a 1.3 M soln. in hexanes; 3 eq.) is added dropwise to a -70°C cooled stirred solution of *cis*-5,6-epoxy decane (0.2 g; 1.28 mmol.; 1 eq.) in 13 ml of dry THF. The reaction is warmed to room temperature over a period of 90 minutes and then quenched with a sodium chloride solution. The aqueous phase is extracted twice with diethyl ether, the combined organic layers are dried over MgSO_4 , filtrated and the solvent is evaporated under vacuum. The crude material is purified by SiO_2 chromatography (hexane) to give the corresponding alkene **14** (0.22 g; 76%) ¹².

Acknowledgments: We thank Mr Alain Valleix for MS measurements and Dorothée Deuring for reviewing this manuscript. The "Institut de Recherche Servier" is gratefully acknowledged for financial support to E.D.

References and notes:

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- The organo lithium epoxide complex could exist as two conformational structures *syn* or *anti* to the epoxide substituent, the formation of the complex is influenced by steric interactions depending on the bulkiness of the base and of the substituent: Molander, G.A.; Mautner, K. *J.Org.Chem.* **1989**, *54*, 4042-4050.



- All products were fully characterized by ^1H , ^{13}C NMR and by Mass Spectroscopy.
- Spectral data for compound **14**:
 $\text{RMN } ^1\text{H}$ (CDCl_3 , 200 MHz) δ : 0.78-0.99 (m, 12H), 1.20-1.45 (m, 10H), 1.89-2.02 (m, 5H), 5.07 (t, $J=7.1\text{Hz}$, 1H).
 $\text{RMN } ^{13}\text{C}$ (CDCl_3 , 50 MHz) δ : 12.1, 14.0, 20.2, 22.4, 23.2, 27.4, 28.7, 29.3, 31.8, 32.5, 42.2, 123.7, 143.8.
 MS-Cl NH_3 m/z (%): 214, M+18, (100).