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Metalated Epoxides as Carbenoids. Solvent Effect on the Alkyl 1,2-Shift in α-Hydroxy Epoxide Systems[†]

Eric Doris* and Charles Mioskowski

CEA-Saclay, Service des Molécules Marquées, Bât. 547,
Département de Biologie Cellulaire et Moléculaire,
91191 Gif sur Yvette Cedex, France

Luc Dechoux* and Claude Agami

Laboratoire de Synthèse Asymétrique associé au CNRS,
Université Pierre et Marie Curie, 4 place Jussieu,
75005 Paris, France

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Metalated oxiranes are versatile reagents of wide scope and applicability.[1] We recently surveyed the diverse behavior of these epoxide-derived carbenoids in a review article.[2] The purpose of this paper is to report our latest results on the alkyl 1,2-shift in cyclic syn α-hydroxy epoxide systems (Scheme 1). This reaction was first observed in our laboratories in 1995.[3]

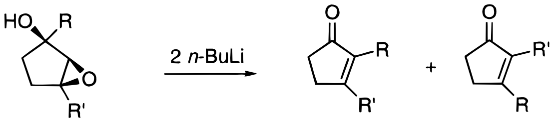
The reaction proceeds across a carbenoid intermediate **2** that is derived from the corresponding epoxide **1** by metalation. The transient thus generated can rearrange along two distinct intramolecular carbenoid insertion routes to yield two regioisomeric α,*β*-unsaturated ketones, **4** and **5**, respectively (Scheme 2).

By varying the substituents R and R′ on the starting hydroxy epoxide **1**, we were able to deduce the following order of migratory aptitude from the product distribution: hydride > methyl > *n*-butyl > aryl > *tert*-butyl.

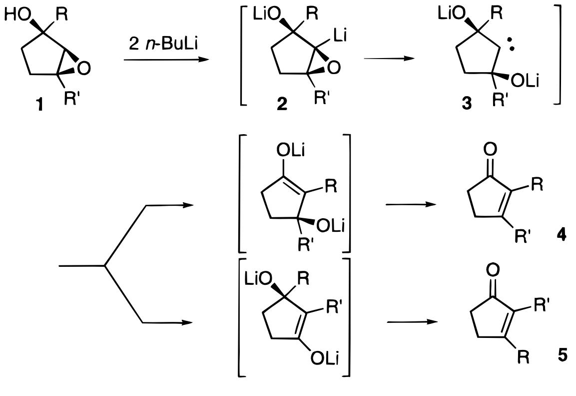
The initial objective of this investigation was to define conditions that would facilitate a highly regioselective alkyl 1,2-shift. Perusal of the literature indicated that the chemoselectivity of carbene-type species is solvent dependent.[4] We thus examined the influence of various solvents on the migratory aptitudes observed in cyclic syn α-hydroxy epoxides. For this purpose, the deuterium-labeled 2-methyl-d_3-5-methyl-6-oxabicyclo[3.1.0]hexan-2-ol (**7**) was synthesized from 3-methyl-2-cyclopenten-1-one oxide (**6**)[5] in a nucleophilic addition reaction with methyl-d_3-lithium[6] at −78 °C. This furnished the expected syn α-hydroxy epoxide in nearly quantitative yield (Scheme 3).[7]

The choice of a CD_3-labeled group was governed by the fact that substituents not only had to be structurally related, but they also had to be distinguishable by NMR spectroscopy. Upon treatment of the deuterated α-hydroxy epoxide **7** with 2 equiv of *n*-BuLi in different solvent systems, **7** suffered an alkyl 1,2-shift to furnish two isomeric α,*β*-unsaturated ketones **8** and **9** in different ratios. The results are collated in Table 1.

Scheme 1



Scheme 2



Scheme 3

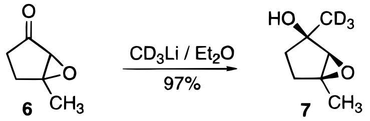
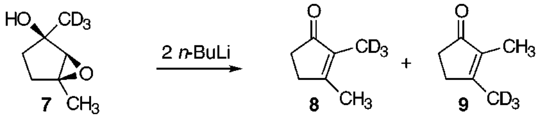


Table 1. Solvent Influence on the Regioselectivity of Alkyl Migration



entry	reaction condns	ratio[a] *8/9*	yield[b] (%)
1	THF, rt, 1h	3.5/1	78
2	Et_2O, rt, 1 h	6.7/1	73
3	pentane, rt, 1 h	13.3/1	69
4	pentane/THF (9:1), rt, 1 h	3.5/1	75
5	THF/TMEDA[c] (9:1), rt, 1 h	2.2/1	78
6	THF/12C4[d] (9:1), rt, 1 h	2/1	70

[a] Ratios determined by ^1H NMR analysis of the crude reaction mixture. [b] Combined GC yields. [c] *N,N,N′,N′*-Tetramethylethylenediamine. [d] 12-Crown-4 ether.

The overall yields are satisfactory and range from 69 to 78%. The major isomer obtained in every case resulted from the preferential migration of the alkyl group originally bound to the α-hydroxy carbon atom (e.g., CD_3).

The utilization of our previously reported conditions[3] (THF) led to a ratio of 3.5/1 in favor of compound **8** (entry 1). When we conducted the same experiment in a slightly less dipolar solvent such as diethyl ether (entry 2), we observed a higher regioselectivity.

The best result obtained was with pentane as solvent (entry 3), where we observed a highly preferential migration of CD_3. This may be rationalized by the anchimeric as-

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[†] This communication is dedicated to the memory of Sir Derek H. R. Barton.

(1) For reviews on metalated oxiranes, see: Crandall, J. K.; Apparu, M. *Org. React.* **1983**, 345−443. Satoh, T. *Chem. Rev.* **1996**, *96*, 3303−3325. See also: Doris, E.; Dechoux, L.; Mioskowski, C. *Tetrahedron Lett.* **1994**, *35*, 7943−7946. Agami, C.; Dechoux, L.; Doris, E.; Mioskowski, C. *Tetrahedron Lett.* **1997**, *38*, 4071−4074.

(2) Doris, E.; Dechoux, L.; Mioskowski, C. *Synlett* **1998**, 337−343.

(3) Doris, E.; Dechoux, L.; Mioskowski, C. *J. Am. Chem. Soc.* **1995**, *117*, 12700−12704.

(4) Köbrich, G. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 473−485.

(5) Felix, D.; Wintner, C.; Eschenmoser, A. *Org. Synth.* **1976**, *55*, 52−56.

(6) CD_3Li was prepared by halogen−metal exchange, see: Bailey, W. F.; Punzalan, E. R. *J. Org. Chem.* **1990**, *55*, 5404−5406.

(7) The preferential formation of syn hydroxy epoxide is due to the steric hindrance of the oxirane, which directs nucleophilic addition to the side opposite to the epoxide. See: Sepùlveda, J.; Soto, S.; Mestres, R. *Bull. Soc. Chim. Fr.* **1983**, *II*, 233−236. Sepùlveda, J.; Soto, S.; Mestres, R. *Bull. Soc. Chim. Fr.* **1983**, *II*, 237−239. Sepùlveda, J.; Soriano, C.; Mestres, R.; Sendra, J. *Bull. Soc. Chim. Fr.* **1983**, *II*, 240−244.

(8) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: New York, 1983.

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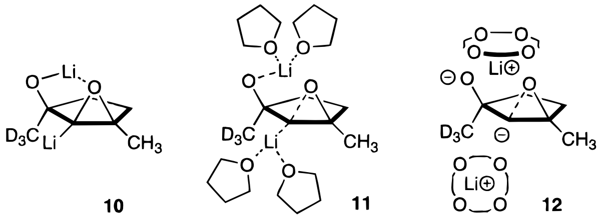
Chart 1



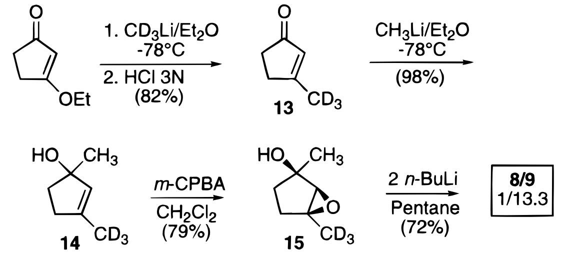
sistance of the oxygen anion, whereby migratory aptitude is enhanced through primary electronic effects.[8] Indeed, in the absence of solvation of the carbenoid lithiums in pentane, the key intermediate **2** does not decompose to the corresponding carbene, thereby permitting a *fully* concerted alkyl 1,2-shift. The carbene stage **3** is circumnavigated in this instance. Furthermore, the intramolecular chelation between the lithium alkoxide and the intracyclic oxygen (Chart 1, structure **10**) does not only decrease the electron- donating potential of the heterocyclic oxygen atom, but it also increases the anionic character of the alkoxide. Thus, migration of the alkyl group adjacent to the negatively charged alcoholate is promoted (vide supra).

This electronic effect is minimized in THF (entry 1), thereby rendering the nonbonding electron pairs of the epoxide oxygen atom "free" to enhance the migratory aptitude of the pendant groups (Chart 1, structure **11**). THF also coordinates the lithium atom of the carbenoid species **2**. This complexation polarizes the C−Li bond and hence promotes the carbene character of the key intermediate. In this case, the alkyl 1,2-shift is *partly* concerted and proceeds more likely through an intermediate that resembles the carbene species **3**. The intermediacy of such a "symmetrical" species is responsible for the poor selectivity observed when running experiments in dipolar solvents (loss of preferential migration).

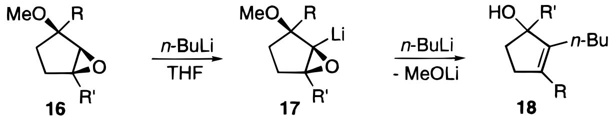
To confirm this conjecture, a number of experiments were conducted with mixed solvents. The addition of 10% THF to pentane dramatically decreased the regioselectivity (entry 4). The same phenomenon was observed in entries 5 and 6, where either TMEDA (entry 5) or the crown ether 12C4 (entry 6 and Chart 1, structure **12**) was added to the reaction mixture. In these cases, we also observed an equilibration of the CD$_3$/CH$_3$ migration imbalance.

The influence of secondary isotope effects on the alkyl 1,2-shift should be negligible.[9] To corroborate this hypothesis, a rearrangement experiment was conducted with compound **15** where the alkyl substituents have been interchanged. The starting α-hydroxy epoxide derivative was prepared according to Scheme 4 in 63% yield. When treated with 2 equiv of *n*-BuLi in pentane, **15** rearranged to **8** and **9** in 72% yield but with an inverted ratio (**8/9** 1/13.3) compared to compound **7**. This result confirms the insignificant influence of isotope effects on the overall process.

Scheme 4



Scheme 5



Interestingly, when the hydroxyl function on the starting α-hydroxy-epoxide **1** was protected as a methyl ether, the resulting α-methoxy-epoxide **16** displayed anomalous behavior (Scheme 5). We did not observe an alkyl 1,2-shift; rather, a product (**18**) that arises from a reductive alkylation process was obtained.[10] The difference in reactivity between the α-alkoxide carbenoid **2** and the α-alkoxy carbenoid **17** can be ascribed to a minimized electrostatic repulsion in the latter case. This favors the insertion reaction above the alkyl 1,2-shift.

This paper describes a highly regioselective access to α,*β*-unsaturated ketone systems. The key carbenoid alkyl 1,2-rearrangement is strongly affected by the nature of the solvent. Solvation of the lithium atoms is decisive in the regiochemical outcome of the reaction.

Acknowledgment. Dr. J. Albert Ferreira is gratefully acknowledged for reviewing this manuscript.

Supporting Information Available: Experimental procedures and spectral data (^{1}H, ^{2}H, ^{13}C) for compounds **7**−**9**, and **13**−**15** (2 pages).

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[9] McLennan, D. J. In *Isotopes in Organic Chemistry*; Buncel, E. B., Lee, C. C., Eds.; Elsevier: New York, 1987; Vol. 7, Chapter 6.

[10] Dechoux, L.; Doris, E.; Mioskowski, C. *Chem. Commun.* **1996**, 549−550.