LOW TEMPERATURE METALLATION OF CYCLIC EPOXIDES:
ENHANCEMENT OF CARBENE DERIVED INSERTION REACTIONS

Robert K. Boeckman, Jr.[1]

Department of Chemistry, Wayne State University

Detroit, Michigan 48202

Since Cope and Tiffany first observed the isomerization of an epoxide initiated by strong base,[2] a considerable effort has been devoted to the study of the scope and mechanism of these processes. Crandall[3] and Rickborn[4] and their collaborators have developed the reaction utilizing lithium di-n-alkyl amides into a synthetically useful and convenient route to a variety of allylic alcohols with good stereo and regioselectivity. Perhaps the most interesting of the reactions observed under these conditions was the formation of bicyclic systems by transannular cyclization of medium ring epoxides discovered by Cope[5] and extended later by Crandall.[3b, c] Cope and Berchtold elegantly demonstrated that these products are most likely derived by transannular insertion of a carbene type intermediate formed by α-elimination of an α-lithioepoxide (Eq. 1).[6] However, in all cases, conditions were not developed which provided cleanly products derived from the carbene pathway.
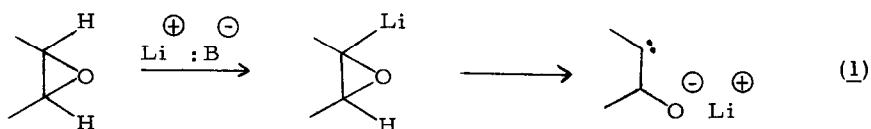

Competition from the other major pathway, β-elimination to form allylic alcohols afforded product mixtures which were difficultly separable. The mechanism leading via syn β-elimination to the allylic alcohols has been nicely elucidated.[7]

We were interested, in this investigation, in developing conditions which would allow clean production of carbene derived products. Since metallation is thought to be reversible[7] and should be enhanced by altering the polarity of the medium, a study of solvent effects was undertaken for cyclooctene oxide. Remarkably, little or no solvent dependence was observed, but the reaction was extremely temperature dependent (Table 1).[8] The ratio of

alcohols was assessed by oxidation and VPC analysis. In all cases, high yields of products ($\geq 80\%$) were obtained. Only in the presence of HMPA is any significant solvent dependence noted, and apparently the more polar medium favors β-elimination to allylic alcohol. However, even a slight increase in the temperature of the medium profoundly affects the selectivity for allylic alcohol.

TABLE 1
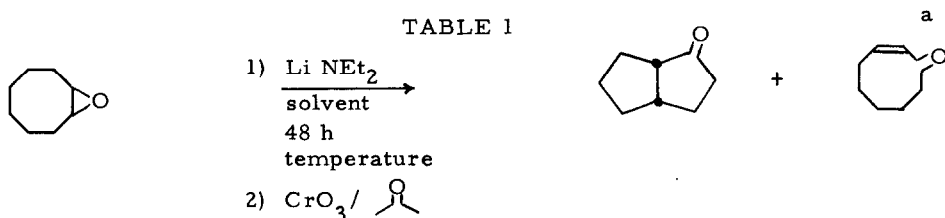
|			
1) Ether/ $\triangle$ /48 h	65	:	35[b]
2) Ether-Hexane (~1 : 1)/ $\triangle$ /48 h	8	:	92
3) THF/ $\triangle$ /48 h	7	:	93
4) THF/HMPA (1 eq.)/ $\triangle$ /48 h	9	:	91
5) Ether/HMPA/r.t. 6 days	4	:	96[c]

a) Analysis by VPC (5', 15% CARBOWAX-20-M at 70°)

b) The difference between these values and those reported by Cope (ref. 5a) (78 : 22) is probably not meaningful since the presence or absence of lithium salts, etc., could play a role, cf. ref. 8.

c) 18% starting epoxide recovered; little reaction occurs at rt without HMPA

In view of this dramatic temperature effect favoring the production of allylic alcohols at higher temperatures, we felt that conditions conducive to formation of the α-lithiated epoxide at lower temperatures might allow the exclusion of β-elimination as a viable pathway leading to clean production of carbene derived products. We have studied the interaction of several cyclic epoxides with nBuLi at lower temperatures ($-78°\rightarrow 25°$) and believe that the spectrum of products observed is consistent with the intermediacy of the α-lithiated epoxide

TABLE 2
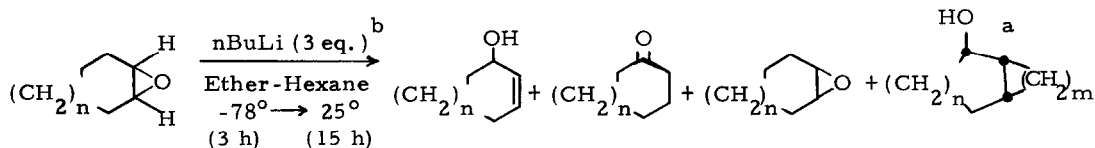
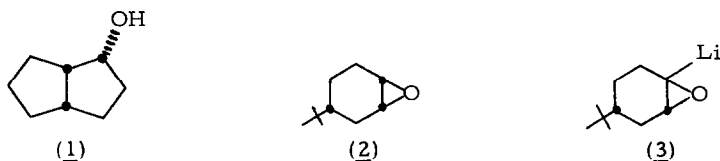|				
n = 1	29	56	15	0
n = 2	0	84	3	13 (m=1, n=2)
n = 3 (cis)	0	0	1	99 (m=3, n=1)
n = 5 (cis)	1	0	0.5	97.5 (m=4, n=2)
				1 (m=3, n=3)
n = 7	80	10	10	0

a) Separated by VPC (15% CARBOWAX-20-M, 5', 65°-150°) and identified by comparison with authentic samples. Yields 60-90%.

b) Reaction occurs more rapidly with the medium ring epoxides, however, it is not usually complete prior to reaching room temperature (TLC)

and derived carbene as the major reaction intermediates (Eq. 1). As shown in Table 2, allylic alcohol is absent in all but the cyclohexane and cyclododecane cases. In a similar experiment except at higher temperature, Rickborn observed substantially more allylic alcohol than ketone (89 : 11).[9] It seems plausible that at least some of the allylic alcohol derived from our experiments (and that of Rickborn's) arises by one of the two possible modes of C-H insertion (paths a, b) available in the cyclohexane system, since no hydrogen is suitably disposed for transannular insertion (path c) (Eq. 2).[6] However, final confirmation of this awaits a labeling study. It is significant, in the case of the seven, eight, and ten membered rings, that essentially no allylic alcohol products are observed, and this provides a synthetically useful route to bicyclic alcohol (1). In all of these cases, the transannular mode of insertion is a lower energy pathway than insertion into the adjacent

$$(2)$$
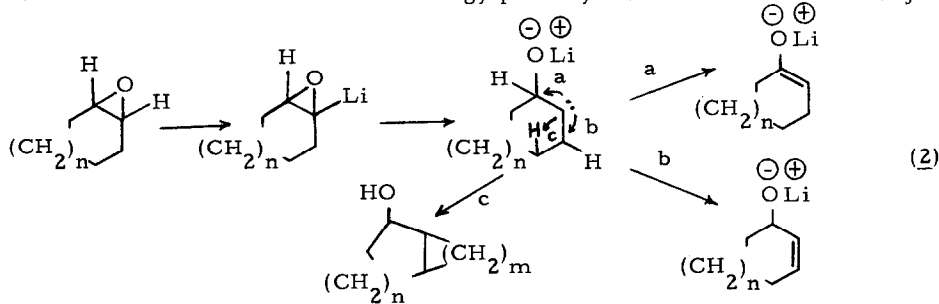
methylene, although undoubtedly conformational factors also influence the results. The insertion of the carbene into the adjacent tertiary hydrogen affording enolate also is a favorable process, whose rate relative to other possible C-H insertion pathways is deter-

mined by conformational factors in the particular ring system. Crandall has conclusively shown that the ketonic products observed do not arise via double bond isomerization and are therefore primary products.[10] The final point which remains to be demonstrated is the mechanism of ketone formation. The alternative of β-elimination of the lithiated epoxide in a concerted formation of the enolate seems implausible and the results of Rickborn bear on this point.[11] The minor ketonic products (26%) of treatment of (2) with Li NEt$_2$ are 3- and 4-tButyl cyclohexanone (85 : 15) which undoubtedly arise via lithiated epoxide. Since the base is sterically demanding (preferring 2° : 3° H for β-elimination to allylic alcohol

2 : 1), it seems reasonable that metallation would occur preferentially at the less hindered site providing (3). Decomposition of (3) via β-elimination to enolate would afford 4-tButyl cyclohexanone, alternatively, carbene insertion would provide 3-tButyl cyclohexanone. It would appear that the latter mechanism is substantially favored, although nonselective metallation may account for the minor amount of 4-tButyl isomer formed. It would indeed be much more difficult to argue that the major product arises selectively from the more hindered metallated epoxide. Again, a conclusive demonstration of the validity of these arguments awaits a definitive labeling study.

In summary, the major products of lithiation of cyclic epoxides at low temperatures are ketones and bicyclic alcohols resulting from adjacent and, transannular C-H insertion, when this pathway is geometrically feasible. This method allows convenient cyclization of certain medium ring epoxides.

References

1. Career Development Award Recipient (CA-00273) of the National Cancer Institute of the National Institutes of Health (1976-1981); Fellow of the Alfred P. Sloan Foundation 1976-1978.
2. A. C. Cope and B. D. Tiffany, J. Amer. Chem. Soc., 73, 4158 (1951).
3. a) J. K. Crandall, J. Org. Chem., 29, 2830 (1964).
   b) J. K. Crandall and L. H. Chang, J. Org. Chem., 32, 435 (1967).
   c) J. K. Crandall and L. H. Chang, J. Org. Chem., 32, 532 (1967).
   d) J. K. Crandall and L. C. Lin, J. Amer. Chem. Soc., 89, 4526 (1967).
   e) J. K. Crandall and L. C. Lin, J. Amer. Chem. Soc., 89, 4527 (1967).
4. a) B. Rickborn and R. P. Thummel, J. Org. Chem., 36, 1365 (1971).
   b) B. Rickborn and R. P. Thummel, J. Org. Chem., 37, 3919 (1972).
   c) B. Rickborn and R. P. Thummel, J. Org. Chem., 37, 4250 (1972).
5. a) A. C. Cope, H. H. Lee, and H. E. Petree, J. Amer. Chem. Soc., 80, 2849 (1958).
   b) A. C. Cope, M. Brown, and H. H. Lee, J. Amer. Chem. Soc., 80, 2855 (1958).
6. A. C. Cope, G. A. Berchtold, P. E. Peterson, and S. H. Sharman, J. Amer. Chem. Soc., 82, 6370 (1960).
7. B. Rickborn and R. P. Thummel, J. Amer. Chem. Soc., 92, 2064 (1970).
8. James K. Whitesell and Patrice D. White, Synthesis, 602 (1975); The difference in product distribution noted for lithium diisopropyl amide is undoubtedly the result of the hindered base preferring metallation over proton abstraction leading to β-elimination. In the cyclooctyl case, temperature does not influence the partition of the α-lithioepoxide-carbene to products. In other cases (cf. ref. 9), the product partition from carbene, as well as metallation-β-elimination partition could be temperature dependent.
9. B. Rickborn and C. L. Kissel, J. Org. Chem., 37, 2060 (1972).
10. J. K. Crandall and L. C. Lim, J. Org. Chem., 33, 2375 (1968).
11. B. Rickborn and R. P. Thummel, J. Org. Chem., 34, 3583 (1969).