

Novel processes for stereoselective organic synthesis

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Abstract - The application of oxiranyl anions in organic synthesis represents a unique means to introduce the epoxide functional group into organic molecules. Unlike simple oxidation procedures, use of these nucleophiles increases molecular complexity in the carbon skeleton at the same time new functionality is created. The generation and utility of trialkylsilyl-substituted oxiranyl anions is highlighted in this paper.

INTRODUCTION

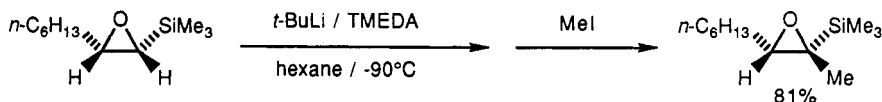
Oxiranes are critical components of many important, biologically active compounds (e.g., the antitumor antibiotics maytansine¹ and ankinomycin,² antibiotics asperlin³ and pseudomonic acids A and B,⁴ and immunosuppressants such as ovalicin⁵). Oxiranes are widely recognized as being extremely versatile synthetic intermediates as well. The high reactivity of epoxides, attributable to ring strain, supports a variety of nucleophilic ring openings, Lewis acid catalyzed rearrangements, and isomerization reactions. Predictable control of regiochemistry and of course stereochemistry in nucleophilic ring-opening reactions of epoxides lends further attraction to their use in selective organic synthesis.

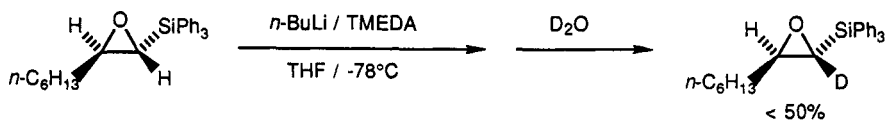
The ready accessibility of oxiranes also contributes significantly to their utility. Oxiranes can be synthesized from olefins utilizing a variety of general reaction conditions. Thus, nucleophilic oxidants such as basic hydrogen peroxide⁶ or electrophilic oxidants like *m*-chloroperbenzoic acid⁷ can be chosen depending on the nature of the olefin. A two-step procedure involving initial halohydrin formation with subsequent base-induced cyclization is another viable route.⁷ Perhaps most importantly, oxiranes can now be generated in high enantiomeric excesses by direct oxidation of allylic alcohols utilizing the elegant procedure developed by Sharpless and his coworkers.⁸

All of the aforementioned procedures involve a simple functional group transformation (i.e., net oxidation of an olefin). However, in general the most efficient synthetic methods are those which not only introduce new functionality, but at the same time dramatically increase molecular complexity in the carbon framework as well. Few methods of oxirane synthesis fulfill both of these criteria. In fact, among the more common methods of oxirane synthesis, only Darzens-type condensation chemistry⁷ and methods based upon ylide chemistry⁹ generate the epoxide functional group in a carbon-carbon bond-forming process. In view of the many roles that epoxides play in organic synthesis, unique, efficient methods for the introduction of this important functional group would be highly valued.

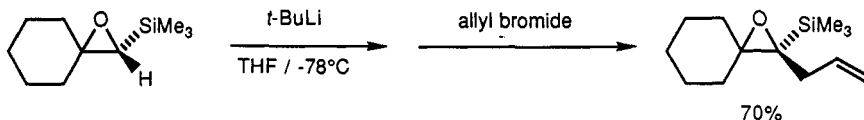
The coupling of oxiranyl organometallics with reactive electrophiles is one method for incorporation of oxiranes that has yet to be fully developed. Although at first glance the stability of such species might be suspect, there is certainly adequate precedent suggesting that these intermediates might be developed into useful synthetic reagents. Oxiranyl anion intermediates were first proposed by House in 1958 in conjunction with his studies on base-catalyzed isomerizations of oxiranes.¹⁰ These anions were examined further in the same context by Cope¹¹ and Crandall.¹² Since that time, numerous processes implicating metalated oxirane intermediates have been recorded.¹³ According to these studies, unstabilized oxiranyl anions are especially prone to α -elimination, providing α -alkoxy carbenes. Products derived from α -alkoxy carbenes have been detected in numerous instances in which oxiranes are subjected to strongly basic conditions.

As might be expected, the ease of metalation of oxiranes as well as the thermal and configurational stability of oxiranyl anions is greatly affected by substituents on the parent oxirane. The first systematic studies of stabilized oxiranyl anions were conducted by Eisch and Galle.¹⁴ Their pioneering research demonstrated the necessity of an anion-stabilizing group to enhance the facility of metalation of epoxides and to increase the thermal stability of the oxiranyl anions produced. Metalation of *cis*-disubstituted trialkylsilyloxiranes and reaction of the resultant oxiranyl anions with simple electrophiles, such as Me₃SiCl, Me₃SnCl, CO₂, MeI, amides, and D₂O, led to high yields of the desired products. Conversely, the reactivity of *trans*-disubstituted trialkylsilyloxiranes toward strong bases proved to be much lower, and only moderate yields of substituted epoxides were obtained. In both cases, however, complete configurational stability was observed.

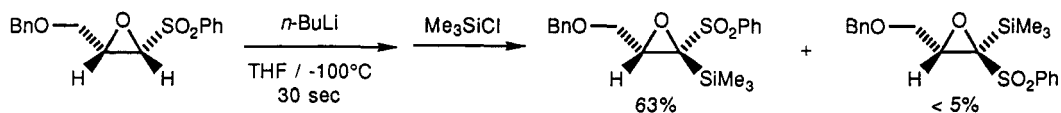




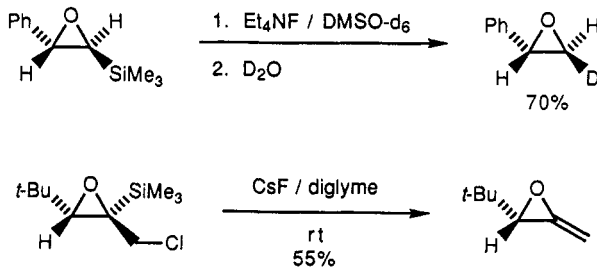
Magnus and coworkers generated a similarly functionalized oxiranyl anion under slightly modified conditions, and briefly examined its reactivity with MeI, allylbromide, and TMSCl.¹⁵



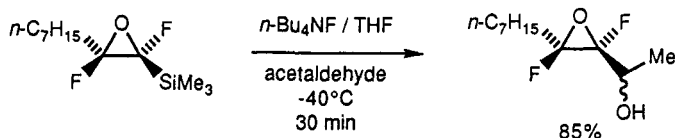
Phenylsulfonyl-substituted oxiranyl anions have also been prepared by direct metalation.¹⁶ Unlike the trialkylsilyloxy-substituted oxiranyl anions, the sulfonyl-stabilized oxiranyl anions apparently exhibit configurational instability even at very low temperatures.



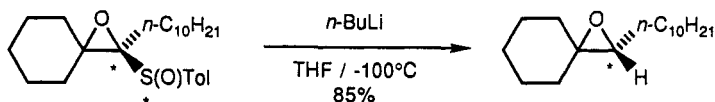
Metal-hydrogen exchange is not the only means to access oxiranyl anions or their synthetic equivalent. For example, desilylation of epoxysilanes with fluoride, first investigated by Chan and coworkers, can be utilized to generate a nucleophilic intermediate (either transient oxiranyl anions or nucleophilic silicon "ate" complexes).¹⁷ In the presence of a proton source, desilylation occurs with strict retention of configuration prior to α -elimination, indicating that the nucleophilic species has some configurational stability. This desilylation reaction has been used in synthetic sequences leading to natural products¹⁸ and as a means of generating allene oxides.¹⁹



In addition, the nucleophilic species produced by reaction of fluoride ions with fluoro-substituted silyloxy epoxides undergo carbonyl addition reactions with a variety of aldehydes and ketones.²⁰



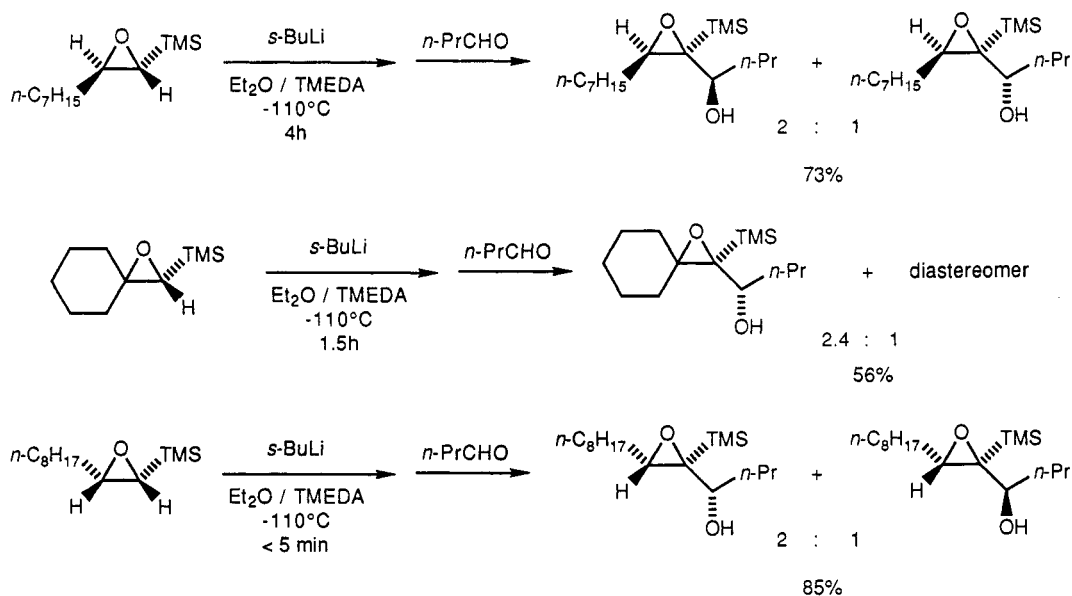
Oxiranyl anions would appear to be likely intermediates in the desulfinylation of epoxy *p*-tolylsulfoxides as well.²¹ Treatment of enantiomerically enriched epoxy *p*-tolylsulfoxides with *n*-butyllithium leads to desulfinylated epoxides, presumably through a configurationally stable oxiranyl anion.



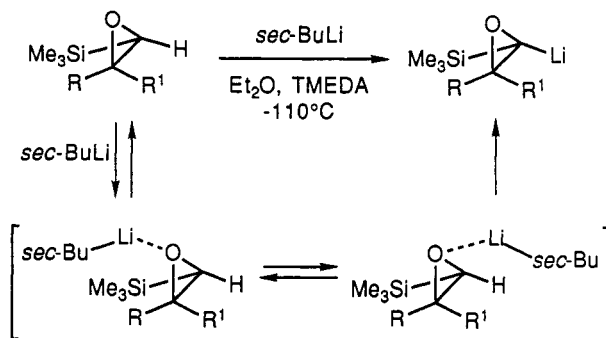
Oxiranyl anions present a clearly unique means to introduce the epoxide functional group into organic molecules. In view of the enormous potential of metalated oxiranes to enhance and significantly expand methods for the construction of epoxides, we have initiated investigations on the application of these unique nucleophiles in organic synthesis. Some of our initial efforts in this area are described below.

RESULTS AND DISCUSSION

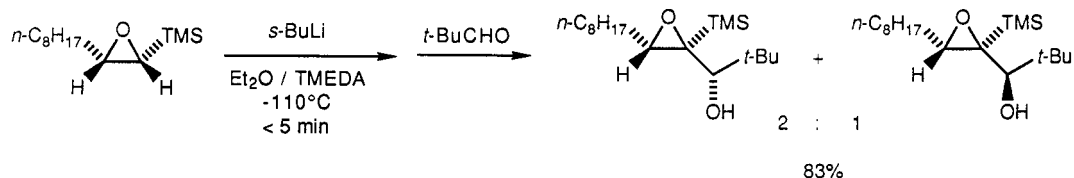
Although it had been demonstrated that trimethylsilyl-substituted oxiranes could be metalated to provide the corresponding oxiranylolithiums,¹⁴ reaction conditions previously reported did not permit efficient metalation of all trimethylsilyl-substituted oxiranes. In particular, those oxiranes possessing a substituent trans to the trialkylsilane were found to be particularly resistant to metalation, and provided low yields of the desired products. As a starting point for our studies, we set out to establish optimized metalation conditions which could be effectively utilized for all substitution patterns of oxiranyl anions. In addition, we wished to examine the reaction of oxiranyl anions with aldehyde and ketone substrates. To date, several metalation conditions have been found which appear to be general, providing high yields of the desired epoxy alcohol products. Although *sec*-BuLi in Et₂O with TMEDA as an additive has been utilized most extensively, use of *t*-BuLi/pentane, *t*-BuLi/pentane/TMEDA or *t*-BuLi/THF/TMEDA appear to be equally effective for these transformations.



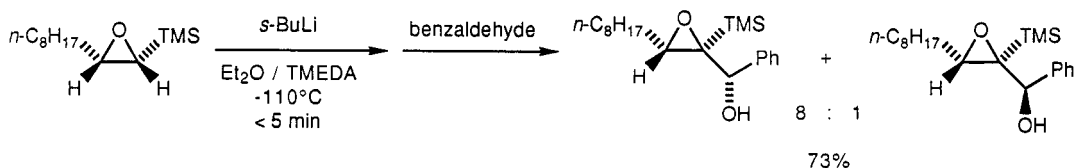
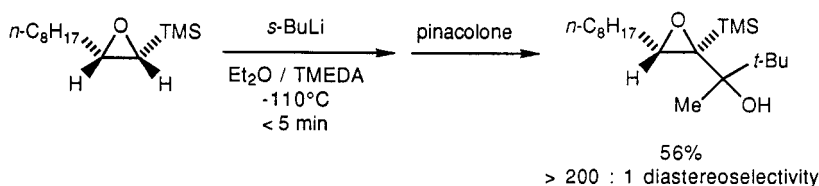
Several points should be noted. The first is that oxiranes with substituents trans to the trimethylsilyl group metalate much more slowly than the corresponding *cis*-disubstituted oxiranes. Although steric hindrance in approach of the base to the C-H bond can be suggested as one explanation for the differential reactivity between *cis*-disubstituted epoxysilanes and oxiranes possessing other substitution patterns,¹⁴ at least one other factor must be considered as well. As in the base-promoted isomerization of epoxides, metalation probably takes place from a base-epoxide complex.¹³ Ignoring any aggregation phenomena, two such complexes exist. The prevalence and stabilities of these complexes will be determined largely by steric interactions between the base and substituents on the oxirane. *Cis*-disubstituted oxiranes will favor a complex placing the base *syn* to the acidic proton, and the equilibrium constant for formation of a complex is expected to be high. The equilibrium constant for formation of an organolithium-epoxide complex in *trans*-disubstituted oxiranes and trisubstituted substrates will be somewhat lower, and more equally split between the two complexes. The rate of deprotonation of oxiranes possessing these substitution patterns is therefore expected to be dramatically lower.



A second feature of the reaction is the low diastereoselectivity ($\cong 2 : 1$) observed in reactions with alkyl aldehydes. Somewhat unexpectedly, increasing the steric demands of the aldehyde has little influence on the diastereomeric ratio of the observed products. For example, pivalaldehyde exhibits virtually the same diastereoselectivity as butanal.

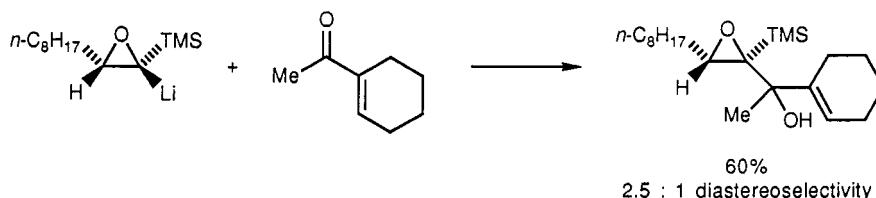
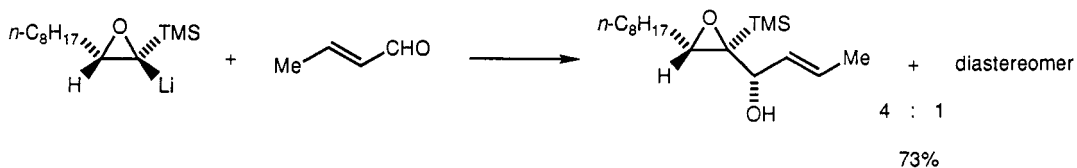


Surprisingly, ketones and conjugated (stabilized) aldehydes such as benzaldehyde provide much higher diastereomeric ratios of products than simple alkyl aldehydes.

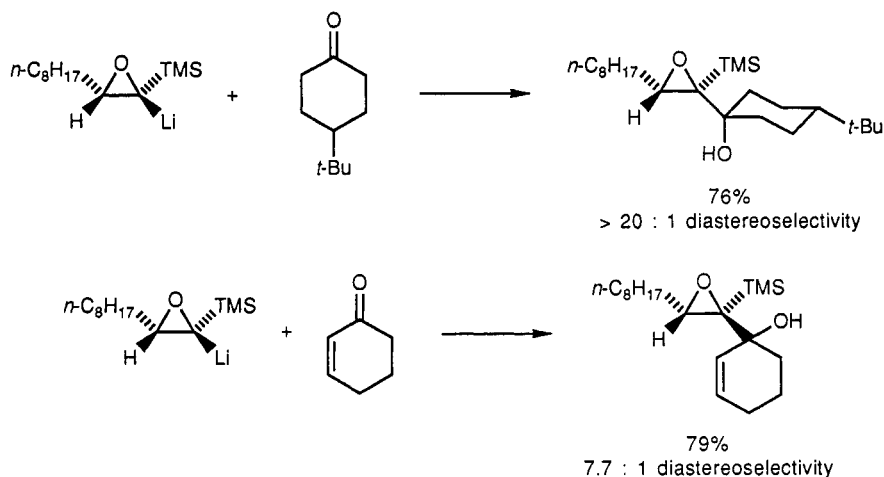


These results may be interpreted in terms of an early transition state reaction. With more reactive aldehydes, carbon-carbon bond formation is established at an early point on the reaction coordinate, and steric demands of the aldehyde substituents are apparently not highly influential. As a consequence, diastereoselectivity is relatively poor. In the case of less reactive aldehydes and ketones, the commitment to carbon-carbon bond formation is established further along the reaction coordinate, permitting steric effects to play a greater role in the determination of the transition state structure. Higher diastereoselectivities are therefore achieved.

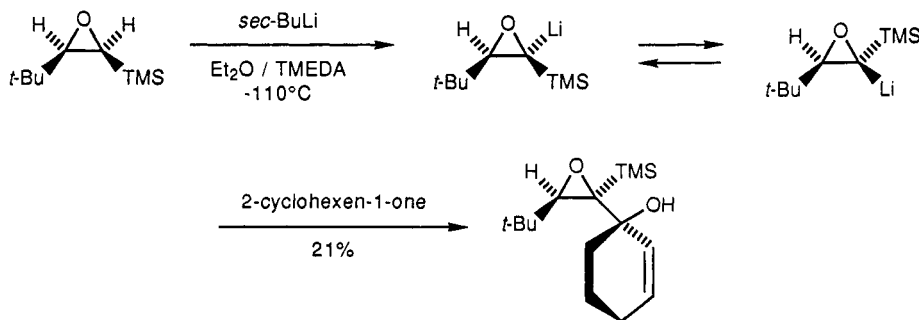
Within the limits of detection, conjugated aldehydes and ketones undergo exclusive 1,2-addition.



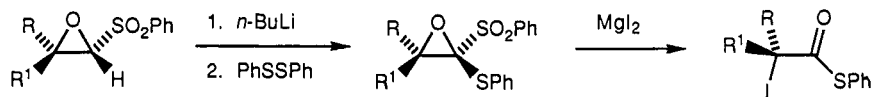
Cyclic ketones also react quite efficiently with trimethylsilyl-substituted oxiranyl anions, in most cases with quite high diastereoselectivity.



During the course of our preliminary studies, we have encountered one example in which configurational inversion appears to be a relatively facile process. When *cis*-1-trimethylsilyl-1,2-epoxy-3,3-dimethylbutane was metalated under the standard reaction conditions and then treated with 2-cyclohexen-1-one, the major product was a solid which was isolated in 21% yield. Single crystal X-ray analysis of this product showed that isomerization of the oxiranyl anion had occurred prior to carbonyl addition.



Studies now in progress are addressing several separate, yet interrelated, issues. The first is the range of stabilizing substituents that may be incorporated into the oxirane as the anion-stabilizing group. These functional groups must be able to facilitate metalation and increase the thermal stability of the resultant anion, but must prevent rapid configurational inversion. It is known that substituents such as esters, nitriles, amides, sulfoxides, and perhaps sulfones fail to meet the required criteria.^{14,16} Current studies with oxazolines are quite promising, and a variety of phosphorus-base substituents are also under consideration. Transmetalation reactions from oxiranyl lithium species to other oxiranyl organometallics are also being explored. To date, oxiranyl titaniums and oxiranyl coppers show the most promise in terms of complementing the parent oxiranyl lithiums. In order to compete with the Sharpless procedure as a means of synthesizing epoxides, routes to enantiomerically enriched oxiranyl anion precursors are also being explored. While some approaches to the oxiranyl anion precursors utilize the Sharpless procedure itself, completely independent routes are being developed as well. Finally, uses of the functionalized oxiranes themselves as synthons in further transformations are being explored. Many of these exhibit unique reactivity patterns that will be of great utility when combined with enantioselective oxiranyl anion chemistry. One example of this is the application of arylsulfonyl-substituted oxiranes as dipolar acetaldehyde synthons.^{16,22}



Clearly, oxiranyl anion chemistry represents an extraordinary means by which epoxides can be incorporated into organic molecules. Full development of these exciting nucleophiles will provide valuable, efficient new routes to epoxides, nicely complementing existing methods for the synthesis of these versatile intermediates.

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