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Base-Induced Rearrangements of Bicyclo[2.2.1] and Bicyclo[2.2.2]alkene-Derived Epoxides to Ketones and Alcohols

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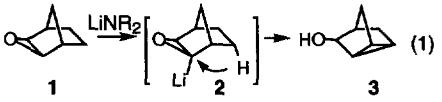
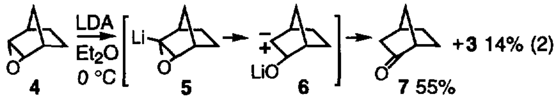
Abstract: Previously unreported base-induced transformations of rigid bicycloalkene-derived epoxides (**4**, **8**, and **16**) are described, providing insight into the rearrangement mechanisms which operate following α-lithiation in such systems. © 1997, Elsevier Science Ltd. All rights reserved.

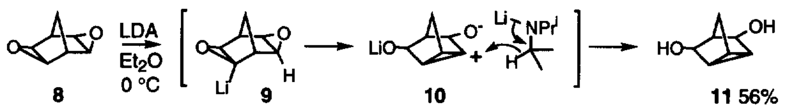
Base-induced rearrangements of epoxides are attracting increasing interest.[1,2] Here we communicate our preliminary results concerning an examination of the α-deprotonation-rearrangement chemistry of some rigid, bicycloalkene-derived epoxides. Our study builds on earlier work[1] to provide significant additional insight into the factors which influence product outcome in such systems.





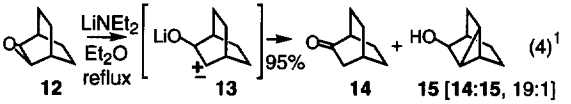
Crandall originally reported the reaction of *exo*-norbornene oxide **1** with $LiNEt_2$ in refluxing benzene to give nortricyclanol **3** (55%, Eq. 1).[1] However, under similar conditions, Crandall and co-workers observed that *endo*-bornylene oxide gives a crude mixture (79%) of camphor, epicamphor and two tricyclanols [ketones: tricyclanols, 3:1 (1.5:1 at room temperature)].[1] In order to make a direct comparison of the effect of epoxide stereochemistry on product outcome, we individually treated *exo*-norbornene oxide **1** and *endo*-norbornene oxide **4**[3] with LDA (2.5 equivs.) in Et_2O at 0 °C for 16 h to give nortricyclanol **3** (90%, no norcamphor **7** observed) and a mixture of norcamphor **7** (55%) and nortricyclanol **3** (14%, **7**:**3**, 4:1 by ^{1}H nmr analysis of the crude product mixture, Eq. 2) respectively.[4] We suggest that for lithiated *exo*-norbornene oxide **2** transannular C-H insertion proceeds readily as hydride migration is able to assist the breaking of the C-O bond (by attack at the C-O σ^* orbital). In contrast, lithiated *endo*-norbornene oxide **5** proceeds to carbene **6** which then partitions between (mainly) insertion into the adjacent LiOC-H bond to give the enolate of norcamphor **7** and transannular C-H insertion to give nortricyclanol **3**.

We also examined the reaction of *exo*,*exo*-norbornadiene diepoxide **8**[5] with LDA (2.5 equivs.) at 0 °C for 16 h which gave *meso*-nortricyclandiol **11**[6] (56%, Eq. 3). In this case, as with *exo*-norbornene oxide **1**, hydride migration may assist transannular C-H insertion from the presumed first-formed lithiated intermediate **9**. However, rather than leading to a highly strained cyclopropyl containing spiro-epoxide, subsequent (or nearly concerted) rupture of the remaining epoxide ring could generate a cyclopropyl cation **10**, which then undergoes reduction by LDA.

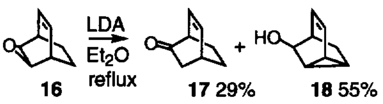


(3)

Crandall and co-workers also reported the rearrangement of bicyclo[2.2.2]octene oxide **12** to give mainly bicyclo[2.2.2]octanone **14** (Eq. 4).[1] This result indicates that, aside from epoxide stereochemistry, the propensity for transannular C-H insertion is very sensitive to the distance between the lithiated epoxide and transannular C-H bonds. However, we find that reaction of structurally related mono-epoxide **16**[7] with LDA (2.5 equivs.) in Et_2O at reflux for 16 h gives a mixture of ketone **17**[8] (29%) and (mainly) alcohol **18**[9] [55%, **17**:**18**, 0.7:1 by ^1H nmr analysis of the crude product mixture (0.5:1 at –10 °C), Eq. 5]. The double bond in mono-epoxide **16** may promote C-H insertion by π- C-H σ* orbital overlap in the lithiated epoxide (and/or at the carbene stage); bicyclo[2.2.2]octene oxide **12**, which lacks such a promoting effect, proceeds entirely to carbene **13** which then partitions between (mainly) insertion into the adjacent LiOC-H bond resulting in the enolate of ketone **14**, and transannular C-H insertion (exclusively[1] *cis* to OLi) to give alcohol **15** (Eq. 4).



(4)[1]



(5)

In summary, in the LDA-induced transformations of bicycloalkene-derived epoxides (a) the first direct comparison of the effects of epoxide stereochemistry have been examined: in the norbornyl system the results are consistent with concerted transannular rearrangement under stereoelectronic control for *exo*-norbornene oxide **1**, and rearrangement first to a carbene for *endo*-norbornene oxide **4**; (b) with *exo*,*exo*-norbornadiene diepoxide **8** a novel rearrangement-concomitant reduction process has been observed; and (c) the presence of a double bond in bicyclo[2.2.2]octyl systems such as **16** results in transannular C-H insertion as the dominant reaction pathway.

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9. The structure of alcohol **18** was determined by X-ray crystallographic analysis of the corresponding 3,5-dinitrobenzoate. Full details will be reported at a later date.

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