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Enantioselective rearrangements of bicyclo[2.2.1]- and bicyclo[2.2.2]alkene-derived achiral epoxides to ketones

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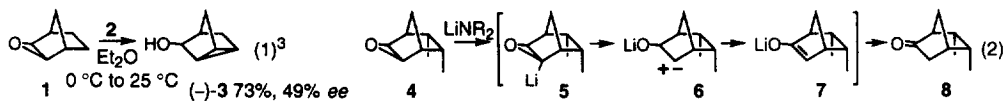
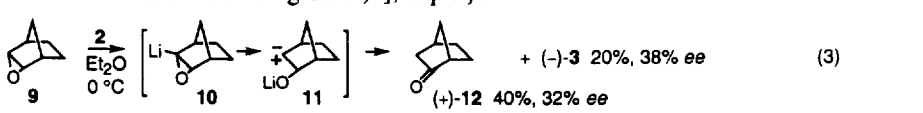
Abstract: The enantioselective α-deprotonation-rearrangement of bicycloalkene-derived epoxides (**4**, **9** and **13**) to ketones (**8**, **12** and **16** respectively) is described. © 1997 Elsevier Science Ltd. All rights reserved.

Base-induced rearrangements of epoxides,[1] particularly enantioselective rearrangements of achiral epoxides,[2] are attracting increasing interest. Here we communicate our preliminary results concerning a study of the enantioselective α-deprotonation-rearrangement of bicycloalkene-derived epoxides for the synthesis of enantioenriched ketones.



We have previously found that chiral, non-racemic lithium amides such as lithium (*S,S*)-bis(1-phenyl)-ethylamide **2** are capable of enantioselective desymmetrisation of *exo*-norbornene oxide **1** by α-deprotonation and subsequent transannular C–H insertion to give (−)-nortricyclanol **3** (Eq. 1).[2,3] However, it was not clear that such an initial enantio-discrimination process could lead to enantioenriched ketones. Firstly, rearrangement of a lithiated epoxide to a ketone (eg **4** to **8**, Eq. 2)[4] is likely to be slower than in the examined case of transannular C–H insertion (compare Eqs. 1 and 2), giving more time for reprotonation. In the presence of a non-racemic base, a lithiated epoxide **5** and its enantiomer could undergo rearrangement to an enolate **7** (or protonation to return to the epoxide **4**) at different rates, potentially compromising the initial, kinetically controlled, enantioselective deprotonation. Secondly, even if a single lithiated epoxide enantiomer **5** was formed it might rearrange to partially or fully racemised enolate **7** if enolate formation occurred competitively by two mechanisms: α-ring opening and insertion of the carbene **6** into the LiOC–H bond (shown in Eq. 2) or electrocyclic β-ring opening (there is experimental evidence in support of both mechanisms).[1,5]

In the event, treatment of epoxide **4**[4] with base **2** (1.85 equivs.) in Et_2O at 0 °C for 24 h gave (−)-ketone **8** (58%, 35% *ee*, Eq. 2);[6] reaction in a variety of solvents at 40 °C was less satisfactory [Et_2O: 87%, 18% *ee*; pentane: 74%, 6% *ee*; THF: 62%, 2% *ee*; THF/LiCl (2 equivs.): 85%, 0% *ee*]. Similarly, reaction of *endo*-norbornene oxide **9**[7] with base **2** gave (+)-norcamphor **12**[8] (40%, 32% *ee*) along with (−)-nortricyclanol **3** {20%, 38% *ee* [**12**:**3**, 4:1 by ^1H nmr analysis of crude product mixture (the same ratio observed using LDA)[7]], Eq. 3}.



Assuming that (+)-norcamphor **12** and (−)-nortricyclanol **3** derive from a common enantioenriched lithiated epoxide **10** (Eq. 3), then this result has important mechanistic consequences because it provides evidence that α-ring opening occurs en route to the enolate of norcamphor. The lower *ee*

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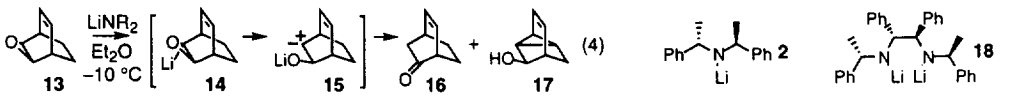
observed for norcamphor **12** compared with nortricyclanol **3** suggests minor competing electrocyclic β-ring opening and/or [probably more likely (*vide infra*)] that base **2** is effecting different partitioning of lithiated epoxide **10** and its enantiomer (and/or carbene **11** and its enantiomer) to norcamphor **12** and nortricyclanol **3**. The selectivity for removal of the *pro-R* hydrogen on the epoxide ring of *endo*-norbornene oxide **9** with base **2** is the same as that observed with *exo*-norbornene oxide **1**.[3] The absolute configuration of the major enantiomer of ketone **8** obtained from epoxide **4** is tentatively assigned by analogy, and is shown in Eq. 2.

Reaction of mono-epoxide **13**[7] with base **2** in Et_2O at 0 °C for 16 h reproducibly gave a mixture of mainly ketone (−)-**16** [40%, 19% optical purity (*op*),[6] major enantiomer shown in Eq. 4] along with alcohol (−)-**17** (30%, 16% *ee*, predominant enantiomer unknown; **16**:**17**, 1.3:1, 1.9:1 at reflux).



For the case of mono-epoxide **13** (Eq. 4), if one again assumes that α-ring-opening operates, then the major ketone enantiomer (−)-**16** formally arises from the opposite sense of predominant asymmetric induction found with base **2** and *endo*-norbornene oxide **9**. No reaction was observed between mono-epoxide **13** and chiral, non-racemic base **18**[9] (shown above) in Et_2O at 0 °C for 16 h. However, reaction at 20 °C for 8 h gave a mixture of mainly ketone (+)-**16** (50%, 12% *op*) along with alcohol (−)-**17** (15%, 20% *ee*, **16**:**17**, 2.7:1). Although bases **2** and **18** both provide ketone **16** as the major product, we had earlier observed that ketone **16** was the minor product when LDA was used as the base in Et_2O (**16**:**17**, 0.5:1 at −10 °C, 0.7:1 at reflux).[7] The nature of the base therefore has a significant effect in determining the ratio of ketone **16** to alcohol **17**. The bases **2** and **18** either retard transannular insertion or accelerate enolate formation from lithiated epoxide **14** and/or carbene **15** (compared with LDA). The results also indicate that bases **2** and **18** generate (in low *ees*) opposite enantiomers of ketone **16** but the same enantiomer of alcohol **17**. Therefore, bases **2** and **18** effect different partitioning of lithiated epoxide **14** and its enantiomer (and/or carbene **15** and its enantiomer) to ketone **16** and alcohol **17**.

Acknowledgements

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