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# Intramolecular Cyclopropanation of Unsaturated Terminal Epoxides

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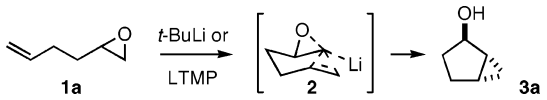
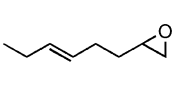
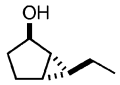
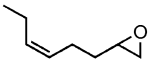
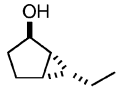
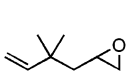
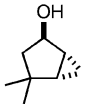
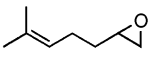
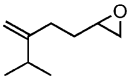
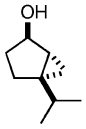
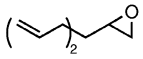
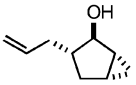
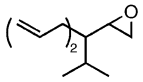
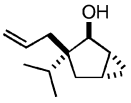
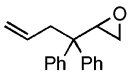
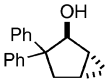
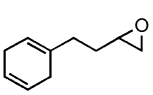
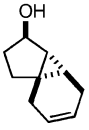
Cyclopropanes fused to five- and six-membered carbocycles are found widely in natural products, and there has been considerable interest in the synthesis of such bicycles, especially in an enantioselective manner.[1] Following the pioneering work of Stork and Ficini,[2] the transition-metal-catalyzed intramolecular cyclopropanation of unsaturated α-diazocarbonyl compounds is now established as important methodology to access such structures.[3] However, the α-diazocarbonyl substrates normally possess limited stability and are typically synthesized in modest yields via one-carbon homologation of carboxylic acids using hazardous diazomethane. For enantioselective cyclopropanation, conditions have recently been developed to obtain high levels of asymmetric induction, but it remains the case that yields and enantioselectivities are highly susceptible to structural variation in the substrate.[4] α-Lithiated epoxides constitute an alternative to diazo compounds as a carbene source.[5] Indeed, in 1967 Crandall and Lin reported that the reaction of *t*-BuLi with 1,2-epoxy-5-hexene **1a** gave small amounts of *trans*-bicyclo[3.1.0]hexan-2-ol (**3a**) (9%), along with other products involving incorporation of the organolithium.[6]




In 1994, Yamamoto and co-workers reported the efficient isomerization of terminal epoxides to aldehydes using lithium 2,2,6,6-tetramethylpiperidide (LTMP), for which deuterium labeling studies indicated that the reaction proceeded via an α-lithiated epoxide.[7] We have recently reinvestigated this reaction and established that it proceeds through trapping of the lithiated epoxide with LTMP to give an enamine, which can be isolated or hydrolyzed to the aldehyde on workup.[8] During this study we considered whether, in the presence of tethered unsaturation, an LTMP-generated lithiated terminal epoxide could preferentially undergo intramolecular cyclopropanation. The present communication reports our promising results of this latter investigation.

Direct application of Yamamoto's conditions to epoxide **1a** (addition of **1a** to LTMP (2 equiv, 0.2 M in THF, 25 °C)) gave after 1 h the alcohol **3a** in 47% yield (volatile 5-hexenal was also observed). Variation of the reaction conditions indicated that the yield of alcohol **3a** was unchanged (48%) if the reaction was initiated at 0 °C and the LTMP (2 equiv, 0.2 M in THF) was added dropwise to the epoxide **1a** (0.2 M in THF). However, under these latter conditions the yield did improve on switching the solvent to hexane (62%) and then to $Et_2O$ (79%). To examine the scope of this cyclopropanation, a variety of bishomoallylic terminal epoxides **1** were examined (Table 1). The reaction works with 1,2-disubstituted alkenes and is stereospecific (entries 1 and 2).[9] A quaternary center adjacent to a terminal alkene presents no problems in the transformation (entry 3), and a trisubstituted alkene and a 2,2-disubstituted-1-alkene also underwent cyclopropanation successfully (entries 4 and 5). However, in these latter two cases the reactions were incomplete after 8 h, and a further 2 equiv of LTMP were subsequently added. *t*-BuOMe was examined as an alternative solvent to $Et_2O$ on the basis that in this solvent LTMP would have a longer half-life;[10] pleasingly, use of *t*-BuOMe allows the reaction shown in entry 5 to proceed without the requirement for a second addition of LTMP, and subsequent examples in this communication use *t*-BuOMe as solvent.

***Table 1.*** Bicyclo[3.1.0]hexanols **3** from Epoxides **1** and LTMP[a]

| Entry | Epoxide **1** | Cyclopropane **3** | | Time (h) | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 |  |  | **3b** | 10 | 81[c] |
| 2 |  |  | **3c** | 12 | 73[c] |
| 3 |  |  | **3d** | 16 | 78[c] |
| 4 |  |  | **3e** | 16 | 65[c] |
| 5 |  |  | **3f** | 16 | 82 |
| 6 |  |  | **3g** | 10 | 69 |
| 7 |  |  | **3h** | 8 | 82 |
| 8 |  |  | **3i** | 16 | 81 |
| 9 |  |  | **3j** | 20 | 76 |

[a] *t*-BuOMe as solvent unless otherwise indicated. [b] Isolated yield. [c] $Et_2O$ as solvent.

The cyclopropanation reaction efficiently distinguishes between diastereotopic allyl groups (entry 6);[9] this presumably reflects the preference for a substituent to reside equatorial if possible in the suggested chairlike transition state **2**. Substitution adjacent to the

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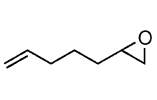
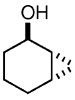
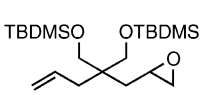
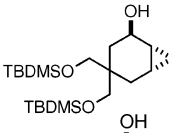
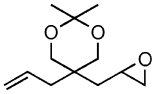
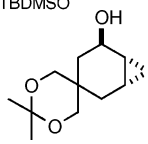
terminal epoxide functionality is tolerated (entries 7 and 8). In entry 7 a quaternary stereocenter is generated in a controlled fashion,[9] and this is likely due to the preference of the *i*-Pr group to be equatorial in the transition state. For entry 8 aromatic insertion was not observed as a competing reaction. Cyclopropanation of a tethered cycloalkene leads to a tricyclic alcohol **3j** (entry 9); possible complications arising from potentially competitive deprotonation in the substrate at the doubly allylic positions were not observed. The structure of tricyclic alcohol **3j** was supported by X-ray crystallographic analysis following dihydroxylation.[11]

The chemistry could be extended to trishomoallylic epoxides **4**, thus allowing access to *trans*-bicyclo[4.1.0]heptan-2-ols **5** (Table 2);[12] allylic C−H insertion was not observed as a competing reaction.

***Table 2.*** Bicyclo[4.1.0]heptanols **5** from Epoxides **4** and LTMP[a]

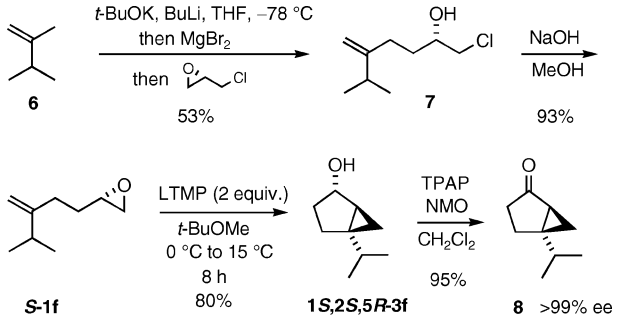
| Entry | Epoxide **4** | Cyclopropane **5** | | Yield (%)[b] |
|---|---|---|---|---|
| 1 |  |  | **5a** | 65 |
| 2 |  |  | **5b** | 71 |
| 3 |  |  | **5c** | 64 |

[a] *t*-BuOMe as solvent, reaction time 20 h. [b] Isolated yield.

It was considered important to ascertain whether an enantioenriched epoxide would undergo cyclopropanation under the reaction conditions without any degradation in ee. This was established by chiral GC analysis on the TBDMS ether of alcohol (+)-**3a** (98% ee)[13] formed using (*R*)-1,2-epoxy-5-hexene ***R*-1a** (99% ee).[14] To illustrate the utility of this chemistry in targeted asymmetric synthesis, (−)-sabina ketone **8**[15] was synthesized according to Scheme 1. The strategy additionally demonstrates the use of readily available highly enantioenriched epichlorohydrin to prepare bishomoallylic epoxides of high ee. Thus, commercially available 2,3-dimethyl-1-butene (**6**) was converted to the corresponding allylic Grignard[16] and reacted with (*S*)-epichlorohydrin (>99% ee) to give chlorohydrin **7** (53%). The derived epoxide ***S*-1f** underwent cyclopropanation in a similar yield (80%) to the racemate (Table 1, entry 5). Cyclopropanation could also be achieved directly from the chlorohydrin **7** using 3 equiv of LTMP (69%). Finally, oxidation using TPAP gave sabina ketone **8** (>99% ee).[13]

In summary, we report conditions for the efficient intramolecular cyclopropanation of bishomoallylic and trishomoallylic epoxides, together with a preliminary evaluation of the scope of this process. The methodology can be considered as a useful alternative to intramolecular cyclopropanation of unsaturated α-diazocarbonyl compounds, because of the ready availability of (highly enantioenriched) epoxides and the completely diastereoselective nature of the transformation. The diastereoselectivity is due to a combination of an initial trans-lithiation of the epoxide,[7] the fact that the cyclopropane must form cis-fused to a five- or six-membered ring, and probably, that the cyclopropanation occurs at the stage of the lithium carbenoid (as suggested in **2**), rather than an α-lithiooxy carbene.[17]

***Scheme 1***

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**Supporting Information Available:** Experimental procedures and NMR spectra of **3a**−**j**, **5a**−**c**, **7**, and **8** and details regarding starting epoxides (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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