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Widening the usefulness of epoxides and aziridines in synthesis*

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Abstract: Deprotonation of terminal epoxides and aziridines with organolithium/diamine combinations or lithium amides allows the regio- and stereoselective formation of α-lithiated species. Judicious choice of reaction conditions allows these species to operate as nucleophiles, enolate equivalents, vinyl cation equivalents, or carbenes.

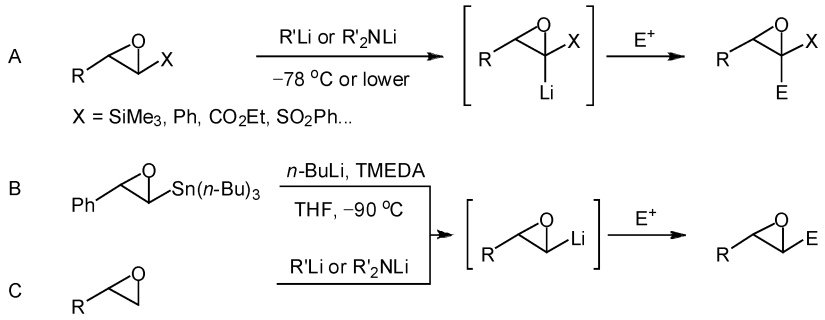
Keywords: asymmetric synthesis; aziridines; carbenoids; epoxides; lithiation.

INTRODUCTION

Epoxides and aziridines are common intermediates in synthesis. Readily accessible in enantioenriched form, they are typically used as electrophiles, taking advantage of their predictable highly regioselective ring-opening reactions. Our work in the area of α-lithiated terminal epoxides and aziridines indicates that there are many other less conventional but useful reactions of these small-ring heterocycles [1].

EPOXIDES AS NUCLEOPHILES

The reaction of an α-lithiated epoxide with an electrophile is potentially an attractive route for the synthesis of more substituted epoxides. This concept was first demonstrated by Eisch and Galle 30 years ago, when an α-lithiated epoxide bearing an anion-stabilizing group was shown to act as a nucleophile to give a more substituted epoxide (Scheme 1, reaction A) [2].



Scheme 1

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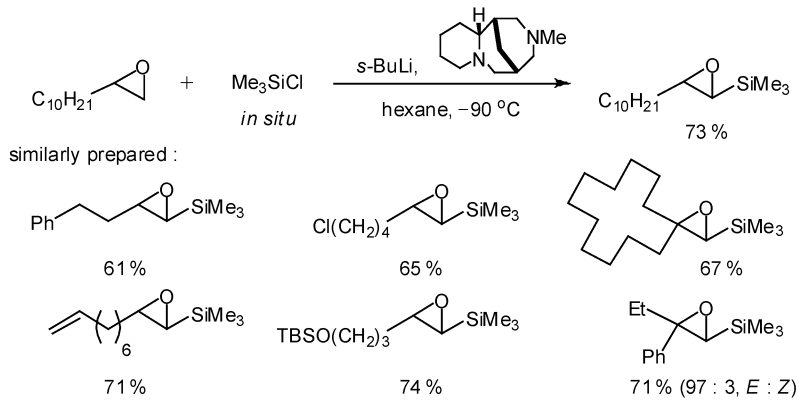
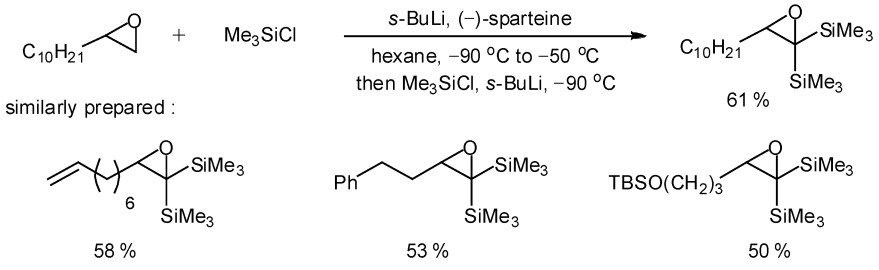
A potential problem with this route is that an anion-stabilizing group needs to be present in the starting material and, if it is not required, removed in subsequent transformations. In order to partially overcome these issues, Pflatz and coworkers were able to indirectly generate a simple α-lithiated terminal epoxide lacking any anion-stabilizing groups, by tin–lithium exchange (Scheme 1, reaction B) [3]. More recently, we considered whether a simple terminal epoxide could be directly regio- and stereoselectively lithiated by treatment with an organolithium or lithium amide to generate a nonstabilized α-lithiated epoxide, which could undergo trapping with an electrophile to access a 1,2-disubstituted epoxide (Scheme 1, reaction C).

After extensive reaction optimization, treatment of terminal epoxides with *s*-BuLi in the presence of a diamine ligand generated α-lithiated terminal epoxides that could trap out Me_3SiCl in situ in good yields (Scheme 2) [4]. Single *trans*-diastereomers of the α,β-epoxysilanes were isolated in all cases, indicating that the less sterically hindered epoxide ring proton was abstracted.



Scheme 2

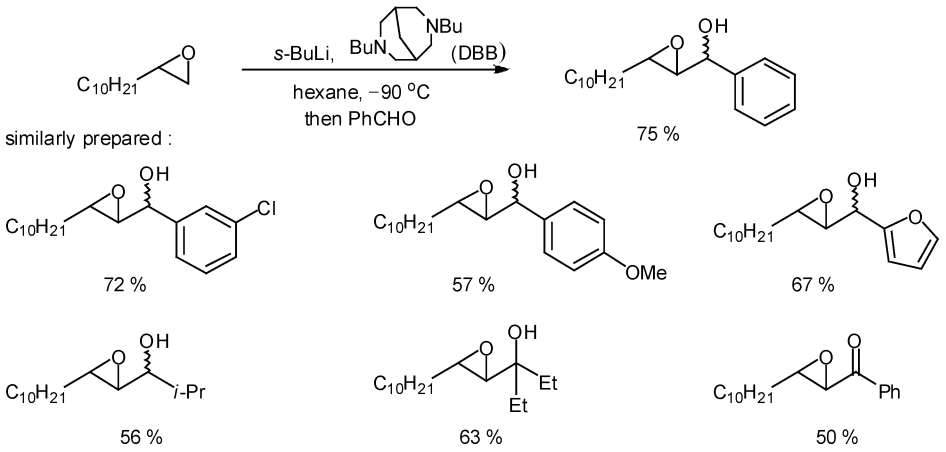
As mentioned above, organosilyl substituents can act as anion-stabilizing groups to promote lithiation, and the in situ lithiation/silylation reaction could be extended into a one-pot method for the synthesis of α,β-epoxydisilanes from simple terminal epoxides by a direct double silylation reaction (Scheme 3) [5].



Scheme 3

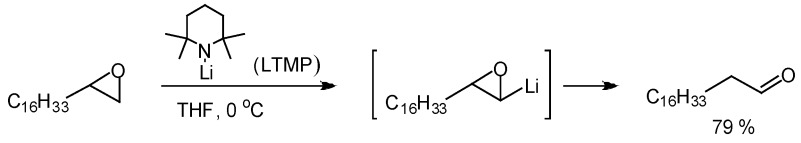
It still remained to establish conditions to trap simple α-lithiated epoxides with external electrophiles, i.e., electrophiles that do not possess compatibility with *s*-BuLi. To this end, a wide variety of diamine ligands were screened in an attempt to not only increase the rate of lithiation, but also to stabilize the transient α-lithiated epoxide. We discovered that *N*,*N*-dibutylbispidine (DBB) was the opti-

mum diamine ligand for this task and a variety of external electrophiles were trapped [6]. It is noteworthy that carbon–carbon bond formation could be achieved in this process (Scheme 4) [7].



Scheme 4

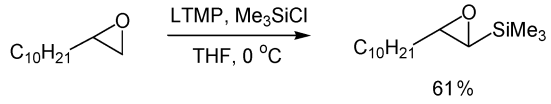
With the aim of improving the experimental simplicity of the above lithiated terminal epoxide chemistry, we were attracted to a publication by Yamamoto and coworkers which described the isomerization of terminal epoxides to aldehydes via an α-lithiated epoxide upon treatment with lithium 2,2,6,6-tetramethylpiperidide (LTMP) (Scheme 5) [8].



Scheme 5

This report demonstrated a straightforward, stereoselective route to α-lithiated terminal epoxides, although it suggested a subsequent "rearrangement" to the enolate of the aldehyde (rather than the ketone) as the reaction pathway, which seemed unusual (vide infra). We considered whether LTMP could be used within the context of electrophile trapping for the synthesis of *trans*-1,2-disubstituted epoxides from terminal epoxides.

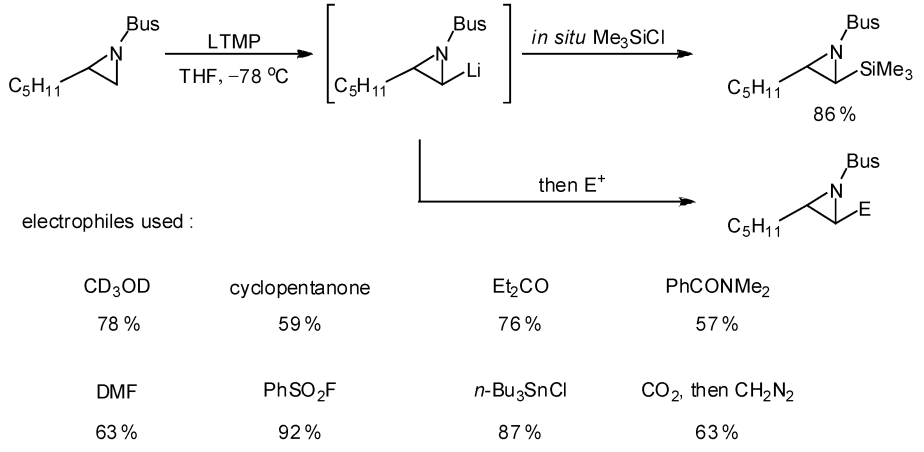
Pleasingly, α-lithiated epoxides could not only be generated at 0 °C (as opposed to the strict –90 °C required when using *s*-BuLi/diamine combinations), but also trapped with Me_3SiCl in situ to give single *trans*-diastereomers of α,β-epoxysilanes (Scheme 6) [9].



Scheme 6

AZIRIDINES AS NUCLEOPHILES

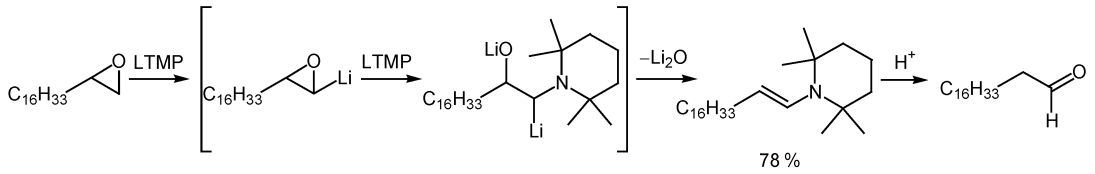
Aziridines and epoxides frequently display similar reactivity, although in the case of aziridines the choice of the *N*-protecting/activating group offers the potential additional advantage of being able to fine-tune the reaction characteristics of the aziridine. Although the LTMP methodology was found unsuitable for trapping external electrophiles with terminal epoxide substrates, it could be extended to terminal aziridines bearing the base-stable acid-labile *N-tert*-butylsulfonyl (Bus) protecting group (Scheme 7) [10].



Scheme 7

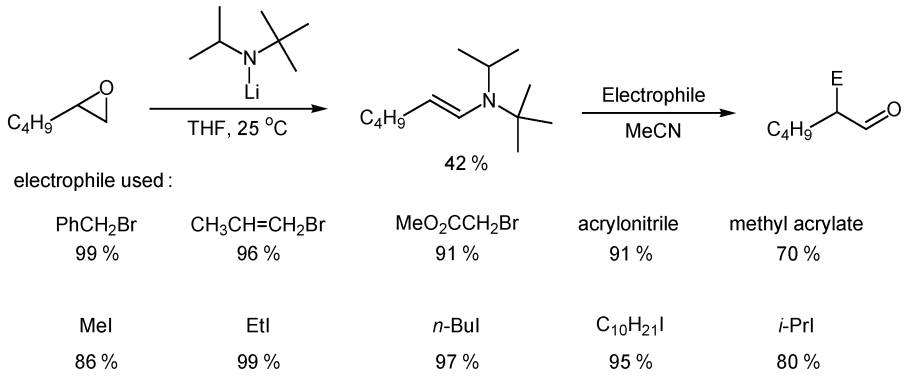
EPOXIDES AS ENOLATE EQUIVALENTS

Upon repeating one of the "isomerization" reactions reported by Yamamoto and coworkers [8], we were surprised to observe olefinic protons in the ^{1}H NMR spectrum of the crude reaction mixture. Closer examination showed that the reaction proceeded via an enamine intermediate, which hydrolyzed on column chromatography on SiO_2 (Scheme 8).



Scheme 8

The enamine derived from LTMP appeared to possess too much steric bulk to undergo successful C-alkylation with typical enamine electrophiles; however, using an alternative, slightly less bulky lithium amide allowed the synthesis of α-alkylated aldehydes from epoxides, in good to excellent yields (Scheme 9) [11].

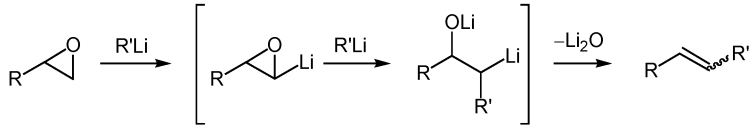


Scheme 9

The novel enamine formation pathway allows terminal epoxides to function overall as aldehyde enolate equivalents for the trapping of electrophiles.

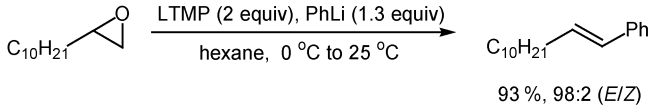
EPOXIDES AS VINYL CATION EQUIVALENTS

Reductive alkylation of epoxides is a potentially powerful synthetic process, involving a (terminal) epoxide functioning as a vinyl cation equivalent in a reaction with organolithiums to generate more substituted olefins (Scheme 10).



Scheme 10

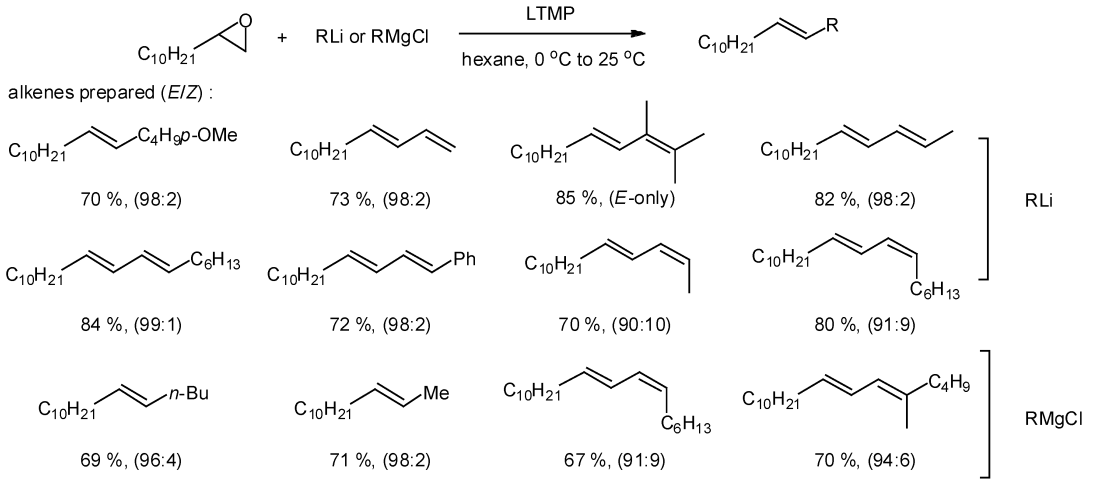
However, following the first observation of this reaction in 1967 [12], it has suffered from a number of drawbacks: only simple alkyllithiums were effective partners in this chemistry, a bulky organolithium was needed for high *E*-selectivity, and at least 2 equiv of organolithium were required. We considered whether LTMP and an organolithium would be an effective combination for the reaction, with LTMP acting to deprotonate the terminal epoxide and the organolithium then acting as a nucleophile on the transient carbenoid (Scheme 11).



Scheme 11

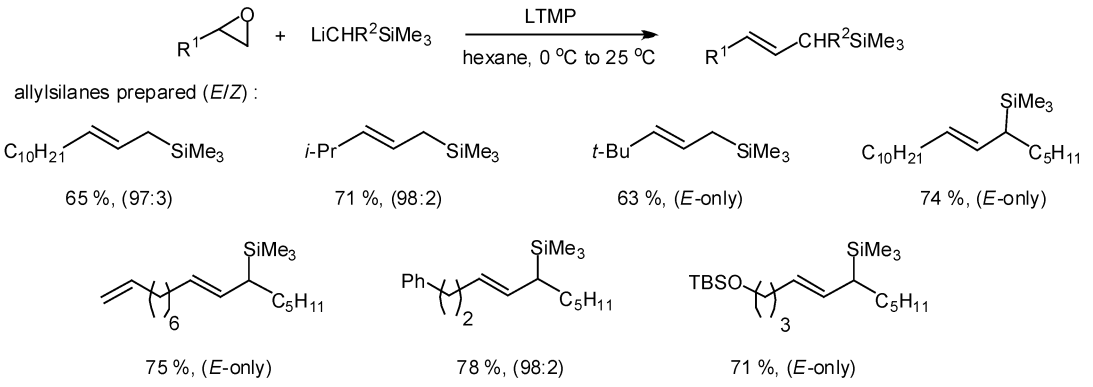
Pleasingly, using a mixture of LTMP and PhLi allowed the synthesis of the desired alkene in excellent yield and *E*-selectivity. This is an interesting transformation when one considers what is happening in the reaction: α-lithiation of 1,2-epoxydodecane by LTMP is faster than by PhLi and faster than direct ring opening by PhLi; the *trans*-lithiated epoxide undergoes reaction with PhLi preferentially over LTMP and PhLi is not consumed in deprotonating the TMP generated by lithiation of the epoxide.

The reaction was successfully extended to a number of other organolithiums and even Grignard reagents to allow the synthesis of a variety of alkenes, all with excellent *E*-selectivity about the newly formed double bond (Scheme 12) [13].



Scheme 12

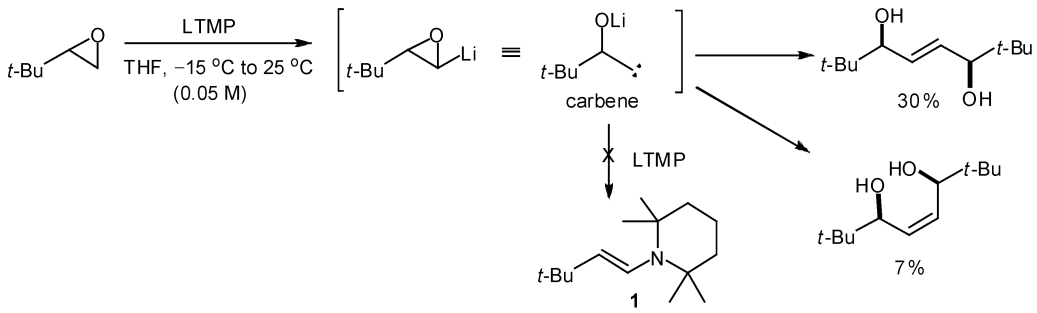
The synthesis of synthetically important allylsilanes was also possible using Me_3SiCH_2Li or 1-(trimethylsilyl)hexyllithium with LTMP (Scheme 13).



Scheme 13

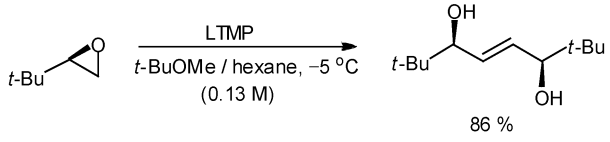
EPOXIDES AS CARBENOIDS IN DIMERIZATION

The carbenoid character of α-lithiated epoxides is exemplified by their ability to undergo eliminative dimerization to 2-ene-1,4-diols, a process first observed in 1980 [14]. We first became interested in the dimerization of carbenoid epoxides as a practical synthetic method for the construction of new carbon–carbon double bonds when during an attempt to form enamine **1** we recovered the *cis* and *trans* enediols of *tert*-butyl oxirane in a combined 37 % yield (Scheme 14).



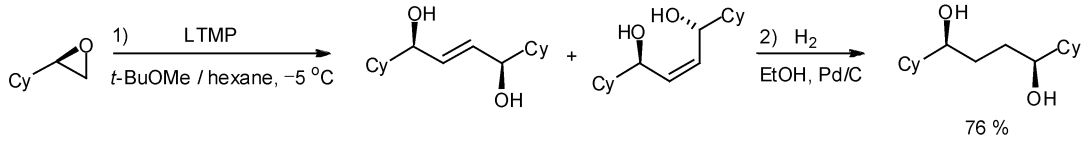
Scheme 14

The combined yield of 2-ene-1,4-diols was successfully increased to 75 % by increasing the concentration of the reaction mixture and by using a less coordinating solvent mixture. It was then considered that if dimerization were to occur with an enantiopure terminal epoxide (easily accessible from the racemate via hydrolytic kinetic resolution), then only homochiral dimerization could occur, potentially resulting in only the (*E*)-enediol as a single diastereomer. Pleasingly, dimerization of enantiopure (*R*)-*tert*-butyloxirane gave the (*S*,*S*)-enediol as a single enantiomer in 86 % yield (Scheme 15).



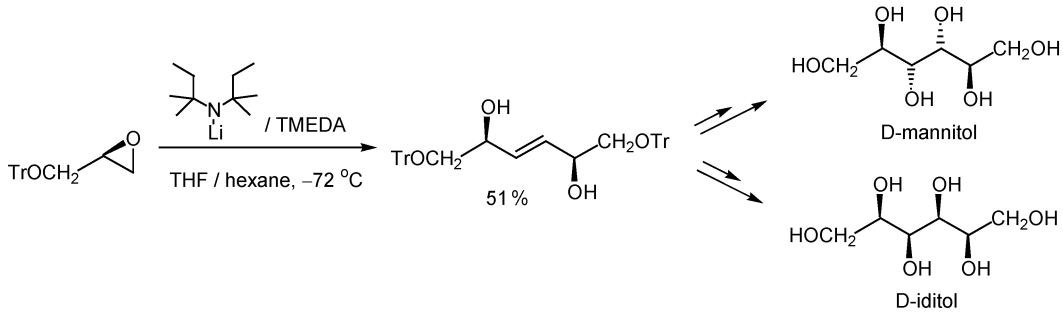
Scheme 15

Despite our finding that decreasing the steric bulk in the γ-position led to competitive formation of the chiral *(Z)*-2-ene-1,4-diol, hydrogenation of the *E*/*Z* mixture of 2-ene-1,4-diols derived from (*R*)-cyclohexyloxirane gave a single (enantiopure) 1,4-diol in 76 % yield over two steps; thus demonstrating the method as a straightforward route to useful C_2-symmetric enantiopure 1,4-diols (Scheme 16).



Scheme 16

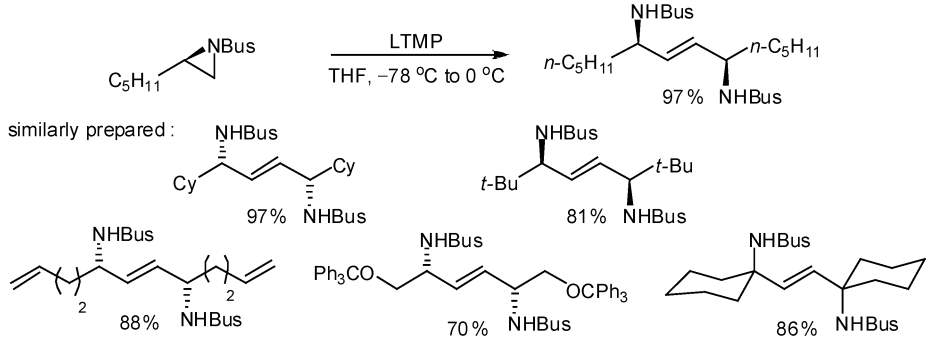
Applying the methodology to a more oxygenated substrate is illustrated with the reaction of enantiopure (*S*)-tritylglycidyl ether to give the corresponding protected 2-ene-1,4,-diol as a single geometric isomer in 51 % yield. This 2-ene-1,4-diol was then used in the syntheses of the hexitols D-mannitol and D-iditol (Scheme 17) [15].



Scheme 17

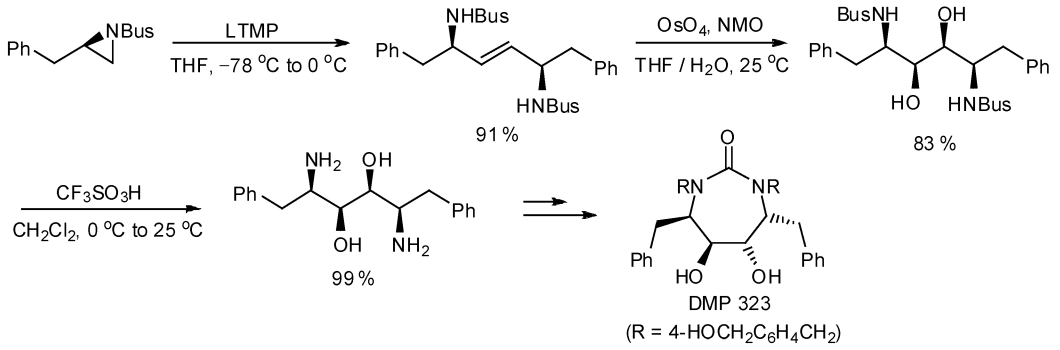
AZIRIDINES AS CARBENOIDS IN DIMERIZATION

Following on from the above studies, we considered that lithiated terminal aziridines might undergo similar dimerization, leading to useful (N-protected) 2-ene-1,4-diamines. Pleasingly, treatment of the racemic *N*-Bus aziridine of 1-heptene with LTMP gave the desired dimer in 90 % yield as a mixture of three protected 2-ene-1,4-diamine diastereomers. Extension of this reaction to a range of enantiopure *N*-Bus protected terminal aziridines gave the desired products of dimerization in high efficiency and as single enantiomers (Scheme 18) [16].



Scheme 18

The utility of this methodology was demonstrated in the synthesis of the core C_2-symmetric unit of a series of extremely potent HIV protease inhibitors, such as the parent DuPont Merck compound DMP 323. The core 1,4-diamine-2,3-diol unit was synthesized from enantiopure (*R*)-benzyl-substituted aziridine in three high yielding steps (Scheme 19).

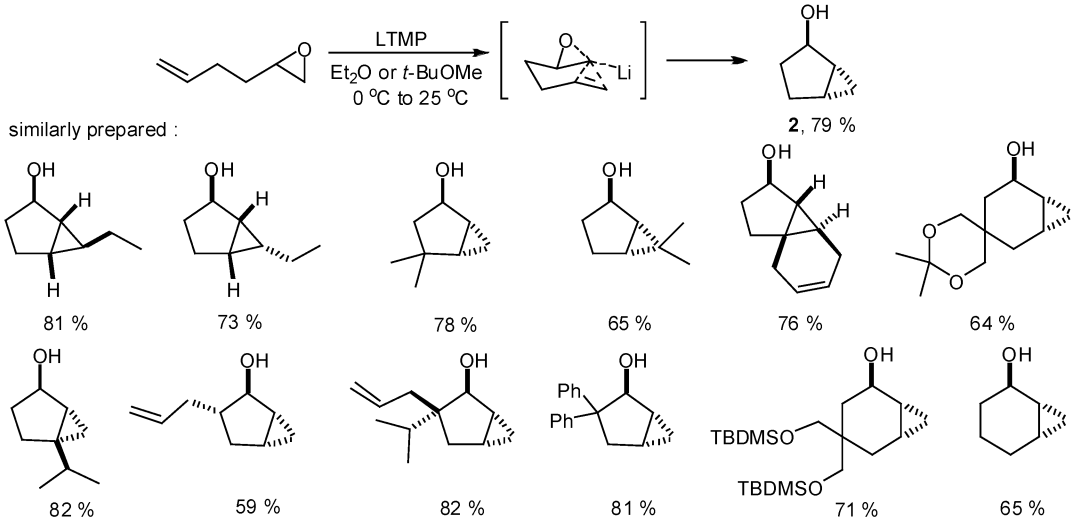


Scheme 19

The dimerization of epoxides and aziridines constitutes a convenient strategy for the construction of 1,4-diols/diamines of defined absolute stereochemistry in one step from simple enantiopure epoxides and aziridines, which in the case of epoxides are frequently commercial and inexpensive.

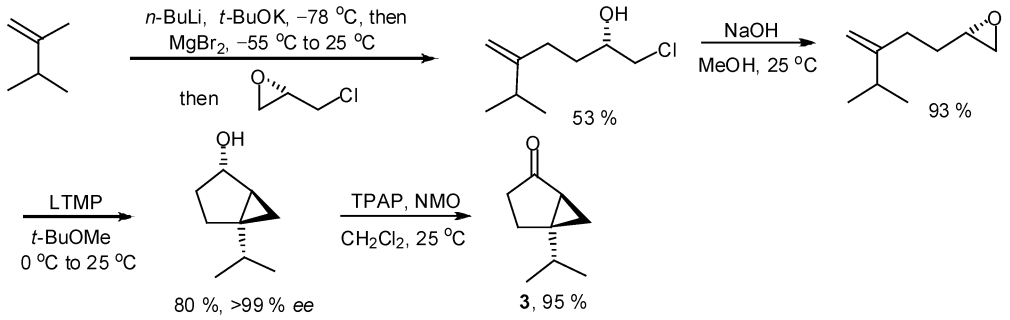
EPOXIDES AS CARBENOIDS IN INTERMOLECULAR CYCLOPROPANATION

During our investigations into the formation of enamines from terminal epoxides and hindered lithium amides, we attempted to react 1,2-epoxy-5-hexene with LTMP. The desired enamine was isolated in low yield and interestingly, bicyclic alcohol **2** was identified as a side-product. The formation of this latter cyclopropane-containing product had previously been reported by Crandall and Lin as a side-product, being isolated in only 9 % yield when 1,2-epoxy-5-hexene was treated with *t*-BuLi [17]. After further investigation, the reaction with LTMP was optimized to give alcohol **2** in 79 % yield. The reaction between the lithiated epoxide and the tethered olefin was found to be completely diastereoselective, which may be due to the reaction proceeding via a chair-like transition state. A variety of bis- and tris-homoallylic terminal epoxides were then synthesized and successfully underwent cyclopropanation using this optimized procedure (Scheme 20) [18].



Scheme 20

To further demonstrate the utility of this methodology, an asymmetric total synthesis of (–)-sabina ketone **3** was carried out in four steps from commercially available (*S*)-epichlorohydrin (Scheme 21).

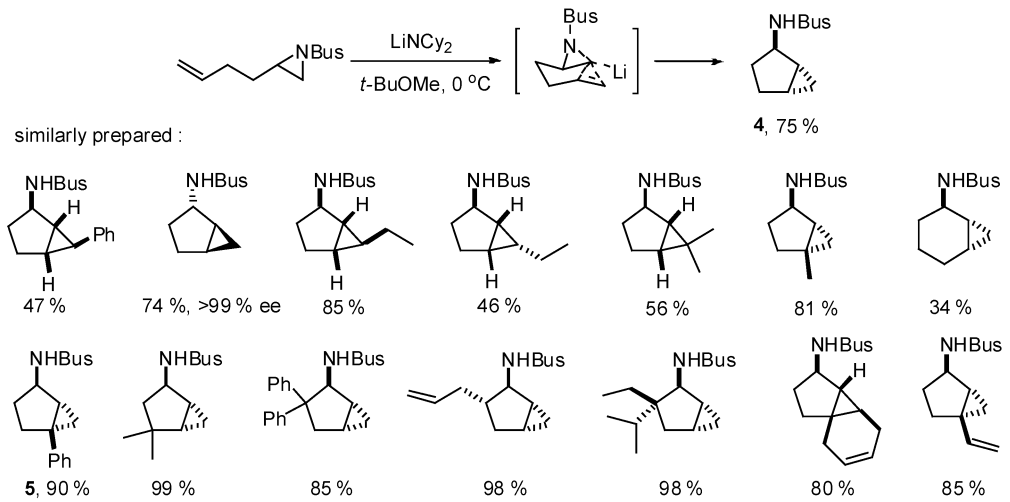


Scheme 21

From a practical point of view, it was found that comparatively less volatile chlorohydrins were also suitable substrates for cyclopropanation, providing an additional equivalent of base was used to form the corresponding epoxides in situ [19].

AZIRIDINES AS CARBENOIDS IN INTERMOLECULAR CYCLOPROPANATION

Following the successful development of epoxide intermolecular cyclopropanation, we decided to investigate the possibility of extending the process to aziridines as a method for accessing 2-aminobicyclo[3.1.0]hexanes **4** (a structural motif found in numerous analgesics, anti-viral agents and anti-obesity therapeutics). After extensive investigation of the reaction conditions to minimize competitive formation of 2-ene-1,4-diamine, optimized conditions using $LiNCy_2$ were applied to a range of unsaturated terminal aziridines (Scheme 22) [20].



Scheme 22

The 2-aminobicyclo[3.1.0]hexanes were all isolated as single diastereomers in good to excellent yields. The successful synthesis of amine **5** is particularly noteworthy in the context of anti-obesity therapeutics, as the latter bear similar aryl substitution in the 5-position.

CONCLUSIONS

In summary, epoxides have been used as masked olefins and aldehydes in synthesis. Epoxides and aziridines have been used as nucleophiles and utilized as *E*-selective olefin precursors during eliminative dimerization. Finally, epoxides and aziridines have been exploited to form bicyclic ring systems found in numerous interesting synthetic targets. We believe that there are further useful reactivity modes for these versatile small-ring systems waiting to be discovered and our studies are ongoing in this area.

ACKNOWLEDGMENTS

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