

isotope effects that might be of importance, and of limitations associated with experimental uncertainties in the two rate constants measured: from their observed k_i/k_α value, an extreme double rotation/single rotation ratio of 85/15 was derived, based on assumptions least favorable to the double rotation process, while a 98/2 ratio was deduced under more plausible assumptions.¹⁰ Yet they harbored no doubt that the theoretically predicted¹¹ double rotation mechanism predominated by a substantial factor.

We believe that this conclusion was based on an extremely accurate experimental estimation of the ratio of the two accessible kinetic parameters, k_i and k_α ,¹² and on some reasonable but nevertheless erroneous assumptions regarding kinetic isotope effects which were employed as this ratio was interpreted. Fresh consideration of the several distinct sorts of secondary deuterium isotope effects which might be of importance in such thermal reactions seems clearly warranted.

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Synthetically Useful Dianions via Reductive Lithiation of Tetrahydrofurans by Aromatic Radical Anions

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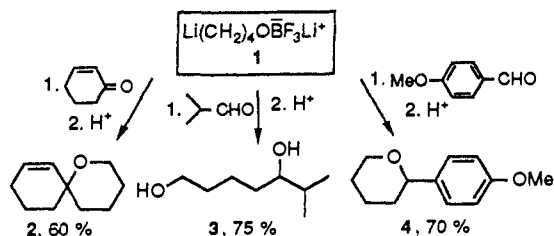
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Reductive cleavages of epoxides¹ (at -78 °C) and oxetanes² (at 0 °C) by lithium 4,4'-di-*tert*-butylbiphenylide³ (LDBB) provide β -lithio- and γ -lithioalkoxides, respectively. Reaction of the latter with carbonyl compounds results in pentaspiroannulation to substituted tetrahydrofurans or spiroacetals.^{2,4} It would be very useful if the six-membered analogues of these heterocycles would be available from δ -lithioalkoxides generated by reductive lithiation of tetrahydrofurans (THFs). However, THFs cleave only at temperatures at which the resulting dianions do not survive.⁵

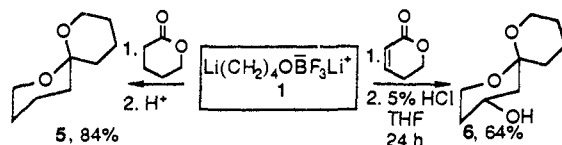
Reductive lithiations of epoxides and oxetanes are thought to involve transfer of an electron to an antibonding orbital (LUMO) of the heterocycle followed by ring cleavage to an intermediate possessing an oxyanion and a carbon radical.⁶ We now report two methods which greatly facilitate the reductive lithiation of THFs by stabilizing both the LUMO and the open-chain intermediate.

The first method involves complexation of the oxygen atom of THF by a Lewis acid. By inducing a formal positive charge on the oxygen atom, the acid should lower the energy of the σ^* orbital that accepts the electron. It should also stabilize the resulting open-chain oxyanion (e.g., the radical precursor of **1**). Gratifyingly, THF is found to be instantaneously cleaved by LDBB (2 equiv) in the presence of boron trifluoride etherate (1 equiv) at

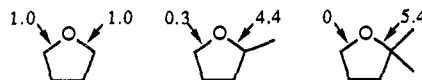
Scheme I



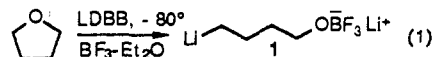
Scheme II



Scheme III



-80 °C, yielding 4-lithiobutoxide probably best represented by **1** (eq 1).⁷

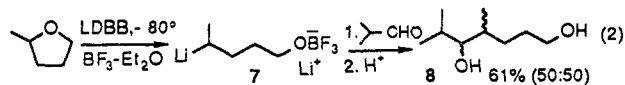


The experimental procedure requires dropwise addition of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (neat) to the preformed 0.4 M solution of LDBB in THF at -80 °C. The reaction is strongly exothermic, and its completion can easily be recognized by the color change of the solution from dark greenish-blue to dark red. We have found that the stability of **1** is limited even under such mild conditions, presumably because of transfer of the BF_3 from oxygen to carbon.⁹

Some reactions of **1** with aldehydes and ketones are shown in Scheme I. Those coupling products (1,5-diols) which are able to form stabilized carbocations can be easily cyclized to useful tetrahydropyrans, as demonstrated for 2-cyclohexen-1-one and 4-methoxybenzaldehyde.¹⁰

δ -Lithiobutoxides are particularly useful synthons in the preparation of [5,*n*] spiroketal units, compounds of great biological interest.⁴ Scheme II presents simple and efficient one-pot syntheses of the major and minor components (**5** and **6**) of the olive fruit fly pheromone. Our preparation of **6**, considering its simplicity and the ready availability of the starting materials, compares very favorably to alternative methods.¹¹ The successful monoaddition of **1** to lactones also indicates that the Lewis acid may help to prevent the opening of the initially formed lactolate ring acting in a manner similar to that of an oxophilic organocerium species.⁴

Whereas substituted epoxides and oxetanes in uncatalyzed reductive lithiations cleave predominantly so as to produce the most branched alcohol,^{1,2,6} the opposite regioselectivity is found in the BF_3 -induced reductive opening of 2-substituted THFs. 2-Methyltetrahydrofuran, also used as solvent, yields predominantly the most substituted carbanion **7** (eq 2). Scheme III



(7) Certain special 4-lithiobutoxides can be produced by reductive lithiation of 4-(phenylthio)- or 4-chloroalkoxides.^{4,8}

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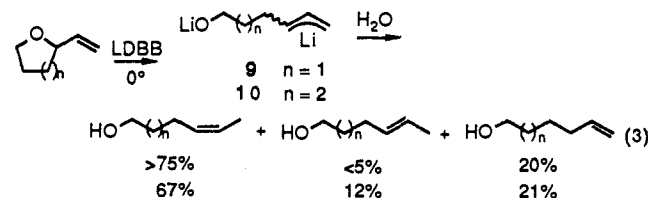
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indicates the relative rates of BF_3 -induced reductive cleavage of the C-O bonds of THFs with different degrees of 2-substitution. They were determined by using large excesses of equimolar quantities of THF and substituted THF followed by protonation of the generated dianions and GC estimation of the alcohols (80-90% yields) produced. In due course, we shall report our success in reversing the regiochemistry of reductive lithiation of substituted oxetanes² by the use of Lewis acids.

We then sought a solvent in which lithium radical anions can be generated but which is not reductively cleaved in the presence of BF_3 so that an expansion of this method to a wider variety of THFs would be possible. To date, a lithium biphenylide-dimethyl ether system has provided the best results,¹² and we were able to isolate the coupling product from the reaction of isobutyraldehyde with our model dianion derived from 2,2-dimethyltetrahydrofuran in a modest 42% yield.

The second method of lowering the energy of the THF LUMO and stabilizing the open-chain radical anion is to append an alkenyl group to the 2-position of the ring. We reasoned that π^* orbitals are lower in energy than σ^* orbitals, that bond rotations would allow the π^* orbital to become parallel to the C-O bond that was cleaving, and that allylic resonance would stabilize the ring-cleaved radical. Encouraging precedents were the reductive cleavage of 4-phenyl-1,3-dioxanes¹³ and the production of benzyl lithium by reductive lithiation of benzyl ethyl ether.^{14,15}

The starting materials were synthesized in 50-70% yield either by employing the previously reported² one-pot procedure involving the addition of γ -lithioalkoxides (generated from oxetanes) to α,β -unsaturated carbonyl compounds followed by acid-induced ring closure of the resulting 1,4-diols,¹⁶ or by treating 2-bromotetrahydrofuran or 2-bromotetrahydropyran with vinylmagnesium bromide.¹⁷ The reductive cleavages of 2-vinyltetrahydrofuran and 2-vinyltetrahydropyran by LDBB in THF were rapid at 0 °C and produced the corresponding terminal oxyallylic dianions **9** and **10**. In both cases the major isolated product after protonation was the (*Z*)-alkenyl alcohol (eq 3), reflecting the predominant existence of terminal *cis*-allyllithiums in THF under thermodynamic conditions.^{18a}



Techniques recently reported from this laboratory¹⁸ can be used to attain excellent regiochemical and stereochemical control in reactions of isobutyraldehyde with the dianion **11** resulting from reductive cleavage of 4,4-dimethyl-2-vinyltetrahydrofuran. Thus, transmetalation with CeCl_3 resulted overwhelmingly (98.7:1.3) in reaction at the least substituted allylic terminus, providing the *cis* olefin **12** and only a trace of the *trans* isomer. Alternatively, the use of titanium isopropoxide gave very largely (regiochemical control 89:11) **13** resulting from attack on the other terminus; as expected,¹⁹ the intermediate *trans*-allyltitanium, with the bulky metal σ -bond to the least substituted terminus, resulted in an

(12) Solutions of LDBB, 0.2 M, could sometimes be generated in dry, deoxygenated DME under ultrasonication, but the reproducibility of this process was low; reactions of lithium and DBB in tetrahydropyran were sluggish and stopped at $\approx 20\%$ conversion.

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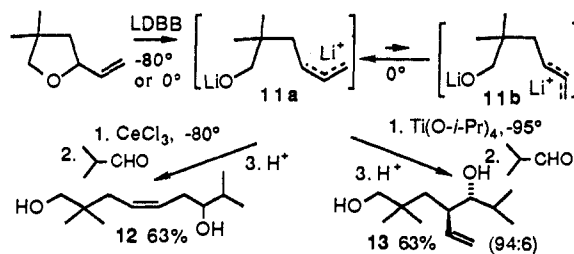
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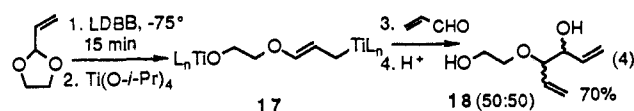
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Scheme IV



almost completely anti configuration of **13** (Scheme IV). The somewhat similar results obtained with other 2-vinyltetrahydrofurans will be chronicled in the full paper.

Preliminary experiments indicate that some cyclic ethylene acetals of enals can also be reductively lithiated by LDBB in THF. The resulting α -alkoxyallyl systems, after transmetalation with Ti^{IV} and trapping with α,β -unsaturated aldehydes and ketones, yield 4-alkoxy 1,5-dien-3-ols such as **18** (e.g., eq 4), starting materials for the anionic oxy-Cope rearrangement.²⁰



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Supplementary Material Available: Sample procedures for generation of δ -lithioalkoxides and terminal oxyallylic dianions and for their reactions with electrophiles and the spectral data of the products (3 pages). Ordering information is given on any current masthead page.

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Kinetic and Thermodynamic Stability of α -Azidobenzyl Carbocations: Putative Intermediates in the Schmidt Reaction

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We report here the first direct demonstration of the formation of α -azido-stabilized carbocations. The azido group is one of the most versatile functionalities in organic chemistry.¹ As a substituent it stabilizes developing positive or negative charge at an adjacent carbon and thereby accelerates both electrophilic and nucleophilic aromatic substitution reactions.² The thermodynamically favorable loss of nitrogen from the azido group drives several rearrangement reactions.³ Azide ion is a good leaving group in $\text{S}_{\text{N}}1$ reactions⁴ and also a reactive nucleophile for capture of carbocations.^{5,6} Recent calculations predict that α -azido carbocations are highly stabilized by resonance electron donation

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