

Free Radical Mediated Reduction and Deoxygenation of Epoxides

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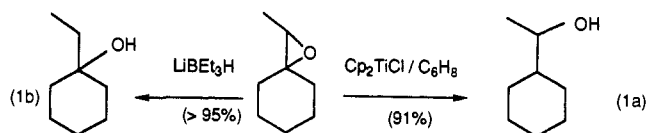
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Because of the ease with which they are generated from unsaturated as well as polyhydroxylic substrates and the stereochemical predictability in their reactions, epoxides play a key role as intermediates in organic synthesis.¹ We have previously shown that radicals generated by reaction of epoxides with paramagnetic Cp_2TiCl can participate in both intramolecular (hex-5-enyl cyclization)^{2a} and intermolecular^{2b} addition reactions. Here we report that the radicals generated this way can also serve as intermediates in an overall reduction or deoxygenation of the epoxide as shown in Scheme I.

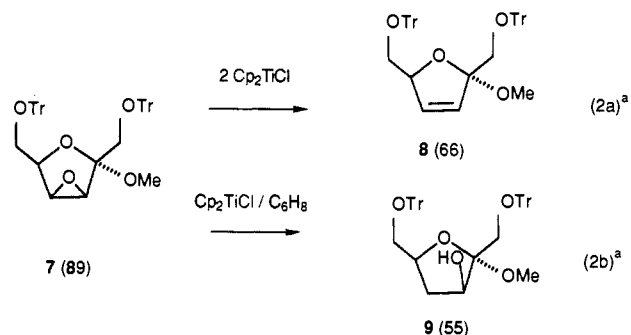
The radical formed upon treating an epoxide with Cp_2TiCl can be trapped by a H atom donor such as cyclohexa-1,4-diene leading to an overall reduction. Since the regio- and stereochemistry of the ring opening will be guided by the relative stability of the intermediate radicals rather than the ease of approach of the hydride reagent such as in the classical $\text{S}_{\text{N}}2$ -type reduction conditions,^{3a} we would expect different product distributions under these conditions.^{3b,c} These expectations have been borne out, and in this communication we report our preliminary results in this area. We also report applications of related chemistry for the deoxygenation of highly functionalized epoxides including epoxy nucleosides. The resulting compounds are potential intermediates for the synthesis of dideoxy nucleosides used in anti-AIDS chemotherapy.⁴

Dropwise addition of 1.05 equiv of a THF solution of Cp_2TiCl to a mixture of 1,1'-epoxyethylcyclohexane and 10 mmol of cyclohexa-1,4-diene in THF at room temperature followed by acidic (1 N HCl) workup yielded 92.0% of 1-cyclohexylethanol. Minor amounts (1.5% and 0.9% respectively) of 1-ethyl-1-cyclohexanol and 1-(1-chlorocyclohexyl)ethanol were also isolated. With lithium triethylborohydride, as expected, the only product formed is 1-ethyl-1-cyclohexanol (eq 1a,b).



Functional-group compatibility and further applications of this mild reduction procedure are illustrated by the reactions of adenosine epoxide **3**^{5a} (Scheme II). Whereas the LiEt_3BH reduction of **3a** gives exclusively **4a**,^{5b} the titanium-mediated reduction gives, in addition, the 2'-deoxy derivative, **5a**.^{5c} Varying amounts (up to 15%) of a deoxygenation product (**6a**) are also obtained under the reaction conditions. This product arises from the competitive electron transfer reduction of the intermediate radical by the Ti^{3+} species followed by elimination of the β leaving group. Indeed, as shown in Scheme II, **6** can be made the exclusive product (69% yield) by carefully adding the epoxide in THF to an excess (2.1 equiv) of the titanium reagent at room temperature.⁶ It should be noted that the reaction is compatible with amino and benzamido groups. For comparison, the super hydride reduction of **3b** removes the benzoyl protecting group from the amine. These results along with the previously demonstrated compatibility^{2a,b} with several other groups including ester groups make this Ti reagent a unique reducing agent.

Important applications of this methodology may be in the carbohydrate area where the Mitsunobu reaction^{7a-c} provides an exceptionally short synthesis of various epoxides. Interesting chiral synthons may now be prepared from these epoxides by the Ti-mediated reactions. For example, deoxygenation of methyl furanoside **7c** cleanly yields 66% of the corresponding olefinic product, **8**, a very sensitive compound that has been the target of an extensive, yet unsuccessful, synthetic effort⁸ (eq 2a,b).



* see scheme 2

Reduction of **7** yields the 4-deoxy derivative **9** under both $\text{S}_{\text{N}}2$ and radical reduction conditions. Likewise, reduction of the anhydro sugar **10**^{9d} gives **11**⁹ and **12**⁹ in a ratio of 5:1. The former is the exclusive product of reduction with super hydride. Deoxygenation, as expected, yields two olefins (**13**¹⁰ and **14**¹⁰ in a ratio

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(6) McMurry has reported the use of $\text{TiCl}_3/\text{LiAlH}_4$ for the deoxygenation of epoxides. The compatibility of this and other related reagent systems (see the following references and ref 11) with sensitive substrates such as **3** remains to be established. McMurry, J. E.; Silvestri, M. G.; Fleming, M. P.; Hoz, T.; Grayston, M. W. *J. Org. Chem.* **1978**, 43, 3249. See also: van Tamelen, E. E.; Gladysz, J. A. *J. Am. Chem. Soc.* **1974**, 96, 5290. Schobert, R. *Angew. Chem., Int. Ed. Engl.* **1988**, 27, 855 and references cited therein. Berry, M.; Davies, S. G.; Green, M. L. H. *J. Chem. Soc., Chem. Commun.* **1978**, 99. For a review of low valent Ti reagents in synthesis, see: Lenoir, D. *Synthesis* **1989**, 883.

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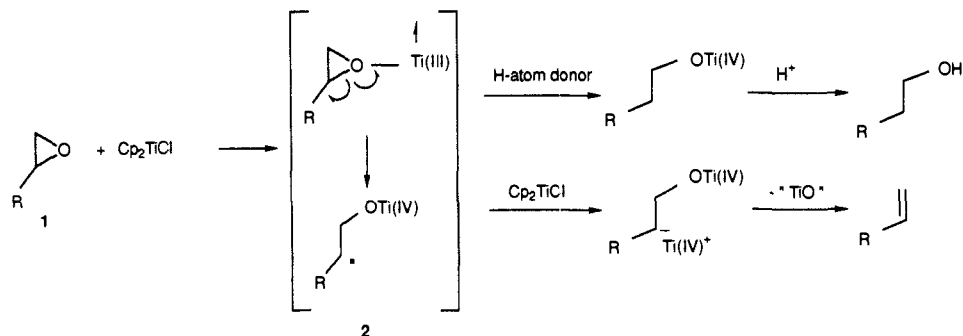
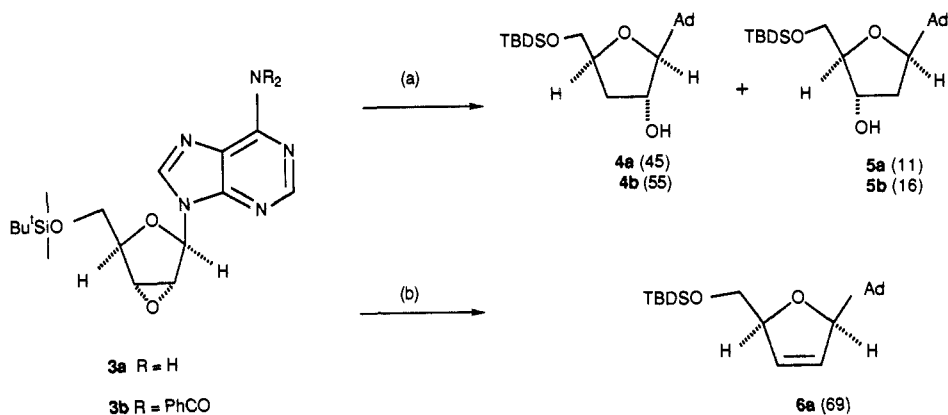
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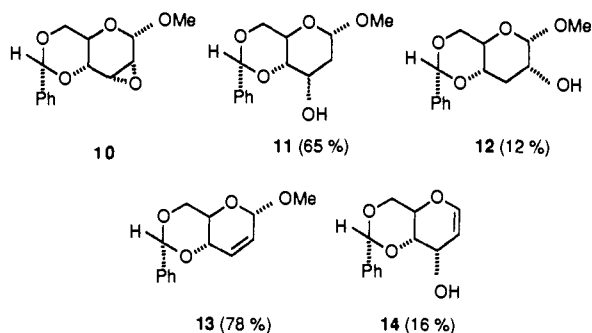
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Scheme I

Scheme II. Reduction and Deoxygenation of Adenosine Epoxide^a

^a (a) $\text{Cp}_2\text{TiCl}/\text{cyclohexa-1,4-diene}/\text{room temperature}$. (b) $2\text{Cp}_2\text{TiCl}/\text{room temperature}$; % yields shown in brackets.

of 5:1) arising from the β -eliminations of either the Ti-oxo or the OMe species, with the former predominating.



One limitation of this reduction protocol is revealed in the attempted reduction of monosubstituted terminal epoxides like 1,2-epoxydecane where up to 33% deoxygenation is observed even in the presence of a 10-fold excess of 1,4-cyclohexadiene. This may be due to the accessibility of the sterically unencumbered secondary/primary radicals to the Ti^{3+} species resulting in further electron transfer reduction and subsequent deoxygenation rather than H atom transfer from cyclohexa-1,4-diene.

Finally, this deoxygenation reaction appears to be mechanistically different from the stereospecific low-valent W-mediated reaction reported by Sharpless et al.¹¹ Addition of either *cis*- or *trans*-5-decene oxide to excess Cp_2TiCl afforded an identical 73:27 mixture of *cis*- and *trans*-5-decenes. The mechanistic details of this reaction remain largely unknown except that the β -eliminations of alkoxides and the need for 2 equiv of Ti^{3+} suggest that

the reaction proceeds via carbanion-like intermediates.

Supplementary Material Available: Details of typical experimental procedures and ^1H NMR, HRMS, and/or elemental analysis of new compounds (7 pages). Ordering information is given on any current masthead page.

Self-Assembly Based on the Cyanuric Acid-Melamine Lattice¹

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Reaction of cyanuric acid (CA) with melamine (M) forms a stable, insoluble 1:1 complex $\text{CA}\cdot\text{M}$.³ We, and others, believe that $\text{CA}\cdot\text{M}$ has a local structure represented by the lattice 1.⁴ We have started a program in the design and synthesis of three-dimensional supramolecular assemblies based on the hydrogen-bonding pattern of $\text{CA}\cdot\text{M}$. This program is an extension of the strategy of molecular self-assembly that has been highly successful in forming quasi-two-dimensional monolayers on solid supports.⁵

(1) Supported by the National Science Foundation (Grants CHE-88-12709 to G.M.W. and DMR 86-14003 to the Harvard University Materials Research Laboratory).

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