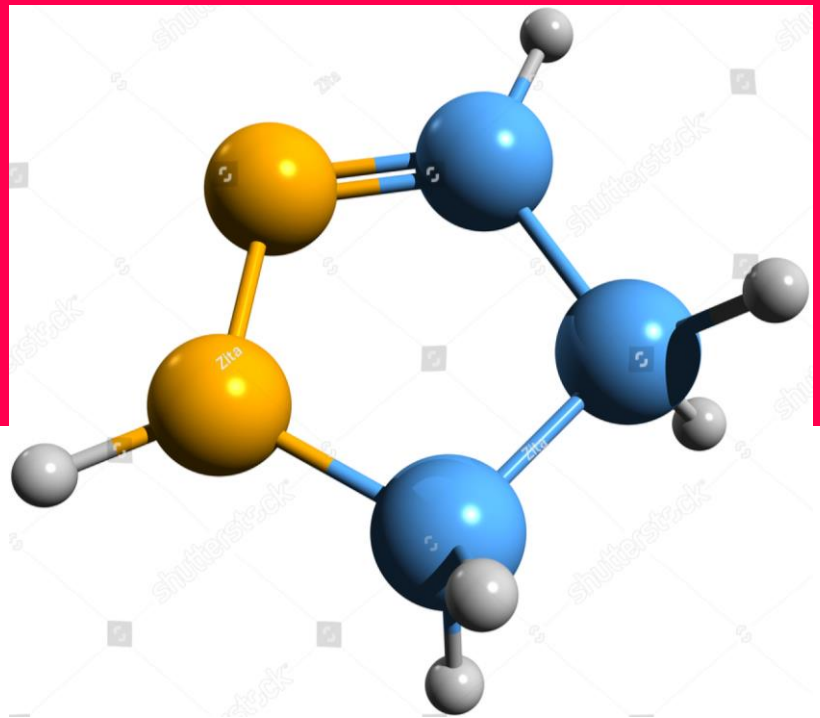


6. Small heterocyclic rings (Epoxides)



by

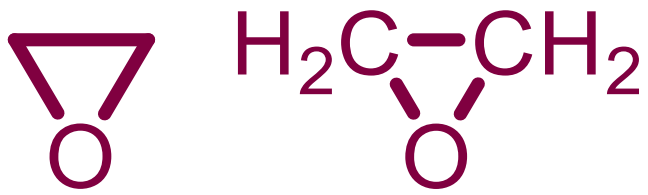
Mohamed M. Khalifa

2nd year

2nd semester

Epoxides

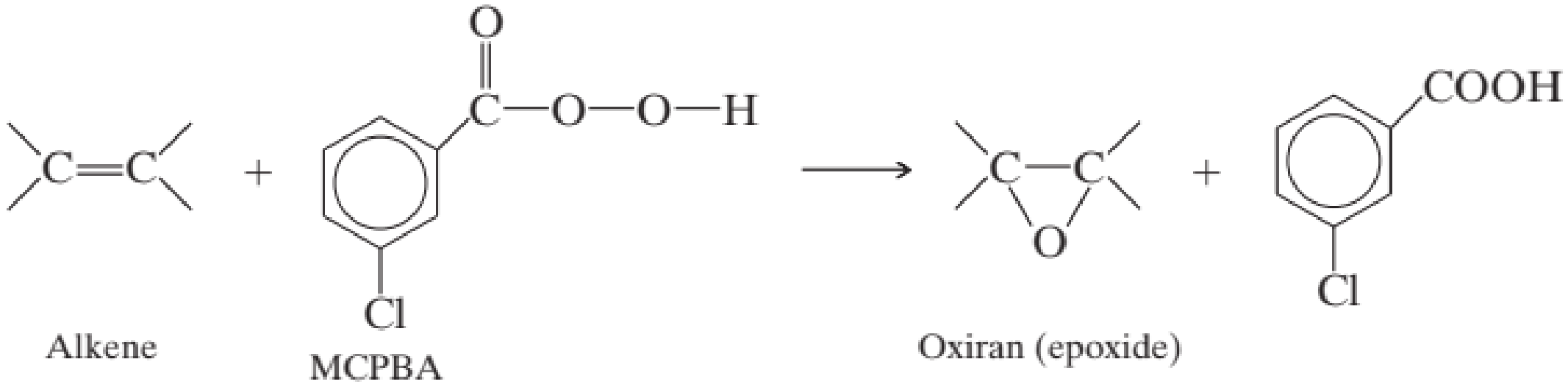
- **Epoxides are compounds containing a three-membered ring with oxygen as a heteroatom.**



- **The IUPAC name of such rings is oxiran.**
- **They are cyclic ethers.**
- **The three-membered ring gives them unusual properties that make them exceedingly important class of compounds having numerous synthetic applications.**

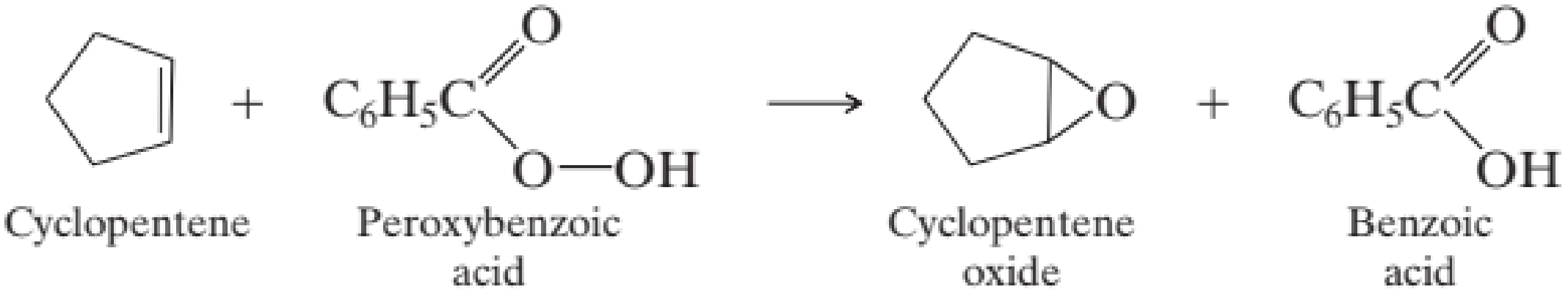
- **Synthesis of Epoxides**

1. **Epoxide is generally synthesized by the oxidation of a C=C bond of alkenes with peracids like *m*-chloroperbenzoic acid (MCPBA).**



- **Synthesis of Epoxides**

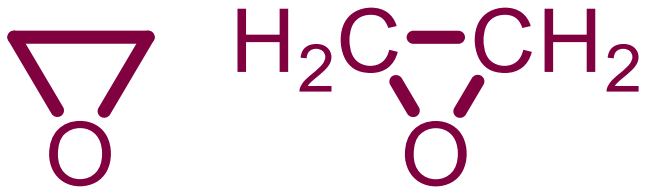
2. When allowed to stand in ether or chloroform solution, the peroxy acid and the unsaturated compound—which need not be a simple alkene—react to yield benzoic acid and the epoxide.



Reactions of Epoxides

- **Reactions of Epoxides are very important. Why????**

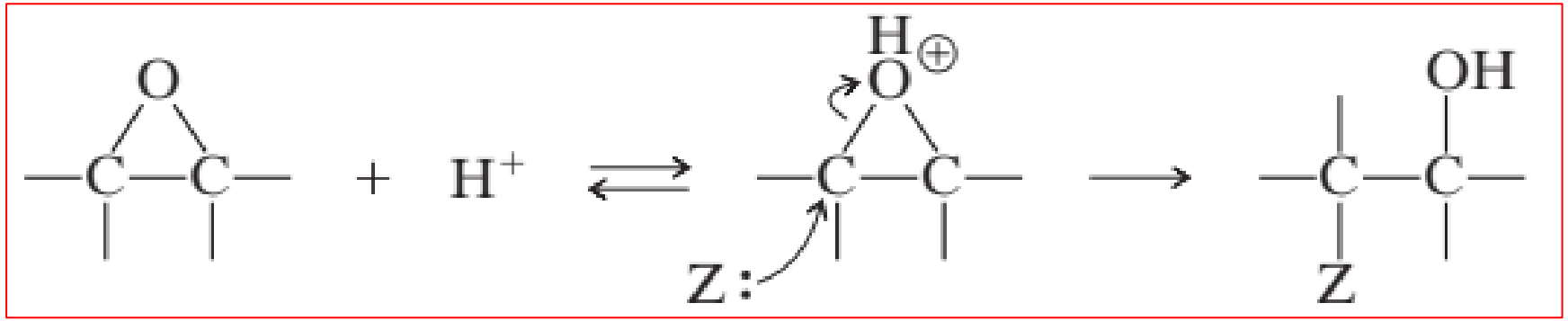
✓ **Due to the ease of opening of the highly strained three-membered ring.**



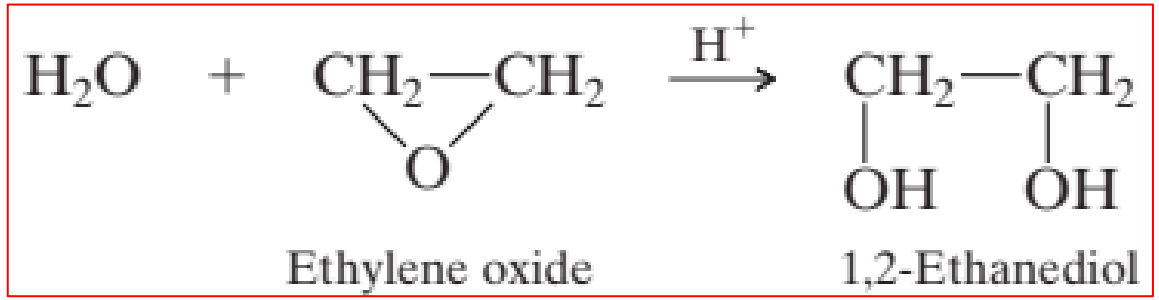
- **Some of their important reactions:**

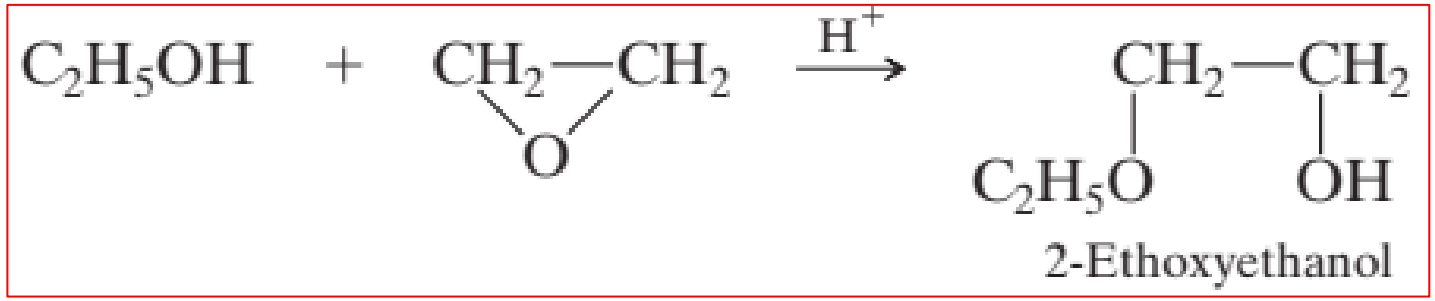
1. **Acid-catalyzed reactions with extreme ease.**
2. **Unlike ordinary ethers Epoxides can even be cleaved by bases.**
3. **They can react with Grignard reagents.**

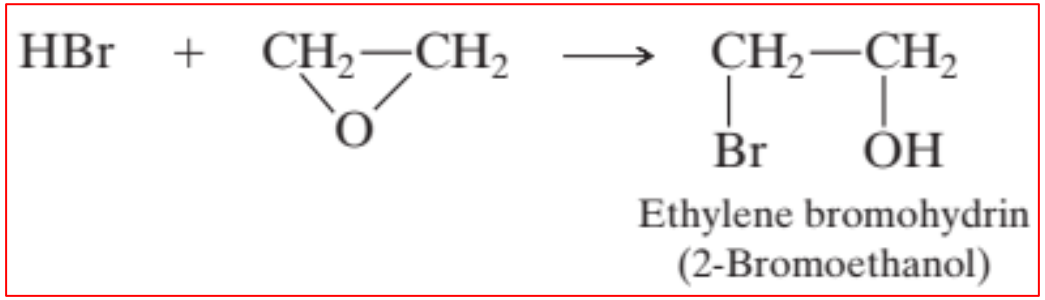
1. Acid-catalyzed reactions



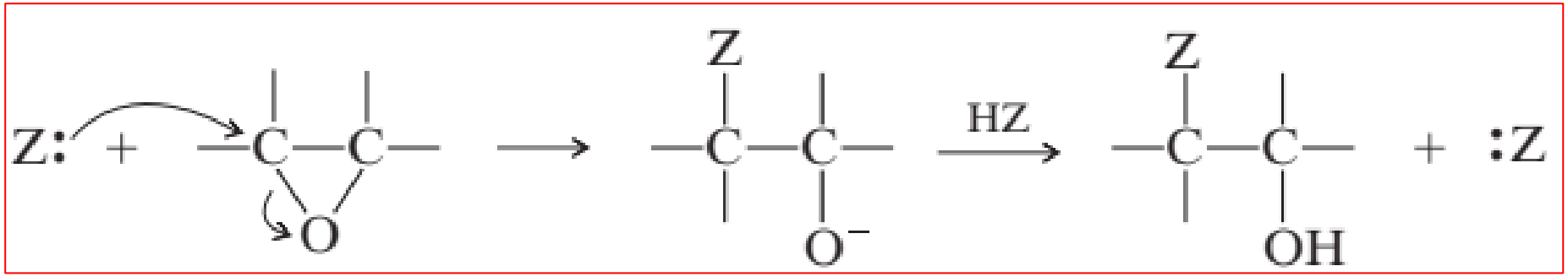
- **Examples**



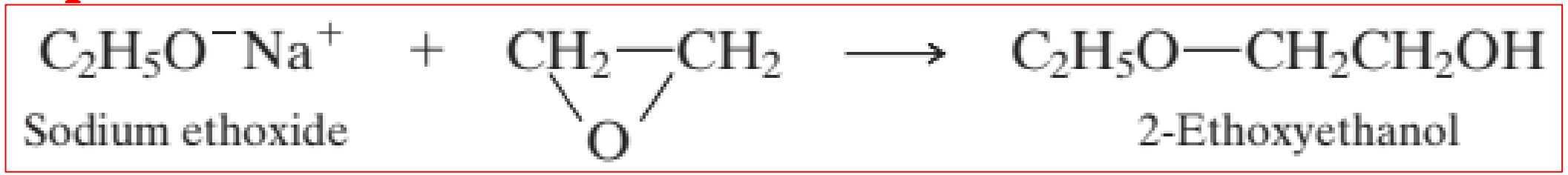


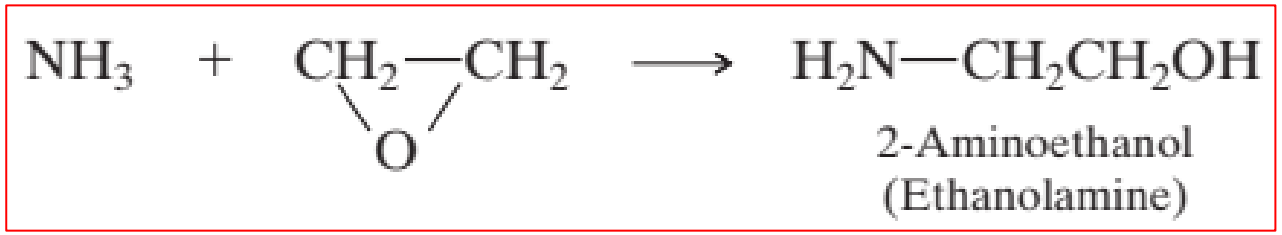


2. Base-catalyzed cleavage

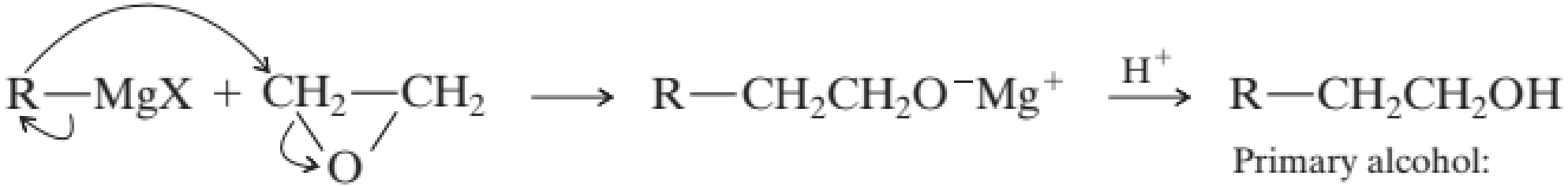


- **Examples**



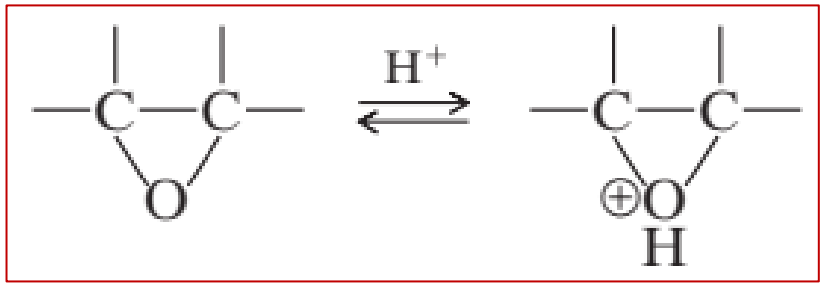


3. Reaction with Grignard reagents.



1. Acid-catalyzed cleavage of epoxides. anti-Hydroxylation

- **Step 1:** an epoxide is protonated by acid;

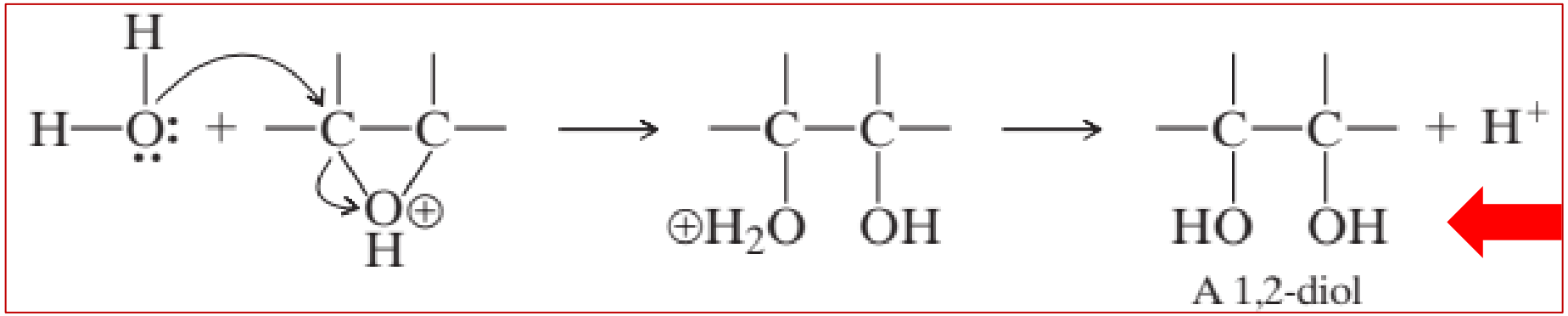


- **Step 2:** the protonated epoxide can then undergo attack by any of several nucleophilic reagents.

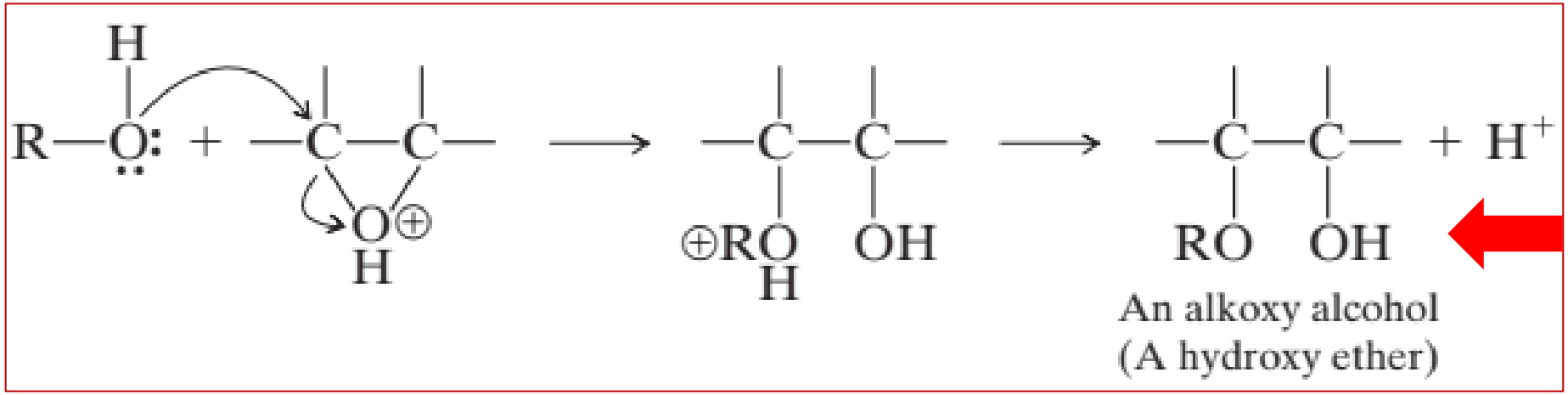
The product compounds contain two functional groups

1. Acid-catalyzed cleavage of epoxides. anti-Hydroxylation

Epoxide + water yields a 1,2-diol

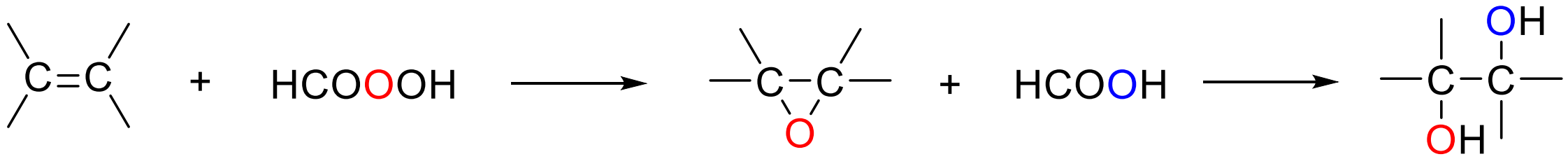


Epoxide + alcohol yields a compound that is both ether and alcohol



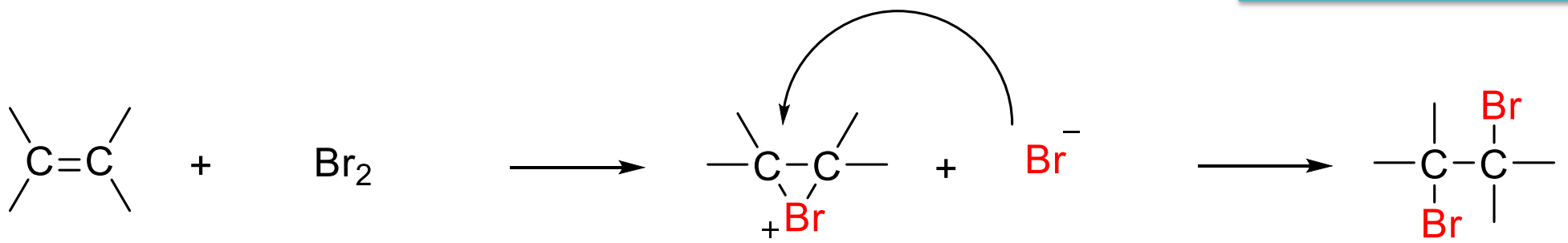
- **The two-stage process of epoxidation followed by hydrolysis is stereoselective, and gives 1,2-diols corresponding to *anti*-addition to the carbon-carbon double bond.**
- **Exactly the same stereochemistry was observed for hydroxylation of alkenes by peroxyformic acid—and for good reason: an epoxide is formed there, too, but is rapidly cleaved in the acidic medium, formic acid.**

المعادلة للتوضيح فقط



- **The interpretation is exactly the same as that given to account for *anti*-addition of halogens; indeed, epoxides and their hydrolysis served as a model on which the halonium ion mechanism was patterned.**

المعادلة للتوضيح فقط



halonium ion

Hydroxylation of alkenes with peroxy Acids gives *anti*-addition

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Hydroxylation of alkenes with permanganate gives *syn*-addition

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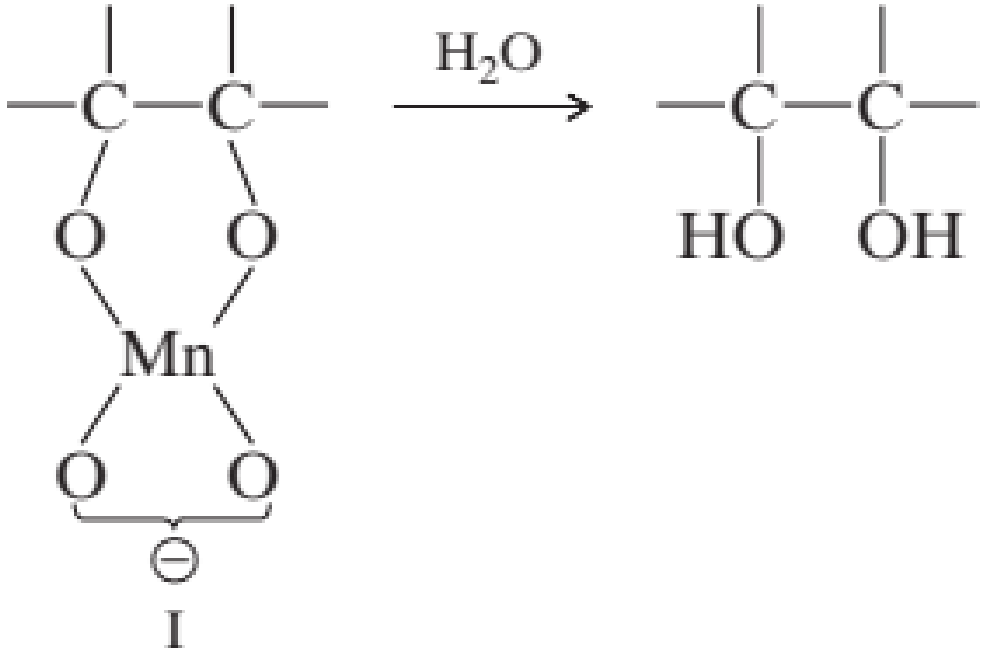
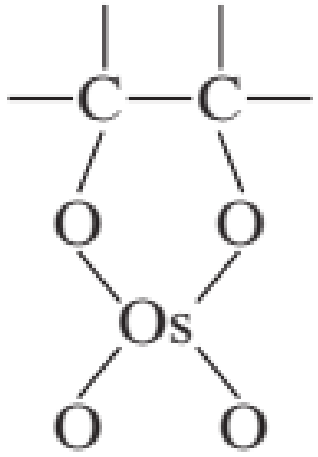
- To account for this stereochemistry it has been suggested that an intermediate like I is involved:



I

- **Hydrolysis of such an intermediate would yield the *cis* diol.**

- **This mechanism is supported by the fact that osmium tetroxide, OsO_4, which also yields the *cis* diol, actually forms stable intermediates of structure II.**

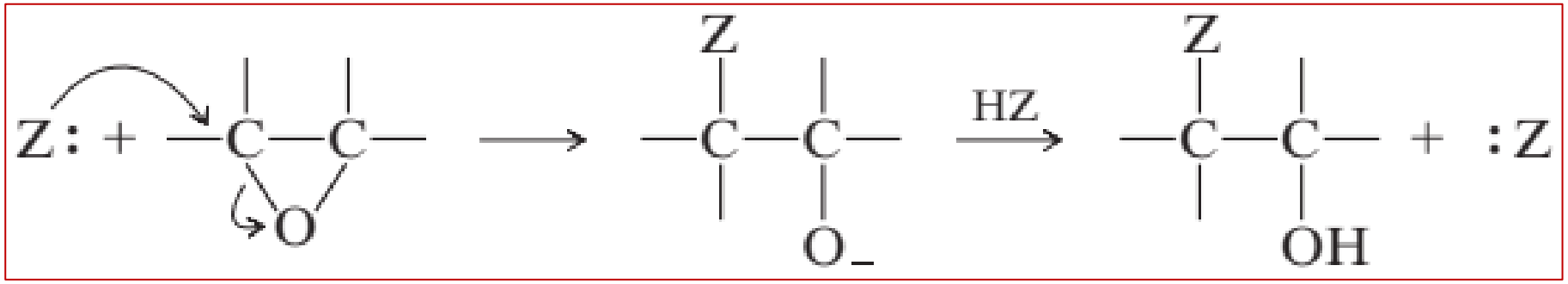


II

Thus, the two methods of hydroxylation—by peroxy acids and by permanganate-differ in stereochemistry because they differ in mechanism.

2. Base-catalyzed cleavage of epoxides

- **Unlike ordinary ethers, epoxides can be cleaved under alkaline conditions.**
- **Here it is the epoxide itself, not the protonated epoxide, that undergoes nucleophilic attack:**



- **The lower reactivity of the non-protonated epoxide is compensated for by the more basic, more strongly nucleophilic reagents that are compatible with the alkaline solution: alkoxides, phenoxides, ammonia.**

2. Base-catalyzed cleavage of epoxides

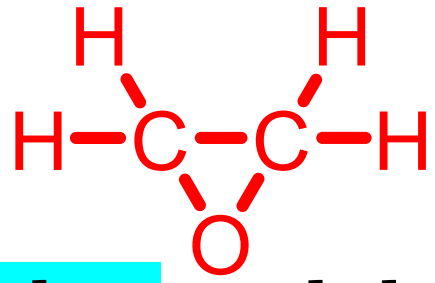
- **Like alkyl halides and sulfonates, and like carbonyl compounds, epoxides are an important source of electrophilic carbon.**
- **Electrophilic carbon is highly susceptible to attack by a wide variety of nucleophiles.**
- **(Epoxides generated from carcinogenic hydrocarbons are even attacked by the nucleophilic portion of the genetic material DNA and thereby induce mutation and tumors.)**

2. Base-catalyzed cleavage of epoxides

Problem 16.23 Write equations for the reaction of ethylene oxide with: (a) methanol in the presence of a little H_2SO_4; (b) methanol in the presence of a little $CH_3O^-\ Na^+$; (c) methylamine, CH_3NH_2.

3. Orientation of cleavage of epoxides

- **There are two carbon atoms in an epoxide ring and, in principle, either one can suffer nucleophilic attack.**
- **In a symmetrical epoxide like ethylene oxide, the two carbons are equivalent, and attack occurs randomly at either.**

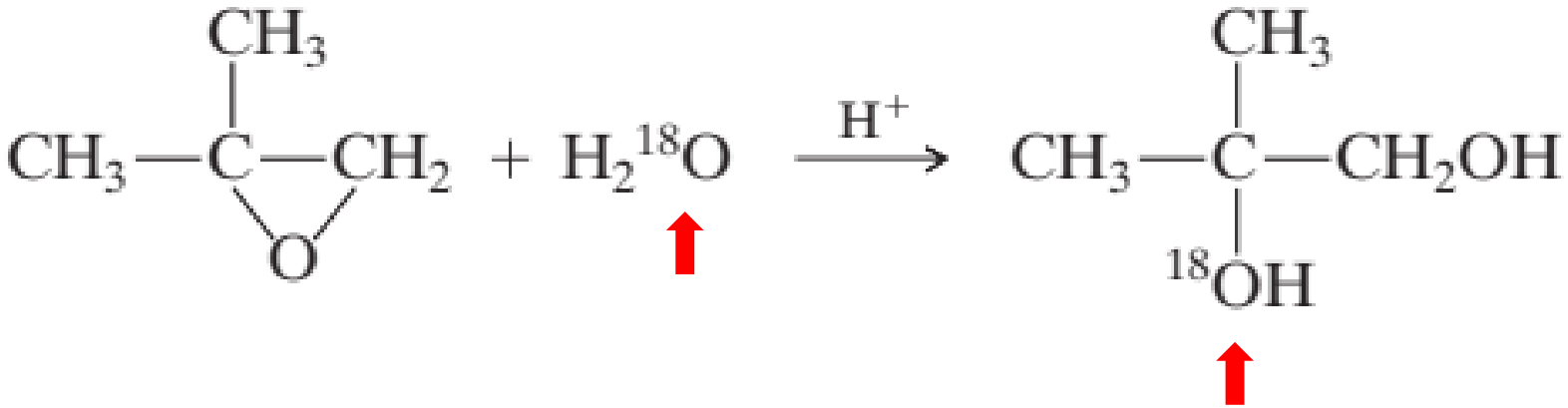


- **In an unsymmetrical epoxide, the carbons are not equivalent, and the product we obtain depends upon which one is preferentially attacked.**

The preferred point of attack depends chiefly on whether the reaction is acid-catalyzed or base-catalyzed.

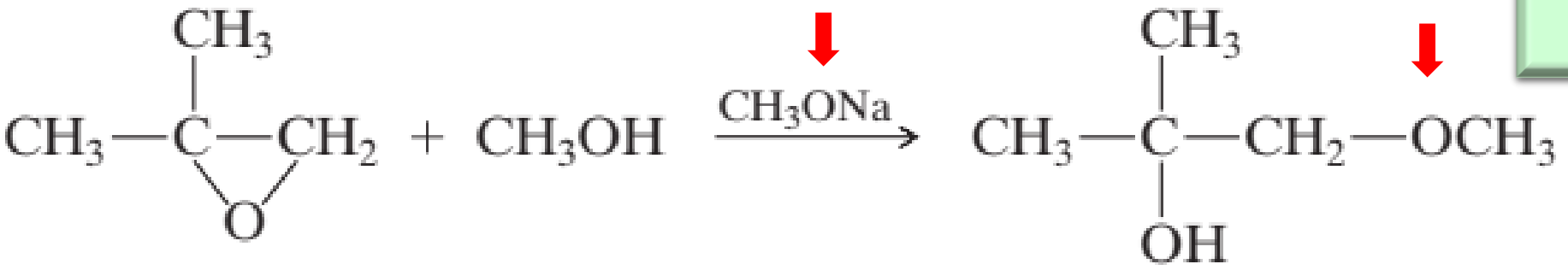
- **Consider, for example, two reactions of isobutylene oxide:**

✓ **In Acid catalyzed cleavage**



Nu⁻ attacks the more substituted carbon

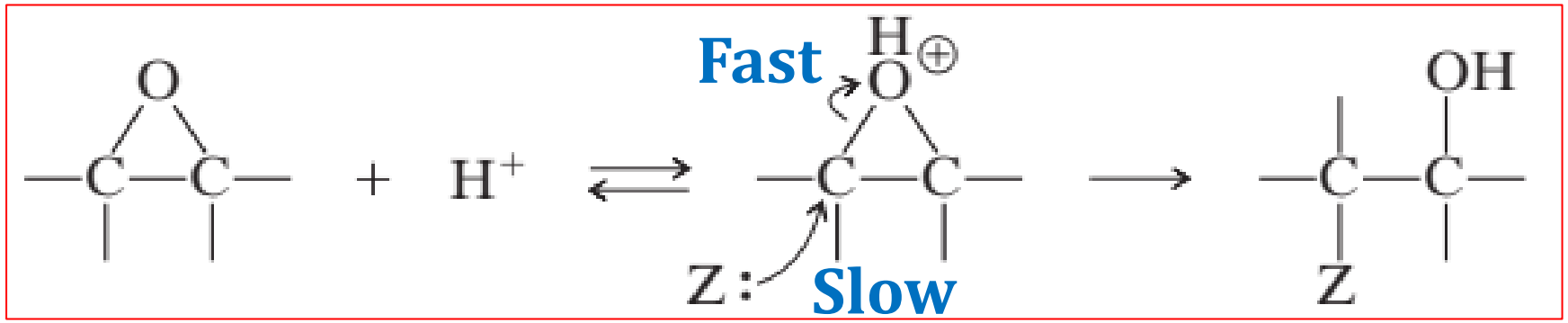
✓ **In Base catalyzed cleavage**



Nu⁻ attacks the less substituted carbon

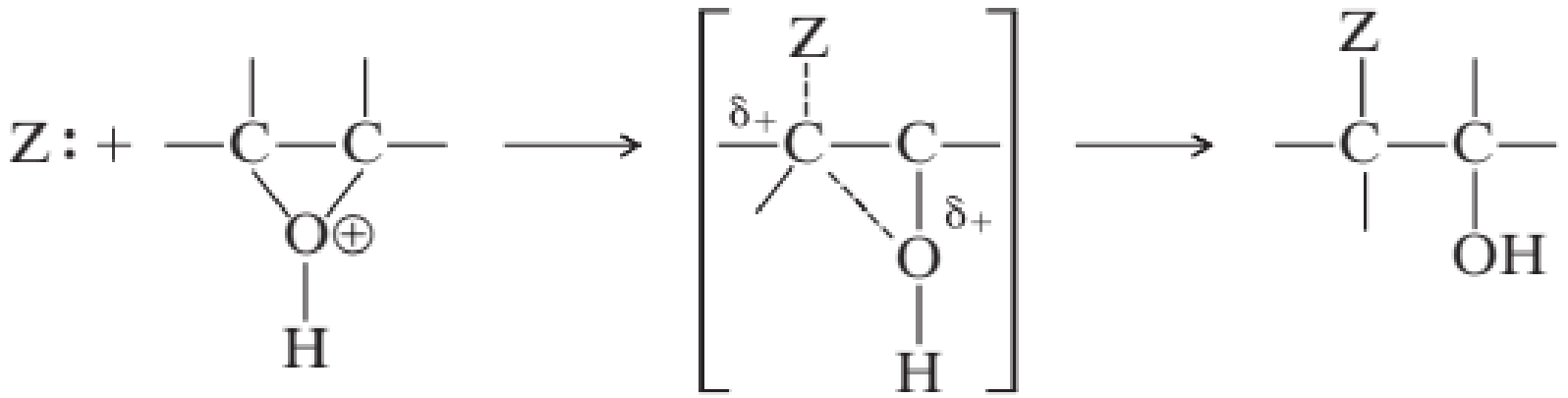
- **Here, as in general, the nucleophile attacks the more substituted carbon in acid catalyzed cleavage, and the less substituted carbon in base-catalyzed cleavage.**
- **Our first thought is that two different mechanisms are involved here, S_N1 and S_N2.**
- **But the evidence indicates that both are of the S_N2 type.**
- **S_N2 means that cleavage of the carbon-oxygen bond and attack by the nucleophile occur in a single step.**
- **How, then, are we to account for the difference in orientation—in particular, for S_N2 attack at the *more hindered* position in acid-catalyzed cleavage?**

- In the transition state of most S_N2 reactions, bond-breaking and bond-making have proceeded to about the same extent, and carbon has not become appreciably positive or negative; as a result steric factors, not electronic factors, chiefly determine reactivity.
- But in acid-catalyzed cleavage of an epoxide, the carbon-oxygen bond, already weak because of the angle strain of the three-membered ring, is further weakened by protonation: the leaving group is a very good one, the weakly basic alcohol hydroxyl.



- **The nucleophile, on the other hand, is a poor one (water, alcohol).**
- **In the transition state bond-breaking has proceeded further than bond-making, and carbon has acquired a considerable positive charge.**
- **Since both leaving group and nucleophile are far away, crowding is relatively unimportant.**
- **The stability of the transition state is determined chiefly by *electronic factors* and not steric factors, and the reaction has considerable S_N1 character.**
- **Attack occurs at the carbon that can best accommodate the positive charge.**

Acid-catalysed S_N2 cleavage

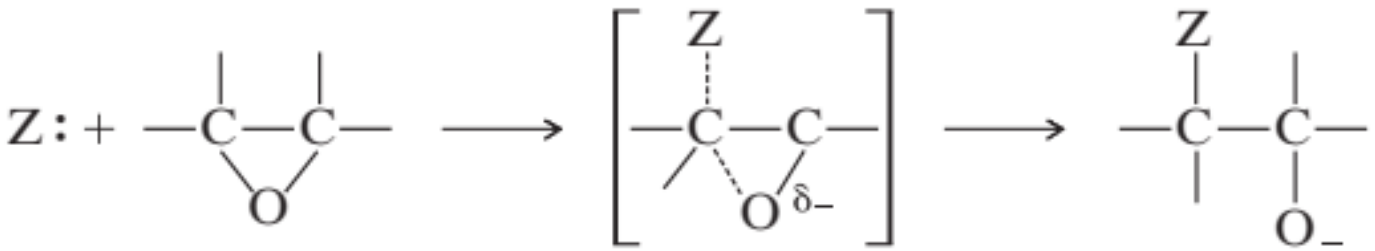


Bond-breaking exceeds bond-making:

Positive charge on carbon

- **In base-catalyzed cleavage, the leaving group is a poorer one—a strongly basic alkoxide oxygen—and the nucleophile is a good one (hydroxide, alkoxide).**
- **Bond breaking and bond-making are more nearly balanced, and reactivity is controlled in the more usual way, *by steric factors*.**
- **Attack occurs at the less hindered carbon.**

Base-catalysed S_N2 cleavage



Bond-making balances bond-breaking:
no particular charge on carbon