Nucleophilic Neighboring Group Participation

Case I:

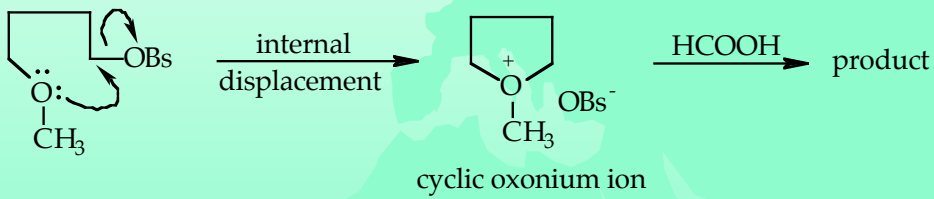
Consider the following data: 

Compound #	R—OBs	$k_{relative}$ (75°C)
1	$CH_3(CH_2)_2CH_2$-OBs	1.00 (reference)
2	$CH_3OCH_2CH_2OBs$	0.10
3	$CH_3OCH_2CH_2CH_2OBs$	0.33
4	**$CH_3OCH_2CH_2CH_2CH_2OBs$**	**461.0**
5	**$CH_3O(CH_2)_4CH_2OBs$**	**32.6**
6	$CH_3O(CH_2)_5CH_2OBs$	1.13

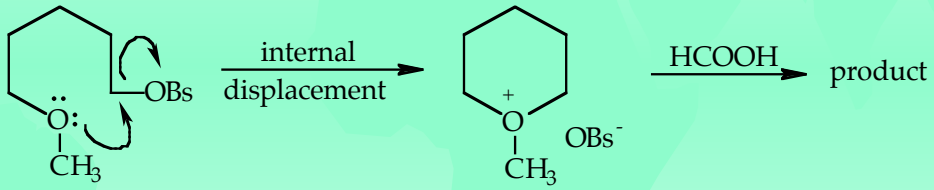
Nucleophilic Neighboring Group Participation

Case I: Rationale

Rationale to explain enhanced rates of substitution for compounds 4 & 5:



cyclic oxonium ion



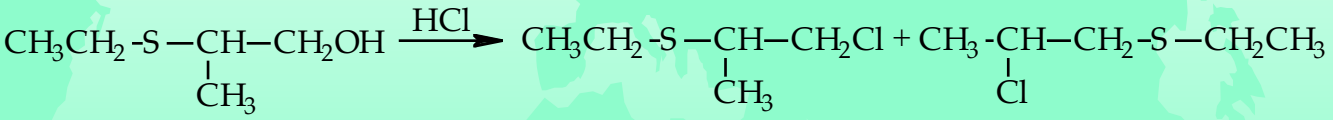
cyclic oxonium ion

In addition to the available S_N2 pathway, a more favorable alternate pathway for displacement of brosylate is possible for compounds 4 & 5. The internal displacement pathway leads to the formation of relatively stable 5- and 6-membered cyclic oxonium salts. As the chain length increases, the likelihood of cyclic oxonium ion formation diminishes, and rates approach that of the reference case where only S_N2 attack by HCOOH is possible.

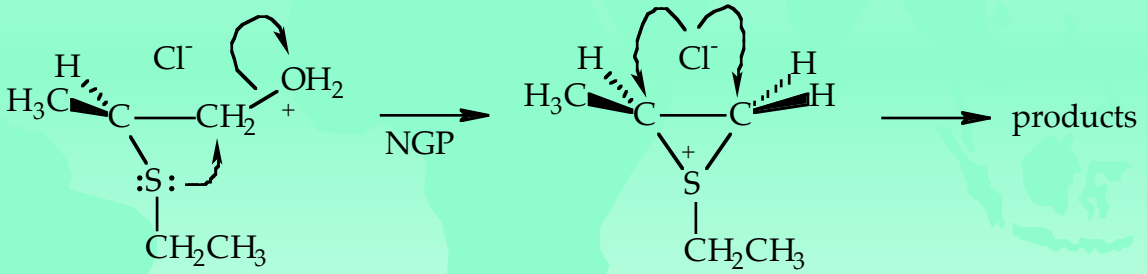
Nucleophilic NGP

Case II

Consider the following:



Rationale:



An S_N1 pathway leading to a primary carbocationic intermediate is not as favorable as a neighboring group participation (internal displacement) pathway leading to an episulfonium ion intermediate.

NUCLEOPHILIC NGP

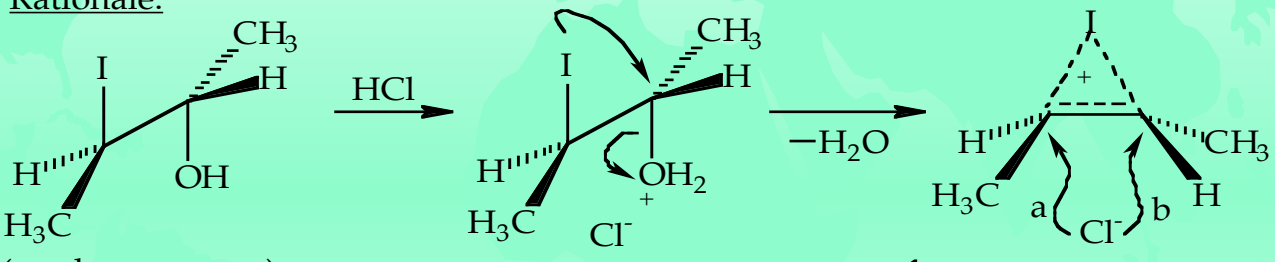
CASE III

Consider the following:

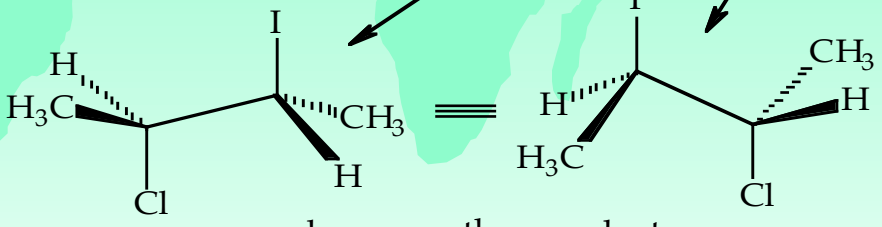
(erythro)-3-iodo-2-butanol $\xrightarrow{HCl}$ (erythro)-2-chloro-3-iodobutane (only product)

(threo)-3-iodo-2-butanol $\xrightarrow{HCl}$ (threo)-2-chloro-3-iodobutane (only product)

Rationale:



(erythro reactant)



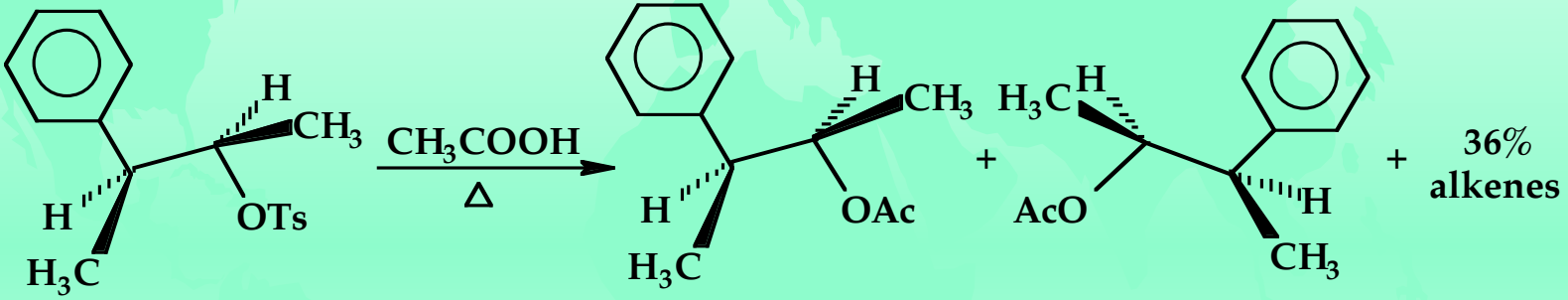
only one erythro product

Likewise, for threo reactant, only one threo product is obtained. In both erythro and threo reactions, neighboring group participation by an iodonium ion intermediate is more favorable than formation of an open carbocationic intermediate.

"Non-nucleophilic" NGP

Acetolysis of Phenyl tosylates

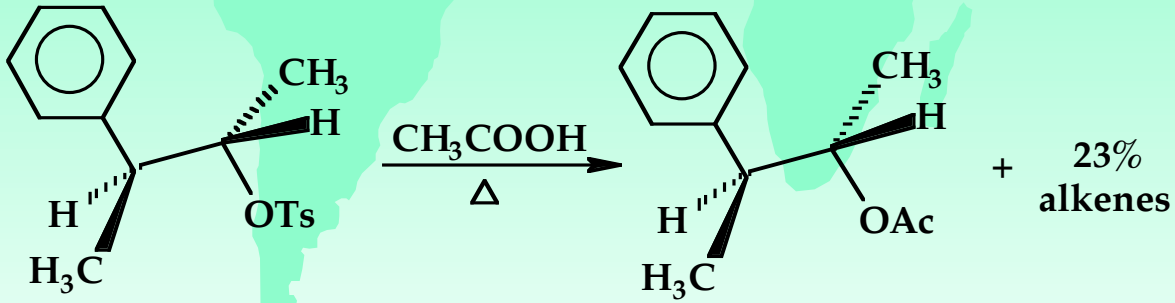
Consider the following:



L-threo-3-phenyl-2-butyl tosylate

L-threo-3-phenyl-2-butyl acetate (32%)

D-threo-3-phenyl-2-butyl acetate (32%)



L-erythro-3-phenyl-2-butyl tosylate

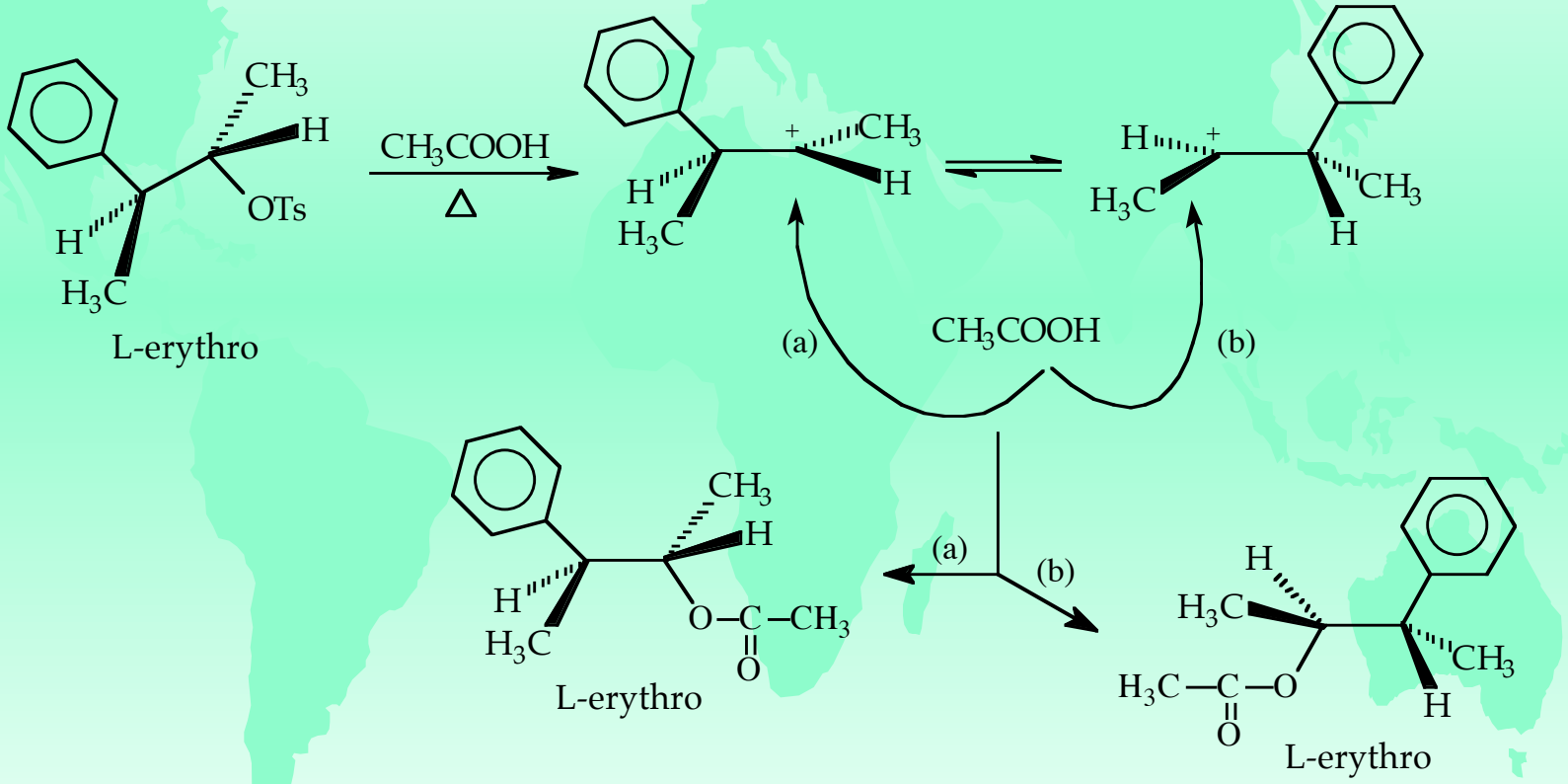
L-erythro-3-phenyl-2-butyl acetate

Possible explanations for the results of the acetolysis reactions

- **Direct bimolecular nucleophilic attack at C-2**
  - **Inconsistent with the experimental data. Why?**
- **Formation of a secondary carbocation at C-2**
  - **Inconsistent with the experimental data. Why?**

Rapidly equilibrating secondary carbocations to account for the acetolysis results?

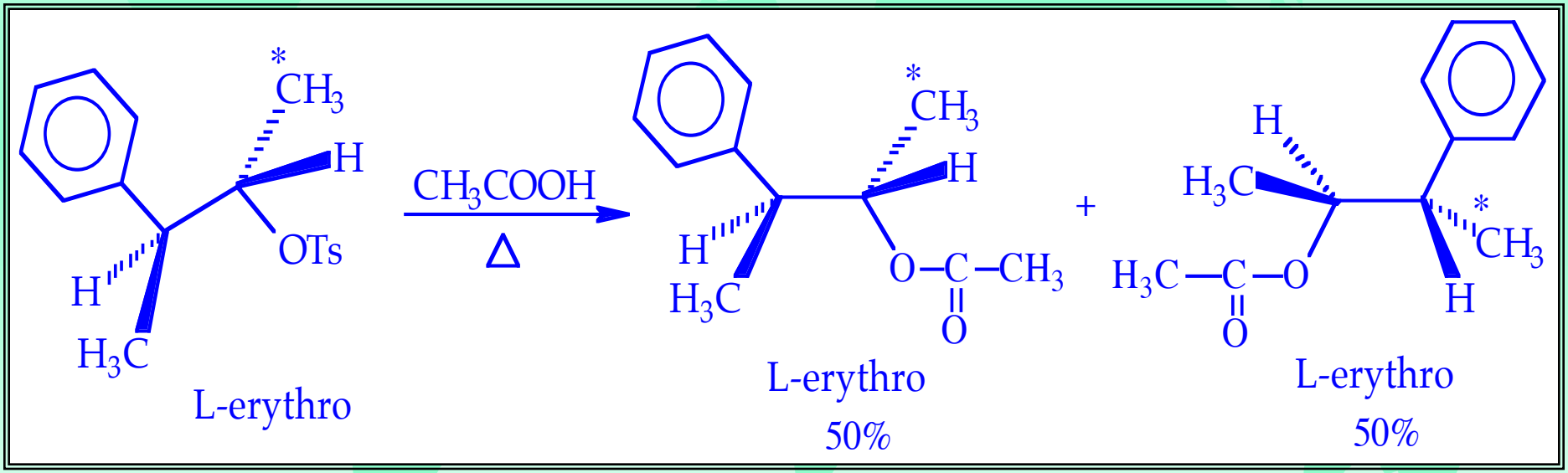
The "Windshield-Wiper" Effect



A rapidly equilibrating pair of secondary carbocations in which 1,2-phenyl shifts effectively prevent topside attack by acetic acid.

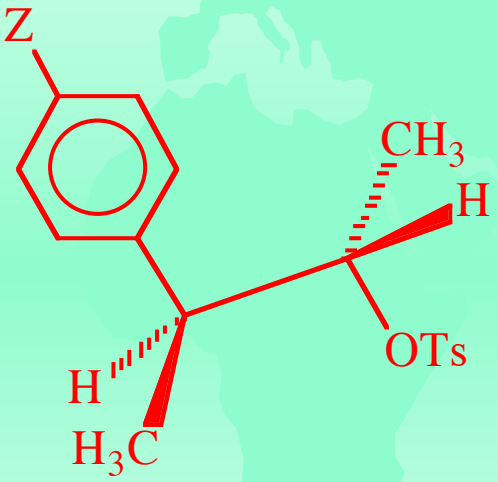
Additional data concerning acetolysis of phenyl tosylates

Fact One - Scrambling of a label



Additional data concerning acetolysis of phenyl tosylates

Fact Two - Substituent effects

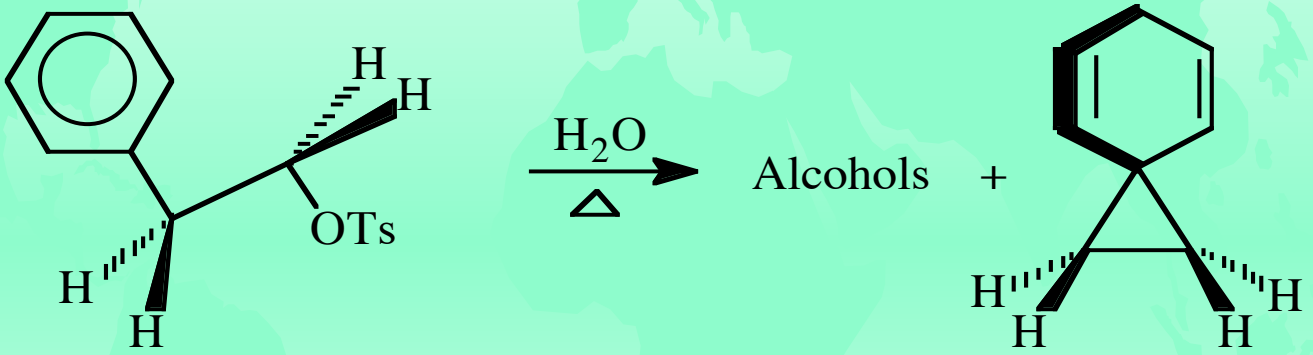


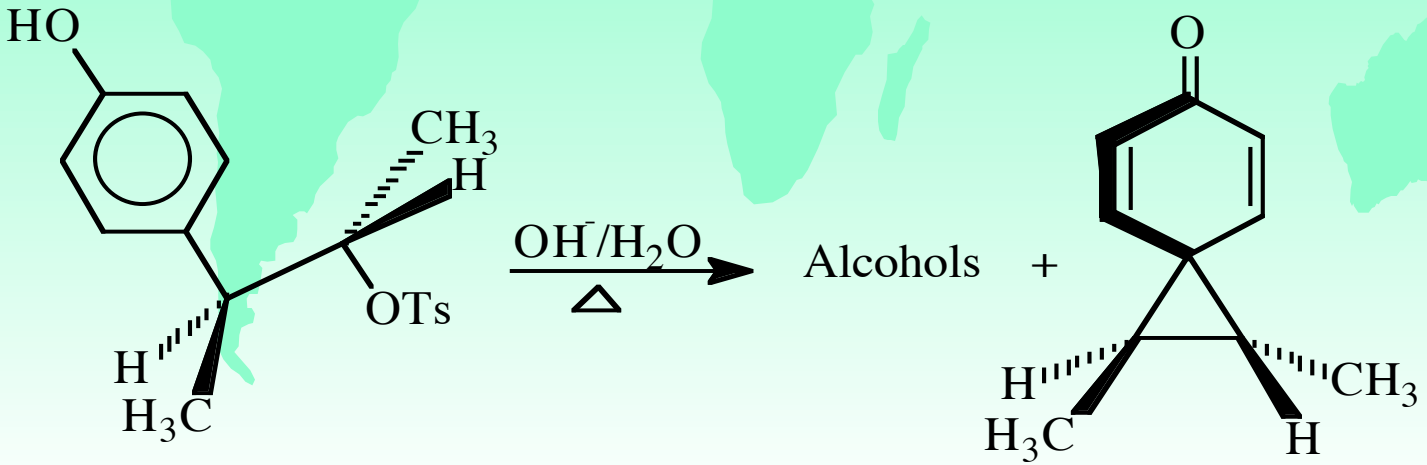
As the electron-donating ability of substituent Z increases, the rate of acetolysis increases.

	Cl	H	CH_3	OCH_3
$k_{acetolysis}$ ($x10^7$)	0.39	2.39	19.0	228.0

Additional data concerning acetolysis of phenyl tosylates

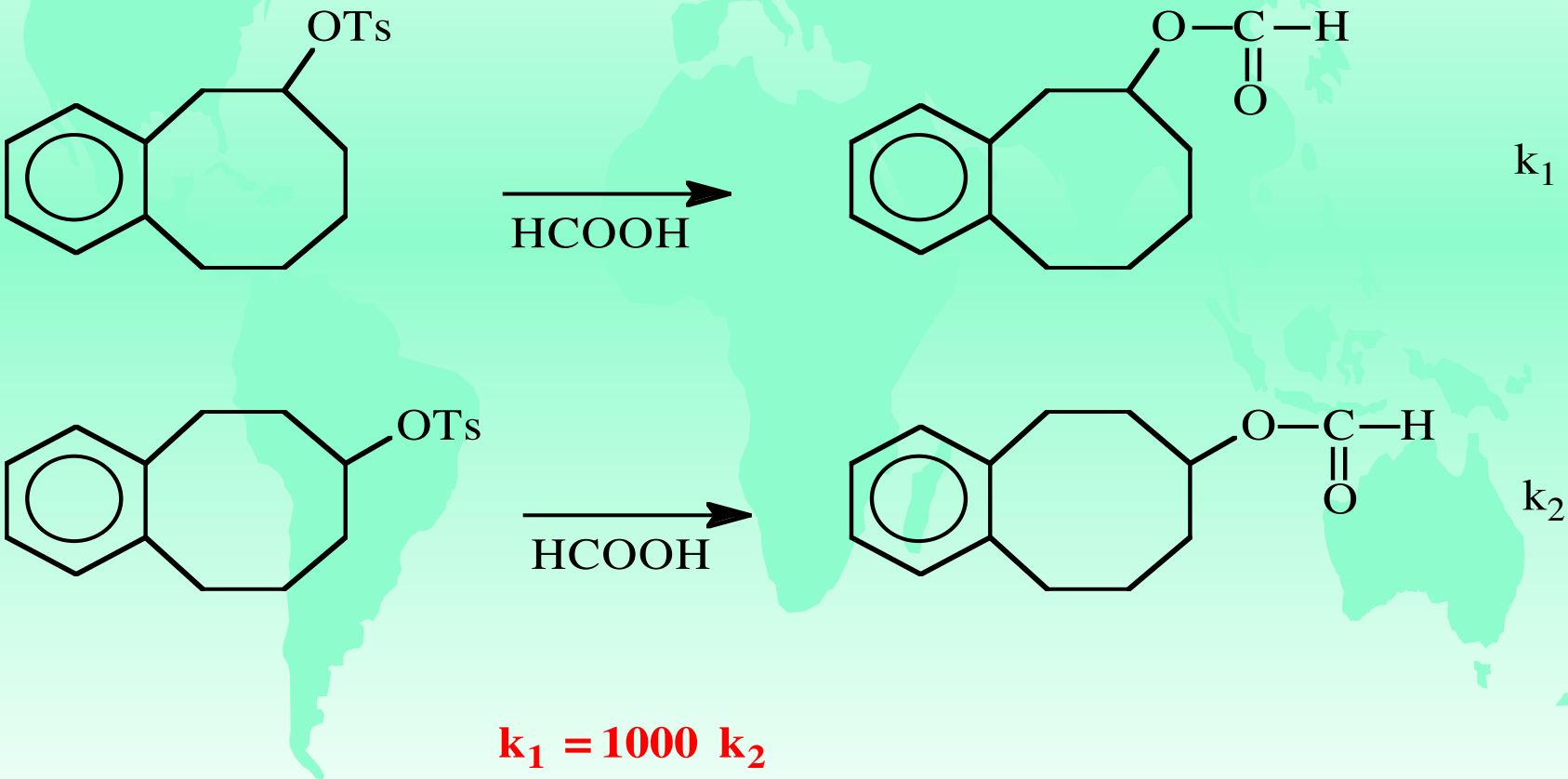
Fact Three - Formation of Spirane products





Additional data concerning acetolysis of phenyl tosylates

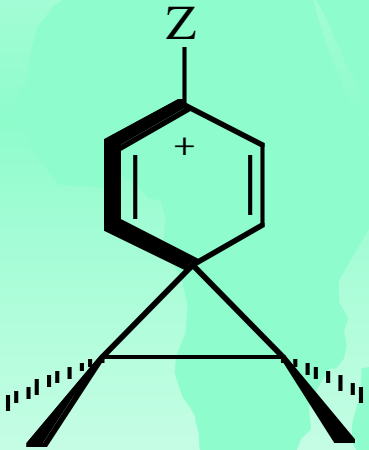
Fact Four - Unusual Kinetics



$k_1 = 1000\ k_2$

EXPLANATION TO ACCOUNT FOR THE ACETOLYSIS RESULTS

Phenonium ion participation

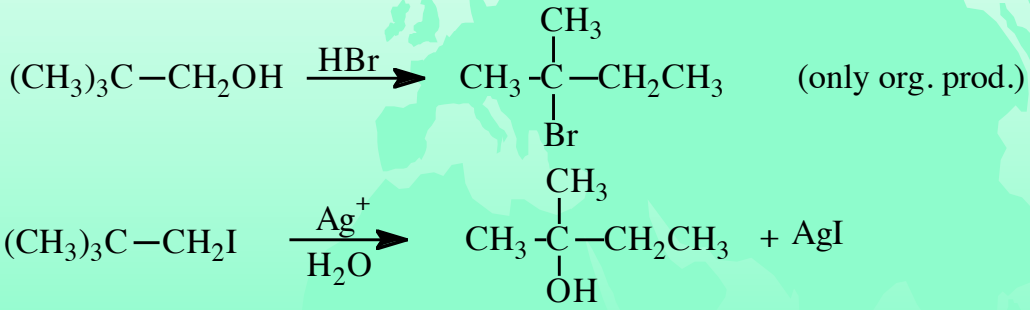


A phenonium ion: π-electron donation from an electron rich benzene π–system leading to internal displacement of the leaving group and formation of a cyclopropyl spirane intermediate.

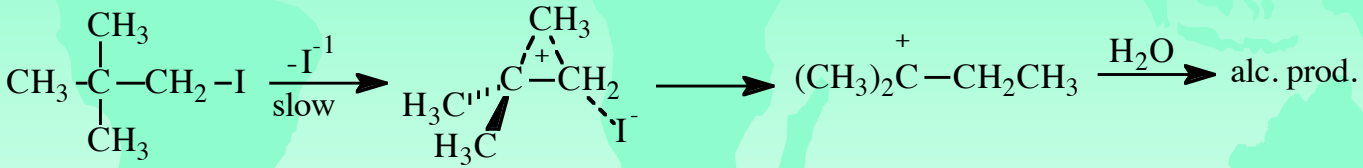
Alkyl Participation

σ - bridged complexes

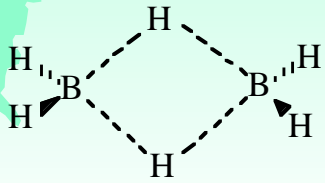
Consider the following reactions:



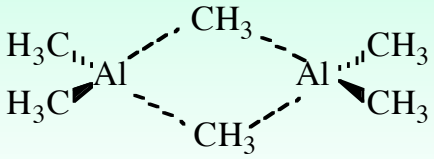
Rationale



Supporting evidence



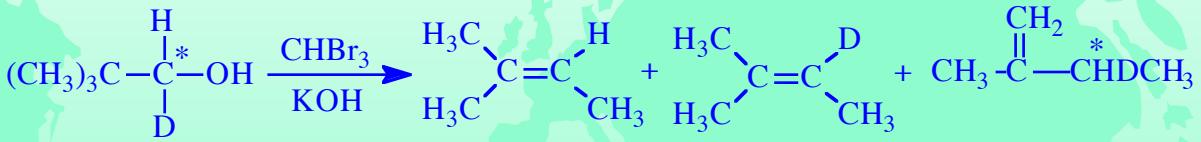
B_2H_6



$Al_2(CH_3)_6$

Corroborating evidence for alkyl participation

Observation:



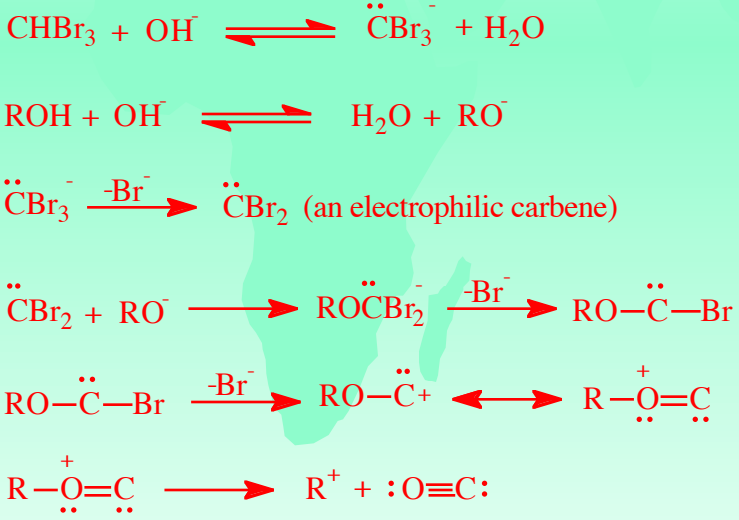
optically active

optically active

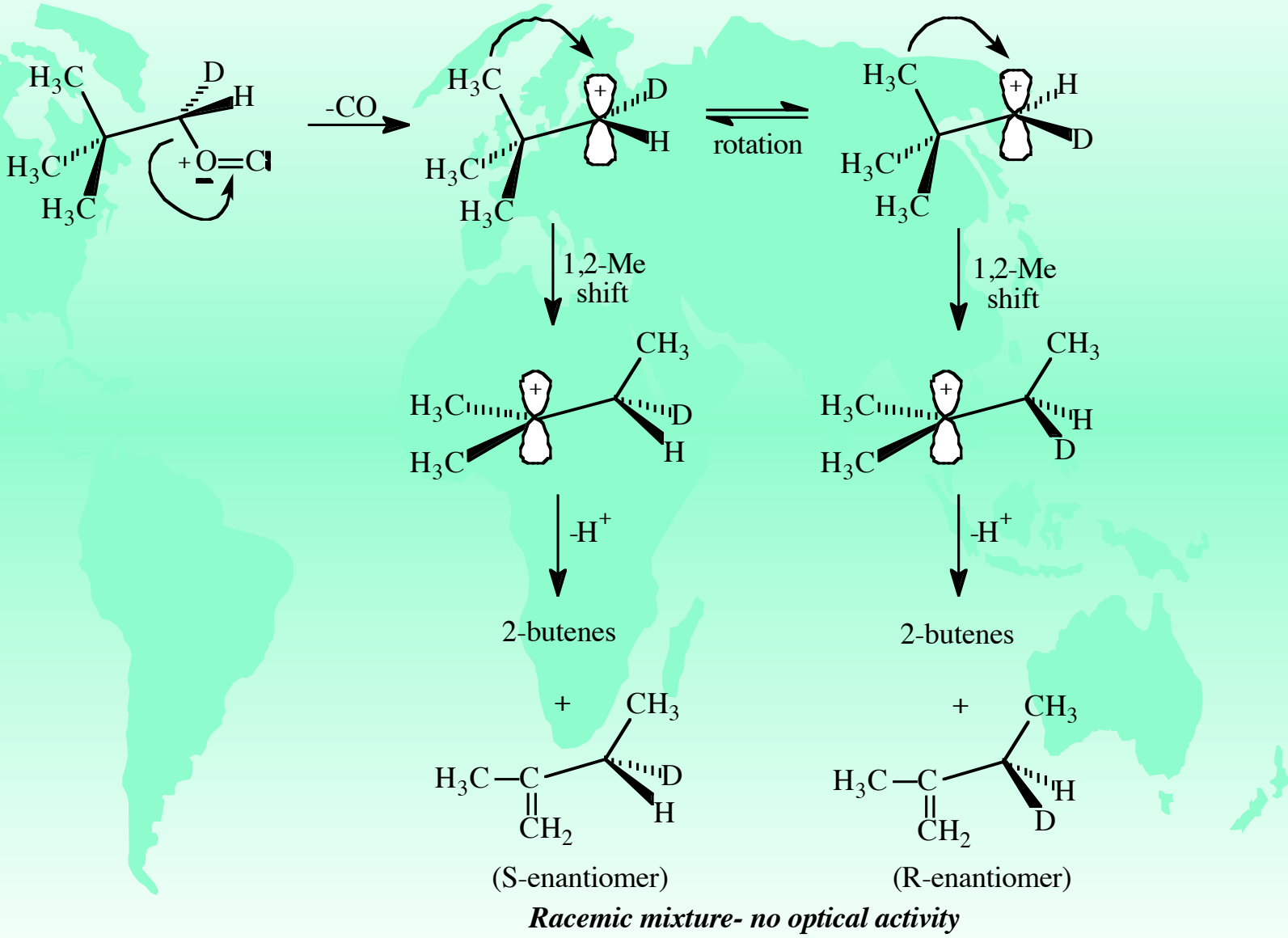
Preliminary explanation:

The above reaction generates carbocationic intermediates under strongly basic conditions.

In general:

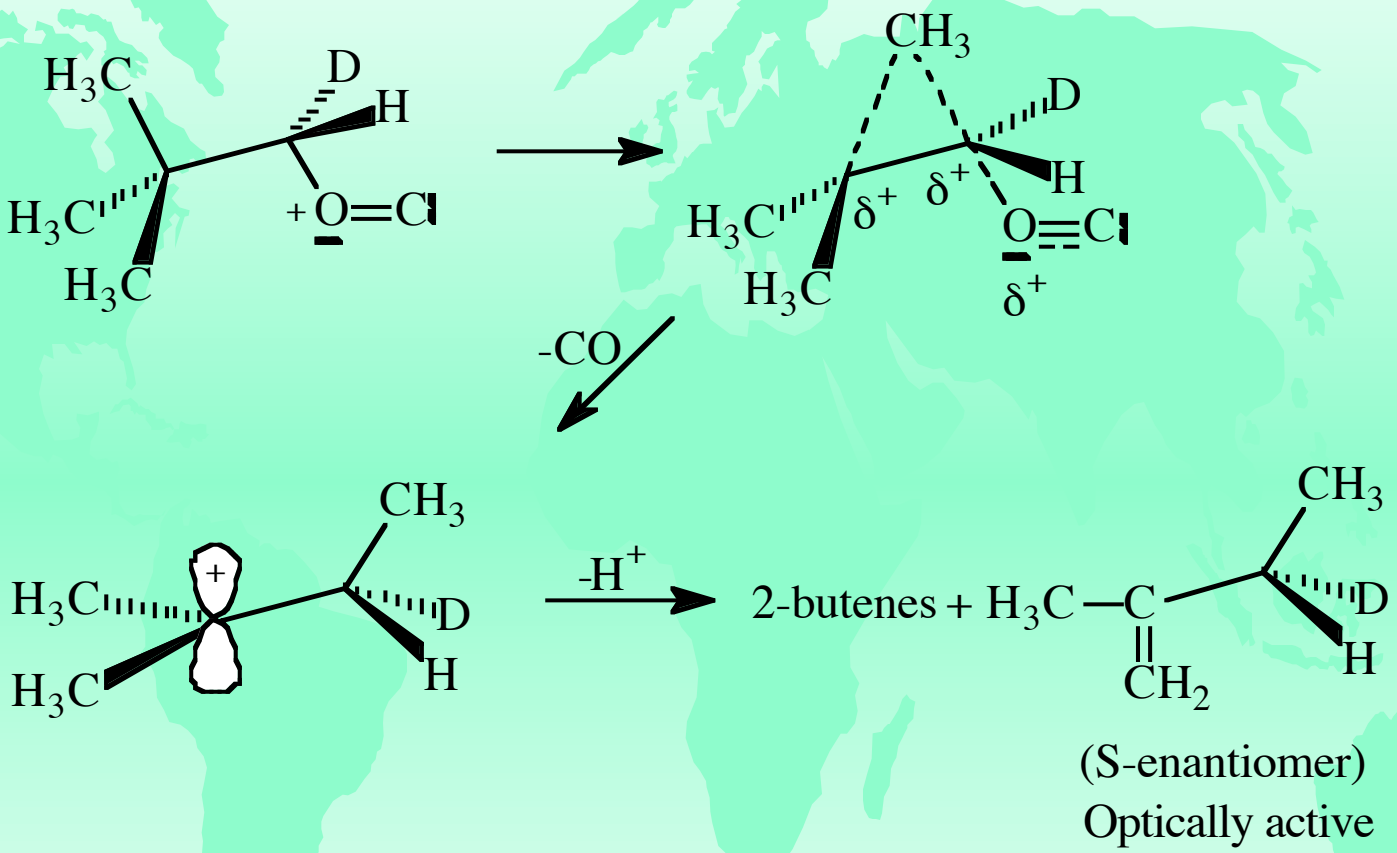


OPEN CARBOCATION POSSIBILITY



Racemic mixture- no optical activity

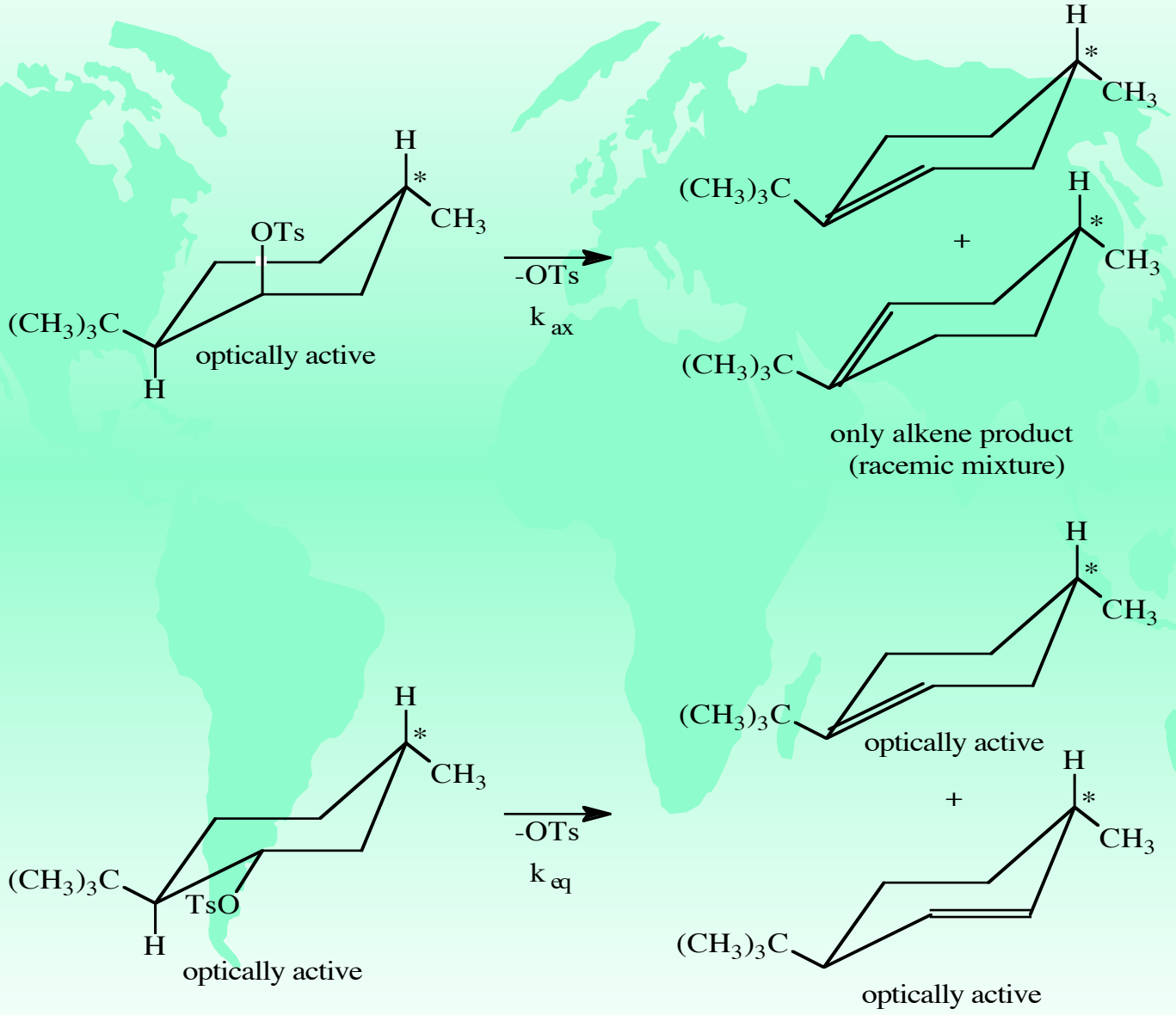
Methyl bridged intermediate



Even if the bridged pathway only competes with the open carbocation pathway, one alkene enantiomer will still be produced in excess, and there will be residual optical activity in the product.

Data for the solvolysis of cyclohexyl tosylates

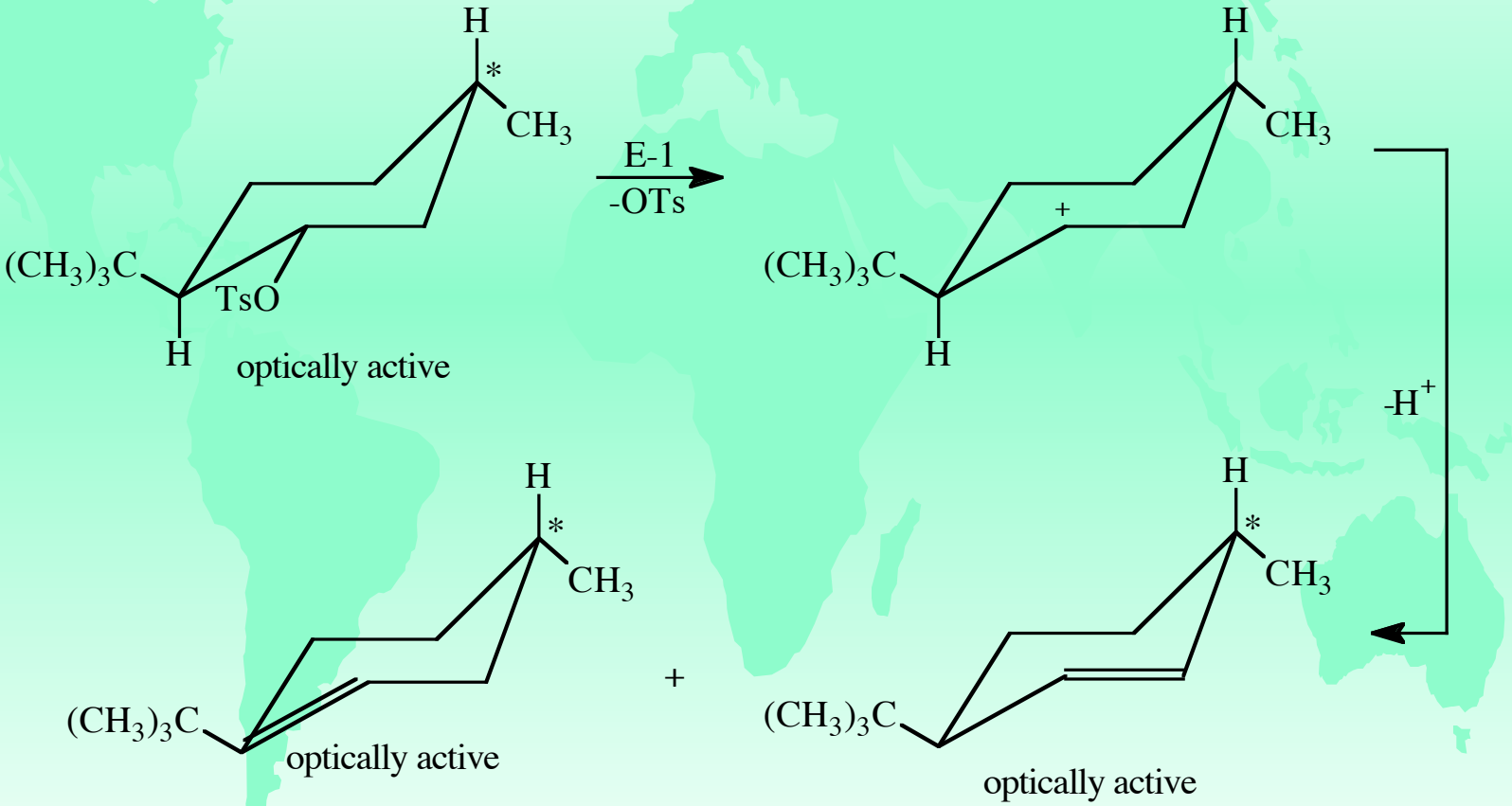
Consisder the following solvolysis data:



$k_{ax} \simeq 70\text{-}80\, k_{eq}$

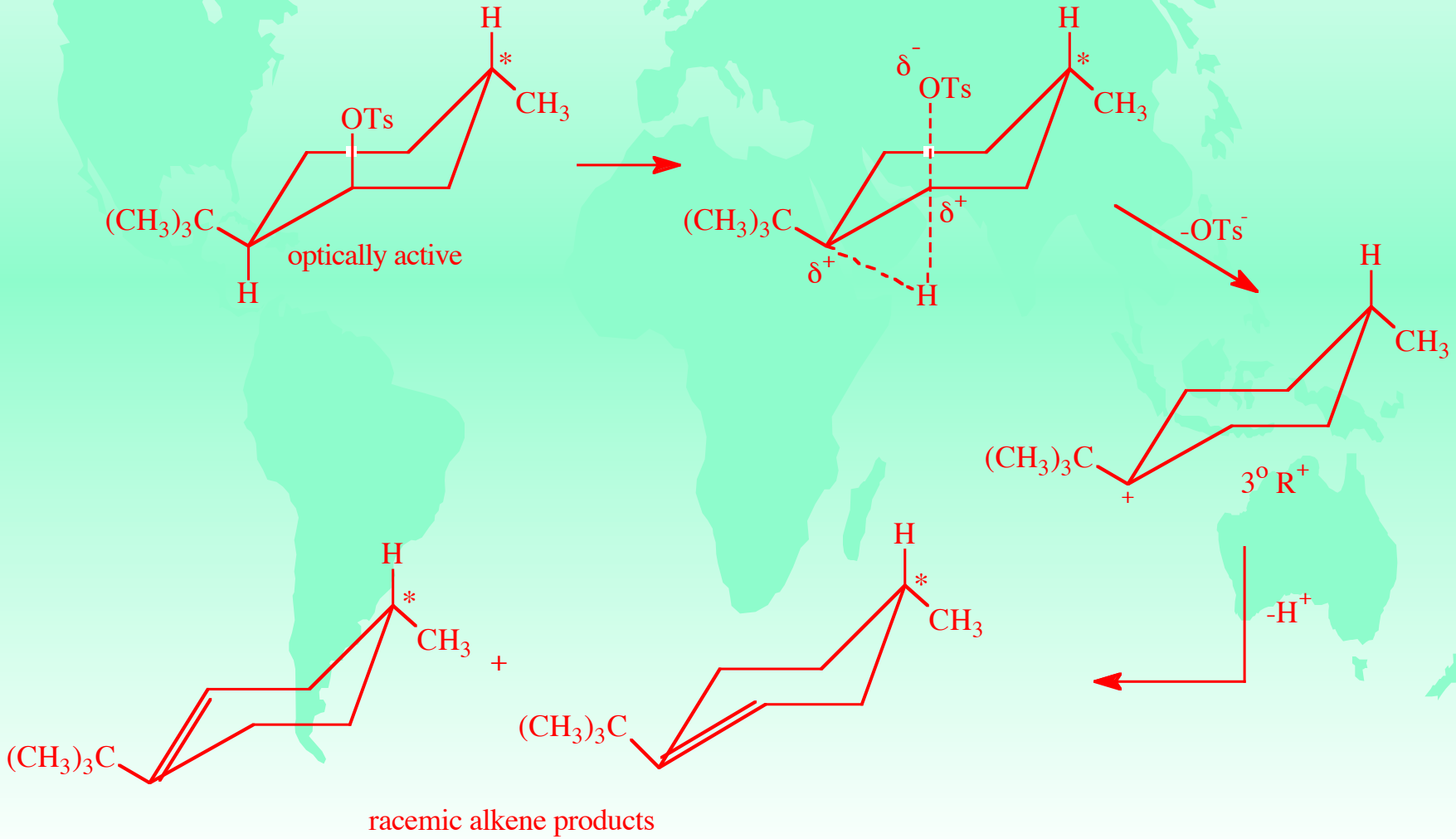
Rationale for cyclohexyl tosylate solvolysis

Ordinarily, an axial leaving group, because it experiences more steric interactions, is solvolyzed 2 to 3 times faster than an equatorial leaving group. The greater rate of solvolysis (70-80 times as fast) for axial tosylate relative to equatorial tosylate is suggestive of neighboring group participation.



Rationale for cyclohexyl tosylate solvolysis cont'd.

β-Hydrogen participation



Solvolysis of unsaturated tosylates

Consider the following observations:

a) $(CH_3)_2C{=}CH{-}CH_2CH_2OTs \xrightarrow[\Delta]{CH_3COOH} (CH_3)_2C{=}CH{-}CH_2CH_2O{-}C(=O){-}CH_3$

b) $(CH_3)_2C{=}CH{-}CD_2CH_2OTs$ or $(CH_3)_2C{=}CH{-}CH_2CD_2OTs \xrightarrow[\Delta]{CH_3COOH}$ $(CH_3)_2C{=}CH{-}CD_2CH_2O{-}C(=O){-}CH_3$ + $(CH_3)_2C{=}CH{-}CH_2CD_2O{-}C(=O){-}CH_3$

both labelled products are obtained from either labelled reactant

c) $(CH_3)_2CHCH_2CH_2CH_2OTs \xrightarrow[\Delta]{CH_3COOH} (CH_3)_2CHCH_2CH_2CH_2O{-}C(=O){-}CH_3$

$(CH_3)_2C{=}CH{-}CH_2CH_2OTs \xrightarrow[\Delta]{CH_3COOH} (CH_3)_2C{=}CH{-}CH_2CH_2O{-}C(=O){-}CH_3$

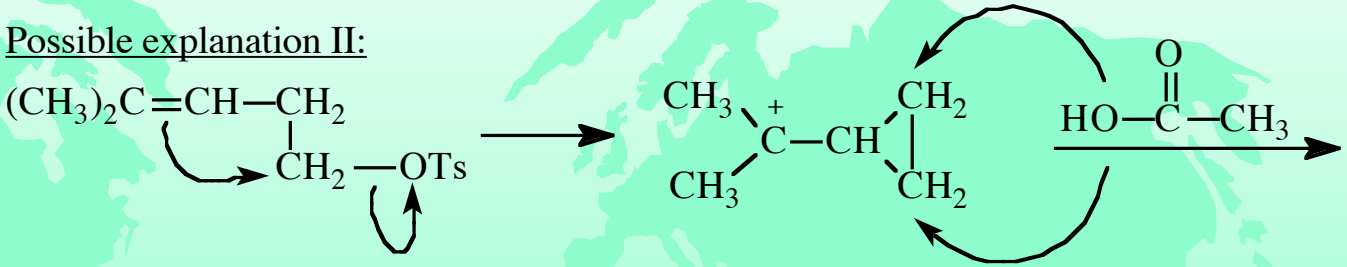
$k_{unsat'd.} \gg k_{sat'd.}$

Possible explanations for solvolysis of unsaturated tosylates

Possible explanation I:

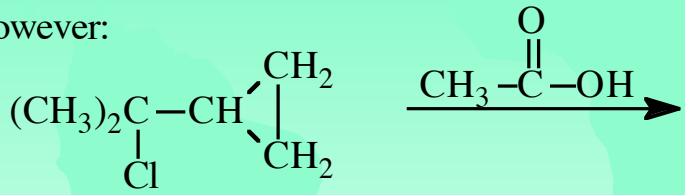
Formation of $(CH_3)_2C{=}CH{-}CH_2CH_2^+$; Unlikely, this is a primary R^+.

Possible explanation II:



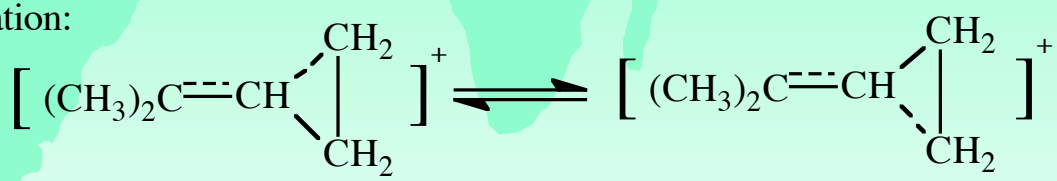
The above explanation invokes the intermediacy of a tertiary carbocation formed with π-electron NGP; no primary carbocation is involved.Further, the above tertiary carbocation can account for the scrambling observed with labelled reactants and for the enhanced rate of solvolysis in the case of the unsaturated vs. saturated tosylate reactants.

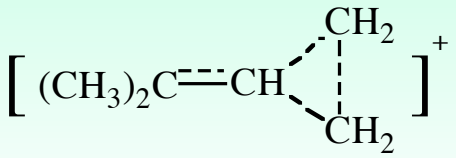
However:



a different set of solvolysis products relative to those obtained from the unsaturated tosylate reactants

Best explanation:





A homoallyl carbocation