

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

نام خداوند بخشنده مهربان

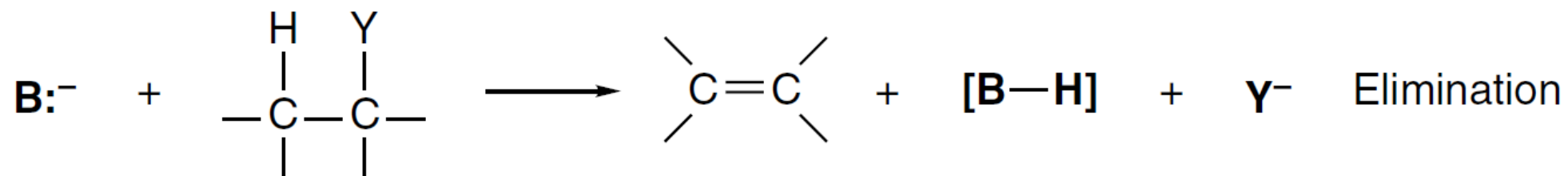
Polar Addition and Elimination Reactions

Addition Reactions



Vicinal addition (two adjacent groups *addition*)
electrophilic polar (*heterolytic*) mechanisms
radical (homolytic), nucleophilic, and concerted
mechanisms.

Elimination reaction

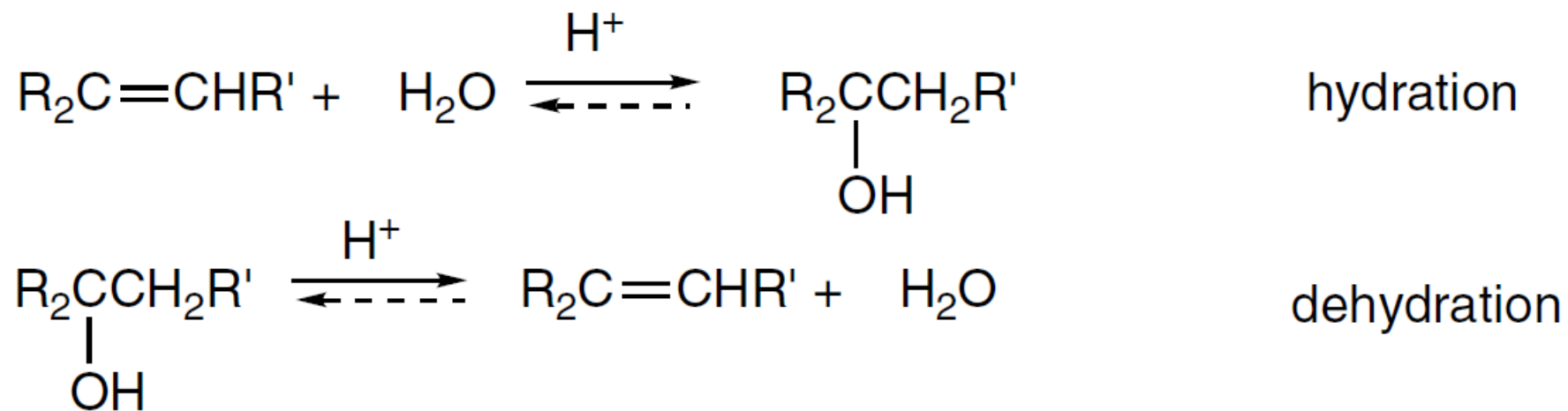


E2, E1, and E1cb eliminations

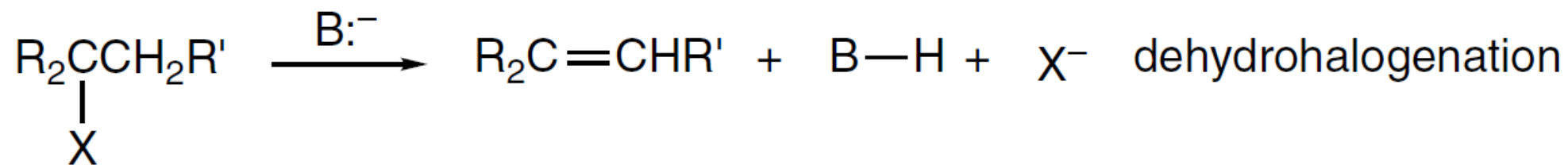
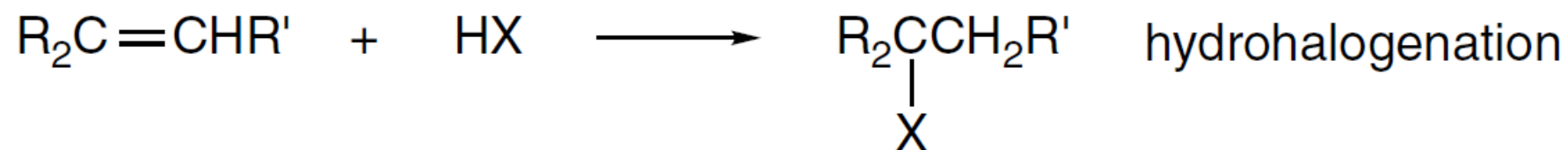
Addition and elimination processes are the formal reverse of one another

Acid-catalyzed hydration of alkenes

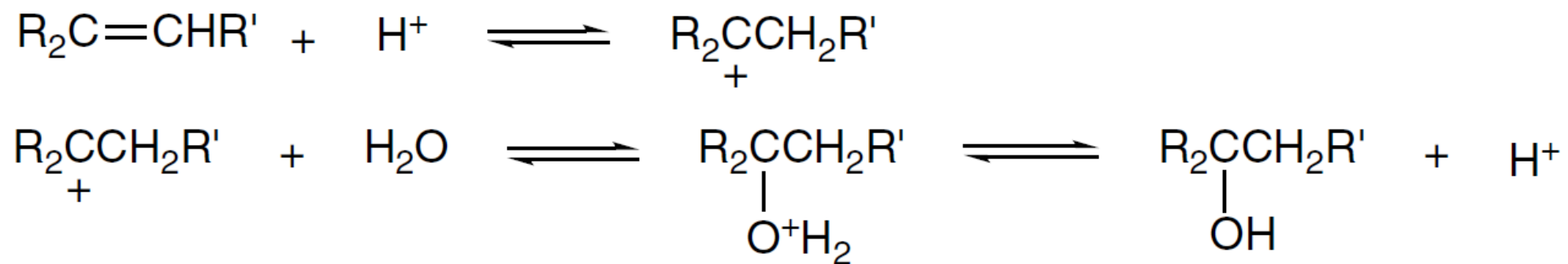
Dehydration of alcohols



Hydrohalogenation and dehydrohalogenation



When reversible addition and elimination reactions are carried out under similar conditions, they follow the same mechanistic path, but in opposite directions. The ***principle of microscopic reversibility*** states that the mechanism of a reversible reaction is the same in the forward and reverse directions.



Two intermediates are involved: a carbocation and a protonated alcohol.

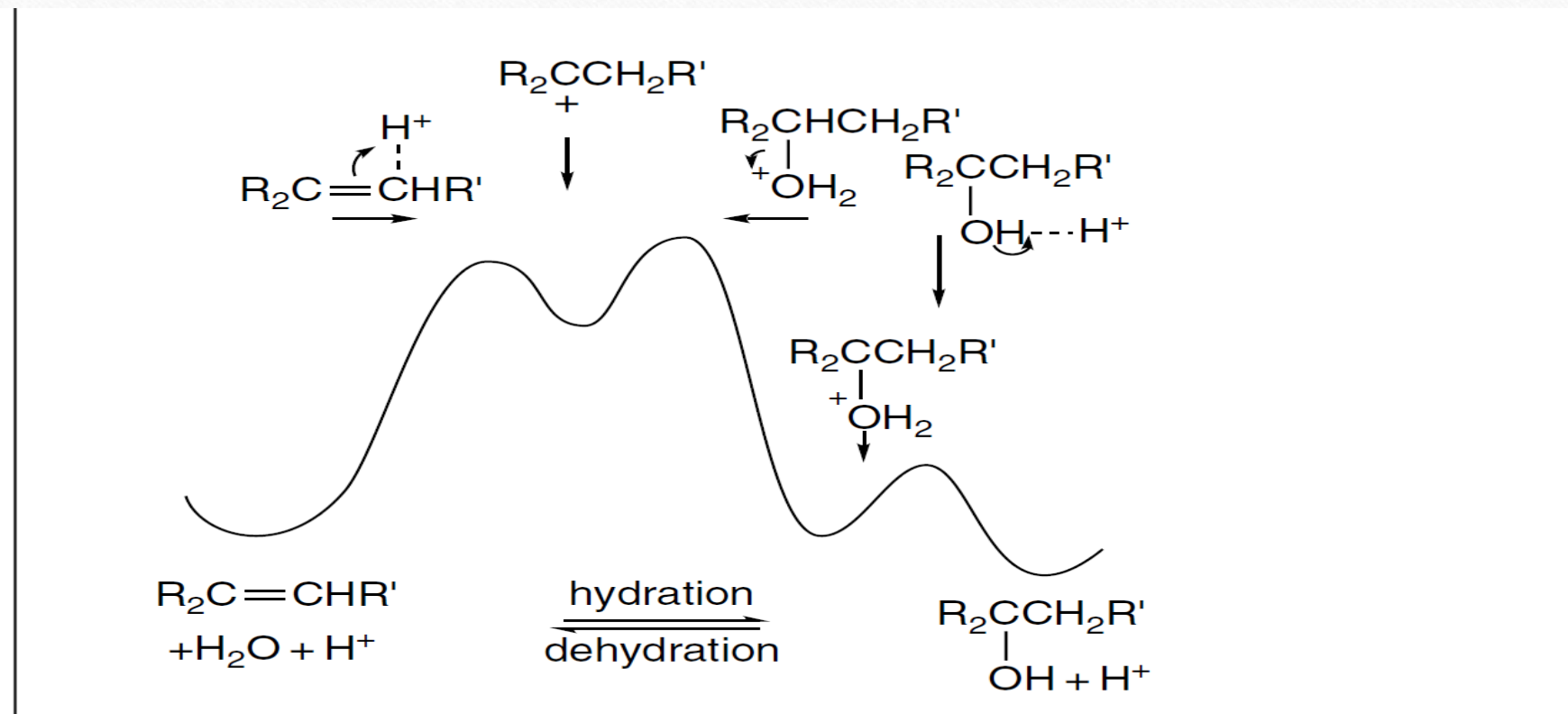
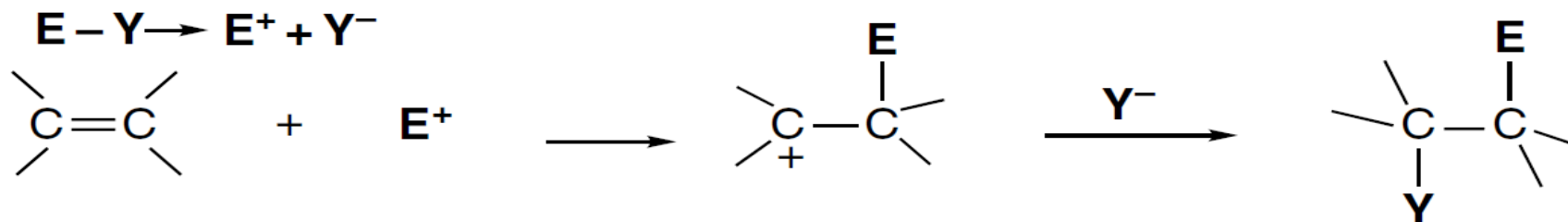
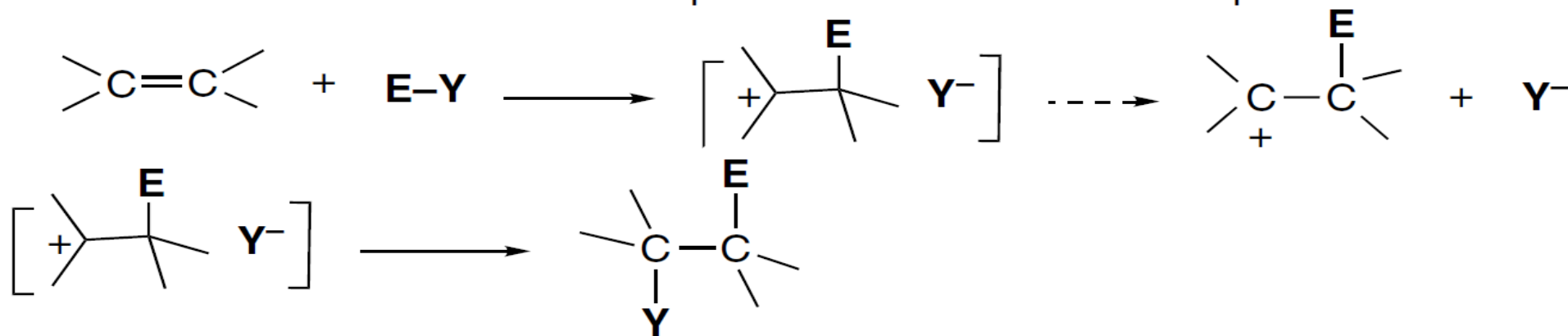


Fig. 5.1. Conceptual representation of the reversible reaction path for the hydration

A. Prior dissociation of electrophile and formation of carbocation intermediate



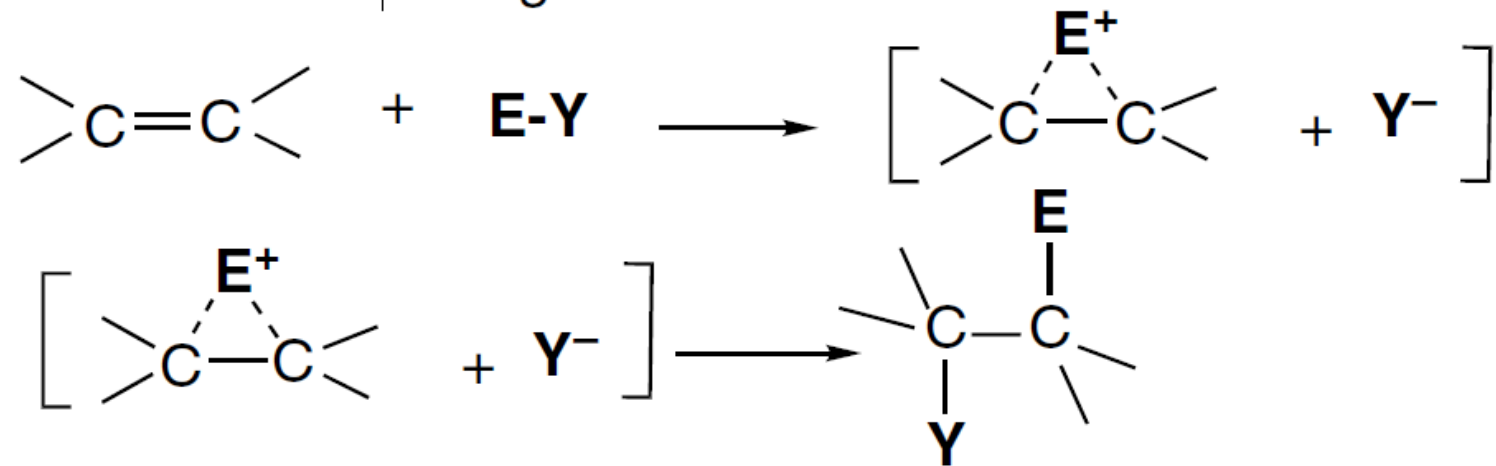
B. Formation of carbocation ion pair from alkene and electrophile



Mechanisms A, and B are **Ad_E2** reaction.

Mechanism B can occur if the carbocation is fairly stable and E^+ is a poor bridging group. The lifetime of the carbocation may be very short, in which case the ion pair would react faster than it dissociates.

C. Formation of bridged cationic intermediate from alkene and electrophile



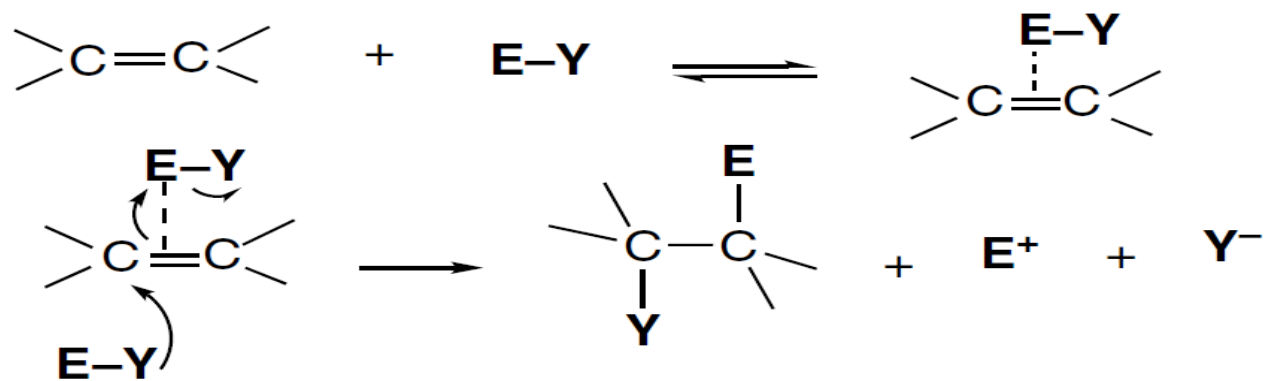
Mechanism C:

a bridged intermediate

stereospecific *anti* addition

Mechanism C is an important general mechanism that involves bonding of E^+ to *both carbons of the alkene* and depends on the ability of the electrophile to function as a bridging group.

D. Concerted addition of electrophile and nucleophile in a termolecular reaction



Mechanism D is:

- A termolecular electrophilic addition, Ad_E3; anti addition

Mechanism D avoids a cationic intermediate by concerted formation of the C-E and C-Y bonds.

The nature of the electrophilic reagent and the relative stabilities of the intermediates determine which mechanism operates.

Because proton is the hardest electrophile and has no free electrons for bridging, it is most likely to react via a carbocation mechanism.

Similarly, reactions in which E^+ is the equivalent of F^+ are unlikely to proceed through bridged intermediates.

Bridged intermediates become more important as the electrophile becomes softer (more polarizable).

Bridged halonium ions are involved in many bromination and chlorination reactions.

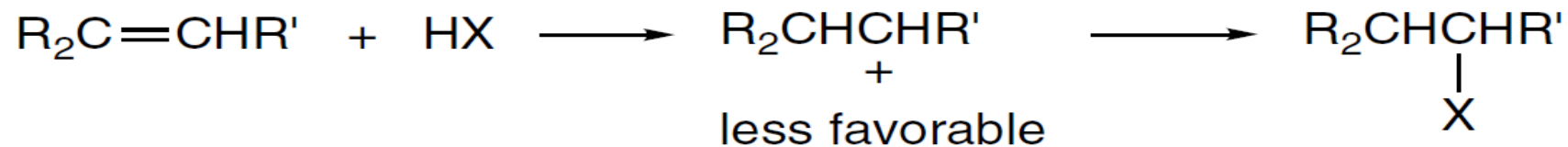
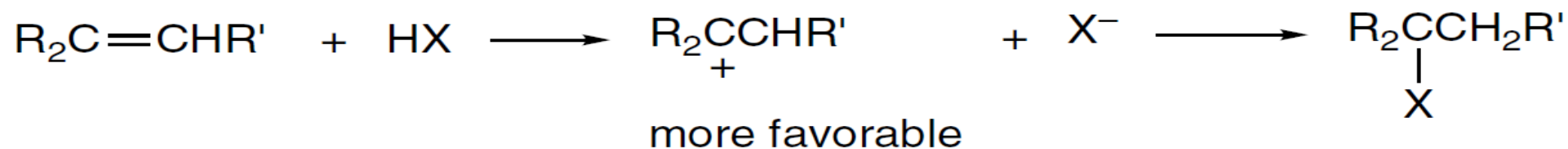
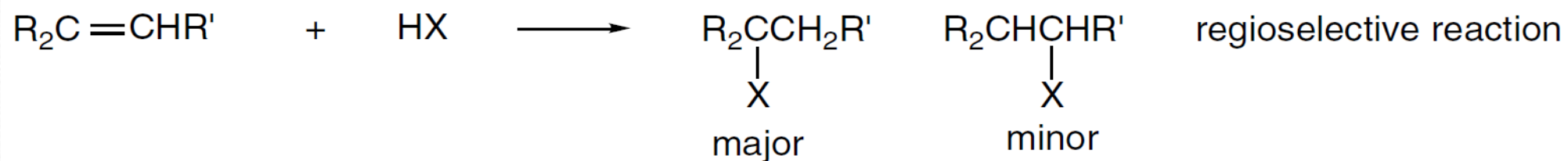
Bridged intermediates are also important with sulfur and selenium electrophiles.

Productive termolecular collisions are improbable, and mechanism D involves a prior complex of the alkene and electrophilic reagent.

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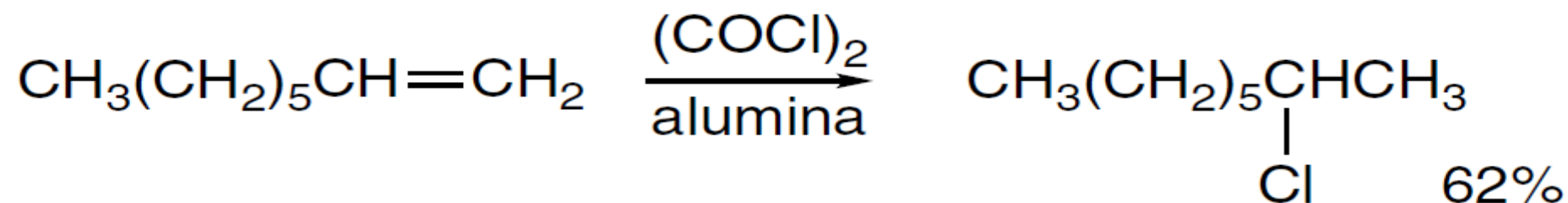
Addition of Hydrogen Halides to Alkenes

Regioselective addition; Markovnikov's rule



Addition of hydrogen bromide to alkenes free-radical chain addition

- Initiated by: 1-peroxidic impurities; 2-light
- anti Markovnikov addition
- Conditions that minimize the competing radical addition include:
 - 1-Use of high-purity alkene and solvent; 2-Exclusion of light; 3-Addition of a radical inhibitor



- **The order of reactivity of the hydrogen halides is:** $\text{HI} > \text{HBr} > \text{HCl}$.
- Reactions of simple alkenes with HCl are quite slow.
- The reaction occurs more readily in the presence of silica or alumina.
- In the presence of these adsorbents, HBr undergoes exclusively ionic addition.
- In addition to the gaseous hydrogen halides, liquid sources of hydrogen halide such as SOCl_2 , $(\text{COCl})_2$, $(\text{CH}_3)_3\text{SiCl}$, $(\text{CH}_3)_3\text{SiBr}$, and $(\text{CH}_3)_3\text{SiI}$ can be used.
- The hydrogen halide is generated by reaction with water and/or hydroxyl group on the adsorbent.

Mechanistic details of hydrogen halide addition to alkenes have focused on the 1-kinetics and 2-stereochemistry of the reaction and on the 3-effect of added nucleophiles.

For addition of hydrogen bromide or hydrogen chloride to alkenes:

$$\text{Rate} = k[\text{alkene}][\text{HX}]^2$$

Addition of HCl to 2-methyl-1-butene, 2-methyl-2-butene, 1-methylcyclopentene, and cyclohexene.

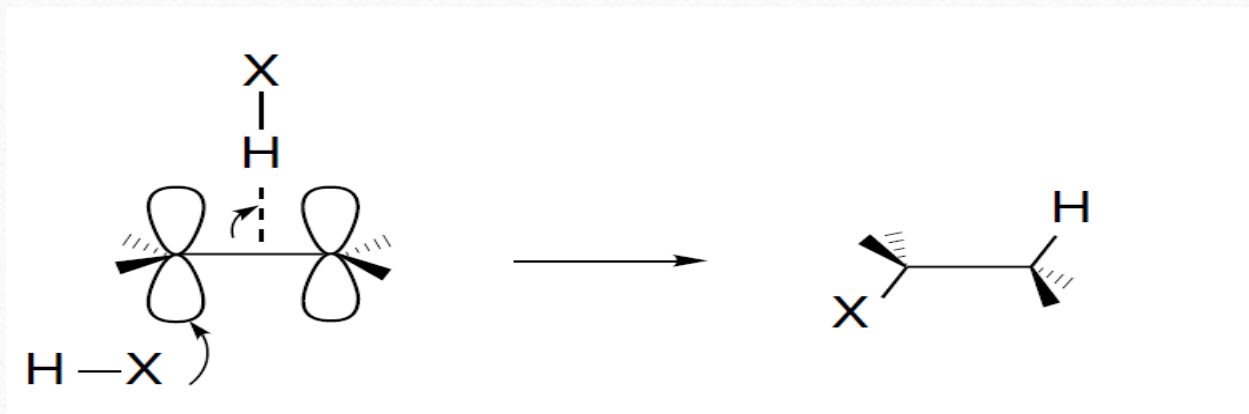
The addition of HBr to cyclopentene

The stereochemistry of addition of hydrogen halides to unconjugated alkenes is usually *anti*

- addition of **HBr** to 1,2-dimethylcyclohexene, cyclohexene, 1,2-dimethylcyclopentene, cyclopentene, Z- and E-2-butene, 2 and 3-hexene.
- **Anti** stereochemistry is also **dominant** for addition of **HCl** to:
- 1,2-dimethylcyclohexene and 1-methylcyclopentene.

Temperature and solvent can modify the stereochemistry

For example, although the addition of HCl to 1,2-dimethylcyclohexene is *anti* near room temperature, *syn* addition dominates at $-78\text{ }^{\circ}\text{C}$.

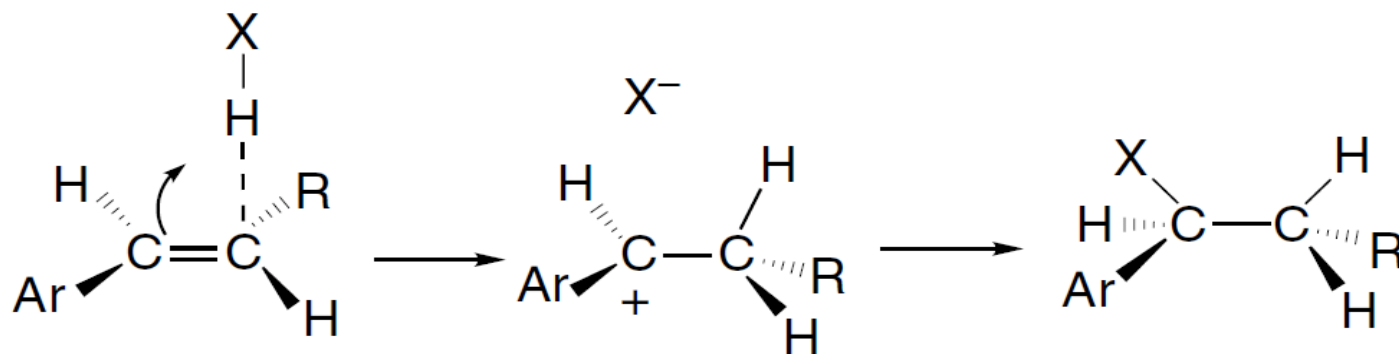


A change in the stereoselectivity is observed

- when the double bond is conjugated with a group that can stabilize a carbocation intermediate.
- Most of the specific cases involve an aryl substituent. Examples of syn addition are:
- Z- and E-1-phenylpropene, cis- and trans- β -t-butylstyrene, 1-phenyl-4-t-butylcyclohexene

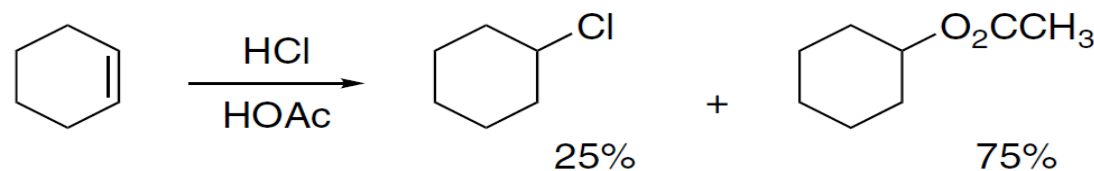
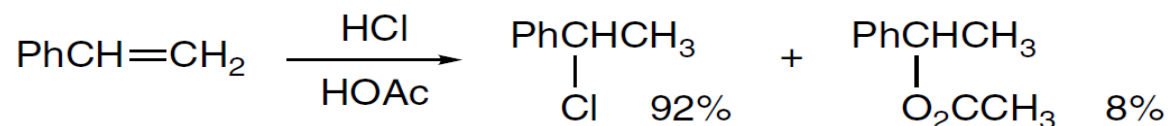
The mechanism proposed for these reactions features an ion pair as the key intermediate

- Owing to the greater stability of the benzylic carbocations formed in these reactions, concerted attack by halide ion is not required for protonation. If the ion pair formed by alkene protonation collapses to product faster than rotation takes place, *syn* addition occurs because the proton and halide ion are initially on the same face of the molecule.



Kinetic studies of the addition

- Addition of hydrogen chloride to styrene support the conclusion that an ion pair mechanism operates. The reaction is first order in hydrogen chloride.
- There is a competing reaction with solvent when hydrogen halide additions to alkenes are carried out in nucleophilic solvents.

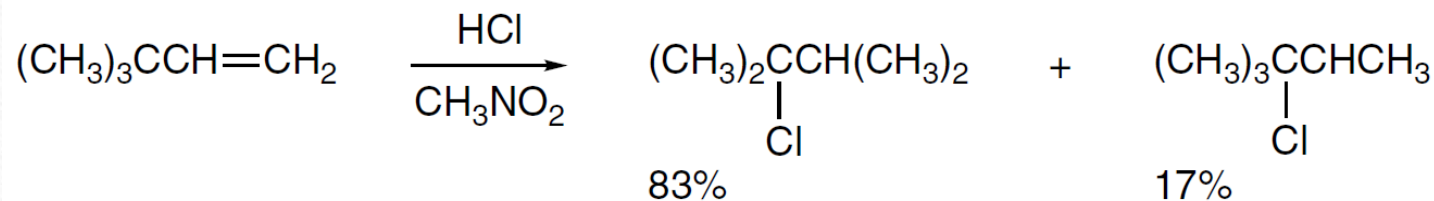
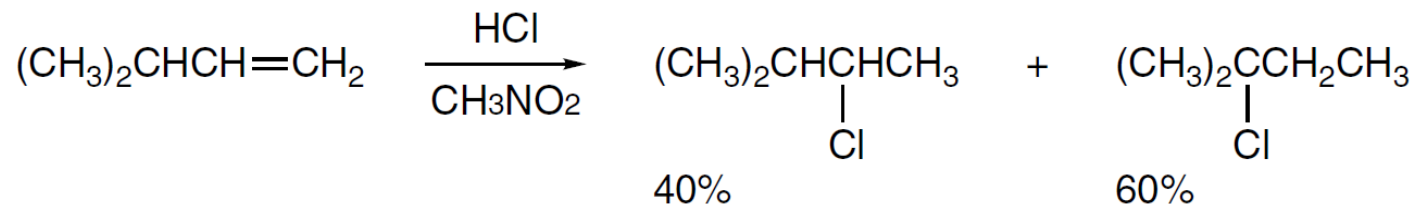


Addition of a halide salt

- Addition of a halide salt increases the likelihood of capture of a carbocation intermediate by halide ion.
- The effect of added halide salt can be detected kinetically. For example, the presence of tetramethylammonium chloride increases the rate of addition of hydrogen chloride to cyclohexene.
- Similarly, lithium bromide increases the rate of addition of hydrogen bromide to cyclopentene.

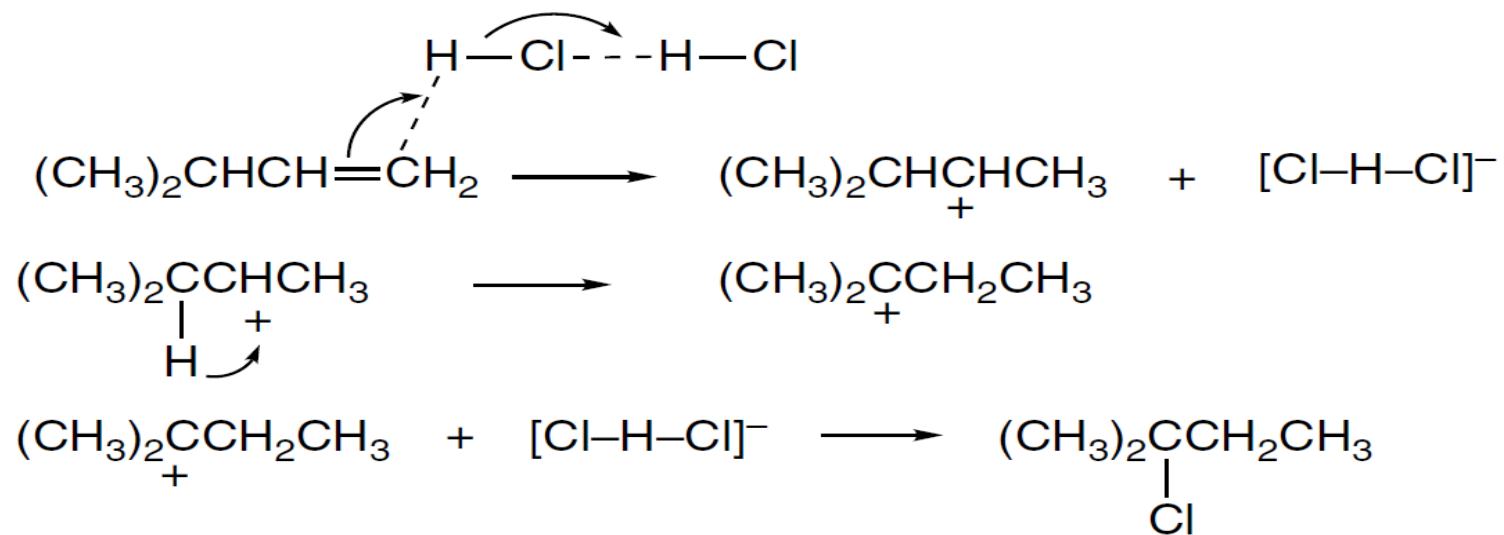
Skeletal rearrangements

- Skeletal rearrangements are possible in hydrogen halide additions if hydride or alkyl migration can give a more stable carbocation.



The key intermediate

The key intermediate in this mechanism is an ion sandwich involving the acid ion and a halide ion.

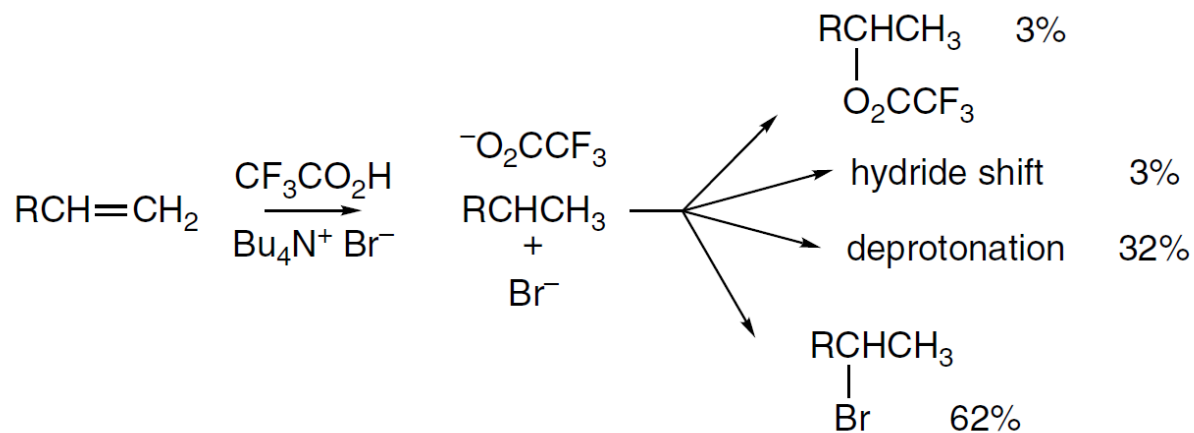


Bromide ion accelerates addition of HBr

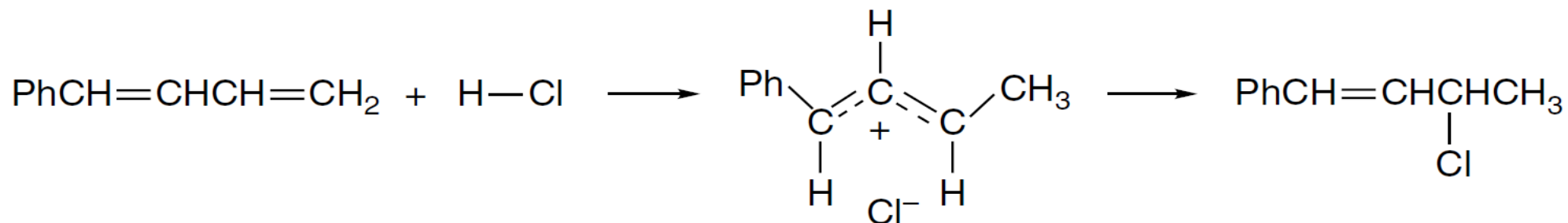
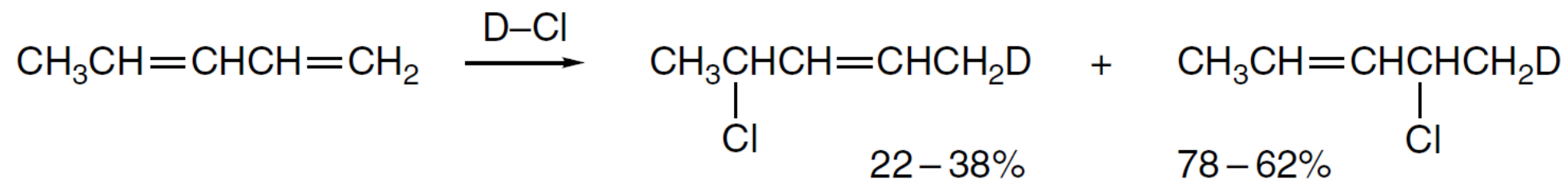
Bromide ion accelerates addition of HBr to 1-, 2-, and 4-octene in 20% TFA in CH_2Cl_2 .

In the same system, 3,3-dimethyl-1-butene shows substantial rearrangement, indicating formation of a carbocation intermediate.

Even 1- and 2-octene show some evidence of rearrangement, as detected by hydride shifts.



Second order an $\text{Ad}_\text{E}2$ mechanism

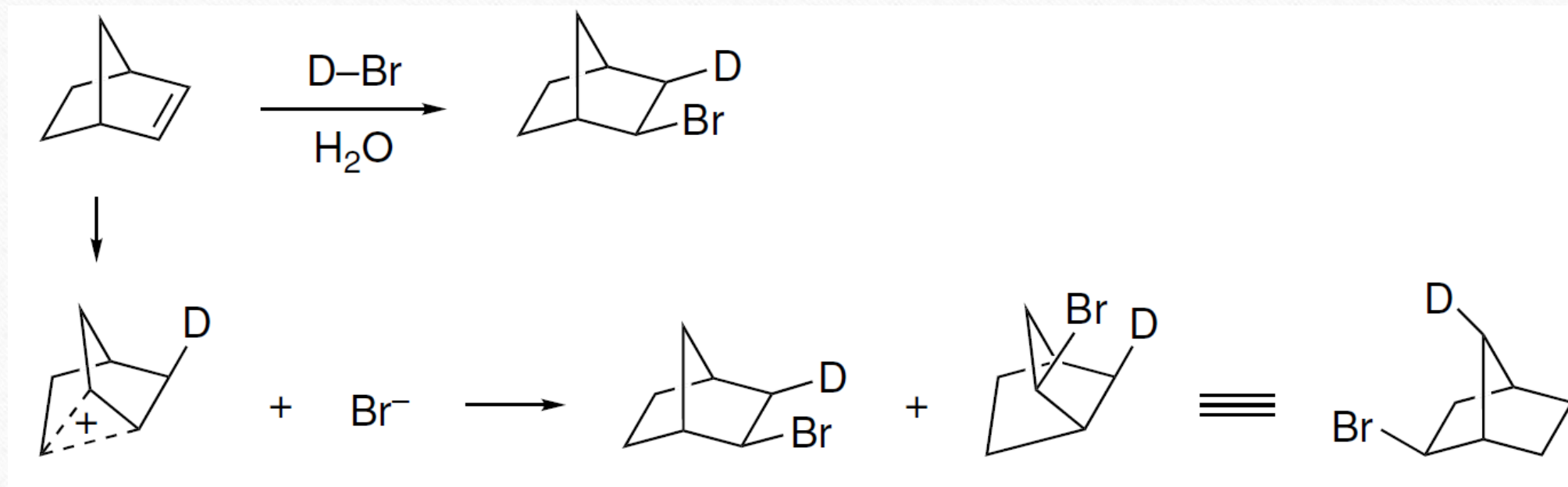


The kinetics of this reaction are second order an $\text{Ad}_\text{E}2$ mechanism.

Additions of HCl or HBr to norbornene

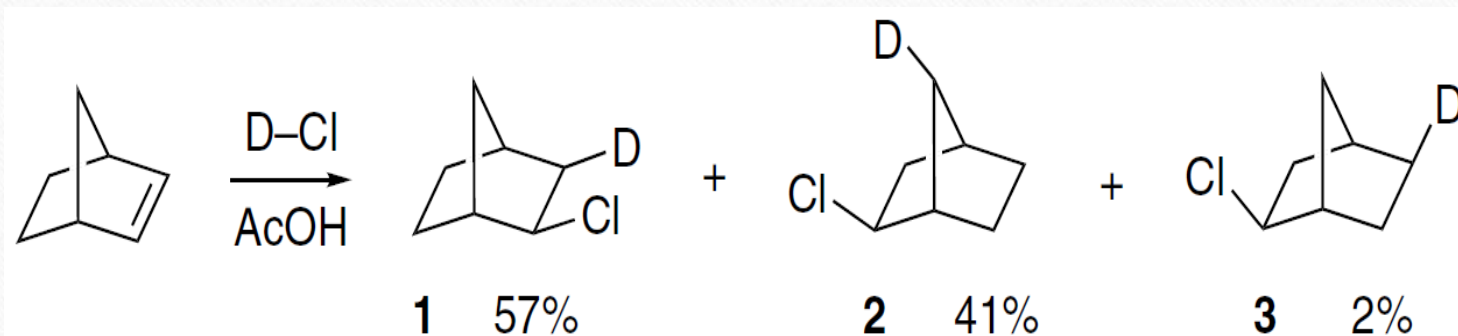
- In the additions of HCl or HBr to norbornene, the **stability and facile rearrangement** of the norbornyl cation come into consideration.
- Addition of deuterium bromide to norbornene gives ***exo***-norbornyl bromide.
- Degradation shows that about ***half of the product is formed via the bridged norbornyl cation***, which leads to ***deuterium at both the 3- and 7-positions***.
- The ***exo*** orientation of the ***bromine atom*** and the ***redistribution of the deuterium*** indicate the ***involvement of the bridged ion***.

Additions of HCl or HBr to norbornene



Addition of HCl to norbornene

- The chloride is almost exclusively the *exo* isomer.
- The fact that **1** and **2** are formed in unequal amounts excludes the possibility that the symmetrical bridged ion is the only intermediate.



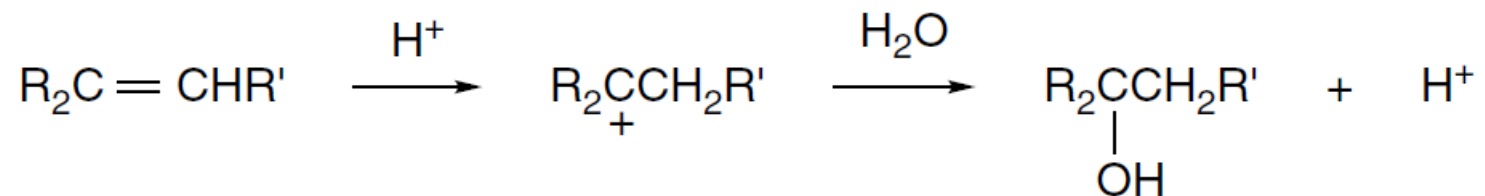
Addition of HCl to norbornene

- The excess of **1** over **2** indicates that some *syn* addition occurs by ion pair collapse before the bridged ion achieves symmetry with respect to the chloride ion.
- If the amount of **2** is taken as an indication of the extent of bridged ion involvement, one can conclude that 82% of the reaction proceeds through this intermediate, which must give equal amounts of **1** and **2**.
- Product **3** results from the C (6) $\rightarrow$ C (2) hydride shift that is known to occur in the 2-norbornyl cation with an activation energy of about 6 kcal/mol.

Mechanistic and stereochemical dependency

- The *mechanistic* and *stereochemical* details of hydrogen halide addition depend on *the reactant structure*.
- Alkenes that form relatively *unstable carbocations* are likely to react via a *termolecular complex* and exhibit *anti* stereospecificity.
- Alkenes that can form *more stable cations* can react via *rate-determining protonation* and the *structure and stereochemistry* of the product are determined by the *specific properties of the cation*.

Acid-Catalyzed Hydration Addition Reactions



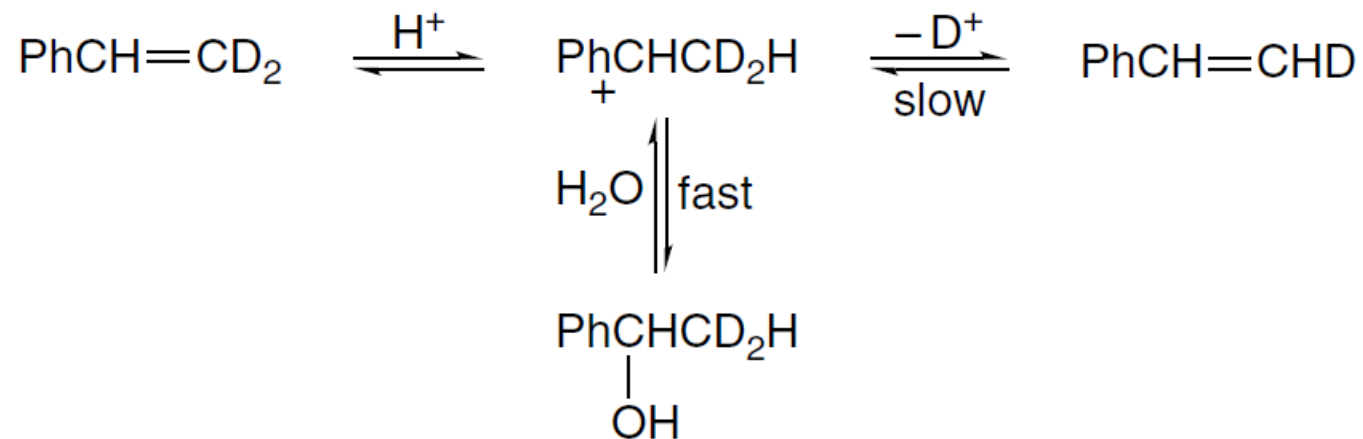
Markovnikov's rule

1- Is the protonation step reversible? 2- Is there a discrete carbocation intermediate, or does the nucleophile become involved before proton transfer is complete? 3- Can other reactions of the carbocation, such as rearrangement, compete with capture by water?

Substituents and Isotope Effects

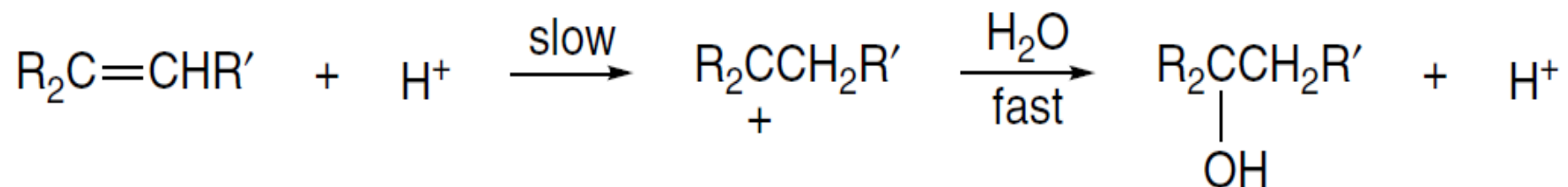
- With styrenes, the rate of hydration is increased by ERG substituents and there is an excellent correlation with σ^+ .
- A substantial solvent isotope effect $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}}$ equal to 2 to 4 is observed.
- Both of these observations are in accord with a rate-determining protonation to give a carbocation intermediate. Capture of the resulting cation by water is usually fast relative to deprotonation.

Reversibility and Isotope Exchange



The overall process is reversible, however, and some styrene remains in equilibrium with the alcohol, so isotopic exchange eventually occurs.

Alkenes Lacking Phenyl Substituents Mechanism



Alkenes lacking phenyl substituents appear to react by a *similar mechanism*.

Both the observation of *general acid catalysis and solvent isotope effect* are consistent with *rate-limiting protonation of alkenes* such as 2-methylpropene and 2,3-dimethyl-2-butene.

Alkenes Lacking Phenyl Substituents Mechanism

- The $1:10^7:10^{12}$ relative rates for ethene, propene, and 2-methylpropene illustrate the dramatic *rate enhancement by alkyl substituents*.
- *Strained alkenes* show *enhanced reactivity* toward *acid-catalyzed hydration*.
- *trans-Cyclooctene* is about **2500 times** as reactive as the *cis isomer*, which reflects the **higher ground state energy** of the strained alkene.

Table 5.1. Rates of Alkene Hydration in Aqueous Sulfuric Acid^a

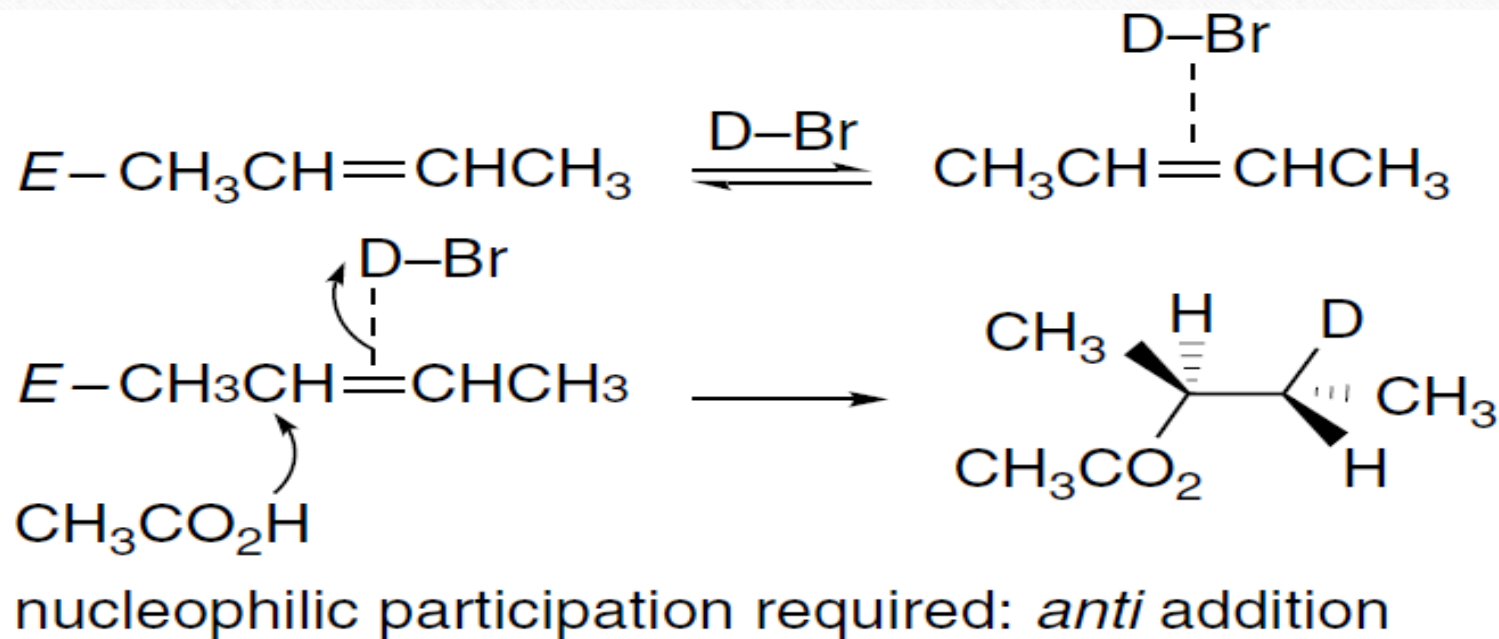
Alkene	$k_2 (M^{-1}s^{-1})$	k_{rel}
$\text{CH}_2=\text{CH}_2$	1.56×10^{-15}	1
$\text{CH}_3\text{CH}=\text{CH}_2$	2.38×10^{-8}	1.6×10^7
$\text{CH}_3(\text{CH}_2)_3\text{CH}=\text{CH}_2$	4.32×10^{-8}	3.0×10^7
$(\text{CH}_3)_2\text{C}=\text{CHCH}_3$	2.14×10^{-3}	1.5×10^{12}
$(\text{CH}_3)_2\text{C}=\text{CH}_2$	3.71×10^{-3}	2.5×10^{12}
$\text{PhCH}=\text{CH}_2$	2.4×10^{-6}	1.6×10^9

a. W. K. Chwang, V. J. Nowlan, and T. T. Tidwell, *J. Am. Chem. Soc.*, **99**, 7233 (1977).

Addition of alcohols

- The **strongest acid** catalysts probably react via **discrete carbocation intermediates**, whereas **weaker acids** may involve **reaction of the solvent with an alkene-acid complex**.
- In the addition of **acetic acid** to Z- or E-2-butene, **the use of DBr as the catalyst results in stereospecific *anti* addition**, whereas the **stronger acid $\text{CF}_3\text{SO}_3\text{H}$ leads to loss of stereospecificity**.
- **This difference in stereochemistry** can be explained by a **stereospecific $\text{Ad}_\text{E}3$ mechanism** in the case of **DBr** and an **$\text{Ad}_\text{E}2$ mechanism** in the case of **$\text{CF}_3\text{SO}_3\text{D}$** .

Dependence of Stereochemistry on Acid Strength

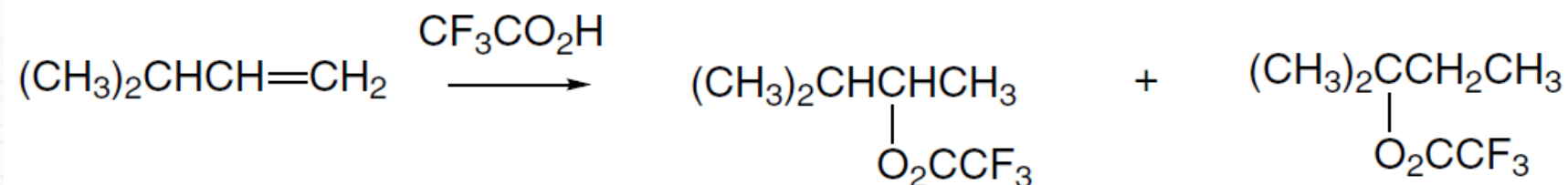


The dependence of stereochemistry on acid strength reflects the degree to which nucleophilic participation is required to complete proton transfer.

No Need for Stronger Acid Catalyst

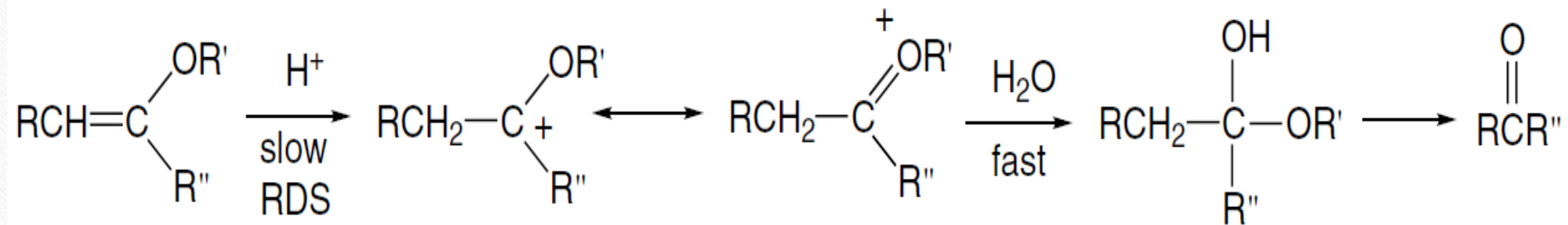
- Trifluoroacetic acid adds to alkenes without the necessity of a stronger acid catalyst. The mechanistic features of this reaction are similar to addition of water catalyzed by strong acids.
- For example, there is a substantial isotope effect when $\text{CF}_3\text{CO}_2\text{D}$ is used ($k_{\text{H}}/k_{\text{D}} = 4.33$) and the reaction rates of substituted styrene are correlated with σ^+ .

No Need for Stronger Acid Catalyst



2-Methyl-1-butene and 2-methyl-2-butene appear to react via the 2-methylbutyl cation, and 3-methyl-1-butene gives the products expected for a carbocation mechanism, including rearrangement. These results are consistent with rate-determining protonation.

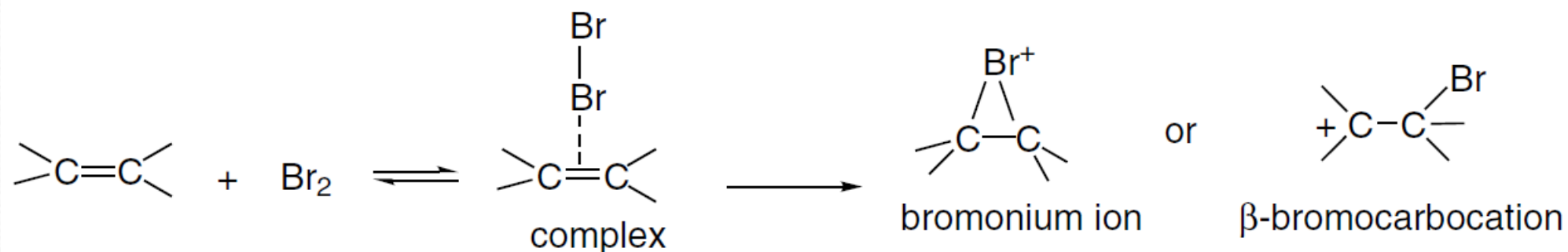
The reaction of vinyl ethers with water in acidic solution



Addition of Halogens

- The order of reactivity is $F_2 > Cl_2 > Br_2 > I_2$.
- Fluorination is strongly exothermic and difficult to control, whereas for iodine the reaction is easily reversible.
- Whether a bridged intermediate or a carbocation is formed depends on the stability of the potential cation.
- Aliphatic systems normally react through the bridged intermediate but styrene are borderline cases.
- When the phenyl ring has an ERG substituent, there is sufficient stabilization to permit carbocation formation, whereas EWGs favor the bridged intermediate.

Solvent Dependence



Because this step involves formation of charged intermediates, it is strongly solvent dependent. Even a change from CCl_4 to 1,2-dichloroethane accelerates the reaction (with cyclohexene) by a factor of 10^5 .

Kinetics of Bromination

The kinetics of bromination reactions are often complex, with at least three terms making contributions under given conditions.

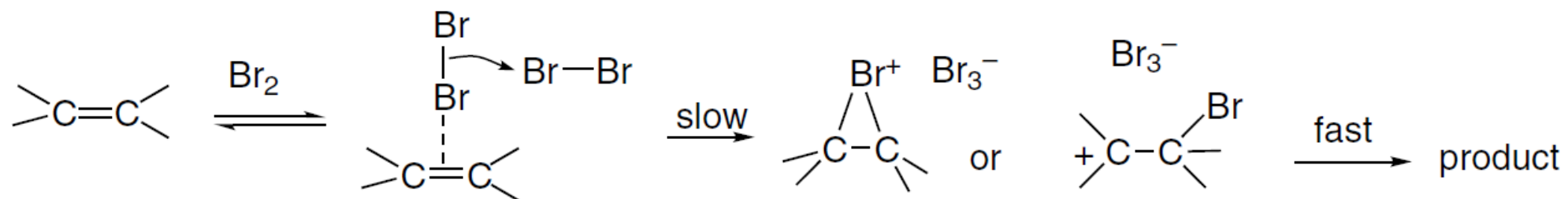
$$\text{Rate} = k_1[\text{alkene}][\text{Br}_2] + k_2[\text{alkene}][\text{Br}_2]^2 + k_3[\text{alkene}][\text{Br}_2][\text{Br}^-]$$

In methanol, pseudo-second-order kinetics are observed when a high concentration of Br^- is present.

Under these conditions, the dominant contribution to the overall rate comes from the third term of the general expression.

In nonpolar solvents, the observed rate is frequently described as a sum of the first two terms in the general expression.

Mechanism of the Third-Order Reaction



*The mechanism of the third-order reaction is similar to the process that is first order in Br_2 , but with a **second Br_2 molecule replacing solvent in the rate-determining** conversion of the complex to an ion pair.*

Similarities in the Second- and Third-Order Reaction

- There are strong similarities in the second- and third-order reaction in terms of magnitude of values and product distribution. In fact, there is a quantitative correlation between the rate of the two reactions over a broad series of alkenes, which can be expressed as:

$$\Delta G_3^\ddagger = \Delta G_2^\ddagger + \text{constant}$$

where $\Delta G_3^\ddagger$ and $\Delta G_2^\ddagger$ are the free energies of activation for the third- and second-order processes, respectively. ***These correlations suggest that the two mechanisms must be very similar.***

Table 5.2. Relative Reactivity of Alkenes toward Halogenation

Alkene	Relative reactivity		
	Chlorination ^a	Bromination ^b	Bromination ^c
Ethene		0.01	0.0045
1-Butene	1.00	1.00	1.00
3,3-Dimethyl-1-butene	1.15	0.27	1.81
<i>Z</i> -2-Butene	63	27	173
<i>E</i> -2-Butene	50	17.5	159
2-Methylpropene	58	57	109
2-Methyl-2-butene	1.1×10^4	1.38×10^4	
2,3-Dimethyl-2-butene	4.3×10^5	19.0×10^4	

a) In excess alkene; b) in methanol; c) in $\text{ClCH}_2\text{CH}_2\text{Cl}$.

Impurity

- Observed bromination rates are very sensitive to common *impurities such as HBr and water*, which can assist in formation of the *bromonium ion*.
- Chlorination generally exhibits second-order kinetics, first-order in both alkene and chlorine. The reaction rate increases with alkyl substitution, as would be expected for an electrophilic process.
- The magnitude of the rate increase is quite large, but not as large as for protonation.

Syn and Anti Addition

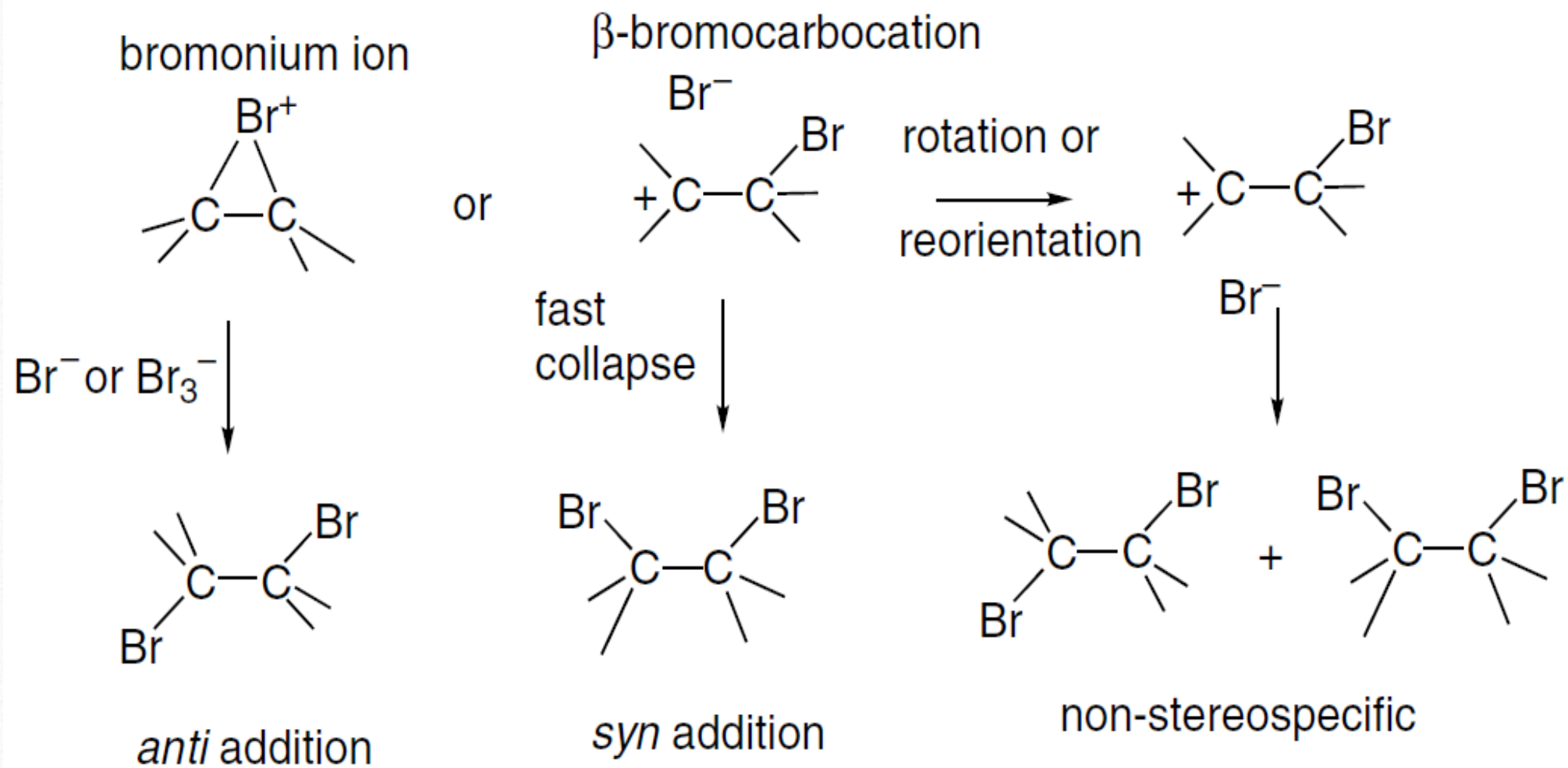
- All these features are in accord with an electrophilic mechanism.
- For brominations, *anti* addition is preferred for *alkenes lacking substituent groups* that can strongly stabilize a carbocation intermediate.
- When the *alkene is conjugated with an aryl group*, the extent of *sin* addition increases and can become the dominant pathway.
- Chlorination is not *as likely to be as stereospecific* as bromination, but tends to follow the same pattern.
- The Hammett correlation for bromination of styrenes is best with σ^+ substituent constants, and gives $\rho = -4.8$.

Table 5.3. Stereochemistry of Alkene Halogenation

Alkene	Solvent	Ratio <i>anti:syn</i>
A. Bromination		
Z-2-Butene ^a	CH ₃ CO ₂ H	> 100 : 1
E-2-Butene ^a	CH ₃ CO ₂ H	> 100 : 1
Cyclohexene ^b	CCl ₄	Very large
Z-1-Phenylpropene ^c	CCl ₄	83:17
E-1-Phenylpropene ^c	CCl ₄	88:12
Z-2-Phenylbutene ^a	CH ₃ CO ₂ H	68:32
E-2-Phenylbutene ^a	CH ₃ CO ₂ H	63:37
<i>cis</i> -Stilbene ^d	CCl ₄	> 10 : 1
	CH ₃ NO ₂ ^d	1:9
B. Chlorination		
Z-2-Butene ^e	None	> 100 : 1
	CH ₃ CO ₂ H ^f	> 100 : 1
E-2-Butene ^e	None	> 100 : 1
	CH ₃ CO ₂ H ^f	> 100 : 1
Cyclohexene ^g	None	> 100 : 1
E-1-Phenylpropene ^f	CCl ₄	45:55
	CH ₃ CO ₂ H ^f	41:59
Z-1-Phenylpropene ^f	CCl ₄	32:68
	CH ₃ CO ₂ H ^f	22:78
<i>Cis</i> -Stilbene ^h	ClCH ₂ CH ₂ Cl	8:92
<i>Trans</i> -Stilbene ^h	ClCH ₂ CH ₂ Cl	35:65

Syn and Anti Additions

- When the reaction with Br₂ involves a bromonium ion, the *anti* stereochemistry can be readily explained.
- On the other hand, a freely rotating open β-bromo carbocation can give both the *syn* and *anti* addition products.
- If the principal intermediate is an ion pair that collapses faster than rotation occurs about the C–C bond, *syn* addition can predominate.



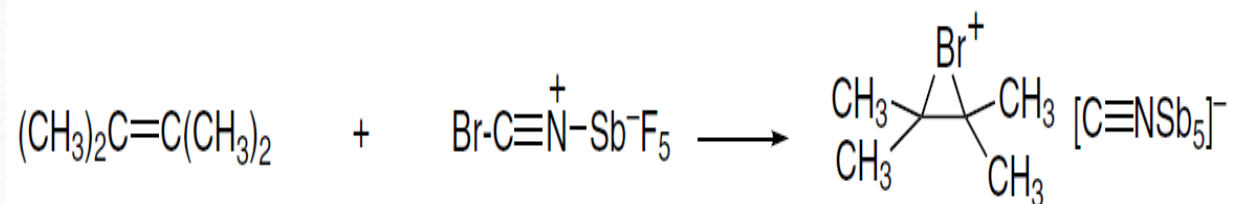
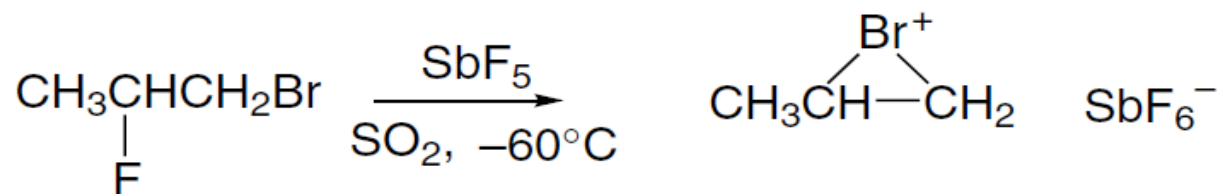
Bridged Carbocation

- Substituent effects on stilbenes show the role of bridged ions versus nonbridged carbocation intermediates.
- In aprotic solvents, stilbene gives clean *anti* addition, but 4, 4'-dimethoxystilbene gives a mixture of the *syn* and *anti* addition products indicating a carbocation intermediate.
- Nucleophilic solvents compete with bromide, but *anti* stereoselectivity is still observed, except when ERG substituents are present.
- It is proposed that *anti* stereoselectivity can result not only from a bridged ion intermediate, but also from very fast capture of a carbocation intermediate.

Bridged Carbocation

- Interpretation of the ratio of capture by competing nucleophiles has led to the estimate that the bromonium ion derived from cyclohexene has a lifetime on the order of 10^{-10} s in methanol, which is about 100 times longer than for secondary carbocations.
- Chlorine is a somewhat poorer bridging group than bromine because it is less polarizable and more resistant to becoming positively charged.
- Comparison of the data for E- and Z-1-phenylpropene in bromination and chlorination confirms this trend (see Table 5.3).
- Although *anti* addition is dominant for bromination, *syn* addition is slightly preferred for chlorination.

Bridged Carbocation



There is direct evidence for the existence of bromonium ions. The bromonium ion related to propene can be observed by NMR when 1-bromo-2-fluoropropane is subjected to *superacid conditions*.

Styrenes generally appear to react with chlorine via ion pair intermediates.

Highly Hindered Alkene

- The highly hindered alkene adamantylideneadamantane forms a bromonium ion that crystallizes as a tribromide salt.
- This particular bromonium ion does not react further because of extreme steric hindrance to back-side approach by bromide ion.
- Other very hindered alkenes allow observation of both the initial complex with Br_2 and the bromonium ion.
- An X-ray crystal structure has confirmed the cyclic nature of the bromonium ion species (Figure 5.2).

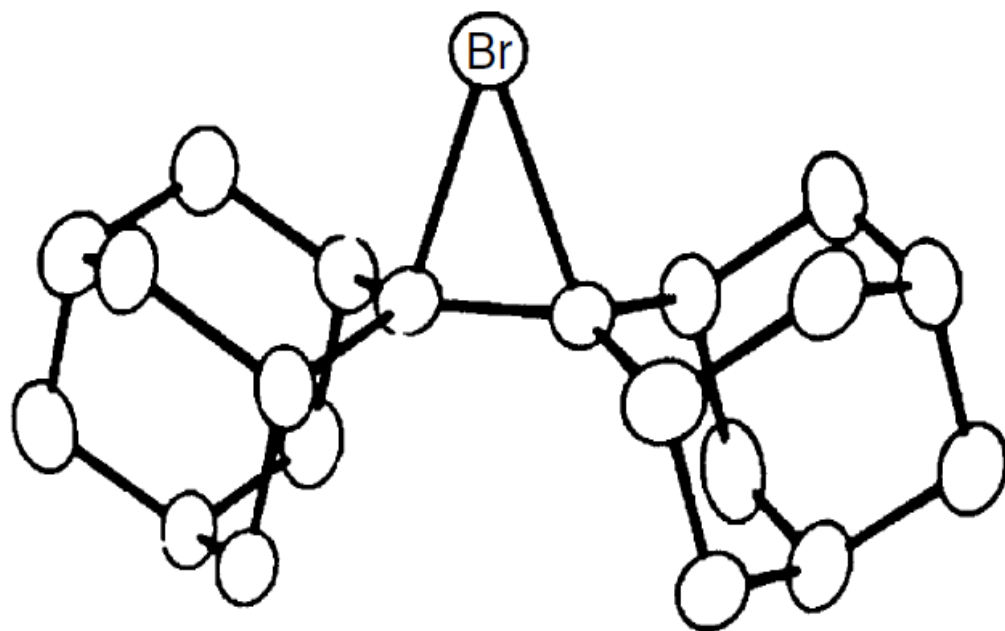
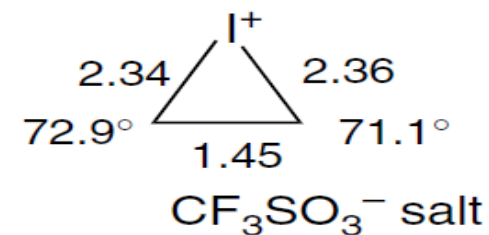
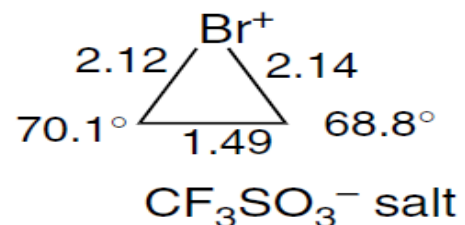
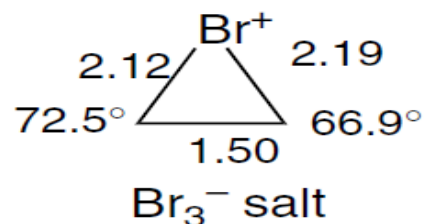
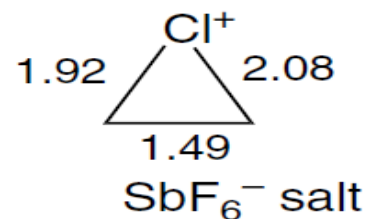


Fig. 5.2. X-ray crystal structure of the bromonium ion from adamantylideneadamantane. Reproduced from *J. Am. Chem. Soc.*, **107**, 4504 (1985), by permission of the American Chemical Society.

- Crystal structures have also been obtained for the corresponding chloronium and iodonium ions and for the bromonium ion with a triflate counterion.



- Each of these structures is somewhat unsymmetrical, as shown by the dimensions above. The significance of this asymmetry is not entirely clear.
- It has been suggested that the bromonium ion geometry is *affected by the counter ion* and it can be noted that the *triflate salt* is more symmetrical than the *tribromide*.
- On the other hand, the dimensions of the unsymmetrical chloronium ion, where the difference is considerably larger, has been taken as evidence that the bridging is inherently unsymmetrical⁶⁰

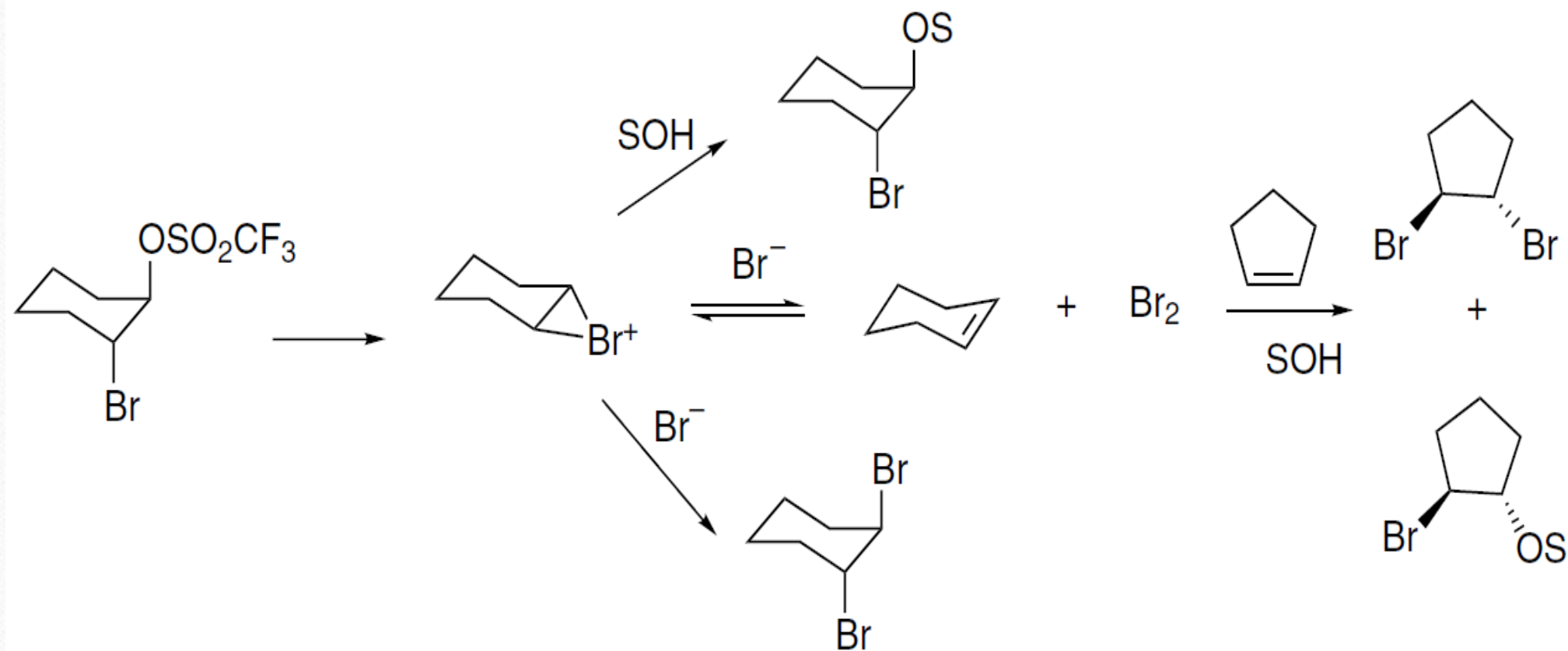
Reversibility

Reversibility has been demonstrated for *highly hindered alkenes*, and attributed to a relatively *slow rate of nucleophilic capture*. However, even the bromonium ion from cyclohexene appears to be able to release Br_2 on the reaction with Br^- .

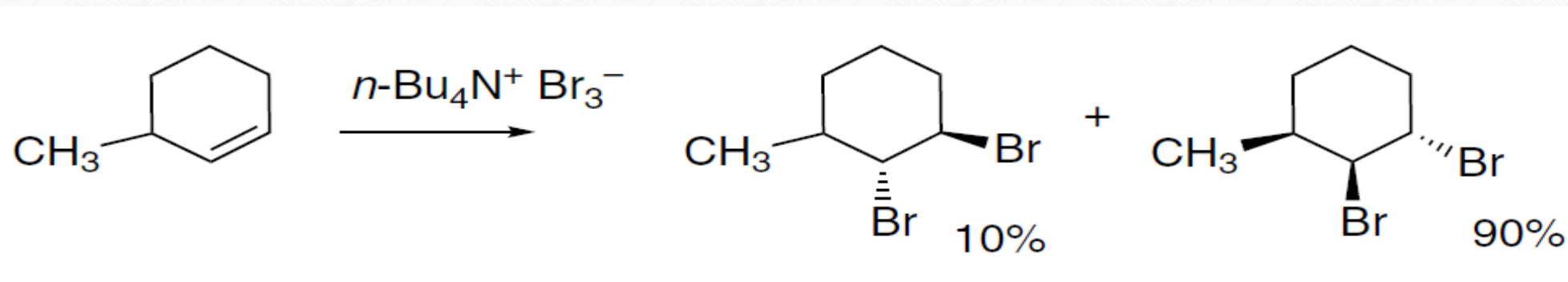
The bromonium ion can be generated by neighboring-group participation by solvolysis of *trans*-2-bromocyclohexyl triflate.

If cyclopentene, which is more reactive than cyclohexene, is included in the reaction mixture, bromination products from cyclopentene are formed.

This indicates that free Br_2 is generated by reversal of bromonium ion formation. Other examples of reversible bromonium ion formation have been found.



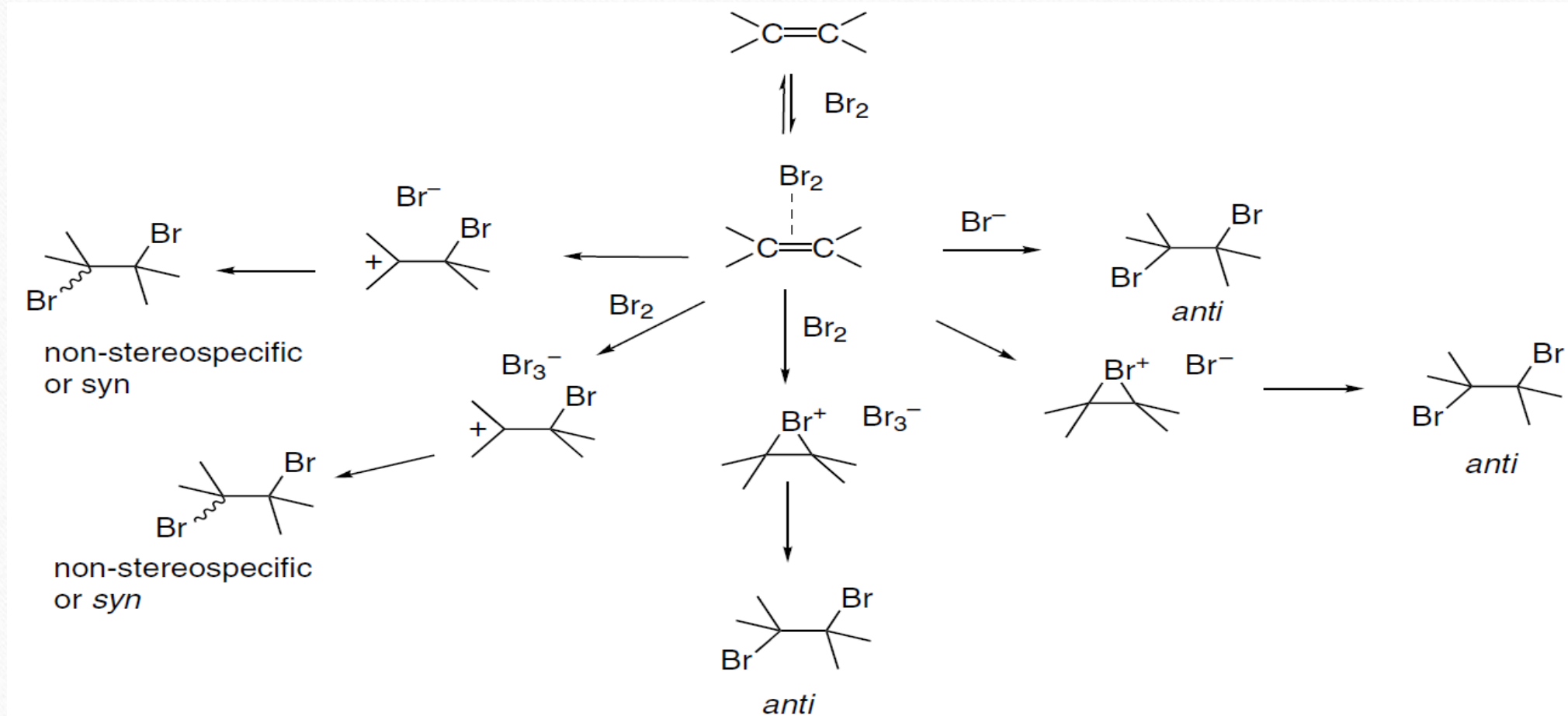
Bromination with Br^{-3}



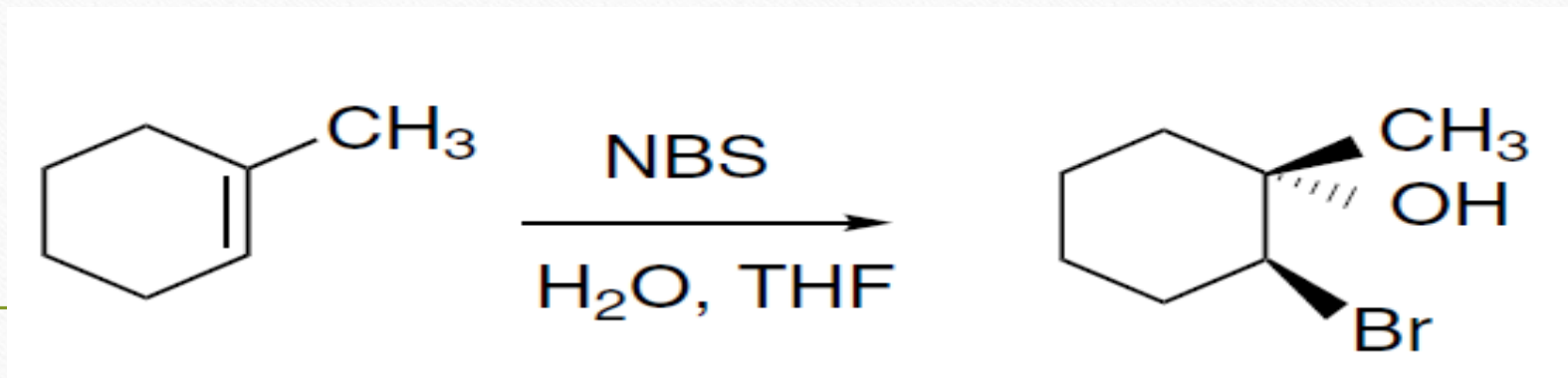
- **Bromination** also can be carried out with reagents that supply **bromine** in the form of the Br^{-3} **anion**.
- One such reagent is **pyridinium bromide tribromide**. Another is **tetrabutylammonium tribromide**.
- These reagents are believed to react **via the Br_2 -alkene complex** and have a strong preference for ***anti* addition**.

Summery

- In summary, it appears that **bromination** usually involves a **complex** that collapses to ***an ion pair intermediate***.
- The **ionization generates charge separation** and is assisted by ***solvent, acids, or a second molecule of bromine***.
- The **cation** can be a **β -carbocation**, as in the case of styrenes, or ***a bromonium ion***.
- Reactions that proceed through **bromonium ions** are ***stereospecific anti additions***.

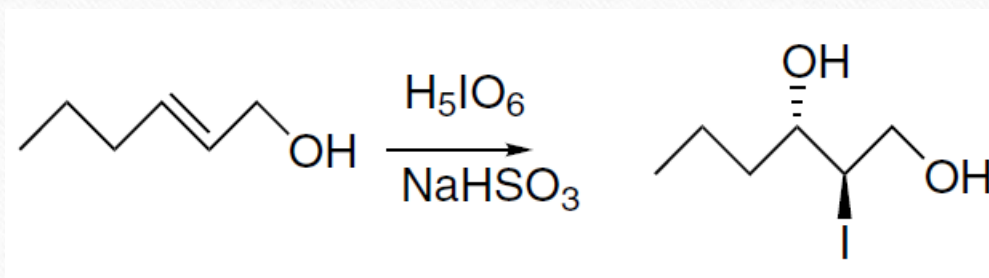


Reactions that proceed through open carbocations can be syn selective or nonstereospecific.



- The carbocation can be *captured by solvent*.
- Halogenation with solvent capture gives *halohydrins*
- Chloramine T for chlorohydrin (p-CH₃C₆H₄SO₂N⁻Cl Na⁺).
- NBS/Aqueous solvent mixture for bromohydrins.

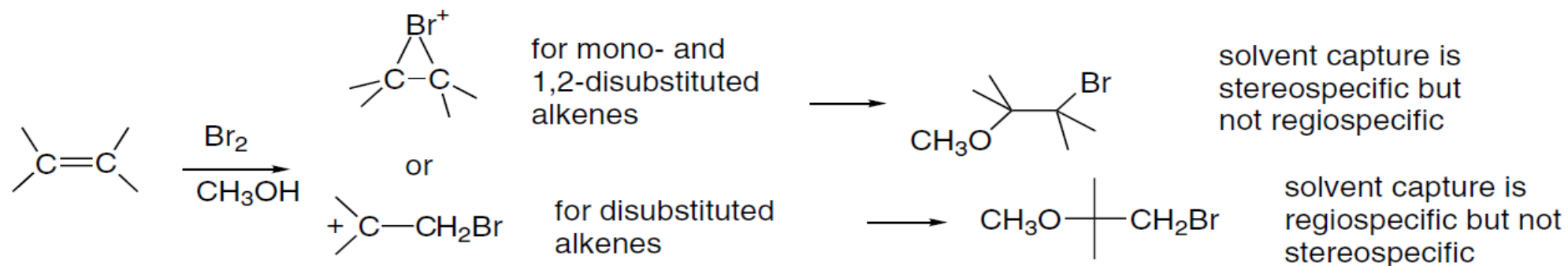
Halohydrins



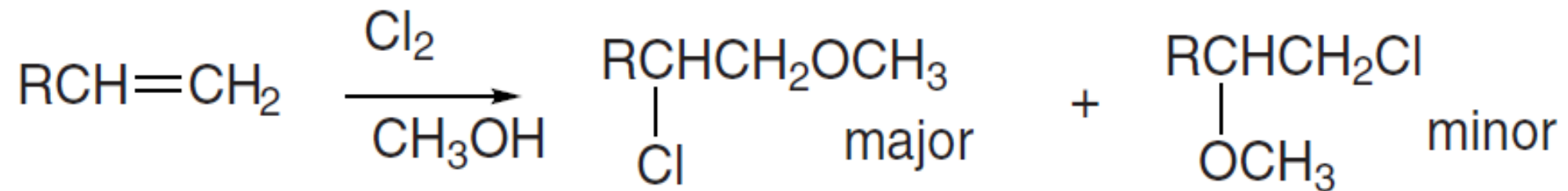
Iodohydrins can be prepared using iodine or phenyliodonium di-trifluoroacetate.

Iodohydrins can be prepared in generally *good yield* and *high anti stereoselectivity* using H_5IO_6 and NaHSO_3 .

These reaction conditions generate *hypoiodous acid*.

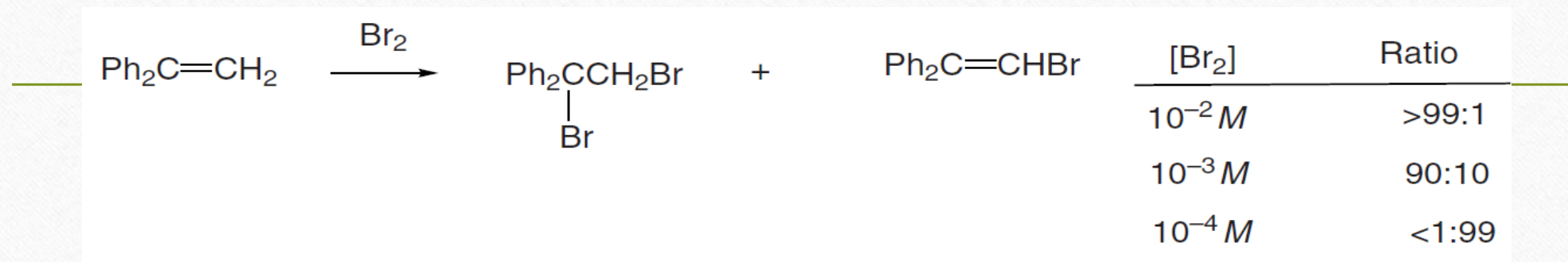


- For both E- and Z-disubstituted alkenes, the addition of both methanol and Br^- was completely:
- **1. anti**
- **2. stereospecific**
- **regioselective**, in accordance with Markovnikov's rule, for disubstituted alkenes, *but not for monosubstituted alkenes*.



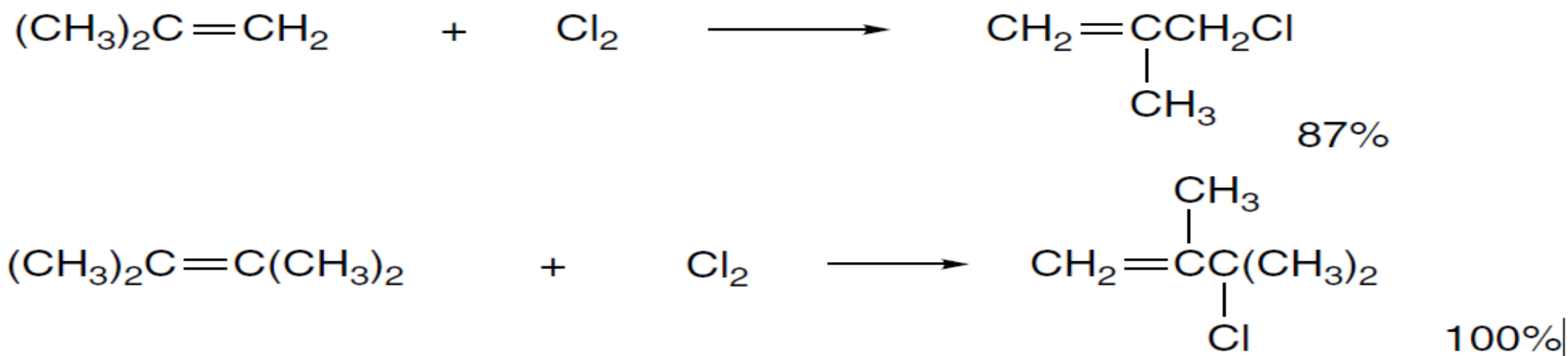
- **Similar results** were obtained for chlorination of several of alkenes in methanol.
- This result is *indicative of strong bridging* in the chloronium ion.
- Styrene gave only the Markovnikov product.
- Propene, hexene, and similar alkenes gave more of the *anti* Markovnikov product.

Substitution Reactions



Some alkenes react with halogens to give *substitution rather than addition*.

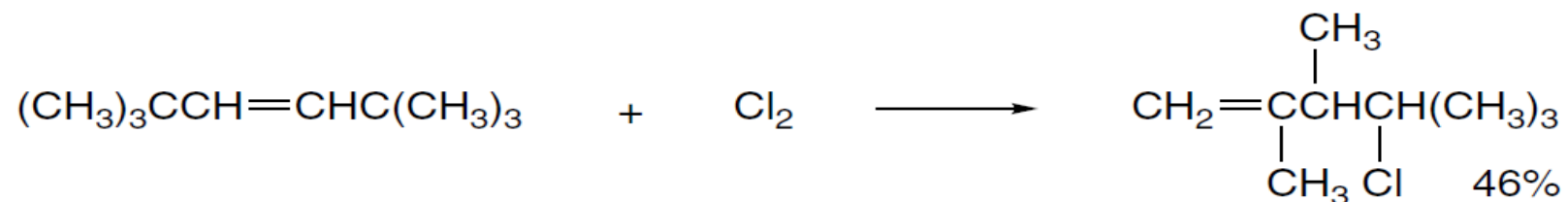
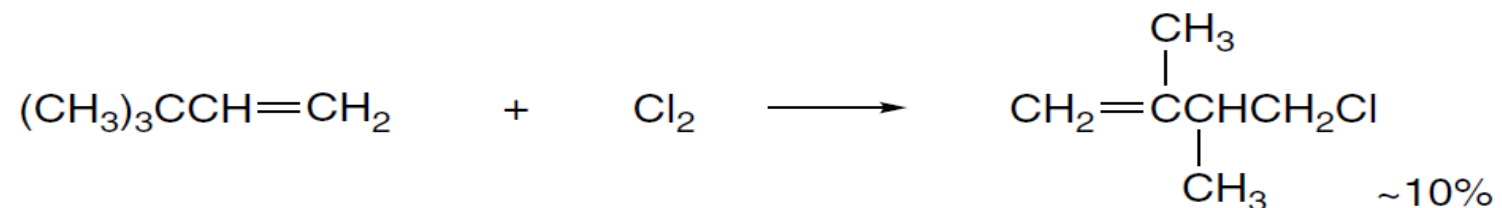
For example, with *1,1-diphenylethene*, *substitution is the main reaction at low bromine concentration*. Substitution occurs when loss of a proton is faster than capture by bromide.



Similarly, in chlorination, **loss of a proton can be a competitive reaction** of the cationic intermediate. 2-Methylpropene and 2,3-dimethyl-2-butene give products of this type.

Alkyl Migration

Alkyl migrations can also occur.

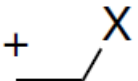
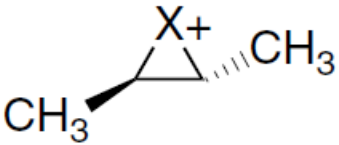
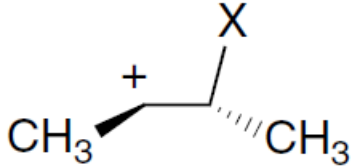


Both *proton loss* and *rearrangement* are more likely in *chlorination* than in *bromination* because of the *weaker bridging by chlorine*.

Computational Investigation

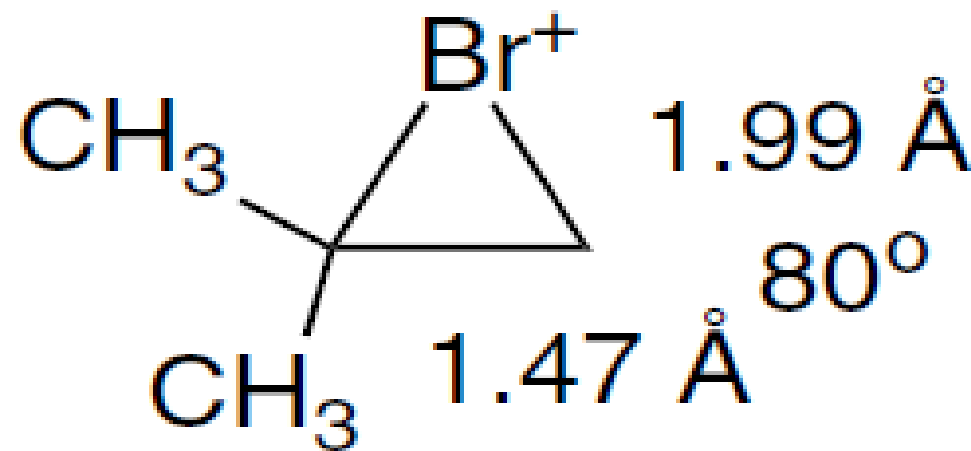
- In the gas phase, formation of the charged halonium ions from halogen and alkene is energetically prohibitive, and halonium ions are not usually found to be stable by these calculations.
- Bromonium ions were found to be unsymmetrical, with weaker bridging to the more stabilized carbocation.
- Open and bridged $[\text{CH}_2\text{CH}_2\text{X}]^+$ and $[\text{CH}_3\text{CHCHXCH}_3]^+$ ions are compared. The bridged halo ethyl ion was favored slightly for $\text{X} = \text{F}$ and strongly for $\text{X} = \text{Cl}$ and Br .
- For the 3-halo-2-butyl ions, open structures were favored for F and Cl , but the bridged structure remained slightly favored for Br .

Relative Stabilities

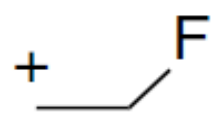
X		+ 		
F	274.3	278.6	249.9	227.6
Cl	253.4	277.8	233.8	230.6
Br	239.9	270.8	221.6	225.0

Hydride affinity in kcal/mol

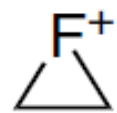
The relative stabilities, as measured by hydride affinity are given below



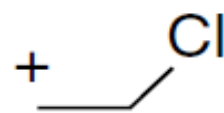
- The computed structure of bromonium ions from alkenes such as *2-methylpropene* are highly *dependent on the computational method* used and inclusion of correlation is essential. CISD/DZV calculations gave the above structural characteristics.



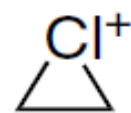
0.0



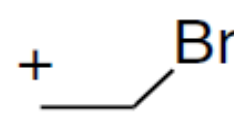
27.7



0.0



3.3



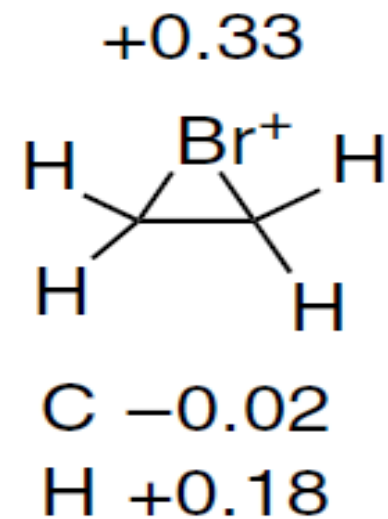
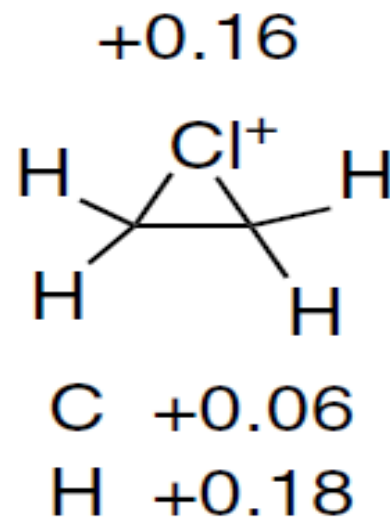
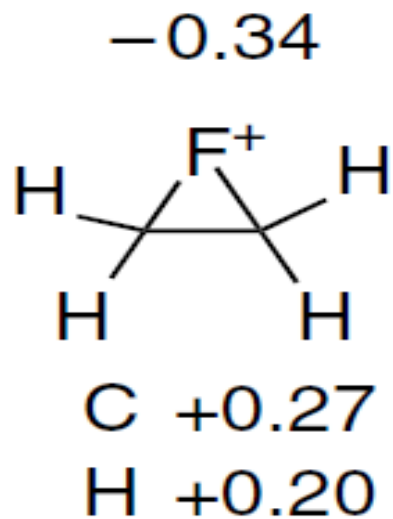
2.4



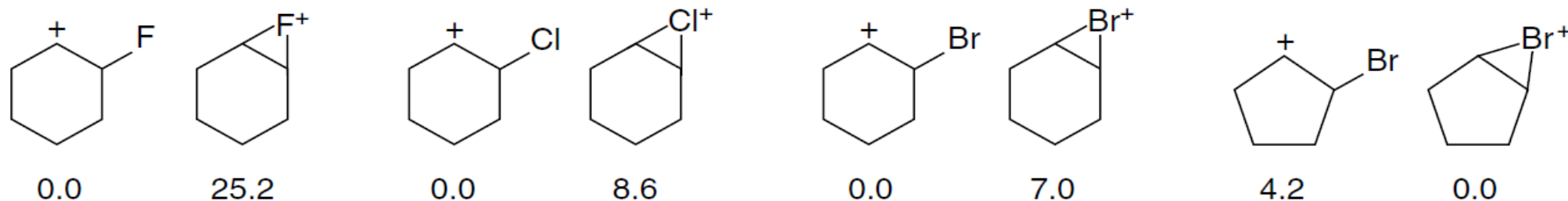
0.0

Relative energy in kcal/mol of open and bridged $[\text{C}_2\text{H}_4\text{X}]^+$ ions

Another study gives some basis for comparison of the halogens. QCISD(T)/6- 311(d,p) calculations found the open carbocation to be the most stable for $[\text{C}_2\text{H}_4\text{F}]^+$ and $[\text{C}_2\text{H}_4\text{Cl}]^+$ but the bridged ion was more stable for $[\text{C}_2\text{H}_4\text{Br}]^+$. The differences were small for Cl and Br.



AIM charges for the bridged ions were as above (MP2/6-311G(d,p)). Note the very different net charge for the different halogens.



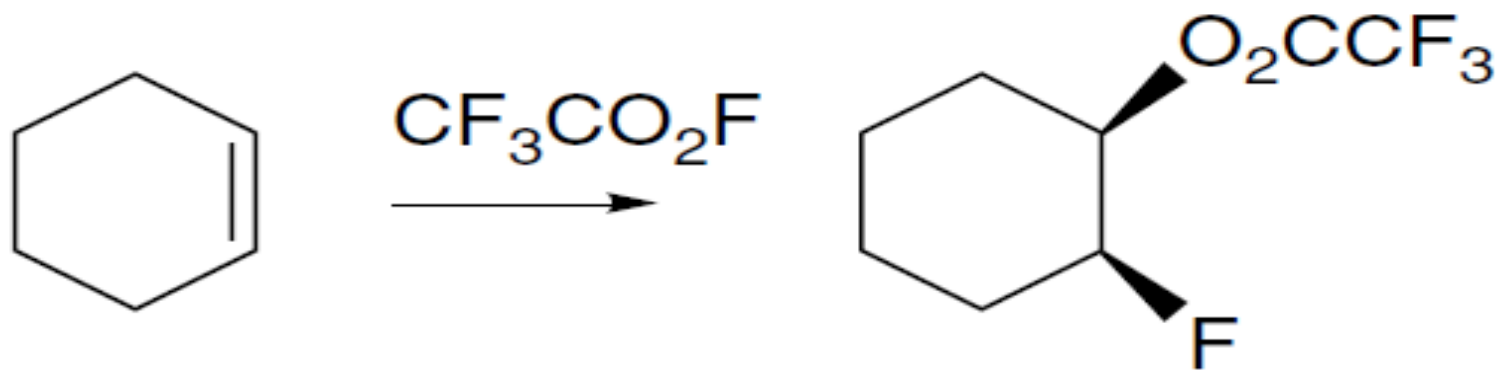
Relative stability of open and bridged cations in kcal/mol

MP2/6-311G(d,p) calculations favored open carbocations for the ions derived from cyclohexene.

On the other hand, the bridged bromonium ion from cyclopentene was found to be stable relative to the open cation.

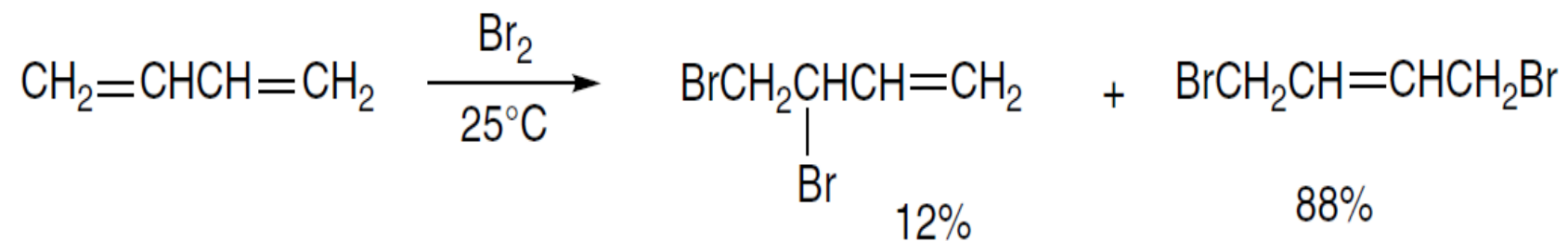
This result is in qualitative agreement with an NMR study under stable ion conditions.

- The computational results agree with the $F < Cl < Br$ order in terms of bridging.
-
- Elemental fluorine reacts violently with alkenes giving mixtures including products resulting from degradation of the carbon chain.
 - Electrophilic additions of fluorine to alkenes can be achieved with xenon difluoride, electrophilic derivatives of fluorine, or by use of highly dilute elemental fluorine at low temperature.
 - Under the last conditions, *syn* stereochemistry is observed. The reaction is believed to proceed by rapid formation and then collapse of an β -fluorocarocationfluoride ion pair.



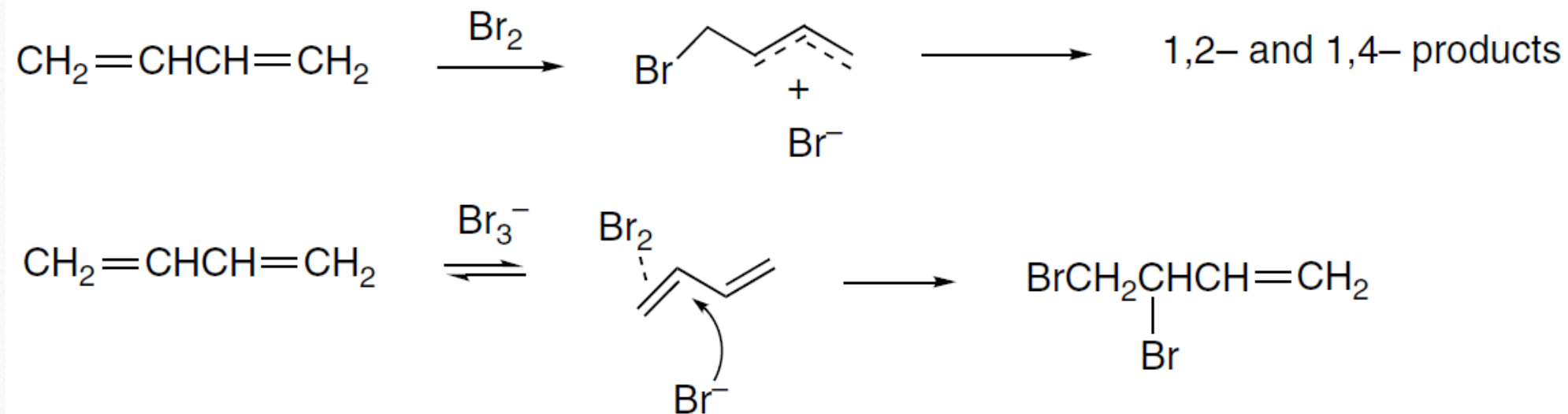
- Both from the stereochemical results and theoretical calculations, it appears *unlikely that a bridged fluoronium species is formed*.
- Acetyl hypofluorite (CH_3COOF) reacts with alkenes to give β -acetoxyalkyl fluorides.
- The reaction gives predominantly *syn* addition, which is also consistent *with rapid collapse* of a β -fluorocarocation-acetate ion pair.

-
- There are a *few mechanistic studies* on the addition of *iodine*.
 - One significant feature of *iodination* is that it is *easily reversible*, even in the presence of *excess alkene*.
 - The addition is *stereospecifically anti* but it is not entirely clear whether *a polar or a radical mechanism* is involved.



Halogenation can give **1,2- or 1,4-addition** products from conjugated dienes

The product distribution can be shifted to ***favor the 1,2-product by use of milder brominating agents*** such as the ***pyridine-bromine complex*** or the ***tribromide ion, Br^{-3}*** .



- Br_2 reacts through a cationic intermediate.
- The less reactive brominating agents reacts through the $\text{Ad}_\text{E}3$ *anti*-addition.

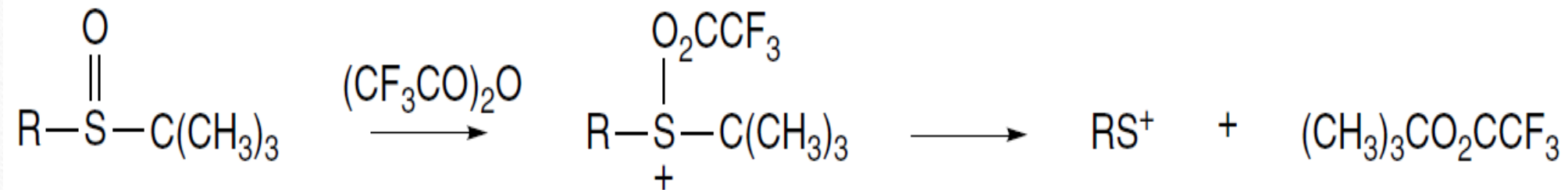
-
- ***Bromination*** is ***often*** stereospecifically ***anti*** for the ***1,2-addition*** process, whereas ***syn addition*** is preferred for ***1,4-addition***.
 - Comparable results for ***chlorination*** show ***much less stereospecificity***.

Sulfenylation and Selenenylation

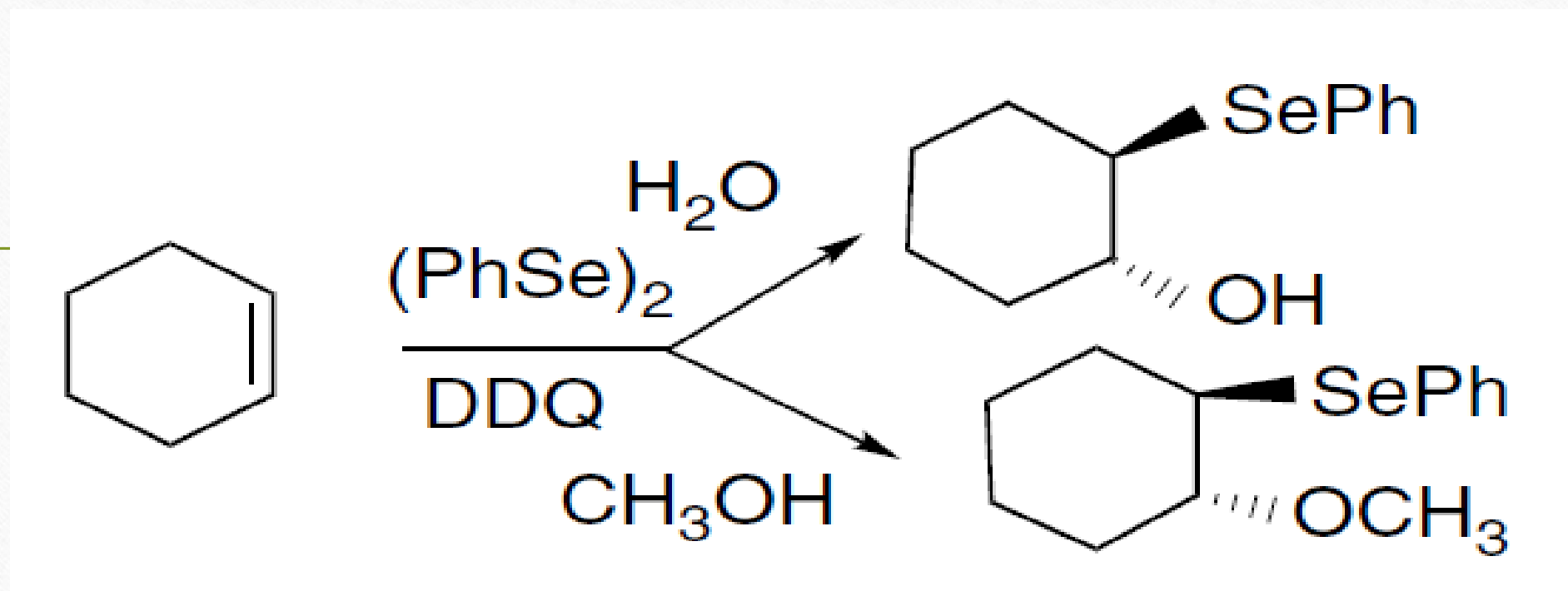
Electrophilic derivatives of both sulfur and selenium can add to alkenes.

These compounds characterized by the formulas RS-X and RSe-X , where X is a group that is more electronegative than sulfur or selenium.

The reactivity of these reagents is sensitive to the nature of both the R and the X group.



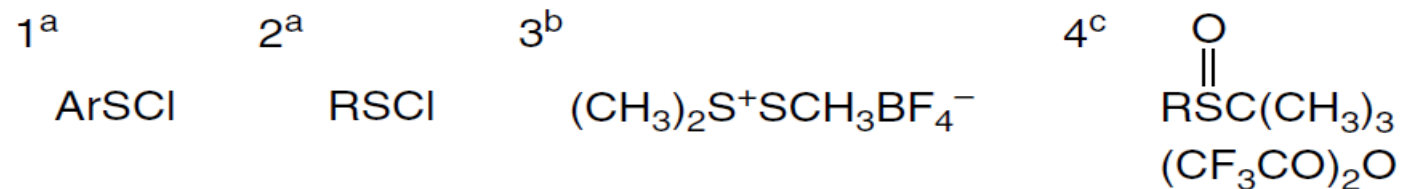
- Entry 4 is a special type of sulfenylation agent.
- The sulfoxide fragments after O-acylation, generating a **sulfenyl electrophile**.



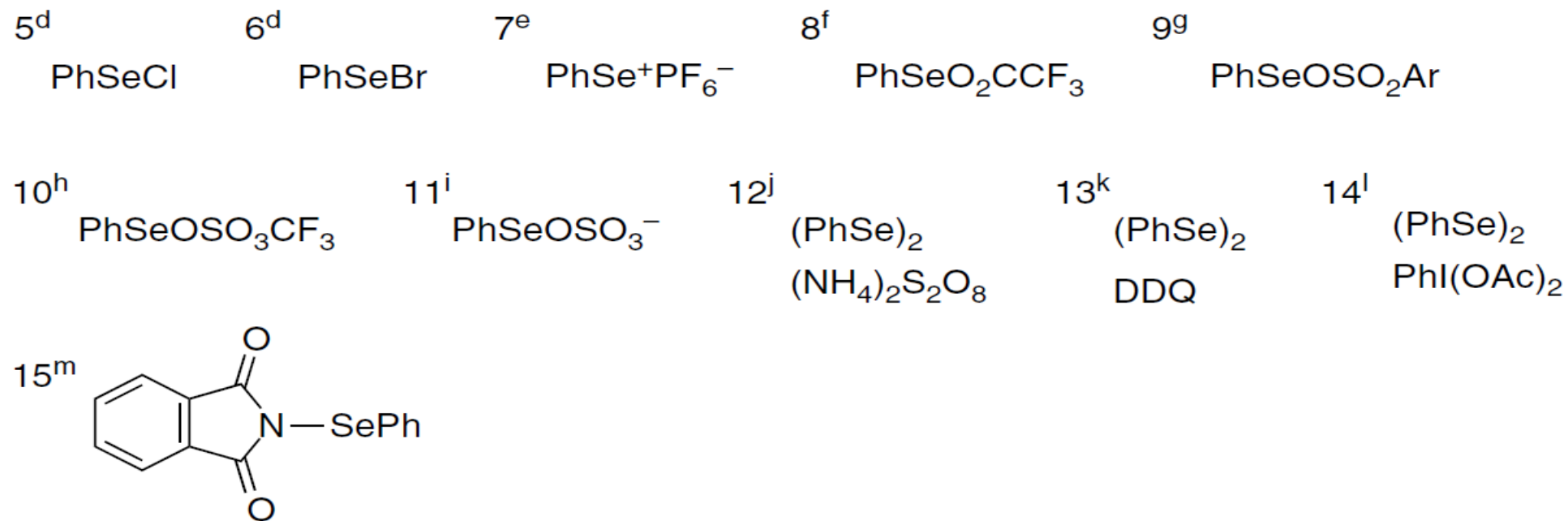
Oxidative generation of selenenylation reagents

Scheme 5.1. Electrophilic Sulfur and Selenium Reagents

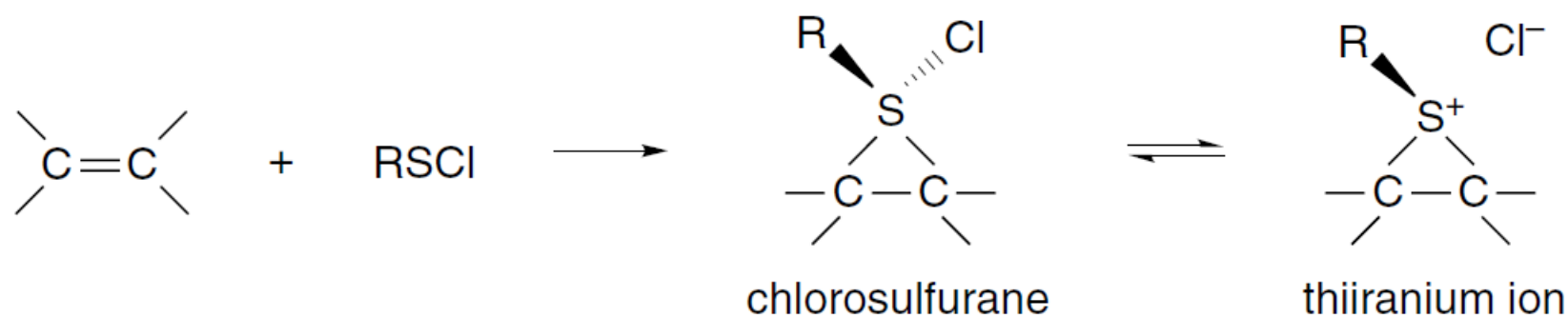
A. Sulfonylation Reagents



B. Selenenylation Reagents

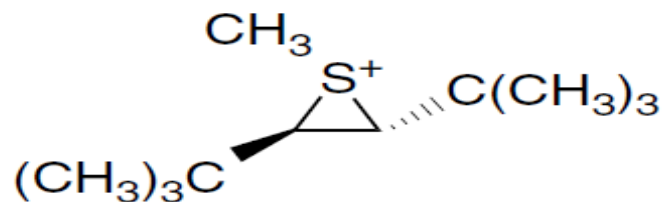
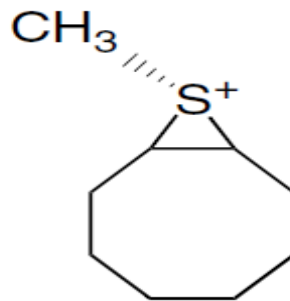


Sulfenylation



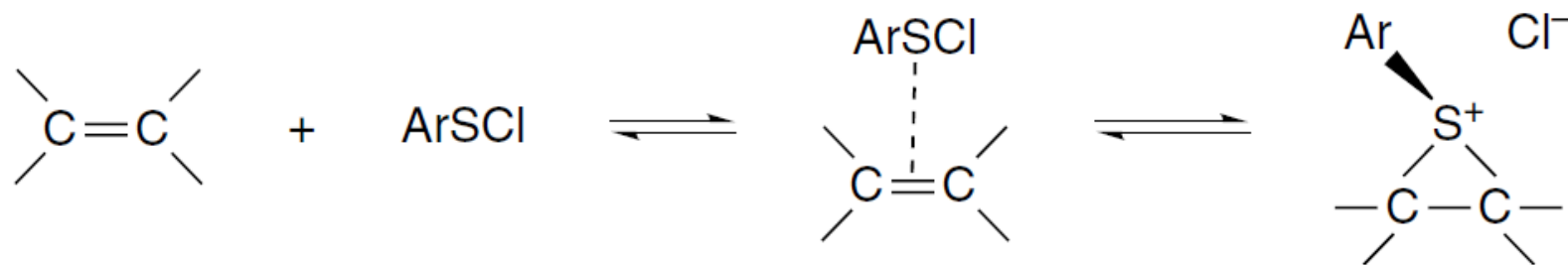
By analogy with halogenation, ***thiiranium ions can be intermediates*** in electrophilic sulfenylation.

However, the corresponding tetravalent sulfur compounds, which are called *sulfuranes*, may also lie on the reaction path.



The ***sulfur atom is a stereogenic center*** in *both* the ***sulfurane*** and the ***thiiranium ion***, and this may influence the stereochemistry of the reactions of stereoisomeric alkenes.

Perhaps the closest analog to the sulfenyl chlorides is chlorine (both are 3rd row elements).



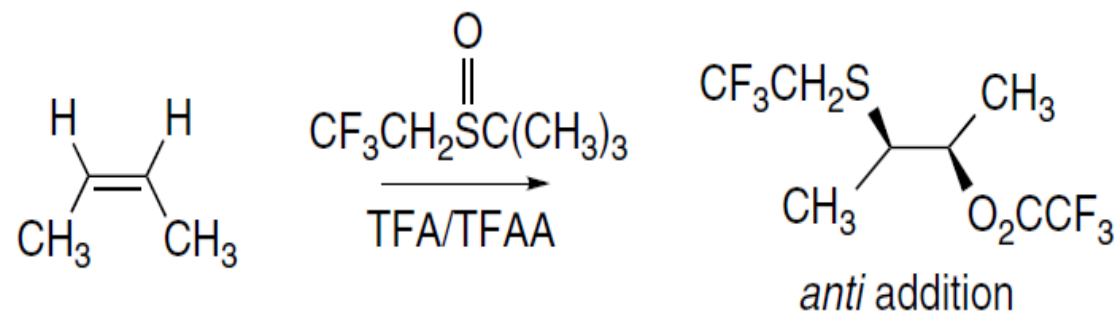
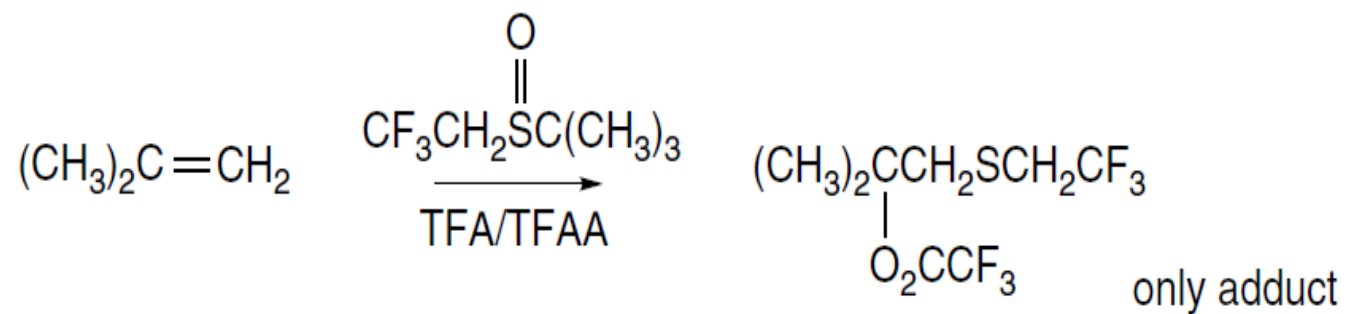
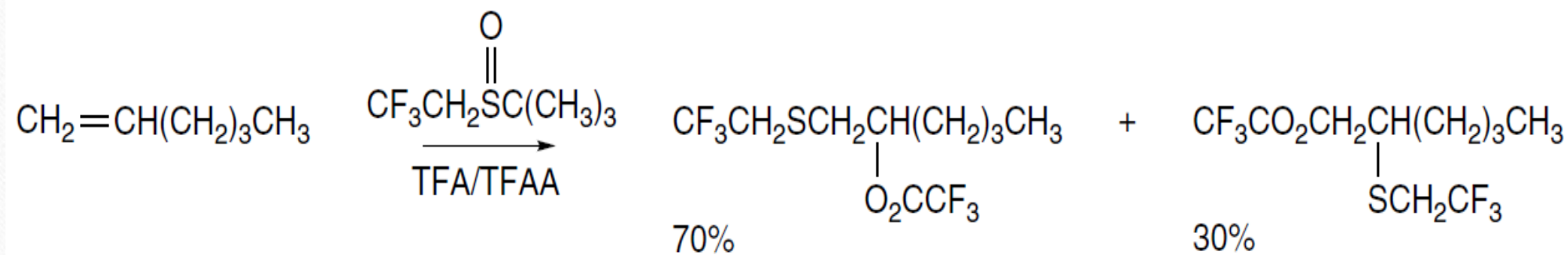
- However, the *sulfur is less electronegative* and is a much *better bridging element than chlorine*.
- Although *sulfenylation reagents are electrophilic* in character, *they are much less so than chlorine*.
- The *extent of rate acceleration* from *ethene to 2,3-dimethyl-2-butene* is only 10^2 , as compared to 10^6 for chlorination and 10^7 for bromination (see Table 5.2). The sulfur substituent can influence reactivity.

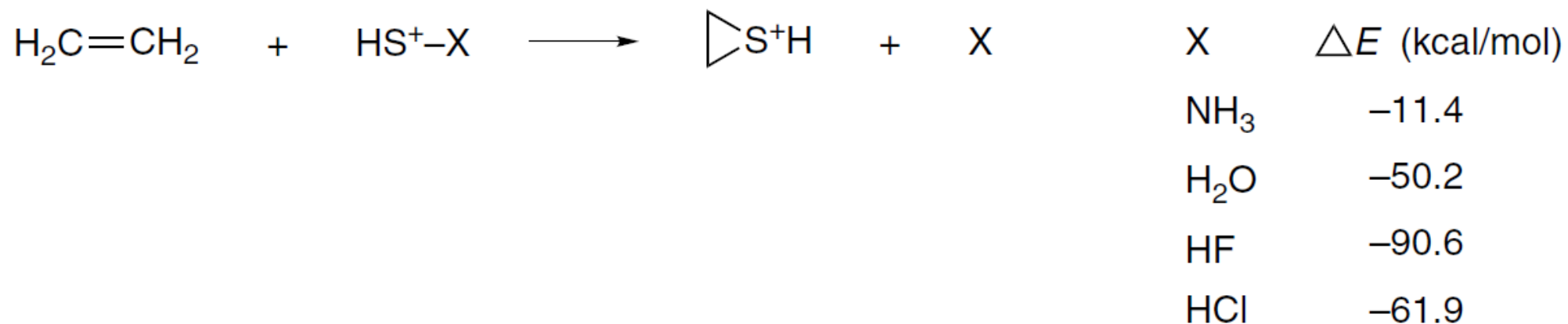
- As sulfur is less electronegative and more polarizable than chlorine, a strongly bridged intermediate, rather than an open carbocation, is expected for alkenes without ERG stabilization.
-
- Consistent with this expectation, sulfenylation is weakly regioselective and often shows a preference for anti-Markovnikov addition as the result of steric factors.
 - When bridging is strong, nucleophilic attack occurs at the less-substituted position. Table 5.4 gives some data for methyl- and phenyl- sulfenyl chloride.
 - For bridged intermediates, the stereochemistry of addition is anti. Loss of stereospecificity with strong regioselectivity is observed when highly stabilizing ERG substituents are present on the alkene, as in 4-methoxyphenylstyrene.

Table 5.4. Regiochemistry of Some Sulfenylation Reactions with Sulfenyl Chlorides

Alkene	Percent Markovnikov: <i>anti</i> -Markovnikov	
	CH ₃ SCl	PhSCl
Propene	18:82	32:68
3-Methylbutene	6:94	13:87
2-Methylpropene	20:80	
Styrene	98:2	

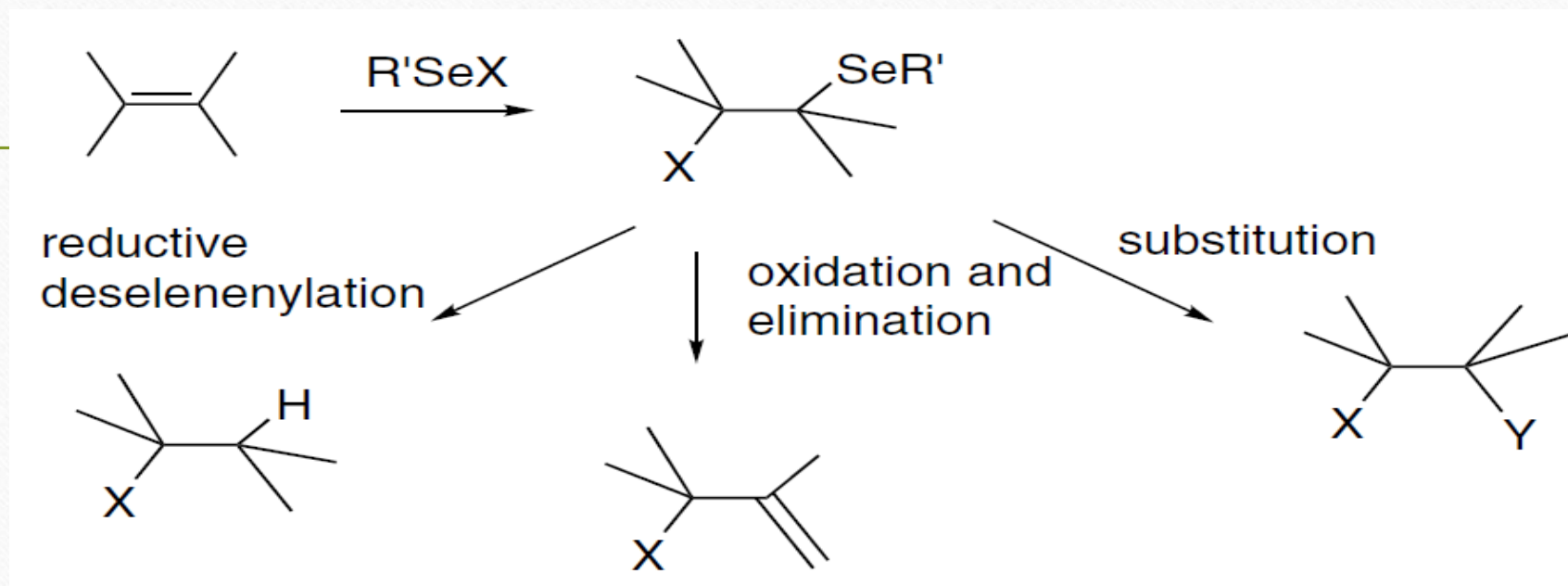
The somewhat *more electrophilic* trifluoroethylsulfenyl group shows a *shift toward Markovnikov regioselectivity* but *retains anti stereospecificity*, indicating a bridged intermediate.



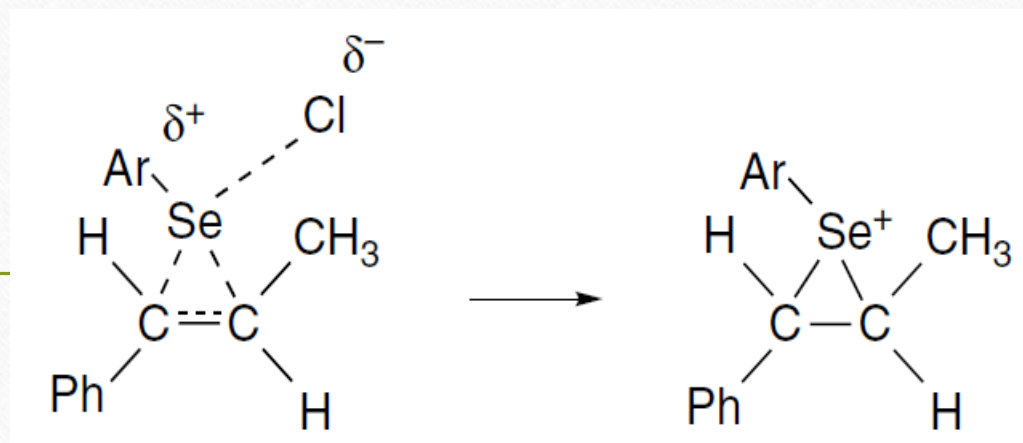


- G2 computations have been used to model the reaction of sulfenyl electrophiles with alkenes. The reactions were modeled by $\text{HS}-\text{X}^+$, where $\text{X} = \text{FH}, \text{OH}_2, \text{NH}_3$, and ClH .
- This is similar to halogenation. The overall *exothermicity calculated* for the reactions correlated with the *leaving-group ability of HX*.

Selenenylation

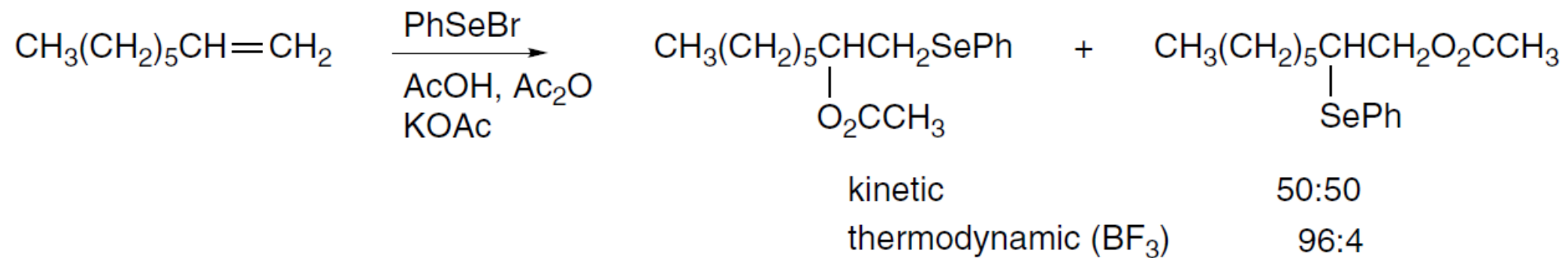


- Selenenyl substituents can be removed both reductively and oxidatively. In some cases, the selenenyl substituent can undergo substitution reactions.



- The reaction is accelerated by an *ERG* in the arylselenenides. These data were *interpreted* in terms of a *concerted addition with ionization* of the Se–Cl bond leads C–Se bond formation.
- *Bridged seleniranium* ions are considered to be *intermediates*.

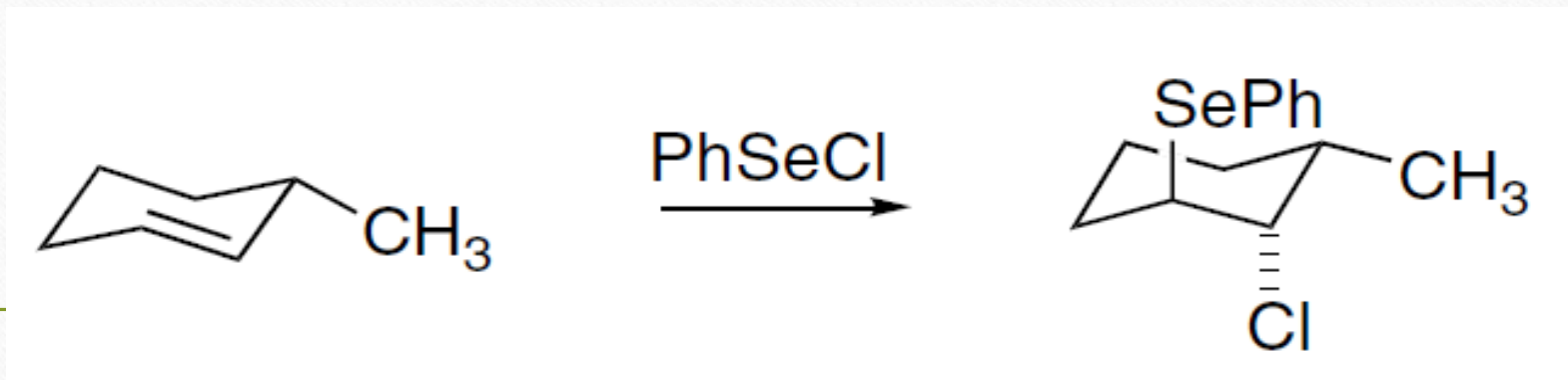
- As shown in Table 5.5, *alkyl substitution enhances the reactivity of alkenes*, but the *effect is very small* in comparison with *halogenation* (Table 5.2).
-
- *Selenenylation* seems to be particularly *sensitive to steric effects*. Note that a *phenyl substituent is rate retarding for selenenylation*. This may be *due to both steric factors and alkene stabilization*.
 - The *Hammett correlation with σ^+ gives a ρ value of -0.715* , also *indicating only modest electron demand at the TS*. Indeed, positive values of ρ have been observed in some cases.



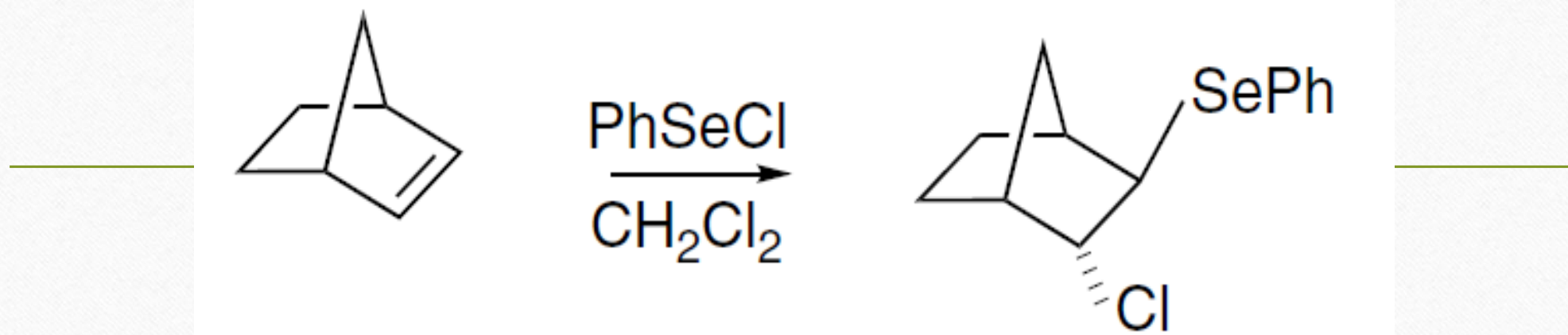
*Terminal alkenes show anti-Markovnikov regioselectivity, but rearrangement is facile.
The Markovnikov product is thermodynamically more stable.*

Table 5.5. Relative Reactivity of Some Alkenes toward 4-Chlorophenylsulfenyl Chloride and Phenylselenenyl Chloride^a

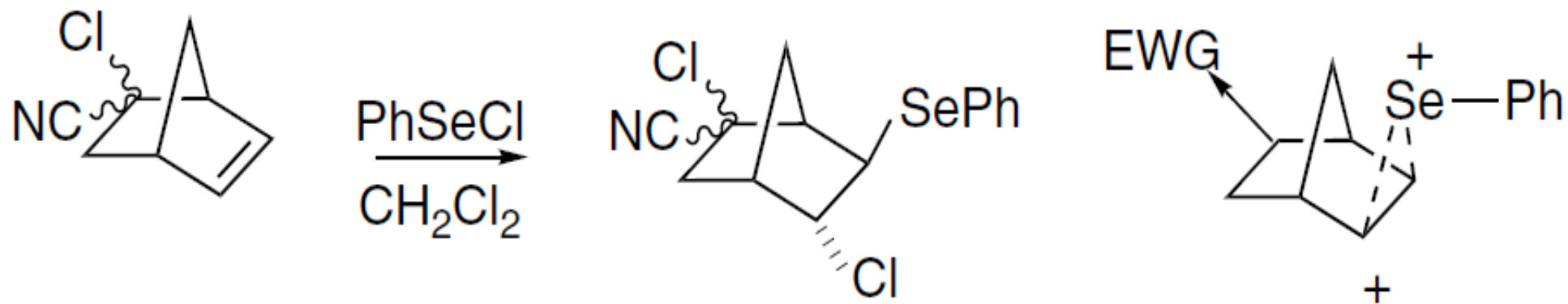
Alkene	<i>p</i> -ClPhSCl k_{rel}	PhSeCl k_{rel}
Ethene	1.00	1.00
Propene	3.15	8.76
1-Butene	3.81	6.67
<i>Z</i> -2-Butene	20.6	3.75
<i>E</i> -2-Butene	6.67	2.08
<i>Z</i> -3-Hexene	54.8	5.24
<i>E</i> -3-Hexene	5.96	2.79
2-Methylpropene	8.46	6.76
2-Methyl-2-butene	46.5	3.76
2,3-Dimethyl-2-butene	119	2.46
Styrene	0.95	0.050
<i>Z</i> -1-Phenylpropene	0.66	0.010
<i>E</i> -1-Phenylpropene	1.82	0.016



- Styrene, on the other hand, is *regioselective for the Markovnikov* product, with the nucleophilic component bonding to the aryl-substituted carbon as the result of *weakening of the bridging by the phenyl group*.
- Selenenylation is a stereospecific *anti* addition with *acyclic alkenes*. Cyclohexenes undergo preferential *diaxial addition*.



- Norbornene gives highly stereoselective *exo-anti* addition, pointing to an *exo* bridged intermediate.



The *regiochemistry* of addition to substituted norbornenes appears to be controlled by *polar substituent effects*.

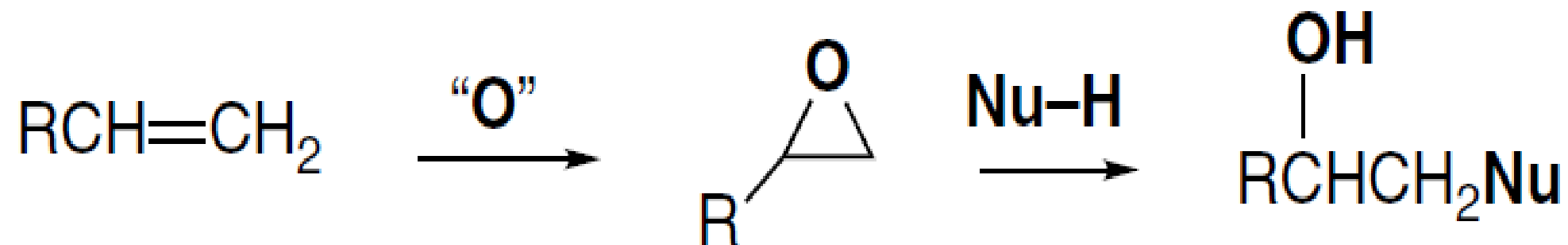
-
- This regioselectivity is consistent with an unsymmetrically bridged seleniranium intermediate in which the more positive charge is remote from the EWG substituent.
 - The enantioselectivity is attributed to the relative ease of nucleophilic approach on the seleniranium ion intermediate, which is consistent with viewing the intermediate as being strongly bridged.

Bridged Intermediates

- Broadly comparing sulfur and selenium electrophiles to the halogens, we see that they are *less electrophilic* and characterized by *more strongly bridged intermediates*.
- This is consistent with reduced sensitivity to electronic effects in alkenes (e.g., alkyl or aryl substituents) and an increased tendency to anti-Markovnikov regiochemistry.
- The strongly bridged intermediates favor *anti* stereochemistry.

Addition Reactions Involving Epoxides

- Epoxidation is an electrophilic addition to form a three-membered ring.
- It is closely analogous to halogenation, sulfenylation, and selenenylation
- In contrast to these reactions, however, the resulting epoxides are neutral and stable and normally can be isolated.
- The epoxides are susceptible to nucleophilic ring opening.



- As the regiochemistry of the ring opening is usually controlled by the ease of nucleophilic approach, *the oxygen is introduced at the more-substituted carbon.*

Epoxides from Alkenes and Peroxidic Reagents

- m-Chloroperoxybenzoic acid (MCPBA)
- Magnesium salt of monoperoxyphthalic acid
- Potassium hydrogen peroxysulfate (Oxone)

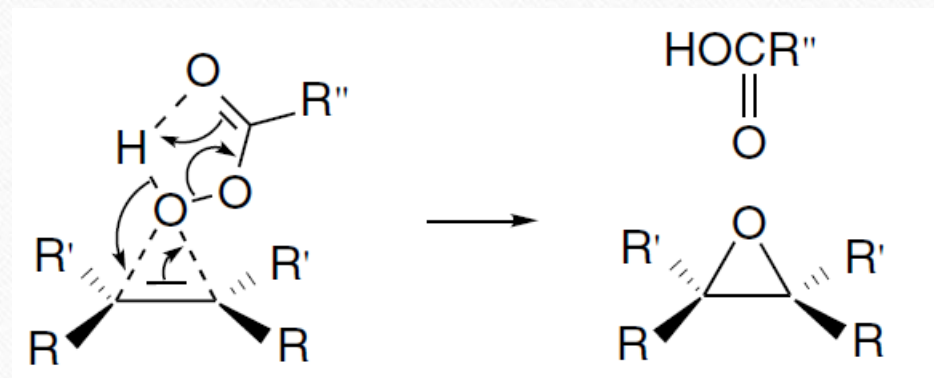
Epoxides from Alkenes and Peroxidic Reagents

No ionic intermediates

Not very sensitive to solvent polarity.

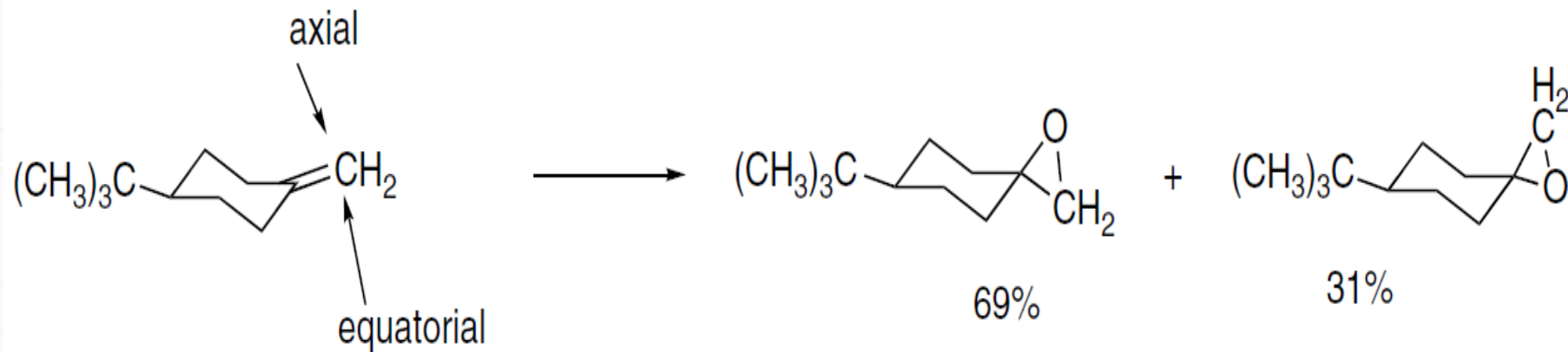
Stereospecific *syn* addition

A concerted process (TS shown below)

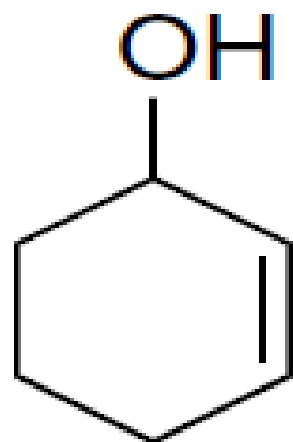


-
- *Alkyl groups and other ERG increases the rate of epoxidation.*
 - *The reactivity of the peroxy acids is increased by EWG substituents.*
 - *The peroxy acid acts as an electrophile in the reaction.*
 - *Double bonds that are conjugated with strongly EWG groups have low reactivity and need very reactive peroxy acids, such as trifluoroperoxyacetic acid.*

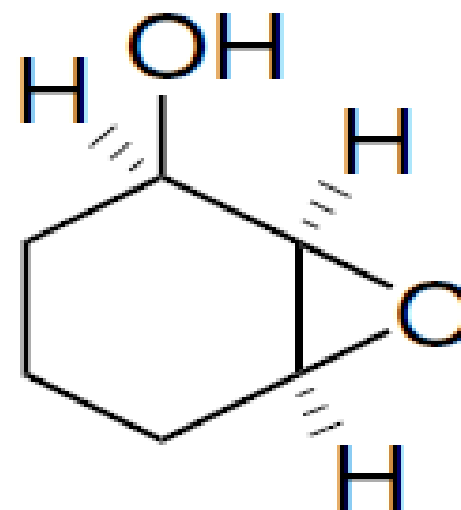
-
- *Strain increases the reactivity of alkenes toward epoxidation.*
 - *Norbornene is about twice as reactive as cyclopentene toward peroxyacetic acid.*
 - *trans-Cyclooctene is 90 times more reactive than cyclohexene.*
 - *Alkenes with aryl substituents are less reactive than unconjugated alkenes because of ground state stabilization and this is consistent with a lack of carbocation character in the TS.*



- Addition of oxygen occurs preferentially from the *less hindered side* of nonpolar molecules.
- *Norbornene*, for example, gives a 96:4 *exo:endo* ratio.

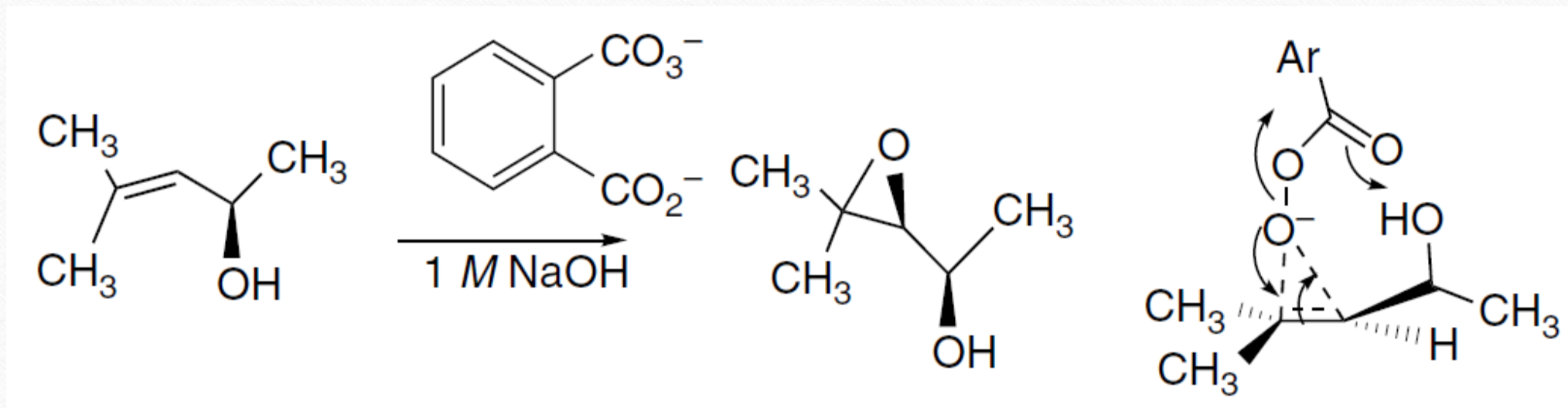


peroxybenzoic
acid

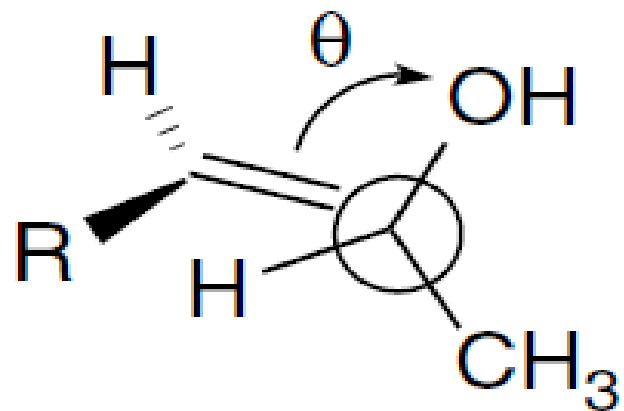


- Hydroxy groups exert a directive effect on epoxidation and favor approach from the side of the double bond closest to the hydroxy group.
- Hydrogen bonding between the hydroxy group and the peroxidic reagent evidently stabilize the TS.

-
- This is a strong directing effect that can exert stereochemical control even when steric effects are opposed.
 - Other substituents capable of hydrogen bonding, in particular amides, also exert a syn-directing effect.
 - The hydroxy-directing effect also operates in alkaline epoxidation in aqueous solution.



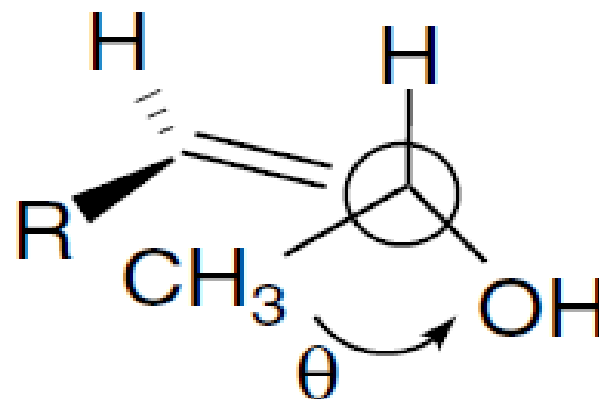
Here the alcohol group can supply a hydrogen bond to assist the oxygen transfer.



$$\theta = +120^\circ$$

R=H 0.0 kcal/mol

R=CH₃ 0.0 kcal/mol

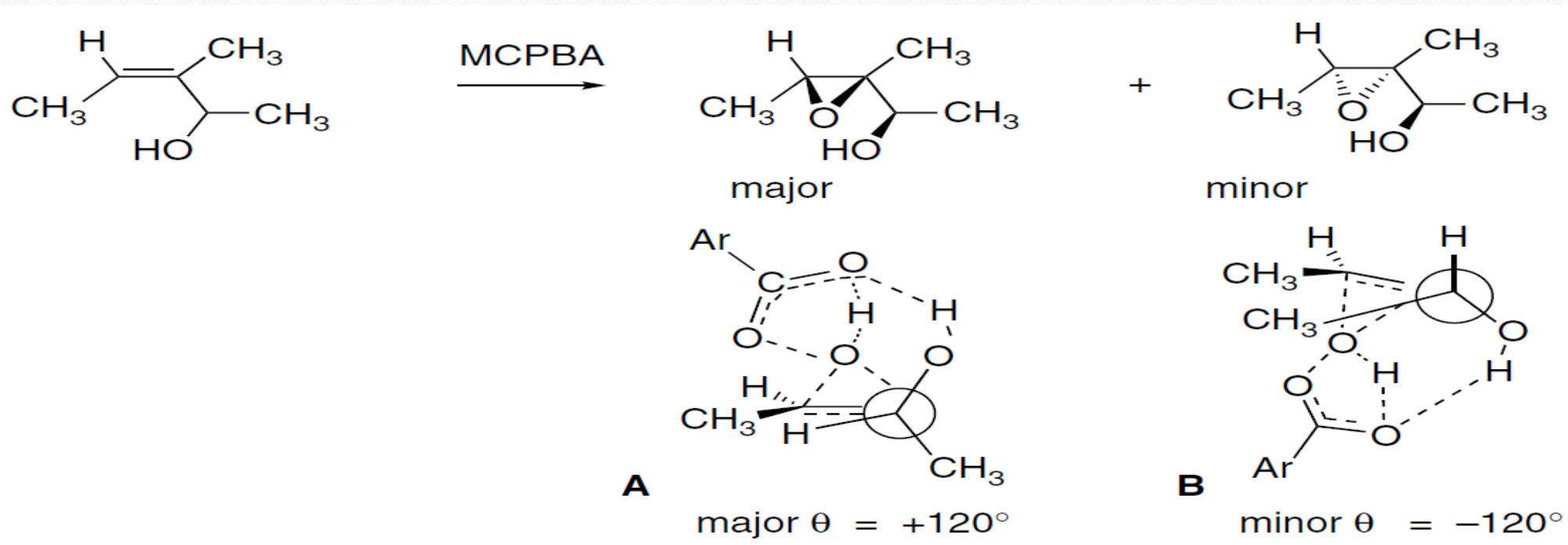


$$\theta = -120^\circ$$

0.7 kcal/mol

> 4.0 kcal/mol

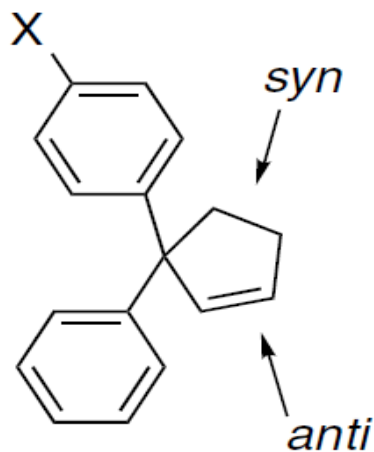
- The analysis begins with the reactant conformation, which is dominated by allylic strain.



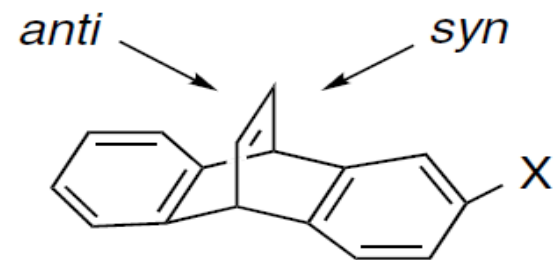
The epoxidation goes through TSA, with 9:1 diastereoselectivity.

The preference is the result of the $\text{CH}_3\text{--CH}_3$ steric interaction that is present in TSB.

The results of two such studies are shown below. Generally, EWGs are *syn* directing, whereas ERGs are *anti* directing, but the effects are not very large.

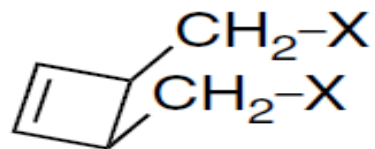


X	<i>syn:anti</i>
NO ₂	73:27
Br	57:43
Cl	57:43
H	50:50
CH ₃ O	48:52



X	<i>syn:anti</i>
NO ₂	77:23
F	58:42
H	50:50
CH ₃ O	48:52

-
- There would be a more favorable electronic environment *anti* to the ERG substituents and *syn* to the EWGs.
 - A related study of 3,4-disubstituted oxymethylcyclobutenes showed moderate *syn* directive effects on MCPBA epoxidation.



X	<i>syn:anti</i>
H	55:45
OH	67:33
OCH ₃	62:38
O ₂ CCH ₃	72:28
OSO ₂ CH ₃	79:21
OSO ₂	70:30
(cyclic sulfite)	

In this case, the effect was attributed to interaction of the relatively electron-rich peroxide oxygens with the positively charged methylene hydrogens, but the electrostatic effect of the bond dipoles would be in the same direction.

- There have been several computational studies of the peroxy acid–alkene reaction.
 - The proposed spiro TS has been supported in these studies for alkenes that do not present insurmountable steric barriers.
-
- The spiro TS has been found for ethene (B3LYP/6-31G*), propene and 2-methylpropene (QCISD/6-31G*), and 2,3- dimethylbutene and norbornene (B3LYP/6-311+G (d,p)).
 - These computational studies also correctly predict the effect of substituents on the E_a and account for these effects in terms of less synchronous bond formation.

- This is illustrated by the calculated and E_a (B3LYP/6-31G*) of the TS for ethene, propene, methoxyethene, 1,3-butadiene, and cyanoethene, as shown in Figure 5.3.
-
- Note that the TSs become somewhat unsymmetrical with ERG substituents, as in propene, methoxyethene, and butadiene.
 - The TS for acrylonitrile with an EWG substituent is even more unsymmetrical and has a considerably shorter C (3)–O bond, which reflects the electronic influence of the cyano group.
 - In this a synchronous TS, the nucleophilic character of the peroxidic oxygen toward the β -carbon is important.
 - Note also that the E_a is increased considerably by the EWG.

Spiro TS

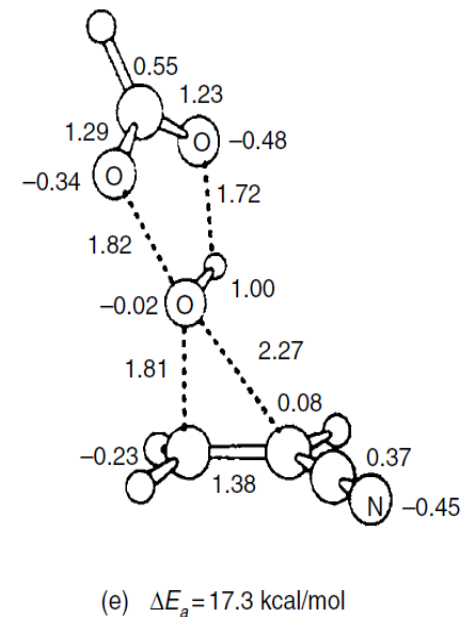
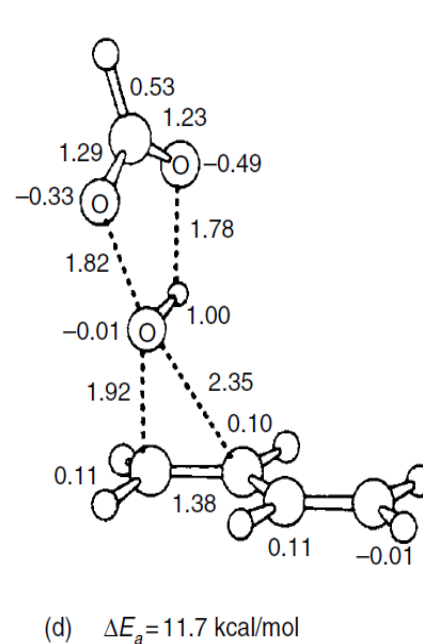
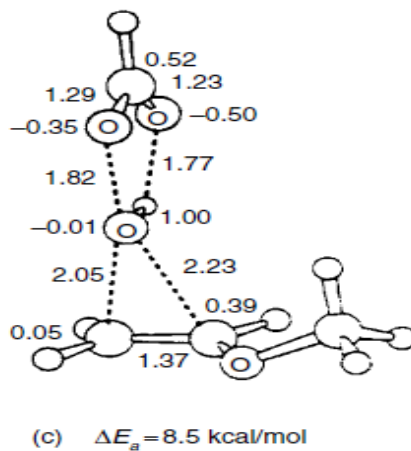
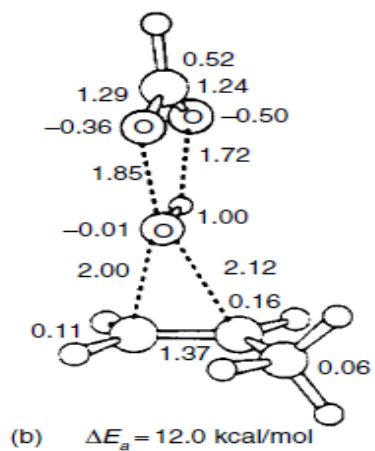
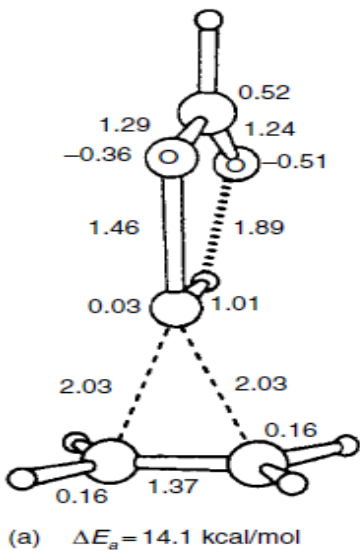
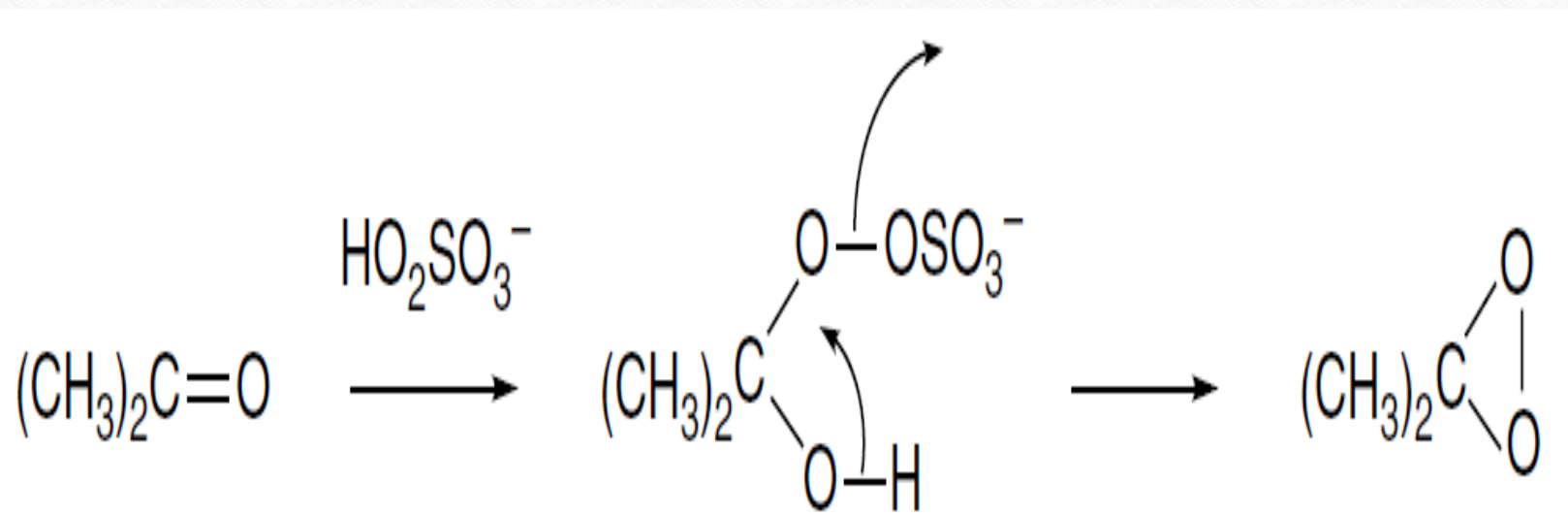
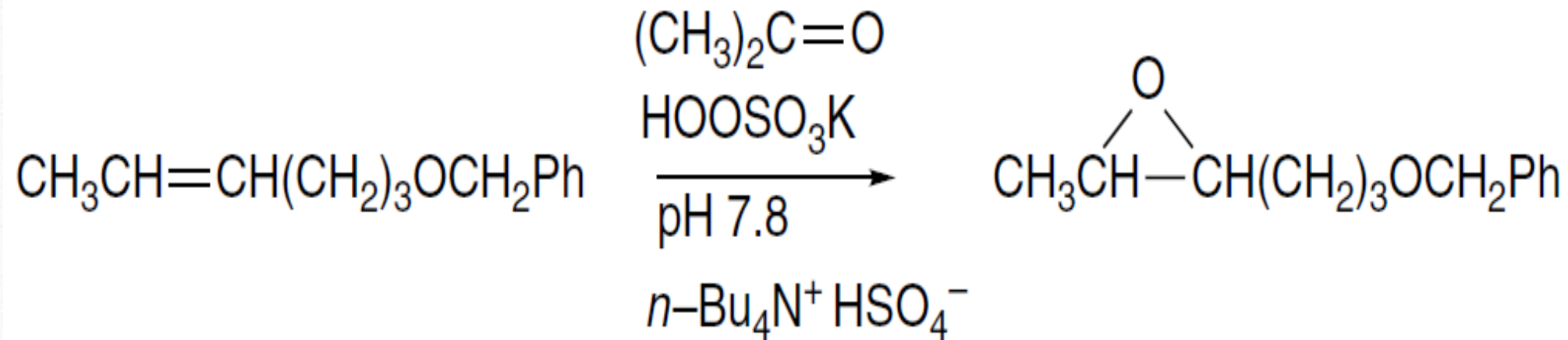


Fig. 5.3. Comparison of B3LYP/6-31G* TS structures and E_a for epoxidation by HCO_3H for: (a) ethene; (b) propene; (c) methoxyethene; (d) 1,3-butadiene, and (e) cyanoethene. Reproduced from *J. Am. Chem. Soc.*, **119**, 10147 (1997), by permission of the American Chemical Society.

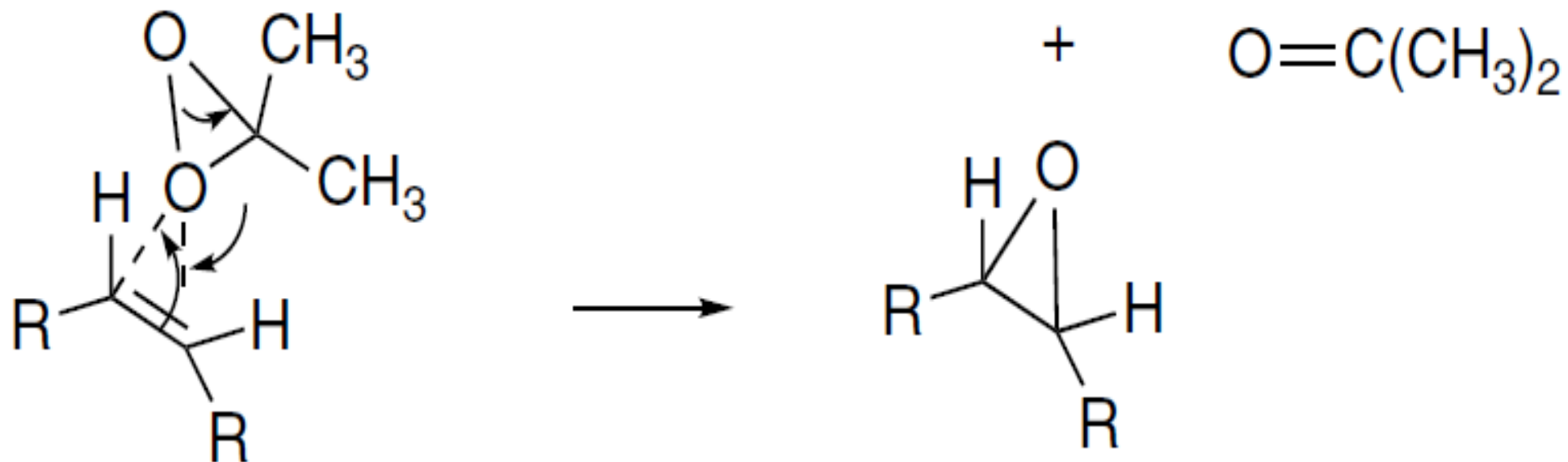


Another useful *epoxidizing agent* is *dimethyldioxirane (DMDO)*. This reagent is generated by an in situ reaction of acetone and peroxymonosulfate in buffered aqueous solution.

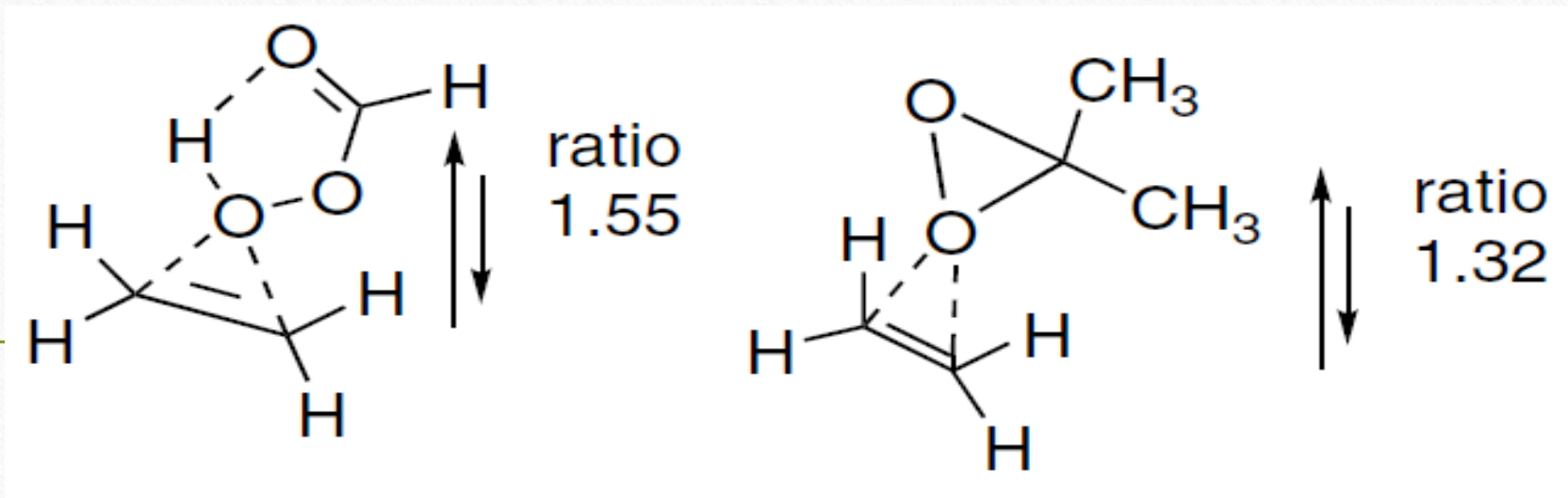


Other *improvements* in convenience is including *in situ generation* of DMDO under *phase transfer conditions*.

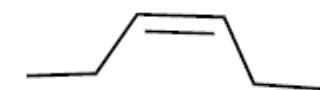
The ***yields and rates*** of this reaction depend on ***pH*** and other reaction conditions.



- *Various computational models of the TS show that the reaction occurs by a concerted mechanism that is quite similar to that for peroxy acids.*
- *Kinetics and isotope effects are consistent with this mechanism.*



- For example, the *NPA charges* for the *DMDO* and *performic oxidations* of *ethane* have been compared.
- The *ratio of the electrophilic interaction* involving *electron density transfer* from the *alkene* to the *O–O σ^* orbitals* can be compared with the *nucleophilic component* involving *back donation* from the *oxidant* to the *alkene π^* orbital*. By this comparison, *performic acid* is somewhat more electrophilic.

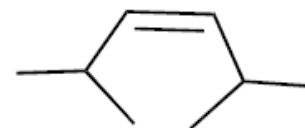


Z-3-hexene

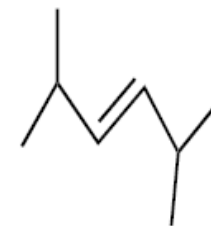


E-3-hexene

rate ratio: 8.3:1



Z-2,5-dimethyl
-3-hexene

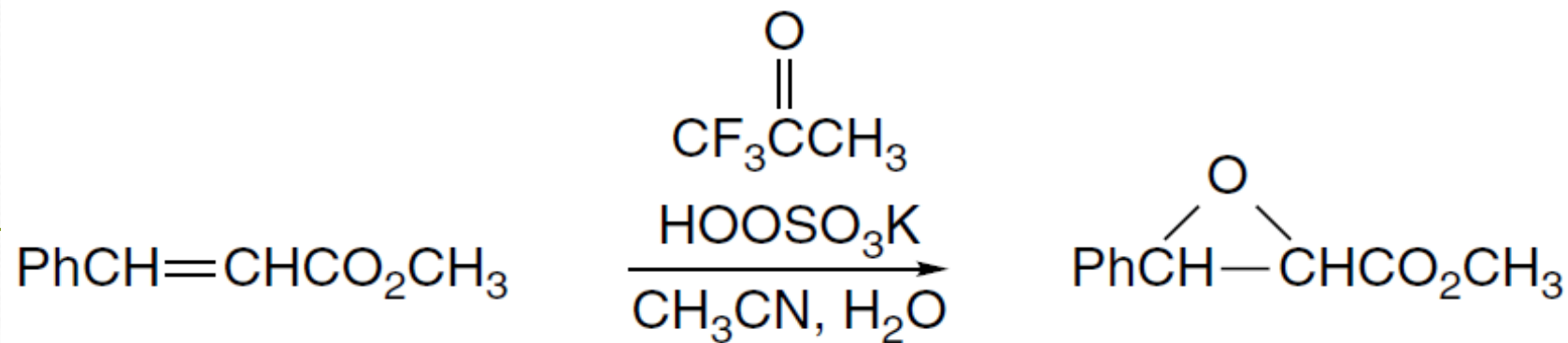


E-2,5-dimethyl
-3-hexene

rate ratio: 17:1

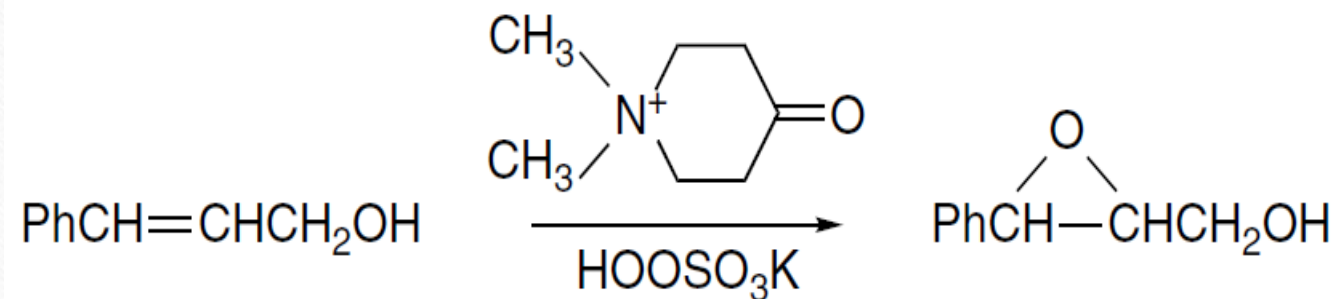
- It has been suggested that the *TS* for *DMDO* oxidation of *electron-poor alkenes*, such as acrylonitrile, has a *dominant nucleophilic component*.
- *DMDO* oxidations have a fairly *high sensitivity to steric effect*. The *Z*-isomers of alkenes are usually more reactive than the *E*-isomers because in the *former case* the reagent can *avoid the alkyl groups*.

-
- Similarly to peroxycarboxylic acids, DMDO is subject to *cis* or *syn* stereoselectivity by hydroxy and other hydrogen-bonding functional groups.
 - The effect is strongest in nonpolar solvents.
 - For other substituents, both steric and polar factors seem to have an influence, but the precise origin of the stereoselectivity is not always evident.



Other ketones apart from acetone *can be used* for in situ generation of dioxiranes by reaction with peroxysulfate or another suitable peroxide.

More electrophilic ketones give more reactive dioxiranes. 3-Methyl-3-trifluoromethyldioxirane is a more reactive analog of DMDO and it is capable of oxidizing less reactive compounds such as methyl cinnamate.



- Hexafluoroacetone and hydrogen peroxide in buffered aqueous solution epoxidizes alkenes and allylic alcohols.
- N,N-dialkylpiperidin-4-one salts are also good catalysts for epoxidation.
- The positively charged quaternary nitrogen enhances the reactivity of the carbonyl group toward nucleophilic addition and also makes the dioxirane intermediate more reactive.

Subsequent Transformations of Epoxides

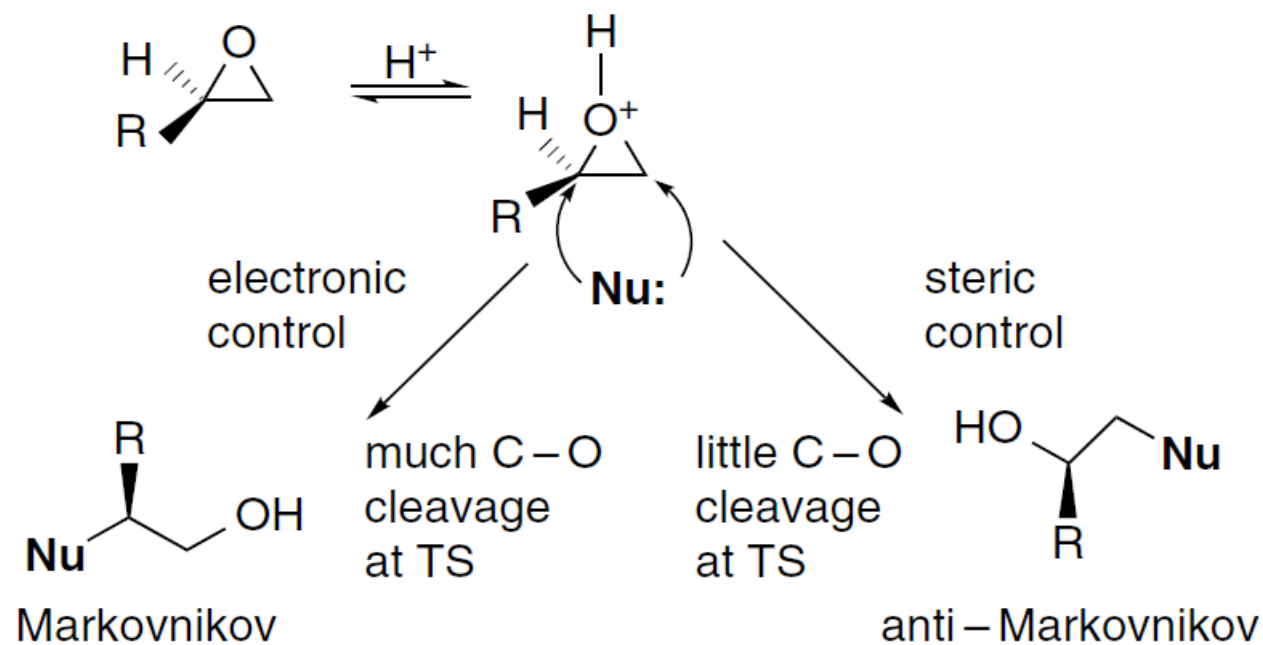
- Such two- or three-step operations can achieve specific oxidative transformations of an alkene that might not be easily accomplished in a single step.
- *Ring opening of epoxides* can be carried out *under either acidic or basic conditions*.
- The *regiochemistry* of the ring opening depends on *whether steric or electronic factors are dominant*.

Base-catalyzed reactions usually involve breaking the epoxide bond at the less-substituted carbon (*steric factor dominates*).

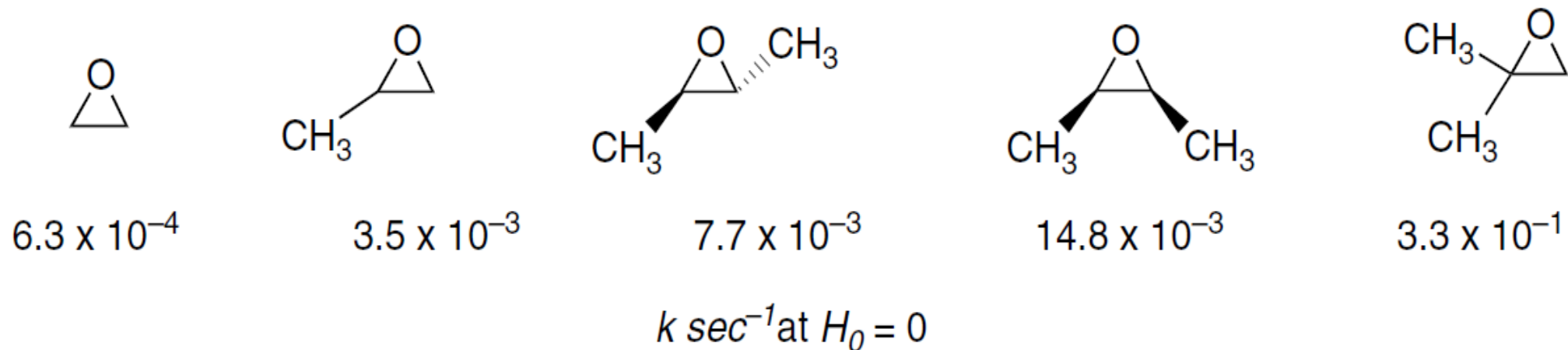
The situation in acid-catalyzed reactions is more complicated. The bonding of a proton to the oxygen weakens the C–O bonds and facilitates rupture of the ring by weak nucleophiles.

If the C–O bond is largely intact at the TS, the nucleophile will become attached to the less-substituted position for the same steric reasons that were cited for nucleophilic ring opening.

If, on the other hand, C–O rupture is more complete when the TS is reached, the opposite orientation is observed.



- This results from the ability of the *more-substituted carbon* to stabilize the developing positive charge (*electronic factor dominates*).
- Steric control corresponds to anti-Markovnikov regioselectivity, whereas electronic control leads to Markovnikov regioselectivity.



- The dominant role of bond cleavage in acidic hydrolysis is indicated by the increase in rates with additional substitution.
- Note in particular that the 2,2-dimethyl derivative is much more reactive than the *cis* and *trans* disubstituted derivative, as expected for an intermediate with carbocation character.

$$k_{\text{H}^+} = 25.8 \pm 1.7 \text{ M}^{-1} \text{ s}^{-1}$$

$$k_{\text{H}_2\text{O}} = 2.19 \pm 10^{-6} \text{ M}^{-1} \text{ s}^{-1}$$

$$k_{-\text{OH}} = 1.95 \pm 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$$

The profile for 2,2-dimethyloxirane, shown in Figure 5.4, leads to the following rate constants for the acid-catalyzed, uncatalyzed, and base catalyzed reactions.

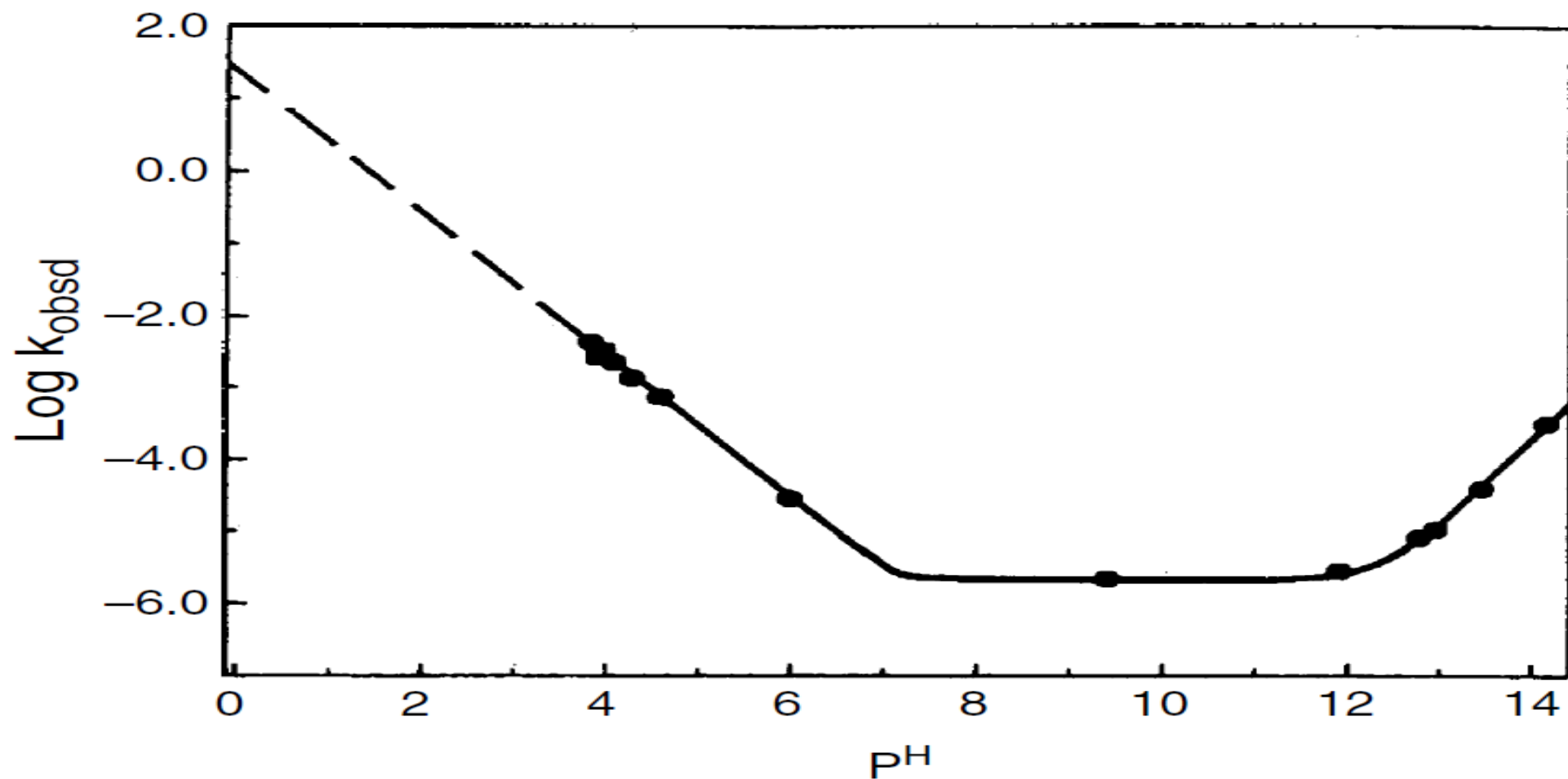
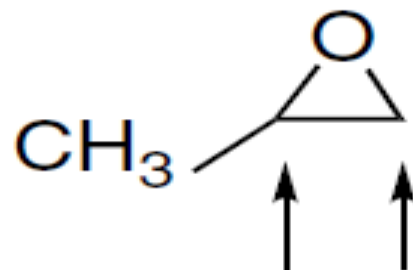
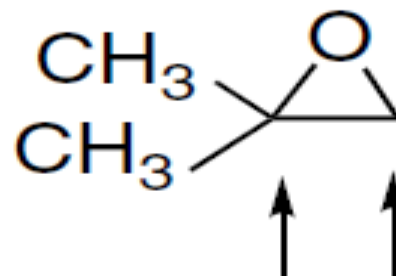


Fig. 5.4. pH-Rate profile for hydrolysis of 2,2-dimethyloxirane. Reproduced from *J. Am. Chem. Soc.*, **110**, 6492 (1988), by permission of the American Chemical Society.



pH = 1 70 30

pH = 7 36 64



80–90 10–20

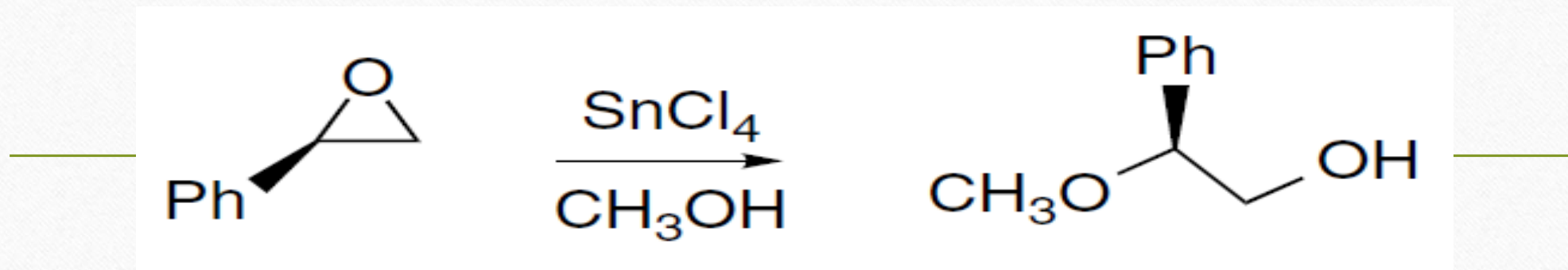
99 1

Nucleophilic attack occurs at both the more-substituted and the less-substituted carbon, as determined by isotopic labeling.

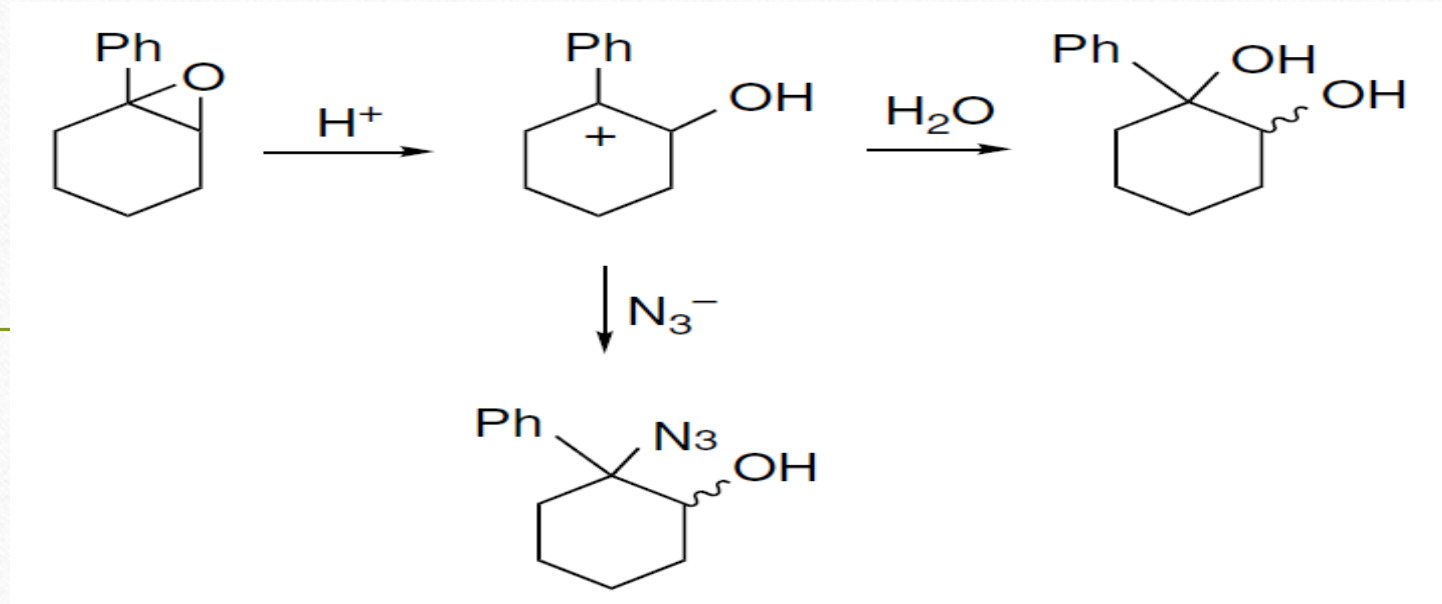
- The opening of *cis*- and *trans*-2,3-dimethyloxirane in methanol or acetic acid is a stereospecific *anti* addition.

- The presence of an aryl substituent favors cleavage of the benzylic C–O bond.
- The case of styrene oxide hydrolysis has been carefully examined. Under acidic conditions the bond breaking is exclusively at the benzylic position (electronic control).
- Under basic conditions, ring opening occurs at both epoxide carbons.

Inversion of Configuration



- Styrene also undergoes highly *regioselective* ring opening ***in the presence of Lewis acids***. For example, methanolysis is catalyzed by SnCl_4 ; it occurs with more than a 95% attack at the *benzyl carbon* and with *high inversion of configuration*.
- Similar results are observed with BF_3 . The *stereospecificity* indicates a *concerted nucleophilic* opening of the complexed epoxide, with *bond-weakening factors* (electronic control) determining the *regiochemistry*.

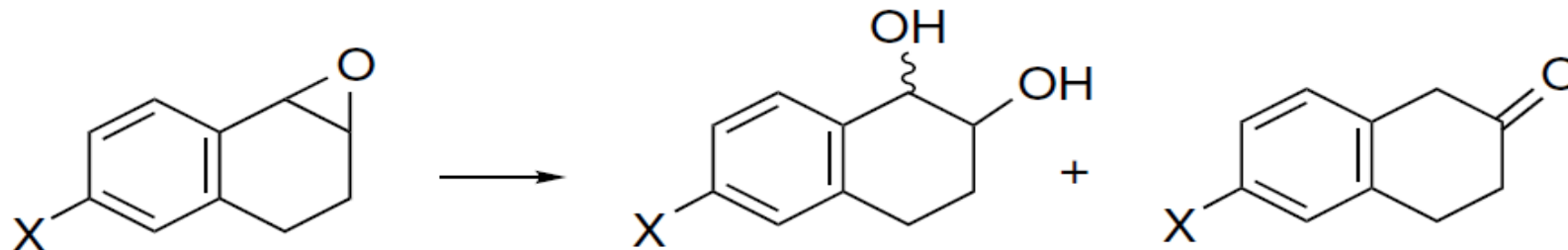


- In the case of epoxides of 1-arylcyclohexene, there is direct evidence for a carbocation intermediate.
- The hydrolysis product can be diverted by addition of azide ion as a competing nucleophile. As expected for a carbocation intermediate, both the *cis* and *trans* diols are formed.

- Similarly, comparison of the epoxide of 1,2-dihydronaphthalene and its 6-methoxy analog provided interesting contrasts.
-

- The product was partitioned into the components formed by the acid-catalyzed and uncatalyzed mechanisms.
- The unsubstituted compound gives the *trans* diol exclusively, indicating participation of the nucleophile in the ring opening.
- The 6-methoxy derivative gives a substantial amount of a rearrangement product and the diol is a mixture of the *cis* and *trans* stereoisomers.

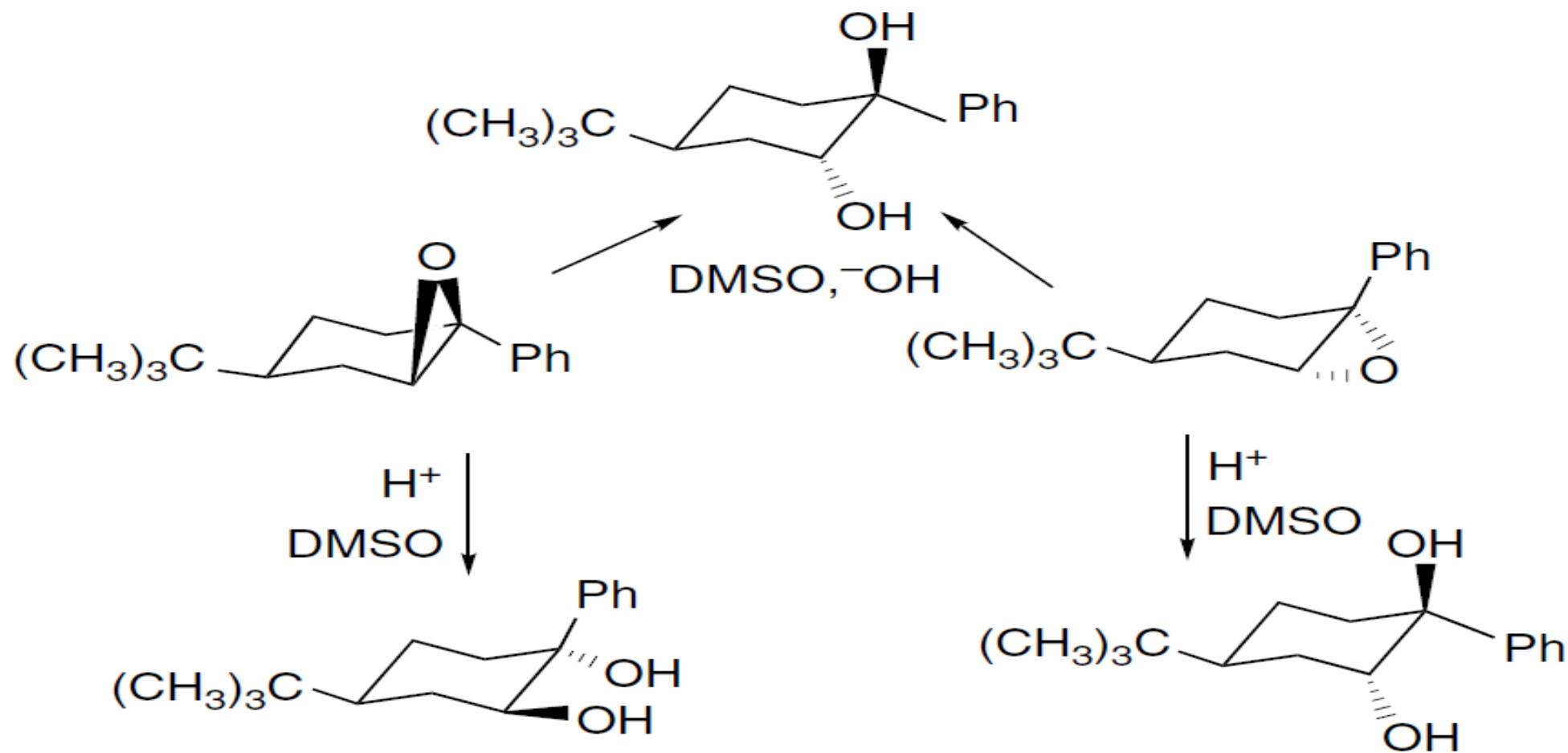




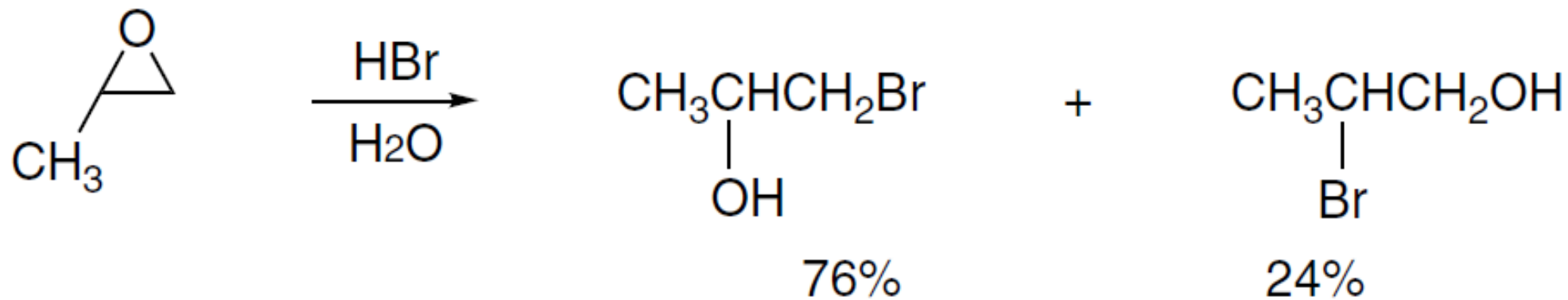
X	<i>cis</i>	<i>trans</i>	
H			
H ⁺ – catalyzed	6	94	0
uncatalyzed	0	100	0
CH ₃ O			
H ⁺ – catalyzed	81	19	<1
uncatalyzed	17	7	76

These differences indicate that the more stabilized carbocation has a significant lifetime.

-
- The conformationally biased *cis*- and *trans*-4-*t*-butyl derivatives were examined.
 - The stereochemistry of both acid- and base-catalyzed reactions was investigated in 85:15 DMSO-H₂O.
 - Under acidic conditions the epoxides give *anti* ring opening and the reaction is stereospecific.
 - The base-catalyzed reactions involve *trans*-diaxial ring opening.



The acid-catalyzed reactions occur by preferential opening of the benzylic bond with inversion.



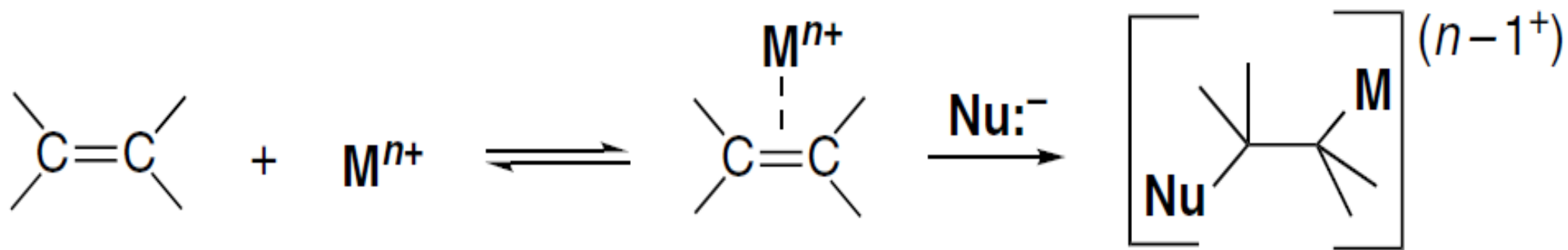
When saturated epoxides such as propylene oxide react with hydrogen halides, the dominant mode of reaction introduces halide at the less-substituted primary carbon (anti-Markovnikov).

Ring opening that is dominated by the nucleophilic reagent is determined by steric access.

Ring opening that is electrophilic in character introduces the nucleophile at the position that has the largest cationic character.

Electrophilic Additions Involving Metal Ions

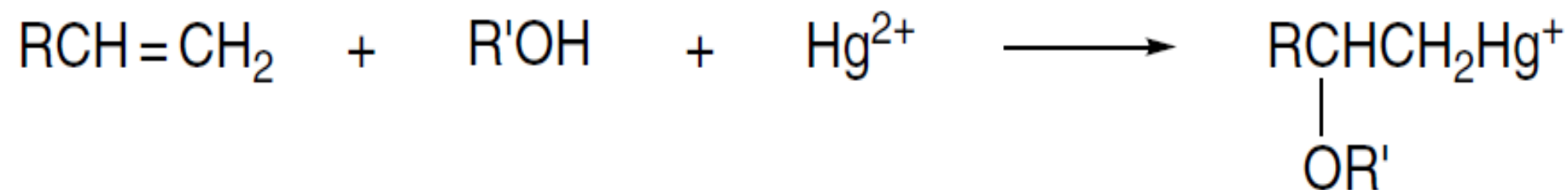
- Certain metal cations promote addition by electrophilic attack on alkenes.
- Addition is completed when a nucleophile adds to the alkene-cation complex.
- We also consider reactions of the Ag^+ ion, which give complexes, but usually do not proceed to adducts.



Substituents that further stabilize a carbocation intermediate lead to *reversal of the stereochemistry* and *regiochemistry* of epoxides can be controlled by the reaction *conditions*.

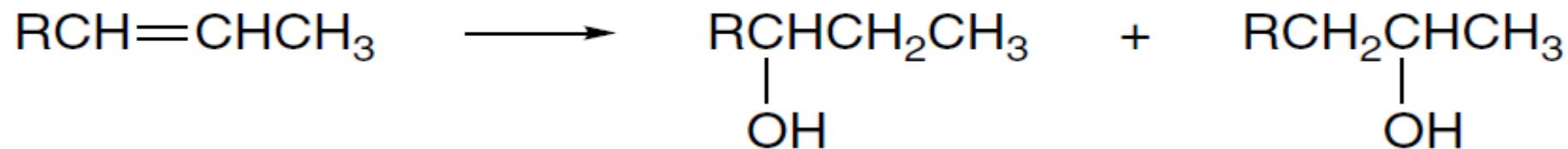
Solvomercuration

- Mercuric ion, Hg^{2+} , as the cation
- The usual nucleophile is the solvent
- The term *oxymercuration* is used to refer to reactions in which water or an alcohol acts as the nucleophile.



The adducts can be isolated as halide salts, but in synthetic applications the mercury is often replaced by hydrogen (*oxymercuration reduction*).

- The *reactivity* of mercury salts is a function of both the *solvent and the counterion*.
- *Mercuric chloride*, for example, is *unreactive* and mercuric acetate is the most commonly used reagent, but the trifluoroacetate, trifluoromethanesulfonate, nitrate, or perchlorate salts are preferable in some applications.
- *Dialkyl terminal alkenes* are more *reactive* than *monosubstituted ones*, but *internal disubstituted alkenes* are less reactive.
- For example, *1-pentene* is about *ten times* more reactive than *Z-2-pentene* and *40 times* more reactive than *E-2-pentene*.
- As expected for an *electrophilic reaction*, the *ρ values* for oxymercuration of styrene (-3.6) and α -methylstyrene (-3.12) derivatives are *negative*.



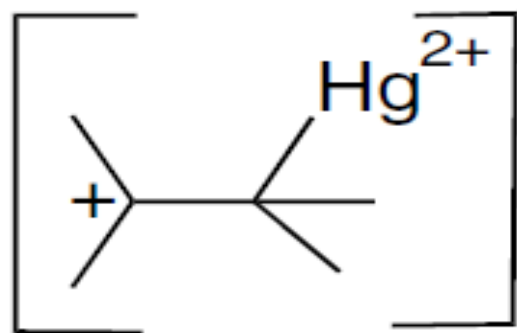
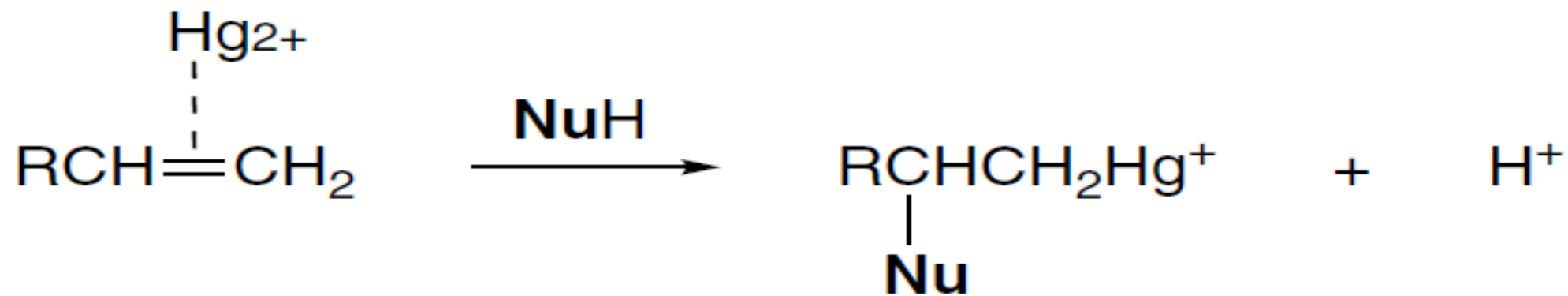
R		
CH ₃ CH ₂	36%	64%
(CH ₃) ₂ CH	9%	91%
(CH ₃) ₃ C	2%	98%

- The addition of the nucleophile follows Markovnikov's rule and the regioselectivity of oxymercuration is ordinarily very high.
- Terminal alkenes are usually more than 9% regioselective and even disubstituted alkenes show significant regioselectivity, which is enhanced by steric effects.

Table 5.6. Relative Reactivity of Some Alkenes in Oxymercuration

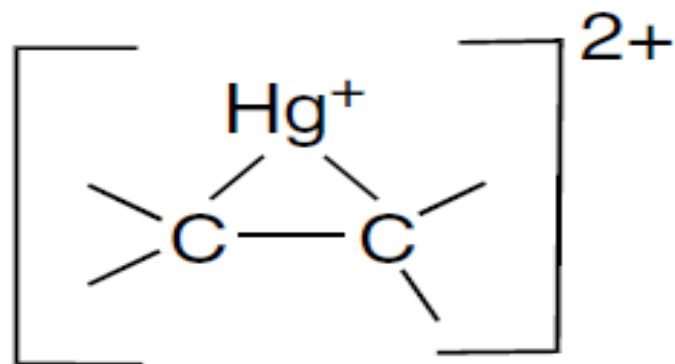
Alkene	Relative reactivity ^a
1-Pentene	6.6
2-Methyl-1-pentene	48
Z-2-Pentene	0.56
E-2-Pentene	0.17
2-Methyl-2-pentene	1.24
Cyclohexene	1.00

a. H. C. Brown and P. J. Geogheagan, Jr., *J. Org. Chem.*, **37**, 1937 (1972).



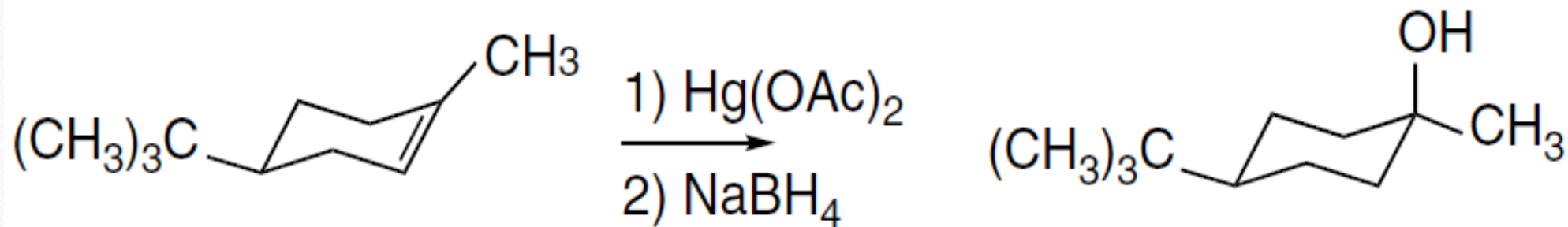
open

or



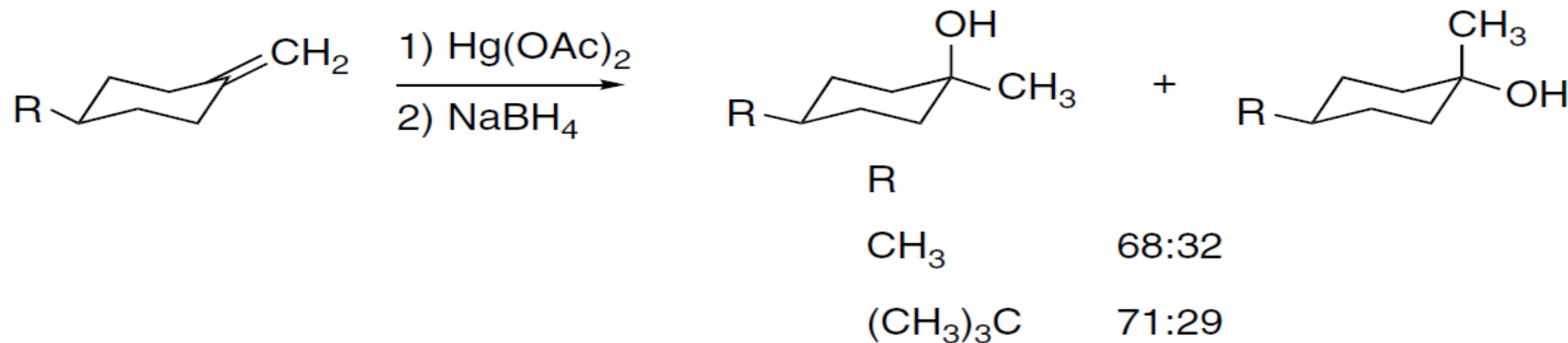
bridged

Oxymercuration Reduction



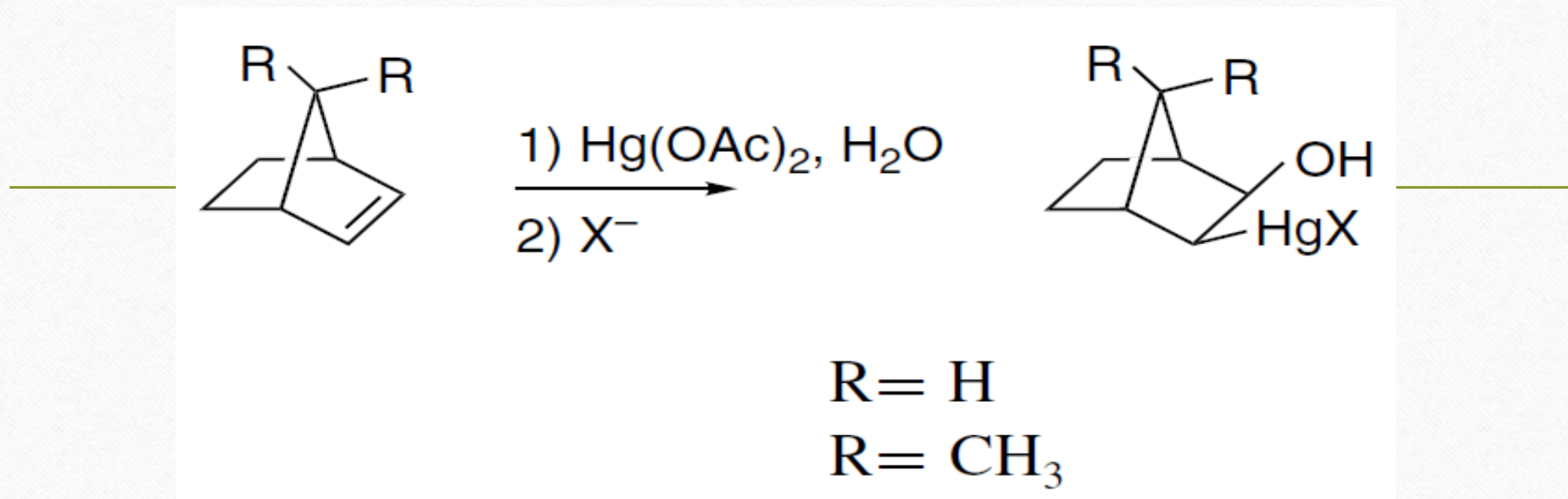
Oxymercuration of unhindered alkenes is usually a stereospecific *anti* addition.

Conformationally biased cyclic alkenes such as 4-*t*-butylcyclohexene and 4-*t*-butyl-1-methylcyclohexene give exclusively the product of *anti*-diaxial addition.

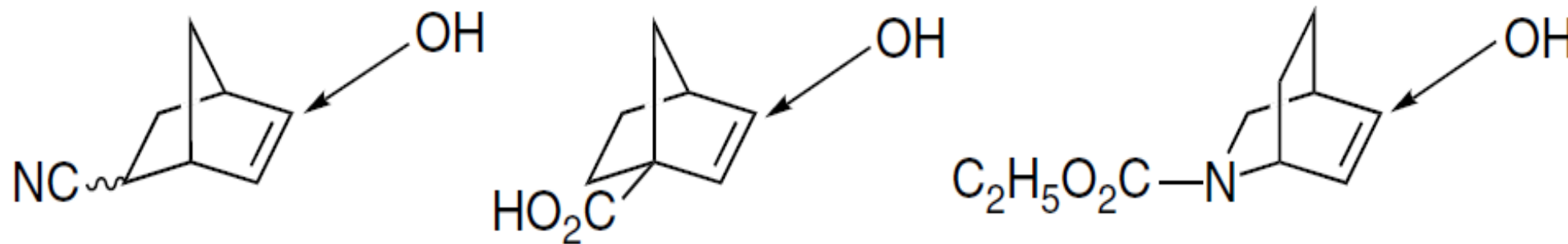


Methylenecyclohexenes are not very stereoselective, showing a small preference for the axial alcohol, which corresponds to mercuration from the equatorial face.

-
- In contrast to the *anti* addition observed with acyclic and monocyclic alkenes, *bicyclic alkenes* frequently show *syn* addition.
 - Norbornene gives exclusively *exo-syn* addition. Even 7,7-dimethylnorbornene gives the *exo-syn* product, in sharp contrast to the usual *endo*-directing effects of 7-substitution.
 - These results are difficult to reconcile with a bridged mercurinium ion and suggest that *intramolecular transfer of the nucleophile from mercury* occurs.



In norbornene derivatives, the competing *anti* addition is sterically restricted by the *endo* bridge.



Other bicyclic alkenes have been observed to give largely or exclusively *syn* addition.

Oxymercuration shows considerable sensitivity to polar substituents. Several early examples set the pattern, which is for the nucleophile to add at the carbon that is more remote from a polar EWG substituent.



X	5:6 (<i>exo</i>)	5:6 (<i>endo</i>)
CH ₂ OTBS	1:1	1:1
CO ₂ CH ₃	5:1	5:1
OH	6:1	3:1
OCH ₂ Ph	9:1	6:1
O ₂ CCH ₃	14:1	9:1

EWGs make the unsymmetrical TS having less positive charge near the substituted position the one of lowest energy.”

The directive effect of substitution was found for both *exo* and *endo* substituents, but was somewhat stronger for *exo* groups.

Probe TS by Calculation

- They used calculations to probe the TS using $\text{Hg}(\text{O}_2\text{CH})_2$ as the reagent and **ethene** as the reactant, they found a **symmetrical bridged structure** to be a stable prereaction complex.
- The TS for addition is **very unsymmetrical** with **partial bonding** by one of the **formate ligands**.
- The TS for addition to **norbornenes** was **somewhat looser** and the addition corresponded to a **four-center *syn* mechanism**.

- These gas phase computations may bias the *ethene TS toward syn addition* by virtue of the *attachment of the nucleophile to Hg^{2+}* .
-
- However, the results with *both ethene and norbornene* suggest that there is *no strong prohibition against a syn addition*, in agreement with the experimental results.
 - The *regioselectivity in substituted norbornenes* is the result of *polarization of the double bond*, with the Hg^{2+} *attacking the more negative carbon*.
 - The *NPA charges calculated for the TS* show that *this polarization becomes much larger as the C–Hg bond is formed and the TS is approached*.

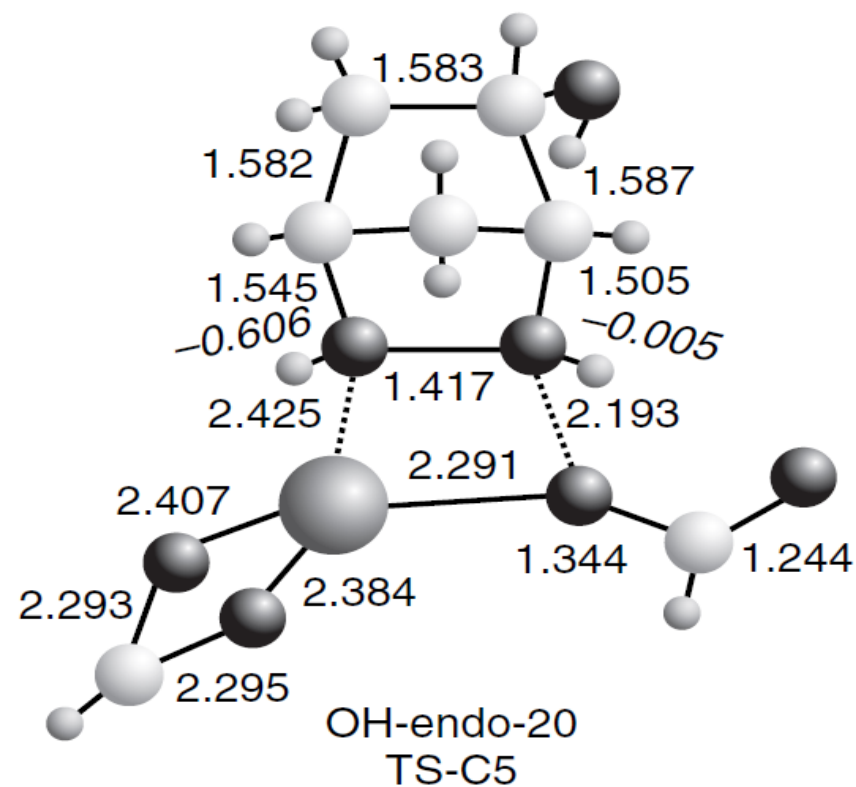
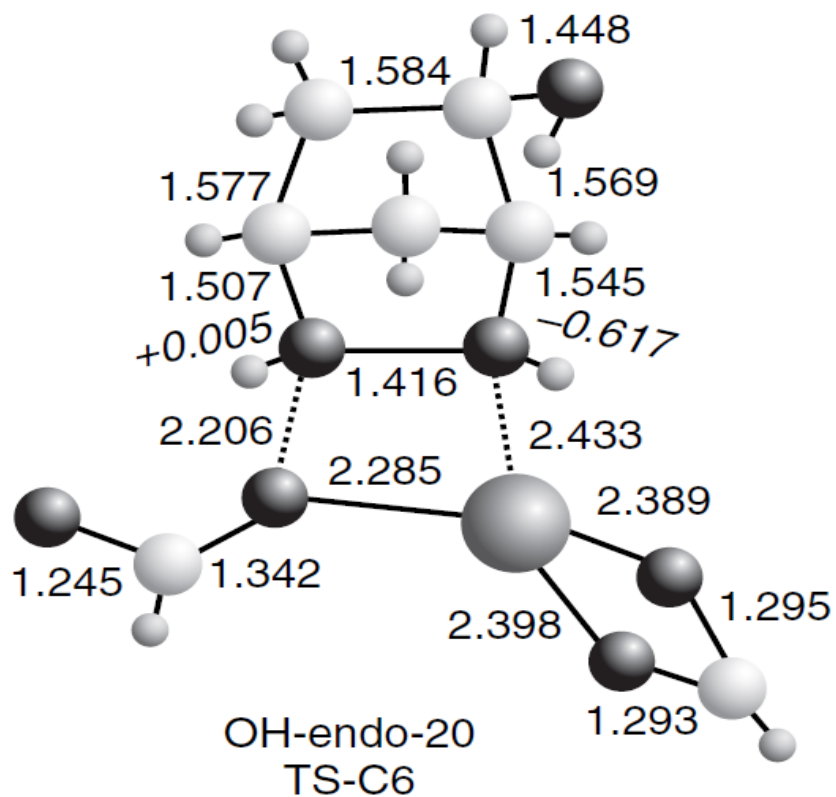
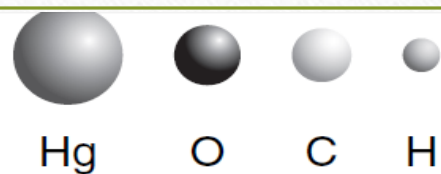
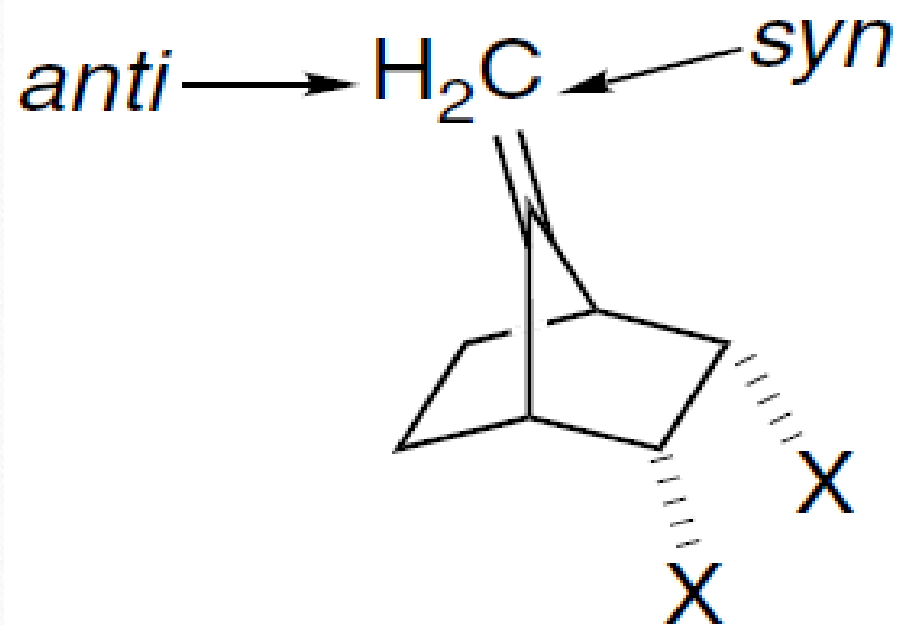


Fig. 5.5. Transition structures for C(6) and C(5) mercuration of the *endo* hydroxy derivative of norbornene. Italic numbers give the NPA charges at the reacting carbons. Reproduced from *J. Org. Chem.*, **66**, 5182 (2001), by permission of the American Chemical Society.



	<i>syn</i>	<i>anti</i>
X CO_2CH_3	>95	>5
CH_2OCH_3	40	60
CH_2CH_3	17	83

Ester groups are strongly *syn* directing, whereas ethyl groups are *anti* directing. These results were attributed to differential polarization of the faces of the π bond (see Section 2.4).

Similar, but much weaker, directive effects are seen for epoxidation and hydroboration.

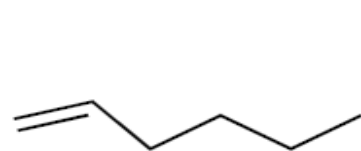


-
- A broad mechanistic interpretation that can encompass most of these results suggests that the Hg^{2+} ion is rather loosely bound prior to the rate-determining nucleophilic addition.
 -
 - The bonding is weaker at the carbon best able to accommodate positive charge, resulting in Markovnikov regioselectivity.
 -
 - If there is little steric hindrance, *anti* addition of a nucleophile is preferred, but the *syn* mechanism is available.

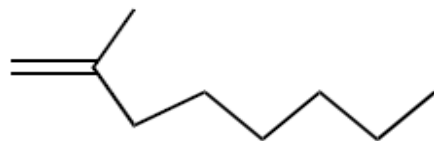
- The *syn* mechanism, at least as modeled in the *gas phase*, seems to involve *migration of a ligand* from Hg^{2+} to carbon.
-
- It is the *nucleophilic capture* that determines the *regiochemistry and stereochemistry* of the product, *since the mercuriation step is reversible*.
 - It should also be noted that *oxymercuration* has a *different electronic pattern* from most of the *other electrophilic additions* in that the *Hg-substituted carbon* becomes *negatively charged* as bonding occurs (see Figure 5.5).
 - This is also *true in hydroboration*, although *less so*, whereas *halogenation, sulfenylation, and selenylation* result in placing a *more electronegative substituent* on *both carbons of the double bond*.

Argentation-the Formation of Silver Complexes

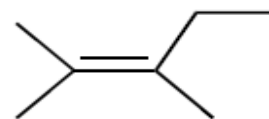
- Several analytical and separation techniques are based on the reversible formation of Complexes between alkenes and Ag^+ ions.
- Analytical methods for terpenes, unsaturated acids and esters, and other unsaturated nonpolar compounds are based on the use of Ag^+ - impregnated materials for thin-layer (TLC) and high-pressure (HPLC) as well as gas liquid (GLC) chromatography.



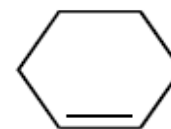
1.0



0.49



0.054



0.24



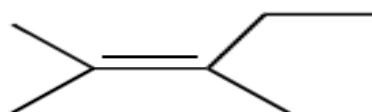
14.4

Relative affinity

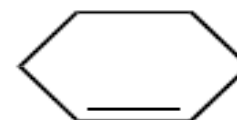
GLC measurements done some years ago suggest that the *affinity decreases* with *additional substituents*, but *increases with strain*.



1.0



0.18



0.86



24.2

Relative affinity

An NMR study in methanol showed a similar trend in relative stability of the Ag(I) complexes.

- In contrast to Hg(II), Ag(I) does not normally induce intermolecular nucleophilic addition to alkenes.
-
- However, internal nucleophiles can sometimes be captured, leading to cyclization reactions.
 - The structure and stability of alkene-Ag⁺ complexes has also been examined by computation. MP2/SBK(d) calculations indicate that three ethene molecules are accommodated at Ag⁺ with ΔE of -30 ± 3 kcal/mol, but subsequent ethenes are less strongly bound.
 - The computations find stronger complexation with alkyl-substituted alkenes in the gas phase, which is in contrast to the trend in the solution stabilities.

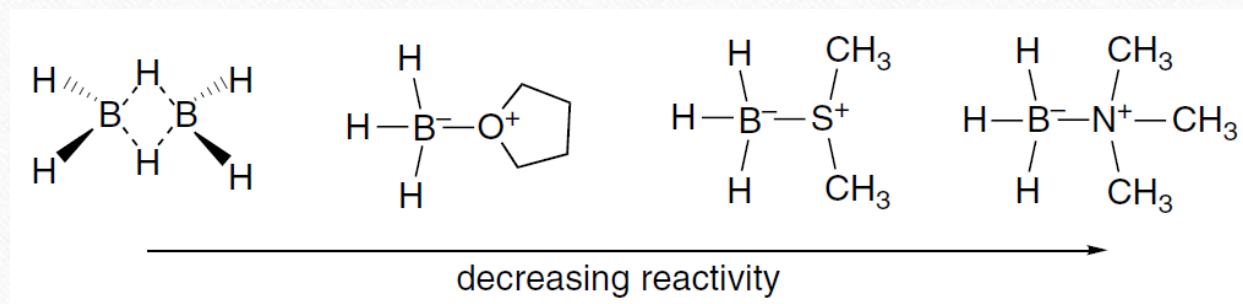
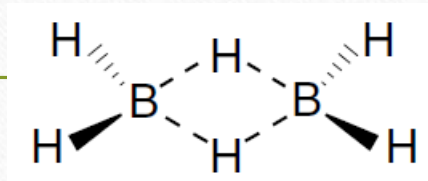


The computations find stronger complexation with alkyl-substituted alkenes in the gas phase, which is in contrast to the trend in the solution stabilities

	Solution ^a	ΔE (gas phase) ^b kcal/mol
Ethene	1.32	−33.7
Propene	0.98	−36.6
<i>Z</i> -2-Butene	0.49	−38.0
<i>E</i> -2-Butene	0.27	−38.3
2-Methylpropene	0.16	−41.3
2,3-Dimethyl-2-butene	0.04	−43.5

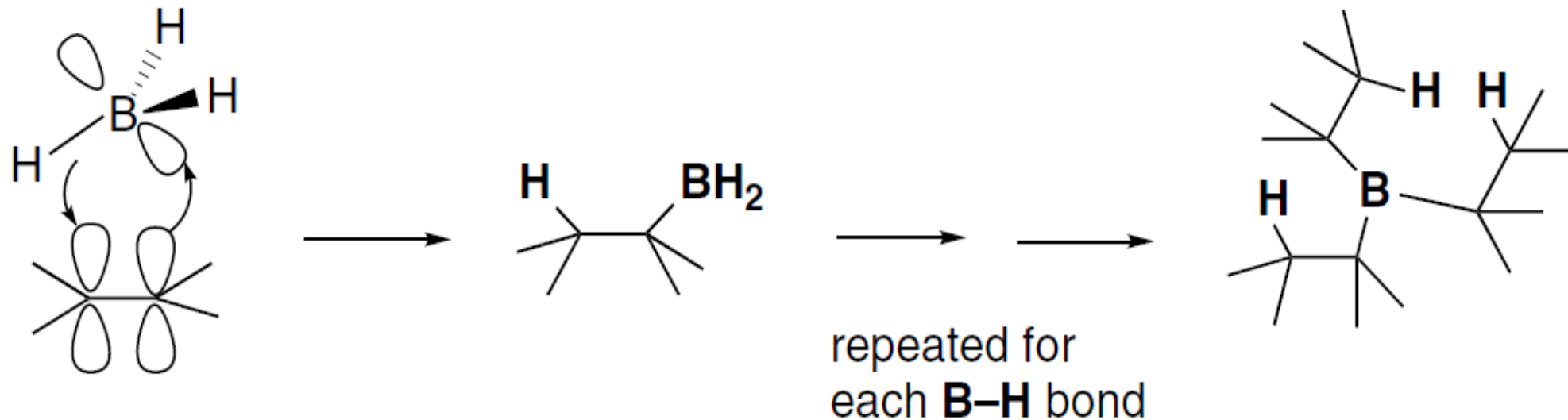
- This might be the result of the greater importance of solvation in the liquid phase, whereas polarization might be the dominant factor in the gas phase.

Synthesis and Reactions of Alkylboranes

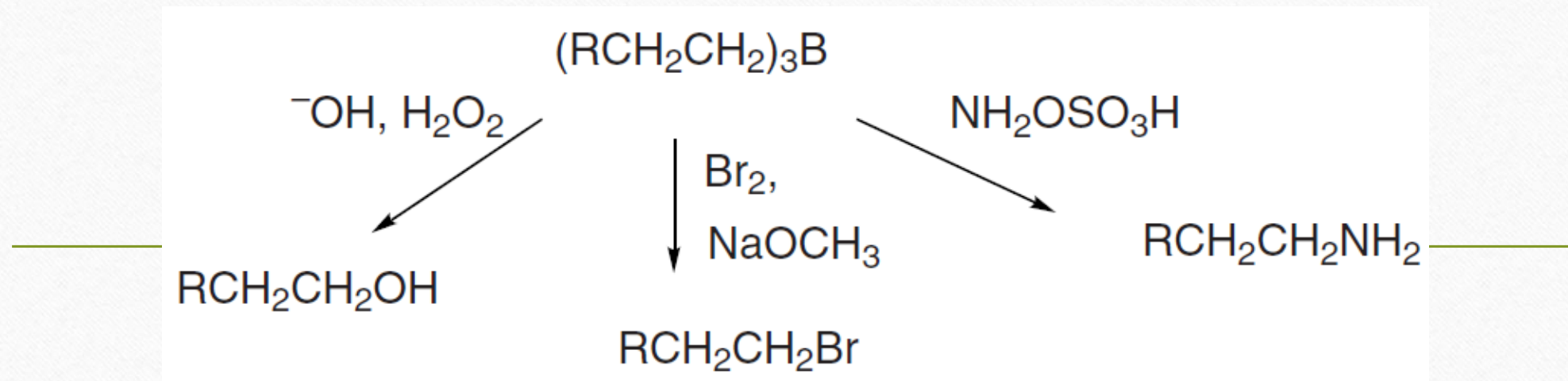


The addition of borane to alkenes is an electrophilic process, but it is concerted.

The alkene donates electron density to the borane but a hydrogen shifts to carbon, resulting in an overall *syn* addition.



- In MO terms, the addition is viewed as taking place by interaction of the alkene π orbital with the vacant p orbital on boron, accompanied by concerted C-H bond formation by interaction with the empty π^* orbital.
- Unhindered alkenes proceed to the trialkylborane stage by three successive additions.



As a result of a combination of steric and electronic factors, hydroboration is highly regioselective, with boron becoming bonded to the *less-substituted carbon*.

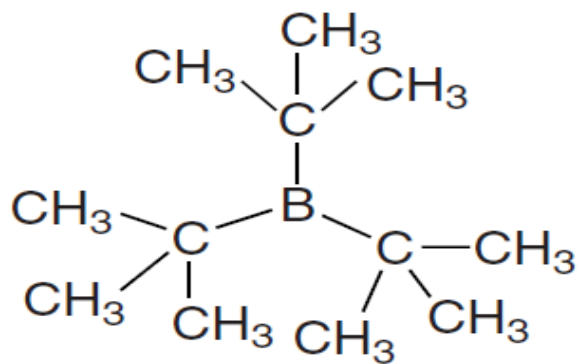
The boron can eventually be replaced by hydroxy, carbonyl, amino, or halogen substituents.

These reactions occur with retention of configuration. The overall transformations occur by *syn* addition with anti-Markovnikov regiochemistry.

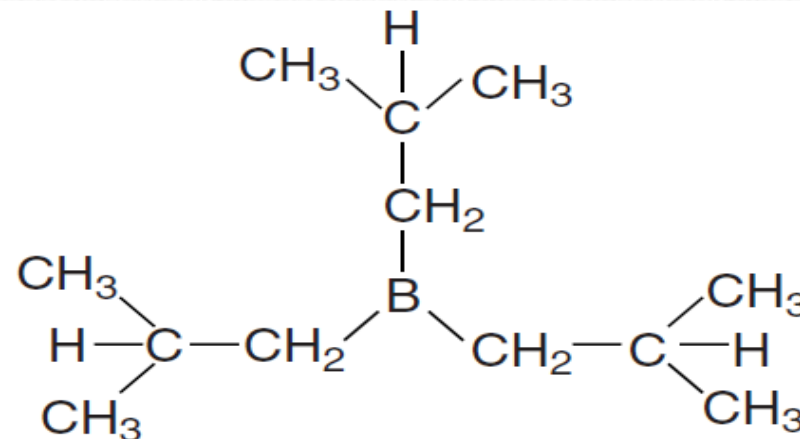
Hydroboration

- Hydroboration can be used to make alcohols and halides, and these reactions usually lead to the opposite (anti-Markovnikov) regiochemistry from reactions that proceed through cationic intermediates.
- The reactions are also stereospecific *syn* additions, as compared to the *anti* stereoselectivity for many reactions proceeding through cationic intermediates.
- The reaction is diverted to *syn* addition by the presence of the potentially nucleophilic hydrogen on boron.
- As the electron-deficient boron bonds to one carbon, the hydrogen with two electrons shifts to the other carbon.

- The addition occurs through a four-center TS. Both the new C–B and C–H bonds are thus formed from the same side of the double bond.
-
- Hydroboration is highly regioselective. The boron becomes bonded predominantly to the *less-substituted* carbon atom of the alkene.
 - A combination of steric and electronic effects favors this orientation. Borane is an electrophilic reagent. The reaction with substituted styrenes exhibits a negative ρ value (–0.5).
 - Compared with bromination ($\rho^+ = -4.3$), this is a weak substituent effect, but it does favor addition of the electrophilic boron at the more nucleophilic end of the double bond.



severe non-bonded
repulsions



non-bonded repulsions
reduced

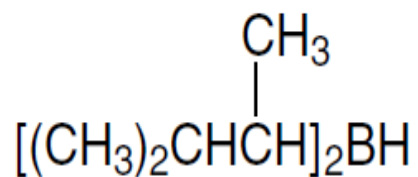
In contrast to the case of addition of protic acids to alkenes, it is boron, not hydrogen, that is the more electrophilic atom.

This electronic effect is reinforced by steric factors. Hydroboration is usually done under conditions in which the borane eventually reacts with three alkene molecules to give a trialkylborane.

The second and third alkyl groups encounter severe steric repulsion if the boron is added at the internal carbon.

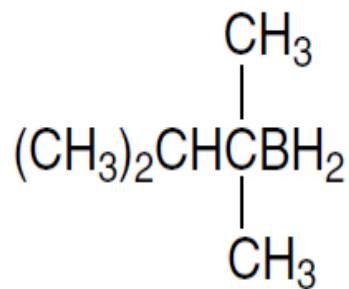
Table 5.7. Regioselectivity of Diborane and Derivatives toward Representative Alkenes

Hydroborating Reagent	Percent added at less-substituted carbon			
	1-Hexene	2-Methyl-1- Butene	4-Methyl-2- Pentene	Styrene
Diborane ^a	94	99	57	80
Chloroborane-dimethylsulfide ^b	99	99.5	—	98
Disiamylborane ^a	99	—	97	98
Thexylborane ^c	94	—	66	95
Chlorothexylborane-dimethylsulfide ^d	99	99	97	99
9-Borabicyclo[3.3.1]nonane (9-BBN) ^e	99.9	99.8 ^f	99.8	98.5



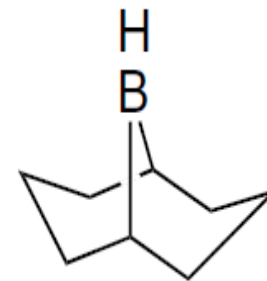
disiamylborane

bis-(1,2-dimethylpropyl)borane



thexylborane

1,1,2-trimethylpropylborane

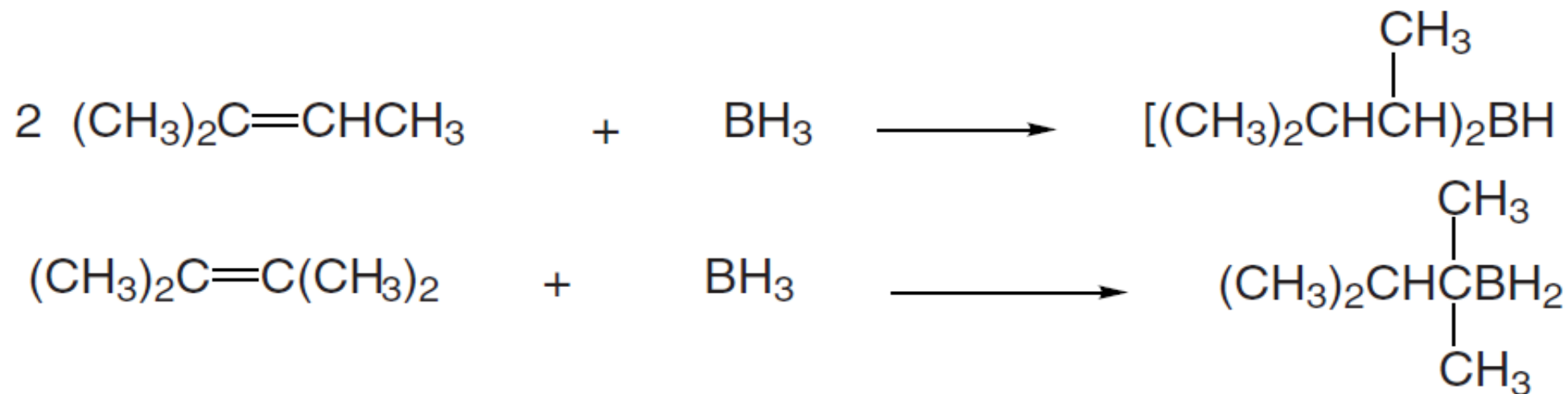


9-BBN

9-borabicyclo[3.3.1]nonane

Table 5.7 includes data for some mono- and dialkylboranes that show even higher regioselectivity than diborane itself.

These derivatives are widely used in synthesis and are frequently referred to by the shortened names shown with the structures.



These reagents are prepared by hydroboration of the appropriate alkene, using control of stoichiometry to achieve the desired degree of alkylation.

9-BBN is prepared from 1,4-cyclooctadiene.

As is true for most addition reactions, there is a preference for approach of the borane from the less hindered face of the double bond.

Since diborane itself is a relatively small molecule, the stereoselectivity is not high for unhindered molecules.

-
- As is true for most addition reactions, there is a preference for approach of the borane from the less hindered face of the double bond.
 - Since diborane itself is a relatively small molecule, the stereoselectivity is not high for unhindered molecules.

- Even 7,7- dimethylnorbornene shows only a modest preference for *endo* addition with diborane.
-
- The selectivity is much enhanced with the bulkier reagent 9-BBN.
 - The haloboranes BH_2Cl , BH_2Br , BHCl_2 , and BHBr_2 are also useful hydroborating reagents.
 - These compounds are somewhat more regioselective than borane itself, but otherwise show similar reactivity.

Table 5.8. Stereoselectivity of Hydroboration with Cyclic Alkenes^a

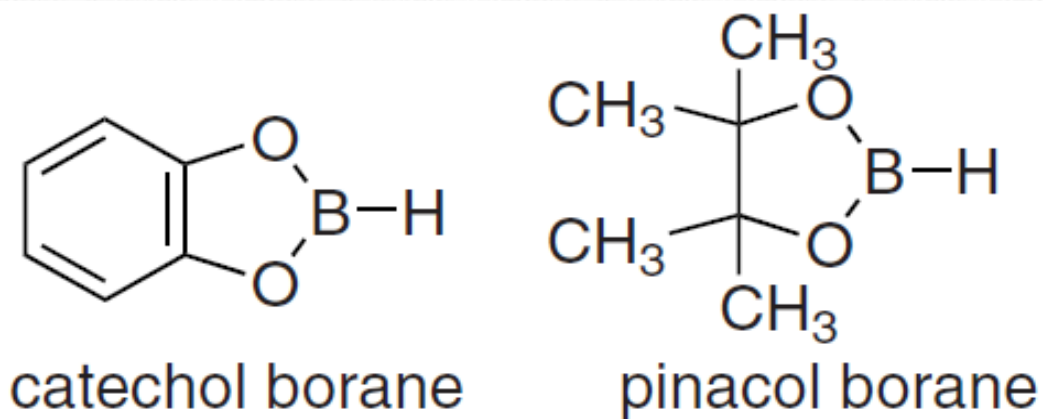
Hydroboration Reagent	Product composition ^b							
	3-Methyl- cyclopentene			3-Methyl- cyclohexene				7,7-Dimethyl norbornene
	<i>trans</i> -2	<i>cis</i> -3	<i>trans</i> -3	<i>cis</i> -2	<i>trans</i> -2	<i>cis</i> -3	<i>trans</i> -3	<i>exo</i> <i>endo</i>
Diborane	45		55	16	34	18	32	22 ^c 78 ^c
Disiamylborane	40		60	18	30	27	25	– –
9-BBN	25	50	25	0	20	40	40	3 97

The products in all cases result from *syn* addition, but the mixtures result from both the low regioselectivity and from addition to both faces of the double bond.

The halogen(s) can be replaced by hydride and a second hydroboration step can then be carried out. This allows for preparation of unsymmetrically substituted boranes. *



Catecholborane and pinacolborane, in which the boron has two oxygen substituents, are much less reactive hydroborating reagents than alkyl or haloboranes.

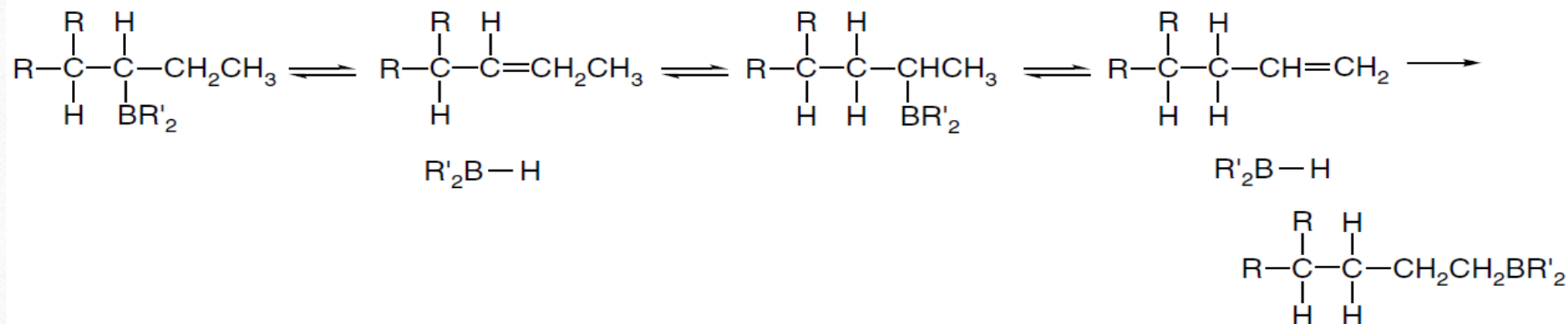


The boron electron deficiency is attenuated by the oxygen atoms.

Nevertheless, they are useful reagents for certain applications. The reactivity of catecholborane has been found to be substantially enhanced by addition of 10–20% of N,N-dimethylacetamide to CH_2Cl_2 .

Hydroboration is thermally reversible. At 160 °C and above, B–H moieties are eliminated from alkylboranes, but the equilibrium is still in favor of the addition products.

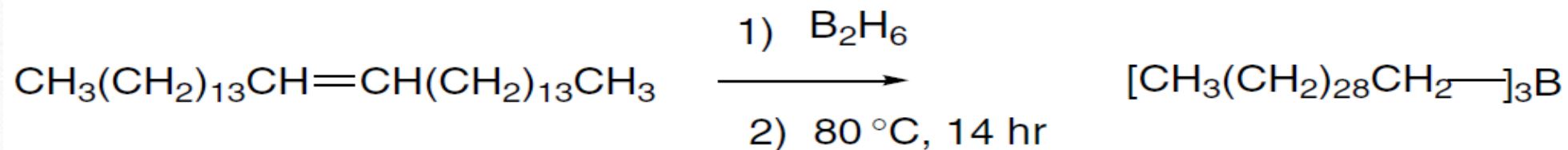
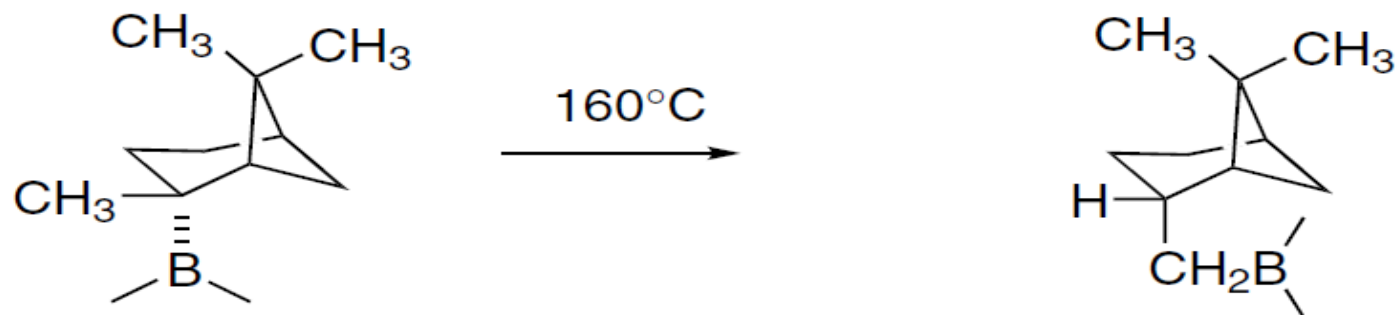
Borane Migration



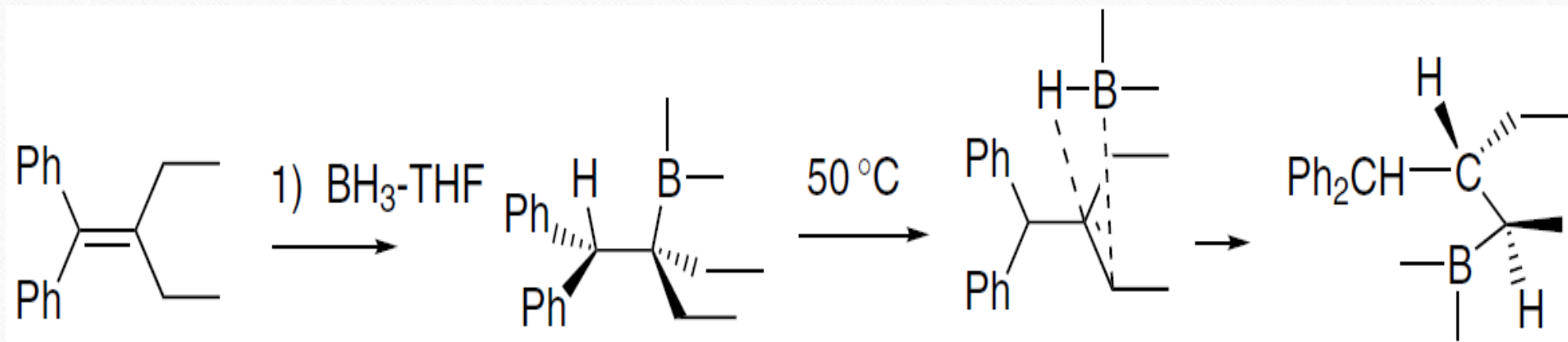
This provides a mechanism for migration of the boron group along the carbon chain by a series of eliminations and additions.

Migration cannot occur past a quaternary carbon, however, since the required elimination is blocked.



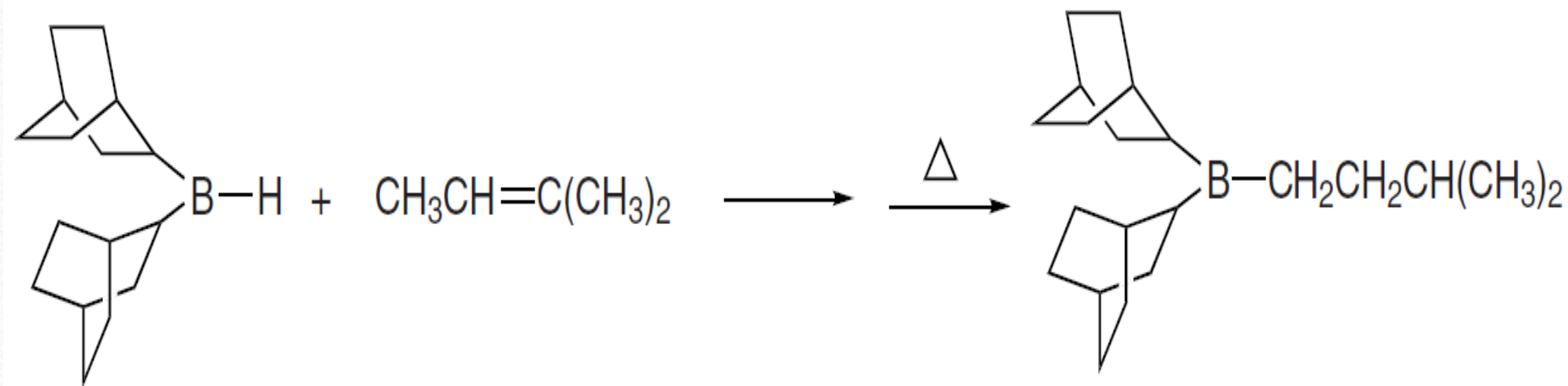


Migrations are especially facile for *tetra*-substituted alkenes; they occur at 50–60 °C and exhibit both regio- and stereoselectivity.



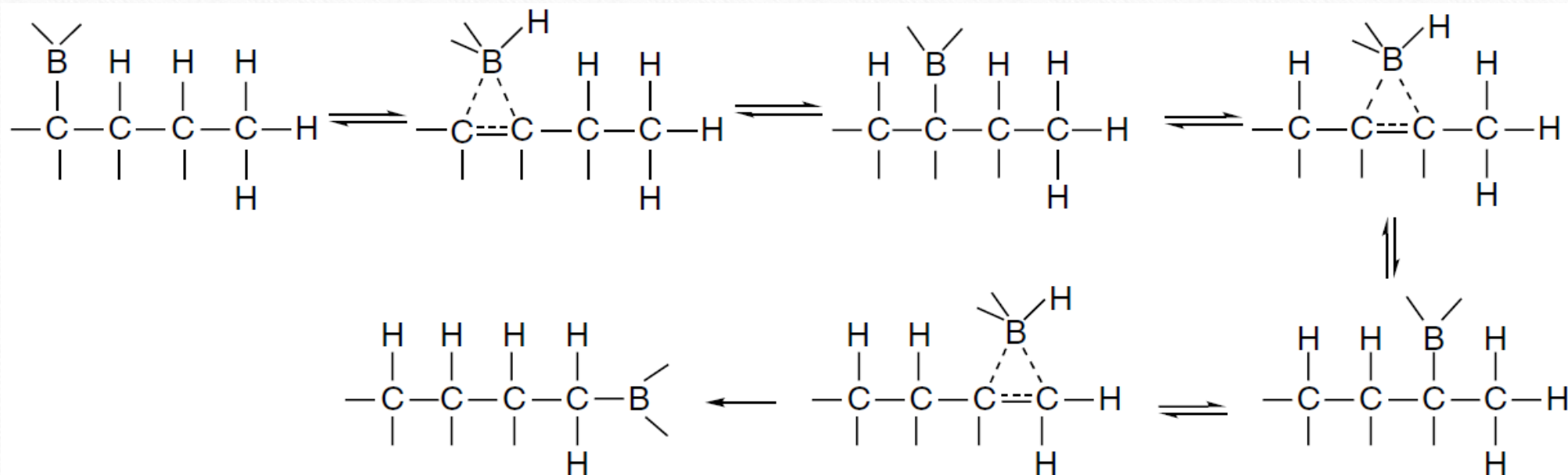
The course of the reactions is dictated by the relative energy of the reversibly formed borane alkene complexes.

Unstrained bicyclic rings have little tendency to rearrange. **bis-Bicyclo[2.2.2] octanylborane** has been found to be particularly useful for formation and isomerization of **monoalkyl derivatives**.



There is evidence that boron migration occurs *intramolecularly*.

A TS that describes this process has been located computationally (Figure 5.6). It involves an electron-deficient π -complex about 20–25 kcal above the trialkylborane. These structures are analogous to the bridged carbocations in carbocation rearrangements.



The boron can migrate to the end of the chain through a series of such structures.

Methods by which the boron atom can be efficiently replaced by hydroxy, halogen, or amino groups.

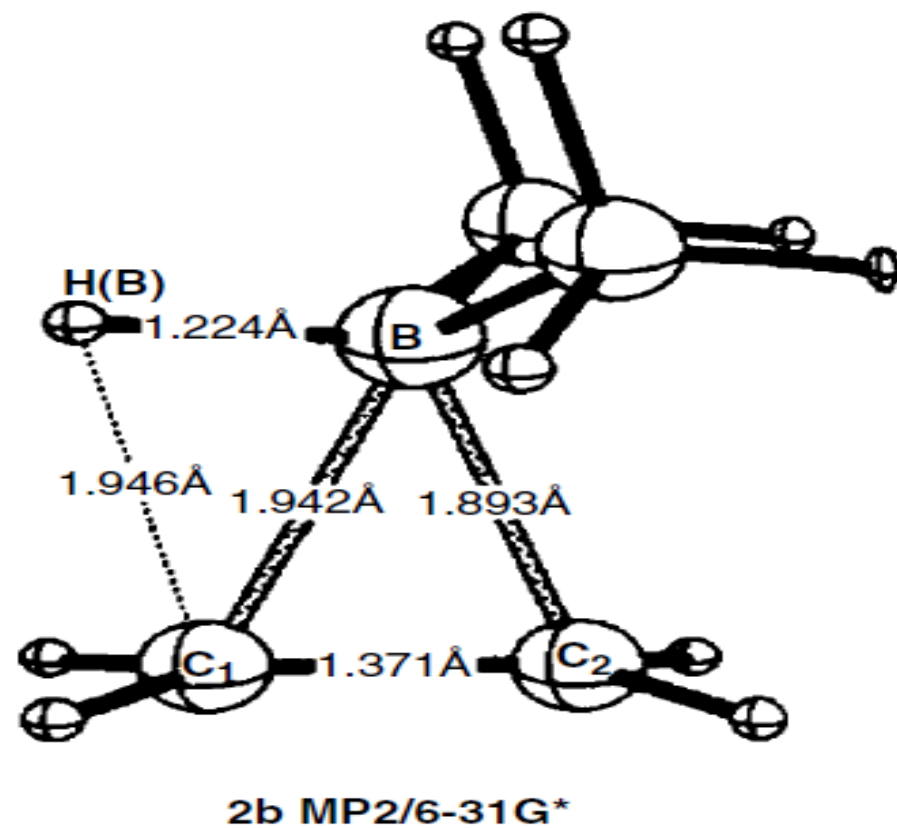
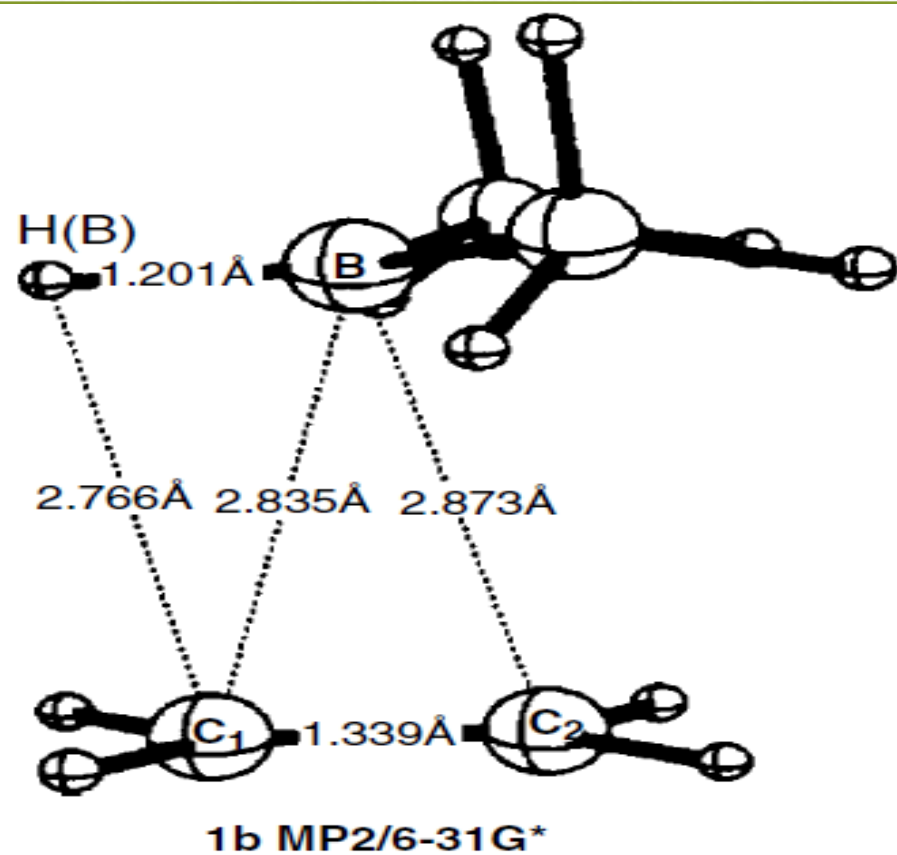


Fig. 5.6. Geometries (MP2/6-31G*) of (a) π complex and (b) transition state in reaction of ethene and dimethylborane. Reproduced from *J. Org. Chem.*, **56**, 4074 (1991), by permission of the American Chemical Society.

Reactions of Organoboranes

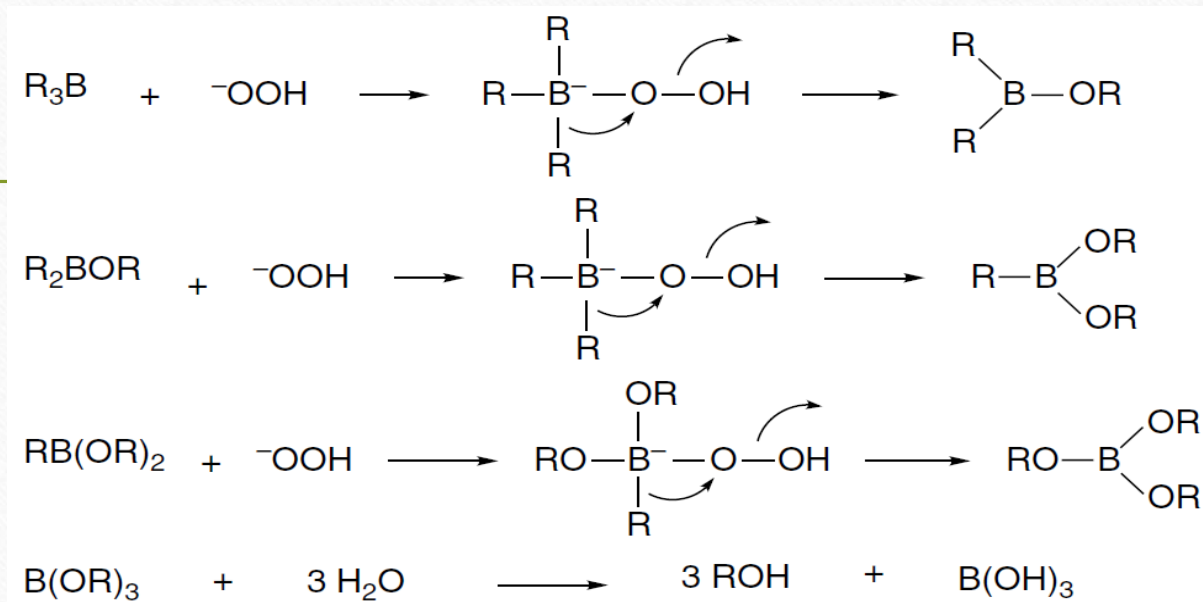
The most widely used reaction of organoboranes is the oxidation to alcohols.

Alkaline hydrogen peroxide is the reagent usually employed to effect the oxidation.

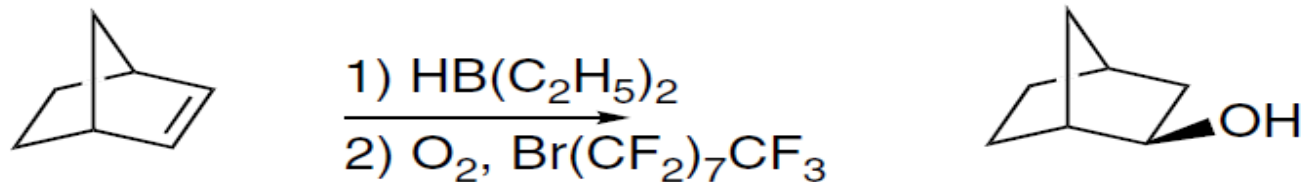
The trialkylborane is converted to a trialkoxyborane (trialkyl borate) by a series of $B \rightarrow O$ migrations.

The $R-O-B$ bonds are hydrolyzed in the alkaline aqueous solution, generating the alcohol.

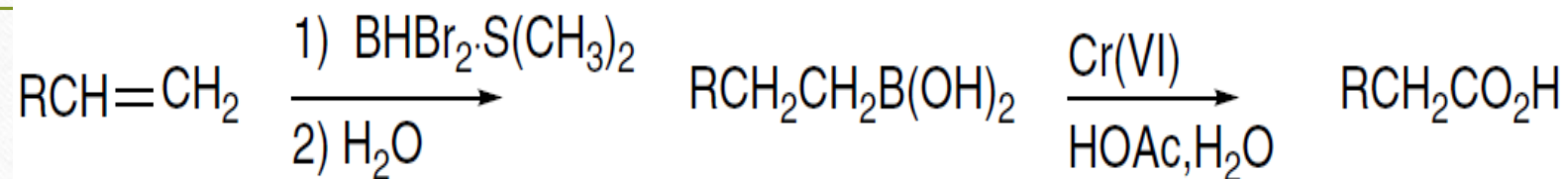
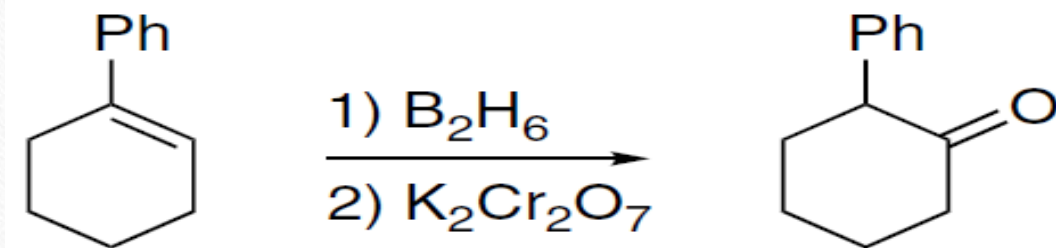
The Mechanism of Oxidation of Alkyl borane



The preference for boronation at the less-substituted carbon of a double bond results in the alcohol being formed with regiochemistry that is complementary to that observed by direct hydration or oxymercuration, i.e., anti-Markovnikov.



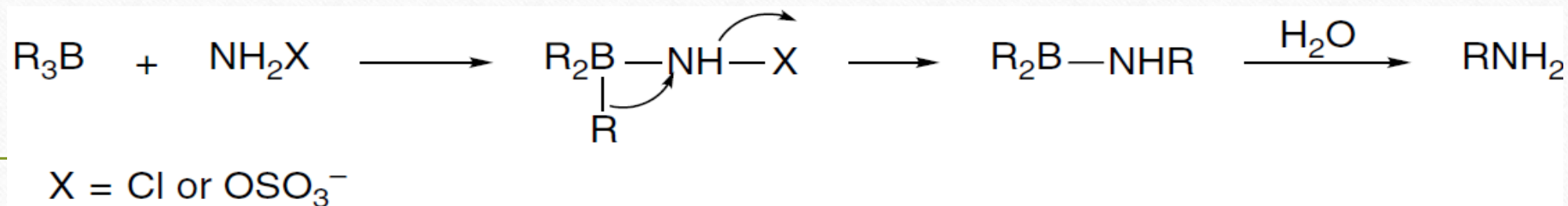
- Conditions that permit oxidation of organoboranes to alcohols using other oxidants, including molecular oxygen, sodium peroxycarbonate, or amine oxides have been developed.
- Oxone has been recommended for oxidations done on a large scale.
- The reaction with molecular oxygen is particularly effective in perfluoroalkane solvents.



More vigorous oxidizing agents such as **Cr (VI)** reagents effect replacement of boron with oxidation to the **carbonyl level**.

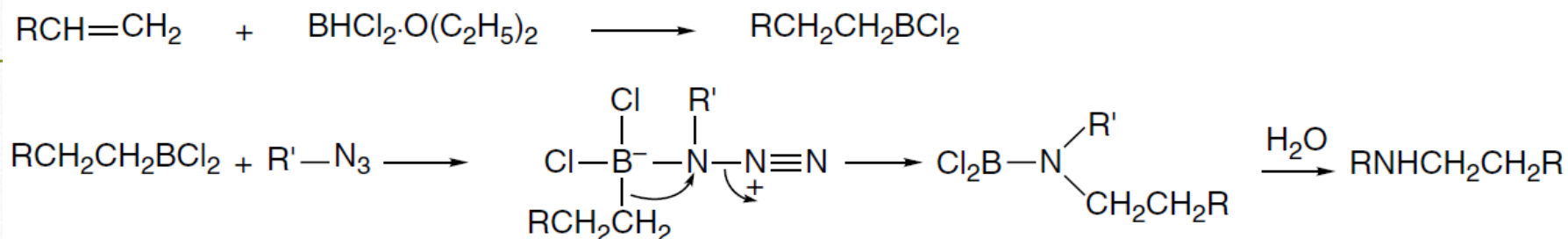
An alternative procedure for oxidation to **ketones** involves treatment of the alkylborane with a **quaternary ammonium perruthenate** salt and an amine oxide.

Replacement by Amino Group



- The nitrogen-containing reagent initially reacts as a nucleophile by adding at boron; then a B→N shift occurs with expulsion of chloride or sulfate.
- As in the oxidation, the **migration step** occurs with **retention** of configuration. The amine is freed from the borane by hydrolysis.
- The reagents that effect this conversion are **chloramine or hydroxylamine-O-sulfonic acid**.
- The mechanisms of these reactions are very similar to that of the **hydrogen peroxide oxidation of organoboranes**.

Secondary amines



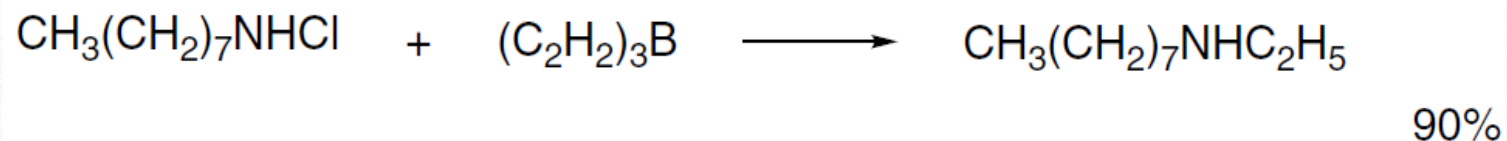
Secondary amines are formed by reaction of boranes with **alkyl or aryl azides**.

The most efficient borane reagents are **monoalkyldichloroboranes**, which are generated by the reaction of an alkene with **BHCl₂ · Et₂O**.

The entire sequence of steps and the mechanism of the final stages are summarized by the above equation.

Secondary Amines

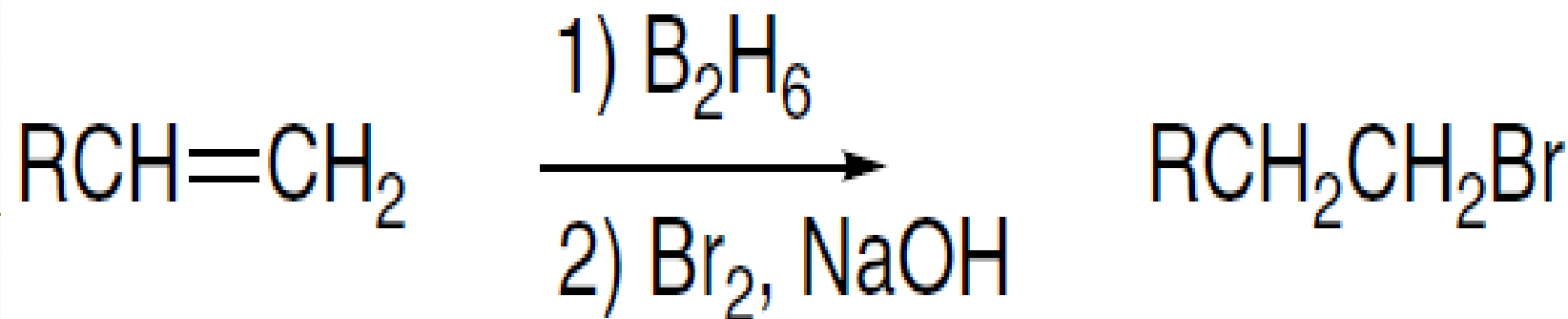
Another method is using N-chloro derivatives of primary amines.



Organoborane intermediates can also be used to synthesize alkyl halides.

Replacement of boron by iodine is rapid in the presence of base.

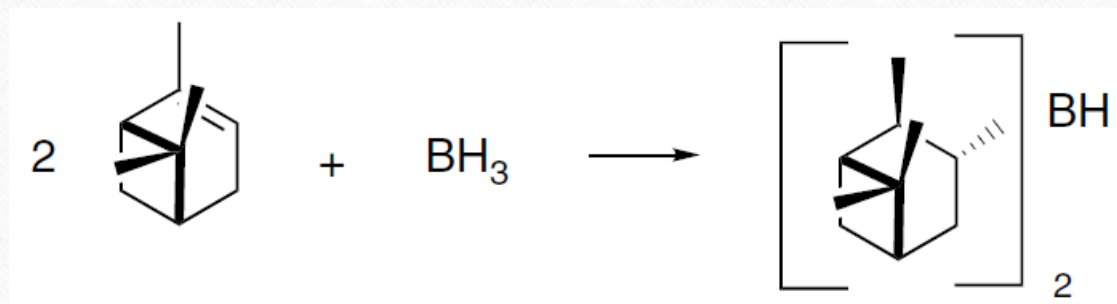
The best yields are obtained using sodium methoxide in methanol. If less basic conditions are desirable, the use of iodine monochloride and sodium acetate gives good yields.



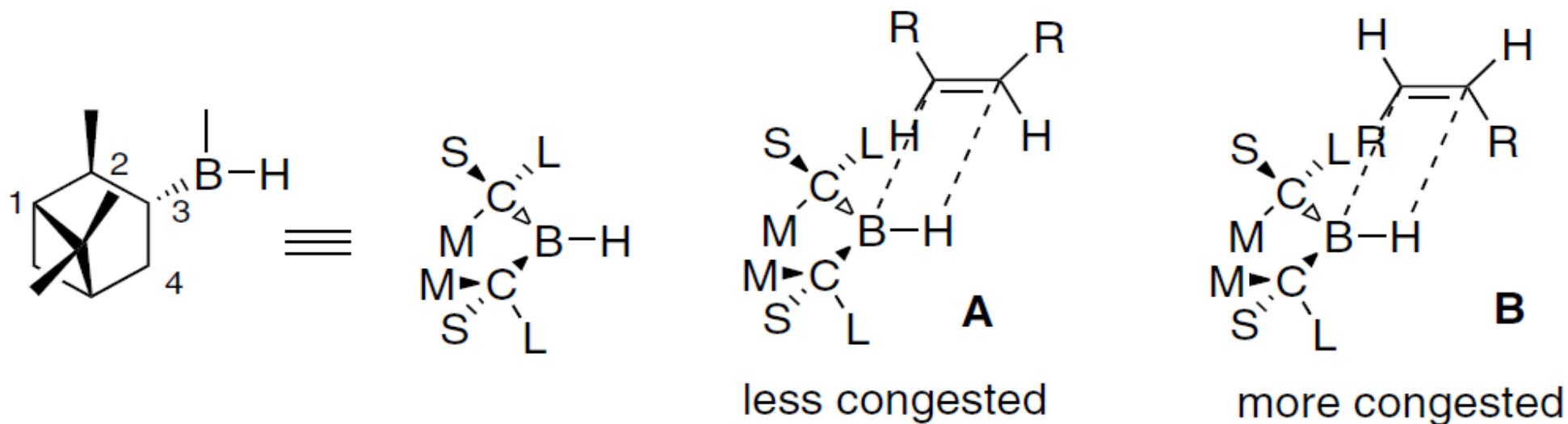
- As is the case in hydroboration-oxidation, the **regioselectivity** of **hydroboration-halogenation** is **opposite** to that observed with direct ionic addition of hydrogen halides to alkenes.
- Terminal alkenes give primary halides.

Enantioselective Hydroboration

The most thoroughly investigated of these boranes is *bis*-(isopinocampheyl)borane, $(\text{Ipc})_2\text{BH}$, which can be prepared in 100% enantiomeric purity from the readily available terpene α -pinene. Both enantiomers are available.



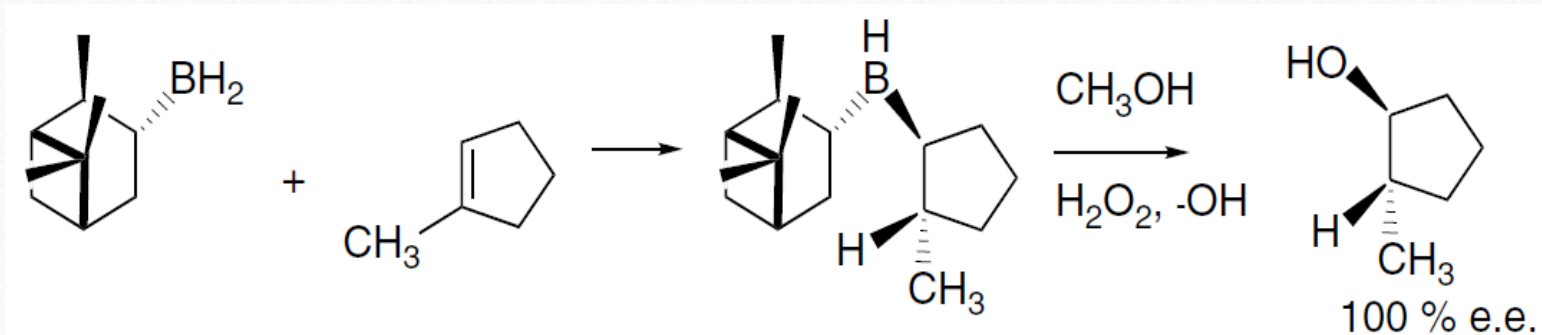
$(\text{Ipc})_2\text{BH}$ adopts a conformation that minimizes steric interactions.



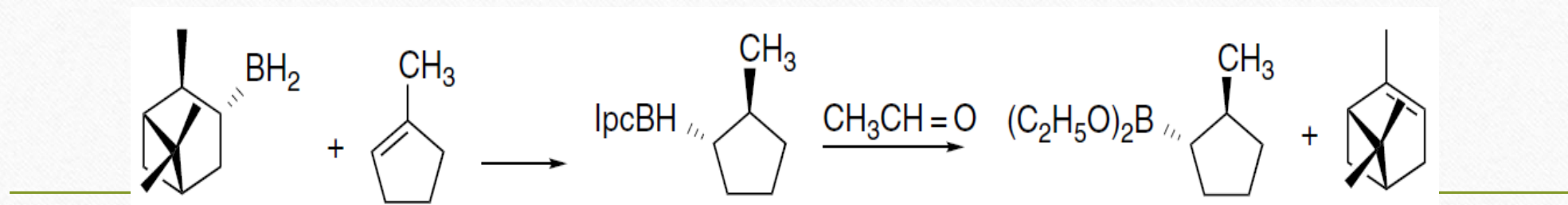
This conformation can be represented schematically, where the S, M, and L substituents are, respectively, the 3-H, 4-CH₂, and 2-CHCH₃ groups of the carbocyclic structure.

The steric environment at boron in this conformation is such that Z-alkenes encounter less steric encumbrance in TS **A** than in **B**.

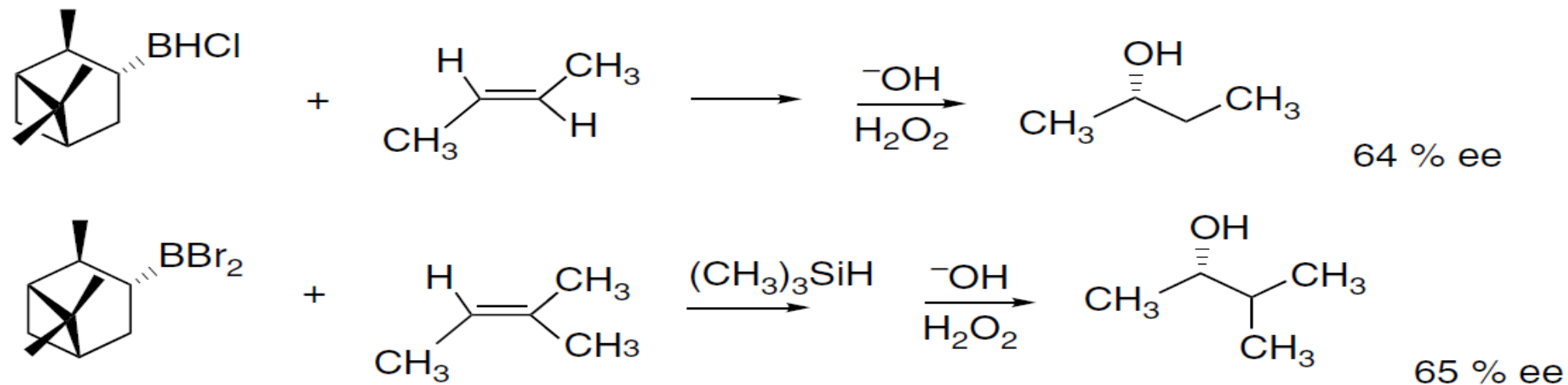
Z-2-Butene undergoes hydroboration with 98% enantioselectivity with (Ipc)₂BH.



- Other *Z*-disubstituted alkenes give good enantioselectivity (75–90%) but *E*-alkenes and simple cycloalkenes give low enantioselectivity (5–30%).
- Monoisopinocampheylborane (IpcBH₂) can be prepared in enantiomerically pure form by purification of its TMEDA adduct.
- When this *monoalkylborane* reacts with a *prochiral alkene*, one of the *diastereomeric products* is normally formed in *excess* and can be obtained in high enantiomeric purity by an appropriate separation. *Oxidation* of the borane then provides the corresponding *enantiomerically enriched alcohol*.



- Although this is not a problem with inexpensive materials, the overall efficiency of generation of enantiomerically pure product is improved by procedures that can regenerate the original terpene.
- This can be done by heating the dialkylborane intermediate with acetaldehyde.
- The α -pinene is released and a diethoxyborane is produced. The usual oxidation conditions then convert this boronate ester to an alcohol



- The corresponding haloboranes are also useful for enantioselective hydroboration.
- Isopinocampheylchloroborane can achieve 45–80% e.e. with representative alkenes.
- The corresponding bromoborane achieves 65–85% enantioselectivity with simple alkenes when used at $-78\text{ }^{\circ}\text{C}$.

Comparison of Electrophilic Addition Reactions

- In this section, we make some broad comparisons among the electrophilic addition reactions that have been discussed.
- We have presented data on substituent effects, regioselectivity, and stereochemistry for protonation, halogenation, sulfenylation and selenenylation, epoxidation, mercuration, and hydroboration.
- What general trends and insights can be gained by comparing these reactions? There have been several efforts at elucidating correlations among the different reactions.

-
- Fukuzumi and Kochi showed that when **steric effects** are considered in a quantitative way, there is a **strong correlation between bromination and mercuration rates**.
 - Nelson and co-workers examined most of the reaction series and found **correlations between the reactivity of various alkenes and the IP of the alkene**.
 - For some of these correlations, **there were separate lines for mono- , di- , and trisubstituted alkenes, reflecting different steric environments**.
 - We take a similar but less detailed look at relative reactivity of several representative alkenes. Figure 5.7 is a graph of the relative reactivity (with ethene as the standard) for the various reactions.

-
- The log of the relative reactivity, as shown in Table 5.9, is plotted against alkene IP. A separate symbol is used for each reaction.
 - The alkenes are in order of decreasing IP.
 - We make comparisons based on these data in very broad terms. Looking first at **protonation**, represented in Figure 5.7 by circles, we see that **reactivity rises sharply** with **substitution** from **ethene to propene to 2-methylpropene**, but *2-methyl-2-butene and 2,3-dimethyl-2-butene have rates roughly similar to 2-methylpropene.*

- *The degree of substitution at the more-substituted carbon is the major factor in reactivity.*
-

- We can surmise from this trend that *carbocation stability* is the major factor in determining the protonation rates.
- Note also that styrene is *more reactive* than propene, again consistent with carbocation stability as the major influence on reactivity.
- In terms of the Hammond postulate, the carbocation is a good model of the TS because the protonation step is substantially *endothermic* and the TS is late.

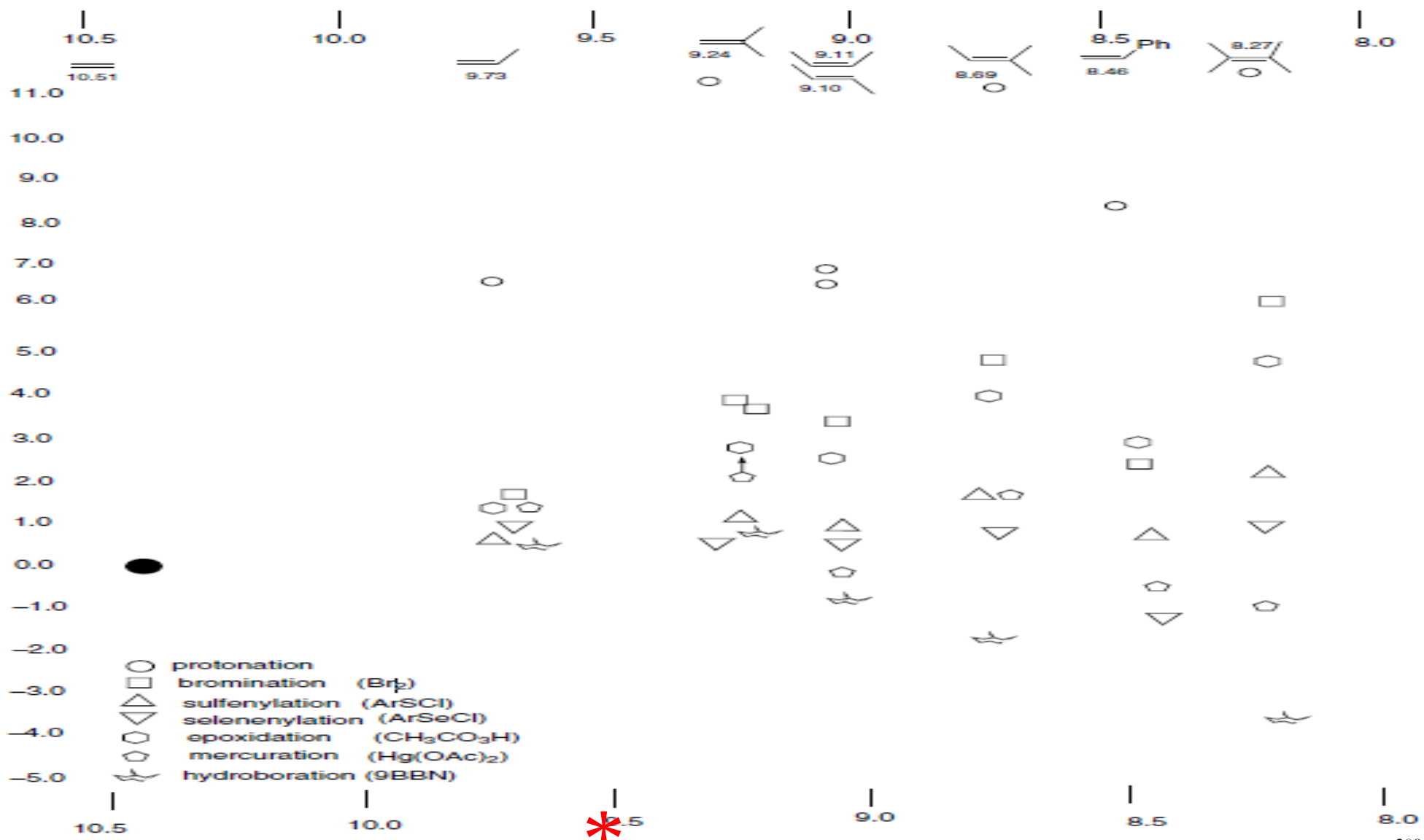


Fig. 5.7. Relationship between reactivity and IP for several alkenes.

-
- Moving to *bromination*, represented by *squares* in the figure, we again see an *increase of reactivity with alkyl substitution*.
 - Now, however, the *total number of substituents is important*. The rate continues to increase as substitution increases from ethene through 2,3-dimethyl-2-butene.
 - This pattern is consistent with the more symmetrical (bridged) nature of the rate-determining TS. All of the substituents contribute to stabilization.

Table 5.9. Log of Relative Reactivity of Representative Alkenes.

Alkene	IP(ev) ^a	H ⁺ ^b	Br ₂ ^c	ArSCl ^d	ArSeCl ^d	RCO ₃ H ^e	Hg ²⁺ ^f	9-BBN ^g
Ethene	10.51	0	0	0	0	0	0	—
Propene	9.73	6.2	1.8	0.50	0.94	1.3	1.3	0.3
2-Methylpropene	9.24	11.5	3.7	0.93	0.83	2.5	>2	0.6
<i>Z</i> -2-Butene	9.11	6.0	3.4	1.30	0.57	2.3	0.04	-1.0
<i>E</i> -2-Butene	9.10	6.4	3.2	0.82	0.32	2.3	-0.5	
<i>Z</i> -3-Hexene	9.0 ^h							-1.2
<i>E</i> -3-Hexene	9.0 ^h							-1.5
Cyclohexene	8.95	7.5				2.8	0.0	
2-Methyl-2-butene	8.69	11.2	5.1	1.6	0.57	3.8	1.6	-2.0
Styrene	8.46	8.2	2.4 ⁱ	-0.03	-1.3	2.7	-0.6	
2,3-Dimethyl-2-butene	8.27	11.3	6.0	2.1	0.39	4.8	-1.2	-4.2



-
- The most noteworthy feature of the **sulfenylation and selenenylation rates** (represented by the triangles) is their **much diminished sensitivity to substitution**.
 - This reflects both **smaller electron demand in the TS** and **increased sensitivity to steric factors**.
 - The **relatively low rate of styrene** toward **selenenylation** is somewhat of an anomaly, and may reflect **both ground state stabilization and steric factors in the TS**.
 - The **epoxidation data** ($\text{CH}_3\text{CO}_3\text{H}$, hexagons) show a **trend similar to bromination**, but **with a reduced slope**.

- Mercuration exhibits a *carbocation-like pattern*, but with the superposition of a large steric effect.
 - For *unsubstituted terminal carbons*, the rate increases from *ethane* to *propene* to *2-methylpropene*.
-
- This trend also holds *for internal alkenes*, as *2-methyl-2-butene* is more reactive than *2-butene*.
 - However, *steric effects become dominant for 2,3-dimethylbutene*.
 - There is *no evidence* of a *rate-retarding steric component*. One indicator of a *strong steric component* is *decreased reactivity of the E-isomer in an E,Z-disubstituted alkene pair*, but the rates for the *2-butene isomers toward epoxidation* are very similar (Table 5.9).

-
- This *incursion of steric effects in oxymercuration* has long been *recognized*, he found *separate correlation lines for mono- and disubstituted alkenes*.
 - *Hydroboration by 9-BBN (structures)* shows a *different trend: steric effects are dominant* and reactivity decreases with substitution.
 - *Similar trends* apply to rates of *addition of dibromoborane and disiamylborane*. The importance of steric factors is no doubt due in part to the relatively bulky nature of these boranes.
 - However, it also reflects *a decreased electron demand in the hydroboration TS*.

- An overall perspective of the data in Table 5.9 and Figure 5.7 can be gained by simply comparing the relative rates of ethene and 2,3-dimethyl-2-butene.
- These go from *very large for protonation* ($10^{11.4}$) *to small* ($10^{-4.2}$) *for hydroboration by 9-BBN as the dominance of carbocation stability effects for protonation is replaced by dominant steric effects for hydroboration by 9-BBN.*
- *Another useful perspective from which to compare the electrophilic addition reactions is to focus on structure of the TS and intermediates.*
- Figure 5.8 *arranges the cationic and neutral species in relation to the periodic table. Some of these structures are stable products, others are reaction intermediates, and still other are transition structures.*
- If the bridged and open versions of a species are comparable in energy, both are shown.

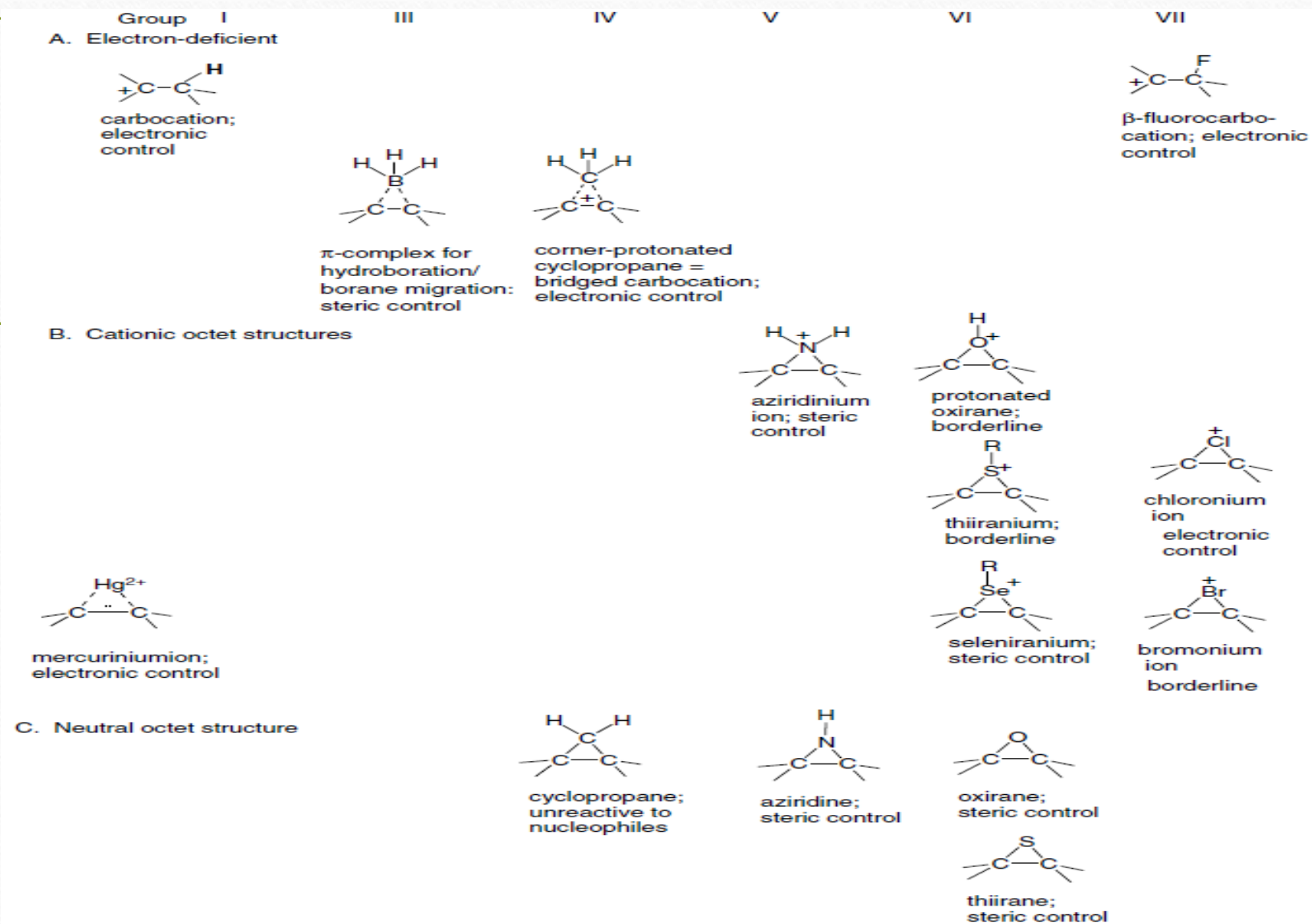
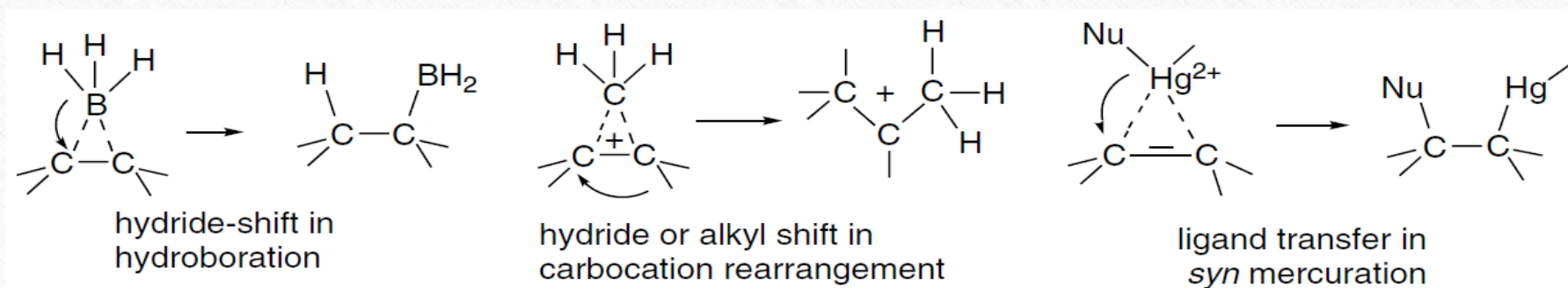


Fig. 5.8. Relationship between small ring structures and regiochemistry of addition reactions.

- Taking the view that *protonation of alkenes gives open carbocations*, at least in solution, gives us a starting point for comparing the various addition reaction intermediates.
-
- The reactions that are *characteristic of carbocations*, namely *nucleophilic capture, elimination of a proton, and rearrangement*.
 - These reactions are controlled by *electronic factors*, as illustrated by *Markovnikov regioselectivity for nucleophile capture* and *Saytzeff regiochemistry for elimination*.
 - The TSs for hydroboration and protonated cyclopropanes are related to open carbocations in being *electron deficient*.



- The *hydroboration TS collapses* by a *hydride shift* from boron to carbon that is *driven by both electronegativity and steric factors*.
- *Corner-protonated cyclopropanes* are converted to the *carbocation* best able to support *positive charge*. It is also clear from the *mercuration reaction* that a *ligand transfer* process is *available* when *anti nucleophilic addition* is *sterically hindered*.
- The *syn addition* is similar to the *hydride migration* that occurs during hydroboration. The *regiochemistry of the migration* is dictated by *electronic factors*.

- Moving to the right in the periodic table, aziridinium ions and protonated epoxides are no longer electron deficient, although they are electrophilic.
-
- Ring opening of aziridinium ions is normally controlled by *steric access*, because of the *need for nucleophilic participation*.
 - The *regioselectivity of solvo-fluorination*, by contrast, is subject to *electronic control* and strictly follows *Markovnikov's rule* because of the *carbocationic character* of the species.
 - An *O-protonated or Lewis acid-activated oxirane is borderline*, with instances of both Markovnikov and anti- Markovnikov ring opening.

- When we drop down to the next two rows of the periodic table, *bridging becomes more important*.
-
- For *chloronium ions and bromonium ions* (as in halohydrin formation, *Markovnikov orientation (electronic control) usually prevails* because *the bridging bonds are relatively weak*. However, the mixed regiochemistry of *methoxybromination in methanol is an exception*.
 - For *sulfenylation and selenenylation*, the *bridging bonds are stronger* and *anti-Markovnikov regiochemistry* frequently observed because *nucleophilic engagement (steric access) is a critical feature for ring opening*.
 - For the *neutral small rings, cyclopropane is resistant to nucleophilic attack*.

-
- *Aziridines and epoxides are successively more reactive toward nucleophiles, but the regiochemistry is controlled by steric approach factors.*
 - The *proton* that initiates acid-catalyzed addition processes is a hard acid and has no unshared electrons. It can form *either a carbocation or a hydrogen-bridged cation.*
 - Both species are *electron deficient* and highly reactive. The *formation of the cationic intermediate is rate determining and nucleophilic capture is fast.*

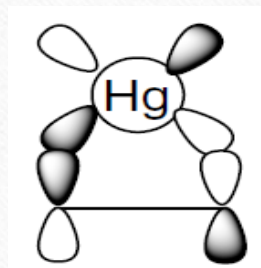
The *positive bromine in a bromonium ion intermediate is a softer electrophile and also has unshared electron pairs* that permit a total of *four electrons* to participate in the bonding.

The bromonium ion can be represented as *having two covalent bonds to bromine* and is *electrophilic* but not *electron deficient*.

This results in a more strongly bridged and more stable species than is possible for the proton.

-
- Where do mercuration reactions fit into this picture? A mercurinium ion has both similarities and differences, as compared with the intermediates that have been described for other electrophilic additions.
 - The electrophile in oxymercuration reactions, $+HgX$ or Hg^{2+} , is a soft Lewis acid and polarizes the π -electrons of an alkene to the extent that a three-center two-electron bond is formed between mercury and the two carbons of the double bond.

- However, there is also back bonding from Hg^{2+} d orbitals to the alkene π^* orbital. There is weaker bridging in the mercurinium ion than in the three-center four-electron bonding of the bromonium ion.



Another perspective on the nature of some the cyclic structures represented in Figure 5.9 by focusing on the bond paths for the three-membered ring. (See p. 63 to review the discussion of bond paths.)

- Neutral cyclopropane, aziridine, and oxirane rings are well described by the *bent bond model*, but the *C–O bonds are somewhat less bent than those in cyclopropane*.
-
- On the other hand, in *protonated oxirane*, the *bonds begin to bend inward*.
 - For the *bridged fluorine species*, there is *no longer a ring*; instead the structure is that of a *π complex* (a bridged fluoronium ion is unstable relative to the corresponding carbocation.)
 - The differences in the nature of the bonds result from the relative ability of the bridging atom to donate electron density to the ring forming orbitals, which is in the order $CH_2 > NH > O > O^+H > F^+$ (Figures 5.9).

Additions to Alkynes and Allenes

- Reactions of alkynes with electrophiles are generally similar to those of alkenes.
- Since the HOMO of alkynes is also a π type orbital, it is not surprising that there is a good deal of similarity to the reactivity of alkenes.
- The fundamental questions about additions to alkynes include the following: How reactive are alkynes in comparison with alkenes? What is the stereochemistry of additions to alkynes? What is the regiochemistry of additions to alkynes?
- The important role of bridged ions in addition reactions of alkenes raises the question of whether similar species are involved with alkynes, where the ring includes a double bond and bridged intermediates and would be expected to be substantially more strained.

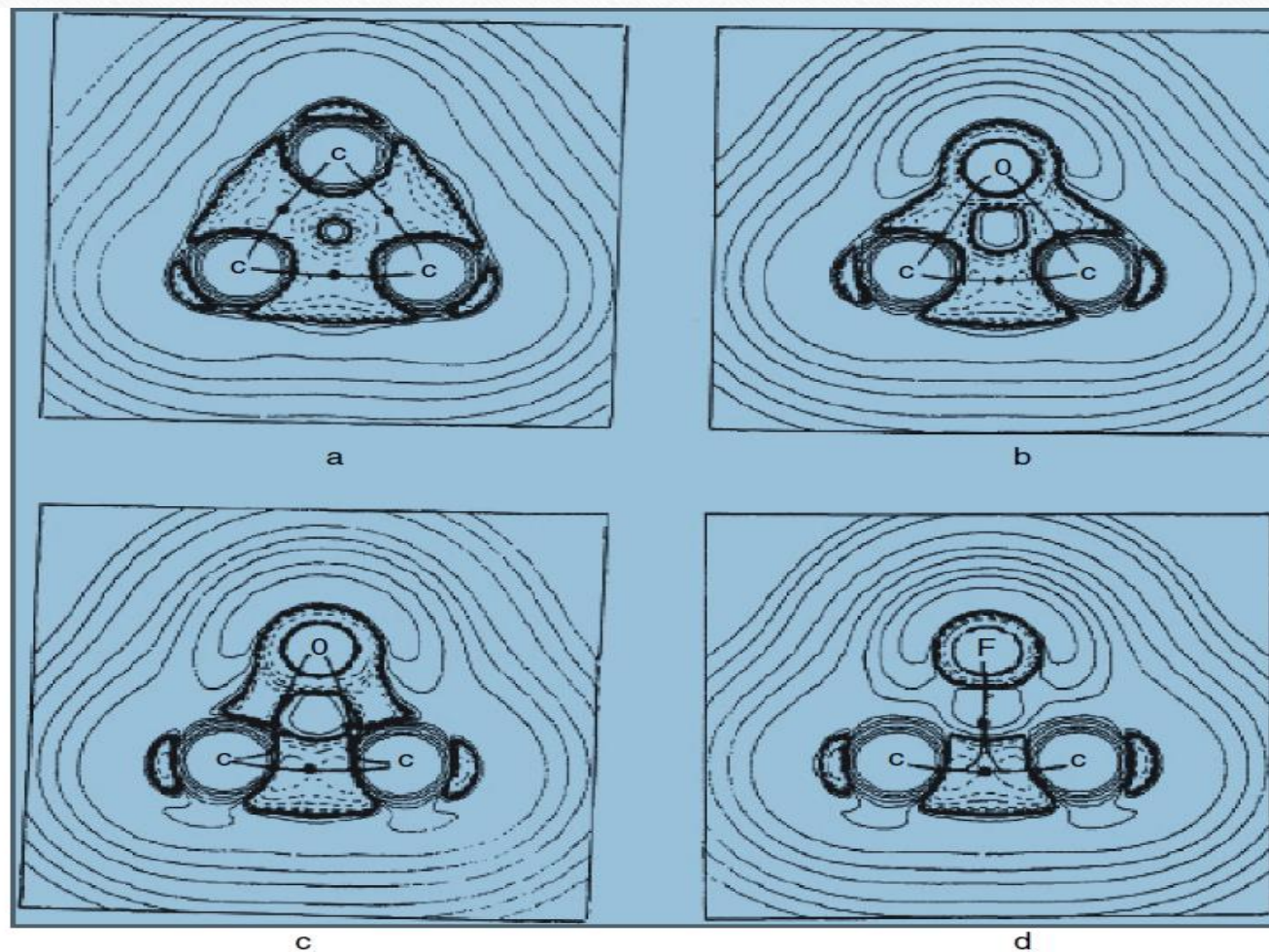
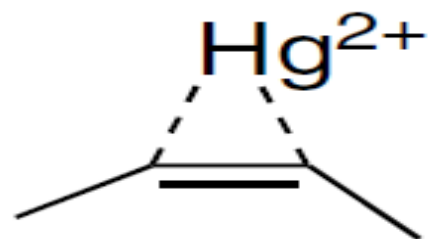
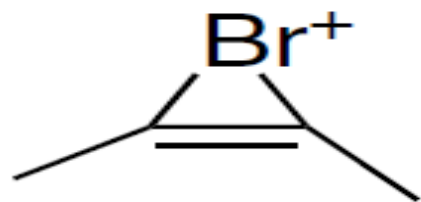
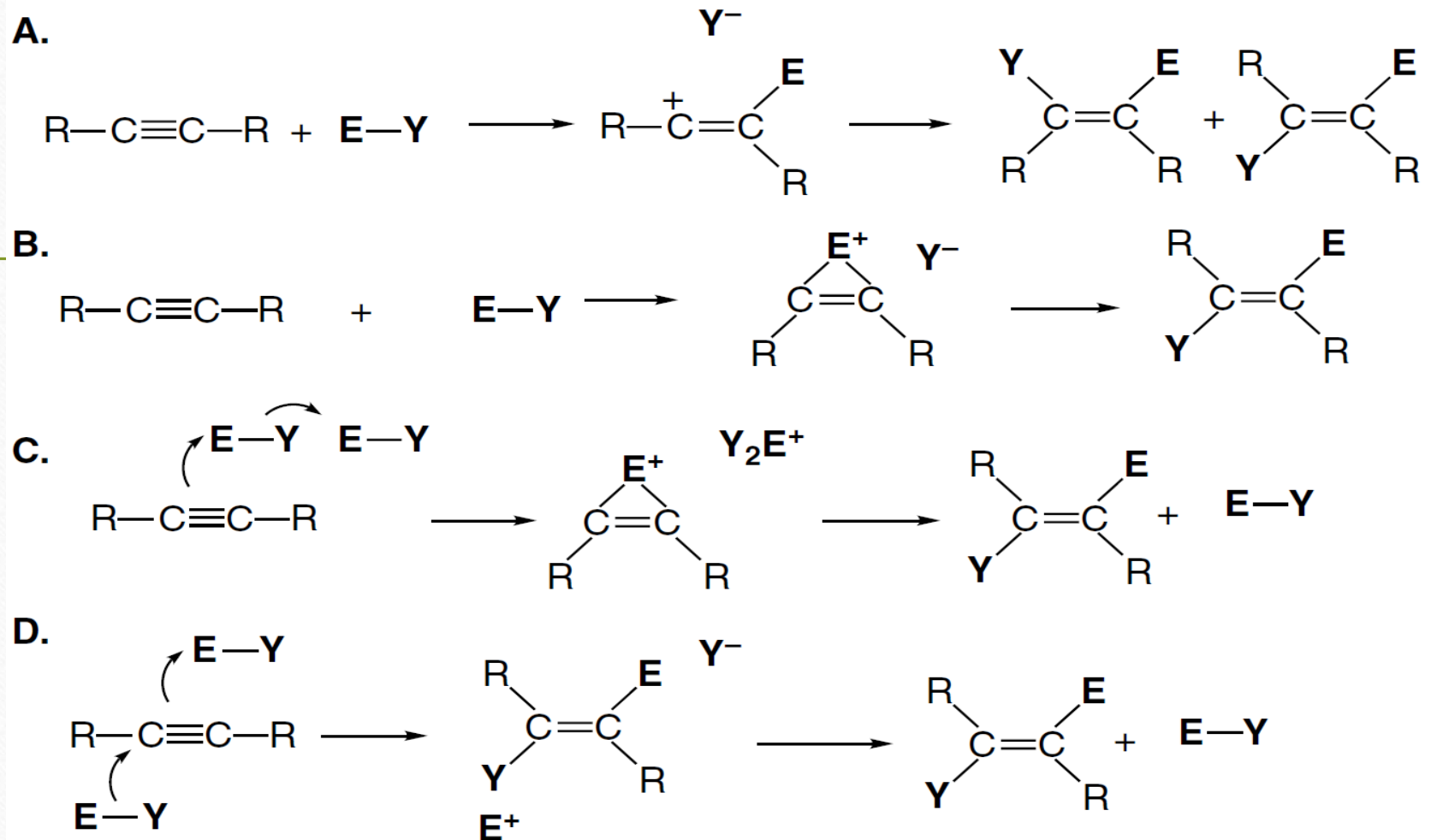


Fig. 5.9. Molecular graphs showing the Laplacian $-\nabla^2\rho(\mathbf{r})$ and bond paths. Bond paths are shown as solid lines and bond critical points as dots. Dashed contours show areas of electronic charge concentration and solid contours show regions of charge depletion. (a) cyclopropane, (b) oxirane, (c) protonated oxirane, and (d) fluorine-bridged cation. Reproduced from *J. Am. Chem. Soc.*, **107**, 3800 (1985), by permission of the American Chemical Society.



The first involves a discrete vinyl cation.

In general, this reaction will lead to a mixture of the two stereoisomeric addition products.



-
- Mechanisms **B** and **C** depict bridged intermediates formed without (**B**) or with (**C**) participation of a second electrophilic molecule. Mechanisms **B** and **C** should lead to *anti* addition.
 - Mechanism **D** is a termolecular process that would be expected to be a stereospecific *anti* addition.
 - Mechanisms **A** and **B** are of the AdE2 type, whereas **C** and **D** are classified as AdE3. Each of these mechanisms may involve a prior complex formation between the alkyne and an electrophile.

- Alkynes are somewhat less reactive than alkenes toward many electrophiles. A major reason is the substantially higher energy of the vinyl cation intermediate.
-
- Vinyl cations are about 10 kcal/mol less stable than an alkyl cation with similar substitution.
 - For additions that proceed through bridged intermediates, the alkynes are also less reactive because of additional strain in the intermediate.
 - The differences in the rate of addition between alkenes and alkynes depends upon the specific electrophile and the reaction conditions.

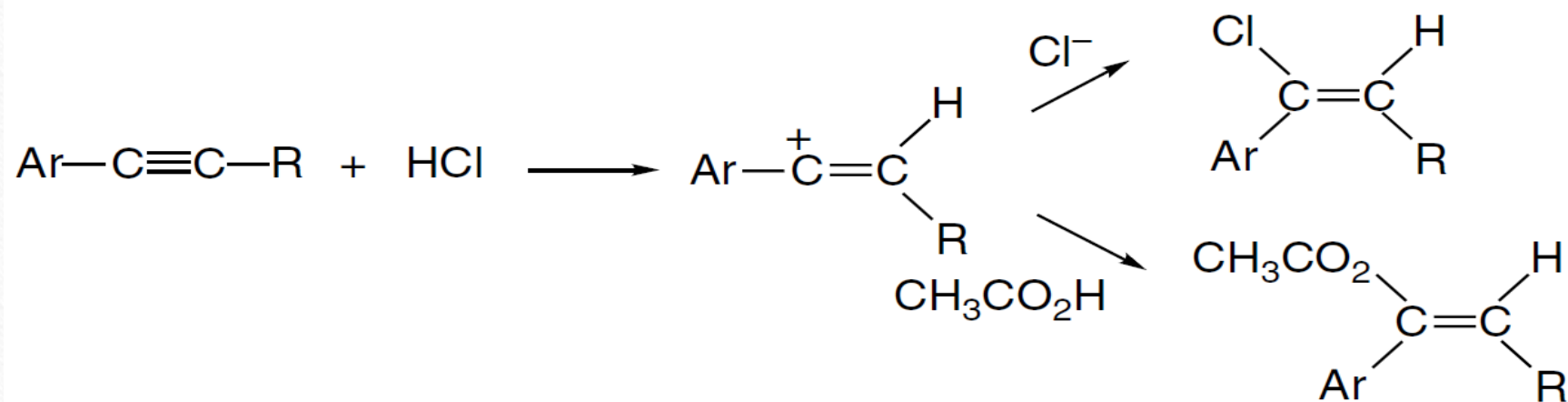
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- Table 5.10 summarizes some specific rate comparisons. These results show large differences for bromination and chlorination but relatively small differences for protonation.
 - The presence of a carbocation-stabilizing phenyl group reduces the difference for bromination and chlorination.

Hydrohalogenation and Hydration of Alkynes

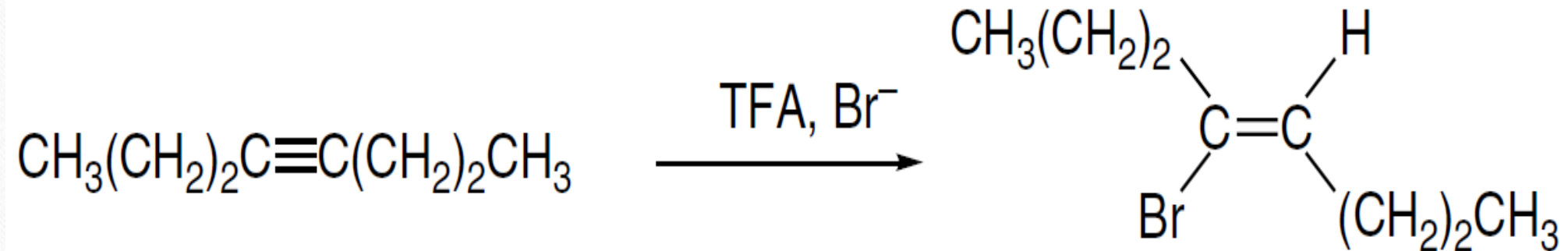
- Hydrogen chloride adds to aryl alkynes in acetic acid to give mixtures of α -chlorostyrenes and the corresponding vinyl acetate.
- A vinyl cation, which is stabilized by the aryl substituent, is believed to be an intermediate. The ion pair formed by protonation can either collapse to give the vinyl halide or capture solvent to give the acetate.
- Aryl-substituted acetylenes give mainly the *syn* addition product.

Table 5.10. Relative Reactivity of Alkenes and Alkynes^a

Alkene/alkyne pair	Bromination, HOAc	Chlorination, HOAc	Acid-catalyzed hydration
1-Hexene/1-hexyne	1.8×10^5	5.3×10^5	3.6
<i>E</i> -3-Hexene/3-hexyne	3.4×10^5	$\sim 1 \times 10^5$	16.6
Styrene/phenylethyne	2.6×10^3	7.2×10^2	0.65

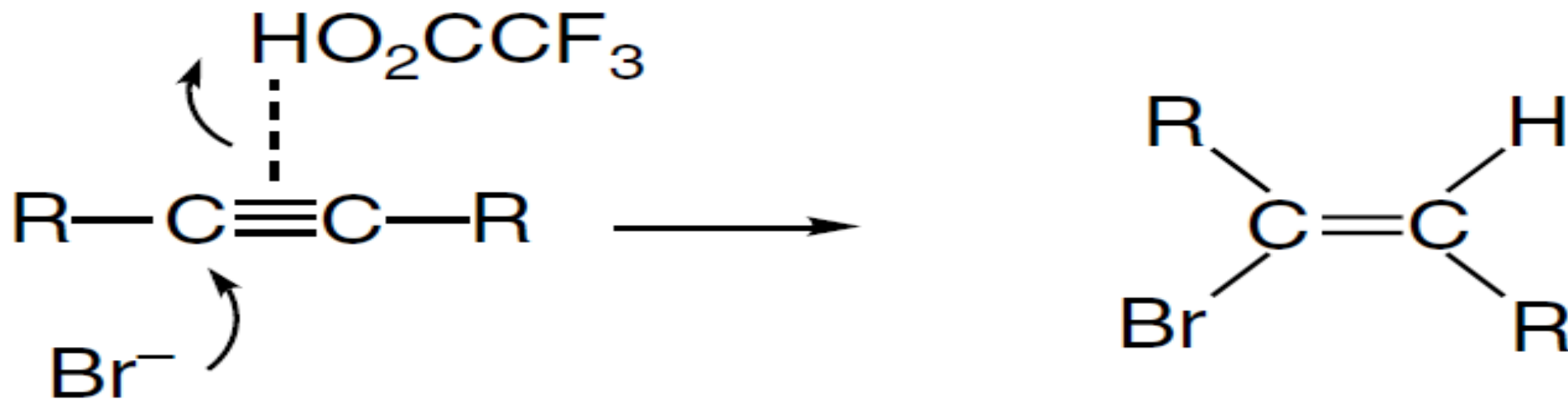


-
- Alkyl-substituted acetylenes can react with HCl by either the AdE3 or the AdE2 mechanism.
 - The AdE3 mechanism leads to *anti* addition. The preference for one or the other mechanism depends on the reactant structure and the reaction conditions.
 - Added halide ion promotes the AdE3 mechanism and increases the overall rate of reaction.
 - Reaction of 4-octyne with TFA in CH₂Cl₂ containing 0.1–1.0M Br[−] leads mainly to Z-4-bromo-4-octene by an *anti* addition.



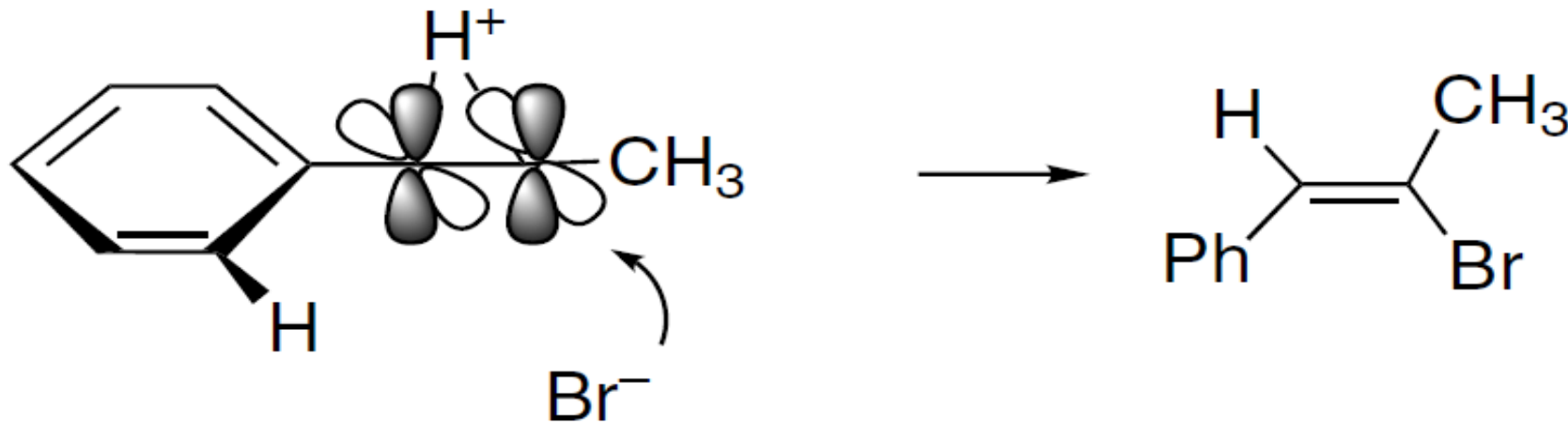
- The presence of Br^- greatly accelerates the reaction as compared to reaction with TFA alone, indicating the involvement of the Br^- in the rate-determining protonation step.

1-Octyne and 2-octyne also give more than 95% *anti* addition under these conditions.



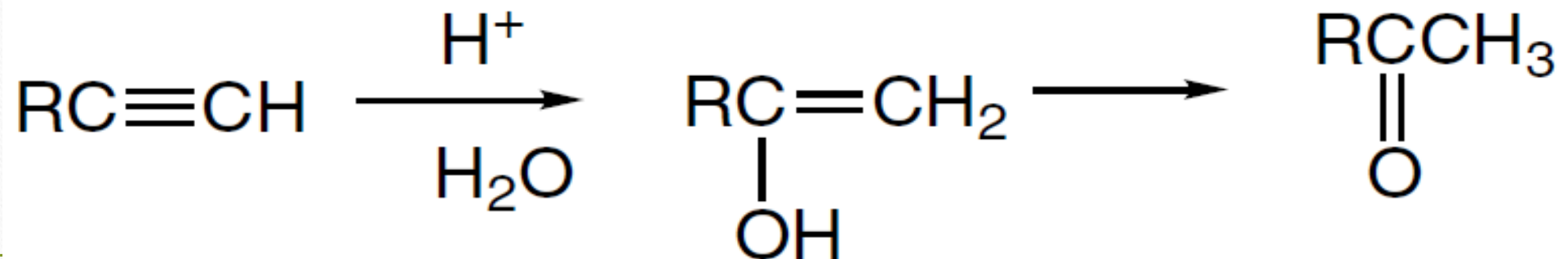
The reactions are formulated as *concerted AdE3* processes, involving bromide attack on an alkene-acid complex.

Under these conditions, 1-aryalkynes react by a mixture of *AdE2 and AdE3* mechanisms with the *proportion of AdE3* reaction *increasing* with *increasing bromide concentration and decreasing effective acidity*.



The AdE3 reaction of 1-phenylpropyne gives the anti-Markovnikov product. This is believed to be due to a steric effect of the phenyl group.

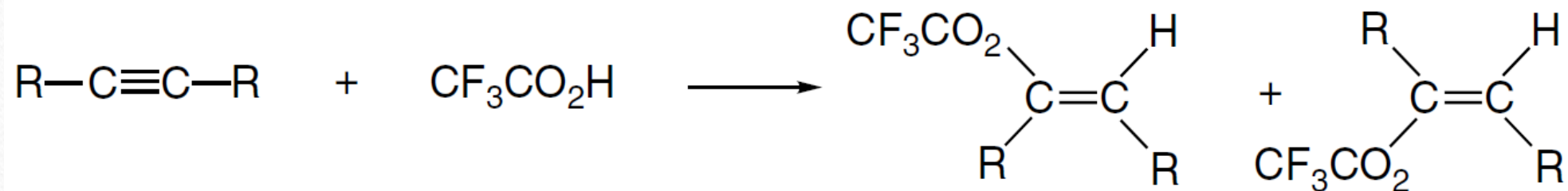
Compared to alkene additions carried out under similar conditions, there is less likely to be involvement of a cationic intermediate because of the higher energy of the vinyl cation.



Alkynes can be hydrated in concentrated aqueous acid solutions. The initial product is an enol, which isomerizes to the more stable ketone.

Alkynes are somewhat less reactive than alkenes. For example, 1-butene is 20 times more reactive than 1-butyne in 8.24 M H_2SO_4 .

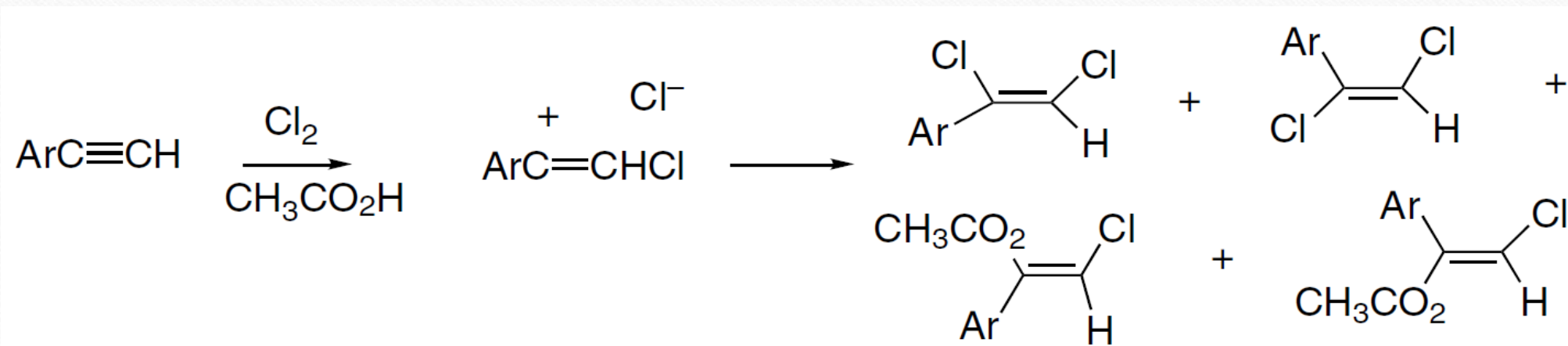
Alkyne reactivity increases with the addition of ERG substituents. Solvent isotope effects are indicative of a rate determining protonation.



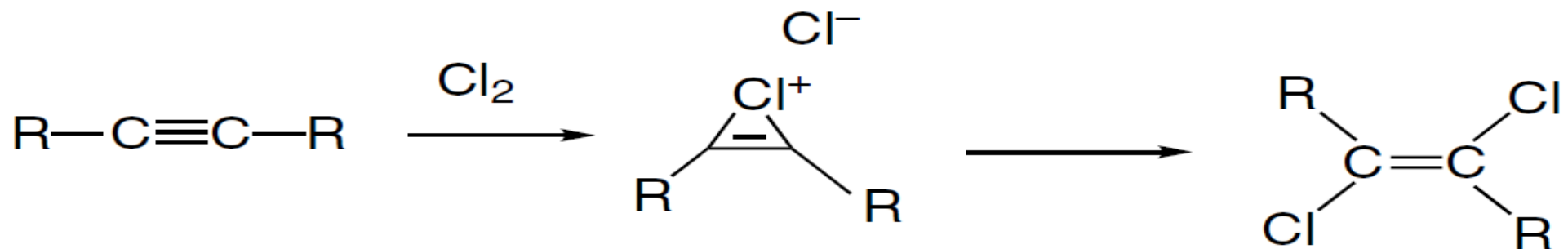
- These reactions are believed to proceed by rate-determining proton transfer to give a vinyl cation.
- Reactions proceeding through a vinyl cation would not be expected to be stereospecific, since the cation will adopt *sp* hybridization.
- Alkynes react when heated with TFA to give addition products. Mixtures of *syn* and *anti* addition products are obtained.
- Similar addition reactions occur with trifluoromethanesulfonic acid. These reactions are analogous to acid-catalyzed hydration and proceed through a vinyl cation intermediate.

Halogenation of Alkynes

- Alkynes undergo addition reactions with halogens. In the presence of excess halogen, tetrahaloalkanes are formed but mechanistic studies can be carried out with a limited amount of halogen so that the first addition step can be characterized.
- In general, halogenation of alkynes is slower than for the corresponding alkenes.
- The reaction shows typical characteristics of an electrophilic reaction. For example, the rates of chlorination of substituted phenyl acetylenes are correlated by σ^+ with $\rho = -4.2$.

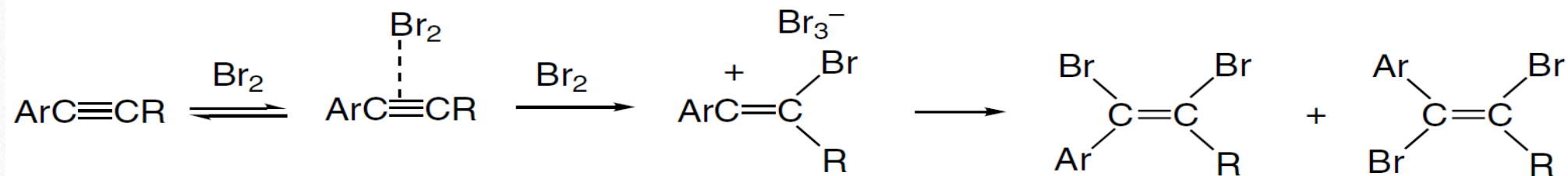


- In acetic acid, the reaction is overall second order, first order in both reactants. The addition is not very stereoselective and a considerable amount of solvent capture product is formed.
- All of these features are consistent with the reaction proceeding through a vinyl cation intermediate.



- For alkyl-substituted alkynes, there is a difference in stereochemistry between mono- and disubstituted derivatives.
- The former give *syn* addition, whereas the latter react by *anti* addition. The disubstituted (internal) compounds are considerably (~ 100 times) more reactive than the monosubstituted (terminal) ones.
- This result suggests that the TS of the rate-determining step is stabilized by *both* alkyl substituents and points to a bridged structure.
- This interpretation is consistent with the *anti* stereochemistry of the reaction for internal alkynes.

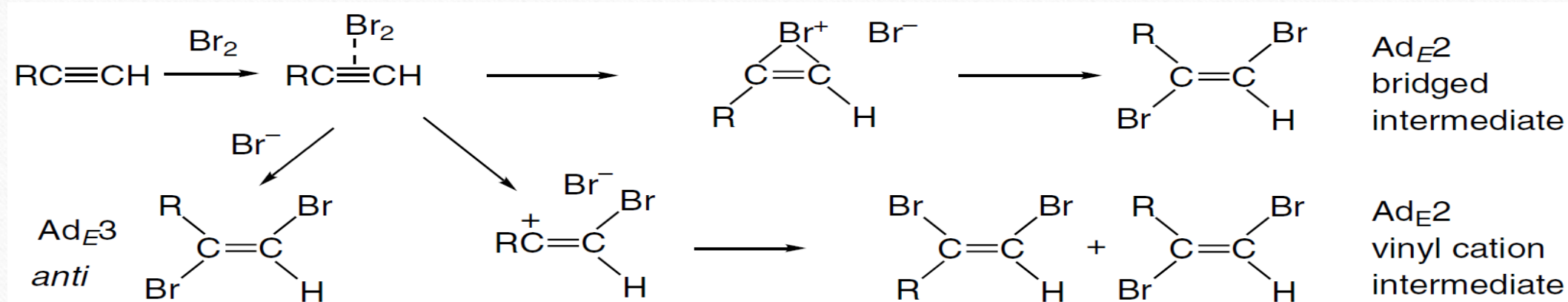
- The monosubstituted intermediates do not seem to be effectively bridged, since *syn* addition predominates.
-
- A very short-lived vinyl cation appears to be the best description of the intermediate in this case.
 - The stereochemistry of bromination is usually *anti* for alkyl-substituted alkynes.
 - A series of substituted arylalkynes has been examined in dichloroethane. As with alkenes, a π -complex intermediate was observable.



The ΔH for formation of the complex with 1-phenylpropyne is about -3.0 kcal/mol. The overall kinetics are third order, as for an $\text{Ad}_\text{E}3$ mechanism.

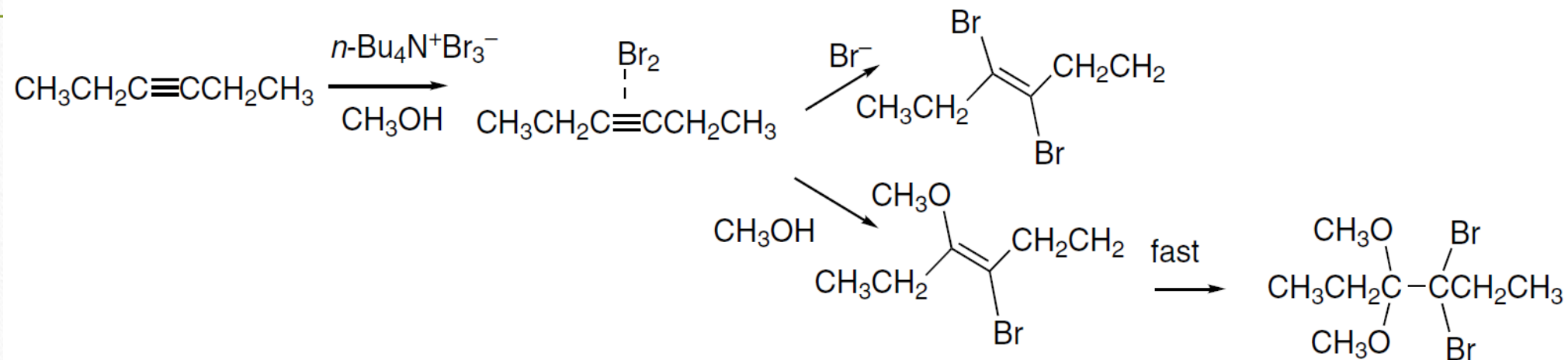
The rate-determining step is the reaction of Br_2 with the π -complex to form a vinyl cation, and both *syn* and *anti* addition products are formed.

For the aryl-substituted alkynes, the reaction stereochemistry is sensitive to the aryl substitution. With EWG substituents (NO_2 , CN) the reaction becomes stereospecifically *anti* and the same is true for 2-hexyne, reflecting the diminished stability of the vinyl cation in these cases.

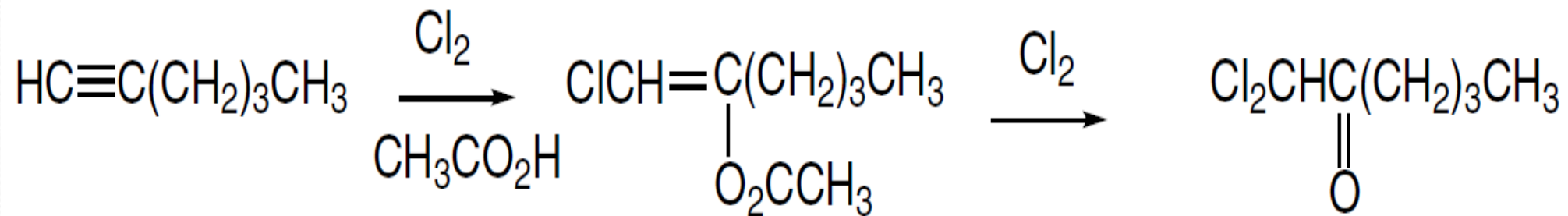


- Aryl-substituted alkynes can be shifted toward *anti* addition by including a bromide salt in the reaction medium.
- Under these conditions, a species preceding the vinyl cation must be intercepted by a bromide ion.
- This intermediate is presumably the complex of molecular bromine with the alkyne. An overall mechanistic summary is shown in the above equations.

- This scheme shows an alkyne-bromine complex as an intermediate in all alkyne brominations, which is analogous to the case of alkenes.
-
- The complex may dissociate to a vinyl cation when the cation is sufficiently stable, as is the case when there is an aryl substituent.
 - It may collapse to a bridged bromonium ion or undergo reaction with a nucleophile. The latter is the dominant reaction for alkyl-substituted alkynes and leads to stereospecific *anti* addition.
 - Reactions proceeding through vinyl cations are nonstereospecific.
 - As for alkenes, the alkyne-Br₂ complex can be intercepted by nucleophilic solvent.



- Alkynes react with $n\text{-Bu}_4\text{N}^+ \text{Br}_3^-$ in methanol to give a mixture of dimethoxydibromo and E-dibromo products.
- A key aspect of this reaction is the high reactivity of the methoxybromo intermediate, which is more reactive than the starting material.
- Evidently, the dibromo intermediate is unreactive toward Br_3^- .



Chlorination of 1-hexyne in acetic acid gives mainly to 1,1-dichlorohexan-2-one via chlorination and deacetylation of the initial product, 2-acetoxy-1-chlorohexene.

The corresponding intermediate, E-3-acetoxy-4-chlorohexene can be isolated from 3-hexyne.

- The rate of bromination of styrene exceeds that of phenylacetylene by about 10³.
-
- For dialkylacetylene disubstituted alkene comparisons, the ratios range from 10³ to 10⁷, being greatest in the least nucleophilic solvents.
 - Bromination of alkyl-substituted alkynes shows rate enhancement by both alkyl substituents, and this indicates that the TS has bridged character.
 - The lower reactivity of the alkynes is probably due to a combination of factors including greater strain in the bridged TS and reduced electron-donating capacity of alkynes.

- The IP of 2-butyne (9.6 eV), for example, is considerably higher than that of 2-butene (9.1 eV).
-
- MP2/6-311+G** and B3LYP/6-311+G** computations have been used to compare the stability of the Br₂ complexes with ethene, ethyne, and allene.
 - The computed structures and ΔE for formation of the complex are shown in Figure 5.10. The structures and energies are quite similar.
 - This indicates that it is the formation of the cationic intermediate that is more difficult for alkynes.

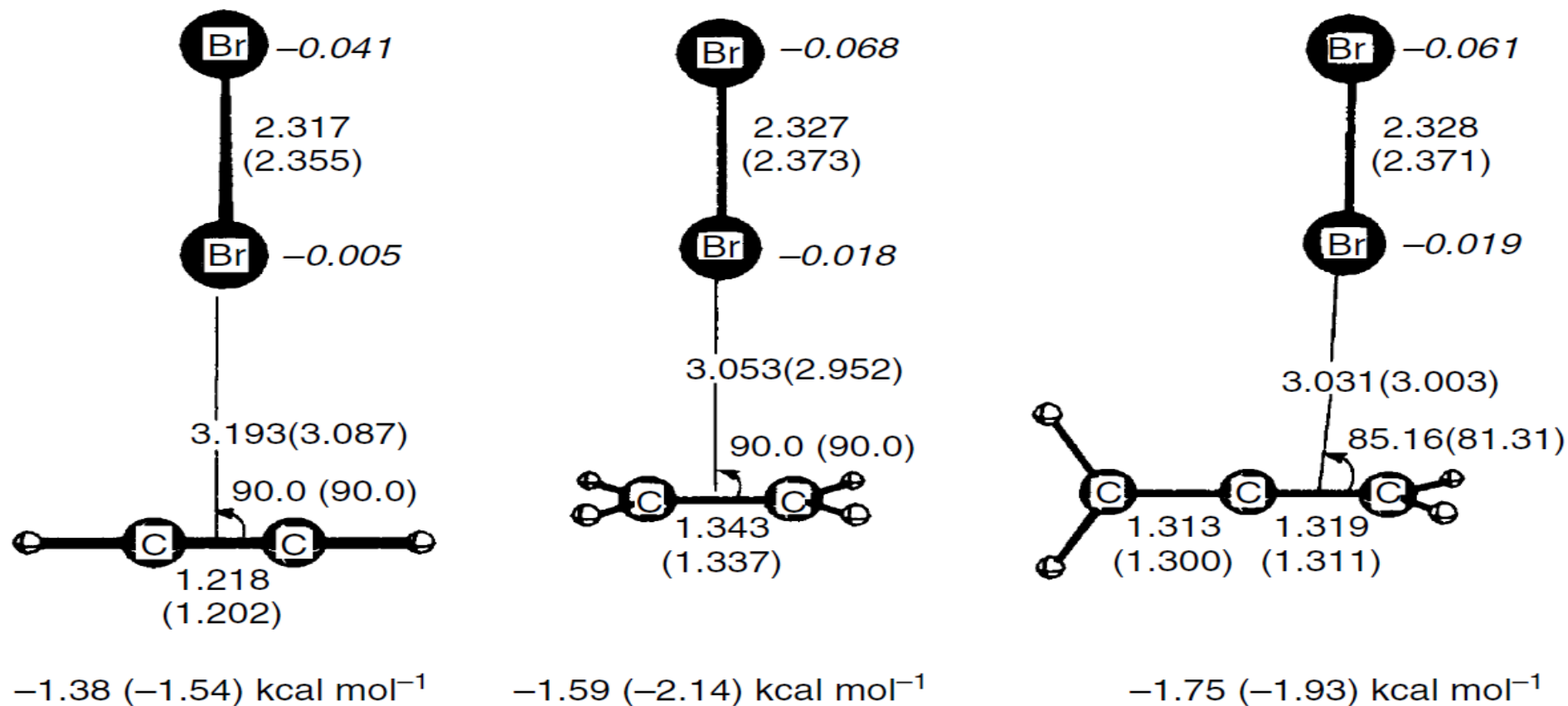
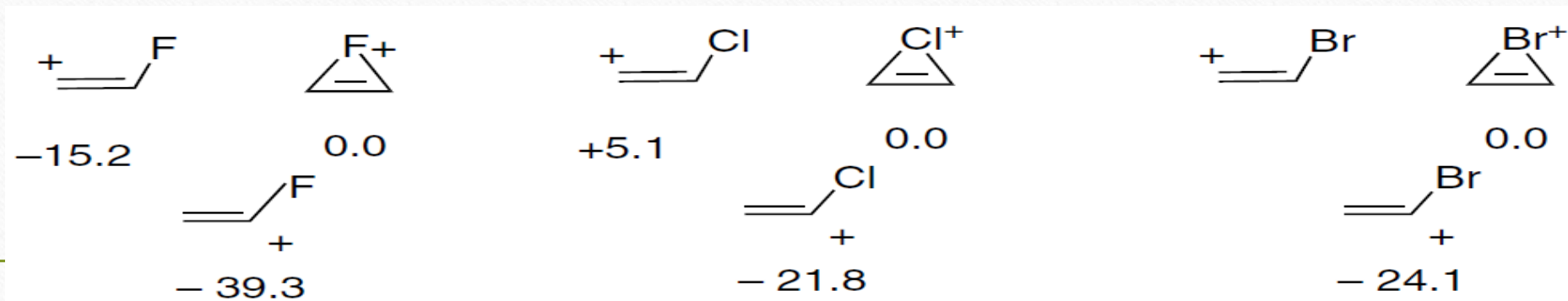


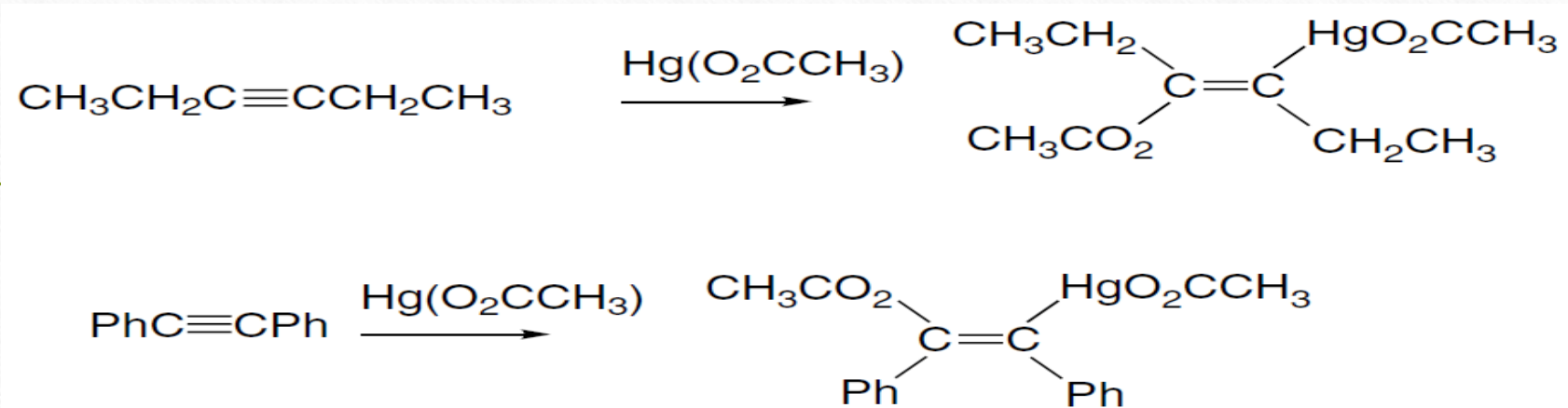
Fig. 5.10. Optimized structures and ΔE for formation of (a) ethyne- Br_2 , (b) ethene- Br_2 , and (c) allene- Br_2 complexes. Values of ΔE from MP2/6-311+G** and B3LYP/6-311G** (the latter in parentheses). Reproduced from *Chem. Eur. J.*, 967 (2002), by permission of Wiley-VCH.



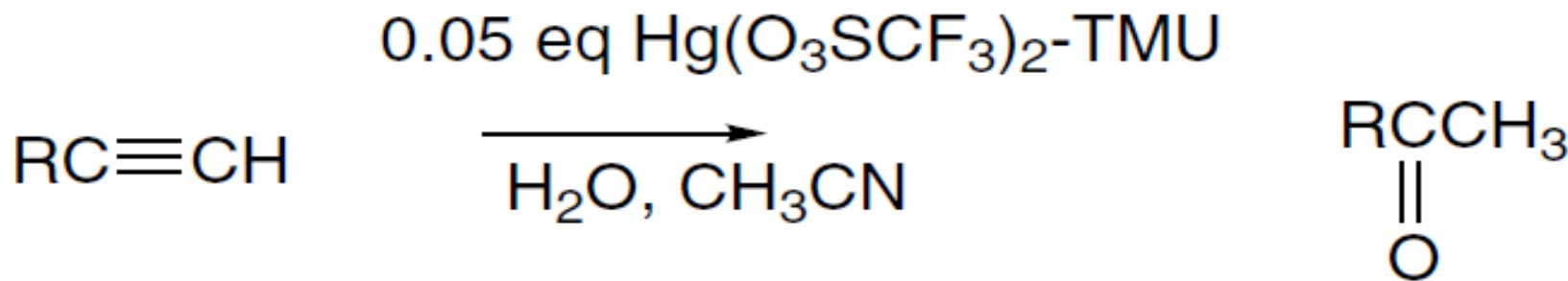
- Calculations comparing the open β -halovinyl and bridged cations have been reported using MP2/6-311G++(3df,3pd)- and B3LYP/6-31+G(d)-level computations.
- The *bridged ions* are found to be favored for *chlorine and bromine* but the *open ion* is favored for *fluorine*.
- The β -chloro and β -bromovinyl cations are found not to be minima. They rearrange to the much more stable α -halovinyl cations by a hydride shift.

- The bridged ions tend to be more strongly stabilized by solvation than the open ions. As was noted for the halonium ions derived from alkenes, the charge on halogen is positive for Cl and Br, but negative for F.
- When a methyl group is added, the vinyl cation is favored. The open cation was also favored for ions derived from 2-butyne.
- Computational studies have also explored the issue of how the π -complex is converted to the intermediate and several potential mechanisms have been described.
- A salient result of these studies is that ionization is energetically prohibitive, at least in the gas phase.
- This finding is consistent with experimental studies that indicate strong acceleration in polar solvents or in the presence of acids that can facilitate ionization.

Mercuration of Alkynes



- Alkynes react with mercuric acetate in acetic acid to give addition products. For 3-hexyne the product has E-stereochemistry but the Z-isomer is isolated from diphenylacetylene.
- The kinetics of the addition reactions are first order in both alkyne and mercuric acetate.



- The most common synthetic application of mercury-catalyzed addition to alkynes is the conversion of alkynes to ketones.
- This reaction is carried out under aqueous conditions, where the addition intermediate undergoes protonation to regenerate Hg^{2+} .
- Mercuric triflate has been found to be a useful reagent for this reaction.

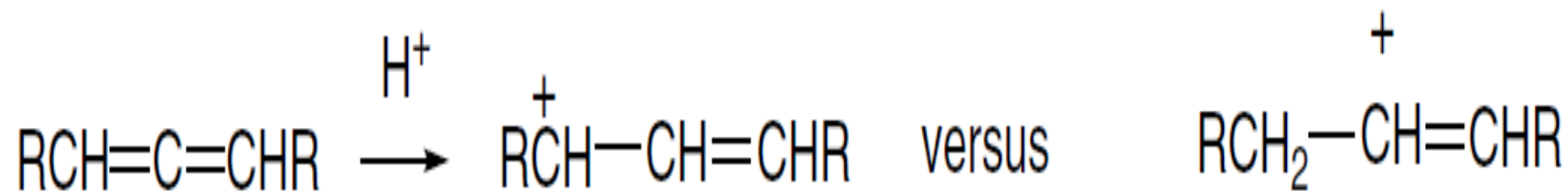
Overview of Alkyne Additions

- We can understand many of the general characteristics of electrophilic additions to alkynes by recognizing the possibility for both bridged ions and vinyl cations as intermediates.
- Reactions proceeding through vinyl cations are expected to be nonstereospecific, with the precise stereochemistry depending upon the lifetime of the vinyl cation and the identity and concentration of the potential nucleophiles.
- Stereospecific *anti* addition is expected from processes involving nucleophilic attack on either a bridged ion intermediate or an alkyne-electrophile complex.
- These general mechanisms also explain the relative reactivity of alkenes and alkynes in comparable addition processes.

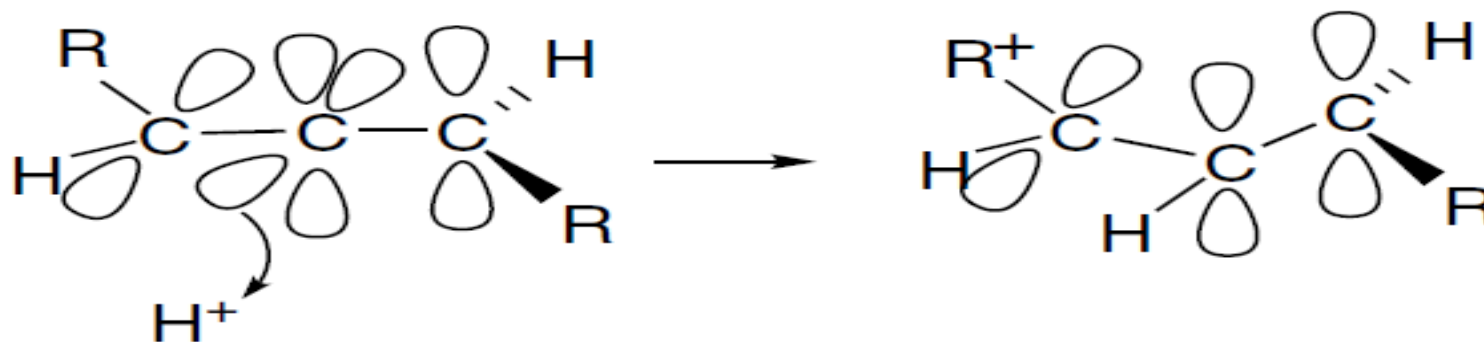
-
- In general, reactions that proceed through vinyl cations, such as those involving rate-determining protonation, are only moderately slower for alkynes as compared to similar alkenes.
 - This is attributed to the somewhat higher energy of vinyl cations compared to cations with sp^2 hybridization.
 - It has been estimated that this difference for secondary ions is around 10^{-15} kcal/mol, a significant but not an enormous difference, which is partially compensated by the higher ground state energy of the alkynes.
 - Reactions that proceed through TSs leading to bridged intermediates typically show much greater rate retardation for the alkyne addition.

-
- Bromination is the best studied example of this type. The lower rate reflects the greater strain of bridged species in the case of alkynes.
 - Bridged intermediates derived from alkynes must incorporate a double bond in the three-membered ring.
 - The activation energies for additions to alkynes through bridged intermediates are thus substantially greater than for alkenes.

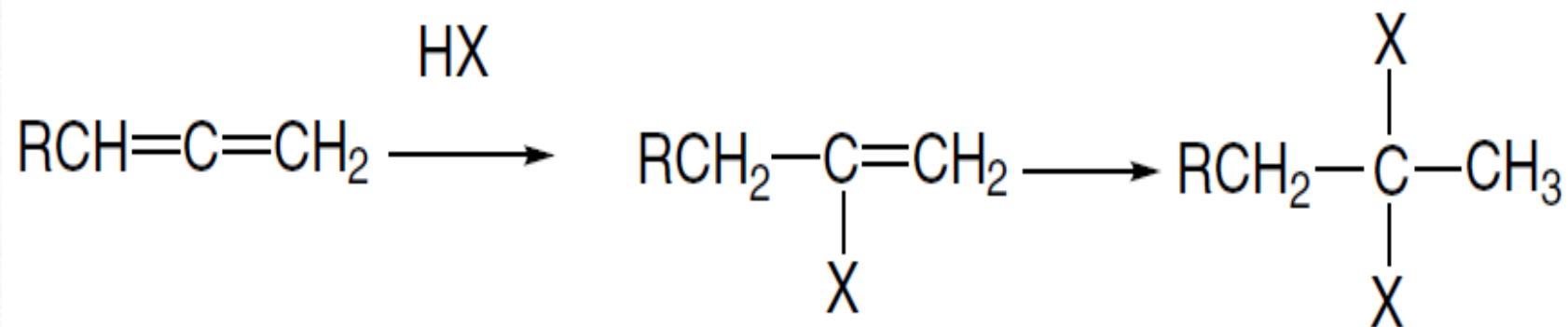
Additions to Allenes



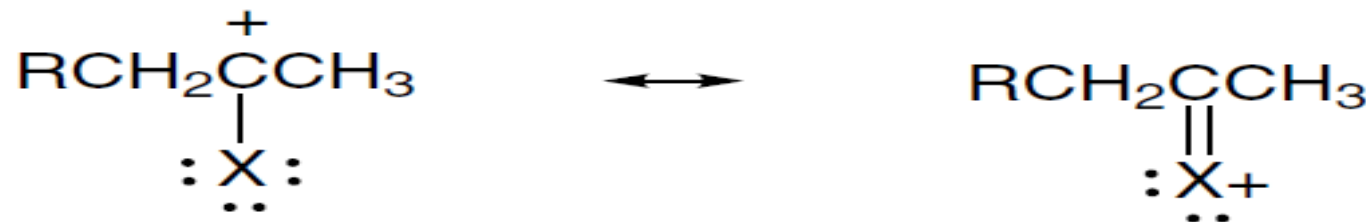
- Electrophilic additions to allenes represent an interesting reaction type that is related to additions to both alkenes and alkynes.
- An allene could, for example, conceivably be protonated at either a terminal sp^2 carbon or the central sp carbon.

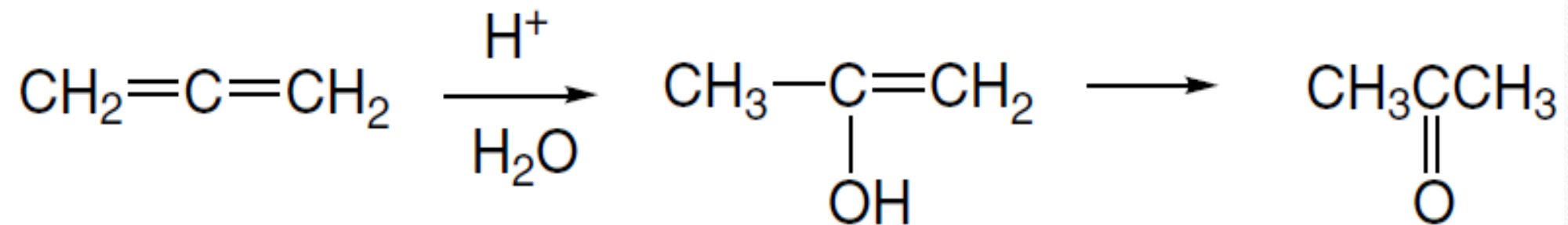


- The allylic carbocation resulting from protonation of the center carbon might seem the obvious choice but, in fact, the kinetically favored protonation at a sp^2 carbon leads to the vinyl cation intermediate. The reason for this is stereoelectronic.
- The allene structure is nonplanar, so that a protonation of the center carbon leads to a twisted structure that lacks of allylic conjugation.
- This twisted cation is calculated to be about 36–38 kcal/mol higher in energy than the cation formed by protonation at a terminal Carbon.

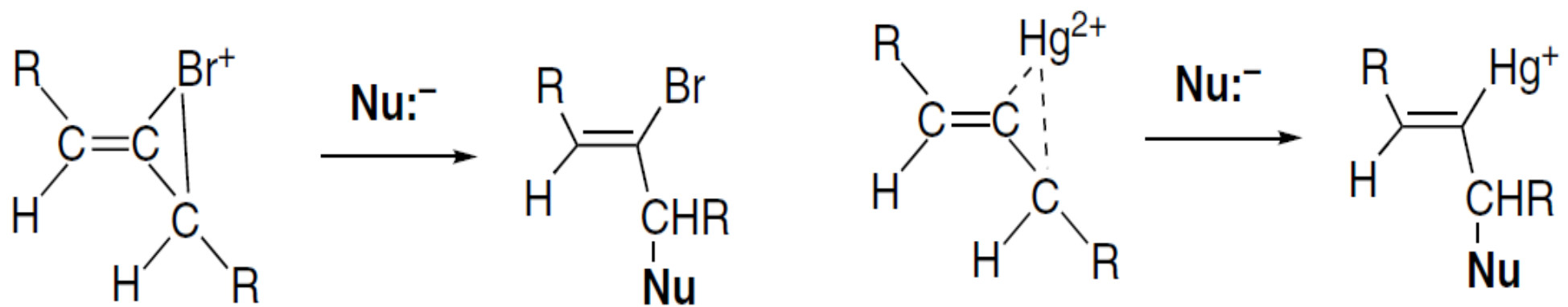


- Consistent with this generalization, addition of hydrogen halides to terminal allenes initially gives the vinyl halide; if the second double bond reacts, a geminal dihalide is formed.
- The regioselectivity of the second step is consistent with Markovnikov's rule because a halogen atom can stabilize a carbocation by resonance.





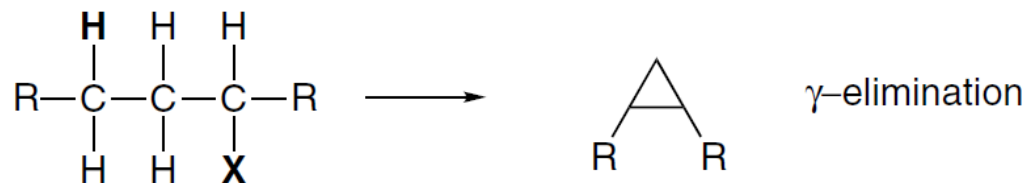
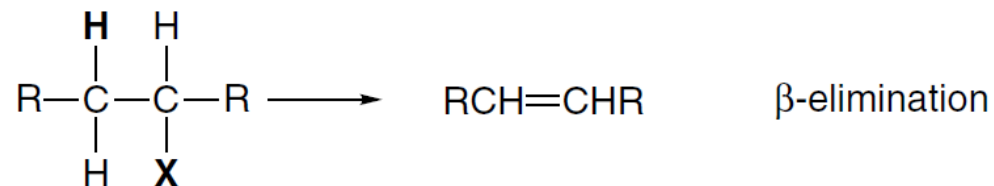
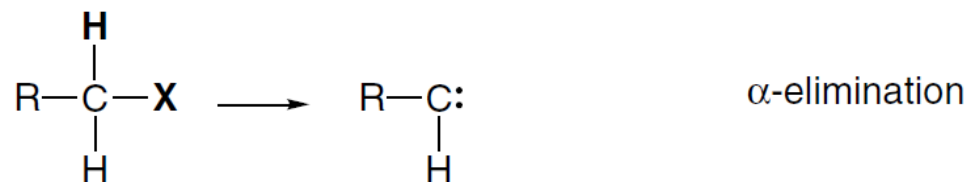
- Strong acids in aqueous solution convert allenes to ketones via an enol intermediate. This process also involves protonation at a terminal carbon.
- The kinetic features of this reaction, including the solvent isotope effect, are consistent with a rate-determining protonation to form a vinyl cation.
- Allenes react with other typical electrophiles such as the halogens and mercuric ion. In systems where bridged ion intermediates would be expected, nucleophilic capture generally occurs at the allylic position.



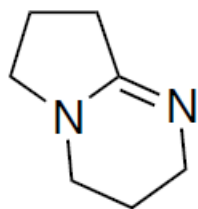
- This pattern is revealed, for example, in the products of solvent capture in halogen additions and by the structures of mercuration products.

Elimination Reactions

Removal of another molecule from a reactant

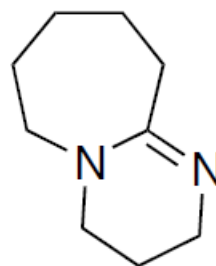


The strong organic bases are particularly effective for reactants that are easily ionized, such as tertiary halides.



DBN

1,3-diazabicyclo[3.2.0]nonene

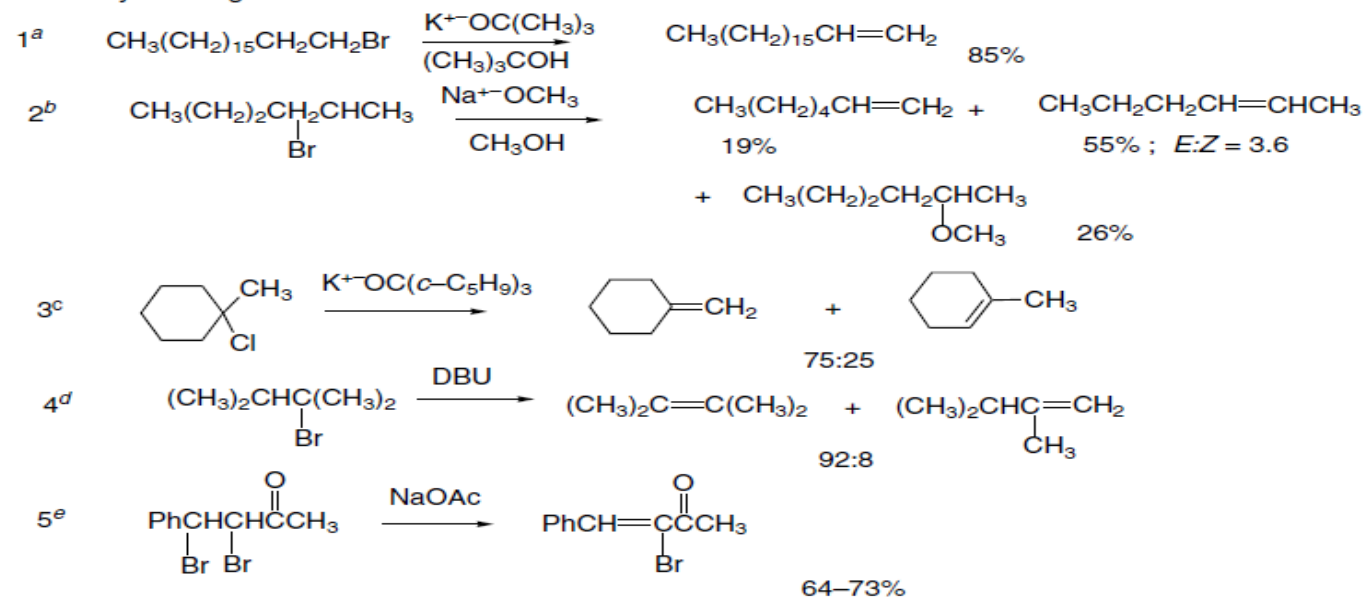


DBU

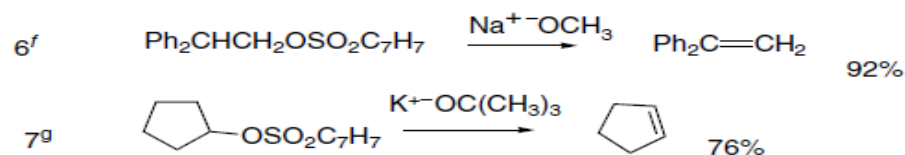
1,3-diazabicyclo[4.3.0]undecene

Scheme 5.2. Representative β -Elimination Reactions

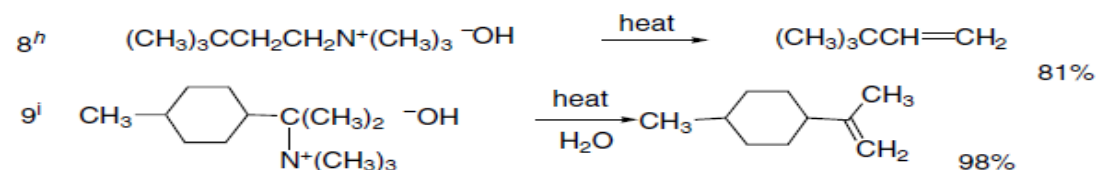
A. Dehydrohalogenation



B. Dehydrosulfonation



C. Eliminations of Quaternary Ammonium Hydroxides



Elimination Reactions

- With primary reactants, the main competing reaction is substitution.
-
- ($\text{K}^+ - \text{O}-t\text{-Bu}$) favors elimination over substitution.
- Substitution can compete with elimination in unhindered systems.
- The use of a very hindered alkoxide to favor the less-substituted product.

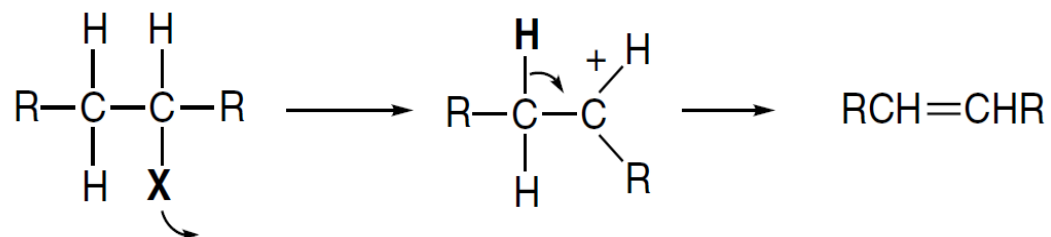
Elimination Reactions

- The strong organic bases DBU and DBN can also effect dehydrohalogenation.
- The carbanion-stabilizing effect of a carbonyl group facilitates elimination by a relatively weak base and controls regiochemistry by favoring deprotonation of the α -carbon.
- Generally speaking, tosylates give a higher proportion of substitution than do halides.
- Hofmann elimination reaction with poor and bulky leaving group (trimethylamine) leads to a preference for formation of the less-substituted alkene.

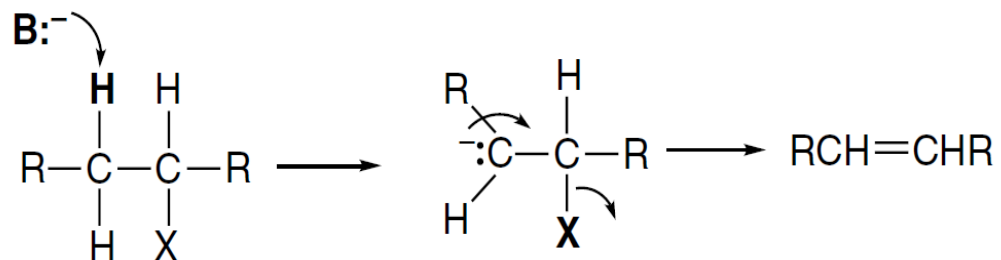
Elimination Reactions

The β -eliminations:

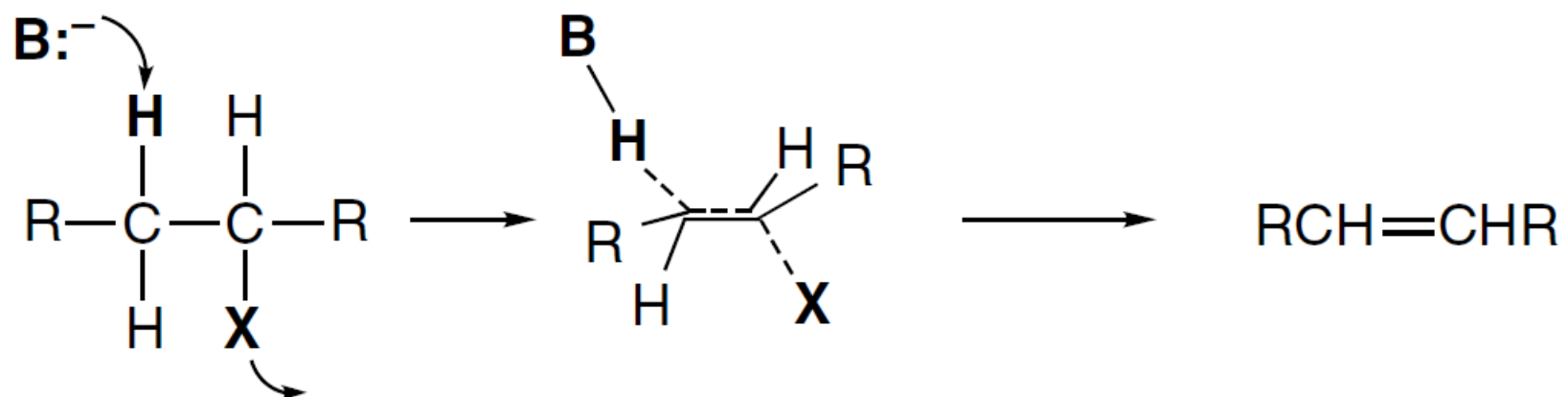
E1 Mechanism (carbocation intermediate)



E1cb Mechanism (carbanion intermediate)

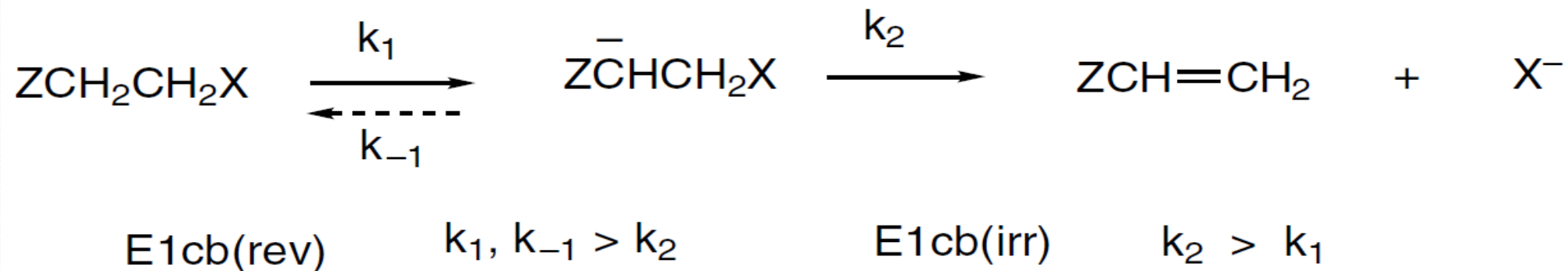


E2 Mechanism (concerted)



Elimination Reactions

- The E2 mechanism: bimolecular TS, concerted
- The E1 mechanism: unimolecular ionization, carbocation intermediate.
- The E1cb mechanism: like the E1, two steps, with reverse order, a carbanion intermediate.



- The E1cb mechanism: (1) E1cb(irr) and (2) E1cb(rev), depending on whether the formation of the carbanion intermediate is or is not rate determining.
- If the anion is formed reversibly it may be possible to detect proton exchange with the solvent (E1cb(rev)). This is not the case if formation of the carbanion is the rate-determining step (E1cb(irr)).

Variants of a continuum of mechanistic possibilities

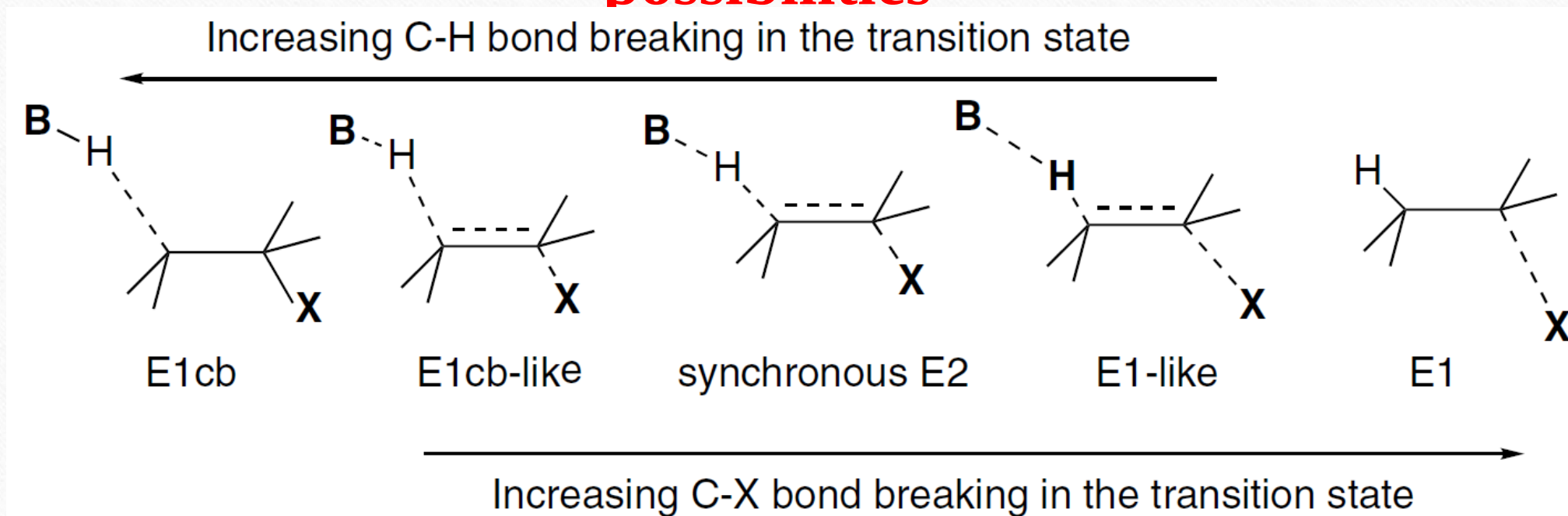
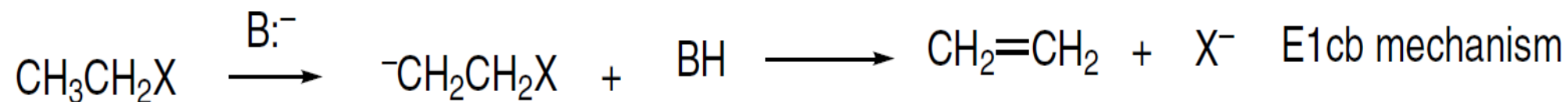
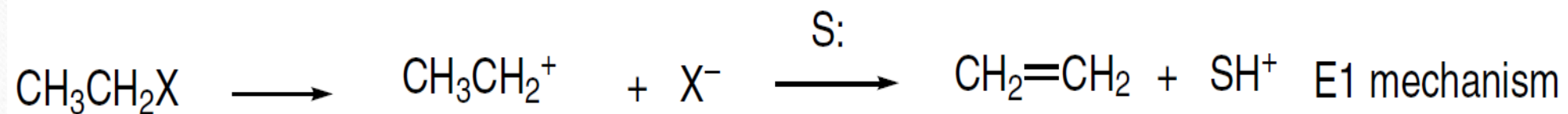


Fig. 5.11. Variable transition state theory of elimination reactions.

Many β -elimination reactions are intermediate between the limiting mechanistic types. This idea, called the *variable E2 transition state theory*.

Mechanism of Elimination

- The most important factors to be considered are:
 - (1) the nature of the leaving group,
 - (2) electronic and steric effect of substituents in the reactant molecule,
 - (3) the nature of the base,
 - (4) solvent effects.



- Consider ethyl halide:
- Both stepwise reaction paths require the formation of high energy intermediates.
- With no stabilizing substituent groups, both a primary carbocation and carbanion are highly unstable intermediates.
- The E1 mechanism: forms primary carbocation
- E1cb mechanism: forms carbanion intermediate

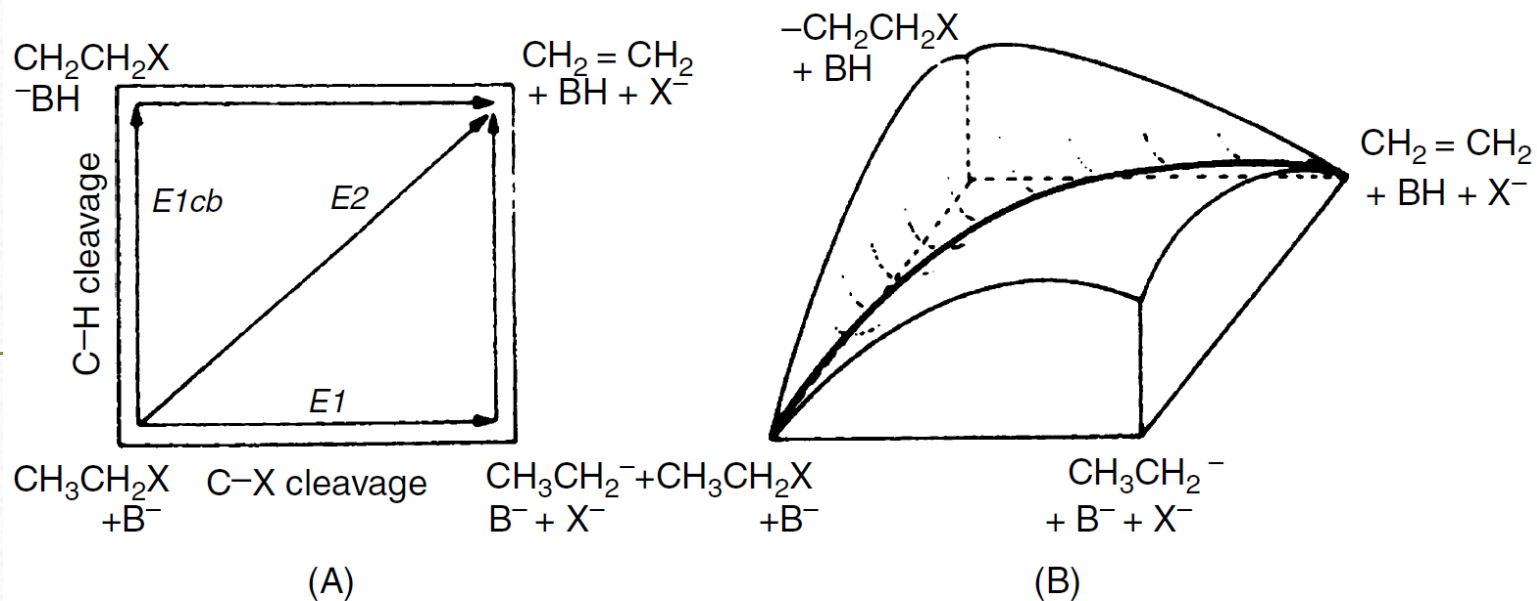


Fig. 5.12. Two-dimensional potential energy diagrams depicting E1, E2, and E1cb mechanisms.

- If we construct a reaction energy diagram in which progress of C–H bond breaking is one dimension, progress of C–X bond breaking is the second, and the energy of the reacting system is the third, we obtain a diagram such as the one in Figure 5.12.

-
- In Figure 5.12A only the two horizontal (bond-breaking) dimensions are shown.
 - In Figure 5.12B the energy dimension is added.
 - Because of the high energy of both the E_1 and E_{1cb} intermediates, the lowest-energy path is the concerted E_2 path, more or less diagonally across the energy surface. This pathway is of lower energy because the partially formed double bond provides some compensation for the energy required to break the C–H and C–X bonds and the high-energy intermediates are avoided.

-
- As a result, substituents that stabilize carbocation character move the E_2 TS to a point that more closely resembles the E_1 TS.
 -
 - A structural change that stabilizes carbanion character shifts the E_2 TS to be more similar to the $E_1\text{cb}$ TS.
 -
 - In the E_1 -like TS, C–X bond cleavage is more advanced than C–H cleavage, whereas in the $E_1\text{cb}$ -like TS, the C–H bond breaking is more advanced.
 -

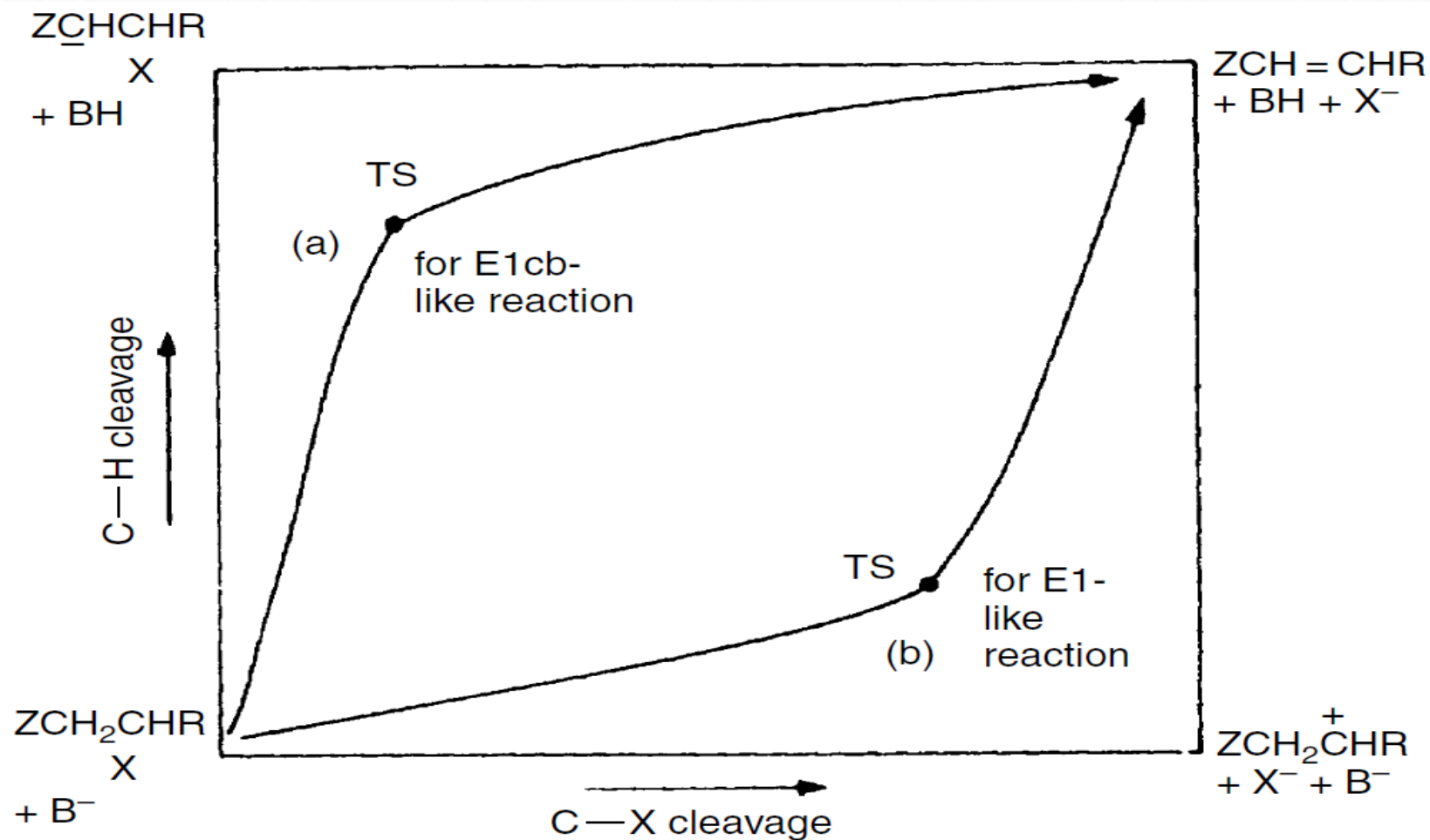
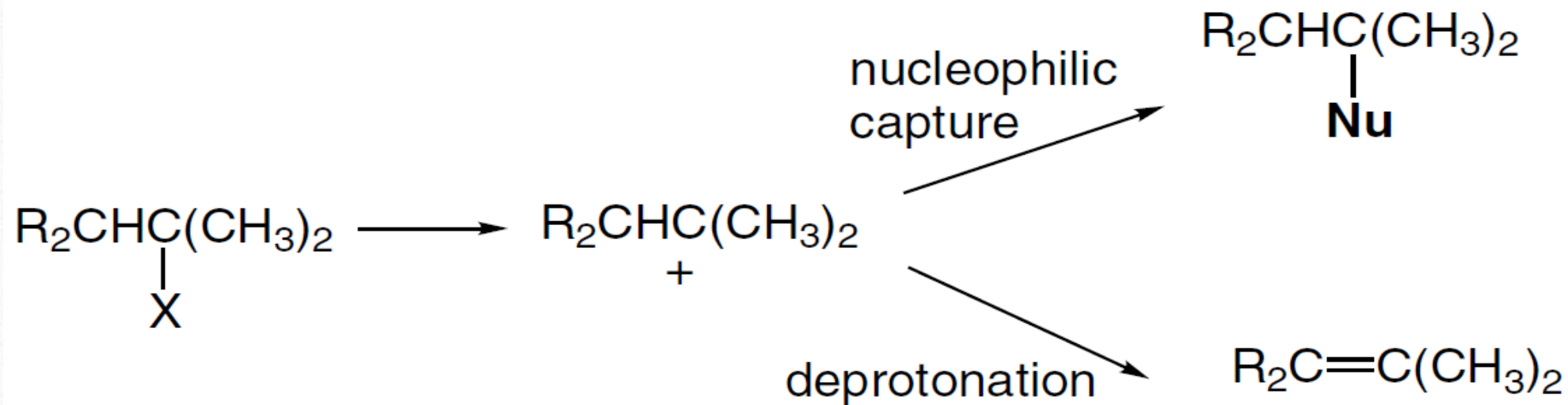


Fig. 5.13. Representation of changes in transition structure character in the E2 elimination reaction as a result of substituent effects: (a) substituent Z stabilizes carbanion character of E1cb-like TS; (b) substituent R stabilizes carbocation character of E1-like TS.

-
- Ionization is favored by:
 - (1) electron releasing groups
 - (2) readily ionized, i.e., “good,” leaving groups
 - (3) solvents that facilitate ionization



After ionization, the cationic intermediate can:

- (1) react with nucleophile ($\text{S}_{\text{N}}1$) or
- (2) remove proton (E_1).

Inherent preference exists for substitution. The reaction can be diverted to elimination by bases.

Use of stronger and harder bases favor the E_1 path over the $\text{S}_{\text{N}}1$ path.

- E_2 reactions are distinguished from E_1 reactions in that the base is present in the TS for the rate-determining step.
-

- The E_2 reactions have second-order kinetics.
- The precise nature of the TS is a function of:
 - Strength of the base
 - The identity of the leaving group
 - Reactant structure
 - The solvent.

- E_2 TS will be moved in the E_1 cb direction by:
-

- 1. An increase in base strength
- 2. By a change to a poorer leaving group.

- E_2 TS will be moved in the E_1 direction by:

- 1. Having a good leaving group
- 2. Having highly ionizing solvent

- The E₁cb mechanism is not observed with simple alkyl halides or sulfonates.

-
- It is more likely to be involved when the leaving group is β to a carbonyl, nitro, cyano, sulfinyl, or other carbanion-stabilizing group.

- The E₁cb mechanism require substituents that can stabilize the carbanion intermediate.

-

-

- From these data, we can conclude that E₁cb reactions generally require *both* carbanion stabilization and a relatively poor leaving group.

Scheme 5.3. Distinguishing Features of Elimination Mechanisms

A. E1 Mechanism

First Order Kinetics: $\text{rate} = k[\text{RX}]$

LFER indicate cationic character of the TS

Strong dependence on leaving group

B. E2 Mechanism

Second Order Kinetics: $\text{rate} = k[\text{RX}][\text{base}]$

Leaving group effect is normally $\text{I} > \text{Br} > \text{Cl} \gg \text{F}$ because bond-breaking occurs in RDS.

Kinetic isotope effect for both β -C-H and leaving group.

Kinetic isotope effect for both α - and β -carbons.

C. E1cb(rev)

Second Order Kinetics: $\text{rate} = k[\text{RX}][\text{base}]$

Exchange of β -H with protic solvent

LFER indicate anionic character in TS

D. E1cb(irr)

Second Order Kinetics: $\text{rate} = k[\text{RX}][\text{base}]$

Leaving group effect may be $\text{F} > \text{Cl} > \text{Br} > \text{I}$, since C-X bond-breaking is not involved in RDS.

LFER indicates anionic character in TS

Scheme 5.4. Examples of Systems Subjected to Mechanistic Characterization

- 1.^a
$$\text{ArCH}_2\text{CH}_2\text{X} \xrightarrow[\text{DMSO, H}_2\text{O}]{\text{OH}^- \text{ and buffer anions}} \text{ArCH=CH}_2$$

E2 for X = TsO⁻, Br⁻, and quinuclidinium, except for Ar = *p*-nitrophenyl and X = quinuclidinium: based on variation of sensitivity to base (Bronsted β) and LFER relationships.
- 2.^b
$$\text{ArCH}_2\text{CH}_2\text{N}^+(\text{CH}_3)_3 \xrightarrow{\text{NaOC}_2\text{H}_5} \text{ArCH=CH}_2$$

E2: based on k¹²C/k¹⁴C isotope effects for both C(1) and C(2)
- 3.^c
$$\text{PhCH(CH}_3\text{)CH}_2\text{Cl} \xrightarrow[\text{EtOH, 75}^\circ\text{C}]{\text{NaOC}_2\text{H}_5} \text{PhC(CH}_3\text{)=CH}_2$$

E2; based on k³⁵Cl:k³⁷Cl = 1.0059; k_H/k_D = 5.37, and k_{Br}/k_{Cl} = 52
- 4.^d
$$\text{O}_2\text{N-C}_6\text{H}_4\text{-CH}_2\text{CH}_2\text{-N}^+\text{C}_6\text{H}_4\text{-X} \xrightarrow{\text{KOH}} \text{O}_2\text{N-C}_6\text{H}_4\text{-CH=CH}_2$$

E1cb: based on kinetics and Bronsted dependence on substituent X; shifts from E1cb(irr) to E1cb(rev) as X becomes ERG
- 5.^e
$$\text{H-N}^+\text{C}_6\text{H}_4\text{-CH}_2\text{CH}_2\text{-N}^+\text{C}_6\text{H}_4 \xrightarrow{\text{buffer}} \text{H-N}^+\text{C}_6\text{H}_4\text{-CH=CH}_2$$

E1cb(rev): based on observation of CH solvent exchange and solvent isotope effect
- 6.^f
$$\text{Indene-1-CH(CH}_3\text{)Cl} \xrightarrow[(\text{C}_2\text{H}_5)_3\text{N}]{\text{CH}_3\text{O}^- \text{ or}} \text{Indene-1-CH=CH}_2$$

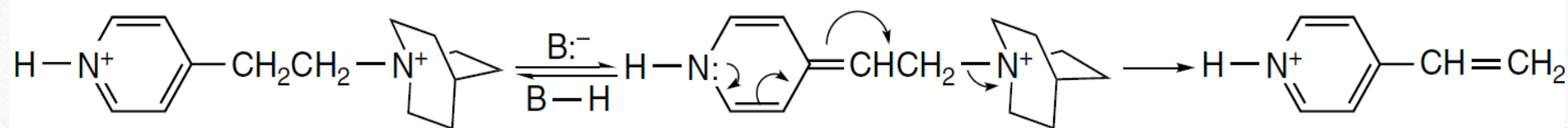
E2: based on both CH and Cl kinetic isotope effects: k_H/k_D = 7.1 (CH₃O⁻); 8.4 ((C₂H₅)₃N)
k³⁵Cl:k³⁷Cl = 1.0086 (CH₃O⁻); 1.0101 ((C₂H₅)₃N)
- 7.^g
$$\text{Indene-1-CH}_2\text{OSO}_2\text{Ar} \xrightarrow[\text{R}_3\text{N}]{\text{CH}_3\text{O}^- \text{ or}} \text{Indene-1-CH=CH}_2$$

E2 with transition to E1cb for ERG in Ar based on curved LFER (Hammett) relationships

Scheme 5.4

- For example, simple 2-arylethyl halides and tosylates react by the E_2 mechanism and only when a p-nitro group is present is there clear evidence of an E_1cb mechanism (Entry 1).
-
- Entry 2 illustrates one of the distinguishing characteristics of E_2 reactions. Both the α - and β -carbons show isotope effects because rehybridization occurs at both carbons.
-
- Entry 3 illustrates some of the kinetic features that characterize E_2 reactions. In addition to second-order kinetics, the concerted mechanism results in kinetic isotope effects at both the β -hydrogen and the leaving group.
-
- The substantial $Br > Cl$ ratio also shows that the bond to the leaving group is involved in the rate determining step.

Scheme 5.4



- The pyridinium system in Entry 5 is an interesting case. Kinetic studies have shown that the reaction occurs through the *conjugate acid* of the reactant. The protonation of the pyridine ring enhances the acidity of the C–H bond.
-
- The reaction occurs with exchange, indicating that the proton removal is reversible. The indenyl (Entry 6) and fluorenyl (Entry 7) ring systems have been studied carefully.
-
- Note that these are cases where (aromatic) anionic stabilization could potentially stabilize an anionic intermediate.
-

Scheme 5.4

- However, the elimination reactions show E₂ characteristics.
 -
-
- The reaction in Entry 7 shifts to an E₁cb mechanism if the leaving group is made less reactive.
 -
 - Because of their crucial role in the ionization step, solvents have a profound effect on the rates of E₁ reactions.
 -
 - These rates for a number of tertiary halides have been determined in a variety of solvents. For t-butyl chloride there are huge differences in the rates in water (log k = -1.54), ethanol (log k = -7.07), and diethyl ether (log k = -12.74).
 -
 - Similarly, the rates of the E1 reaction of 1-methylcyclopentyl bromide range from $1 \times 10^{-3} \text{ s}^{-1}$ in methanol to $2 \times 10^{-9} \text{ s}^{-1}$ in hexane.

- Polar aprotic solvents such as DMSO ($k = 2 \times 10^{-4} \text{ s}^{-1}$) and acetonitrile ($k = 9 \times 10^{-5} \text{ s}^{-1}$) are also conducive for ionization.

-

- The solvent properties that are most important are polarity and the ability to assist leaving group ionization.

-

- These, of course, are the same features that favor S_N1 reactions.

-

- The details of the mechanism as well as the stereochemistry and regiochemistry also depend on the identity and degree of aggregation of the base.

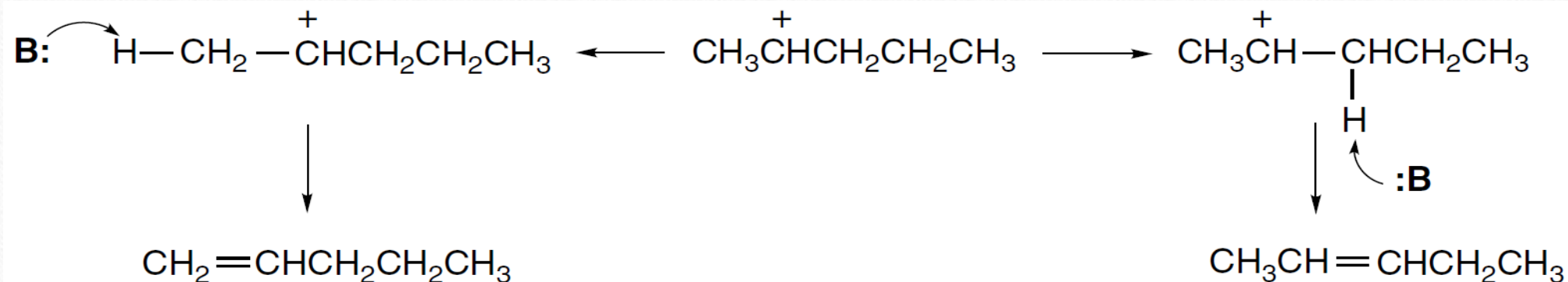
-

-
- This is affected by variables such as the nature of the solvent, the cationic counterions, and the presence of coordinating ligands.
 - Under given reaction conditions, there may be an equilibrium involving a number of different species, which, in turn, have different rates for inducing elimination.
 - The nature of the TS in elimination reactions also controls the regiochemistry of β -elimination.

Regiochemistry of Elimination Reactions

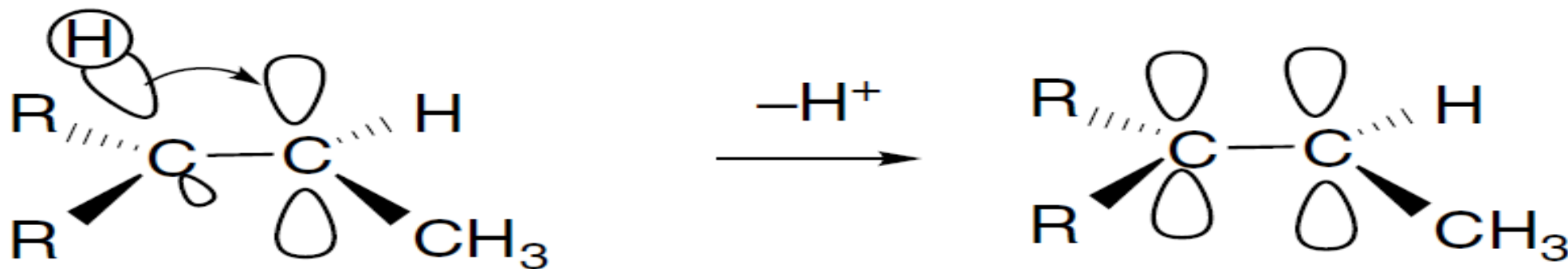
- Useful generalizations and predictions regarding regioselectivity in elimination reactions can be drawn from the variable transition state theory.
-
- As we saw earlier in Figure 5.11, this theory proposes that the TSs in E_2 reactions can vary over a mechanistic range between the E_1 and E_{1cb} extremes.
-
- When the base is present at the TS, the reaction will exhibit second-order kinetics and meet the other criteria of an E_2 mechanism.
-
- There is no intermediate. The cleavage of the C–H and the C–X bonds is concerted, but not necessarily synchronous.
-

- The relative extent of the breaking of the two bonds at the TS may differ, depending on the nature of the leaving group X and the ease of removal of the β -hydrogen as a proton.
-
- If there are several nonequivalent β -hydrogens, competition among them determines which one is removed and the regiochemistry and stereochemistry of the reaction.
 - If one compares E_1 and E_{1cb} eliminations, it is seen that quite different structural features govern the direction of elimination.
 - The variable transition state theory suggests that E_2 elimination proceeding through an “ E_1 -like” TS will have the regiochemistry of E_1 eliminations, whereas E_2 eliminations proceeding through an “ E_{1cb} -like” TS will show regioselectivity similar to E_{1cb} reactions.



- It is therefore instructive to consider these limiting mechanisms before discussing the E₂ case.
- In the E₁ mechanism, the leaving group is completely ionized before C–H bond breaking occurs.
- The direction of the elimination therefore depends on the structure of the carbocation and the identity of the base involved in the proton transfer that follows C–X heterolysis.
- Because of the high energy of the carbocation intermediate, quite weak bases can effect proton removal. The solvent can serve this function. The counterion formed in the ionization step can also act as the proton acceptor.

-
- The product composition of the alkenes formed in E_1 elimination reaction usually favors the more-substituted alkene, and therefore the more stable one.
 -
 - This indicates that the energies of the *product-determining TSs parallel those of the isomeric alkenes*.
 -
 - However, since the activation energy for proton removal from a carbocation is low, the TS should resemble the carbocation intermediate much more than the alkene product.
 -



- In the carbocation there is hyperconjugation involving each β -hydrogen. Since the hyperconjugation structures possess some double-bond character, the interaction with hydrogen is greatest at more highly substituted carbons; that is, there will be greater weakening of C–H bonds and more double-bond character at more highly substituted carbon atoms.
- This structural effect in the carbocation intermediate governs the direction of elimination and leads to the *preferential formation of the more highly substituted alkene*, as illustrated in Figure 5.14.

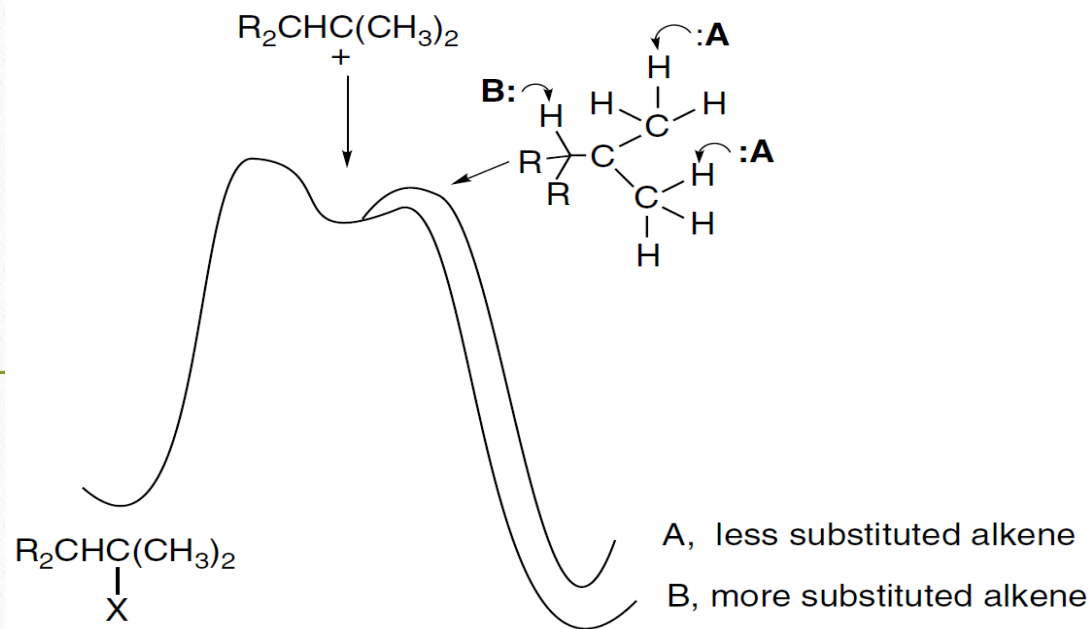


Fig. 5.14. Potential energy profile for product-determining step for E1 elimination.

In the E1cb mechanism, the direction of elimination is governed by the *kinetic acidity* of the individual β -protons, which in turn is determined by the polar and resonance effects of adjacent substituents, and by the degree of steric hindrance to approach of base to the proton.

Alkyl substituents tend to retard proton abstraction both electronically and sterically. Preferential proton abstraction from less-substituted carbons leads to the formation of the less-substituted alkene.

-
- Carbanion-stabilizing substituents control the regiochemistry of E_1cb eliminations by favoring deprotonation at the most acidic carbon.
 - The preferred direction of elimination via the E_2 mechanism depends on the precise nature of the TS. The two extreme TSs for the E_2 elimination resemble the E_1 and E_1cb mechanisms in their orientational effects. At the “ E_1cb -like” end of the E_2 range, a highly developed bond is present between the proton and the base.
 - The leaving group remains tightly bound to carbon, and there is relatively little development of the carbon-carbon double bond. *When the TS of an E_2 reaction has E_1cb character, the direction of the elimination is governed by the ease of proton removal.* In this case, the less-substituted alkene usually dominates.

-
- At the “E₁- like” end of the E₂ spectrum, the TS is characterized by well-advanced cleavage of the C–X bond and a largely intact C–H bonds. An “E₁-like” TS for E₂ reactions leads to formation of the more highly substituted of the possible alkenes.
 -
 - In a more synchronous E₂ reaction, the new double bond is substantially formed at the TS with partial rupture of both the C–H and C–X bonds.
 -
 - E₂ eliminations usually give mainly the more-substituted alkene. This is because the TSs leading to the isomeric alkenes reflect the partial double-bond character and the greater stability of the moresubstituted double bond.
 -

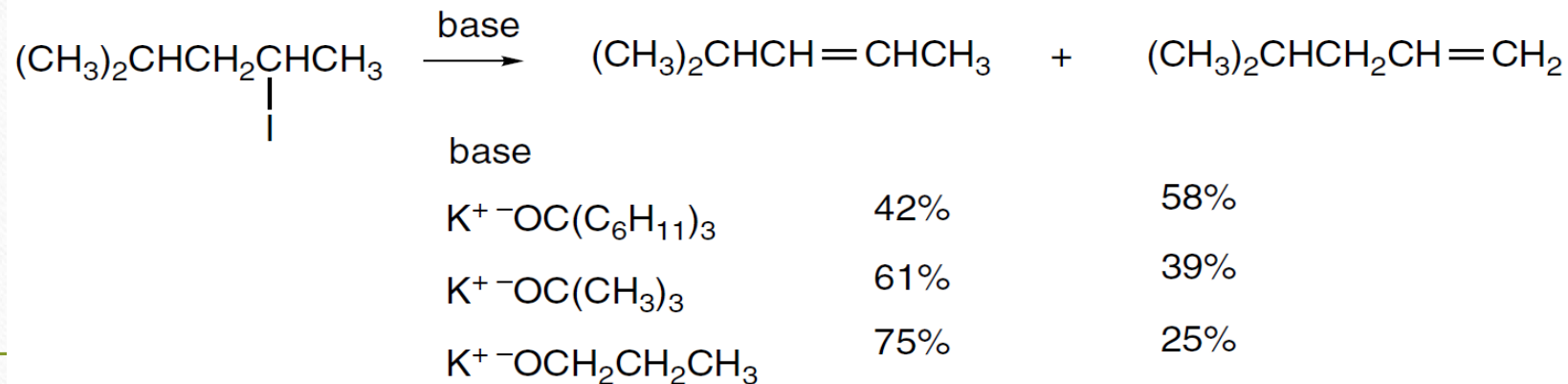
-
- Concerted E_2 reactions are also subject to the stereoelectronic requirement that the reacting C–H and C–X bond be antiperiplanar.
 - This requirement makes reactant conformation a factor in determining the outcome of the reaction.
 - Prior to development of the mechanistic ideas outlined above, it was recognized by experience that some types of elimination reactions give the more substituted alkene as the major product. Such eliminations are said to follow the *Saytzeff rule*.
 - This behavior is characteristic of E_1 reactions and E_2 reactions involving relatively good leaving groups, such as halides and sulfonates.

-
- These are now recognized as reactions in which C–X cleavage is well advanced in the TS. E₂ reactions involving poor leaving groups, particularly those with quaternary ammonium salts, are said to follow the *Hofmann rule* and give primarily the less-substituted alkene.
 - We now recognize that such reactions proceed through TSs with E₁cb character.
 - The data recorded in Table 5.11 for the 2-hexyl system illustrate two general trends that have been recognized in other systems as well.
 - First, poorer leaving groups favor elimination according to the Hofmann rule, as shown, for example, by the increasing amount of terminal olefin in the halogen series as the leaving group is changed from iodide to fluoride.

- Poorer leaving groups move the TS in the $E_1\text{cb}$ direction. A higher negative charge must build up on the β -carbon to induce loss of the leaving group.
 -
 - This charge increase is accomplished by more complete proton abstraction.
-
- Comparison of the data for methoxide with those for t-butoxide in Table 5.11 illustrates a second general trend.
 - Stronger bases favor formation of the less-substituted alkene. A stronger base leads to an increase in the carbanion character at the TS and, thus, shifts it in the $E_1\text{cb}$ direction.
 - A correlation between the strength of the base and the difference in $\Delta G^\ddagger$ for the formation of 1-butene versus 2-butene has been established. Some of the data are given in Table 5.12.

Table 5.11. Product Ratios for Some Elimination Reactions of 2-Hexyl Systems

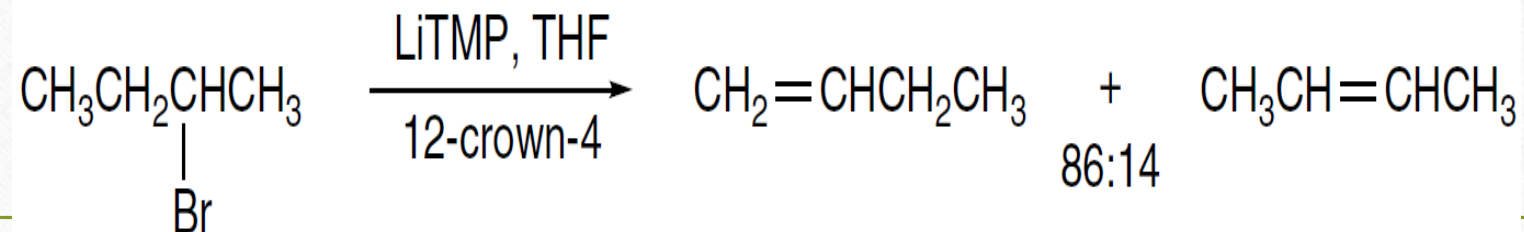
Leaving group	Base/solvent	Product Composition		
		1-Hexene	<i>E</i> -2-Hexene	<i>Z</i> -2-Hexene
I	MeO ⁻ /MeOH	19	63	18
Cl	MeO ⁻ /MeOH	33	50	17
F	MeO ⁻ /MeOH	69	21	9
OSO ₂ C ₇ H ₇	MeO ⁻ /MeOH	33	44	23
I	<i>t</i> -BuO ⁻ / <i>t</i> -BuOH	78	15	7
Cl	<i>t</i> -BuO ⁻ / <i>t</i> -BuOH	91	5	4
F	<i>t</i> -BuO ⁻ / <i>t</i> -BuOH	97	2	1
OSO ₂ C ₇ H ₇	<i>t</i> -BuO ⁻ / <i>t</i> -BuOH	83	4	14



- The direction of elimination is also affected by steric effects, and if both the base and the reactant are highly branched, steric factors may lead to preferential removal of the less hindered hydrogen.
-
- Thus, when 4-methyl-2-pentyl iodide reacts with very hindered bases such as potassium tricyclohexylmethoxide, there is preferential formation of the terminal alkene.
-
- In this case, potassium t-butoxide favors the internal alkene, although by a smaller ratio than for less branched alkoxides.
-

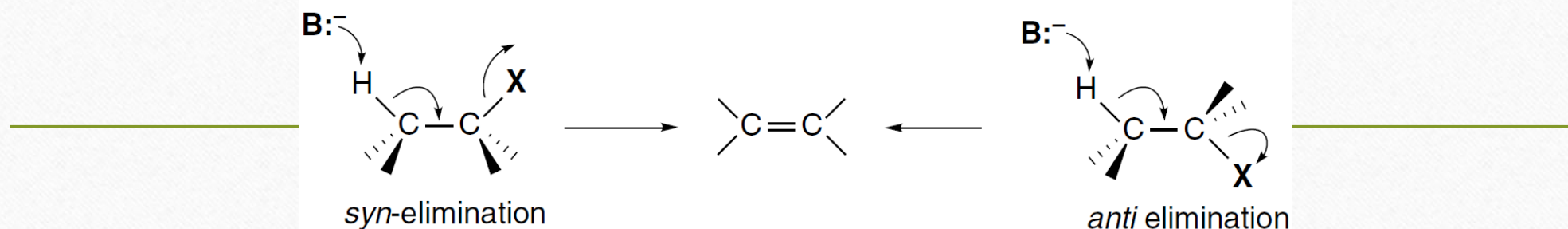
Table 5.12. Orientation of E2 Elimination as a Function of Base Strength

Base (K ⁺ salt)	p <i>K</i> (DMSO)	Percent 1-butene	
		2-Iodobutane ^a	2-Butyl tosylate ^b
<i>p</i> -Nitrobenzoate	8.9	5.8	c
Benzoate	11.0	7.2	c
Acetate	11.6	7.4	c
Phenolate	16.4	11.4	30.6
Trifluoroethoxide	21.6	14.3	46.0
Methoxide	29.0	17.0	c
Ethoxide	29.8	17.1	56.0
<i>t</i> -Butoxide	32.2	20.7	58.5

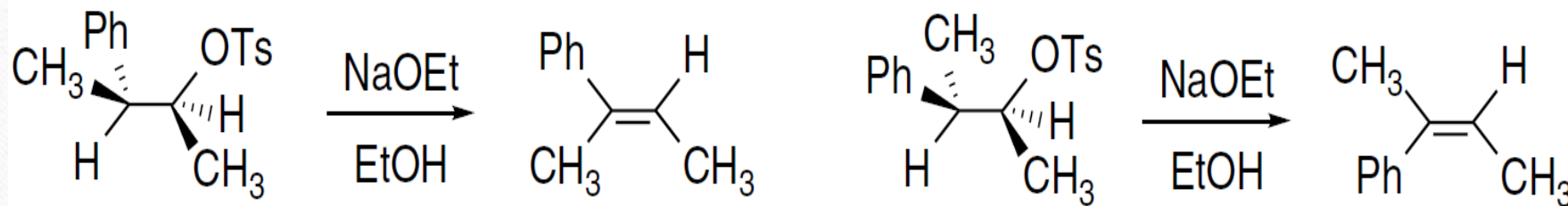


- Branched amide bases can also control the regiochemistry of elimination on the basis of steric effects.
-
- For example LiTMP favors formation of 1-butene from 2-bromobutane. The leaving group also affects the amount of internal versus terminal alkene that is formed. The poorer the leaving group, the more E₁cb-like the TS.
-
- This trend is illustrated for the case of the 2-butyl system by the data in Table 5.13. Positively
- charged leaving groups, such as in dimethylsulfonium and trimethylammonium salts, may also favor a more E₁cb-like TS because their inductive and field effects increase the acidity of the β-protons.
-

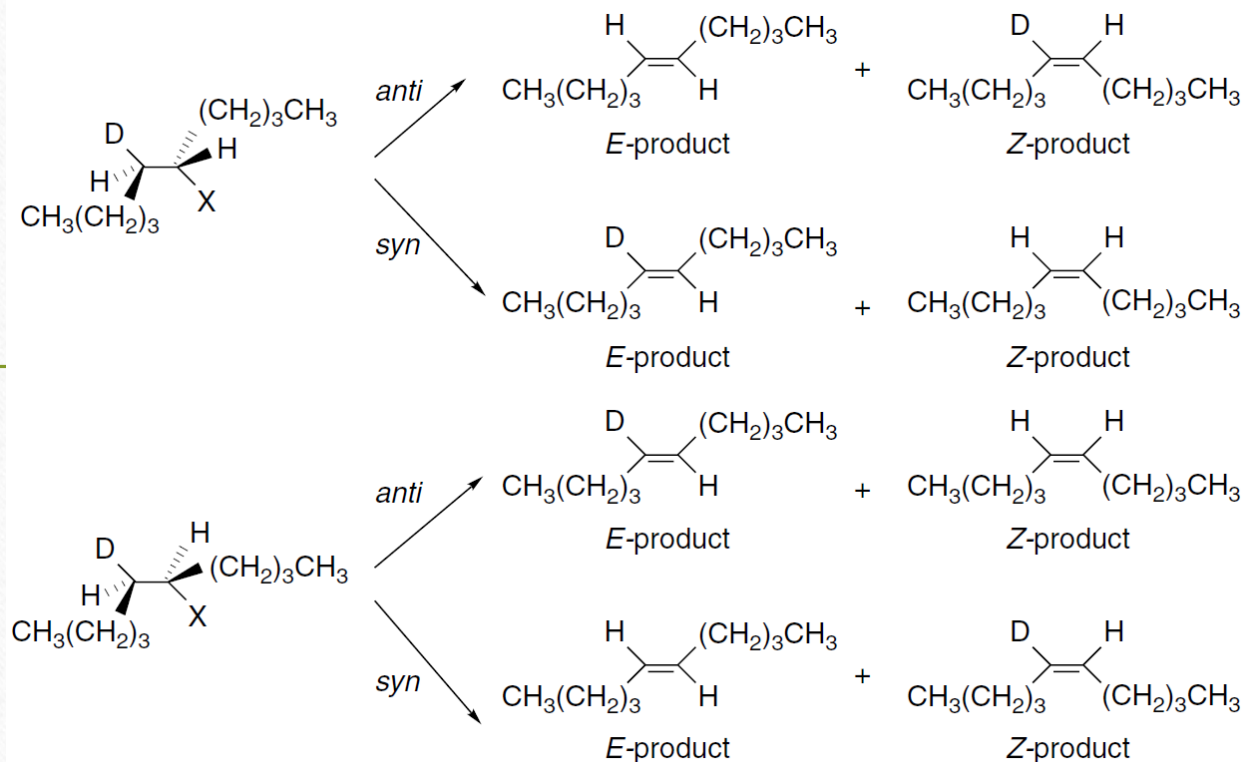
Stereochemistry of E2 Elimination Reactions



- In this section we focus primarily on the stereochemistry of the concerted E2 mechanism. The most familiar examples are dehydrohalogenation and dehydrosulfonylation reactions effected by strong bases.
-
- In principle, elimination can proceed with either *syn* or *anti* stereochemistry. For acyclic systems, there is a preference for *anti* elimination, but this can be overridden if conformational factors favor a *syn* elimination.
-
- The *anti* TS maximizes orbital overlap and avoids the eclipsing that is present in the *syn* TS.
-



- In acyclic systems, the extent of *anti* versus *syn* elimination can be determined by use of either stereospecifically deuterated reactants or diastereomeric reactants that give different products by *syn* and *anti* elimination.
- The latter approach showed that elimination from 3-phenyl-2-butyl tosylate is a stereospecific *anti* process.
- The extent of *syn* elimination in 5-decyl systems was measured using diastereomeric deuterium-labeled substrates.
- Stereospecifically deuterated 5-substituted decane derivatives were prepared and subjected to various elimination conditions.



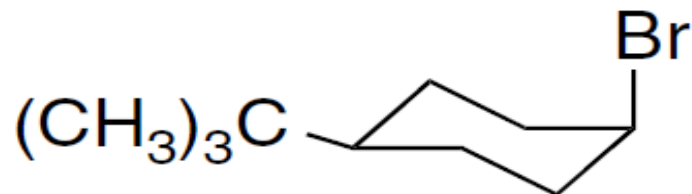
- By comparison of the amount of deuterium in the E- and Z-isomers of the product, it is possible to determine the extent of *syn* and *anti* elimination.
- Data obtained for three different leaving groups are shown in Table 5.14. The results demonstrate that *syn* elimination is extensive for quaternary ammonium salts.

-
- With better leaving groups, the extent of *syn* elimination is small in the polar solvent DMSO but quite significant in benzene.
 -
 - The factors that promote *syn* elimination are discussed below. Table 5.15 summarizes some data on *syn* versus *anti* elimination in other acyclic systems.
 -
 - The general trend revealed by these and other data is that *anti* stereochemistry is normally preferred for reactions involving good leaving groups such as bromide and tosylate. With poorer leaving groups (e.g., fluoride, trimethylamine), *syn* elimination becomes important.
 -
 - The amount of *syn* elimination is small in the 2-butyl system, but it becomes a major pathway with 3-hexyl compounds and longer chains.
 -

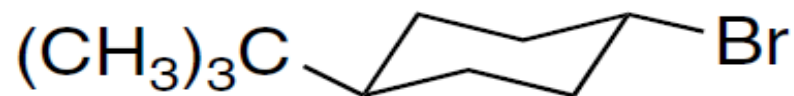
Table 5.14. Extent of *syn* Elimination as a Function of the Leaving Group in the 5-Decyl System^a

Leaving group	Percent <i>syn</i> elimination			
	E-product		Z-product	
	DMSO	Benzene	DMSO	Benzene
Cl	6	62	7	39
OTs	4	27	4	16
(CH ₃) ₃ N ⁺	93	92	76	84

- In cyclic systems, the extent of *anti* and *syn* elimination depends on ring size, among other factors. Cyclohexyl systems have a very strong preference for *anti* elimination via conformations in which both the departing proton and the leaving group occupy axial positions.



$$4.1 \times 10^{-3}$$



$$8.0 \times 10^{-6}$$

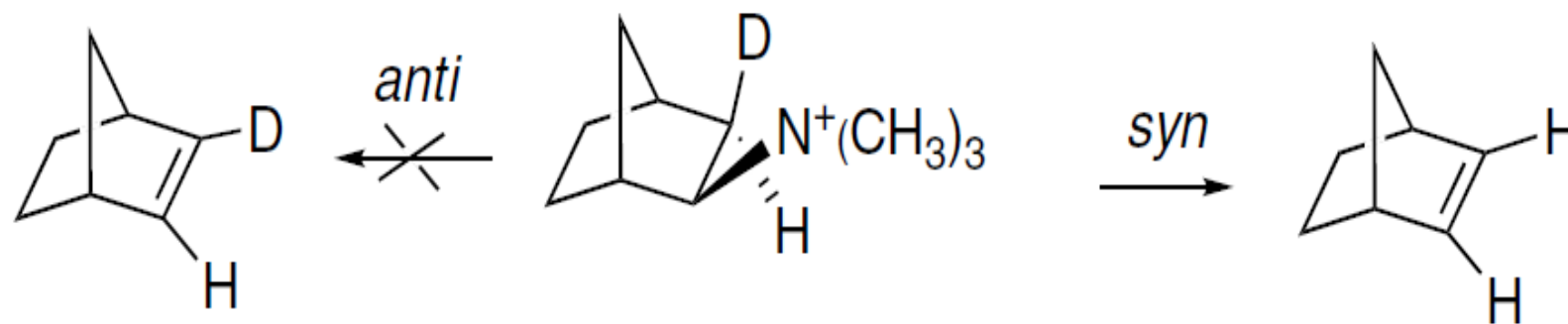
second order rate constants for E2 reaction
with $\text{K}^+ \text{ } ^-\text{OC}(\text{CH}_3)_3$

- This orientation permits alignment of the orbitals so that concerted *anti* elimination can occur.
-
- For example, *cis*-4-*t*-butylcyclohexyl bromide undergoes E_2 elimination at a rate about 500 times greater than the *trans* isomer because only the *cis* isomer permits *anti* elimination from the favored chair conformation.
-

Table 5.15. Stereochemistry of E2 Elimination for Some Acyclic Systems

Reactant	Base/solvent	% <i>anti</i>	% <i>syn</i>
2-Bromobutane ^a	K ⁺ OC(CH ₃) ₃ / <i>t</i> -BuOH	100	0
2-Butyl tosylate ^b	K ⁺ OC(CH ₃) ₃ / <i>t</i> -BuOH	> 98	< 2
<i>N, N, N</i> -trimethyl-2-butylammonium ^c	K ⁺ OC(CH ₃) ₃ /DMSO	100	0
3-Fluorohexane ^d	K ⁺ OC(CH ₃) ₃ / <i>t</i> -BuOH	32	68
<i>N, N, N</i> -trimethyl-4-octylammonium ^e	K ⁺ OC(CH ₃) ₃ /DMSO	24	76
5-Decyl tosylate ^f	K ⁺ OC(CH ₃) ₃ / <i>t</i> -BuOH	93	7
5-Decyl chloride ^g	K ⁺ OC(CH ₃) ₃ /benzene	62	38
5-Decyl fluoride ^g	K ⁺ OC(CH ₃) ₃ /benzene	< 20	> 80
5-Decyl chloride ^g	K ⁺ OC(CH ₃) ₃ /DMSO	93	7
5-Decyl fluoride ^g	K ⁺ OC(CH ₃) ₃ , DMSO	80	20

- Other cyclic systems are not so selective. In the decomposition of *N,N,N*-trimethyl- cyclobutylammonium hydroxide, elimination is 90% *syn*.
- The cyclobutyl ring resists the conformation required for *anti* elimination. The more flexible fivemembered
- ring analog undergoes about 50% *syn* elimination. Elimination from the *N,N,N*-trimethylnorbornylammonium ion is exclusively *syn*.



This is another case where the rigid ring prohibits attainment of an *anti*-elimination process. There is also a steric effect operating against removal of an *endo* proton, which is required for *anti* elimination.

Syn elimination is especially prevalent in the medium-sized ring compounds.

The energy difference between the *anti* and *syn* transition structures has been examined computationally using fluoride as the base and alkyl chlorides as the reactants.

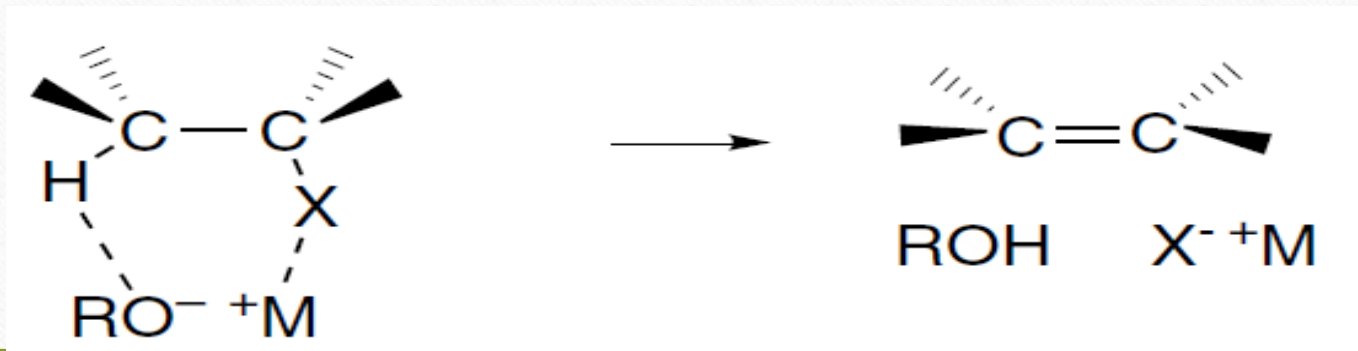
$\text{C}_2\text{H}_5\text{Cl} + \text{F}^- : \quad \Delta E(\text{anti}) = -5.7 \text{ kcal/mole}; \Delta\Delta E(\text{syn} - \text{anti}) = 12.7 \text{ kcal/mol}$

$n\text{-C}_3\text{H}_7\text{Cl} + \text{F}^- : \quad \Delta E(\text{anti}) = -9.9 \text{ kcal/mole}; \Delta\Delta E(\text{syn} - \text{anti}) = 12.8 \text{ kcal/mol}$

$(\text{CH}_3)_2\text{CHCl} + \text{F}^- : \quad \Delta E(\text{anti}) = -10.2 \text{ kcal/mole}; \Delta\Delta E(\text{syn} - \text{anti}) = 12.8 \text{ kcal/mol}$

- Simple primary and secondary chlorides show no barriers for *anti* elimination at the MP4SDQ/6-31+G** level.
-
- The *syn* TSs show positive barriers and the total difference between the *syn* and *anti* TSs is on the order of 13 kcal/mol.

-
- The preferred TS for *syn* elimination is not periplanar, but rather has a torsion angle of about 30 °C.
 - The *syn* TS has more E₁cb character than the *anti*. MP2/6-31+G** computations have been used to compare cyclopentyl and cyclohexyl systems.
 - As noted above, cyclohexyl systems have a much stronger preference for the *anti* stereochemistry.
 - The optimum TSs are shown in Figure 5.15. Both the *anti* and *syn* TSs have negative barriers in the cyclopentyl system (−10.2 and −0.9 kcal/mol), whereas the *syn* system shows a positive barrier in the cyclohexyl system (−10.9 and +5.4 kcal/mol).



- The factors that determine whether *syn* or *anti* elimination predominates are complex. One factor that is believed to be important is whether the base is free or present as an ion pair.
- The evidence suggests that an ion pair promotes *syn* elimination of anionic leaving groups.
- This effect can be explained by a TS in which the anion functions as a base and the cation assists in the departure of the leaving group.
- This interpretation is in agreement with the solvent effect that is evident for the 5-decyl system data in Table 5.15.

-
- The extent of *syn* elimination is much higher in the nondissociating solvent benzene than in DMSO.
 - The ion pair interpretation is also supported by the fact that addition of specific metal ion–complexing agents (crown ethers) that promote dissociation of the ion pair leads to diminished amounts of *syn* elimination.
 - Another factor that affects the *syn:anti* ratio is the strength of the base.
 - Strong bases exhibit a higher proportion of *syn* elimination.

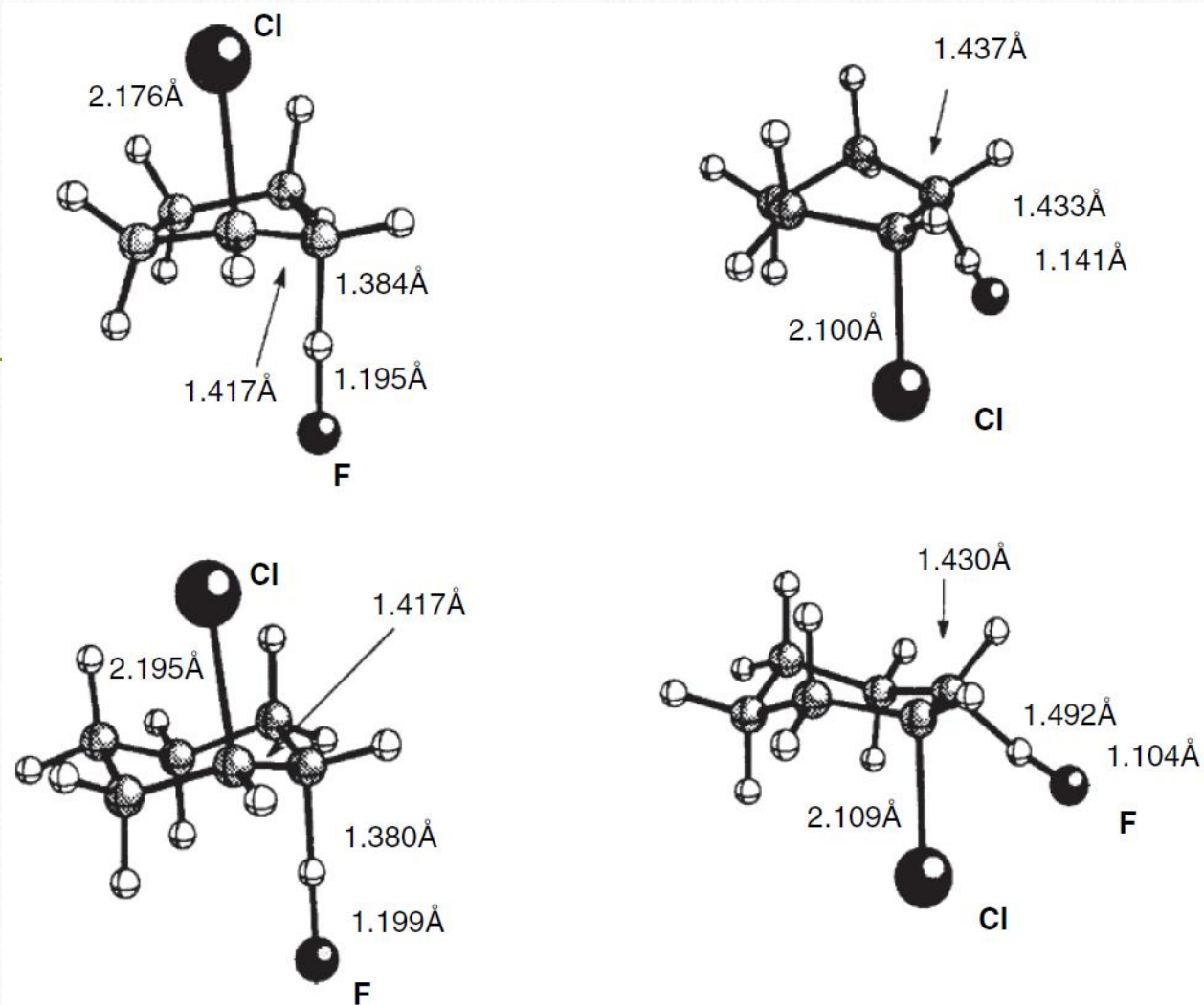
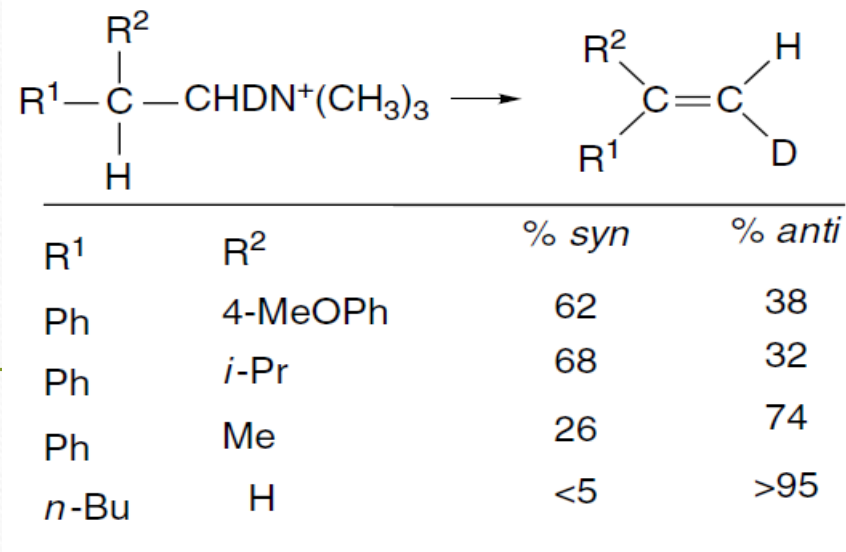
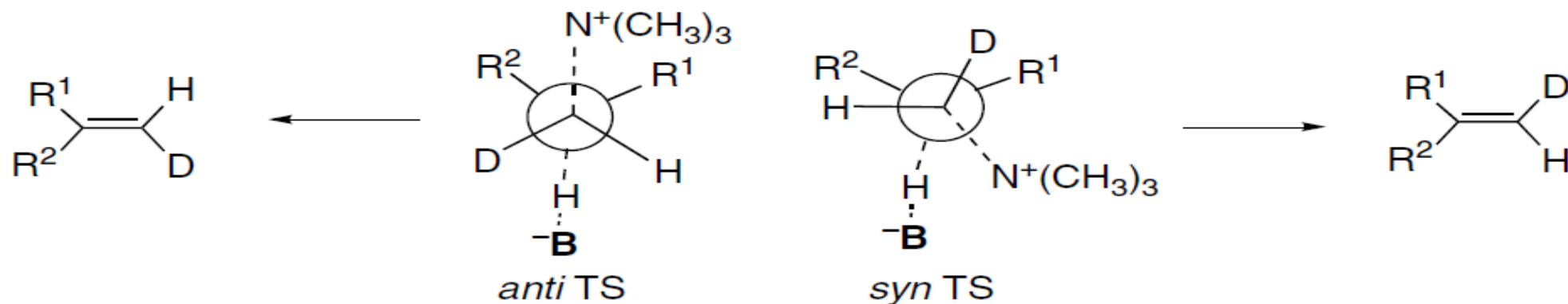


Fig. 5.15. *Anti* and *syn* transition states for fluoride-induced E2 elimination in (a) cyclopentyl and (b) cyclohexyl systems. Reproduced from *J. Org. Chem.*, **59**, 7046 (1994), by permission of the



- Steric and conformational effects also play a significant role in determining the *syn:anti* ratio. With N-(β,β-disubstituted-ethyl)-N,N,N-trimethylammonium ions, *syn* elimination is more prevalent when the β-substituents are aryl or branched.
- As the β-groups become less bulky, the amount of *syn* elimination decreases. This effect is illustrated by the data above. The steric dependence is imposed by the bulky trimethylamine leaving group.

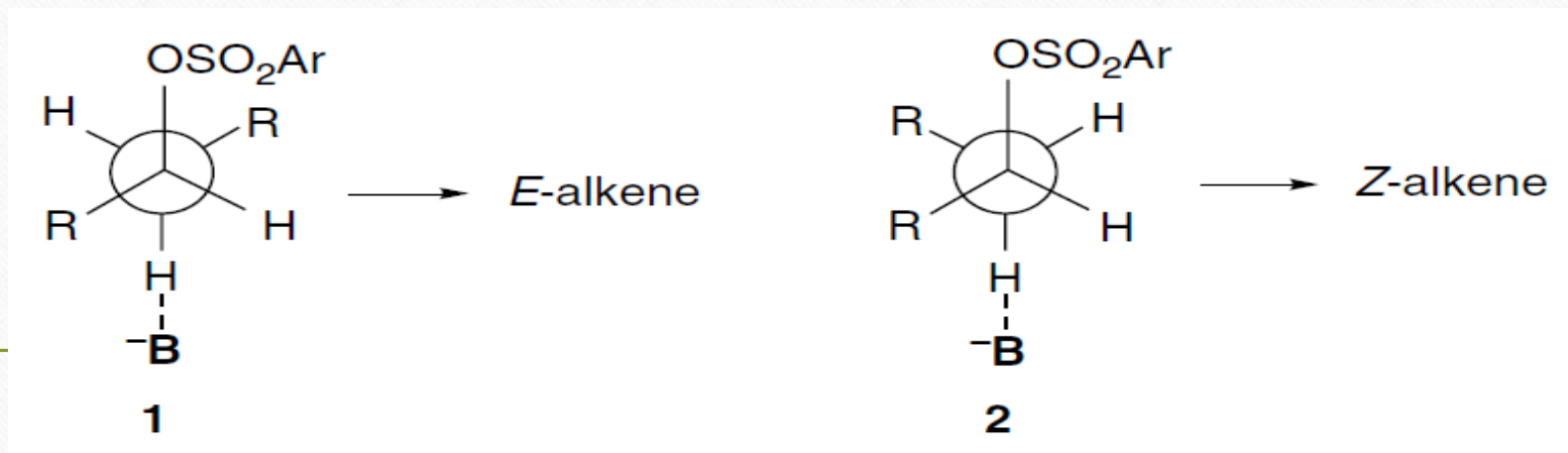


- In the TS for *anti* elimination, steric repulsion is increased as R_1 and R_2 increase in size.
-
- When the repulsion is sufficiently large, the TS for *syn* elimination is preferred.
- Another aspect of the stereochemistry of elimination reactions is the ratio of E-and Z-products.
-
- The proportion of Z-and E-isomers of disubstituted internal alkenes formed during elimination reactions depends on the identity of the leaving group.
-

Halides usually give mainly the E-alkenes. Bulkier groups, particularly arenesulfonates, give higher proportions of the Z-alkene. Sometimes, more Z-isomer is formed than E-isomer.

The preference for E-alkene probably reflects the unfavorable steric repulsions present in the E_2 transition state leading to Z-alkene.

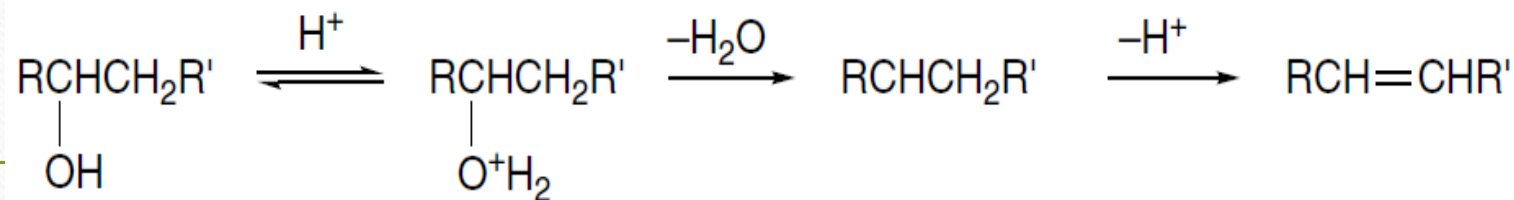
High Z:E ratios are attributed to a second steric effect that becomes important only when the leaving group is large.



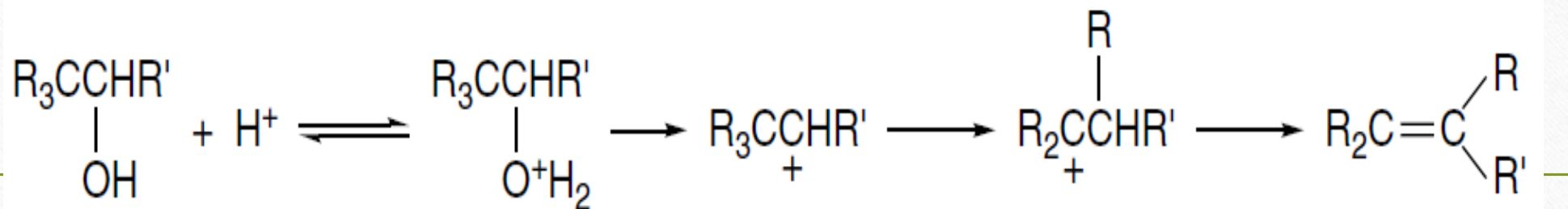
When the leaving group and base are both large, conformation **2** is favored because it permits the leaving group to occupy a position removed from the β -alkyl substituents, while also maintaining an *anti* relationship to the α -hydrogen. *Anti* elimination through a TS arising from conformation **2** gives *Z*-alkene.

The conformations leading to *E*- and *Z*-alkene by *anti* elimination are depicted above.

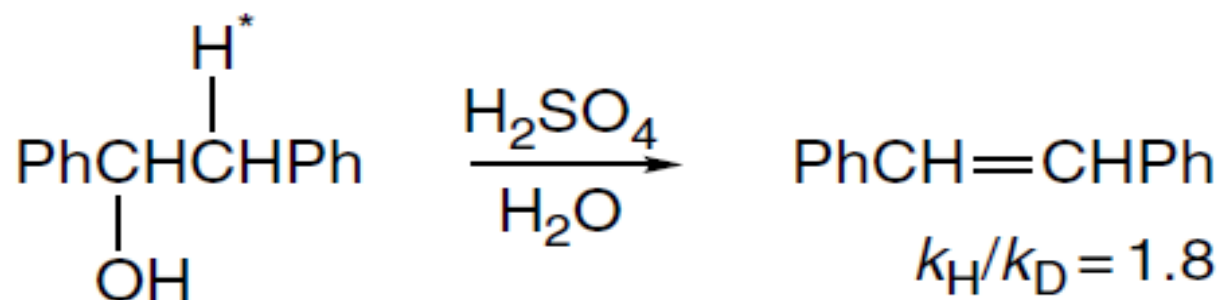
Dehydration of Alcohols



- The dehydration of alcohols is an elimination reaction that takes place under acidic rather than basic conditions and involves an E₁ mechanism.
-
- The function of the acidic reagent is to convert the hydroxyl group to a better leaving group by protonation.
-
- This elimination reaction is the reverse of acid-catalyzed hydration, which was discussed in Section 5.2.
-



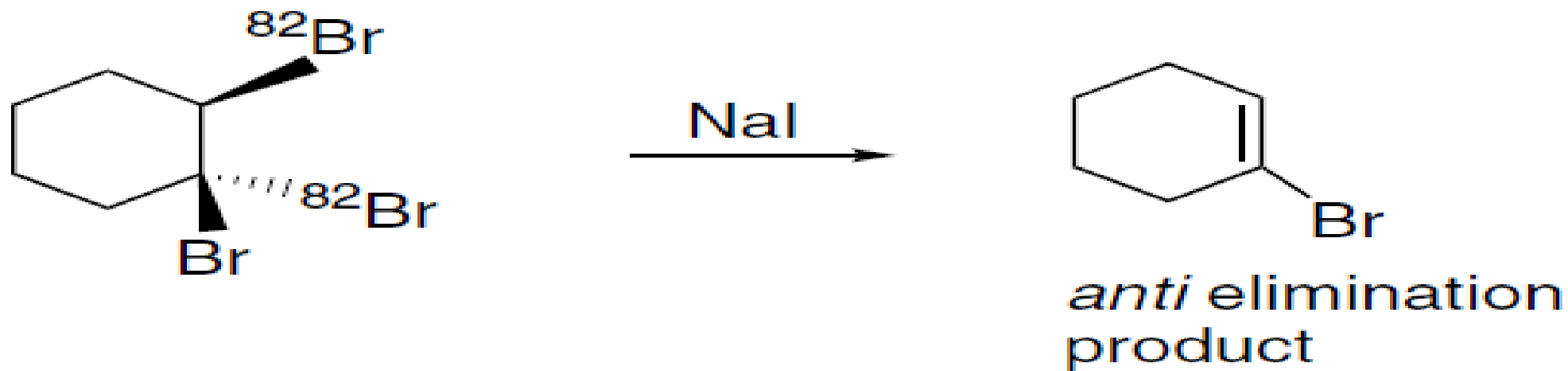
- Since a carbocation or closely related species is the intermediate, the elimination step is expected to favor the more-substituted alkene.
-
- The E₁ mechanism also explains the trends in relative reactivity. Tertiary alcohols are the most reactive, and reactivity decreases going to secondary and primary alcohols.
-
- Also in accord with the E₁ mechanism is the fact that rearranged products are found in cases where a carbocation intermediate would be expected to rearrange.



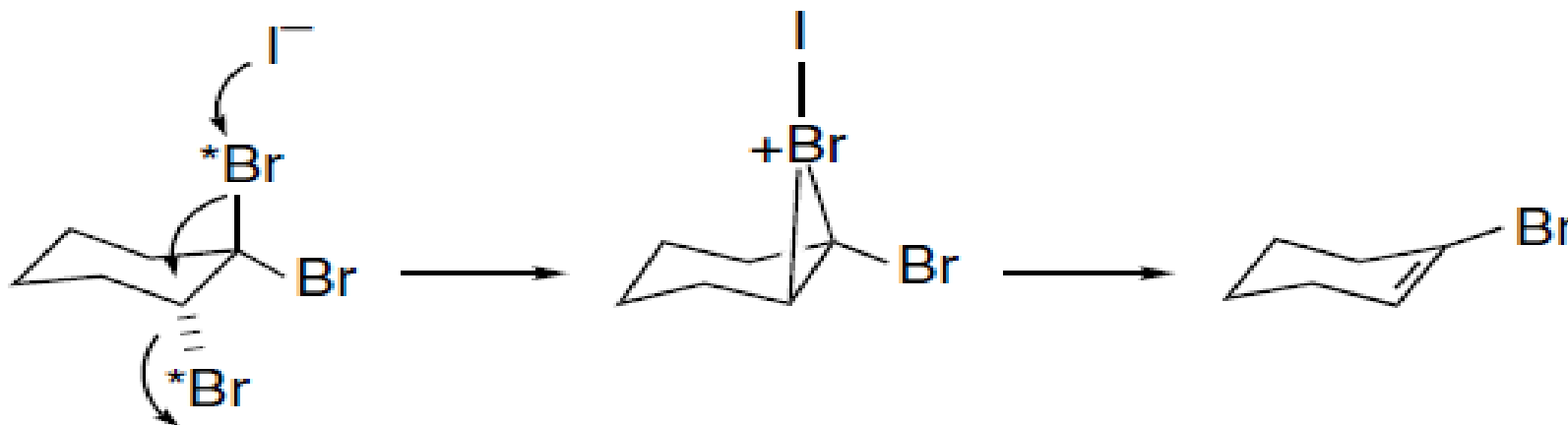
- For some alcohols, exchange of the hydroxyl group with solvent competes with dehydration.
-
- This exchange indicates that the carbocation can undergo $\text{S}_{\text{N}}1$ capture in competition with elimination. Under conditions where proton removal is rate determining,
-
- It would be expected that a significant isotope effect would be seen, which is, in fact, observed.
-

Eliminations Reactions Not Involving C–H Bonds

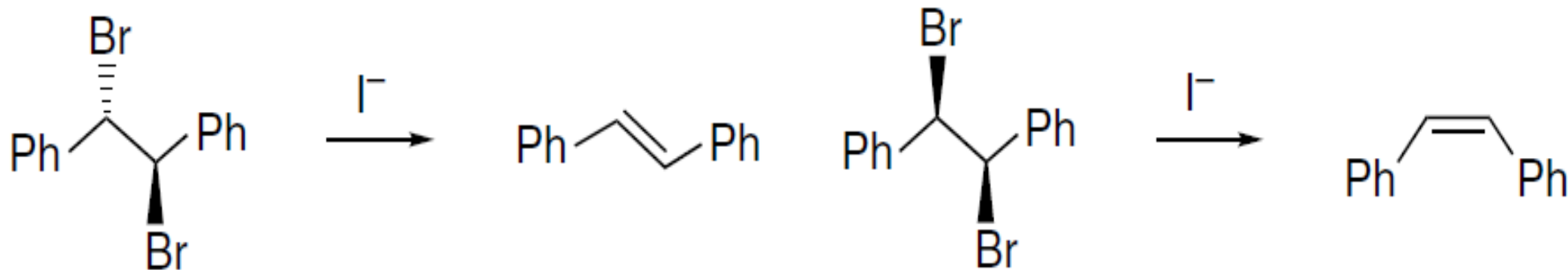
- The discussion of elimination processes thus far has focused on reactions that involve removal of a proton bound to a β -carbon, but it is the electrons in the C–H σ bond that are essential to the elimination process.
- Compounds bearing other substituents that can release electrons undergo β -eliminations. Many such reactions are known, and they are frequently stereospecific.
- Vicinal dibromides can be debrominated by certain reducing agents, including iodide ion.



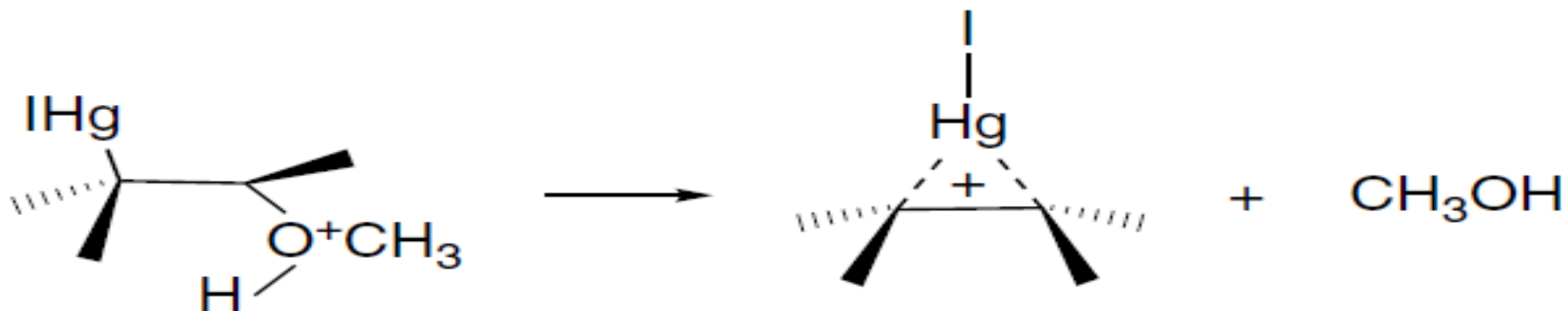
- The stereochemical course in the case of 1,1,2-tribromocyclohexane was determined using a ^{82}Br -labeled sample prepared by *anti* addition of $^{82}\text{Br}_2$ to bromocyclohexene.
-
- Exclusive *anti* elimination gave unlabeled bromocyclohexene, whereas ^{82}Br -labeled product resulted from *syn* elimination. Debromination with sodium iodide was found to be cleanly an *anti* elimination.



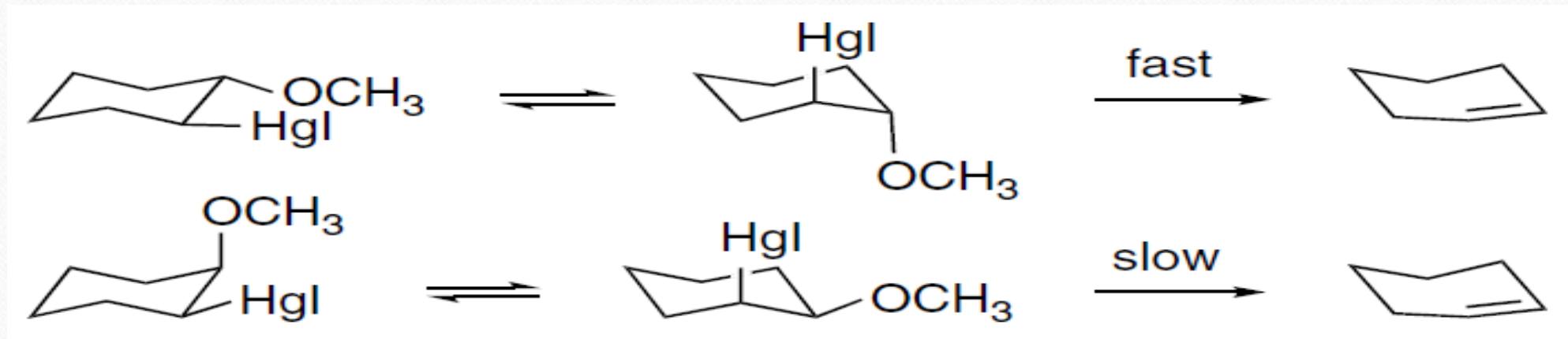
- The iodide-induced reduction is essentially the reverse of a halogenation. Application of the principle of microscopic reversibility suggests that the reaction proceeds through a bridged intermediate.
- The rate-determining expulsion of bromide ion through a bridged intermediate requires an *anti* orientation of the two bromides.
- The nucleophilic attack of iodide at one bromide enhances its nucleophilicity and permits formation of the bridged ion.



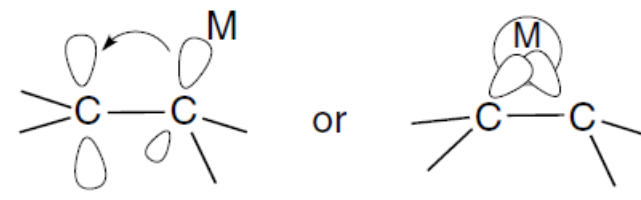
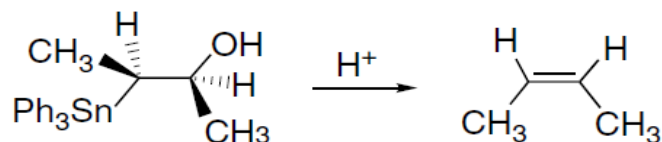
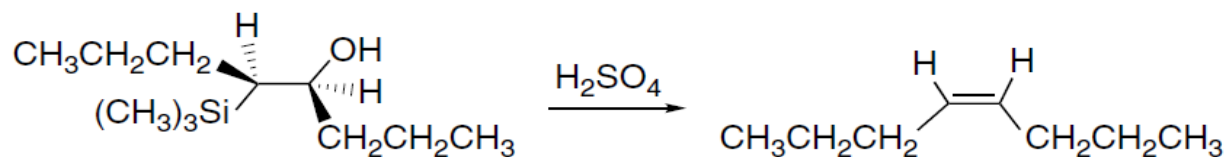
- The stereochemical preference in noncyclic systems is also *anti*, as indicated by the fact that *meso*-stilbene dibromide yields *trans*-stilbene, whereas d,l-stilbene dibromide gives mainly *cis*-stilbene under these conditions.
- Structures of type M–C–C–X in which M is a metal and X is a leaving group are very prone to elimination with formation of a double bond.
- One example is acid-catalyzed deoxymercuration. The β -oxyorganomercurials are more stable than similar reagents derived from more electropositive metals, but are much more reactive than simple alcohols.



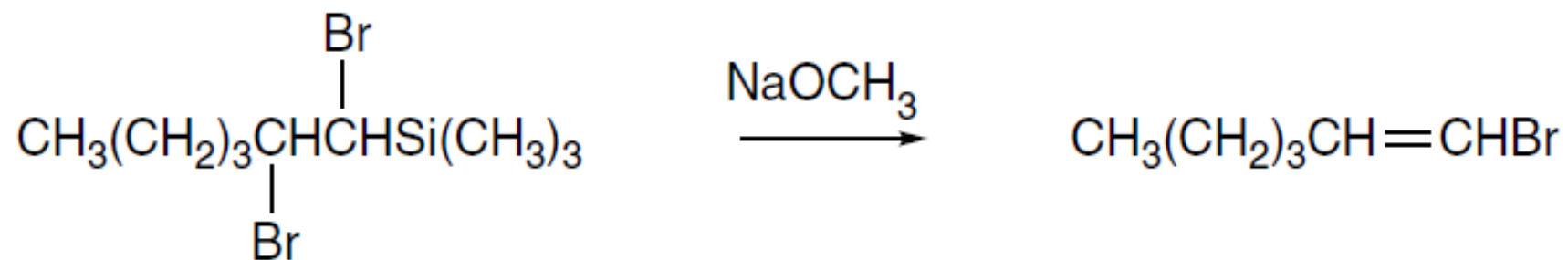
- For example, $\text{CH}_3\text{CH}(\text{OH})\text{CH}_2\text{HgI}$ is converted to propene under acid-catalyzed conditions at a rate that is 1011 times greater than dehydration of 2-propanol under the same conditions.
- Only the *trans* isomer can undergo elimination by an *anti* process through a chair conformation.
-
- These reactions are believed to proceed through a bridged mercurinium ion by a mechanism that is the reverse of oxymercuration.
- One of the pieces of evidence supporting this mechanism is the fact that the $\Delta H^\ddagger$ for deoxymercuration of *trans*-2-methoxycyclohexylmercuric iodide is about 8 kcal/mol less than for the *cis* isomer.



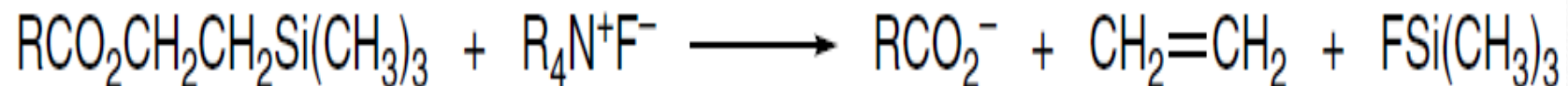
- Comparing the rates of acid-catalyzed β -elimination of compounds of the type MCH_2CH_2OH yields the reactivity order for β -substituents $IHg \sim Ph_3Pb \sim Ph_3Sn > Ph_3Si > H$. The relative rates are within a factor of ten for the first three, but these are 106 greater than for Ph_3Si and 1011 greater than for a proton.
- There are two factors involved in these very large rate accelerations. One is bond energies.
- The relevant values are $Hg-C = 27 < Pb-C = 31 < Sn-C = 54 < Si-C = 60 < H-C = 96$ kcal/mol. The metal substituents also have a very strong stabilizing effect for carbocation character at the p -carbon.



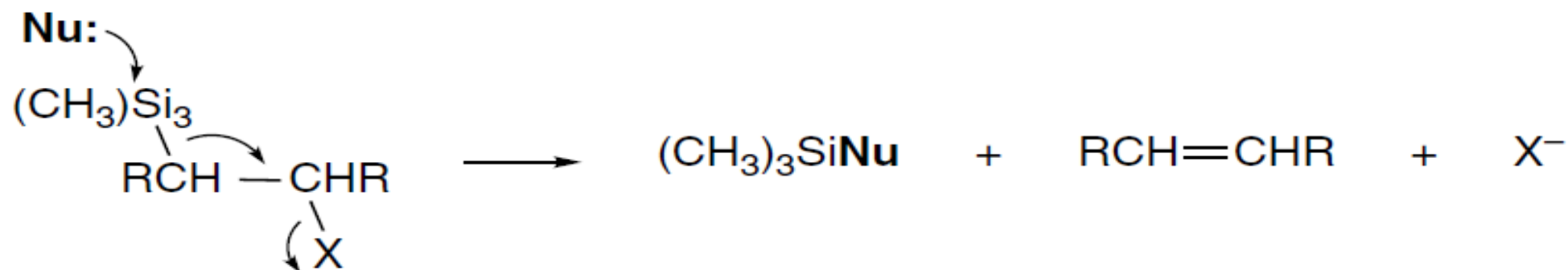
- This stabilization can be pictured either as a orbital-orbital interaction in which the carbon-metal bond donates electron density to the adjacent p orbital, or as formation of a bridged species.
- There are a number of synthetically valuable β -elimination processes involving organosilicon and organotin compounds.
- Treatment of β -hydroxyalkylsilanes or β -hydroxyalkylstannanes with acid results in stereospecific *anti* eliminations that are much more rapid than for compounds lacking the group IV substituent.



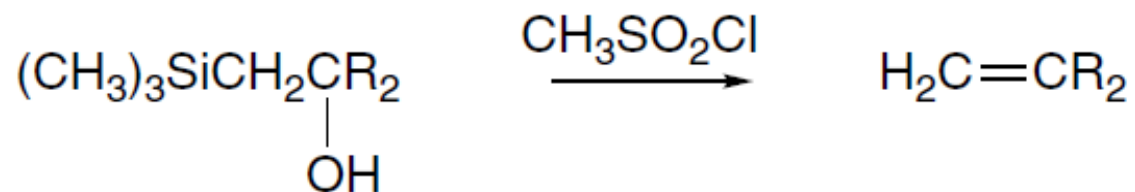
- β -Halosilanes also undergo facile elimination when treated with methoxide ion.



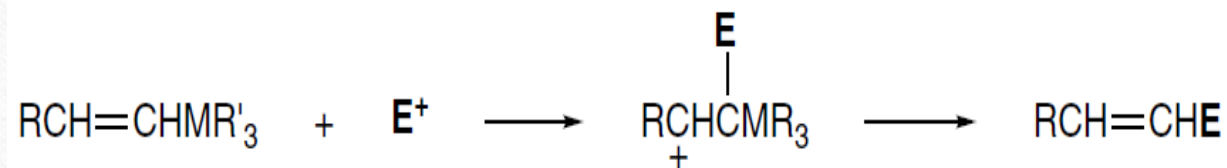
Fluoride-induced β -elimination of silanes having leaving groups in the β -position are important processes in synthetic chemistry, as, for example, in the removal of β -trimethylsilylethoxy groups.



- These reactions proceed by alkoxide or fluoride attack at silicon that results in C–Si bond cleavage and elimination of the leaving group from the β-carbon.
- These reactions are stereospecific *anti* eliminations.



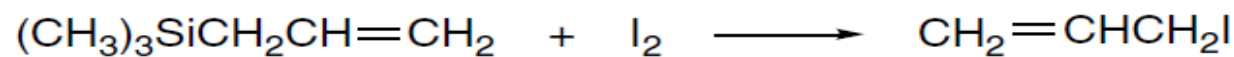
β-Elimination reactions of this type can also be effected by converting a β-hydroxy group to a better leaving group. For example, conversion of β-hydroxyalkylsilanes to the corresponding methane sulfonates leads to rapid elimination.



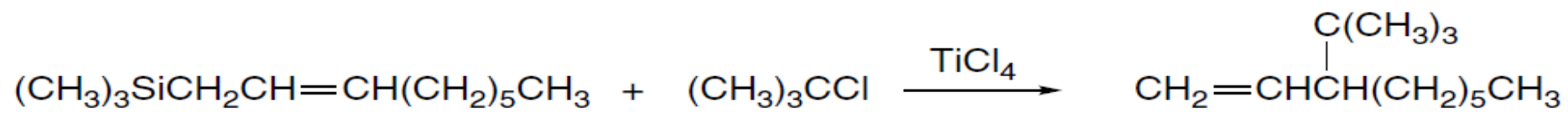
- β -Trimethylsilylalkyl trifluoroacetates also undergo facile *anti* elimination.

- The ability to promote β -elimination and the electron-donor capacity of the β -metalloid substituents can be exploited in a very useful way in synthetic chemistry.
- Vinylstannanes and vinylsilanes react readily with electrophiles. The resulting intermediates then undergo elimination of the stannyl or silyl substituent, so that the net effect is replacement of the stannyl or silyl group by the electrophile.
- The silyl and stannyl substituents are crucial to these reactions in two ways. In the electrophilic addition step, they act as electron-releasing groups that promote addition and control the regiochemistry.
- A silyl or stannyl substituent strongly stabilizes carbocation character at the β -carbon atom and thus directs the electrophile to the α -carbon.

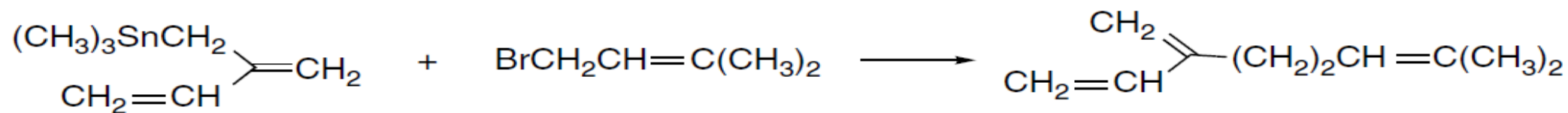
- Computational investigations indicate that there is a ground state interaction between the alkene π orbital and the carbon-silicon bond that raises the energy of the π HOMO and enhances reactivity.
-
- MP3/6-31G* calculations indicate a stabilization of 38 kcal/mol, which is about the same as the value calculated for an α -methyl group.
 - Furthermore, this stereoelectronic interaction favors attack of the electrophile *anti* to the silyl substituent.
 - The reaction is then completed by the elimination step in which the carbon-silicon or carbon-tin bond is broken.
 - Allyl silanes and allyl stannanes are also reactive toward electrophiles and usually undergo a concerted elimination of the silyl substituent.



Ref. 318



Ref. 319



Ref. 320

