Nucleophilic Substitutions, Eliminations & Introduction to Organic Synthesis

Reminders

- Next week, May 16 (6-9 pm) – In class exam review + practice session
- Following week, May 25 (6-9 pm) – Final Exam
- Green Chemistry Presentation Grades
- Evaluations

Outline

- Solvent Role in SN2 reactions
- SN1 reactions
- Differences between SN2 and SN1
- Eliminations (E2, E1 and E1CB)
- Substitution vs. Elimination for 1^o, 2^o and 3^o alkyl halides
- Stereochemical considerations for eliminations
- 12 Principals of Green Chemistry
- Retrosynthetic analysis
- New C-C bond forming reactions

There are Two Types of Nucleophilic Substitution Reactions

S_N2	S_N1
Substitution	Substitution
Nucleophilic	Nucleophilic
Bimolecular (2)	Unimolecular (1)
Rate = k [RX] [Nuc:]	Rate = k [RX]

Keys to a Good SN2 Reactions

- **Reactive Nucleophile**

- Nucleophiles are Lewis Bases (e- donors)

- Nucleophilicity parallels Brønsted basicity when comparing those with same attacking atom (stronger base = weaker conjugate acid, think water (pKa = 15.7) vs. hydronium ion (pKa = -1.7))

- Nucleophilicity increases going down a column of the periodic table (larger e^- cloud = e^-s less bound to nucleus) e.g. HS^- is 7.8x more reactive of a nucleophile as compared to HO^-

- **Stable Leaving Group on Electrophile**

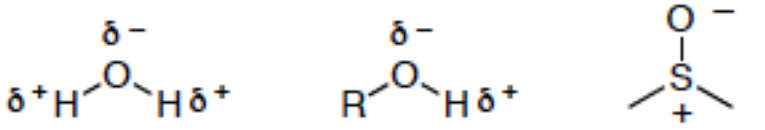
-Best leaving groups are those that can stabilize the negative charge (i.e. *via* resonance)

-Good leaving groups are the weak conjugate bases of strong acids (e.g. Cl^-, Br^-, I^-, TsO^-).

- Poor leaving groups are strong conjugate bases of weak acids (e.g. F^-, OH^-, OR^-, H_2N^-) and must be chemically converted to better leaving groups (e.g. OH to OTos or OH to OH_2^+)

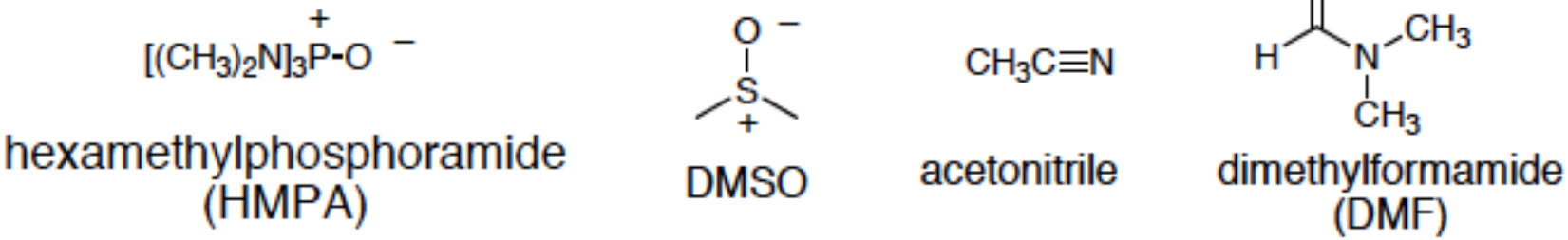
Solvent's Role in S_N2 Reactions

- ***Polar vs. Non-Polar Solvents***
  - *Polar* = High dipole moment (water, alcohols, DMSO, etc.)



  - *Non-polar* = Low dipole moment (hexanes, dichloromethane, benzene, etc.)

- ***Protic vs. Aprotic Solvents***
  - *Protic* = have acidic hydrogen atoms that form H-bonds (water, alcohols)
  - *Aprotic* = no acidic hydrogen atoms



General Solvent Considerations

- *Polar, Protic - Favor step-wise reaction mechanisms with "charge separation" (e.g. SN1)*
- *Polar, Aprotic – Favor concerted reaction mechanisms (e.g. SN2)*
- Non-Polar Aprotic – Limited utility because they do not dissolve many substrates
- No such thing as Non-Polar, Protic solvents

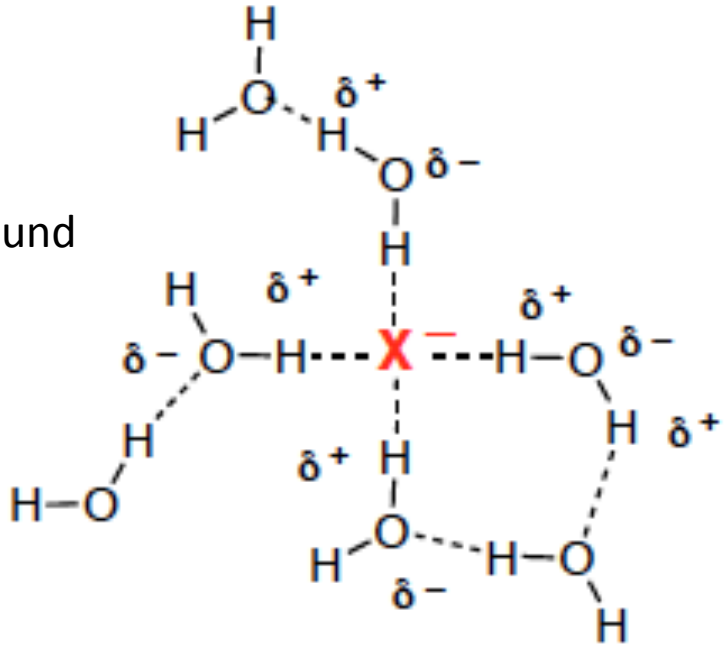
Considerations for solvent/reaction practicality -> e.g. solvent removal from product by:

- distillation: should be "*volatile*" (e.g. boiling point less than 100^{o}C at 1 ATM)
- phase separation: must be "*immiscible*" with water

Unfavorable Solvents for S_N2

- **Polar Protic Solvents:** Selectively solvate and stabilize anion (nucleophile) thus lowering its Free Energy (G) and raising the overall Activation Energy ($\Delta G‡$) of the reaction. *Do not favor S_N2 reactions.*

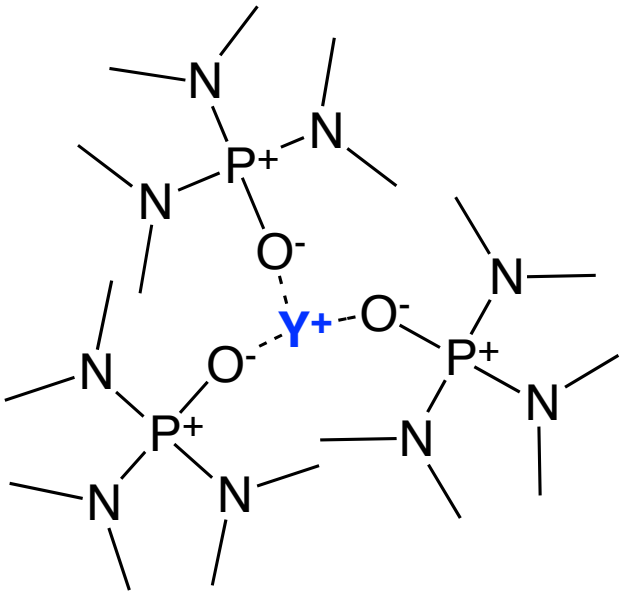
"Solvent Cage" around anion



H_2O lowers energy, and thus stabilizes, the anion (*nucleophile*) by H-bond donation

Favorable Solvents for S_N2

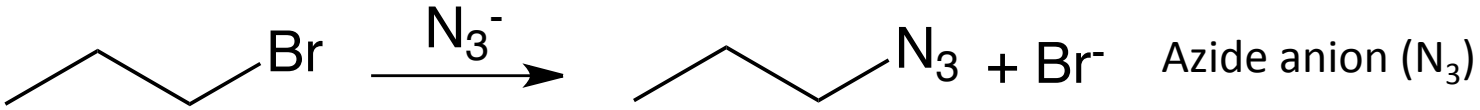
- **Polar Aprotic Solvents:** Selectively solvate and stabilize cation (electrophile), allowing easier reaction with the nucleophile. *Favor S_N2 reactions.*



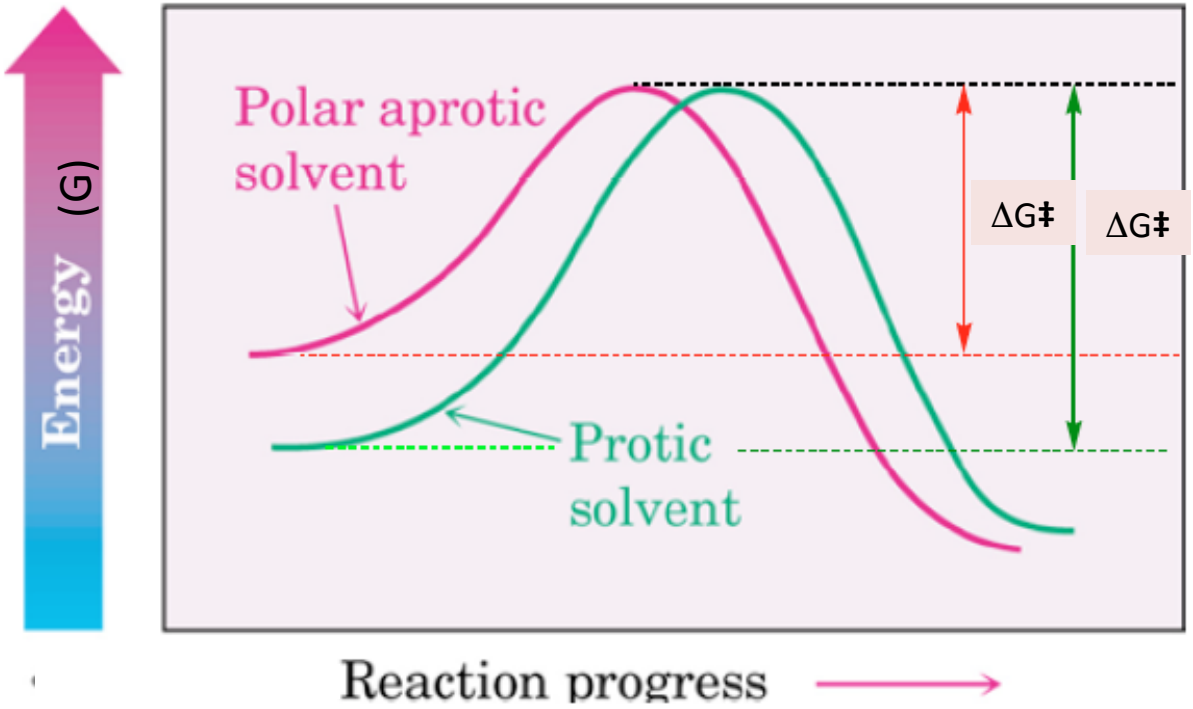
HMPA stabilizing charge of cation (*electrophile*), easing nucleophilic attack

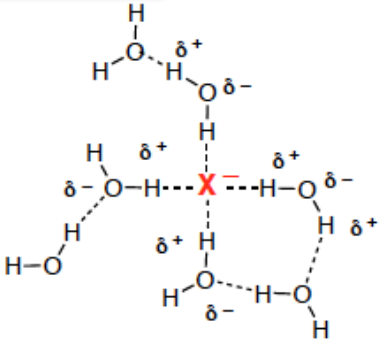
Aprotic solvents also favor reactive nucleophiles, because they do not stabilize the negative charge by H-bond donation

Solvent Effects on S_N2 Reaction

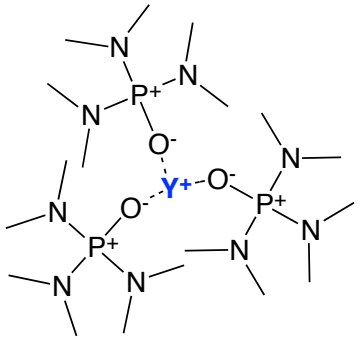


Solvent:	CH_3OH	H_2O	DMSO	DMF	CH_3CN	HMPA
relative reativity:	1	7	1,300	2,800	5,000	200,000



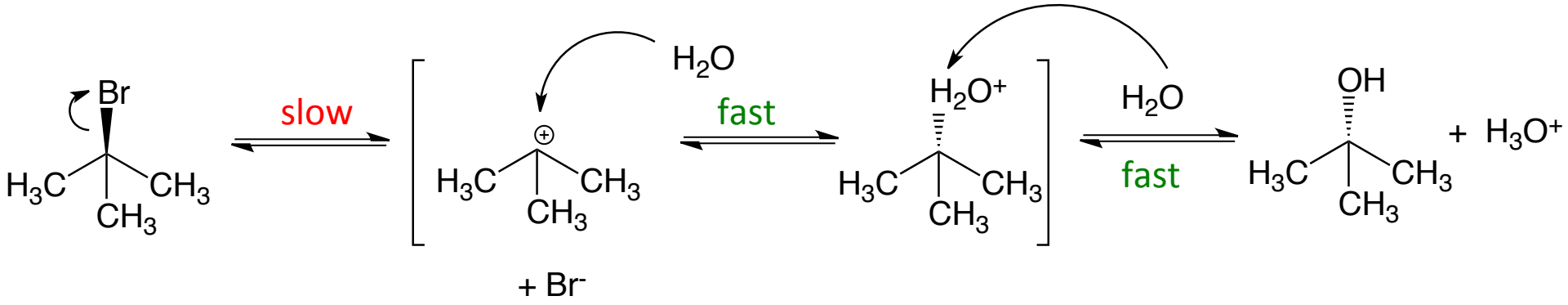


Protic solvents stabilize nucleophiles



Aprotic solvents stabilize electrophiles

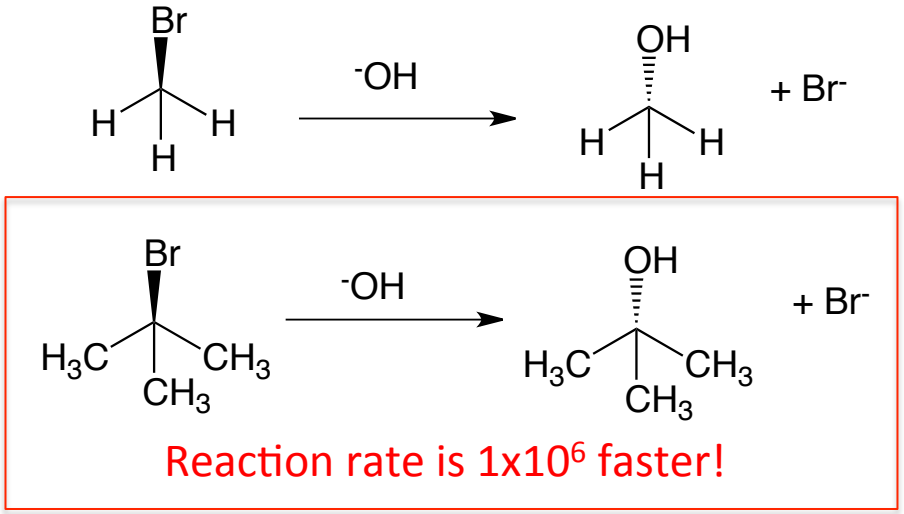
S_N1 Reaction Mechanism



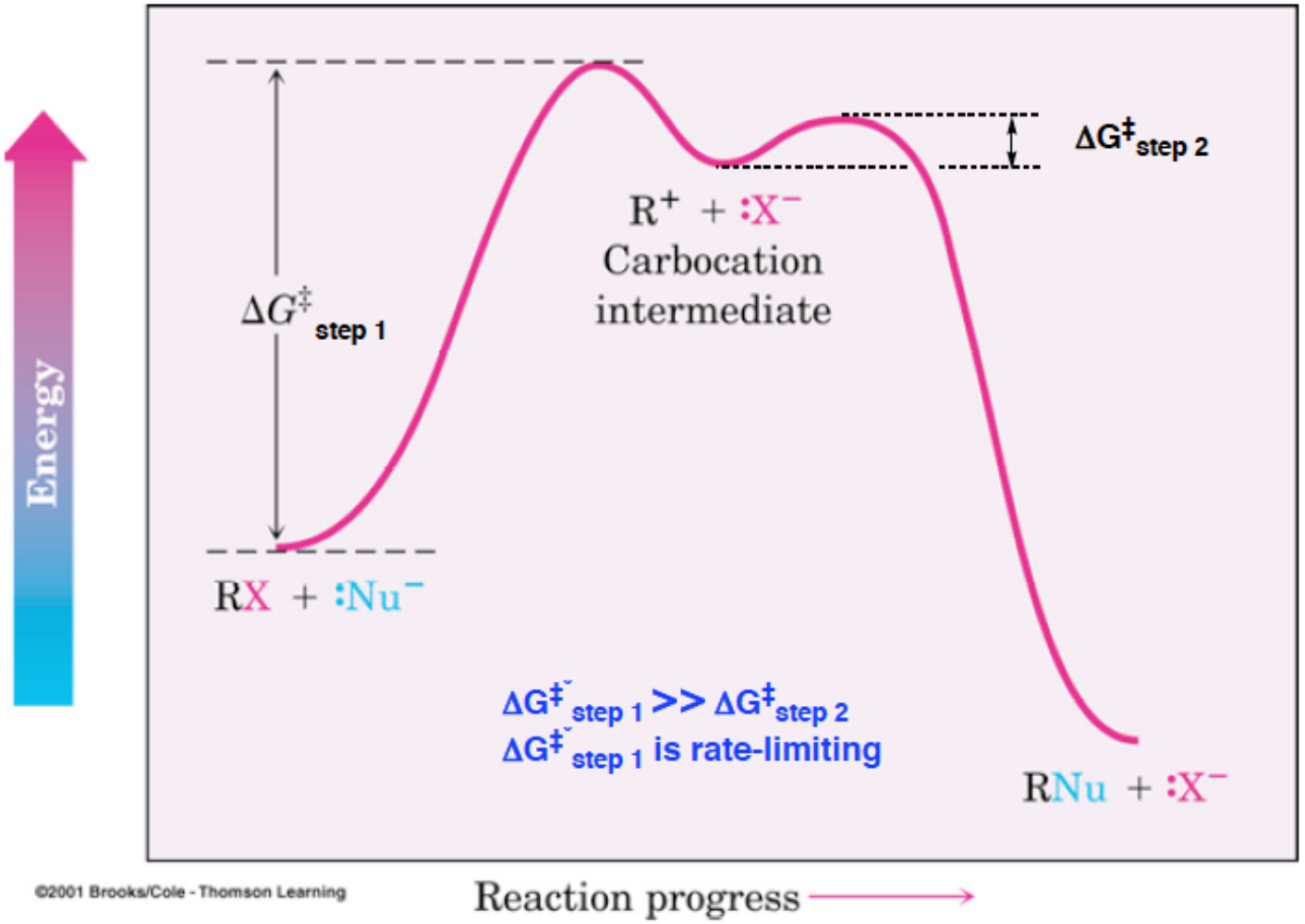
- Loss of bromide is slow and gives carbocation intermediate
- ***Stability of intermediate determines reaction rate***
- Attack by nucleophile and deprotonation is fast

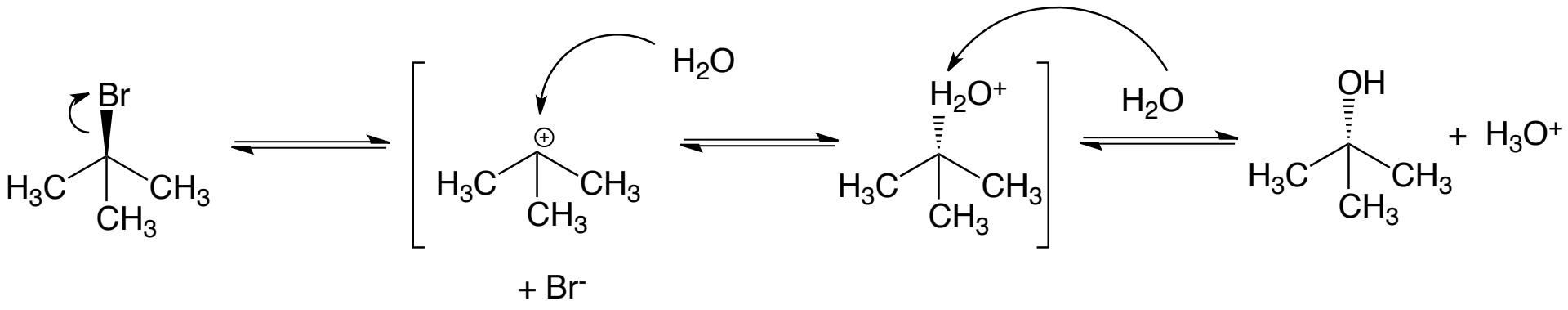
S_N1 Reaction Kinetics

- Why is the reaction of H_2O with *t*-butylbromide *much faster* than the reaction of H_2O with methylbromide?



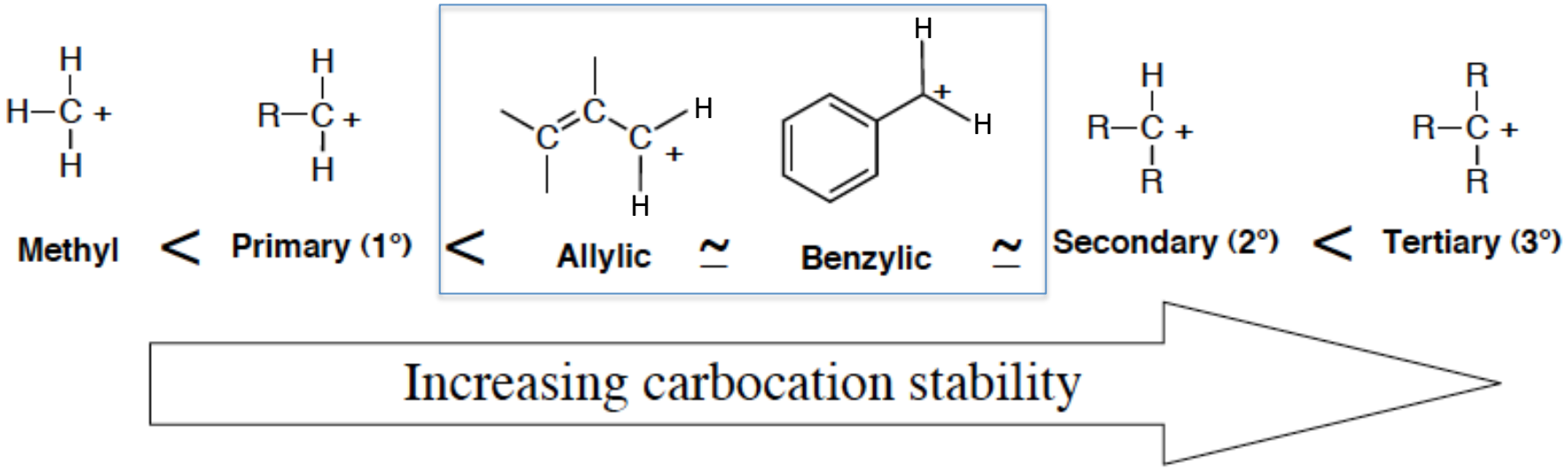
- Rate not dependent on [nucleophile], only [electrophile]
- Rate = k [RX] and rate determining step is formation of the carbocation (methyl vs. tertiary alkyl)


Energy
$\Delta G^{\ddagger}_{\text{step 1}}$
$\Delta G^{\ddagger}_{\text{step 2}}$
$R^+ + :X^-$
Carbocation intermediate
$RX + :Nu^-$
$\Delta G^{\ddagger}_{\text{step 1}} >> \Delta G^{\ddagger}_{\text{step 2}}$
$\Delta G^{\ddagger}_{\text{step 1}}$ is rate-limiting
$RNu + :X^-$
©2001 Brooks/Cole - Thomson Learning
Reaction progress

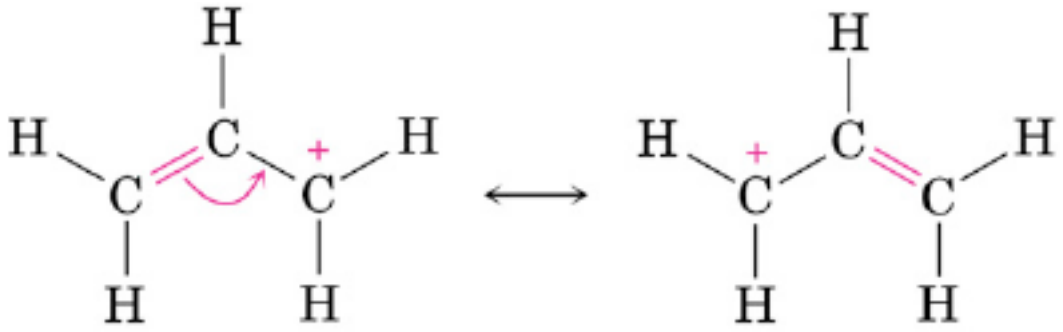

Br
H_3C
CH_3
CH_3
H_2O
H_2O^+
OH
+ H_3O^+
+ Br^-

Carbocation Stability Determines Rate of S_N1 Reaction

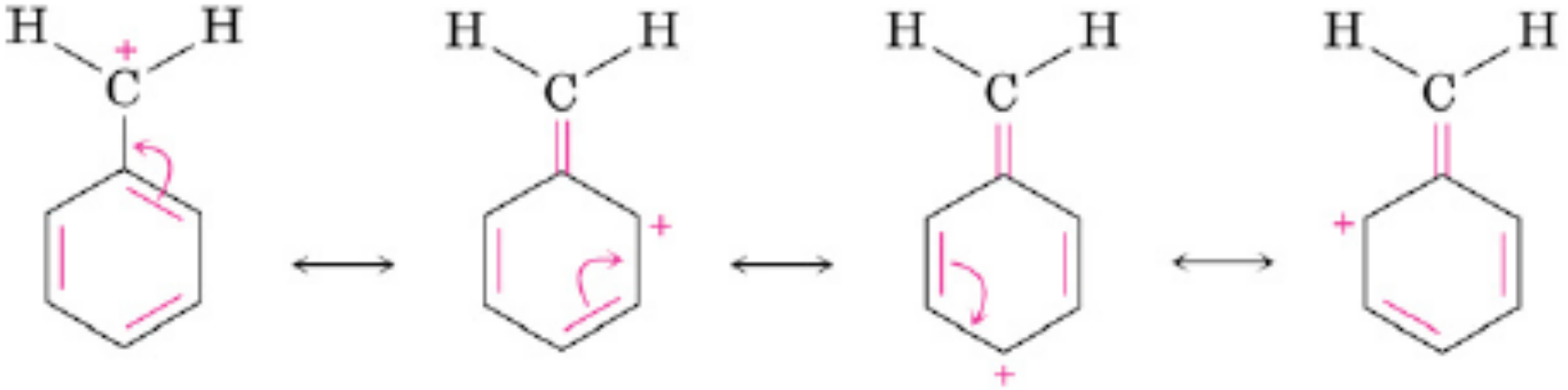
- The stability of the carbocation (electrophile) directly parallels the rate of reaction
- More stable carbocation = faster reaction



Resonance Stabilized Carbocations

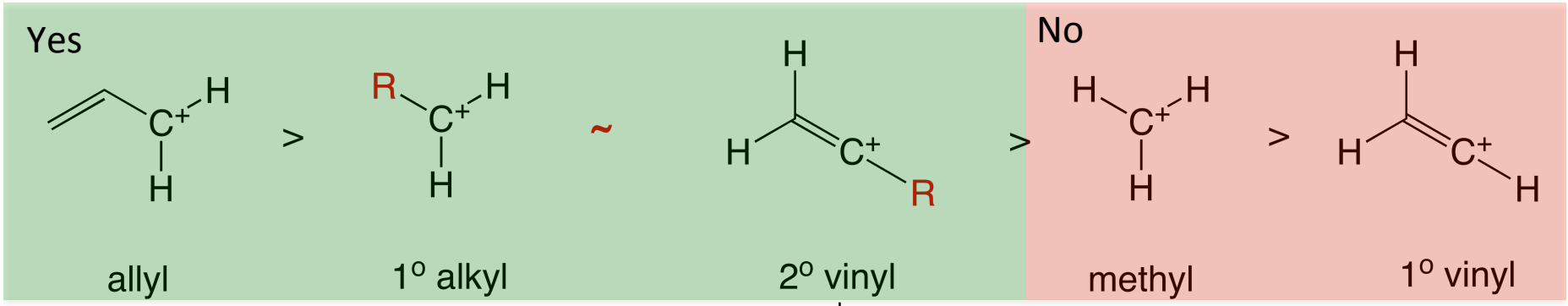


Allyl carbocation



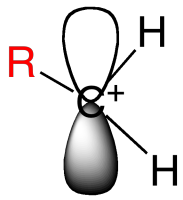
Benzyl carbocation

Vinyl Carbocation Instability

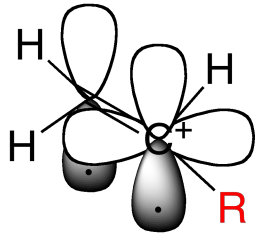


sp2 hybridized carbocation

-0 π bond
-1 σ bond
-vacant p orbital
-only one R group



sp hybridized carbocation
note linear geometry
-1 π bond
-1 σ bond
-vacant p orbital
-only one R group



Vinyl (and aryl) carbocations cannot be stabilized by resonance because π electron clouds are perpendicular to vacant p orbital of carbocation. Resonance requires parallel orbitals for overlap

More stable → Less stable

=

More resonance structures

More hyperconjugation from attached R groups

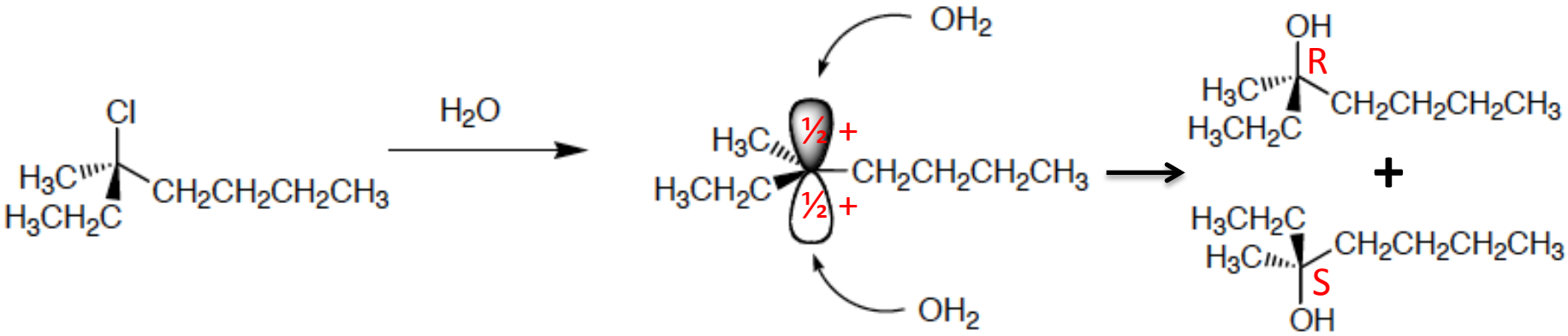
=

Less resonance structures

Less hyperconjugation from attached R groups

Stereochemistry of S_N1 Reaction

- All things equal (e.g. steric bulk of neighboring R groups) the reaction produces a 1:1 racemic mixture of products.



Electrophile is chiral:
sp3 hybridized carbon

Carbocation is achiral:
Attack from either face is possible

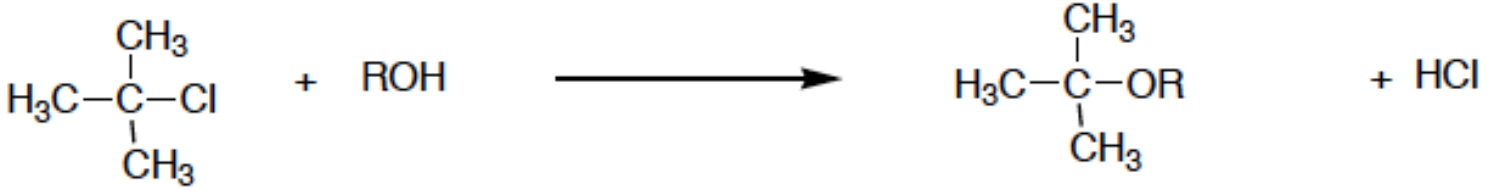
Product is racemic:
1:1 mixture of enantiomers

Solvent Selection for S_N1 Reactions

- ***Polar solvents favored over non-polar solvents****
- ***Protic solvents favored over aprotic solvents***

	Dielectric strength		
Hexane	$\varepsilon =$ 1.9	nonpolar	aprotic
$(CH_3CH_2)_2O$	4.3		
HMPA	30	polar	
DMF	38		
DMSO	48		
CH_3CH_2OH	24		protic
CH_3OH	34		
H_2O	80		

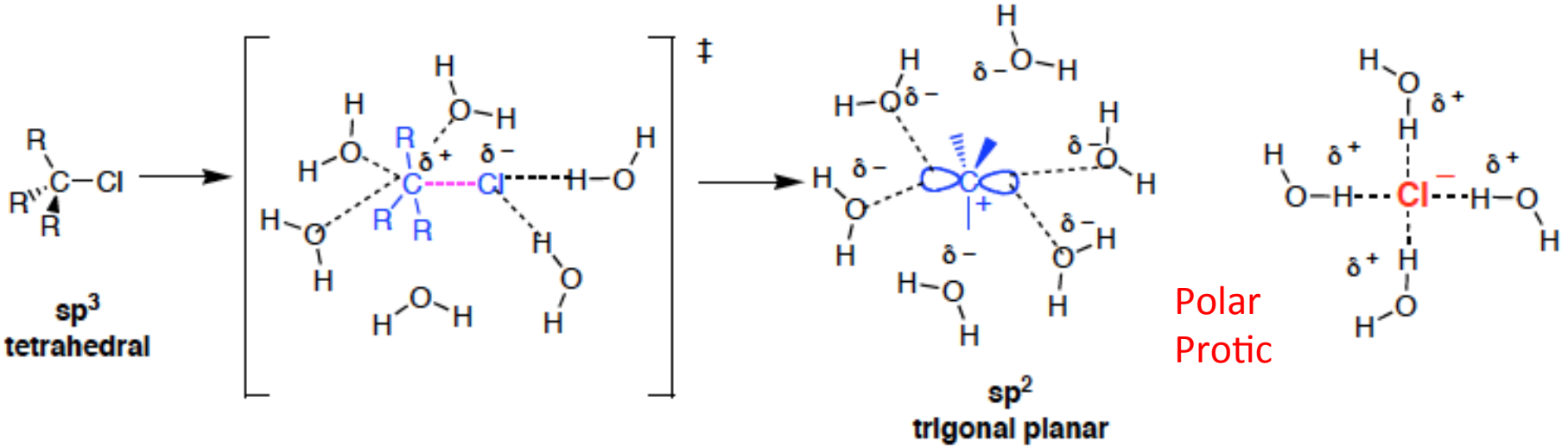
**** Solvent polarity has large influence on reaction rate for S_N1 reactions***



Increasing solvent polarity

Solvent:	Ethanol	40% H_2O 60% Ethanol	80% H_2O 20% Ethanol	H_2O
Rel. reactivity:	1	100	14,000	100,000

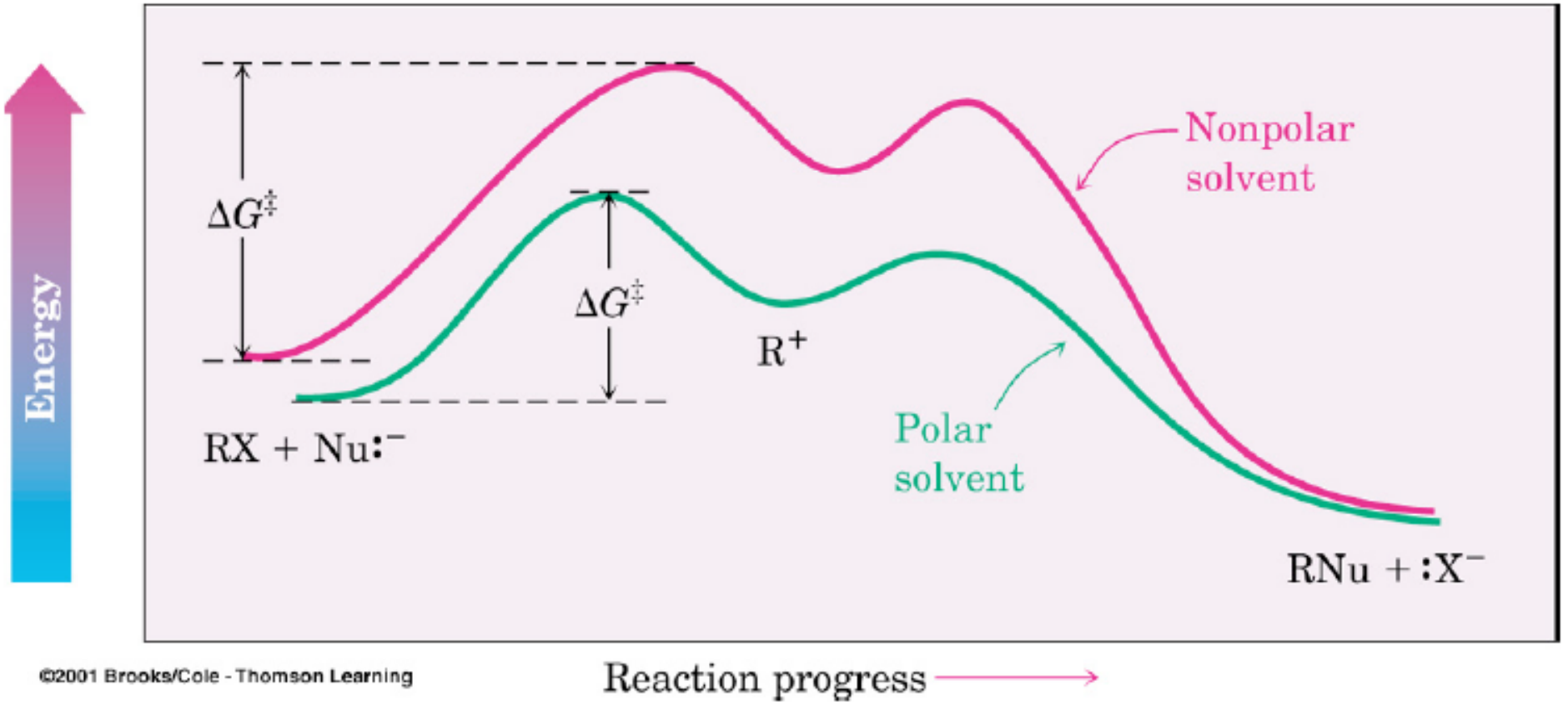
Increasing reactivity in the S_N1 reaction



Solvent stablization of the transition state carbocation and Cl^- leaving group

Solvent stablization of the intermediates

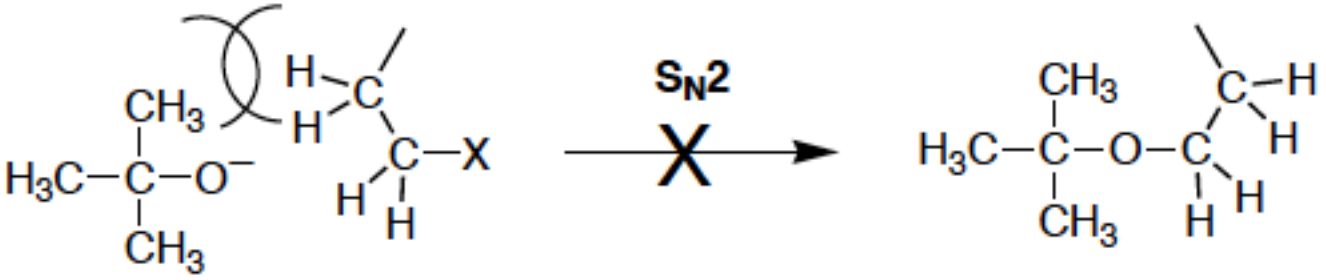
Influence of Solvent Polarity on Kinetics of S_N1 Reactions

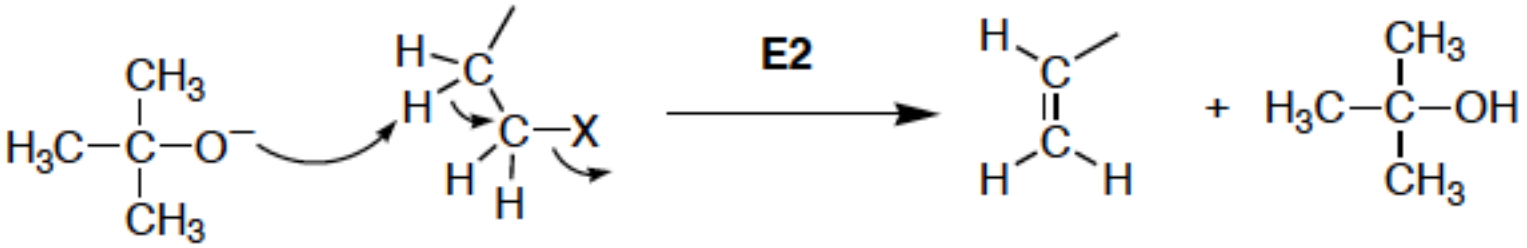


SN1 Reaction Rate: Polar Protic > Polar Aprotic > Non-Polar

S_N2 vs. E2 for 1° Alkyl Halides

- With 1° Alkyl Halides:
- SN1 and E1 do not occur
- S_N2 is favored over E2 for most nucleophiles with primary alkyl halides
- However, sterically hindered, "bulky", "non-nucleophilic" bases like *tert*-butoxide, triethylamine or *N,N*-diisopropylethylamine (Hünig's base) favor E2 reactions





S_N2 and S_N1 vs. Elimination for 2^o Alkyl Halides

With 2^o Alkyl Halides:

- S_N2 and E2 are competitive and a mixture of substitution and elimination products often result.
- S_N1 and Eliminations can also occur
- Solvent selection and nucleophilicity must be considered

Video Summary:

https://www.khanacademy.org/science/organic-chemistry/substitution-elimination-reactions/sn1-sn2-e1-e2-jay/v/sn1-sn2-e1-e2-reactions-secondary-alkyl-halides

Substitutions for 3° Alkyl Halides

With 3° Alkyl Halides:

- S_N2 does not occur with 3° halides

- Elimination vs. Substitution is determined by base strength vs. nucleophilicity

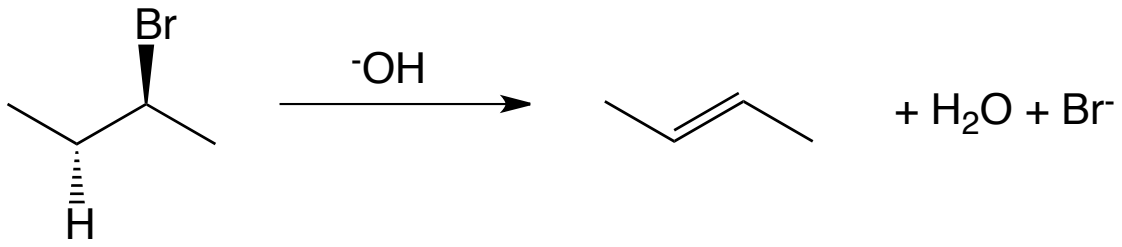
- Good (non-bulky) nucleophile = SN1

Summary of S_N1 vs. S_N2

	S_N1	S_N2
Rate Law	Unimolecular (substrate only)	Bimolecular (substrate and nucleophile)
"Biggest Barrier"	Carbocation stability	Steric hindrance
Alkyl halide (electrophile) effect on likelihood of reaction occurance	$3^o > 2^o >> 1^o$	$1^o > 2^o >> 3^o$
Nucleophile	Weak, generally neutral	Strong, generally bearing a negative charge
Solvent	Polar protic (e.g. alcohols)	Polar aprotic (e.g. DMSO, acetone)
Stereochemistry	Mix of retention and inversion	100% inversion

Elimination Reactions

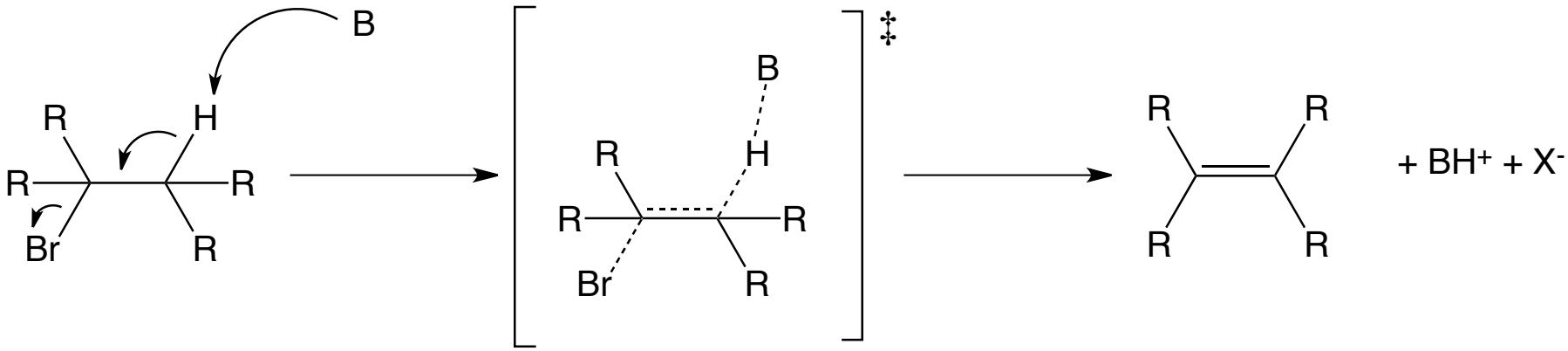
- Nucleophiles are Lewis Bases and when 2° and 3°alkyl halides halides are present, elimination reactions can compete with substitution reactions
- Three types of elimination reaction mechanisms (E1, E2, E1CB)
- Zeitsev vs. Hoffman Products result from different types of bases



E2 Elimination Mechanism and Kinetics

- Single step, no intermediate
- Second order kinetics

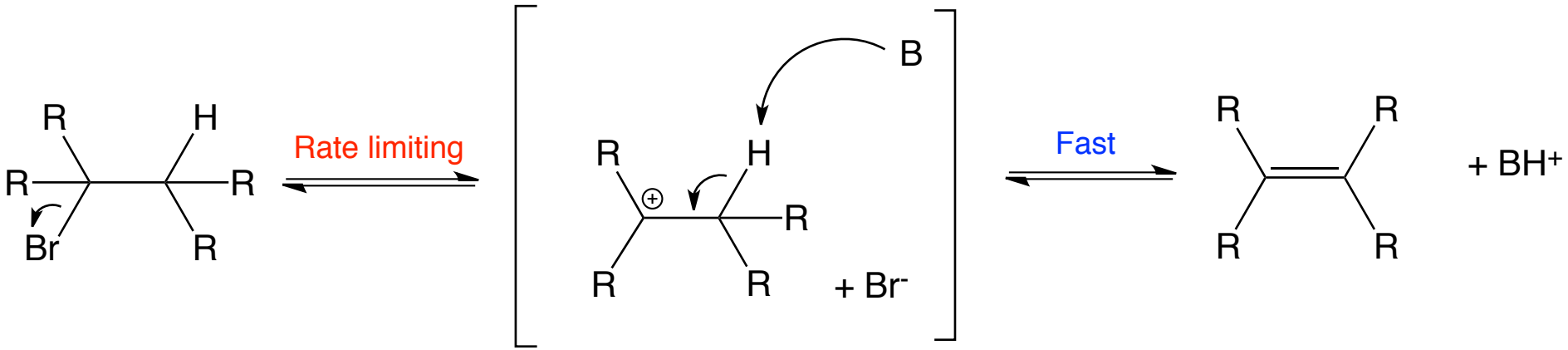
Rate = k [RX][Base]



E1 Elimination Mechanism and Kinetics

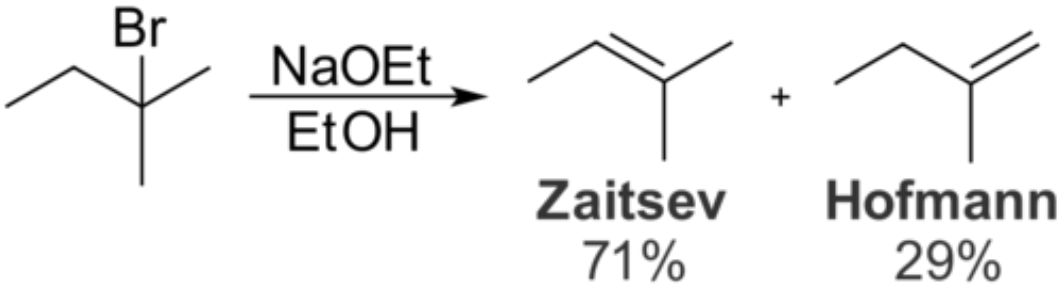
- Carbocation intermediate
- First order kinetics, base concentration is irrelevant

Rate = k [RX]

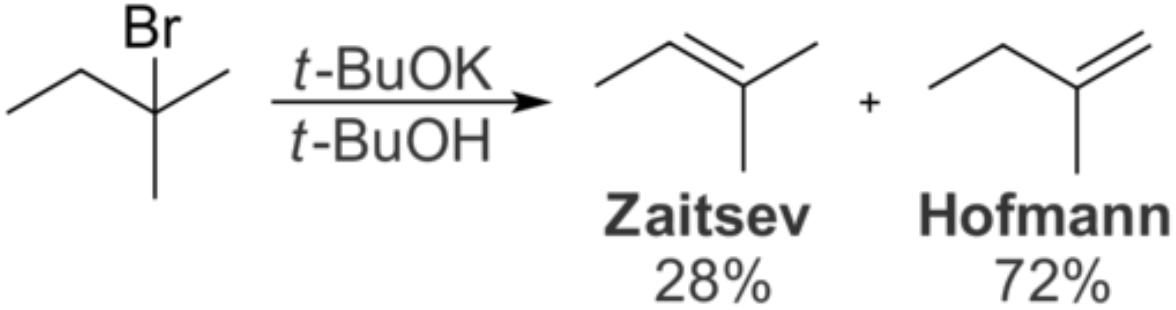


Zaitsev and Hoffman Eliminations

- Small, unhindered bases (NaOH, $NaOCH_3$) favor Zaitsev (more substituted alkene) products



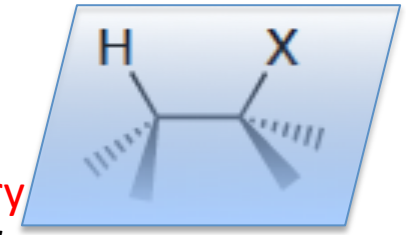
- Bulky bases (sodium *t*-butoxide, trialkylamines) favor Hoffman (less substituted alkene) products

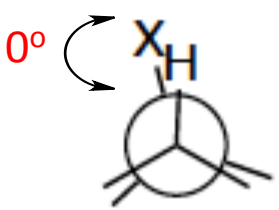


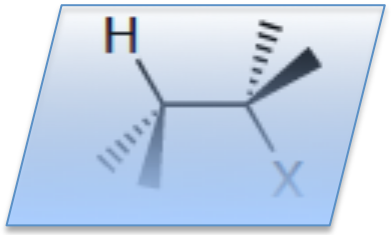
Stereochemistry of E2 Elimination

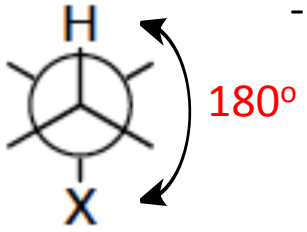
- The Leaving Group (X) and the departing Proton (H) *must be in the same plane*
- ***Anti-periplanar*** geometry is often favored (*anti* conformer is energetically lower than eclipsed (syn-periplanar) conformer)

Syn-periplanar geometry
- H and X are *eclipsed*
- Dihedral angle = 0°





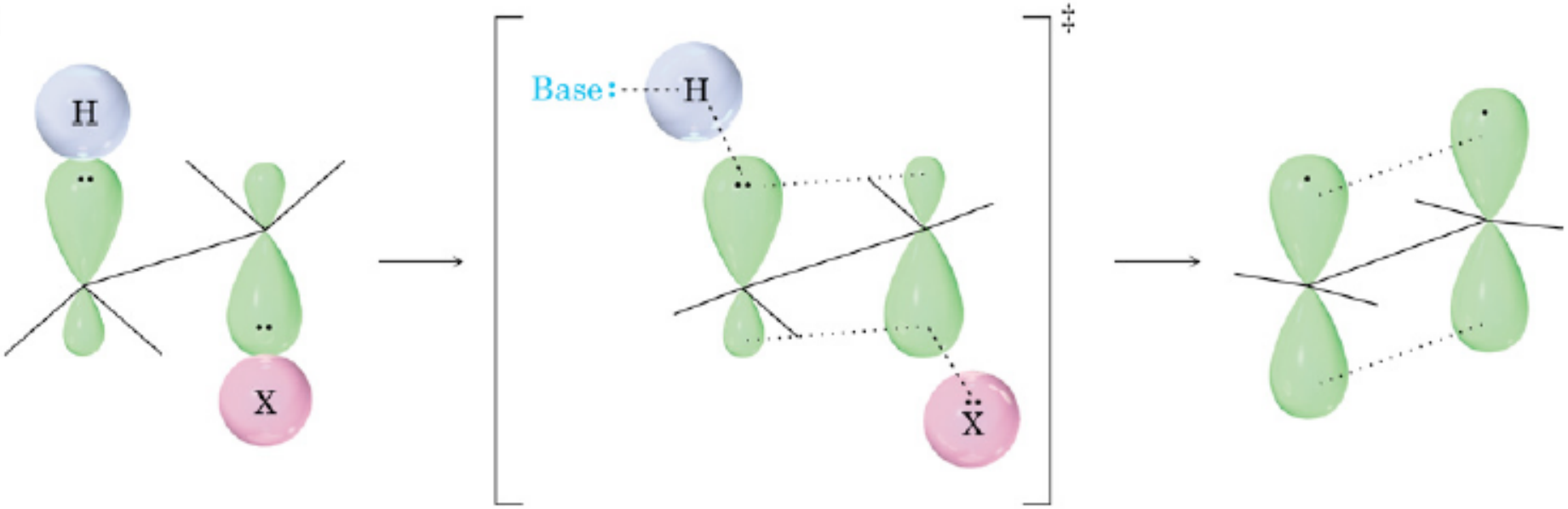




Anti-periplanar geometry
- H and X are *anti*
- Dihedral angle = 180°

Periplanar Geometry Allows sp3 Orbital Alignment

- When orbitals are aligned, π bond forms more readily

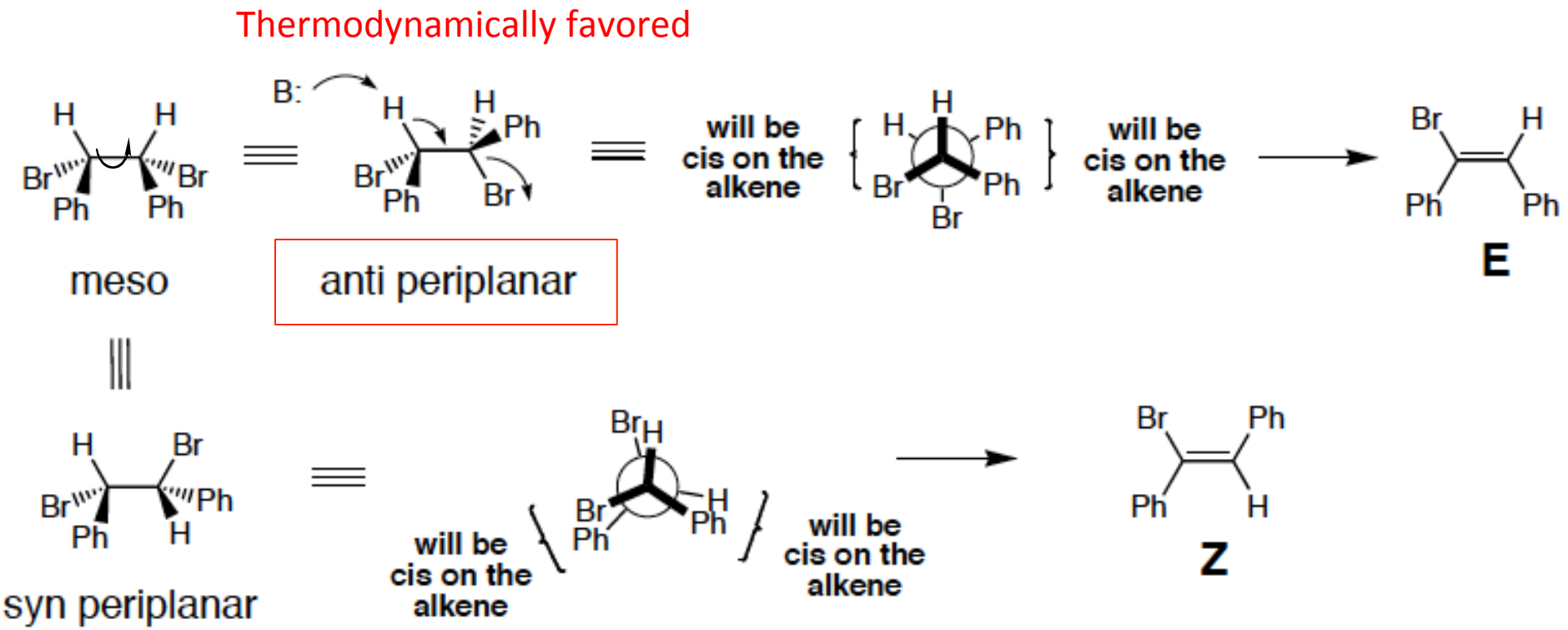


Anti periplanar reactant

Anti transition state

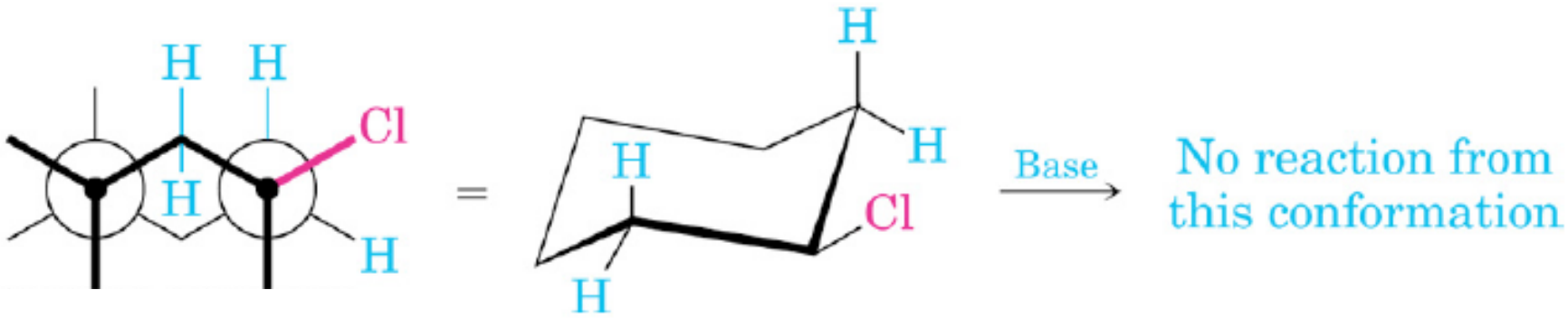
Alkene product

Stereochemical Results of E2 Eliminations

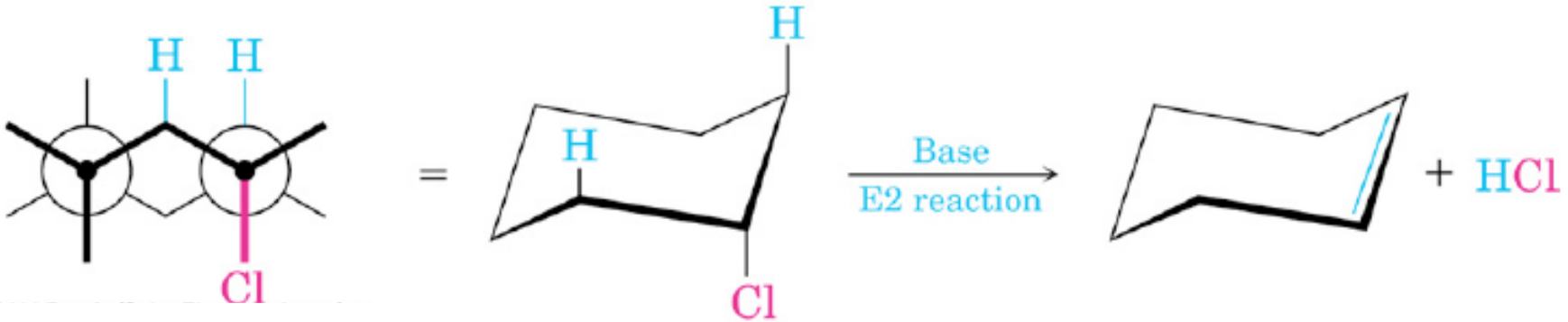


E2 Elimination with Halocyclohexanes

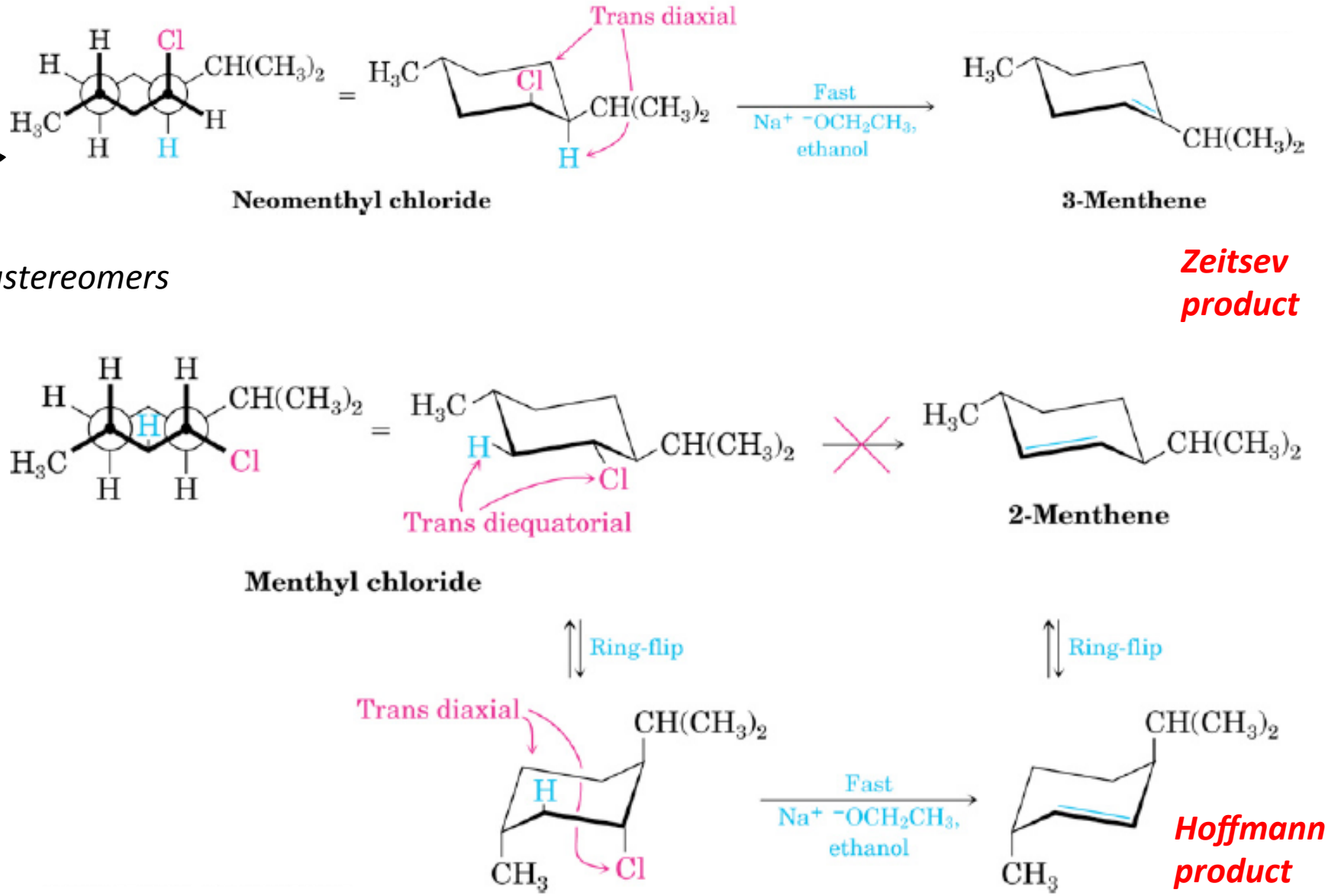
- When Cl is equatorial, H and Cl cannot be periplanar



- When trans diaxial, H and Cl are *anti*-periplanar

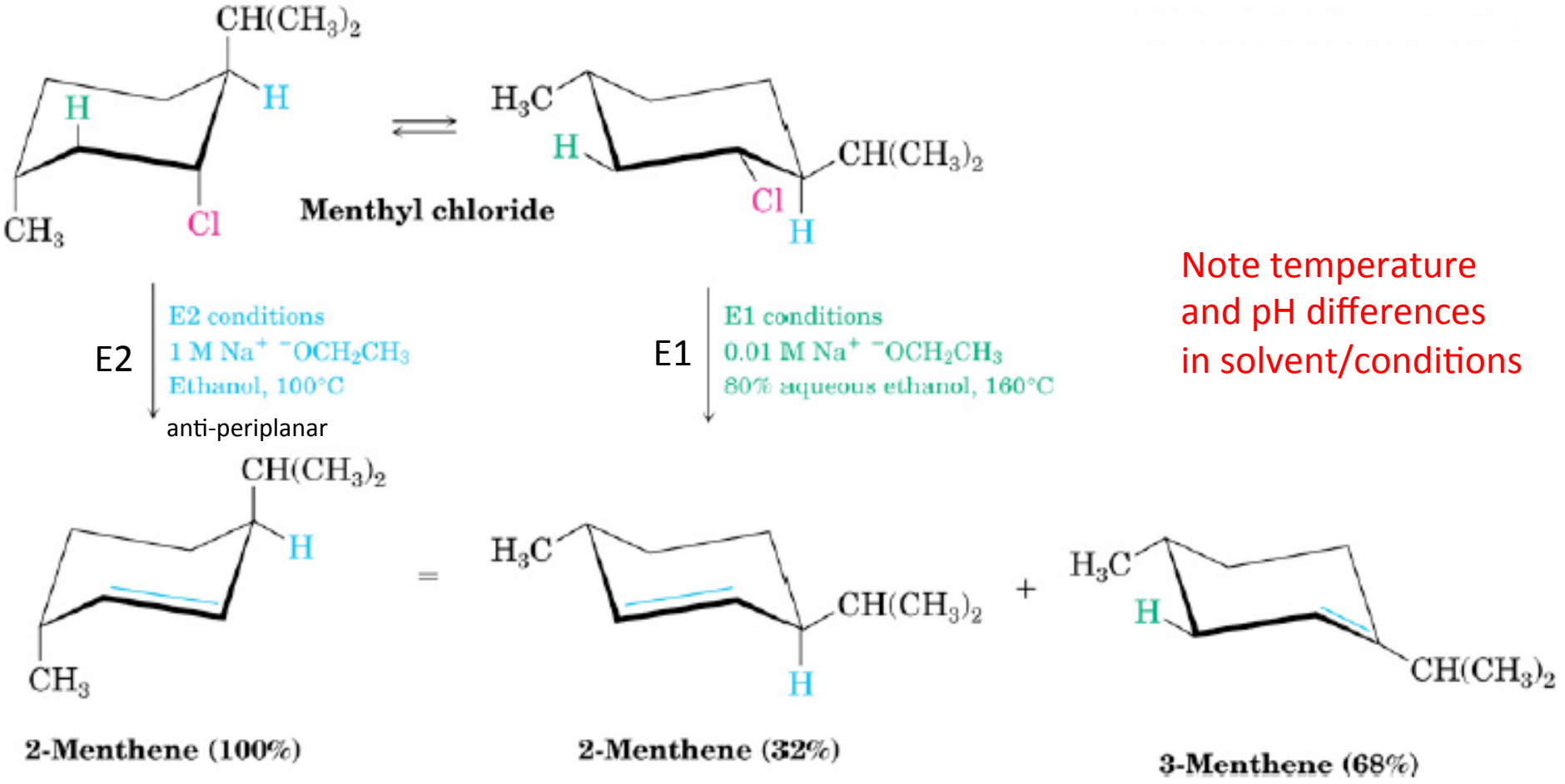


Ring Flip and E2 Regiochemical Outcomes



No Geometric Requirements for E1 Eliminations

- E1 reactions usually follow Zaitsev's Rule



2-Menthene (100%)

2-Menthene (32%)

3-Menthene (68%)

Note temperature and pH differences in solvent/conditions

Eliminations for 3° Alkyl Halides

With 3° Alkyl Halides:

- Elimination vs. Substitution is determined by base strength vs. nucleophilicity

- E2 Elimination occurs with strong bases (OH^-, RO^-, H_2N^-) in strongly basic pH

- E1 Elimination occurs with heating and weak bases (H_2O or ROH) in neutral pH

Summary of E1 vs. E2 Reactions

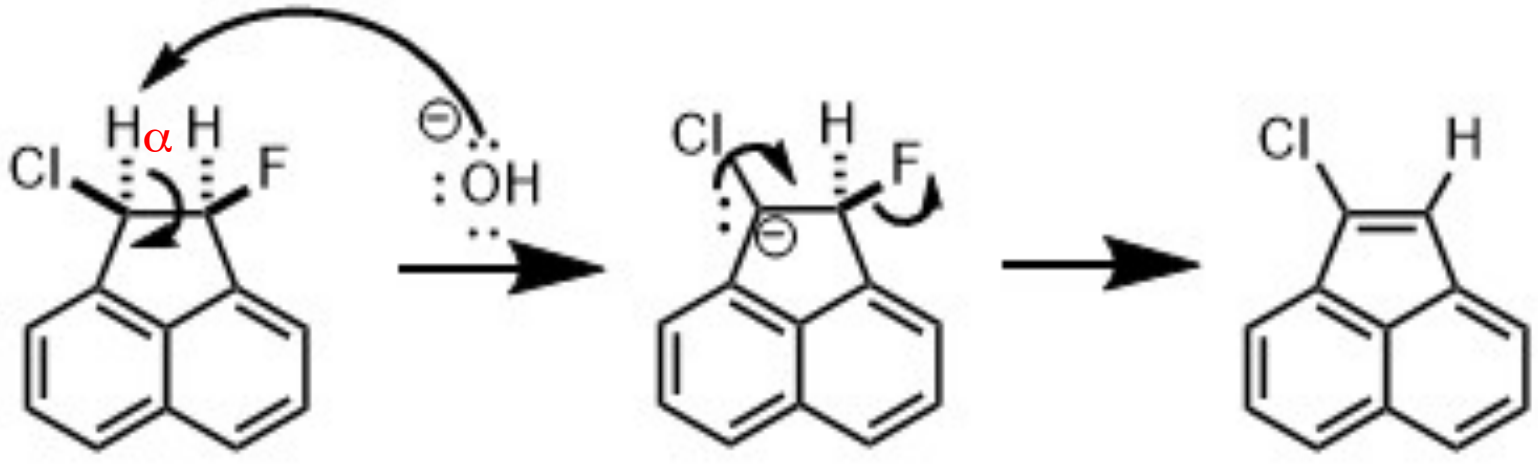
	E1	E2
Rate Law	Unimolecular [carbocation] only	Bimolecular [base] and [carbocation]
Geometry	No requirement	Must be periplanar (anti perferred)
Conditions	Dilute base (0.01M) Aqueous ethanol 160^{o}C	Concentrated base (1M) Pure ethanol 100^{o}C

Good Video Summary of SN2/SN1 + E2/E1:

https://www.khanacademy.org/science/organic-chemistry/substitution-elimination-reactions/sn1-sn2-e1-e2-jay/v/sn1-sn2-e1-e2-reactions-primary-and-tertiary-alkyl-halides

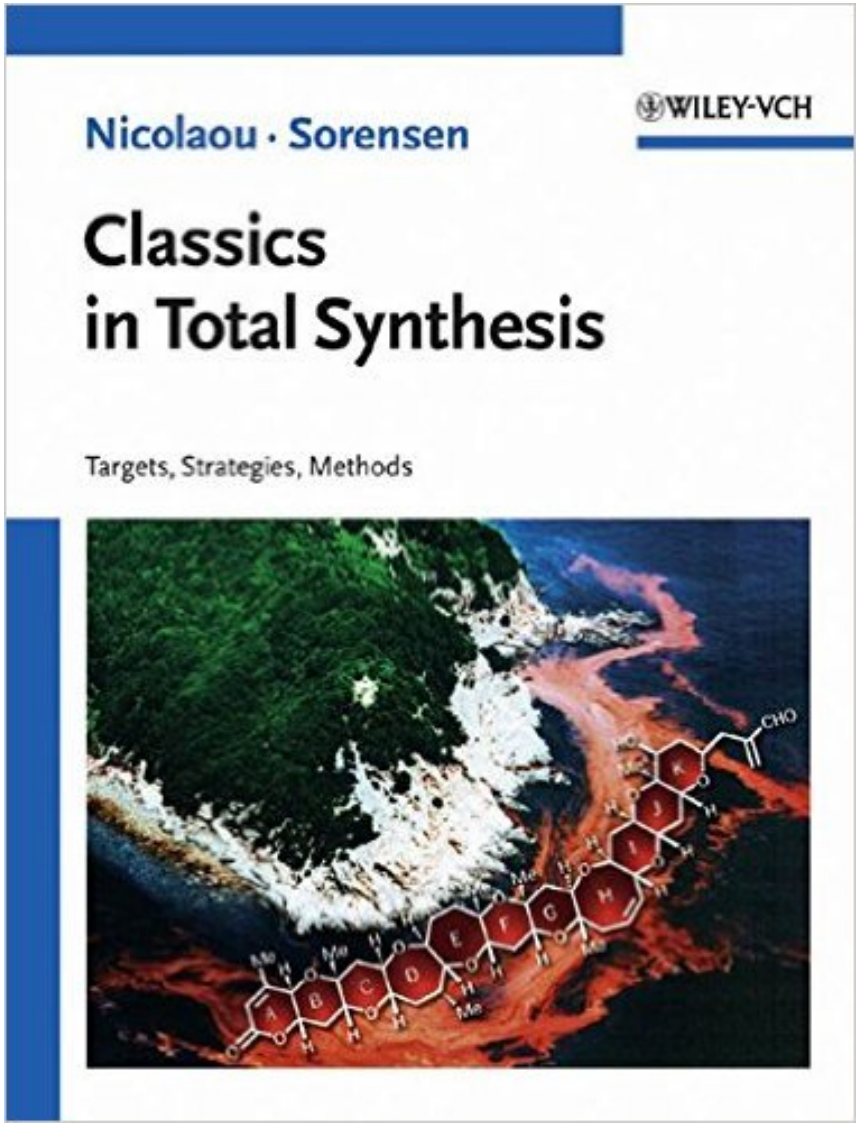
E1 CB

- CB = Conjugate base
- Useful with poor leaving groups (e.g. flourine)
- Stepwise mechanism with carbanion intermediate
- Requires a more acidic alpha proton than E1 or E2



Intro to Organic Synthesis

- Chemical synthesis is a powerful tool (e.g. to prepare compounds for scientific study or commercial sales
- Can be considered an art-form
- Multistep synthesis of a complex (natural product) molecules can take years but the same tricks apply to most reactions and can be learned and refined over a career - e.g. purification, temperature control, solvent selection, limiting reagent selection, protecting groups, retrosynthetic analysis



12 Principals of Green Chemistry

- Prevent Waste (costly to your wallet and the environment to dispose chemical waste)
- Atom Economy (choose syntheses with fewest side products)
- Less Hazardous Synthesis (medical bills and insurance costs reduced)
- Design Benign Chemicals (biodegradation is best)
- Benign Solvents and Auxiliaries (non-toxic, non-volatile, aqueous, ionic liquids)
- Design for Efficient Energy (short, room temperature reactions, microwaves)
- Use of Renewable Feedstocks (cellulose, lignin, chitin, bio-gas, amino acids, etc.)
- Reduce Derivatives (fewer protection/deprotection means better atom economy)
- Catalysis vs. Stoichiometric (atom economy improved and recycling a possibility)
- Design for Degradation (consider all chemicals from cradle to grave)
- Real-Time Analysis for Pollution Prevention (in-situ sensors and monitoring systems)
- Inherently Benign Chemistry for Accident Prevention (no explosions!)

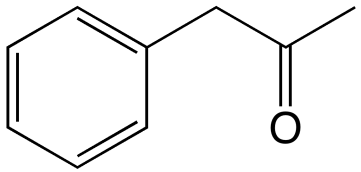
Paul Anastas and John Warner. Green Chemistry: Theory and Practice. Oxford University Press, New York 1998
http://www.acs.org/content/acs/en/greenchemistry/what-is-green-chemistry/principles/12-principles-of-green-chemistry.html

Retrosynthetic Analysis

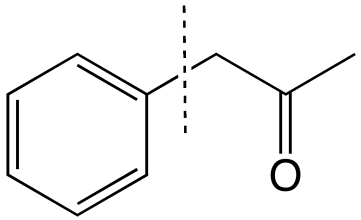
- Devising a plan to prepare a molecule from simple, available, inexpensive starting materials
- Industrially critical for scale-up (cost = number of steps, scale, toxicity of solvent/reagents, waste management, etc.)
- Intellectually challenging (academic, requires mastery of chemistry both in knowledge and practice)
- Total synthesis is often performed on complex natural products

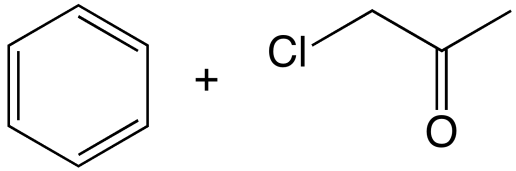
“Retrosynthesis” Terms

- ***Target Molecule*** – The compound we wish to prepare
- ***Disconnection*** – an operation performed “on paper” which imagines the cleavage/ formation of a bond
- ***Synthon*** – The ideal fragments evolved from a disconnection (usually nucleophiles and electrophiles or cations or anions)



phenylacetone





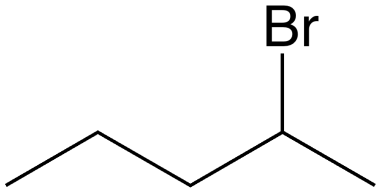
Retrosynthesis Tips

- WORK BACKWARDS, ONE STEP AT A TIME!
- Do not focus solely on the starting material (but keep it in mind so you can work backwards to it)
- Identify functional groups in the product
- Think how can these functional groups be prepared (what reactions do I know)
- First reactions that are simple and high yielding make best syntheses
- Last reactions can be lower yield and more complex

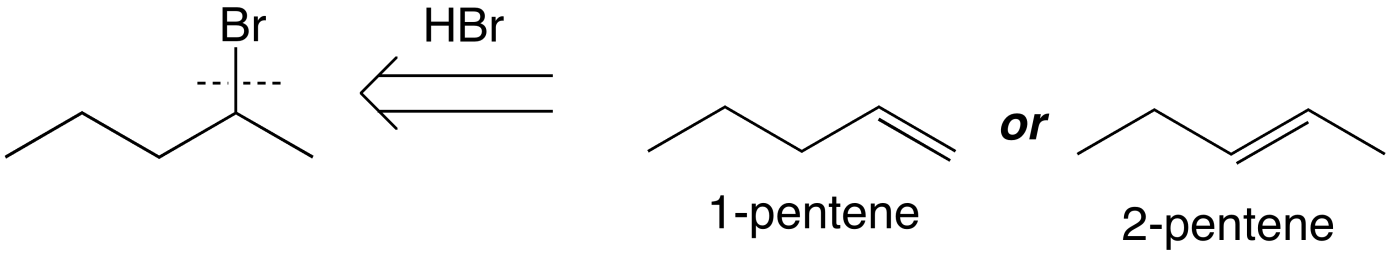
Retrosynthesis of 2-bromopentane

- What is ***key functional group*** in the product?
- What is used to prepare alkyl bromides?
- What are two choices for alkyl bromide preparation? (Markovnikov additions to either 1-pentene or 2-pentene)
- Which has fewest side products?
- What is best starting material?

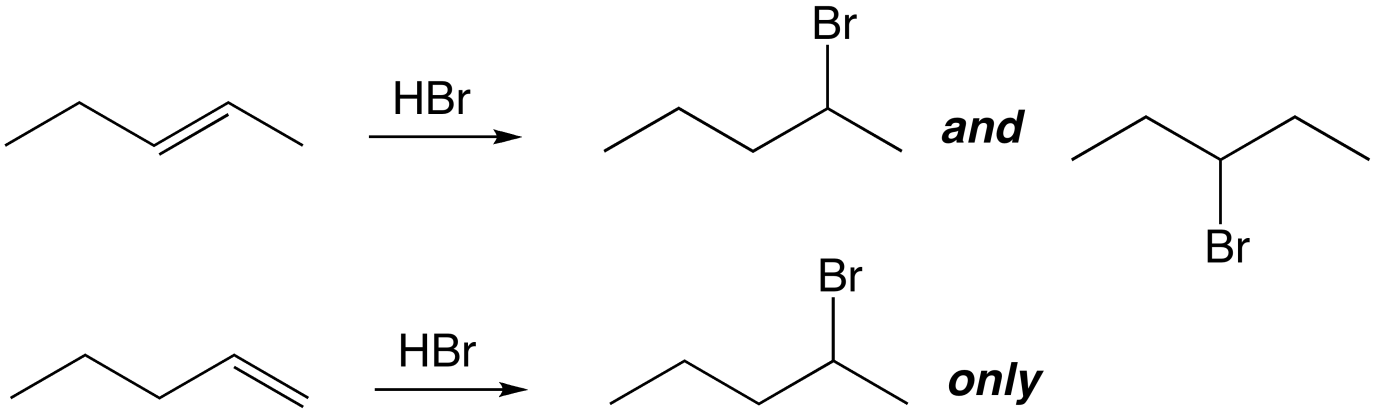
Retrosynthesis Target 1: 2-bromopentane:



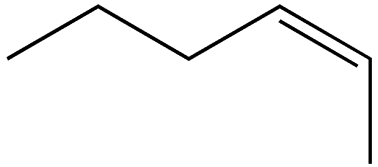
- Alkyl bromides are prepared from alkenes and HBr



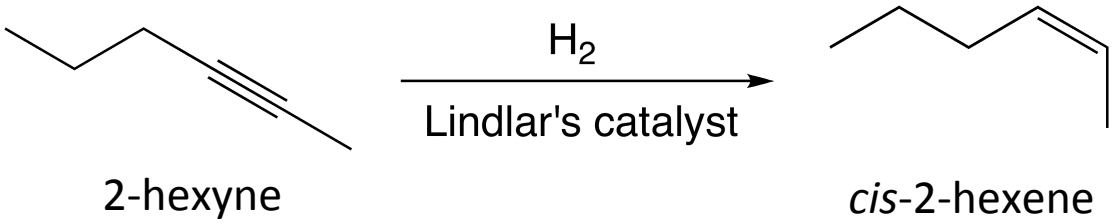
- Which produces fewest side products?



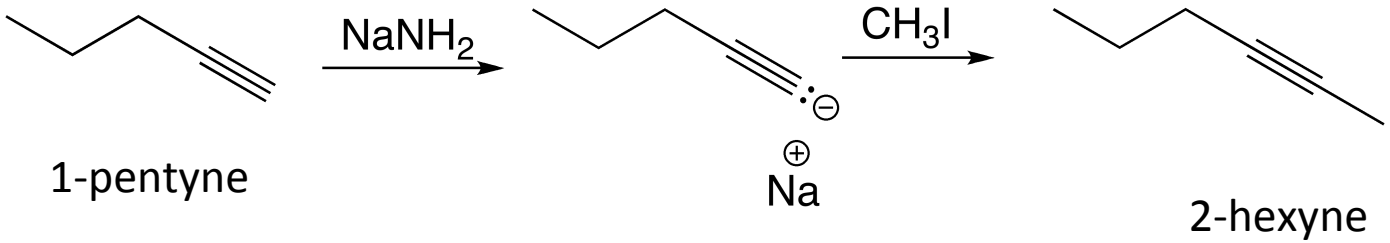
Retrosynthesis Target 2: *cis*-2-hexene



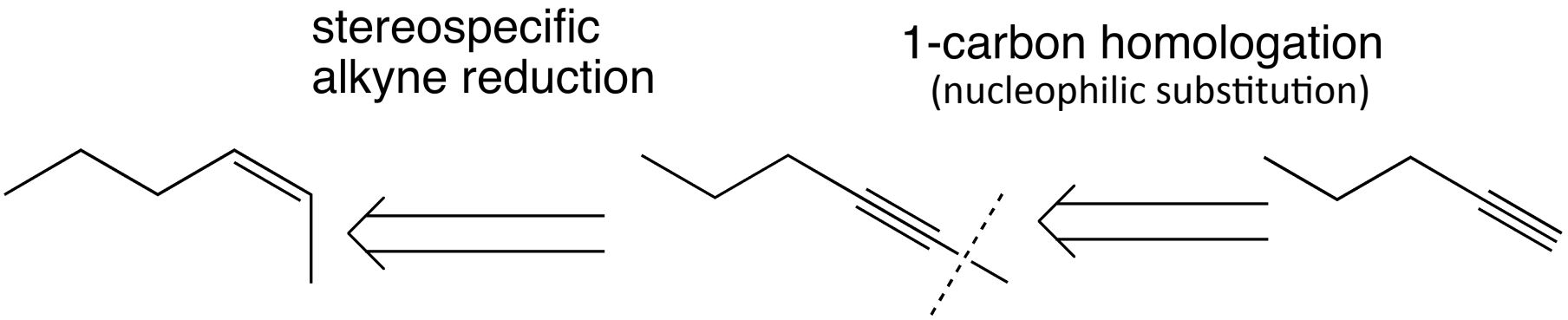
- What reactions have we learned that yield *cis* alkenes?



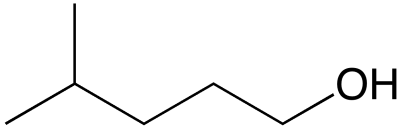
- How could you prepare 2-hexyne?
  - Terminal alkyne + strong base + 1° alkyl halide



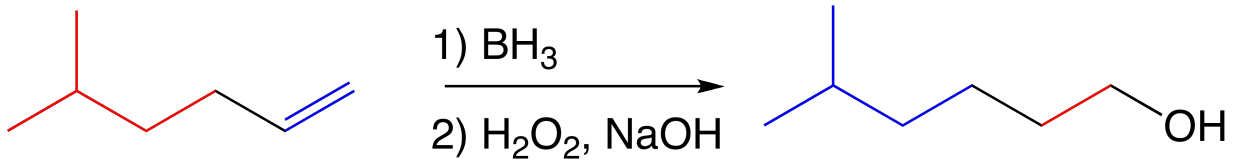
cis-2-hexene overall



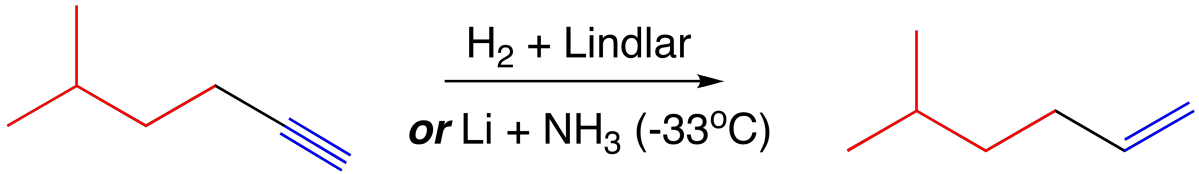
Retrosynthesis Example 3: 5-methyl-1-hexanol



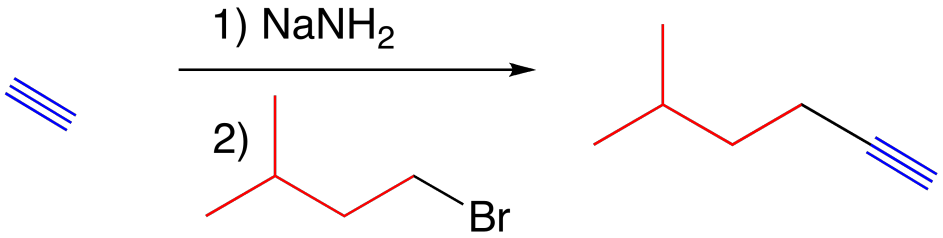
- Immediate precursor of a 1° alcohol is a terminal alkene that can accept non-Markovnikov addition of H_2O.



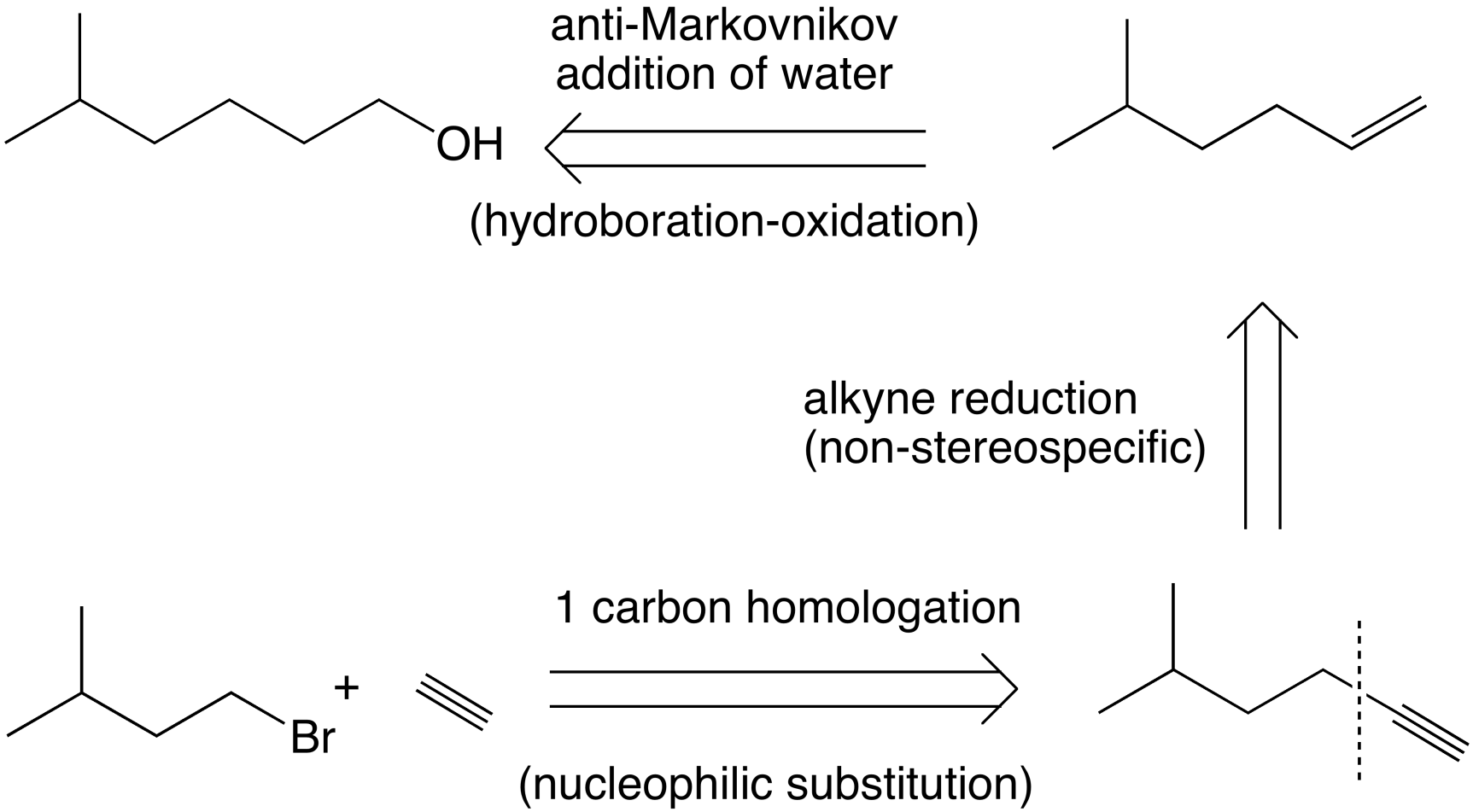
- Terminal alkenes are prepared from reduction of terminal alkynes (stereospecificity not important because alkene will be hydrated)



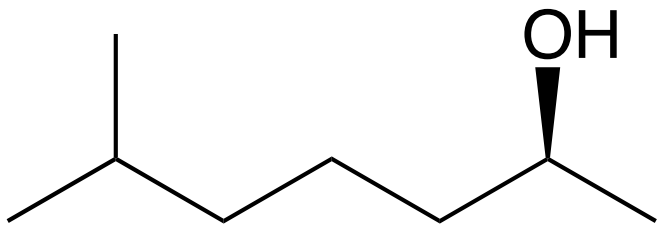
- Immediate precursor of 5-methyl-1-hexyne is acetylene and 1-bromo-3-methylbutane



5-methyl-1-hexanol overall

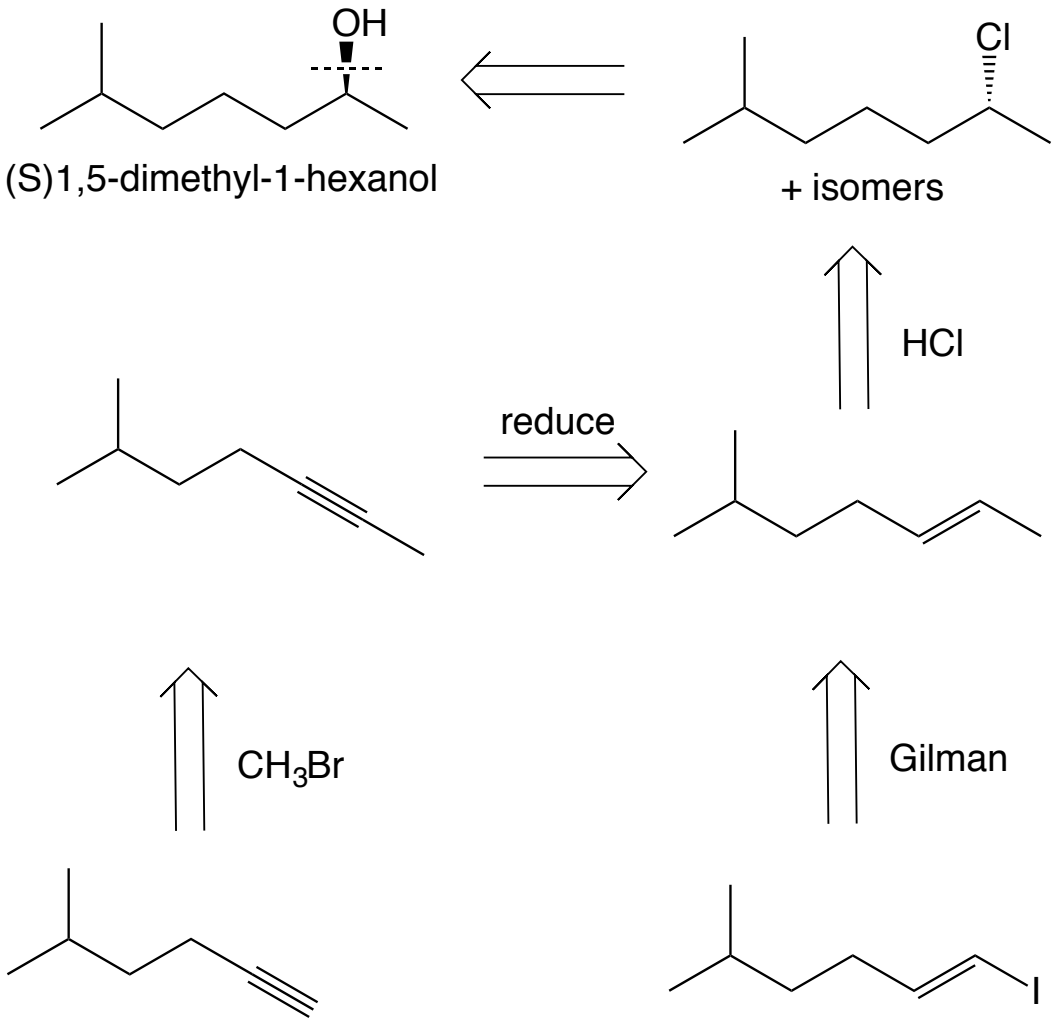


How would you prepare (S) 1,5-dimethyl-1-hexanol?



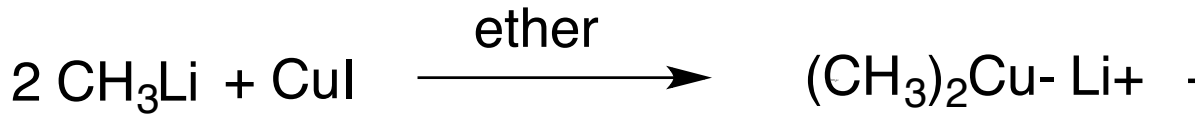
(S)1,5-dimethyl-1-hexanol

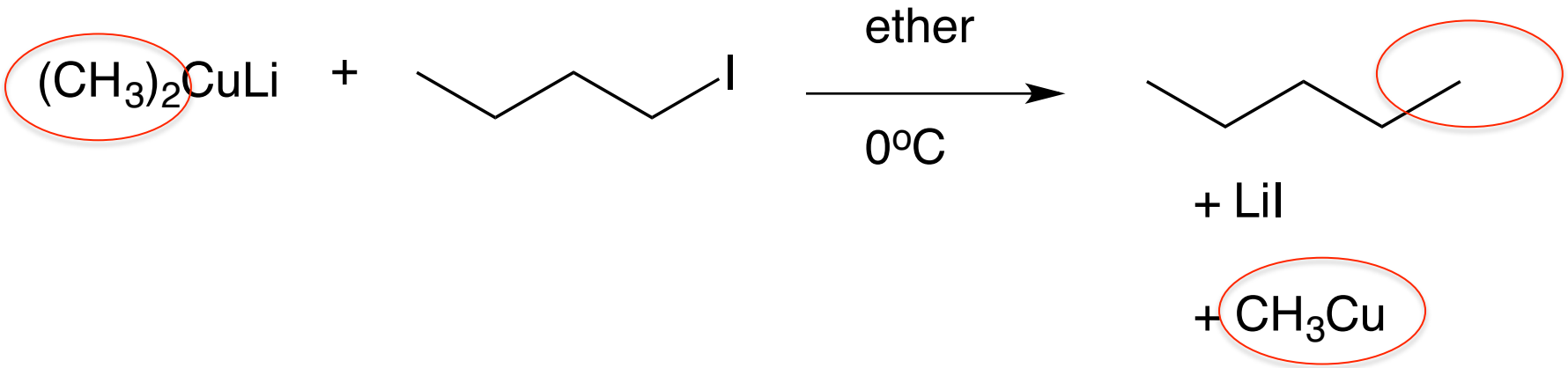
More Reaction Knowledge = More Possible Approaches…



Organometallic Reagents and Reactions for C-C Bond Formation

- "Gilman Chemistry" = Alkyl lithium Reagents
- Alternatives to water sensitive "Grignard" (Mg) Chemistry





Gilman Reagents for Vinyl and Aryl Coupling