# CH4103 Organic and Biological Chemistry
# LCM Lecture 5

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**Autumn Semester**

# Lecture 5 Preparation

**To best prepare yourself for the contents of this lecture, please refresh**

- Atomic and molecular orbitals (Unit 1, Lecture 2)
- Molecular shape and hybridisation (Unit 1, Lecture 2)
- Sigma and pi bonds (Unit 1, Lecture 2)
- Electronegativity and bond polarisation (Unit 1, Lecture 3)
- Stereochemistry (Unit 1, Lecture 4-7)
- Reactive intermediates – carbocations (Unit 1, Lecture 8)
- Acids and bases – p$K_a$ (Unit 1, Lecture 9)
- Reaction thermodynamics (Unit 2, Lecture 1) and kinetics (Unit 2, Lecture 2)
- Curly arrow pushing mechanisms (Unit 2, Lecture 3) and $S_N2$ (Unit 2, Lecture 4)

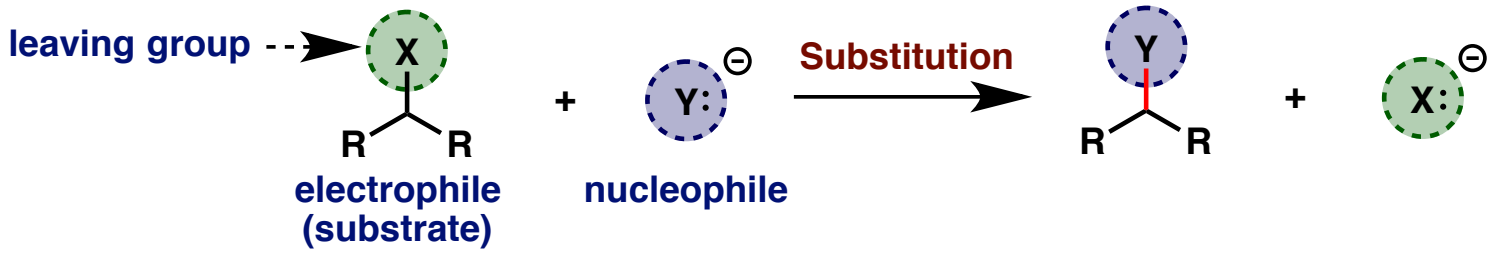
# Lecture 5: Introduction to Substitution Reaction – $S_N1$

**Key learning objectives:**

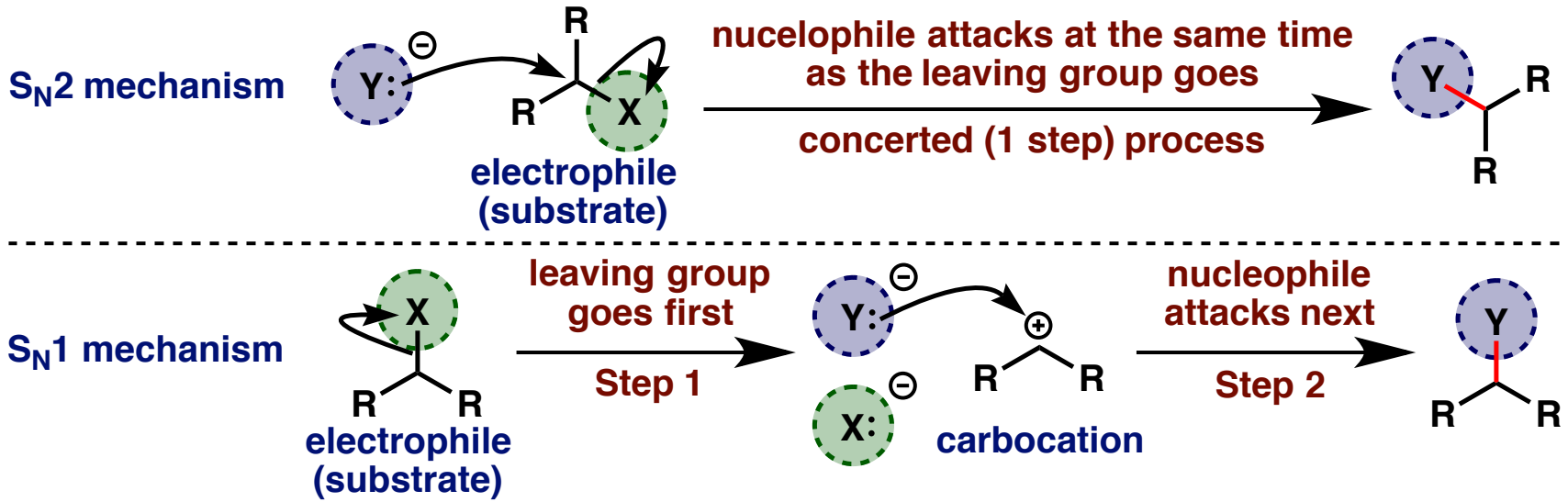
- Know the difference between the possible mechanisms for nucleophilic substitution at saturated carbon – $S_N2$ and $S_N1$
- The rate law for a $S_N1$ reaction
- The free energy diagram for a $S_N1$ reaction
- The curly arrow pushing mechanism, molecular orbital analysis, intermediate and stereochemical outcome of a $S_N1$ reaction
- The factors that favour a $S_N1$ mechanism including the nature of the substrate, nucleophile, solvent and leaving group
- **Synthetic Analysis** – How to favour one substitution mechanism over the other?

# Nucleophilic Substitution at Saturated Carbon

- A substitution reaction exchanges one group for another




- This process can happen in two separate ways:
- 1) Nucleophile attacks at the same time as the leaving group goes – **$S_N2$ mechanism**
- 2) Leaving group goes first, forming a carbocation intermediate that is attacked by a nucleophile in a second step – **$S_N1$ mechanism**

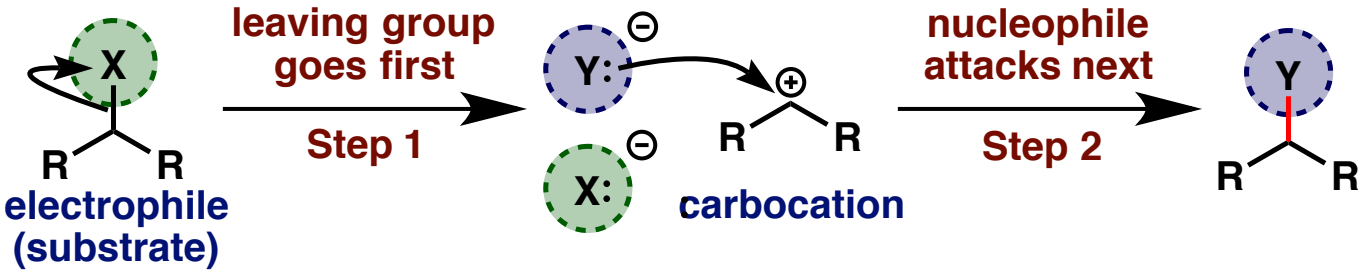


# The $S_N1$ Reaction – Rate Law

- We have already seen that tertiary alkyl halides are unreactive towards $S_N2$ reaction. However, substitution can occur even with fairly poor nucleophiles such as water

- The rate of these processes are dependent only on the electrophile concentration

**Curly Arrow Pushing Mechanism**




**Rate Law**

$$\text{Rate} = \frac{d\,[\text{Products}]}{dt} = k_{obs}[\text{substrate}]^1$$

recap **Reaction Kinetics Unit 2, Lecture 2** recap

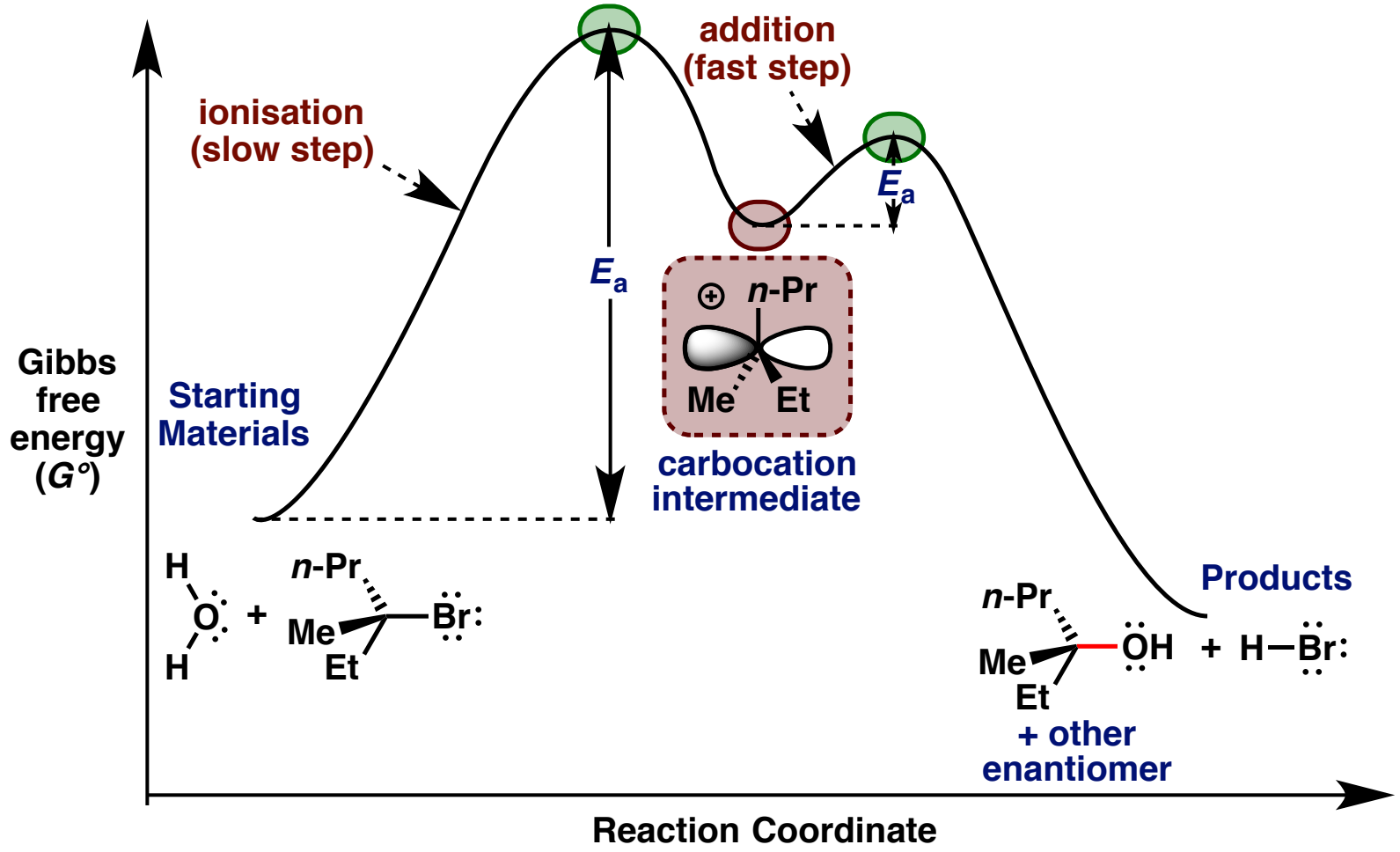
- This dependence implies that only the electrophile is involved in the rate determining step of the reaction, i.e. the step with the highest activation energy, $E_a$.

**Substitution** S N 1 **Nucleophilic**

**Unimolecular - one species involved in rate-determining step**

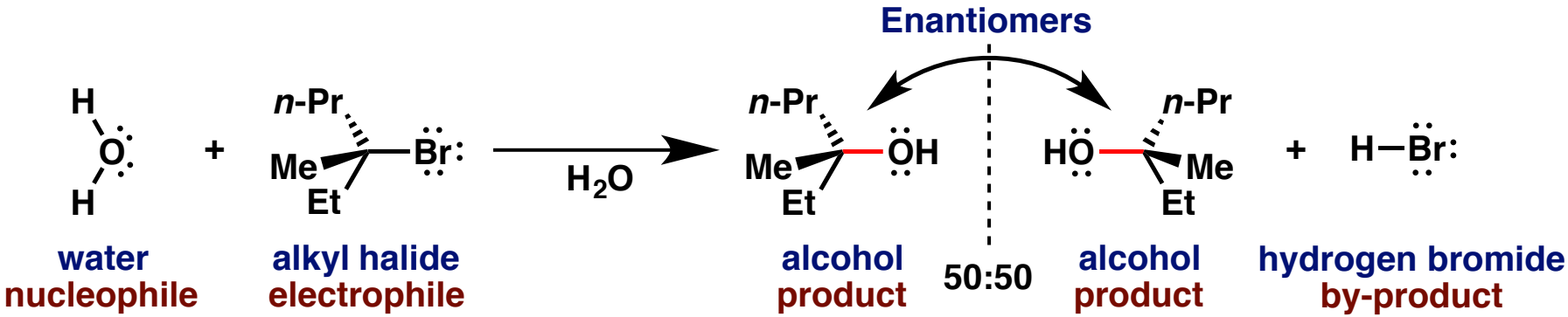
# The $S_N1$ Reaction – Free Energy Diagram

- The $S_N1$ reaction proceeds through a **planar carbocation intermediate**. Ionisation is disfavoured and is associated with the high energy barrier, consistent with rate law

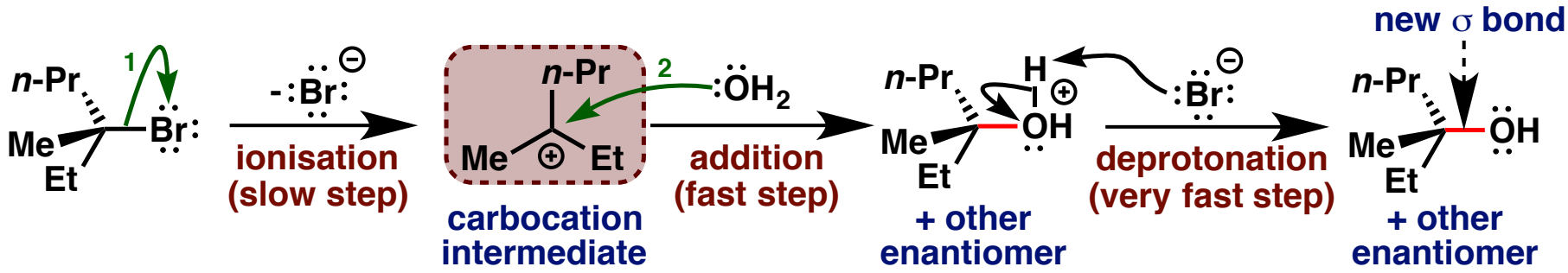


# The $S_N1$ Reaction – Curly Arrow Pushing Mechanism

- Consider the substitution reaction shown below:




- Such processes have a stepwise mechanism involving an intermediate carbocation



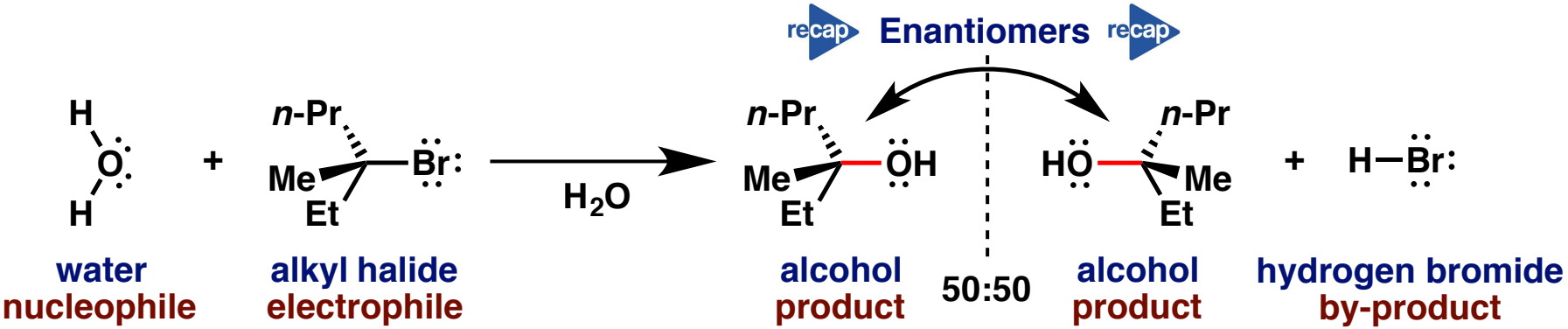

**key orbital interactions**

**Curly arrow 1 - breaking of C-Br σ bond with the two bonding electrons ending up on bromide anion**

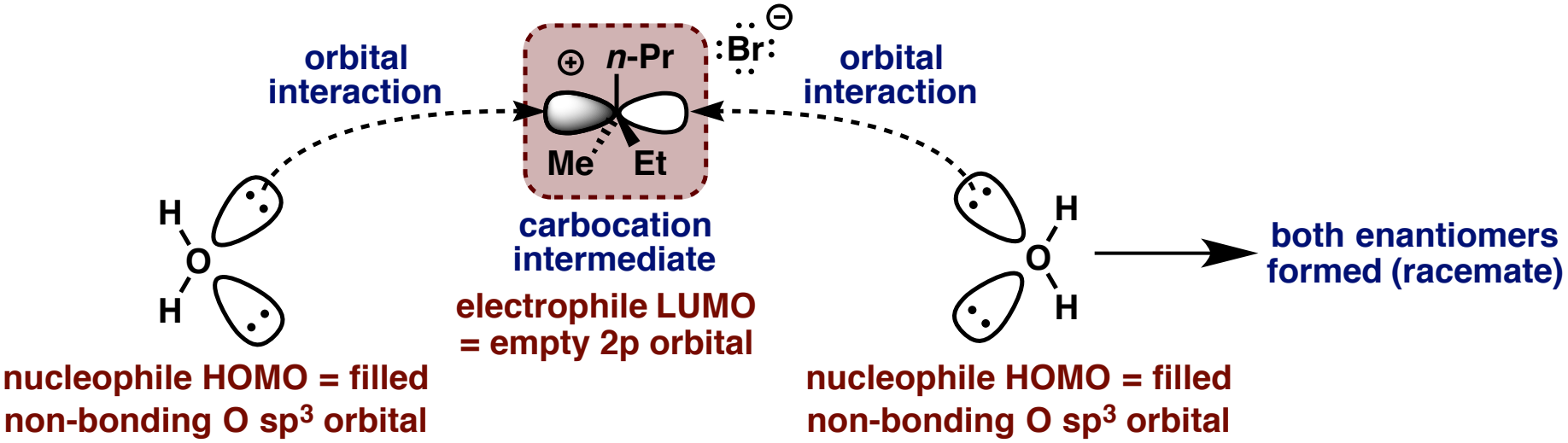
**Curly arrow 2 - filled non-bonding O $sp^3$ orbital to empty C 2p orbital, forming new C-O σ bond**

# The $S_N1$ Reaction – Stereochemistry

- The $S_N1$ reaction proceeds with **racemisation** at the carbon centre

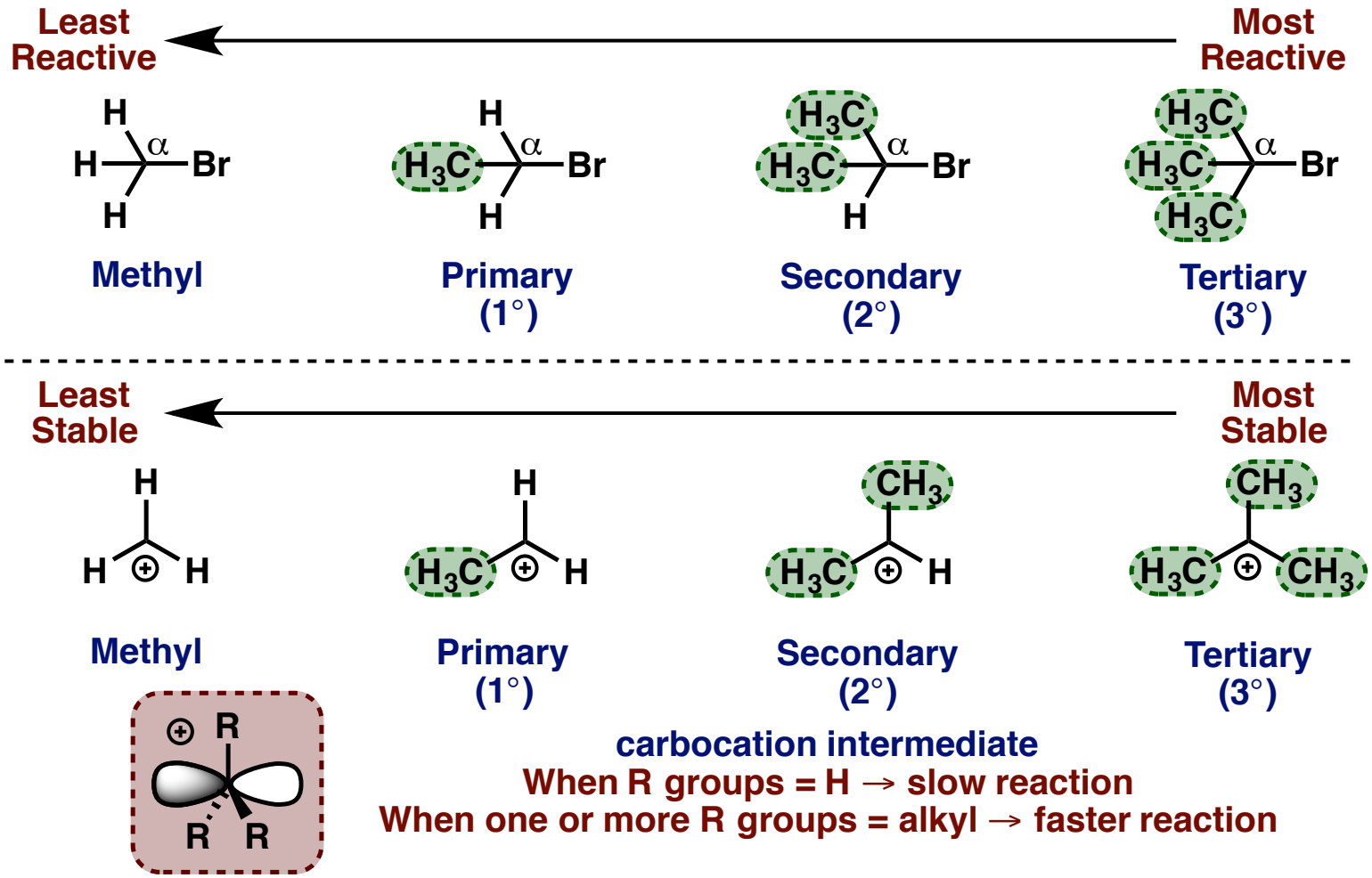



- Since the intermediate carbocation is **planar**, the product will be racemic as the nucleophile can attack the empty 2p orbital from either face.



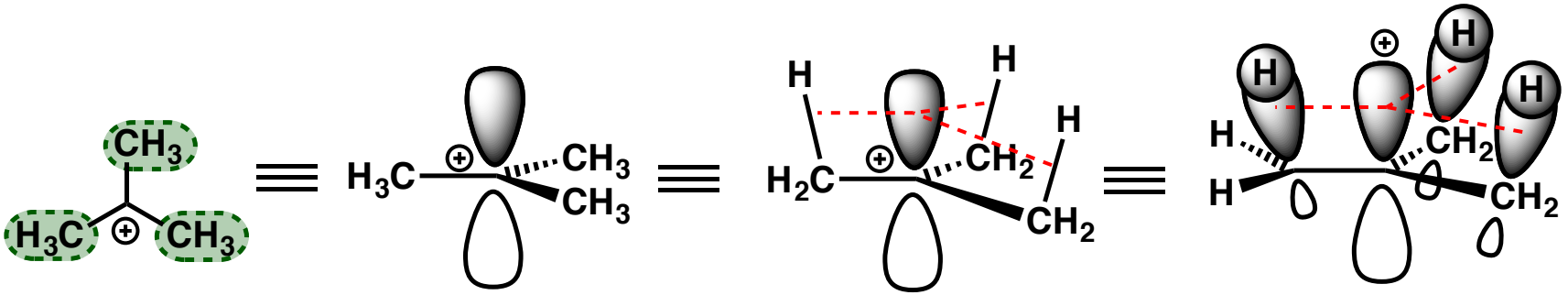
# The $S_N1$ Reaction – Substrate Dependence

- Unimolecular ($S_N1$) substitutions are only observed for substrates that can form a stable carbocation



# The $S_N1$ Reaction – Substrate Dependence

- Tertiary alkyl halides are best for $S_N1$ reactions because alkyl substituents stabilise a carbocation by **hyperconjugation** (inductive effect)




**Tertiary (3°) carbocation** | **empty 2p orbital on carbon** | **stabilisation by donation from filled C-H σ orbitals into empty 2p orbital of planar carbocation**


recap

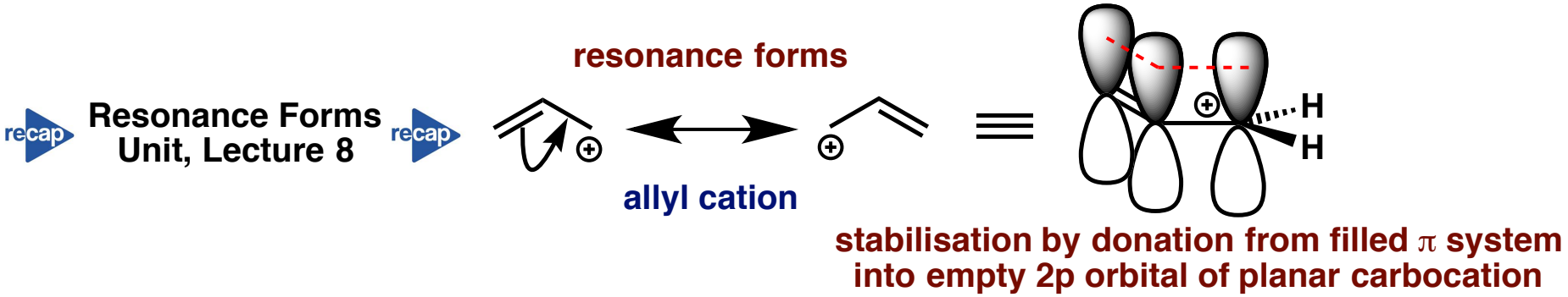
**Reactive Intermediates Unit 1, Lecture 8**

recap

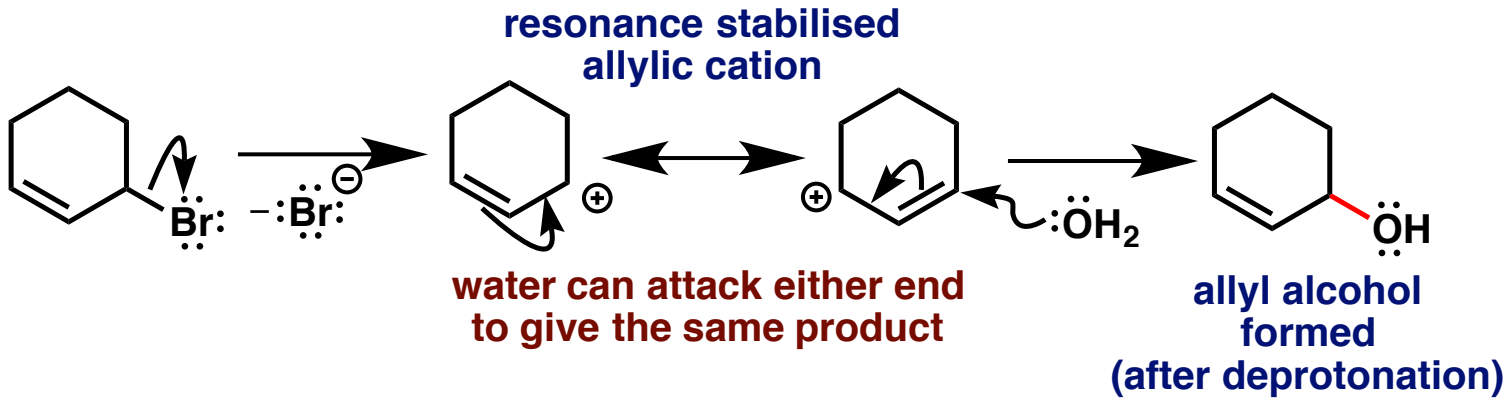
- No stabilisation by hyperconjugation is possible for methyl carbocations. Why?

# The $S_N1$ Reaction – Substrate Dependence

- An adjacent C=C π system also stabilises a carbocation (mesomeric effect)

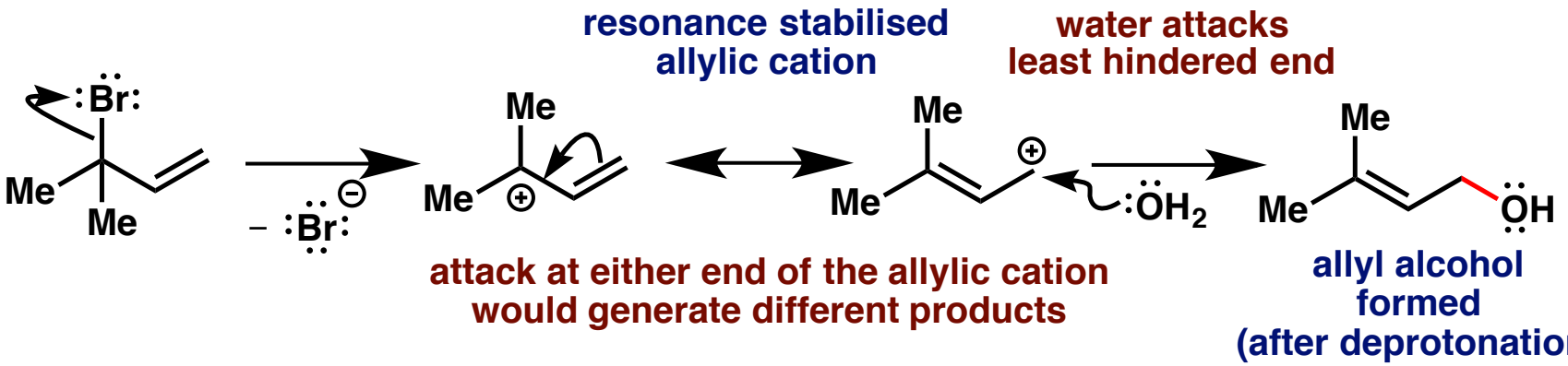



- Allylic electrophiles react well by the $S_N1$ mechanism as the allyl cation is stabilised



# The $S_N1$ Reaction – Substrate Dependence

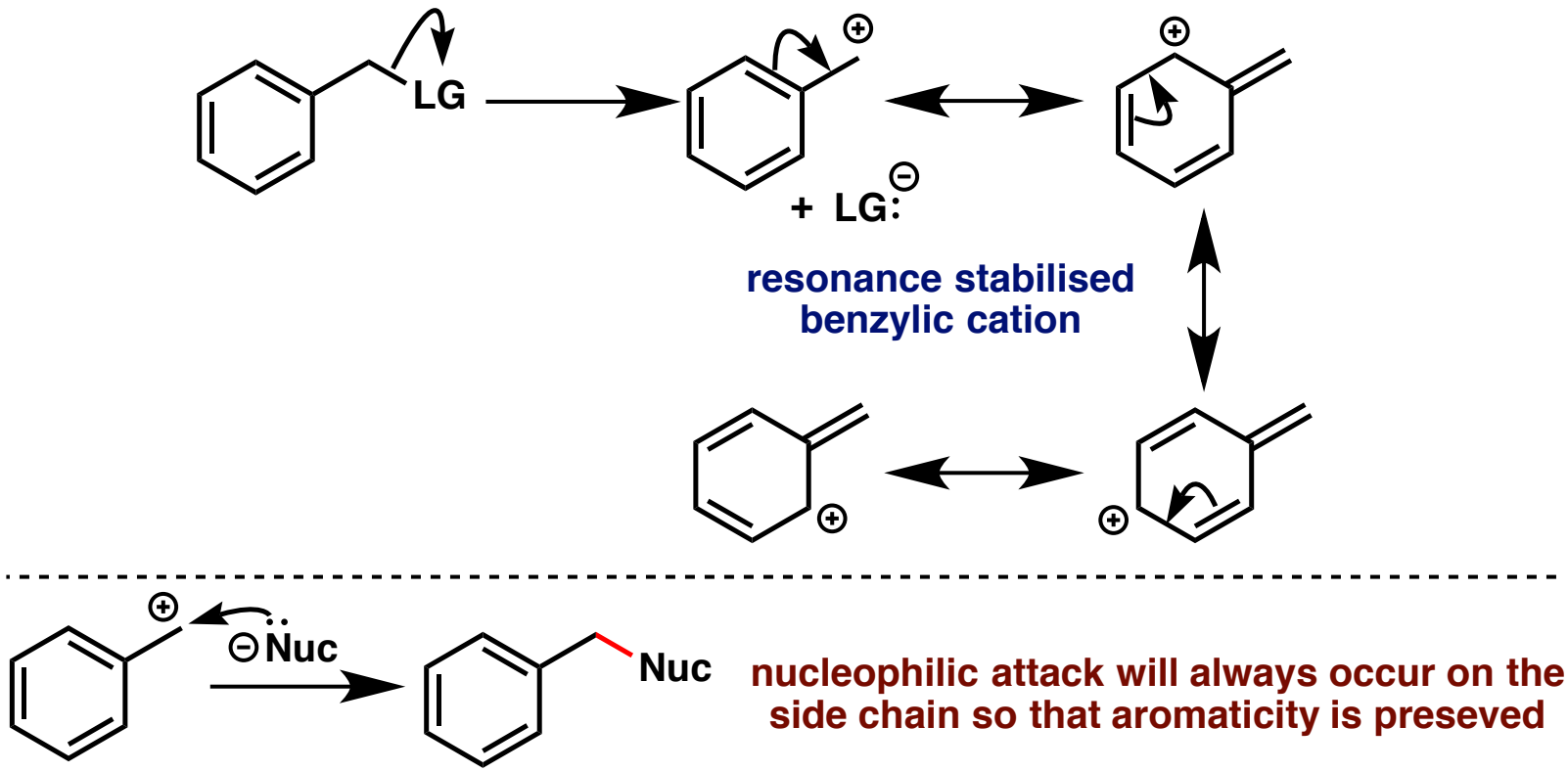
- What about when we generate an unsymmetrical allylic cation?




- In situations where an unsymmetrical allylic cation is generated as a stabilised intermediate, the **regioselectivity** (where the nucleophile attacks) is determined by steric hindrance.
- Nucleophilic attack is faster at the less hindered end of the allylic cation
- What other groups can help stabilise a carbocation intermediate and favour $S_N1$?
- Remember to look out for carbocation rearrangements (cf. Lecture 3)

# The $S_N1$ Reaction – Substrate Dependence

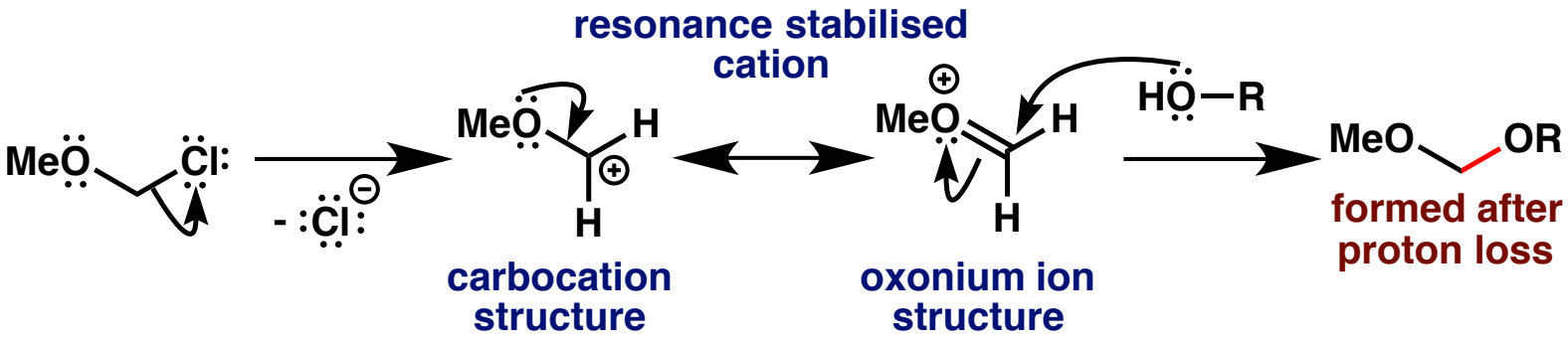
- Benzylic systems also stabilise carbocation intermediates



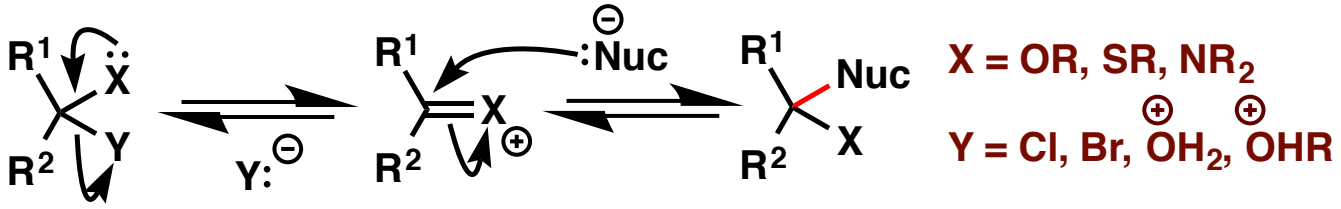

- There is no ambiguity in the site of nucleophilic attack with benzylic systems. Nucleophilic attack will never occur on the ring as this would result in a loss of aromaticity – very disfavoured energetically

# The $S_N1$ Reaction – Substrate Dependence

- Carbocations are also stabilised by an adjacent lone pair of electrons




- You should look out for this type of $S_N1$ reaction whenever there are two atoms such as O, N, S, Cl or Br joined to the same carbon atom. The better leaving groups (Cl and Br) need no acid catalyst but the less good ones (N, O and S) usually do

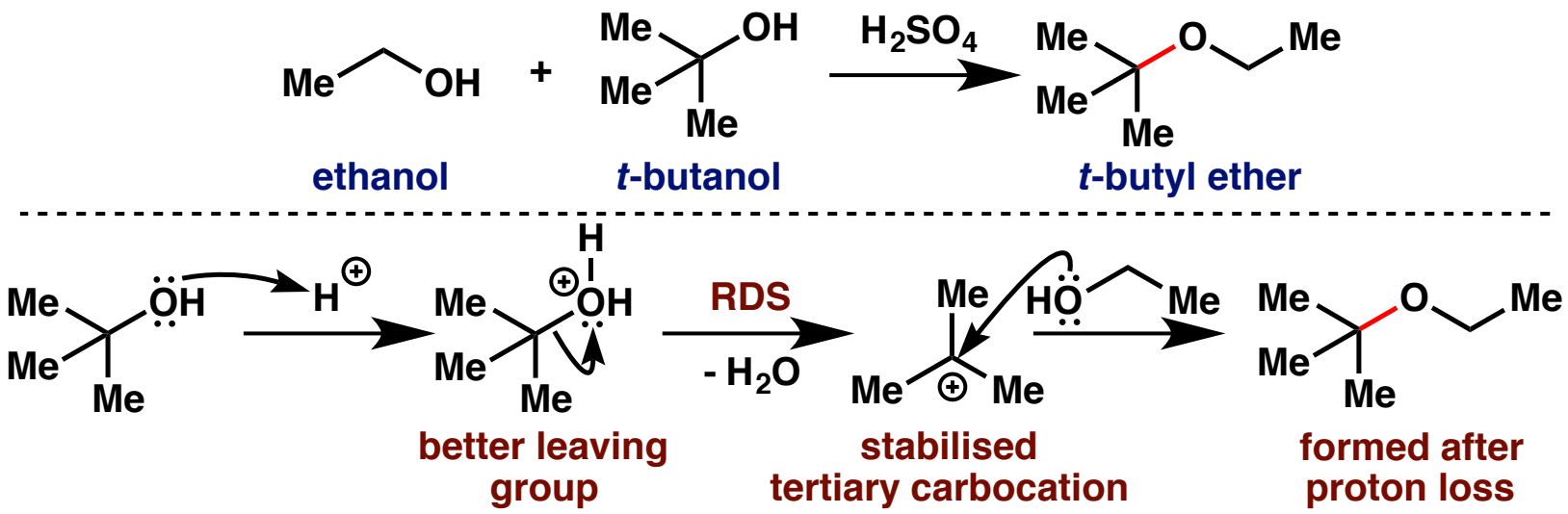


# The $S_N1$ Reaction – Nucleophile

- In an $S_N1$ reaction the **nucleophile** is not important with regard to **rate** – i.e. it is not a component of the rate equation

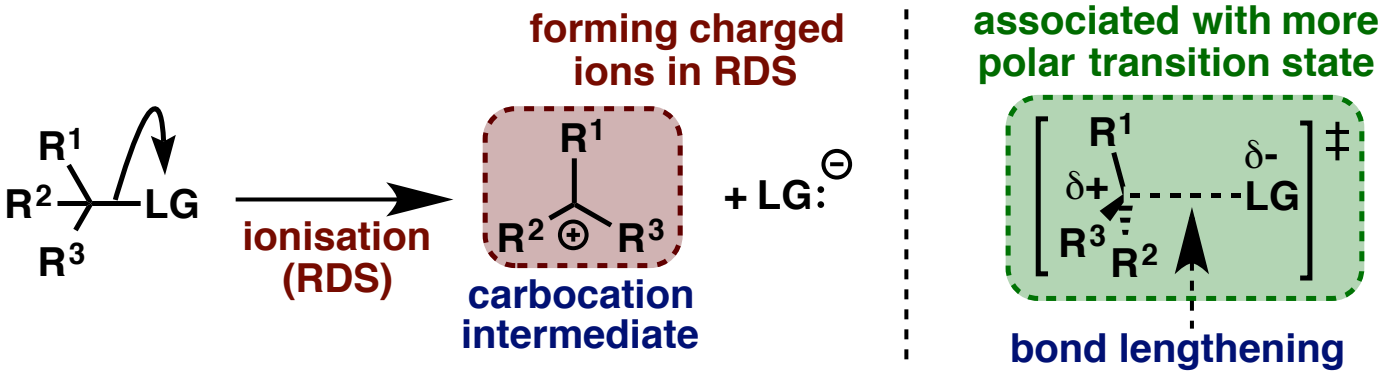
- The rate-determining step of the reaction is loss of the leaving group, so good and bad nucleophiles all give products. We don't need to deprotonate the nucleophile to make it more reactive, e.g. water and hydroxide work equally well

- $S_N1$ reactions on alcohol substrates are carried out under acidic conditions to assist LG departure. For example, consider the formation of a *t*-butyl ether shown below:



# The $S_N1$ Reaction – Solvent

- $S_N1$ reactions are typically carried out in polar protic solvents
- The rate-determining step of a $S_N1$ reaction involves the formation of ions (usually a negatively charged leaving group and a positively charged carbocation) with the associated transition state being more polar than the starting materials
- The rate of $S_N1$ reactions will be increased by polar protic solvents that can solvate these ions and hence stabilise (reduce the energy) of the transition state




- Examples of polar protic solvents that are good for $S_N1$ reactions include methanol, water, acetic acid, sulfuric acid and hydrochloric acid

# The $S_N1$ Reaction – Leaving Group

- The same trends for leaving groups apply to both $S_N1$ and $S_N2$ reactions

Stonger acids
Most stable conjugate base
(low p$K_a$)



Weaker acids
Least stable conjugate base
(high p$K_a$)

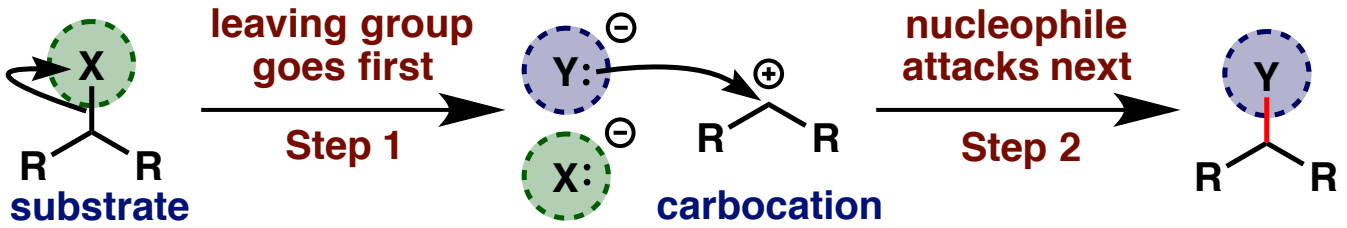
| Acid | p$K_a$ | Conjugate Base / Leaving Group | Name | |
|---|---|---|---|---|
| HI | -10 | $I^-$ | Iodide | Good Leaving Groups |
| HBr | -9 | $Br^-$ | Bromide | |
| HCl | -8 | $Cl^-$ | Chloride | |
| $HOSO_2R$ | -3 | $^-OSO_2R$ | Sulfonate | |
| $H_3O^+$ | -1.7 | $H_2O$ | Water | |
| HF | +3.2 | $F^-$ | Fluoride | Bad Leaving Groups |
| $H_2S$ | +7.0 | $HS^-$ | Thiolate | |
| HCN | +9.4 | $^-CN$ | Cyanide | |
| $H_2O$ | +15.7 | $^-OH$ | Hydroxide | |
| $HOCH_2CH_3$ | +15.9 | $^-OCH_2CH_3$ | Ethoxide | |
| HOR | +16 to +18 | $^-OR$ | Alkoxide | |

recap Reminder: Acids and bases Unit 1, Lecture 9 recap

# The $S_N1$ Reaction – Cheat Sheet

- For the $S_N1$ reaction, you must remember the following key information

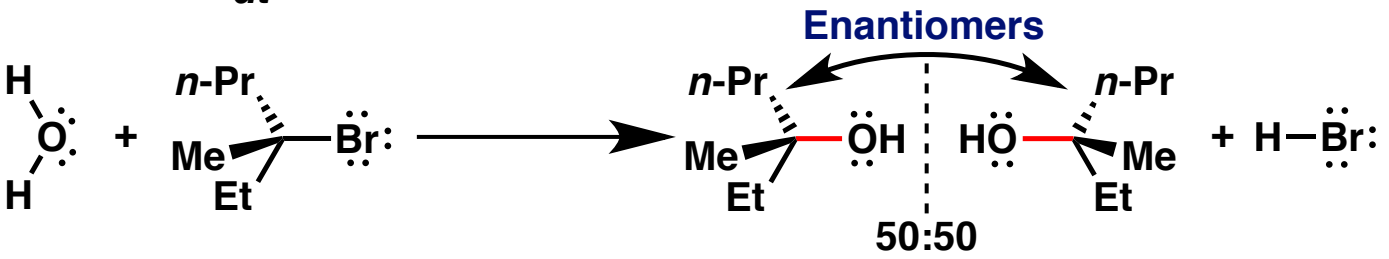
- Mechanism:




- Rate Law:

$$\text{Rate} = \frac{d\,[\text{Products}]}{dt} = k_{obs}[\text{substrate}]^1$$

- Racemisation:




- Factors that favour an $S_N1$ mechanism:

**Substrate**
tertiary, allylic, benzylic, heteroatom-stabilised - all good substrates
secondary - moderate
primary, methyl - bad

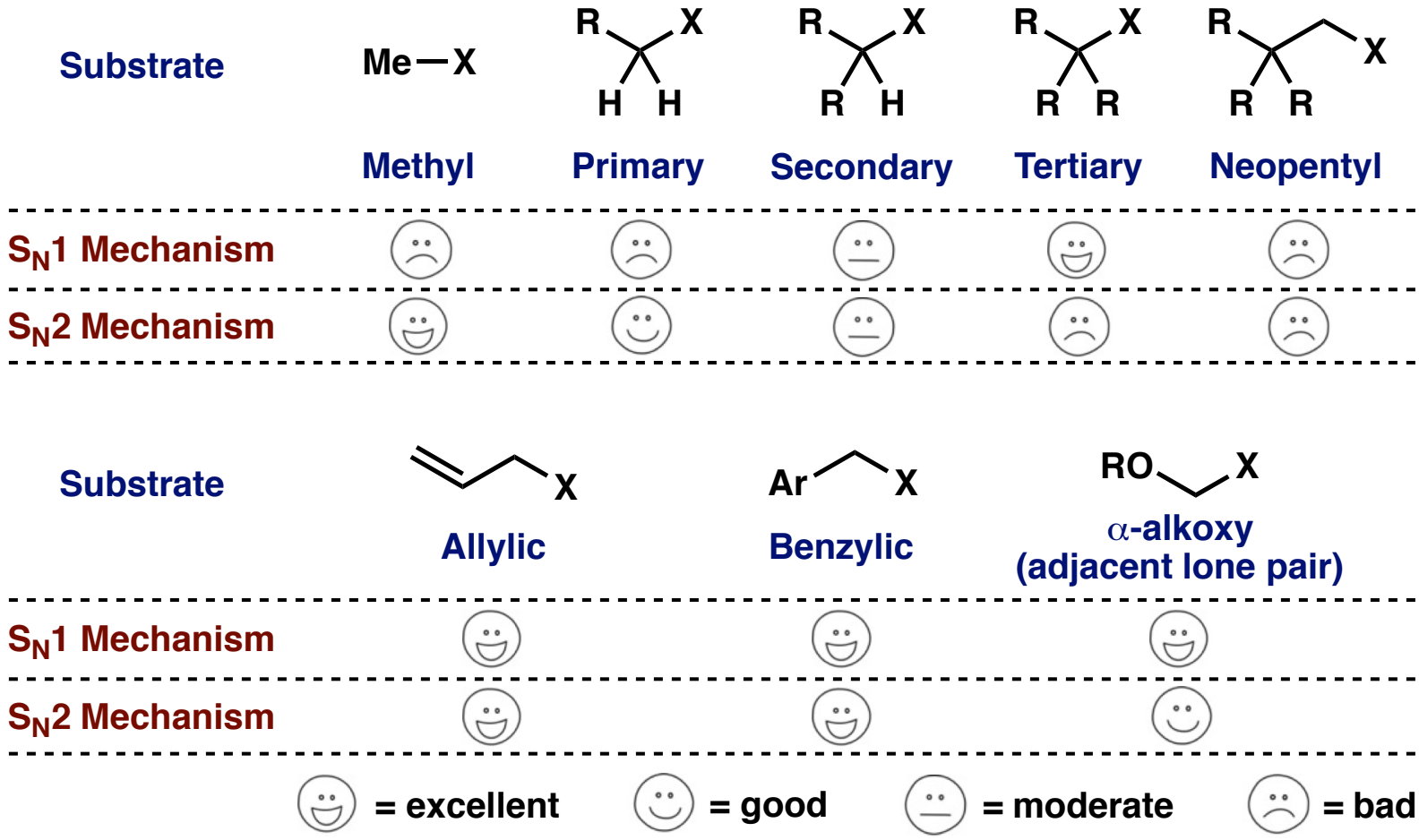
**Nucleophile**
no necessity for strong nucleophiles, neutral nucleophiles are ok too
e.g. MeOH, $H_2O$, AcOH

**Solvent**
polar protic
e.g. $H_2O$, MeOH, AcOH, $H_2SO_4$

**Leaving Group**
highly stabilised / conjugate acid
has a low p$K_a$ value
e.g. $I^-$, $Br^-$, $^-OSO_2R$

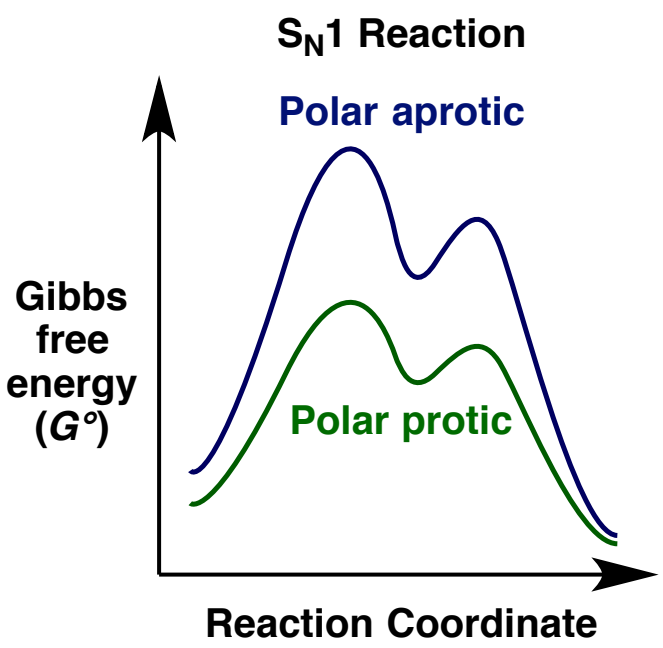
# $S_N1$ vs $S_N2$ – Substrate Dependence

- We are now in a position to draw comparisons between $S_N1$ and $S_N2$ reactions. $S_N2$ best substrate = methyl or primary halides (lowest steric congestion of TS). $S_N1$ best substrate = tertiary halides (best stabilisation of carbocation intermediate)

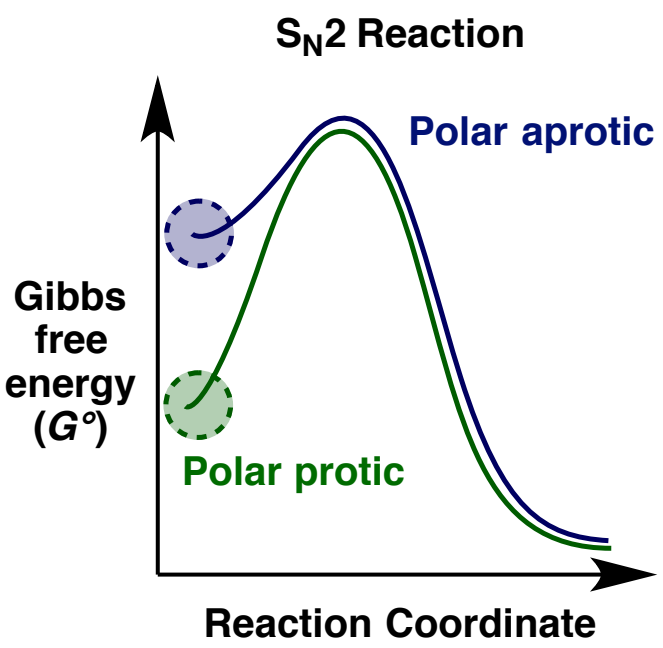


# $S_N1$ vs $S_N2$ – Solvent

- The solvent plays a key role in favouring either $S_N1$ and $S_N2$ mechanisms
- Polar protic solvents favour $S_N1$ by stabilising (lowering the energy of) polar intermediates and transition states. Polar aprotic solvents favour $S_N2$ by raising the energy of the nucleophile, giving a smaller activation energy, $E_a$




**Polar protic solvents favour $S_N1$ by stabilising polar intermediates and transition states**




**Polar aprotic solvents favour $S_N2$ by raising the energy of the nucleophile, giving a smaller $E_a$**

# $S_N1$ vs $S_N2$ – Other Factors and Overall Summary

**Nucleophile**

- $S_N2$ tends to require strong nucleophiles – generally means **negatively charged** nucleophiles such as $NC^-$, $RS^-$, $N_3^-$, $I^-$ and others
- $S_N1$ can also proceed with weak nucleophiles including **neutral** nucleophiles such as MeOH, $H_2O$, AcOH and others

**Leaving Group**

- This is not the most important factor as both $S_N2$ and $S_N1$ mechanisms are favoured by the presence of a good leaving group such as $I^-$, $Br^-$, $^-OSO_2R$ and others

- In summary, $S_N1$ and $S_N2$ reactivity are almost mirror images of each other and can be readily distinguished from each other, as shown below:

| Factor | Favours $S_N2$ Mechanism | Favours $S_N1$ Mechanism |
|---|---|---|
| Substrate | Methyl or primary | Tertiary |
| Nucleophile | Strong nucleophile | Any nucleophile |
| Leaving group | Good leaving group | |
| Solvent | Polar aprotic | Polar protic |

# Lecture 5: Introduction to Substitution Reaction – $S_N1$

**Key learning objectives:**

- Know the difference between the possible mechanisms for nucleophilic substitution at saturated carbon – $S_N2$ and $S_N1$
- The rate law for a $S_N1$ reaction
- The free energy diagram for a $S_N1$ reaction
- The curly arrow pushing mechanism, molecular orbital analysis, intermediate and stereochemical outcome of a $S_N1$ reaction
- The factors that favour a $S_N1$ mechanism including the nature of the substrate, nucleophile, solvent and leaving group
- **Synthetic Analysis** – How to favour one substitution mechanisms over the other?

# Lecture 5 Revision

**To reinforce your understanding of the contents of this lecture, please refer to:**

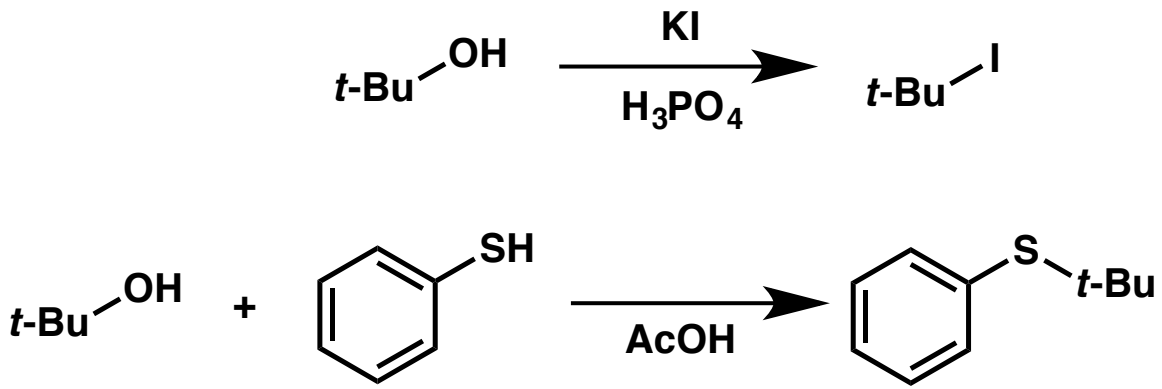
- *Organic Chemistry 2nd Ed.* (J. Clayden et al.) Chapter 15 pp. 328-359.
- Practice questions provided on the next three slides.
- Online practice questions http://www.oxfordtextbooks.co.uk/orc/clayden2e/
  Username: clayden2e  Password: compound
- Online practice questions http://www.chem.ox.ac.uk/vrchemistry/iom/#
- CH4103 Online Test 5
- CH4103 Workshop 2

# Lecture 5 Practice Questions / Guided Self-Study

**For further practice, attempt the following questions in your own time:**

- Q1) Why would both of the following compounds be bad substrates for a $S_N1$ reaction?


- Q2) Draw a curly arrow pushing mechanism for the following reactions, indicating the key orbital interactions involved.

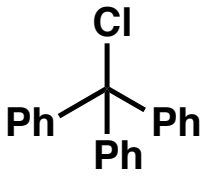


# Lecture 5 Practice Questions / Guided Self-Study

**For further practice, attempt the following questions in your own time:**

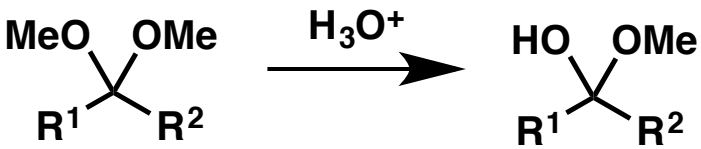
- Q3) What 2 products might be formed from the following $S_N1$ reaction and which might you expect to be the major product?


- Q4) What makes trityl chloride an excellent substrate for a $S_N1$ reaction?




**trityl chloride**

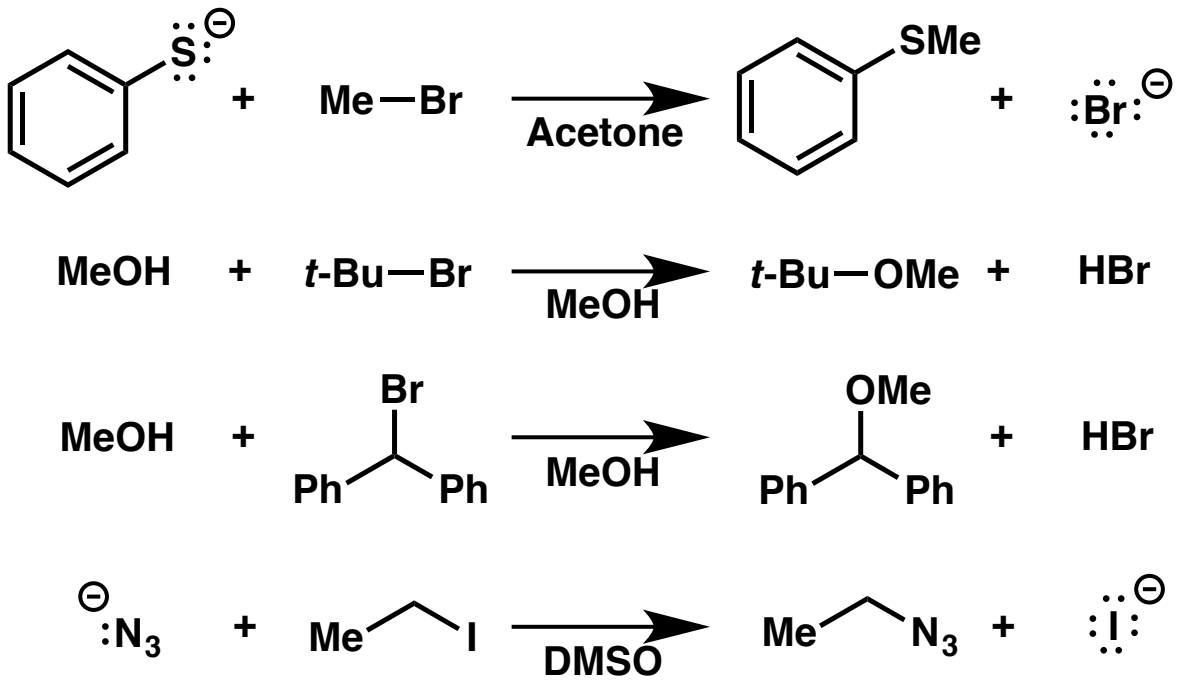
- Q5) Draw a curly arrow mechanism for the following $S_N1$ reaction



# Lecture 5 Practice Questions / Guided Self-Study

**For further practice, attempt the following questions in your own time:**

- Q6) Predict if the following reactions will proceed via an $S_N1$ or $S_N2$ mechanism



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# LCM Lecture 6

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**Autumn Semester**

# Lecture 6 Preparation

**To best prepare yourself for the contents of this lecture, please refresh**

- Sigma and pi bonds (Unit 1, Lecture 2)
- Molecular shape and hybridisation (Unit 1, Lecture 2)
- Stereochemistry (Unit 1, Lecture 4-7)
- Conformation of alkanes and cyclohexanes (Unit 1, Lecture 5)
- Reaction thermodynamics (Unit 2, Lecture 1) and kinetics (Unit 2, Lecture 2)
- Curly arrow pushing mechanisms (Unit 2, Lecture 3)
- The $S_N2$ reaction (Unit 2, Lecture 4)

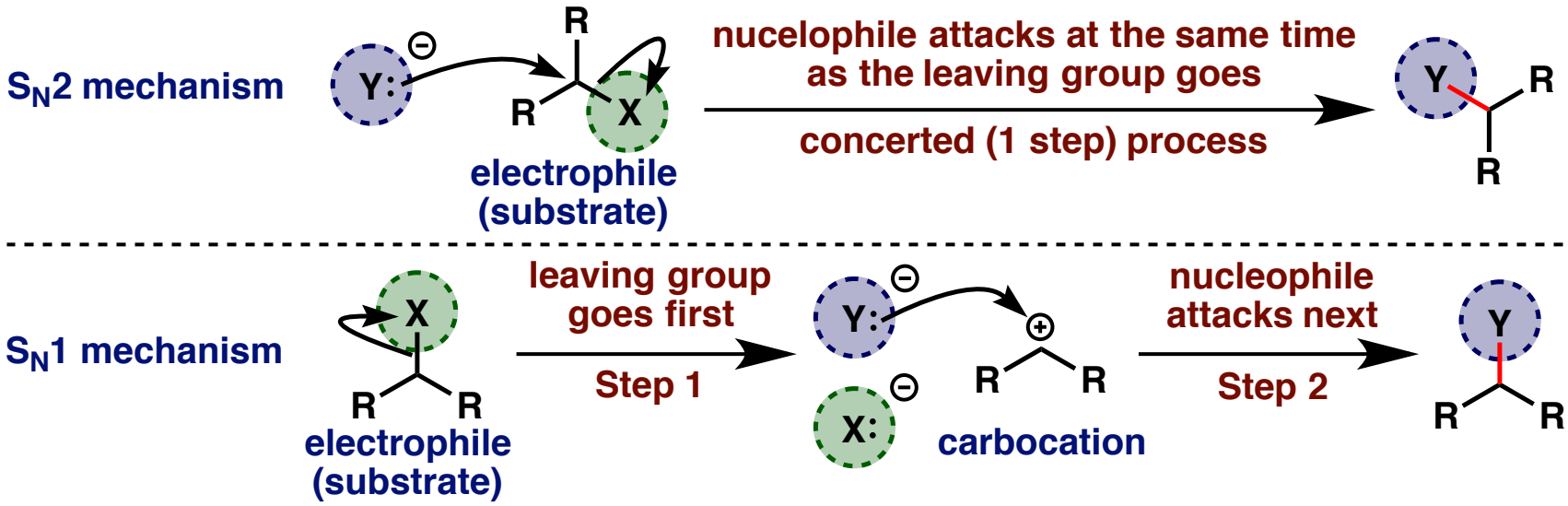
# Lecture 6: Introduction to Elimination Reactions – E2

**Key learning objectives:**

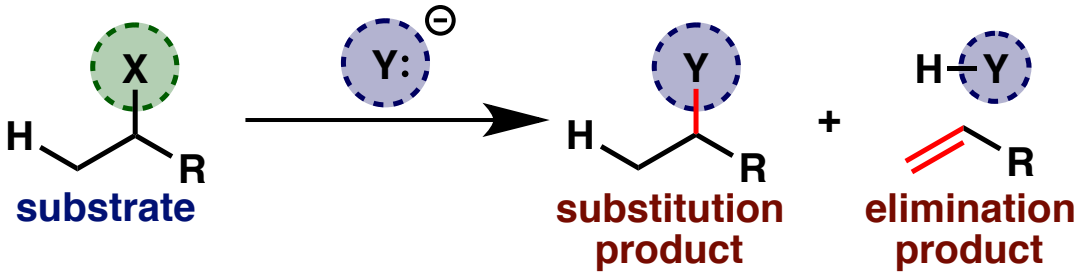
- Know the difference between the possible mechanisms for elimination – E2, E1 and $E1_{cb}$
- The rate law for an E2 reaction
- The curly arrow pushing mechanism, molecular orbital analysis, transition state and stereochemical outcome of an E2 reaction
- The free energy diagram for an E2 reaction
- Regioselectivity of E2 reaction – Zaitsev's rule
- Stereospecificity of E2 reaction
- The factors that favour an E2 mechanism including the nature of the substrate, base, solvent and leaving group

# Substitution vs Elimination

- In the last two lectures we discussed two possible substitution mechanisms

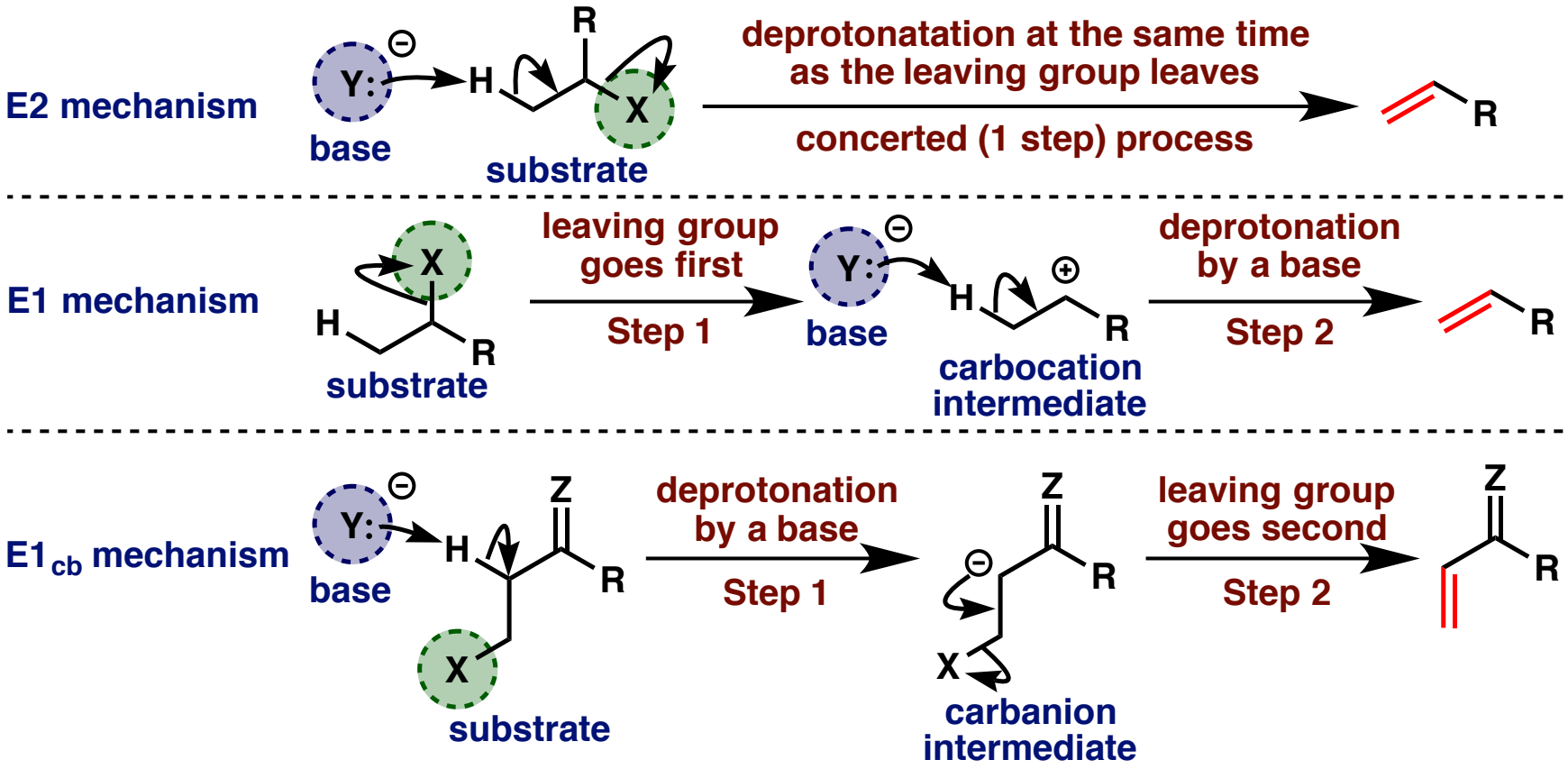



- In practice, most substitution reactions also produce some amount of an alkene that forms *via* a competing elimination process



# Substitution vs Elimination

- In fact, both $S_N2$ and $S_N1$ reactions are always in competition with the corresponding elimination mechanisms, E2 and E1. $E1_{cb}$ is another possible elimination mechanism




- In this lecture we will discuss what factors favour the E2 mechanism and the amount of elimination products that we will observe for a given set of conditions

For further reading refer to *Organic Chemistry 2nd Ed.* (J. Clayden et al.) Chapter 17 pp. 382-406.

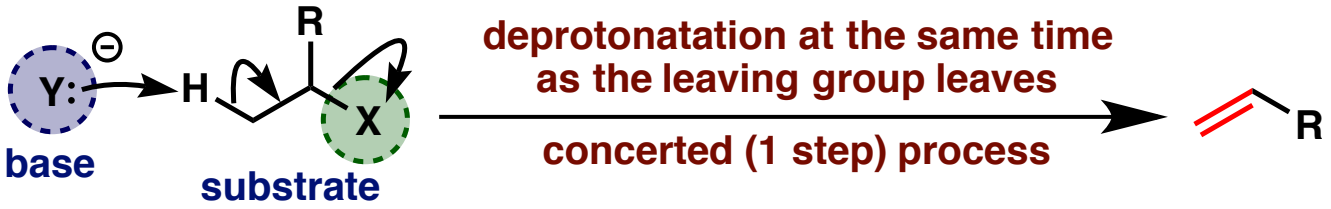
# The E2 Reaction – Rate Law

- The E2 reaction is the **alternative elimination pathway** for the $S_N2$ reaction

- For E2 reactions, the rate is proportional to **both the concentration of the base and the concentration of the substrate**, giving the following rate law:

**Curly Arrow Pushing Mechanism**

**E2 mechanism**




**Rate Law**

$$\text{Rate} = \frac{d[\text{Products}]}{dt} = k_{obs}[\text{base}]^1[\text{substrate}]^1$$

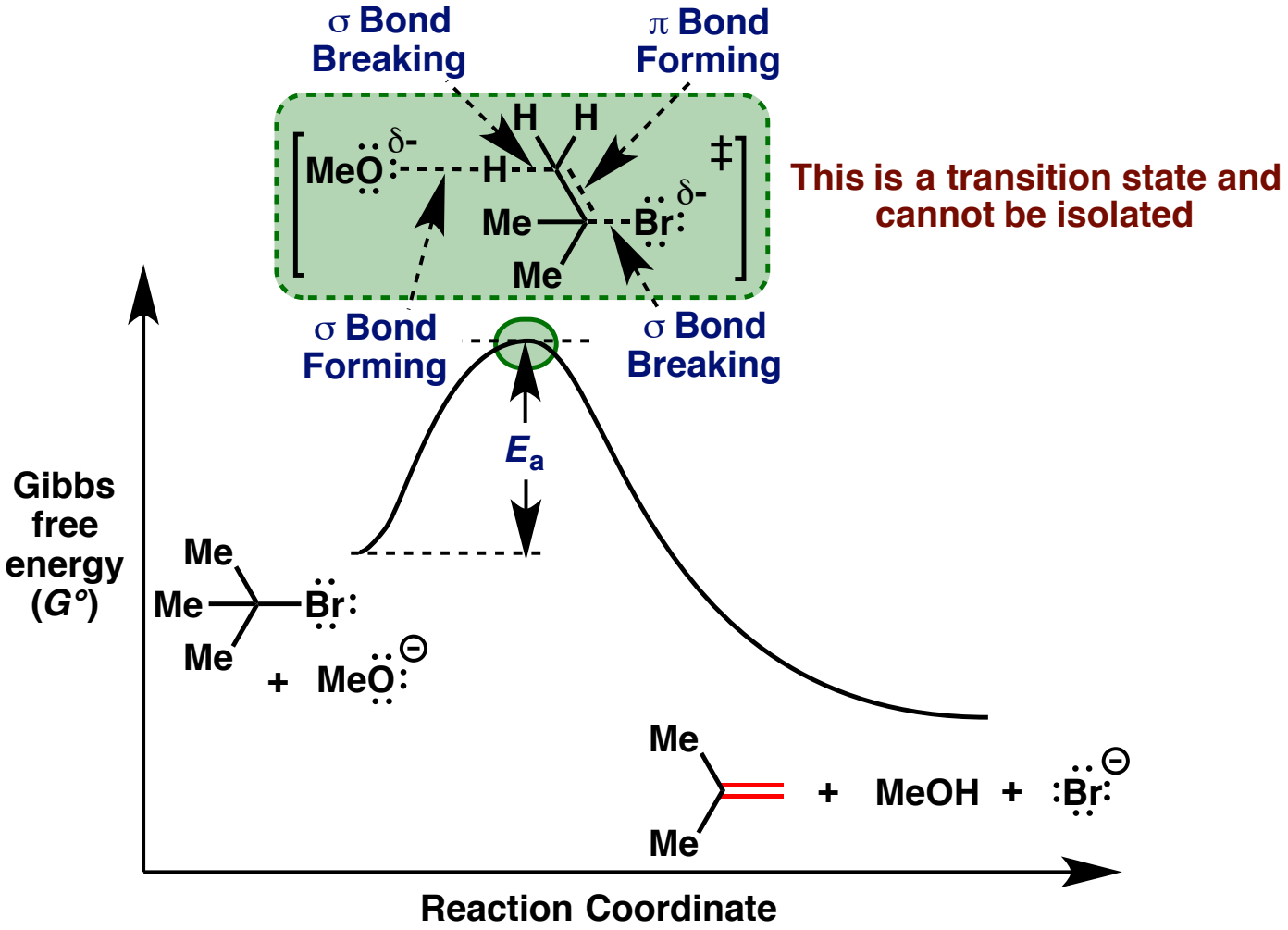
recap **Reaction Kinetics Unit 2, Lecture 2** recap

- This dependence implies that **both** species are involved in the rate determining step of the reaction, i.e. the step with the highest activation energy, $E_a$.

**Elimination** **E** **2** **Bimolecular - two species involved in rate-determining step**

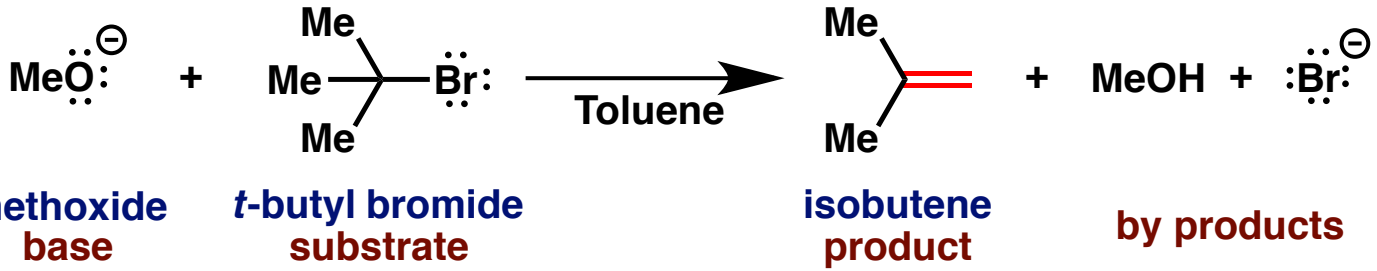
# The E2 Reaction – Free Energy Diagram

- The E2 reaction proceeds through a **transition state** that involves two σ bonds partially broken with one σ bond and one π bond partially formed

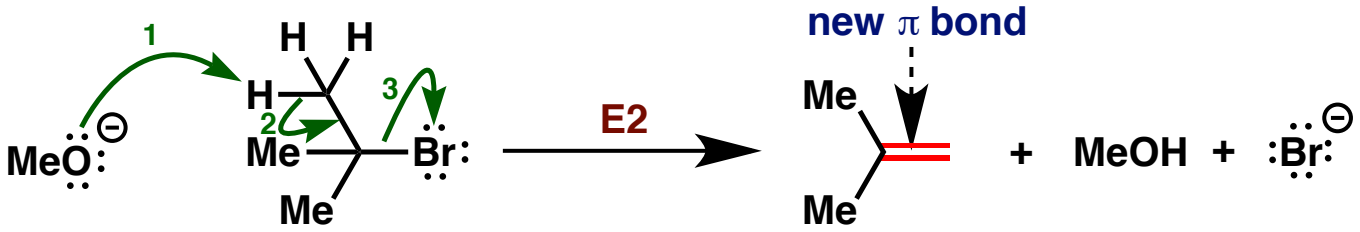


# The E2 Reaction – Curly Arrow Pushing Mechanism

- Consider the elimination reaction shown below:




- We should now be able to draw a curly arrow pushing mechanism and identify the key orbital interaction associated with this movement of electrons




**key orbital interactions**

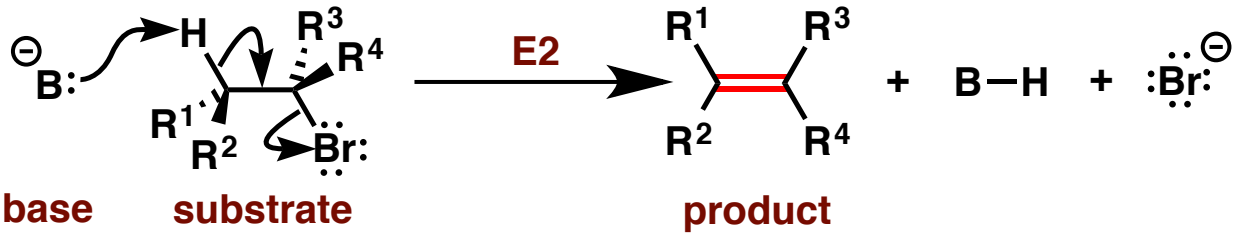
**Curly arrow 1 - filled non-bonding O $sp^3$ orbital to empty C-H $\sigma^*$ orbital, forming new O-H $\sigma$ bond**

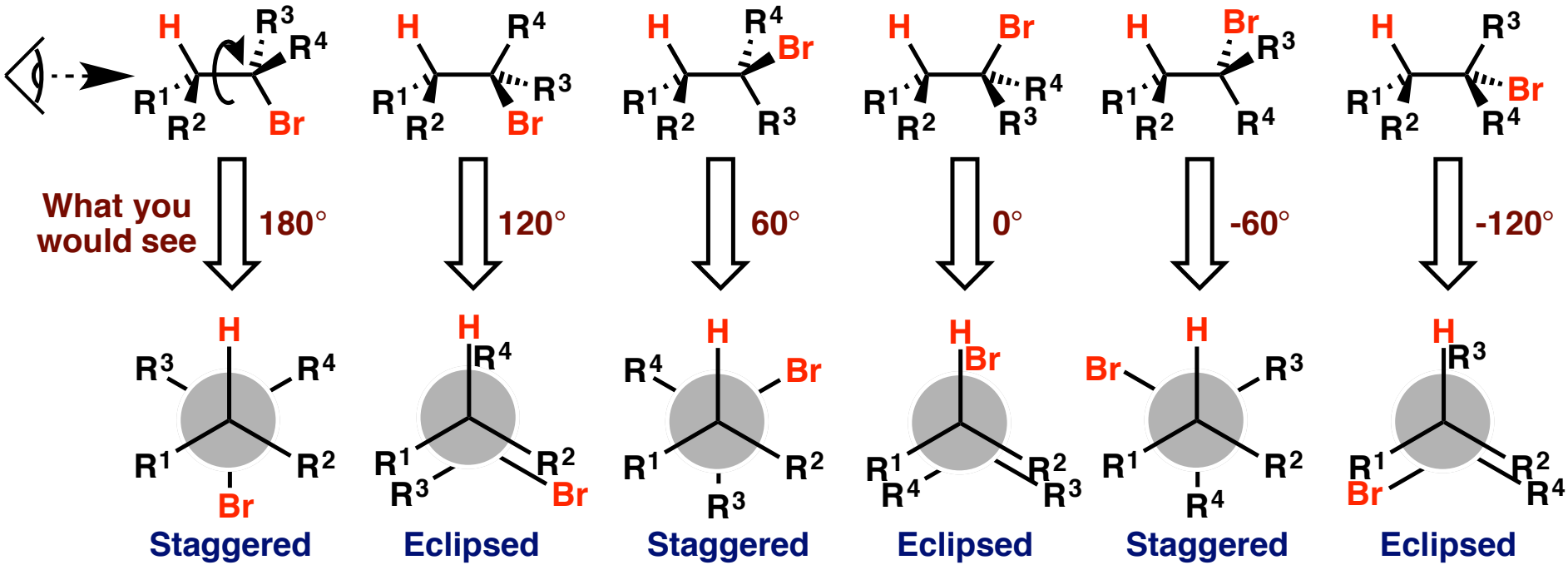
**Curly arrow 2 - filled C-H $\sigma$ bond to empty C-Br $\sigma^*$ orbital, forming new C-C $\pi$ bond**

**Curly arrow 3 - breaking of C-Br $\sigma$ bond with the bonding electrons ending up on bromide anion**

# The E2 Reaction – Conformational Analysis

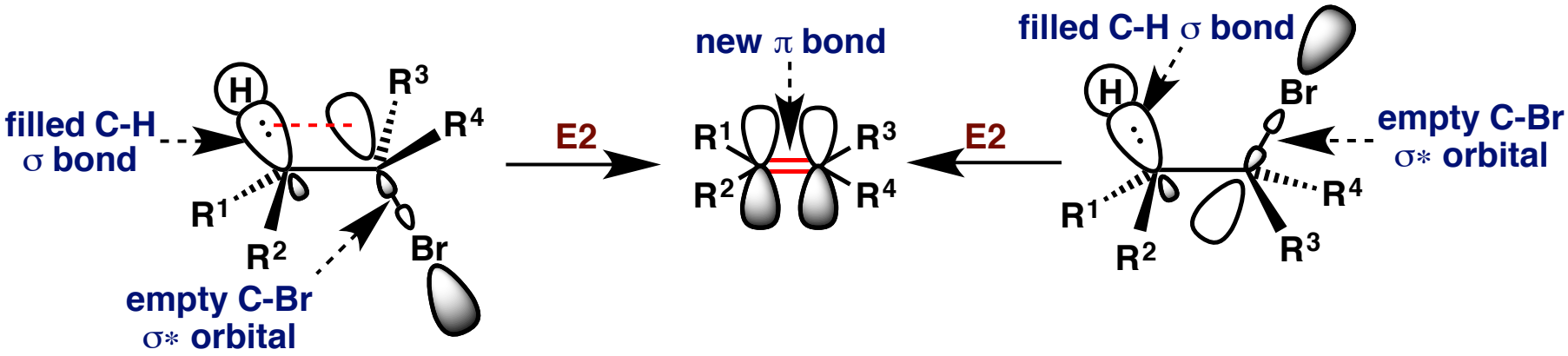
- E2 elimination could occur from one of six possible conformations (MCE Lecture 5)



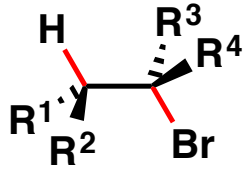



# The E2 Reaction – Stereoelectronic Requirement

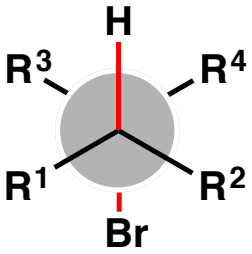
- In an E2 reaction, the new π bond is formed by overlap of the C-H σ bond with the C-X σ* antibonding orbital. The two orbitals have to lie in the same plane for optimal overlap. Only two of the previous conformations allow this and one is better!




**best arrangement - bonds fully parallel**

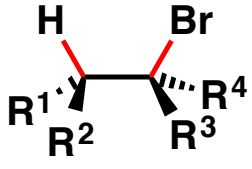


**breaking bonds anti-periplanar**

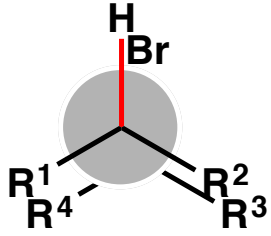


**staggered conformation (more stable)**

**possible but less good arrangement**



**breaking bonds syn-periplanar**

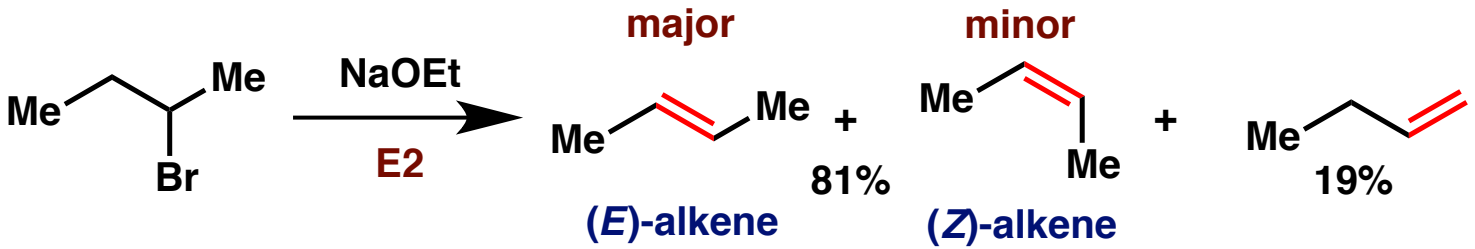


**eclipsed conformation (less stable)**

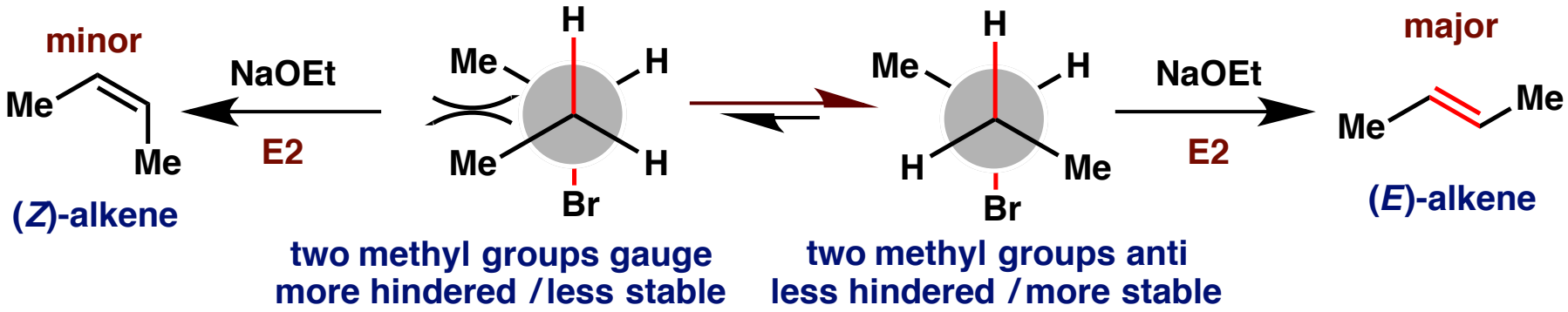
# The E2 Reaction – Regioselectivity

- E2 reactions take place preferentially from the anti-periplanar conformation. What about regioselectivity when multiple different products can still be formed?

- In general the more substituted alkene is formed – Zaitsev's rule

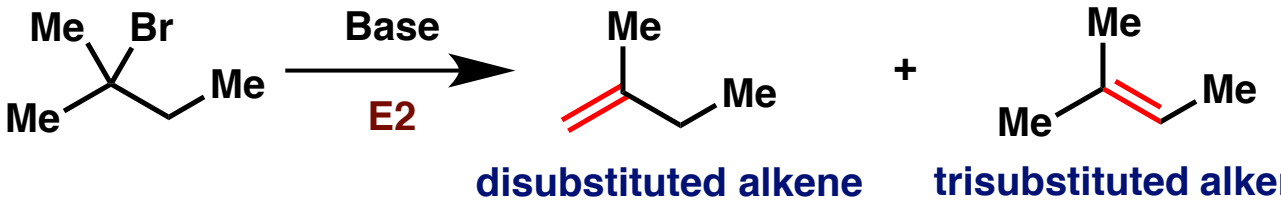



- What about the preference for the (*E*)-alkene? H and Br must be anti-periplanar for E2 reaction but there are two possible conformations



# The E2 Reaction – Regioselectivity

- Alkene stability is not the only factor in determining regioselectivity in E2 reactions
- More hindered bases afford more of the less substituted alkene. Consider the example below:

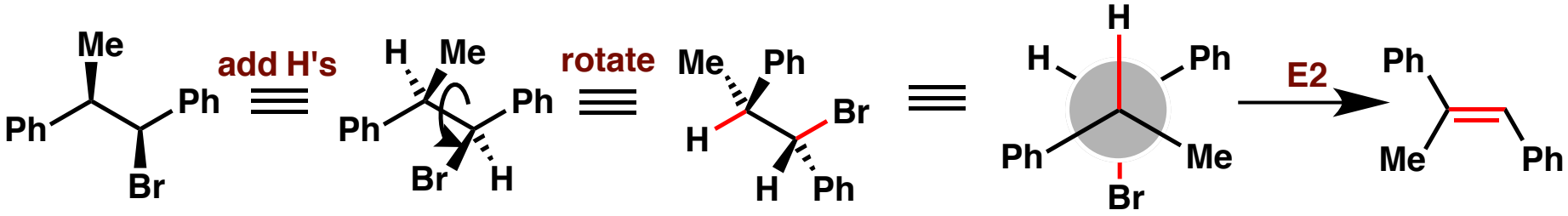



| | | | |
|---|---|---|---|
| more sterically congested base | $EtO^-$ | 29% | 71% |
| | $Me_3CO^-$ | 72% | 28% |
| | $Et_3CO^-$ | 92% | 8% |

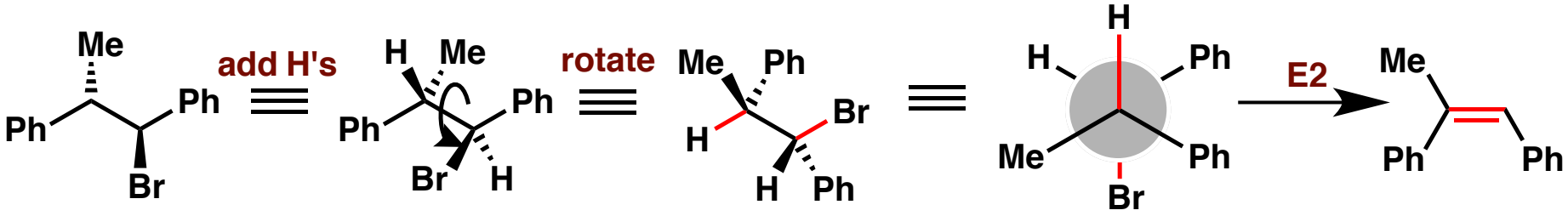
- Refer to the end of the lecture for additional practice questions on this topic

# The E2 Reaction – Stereochemistry

- In some cases the product formed depends on which diastereoisomer of starting material is used – **stereospecific reaction**




**Diastereoisomer 1** — **breaking bonds anti-periplanar** — **staggered conformation (more stable)** — **(*E*)-alkene**




**Diastereoisomer 2** — **breaking bonds anti-periplanar** — **staggered conformation (more stable)** — **(*Z*)-alkene**

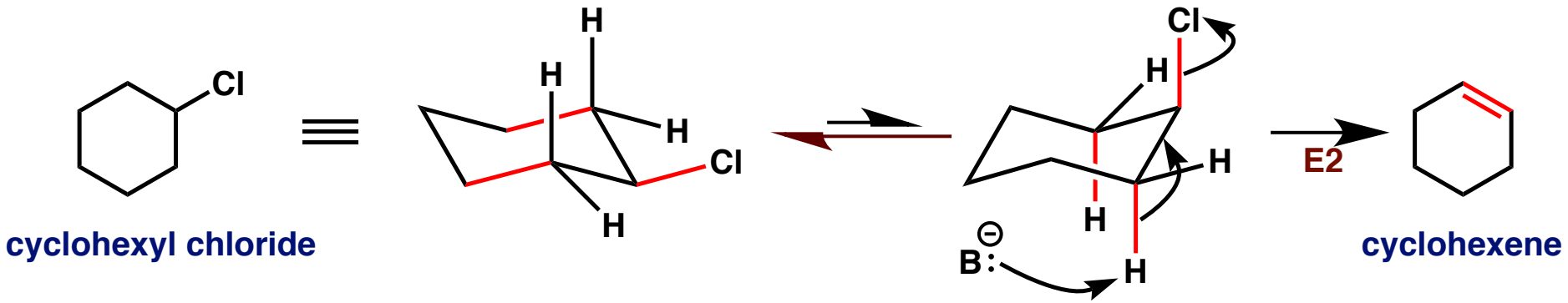
- Only one of the hydrogen atoms can be attacked by a base. Why?

- Reactions in which the stereochemistry of the product is determined by the stereochemistry of the starting material are called **stereospecific**

# The E2 Reaction – Cyclohexane Rings

- The stereoelectronic requirement in an E2 reaction for the breaking bonds to be antiperiplanar has important implications for E2 reactions from cyclohexane systems

- Cyclohexyl chloride can only undergo E2 elimination in one conformation

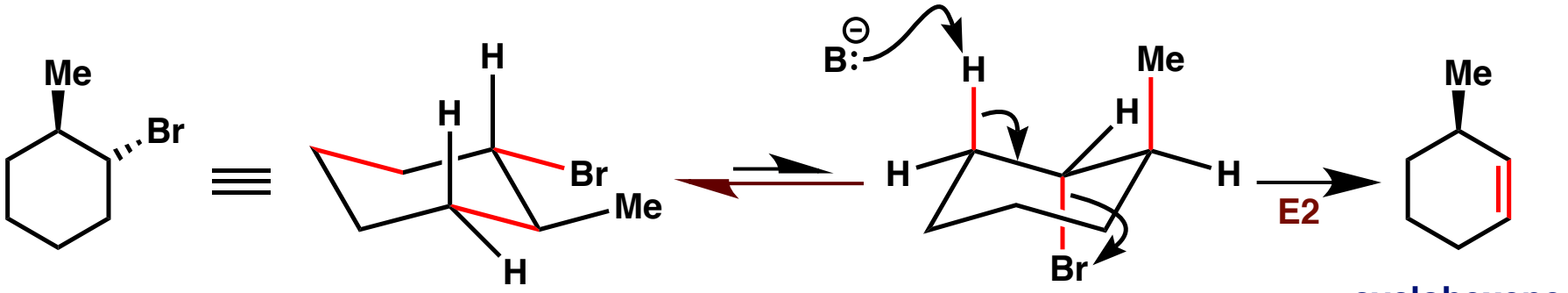



- In cyclohexane systems the leaving group must be axial and there must be an axial β-hydrogen available for E2 reaction to proceed

# The E2 Reaction – Cyclohexane Rings

- The stereoelectronic requirement in an E2 reaction for the breaking bonds to be antiperiplanar has important implications for E2 reactions from cyclohexane systems

- In certain cases regiospecific elimination can occur




**more stable conformer**
**no C-H bonds are antiperiplanar to C-Br bond**
**no E2 reaction possible**

**less stable conformer**
**only one C-H bond is antiperiplanar to C-Br bond**
**regiospecific E2 reaction possible**

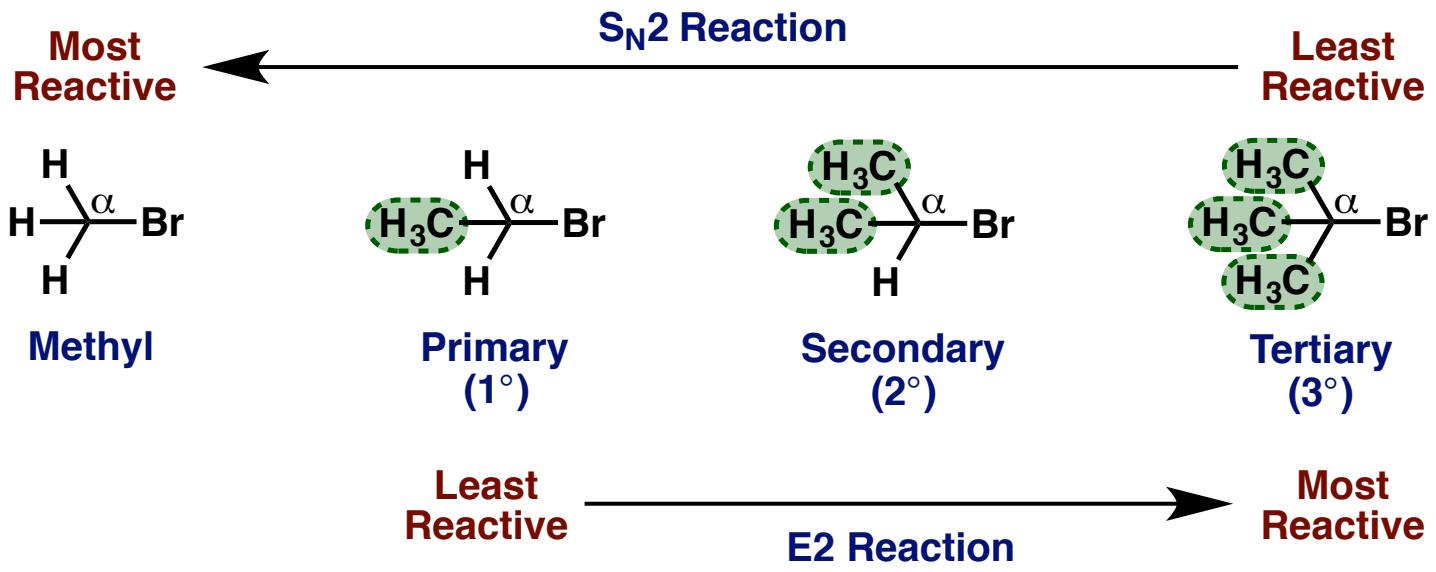
- The other β-hydrogen atom is not removed as it is placed at the equatorial position and is not antiperiplanar to the leaving group. Hence only one alkene product formed

# The E2 Reaction – Substrate Dependence

- $S_N2$ and E2 are always in competition. If we slow down one pathway, the relative importance of the other pathway will increase

- The rate of E2 reactions are dependent upon the **stability to the alkene formed**. A more stable alkene product means a more stable transition state and a faster reaction. Therefore, in terms of alkyl halide starting material 3° > 2° > 1°

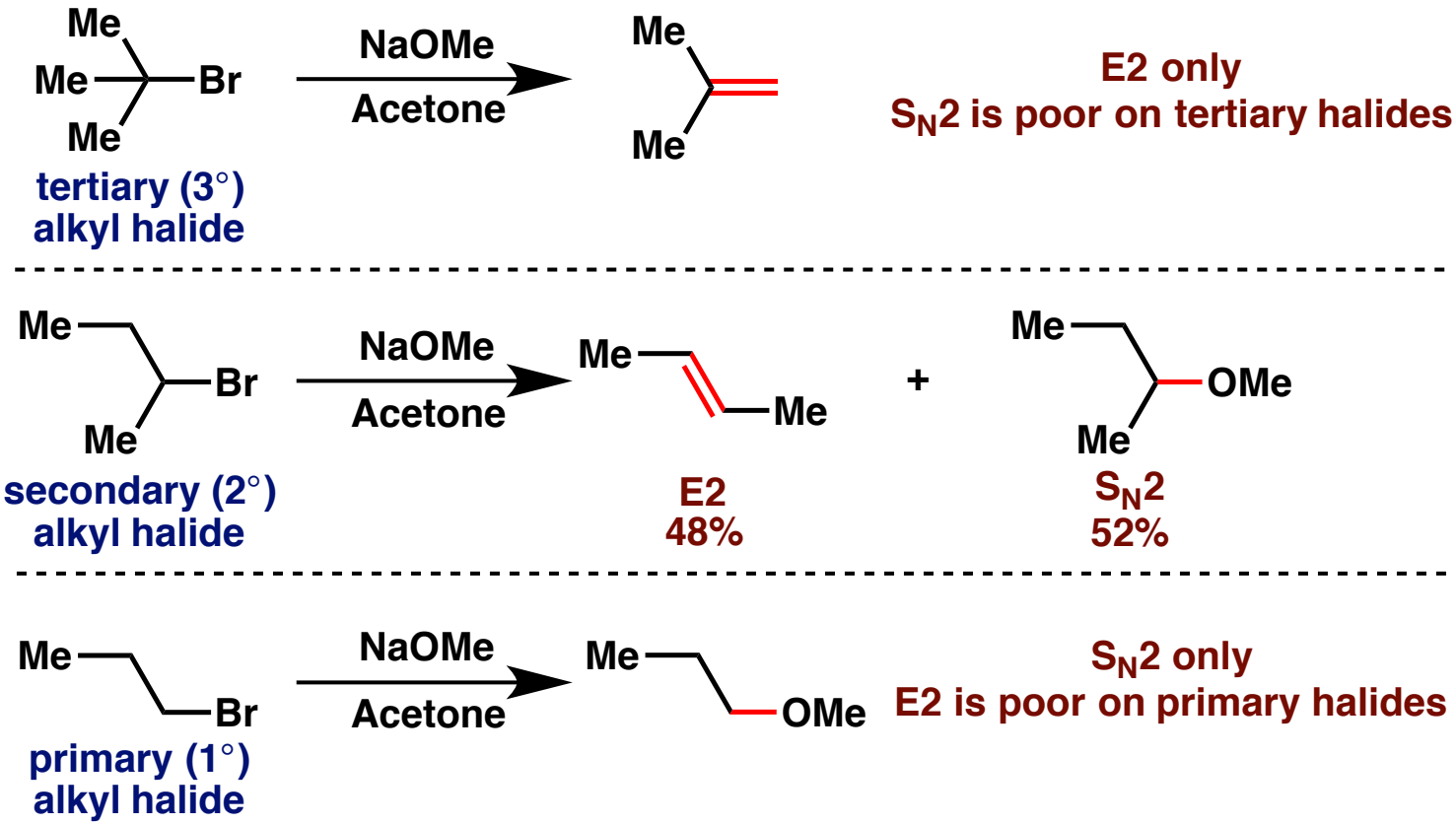
- Remember, for the $S_N2$ reaction, methyl or primary alkyl halides give faster reactions



# The E2 Reaction – Substrate Dependence

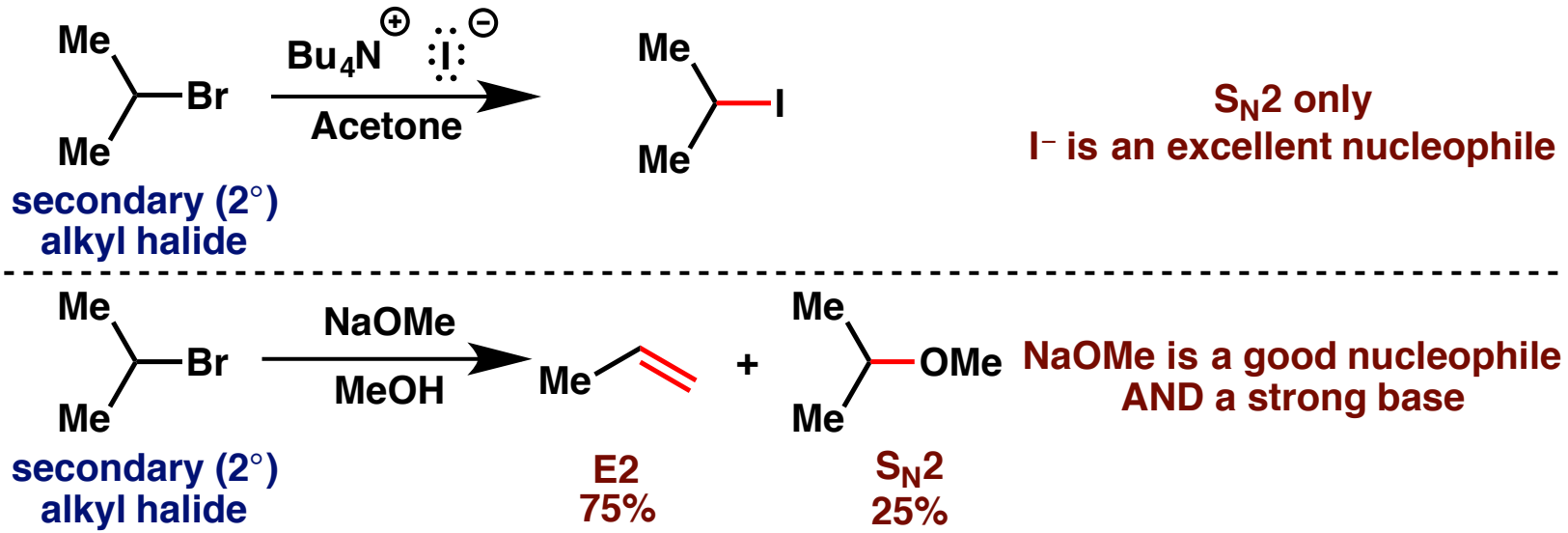
- $S_N2$ and E2 are always in competition. If we slow down one pathway, the relative importance of the other pathway will increase

- Consider the following examples:



# The E2 Reaction – Base and Other Factors

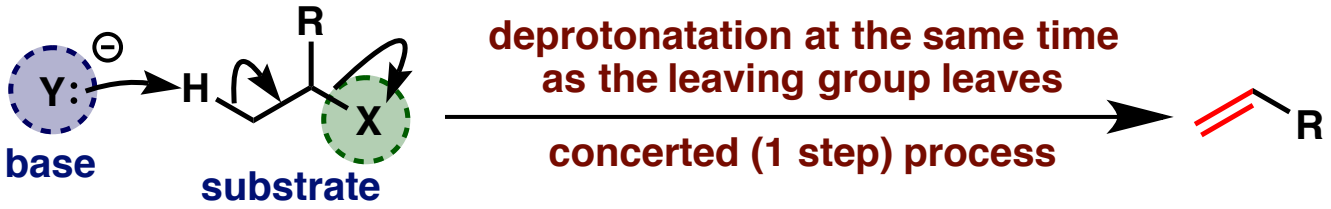
- Remember that good nucleophiles favour $S_N2$ reaction, e.g. $I^-$, $Br^-$, $NC^-$, $RS^-$, RSH, $N_3^-$, $R_2N^-$, $RNH_2$ and $RO^-$
- **Strong Brønsted bases** are required for E2 reaction, e.g. $RO^-$, $R_2N^-$, $H^-$, *t*-$BuO^-$ etc.
- Consider the following examples:




- **Leaving group** – same as for $S_N1$ and $S_N2$ reactions ($I^-$, $Br^-$, $Cl^-$, $^-OSO_2R$, $H_2O$ best)
- **Solvent** – a wide range of solvents can be employed for E2 reactions

# The E2 Reaction – Cheat Sheet

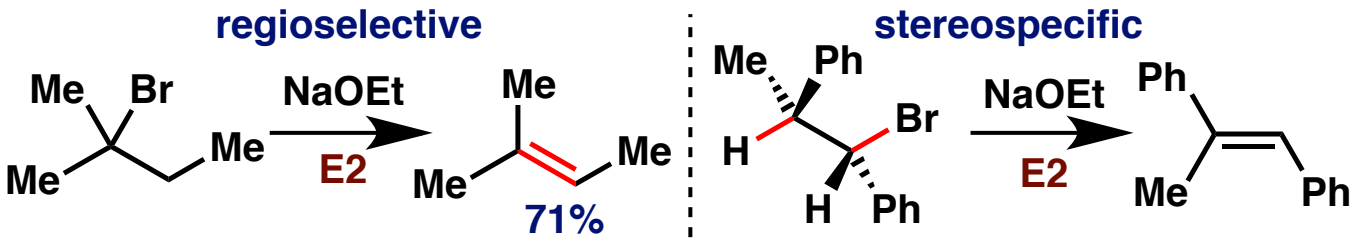
- For the E2 reaction, you must remember the following key information
- Mechanism:




- Rate Law:

$$\text{Rate} = \frac{d[\text{Products}]}{dt} = k_{obs}[\text{base}]^1[\text{substrate}]^1$$

- Regioselective
- Stereospecific




- Factors that favour an E2 mechanism:

**Substrate**
methyl - not possible
primary - moderate
secondary - good
tertiary, allylic, benzylic - excellent

**Base**
strong base required
e.g. $RO^-$, $R_2N^-$, $H^-$
and others

**Solvent**
A wide range of solvents can be used for E2 reactions

**Leaving Group**
highly stabilised / conjugate acid
has a low p$K_a$ value
e.g. $I^-$, $Br^-$, $^-OSO_2R$

# Lecture 6: Introduction to Elimination Reaction – E2

**Key learning objectives:**

- Know the difference between the possible mechanisms for elimination – E2, E1 and $E1_{cb}$
- The rate law for an E2 reaction
- The curly arrow pushing mechanism, molecular orbital analysis, transition state and stereochemical outcome of an E2 reaction
- The free energy diagram for an E2 reaction
- Regioselectivity of E2 reaction – Zaitsev's rule
- Stereospecificity of E2 reaction
- The factors that favour an E2 mechanism including the nature of the substrate, base, solvent and leaving group

# Lecture 6 Revision

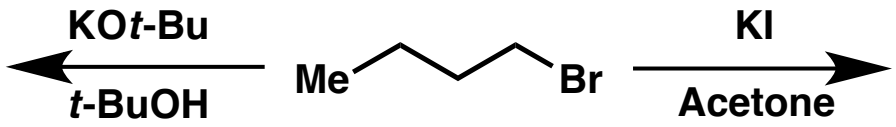
**To reinforce your understanding of the contents of this lecture, please refer to:**

- *Organic Chemistry 2nd Ed.* (J. Clayden et al.) Chapter 17 pp. 382-406.
- Practice questions provided on the next two slides.
- Online practice questions http://www.oxfordtextbooks.co.uk/orc/clayden2e/
  Username: clayden2e  Password: compound
- Online practice questions http://www.chem.ox.ac.uk/vrchemistry/iom/#
- CH4103 Online Test 6

# Lecture 6 Practice Questions / Guided Self-Study

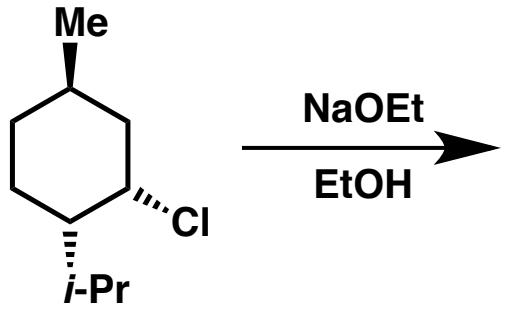
**For further practice, attempt the following questions in your own time:**

- Q1) What would you expect to be the major products formed from the reactions below? Draw curly arrow mechanisms for product formation

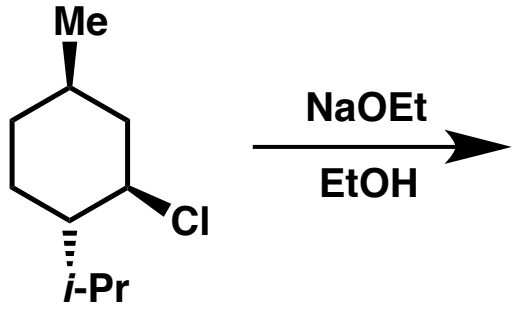



- Q2) Would you expect an increase in temperature to favour a substitution or an elimination pathway?

- Q3) Draw all possible elimination products of the following substituted cyclohexanes. Diastereoisomer B reacts 250 times slower than diastereoisomer A. Why?




**Diastereoisomer A**

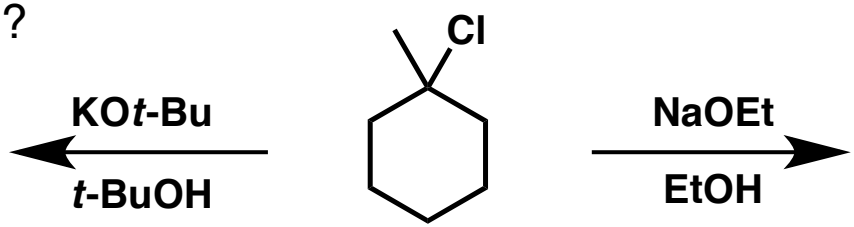



**Diastereoisomer B**

# Lecture 6 Practice Questions / Guided Self-Study

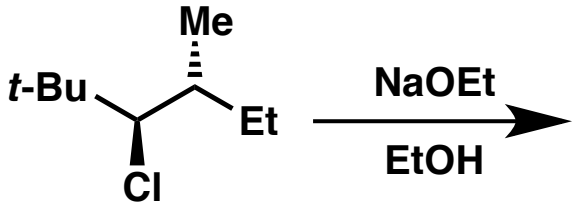
**For further practice, attempt the following questions in your own time:**

- Q4) What product would you expect to be favoured in each of the following elimination reactions?

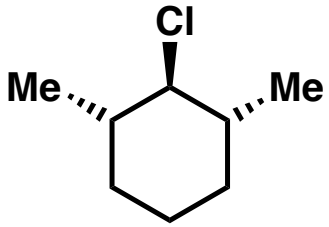



- Q5) Why does *t*-butyl bromide prefer E2 over $S_N2$?

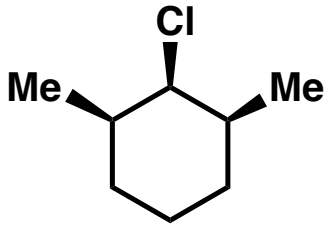
- Q6) Which alkene product is expected from the following reaction?




- Q7) Which of the following diastereoisomers can undergo E2 reaction?




Diastereoisomer 1




Diastereoisomer 2

# CH4103 Organic and Biological Chemistry
# LCM Lecture 7

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**Autumn Semester**

# Lecture 7 Preparation

**To best prepare yourself for the contents of this lecture, please refresh**

- Sigma and pi bonds (Unit 1, Lecture 2)
- Molecular shape and hybridisation (Unit 1, Lecture 2)
- Stereochemistry (Unit 1, Lecture 4-7)
- Conformation of alkanes and cyclohexanes (Unit 1, Lecture 5)
- Reaction thermodynamics (Unit 2, Lecture 1) and kinetics (Unit 2, Lecture 2)
- Curly arrow pushing mechanisms (Unit 2, Lecture 3)
- The $S_N1$ reaction (Unit 2, Lecture 5)
- The E2 reaction (Unit 2, Lecture 6)

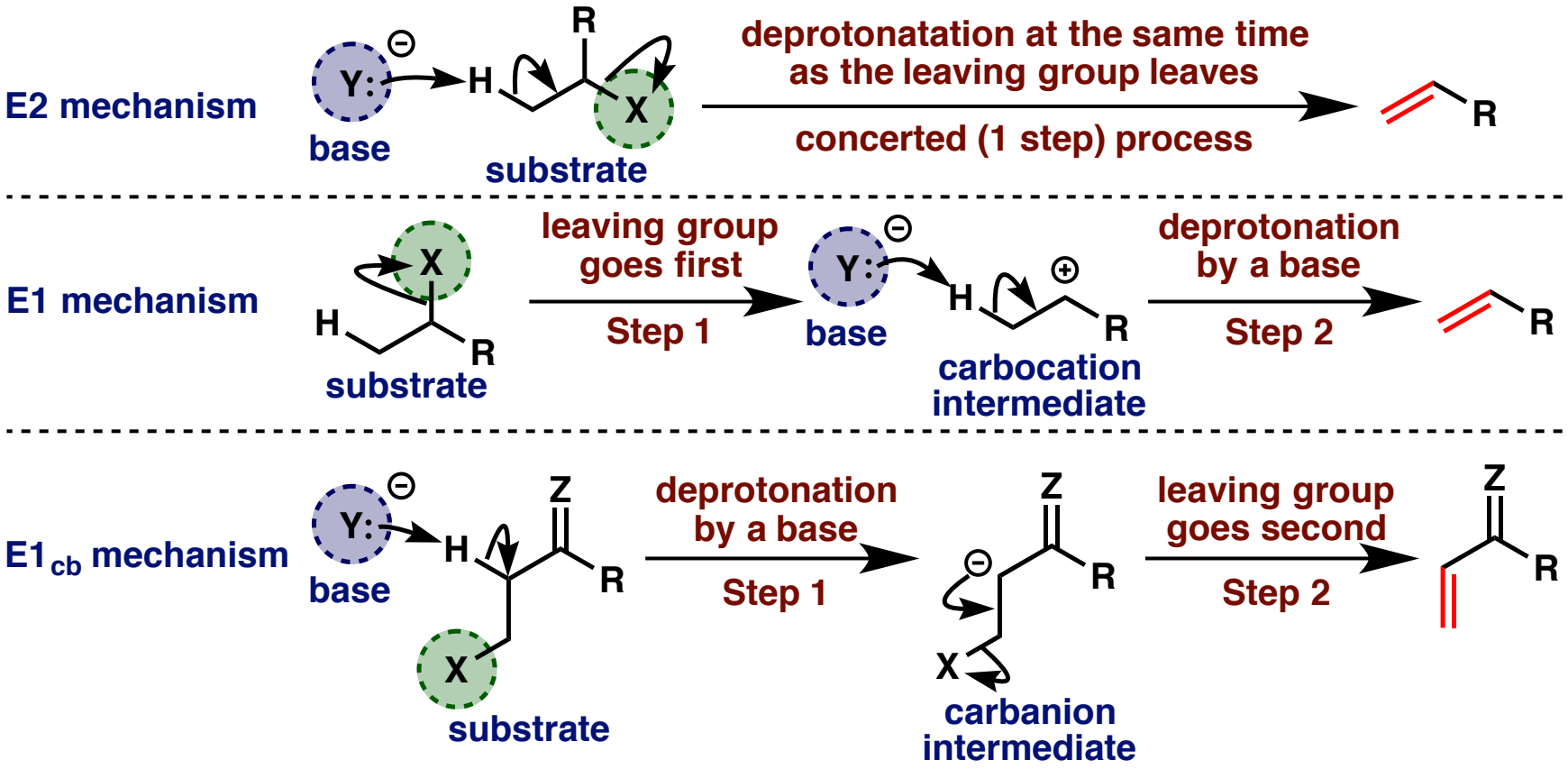
# Lecture 7: Introduction to Elimination Reactions – E1

**Key learning objectives:**

- Know the difference between the possible mechanisms for elimination – E2, E1 and $E1_{cb}$
- The rate law for an E1 reaction
- The free energy diagram for an E1 reaction
- The curly arrow pushing mechanism, molecular orbital analysis and intermediate of an E1 reaction
- Regio- and stereoselectivity of E1 reaction
- The factors that favour an E1 mechanism including the nature of the substrate, base, solvent and leaving group
- Substrates that undergo the E1cb mechanism
- **Synthetic Analysis** – How to favour one elimination mechanism over the other?

# Substitution vs Elimination

- Both $S_N1$ and $S_N2$ reactions are always in competition with the corresponding elimination mechanisms, E1 and E2. $E1_{cb}$ is another possible elimination mechanism



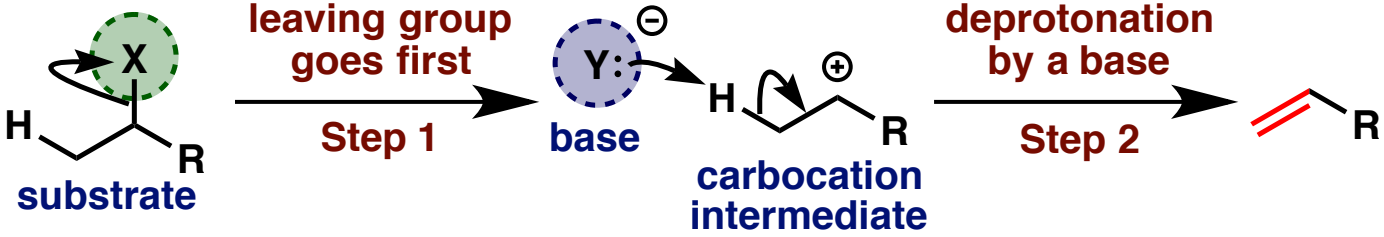

- In this lecture we will discuss what factors favour the E1 and E1cb mechanism and the amount of elimination products that we will observe for a given set of conditions

# The E1 Reaction – Rate Law

- The E1 reaction is the **alternative elimination pathway** for the $S_N1$ reaction
- For E1 reactions, the rate is proportional to the **concentration of the substrate only**, giving the following rate law:

**Curly Arrow Pushing Mechanism**

**E1 mechanism**




**Rate Law**

$$\text{Rate} = \frac{d\,[\text{Products}]}{dt} = k_{obs}[\text{substrate}]^1$$

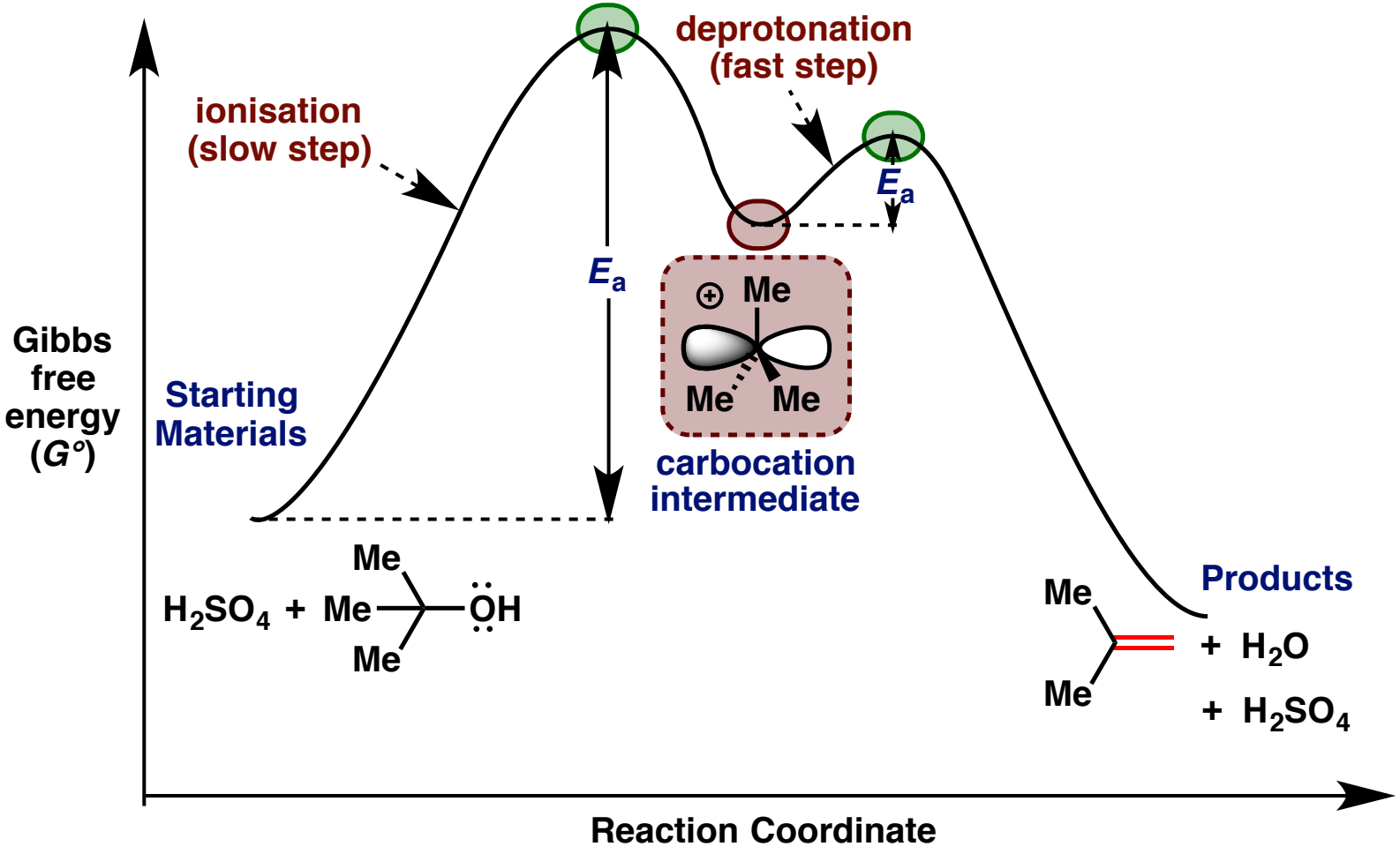
recap **Reaction Kinetics Unit 2, Lecture 2** recap

- This dependence implies that **only** the substrate is involved in the rate determining step of the reaction, i.e. the step with the highest activation energy, $E_a$.

**Elimination** **E** **1** **Unimolecular - one species involved in rate-determining step**

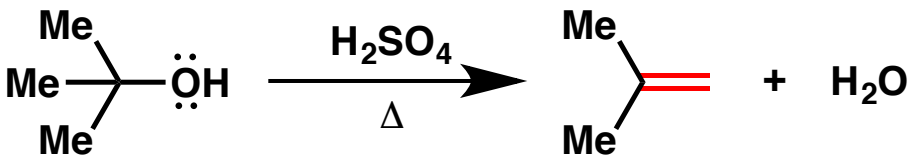
# The E1 Reaction – Free Energy Diagram

- The E1 reaction proceeds through a **planar carbocation intermediate**. Ionisation is disfavoured and is associated with the high energy barrier, consistent with rate law



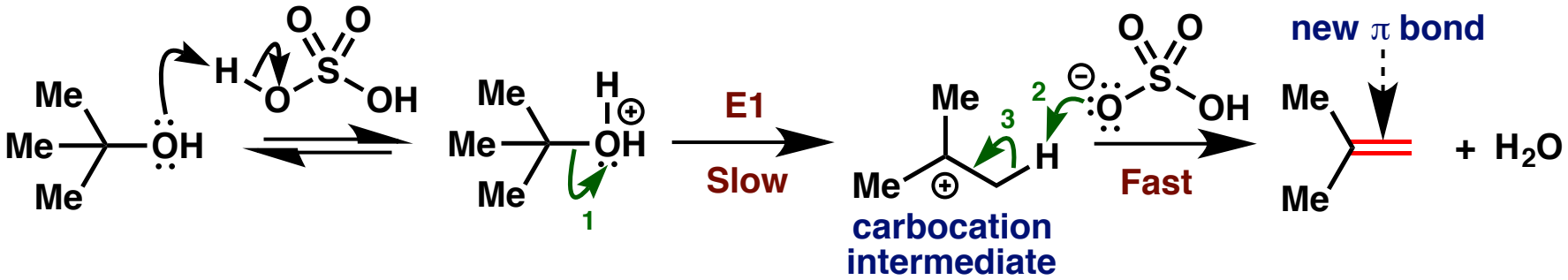
# The E1 Reaction – Curly Arrow Pushing Mechanism

- Consider the elimination reaction shown below that occurs by E1 mechanism:




***t*-butyl alcohol substrate** **isobutene product**

- We should now be able to draw a curly arrow pushing mechanism and identify the orbitals associated with this movement of electrons




**carbocation intermediate**

**key orbital interactions**

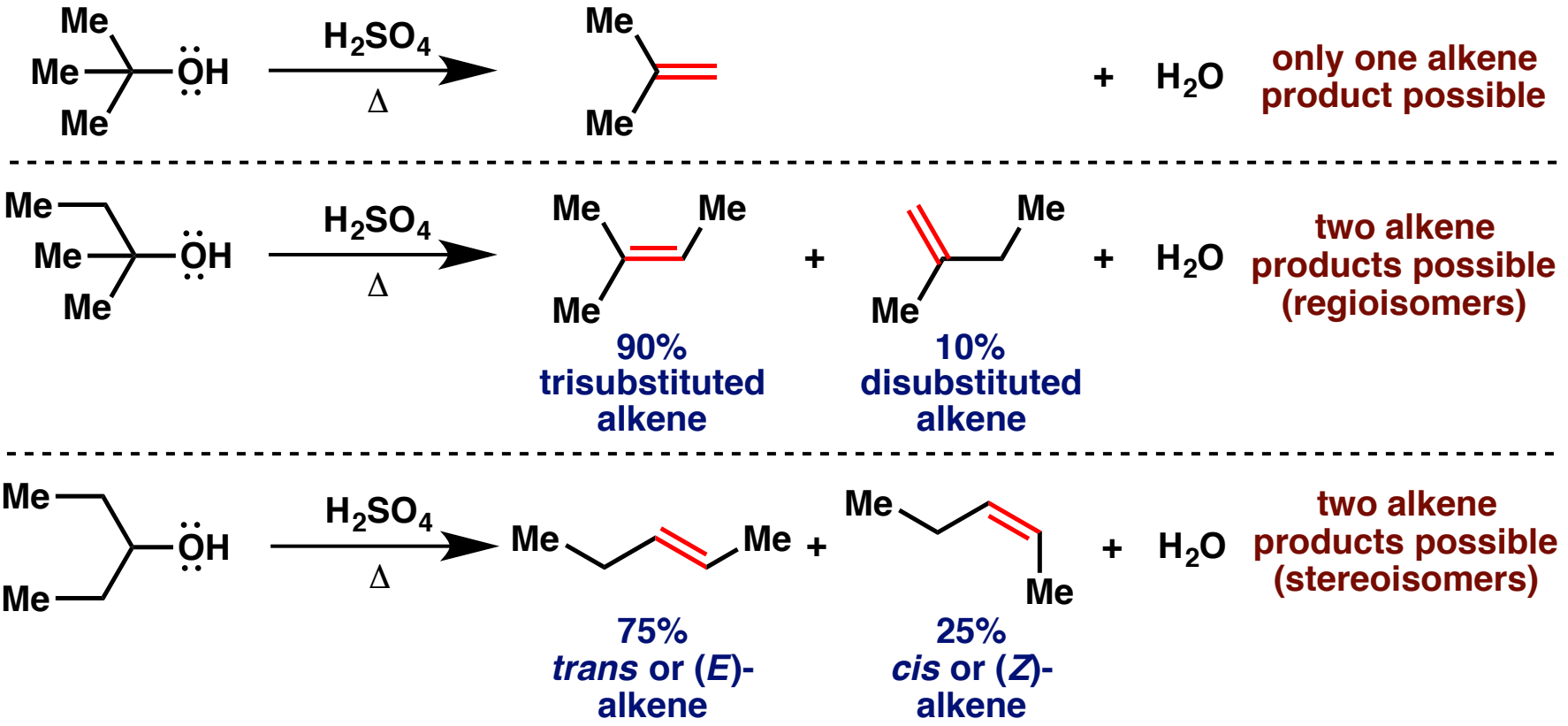
**Curly arrow 1 - breaking C-O σ bond with the bonding electrons ending up on neutral water**

**Curly arrow 2 - filled non-bonding O $sp^3$ orbital to empty C-H σ* orbital, forming new O-H σ bond**

**Curly arrow 3 - filled C-H σ bond to empty C 2p orbital, forming a new C=C π bond**

# The E1 Reaction – Examples

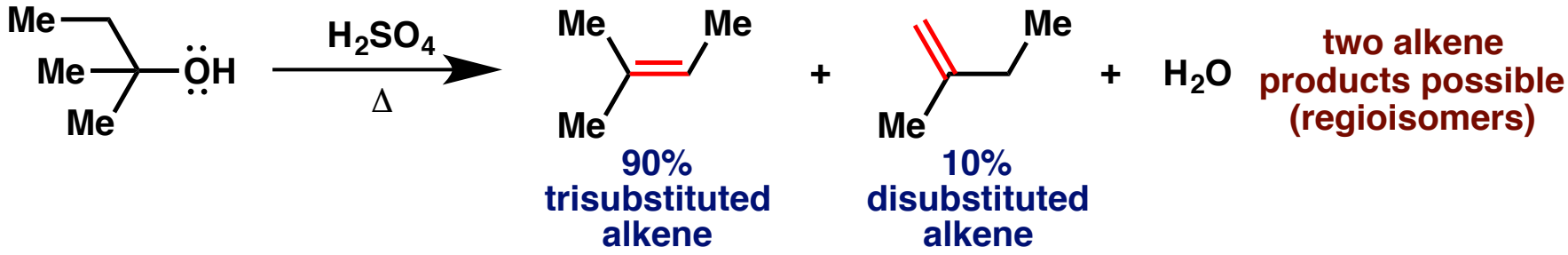
- Consider the following three elimination reactions that proceed *via* an E1 mechanism:




- We can rationalise the amounts of different alkenes formed in each reaction

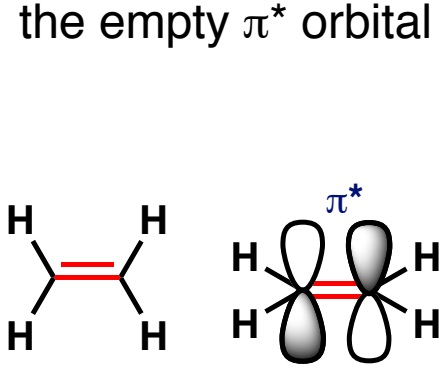
# The E1 Reaction – Regioselectivity

- Consider the following elimination reaction that proceeds *via* an E1 mechanism:

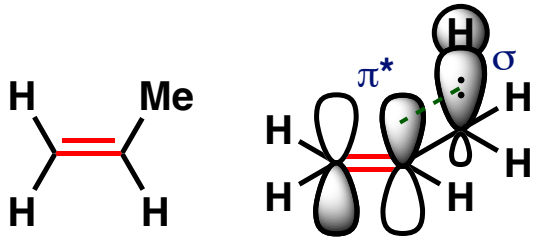



- E1 elimination always favours the **more substituted (and hence more stable)** alkene product – Zaitsev's rule.

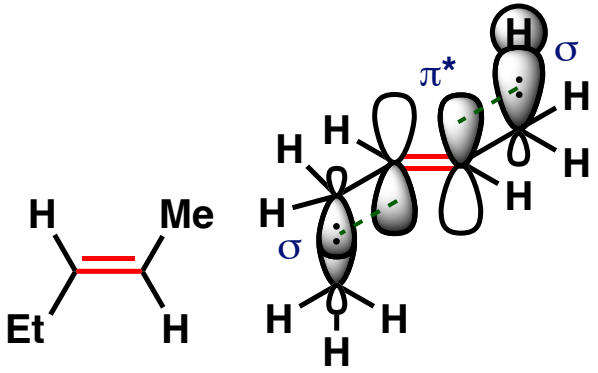
- More substituted alkenes are more stable due to overlap between filled σ orbitals and the empty π* orbital of the alkene:




**Ethene**
**no filled C-H σ bonds parallel with π***



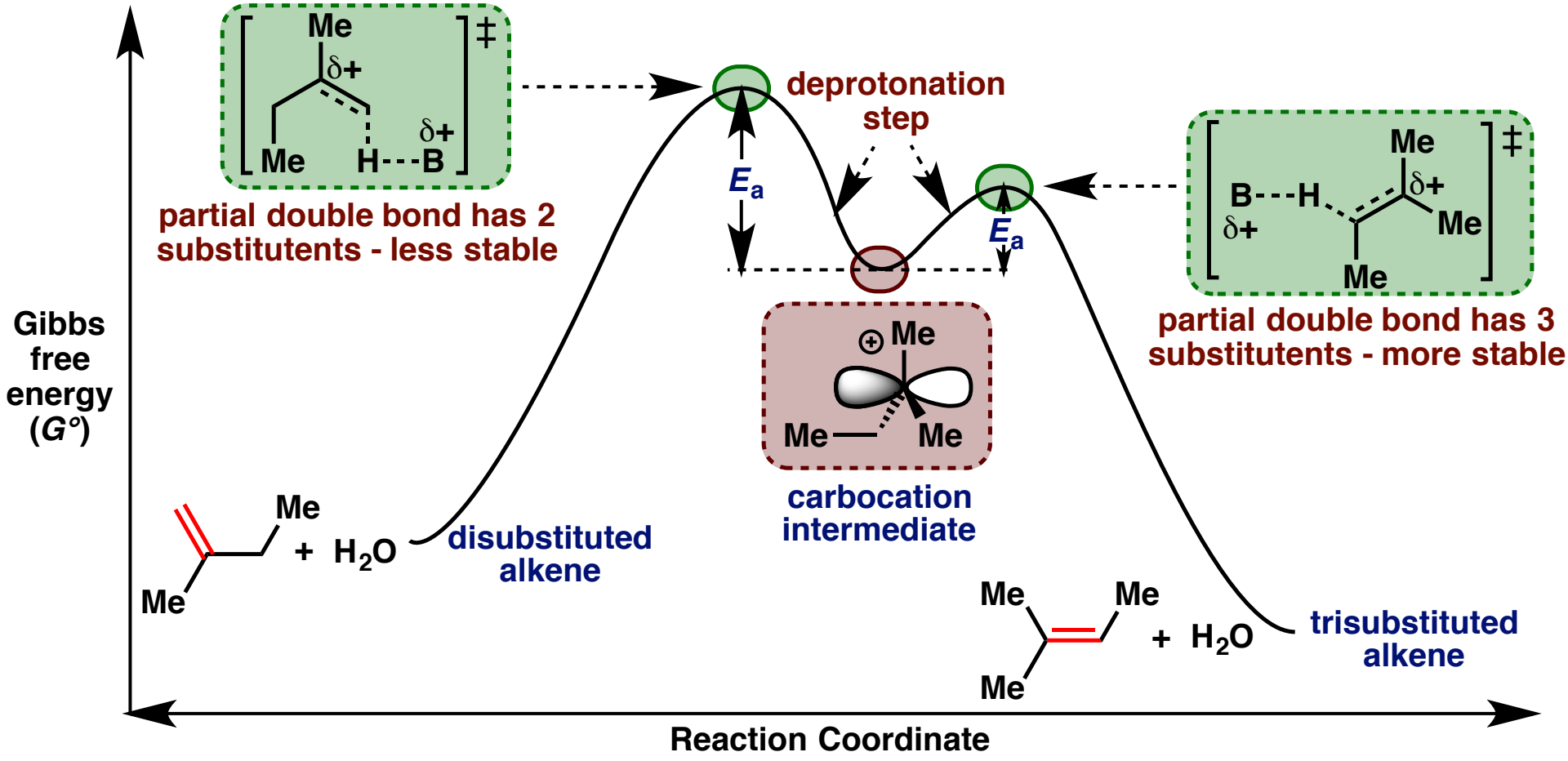

**Propene**
**filled C-H σ bonds parallel with π***




**(*E*)-pent-2-ene**
**filled C-H and C-C σ bonds parallel with π***

# The E1 Reaction – Regioselectivity

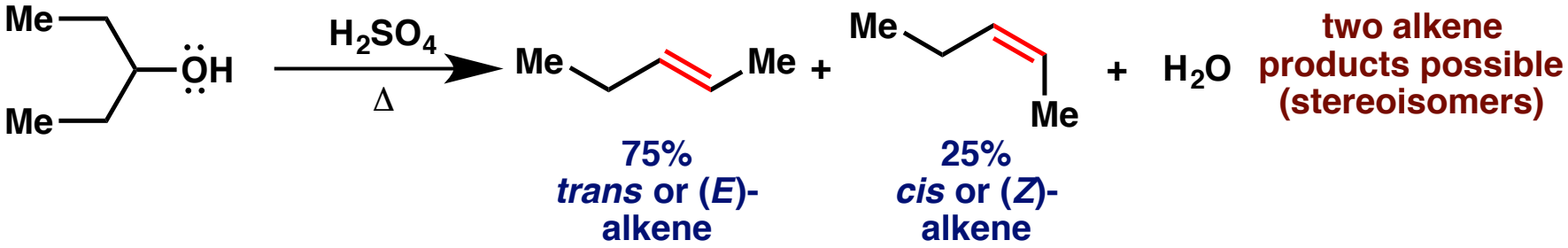
- The stability of the alkene product is reflected at the transitions states for the 2nd deprotonation step. The more stable the alkene product, the lower the energy of the transition state, leading to a smaller activation energy ($E_a$) and a faster reaction




For further reading refer to *Organic Chemistry 2nd Ed.* (J. Clayden et al.) Chapter 17 pp. 382-406.

# The E1 Reaction – Stereoselectivity

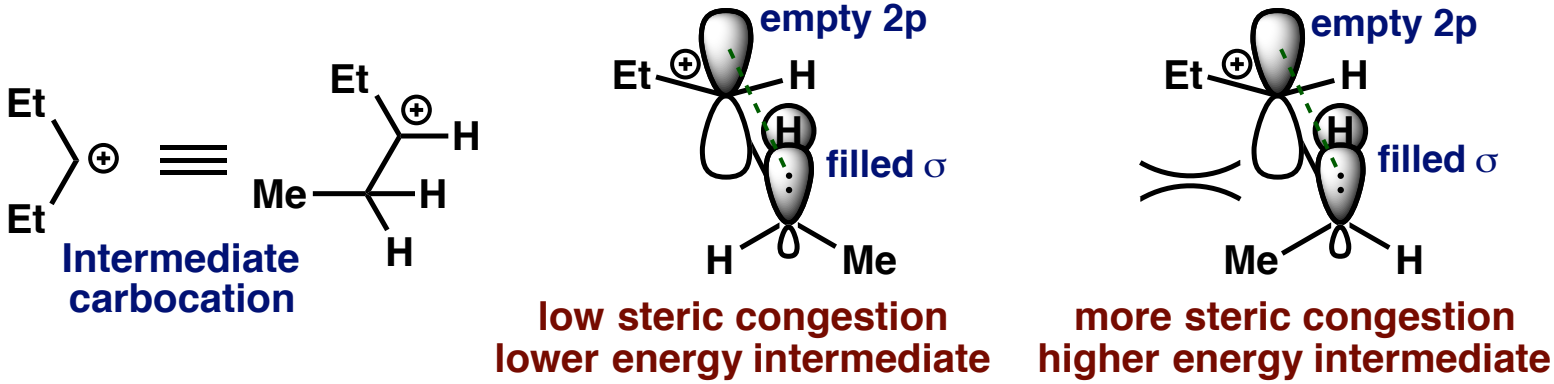
- Consider the following elimination reaction that proceeds *via* an E1 mechanism:




- E1 elimination usually favours the formation of the ***trans* or (E)-alkene** product.

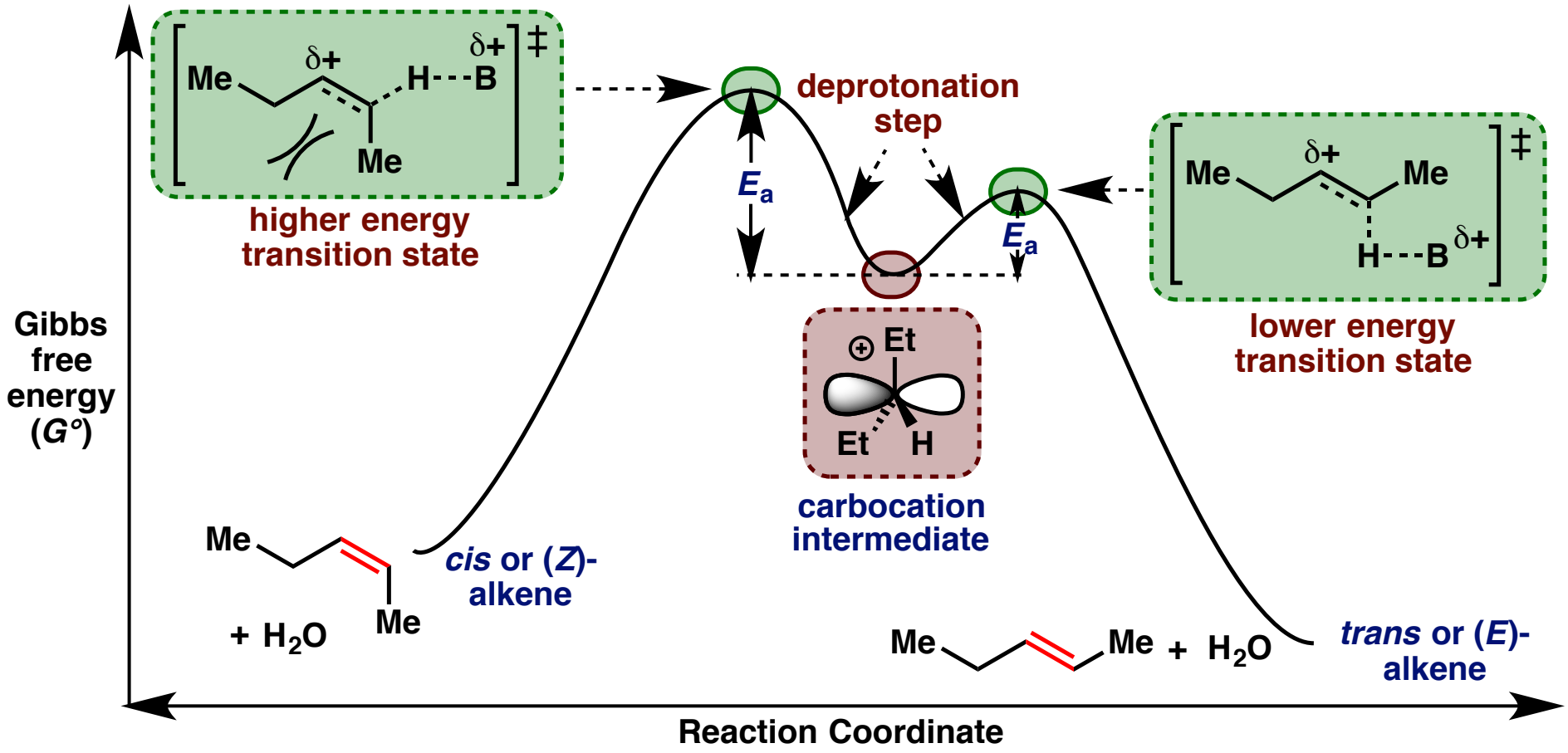
- The new π bond can only form if the vacant p orbital of the carbocation and the breaking filled C-H σ bond are aligned parallel.

- In the example shown, there are two possible conformations with one more stable:



# The E1 Reaction – Stereoselectivity

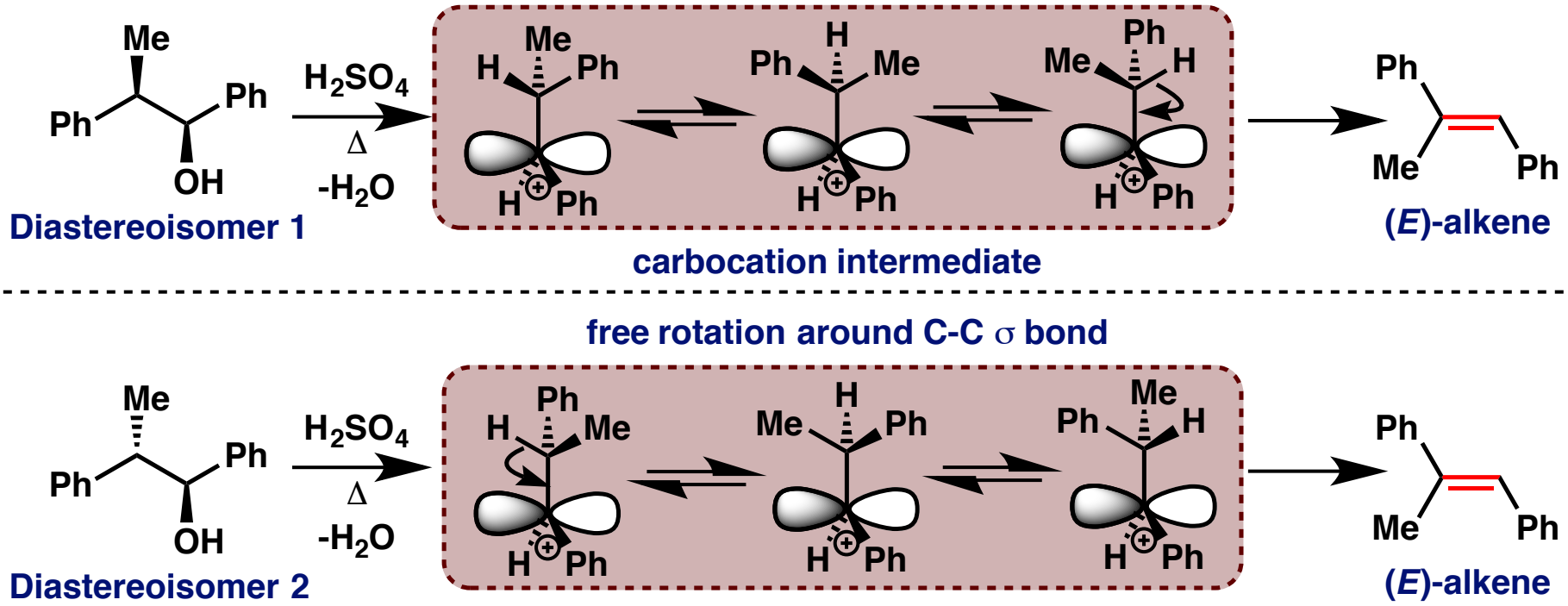
- The stability of the intermediate is reflected at the transitions states for the 2nd deprotonation step. The more stable the intermediate, the lower the energy of the transition state, leading to a smaller activation energy ($E_a$) and a faster reaction



# The E1 Reaction – Stereoselectivity

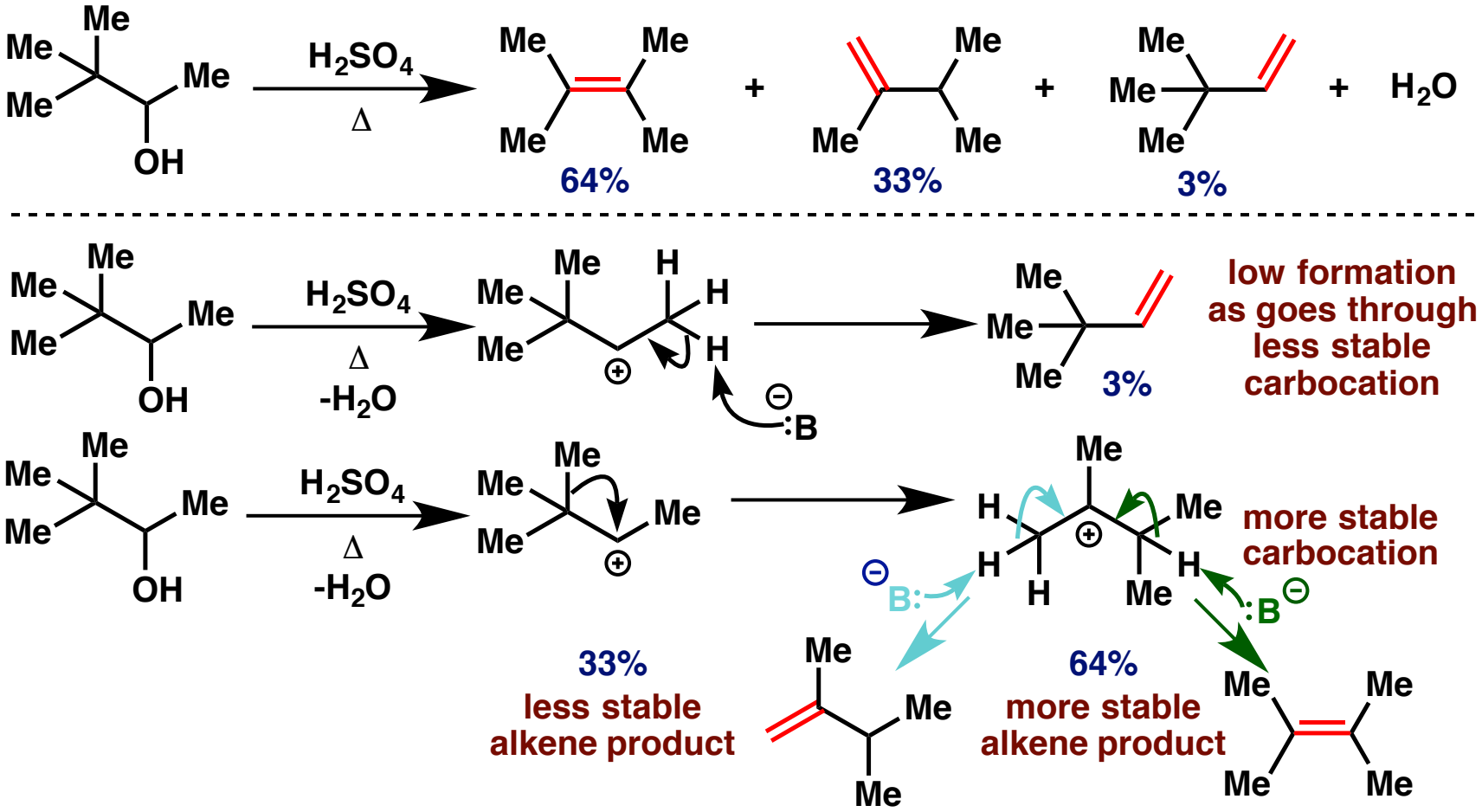
- However, the E1 reaction is **NOT stereospecific**, i.e. the stereochemistry of the products formed are independent of the stereochemistry of the starting materials. In other words, a hydrogen atom is **NOT** required to be anti-periplanar to the LG

- Consider the following example. With both diastereoisomers, elimination occurs from the carbocation intermediate where the two large phenyl groups are on opposite sides, giving rise to the most stable (*E*)-alkene



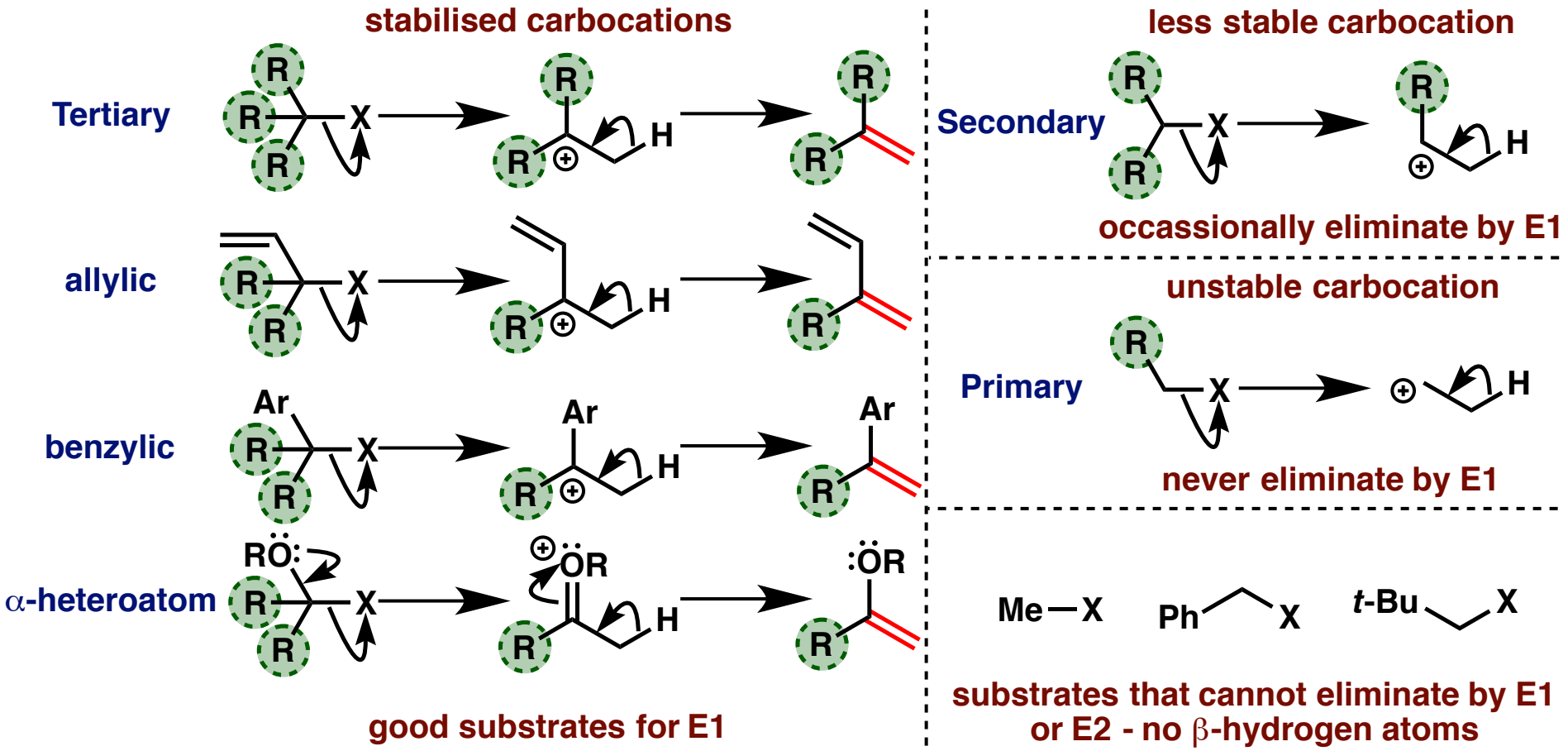
# The E1 Reaction – Carbocation Rearrangements

- Remember from lecture 3, if a carbocation can rearrange to form a more stable carbocation, it will. Consider the reaction below. We should be able to rationalise the quantities of all products formed



# The E1 Reaction – Substrate Dependence

- Just like in the $S_N1$ reaction, substrates that can stabilise the intermediate carbocation are good substrates for the E1 reaction



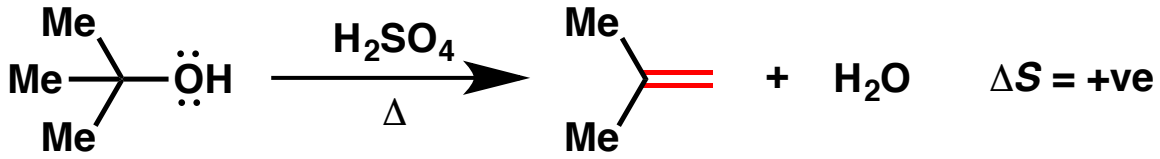
# The E1 Reaction – Base and Other Factors

- In an E1 reaction the **base** is not important with regard to **rate** – i.e. it is not a component of the rate equation. In general a better **nucleophile** favours $S_N1$ and a better **Brønsted base** favours E1. Typical cases for E1 include weak bases (e.g. ROH, $R_2NH$) or the reactions are carried out in acid (e.g. HCl, $H_2SO_4$, $H_3PO_4$)

- **Leaving group** – needs a good leaving group ($I^-$, $Br^-$, $^-OSO_2R$ best, $H_2O$ okay)

- **Solvent** – as for $S_N1$ polar protic solvents are favoured as they stabilise the carbocation intermediate and corresponding TS, lowering $E_a$ and increasing rate

- **Temperature** – In elimination reactions there is an increase in the total number of molecules, representing an increase in entropy (+ve $\Delta S$) for the forward reaction. $\Delta S$ is more +ve for elimination than substitution. Therefore, higher temperatures will favour elimination over substitution as $\Delta G^o$ becomes more negative.

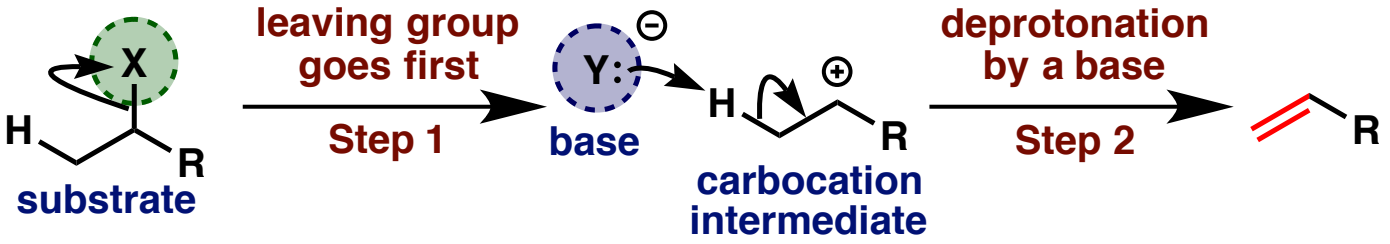



$$\Delta G = \Delta H_{sys} - T\Delta S_{sys}$$

**As T increases, $\Delta G$ decreases, favouring forward reaction**

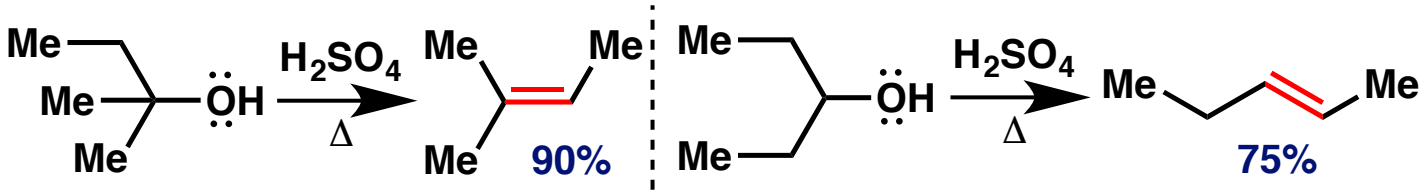
# The E1 Reaction – Cheat Sheet

- For the E1 reaction, you must remember the following key information
- Mechanism:




- Rate Law: $\text{Rate} = \frac{d[\text{Products}]}{dt} = k_{obs}[\text{substrate}]^1$

- Regioselective
- Stereoselective
  (not stereospecific)




- Factors that favour an E1 mechanism:

**Substrate**
methyl - not possible
primary - bad
secondary - moderate
tertiary - good
allylic, benzylic - good

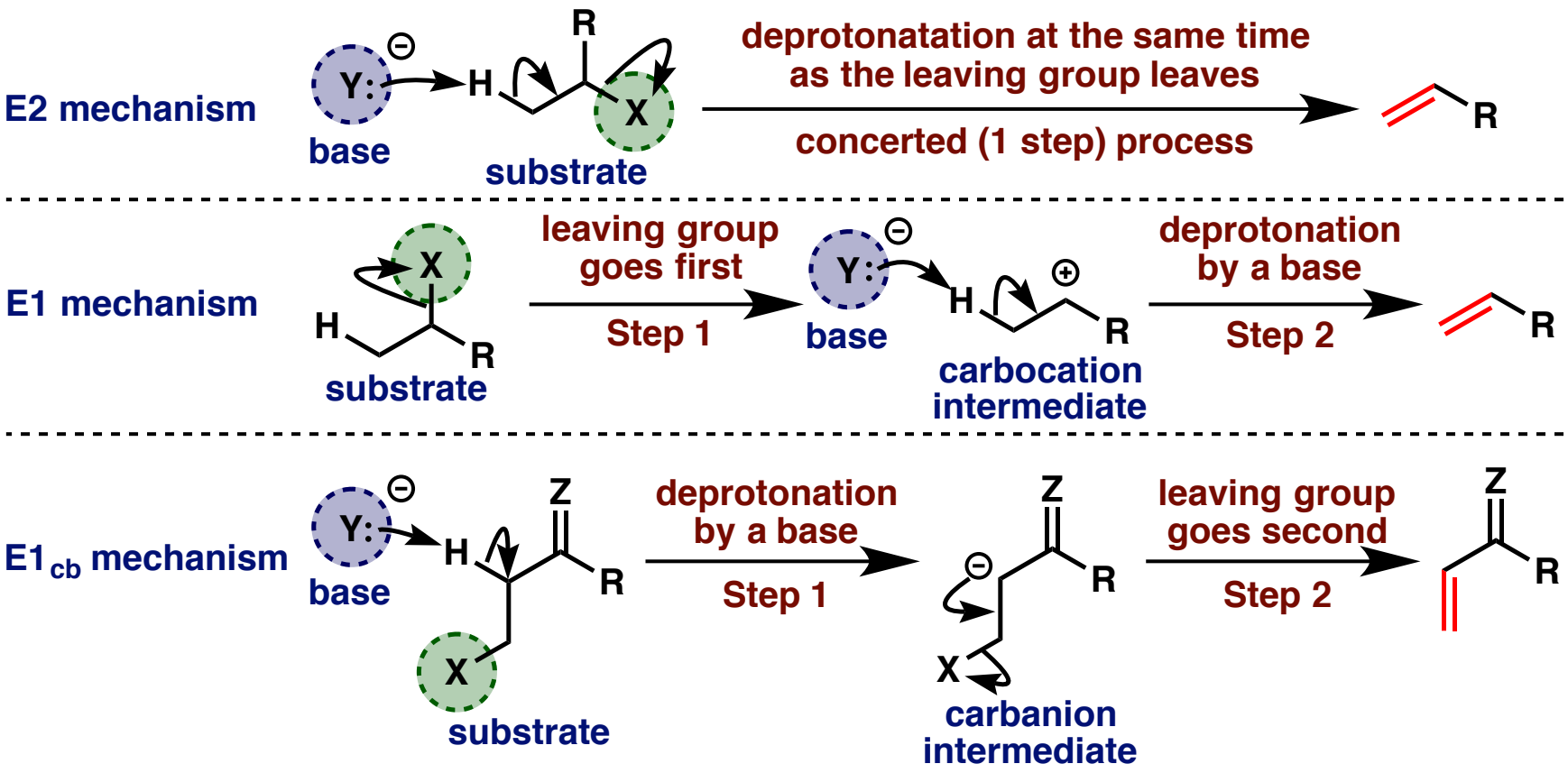
**Base**
not important, usually weak bases (e.g. ROH, $R_2NH$) or done in acid (e.g. $H_2SO_4$, $H_3PO_4$)

**Solvent**
polar protic
e.g. $H_2O$, MeOH, AcOH, $H_2SO_4$

**Leaving Group**
highly stabilised / conjugate acid
has a low p$K_a$ value
e.g. $I^-$, $Br^-$, $^-OSO_2R$

# The $E1_{cb}$ Reaction

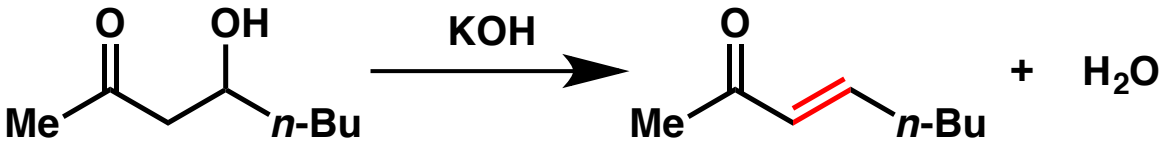
- There is another important elimination mechanism that we need to briefly consider – the $E1_{cb}$ reaction



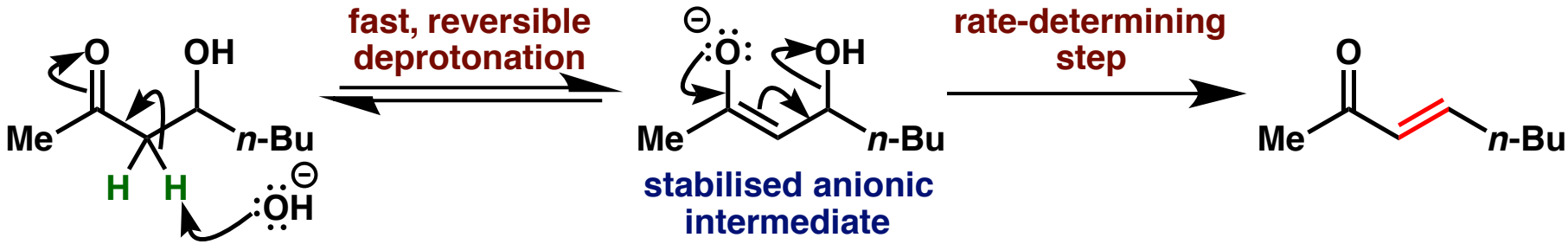
# The E1cb Reaction – Curly Arrow Pushing Mechanism

- The $E1_{cb}$ reaction is an elimination catalysed by a strong base (KOH) and occurs in substrates containing a poor leaving group (e.g. $^-OH$)

**Poor leaving group - unlikely E2**
**Secondary alcohol - unlikely E1**




- The key is the presence of the carbonyl group, making the α-hydrogen atoms more acidic due to stabilisation of the resulting anion. Alkene formation occurs in a second rate-determining step



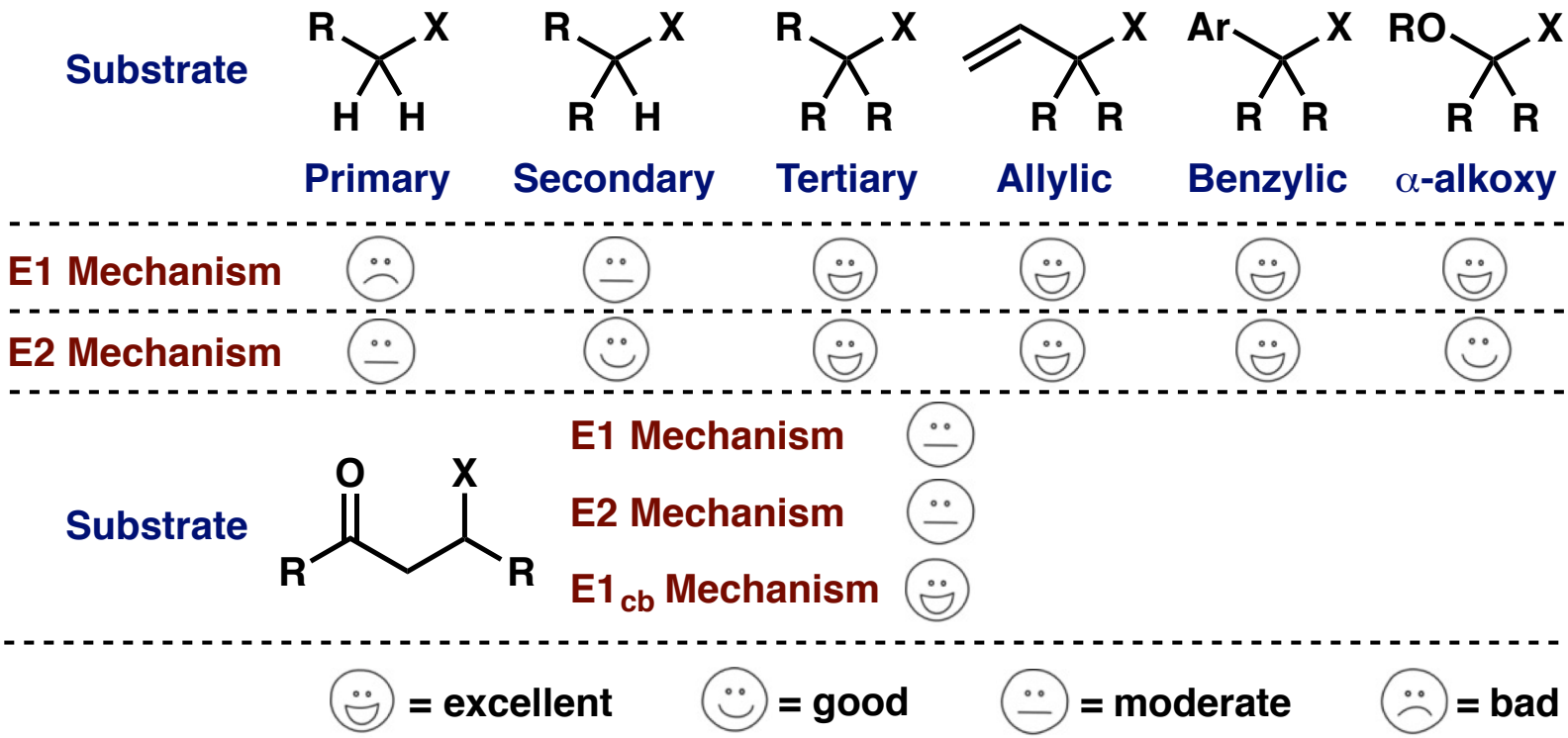

**green protons acidified by adjacent carbonyl**

**stabilised anionic intermediate (conjugate base)**

- The leaving group is lost from the **conjugate base** of the starting material, hence $E1_{cb}$. If the alkene in the product is conjugated with a carbonyl group (or other functionality containing a π bond, e.g. nitrile, imine etc.) mechanism probably $E1_{cb}$

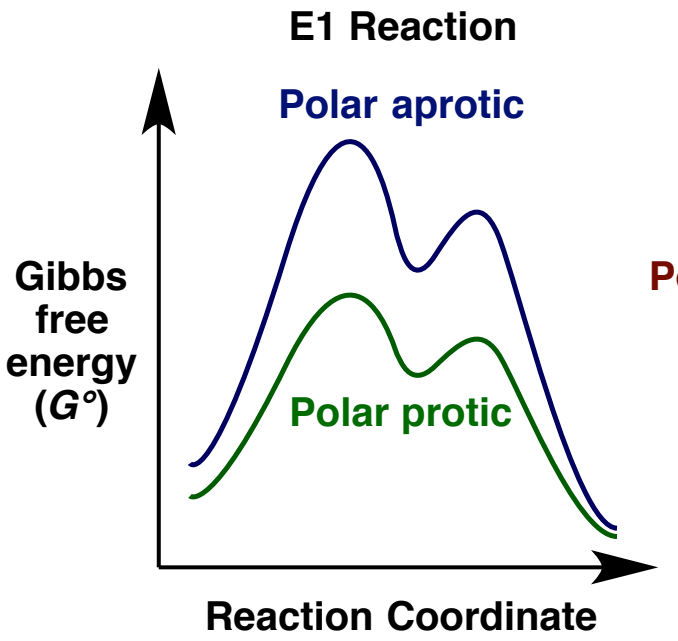
# E1 vs E2 vs $E1_{cb}$ – Substrate Dependence

- We are now in a position to draw comparisons between E1, E2 and $E1_{cb}$ reactions.
- E2 best substrate = tertiary halides, allylic, benzylic (most stable alkene formed).
- E1 best substrate = tertiary halides, allylic, benzylic and α-heteroatom (best stabilisation of carbocation intermediate).
- $E1_{cb}$ occurs for substrates where the LG is β to a π bond (e.g. carbonyl)



# E1 vs E2 – Solvent

- The solvent plays a key role, in determining E1 vs E2
- Polar protic solvents strongly favour E1 by stabilising (lowering the energy of) polar intermediates and transition states.
- The E2 is not significantly affected by the solvent and proceeds in a wide variety




**Polar protic solvents favour E1 by stabilising polar intermediates and transistion states**

# E1 vs E2 – Other Factors and Overall Summary

## Base

- E2 tends to proceed with strong bases – often means **negatively charged** bases such as $MeO^-$, $R_2N^-$ $NC^-$, $H^-$ and others
- E1 can proceed with a variety of bases including both negatively charged and neutral compounds. Also can occur in acid. Stronger bases tend to favour an E2 mechanism

## Leaving Group

- This is not the most important factor as both E2 and E1 mechanisms are favoured by the presence of a good leaving group such as $I^-$, $Br^-$, $^-OSO_2R$ and others.

- In summary, E1 and E2 mechanism are slightly trickier to distinguish. The biggest indicators are choice of base and solvent

| Factor | Favours E2 Mechanism | Favours E1 Mechanism |
|---|---|---|
| Substrate | Tertiary, benzylic, allylic, $\alpha$-heteroatom | |
| Base | Strong and moderate bases | Usually weak bases and acids |
| Leaving group | Good leaving group | |
| Solvent | Wide variety of solvents | Polar protic |

# Lecture 7: Introduction to Elimination Reactions – E1

**Key learning objectives:**

- Know the difference between the possible mechanisms for elimination – E2, E1 and $E1_{cb}$
- The rate law for an E1 reaction
- The curly arrow pushing mechanism, molecular orbital analysis, intermediate and stereo-chemical outcome of an E1 reaction
- The free energy diagram for an E1 reaction
- Regio- and stereoselectivity of E1 reaction
- The factors that favour an E1 mechanism including the nature of the substrate, base, solvent and leaving group
- Substrates that undergo the E1cb mechanism
- **Synthetic Analysis** – How to favour one elimination mechanism over the other?

# Lecture 7 Revision

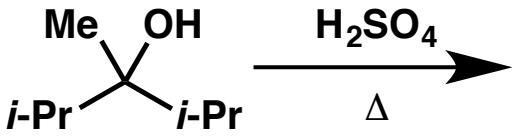
**To reinforce your understanding of the contents of this lecture, please refer to:**

- *Organic Chemistry 2nd Ed.* (J. Clayden et al.) Chapter 17 pp. 382-406.
- Practice questions provided on next slide.
- Online practice questions http://www.oxfordtextbooks.co.uk/orc/clayden2e/
  Username: clayden2e  Password: compound
- Online practice questions http://www.chem.ox.ac.uk/vrchemistry/iom/#
- CH4103 Online Test 7

# Lecture 7 Practice Questions / Guided Self-Study

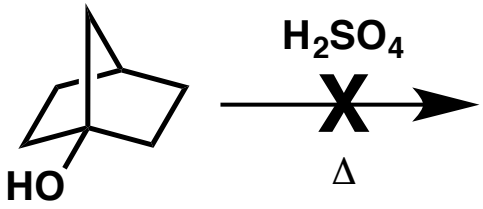
**For further practice, attempt the following questions in your own time:**

- Q1) What would you expect to be the major product formed from the elimination reaction below? Draw an arrow pushing mechanism




- Q2) Write down all possible products for the following E1 reactions. Which would be the major products in each case?


- Q3) Why will the following compound not undergo an E1 reaction?



# CH4103 Organic and Biological Chemistry
# LCM Lecture 8

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**Autumn Semester**

# Lecture 8 Preparation

**To best prepare yourself for the contents of this lecture, please refresh**

- Reaction thermodynamics (Unit 2, Lecture 1)
- Reaction kinetics (Unit 2, Lecture 2)
- Curly arrow pushing mechanisms (Unit 2, Lecture 3)
- The $S_N2$ reaction (Unit 2, Lecture 4)
- The $S_N1$ reaction (Unit 2, Lecture 5)
- The E2 reaction (Unit 2, Lecture 6)
- The E1 reaction (Unit 2, Lecture 7)

# Lecture 8: Substitution vs Elimination

**Key learning objectives:**

- In this final lecture, we will bring everything together!
- Be able to take into account various factors including substrate, nucleophile/base, leaving group and solvent to predict which of the type of substitution or elimination mechanism will dominate under a given set of conditions
- Appreciate that in some situations a mixture of 2 or more mechanisms may be in operation, resulting in the formation of multiple products

# Substitution vs Elimination

- Substitution and elimination reactions are almost always in competition with each other

- In order to predict the products of a reaction, it is necessary to determine which mechanisms are likely to occur

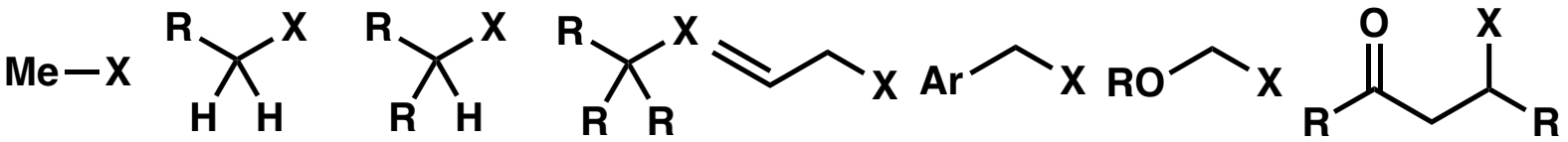
- Don't assume that there must always be one clear winner. In some cases there is, but often there are multiple products arising from multiple mechanisms

- The goal is to predict all of the products and to predict which will be major and which will be minor

- To accomplish this goal, for a given reaction we must:
- 1) Classify the substrate as methyl, 1°, 2°, 3°, allylic, benzylic, $\alpha$-heteroatom or $\beta$-LG-carbonyl
- 2) Classify the reagent as one of the following: a) strong nucleophile only; b) strong base only; c) strong nucleophile and strong base; d) weak nucleophile and weak base
- 3) Consider any solvent and temperature effects
- 4) Consider any relevant regiochemical and stereochemical requirements

# Substitution vs Elimination - Substrate

- An important factor in predicting the mechanism is the substrate

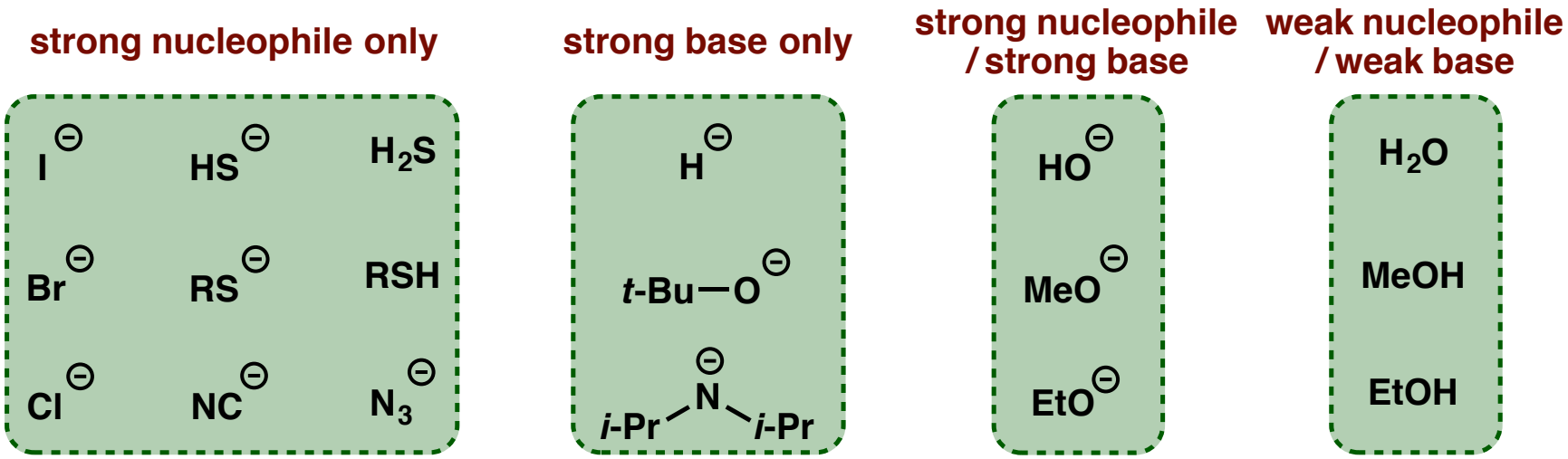
| Substrate |  | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Methyl | Primary | Secondary | Tertiary | Allylic | Benzylic | α-alkoxy | β-LG-carbonyl |
| $S_N1$ Mechanism | ☹ | ☹ | 😐 | 😊 | 😊 | 😊 | 😊 | 😐 |
| $S_N2$ Mechanism | 😊 | 🙂 | 😐 | ☹ | 😊 | 😊 | 🙂 | 😐 |
| E1 Mechanism | X | ☹ | 😐 | 😊 | 😊 | 😊 | 😊 | 😐 |
| E2 Mechanism | X | 😐 | 🙂 | 😊 | 😊 | 😊 | 🙂 | 😐 |
| $E1_{cb}$ Mechanism | X | X | X | X | X | X | X | 😊 |

😊 = excellent 🙂 = good 😐 = moderate ☹ = bad

- This table gives an indication of how complex the situation can be. However, we can make some general observations…

# Substitution vs Elimination – Reagent

- After we know what is possible for a substrate, we now inspect the reagent to see what will happen. We can divide reagents into categories:

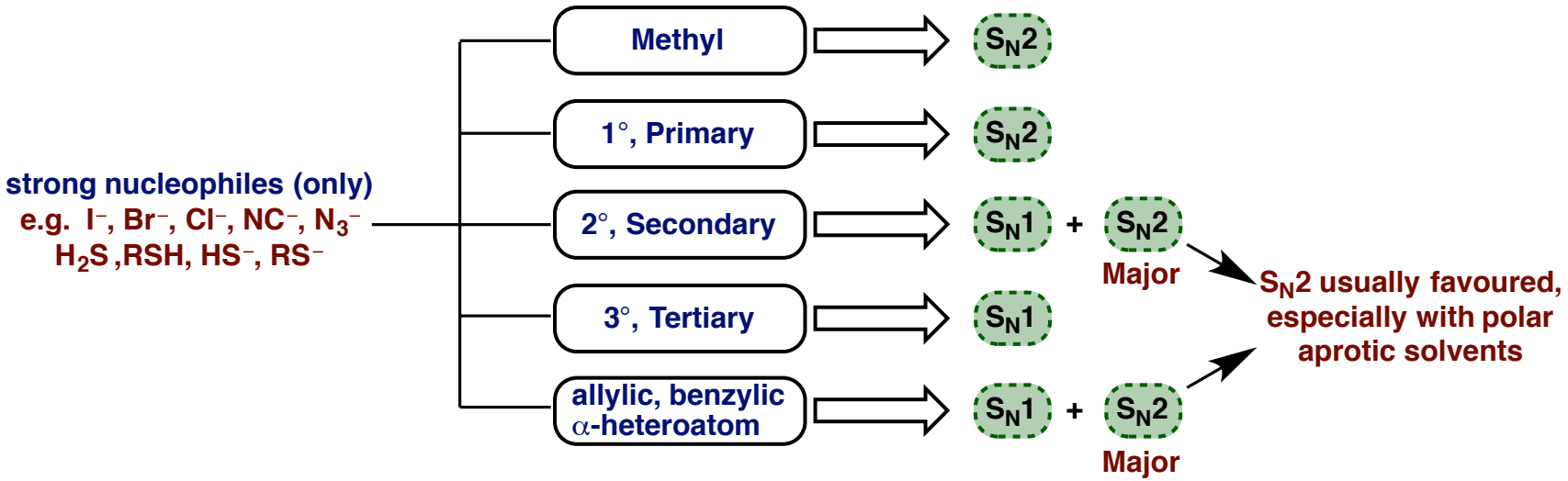



- Assigning the reagent (nucleophile/base) to one of the above categories gives us more information about the mechanism

# Substitution vs Elimination – Reagent

- When the reagent functions exclusively as a strong nucleophile (and not as a base):

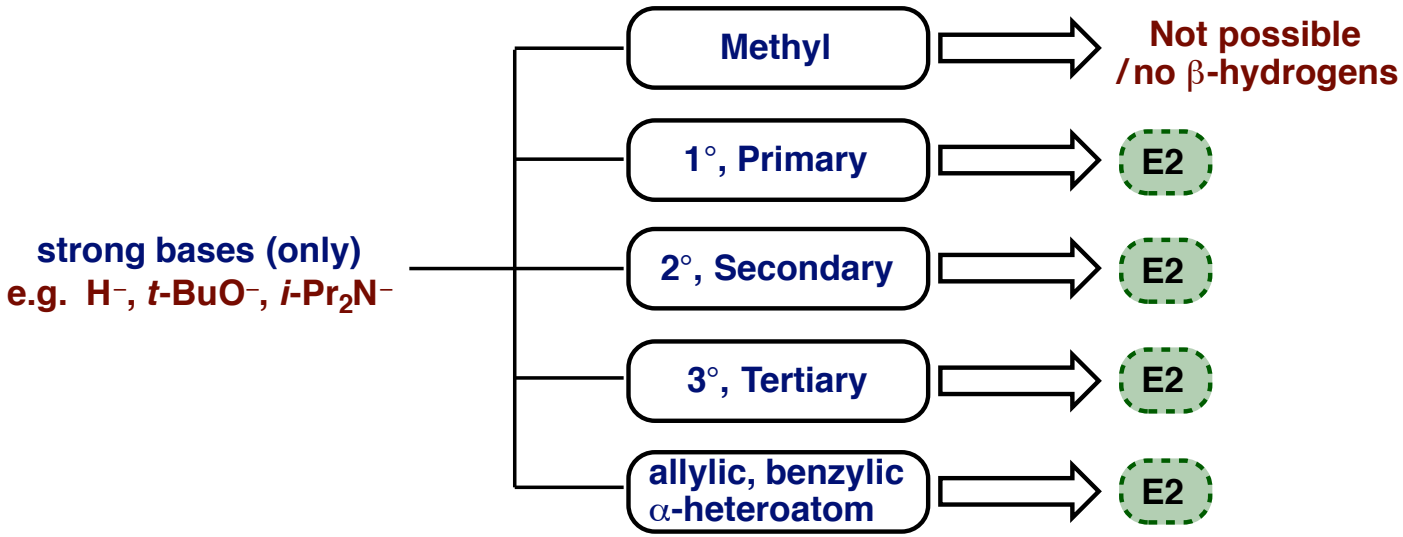
1) Only substitution reactions can occur, with no elimination
2) The substrate determines which mechanism operates
3) $S_N2$ predominates for methyl and primary substrates
4) $S_N1$ predominates for tertiary substrates
5) For secondary, allylic, benzylic and α-heteroatom substrates, both $S_N1$ and $S_N2$ can occur, although $S_N2$ is generally favoured (especially with polar aprotic solvents)



# Substitution vs Elimination – Reagent

- When the reagent functions exclusively as a strong base (and not as a nucleophile):

1) Only elimination reactions can occur, with no substitution
2) Such reagents are generally strong bases, resulting in a E2 process
3) This mechanism is not largely sensitive to steric hindrance and can occur for all the substrate classes discussed in this course except methyl
4) E1 reactions are strictly possible with these substrates but with strong bases, the E2 mechanism is favoured



# Substitution vs Elimination – Reagent

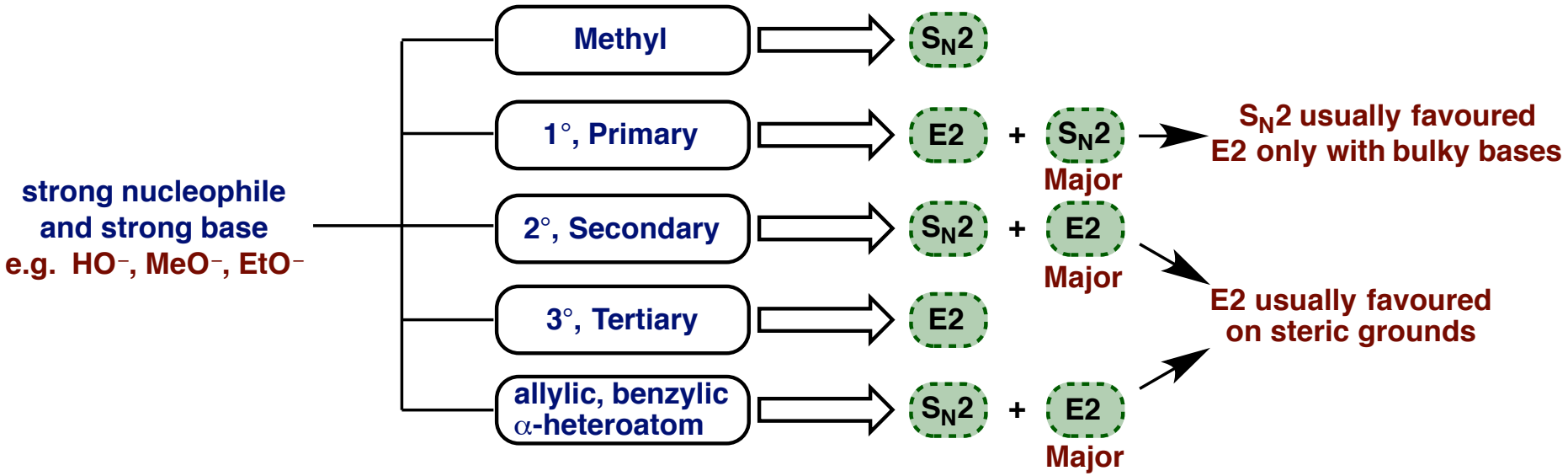
- When the reagent is both a strong nucleophile and a strong base:

1) Bimolecular reactions are favoured ($S_N2$ and E2)

2) For primary substrates, $S_N2$ predominates over E2 unless a bulky reagent is used (e.g. *t*-BuOK) in which case E2 predominates

3) For secondary, allylic, benzylic and α-heteroatom substrates substrates, E2 predominates as it is less sensitive to steric congestion than the corresponding $S_N2$

4) For tertiary substrates, E2 predominates due to the same steric argument



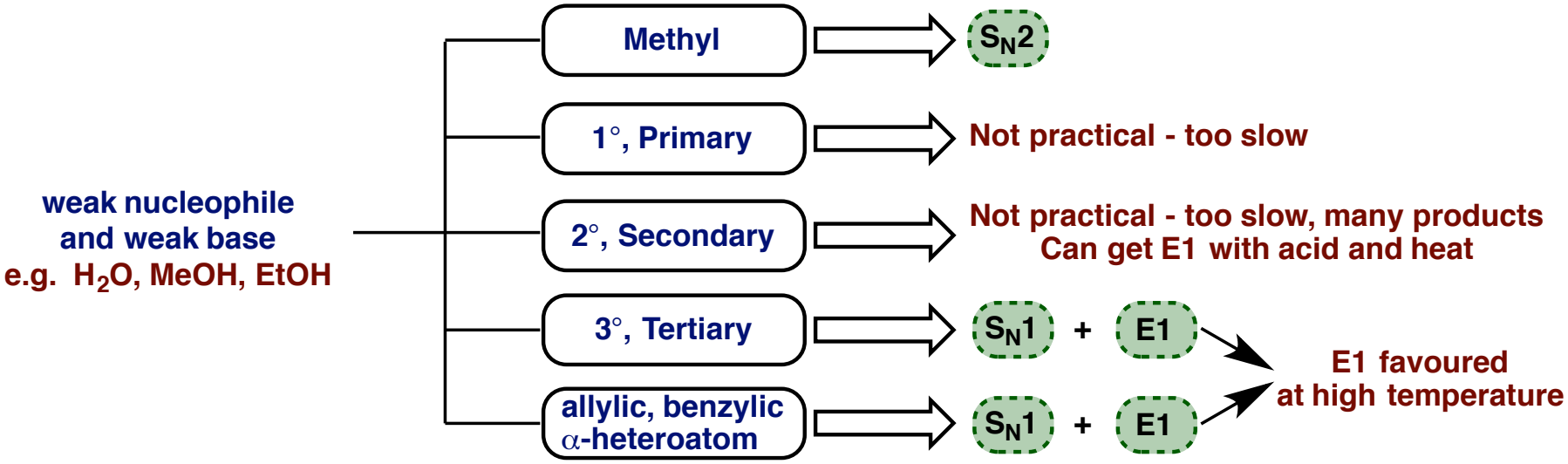
# Substitution vs Elimination – Reagent

- When the reagent is both a weak nucleophile and a weak base:

1) For primary substrates these reactions are not practical as they are too slow

2) For secondary substrates in general, these reactions are not practical as they are too slow and too many products can be formed. However, a secondary alcohol can undergo E1 reaction when treated with strong acid and heat.

3) For tertiary, allylic, benzylic and α-heteroatom substrates substrates, unimolecular reactions are favoured ($S_N1$ and E1). High temperature favours E1

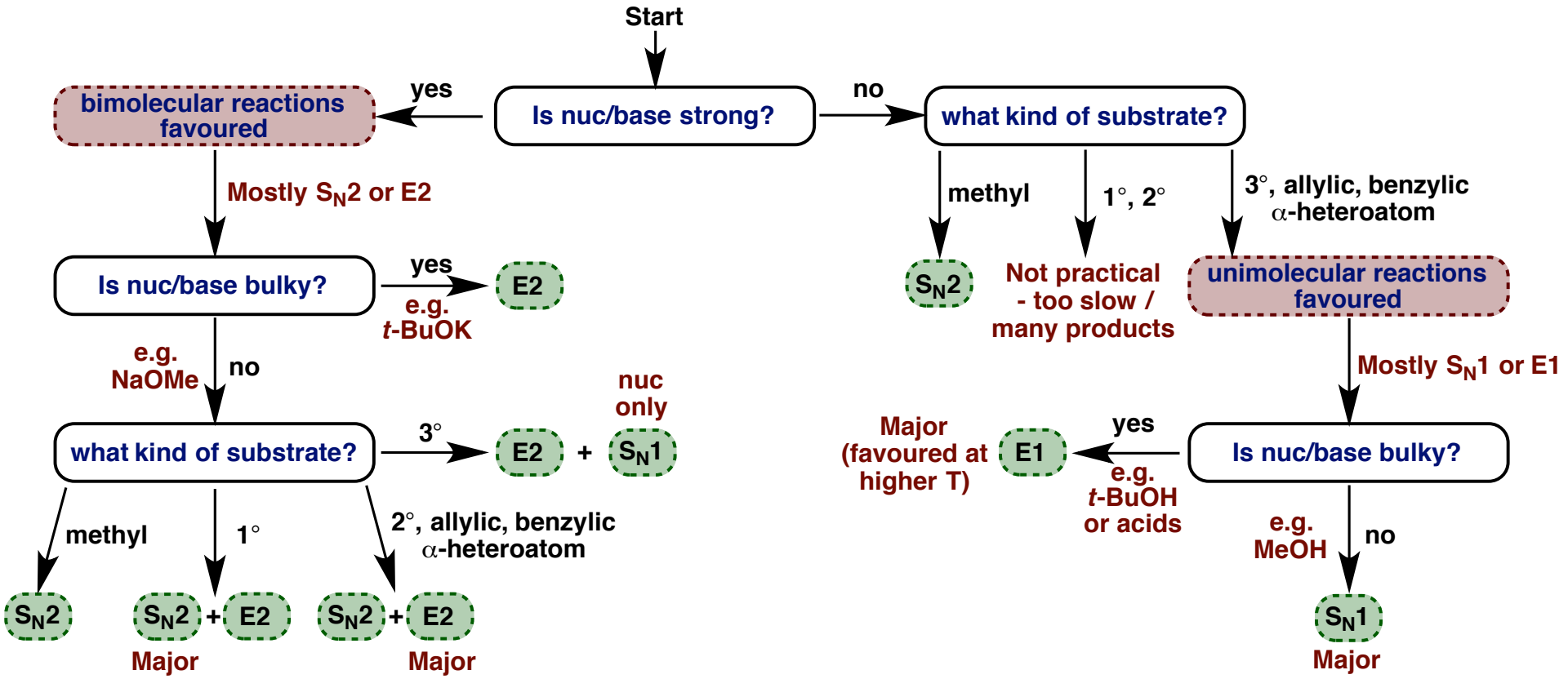


# Substitution vs Elimination – Other Indicators

- **Polar aprotic solvents** favour the $S_N2$ mechanism whereas **polar protic solvents** favour unimolecular mechanisms ($S_N1$ and E1) for all substrates
- An **increase in reaction temperature** favours elimination mechanisms (E1 and E2)
- Remember that a $S_N2$ reaction proceeds with **inversion of stereochemistry** whereas a $S_N1$ reaction proceeds **loss of stereochemistry (racemisation)**
- Remember that a E2 reaction is **stereospecific** – the stereoisomer of the product formed is dependent upon the stereoisomer of the starting material – whereas a E1 reaction is not
- The **rate equations** for each mechanism can also provide valuable insight if kinetic data is provided. The rate of biomolecular reactions ($S_N2$ and E2) are dependent upon the concentration of both substrate and nucleophile/base whereas the rate of unimolecular reactions ($S_N1$ and E1) are only dependent upon substrate concentration
- Time to put it all together!

# Substitution vs Elimination – Predicting Mechanism

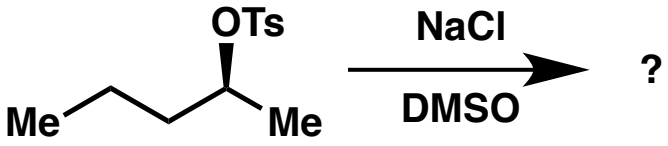
- The flow chart below puts everything together and simplifies the decision making process. Don't forget $E1_{cb}$ for substrates containing a leaving group β to a carbonyl.



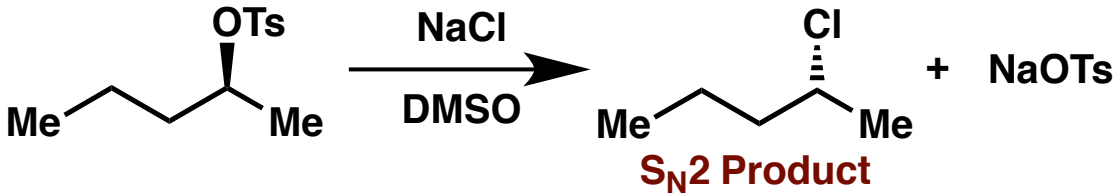

- It is time to put everything into practice by working through several examples

# Worked Example 1 – Substitution vs Elimination

- Predict the major product(s) of the following reaction. You must always be able to rationalise any regio- and/or stereoselectivity and draw curly arrow mechanisms

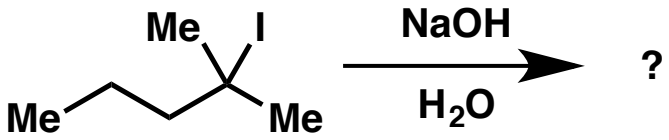



- The reaction shown has the following characteristics:
- 1) Substrate = secondary tosylate (treat tosylates/mesylates the same as halides)
- 2) Reagent = $Cl^-$ which is a non-bulky strong nucleophile and a poor base
- 3) Solvent = DMSO which is a polar aprotic solvent
- Major pathway = **$S_N2$** – substrate favours $S_N2$ and E2, reagent and solvent favour $S_N2$. Remember that this proceeds with inversion of stereochemistry.

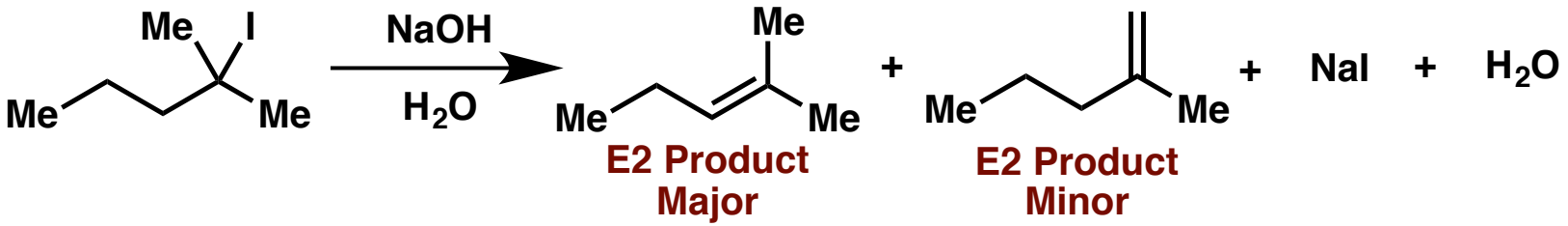


# Worked Example 2 – Substitution vs Elimination

- Predict the major product(s) of the following reaction. You must always be able to rationalise any regio- and/or stereoselectivity and draw curly arrow mechanisms

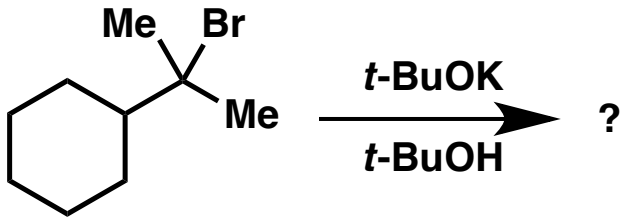



- The reaction shown has the following characteristics:
- 1) Substrate = tertiary iodide
- 2) Reagent = $HO^-$ which is a non-bulky strong nucleophile and a strong base
- 3) Solvent = $H_2O$ which is a polar protic solvent
- Major pathway = **E2** – substrate favours $S_N1$, E1 or E2, reagent favours E2, solvent not important here. The trisubstituted alkene is the favoured product – Zaitsev's rule.



# Worked Example 3 – Substitution vs Elimination

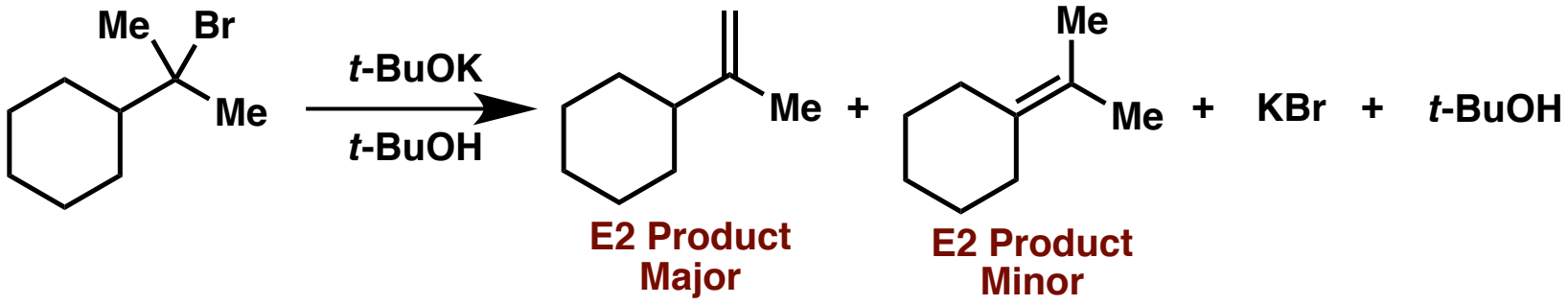
- Predict the major product(s) of the following reaction. You must always be able to rationalise any regio- and/or stereoselectivity and draw curly arrow mechanisms




- The reaction shown has the following characteristics:

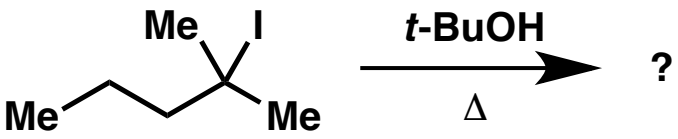
- 1) Substrate = tertiary bromide
- 2) Reagent = *t*-BuOK which is a bulky strong base and a poor nucleophile
- 3) Solvent = *t*-BuOH which is a polar protic solvent

- Major pathway = **E2** – substrate favours $S_N1$, E1 or E2, reagent favours E2, solvent not important here. The disubstituted alkene is the favoured product – bulky base.



# Worked Example 4 – Substitution vs Elimination

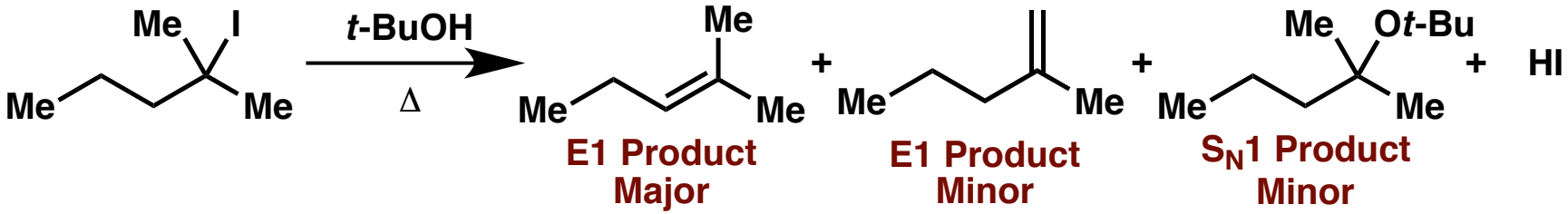
- Predict the major product(s) of the following reaction. You must always be able to rationalise any regio- and/or stereoselectivity and draw curly arrow mechanisms




- The reaction shown has the following characteristics:

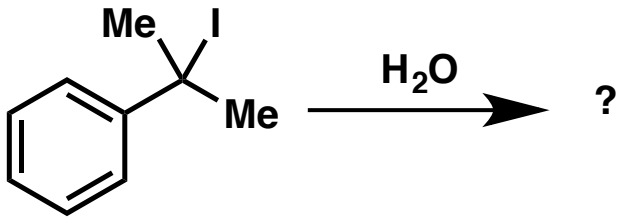
- 1) Substrate = tertiary iodide
- 2) Reagent = *t*-BuOH which is a bulky weak nucleophile and a poor base
- 3) Solvent = *t*-BuOH which is a polar protic solvent
- 4) Temperature = high

- Major pathway = **E1** – substrate favours $S_N1$, E1 or E2, solvent favour $S_N1$ or E1, reagent and high temperature favours elimination, so E1.



# Worked Example 5 – Substitution vs Elimination

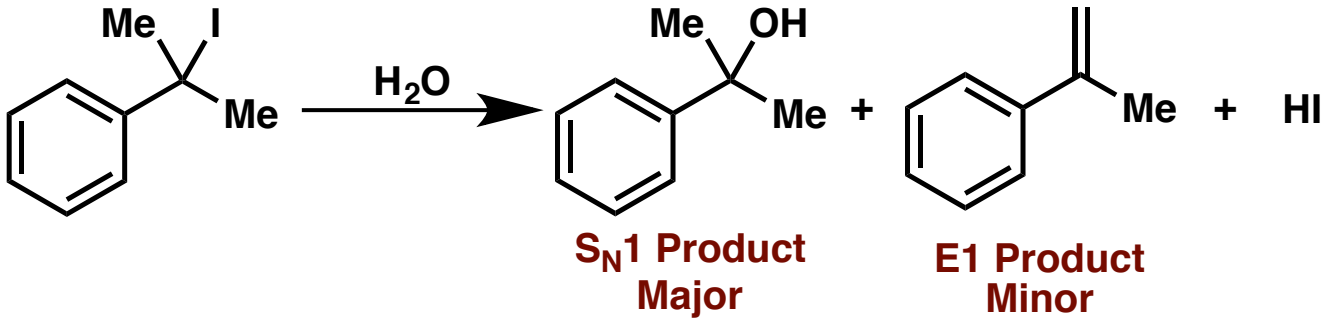
- Predict the major product(s) of the following reaction. You must always be able to rationalise any regio- and/or stereoselectivity and draw curly arrow mechanisms




- The reaction shown has the following characteristics:

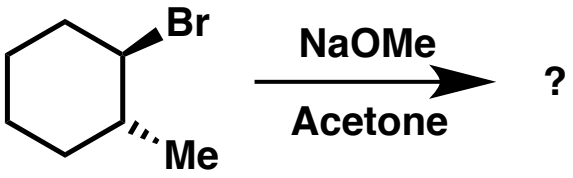
- 1) Substrate = benzyl iodide
- 2) Reagent = $H_2O$ which is a non-bulky weak nucleophile and a poor base
- 3) Solvent = $H_2O$ which is a polar protic solvent

- Major pathway = **$S_N1$** – substrate favours $S_N1$, E1 or E2, solvent favours $S_N1$ or E1, reagent and no heat favours substitution, so $S_N1$.



# Worked Example 6 – Substitution vs Elimination

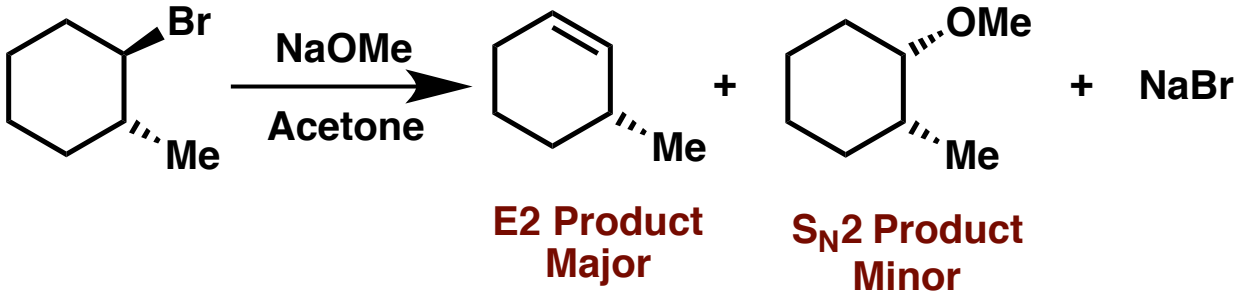
- Predict the major product(s) of the following reaction. You must always be able to rationalise any regio- and/or stereoselectivity and draw curly arrow mechanisms




- The reaction shown has the following characteristics:

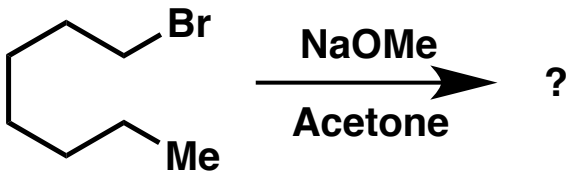
- 1) Substrate = secondary bromide
- 2) Reagent = NaOMe which is a non-bulky strong nucleophile and a strong base
- 3) Solvent = acetone which is a polar aprotic solvent

- Major pathway = **E2** – substrate, solvent and reagent all favour $S_N2$ and E2, in such situations E2 is favoured due to increased steric congestion with 2° substrates, so E2



# Worked Example 7 – Substitution vs Elimination

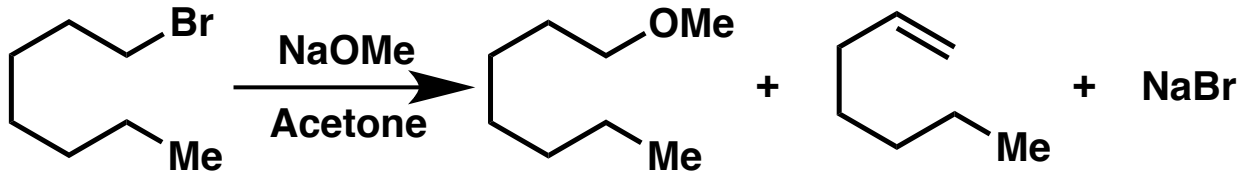
- Predict the major product(s) of the following reaction. You must always be able to rationalise any regio- and/or stereoselectivity and draw curly arrow mechanisms




- The reaction shown has the following characteristics:

- 1) Substrate = primary bromide
- 2) Reagent = NaOMe which is a non-bulky strong nucleophile and a strong base
- 3) Solvent = acetone which is a polar aprotic solvent

- Major pathway = **$S_N2$** – substrate, solvent and reagent all favour $S_N2$ and E2, in such situations $S_N2$ is favoured due to reduced steric congestion with 1° substrates, so $S_N2$

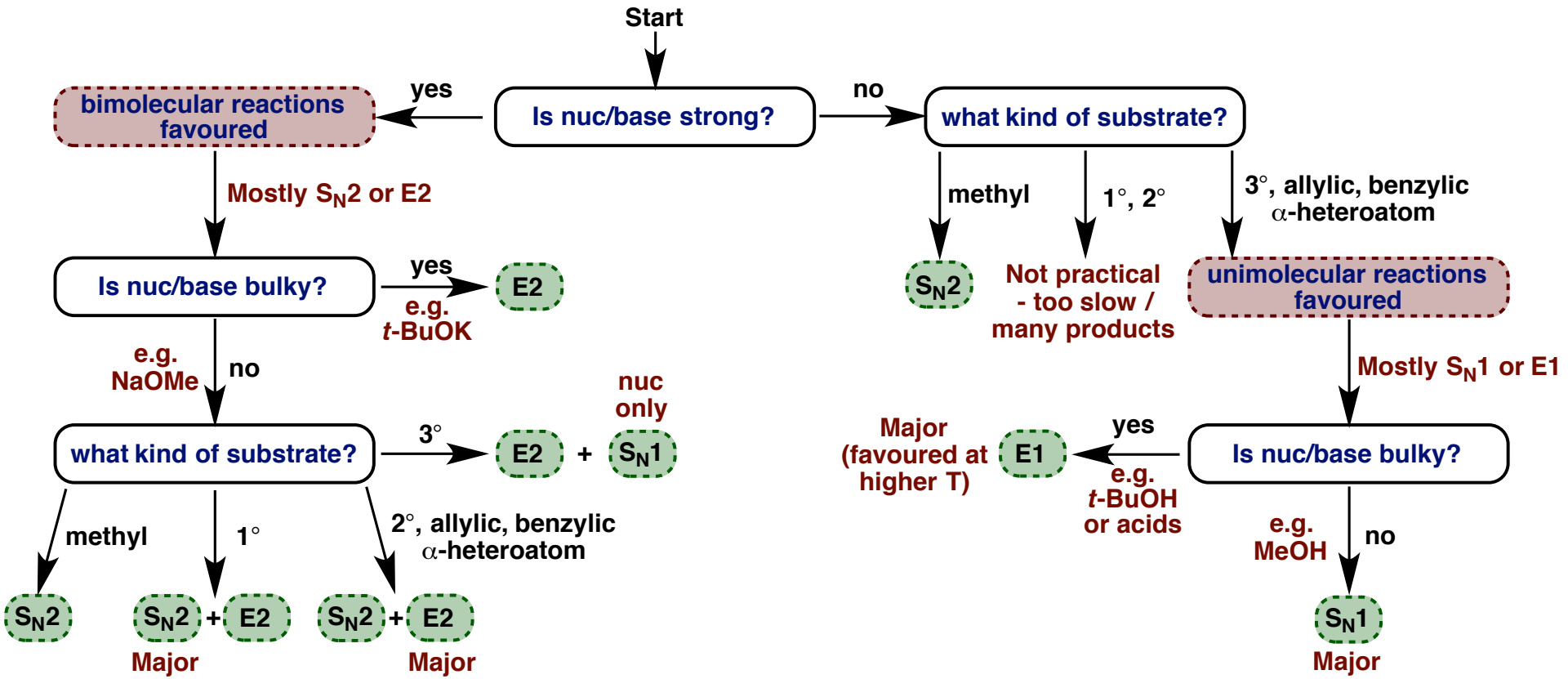



**$S_N2$ Product Major**

**E2 Product Minor**

# Substitution vs Elimination – Predicting Mechanism

- The flow chart below puts everything together and simplifies the decision making process. Don't forget $E1_{cb}$ for substrates containing a leaving group β to a carbonyl.




- You will **NOT** get this flow chart in exams, so you must learn the reactivity patterns!

# Lecture 8: Substitution vs Elimination

**Key learning objectives:**

- In this final lecture, we will bring everything together!
- Be able to take into account various factors including substrate, nucleophile/base, leaving group and solvent to predict which of the type of substitution or elimination mechanism will dominate under a given set of conditions
- Appreciate that in some situations a mixture of 2 or more mechanisms may be in operation, resulting in the formation of multiple products

# Lecture 8 Revision

**To reinforce your understanding of the contents of this lecture, please refer to:**

- *Organic Chemistry 2nd Ed.* (J. Clayden et al.) Chapter 15 pp. 328-359 and Chapter 17 pp. 382-406.
- Worked examples provided in this lecture.
- Online practice questions http://www.oxfordtextbooks.co.uk/orc/clayden2e/
  Username: clayden2e  Password: compound
- Online practice questions http://www.chem.ox.ac.uk/vrchemistry/iom/#
- CH4103 Online Test 8

# Organic Chemistry Industrial Placements

**There are lots of opportunities to do organic chemistry placements within industry or during a year abroad**








**Key info:**

- Application deadlines are usually around Sept – Feb (start of 2nd year)
- Require up-to-date CV, covering letter and referees
- Interview practice available with Dr Louis C. Morrill and Dr Duncan L. Browne