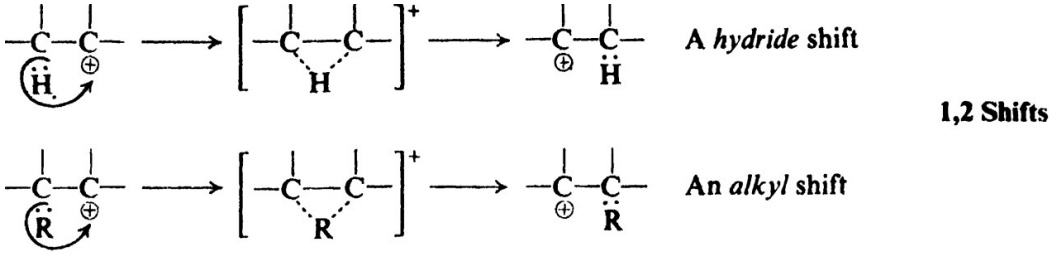
Introduction:

Rearrangements are moves the migrating group from one atom to the very next atom. A hydrogen atom or alkyl group migrates with a pair of electrons from an adjacent carbon to the carbon bearing the positive charge.

The carbon that loses the migrating group acquires the positive charge. A **migration of hydrogen with a pair of electrons** is known as a **hydride shift**; a similar **migration of an alkyl group** is known as an **alkyl shift**. These are just two examples of the most common kind of rearrangement, the 1,2-shifts: rearrangements in which the migrating group **moves from one atom to the very next atom**.



Rearrangement of carbonium ions:

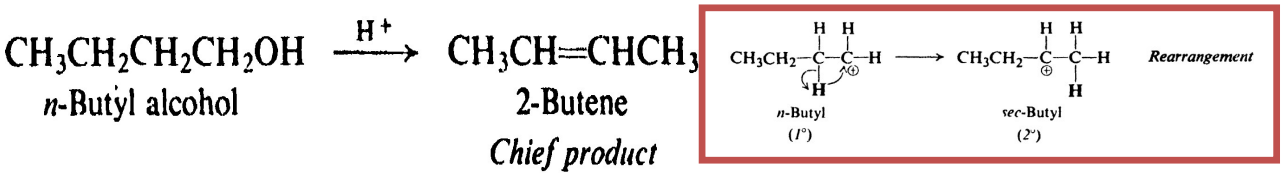
Form method to formed carbonium ion (C+):

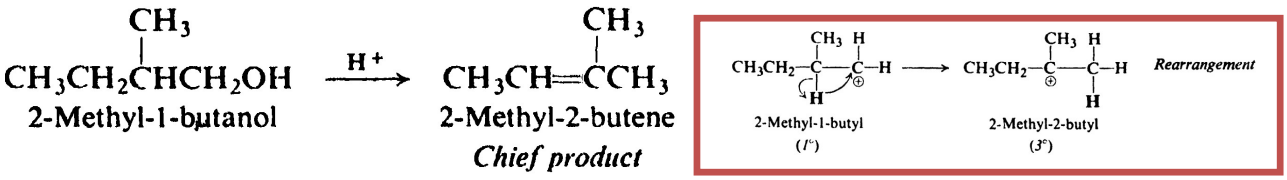
1- dehydration of alcohol (carbonium ion is formed by the loss of water from the protonated alcohol).

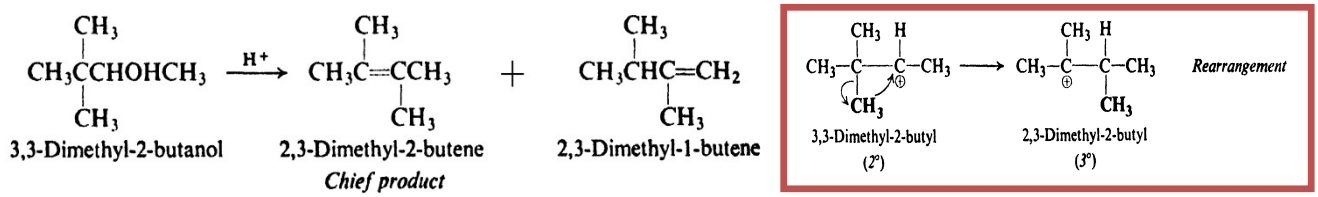
The idea of form intermediate carbonium ions: a **carbonium ion can rearrange to form a more stable carbonium ion**, **If a 1,2-shift of hydrogen or alkyl can form a more stable carbonium ion, then such a rearrangement takes place**.

Stability of carbonium ions	$3° > 2° > 1° > CH_3^+$
Ease of formation of carbonium ions	$3° > 2° > 1° > CH_3^+$

Example:





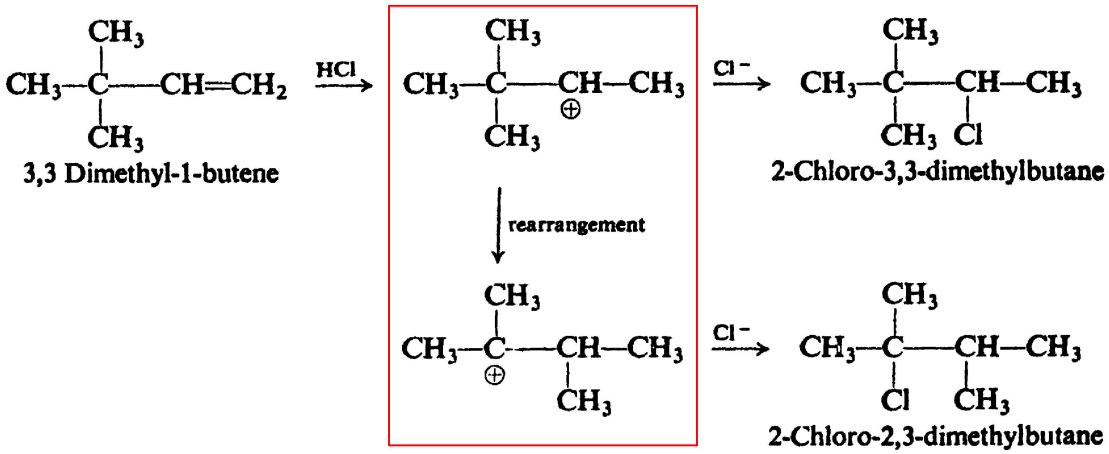


2- **Electrophilic addition to a carbon-carbon double bond(C=C) involves the intermediate formation of the more stable carbonium ion (**Markovnikov's rule, in acidic reagents).

The mechanism of electrophilic addition is consistent with the occurrence of rearrangements.

If carbonium ions are intermediates in electrophilic addition, then we should expect the reaction to be accompanied by the kind of rearrangement that we said earlier is highly characteristic of carbonium ions.

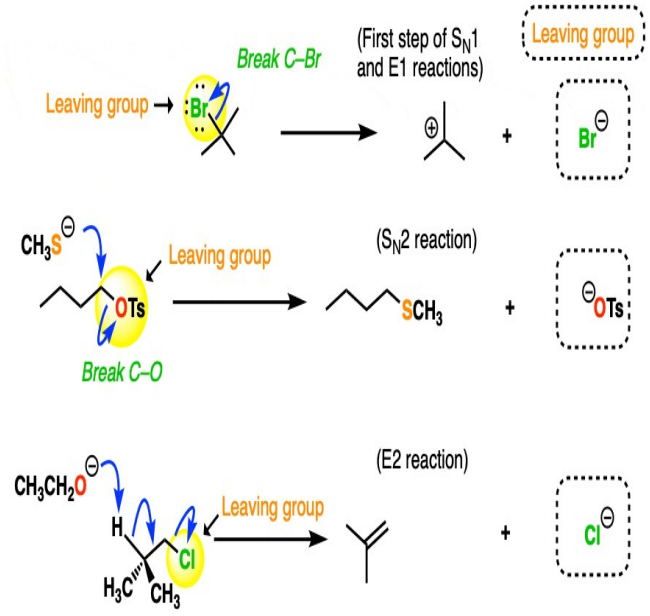
Example:



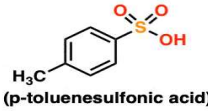
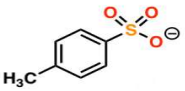
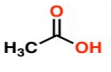
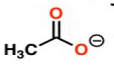
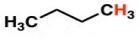
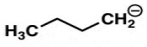
leaving group (nucleofuge):

Is the **new Lewis base** that is generated in various **substitution** and **elimination reactions** when a **new bond is formed to carbon**.

Examples:



- Good leaving groups tend to be **weak bases**. The conjugate bases of strong acids (e.g. I(-), Br(-), Cl(-), H_2O, TsO(-) tend to be excellent leaving groups
- Poor leaving groups can be turned into better leaving groups by converting them into their conjugate acids
- In general, substitution and elimination reactions tend to favor the direction in which the leaving group is a weaker base than the nucleophile/base.

Functional group / Example		pKa	Conjugate base (Leaving group)	
Hydroiodic acid	HI	–10	I^-	Excellent leaving groups (extremely weak bases)
Hydrobromic acid	HBr	–9	Br^-	
Hydrochloric acid	HCl	–6	Cl^-	
Sulfuric acid	H_2SO_4	–3	HSO_4^-	
Sulfonic acids	 (p-toluenesulfonic acid)	–3		
Hydronium ion	H_3O^+	–1.7	H_2O	
Hydrofluoric acid	H–F	3.2	F^-	Exception: F^- is typically an extremely poor leaving group (forms strong bonds to carbon)
Carboxylic acids		4		Moderate leaving groups (weak bases)
Protonated amines	$NH_4^+ Cl^-$	9-11	NH_3	
Water	HO–H	14	HO^-	Poor leaving groups (strong bases)
Alcohols	CH_3O–H	16-18	CH_3O^-	
Amine	NH_3	~35	NH_2^-	Extremely poor leaving groups (very strong bases)
Hydrogen	H–H	42	H^-	
Alkane		~50		

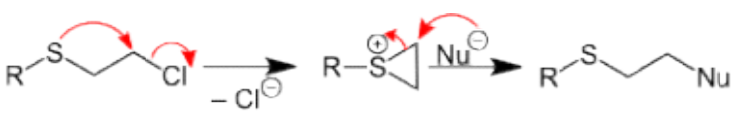
Neighbouring group participation (NGP), known as anchimeric assistance (Greek anchi = neighbouring; mer = part):

Is the **interaction of a reaction centre** with a **lone pair** of **electrons** in an **atom** or the **electrons** present in a **π bond** contained within the **parent molecule but not conjugated with the reaction centre**.

Note: when NGP is in operation it is normal for the **reaction rate** to be **increased**. It is also possible for the **stereochemistry** of the reaction to be **abnormal** (or **unexpected**) when compared with a normal reaction.

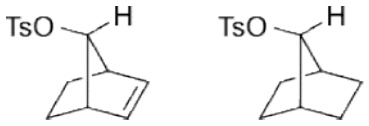
Types of Neighbouring groups:

1- **lone pairs in the heteroatoms (N, O, S)**: is the reaction of sulfur or nitrogen with a nucleophile (type of reaction is substitution).

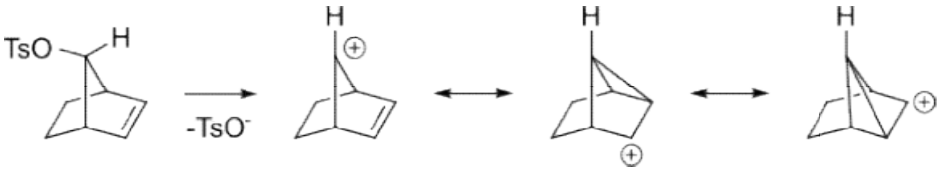


Note: Important atoms and groups that can act as neighbouring groups are **COO-, COOR, COAr, OCOR, OR, OH, O-, NH_2, NHR, NR_2, NHCOR, SH, SR, S-, SO_2Ph, I, Br,** and **Cl**. The effectiveness of halogens as neighbouring groups decreases in the order **I>Br>Cl**. The **chloride is a very weak neighbouring group and can be shown to act in this way only when the solvent does not interfere**.

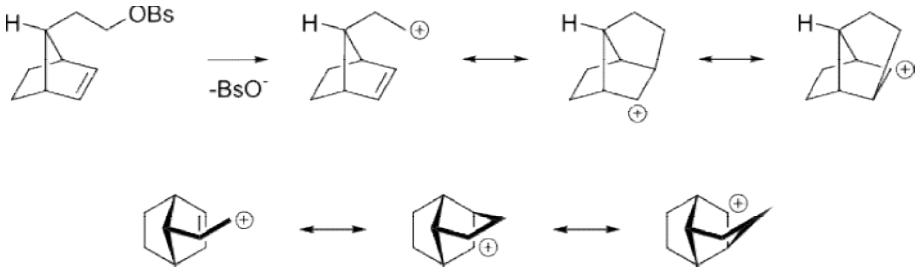
2- **Alkene (=):** The **π orbitals** of an alkene can stabilize a transition state by helping to **delocalize the positive charge of the carbocation**.



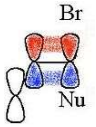
The carbocationic intermediate will be stabilized by resonance where the positive charge is spread over several atoms.



Even if the alkene is more remote from the reacting centre the alkene can still act in this way. For instance, in the following **alkyl benzenesulfonate**, the **alkene is able to delocalised the carbocation**.



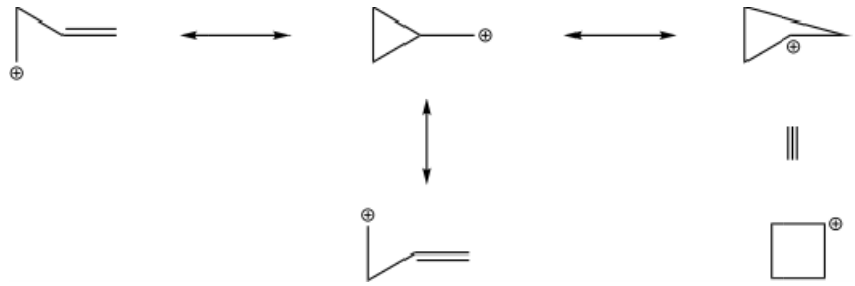
Also, the increase in the rate of the S_N2 reaction of allyl bromide with a nucleophile compared with the reaction of n-propyl bromide is **because the orbitals of the π bond overlap with those of the transition state**. In the allyl system, the **alkene orbitals overlap with the orbitals of an S_N2 transition state**.



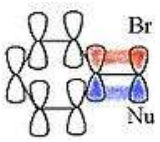
Note: the mechanism of S_N2 is such that the nucleophile attacks from the rear of the leaving group, leading to an inversion of configuration. However, there are some examples of retention of configuration in S_N2

reactions, where an atom or group (Z) close to the carbon undergoing substitution assists in the reaction with its available pair of electrons.

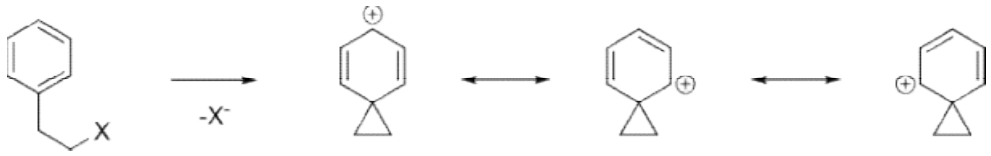
3- **Cyclopropane, Cyclobutane or a homoallyl group:** If Cyclopropylmethyl chloride is reacted with ethanol and water then a mixture of **48% cyclopropylmethyl alcohol**, **47% cyclobutanol** and **5% homoallyl alcohol (but-3-enol)** is obtained. This is because the **carbocationic intermediate is delocalised onto many different carbons through a reversible ring opening**.



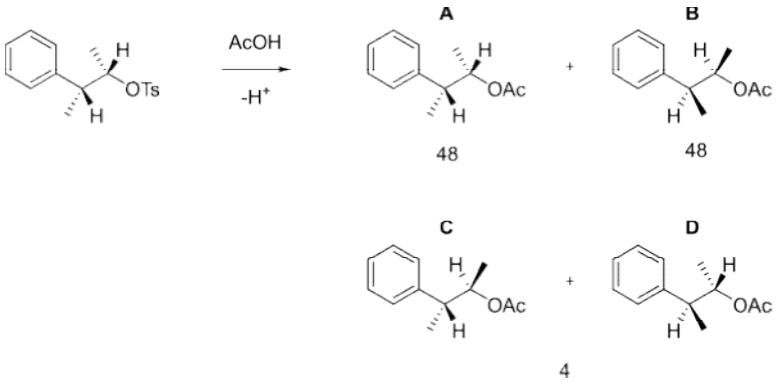
4- **Aromatic ring**: In the case of a **benzyl halide**, the reactivity is higher because the **S_N2 transition state enjoys a similar overlap effect** to that in the **allyl system according to the molecular orbital theory**.



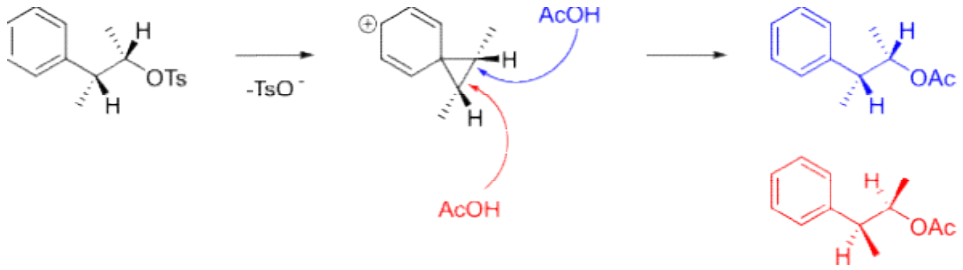
An aromatic ring can assist in the formation of a **carbocationic intermediate called a phenonium ion by delocalised the positive charge**.



When the following tosylate reacts with acetic acid in solvolysis then rather than a simple S_N2 reaction forming B, a **48:48:4** mixture of **A, B (which are enantiomers)** and C+D was obtained.



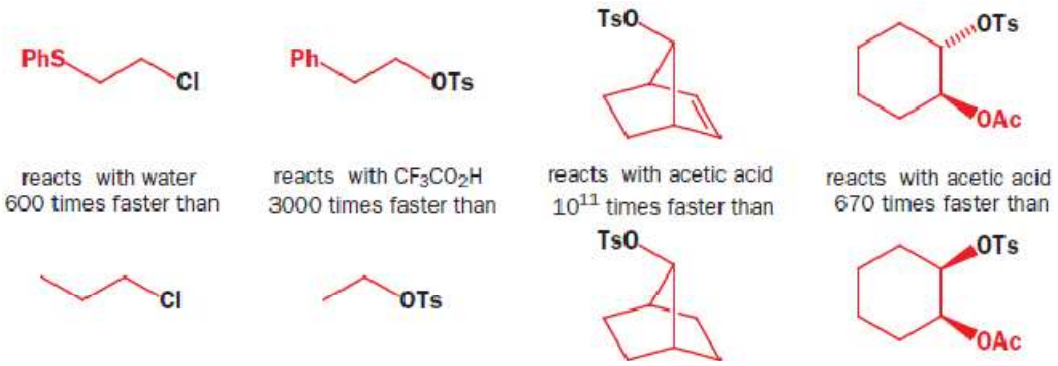
Mechanism: which forms A and B are shown below.



5- **Aliphatic C-C or C-H bonds**: Aliphatic C-C or C-H bonds can lead to **charge delocalization if these bonds are close and antiperiplanar to the leaving group. Corresponding intermediates are referred to as nonclassical ions**, with the 2-norbornyl system as the most well-known case.

-Neighbouring groups can accelerate substitution reactions.

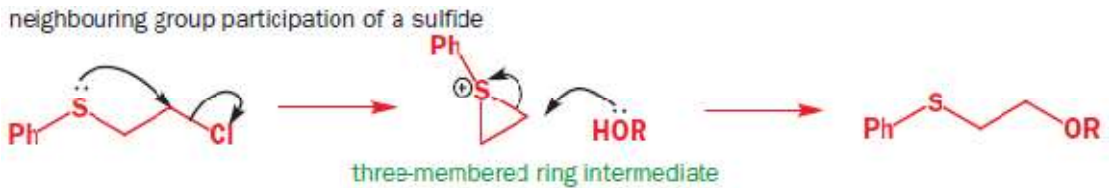
Examples: Each of these reactions is a substitution of the leaving group (OTs or Cl) by solvent, known as **solvolysis (is the reaction in which the solvent is also the nucleophile**). Where the functional groups change at the carbon next to the reaction center, and we call these groups neighbouring groups.



Nearby groups can evidently **increase the rate** of substitution reactions significantly. The mechanism by which they speed up the reactions is known as neighbouring group participation.

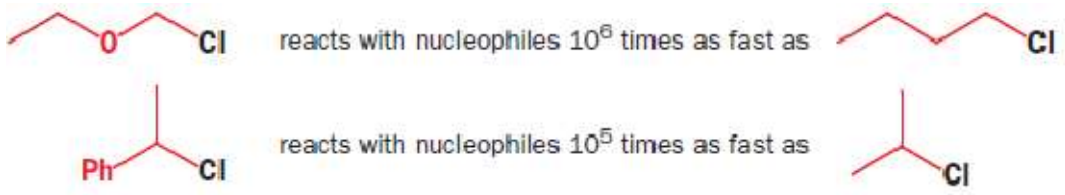
Note: All **mechanisms** involving **neighbouring group participation** is the **formation of a cyclic intermediate.**

Mechanism: The **sulfide** assists by **forming a three-membered ring**.



-While the **cation-stabilizing group** at the reaction center makes S_N1 reactions **very fast** by **lone pair** in **atom** or **phenyl group**.

Examples:

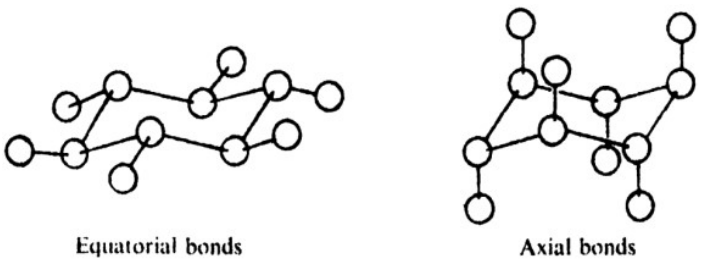


Mechanism: The ether assists by forming a **π bond**

Note: In both cases, ionization of the starting material is **assisted by the lone pair of an electron-rich functional group**.

Conformations of cyclohexane:

One conformations of cyclohexane is **Chair**, although the cyclohexane ring is **not flat**, we can consider that the carbon atoms lie roughly in a plane. If we look at the molecule in this way, we see that the hydrogen atoms occupy **two kinds of position**: six hydrogens lie in the plane, while six hydrogens lie above or below the plane. The bonds holding the **hydrogens that are in the plane** of the ring lie in a belt about the "**equator**" of the ring, and are called **equatorial (eq) bonds**. The bonds holding **the hydrogen atoms that are above and below the plane** are pointed along an axis perpendicular to the plane and are called **axial (ax) bonds**. In the **chair conformation each carbon atom has one equatorial bond and one axial bond**.

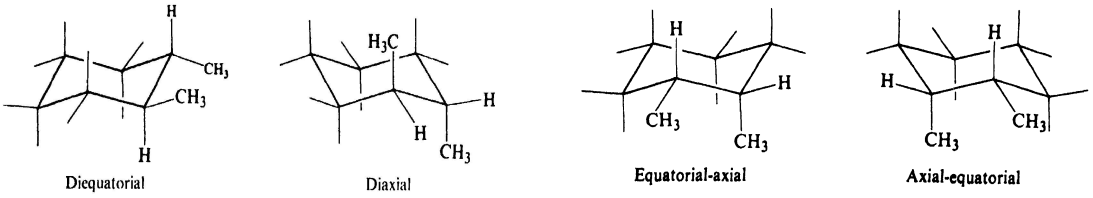


Equatorial bonds Axial bonds

Note: the equatorial conformation to be the more stable than axial conformation.

a- Chair conformations of l,2-dimethylcyclohexane: form **four conformations {*trans* (dieq, diax) , *cis* (eq-ax, ax-eq)}**.

***trans*-l,2-dimethylcyclohexane** **_cis_- 1 ,2-dimethyicyclohexane**



Note: In the **most stable** conformation of ***trans*** -l,2-dimethylcyclohexane, **both CH_3 groups occupy uncrowded equatorial positions**. In either conformation of the ***cis***-l,2-dimethylcyclohexane, only **one CH_3 group can occupy an equatorial position**. **It is not surprising to find that *trans*-l,2-dimethylcyclohexane is more stable than *cis*-l,2-dimethylcyclohexane**.

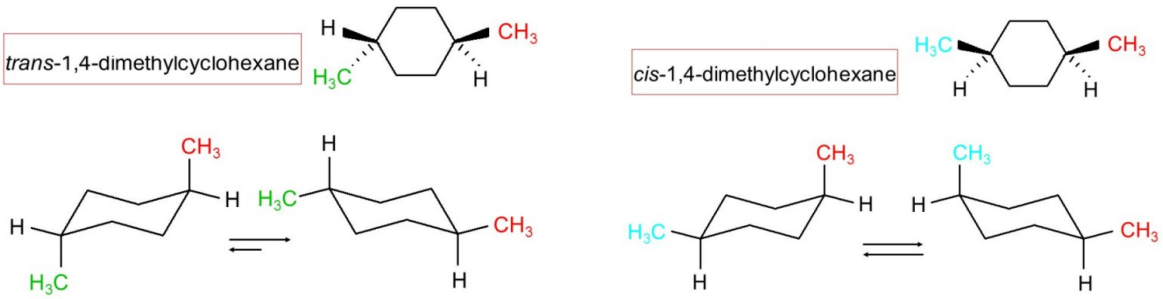
Note: the *trans* conformation to be the more stable than *cis* conformation.

b- Chair conformations of l,3-dimethylcyclohexane: form **four conformations {*cis* (dieq, diax) , *trans* (eq-ax, ax-eq)}**.

Cis-1,3-dimethylcyclohexane *Trans*-1,3-dimethylcyclohexane

Note: *cis*-l,3-dimethylcyclohexane is more stable than *trans*-l,3-dimethylcyclohexane.

c- Chair conformations of l,4-dimethylcyclohexane: form **four conformations {*trans* (dieq, diax) , *cis* (eq-ax, ax-eq)}**.



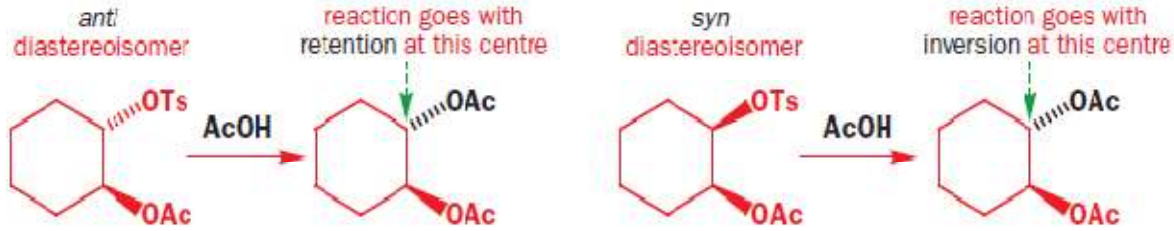
Note: *trans*-l,4-dimethylcyclohexane is more stable than *cis*-l,4-dimethylcyclohexane.

Neighbouring group participation role in the stereochemistry of reaction:

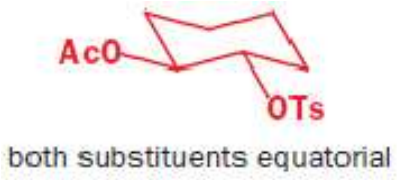
Stereochemistry can indicate neighbouring group participation through the **first evidence** is the **increase in rate**. The **neighbouring groups** will become involved only if they can **increase the rate** of the **substitution reaction** otherwise, the mechanism will just follow the ordinary **S_N2** pathway. But more important information comes from reactions where stereochemistry is involved. Not only does the **first of these reactions go faster than the second its stereochemical course is different too**.

1- If you see a substitution reaction at a stereogenic saturated carbon atom that goes with the **retention of stereochemistry**, indicates the presence neighbouring group participation.
2- Neighbouring groups participate only if they speed up the reaction.
3- Neighbouring groups participate **can be used to form the cyclic intermediate**(**three-, five-, six-**membered rings).

Examples:

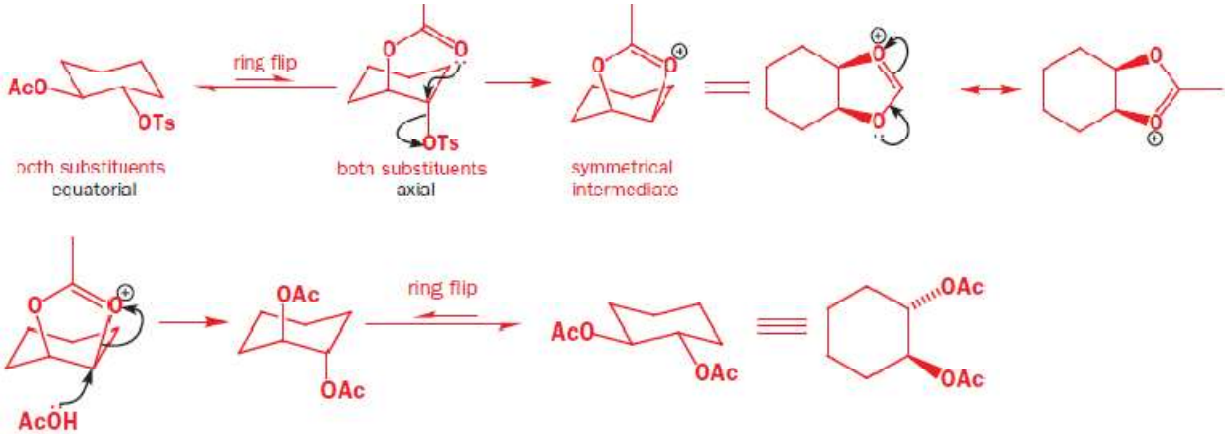


Although one starting material has ***syn*** and the other ***anti*** stereochemistry, the **products have the same (anti) stereochemistry**: one substitution goes with **retention** and one goes with **inversion because of the neighbouring group's participation**. To explain this, we should first **draw the six-membered rings in their real conformation**. For the **anti** compound, **both substituents** can be **equatorial**.

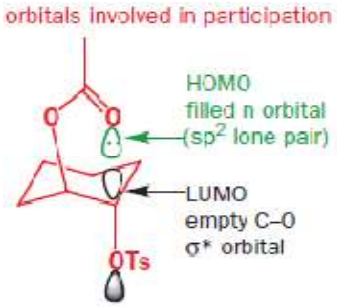


However, not much can happen in this conformation but, if we allow the **ring to flip**, you can see immediately that the **acetate substituent is ideally placed to participate in the departure of the tosylate group**.

Mechanism:



The result is an entirely **symmetrical intermediate the positive charge on one of the oxygens atoms**, by **delocalization of the positive charge over both oxygens atoms**. The **intramolecular S_N2** reaction takes place with **inversion**, as required by the orbitals, so now the junction of the two rings is ***cis***.



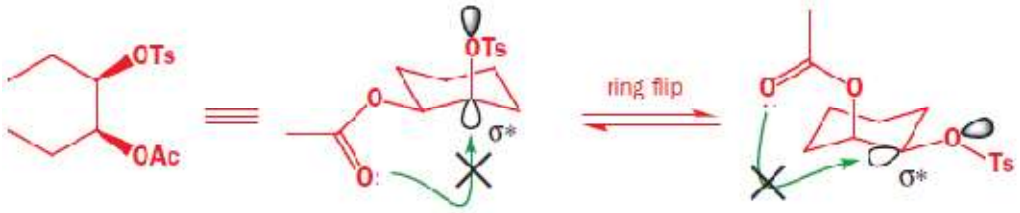
The next step is **attack of acetic acid on the intermediate**. This is another S_N2 reaction, which also proceeds with **inversion and gives back a *trans* product**.

Note: While the mechanism of this first step of the substitution reaction is S_N2 in appearance a nucleophile (the acetate group) arrives just as a leaving group (the tosylate group) departs it is also, of course, only **unimolecular**.

Overall, **the reactions have retention of stereochemistry**. **S_N2** reactions go with **inversion**, and **S_N1** reactions with **loss of stereochemical** information so this result is **possible only** if we **have two sequential S_N2 reactions taking place in other words neighbouring group participation**.

-While the **other diastereoisomer** reacts (***syn***) with the **inversion of stereochemistry**. By drawing the **mechanism** for the **intramolecular displacement of the tosyl group**. Whether you **put the tosylate or the acetate group equatorial doesn't matter**; there is **no way in which the**

acetate oxygen's lone pair can reach the σ* orbital of the tosylate C–O bond.

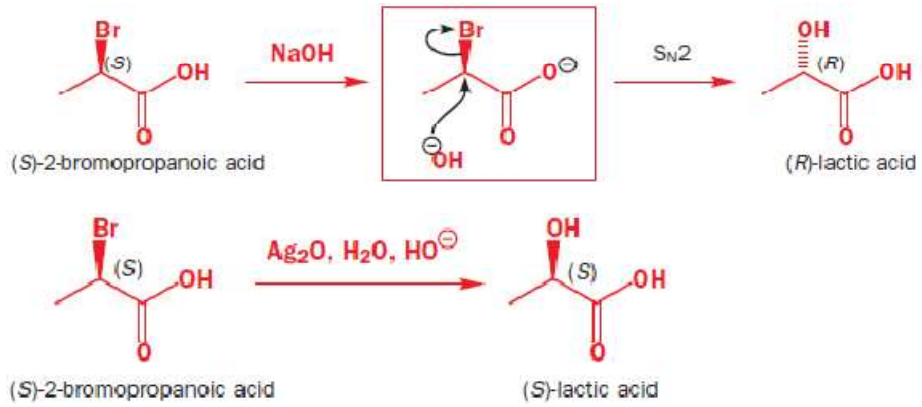


Neighbouring group participation is **impossible**, and **substitution goes simply by intermolecular displacement of OTs by AcOH**. Just **one S_N2 step means an overall inversion of configuration, and no participation means a slower reaction**.

Mechanism:

-Retention of configuration is an **indication of neighbouring group participation** Enantiomerically pure (*S*)-2-bromopropanoic acid reacts with concentrated sodium hydroxide to give (*R*)-lactic acid. The reaction goes with **inversion and is a typical S_N2 reaction** and a good **one too since the reaction center is adjacent to a carbonyl group**.

Examples:

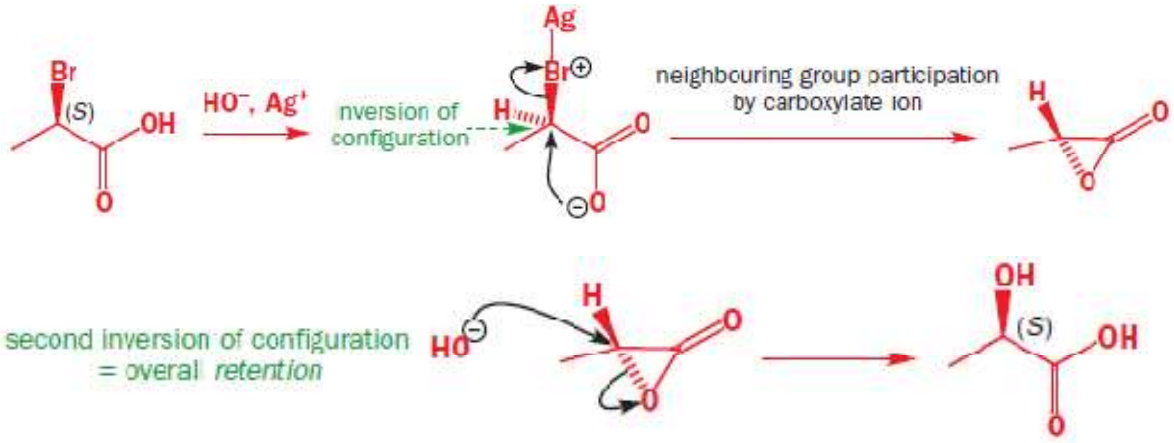


When the reaction is run **using Ag_2O** and a **low concentration of sodium hydroxide**, (S)-lactic acid is obtained there is overall **retention of stereochemistry**.

-Nucleophilic substitution reactions that go with **retention** of stereochemistry are rather rare and mostly go **through two successive**

inversions with neighbouring group participation. This time the neighbouring group is **carboxylate: the silver oxide is important because it encourages the ionization of the starting material by acting as a halogen-selective Lewis acid**. Three-membered ring intermediate forms, which then gets opened by hydroxide in a second S_N2 step.

Mechanism:

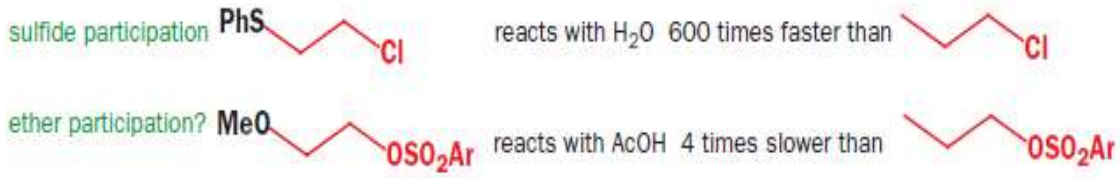


Why does the carboxylate group participate only at low HO^- concentration and in the presence of Ag^+? You can explain the two reactions in **depend on terms of the factors that favour S_N1 and S_N2** reactions. In the first, we have conditions suited to an **S_N2** reaction: a **very good nucleophile** (HO^-) and a **good leaving group** (Br^-). Improve the leaving group by adding Ag^+ (Ag^+ assists Br^- departure much as H^+ assists the departure of OH^- by allowing it to leave as H_2O), and worsen the nucleophile (H_2O instead of HO^-, of which there is now only a **low concentration**), and we have the sorts of conditions that would favour an S_N1 reaction. The trouble is, without neighbouring group participation, the **cation here would be rather unstable right next to a carbonyl group**. The carboxylate saves the day by participating in the departure of the Br^- and forming the lactone. The key thing to remember is that a reaction always goes by the mechanism with the **fastest** rate.

Type of neighbouring groups participate:

Sulfides, **esters**, and **carboxylates**, **Ethers**, and **amines** can also assist substitution reactions through neighbouring group participation.

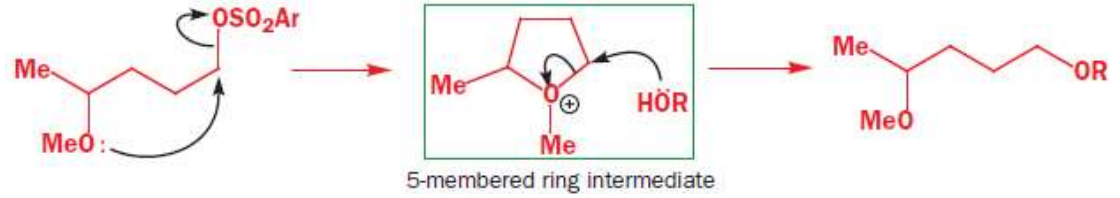
The **important thing that they have in common is an electron-rich heteroatom with a lone pair that can be used to form the cyclic intermediate**. Sulfides are rather better than ethers this sulfide reacts with water much **faster** than *n*-PrCl (*n*-Propylchloride) but the ether reacts with acetic acid four times more **slowly** than *n*-$PrOSO_2Ar$.



The OMe group **slows** the reaction down just **because it is electronegative more than it accelerates it by participation**. A more distant OMe group can participate: this 4-MeO alkyl sulfonate reacts with alcohols 4000 times **faster** than the *n*-Bu sulfonate.

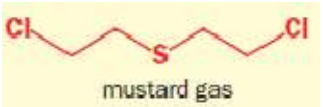
Note: Neighbouring group participation is involved, but this time through a **five-** rather than a **three-membered** ring. Participation is most commonly through **three-** and **five-membered** rings depending on kinetics (rates) of formation and thermodynamics (stability) of different ring sizes, less often **six-membered** ones, and very rarely **four-** or more than **seven-membered** ones.

Mechanism:



5-membered ring intermediate

Note: Mustard gas (Participation of **sulfides through three-membered rings** was used to gruesome effect in the development of mustard gas during the Second World War. Mustard gas itself owes its toxicity to the neighbouring group's participation in sulfur, which accelerates its alkylation reactions).

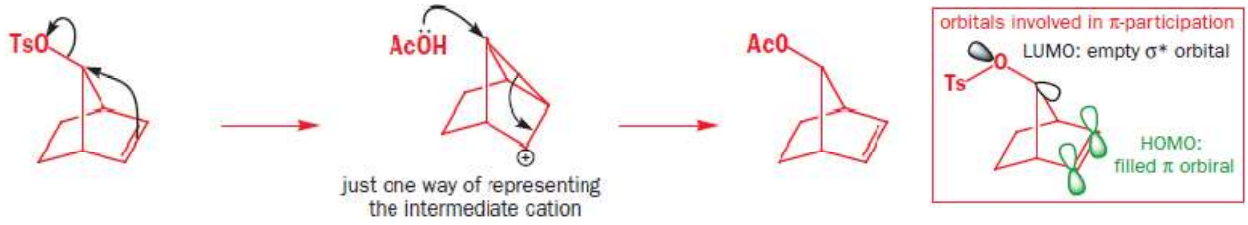


mustard gas

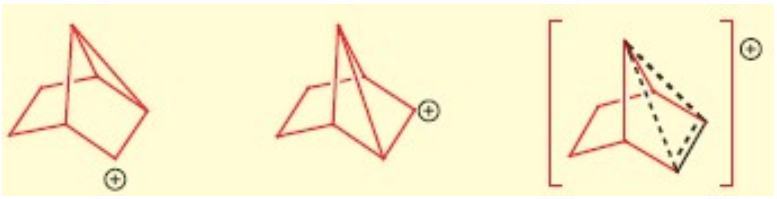
Use π electrons of a C=C double bond (alkene) as neighbouring groups' participation:

Retention of stereochemistry in the product (the starting tosylate and product acetate are both **anti** to the double bond) and the extremely fast reaction (10^{11} times that of the saturated analogue).

Examples:



The structure of the **intermediate** in this reaction is **symmetrical** and could be represented by **two structures** with **three-membered rings** or by a **delocalized structure in which two electrons are shared between three atoms**.



Note: Aryl participation is more common than simple alkene participation.

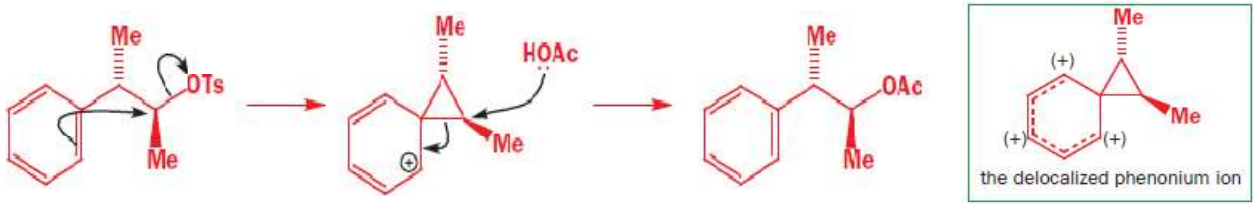
Neighbouring phenyl group participation:

Participation is hinted at by the **retention** of **relative stereochemistry**.

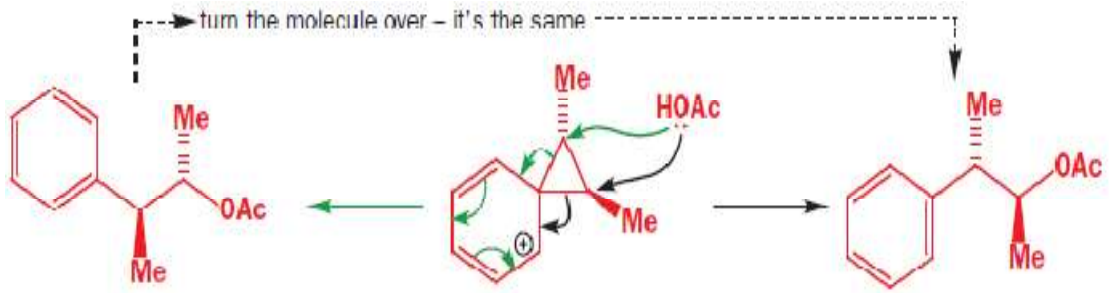
Examples:

The reaction involved π electrons, but the reaction is now **electrophilic aromatic substitution** rather like an intramolecular Friedel–Crafts alkylation with a **delocalized intermediate often termed a phenonium ion**.

Mechanism:

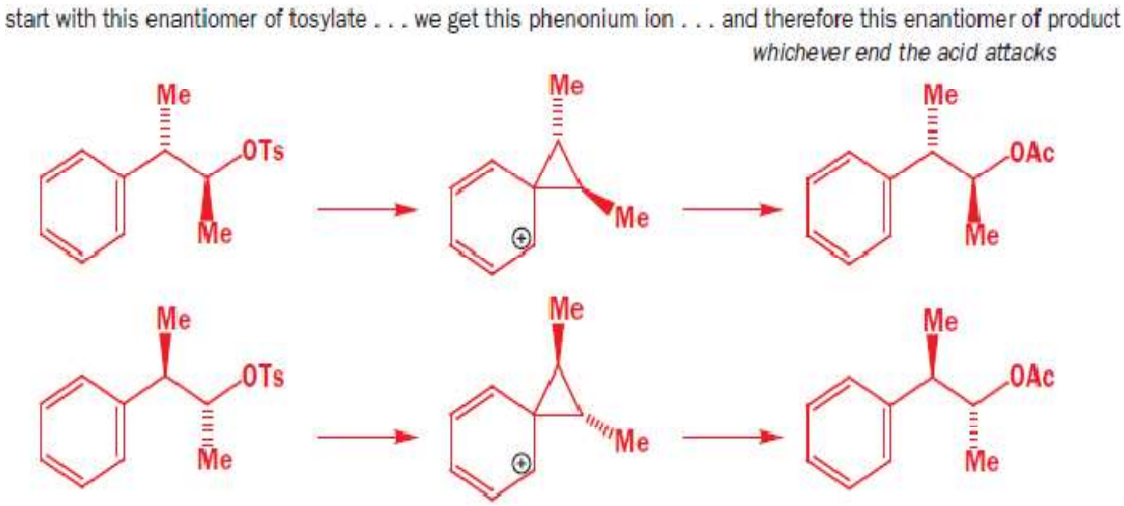


The **phenonium ion** is **symmetrical**. The acetic acid can **attack either atom in the three-membered ring** to give the **same product**.



The phenonium ion is nonetheless still **chiral**, since it has an **axis** (and **not a plane or center**) of **symmetry**, so if we use an enantiomerically **pure starting** material we get an **enantiomerically pure product**.

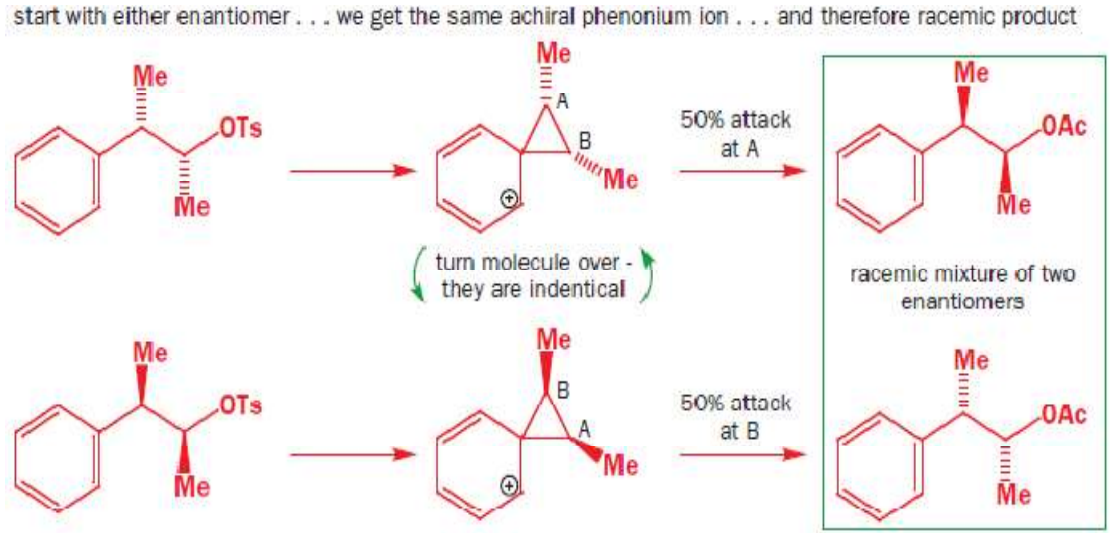
Examples:



Not so with the other diastereoisomer of this compound. Now, the **phenonium ion is symmetrical with a plane of symmetry it is therefore achiral**, and the same whichever enantiomer we start from. **Attack on each end** of the phenonium ion gives a **different enantiomer**, so whichever **enantiomer** of starting material we use we get the **same racemic mixture of products**.

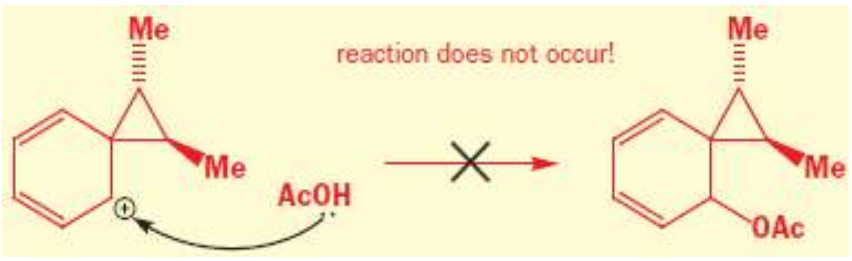
You can compare this reaction with the **loss of stereochemical** information that occurs during an S_N1 reaction of enantiomerically pure compounds. **Both reactions** pass through an **achiral intermediate**.

Examples:



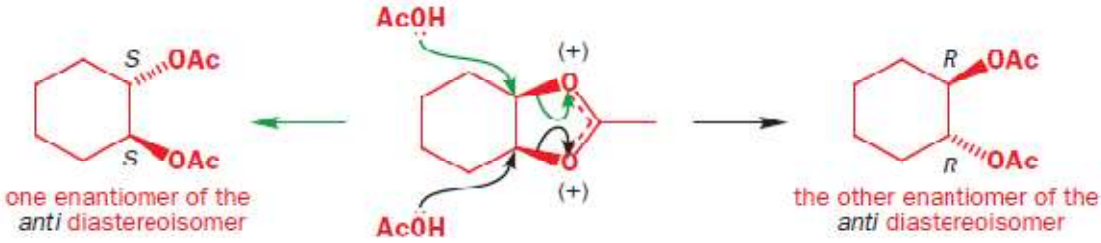
Note: Both of these reactions are stereospecific: the relative stereochemistry of the products depends on the relative stereochemistry of the starting materials. while the absolute stereochemistry of the starting materials is retained in one case (we get a single enantiomer of a single diastereoisomer), it is lost in the other (we get a racemic mixture of both enantiomers of a single diastereoisomer). These are important distinctions. and the development and use of molecules with structure-specific interactions of high selectivity.

Note: Acetic acid does not intercept with the phenonium ion directly at one of the positively charged carbon atoms, because the product hasn't aromatic and would contain a strained three-membered ring. The same sort of intermediates occur in electrophilic aromatic substitution and addition to the cation does not occur there either. **The reaction that does occur here is fragmentation: a C–C bond is broken**.

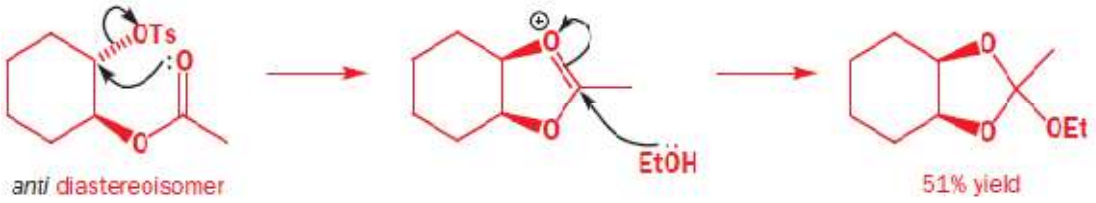


The same loss of absolute stereochemical information (but retention of relative stereochemistry) occurs in another reaction. The acceleration in rate and the retention of stereochemistry.

The **intermediate oxonium ion** is **delocalized and achiral**. If a single **enantiomer** of the starting material is used, **a racemic product** is formed through this achiral intermediate. Attack at **one carbon atom gives one enantiomer**; attack at the other gives the mirror image.



In this case, the neighbouring group can be caught in the act when the **rearrangement is carried out in ethanol**, the **intermediate** is trapped **by the attack at the central carbon atom**, The product is an **orthoester** and is **achiral** too.

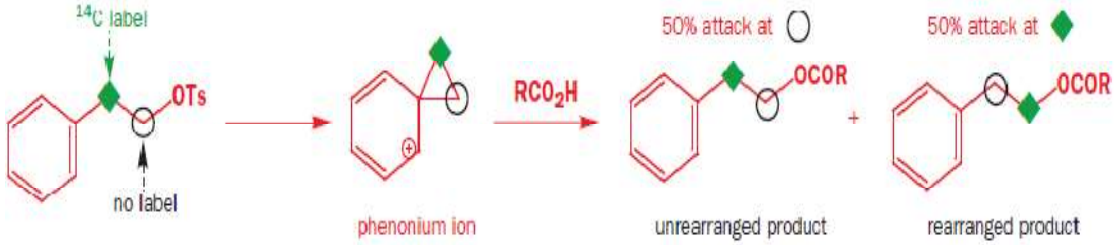


<u>Rearrangements occur when a participating group ends up bonded to a different atom:</u>

Because the **intermediates** in these examples are **symmetrical**, 50% of the time one substituent ends up moving from one carbon atom to another during the reaction. This is clearer in the following.

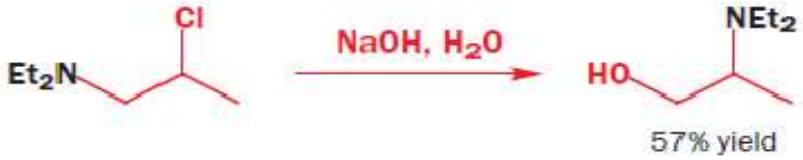
Example: the starting material is prepared such that the carbon atom carrying the phenyl group is an unusual isotope of carbon 14. This doesn't affect the chemistry but means that the two carbon atoms are easily distinguishable. Reacting the compound with trifluoroacetic acid scrambles the label between the **two positions**: the **intermediate** is **symmetrical** and, in the **50%** of reactions with the nucleophile that take place at the **labeled carbon atom**, the phenyl ends up migrating to the **unlabelled carbon atom** in a rearrangement reaction.

Example:

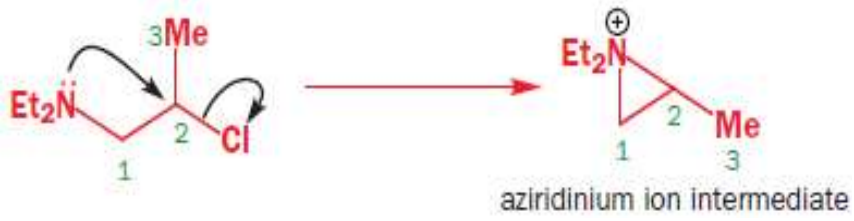


Note: Radioactive ^{3}H (tritium) or ^{14}C used to be used but, with the advent of high-field NMR, nonradioactive ^{2}H (deuterium) and ^{13}C have become more popular.

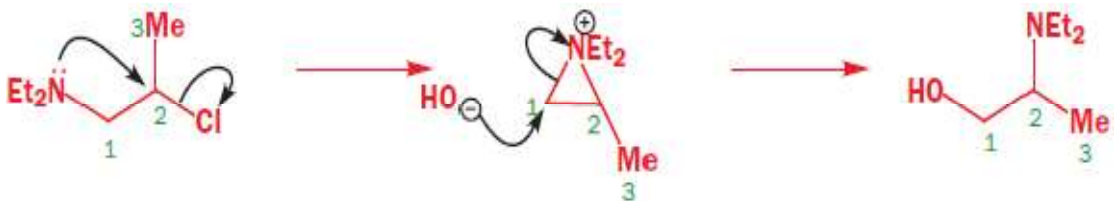
Example:



Consider this substitution reaction in which OH replaces Cl but with a change in the molecular structure. The substitution goes with **complete rearrangement the amine ends up attached to a different carbon atom**.The reaction starts off looking like a neighbouring group participation of the sort you are now familiar with.

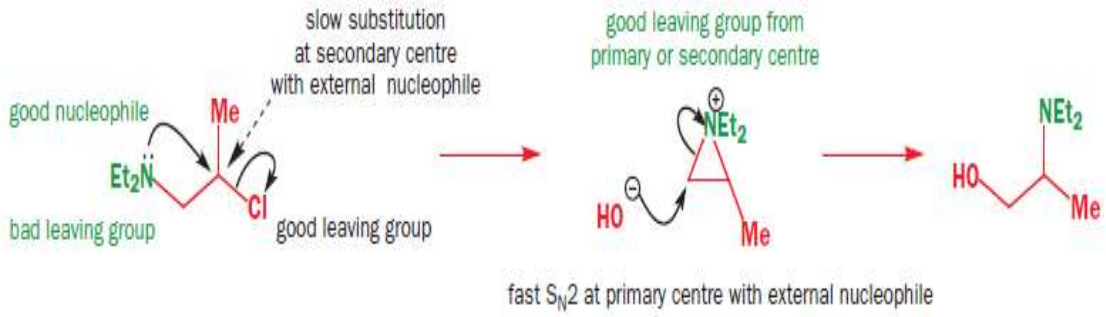


Note: The **intermediate** is an **aziridinium ion** (**aziridines are three-membered rings containing nitrogen the nitrogen analogues of epoxides**). The **hydroxide ion chooses to attack only the less hindered terminal carbon 1**, and **a rearrangement results the amine has migrated from carbon 1 to carbon 2**.



The rearrangement happened because the **secondary alkyl chloride contains** a very bad leaving group (Et_2N) and a good one (Cl^-) **but the good one is hard for HO^- to displace because it is at a secondary center** (**remember secondary alkyl halides are slow to react by S_N1 or S_N2**). But the **NEt_2 can participate to make an aziridinium intermediate** now there is a **good leaving group** ($RNEt_2$ without the negative charge) at the primary as well as the secondary carbon, so HO^- does a **fast S_N2 reaction at the primary carbon**.

Mechanism:



-The good internal **nucleophile Et_2N** will compete successfully for the **electrophile** with the **external nucleophile HO^-**. Intramolecular reactions are usually faster than bimolecular reactions, Intramolecular reactions, including participation, that give three-, five-, or six-membered rings are usually faster than intermolecular reactions.