

Organic Chemistry-4
Semester-4, CBCS
Course: CEMA CC-4-8-TH

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Recommended texts:

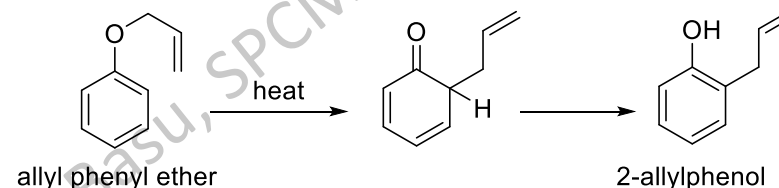
1. Study Guide to Organic Chemistry, Volume 2, by Saha, Chakraborty, Saha & Basu, Techno World, ISBN 9788192669588,
2. Study Guide to Organic Chemistry, Volume 4, by Saha, Chakraborty, Saha & Basu, Techno World, ISBN 9788192695259,
3. Organic Chemistry, Second Ed. by Clayden, Greeves & Warren, OUP, ISBN 9780198728719

Rearrangements in Organic Chemistry

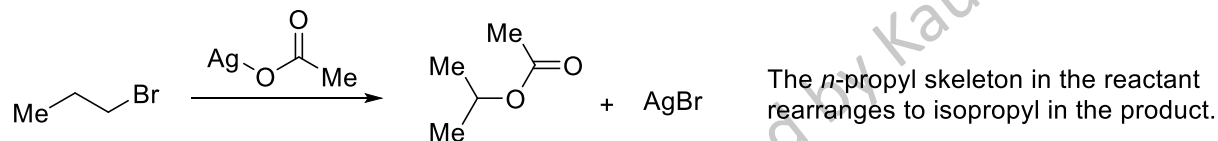
Molecular rearrangement:

The term is traditionally applied to any reaction that involves a *change of connectivity* (sometimes including hydrogen), and violates the so-called '*principle of minimum structural change*'. According to this *oversimplified* principle, chemical species do not isomerize in the course of a transformation, e.g. substitution, or the change of a functional group of a chemical species into a different functional group is not expected to involve the making or breaking of more than the minimum number of bonds required to effect that transformation. For example, any new substituents are expected to enter the precise positions previously occupied by displaced groups. Rearrangement reactions are directly contrary to this expectation.

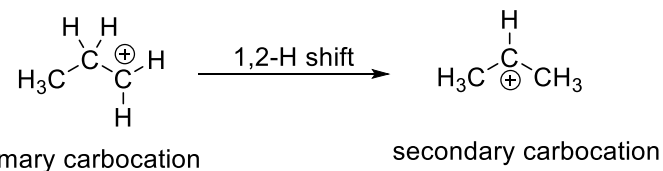
The simplest type of rearrangement is an intramolecular reaction in which the product is isomeric with the reactant (one type of '*intramolecular isomerization*'). An example is the first step of the Claisen rearrangement:



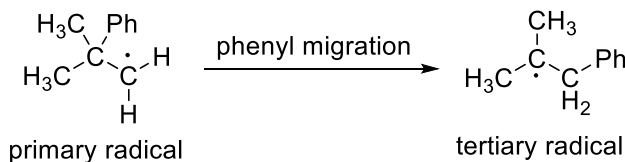
The definition of molecular rearrangement includes changes in which there is a bond migration of an atom or bond (unexpected on the basis of the principle of minimum structural change), as in the reaction:



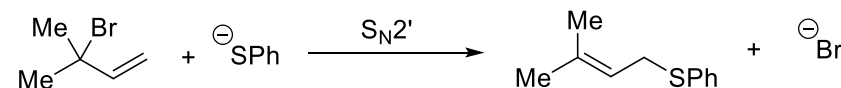
where the rearrangement stage can formally be represented as the '1,2-shift' of hydride between adjacent carbon atoms in the carbocation:



Such migrations occur also in radicals, e.g.:



The definition also includes reactions in which an entering group takes up a different position from the leaving group, with accompanying bond migration. An example of the latter type is the 'allylic rearrangement':



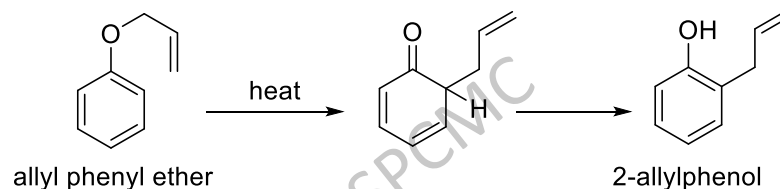
This is also an example of tele-substitution where the entering group (thiophenate) takes up a position more than one atom away from the atom to which the leaving group (bromide) was attached.

Rearrangements in Organic Chemistry

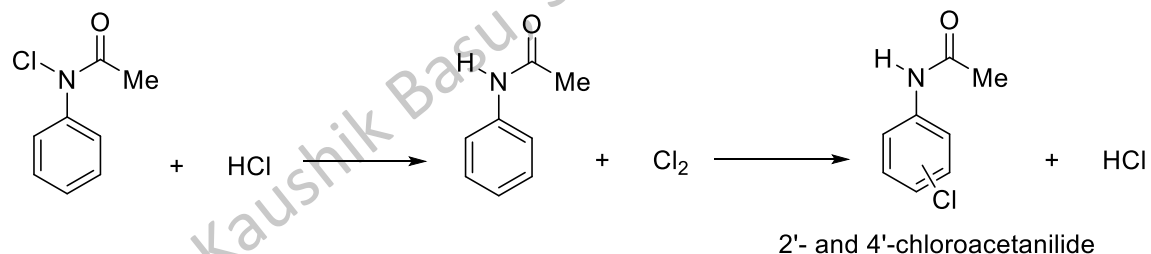
Molecular rearrangement:

A distinction is made between 'intramolecular rearrangements' (or 'true molecular rearrangements') and 'intermolecular rearrangements' (or 'apparent rearrangements').

In the former case the atoms and groups that are common to a reactant and a product never separate into independent fragments during the rearrangement stage (i.e. the change is intramolecular) as in Claisen rearrangement,

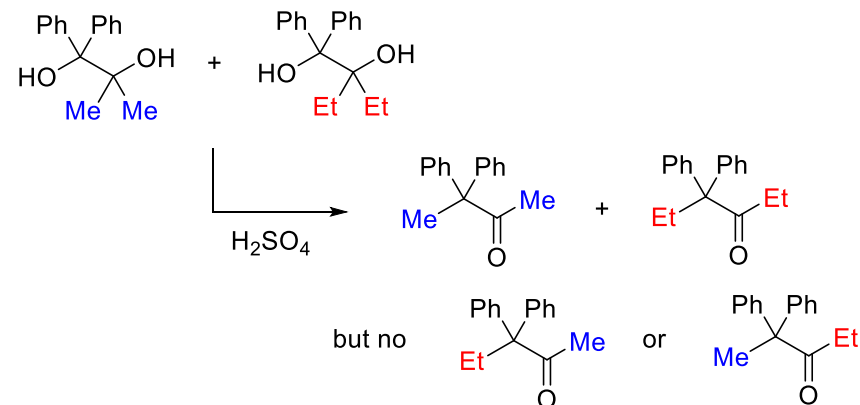


whereas in an 'intermolecular rearrangement' a migrating group is completely free from the parent molecule and is re-attached to a different position in a subsequent step, as in the Orton reaction:

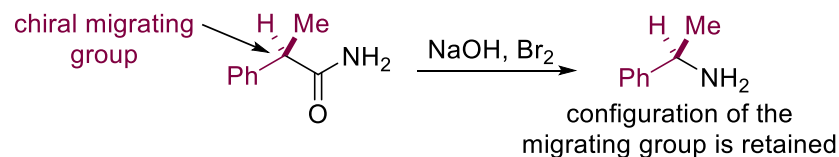


The ways to distinguish between intra- and intermolecular reactions:

i) **Crossover experiment:** In this experiment, two similar but distinguishable reactants *simultaneously* undergo a reaction as part of the same reaction mixture. The products formed will either correspond directly to one of the two reactants (non-crossover products) or will include components of both reactants (crossover products). If crossover products are found, we can say that the reaction (at least partly) proceeds in an intermolecular way where one fragment has completely detached from one of reactants and can now react with either intermediates in the reaction medium that arise from both starting materials.



ii) **Checking the configuration of chiral migrating group:** If the migration is intramolecular, then we see retention of configuration as the migrating group is never completely dissociated from the rest of the molecule and the new position of attachment happens from the same face/side from where the detachment had occurred:



i.e. no crossover product, the reaction is strictly intramolecular

Rearrangements in Organic Chemistry

Migration from carbon to electron-deficient carbon:

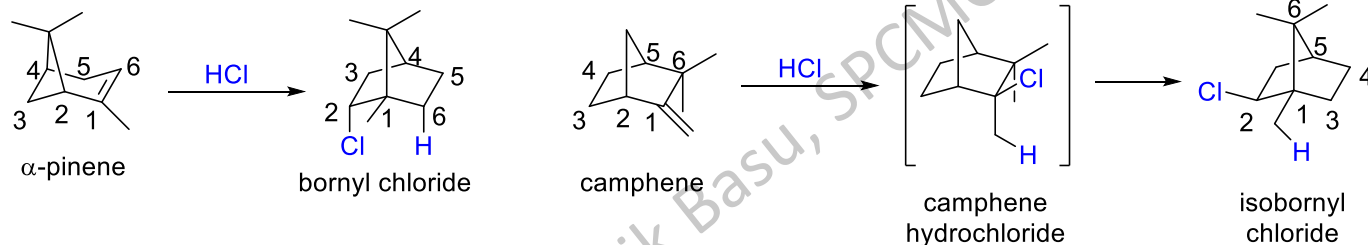
Wagner-Meerwein rearrangement: The generation of a carbocation followed by the [1,2]-shift of an adjacent carbon-carbon bond to generate a new carbocation is known as the Wagner-Meerwein rearrangement. Originally this name referred only to skeletal rearrangements in bicyclic systems, but today it is used to describe all [1,2]-shifts of hydrogen, alkyl, and aryl groups.



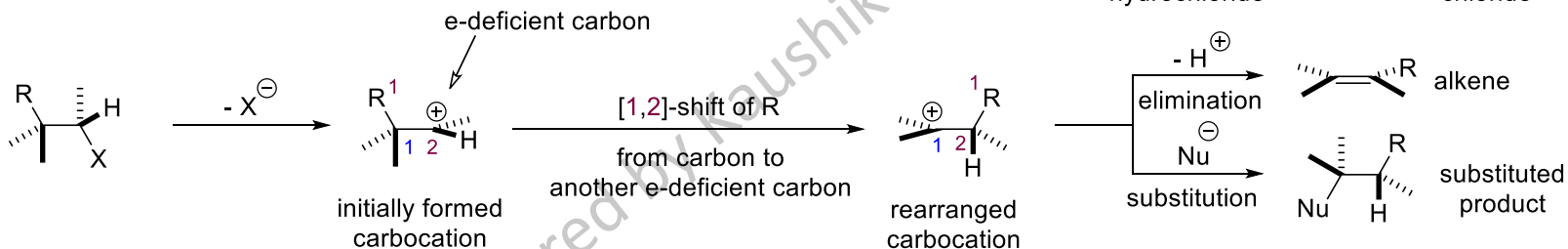
Igor Wagner
(1849-1903)



Hans Meerwein
(1879-1965)

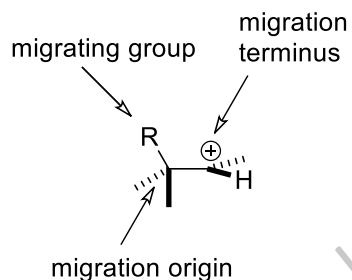


General scheme:

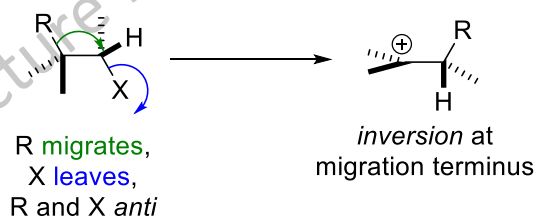


Recall that $\text{S}_{\text{N}}1$ and $\text{E}1$ occur hand in hand

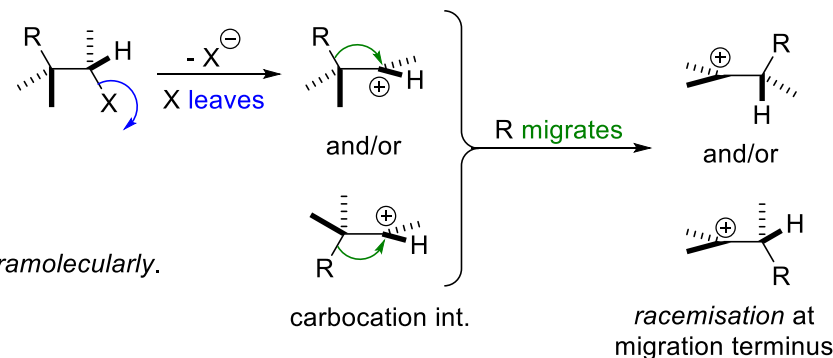
Depending on the structure and stereochemistry of the substrate, the rearrangement may proceed in a concerted or stepwise fashion. When the leaving group and the migrating groups are antiperiplanar to each other, the rearrangement is concerted (especially in rigid polycyclic systems), but in most other cases the formation of a carbocation intermediate is expected.



concerted migration:



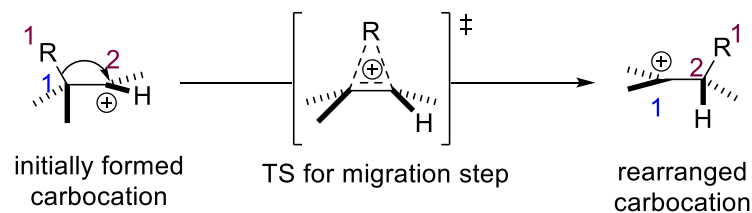
stepwise migration:



In both cases, R migrates *intramolecularly*.

Rearrangements in Organic Chemistry

Migration from carbon to electron-deficient carbon: Wagner-Meerwein rearrangement

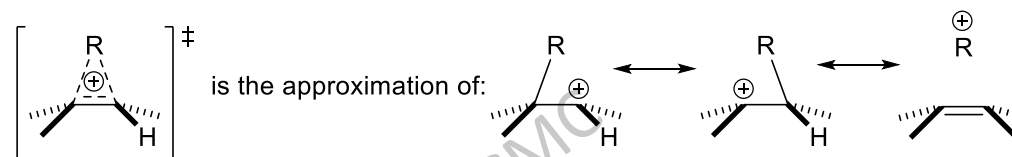


The 1,1-sigma bond breaks and new bond forms b/w 1 and 2, this is why it is called [1,2]-shift of R. It is a pericyclic reaction, a sigmatropic shift.

The position of H in the series of migrating groups is controversial. H is found to migrate much better than ordinary alkyls, but this tendency is probably due to the intrinsic stabilisation by the non-migrating alkyl group of the carbocation resulting from H-migration, in preference to the cation that forms by migration of the same alkyl.

The first clear formulation of the involvement of carbocations in molecular rearrangements was proposed by F. C. Whitmore. The 1,2-shifts of the migrating group that occur in these rearrangements are known as "Whitmore shifts".

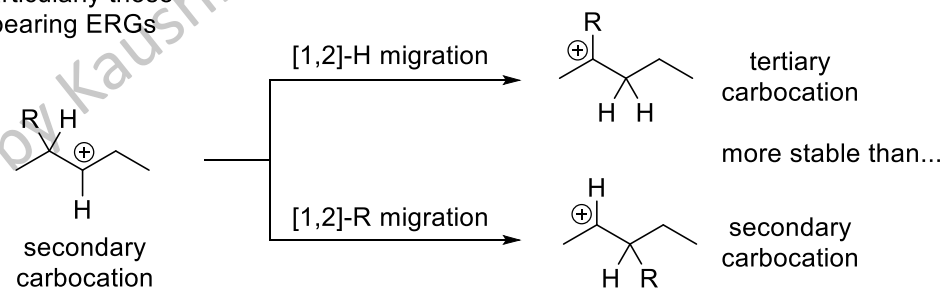
Whitmore said that carbocation rearrangements result when "an atom in an electron-hungry condition seeks its missing electron pair from the next atom in the molecule." Whitmore's description emphasizes the Lewis acid-base character of the reaction. Note that the 1,2-shift can be imagined as the extreme form of hyperconjugation.



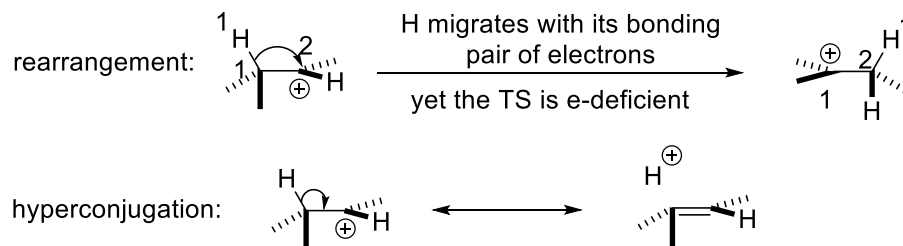
This implies that *the group that can sustain the positive charge better will also have a greater migration tendency*. Thus:

Aryl > *tert.* alkyl > *sec.* alkyl > *prim.* alkyl > methyl
migration tendency decreases →

particularly those bearing ERGs



Thus H migrates in preference to R, although the inherent migratory aptitude of H is only slightly greater than methyl, and lot less than other alkyls.

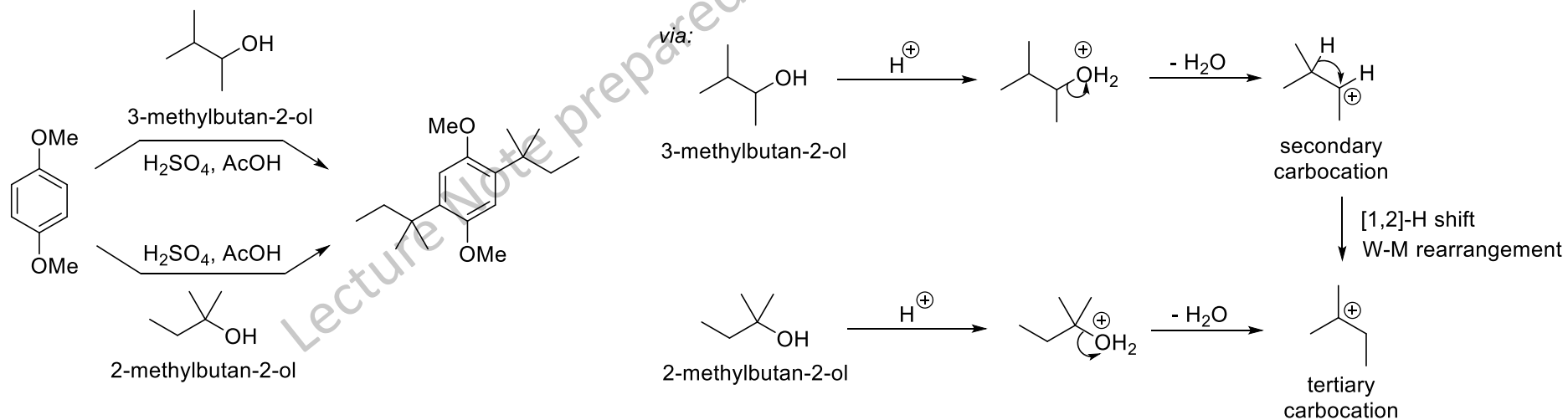
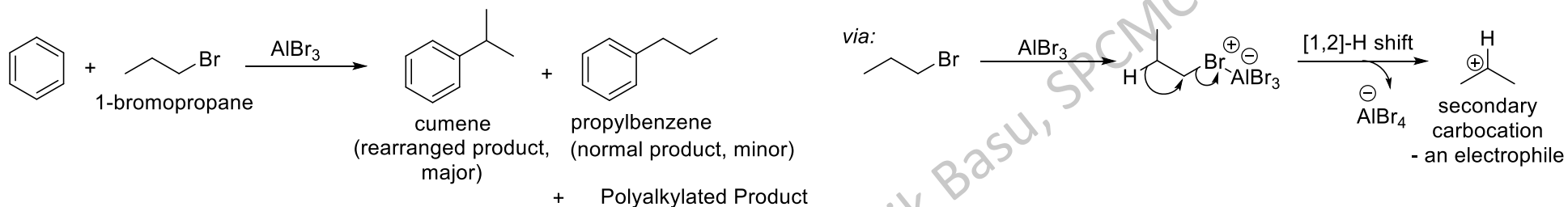


Rearrangements in Organic Chemistry

Migration from carbon to electron-deficient carbon: Wagner-Meerwein rearrangement

The carbocation can be generated in a variety of ways. Let us consider a few examples of the W-M rearrangements:

1. W-M rearrangement is abundant in Friedel-Crafts alkylation reaction where the alkylating agent is a primary halide:



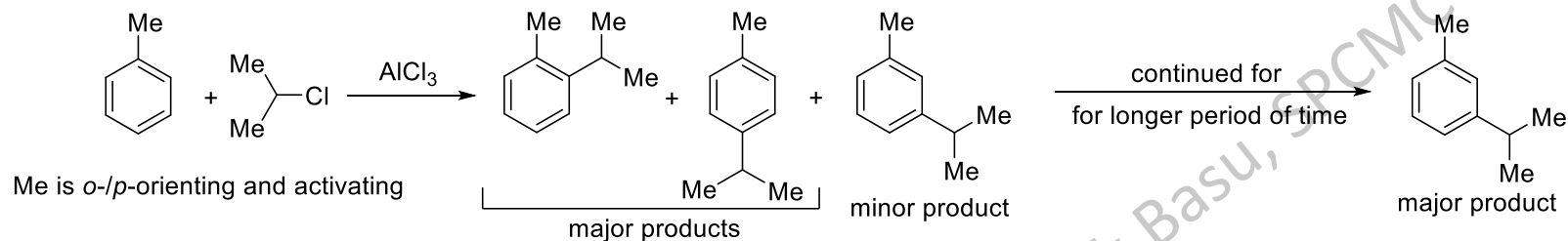
this is the common int. generated from both isomeric alcohols. SEAr on the highly activated aromatic ring (twice) affords the substitution product.

Rearrangements in Organic Chemistry

Migration from carbon to electron-deficient carbon: Wagner-Meerwein rearrangement

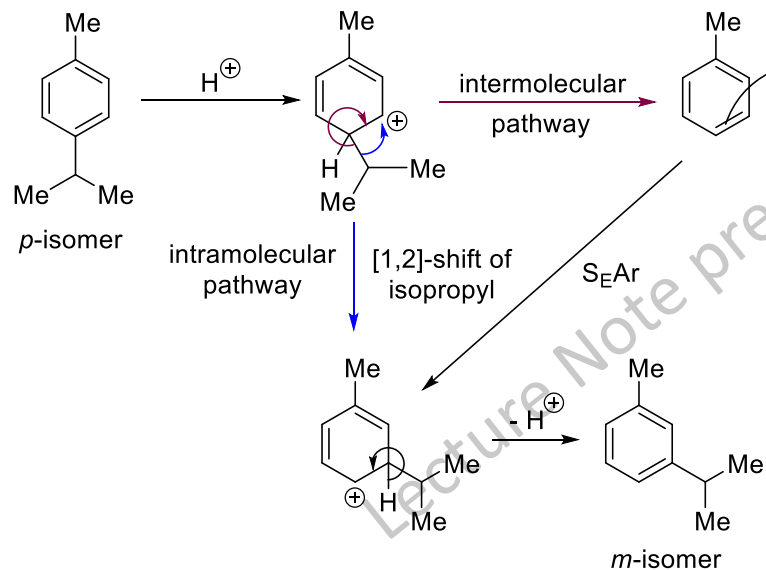
2. W-M rearrangement in isomerisation of alkylbenzenes:

Recall that if the Friedel-Crafts Alkylation is continued on alkylbenzene for a considerable time period, we get mainly the *meta*-product. For example:

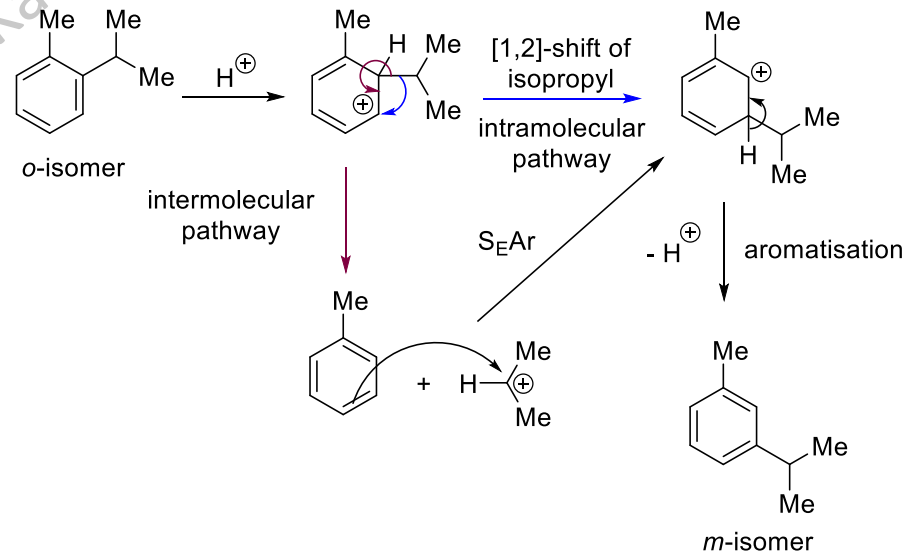


The isomerisation is believed to proceed in the following way:

From *p*-isomer:



From *o*-isomer:



Similarly, both *o*- and *p*-xylene isomerizes to a mixture dominated by the *m*-isomer when treated with appropriate catalysts for a long period of time.

The driving force of this isomerisation is the formation of the thermodynamically more stable *m*-disubstituted product from the relatively less stable *o*- and *p*-disubstituted products.

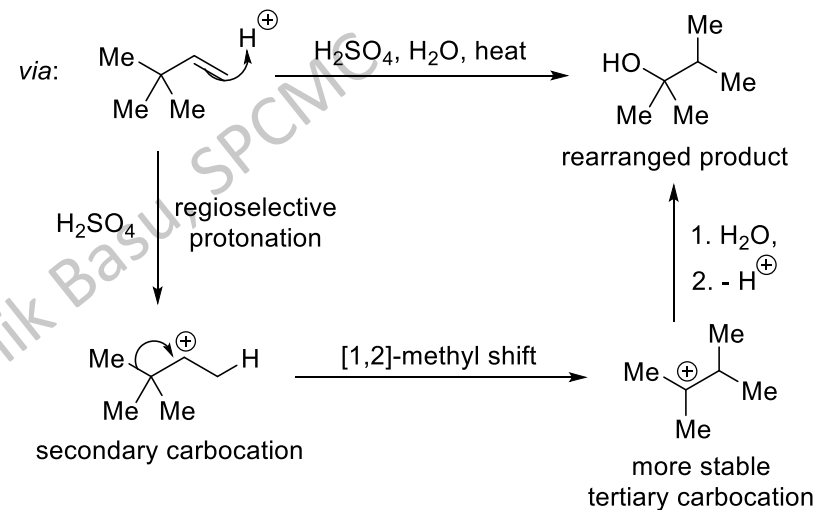
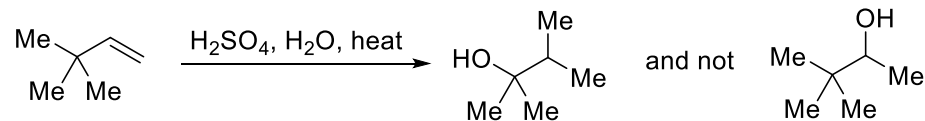
Rearrangements in Organic Chemistry

Migration from carbon to electron-deficient carbon: Wagner-Meerwein rearrangement

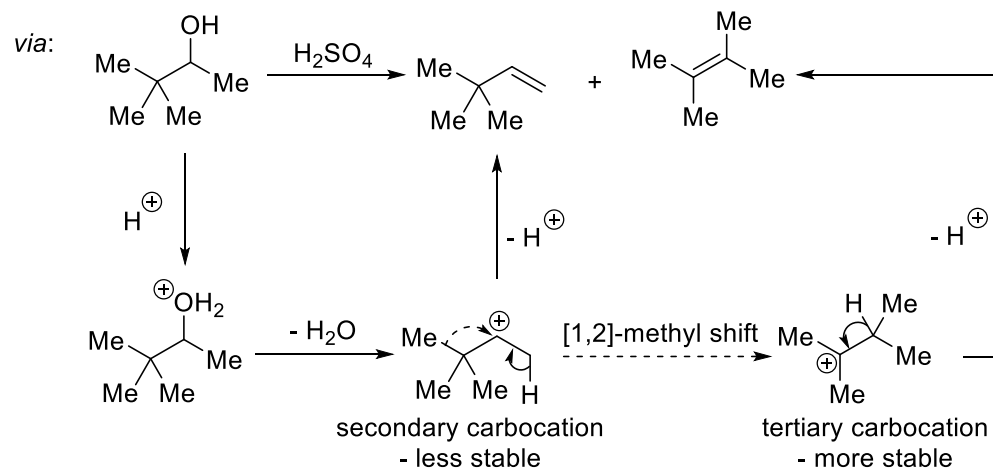
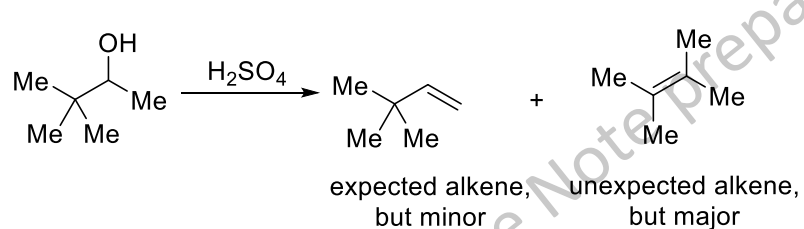
3. W-M rearrangement in acid-catalysed dehydration of alcohols and hydration of alkenes:

These reactions are plagued by the undesired W-M rearrangements, as we have already seen.

For example, in the following acid-catalysed hydration of an alkene:



And in the following acid-catalysed dehydration of alcohol:

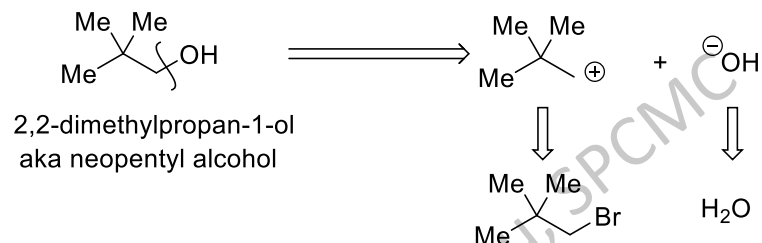


Rearrangements in Organic Chemistry

Migration from carbon to electron-deficient carbon: Wagner-Meerwein rearrangement

4. W-M rearrangement often intervenes in S_N1 solvolysis of primary halides:

For synthesis of neopentyl alcohol, one may go for the retrosynthetic scheme:

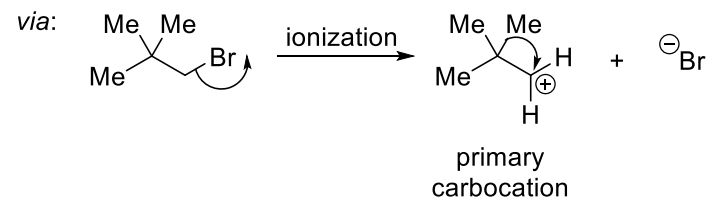
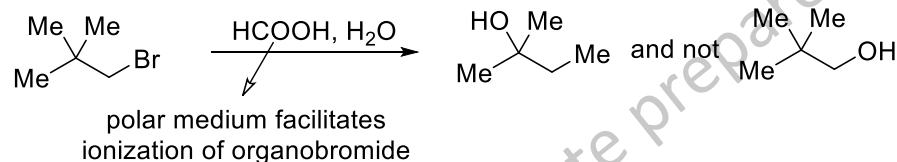


i.e. looking to achieve a nucleophilic substitution on neopentyl bromide

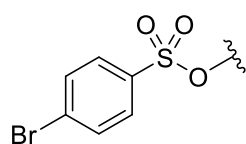
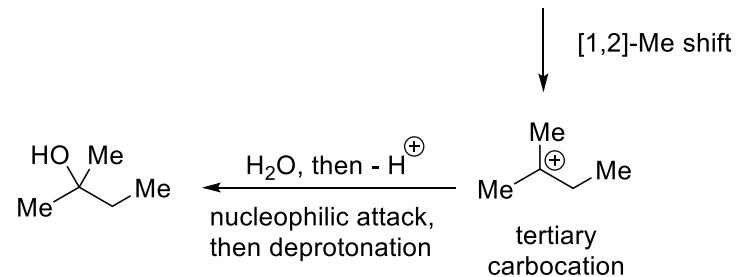
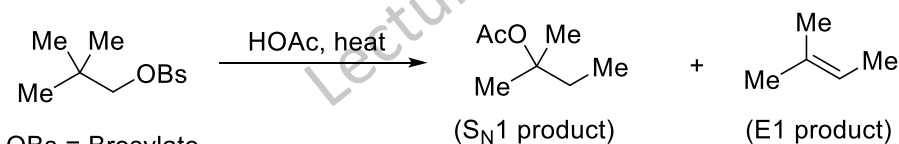
However, the nucleophilic substitution strategy does not work here:



and attempted S_N1 affords an unexpected, rearranged product:



Similarly,

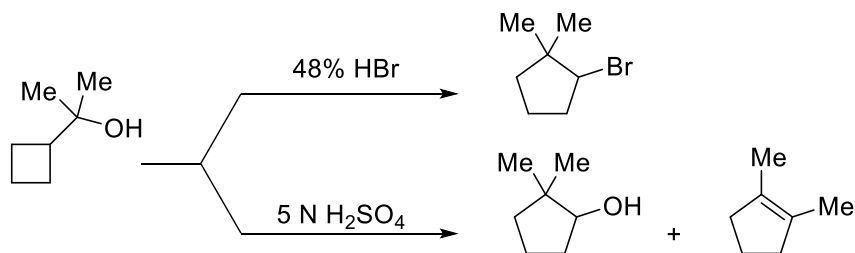


both products arise from rearranged, tertiary carbocation

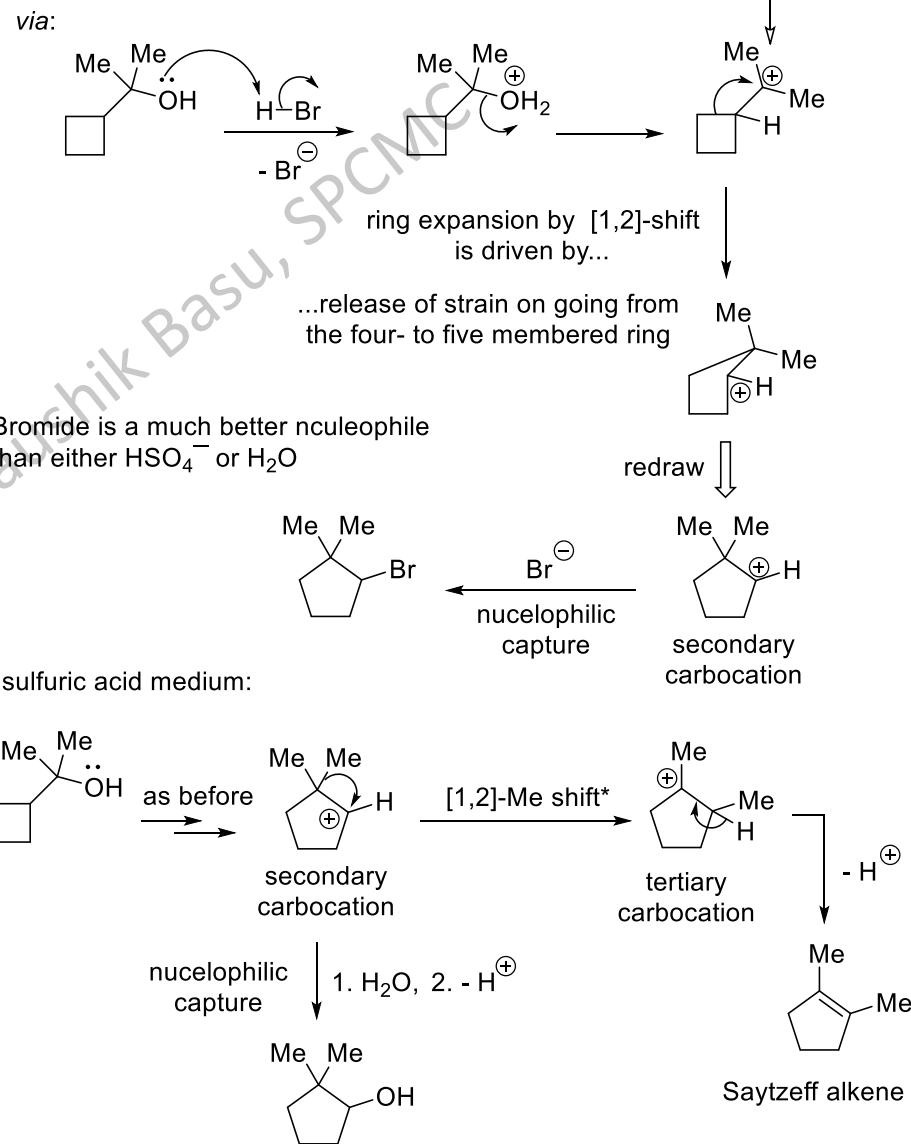
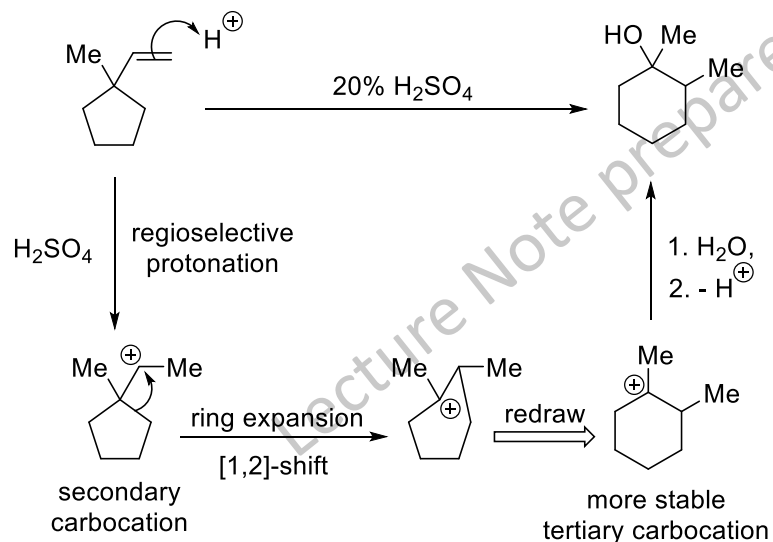
Rearrangements in Organic Chemistry

Migration from carbon to electron-deficient carbon: Wagner-Meerwein rearrangement

5. W-M rearrangement is often driven by relief of ring strain:



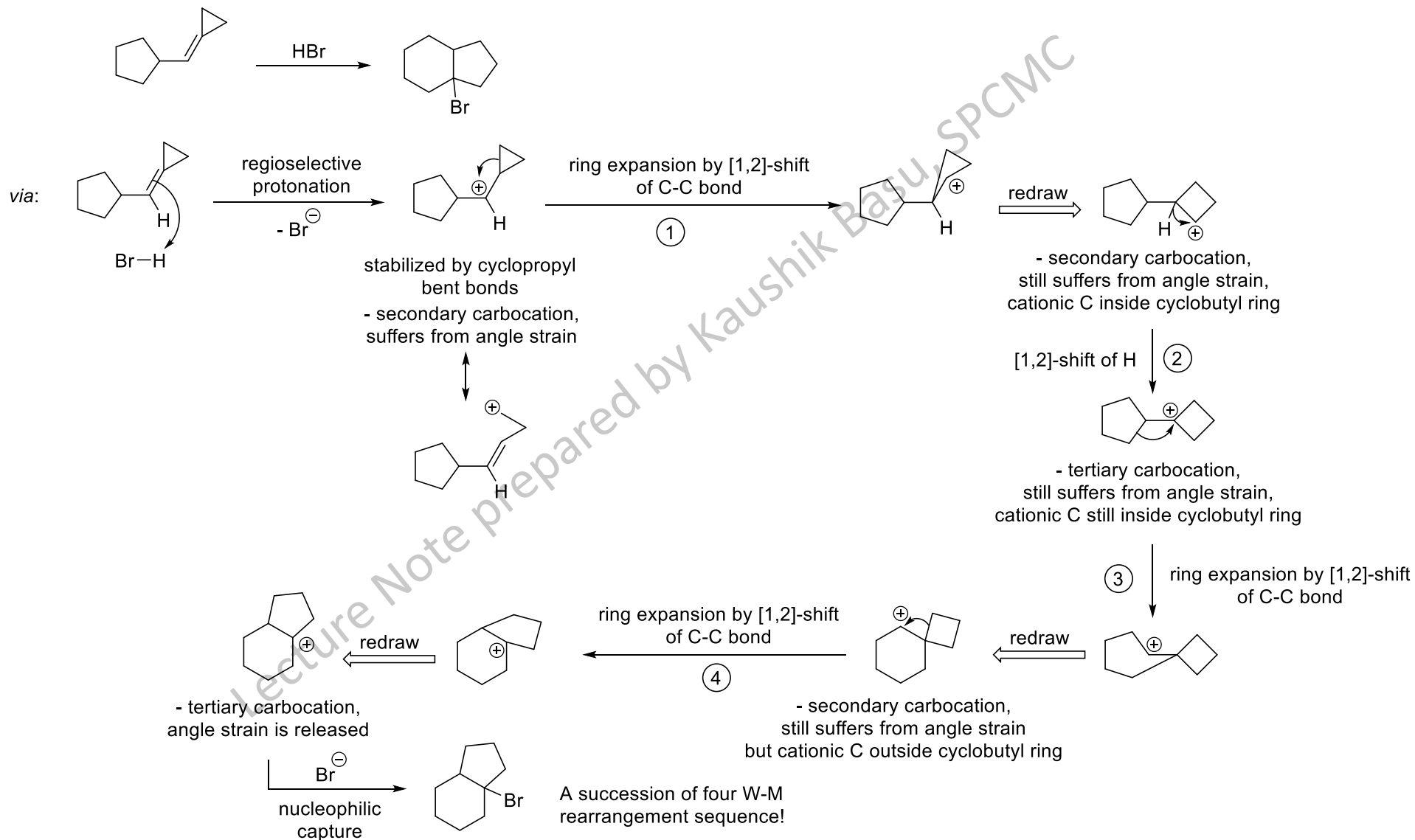
Ring expansion can also be driven by formation of more stable carbocation:



Rearrangements in Organic Chemistry

Migration from carbon to electron-deficient carbon: Wagner-Meerwein rearrangement

5. W-M rearrangement is often driven by relief of ring strain:

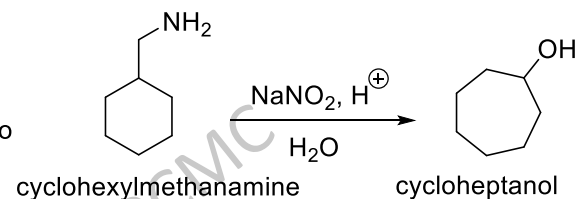


Rearrangements in Organic Chemistry

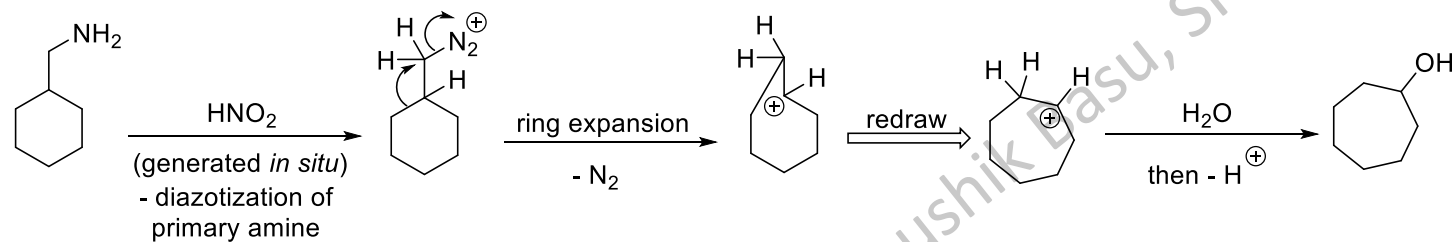
Migration from carbon to electron-deficient carbon: Wagner-Meerwein rearrangement

6. W-M rearrangement in expanding the ring: The Demjanov rearrangement:

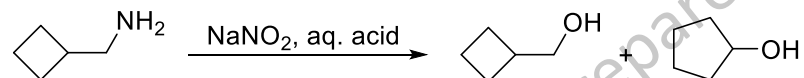
The ring enlargement of aminomethylcycloalkanes upon treatment with nitrous acid (HNO_2) to the corresponding homologous cycloalkanols is called the Demjanov rearrangement. This name is also given to the rearrangement of acyclic primary amines with nitrous acid.



via:



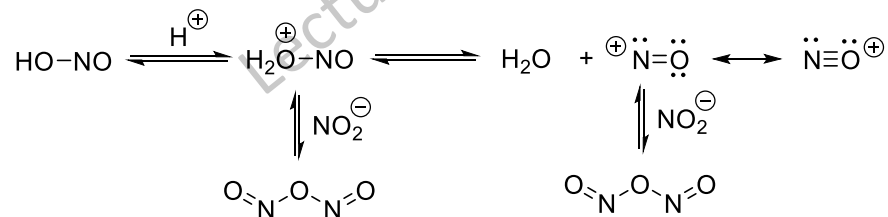
The diazonium ion is very labile due to the lack of stabilization and it readily undergoes a [1,2]-alkyl shift accompanied by the loss of nitrogen, a super leaving group. The rearrangement is competitive with the substitution of the diazonium leaving group by the solvent (i.e. water) and we have the following observation:



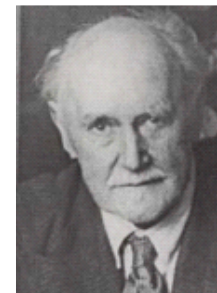
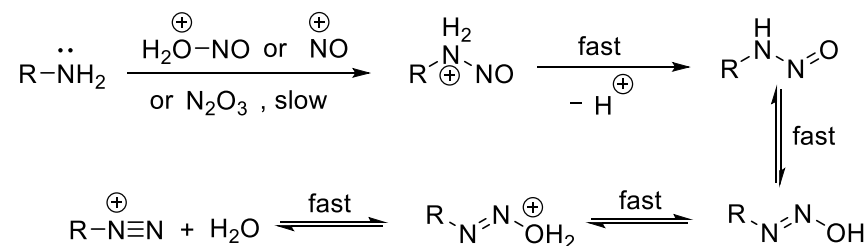
(Write out the mechanisms for the formation of these two products)

Aside: mechanism of diazotization:

Generation of nitrosonium ion (^+NO):



Diazotization:



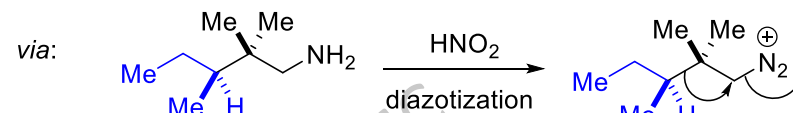
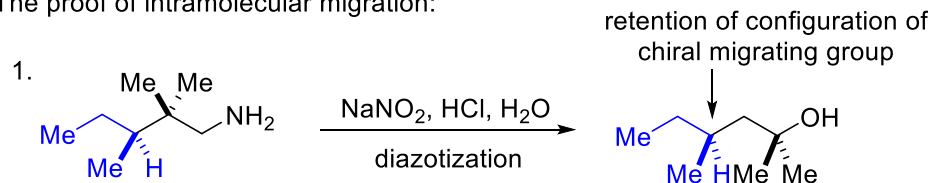
N. Y. Demjanov
(1861-1938)

Synthetically, the Demjanov rearrangement is best applied for the preparation of five-, six-, and seven-membered rings, but it is not well-suited for the preparation of smaller or larger rings due to low yields.

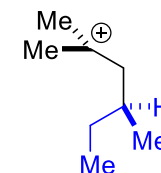
Rearrangements in Organic Chemistry

Migration from carbon to electron-deficient carbon: Wagner-Meerwein rearrangement

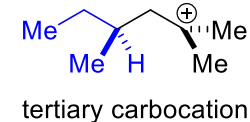
The proof of intramolecular migration:



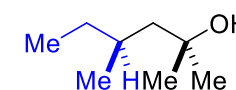
[1,2]-shift,
intramolecular migration



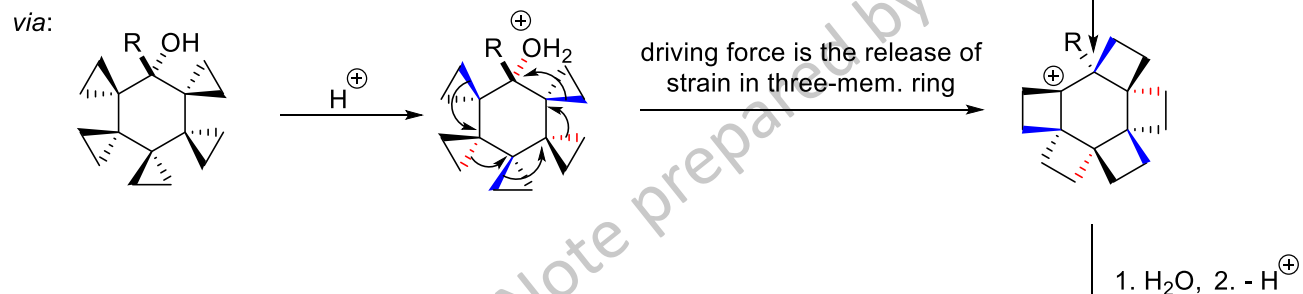
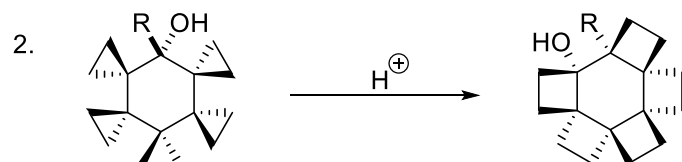
redraw



1. H_2O , 2. $-\text{H}^+$



The rearrangement of acyclic primary amines to alcohols with nitrous acid is known as Demjanov rearrangement.



After migration, the migrating groups remain in the same face from which they have started the migration.

migrators that start off the α -face remain on the α -face
migrators that start off the β -face remain on the β -face

α -face : below the plane of the ring,
 β -face : above the plane of the ring

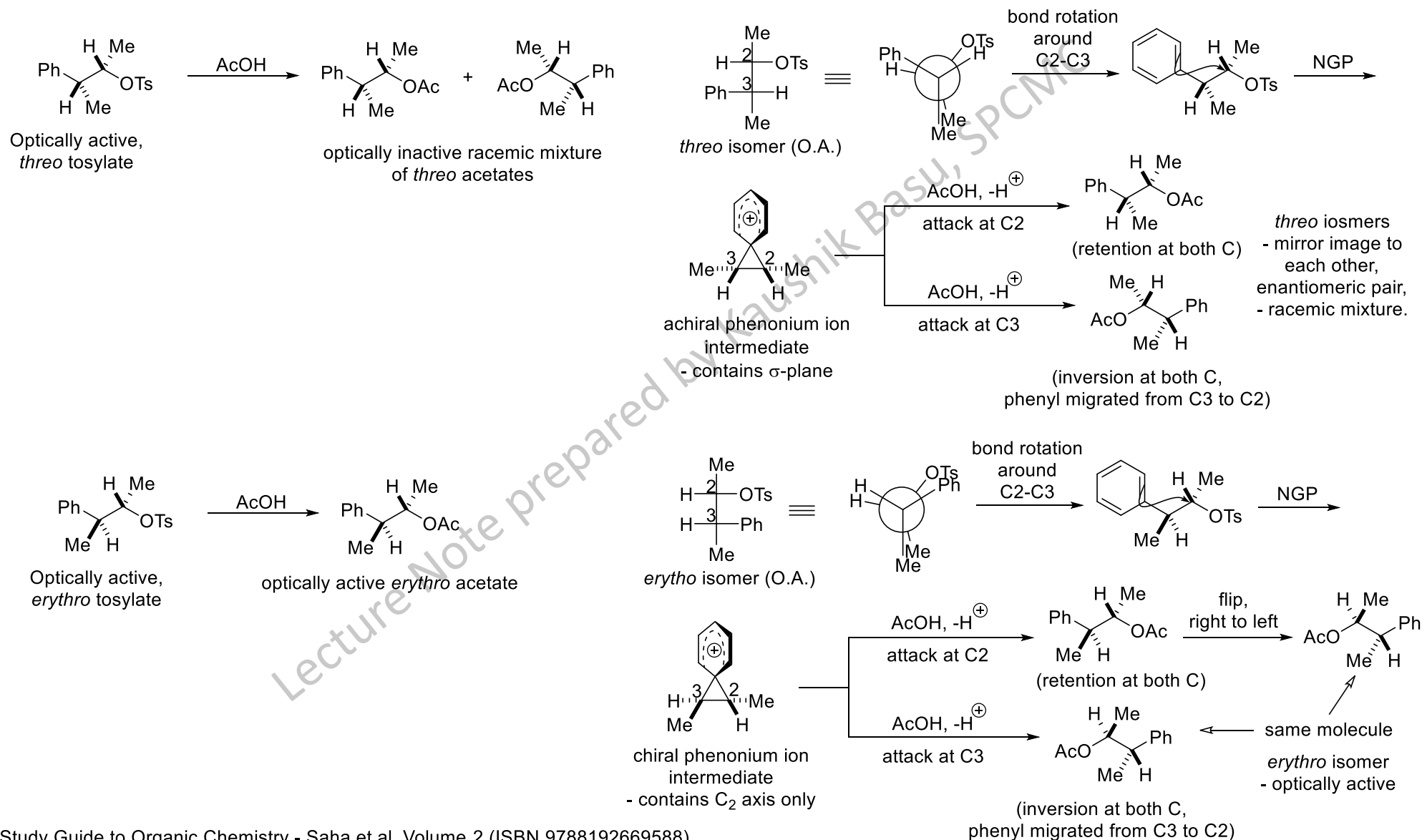
This proves the intramolecular nature of the migration.

(nucleophilic attack of water must be from α -face as the β -face of the carbocation is sterically blocked)

Rearrangements in Organic Chemistry

Migration from carbon to electron-deficient carbon: Wagner-Meerwein rearrangement

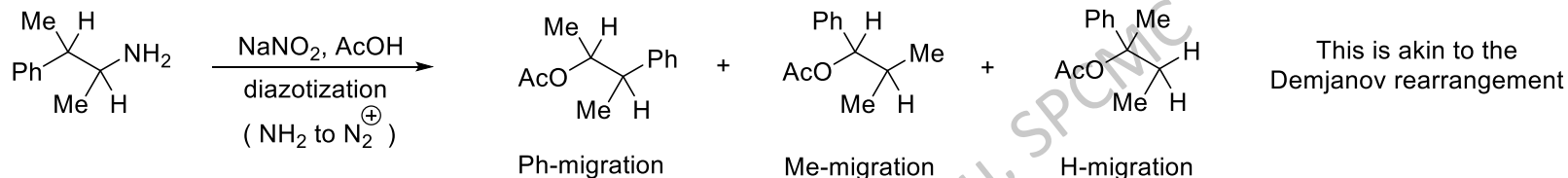
[1,2]-shift of aryl rings are often associated with anchimeric assistance towards the departure of the leaving group:



Rearrangements in Organic Chemistry

Migration from carbon to electron-deficient carbon: Wagner-Meerwein rearrangement

If the leaving group is an excellent one, the tendency for NGP decreases and other groups compete successfully with phenyl in migrating:



The tendency for N_2^+ to depart is so great that it does not require any particular anchimeric assistance from the phenyl group.

