

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

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Recommended texts:

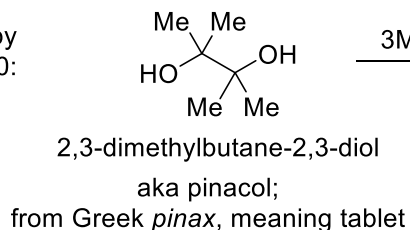
1. Study Guide to Organic Chemistry, Volume 2, by Saha, Chakraborty, Saha & Basu, Techno World, ISBN 9788192669588,
2. Study Guide to Organic Chemistry, Volume 4, by Saha, Chakraborty, Saha & Basu, Techno World, ISBN 9788192695259,
3. Organic Chemistry, Second Ed. by Clayden, Greeves & Warren, OUP, ISBN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

Rearrangements in Organic Chemistry

Migration from carbon to electron-deficient carbon: Pinacol-pinacolone rearrangement

A general transformation for acyclic and cyclic vicinal diols (also known as glycols or 1,2-diols), which, upon treatment with catalytic amounts of acid, undergo dehydration with concomitant [1,2]-alkyl-, aryl- or hydride shift to afford ketones or aldehydes. This acid-catalyzed transformation of vicinal diols is also known as the pinacol rearrangement.

First reported by
R. Fittig in 1860:



structure elucidated by
A. M. Butlerov in 1874

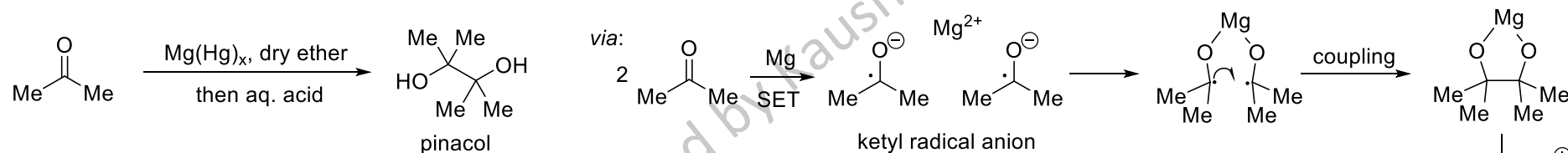


W. R. Fittig
(1835-1910)



A. M. Butlerov
(1828-1886)

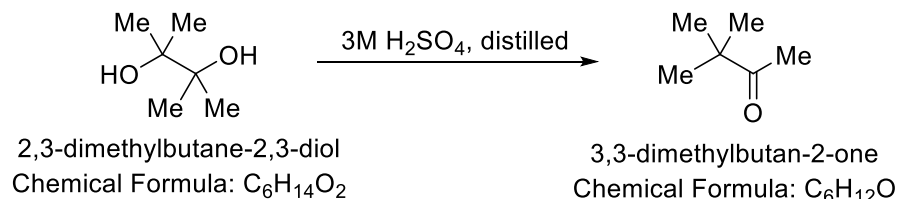
Pinacol preparation: by reductive coupling of acetone



Pinacol can undergo an alternative double dehydration:



Point to note that pinacol rearrangement is also a dehydration accompanied by a rearrangement of carbon skeleton:



Alternative reagents:

Protic acids: HClO₄, H₃PO₂,
TFA, TsOH;

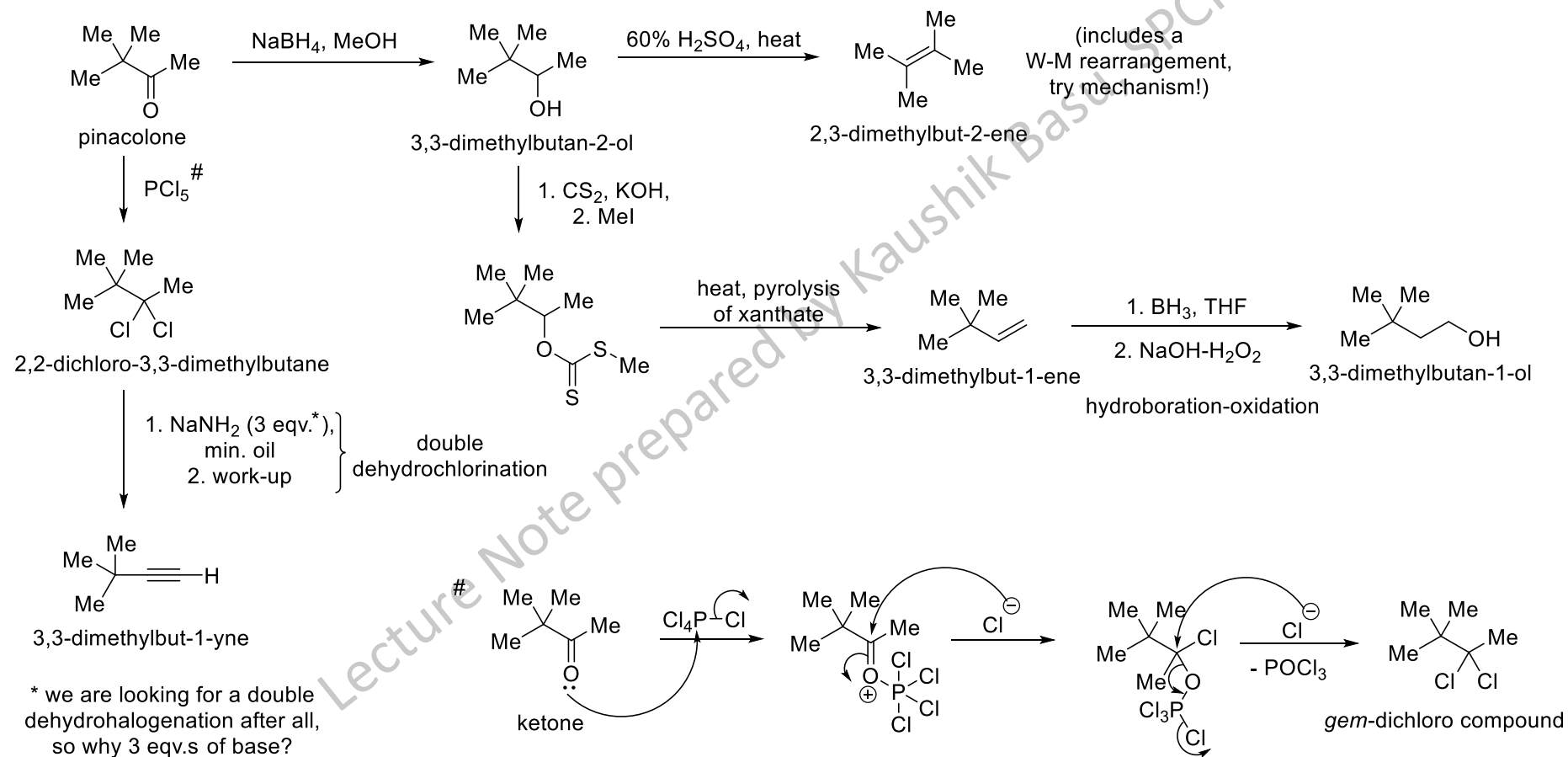
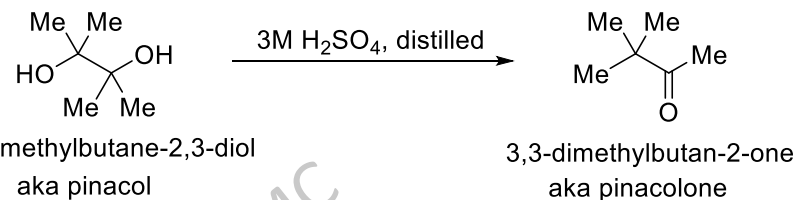
Lewis acid: BF₃-OEt₂

basically, a combination of
dehydration and skeletal rearrangement

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Migration from carbon to electron-deficient carbon: Pinacol-pinacolone rearrangement

Synthetic utility of pinacol rearrangement: pinacolone is an important synthetic intermediate

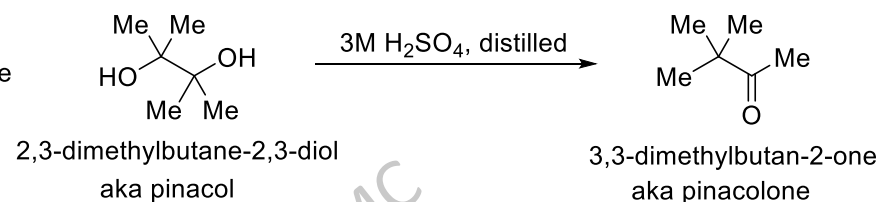


deoxygenation is driven by formation of the strong P=O bond

Rearrangements in Organic Chemistry

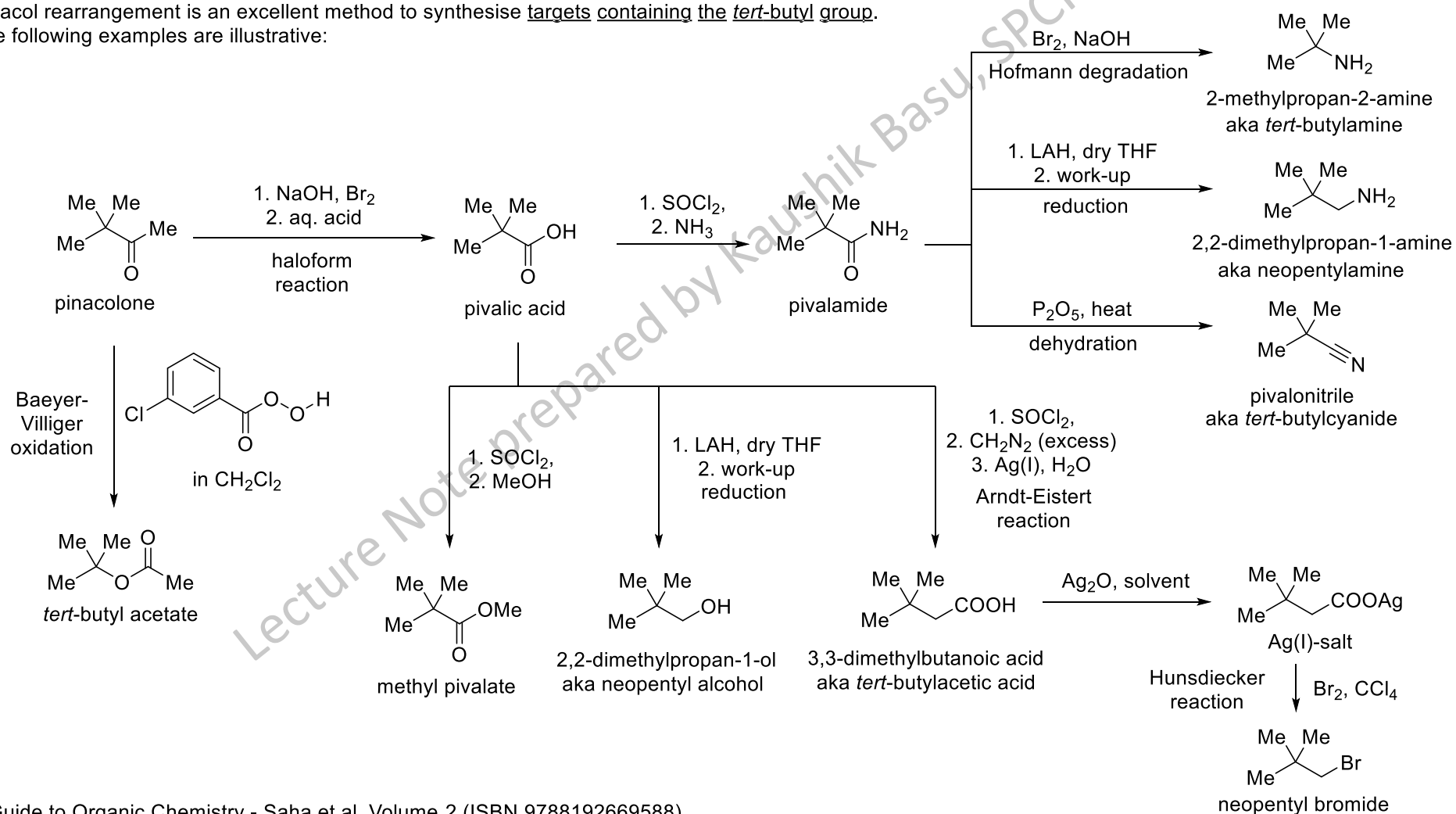
Migration from carbon to electron-deficient carbon: Pinacol-pinacolone rearrangement

Synthetic utility of pinacol rearrangement: pinacolone is an important synthetic intermediate



Pinacol rearrangement is an excellent method to synthesise targets containing the *tert*-butyl group.

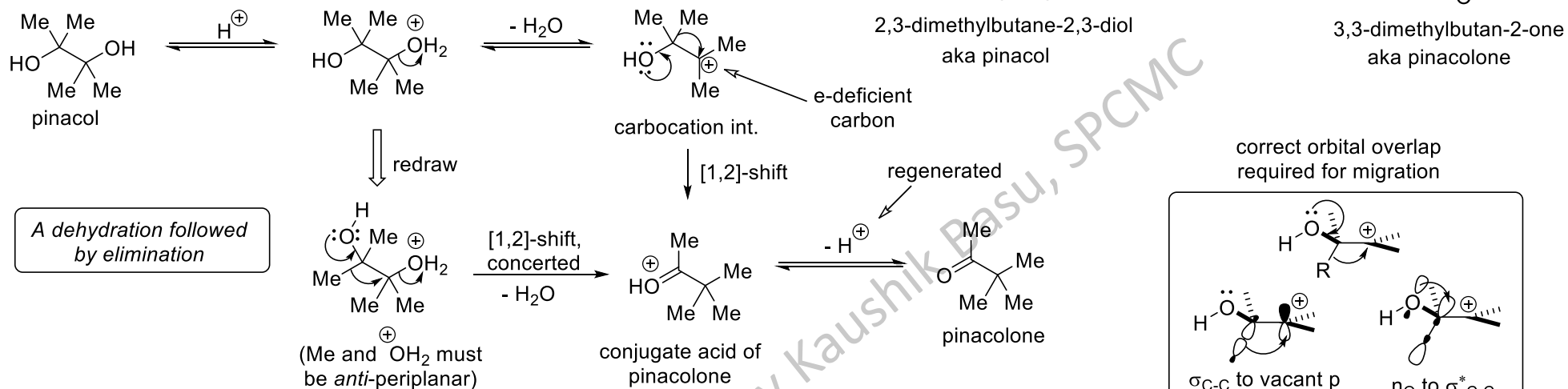
The following examples are illustrative:



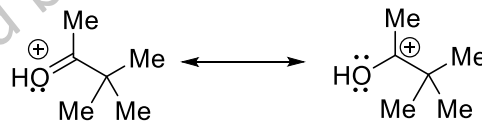
Rearrangements in Organic Chemistry

Migration from carbon to electron-deficient carbon: Pinacol-pinacolone rearrangement

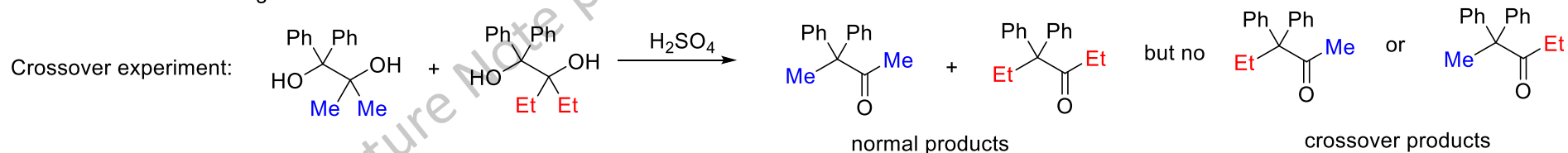
Mechanism:



The driving force of the reaction is the formation of the strong C=O bond via rearrangement to a resonance-stabilised oxocarbenium ion:



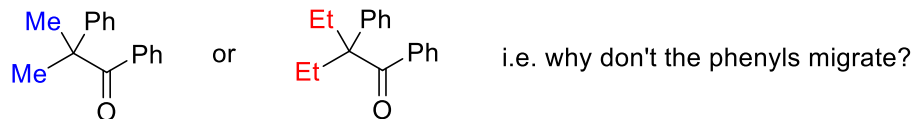
Proof of intramolecular migration:



Absence of crossover products indicates that the rearrangement is *strictly intramolecular*, be it concerted or stepwise.

Question:

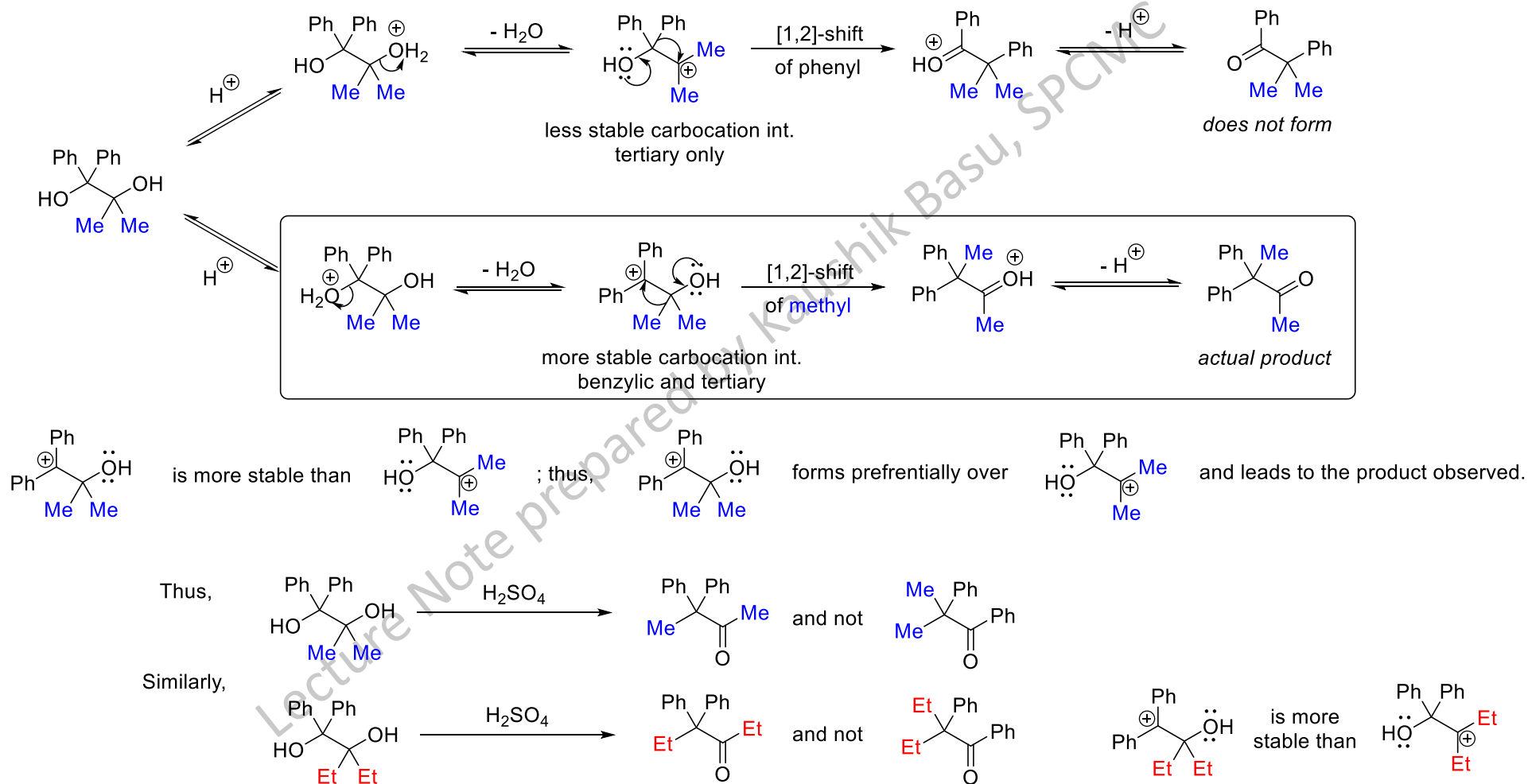
Why are the following not formed in this reaction?



Rearrangements in Organic Chemistry

Migration from carbon to electron-deficient carbon: Pinacol-pinacolone rearrangement

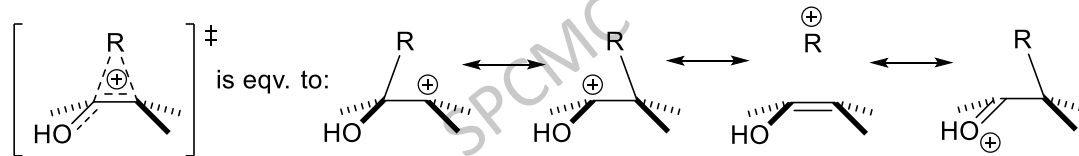
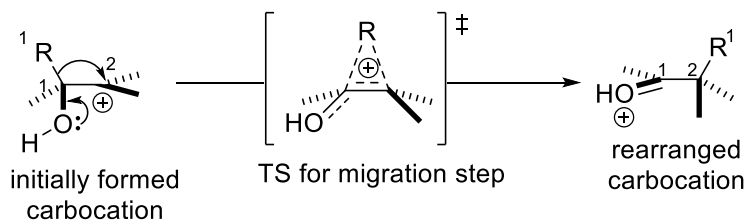
The issue of regioselectivity: when all four substituents of the diol are identical (as in pinacol), the rearrangement yields a single product (as in pinacolone) and there is no debate about which group should migrate (Me migrates); however, when the glycol substrate is unsymmetrical the product is usually formed via the *most stable carbocation intermediate*:



Therefore the protonation in such cases is regioselective, so it is *pre-determined* which group should migrate.

Migration from carbon to electron-deficient carbon: Pinacol-pinacolone rearrangement

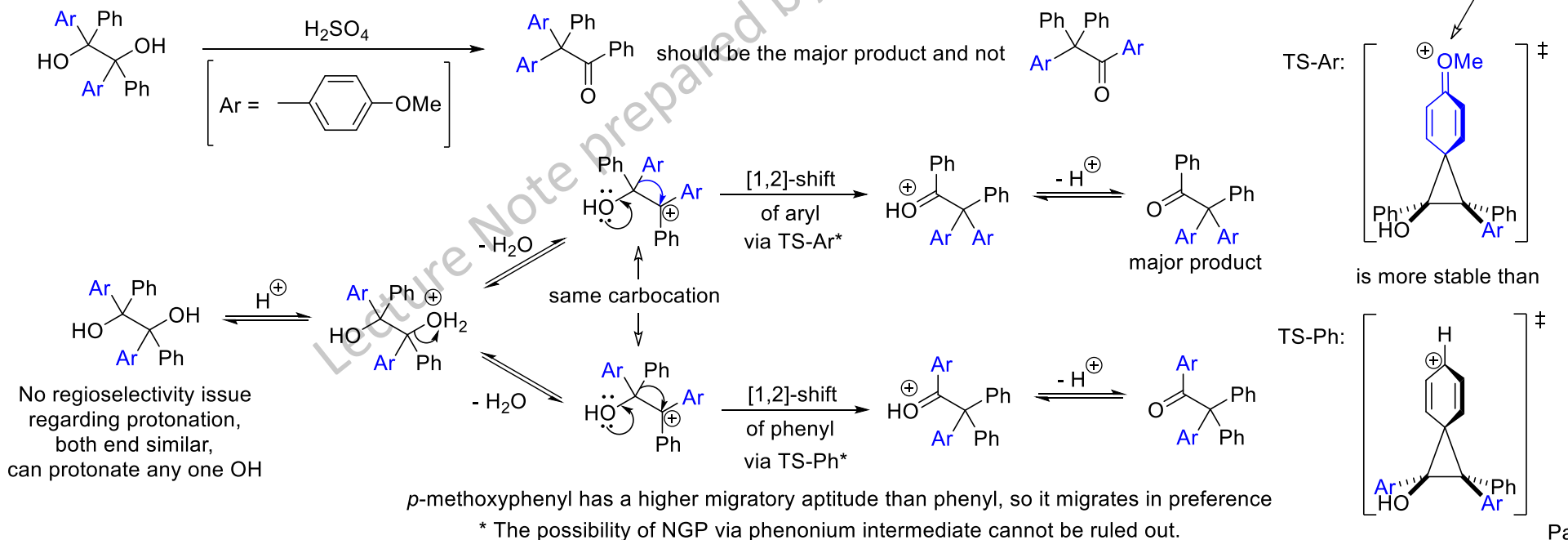
The issue of regioselectivity: when the glycol substrate is symmetrical but contains two different groups at one end the product is usually formed via the migration of the group that has a higher migratory aptitude. As this is a migration to an e-deficient centre, that group should have a greater migratory aptitude which has a better ER capacity:



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

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. The migration is assisted by the oxygen l.p.

Thus,



Aryl > *tert.* alkyl > *sec.* alkyl > *prim.* alkyl > methyl

migration tendency decreases

particularly those bearing ERGs

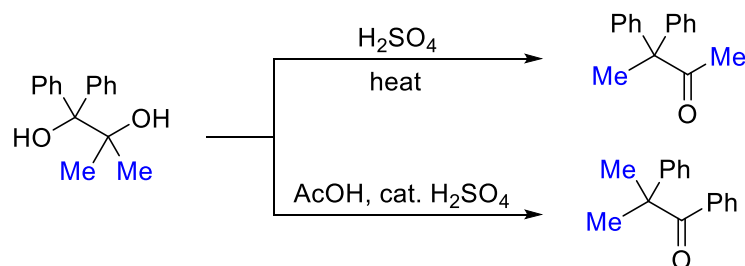
H's position is debatable, as we have already discussed

Rearrangements in Organic Chemistry

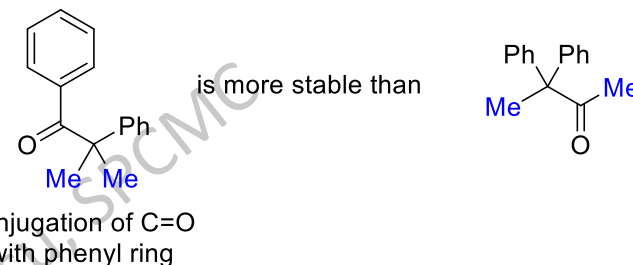
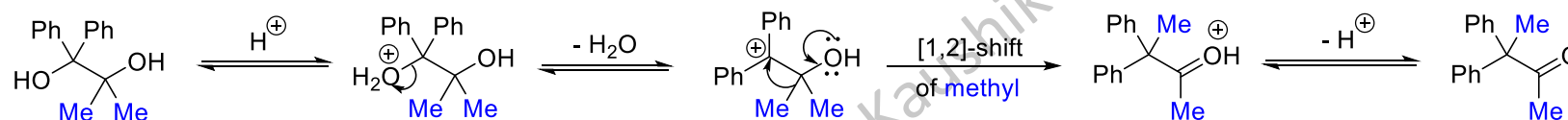
Migration from carbon to electron-deficient carbon: Pinacol-pinacolone rearrangement

Importance of reaction condition in dictating the product composition: The outcome of pinacol rearrangement may completely alter from one reaction condition to the other. Consider the following:

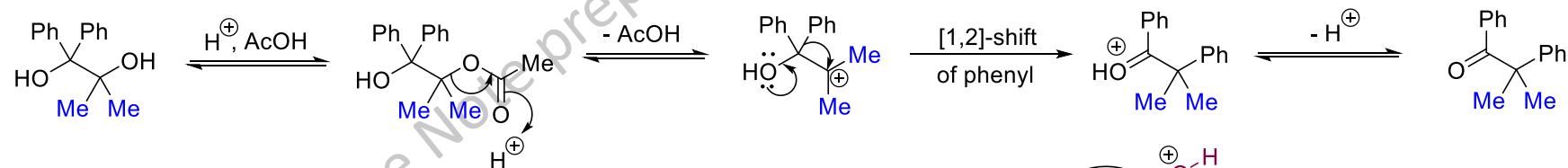
Thus,



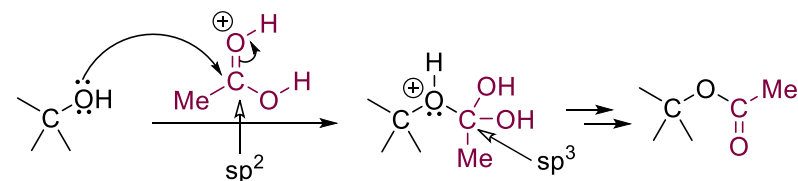
Point to note:

With H_2SO_4 :

reaction outcome determined by regioselective protonation that leads to the formation of the more stable carbocation int. (which is benzylic and tertiary); phenyl is a better migrator but it does not matter.

With AcOH , cat. H_2SO_4 :

Reaction outcome determined by regioselective acetylation of the less hindered OH group that leads to the formation of the *less stable* carbocation int. (which is only tertiary but not benzylic); phenyl now migrates.

hybridization changes from sp^2 to sp^3 during acetylation

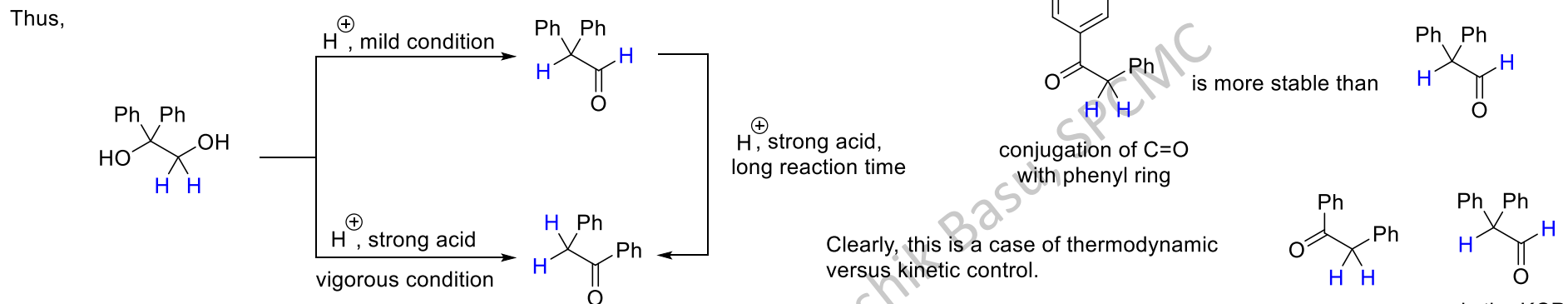
- reaction susceptible to steric crowding
- less hindered $-\text{OH}$ reacts at a faster rate leading to regioselective acetylation - $\text{A}_{\text{Ac}2}$ mechanism

Take home lesson: It is rather difficult to predict which group will migrate and what will be the major product. Along with the relative migratory aptitude of the different groups, reaction condition may also dictate the outcome.

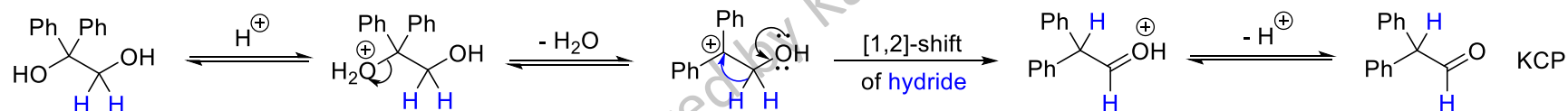
Rearrangements in Organic Chemistry

Migration from carbon to electron-deficient carbon: Pinacol-pinacolone rearrangement

Importance of reaction condition in dictating the product composition: The outcome of pinacol rearrangement may completely alter from one reaction condition to the other. Consider the following:

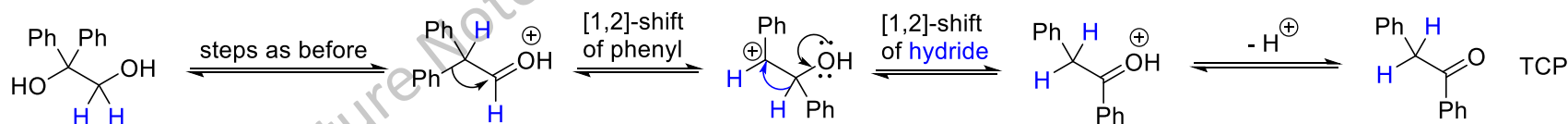


Under milder conditions:

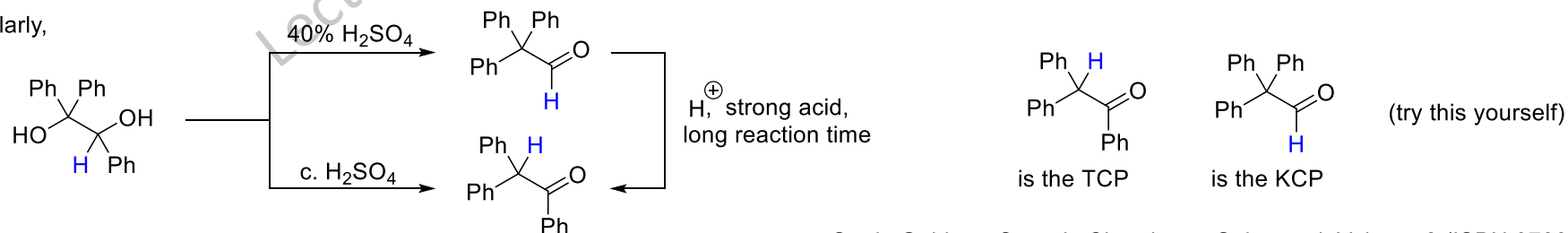


Reaction outcome determined by which carbocation forms fastest as it is under kinetic control. A regioselective protonation leads to formation of the more stable carbocation int. (which is benzylic and tertiary). This eventually dictates that hydride shift will take place.

Under more vigorous conditions, all reactions are reversible and the KCP interconverts to the TCP, via:



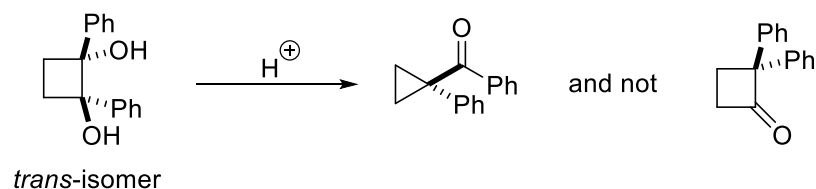
Similarly,



Rearrangements in Organic Chemistry

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A curious observation regarding ring contraction is the following:

The same observation for the *cis*-isomer

The four-membered ring contracts to a three-membered ring.

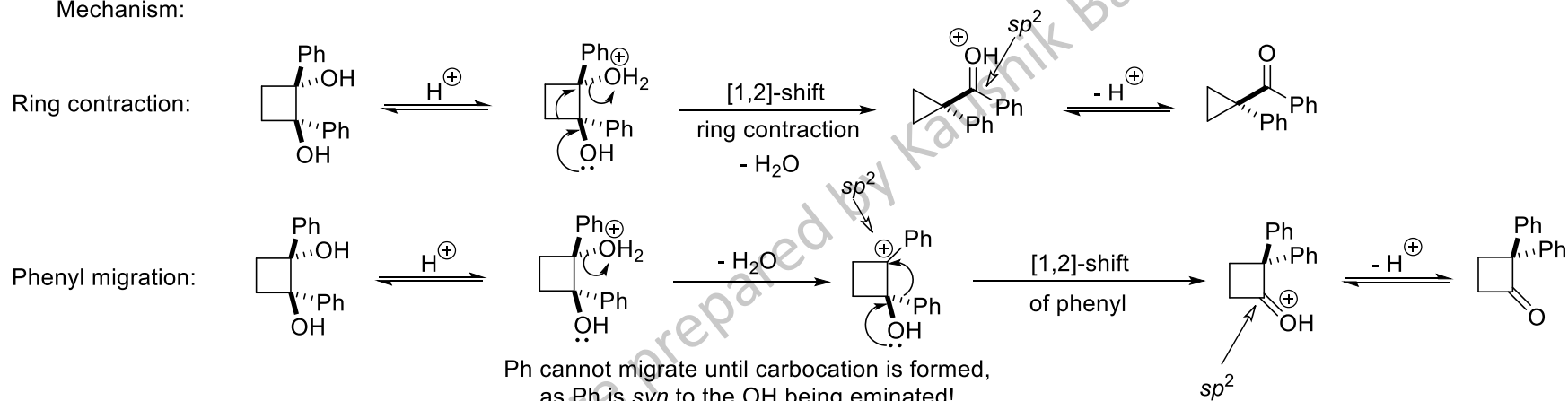
This is unusual because the three-membered ring should be more strained than the four-membered one.

We have seen the opposite happen, rings expanding to release the strain, but here the outcome is different.

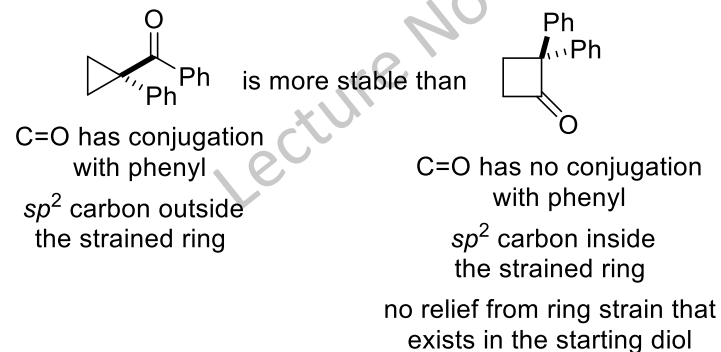
This is even more surprising, considering the relatively high migratory aptitude of phenyl group.

So why is this happening?

Mechanism:



Note:



i) The species resulting from the phenyl shift will be just as strained as the precursor; also, an unsaturated appears inside the four-membered ring in this pathway.

ii) Ring contraction introduces ring strain but also provides stabilisation by bringing the unsaturated carbon outside the strained ring system.

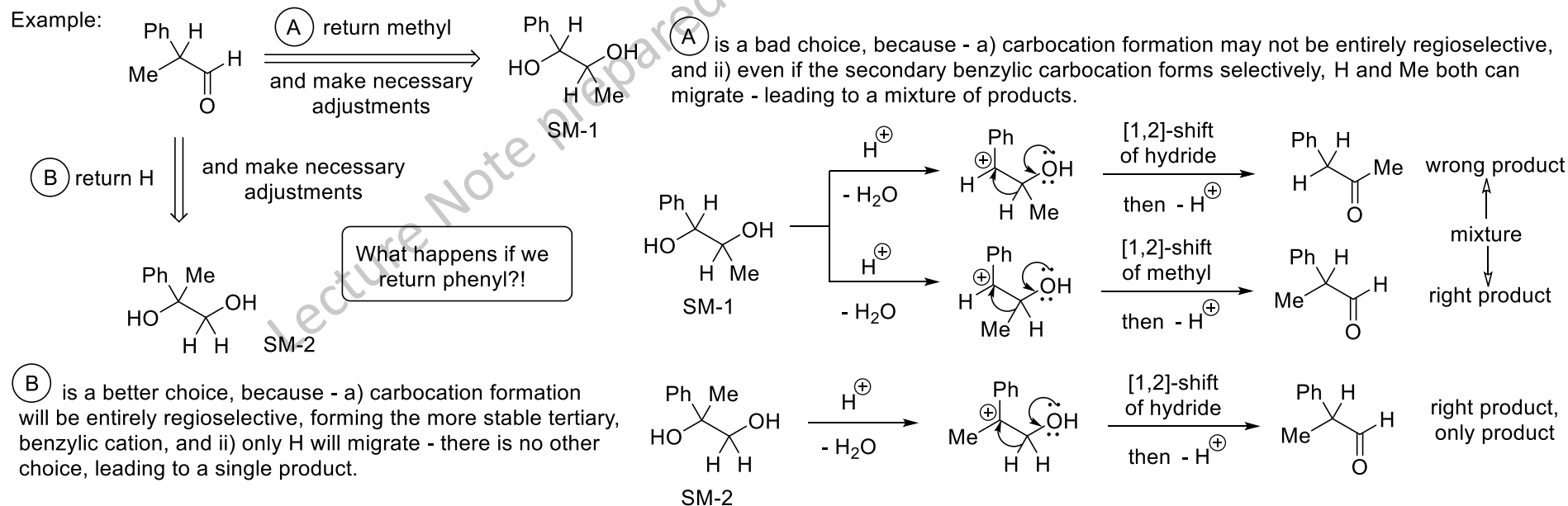
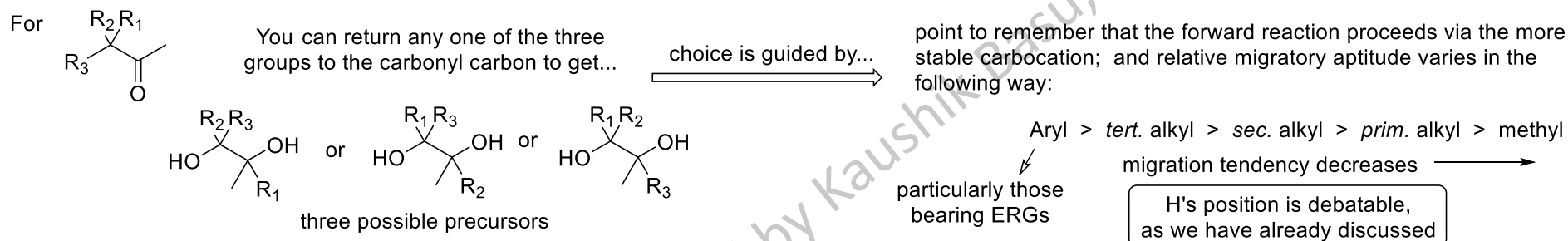
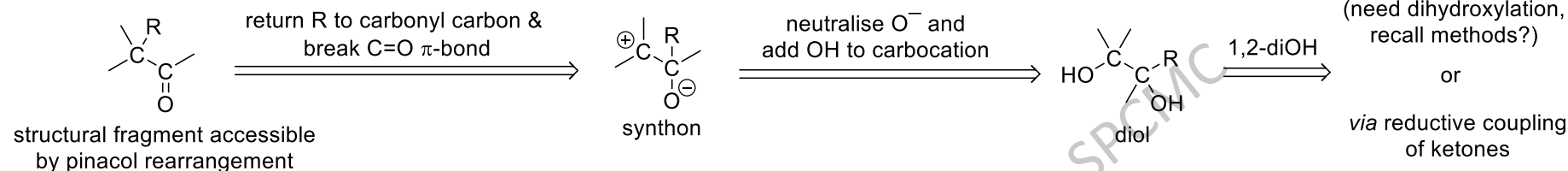
iii) There is also the matter of conjugative stabilisation of the $\text{C}=\text{O}$ in the product ketone in the phenyl in the ring contraction product..

All these factors operating in unison decides the optimum outcome which is ring contraction and not phenyl migration.

Rearrangements in organic Chemistry

Migration from carbon to electron-deficient carbon: Pinacol-pinacolone rearrangement

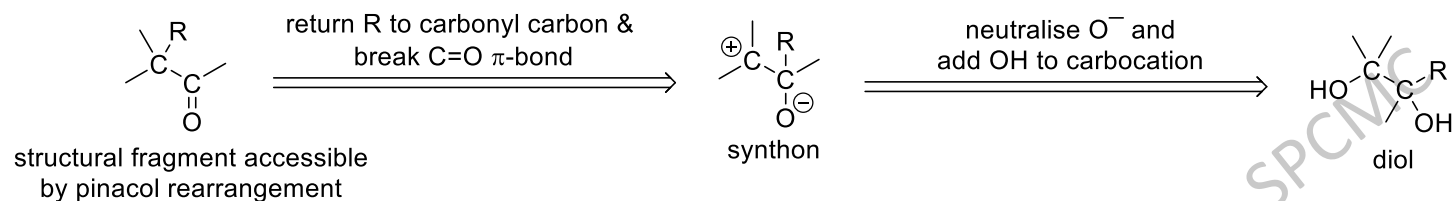
Synthetic utility: How to think of pinacol rearrangement retrosynthetically



Rearrangements in Organic Chemistry

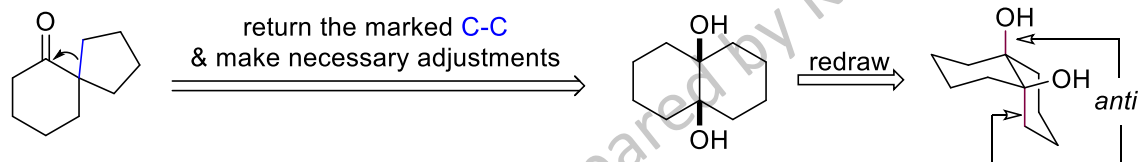
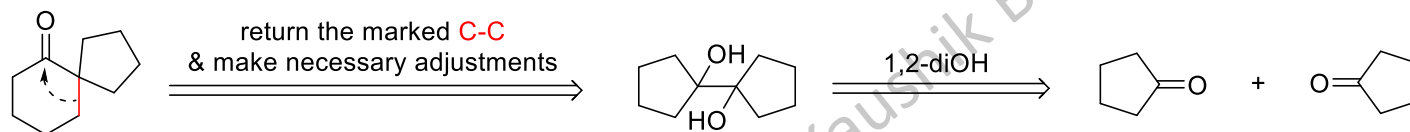
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Synthetic utility: How to think of pinacol rearrangement retrosynthetically



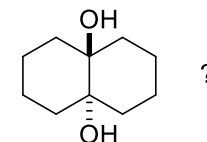
Synthesis of spirocyclic ketone targets:

Example:

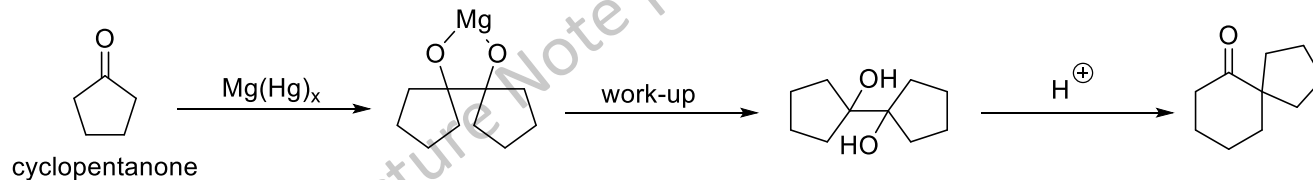


starting diol not so easily obtained

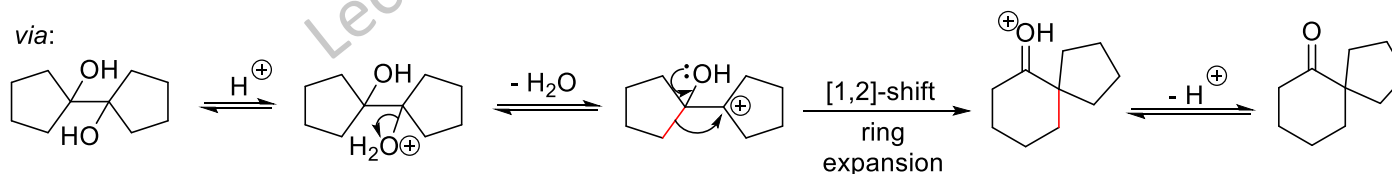
Question: Why not take:



Thus we have the following synthesis:

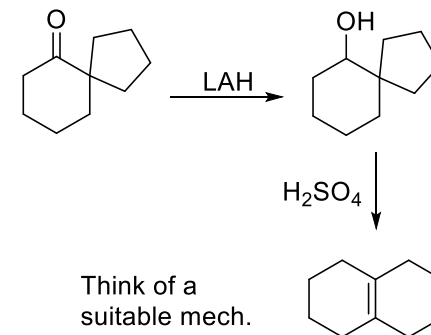


via:



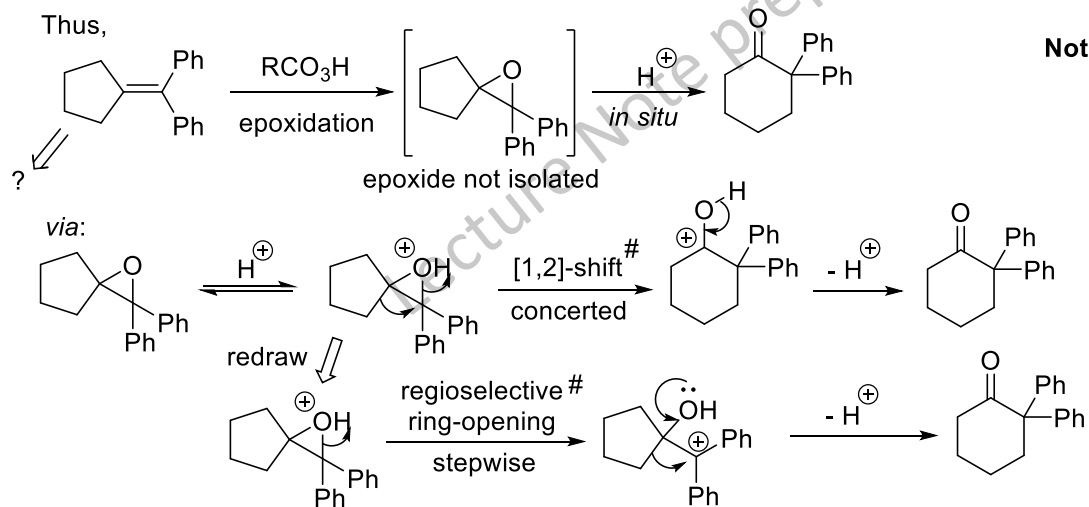
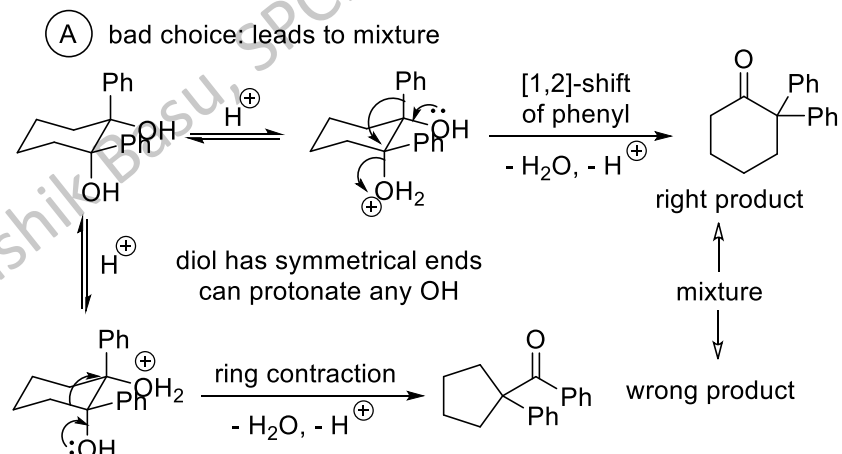
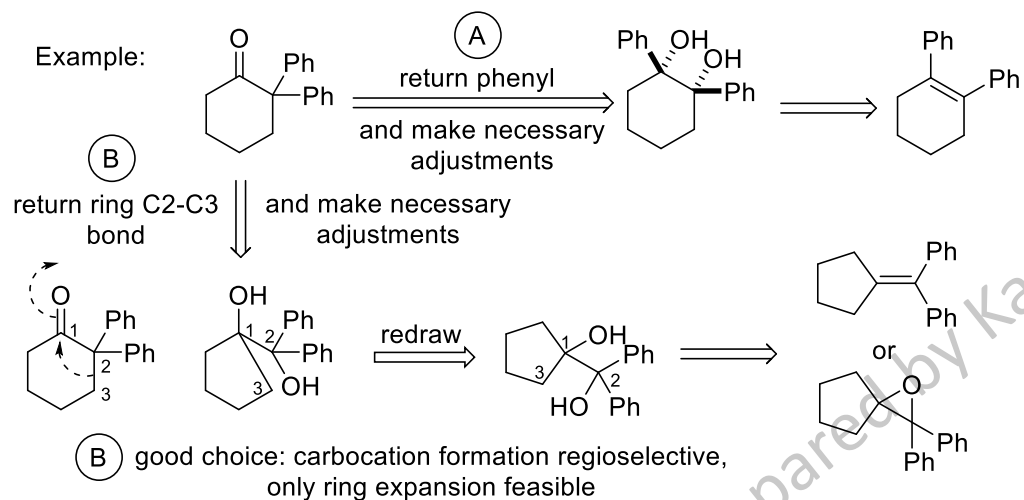
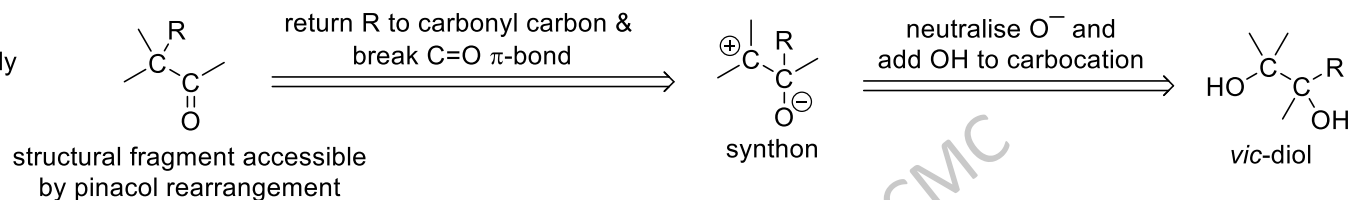
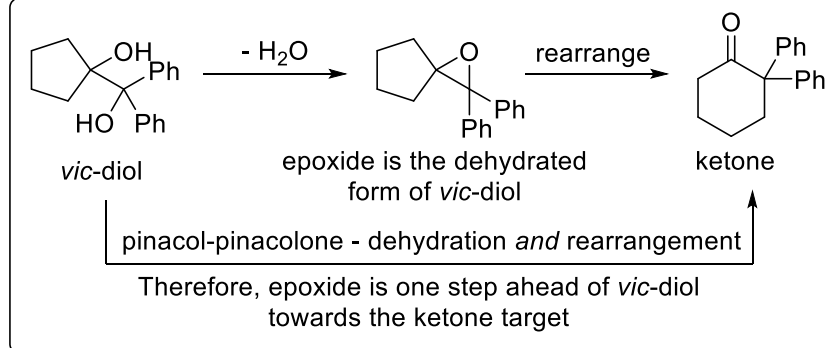
no regioselectivity issue
- diol is symmetrical

aside:



Migration from carbon to electron-deficient carbon: Pinacol-pinacolone rearrangement

Synthetic utility: How to think of pinacol rearrangement retrosynthetically

**Note:**

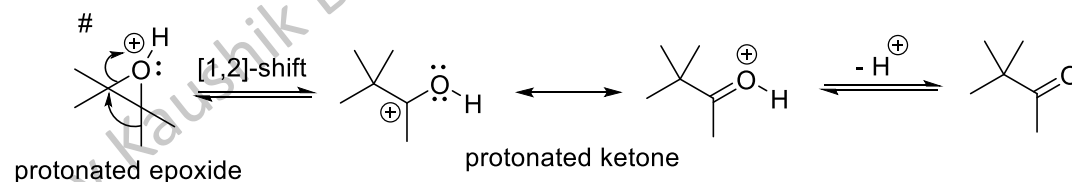
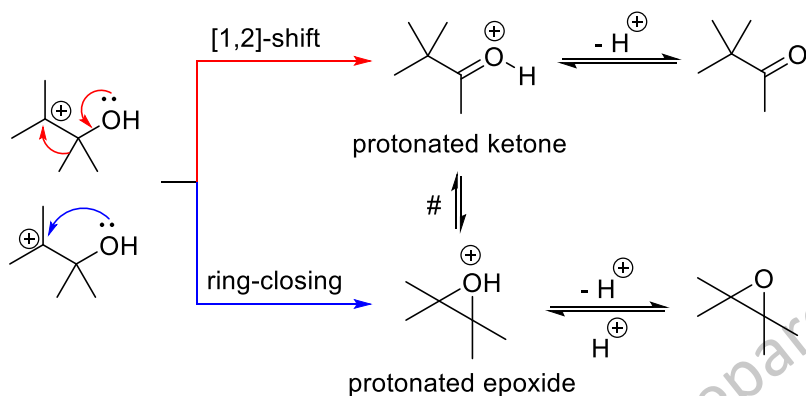
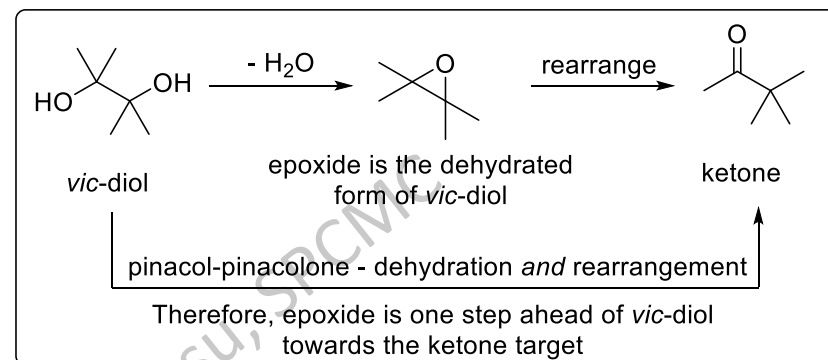
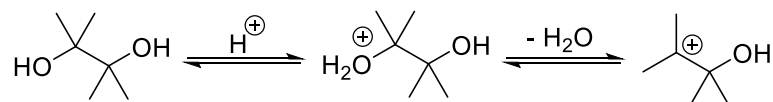
regioselective epoxide ring-opening is guided by formation of the more stable tertiary, benzylic cation

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Cultivating epoxide-involvement in pinacol rearrangement:

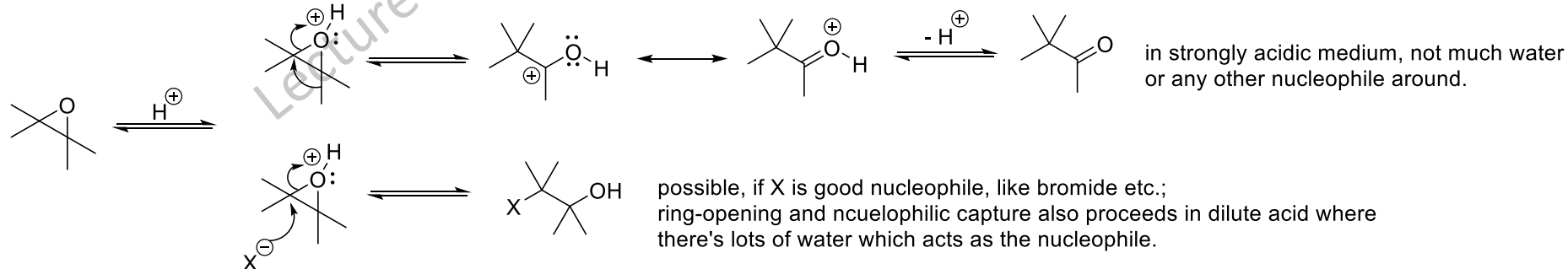
There is always a possibility of involvement of an epoxide in the pinacol rearrangement pathway:



Possible driving force of conversion of epoxide to ketone:

a) release of ring strain, b) formation of strong C=O, c) gain in entropy on going to the acyclic product from cyclic precursor.

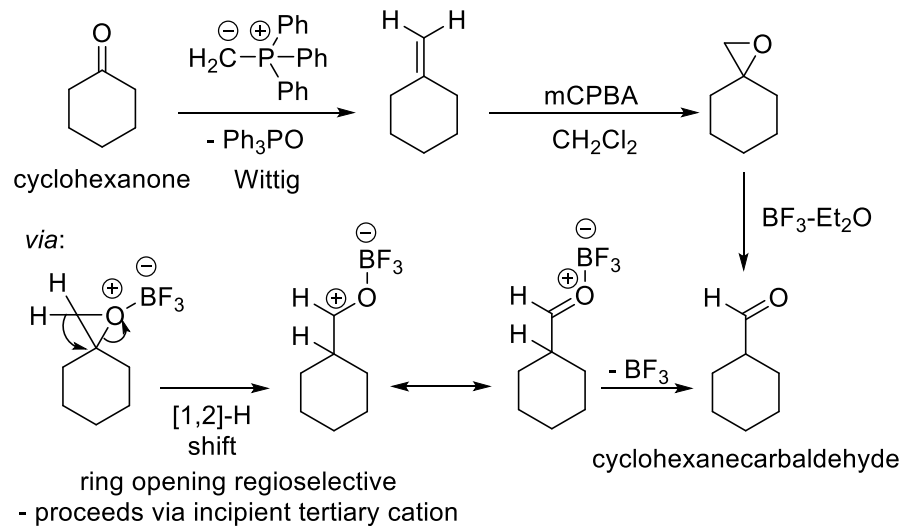
Thus, pinacol rearrangement and acid-catalysed epoxide ring-opening are two closely related transformations. If the epoxide ring-closing is faster than the 1,2-shift then the vic-diol and the epoxide are, in all purposes, equivalent. If we use strongly acidic medium and stabilizing substituents, the two pathways will merge. OTOH, if we use milder acids with good nucleophiles present in the medium, epoxide ring-opening leads not to rearrangement, but to covalent bond-forming reactions, such as halohydrin formation.



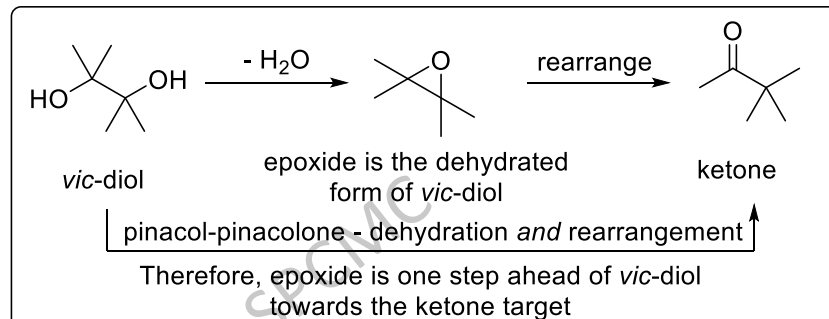
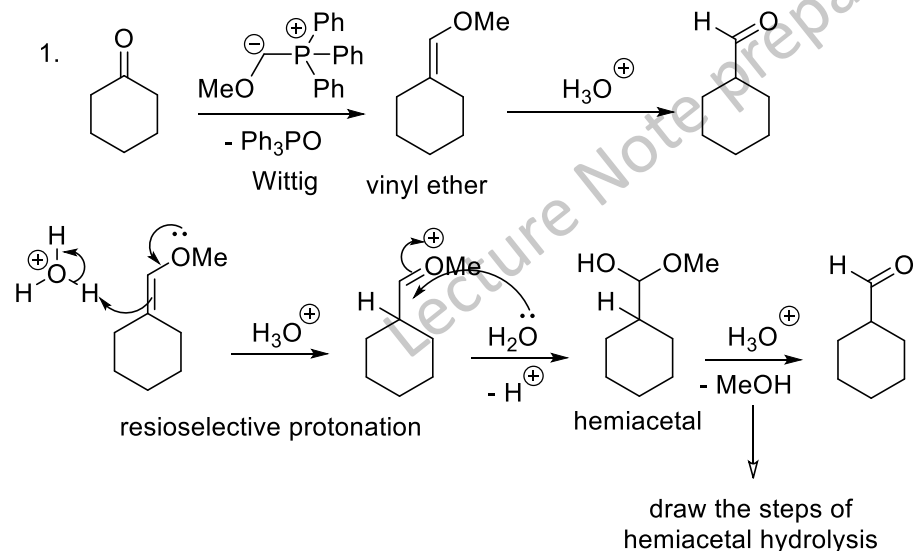
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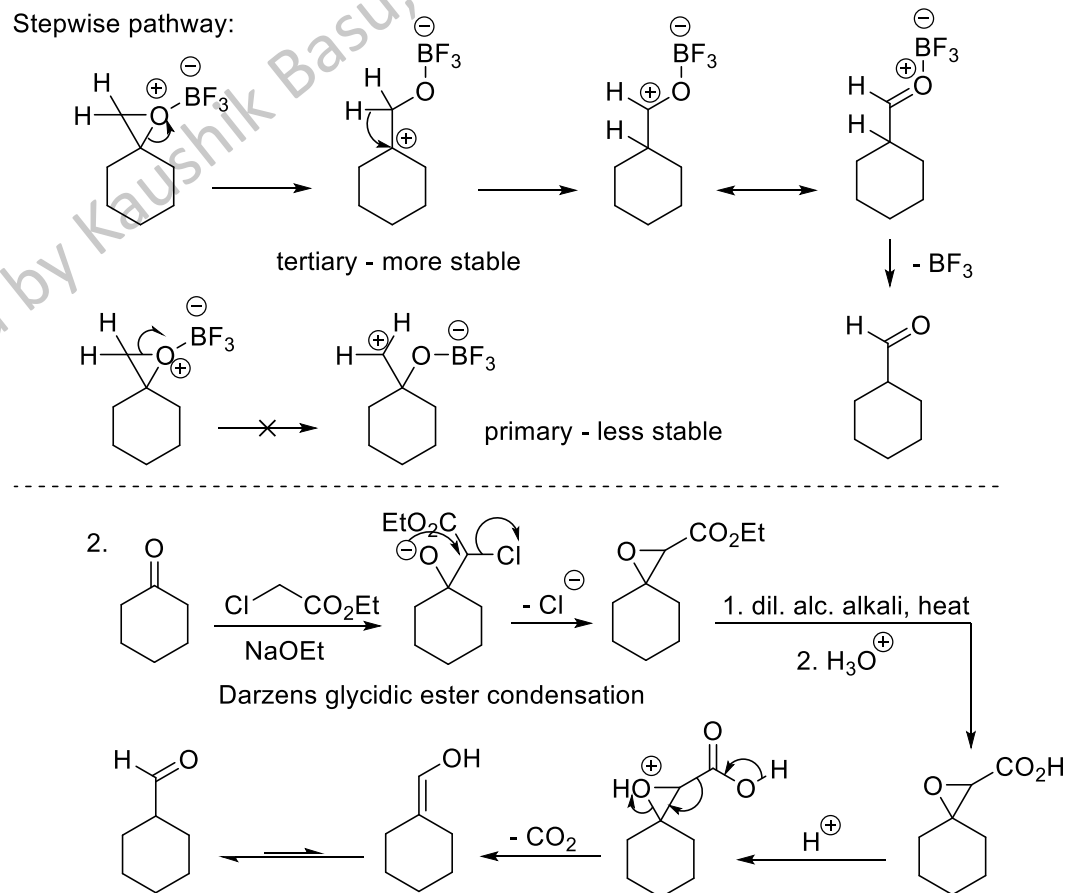
Cultivating epoxide-involvement in pinacol rearrangement:



Alternative ways to achieve this transformation:



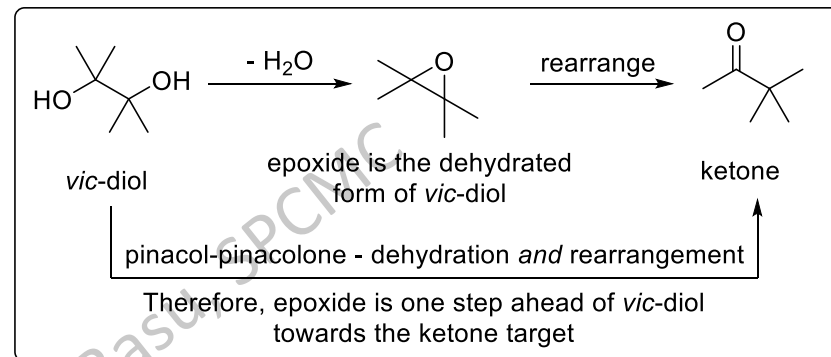
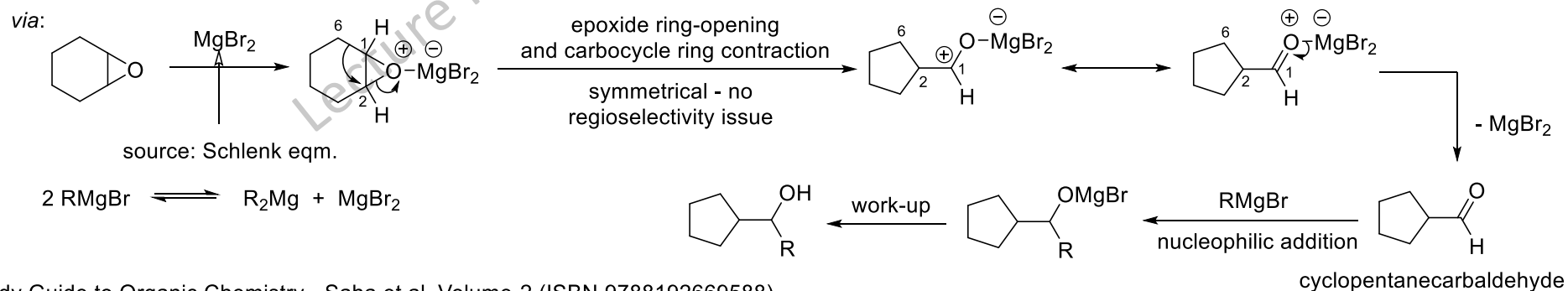
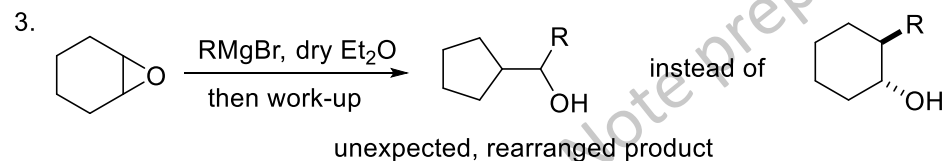
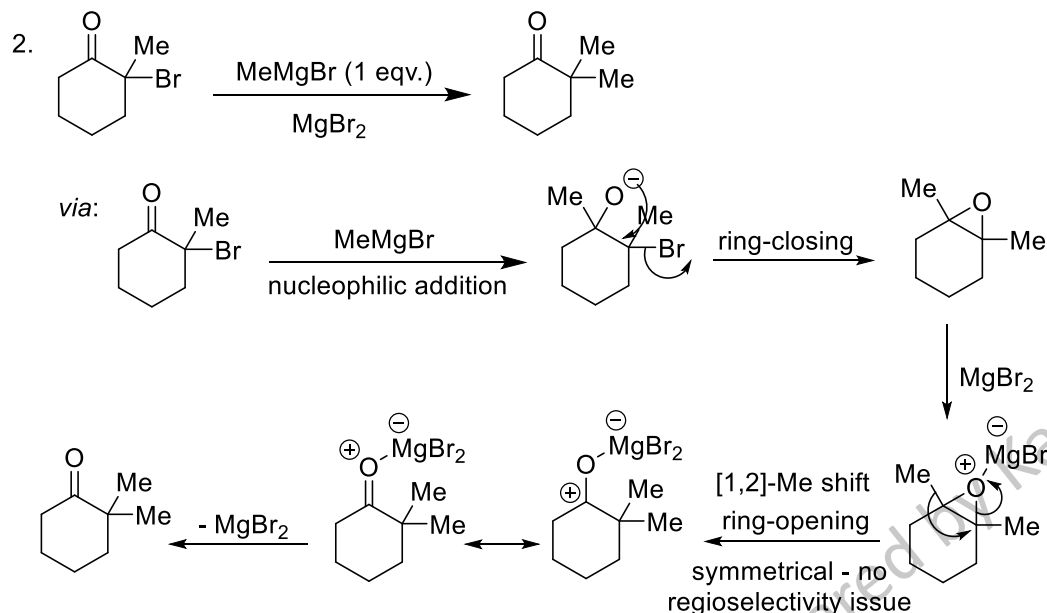
Stepwise pathway:



Rearrangements in Organic Chemistry

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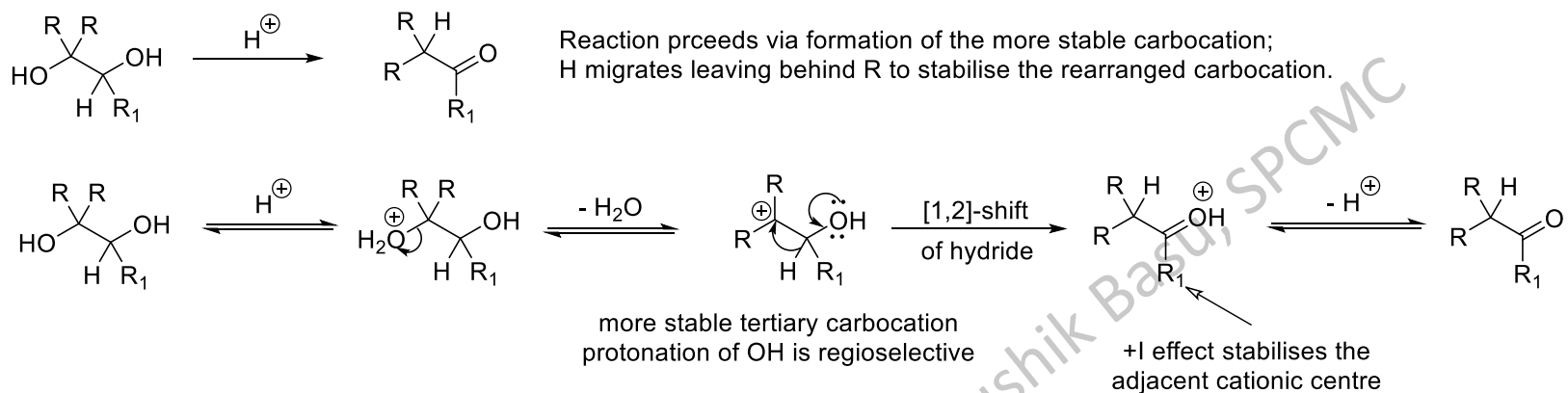
Cultivating epoxide-involvement in pinacol rearrangement:

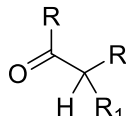


Rearrangements in Organic Chemistry

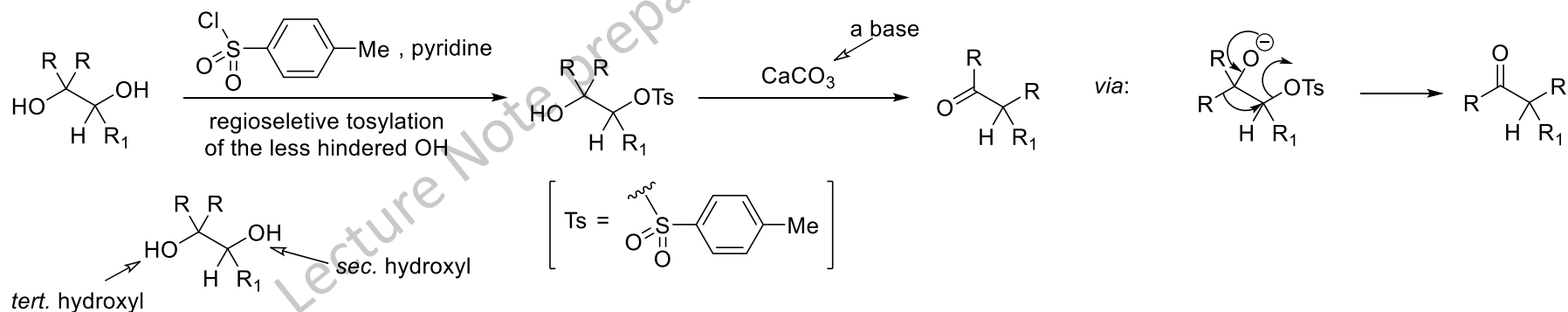
Migration from carbon to electron-deficient carbon: Pinacol-pinacolone rearrangement

Pinacol rearrangement under basic condition: Complementing the acid condition



But what if the target is:  ? For this we need to selectively make the secondary hydroxyl group a better leaving group and keep the more hindered, tertiary hydroxyl unreacted.

We have already seen that regioselective acetylation of the less hindered OH can solve this problem. The same feat can be achieved by tosylation

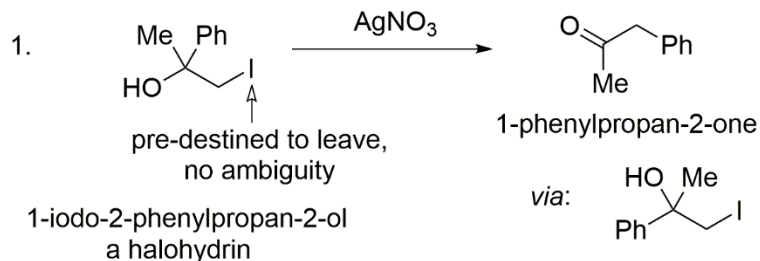


When one of the hydroxyl groups is converted to a good leaving group, one of the two possible products can be generated regioselectively. Similarly, selective generation of carbocations can be realized when 2-heterosubstituted alcohols (e.g., halohydrins and 2-aminoalcohols etc.) are used as substrates. The pinacol-type rearrangement of these compounds is referred to as the semipinacol rearrangement, a term first coined by M. Tiffeneau. Owing to its predictability and the mild reaction conditions, the semipinacol rearrangement is almost exclusively utilized in complex molecule synthesis.

Rearrangements in Organic Chemistry

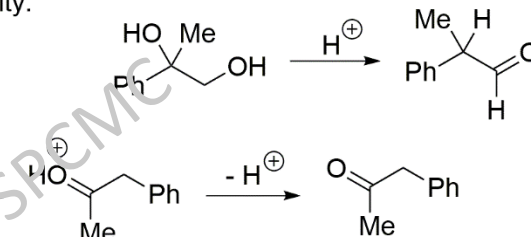
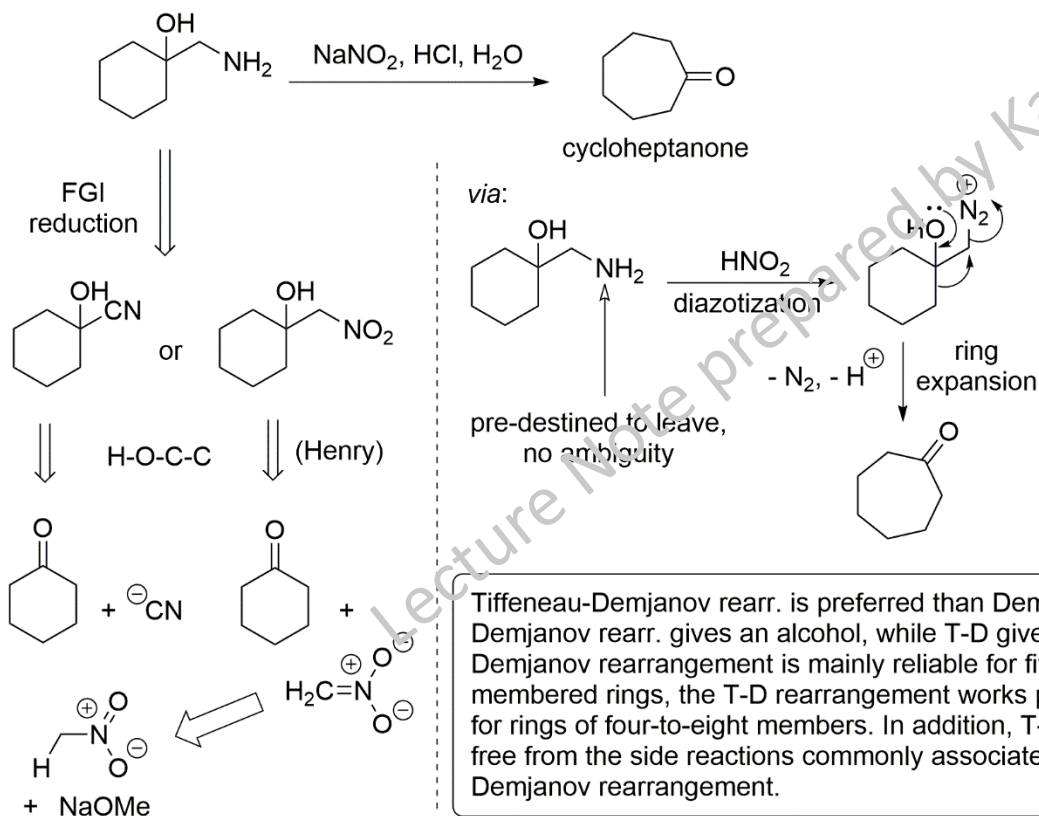
Migration from carbon to electron-deficient carbon: Pinacol-pinacolone rearrangement

Semipinacol rearrangement:

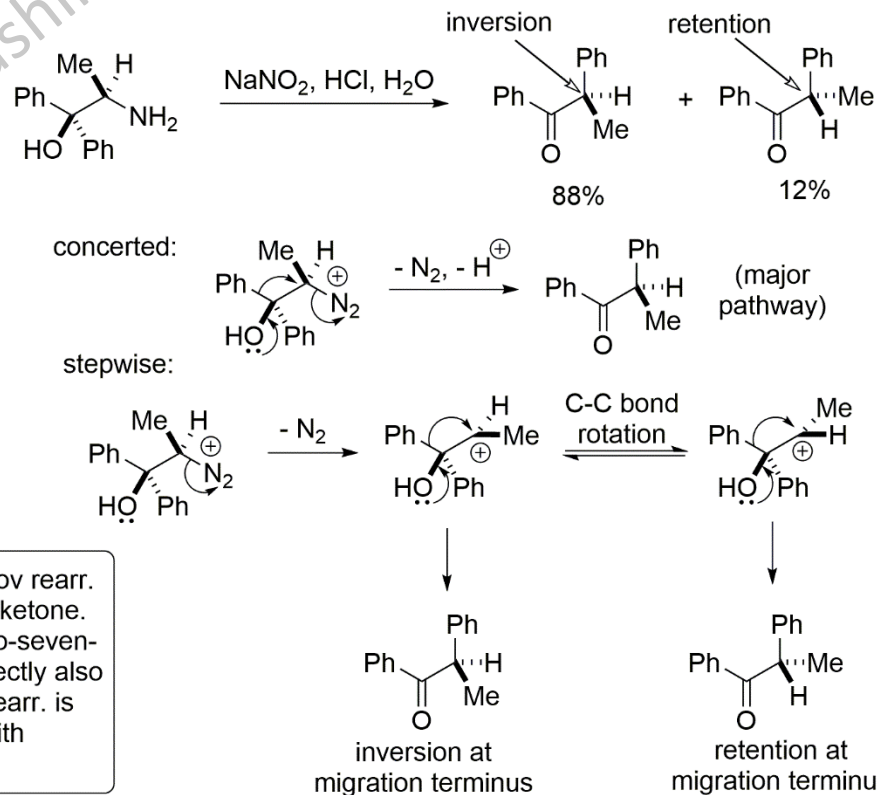


Under the given condition, it is pre-ordained which heteroatom-substituted carbon would lose the leaving group. There is no ambiguity.

Outcome just opposite to pinacol rearr. of

2. Pinacolic demination of β -aminoalcohols: Tiffeneau-Demjanov rearrangement:

Stereochemical outcome indicates both stepwise and concerted paths are operating:



Tiffeneau-Demjanov rearr. is preferred than Demjanov rearr. Demjanov rearr. gives an alcohol, while T-D gives a ketone. Demjanov rearrangement is mainly reliable for five-to-seven-membered rings, the T-D rearrangement works perfectly also for rings of four-to-eight members. In addition, T-D rearr. is free from the side reactions commonly associated with Demjanov rearrangement.