

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

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Recommended texts:

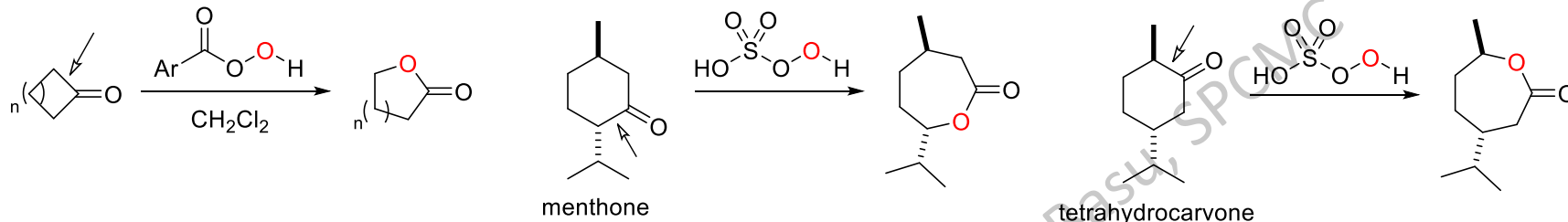
1. Study Guide to Organic Chemistry, Volume 2, by Saha, Chakraborty, Saha & Basu, Techno World, ISBN 9788192669588,
2. Study Guide to Organic Chemistry, Volume 4, by Saha, Chakraborty, Saha & Basu, Techno World, ISBN 9788192695259,
3. Organic Chemistry, Second Ed. by Clayden, Greeves & Warren, OUP, ISBN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

Rearrangements in Organic Chemistry

Migration from carbon to electron-deficient oxygen: Baeyer-Villiger oxidation, Dakin oxidation, cumene-phenol reaction

Baeyer-Villiger oxidation/rearrangement: The transformation of ketones into esters and cyclic ketones into lactones or hydroxy acids by peroxyacids.

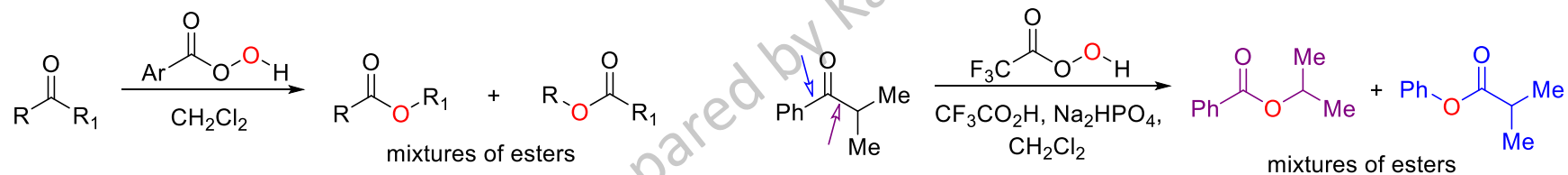
Cyclic ketones to lactones: ring expansion



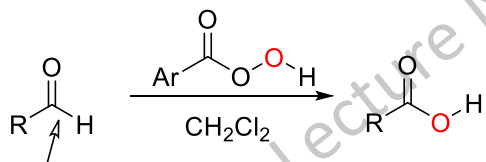
Oxygen insertion at the marked bonds.

Note the retention of configuration of the asymmetric centres.

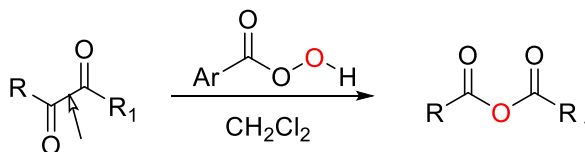
Ketones to esters:



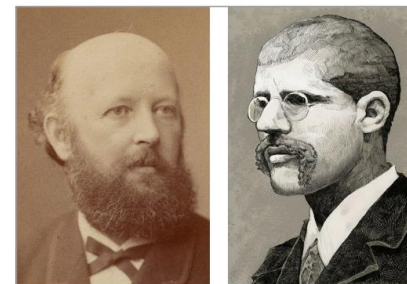
Aldehydes to carboxylic acids:



1,2-diketones to mixed anhydrides:



This is an oxidation reaction as insertion of O into the C-C bond increases the oxidation number of both atoms between which the O is inserted.



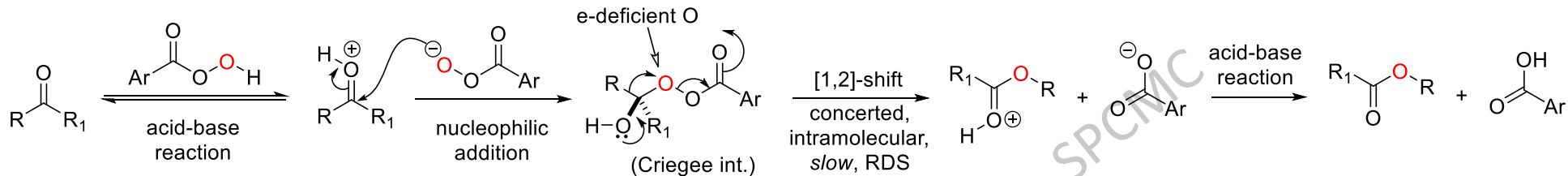
A. von Baeyer
(1835-1917)

V. Villiger
(1868-1934)

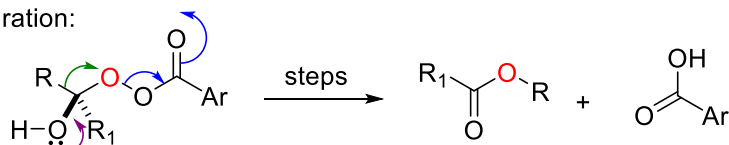
Rearrangements in Organic Chemistry

Migration from carbon to electron-deficient oxygen: Baeyer-Villiger oxidation, Dakin oxidation, cumene-phenol reaction

Baeyer-Villiger oxidation/rearrangement: Mechanism:

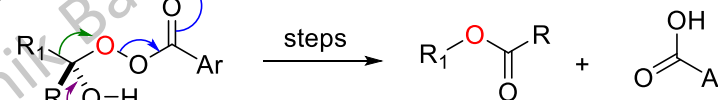


For R migration:



carboxylate leaves, R migrates,
oxygen stabilises the incipient cation
R and OCOAr anti

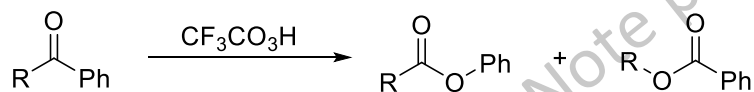
Similarly, R_1 can also migrate:



carboxylate leaves, R_1 migrates,
oxygen stabilises the incipient cation
 R_1 and OCOAr anti

Which group migrates?

As this is a migration to an e-deficient centre, it is expected that the group that has the better ER ability should migrate better. Consider the following data:

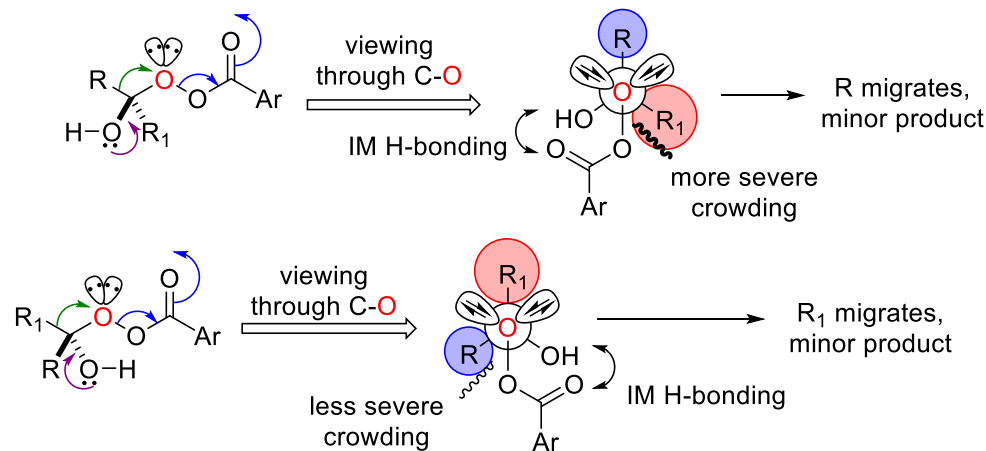


Product arising out of migration of...

R	... Ph	... R
Me	90	0
Et	87	6
i-Pr	33	63
t-Bu	2	77

Migratory aptitude: t -alkyl > sec. alkyl > phenyl > prim. alkyl > methyl

The role of steric bulk: Let the size of $R <$ that of R_1



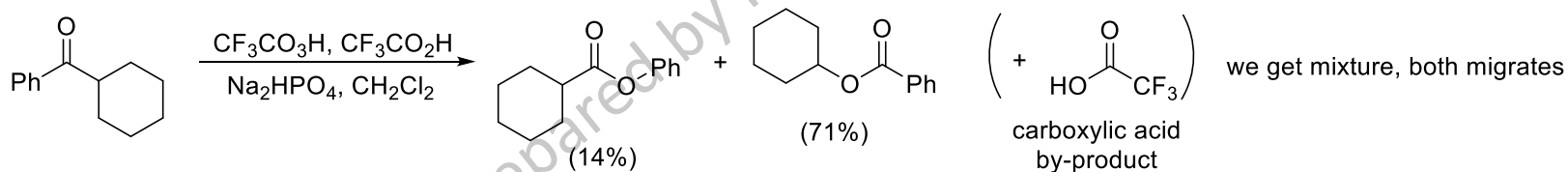
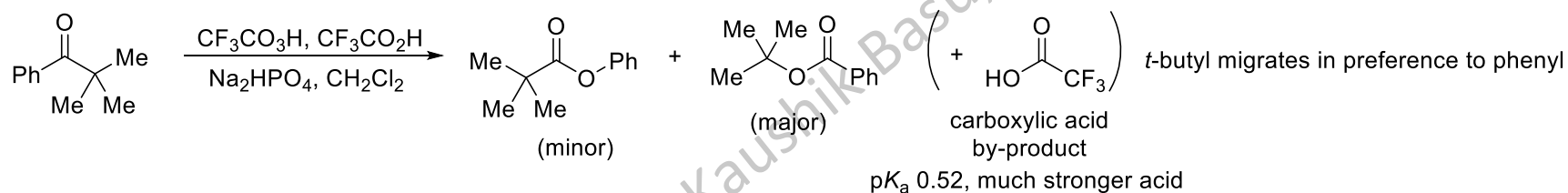
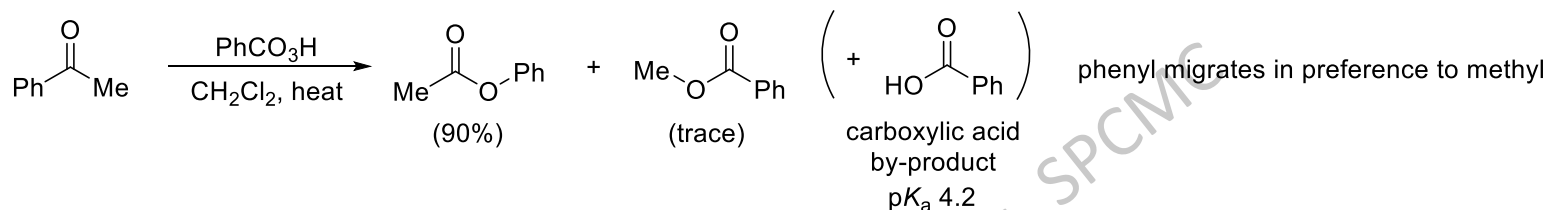
tert-butyl has unusually high tendency for migration

Rearrangements in Organic Chemistry

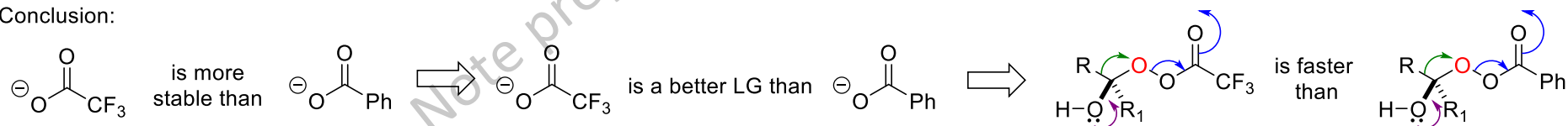
Migration from carbon to electron-deficient oxygen: Baeyer-Villiger oxidation

The identity of the peracid:

Migratory aptitude: *t*-alkyl > sec. alkyl > phenyl > prim. alkyl > methyl

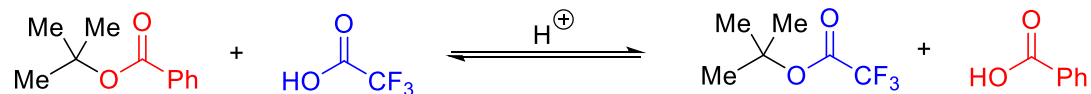


Conclusion:



So $\text{CF}_3\text{CO}_3\text{H}$ should be the reagent of choice. But there is a trade-off. TFA is a very strong acid in organic standard.

It may lower the pH of the medium to such levels where the following *transesterification* reaction may take over, leading to the formation of undesired side products:



So, the pH must be controlled from getting too low. For that a buffer like Na_2HPO_4 is used that consumes the $\text{CF}_3\text{CO}_2\text{H}$ produced *in situ*. Recall that Na_2HPO_4 is a salt derived from the strong base NaOH and weak acid H_3PO_4 .

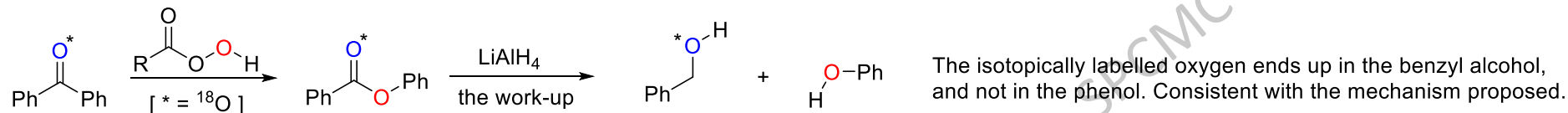
Also note that a peracid RCO_3H is less acidic than the corresponding carboxylic acid RCO_2H . (Why?)

Rearrangements in Organic Chemistry

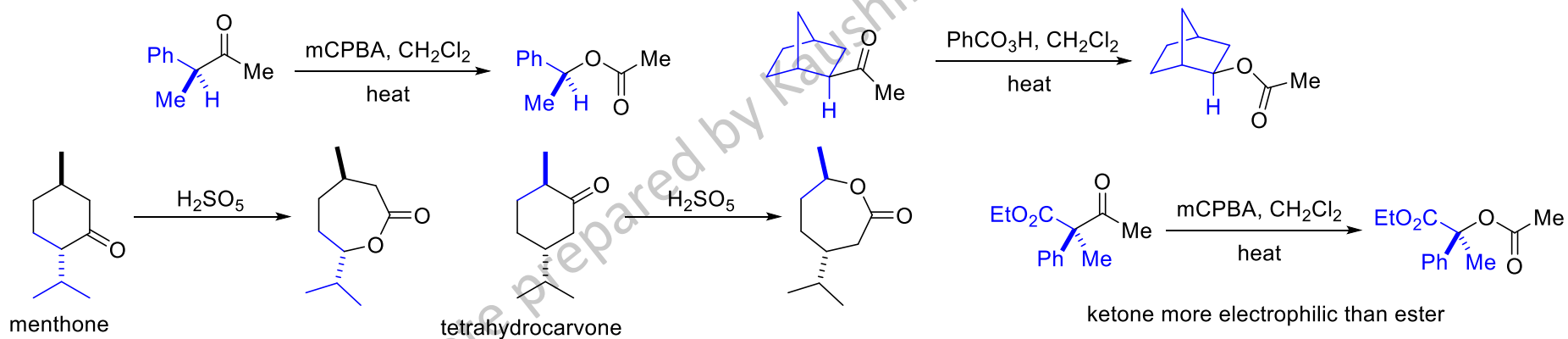
Migration from carbon to electron-deficient oxygen: Baeyer-Villiger oxidation

Proof in favour of the mechanism:

1. The fate of the carbonyl oxygen is determined by isotopic labelling study:

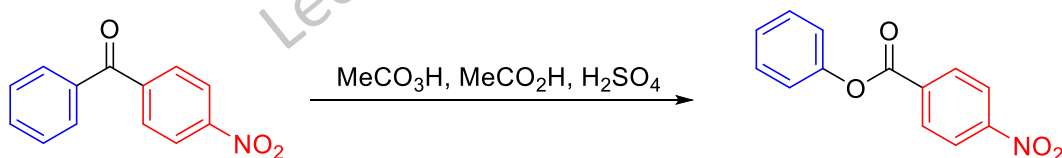


2. Intramolecular migration is proved by complete retention of configuration for chiral migrators:



Note the regioselectivity in each case - the more substituted group of the ketone migrates in each case

3. When steric bulk does not matter, the more ER group migrates preferentially - indicates e-deficient nature of the RDS TS:

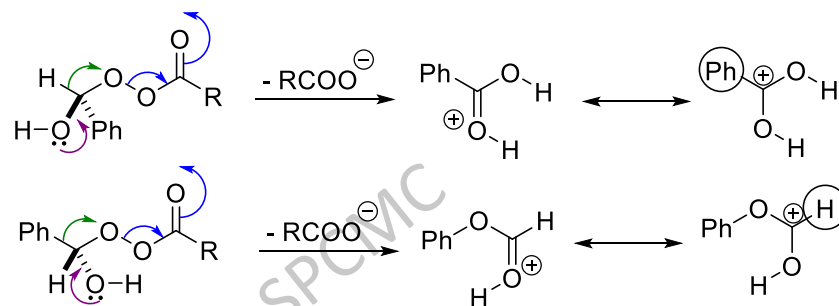
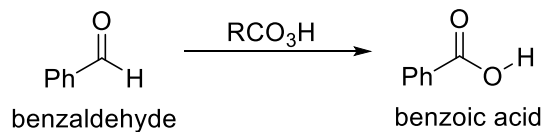


Electron-rich phenyl ring migrates preferentially. The e-deficient red aryl ring does not migrate, NO₂ is an -I, -R effect exerting group.

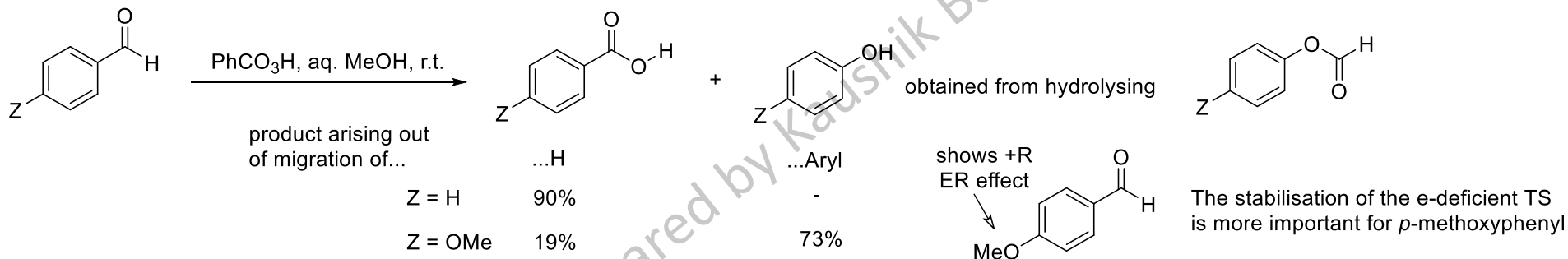
Rearrangements in Organic Chemistry

Migration from carbon to electron-deficient oxygen: Baeyer-Villiger oxidation

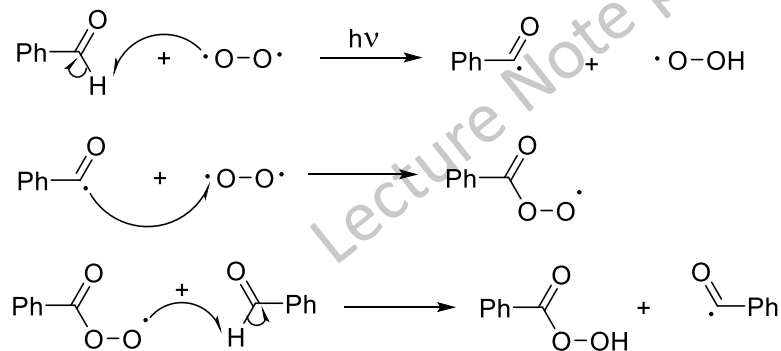
For aldehydes, hydrogen migrates, leading to the formation of carboxylic acid:



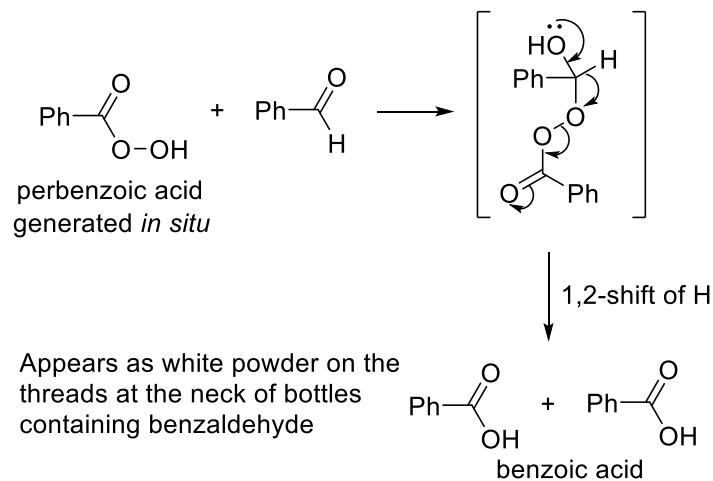
However, if the aryl group has a strong ERG then it may compete with H when migrating, consider the following:



Aerial oxidation of benzaldehyde proceeds via a Baeyer-Villiger oxidation mechanism:



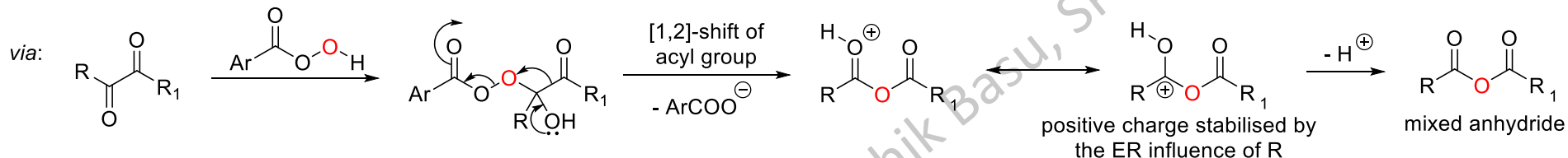
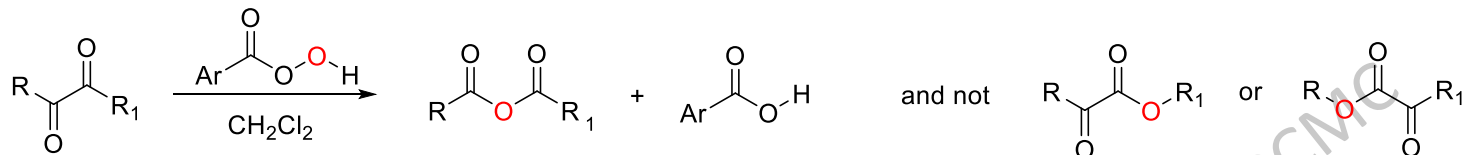
and so on.



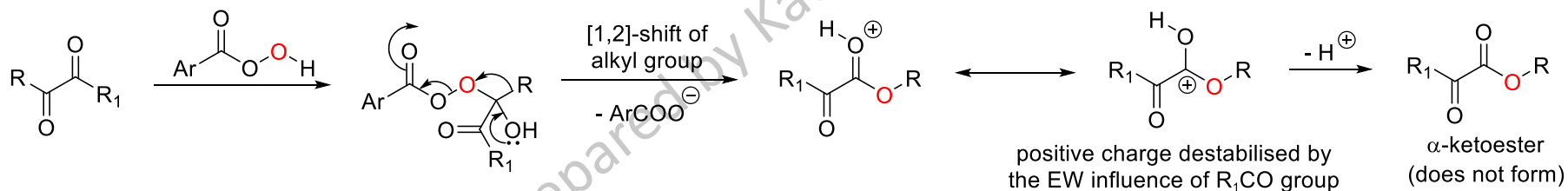
Rearrangements in Organic Chemistry

Migration from carbon to electron-deficient oxygen: Baeyer-Villiger oxidation

For a 1,2-dicarbonyl compounds, a mixed anhydride results:

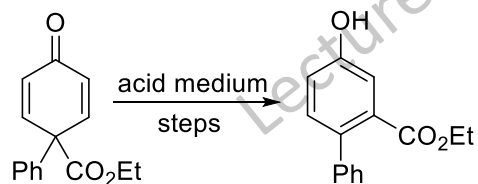


alternative outcome:

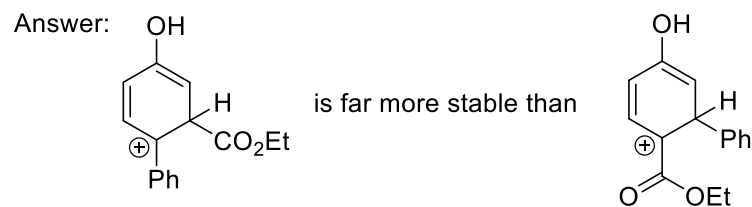


Therefore, the acyl migration is favourable because the alternative leaves the same EW acyl group right next to the positively-charged carbon - a species rather unstable and difficult to form.

Compare this situation with an earlier example seen for dienone-phenol rearrangement:



Ph has a greater migratory apt. than CO_2Et , then?



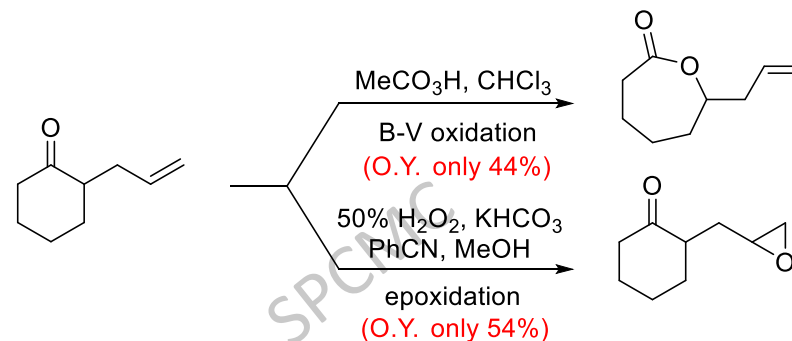
CO_2Et migrates because phenyl migration leaves the positively-charged carbon right next to EW CO_2Et , that is bad.

Rearrangements in Organic Chemistry

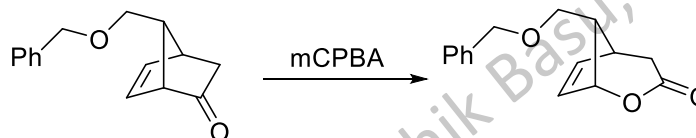
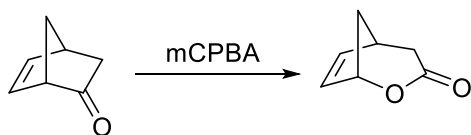
Migration from carbon to electron-deficient oxygen: Baeyer-Villiger oxidation

Presence of C=C in the substrate for B-V oxidation:

Epoxidation can be a seriously competing side reaction, particularly so if the C=C is e-rich in nature. The reactivity of ketones and olefins towards peracids are comparable, so a mixture of products is expected. However, careful control of reaction condition and judicious selection of reagents can favour one reaction over the other. Thus,

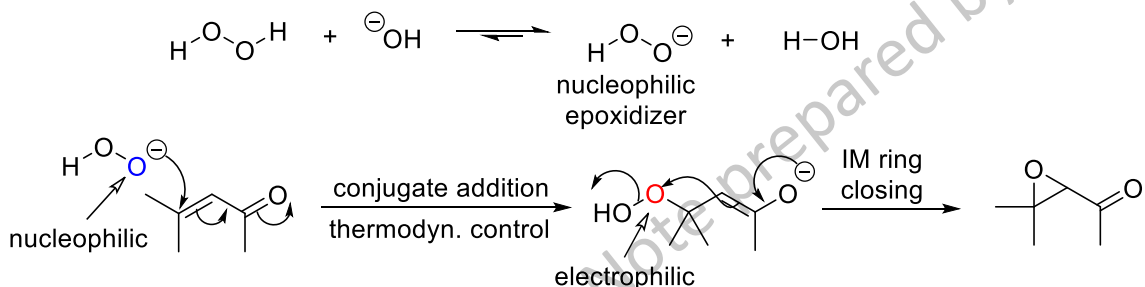


And also the following examples:

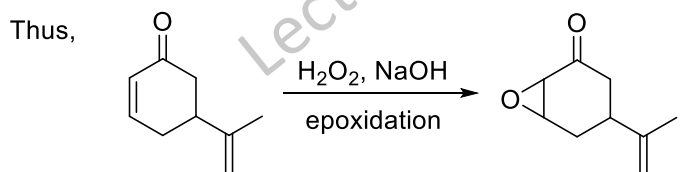


In all the examples, the more substituted group migrates in the B-V reaction

Recall that for epoxidation of α,β -unsaturated carbonyl compounds, peracids are not recommended. The reason is two-fold - a) peracid is an electrophilic epoxidizer and the C=C of enones are also electrophilic; so it is not a compatible combination, and b) there is a possibility of Baeyer-Villiger oxidation. The epoxidation is conveniently carried out by alkaline H_2O_2 , which proceeds via the hydroperoxide anion - a nucleophilic epoxidizer.

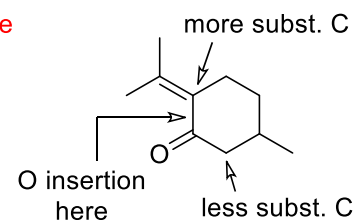
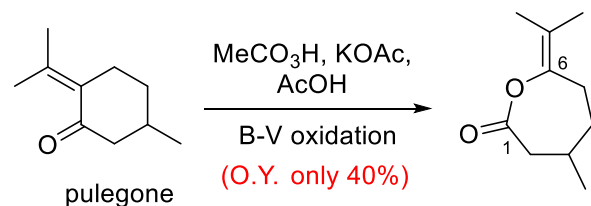


$\text{H}-\text{O}-\text{O}^-$: Marked O-atom acts first as a **nucleophilic centre**, then as an **electrophilic centre**



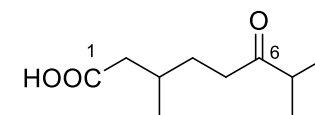
regioselective epoxidation of the electrophilic alkene

B-V oxidation of an enone:



1. NaOH, H_2O
2. aq. acid

hydrolysis
of lactone

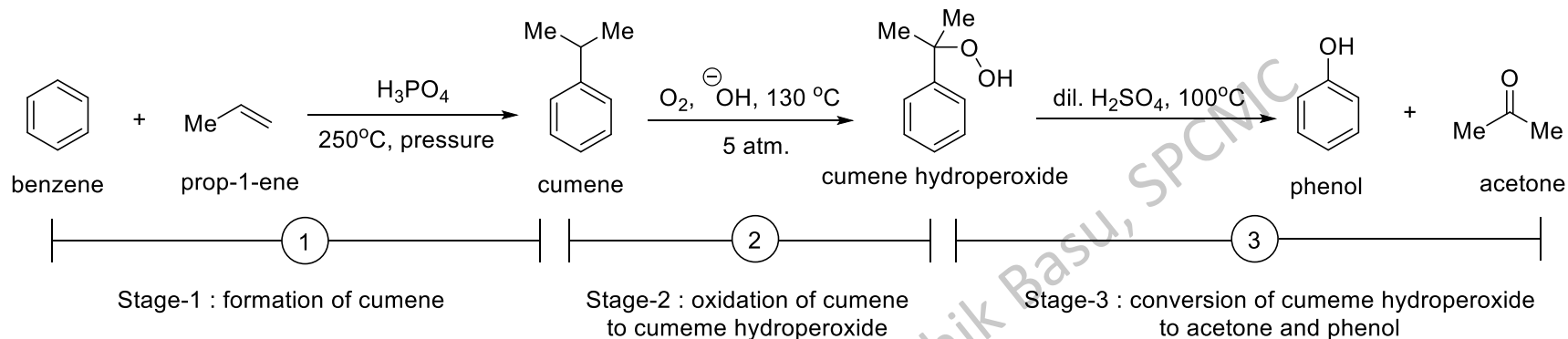


Take home lesson: It is difficult to predict exactly which reaction will dominate. However, for enones, alk. H_2O_2 is the best bet for effecting epoxidation. using peracid will probably give more B-V oxidation.

Rearrangements in Organic Chemistry

Migration from carbon to electron-deficient oxygen: Cumene-phenol process

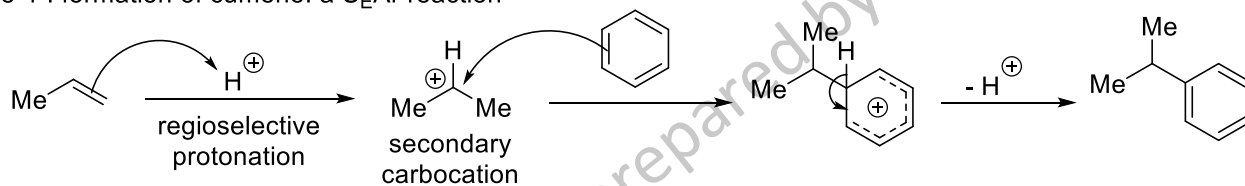
Stepwise conversion of benzene and propylene into phenol and acetone via cumene and cumene hydroperoxide.



This is the rearrangement step.

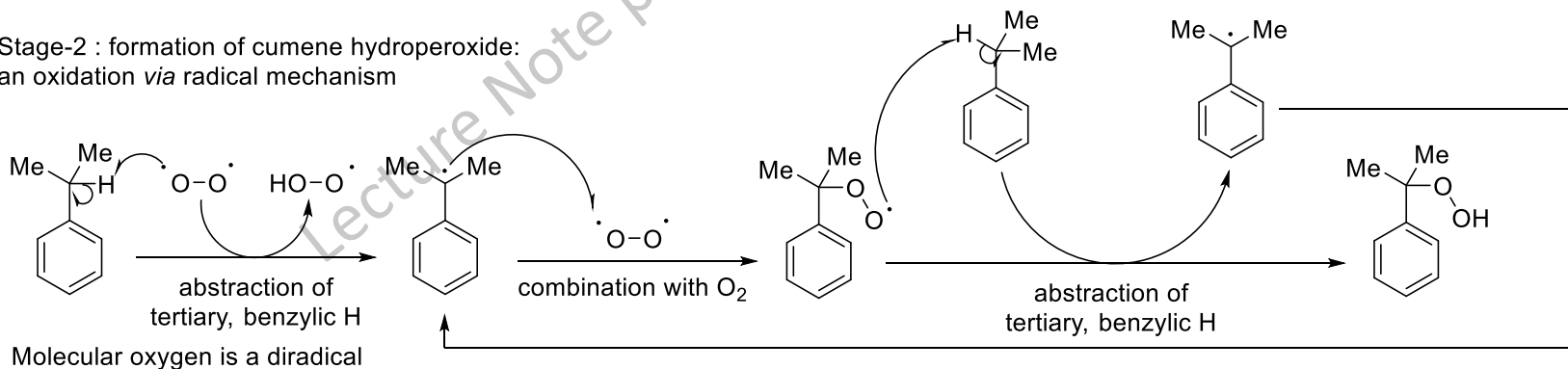
Mechanism:

Stage-1 : formation of cumene: a $\text{S}_{\text{E}}\text{Ar}$ reaction



What is/are the possible side reaction(s) that may happen here?
How may you prevent those?
[Hint: this is a Friedel-Crafts alkylation.]

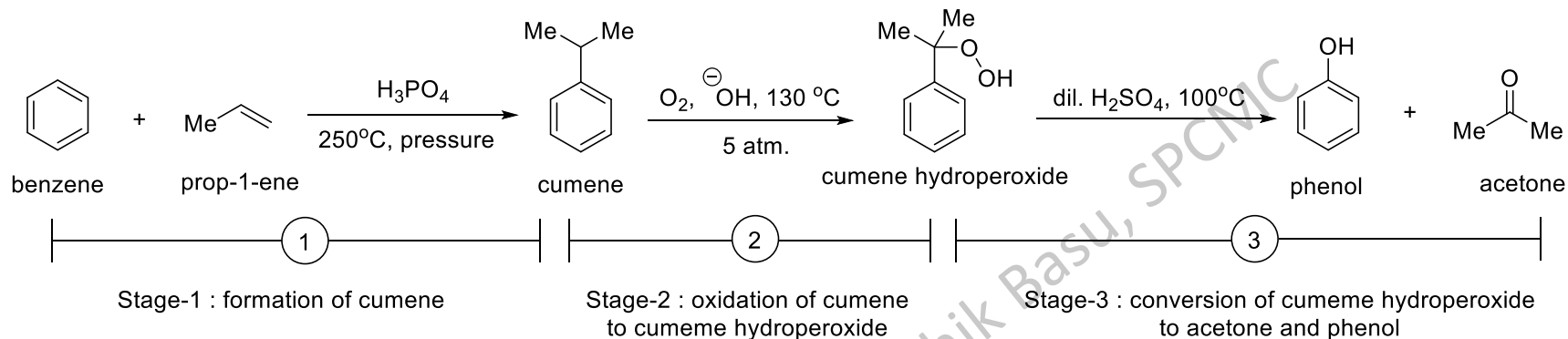
Stage-2 : formation of cumene hydroperoxide: an oxidation via radical mechanism



Rearrangements in Organic Chemistry

Migration from carbon to electron-deficient oxygen: Cumene-phenol process

Stepwise conversion of benzene and propylene into phenol and acetone via cumene and cumene hydroperoxide.

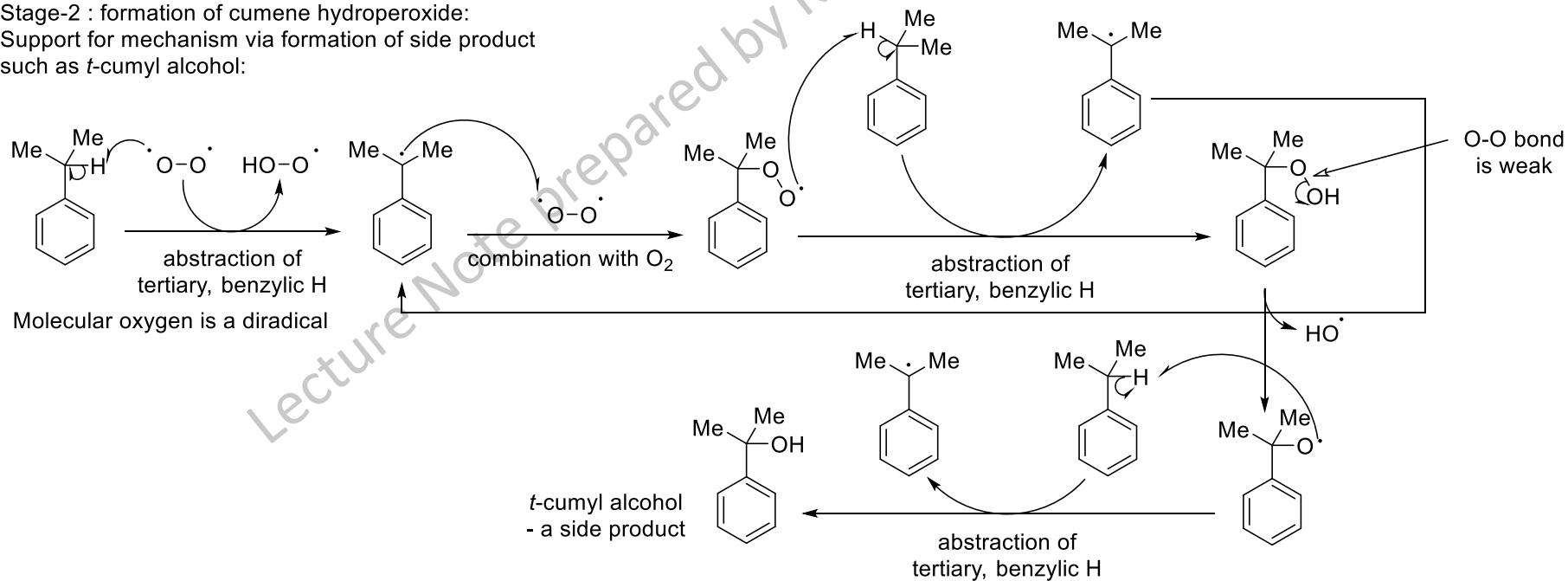


This is the rearrangement step.

Mechanism:

Stage-2 : formation of cumene hydroperoxide:

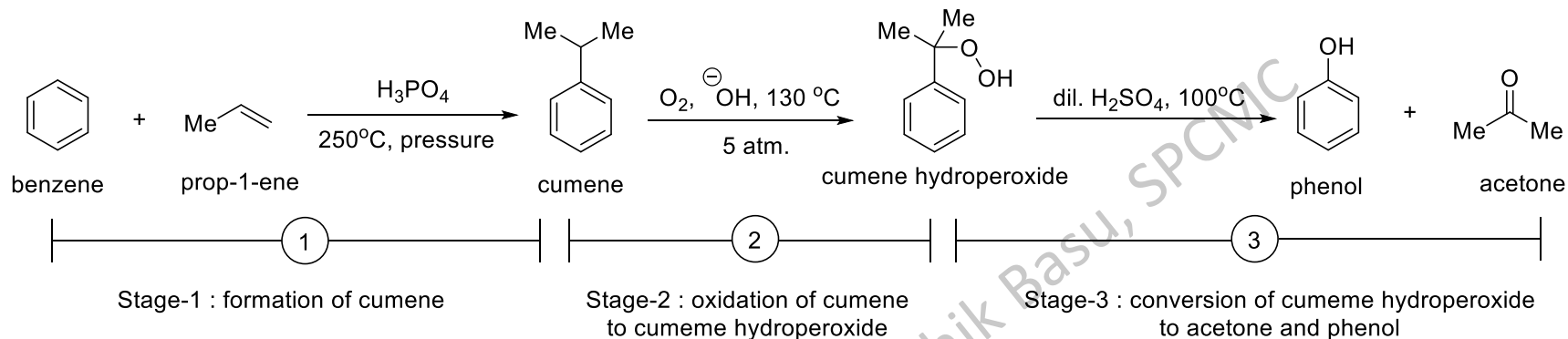
Support for mechanism via formation of side product such as *t*-cumyl alcohol:



Rearrangements in Organic Chemistry

Migration from carbon to electron-deficient oxygen: Cumene-phenol process

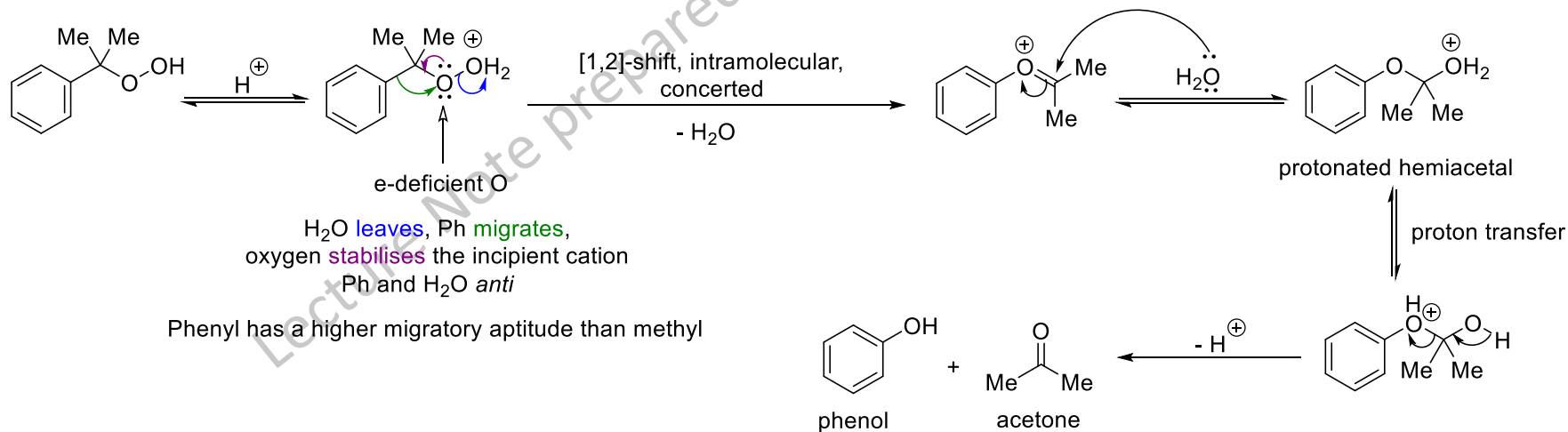
Stepwise conversion of benzene and propylene into phenol and acetone via cumene and cumene hydroperoxide.



This is the rearrangement step.

Mechanism:

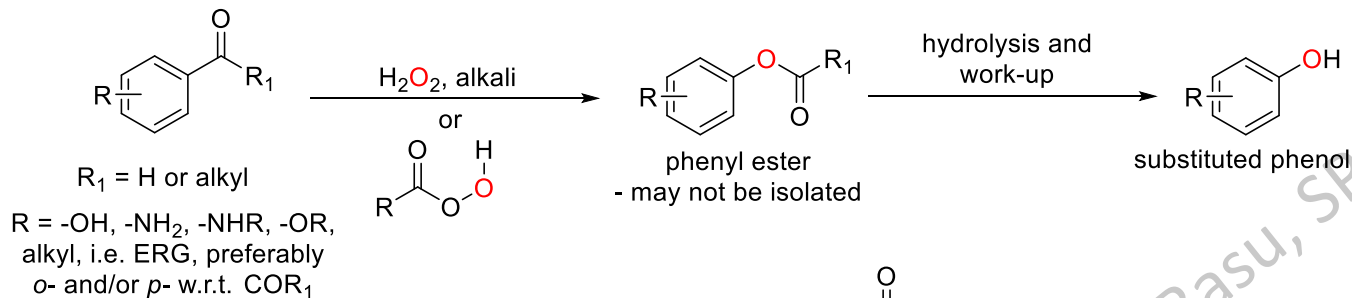
Stage-3 : Rearrangement of cumene hydroperoxide: Migration of an aromatic ring to an e-deficient, electrophilic oxygen atom



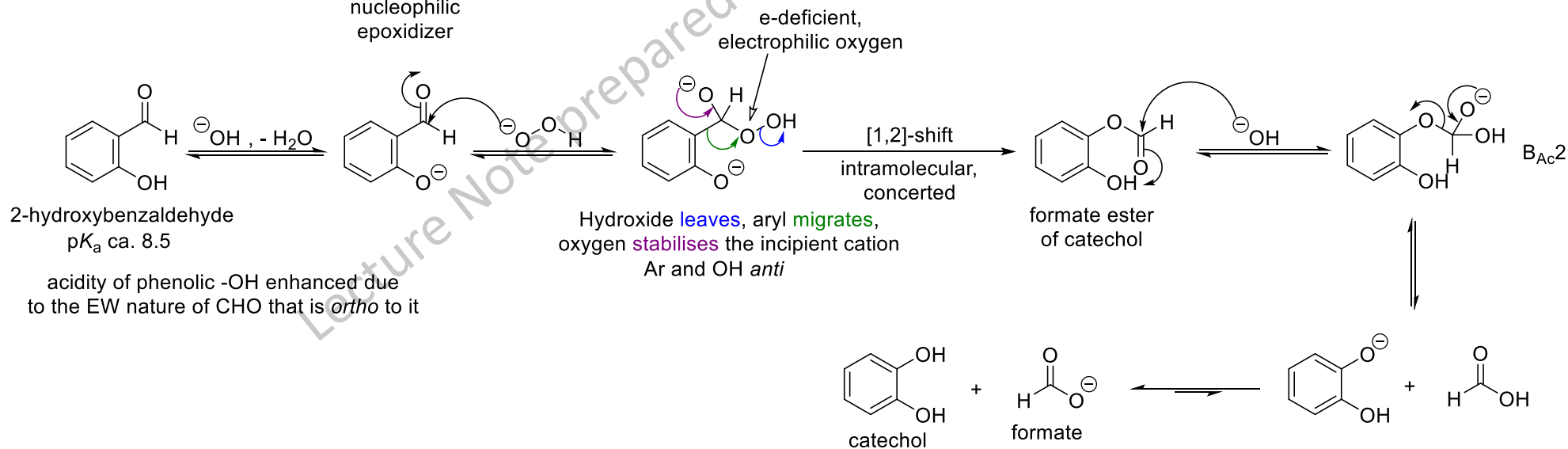
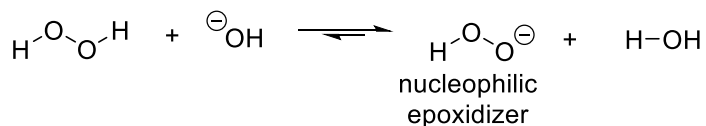
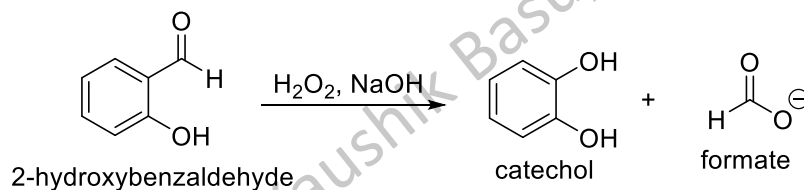
Rearrangements in Organic Chemistry

Migration from carbon to electron-deficient oxygen: Dakin reaction/oxidation:

The oxidation of aromatic aldehydes and ketones to the corresponding phenols by peroxy compounds.

H. D. Dakin
(1880-1952)

Mechanism: Illustrated using salicylaldehyde as example:

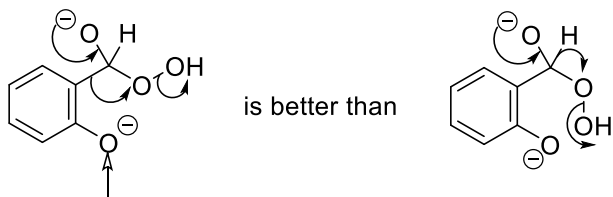


Rearrangements in Organic Chemistry

Migration from carbon to electron-deficient oxygen: Dakin reaction/oxidation:

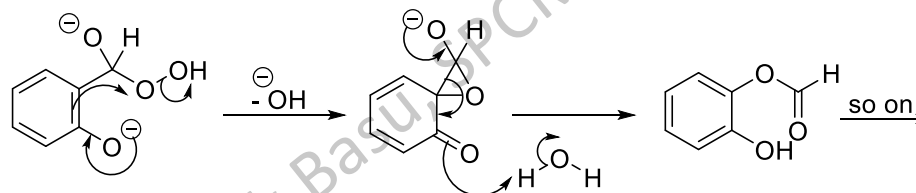
The oxidation of aromatic aldehydes and ketones to the corresponding phenols by peroxy compounds.

Migration of aryl versus hydrogen: aryl migrates in preference to H



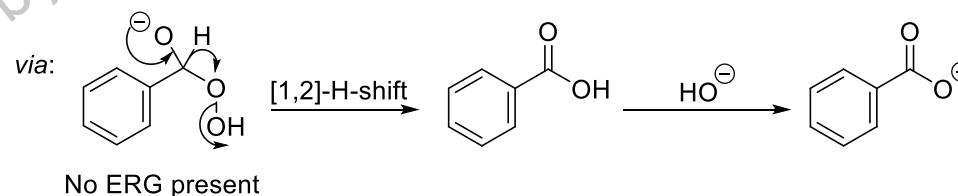
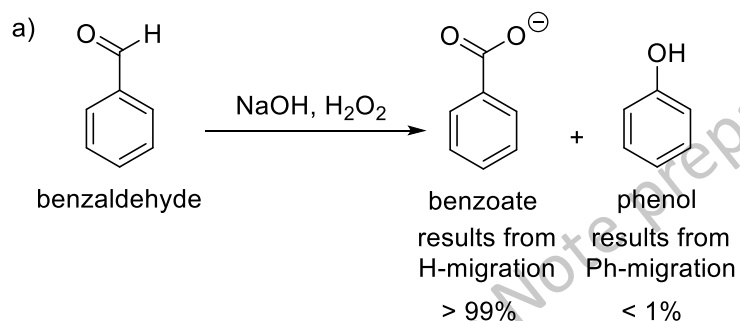
+I and +R effect of ER O⁻ helps the aryl in migrating

i.e. the migration of aryl can be assisted by the *ortho* substituent in the following way:

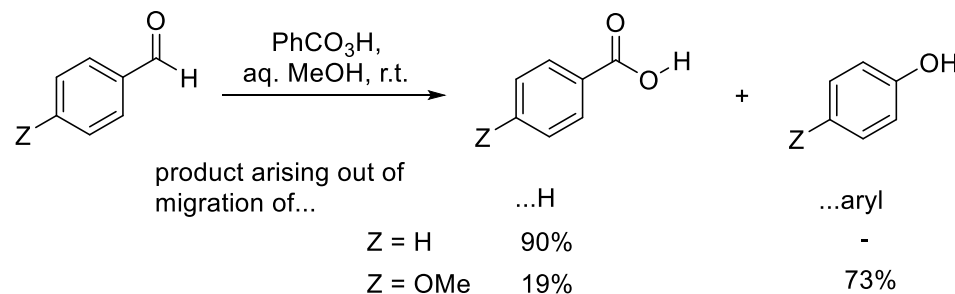
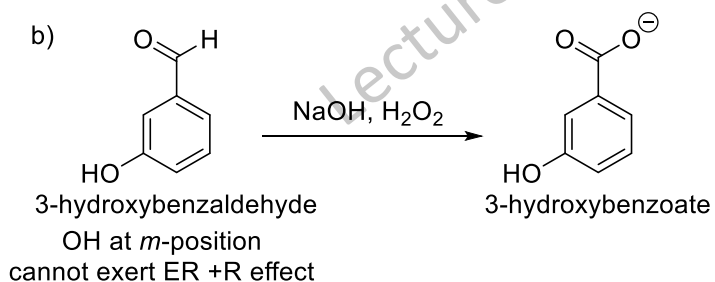


For this +R effect to operate, the ERG must be at the *o*- or at the *p*-position

If this reasoning were true, then - a) absence of such ER group should prompt H to migrate in presence of the aryls in such substrates, and b) placing the ER group at the *m*-position should also result in preferential migration of H as the +R effect of the ERG would not operate in that case. Both are observed.



Compare this with the B-V oxidation of benzaldehyde. Benzoic acid is the product there as well. A 4-methoxy group encourages aryl migration.

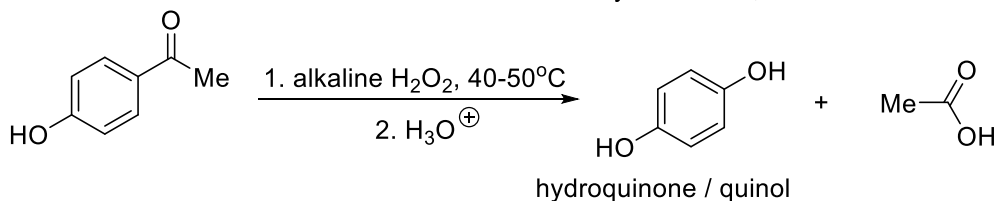
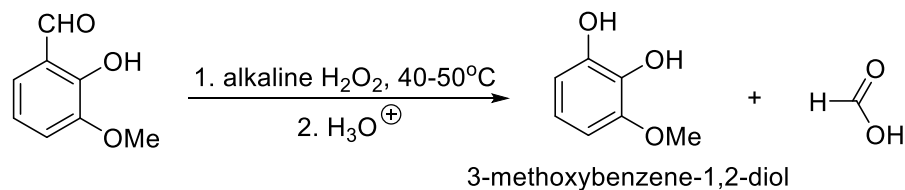


Homework: What is the Dakin oxidation product of *p*-nitrobenzaldehyde?

Rearrangements in Organic Chemistry

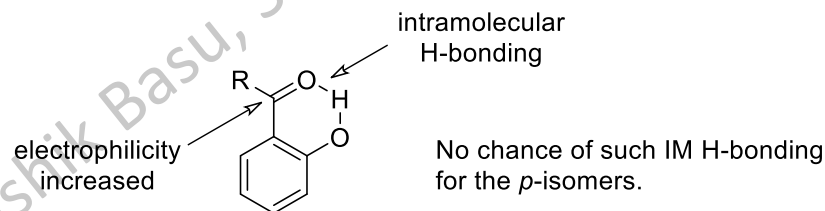
Migration from carbon to electron-deficient oxygen: Dakin reaction/oxidation:

Synthetic utility: Accessing functionalised phenols

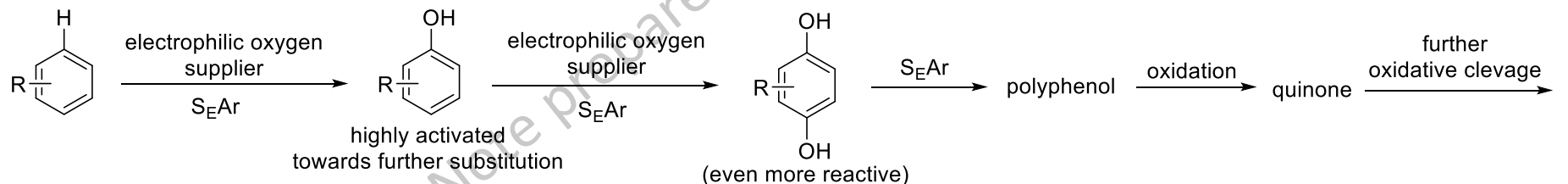


In general, aldehydes are more reactive than ketones because the keto carbonyl carbon is less electrophilic than the carbonyl carbon of an aldehyde.

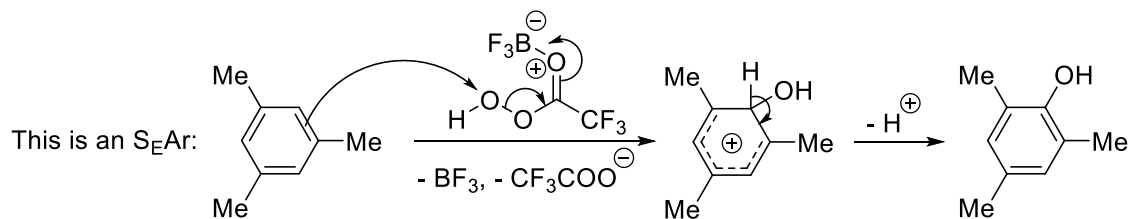
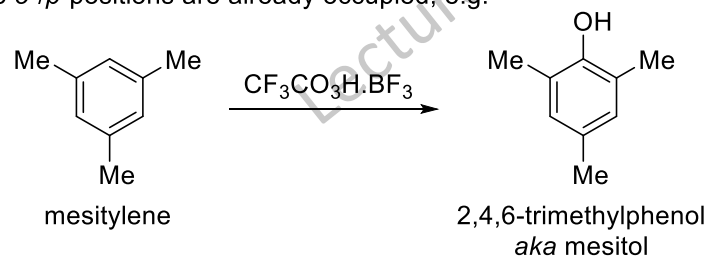
o-Hydroxyphenyl aldehydes and ketones oxidize faster than the corresponding *p*-hydroxy isomers in weakly basic conditions.



An important application of these rearrangements (B-V, cumene-phenol, Dakin) is the introduction of an electrophilic oxygen atom into an aryl ring, thereby making substituted phenols easily accessible. Ordinarily, electrophilic hydroxylation on aromatic ring is not very successful, because introduction of OH powerfully activates the *o*- and *p*-positions of the ring making it vulnerable towards further hydroxylations. Polyphenolic compounds are formed which are converted to quinones resulting in subsequent rupture of the ring.



The method is however, successful on substrates where those *o*-/*p*-positions are already occupied, e.g.



Homework:

Recall the other methods available for synthesising phenols.

Propose an alternative route for converting mesitylene to mesitol.