

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

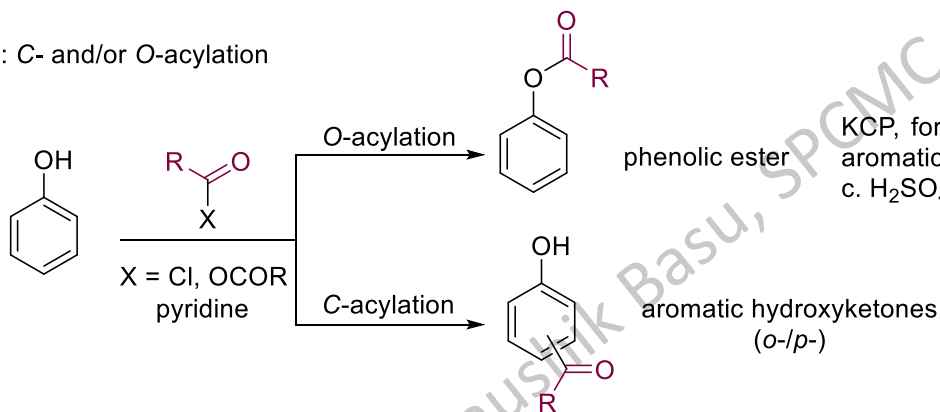
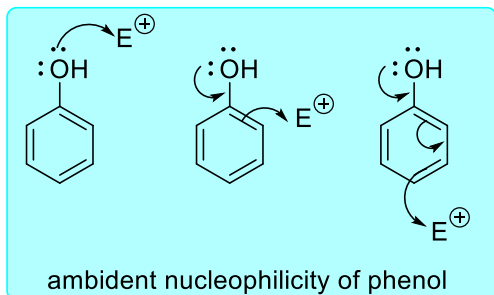
Rearrangements in Organic Chemistry

Molecular rearrangement: Migration from side chain to aromatic rings:

Fries rearrangement: conversion of phenolic esters to the corresponding *ortho* and/or *para*-substituted phenolic ketones and aldehydes, in the presence of Lewis or Brønsted acids

Background information:

Acylation of phenols - two possible outcomes : C- and/or O-acylation

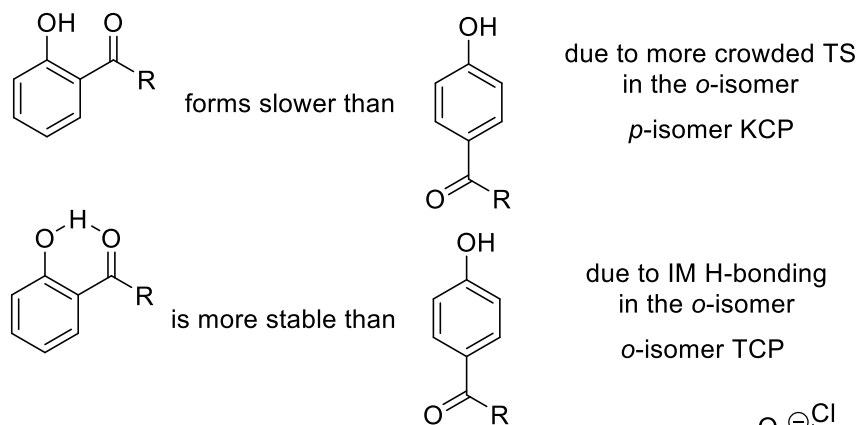
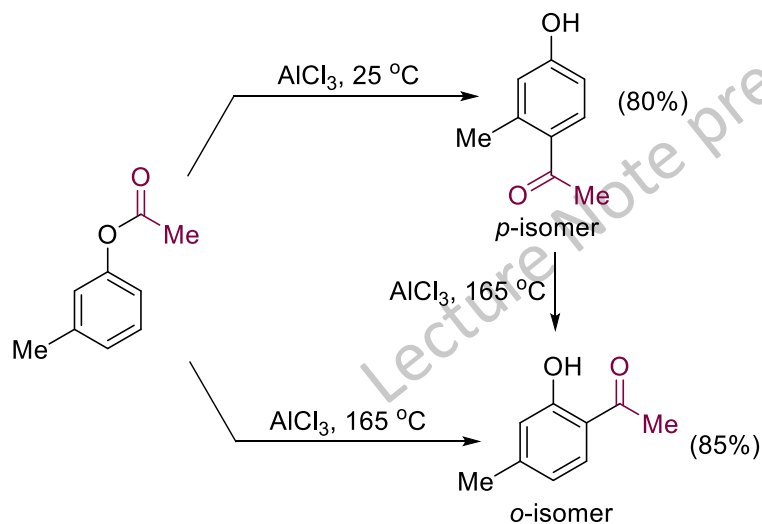


KCP, formation does not disrupt aromaticity, formed under cat. by c. H_2SO_4 or aq. NaOH.

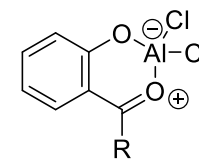
TCP, formation disrupts aromaticity, formed with AlCl_3 but w/ poor yield, more stable product, C=O conjugated with Ar and OH.

Then, how to prepare aromatic hydroxyketones?

Phenolic esters rearrange under Lewis acids such as AlCl_3 to the corresponding phenolic ketones - *o*- and *p*-isomers - this is the Fries rearrangement. The major regioisomer depends upon the reaction condition:



In presence of AlCl_3 , the *o*-isomer forms chelate: Not possible for *p*-isomer; yet another stabilizing factor for *o*-isomer



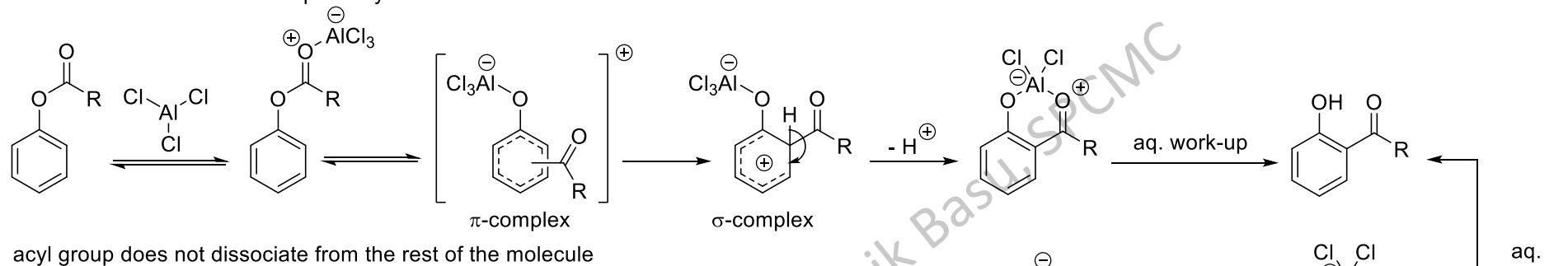
In each case, an aq. acid work-up is required to liberate the ketone from the complex that it forms with AlCl_3 .

Rearrangements in Organic Chemistry

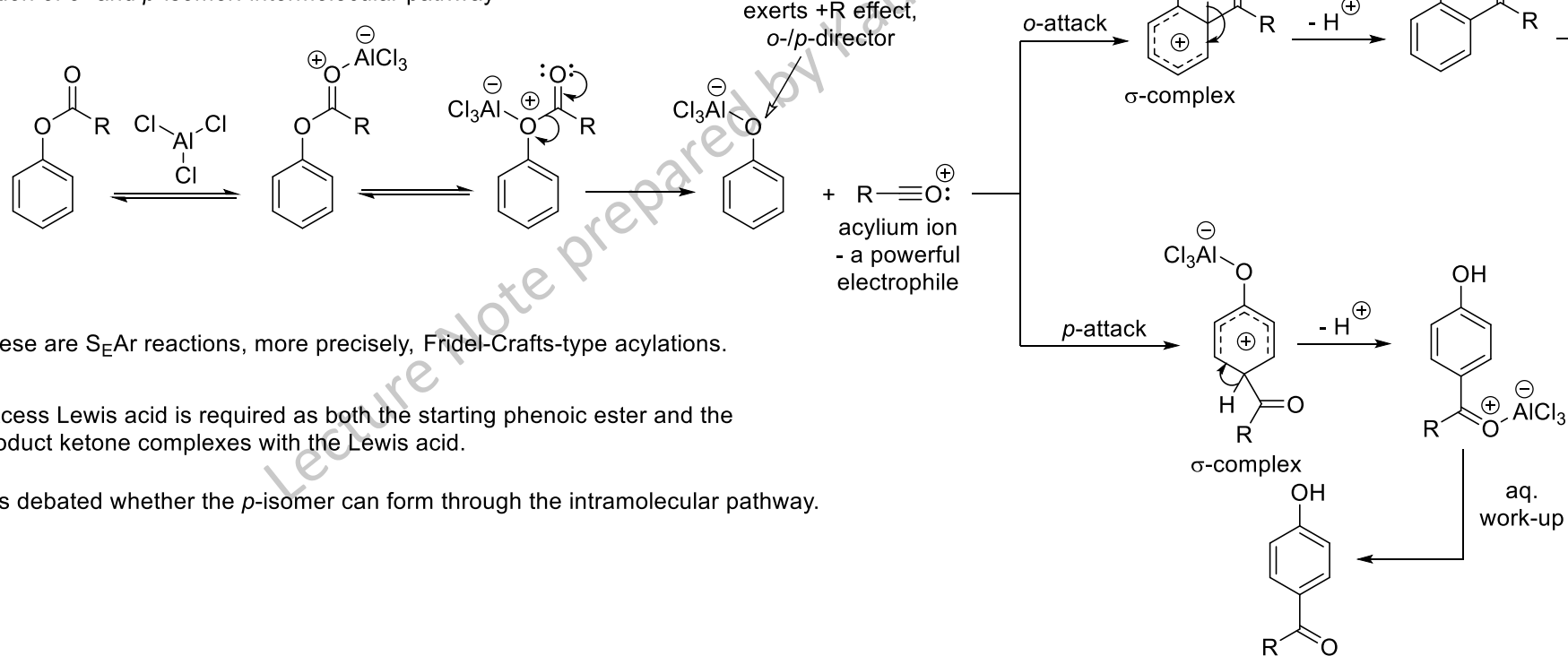
Molecular rearrangement: Migration from side chain to aromatic rings: Fries rearrangement

Mechanism: Evidences are found for both intra- and intermolecular pathways. Exact nature of mechanism depends on substrate structure and the reaction condition.

Formation of *o*-isomer: intramolecular pathway



Formation of *o*- and *p*-isomer: intermolecular pathway



These are $\text{S}_{\text{E}}\text{Ar}$ reactions, more precisely, Friedel-Crafts-type acylations.

Excess Lewis acid is required as both the starting phenolic ester and the product ketone complexes with the Lewis acid.

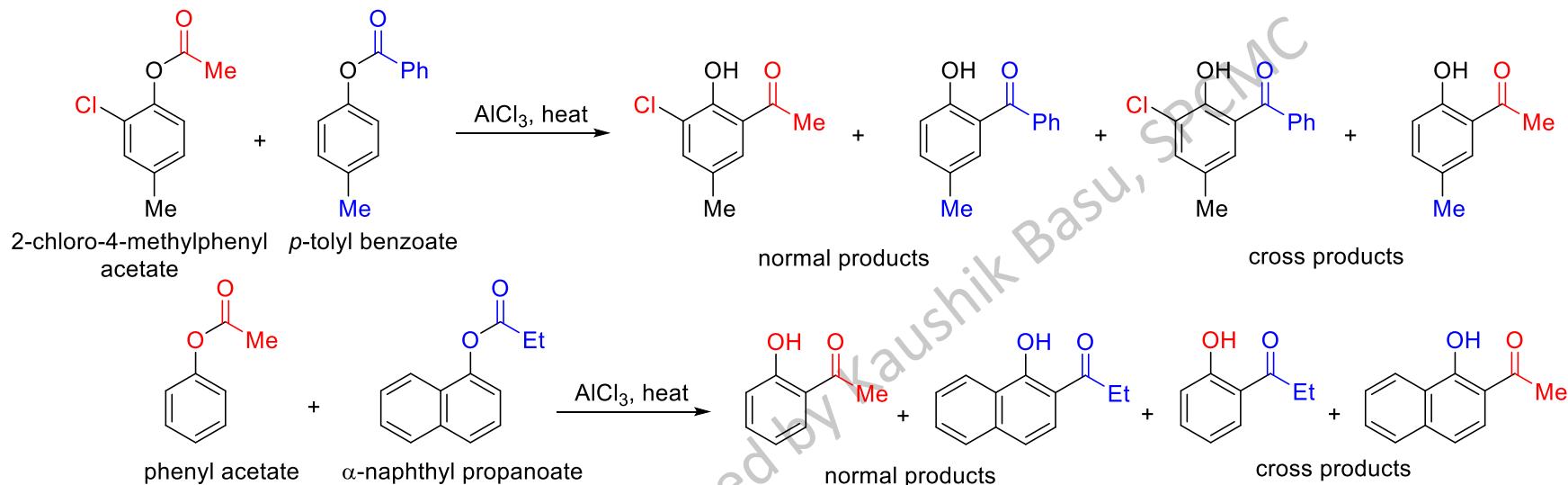
It is debated whether the *p*-isomer can form through the intramolecular pathway.

Rearrangements in Organic Chemistry

Molecular rearrangement: Migration from side chain to aromatic rings: Fries rearrangement

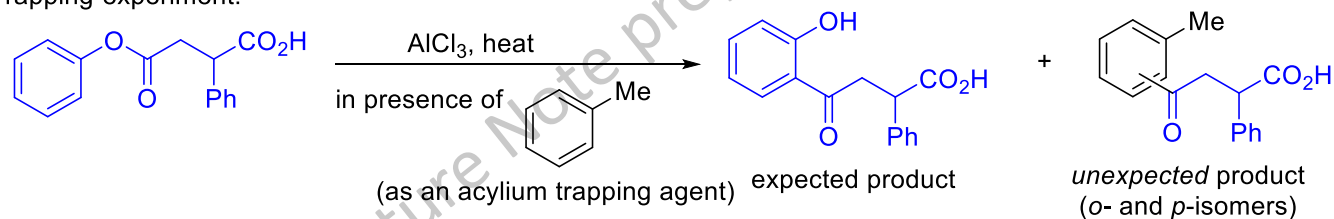
Mechanism: Proof in favour of intermolecularity:

Crossover experiment: Cross products are often found:



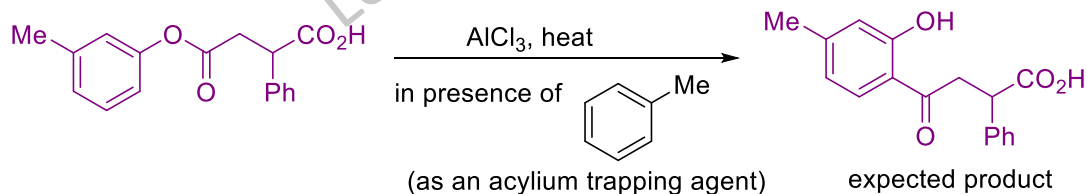
Formation of cross products indicate that the reaction in these cases are, *at least partly*, intermolecular.

Trapping experiment:



Formation of the additional products points to intermolecular nature of reaction where the acylium is detached from the phenolic ester and trapped by toluene (*transacylation*).

Proof in favour of intramolecularity: Fries rearrangement can, in some cases, be *totally* intramolecular.



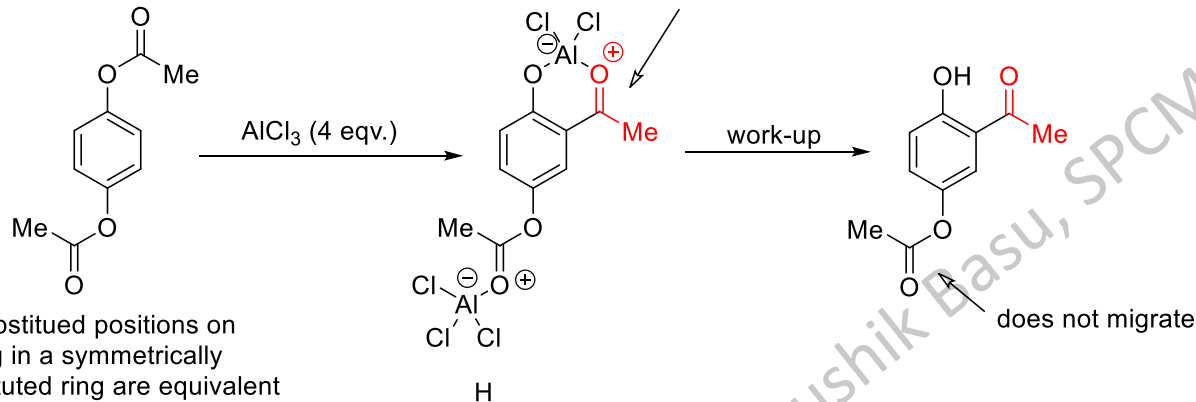
No acyl dev. of toluene is found in this case. Proves that acylium ion *does not* form in the medium and reaction is strictly intramolecular.

Rearrangements in Organic Chemistry

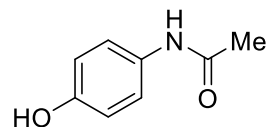
Molecular rearrangement: Migration from side chain to aromatic rings: Fries rearrangement

After introduction of one acyl group into the aromatic ring, no further acyl migration from side chain proceeds.

EW C=O group deactivates the ring towards further electrophilic attack. Complexation with Lewis acid enhances the EW capacity of C=O, further deactivating the ring.



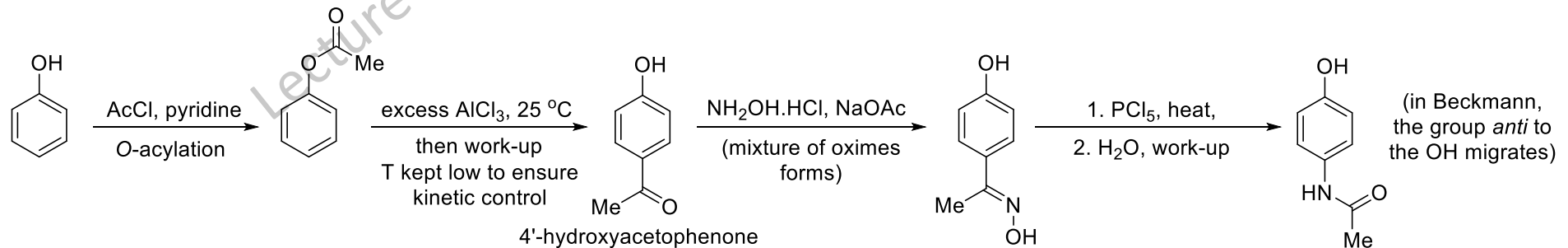
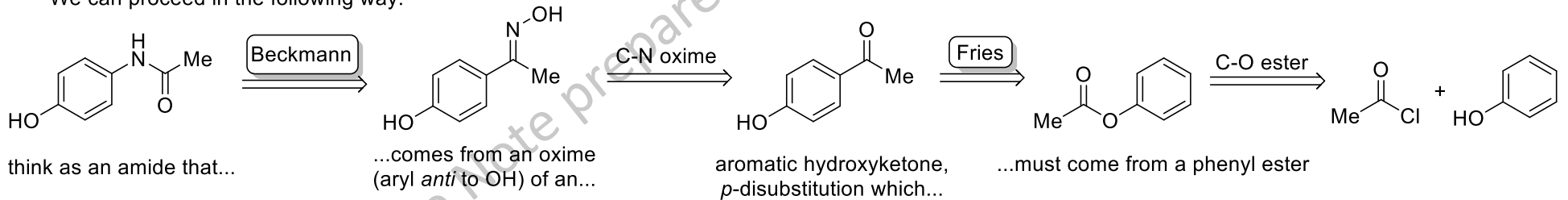
Synthetic utility of Fries rearrangement:



paracetamol aka acetaminophen

You have been asked to devise a strategy for synthesis of this TM using **two different rearrangement reactions**

We can proceed in the following way:



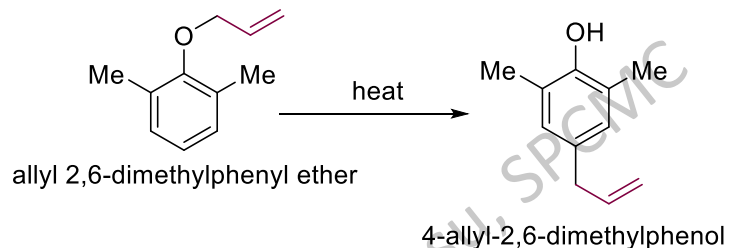
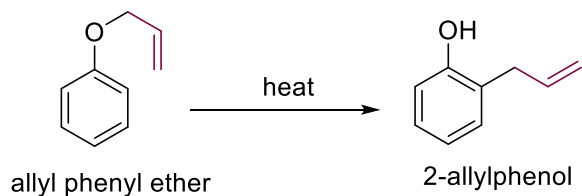
Also recall conversion of 2'-hydroxyacetophenone to catechol via Dakin oxidation.

(sepn. from the other diastereomer)

Rearrangements in Organic Chemistry

Molecular rearrangement: Migration from side chain to aromatic rings: Claisen rearrangement (*aromatic variant*)

Thermal rearrangement of allyl phenyl ethers to the corresponding C-allyl phenols. It is a unimolecular, pericyclic process; more precisely, a [3,3]-sigmatropic shift.

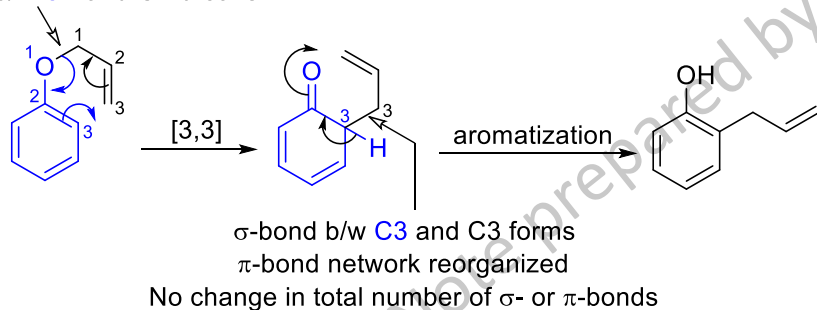


R. L. Claisen
(1851-1930)

Mechanism: Involves [3,3]-sigmatropic shift.

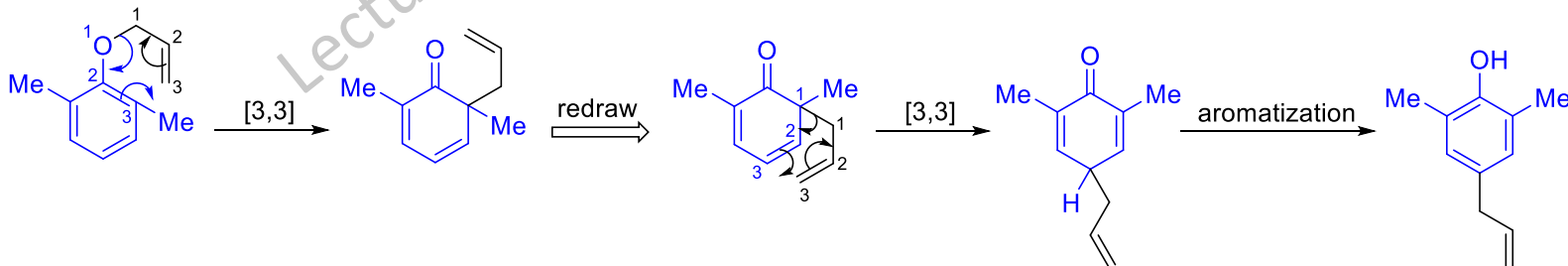
Sigmatropic rearrangement: A molecular rearrangement that involves both the creation of a new σ -bond between atoms previously not directly linked and the breaking of an existing σ -bond. There is normally a concurrent relocation of π -bonds in the molecule concerned, but the total number of π - and σ -bonds does not change, i.e. $\Delta\sigma = 0$ and $\Delta\pi = 0$.

σ -bond b/w O1 and C1 breaks



The first step of this Claisen rearrangement is the pericyclic step. The second step is aromatization and not pericyclic in nature. It is, in fact, ionic in nature.

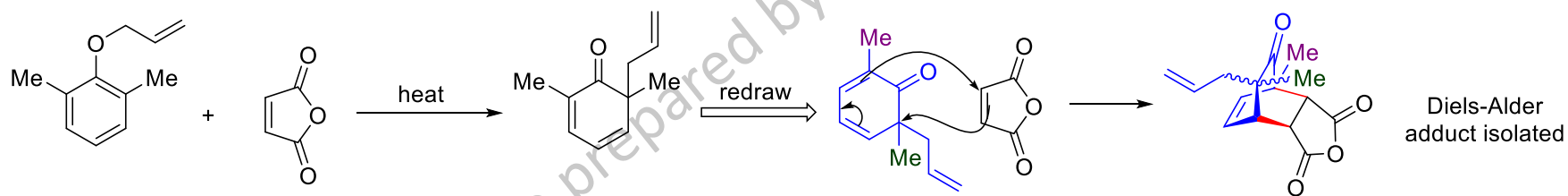
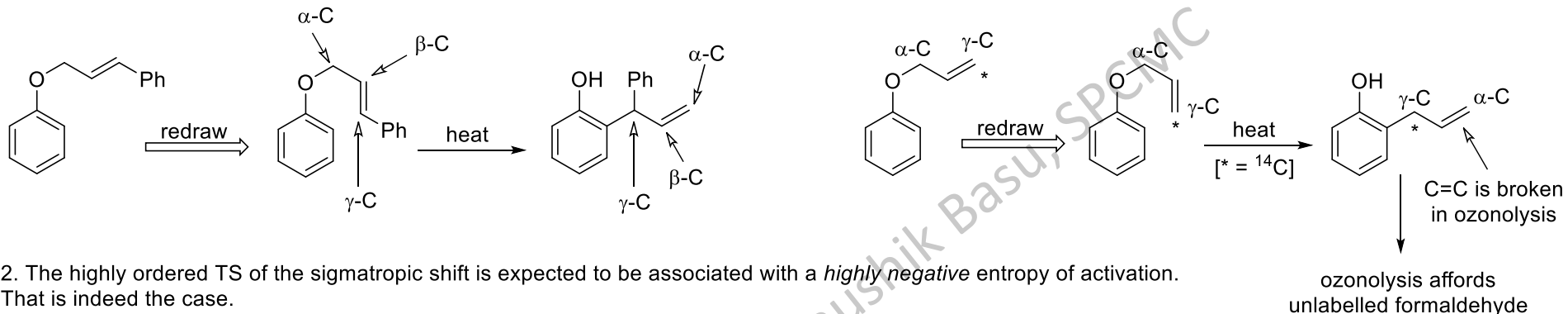
Similarly, if both the *ortho*-positions are substituted, aromatization is not feasible and a second [3,3] shift occurs to bring the allyl group to the *p*-position. Then aromatization takes place and the 4-allyl substituted phenol dev. is formed.



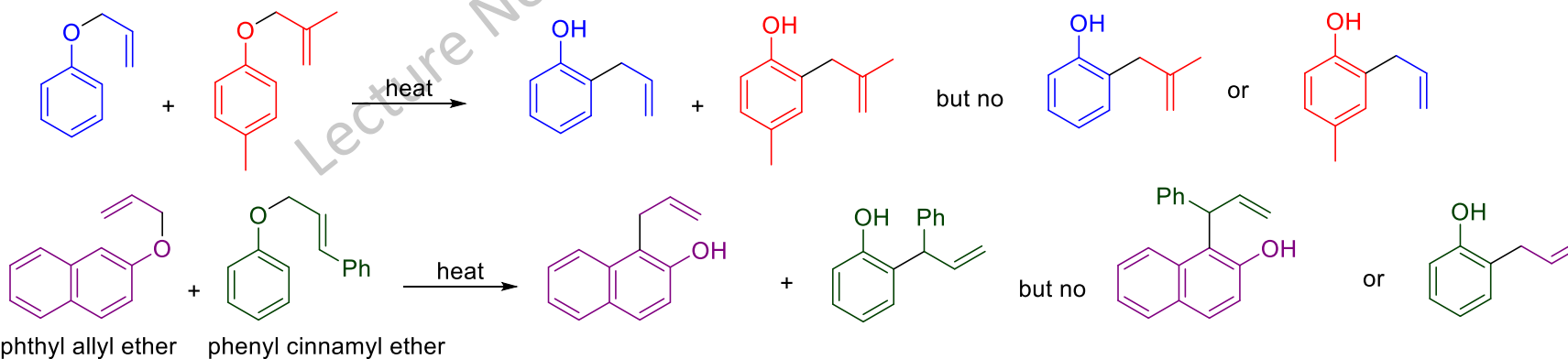
Molecular rearrangement: Migration from side chain to aromatic rings: Claisen rearrangement

Proof of mechanism:

1. The position of attachment of the allyl chain with the ring changes from α - to γ -, that is demonstrated in the following way::



4. No cross products in crossover experiments indicates intramolecular nature of the rearrangement step:

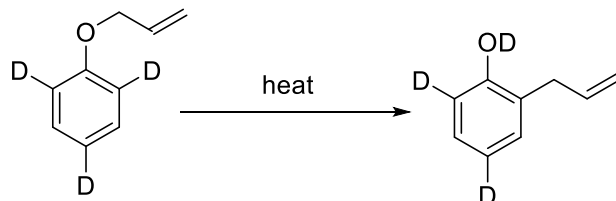


Rearrangements in Organic Chemistry

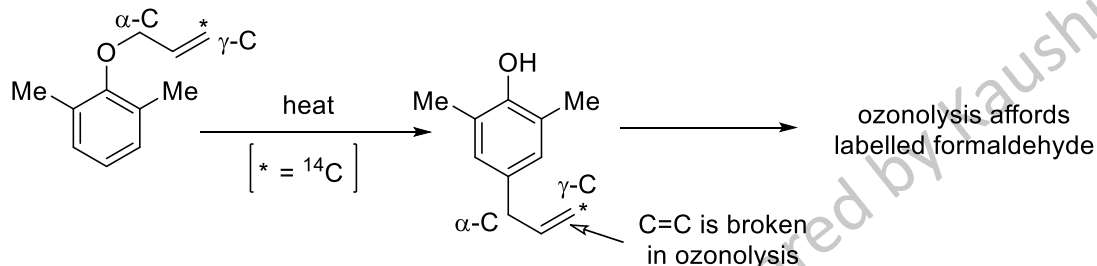
Molecular rearrangement: Migration from side chain to aromatic rings: Claisen rearrangement

Proof of mechanism (contd.):

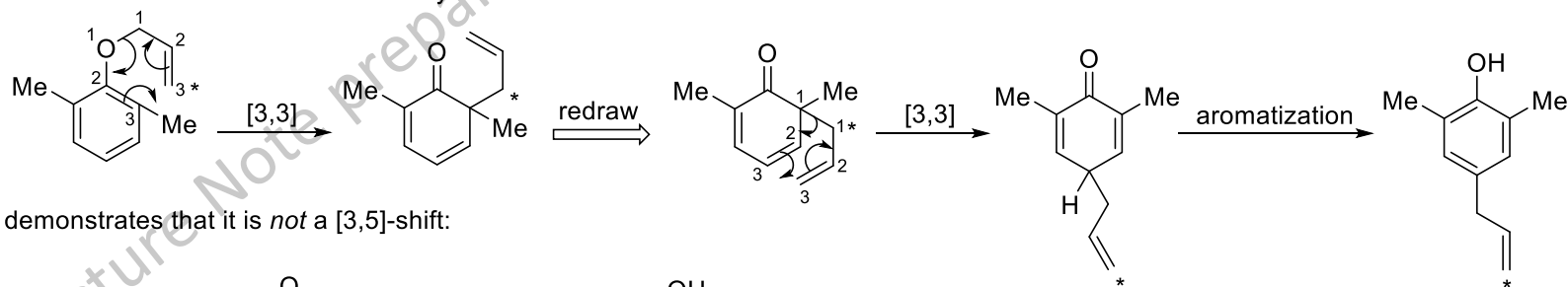
5. Migration of *ortho*-hydrogen in the dienone intermediate is proved by the following experiment:



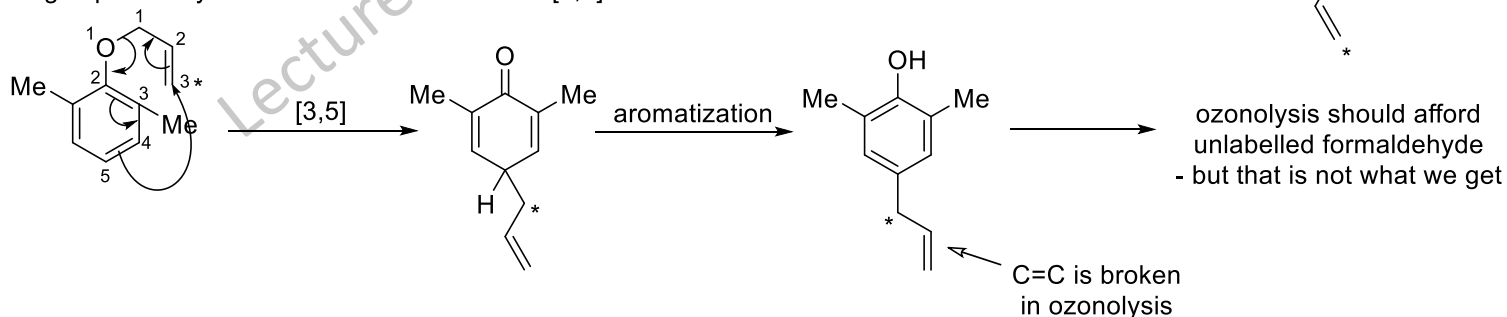
6. Reattachment of the α -carbon in case of *para*-migration has been proved in the following way:



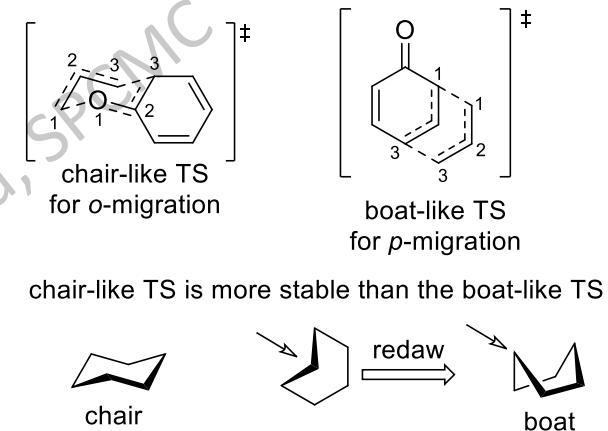
Recall how the reaction proceeds via consecutive [3,3]-shifts:



This labelling expt. clearly demonstrates that it is *not* a [3,5]-shift:



The reason behind the preference for *o*-migration:

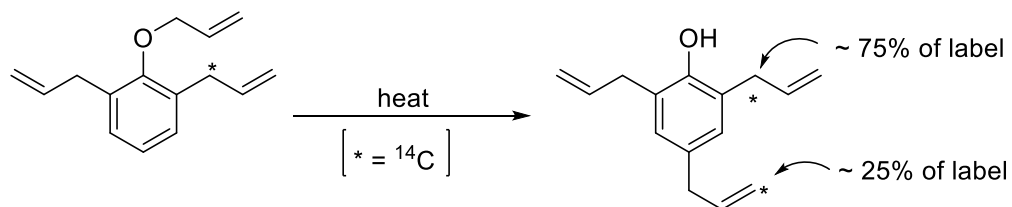


Rearrangements in Organic Chemistry

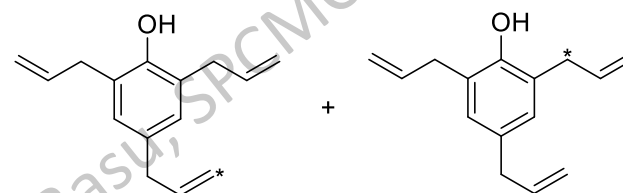
Molecular rearrangement: Migration from side chain to aromatic rings: Claisen rearrangement

Proof of mechanism (contd.):

7. The following labelling study again supports the double [3,3] shift mechanism:



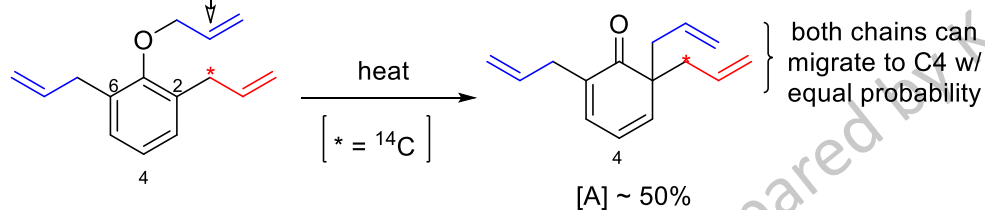
i.e.



(1 : 3)

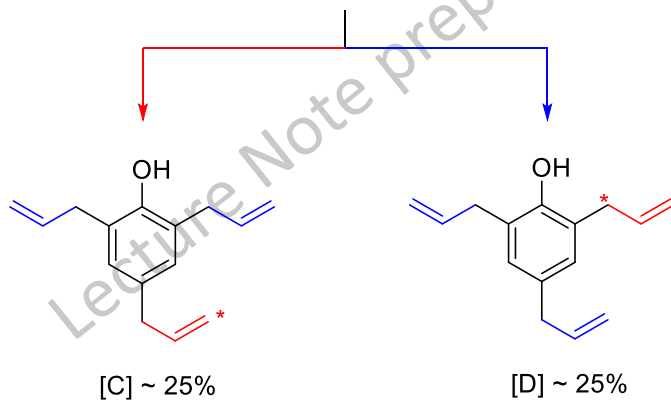
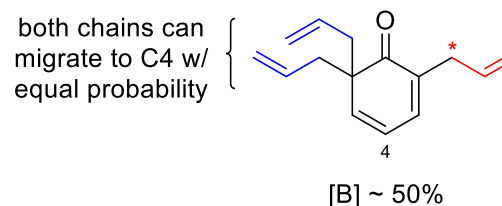
Explanation:

can migrate to C2 or C6
w/ equal probability



both chains can
migrate to C4 w/
equal probability

+



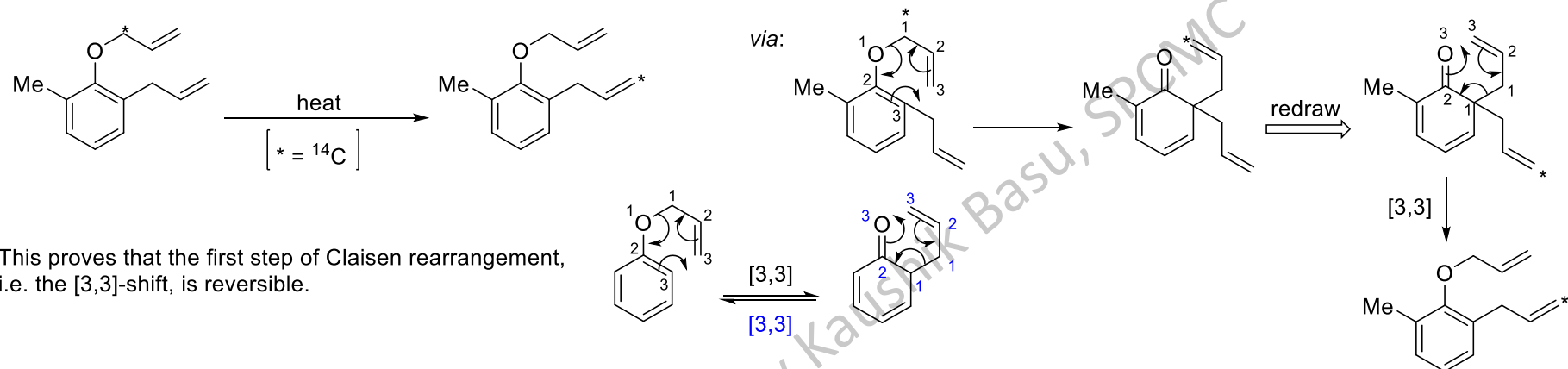
[C] : [D] = 1 : 3

Rearrangements in Organic Chemistry

Molecular rearrangement: Migration from side chain to aromatic rings: Claisen rearrangement

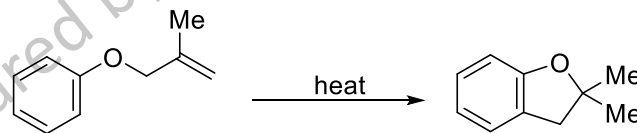
Proof of mechanism (contd.):

8. When stopped before completion, the recovered starting material shows scrambling of radioactive label:

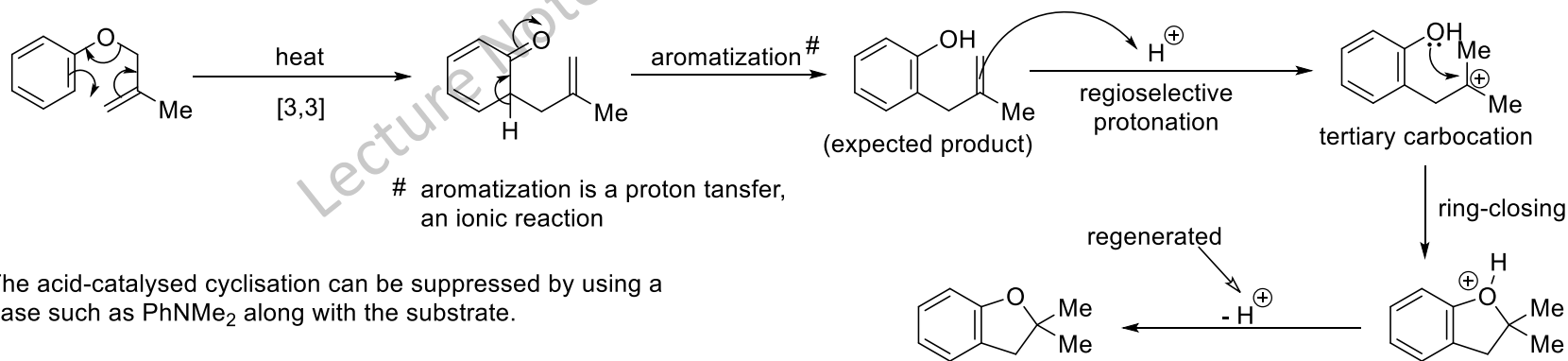


A curious observation:

Carelessly carried out Claisen rearrangement in some cases may lead to cyclisation:



The cyclisation takes place after the C-allylated phenol is produced in the normal way:

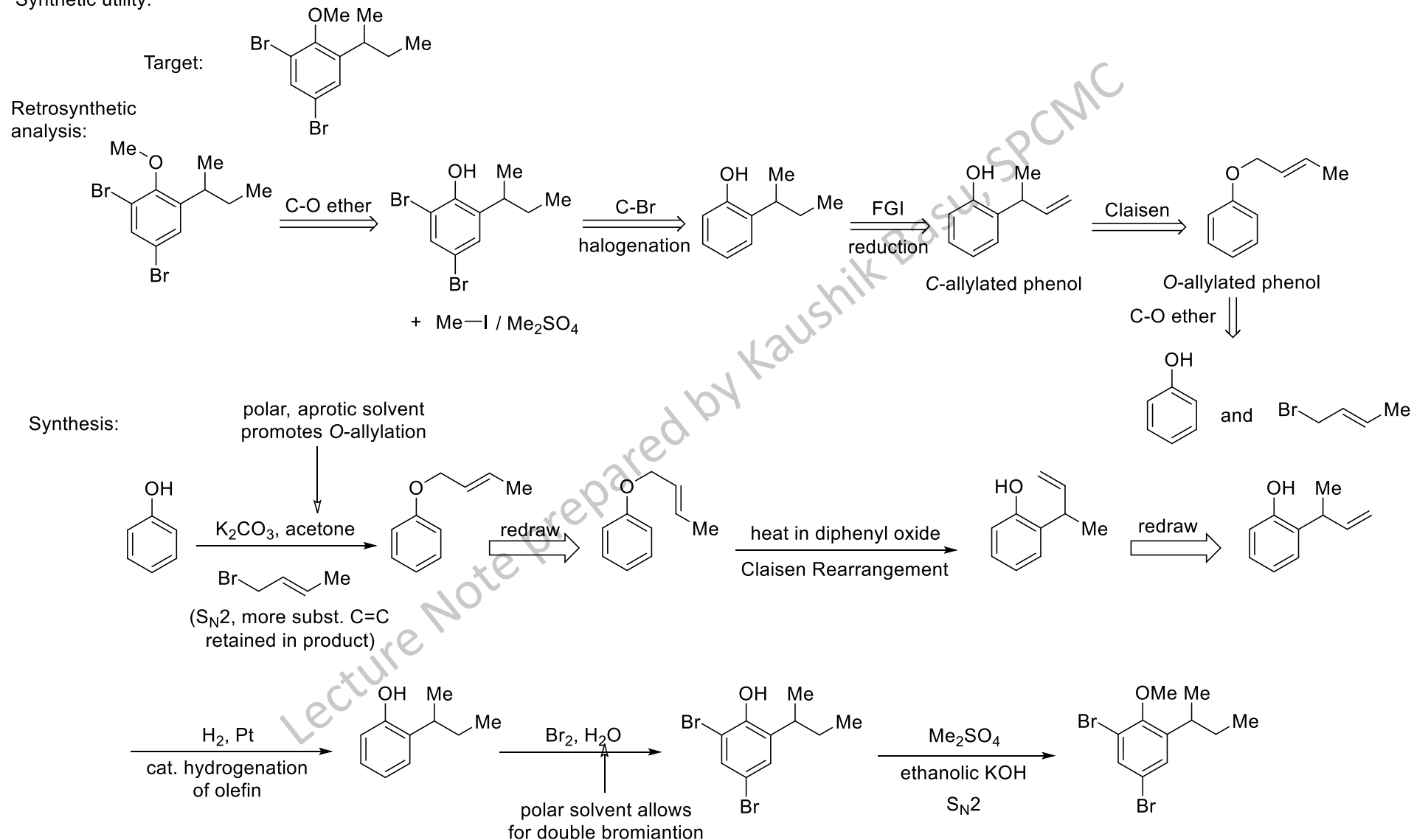


The acid-catalysed cyclisation can be suppressed by using a base such as PhNMe_2 along with the substrate.

Rearrangements in Organic Chemistry

Molecular rearrangement: Migration from side chain to aromatic rings: Claisen rearrangement

Synthetic utility:

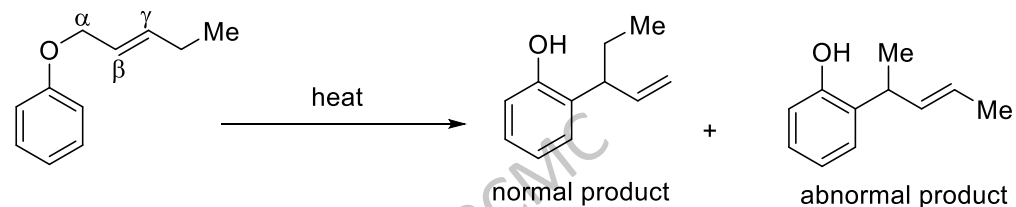


Rearrangements in Organic Chemistry

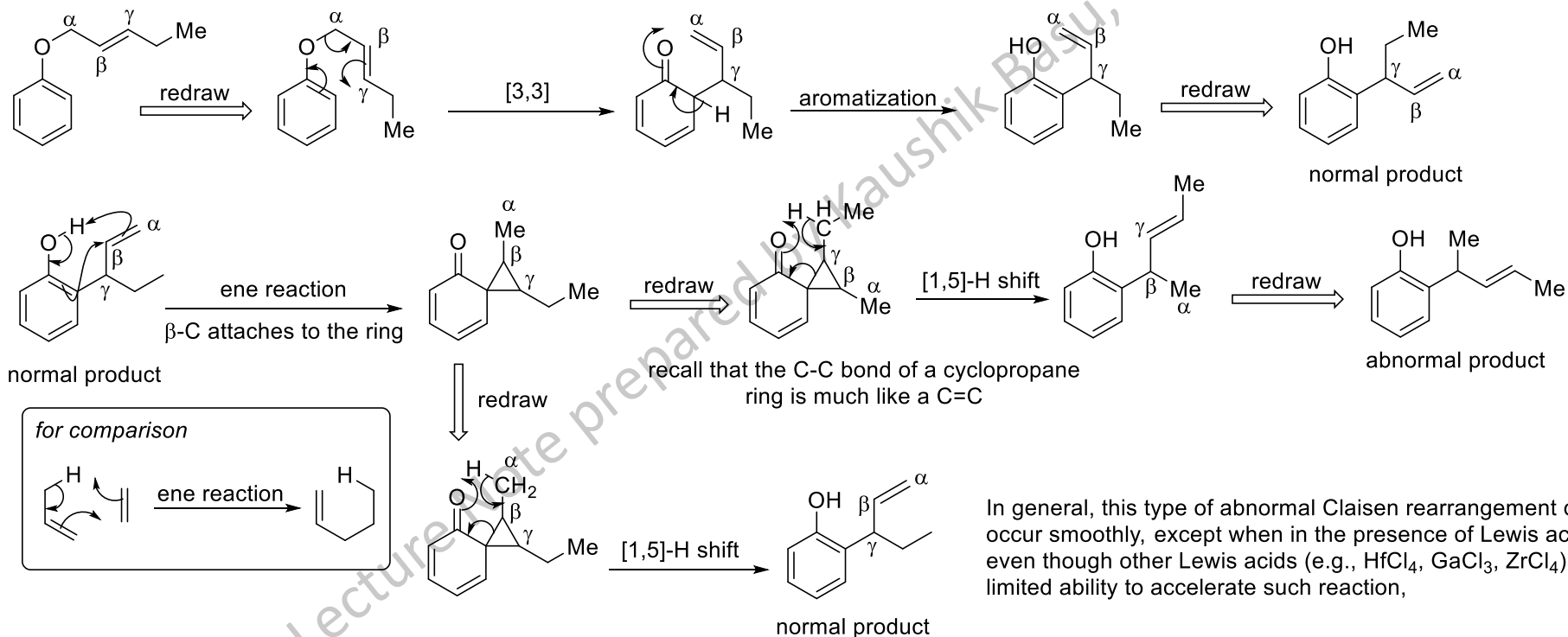
Molecular rearrangement: Migration from side chain to aromatic rings: Claisen rearrangement

Abnormal Claisen rearrangement:

Claisen Rearrangement with allyl phenyl ethers that have an alkyl group in the γ -position sometimes afford an abnormal product.



Mechanism: The abnormal product is believed to form from further rearrangement of the normal product under reaction condition.



In general, this type of abnormal Claisen rearrangement does not occur smoothly, except when in the presence of Lewis acids FeCl_3 , even though other Lewis acids (e.g., HfCl_4 , GaCl_3 , ZrCl_4) have limited ability to accelerate such reaction,

