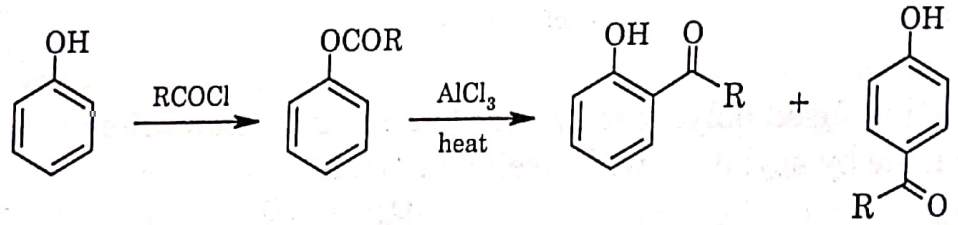
Sem 4 - Remaining Portion of the Syllabus

- **Aromatic rearrangements: Migration from oxygen to ring carbon:**

1. Fries rearrangement
2. Claisen rearrangement

FRIES REARRANGEMENT

The rearrangement of phenyl esters to isomeric phenolic ketones in presence of Lewis acid catalysts like $AlCl_3$ is called Fries rearrangement, after the name of its inventor K. Fries. Brønsted acids like HF, $HClO_4$ and PPA can also be used as catalysts. Phenolic esters are prepared by acylation of phenol with acyl halides.



Fries rearrangemen has the following general features.

(i) It is usually carried out at high temperature (80-180°C). The reaction is catalysed by Brønsted or Lewis acids such as HF, $AlCl_3$, BF_3, $TiCl_4$ or $SnCl_4$. The acids are used in excess of the stoichiometric amount, especially the Lewis acids, since they form complexes with both the starting materials and products.

(ii) Reaction time can vary from a few minutes and several hours.

(iii) The reaction gives good yield when there are electron-donating substituents in phenolic component of the phenolic esters. Presence of electron-withdraing group in phenol retards the reaction.

(iv) The reaction is equivalent to two-step Friedel-Crafts acylation of phenol, i.e. conversion into phenolic esters followed by ring acylation in presence of Lewis acid.

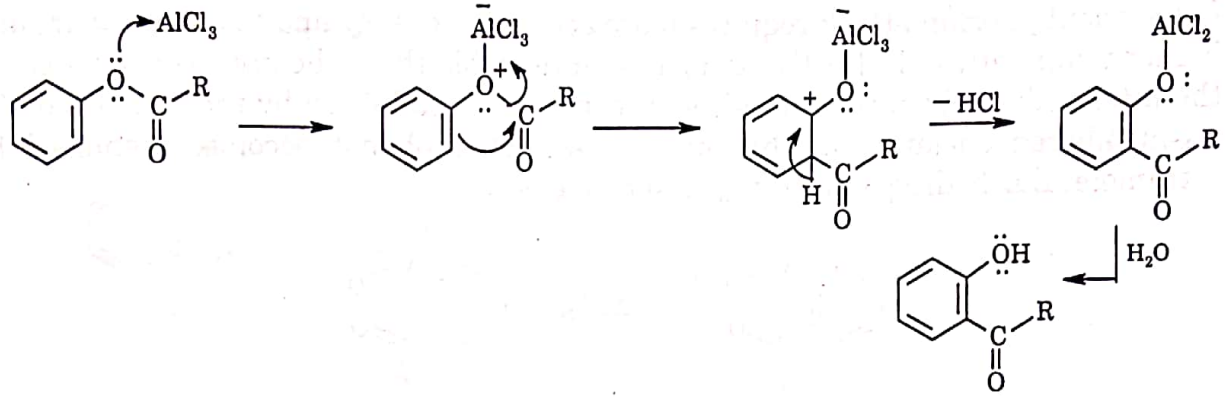
(v) With high temperature and without any solvent the *ortho*-acylated product dominates while the low temperature favours *para*-acylated product.

(vi) Optically active phenolic esters rearrange to optically acive phenolic ketones.

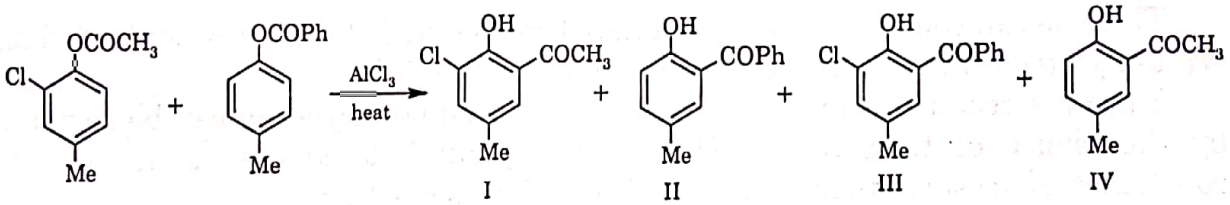
(vii) Fries rearrangement can also be done photochemically. It is specifically called *photo-Fries rearrangement.*

Mechanism:

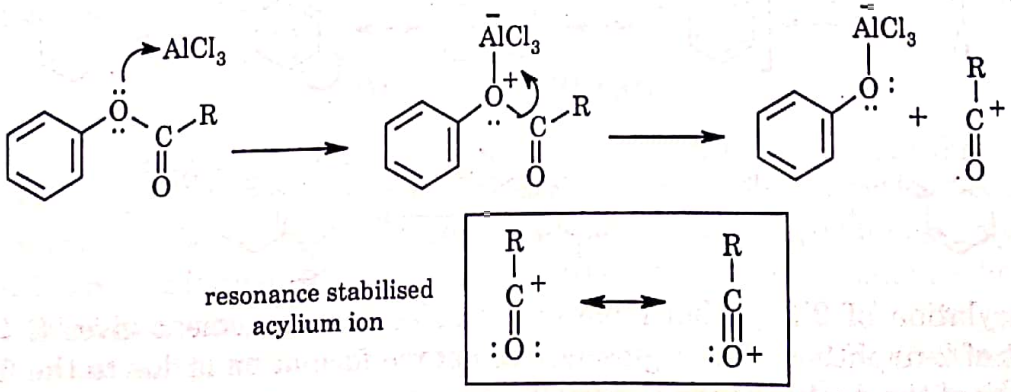
The mechanism of the Fries rearrangement may be both intramolecular and intermolecular. For mation of *ortho*-isomer can be explaind by intramolecular mechanism as follows.

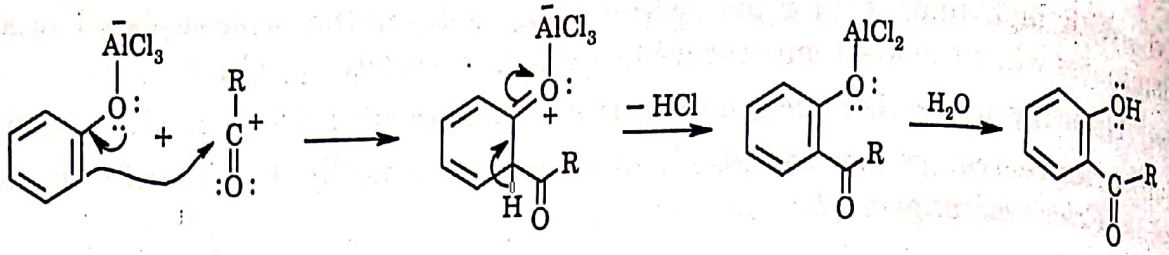


However, when the mixture of following two phenolic esters is subjected to Fries rearrangement, four products are obtained.



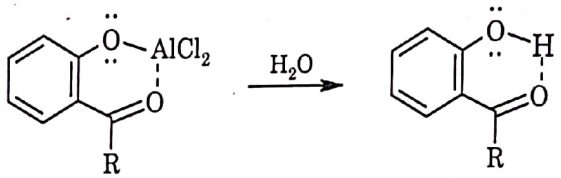
In the above reaction, I and II are self products but III and IV are cross-products. Formation of *ortho*-rearranged cross-products confirms that free acylium ion is involved in the reaction and consequently the reaction is also intermolecular in nature. Intermolecular mechanism can be shown as follows.





Similarly, acylium electrophile can attack the para position leading to the formation of *p*-acylated compound.

It has already been mentioned that low temperature favours *para*-isomer. It may be, *ortho*-attack involves steric interaction with the bulky $-OAlCl_3$ group. Consequently, *ortho*-attack requires more activation energy and reaction occurs at a higher temperature. But *ortho*-osomer is more stable than the *para*-isomer because the intermediate from the *ortho*-isomer can become stabilised by the formation of a six-membered chelate and the the *ortho*-acylated phenol becomes stabilised by intramolecular hydrogen bonding, as shown below.



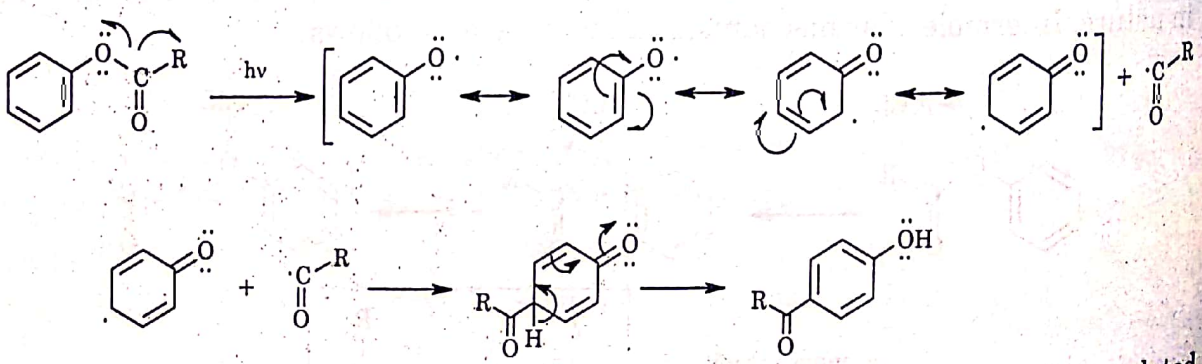
stabilised by chelation

stabilised by intramolecular hydrogen bonding

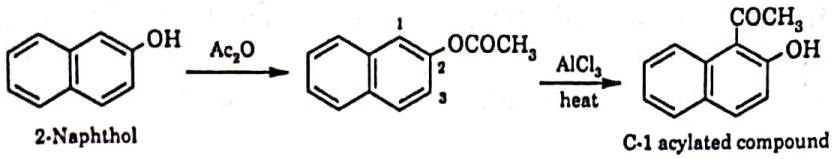
Thus we can conclude that para-acylated compound is kinetically controlled and *ortho*-acylated compound is thermodynamically controlled.

Since the reaction is *ortho, para*-selective, the site of acylation can be regulated by the choice of temperature. Only sterically unhindered arenes are suitable substrates, since substituents will interfere with this reaction.

An additional option for inducing a Fries Rearrangement is photochemical excitation, but this method is only feasible in the laboratory. The course of the photochemical Fries rearrangement is shown below.

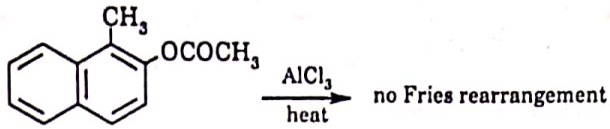


O-acylation of 2-naphthol followed by Fries rearrangement gives C-1 acylated product of 2-naphthol. This regioselective ketone formation is due to the fixed-bond character of the double bonds of naphthalene.



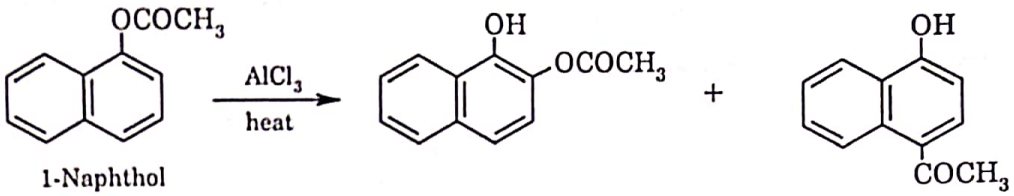
2-Naphthol C-1 acylated compound

If C-position of 2-naphthol acetate remains substituted, Fries rearrangement fails.

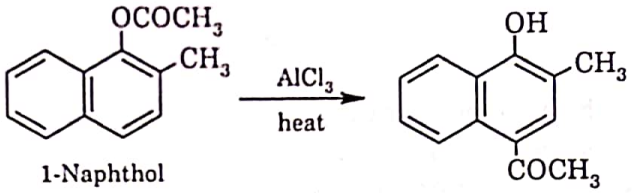


2-Naphthol dervativel with *otho* methyl group

However, following reactions from *O*-acetl derivatives of 1-naphthol undergoes Fries rearrangement.



1-Naphthol



1-Naphthol

References:

1. Blatt, A.H. Fries reaction. *Org. React.* **1942**, 1, 342-369.

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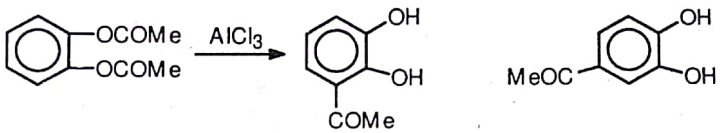
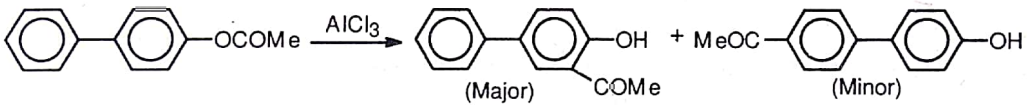


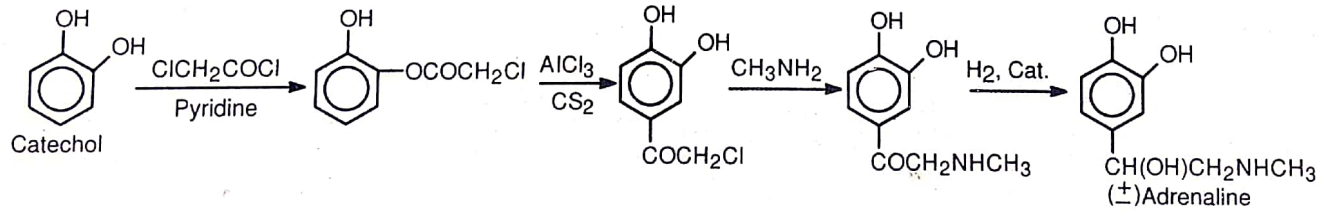
2, 3-Dihydroxy-acetophenone(minor) 3, 4-Dihydroxy-acetophenone(major)

(iii) Diphenyl esters also undergo Fries rearrangement.



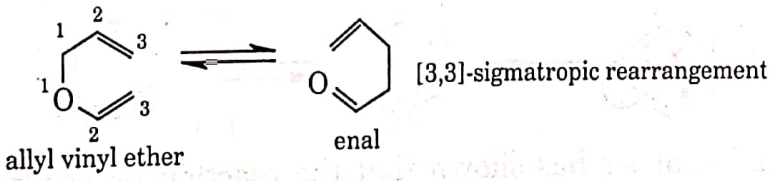
4-Hydroxy-3-methoxybiphenyl 4-Hydroxy-4'-methoxybiphenyl

(iv) A very useful application is in the synthesis of (±) adrenaline which is a heart stimulant.

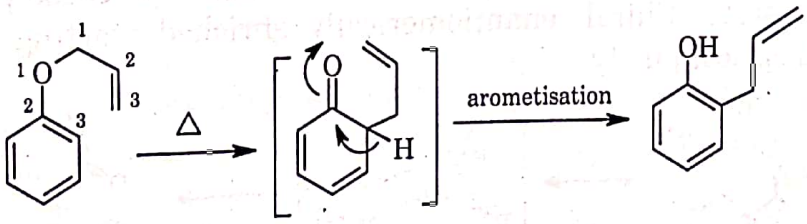


CLAISEN REARRANGEMENT

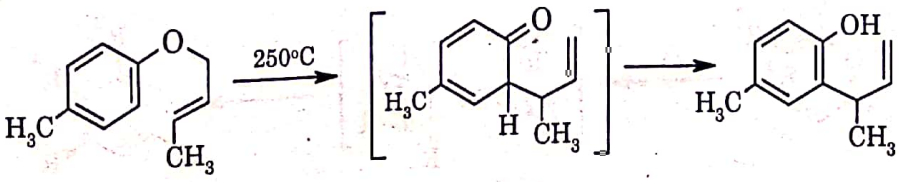
The Claisen rearrangement is a thermal [3,3]-sigmatropic rearrangement of ethers. Both aliphatic and aromatic ethers are found to undergo this reaction. In case of aliphatic ethers like allyl vinyl ether, the reaction closely resembles the Cope rearrangement.

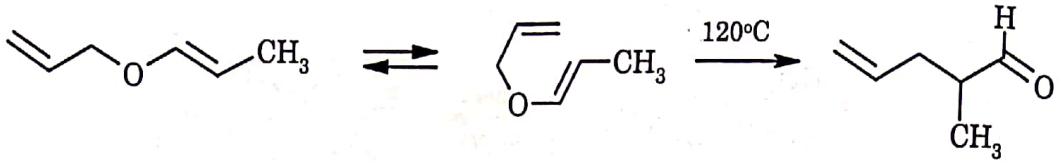


allyl vinyl ether — enal

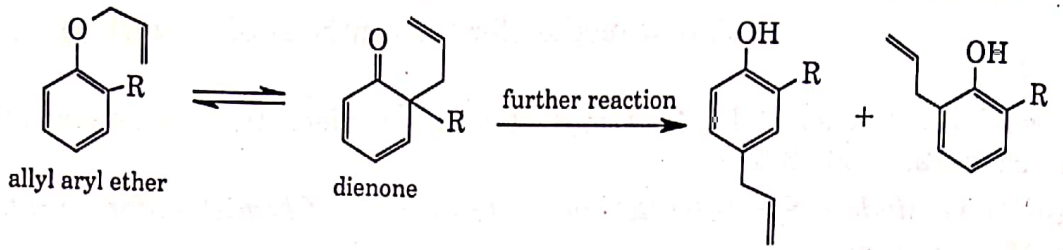


[3,3]-sigmatropic rearrangement





Claisen rearrangement involving allyl aryl ethers is more complex because the first product, an *ortho*-dienone, may react further. An example is given below.



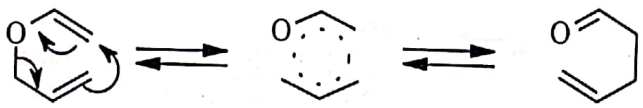
Claisen rearrangement is of first order with respect to rate and has large negative entropy of activation ($\Delta S^{\neq}$=–ve) consistent with cyclic transition state. The allylic group is inverted in the rearrangement, and optical activity is retained if the starting ether is optically active. Polar solvents increase the rate of the Claisen rearrangement, indicating some charge separation in the transition state.

All Claisen Rearrangement reactions described to date require temperatures of > 100°C,,if uncatalyzed. The observation that electron withdrawing groups at C-1 of the vinyl moiety exert a positive influence on the reaction rate.

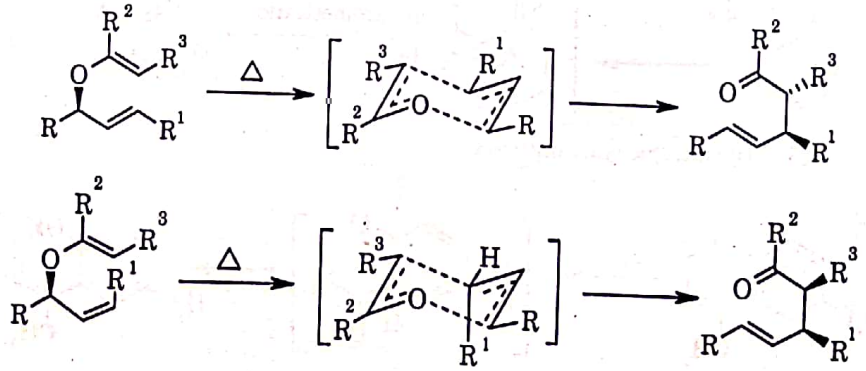
The etherification of alcohols or phenols and their subsequent Claisen rearrangement under thermal conditions makes possible an extension of the carbon chain of the molecule.

Mechanism:

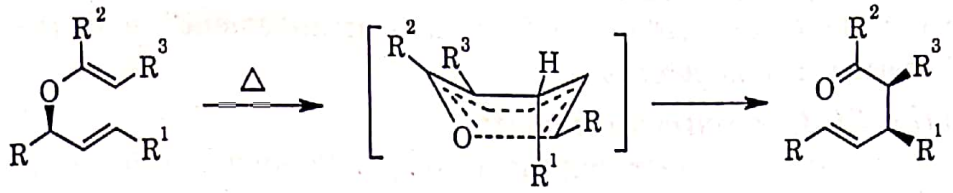
The Claisen Rearrangement may be viewed as the oxa-variant of the Cope Rearrangement (discussed later)



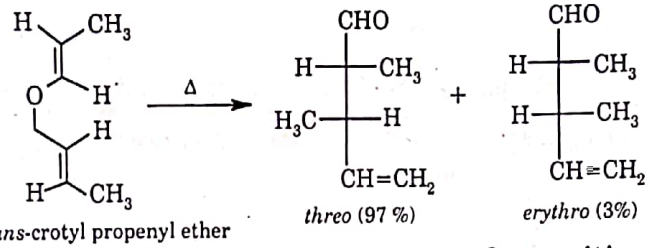
Conformational analysis has shown that the reaction proceeds preferably *via* a chair transition state. Chiral, enantiomerically enriched starting materials give products of high optical purity.



A less stable boat transition state is also possible, and can lead to side products:



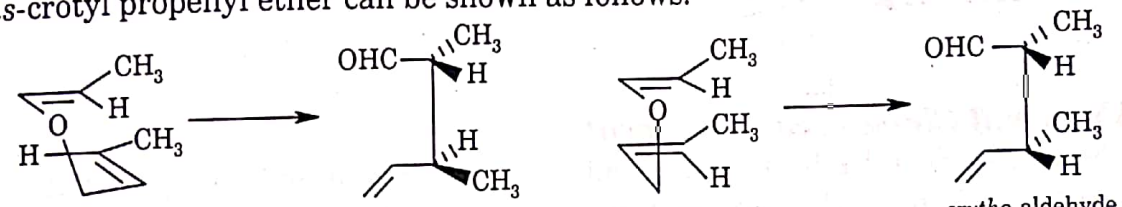
The Claisen rearrangement goes through a *chair* like transition state has been confirmed from product composition from a substrate of known stereochemistry. For example, *trans-trans*-crotyl propenyl ether gives almost 100% of the *threo*-aldehyde, and very small amount of *erythro* aldehyde. This shows that the transition state has a preference for *chair* conformation rather than *boat* conformation.



trans-trans-crotyl propenyl ether

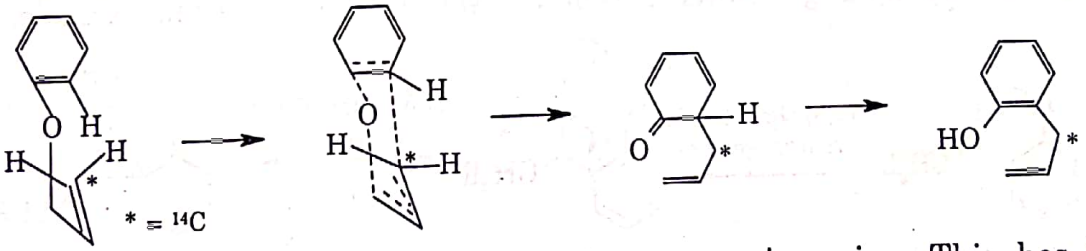
threo (97 %) *erythro* (3%)

Reactions through chair and boat conformations of transition states of *trans-trans*-crotyl propenyl ether can be shown as follows.



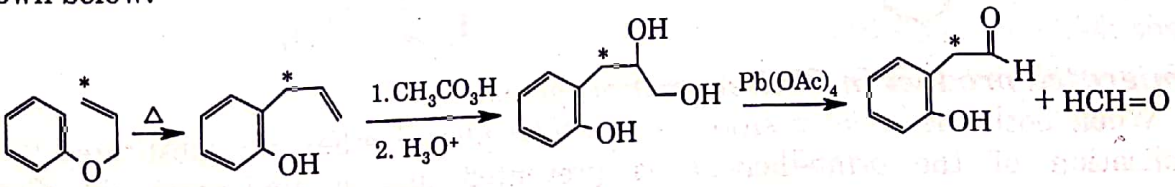
chair conformation *threo*-aldehyde boat conformation *erytho*-aldehyde

In case of allyl aryl ethers, the cyclic transition state for *ortho*-migration can be shown as follows.



* = ^{14}C

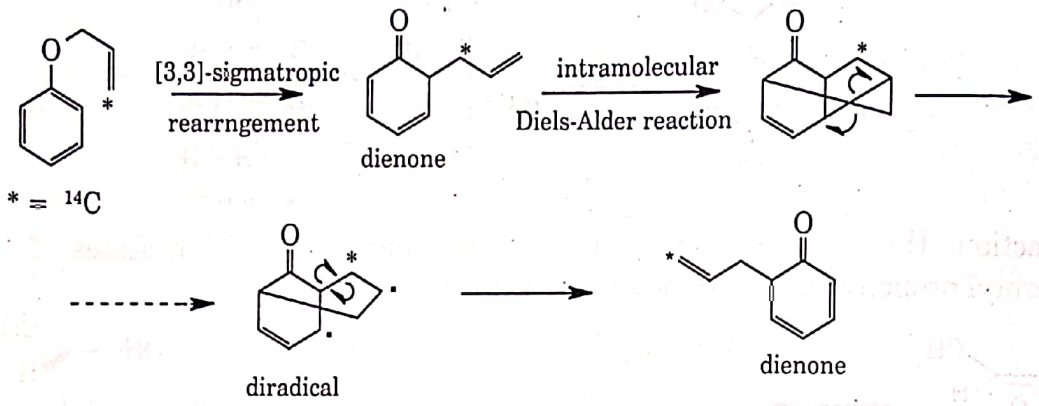
In *ortho*-migration, the allyl chain undergoes an inversion. This has been confirmed by ^{14}C labelled experiment. When the rearranged *ortho*-allylphenol is subjected to hydroxylation with peracid–dilute acid and then oxidised with lead tetraacetate, HCHO is obtained without ^{14}C, starting from the labelled compound as shown below.



Two interesting side reactions have been observed during *ortho*-Claisen rearrangement. One is "*ortho-ortho*-Claisen rearrangement" and the other is "abnormal Claisen rearrangement".

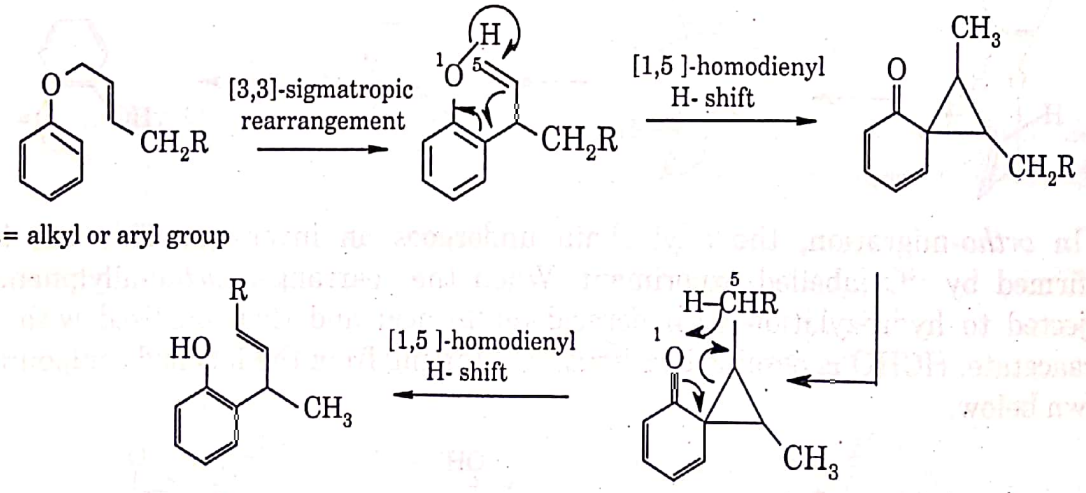
● ***ortho-ortho-Claisen rearrangement*:**

In *ortho-ortho*-Claisen rearrangement, one *ortho*-dienone is converted into another *ortho*-dienone before enolisation to a phenolic compound. This conversion is not a concerted [3,5] shift because geometry for a concerted thermal process would require a *suprafacial-antarafacial* process and the transition state-geometry for such a process would be difficult to attain. It is, therefore, assumed to be a stepwise reaction, as shown below. There is some evidence in favour of this stepwise reaction.



● ***Abnormal Claisen rearrangement*:**

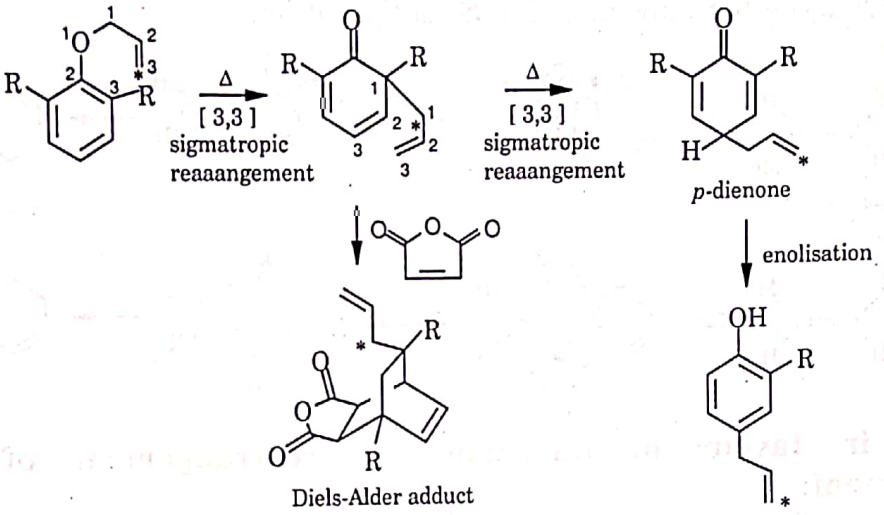
Certain allyl aryl ethers with an alkyl or aryl substituent (-CH_2R) at the end carbon atom of the allyl group rearrange to give a mixture of normal *ortho*-Claisen product and another isomeric *o*-allylphenol. The second *o*-allylphenol is called abnormal Claisen product. This abnormal product is believed to be formed by two [1,5]-homodienyl hydrogen shifts. This may be shown by the following example.



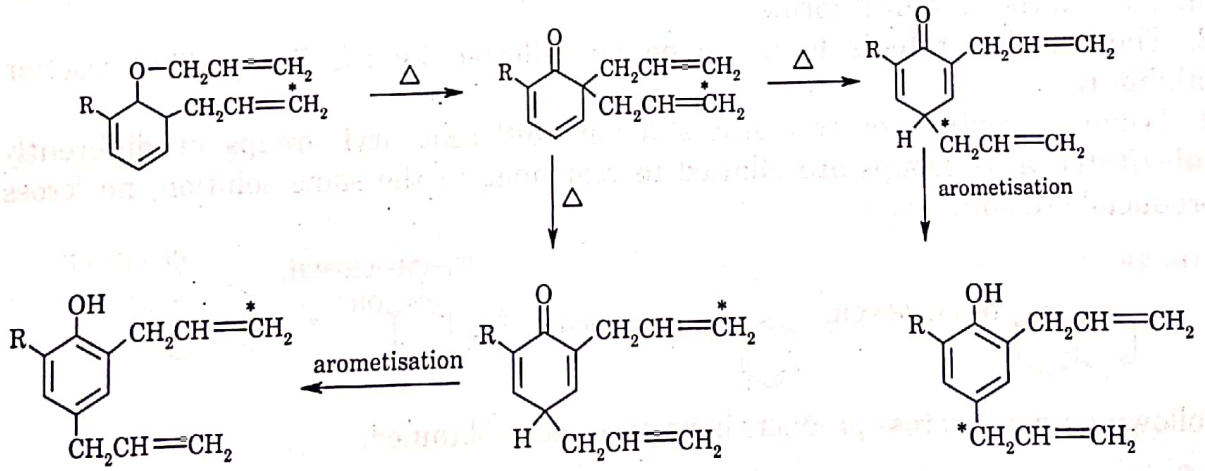
***p-migrated product in Claisen rearrangement*:**

When both the *ortho* positions of an allyl phenyl ether are substituted then enolisation of the *ortho*-dienone is prevented and it undergoes the Cope

rearrangement to give *para*-allylphenol. The allyl chain undergoes one inversion to give the *ortho*-isomer and second inversion to give the *para*-isomer. Through such double inversions, the original order of the carbon atoms in the allyl group in allyl phenyl ether is restored. This has been confirmed by isotope (^{14}C) labelled experiment. The intermediate *ortho*-dienone has also been trapped as a Diels-Alder adduct using maleic anhydride as dienophile. When the *para*-position is also occupied then none of the dienones can enolise and equilibrium is set up among the dienones and the ether.

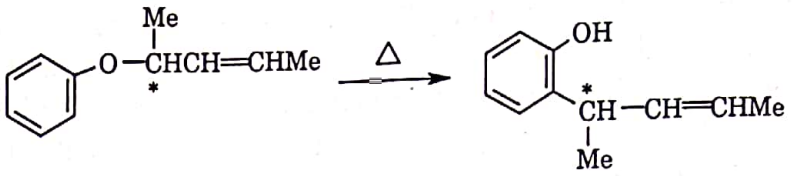


When an aryl vinyl ether also contains another allyl group at the *ortho* position labelled with ^{14}C then two types of *p*-migrated products are obtained with the labelled-carbon containg allyl chain in different position of the aromatic ring. This fact confirms that *p*-migration occurs after an intramolecular *ortho* migration.

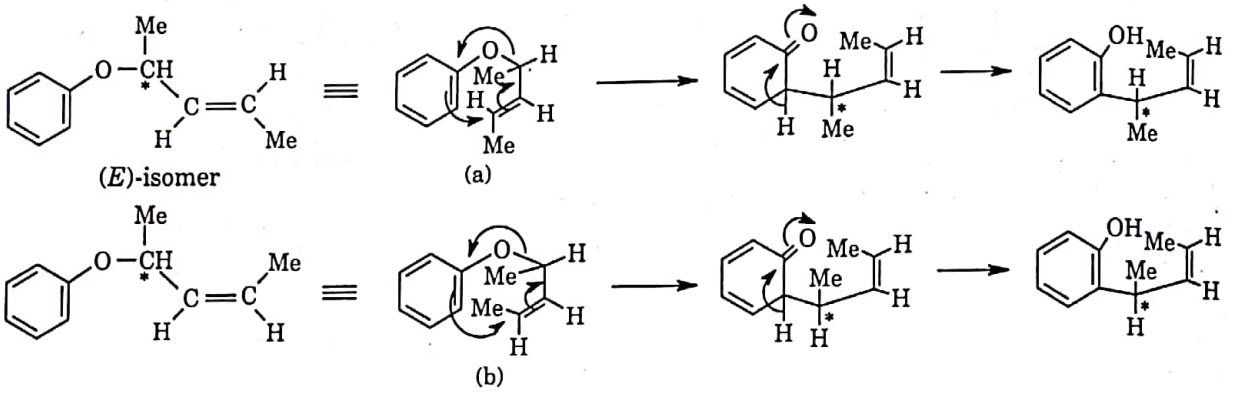


Claisen rearrangement of a chiral aryl vinyl ether:

It is interesting that the Claisen rearrangement of a chiral ether in which the asterisked carbon is an asymmetric centre leads to an optically active phenol in which a new carbon has become asymmetric. This reaction may, therefore, be considered as a case of special type of asymmetric induction.



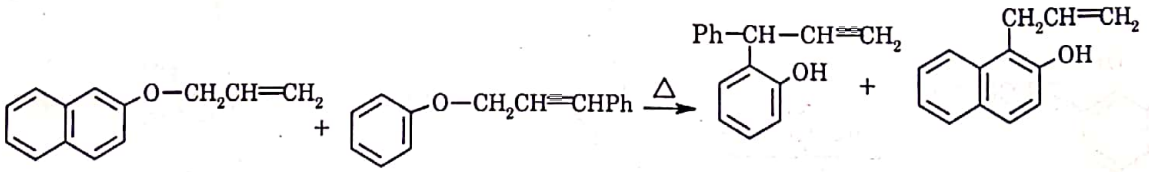
The reaction is shown below taking *E* and *Z* isomers. The transition state (a) from (*E*)-isomer, in which the methyl groups are *trans*, is sterically favoured over the transion state (b) from the (*Z*)-isomer, in which they are *cis*. The chiral centre (*) of the allyl aryl ether may have *R* or *S* configuration.



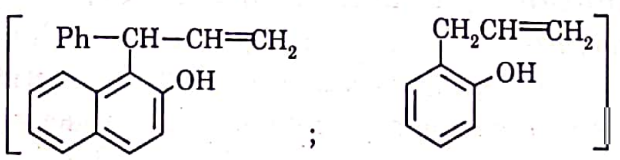
Evidence in favour of intramolecular rearrangement of Claisen rearrangement:

That the Claisen rearrangement is an intramolecular rearrangement are supported by the following facts.

1. All attempts to detect fragmant (ions or radicals) as intermediate in the Claisen rearrangement have failed. When the rearrangement is carried out in a nucleophilic solvents like phenol or dimethylaniline, no product resulting from the attack by the allyl ion on the solvent is formed.
2. The reaction rate is found to be not affected by the free–radical reaction inhibitors.
3. When a mixture of two ethers having different aryl groups or differently substituted allyl groups are allowed to rearrange in the same solution, no 'cross products' are obtained.



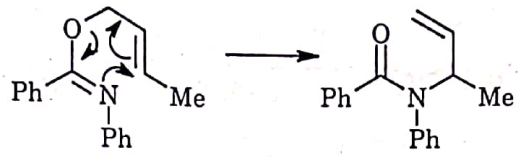
Following types of cross products have never been obtained.



4. The reaction shows a first-order rate law and the negative entropies of activation.

Some reactions analogous to Claisen rearrangement:

A few reactions analogous to Claisen rearrangements are shown below. The reactions follow first-order rate laws and high negative entropies of activation consistent with the cyclic mechanism shown.

1. 

2. 

3. 

References:

1. Claisen, L. Rearrangements of phenol allyl ethers into C-allylphenols. **Ber, 1913,** 45, 3157-3166.

2. Claisen, L., Eisleb, O. Rearrangements of phenol allyl ethers into the isomeric allylphenols. *Ann.* **1914**, 401, 21-119.

3. Rhaods, S. J. Raulilins, N. R. Claisen and Cope rearrangements. *Org. React.* **1975,** 22, 1-252.

4. Bennett, G. B., The Claisen rearrangement in organic synthesis : 1967 to January 1977. *Synthesis*, **1977**, 589-606.

5. Zeigler, F.E. Stereo-regiochemistry of the Claisen rearrangement : application to natural products synthesis. *Acc. Chem. Res.* **1977**, 10, 227-232.

6. Zeigler, F.E. The thermal aliphatic Claisen rearrangement. *Chem Rev.* **1988**, 88, 1423-1452.

7. Ganem, B. The mechanism of the Claisen rearrangement : déjà vu all over again. *Angew. Chem., Int. Ed. Engl.* **1996**, 35, 936-945.