

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

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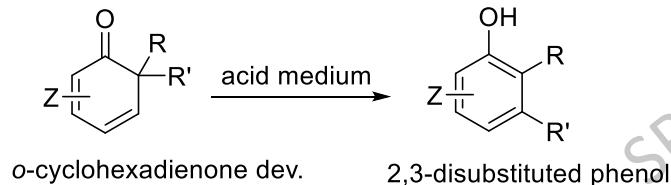
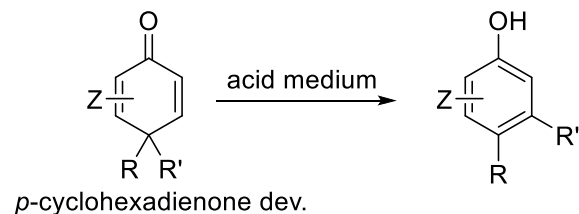
Recommended texts:

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: Dienone-phenol rearrangement

Thematically similar to the Wagner-Meerwein rearrangement in the sense that this is also a [1,2]-shift of migrating group from a carbon to another e-deficient carbon.



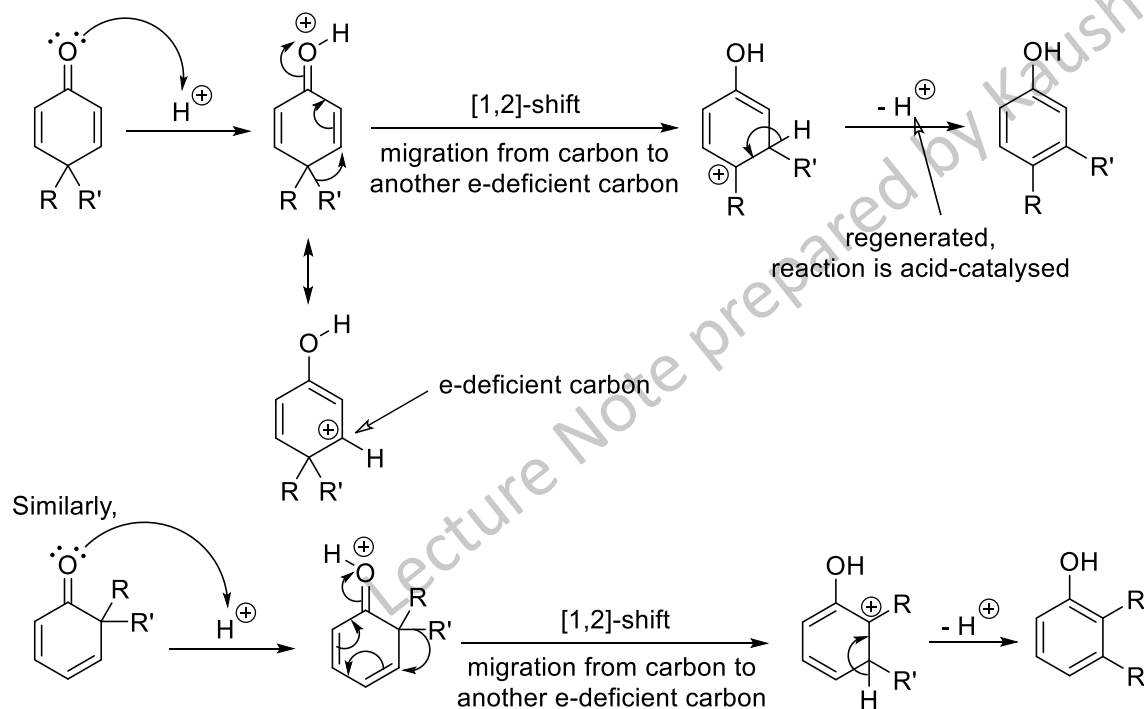
K. von Auwers  
(1863-1939)



K. W. Ziegler  
(1893-1973,  
Nobel Prize in 1963)

The driving force for this rearrangement is gaining the aromatic stabilisation.

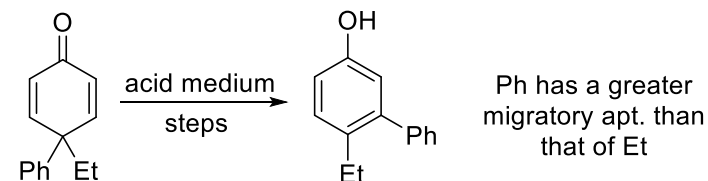
Mechanism:



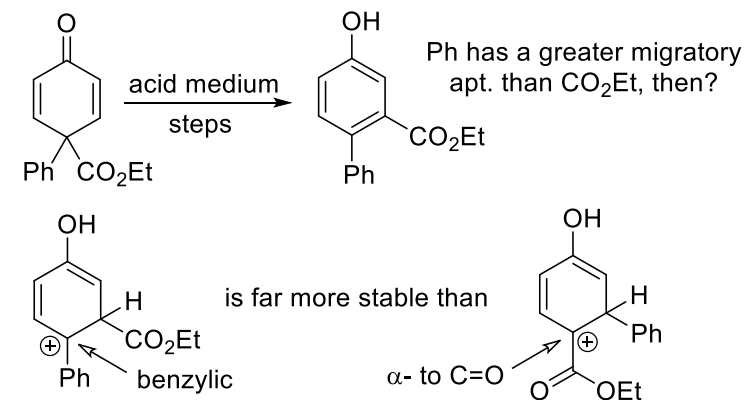
Which group would migrate?

That depends upon the following factors:

i) As this is again a migration to an e-deficient centre, the group that can release electrons better also migrates better, i.e. the group that has greater migratory aptitude migrates better:



ii) Stability of the carbocation formed *after* migration:

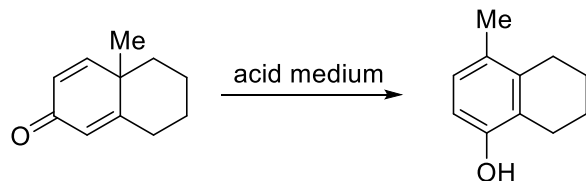


## Rearrangements in Organic Chemistry

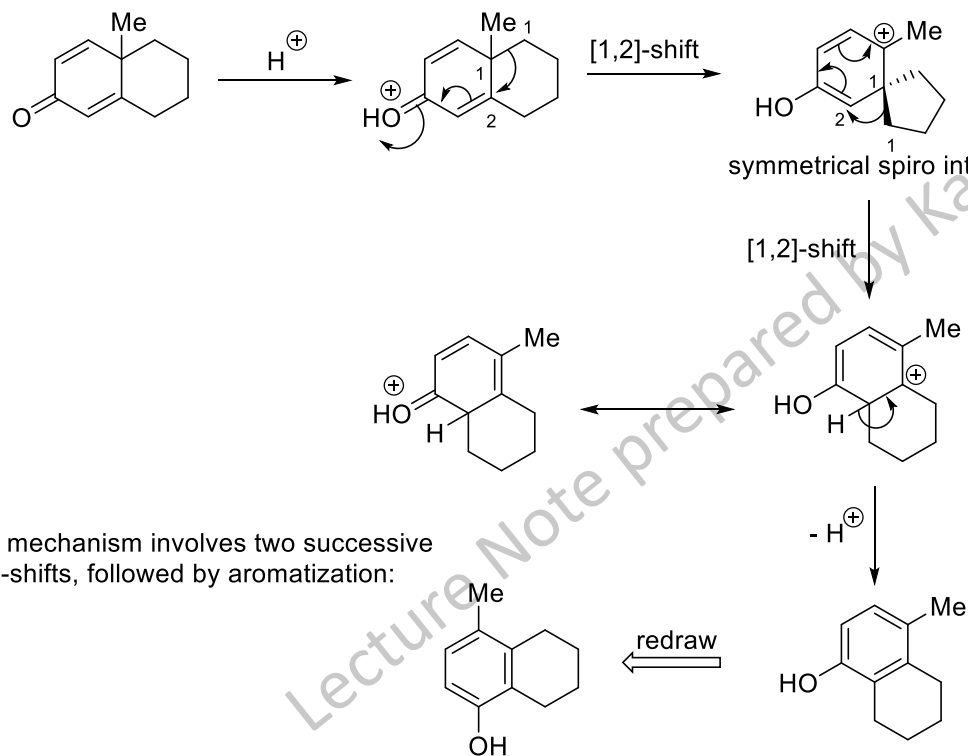
Migration from carbon to electron-deficient carbon: Dienone-phenol rearrangement

An alternative mechanism and how to disprove it:

Consider the following:

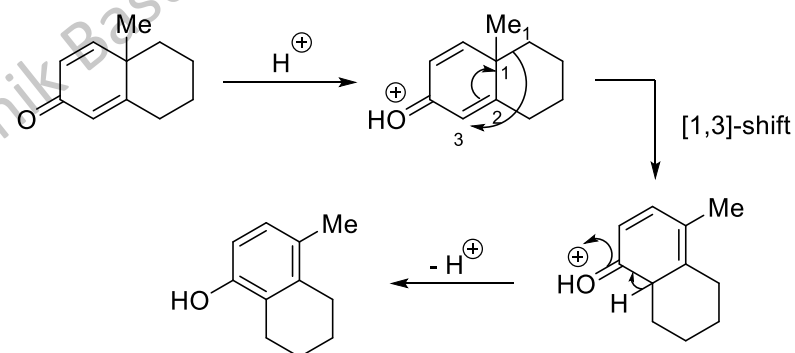


Based on what we have learnt, we can propose the following mechanistic pathway:



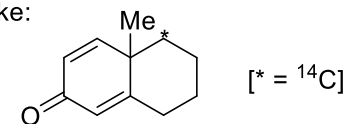
This mechanism involves two successive [1,2]-shifts, followed by aromatization:

However, an alternative description involving a [1,3]-shift is also possible:



Theory predicts that such [1,3]-shift is forbidden on symmetry grounds and we can verify that by isotopic labelling experiment:

We need to take:



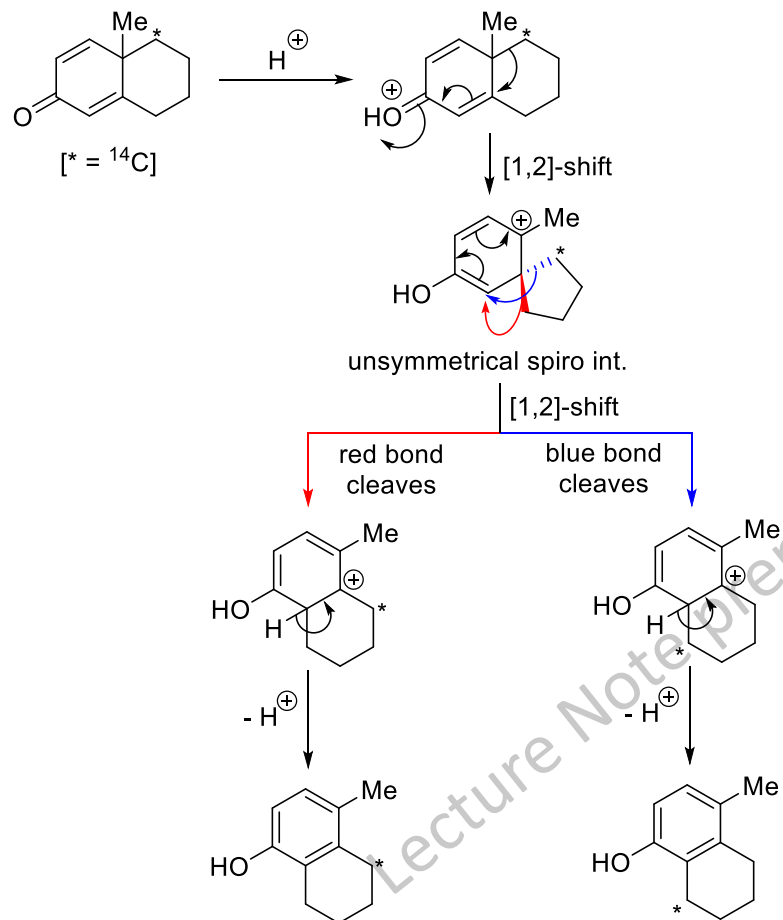
and analyse the product mixture.

## Rearrangements in Organic Chemistry

Migration from carbon to electron-deficient carbon: Dienone-phenol rearrangement

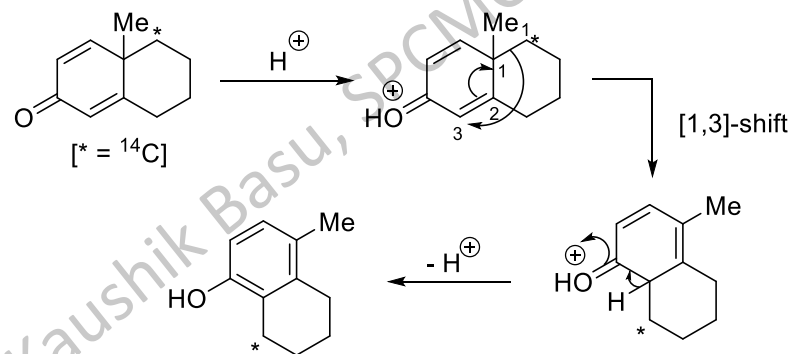
An alternative mechanism and how to disprove it (contd.):

Based on the first mechanism (two successive [1,2]-shifts) we expect:



we should get these two products in approximately 1:1 ratio, i.e. the isotopic label should be scrambled over two different positions

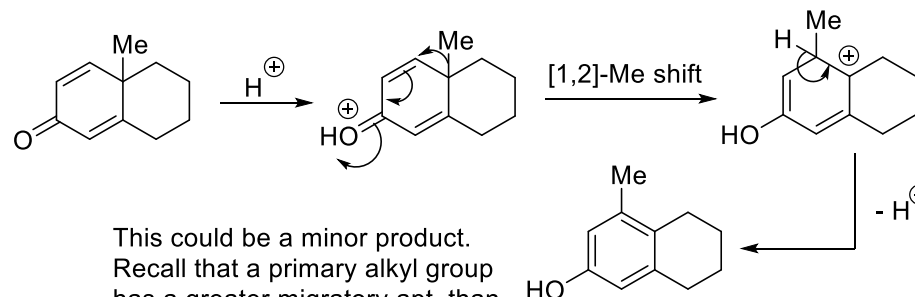
Based on the second mechanism (the [1,3]-shift) we expect:



we should get only this product, i.e. the isotopic label should not be scrambled at all.

In reality we get the mixture of the two products where scrambling is seen. So the actual mechanism is the one involving two successive [1,2]-shifts and not a [1,3]-shift.

Possibility of other product formation:

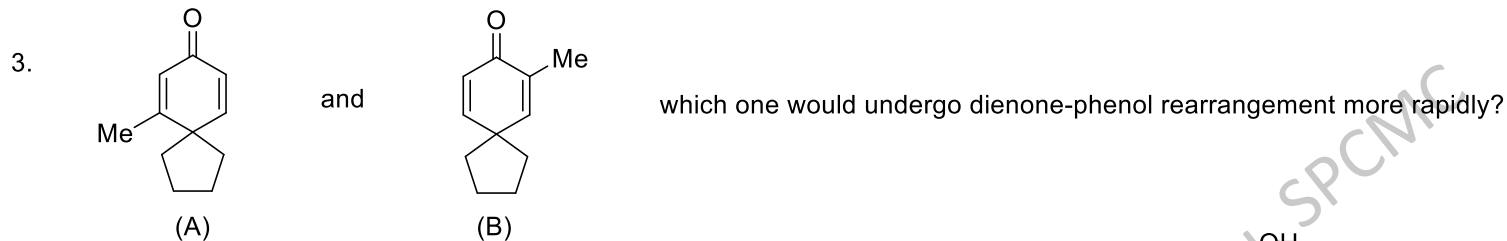


This could be a minor product. Recall that a primary alkyl group has a greater migratory apt. than a methyl does.

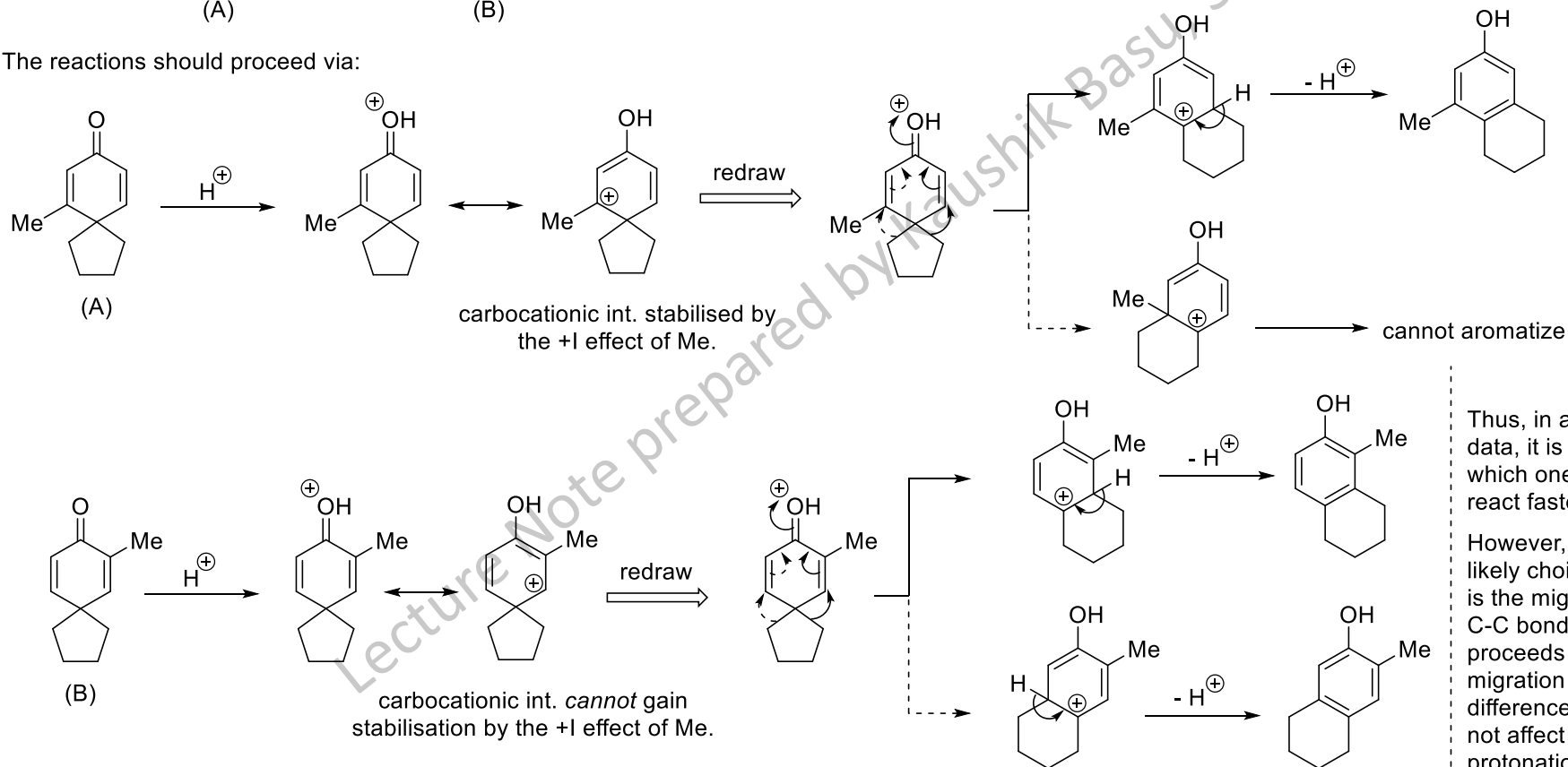


Migration from carbon to electron-deficient carbon: Dienone-phenol rearrangement

A few interesting cases:



The reactions should proceed via:



Thus, in absence of real data, it is difficult to predict which one would actually react faster.

However, A is the more likely choice, as the RDS is the migration of the C-C bond. Aromatization proceeds only when the migration is over so any difference in there should not affect the rate. The protonation, OTOH, is before the RDS and the concentration of the cation matters a lot.

Considering the rel. stability of cationic int.s from A and B, A should react at a faster rate as the int. is more stable there and should form at a faster rate.

However, the rearranged cation from B has a greater chance of aromatization than that from A. So in that respect B, should react faster.

## Rearrangements in Organic Chemistry

Migration from carbon to electron-deficient carbon: Benzilic acid rearrangement (aka benzil-benzilic acid rearrangement)

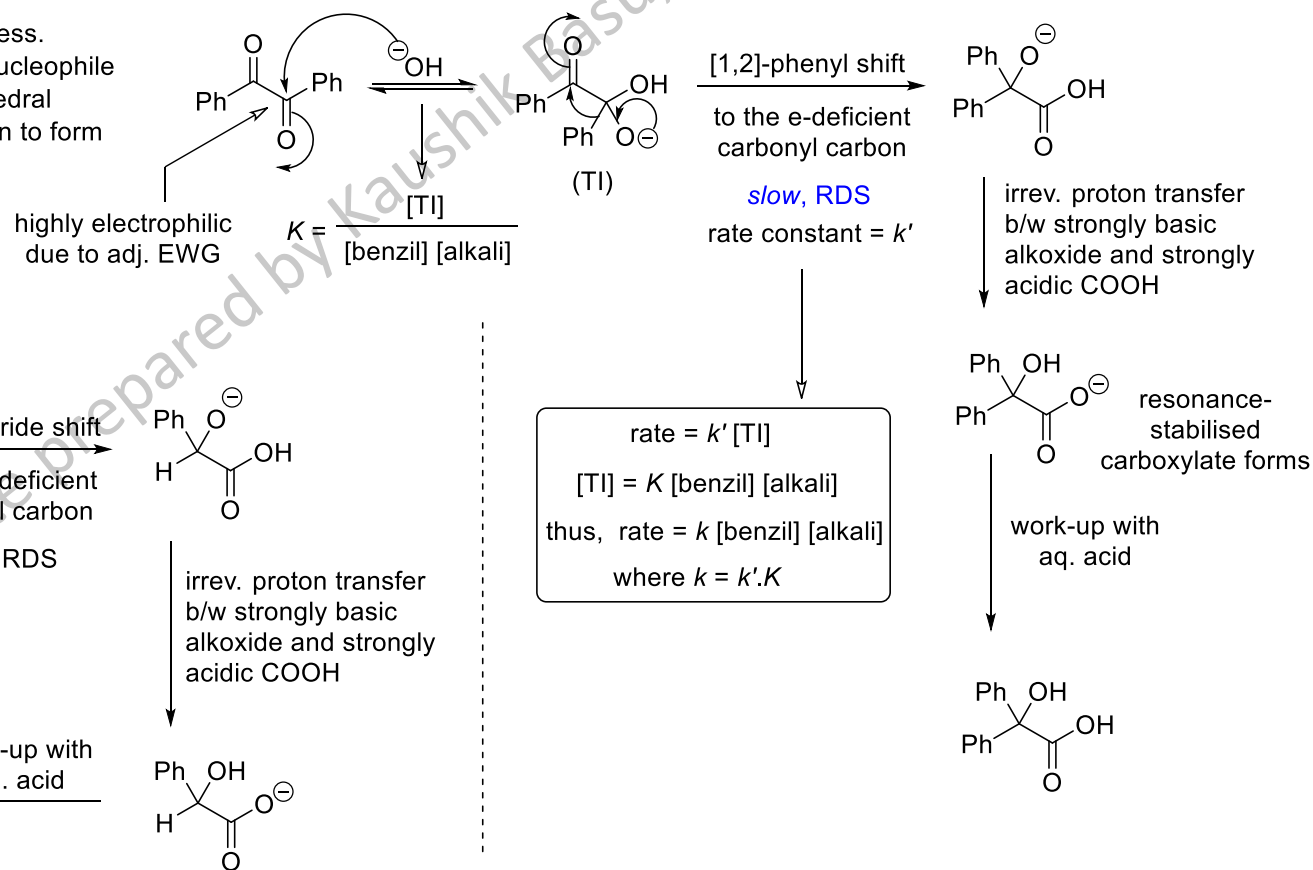
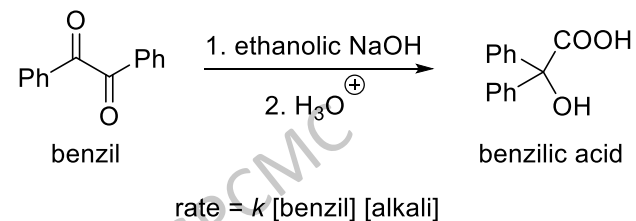
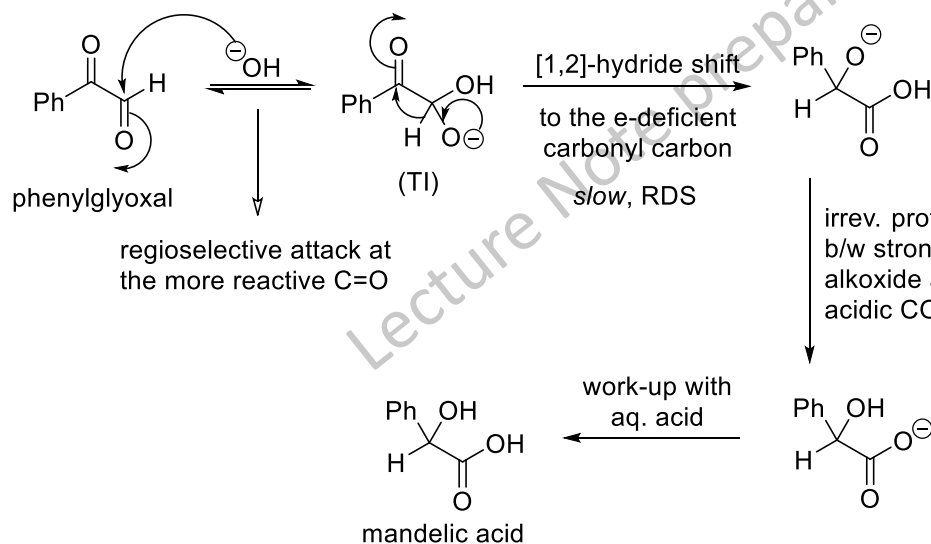
Upon treatment with base (e.g., NaOH),  $\alpha$ -diketones (1,2-diketones) rearrange to give salts of  $\alpha$ -hydroxy acids. This process is called the benzilic acid rearrangement.

The reaction takes place with both aliphatic and aromatic  $\alpha$ -diketones and  $\alpha$ -keto aldehydes. Usually diaryl diketones undergo benzilic acid rearrangements in excellent yields, but aliphatic  $\alpha$ -diketones that have enolizable  $\alpha$ -protons give low yields due to competing aldol condensation reactions.

Mechanism:

The benzilic acid rearrangement is an irreversible process. The first step of the mechanism is the addition of the nucleophile (here hydroxide) across the C=O bond to give a tetrahedral intermediate (TI). The next step is aryl or alkyl migration to form the corresponding  $\alpha$ -hydroxy acid salt.

This has strong mechanistic similarity with intramolecular Cannizzaro reactions, e.g.

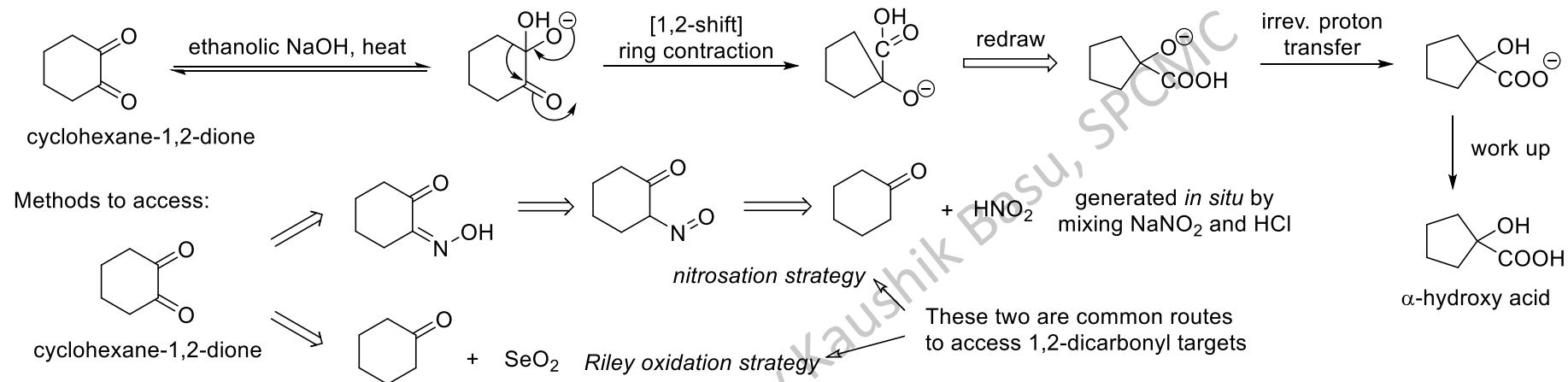


## Rearrangements in Organic Chemistry

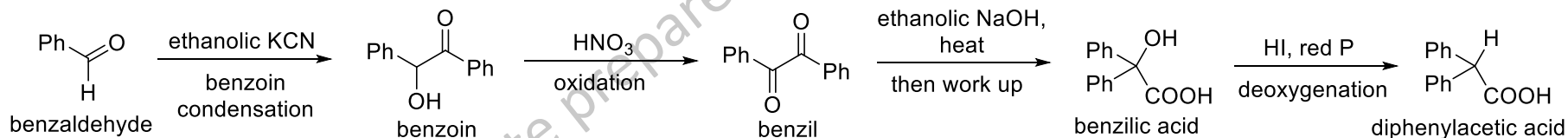
Migration from carbon to electron-deficient carbon: Benzilic acid rearrangement (aka benzil-benzilic acid rearrangement)

Synthetic utility:

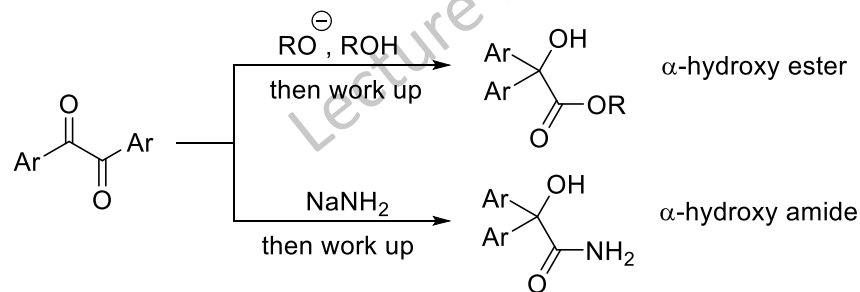
1. Cyclic  $\alpha$ -diketones undergo the synthetically useful ring-contraction benzilic acid rearrangement reaction to afford cyclic  $\alpha$ -hydroxy acid



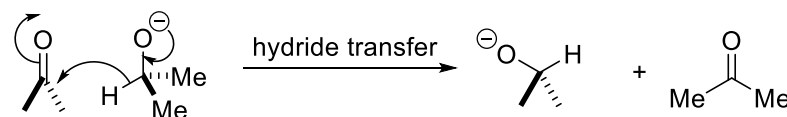
2. Synthesis of diphenylacetic acid from benzaldehyde:



3. Synthesis of  $\alpha$ -hydroxy esters and amides by changing the nucleophile to an alkoxide or an amide:



Not all alkoxides are, however, suitable for this purpose; those that are prone to hydride donation, like isopropoxide or ethoxide have a tendency to reduce the 1,2-diketone (recall MPVO reaction):



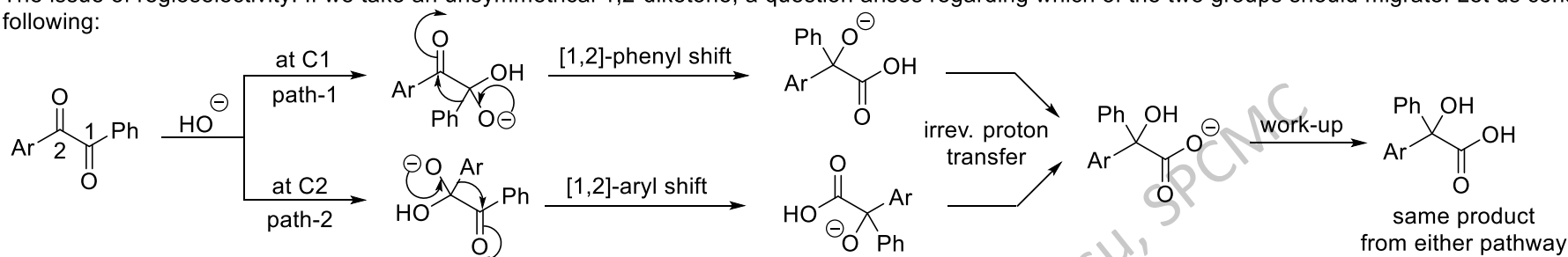
1,2-dicarbonyl compounds are particularly susceptible towards nucleophilic addition due to unusually low LUMO - hence this reduction is facile.



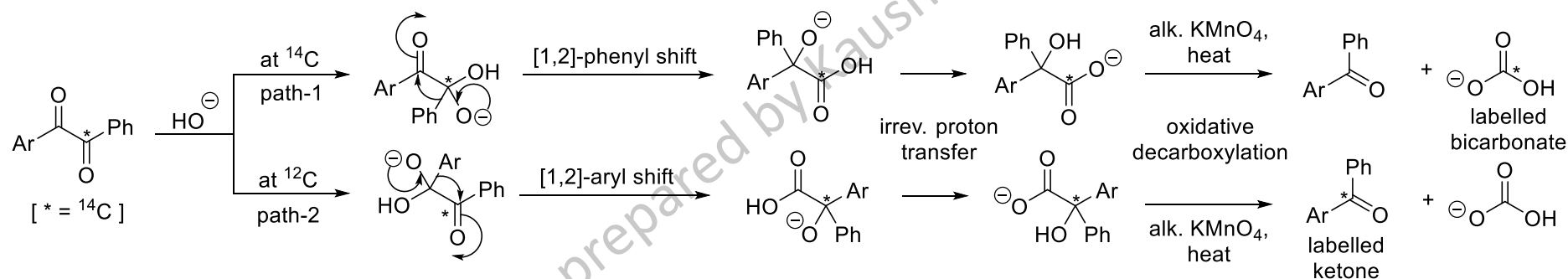
## Rearrangements in Organic Chemistry

Migration from carbon to electron-deficient carbon: Benzilic acid rearrangement (aka benzil-benzilic acid rearrangement)

The issue of regioselectivity: If we take an unsymmetrical 1,2-diketone, a question arises regarding which of the two groups should migrate. Let us consider the following:



The same product is formed by either migration. So we cannot say which group has actually migrated more. In fact, it depends upon which of the two carbonyl carbons is regioselectively attacked by the nucleophile, but we cannot resolve this issue in this approach. To decide in this case, we need to revise the structure of the starting 1,2-diketone in such a way that each migration affords different end product. Thus we have the following:

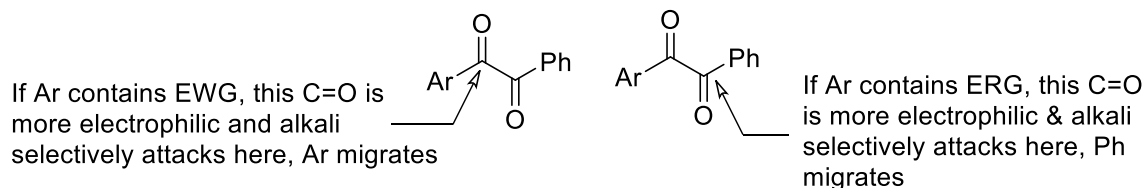


Therefore, by measuring the % of radiolabelled carbon in the ketone product and in the bicarbonate, we can calculate how much of path-1 and path-2 are operating. We have the following result:

for	Identity of Aryl (Ar):	$\frac{\% \text{ migration of Ar}}{\% \text{ migration of Ph}}$
	Me-	0.63
	Cl-	2.05
	MeO-	0.46

Thus, the aryl ring with EWG migrates better than phenyl, which in turn migrates better than aryls with ERG. But this is a migration from carbon to another e-deficient carbon. So why this *apparently* anomalous result?

The regioselectivity of nucleophilic attack determines which group should migrate. Carbonyl carbon adjacent to aryl rings bearing EWG is more electrophilic, thus initial nucleophilic attack is more favourable there; this results in preferential migration of the EW aryl ring. For ER aryls the reverse is true and phenyl migrates.

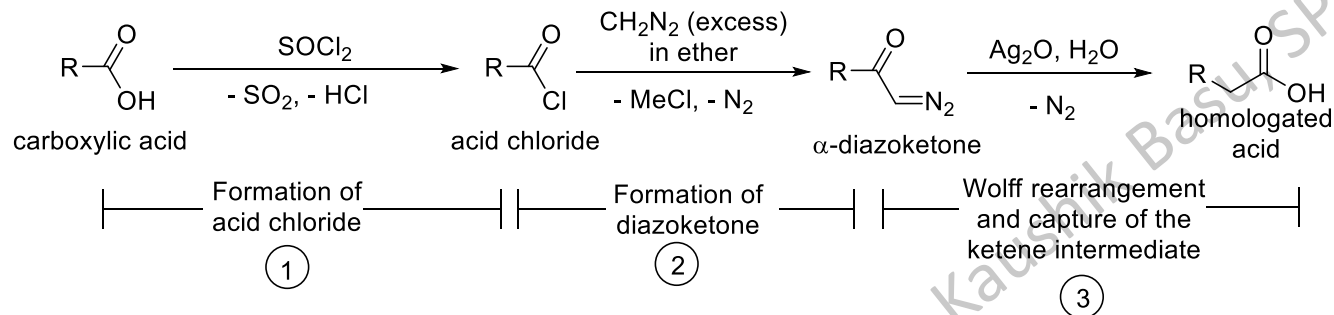


## Rearrangements in Organic Chemistry

Migration from carbon to electron-deficient carbon: Arndt-Eistert reaction/homologation

A method for converting a carboxylic acid to its immediate higher homologue (one CH<sub>2</sub> group longer) or to a derivative (like an amide or an ester) of the homologous acid.

The conversion is achieved in three stages. This homologation is the best preparative method for the chain elongation of carboxylic acids. In the first stage of the process the acid is converted to the corresponding acid chloride. The second stage involves the formation of a  $\alpha$ -diazomethylketone, followed by a Wolff rearrangement in the third stage.



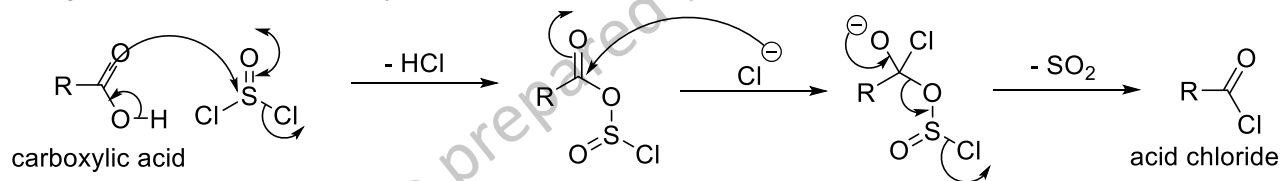
F. Arndt  
(1885-1969)



B. Eistert  
(1902-1978)

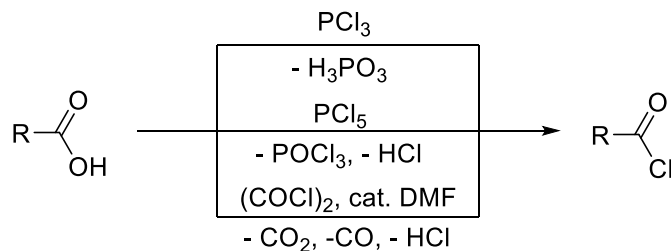
Mechanism:

Stage-1: Conversion of carboxylic acid to acid chloride:



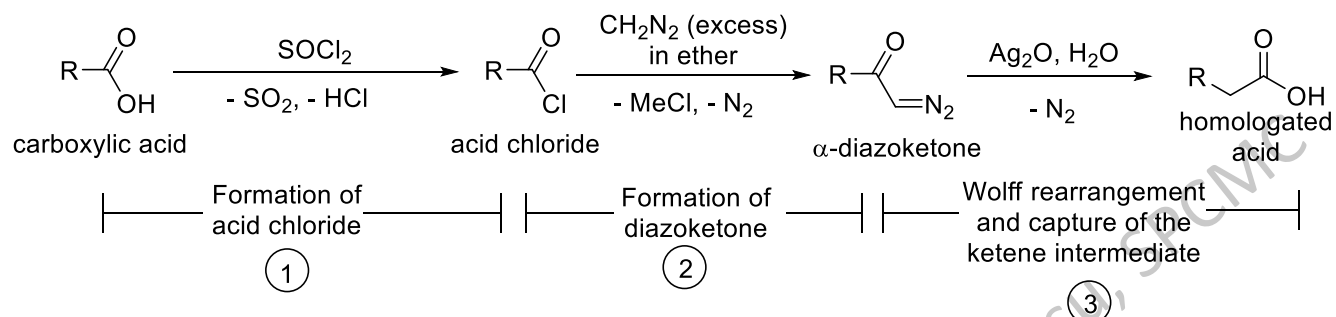
The driving force of this reaction is the formation of gaseous by products SO<sub>2</sub> and hydrogen chloride, both of which can be perged easily from the reaction medium by a stream of N<sub>2</sub>, thereby making the separation of the acid chloride much easier. One of the oxygens of the carboxylic acid is made to leave by converting into a good leaving group. Recall that the S-O bond is strong.

Alternative reagents for conversion of RCO<sub>2</sub>H to RCOCl:



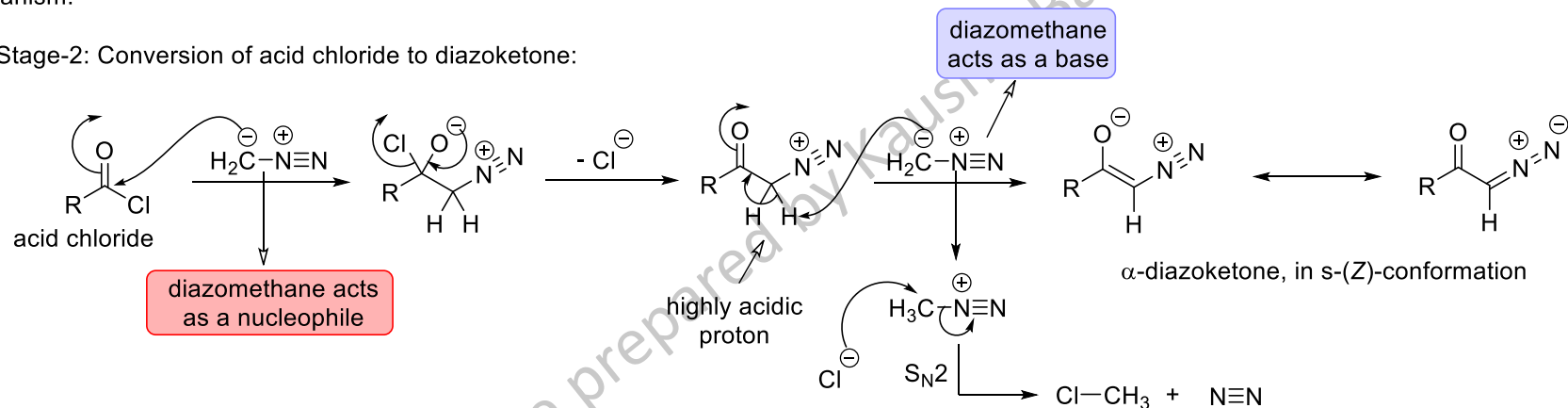
## Rearrangements in Organic Chemistry

Migration from carbon to electron-deficient carbon: Arndt-Eistert reaction/homologation



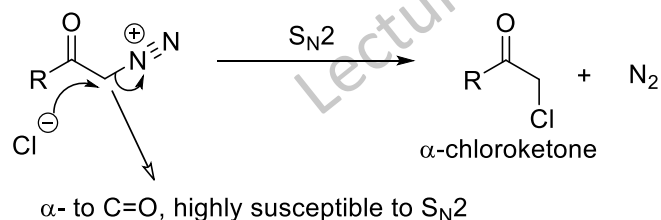
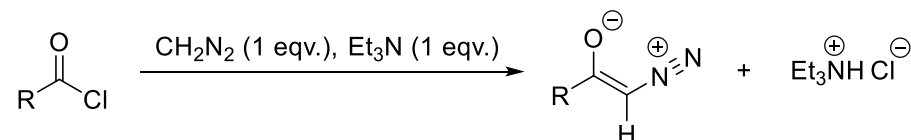
Mechanism:

Stage-2: Conversion of acid chloride to diazoketone:



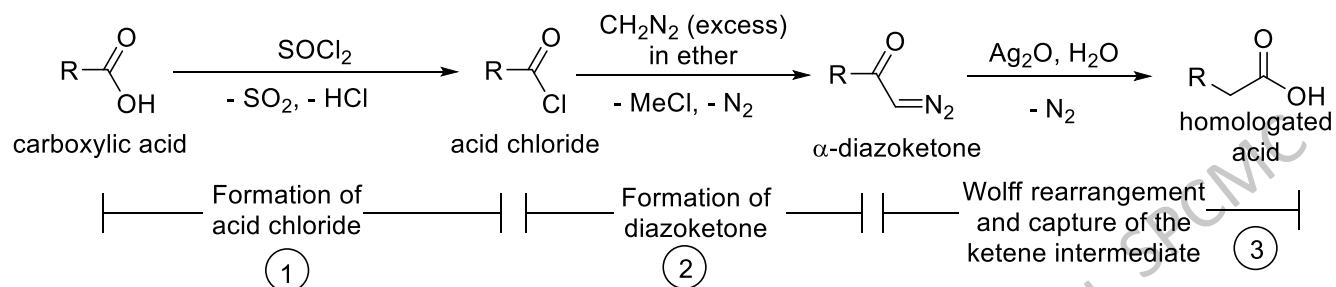
The diazomethane has a dual role in this reaction. It acts as a nucleophile as well as a base. So at least two eqv. of diazomethane must be used.

If we do not use excess diazomethane, the diazoketone cannot form and the following side reaction takes over:

OTOH, if one eqv. of an additional base such as  $\text{Et}_3\text{N}$  is used, only one eqv. of diazomethane is sufficient:

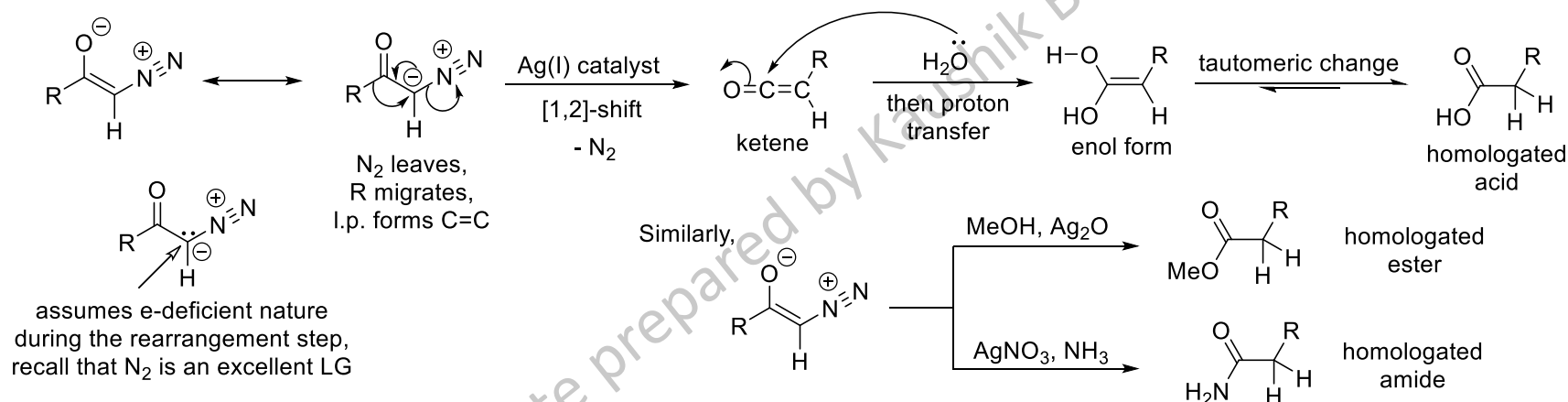
In fact this is a good strategy for synthesis of such chloroketone targets.

Migration from carbon to electron-deficient carbon: Arndt-Eistert reaction/homologation

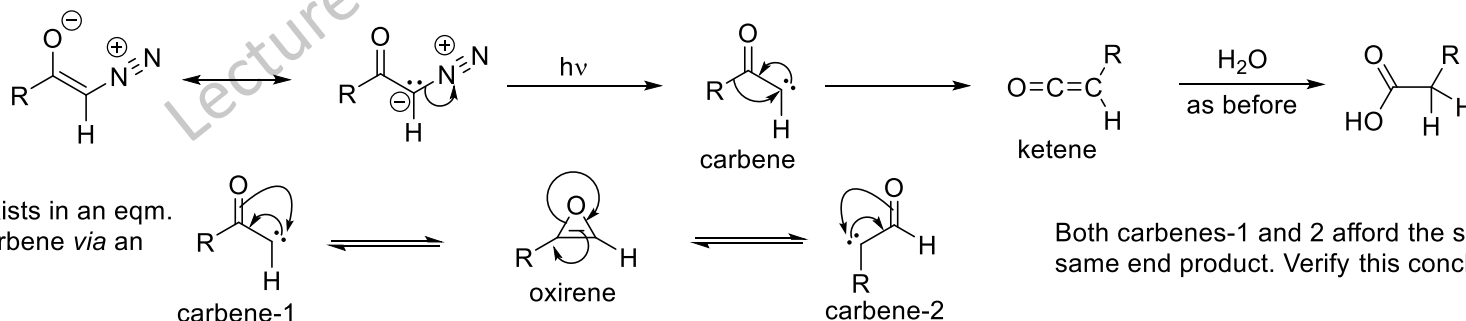


Mechanism:

Stage-3: Rearrangement of the diazoketone and nucleophilic capture of the ketene intermediate:



The rearrangement of diazoketone to ketene is concerted where departure of N<sub>2</sub> and migration of R proceeds in a single step. However, the Wolff rearrangement can also be triggered photochemically. In that case, the rearrangement proceeds in a stepwise manner via a carbene intermediate.

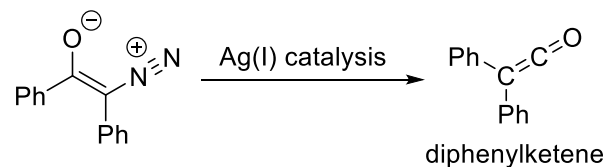


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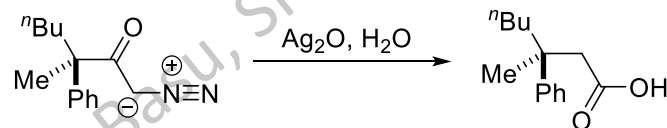
Migration from carbon to electron-deficient carbon: Arndt-Eistert reaction/homologation

Proof of mechanism:

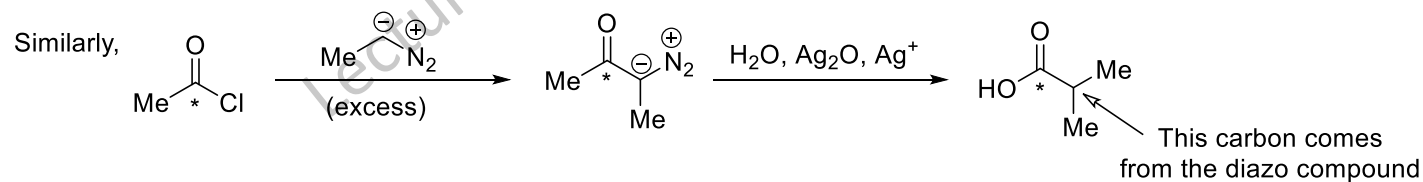
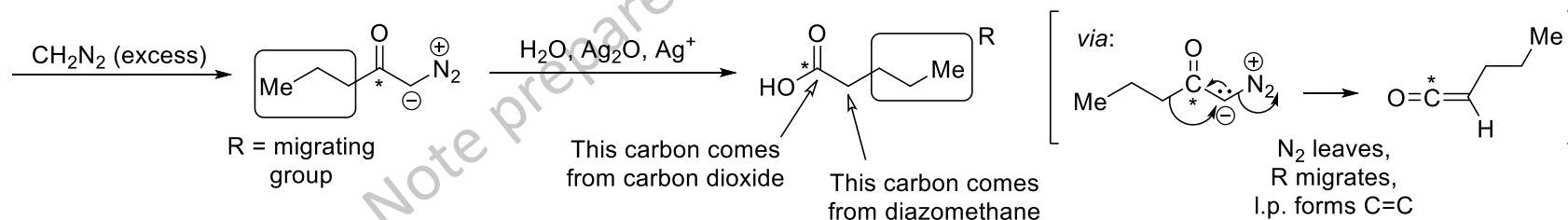
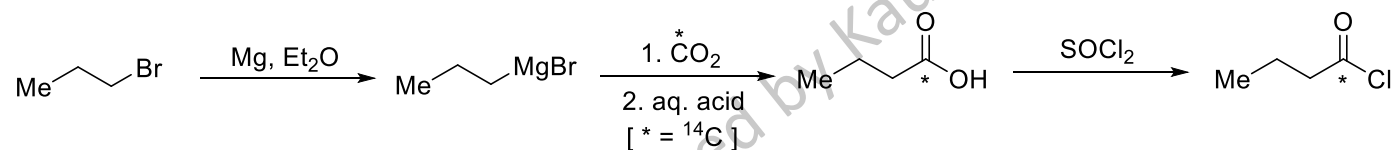
1. Stable ketene int. has been isolated:



2. A chiral R group migrates with retention of configuration which proves that the migration is intramolecular in nature, as indicated by the proposed mechanism:



3. Isotopic labelling studies prove to which carbon the migration happens and where does the diazomethane carbon end up:

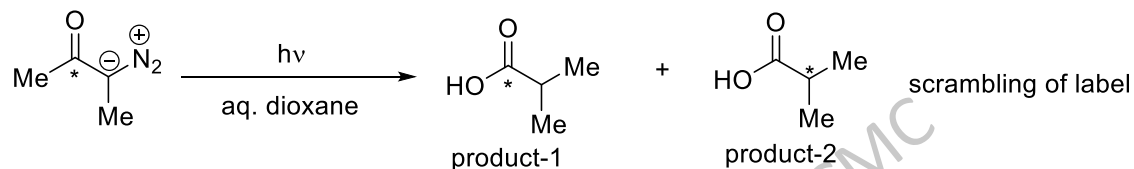


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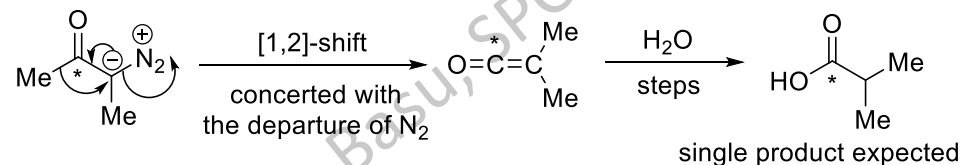
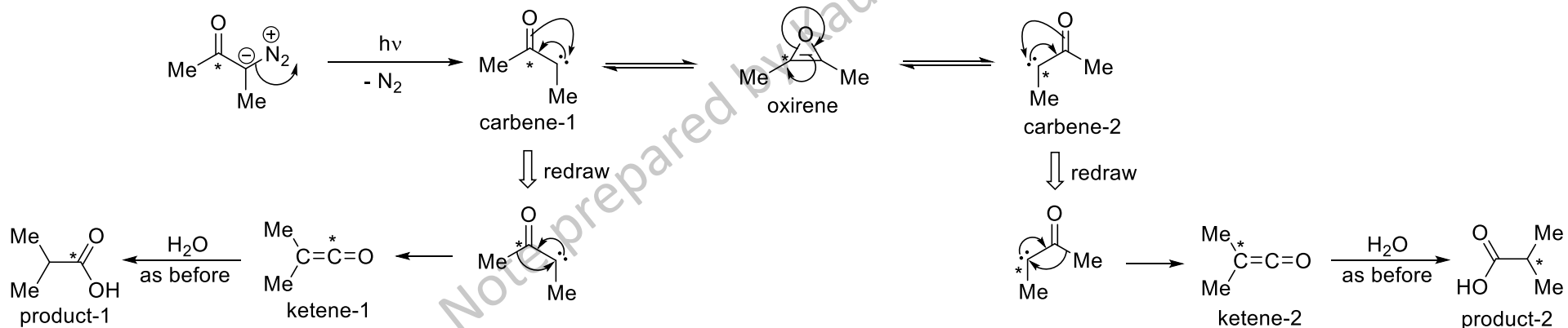
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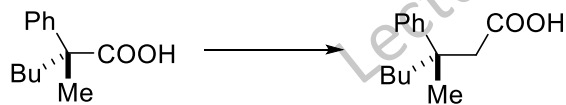
Isotopic labelling: unusual observation:



Formation of this mixture of products rules out the concerted pathway as through that only one product may form:

Recall that photochemical A-E reaction proceeds in a stepwise manner through a carbene intermediate. Also, this carbene can exist in eqm. with another carbene *via* the intermediacy of an oxirene int. These two carbenes give rise to two different ketenes and eventually two different products in this case:

A trick question:



This transformation can be achieved by a straightforward A-E homologation.

treat with excss  $\text{CH}_2\text{N}_2$ , then  $\text{Ag}(\text{I})$ , cat.  $\text{H}_2\text{O}$ But how carry out the *opposite* transformation?