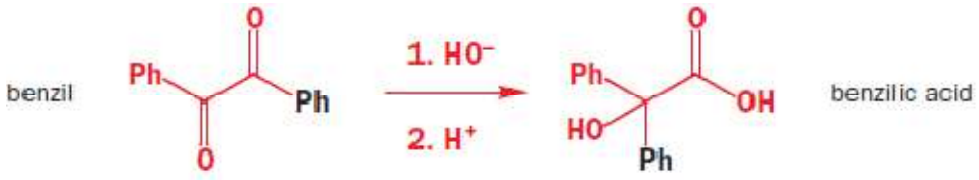
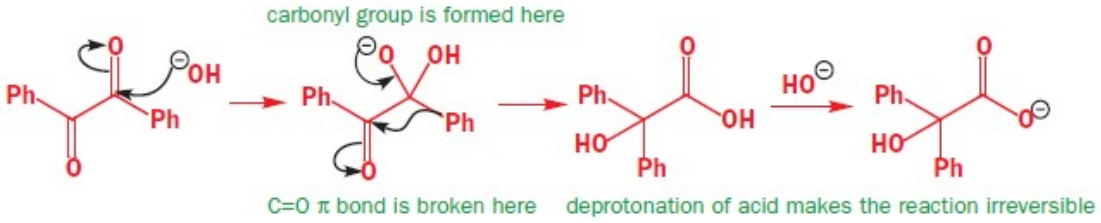
The benzilic acid rearrangement:

The migrating group in the **pinacol and semipinacol** rearrangements is '**pushed**' by the oxygen's lone pair as it **forms the new carbonyl group**, the rearrangements in which carbonyl groups form at the migration origin. While in the **dienone–phenol** rearrangement the migrating group is '**pulled**' towards the protonated carbonyl group if the **carbonyl groups being destroyed** at the migration terminus. The **benzilic acid rearrangement** reaction **has both of these at once**.

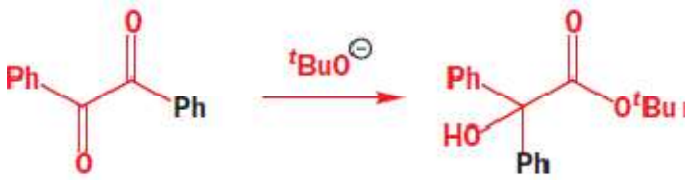
Example: In 1838, **Justus von Liebig** found that treating '**benzil**' (**1,2-diphenylethan-1,2-dione**) with **hydroxide gave**, **after acid** quench, **2-hydroxy-2,2-diphenylacetic acid**, which he called '**benzilic acid**'.



Mechanism: Starts the benzilic acid rearrangement with the attack of hydroxide on one of the carbonyl groups. The tetrahedral intermediate can collapse in a reaction reminiscent of a semipinacol rearrangement.

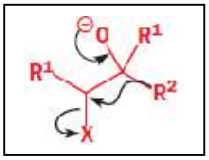


- The **benzilic acid rearrangement** can lead directly to **esters** when **reacting with alkoxides** by the same sort of mechanism.



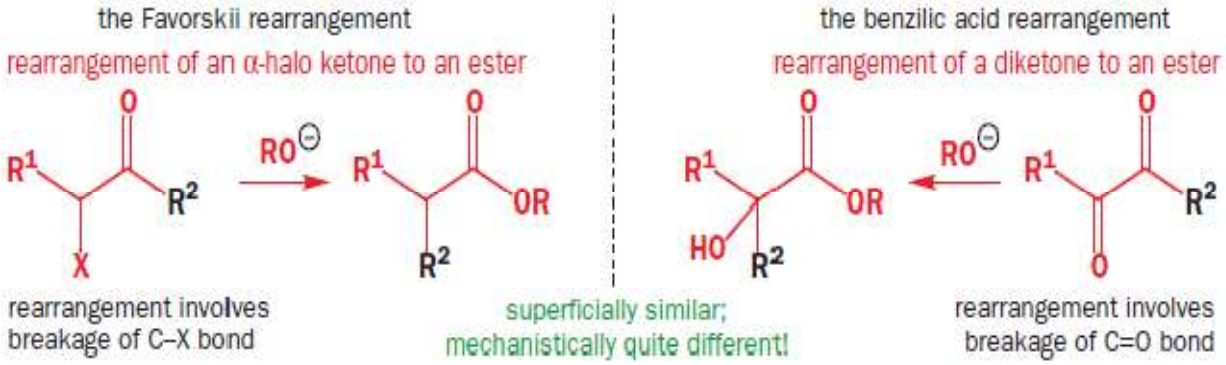
Note: The benzilic acid rearrangement **same** as a semipinacol rearrangement in which we have a **breaking C=O π bond** instead of a leaving group.

Compare the migration step with this semipinacol rearrangement.

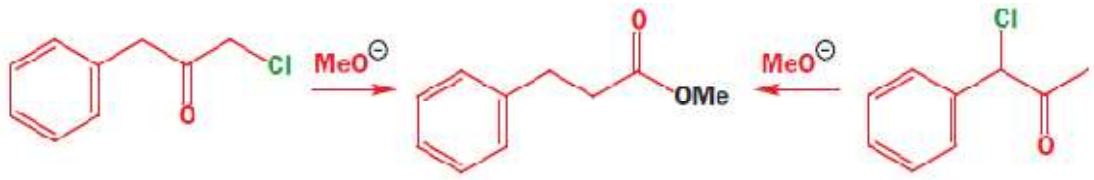


The Favorskii rearrangement:

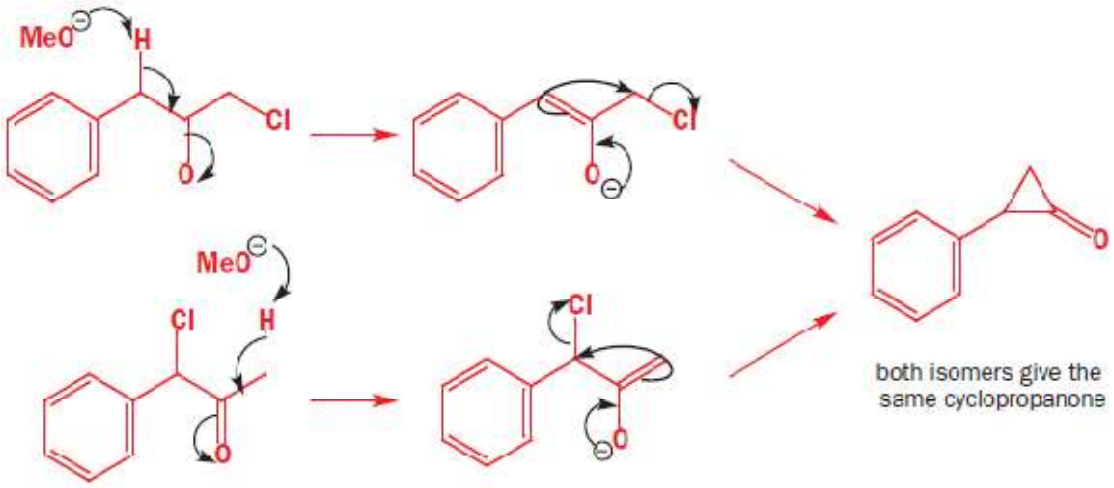
The **Favorskii rearrangement is rather like a variant** of the **benzilic acid rearrangement**.



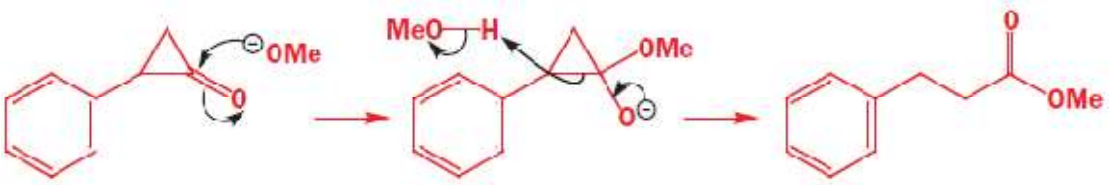
Example: Until 1944 when some Americans found that two isomeric **α-chloro ketones** gave exactly the **same product on treatment with methoxide**. They suggested that both reactions went through the same intermediate.



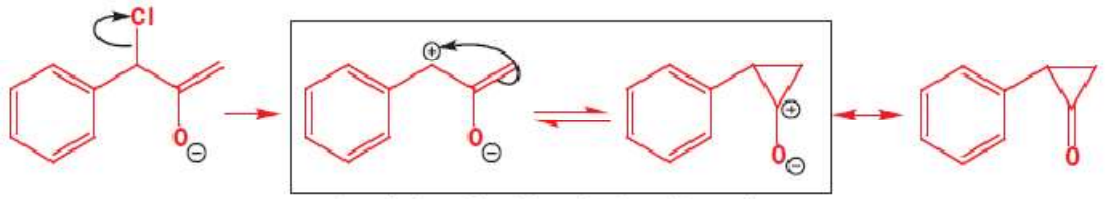
Mechanism: That **intermediate** is a **three-membered cyclic ketone**, a **cyclopropanone**: the **alkoxide acts not as a nucleophile (its role in the benzilic acid rearrangement) but as a base**, **enolizing the ketone**. The **enolate can alkylate itself intramolecularly in a reaction** that looks bizarre. The **product** is the **same cyclopropanone** in each case.



Cyclopropanones are **very reactive** towards **nucleophiles**, and the **tetrahedral intermediate** arising from the **attack of methoxide springs open** to give the **ester product**. The **more stable carbanion leaves**: though the **carbanion is not actually formed as a free species**, there must be a **considerable negative charge** at the **carbon atom as the three-membered ring opens**. Here the **benzyl group** is the **better-leaving group**.

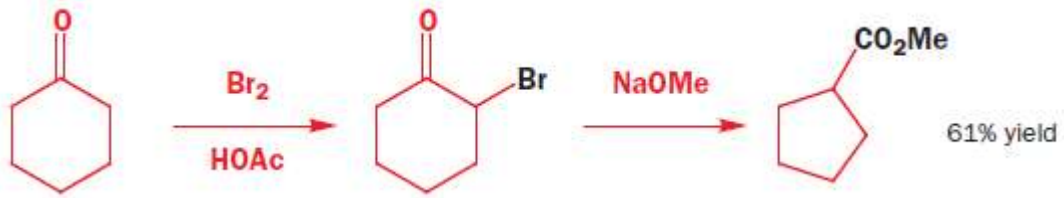


-The other description of the **pericyclic of the ring-closure step**. The **same enolate simply loses chloride to give an 'oxyallyl cation' a dipolar species with an oxyanion and a delocalized allylic cation**. This species can **cyclize in a two-electron disrotatory electrocyclic reaction** to **give the same cyclopropanone**. Whatever the mechanism, the intermediate is cyclopropanone.

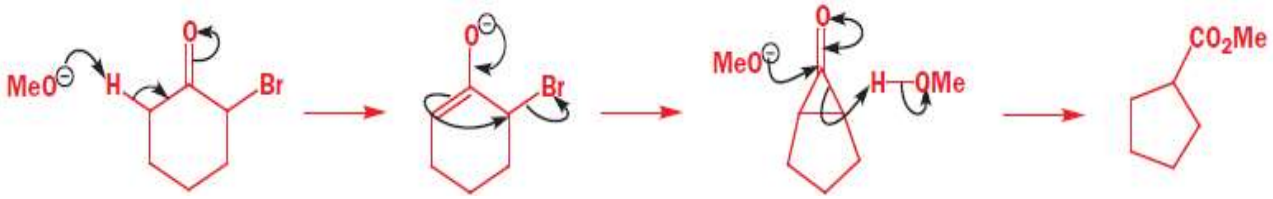


Note: Cyclopropanones and **cyclobutanones** are **very reactive**, rather **like epoxides**, because, **while the 60° or 90° angle in the ring is nowhere near the tetrahedral angle (108°), it is nearer 108° than the 120° preferred by the sp^2 C of the C=O group**. Conversely, the **small ring ketones are resistant to enolization, because that would place two sp^2 carbon atoms in the ring**.

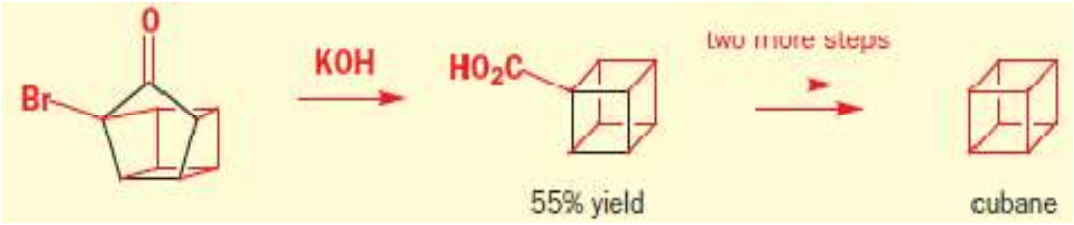
Example: **Favorskii rearrangement** of **cyclic 2-bromoketones** leads to **ring contraction** and this has **become one of the most fruitful uses of the rearrangement in synthesis**. **Bromination of cyclohexanone** is a simple reaction and **treatment with methoxide** give the **methyl ester** of **cyclopentane carboxylic acid** in **good yield**.



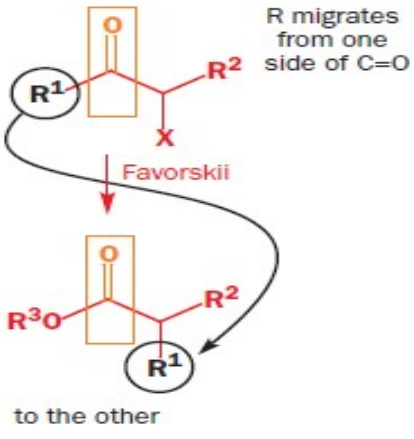
Mechanism: **Enolization** occurs on the **side of the ketone away from the bromine atom** and the **enolate cyclizes** as before but the **cyclopropanone intermediate** is **symmetrical** so that the product is the same whichever **C–C bond breaks after nucleophilic attack by the methoxide ion**.



Note: In 1964, two American chemists synthesized for the first time a remarkable molecule, **cubane**. Two of the key steps were Favorskii rearrangements, which allowed the chemists to contract **five-membered** rings to **four-membered** rings. Here is one of them. Two more steps decarboxylate the product to give **cubane** itself.

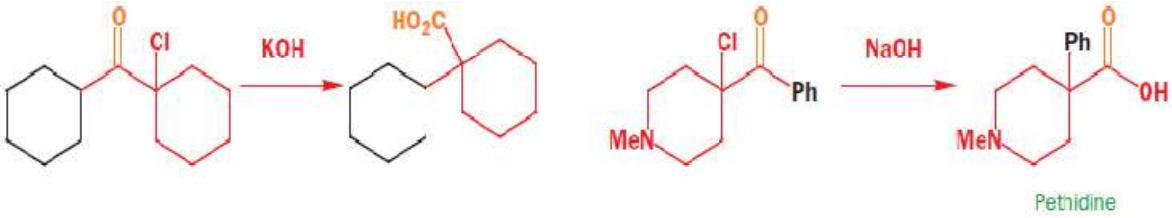


The overall consequence of the **Favorskii rearrangement** is that an **alkyl group is transferred from one side of a carbonyl group to the other**.

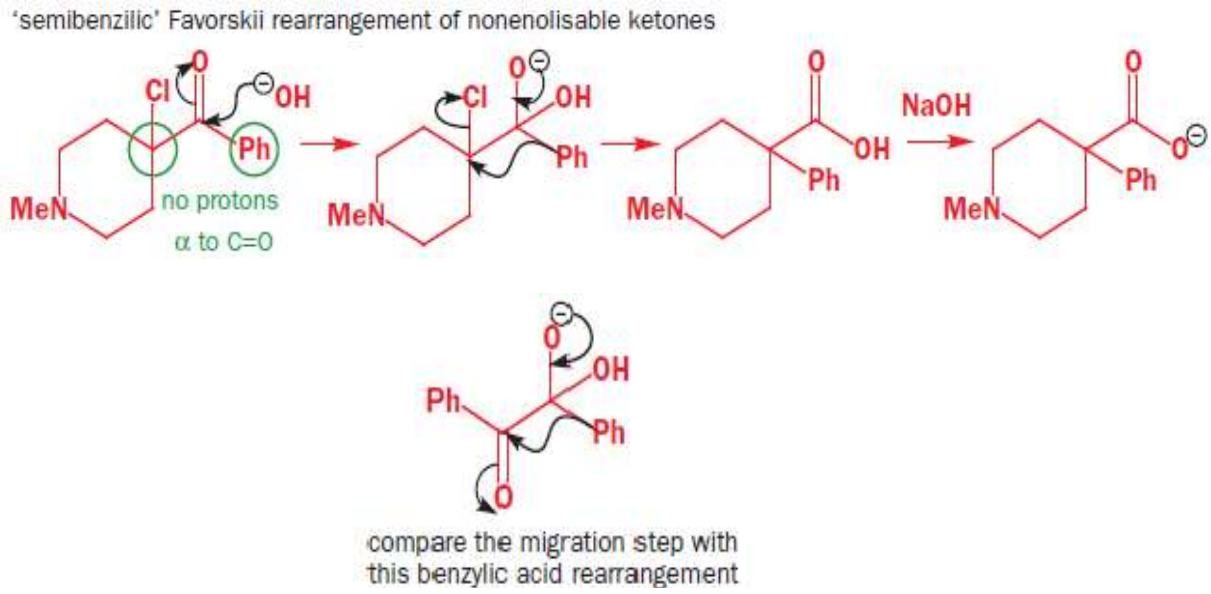


This means that it can be **used to build up heavily branched esters and carboxylic acids the sort that is hard to make by alkylation because of the problems of hindered enolates and unreactive secondary alkyl halides**. Heavily **substituted acids**, where **CO_2H is attached to a tertiary carbon atom, would be hard to make by any other method**. And the **Favorskii rearrangement** is a key step in this **synthesis** of the powerful painkiller **Pethidine**.

Example:



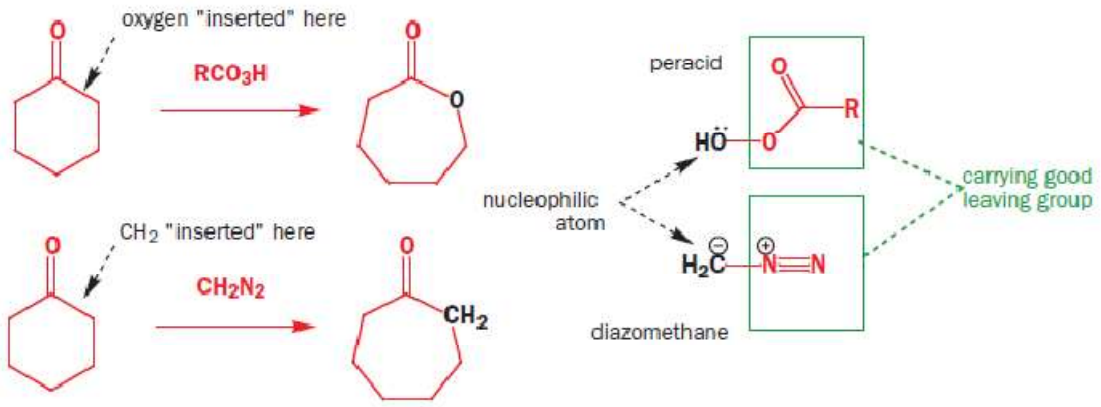
Mechanism: The **Favorskii rearrangement** whene **no acidic hydrogens available**, follows a **benzilic** (or 'semibenzilic', by analogy with the semipinacol) rearrangement mechanism.



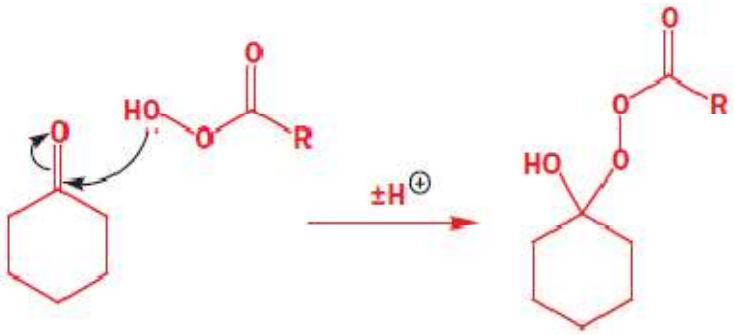
The Baeyer–Villiger reaction (Migration to oxygen):

In 1899, the Germans, A. Baeyer and V. Villiger found that **treating a ketone with a peroxy-acid (RCO_3H) can produce an ester**. An **oxygen** atom is '**inserted**' next to the **carbonyl group**.

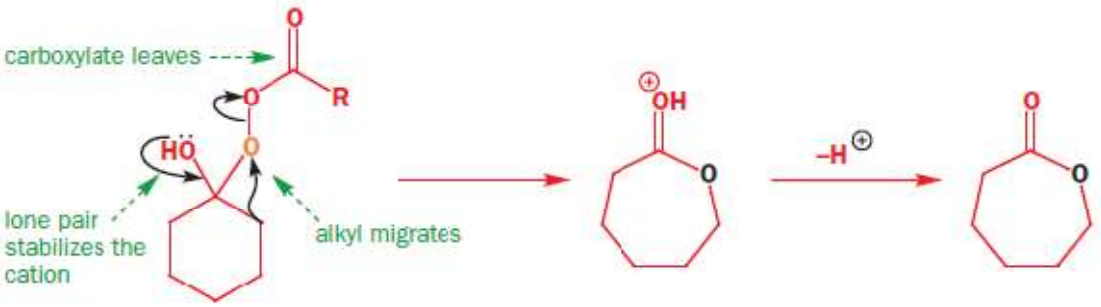
Examples:



Mechanism: Both **peracids and diazomethane contain a nucleophilic center that carries a good leaving group**, **and the addition of peracid to the carbonyl group gives a structure that should remind you of a semipinacol intermediate** with one of the **carbon** atoms replaced by **oxygen**.



Carboxylates are **not** such **good leaving** groups **as nitrogen**, but the **oxygen–oxygen single bond** is **very weak**, and **monovalent oxygen cannot bear to carry a positive charge** so that, **once the peracid has added, loss of carboxylate is concerted with a rearrangement driven**, as in the case of the pinacol and semipinacol, by **the formation** of a **carbonyl** group.



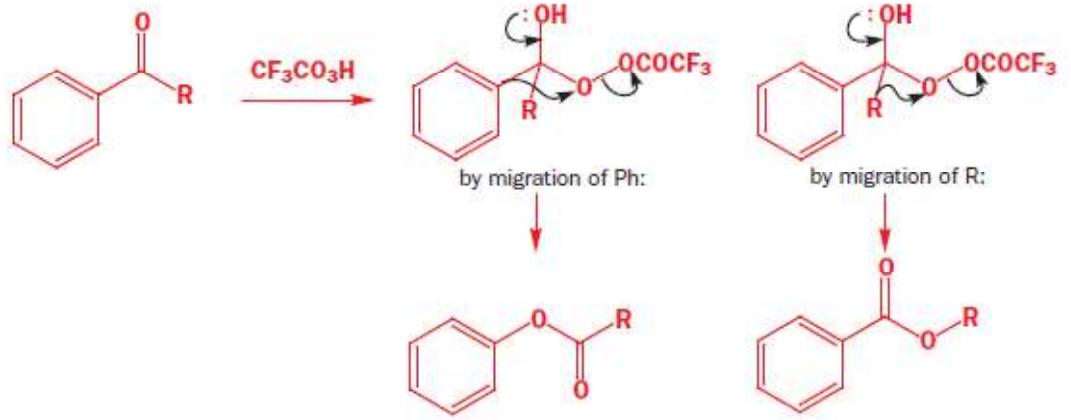
-Baeyer–Villiger reactions are among the **most useful** of all rearrangement reactions, and the **most common reagent is *m*-CPBA (*meta*-chloroperbenzoic acid) because it is commercially available**.

What type of group migrates:

When there is competition between **two migrating groups**, which group migrates?

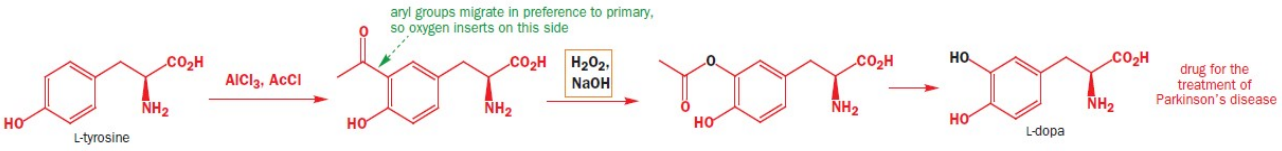
In pinacol, semipinacol, and dienone–phenol rearrangements and in Baeyer–Villiger reactions (in the benzilic acid and Favorskii rearrangements, there is no choice).

In the **Baeyer–Villiger** reaction **except the ketone is oxidized is symmetrical**.



R =	Yield for R (%)	Yield for R (%)
Me	90	0
Et	87	6
i-Pr	33	63
t-Bu	2	77

The order, **t-alkyl** is the **best** at migrating, then **s-alkyl** closely followed by **Ph**, and then **Et**, then **Me**, very roughly **follows the order in which the groups are able to stabilize a positive charge. Primary groups are much more reluctant to undergo migration than secondary ones or aryl groups**, and this makes **regioselective Baeyer–Villiger reactions possible**.



L-tyrosine, a **relatively cheap amino acid**, can be **converted to the important drug L-dopa** provided it can be **hydroxylated ortho to the OH** group. This is where **electrophilic substitutions of the phenol take place**, but **electrophilic substitutions with 'HO$^+$' are not possible**. However, **after a Friedel–Crafts acylation**, the **acyl group can be converted to hydroxyl by the Baeyer–Villiger reaction and hydrolysis**. The Baeyer–Villiger reaction means that **MeCO$^+$ can be used as a synthetic equivalent for 'HO$^+$'**. Note the **unusual use of the less reactive H_2O_2 as an oxidizing** agent in this reaction. This is **possible only when the migrating group is an electron-rich aromatic ring**; these **reactions** are sometimes **called Dakin reactions**.

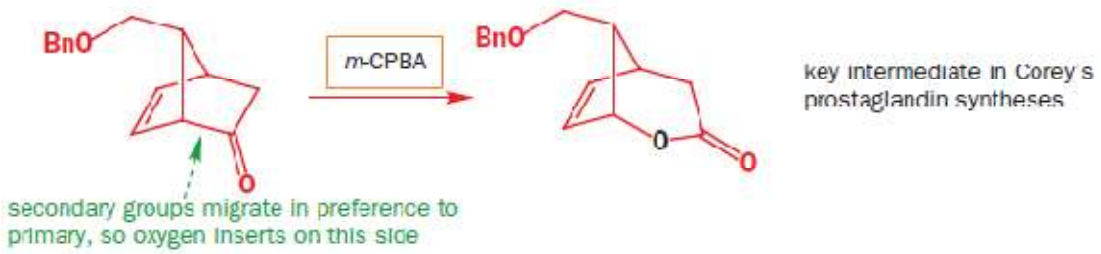
Unsaturated ketones may epoxidize or undergo Baeyer–Villiger rearrangement:

Peracids may epoxidize alkenes faster than they **take part in Baeyer–Villiger reactions**, so **unsaturated ketones are not often good substrates for Baeyer–Villiger reactions**. **The balance is rather delicate**.

The two factors that matter are: how electrophilic is the ketone and how nucleophilic is the alkene?

Why the **C=C double bond here is particularly unreactive**.

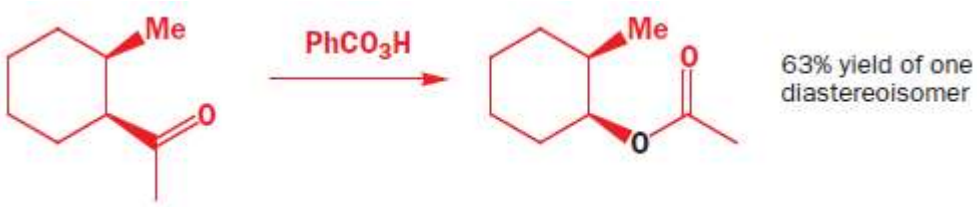
Example:



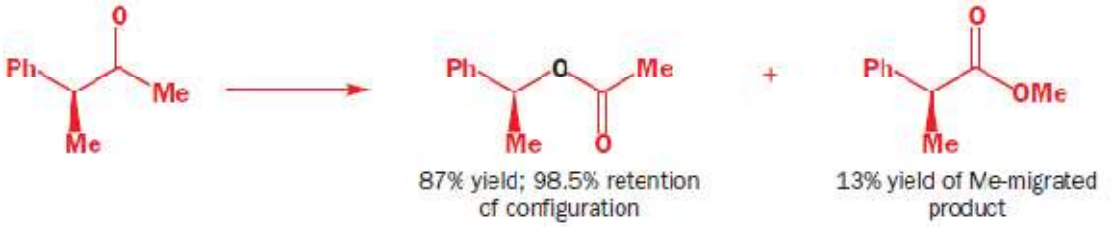
Small-ring ketones can relieve ring strain by undergoing Baeyer–Villiger reactions this **cyclobutanone** (an intermediate in a synthesis of the perfumery compound cis-jasmone) is made by a **ketene [2+2] cycloaddition**, and is so reactive that it needs only **H_2O_2 to rearrange**. **Unlike CF_3CO_3H or m-CPBA**, **H_2O_2** will not **epoxidize double bonds (unless they are electron-deficient)**.

One point to note about both of the last two reactions is that the **insertion of oxygen goes with the retention of stereochemistry**. The **first** of the two cannot possibly go with **inversion**. However, this is a general feature of **Baeyer–Villiger reactions**, **even when inversion would give a more stable product**.

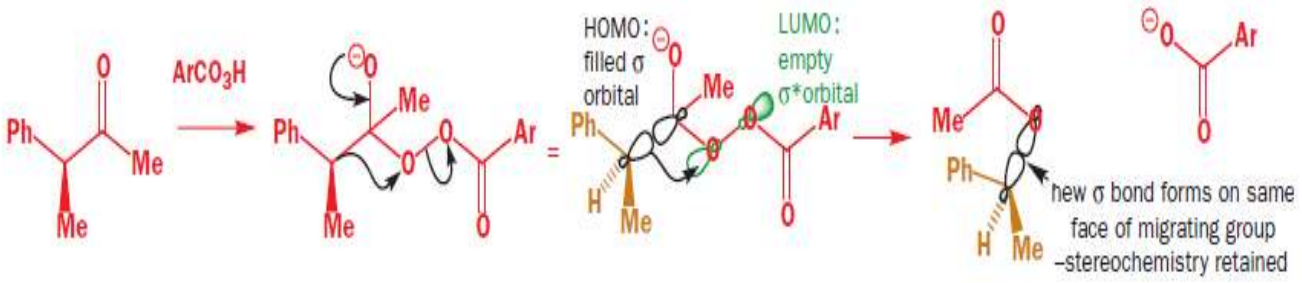
Example:



Example: Even when that **racemization** would occur, as in this **benzylic ketone, retention is the rule.**



By looking at the orbitals involved. **The sp^3 orbital of the migrating carbon just slips from one orbital to the next with the minimum amount of structural reorganization. The large lobe of the sp^3 orbital is used so the new bond forms to the same face of the migrating group as the old one, and stereochemistry is retained**.



Note: The **orbital interactions in all 1,2-migrations are similar**, and the **migrating group retains its stereochemistry** in these too. In the more familiar **S_N2** reaction, an **inversion occurs because the anti bonding σ* orbital rather than the bonding σ orbital is used**. In the **S_N2** reaction, **carbon undergoes nucleophilic attack with inversion**; in **rearrangements the migrating carbon atom undergoes electrophilic attack with retention of configuration**.

In 1,2-migrations, the migrating group retains its stereochemistry