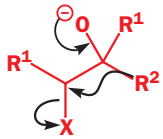
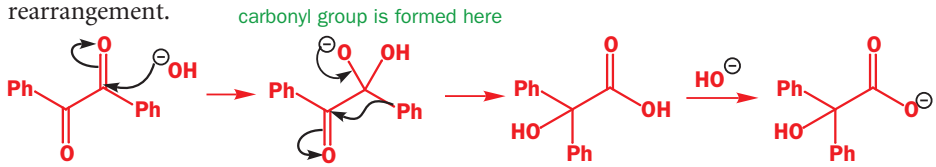
▶ You may find it helpful to think of the benzilic acid rearrangement as a semipinacol rearrangement in which we have a breaking C=O π bond instead of a leaving group.



compare the migration step with this semipinacol rearrangement

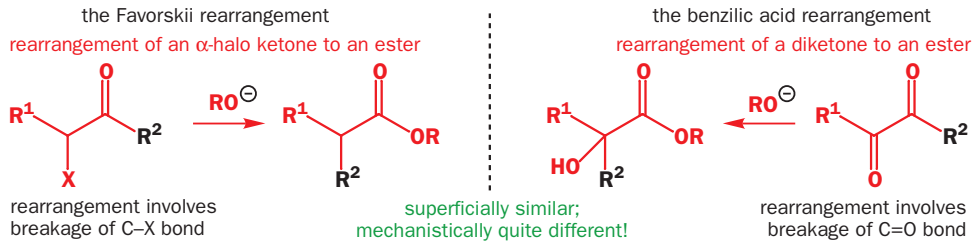
The mechanism of this **benzilic acid rearrangement** starts with attack of hydroxide on one of the carbonyl groups. The tetrahedral intermediate can collapse in a reaction reminiscent of a semipinacol rearrangement.



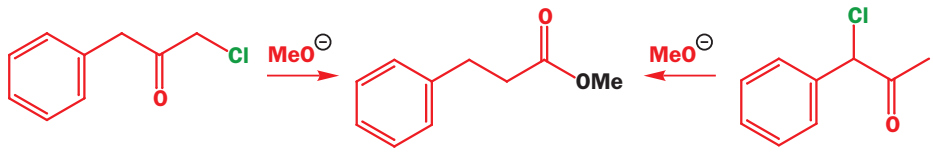
With alkoxides, the benzilic acid rearrangement can lead directly to esters by the same sort of mechanism.

The Favorskii rearrangement

We hope you have appreciated the smooth mechanistic progression so far in this chapter, from Wagner–Meerwein to pinacol and semipinacol through dienone–phenol to benzilic acid. Our aim is to help you gain an overall view of the types of rearrangements that take place (and why) and not to present you with lots of disconnected facts. It is at this point, however, that our mechanistic journey takes a hairpin bend. A surprising one, too, because, when we show you the Favorskii rearrangement, you would be forgiven for wondering what the fuss is about: surely it's rather like a variant of the benzilic acid rearrangement?

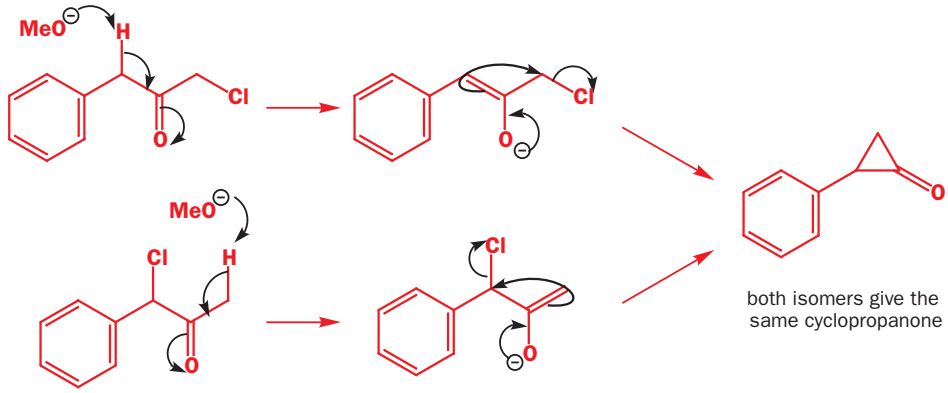


Well, this is what chemists thought until 1944, when some Americans found that two isomeric α-chloro ketones gave exactly the same product on treatment with methoxide. They suggested that both reactions went through the same intermediate.

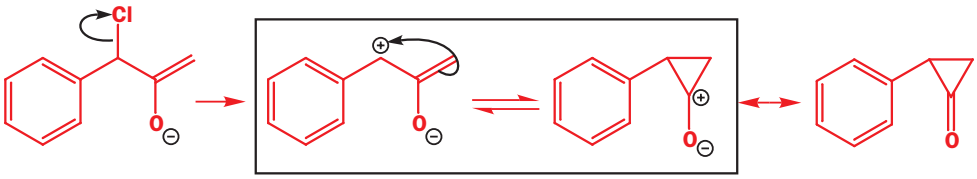


■ A full discussion of this point requires Baldwin's rules, which appear in Chapter 41.

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 but that many chemists think is not unreasonable. The product is the same cyclopropanone in each case.

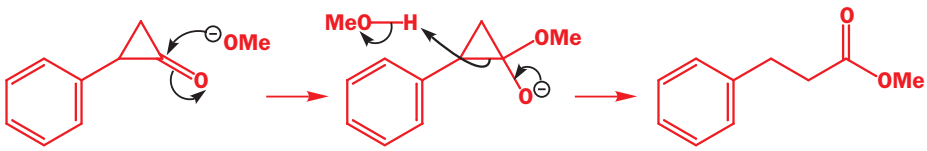


Other chemists prefer a pericyclic description of the ring-closure step. The same enolate simply loses chloride to give an 'oxyallyl cation'—a dipolar species with an oxyanion and a delocalized allylic cation. This species can cyclize in a two-electron disrotatory electrocyclic reaction (Chapter 36) to give the same cyclopropanone. We shall return to this discussion in the next chapter but, whatever the mechanism, there is no doubt that a cyclopropanone is an intermediate.

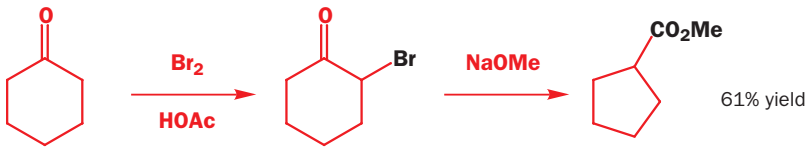


two-electron disrotatory electrocyclic reaction

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 considerable negative charge at the carbon atom as the three-membered ring opens. Here the benzyl group is the better leaving group.



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 (Chapter 21) and treatment with methoxide gives the methyl ester of cyclopentane carboxylic acid in good yield.

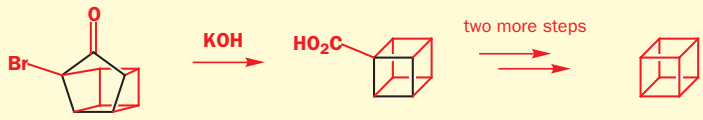


61% yield

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.

Heading

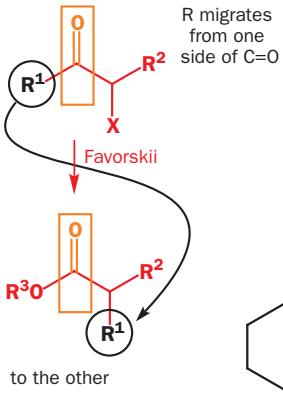
In 1964, two American chemists synthesized for the first time a remarkable molecule, cubane. Two of the key steps were Favorskii rearrangements, which allowed the chemists to contract five-membered rings to four-membered rings. Here is one of them. Two more steps decarboxylate the product to give cubane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



55% yield

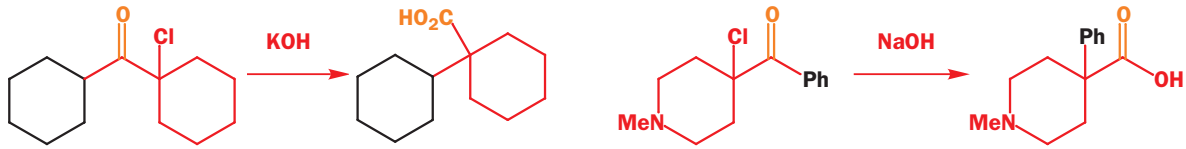
cubane

▶ 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.



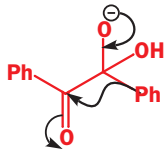
The overall consequence of the Favorskii rearrangement is that an alkyl group is transferred from one side of a carbonyl group to the other.

This means that it can be used to build up heavily branched esters and carboxylic acids—the sort that are 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.



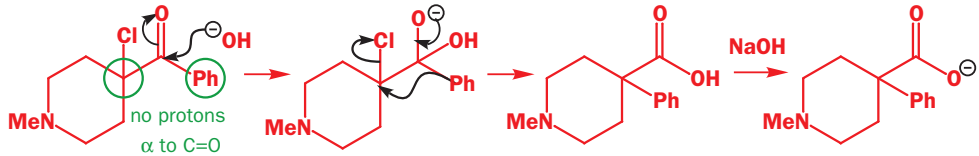
▶ The Favorskii mechanism will help you understand the Ramberg–Bäcklund reaction in Chapter 46—the two reactions have quite similar mechanisms.

Try writing a mechanism for this last reaction and you run into a problem—there are no acidic protons so the ketone cannot be enolized! Yet the Favorskii rearrangement still works. Despite our warnings against confusing the mechanisms of the Favorskii and benzilic acid rearrangements, the Favorskii rearrangement may, in fact, follow a benzilic (or 'semibenzilic', by analogy with the semipinacol) rearrangement mechanism, *if* there are no acidic hydrogens available.



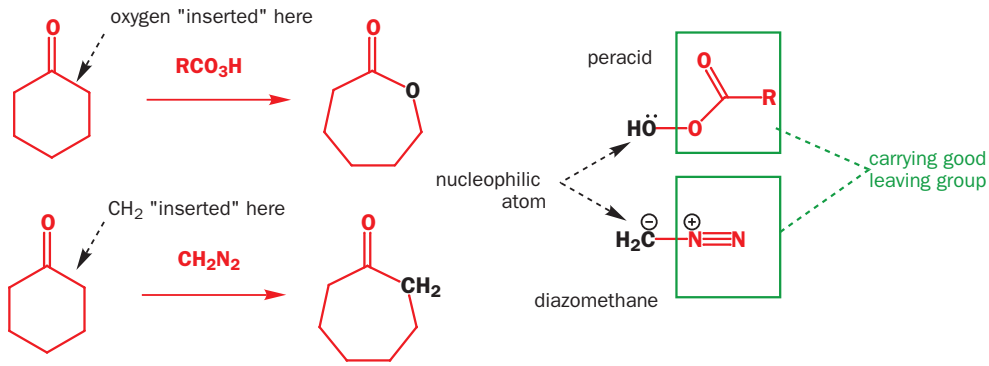
compare the migration step with this benzylic acid rearrangement

'semibenzilic' Favorskii rearrangement of nonenolisable ketones

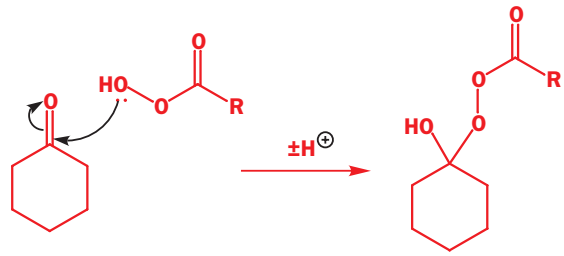


Migration to oxygen: the Baeyer–Villiger reaction

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.



Now, you saw a similar 'insertion' reaction earlier in the chapter, and the mechanism here is not dissimilar. Both peracids and diazomethane contain a nucleophilic centre that carries a good leaving group, and 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