

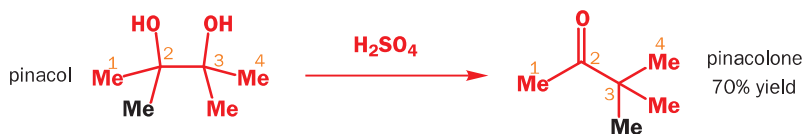
The Friedel–Crafts alkylation illustrates the problems of trying to use carbocation rearrangements to make single products in high yield. We can give three guidelines to spotting this type of reaction.

- 1 The rearrangement must be fast so that other reactions do not compete
- 2 The product cation must be sufficiently more stable than the starting one so that the rearrangement happens in high yield
- 3 Subsequent trapping of the product cation must be reliable: cations are high-energy intermediates, and are therefore unselective about how they react

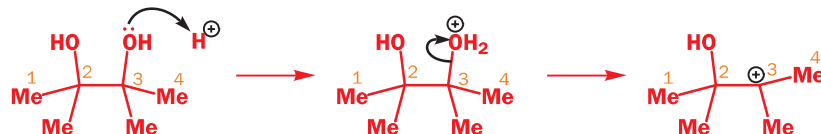
A reaction is no good if the cation reacts in more than one way—it may react with a nucleophile, eliminate, or undergo further rearrangement—but it must do only one of these! For the rest of the chapter, we will address only reactions that, unlike this Friedel–Crafts reaction, follow these guidelines. The reactions we will talk about all happen in good yield.

The pinacol rearrangement

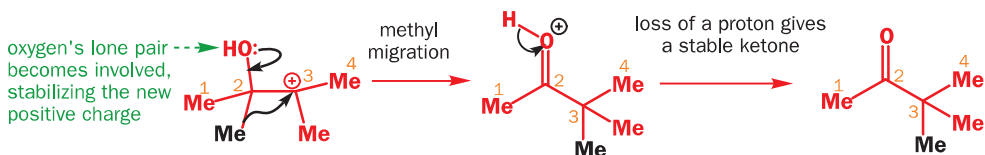
When the 1,2-diol ‘pinacol’ is treated with acid, a rearrangement takes place.



Whenever you see a rearrangement, you should now think ‘carbocation’. Here, protonation of one of the hydroxyl groups allows it to leave as water, giving the carbocation.



You now know that carbocations rearrange by alkyl shifts to get as stable as they can be—but this carbocation is already tertiary, and there is no ring strain, so why should it rearrange? Well, here we have another source of electrons to stabilize the carbocation: lone pairs on an oxygen atom. We pointed out early in the chapter that oxygen is very good at stabilizing a positive charge on an adjacent atom, and somewhat less good at stabilizing a positive charge two atoms away. By rearranging, the first-formed carbocation gets the positive charge into a position where the oxygen can stabilize it, and loss of a proton from oxygen then gives a stable ketone.



You can view the pinacol as a rearrangement with a ‘push’ and a ‘pull’. The carbocation left by the departure of water ‘pulls’ the migrating group across at the same time as the oxygen’s lone pair ‘pushes’ it. A particularly valuable type of pinacol rearrangement forms spirocyclic ring systems. You may find this one harder to follow, though the mechanism is identical with that of the last example. Our ‘top tip’ of numbering the atoms should help you to see what has happened: atom 2 has migrated from atom 1 to atom 6.



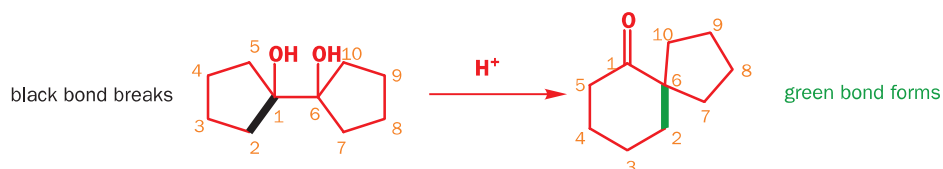
Pinacol, the trivial name for the starting material, which is made from acetone by a reaction you will meet in Chapter 39, gives its name to this class of rearrangements, and to the product, ‘pinacolone’.



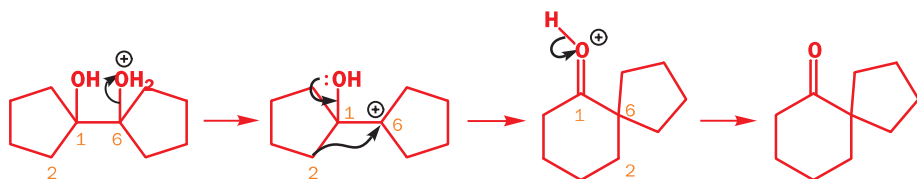
Unlike sulfur, which stabilizes a charge 2 atoms away better than it stabilizes a charge on an adjacent atom.



Spirocycles are pairs of rings joined at a single carbon atom (Chapter 33).



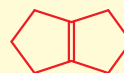
When drawing the mechanism it doesn't matter which hydroxyl group you protonate or which adjacent C–C bond migrates—they are all the same. One five-membered ring expands to a six-membered ring but the reason this reaction happens is the formation of a carbonyl group, as in all pinacol rearrangements.



Of course, it doesn't matter how you number the atoms, but the numbering must be consistent. Usually, your initial impression of a greatly changed molecule will come down to just one or two atoms changing their substitution pattern, and numbering will help you to work out which ones they are.

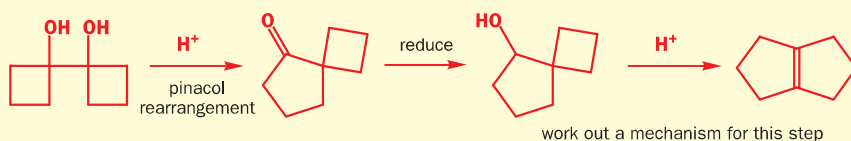
The pinacol reaction in synthesis

A nice synthesis of the bicyclic alkene on the right starts with a pinacol reaction.



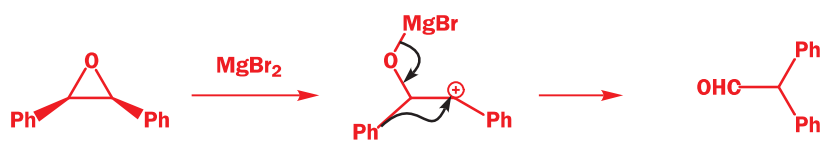
The first step is straightforward—just like the one you have just met. The 'pinacol' dimer from cyclobutanone rearranges with the expansion of one of the rings to give a cyclopentanone fused *spiro* to the remaining four-membered ring. Reduction of the ketone then gives an

alcohol that rearranges to the alkene in acid. Try working out a mechanism for this transformation—start by protonating of the alcohol and allowing water to leave to give a cation. You might also like to think about why the rearrangement happens—for a clue go back to p. 000.

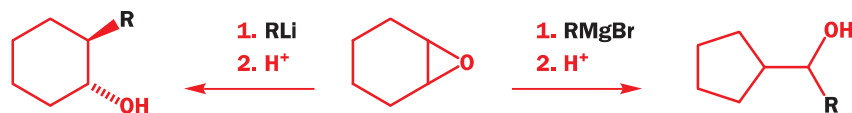


Epoxides rearrange with Lewis acids in a pinacol fashion

The intermediate cation in a pinacol rearrangement can equally well be formed from an epoxide, and treating epoxides with acid, including Lewis acids such as MgBr_2 , promotes the same type of reaction.



Rearrangement of epoxides with magnesium salts means that opening epoxides with Grignard reagents can give surprising results.



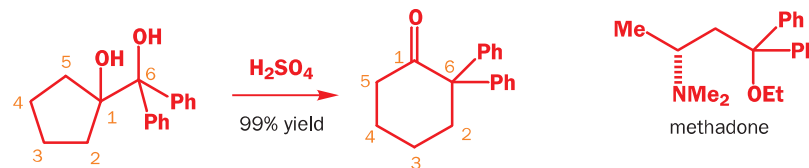
The alkyllithium reaction is quite straightforward as long as the alkyllithium is free of lithium salts. A clue to what has happened with the Grignard reagents comes from the fact that treating this epoxide with just MgBr_2 (no RMgBr) gives an aldehyde.



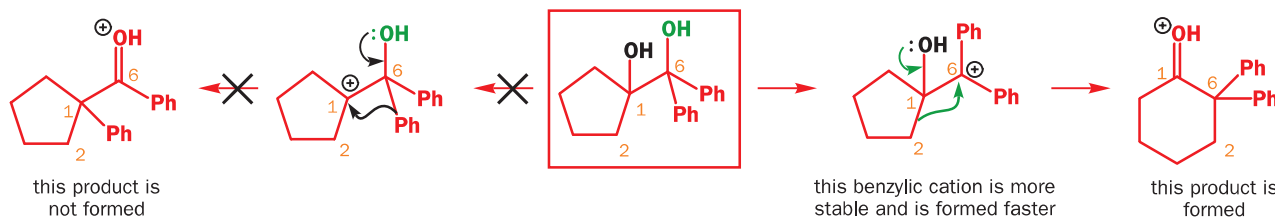
With a Grignard reagent, rearrangement occurs faster than addition to the epoxide, and then the Grignard reagent adds to the aldehyde.

Some pinacol rearrangements have a choice of migrating group

With these symmetrical diols and epoxides, it does not matter which hydroxyl group is protonated and leaves, nor which end the epoxide opens, nor which group migrates. When an unsymmetrical diol or epoxide rearranges, it is important which way the reaction goes. Usually, the reaction leaves behind the more stable cation. So, for example, this unsymmetrical diol gives the ring-expanded ketone, a starting material for the synthesis of analogues of the drug methadone.



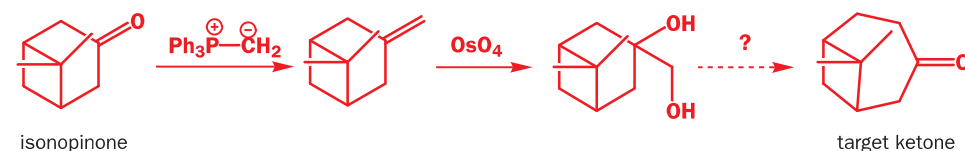
This product is formed because the green OH group leaves more readily than the black because the carbocation stabilized by two phenyl groups forms more readily than the carbocation stabilized by two alkyl groups. The migration step follows without selectivity as both alkyl groups on the black alcohol are the same.



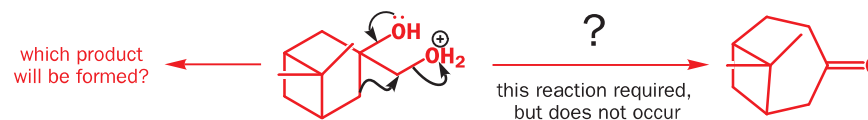
Most unsymmetrical diols or epoxides give mixtures of products upon rearrangement. The problem is that there is a choice of two leaving groups and two alternative rearrangement directions, and only for certain substitution patterns is the choice clear-cut.

Semipinacol rearrangements are pinacol reactions with no choice about which way to go

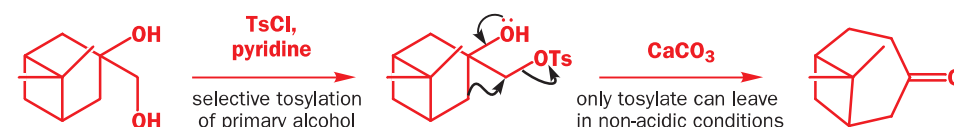
In 1971, French chemists needed this seven-membered cyclic ketone. A reasonable starting material to use is this diol, because it can be made in two steps from the natural product isonopinone.



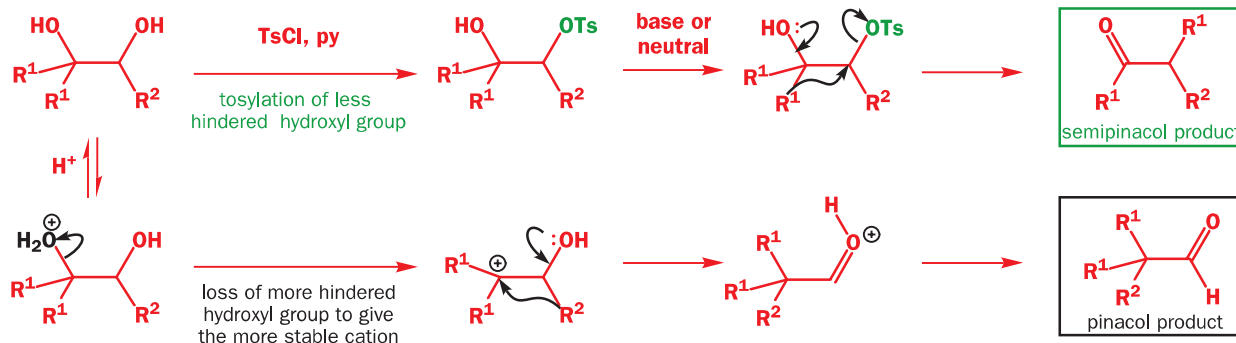
The reaction they needed for the last stage is a pinacol rearrangement—the *primary* hydroxyl group needs persuading to leave as the ring expands. The problem is, of course, that the tertiary hydroxyl group is much more likely to leave since it leaves behind a more stable carbocation.



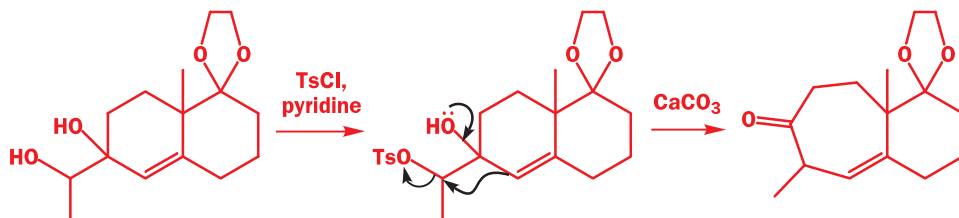
The solution to this problem is to force the primary hydroxyl group to be the leaving group by making it into a tosylate. The primary hydroxyl group reacts more rapidly with TsCl than the tertiary one because it is less hindered. A weak base is now all that is needed to make the compound rearrange in what is known as a **semipinacol rearrangement**.



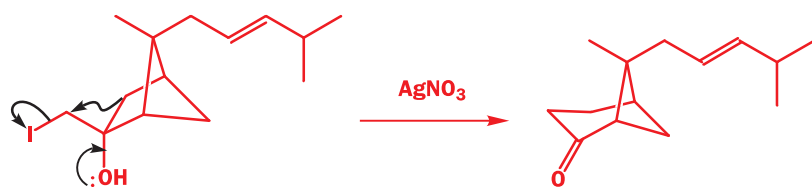
Semipinacol rearrangements are rearrangements in which a hydroxyl group provides the electrons to ‘push’ the migrating group across, but the ‘pull’ comes from the departure of leaving groups other than water—tosylate in this example, but typically also halide or nitrogen (N_2). Since tosylation occurs at the *less* hindered hydroxyl group of a diol, not only can semipinacol rearrangements be more regioselective than pinacol rearrangements, but their regioselectivity may be in the opposite direction.



Corey exploited this in a synthesis of the natural product longifolene. He needed to persuade an easily made 6,6-fused ring system to undergo rearrangement to a ring-expanded ketone. Again, a normal acid-catalysed pinacol rearrangement is no good—the tertiary, allylic hydroxyl group is much more likely to ionize, and the acid-sensitive protecting group would be hydrolysed too. Tosylation of the secondary alcohol in the presence of the tertiary is possible, and semipinacol rearrangement gives the required ketone.



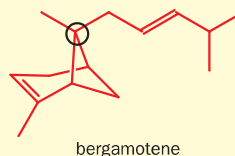
The leaving group need not be tosylate: in the following example, part of a synthesis of bergamotene (a component of valerian root oil and the aroma of Earl Grey tea), a 2-iodo alcohol rearranges.



▶ Treating 2-halo alcohols with base is, of course, a good way to make epoxides. Using $AgNO_3$ to improve iodide's leaving ability without increasing the nucleophilicity of the hydroxyl group favours rearrangement at the expense of epoxide formation. There would certainly be a danger of epoxide formation in strong base.

The structure of bergamotene

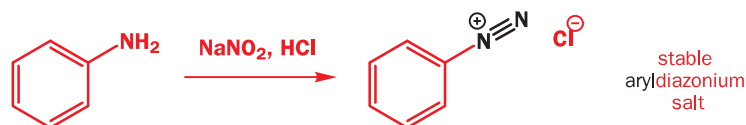
The structure of bergamotene was, for some years during the 1960s, a matter of debate. The difficult question was the configuration of the chiral centre ringed in black. With modern spectroscopic techniques, we can now solve this type of problem simply, but the only solution then was to synthesise the two isomers and compare them with the natural material. There is more about bergamotene in Chapter 46.



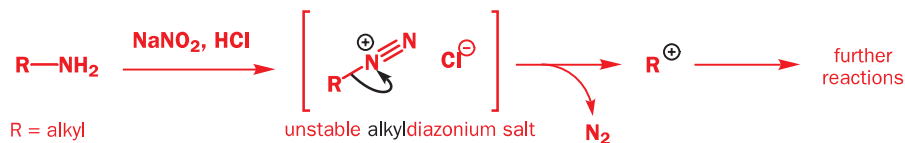
Semipinacol rearrangements of diazonium salts

You saw in Chapter 22 how aromatic amines can be converted to diazonium salts by treatment with acidic sodium nitrite.

It might be an idea to review pp. 000–00 of Chapter 22 to be sure you understand the mechanism of this reaction.

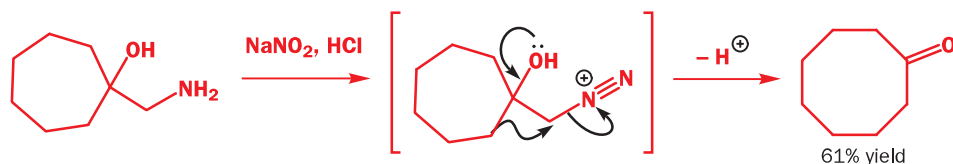


Aryldiazonium salts are stable but *alkyldiazonium* salts are not: nitrogen gas is the world's best leaving group, and, when it goes, it leaves behind a carbocation.

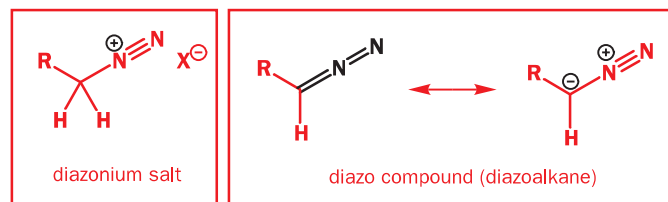


Semipinacol rearrangements of diazonium salts derived from 2-amino alcohols are sometimes called **Tiffeneau–Demjanov rearrangements**.

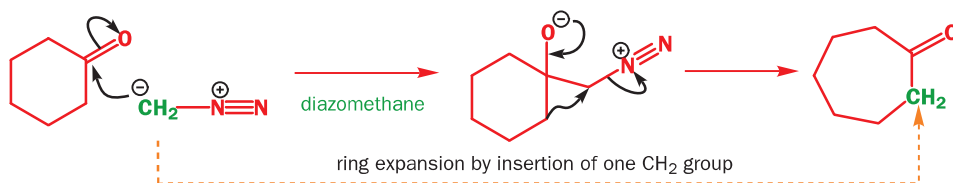
One of the 'further reactions' this carbocation can undergo is rearrangement. If the starting amine is a 2-amino alcohol, the cation can be stabilized by a semipinacol rearrangement.



While alkyldiazonium salts are unstable, their conjugate bases, diazoalkanes, are stable enough to be prepared and are nucleophilic towards carbonyl compounds. **Diazoalkanes** are neutral compounds having one fewer proton than diazonium salts and are delocalized structures with a central sp nitrogen atom.



When diazomethane (a compound we will investigate in more detail in Chapter 40) adds to a ketone, the product undergoes a ring expansion by rearrangement of the same type of intermediate.



The problem with reactions like this is that both the starting material and product are ketones, so they work cleanly only if the starting material is more reactive than the product. Cyclohexanone is more reactive as an electrophile than either cyclopentanone or cycloheptanone, so it ring expands cleanly to cycloheptanone. But expansion of cyclopentanone to cyclohexanone is messy and gives a mixture of products. We shall come back to diazo compounds in more detail in Chapter 40; diazonium salts will reappear in Chapter 38 where their decomposition will provide the driving force for fragmentation reactions.

The dienone–phenol rearrangement

The female sex hormone oestrone is the metabolic product of another hormone, progesterone, itself made in the body from cholesterol.