

6.34 Cationic Rearrangements

11/27:

- Lecture 33 recap.
 - Order of stability: benzyl > allyl > 3° > 2° > 1° > Me > vinyl > phenyl.
 - Primary, methyl, vinyl, and phenyl cations are very unstable and will not be discussed in 5.13.
 - Particularly stable carbocations: Benzyl, allyl, heteroatom-stabilized carbocations, and aromatic (e.g., see Figure 6.2b).
- Generation of carbocations.
 - 1) Addition of an electrophile to a multiple bond (Figure 6.4).
 - 2) Heterolytic cleavage of C–X bonds (Figure 6.5a).
- Reactions.
 - 1) E₁ elimination (Figure 6.6).
 - 2) Reactions with nucleophiles (e.g., lone pairs in S_N1, aromatic rings in Friedel-Crafts); reactions with olefins.
- Rearrangements and fragmentations.
 - Most common type: 1,2-shifts.
 - Driving force: Converting a secondary carbocation into a tertiary carbocation.
 - Nomenclature.
 - Hydride shift: When H is the migrating group (MG).
 - Alkyl shift: When R is the MG.
 - Concerted vs. stepwise mechanisms (Figure 6.11).
- Today: More on rearrangements with carbocation intermediates.
- Lecture outline.

C. Reactions.

- 3) Rearrangements and fragmentations.
 - Hydride shifts in hydrohalogenations.
 - Methyl shifts driven by the need for a concerted shift.
 - Alkyl shifts induced by angle strain.
 - Dienone-phenol rearrangement.
 - Epoxide-aldehyde rearrangement.
 - Pinacol-pinacolone rearrangement (symmetric and asymmetric).
 - Baeyer-Villiger oxidation.
- We now return to Subtopic C.3: Rearrangements and fragmentations.
- H-shifts vs. alkyl shifts.

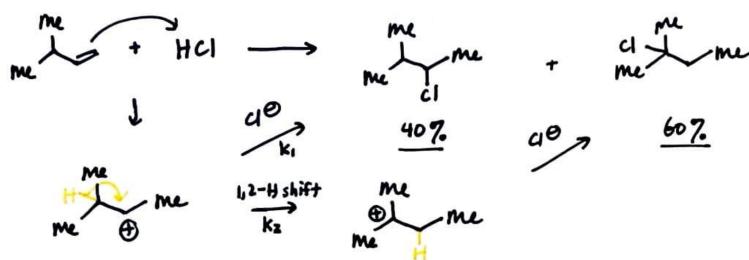


Figure 6.13: Hydride shifts in hydrohalogenations.

- Consider the reaction of 3-methylbut-1-ene with HCl.
 - We might expect the major product to be the 2-chlorinated alkene.
 - This would arise from formation of the more substituted, secondary carbocation.
 - However, this is only 40% of the product.
 - However, the major product (60%) is the 3-chlorinated species!
 - This product occurs because the carbocation undergoes a 1,2-hydride shift prior to trapping by chloride.
 - Indeed,
- $$\frac{k_1}{k_2} = \frac{40}{60} = 0.67$$
- if the k_2 step is irreversible.
- But why do we get a hydride shift instead of a methyl shift?
 - Because a methyl shift would not generate a more stable carbocation! It would still be secondary.
 - General rule: H-shifts are better than alkyl shifts because they form more substituted carbocations.
 - We now look at a case where we have to distinguish between two mechanistic possibilities that form carbocations.

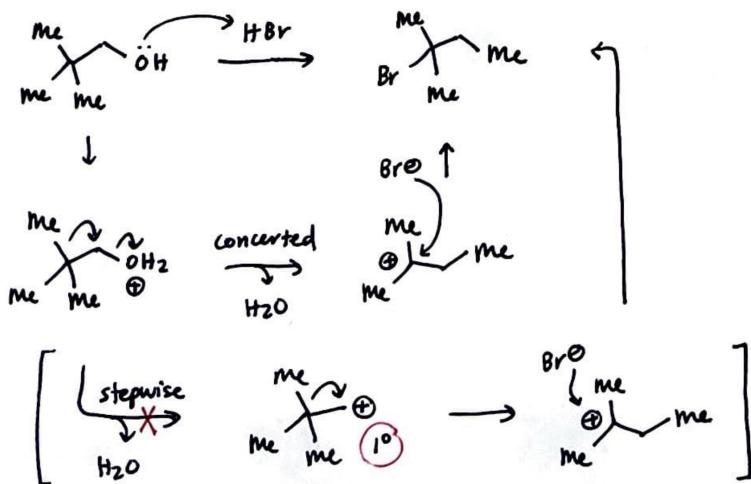


Figure 6.14: Concerted vs. stepwise mechanisms with methyl shifts.

- Consider the reaction of neopentyl alcohol with HBr. What is the most plausible mechanism?
- The alcohol will get protonated and *could* leave to yield a primary carbocation, which could then stepwise rearrange into a secondary cation that could be trapped.
 - But we've said that in this class, primary carbocations are not allowed!
- Thus, we can make use of a concerted pathway (Figure 6.11b).
 - This mechanism affords the secondary carbocation directly, which can then react.
- Thinking about the relative energies of competing transition states is useful here.

- Chemists love small rings; let's look at a strain-releasing reaction with them.

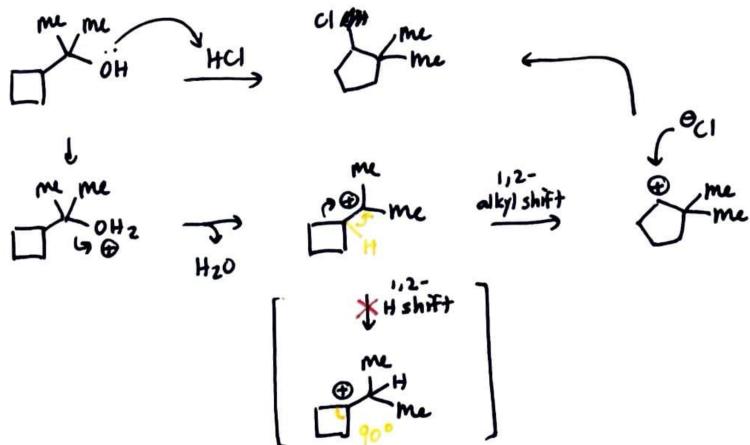


Figure 6.15: Angle strain can induce alkyl shifts.

- Consider the reaction of 2-cyclobutylpropan-2-ol with HCl.
- If we form the tertiary carbocation and then do an H-shift to put the cation in the 4-membered ring, we will induce immense strain.
 - sp^2 likes to be 120° , and we've got it confined to 60° !
- Instead, we can do an alkyl shift to release strain, even though it forms a secondary carbocation.
- Takeaway: In cases where all else is equal, prefer H-shifts. But there do exist cases in which all else is *not* equal!
- Let's now look at some rearrangements.
 - We're going to teach 7-10 rearrangements that involve carbocation intermediates.
 - You can probably find another 500 if you go looking; most will have somebody's name on them.
- Dienone-phenol rearrangement.

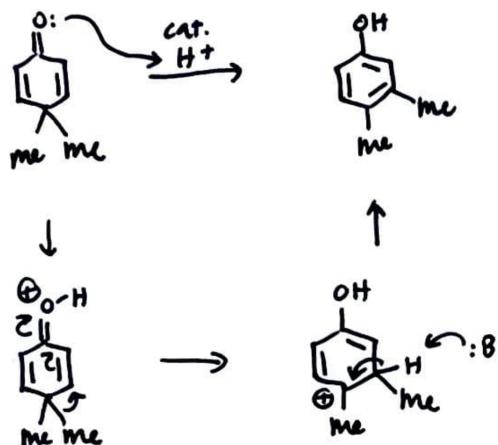


Figure 6.16: Dienone-phenol rearrangement.

- If we didn't have blocking methyl groups, we would tautomerize to the fully aromatic system.
- But in the presence of catalytic acid, we get 3,4-dimethylphenol!
- Protonating the carbonyl makes the β -positions *very, very* electron-deficient; consider the enol resonance structure!
 - Thus, a 1,2-migration can give us a stabilized tertiary, allylic carbocation.
- Then some group (doesn't have to be very basic) can come in to deprotonate and aromatize the system.
- TTQ: What happens to this species at top-left below in the presence of acid?

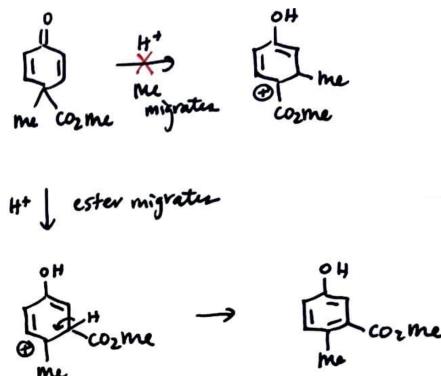


Figure 6.17: TTQ: Ester shifts.

- Two things can happen: Either the methyl group or the ester group can migrate.
- However, having the carbocation be next to a methyl group is far more favorable than having it next to a destabilizing EWG like an ester.
- Thus, the reaction proceeds via an ester shift to yield the drawn phenol!
- Converting epoxides to aldehydes.

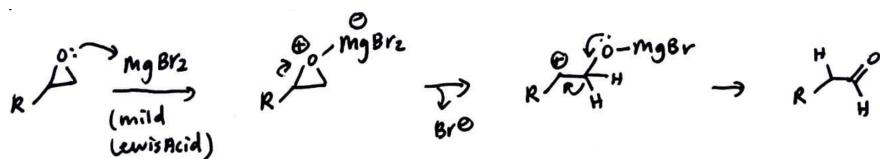


Figure 6.18: Epoxide-aldehyde rearrangement.

- MgBr_2 is a mild Lewis acid that will coordinate to the epoxide oxygen.
- The epoxide can then open, formally bonding to magnesium and kicking out one bromide.
- The O–Mg bond then collapses into the forming aldehyde π -system with a concurrent 1,2-H shift.
- Synthetic utility of the epoxide-aldehyde rearrangement.

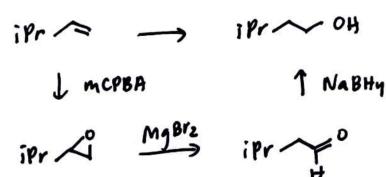
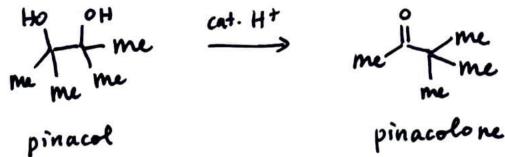
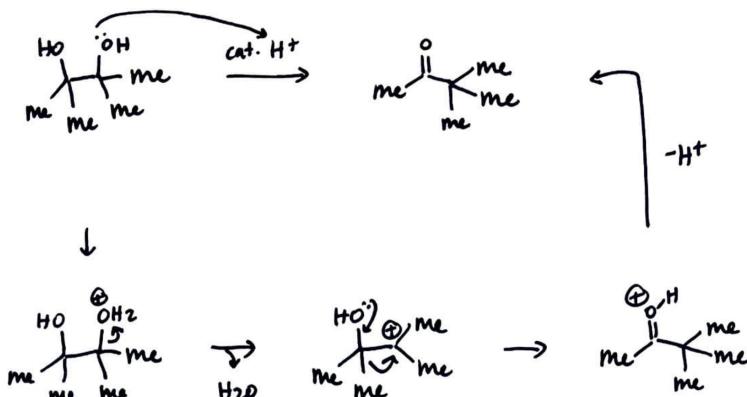


Figure 6.19: Epoxide-aldehyde rearrangement: Synthetic utility.

- We start with an alkene, turn it into an epoxide, open it as in Figure 6.18, and then reduce it.
- This is an alternative to hydroboration!
- Alternatives are important as they can be safer, cleaner, and more generally applicable to complicated systems.
 - Both Profs. Buchwald and Elkin research such reaction alternatives in their labs!
- Pinacol rearrangement of 1,2-diols.



(a) General form.



(b) Mechanism.

Figure 6.20: Pinacol-pinacolone rearrangement.

- Mechanistically, we begin by protonating a hydroxyl group to form a good leaving group.
- Then we get a rearrangement, thermodynamically driven by the formation of a carbonyl.
- Final deprotonation yields the pinacolone product.
- Asymmetric pinacol rearrangements.

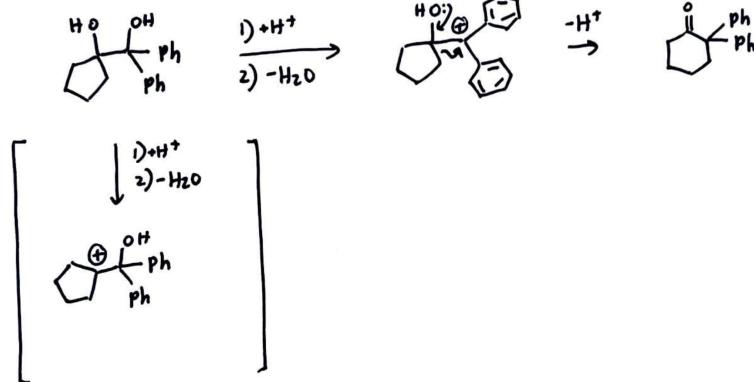
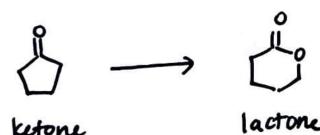
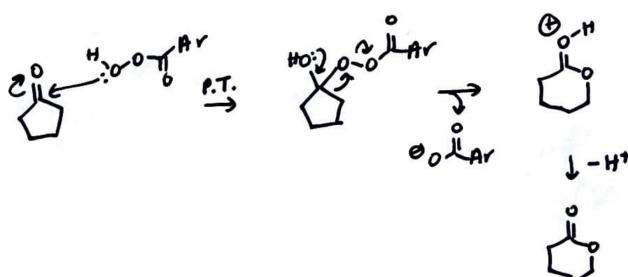


Figure 6.21: Asymmetric pinacol-pinacolone rearrangement.

- Both possible carbocations we could form from this substrate are quite good!
 - However, while the tertiary carbocation is good, the tertiary diphenyl carbocation is *awesome*; it should be in the carbocation hall of fame!
- Thus, we get another alkyl shift, yielding a product with a six-membered ring.
- Baeyer-Villiger oxidation.



(a) General form.



(b) Mechanism.

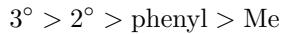
Figure 6.22: Baeyer-Villiger oxidation.

- Here, we convert a ketone into a lactone.
- We generally use a peracid (like *m*CPBA) to make this reaction proceed.
 - We can just use a peroxide sometimes, though.
- There's a very good depiction of the mechanism on Clayden et al. (2012, p. 956).
- Regioselectivity of the Baeyer-Villiger oxidation.



Figure 6.23: Baeyer-Villiger oxidation regioselectivity.

- The example in Figure 6.22 was symmetric, but what if our ketone is asymmetric?
- Here, we get exclusively the drawn enantiopure product from the drawn enantiopure starting material.
- To decide regioselectivity, consider the migratory aptitude of various groups.



- The drawing on Clayden et al. (2012, p. 956) has a good rationalization for this!
- The typical rationalization is for which can best stabilize a positive charge; note that phenyl is the odd one out because it's weird.
- Vinyl is not included because double bonds in the presence of *m*CPBA will lead to an epoxidation more rapidly than a Baeyer-Villiger.
- Thus, we form the drawn product because a 2° carbons migrates instead of a methyl group.