

Unit 6

Cations

6.33 Cations

11/25:

- Lecture 32 recap.
 - Claisen condensations provide 1,3-dicarbonyls (Figure 5.35).
 - Remember that we need two hydrogens to deprotonate!
 - These reactions proceed under 1 equivalent of base.
 - Driving force: Formation of the enolate.
 - Workup yields the final 1,3-dicarbonyl, also known as a β -dicarbonyl.
 - Michael reactions provide 1,5-dicarbonyls (Figure 5.45).
 - We mostly discussed carbonyl enolates, sometimes from β -dicarbonyls!
- Today: We'll begin Unit 6 (carbocations).
 - The beginning of this unit is a recap of what you already know about carbocations.
 - Review your 5.12 notes!!
 - And/or read Clayden et al. (2012, pp. 333–339).
 - We'll cover Chapter 36 of Clayden et al. (2012) toward the end of this unit.
 - Aside (history): Carbocations were called “carbocations” when Prof. Buchwald was in school, then “carbenium ions” for a time, and now are known as “carbocations” again.
- Lecture outline.
 - A. Introduction to carbocations.
 - B. Generating carbocations.
 - 1) Addition of an electrophile to a multiple bond.
 - 2) Heterolytic cleavage of C–X bonds.
 - C. Reactions.
 - 1) Eliminations.
 - 2) Combinations with nucleophiles.
 - b) Reactions with aromatic rings.
 - Friedel-Crafts alkylation.
 - Friedel-Crafts acylation.
 - c) Reactions with olefins.
 - 3) Rearrangements and fragmentations.
 - Friedel-Crafts alkylation (revisited).

- We'll begin with Topic A: Introduction to carbocations.
 - **Carbocation:** A species that contains a carbon bearing a positive charge. *Structure*



Figure 6.1: Carbocation.

- These are sp^2 -hybridized species, so typically with three 120° bond angles.
 - However, carbocation bond angles can be strained in rings, for example.

• Stabilizing cations.



Figure 6.2: Stabilized carbocations.

- The allyl cation is stabilized by resonance.
 - The cyclopropenyl cation is stabilized by $4(0) + 2 = 2\pi$ electron Hückel aromaticity, even though it has significant angle strain ($120^\circ \rightarrow 60^\circ$).
 - Heteroatom-stabilized carbocations are good.

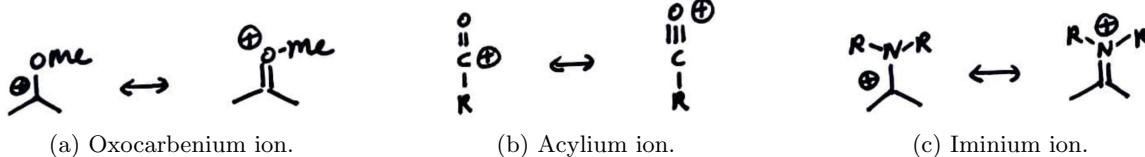
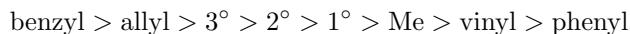


Figure 6.3: Heteroatom-stabilized carbocations.

- Figure 6.3a depicts an intermediate in the hydrolysis of ketals.
 - Heteroatom-stabilized cations can have synthetic utility, e.g., the acylium ion present in the mechanism of Friedel-Crafts acylations.
 - Iminium ions are also technically heteroatom-stabilized carbocations.

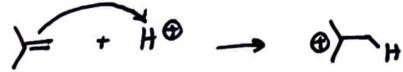
• Ordering carbocation stability.

- Ordering carbocation stability.



- 1° , methyl, vinyl, and phenyl cations will not be discussed further in 5.13.
 - Possible exception: Know that they exist, and that they're bad.
 - Benzyl cations are stabilized by significant resonance delocalization of their positive charge.
 - This resonance implies that the *ortho*- and *para*-positions have δ^+ charges on them.
 - Thus, substitutions at these positions affect carbocation stability!
 - Example: Compare the relative stability of the *para*-trifluoromethylbenzyl cation, *para*-methylbenzyl cation, and *para*-methoxybenzyl cation.
 - Trifluoromethyl is a destabilizing EWG, methyl is an inductively stabilizing EDG, and methoxy is a resonance stabilizing EDG.

- Allyl is good; any time we can add additional resonance forms *of the same energy*, we get stabilization.
 - More substituted carbocations are stabilized by hyperconjugation (see Figure 2.3).
 - Recall that such resonance structures are sometimes referred to as “no-bond resonance forms.”
 - No-bond resonance structures are ok because they do not violate the fundamental principle that *atoms must not move between resonance structures*.
 - This is a very easy thing to forget, for intro students up to tenured professors at MIT! So be careful!!
 - The active mode of stabilization here is σ -donation.
 - We now move onto Topic B: Generating carbocations.
 - We'll begin with Subtopic B.1: Addition of an electrophile to a multiple bond.



(a) Markovnikov addition to an olefin.



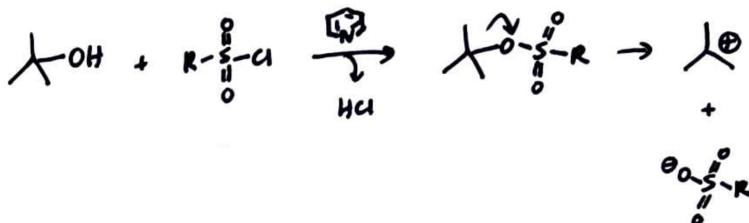
(b) Lewis acid coordination.

Figure 6.4: Multiple bonds can cleave to generate carbocations.

- We protonate in accordance with **Markovnikov's rule**.
 - Additionally, just like silicon is **oxophilic**, aluminum is an oxophilic Lewis acid.
 - **Markovnikov's rule:** Protonate so as to generate the most highly-substituted carbocation.
 - **Oxophilic** (element): An element that has a strong affinity for binding to oxygen. *Etymology* from Latin “lover of oxygen.”
 - We now move onto Subtopic B.2: Heterolytic cleavage of C–X bonds.



(a) General form.

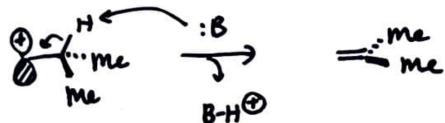


(b) Sulfonate leaving groups.

Figure 6.5: Generating carbocations from heterolytic C–X bond cleavage.

- Acid promotes the departure of the leaving group.
 - We often run these reactions in polar solvents (e.g., DMF) to help stabilize the leaving group.
 - If we make a sulfonate out of a tertiary alcohol (using base), this can then leave — water, by itself, isn't a great leaving group.

- What's to stop the leaving group from just reattacking the carbocation?
 - It can! Leaving group departure is most certainly a reversible process.
 - Leaving group departure is just a way to generate a carbocation if you have a reaction in mind *other than* the transiently formed carbocation just reattracting the lone pair of the leaving group.
- We now move onto Topic C: Reactions.
- We'll begin with Subtopic C.1: Eliminations.

Figure 6.6: E₁ elimination of carbocations.

- This is the simplest carbocation reaction.
- This can be useful for isomerizing alkenes because you will preferentially eliminate to form the more substituted alkene.^[1]
- We now move onto Subtopic C.2: Combinations with nucleophiles.
- We now move onto Subtopic C.2.b: Reactions with aromatic rings.
- Consider the reaction of benzene, *t*-butyl chloride, and a Lewis acid (LA).

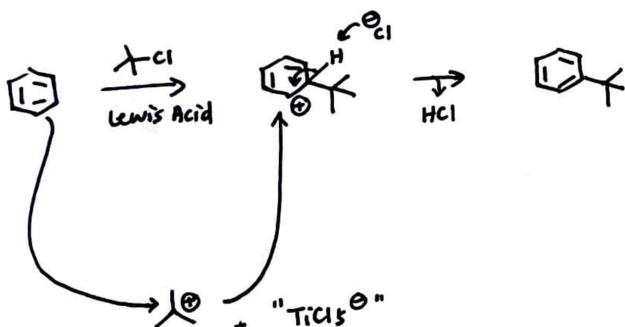


Figure 6.7: Friedel-Crafts alkylation.

- As an example of a Lewis acid, you can use titanium tetrachloride ($TiCl_4$).
 - $TiCl_4$ is chlorophilic, and wants to form the $TiCl_5^-$ adduct.
 - You can form a carbocation that will be attacked by benzene and then eliminated by chloride.
- You can also form a cation from an alkene and then react that with benzene.

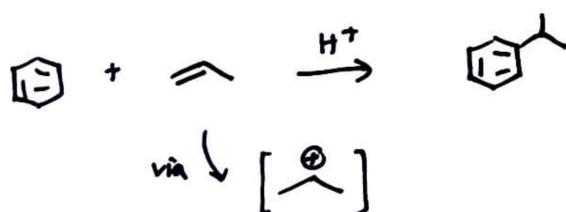


Figure 6.8: Hock process (stage 1).

¹The more substituted alkene is more stable per **Zaitsev's rule**.

- This is the primary method of producing acetone.^[2]
- It astounds Prof. Buchwald that this is economical: Indeed, it's easier to attach the isopropyl group to benzene and then rip it apart again, then it is to convert it directly to acetone.
- Friedel-Crafts acylation.



Figure 6.9: Friedel-Crafts acylation.

- Asides on Friedel-Crafts acylation.
 - Crafts was the president of MIT at one point, once he got tired of running these reactions!
 - If you open a bottle of AlCl₃, it reacts with water in the air to release HCl (very toxic).
- We now move onto Subtopic C.2.c: Reactions with olefins.

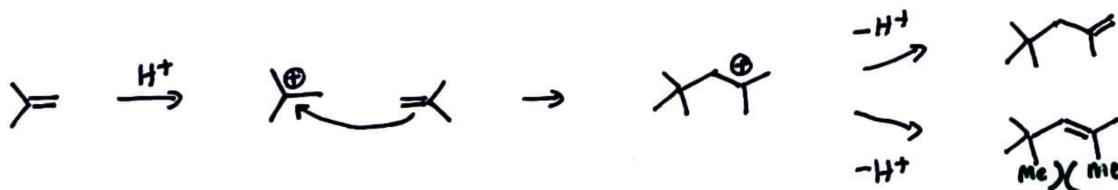


Figure 6.10: Olefin dimerization via carbocations.

- Dimerization under equilibrating conditions would give *mostly* the trisubstituted olefin, but not 100 : 0 because the trisubstituted olefin has some steric clash between the methyl and *t*-butyl group. This steric clash raises its energy relative to the disubstituted alkene product.
- We now move onto Subtopic C.3: Rearrangements and fragmentations.



(a) Stepwise pathway.



(b) Concerted pathway.

Figure 6.11: Carbocation rearrangement.

- The MG is the “migrating group,” and the LG is the “leaving group.”
- When the leaving group departs, we form a 2° carbocation.

²You can read more about this process — called the **Hock process** — on [Wikipedia](#).

- The migrating group can then hop over to give us a 3° carbocation!
- Alternative pathway: A concerted process in which migrating and leaving happen simultaneously.
 - This might be favored because we can avoid the high-energy carbocation intermediate!
 - Following lower-energy pathways is favorable.
- The driving force for this reaction is the formation of the 3° carbocation.

- A case in which we thought a reaction would do one thing, and it does another.

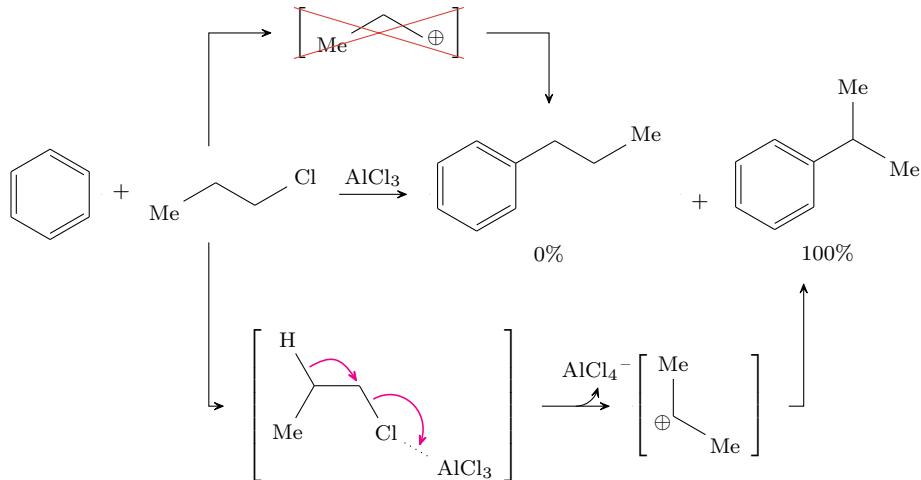


Figure 6.12: Carbocation rearrangements can explain Friedel-Crafts alkylation product distributions.

- These are often the times where we get the most interesting results; serendipity often leads to the most interesting discoveries.
 - Here, the primary carbocation is too high energy, so instead, we get concerted migration of the hydrogen to form the same secondary carbocation that we saw in Figure 6.8 from the protonation of propene.
 - This secondary cation can then react, as before, to form isopropyl benzene again.
- Why wouldn't the activated isopropylbenzene react further?
 - We're doing this in benzene as a solvent, so there's just far more of it around.
 - Example of when it does happen twice: Butylated hydroxytoluene (BHT) is a radical chain inhibitor often present as a preservative in our food!
 - It is made from *para*-methylphenol and isobutylene in acid.
 - This does happen two times!
 - Naming.
 - If MG = H, then it's a **hydride shift**.
 - If MG = R, then it's an **alkyl shift**, also known as a **Wagner-Meerwein rearrangement**.
 - There *might* be a guest in Wednesday's lecture!!

6.34 Cationic Rearrangements - 1

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.

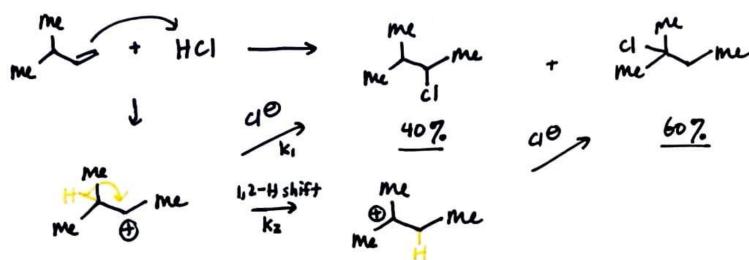


Figure 6.13: Hydride shifts in hydrohalogenations.

- 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.

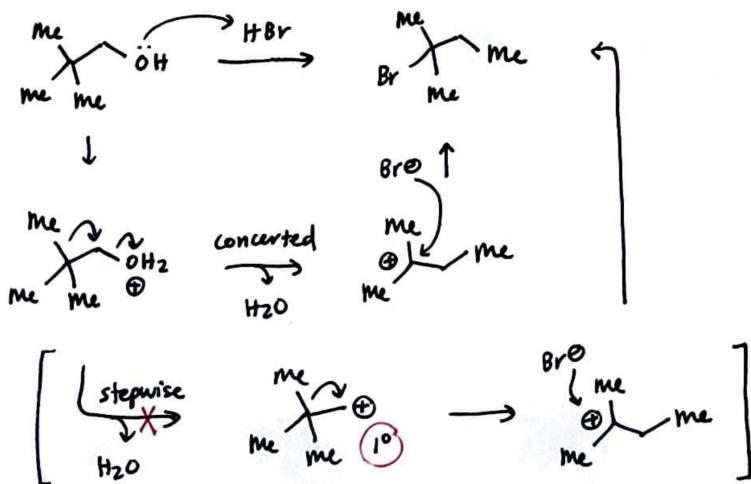


Figure 6.14: Concerted vs. stepwise mechanisms with methyl shifts.

- 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.

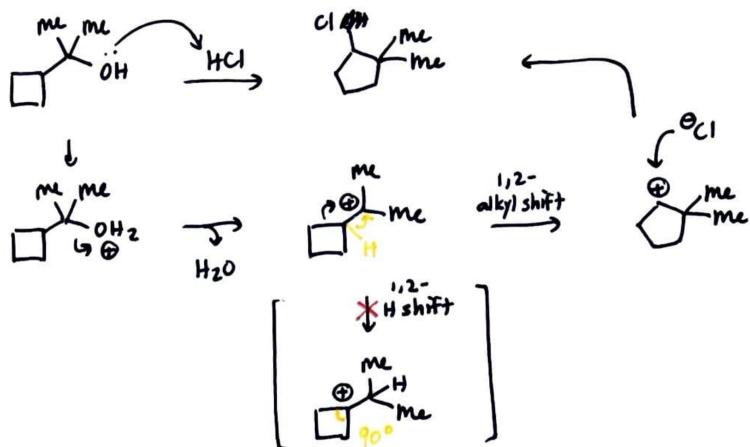


Figure 6.15: Angle strain can induce alkyl shifts.

- 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.

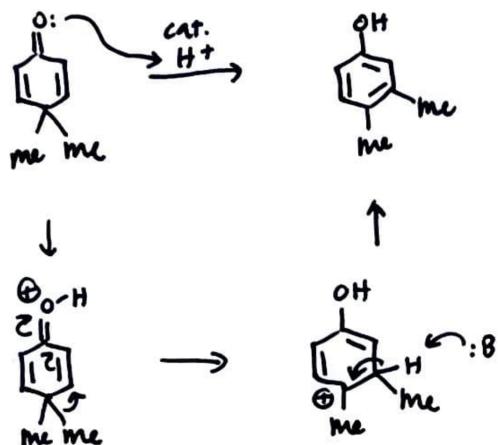


Figure 6.16: Dienone-phenol rearrangement.

- 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?

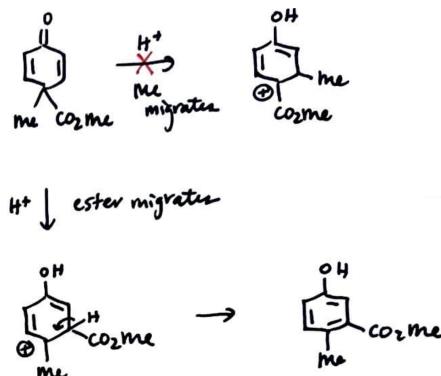


Figure 6.17: TTQ: Ester shifts.

- 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.

- MgBr₂ 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.

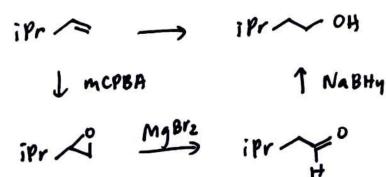
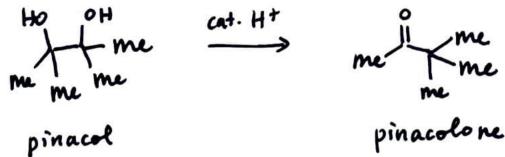
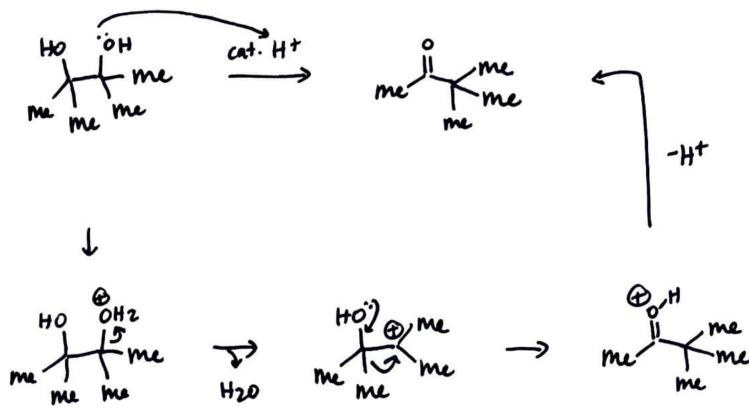


Figure 6.19: Epoxide-aldehyde rearrangement: Synthetic utility.

- 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.

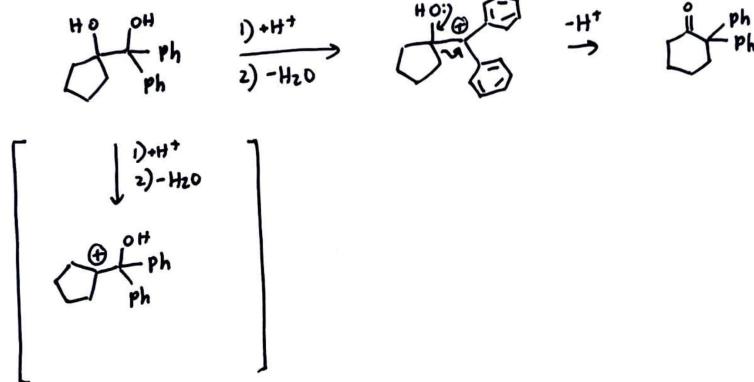


Figure 6.21: Asymmetric pinacol-pinacolone rearrangement.

- 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.

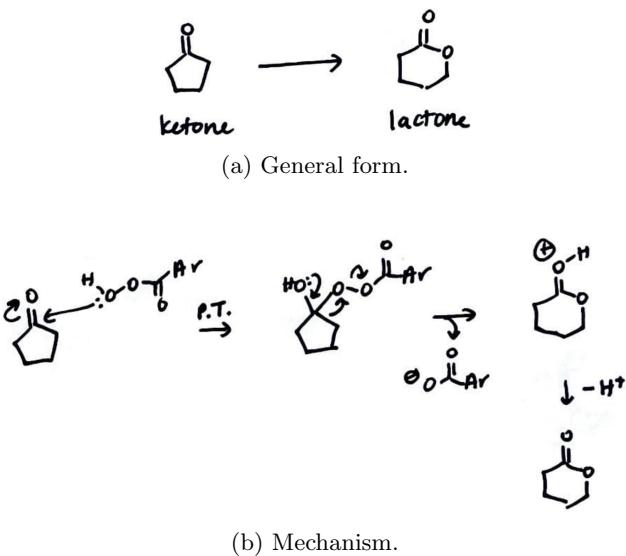


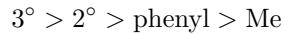
Figure 6.22: Baeyer-Villiger oxidation.

- 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.

6.35 Cationic Rearrangements - 2

- 11/27:
- Lecture 34 recap.
 - 1,2-hydride shifts are generally favored (all else being equal).
 - This is because shifting a hydride typically produces a more substituted carbocation.
 - 1,2-alkyl shifts will happen if they generate a more stable carbocation.
 - Epoxide openings (Figure 6.18).
 - This is the **Meinwald rearrangement**, named after a Cornell chemist.
 - Pinacol rearrangement (Figure 6.20).
 - Takes a 1,2-diol (also known as a **vicinal diol**) to a ketone.
 - Baeyer-Villiger oxidation (Figure 6.22).
 - Converts a ketone into an ester, or a cyclic ketone into a lactone.
 - Know the migratory aptitudes! Example: In *tert*-butyl methyl ketone, the *tert*-butyl group will migrate first.
 - Today: More carbocation rearrangements.
 - Lecture outline.
- C. Reactions.
- Rearrangements and fragmentations.
 - Beckmann rearrangement.
 - Neighboring group participation.
 - Aromatic rings as neighboring groups.
 - Carbonyls as neighboring groups.
- We now return to Subtopic C.3: Rearrangements and fragmentations.
 - The Beckmann rearrangement.

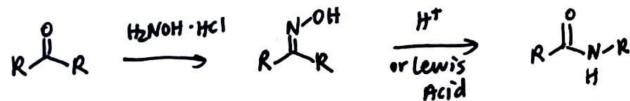


Figure 6.24: Beckmann rearrangement.

- Take a ketone and add hydroxylamine hydrochloride (recall from Figure 3.18b) to form an oxime, and then use an acid catalyst to make an amide.
- This reaction is more important at scale than the previous rearrangements we've discussed (not testable content).

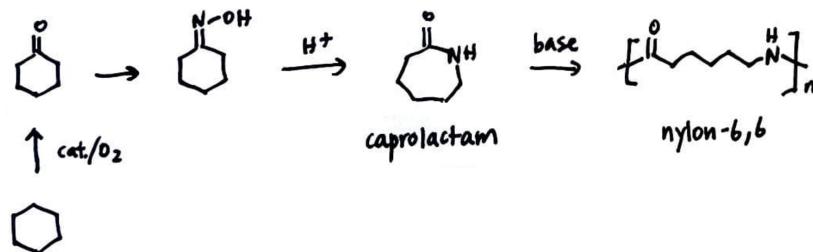


Figure 6.25: Synthesizing nylon!

- This reaction is important because if you want to make a billion of tons of cyclohexanone, start from cyclohexane and subject it to oxygen and a catalyst.
- Then make the oxime.
- Then use your acid catalyst; it used to be a sulfuric acid catalyst, but now they use an acidic clay.
- This yields caprolactam, the polymerization of which makes nylon-6,6 (or nylon!).
- Prof. Buchwald once did some consulting on improving the efficiency of this reaction from 99.83% to 99.84%, which may seem small but means millions of dollars per year in savings.
- Mechanism of the Beckmann rearrangement.

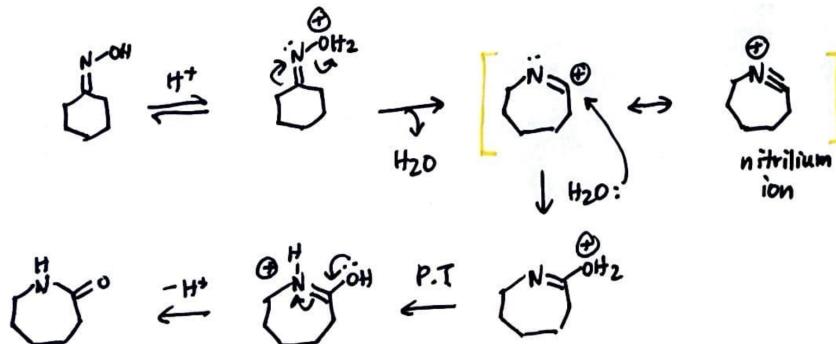


Figure 6.26: Beckmann rearrangement mechanism.

- The nitrogen gets protonated far more often than the oxygen, but every once in a while, the oxygen will be protonated.
- This oxygen protonation allows the rest of the mechanism to proceed, starting with a migration and departure of the leaving group.
- This yields a nitrilium ion, which is very strained.
- The nitrilium ion can then react with water.
- Then, following proton transfer, we get deprotonation to the product.
- Selectivity of the Beckmann rearrangement.

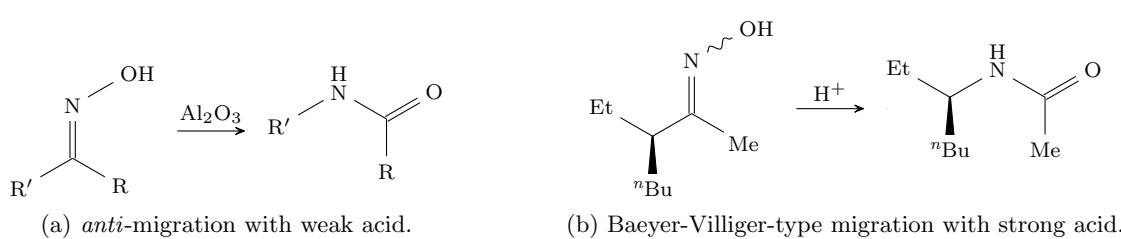


Figure 6.27: Beckmann rearrangement selectivity.

- Only the *anti*-group migrates!
 - This is on full display with the use of a weak Lewis acid like Al_2O_3 .
 - Coordination is weak, so you need the *anti*-oriented push.
- However, there is a caveat: If you use a 10 : 1 mixture of oxime isomers that is enantiomerically pure at the α -carbon, you only form a single stereoretentive product.
 - Indeed, the strong acid makes selectivity identical to that of the Baeyer-Villiger.
- Takeaway: Weak Lewis acid catalysis implies that only the *anti*-group migrates, while strong acid catalysis makes selectivity depend on the Baeyer-Villiger migratory aptitude.

- TTQ: Merging Profs. Elkin's and Buchwald's content.

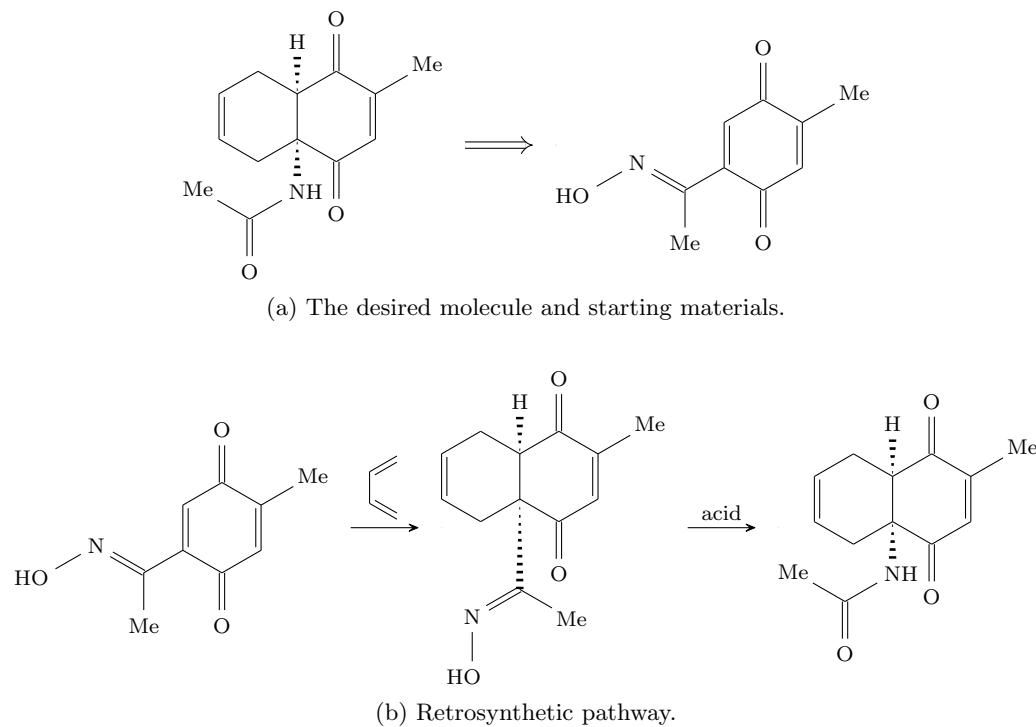


Figure 6.28: TTQ: Merging Unit 2 and Unit 6 content.

- Synthesize the molecule at left in Figure 6.28a from the provided starting material.
- Looking at the cyclohexene in the product, it seems like we might be able to start with a Diels-Alder reaction!
 - Potential ambiguity: Which enantiomer are we forming? We will indeed form both, but we will only form one diastereomer (from the *endo* transition state, etc.)
 - Potential ambiguity: Which side is the stronger dienophile? The left side is because it has the stronger EWG attached.
- Then we just need a Beckmann rearrangement, which we can cause using acid (either H^+ or Al_2O_3 !)
- Recall that we've discussed that substituents can affect reactions, e.g., through steric hindrance or an EWG near a carbonyl. We'll now discuss a topic that's similar to this, but a bit different.
- We now move onto Subtopic C.4: Neighboring group participation.

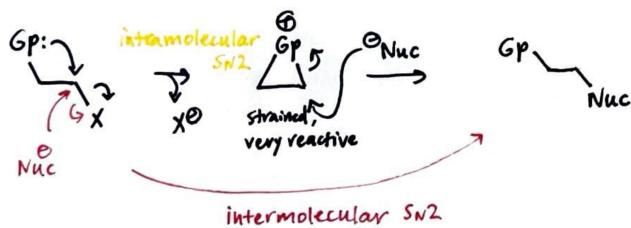


Figure 6.29: Neighboring group participation.

- Consider a group with a lone pair.
- This group can speed up displacement of an adjacent leaving group (because intramolecular chemistry is faster), and speed up subsequent nucleophilic attack because it forms a charged intermediate.
- This wins by $\Delta\Delta G^\ddagger$ over direct S_N2-type displacement.
- We now move onto Subtopic C.4.a: Aromatic rings as neighboring groups.

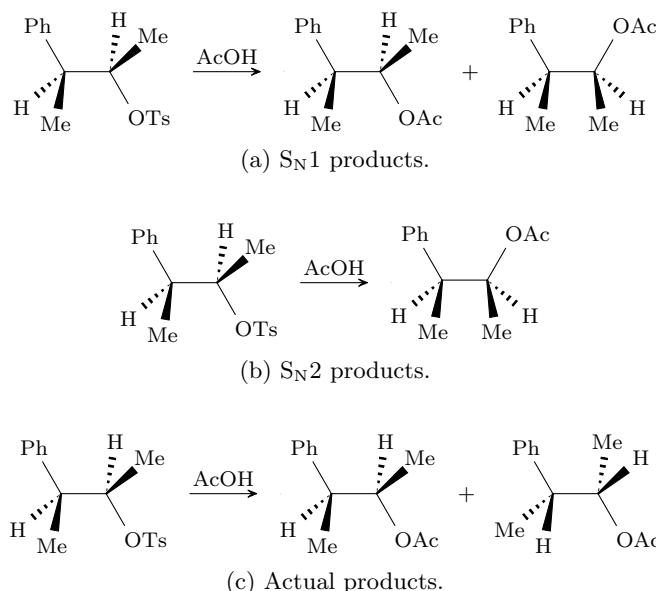


Figure 6.30: Neighboring group participation provides an alternative to S_N1 and S_N2.

- Consider the above **solvolytic** reaction of a single enantiomer, carried out in acetic acid.
- If tosylate is going to leave, it can do so by either an S_N1 or S_N2 mechanism.
- If S_N1...
 - We should form two diastereomers as products (the left stereocenter is retained, and the right one may or may not be flipped).
- If S_N2...
 - We should form exactly 1 diastereomer (the inverted one) as a product.
- However, when we do the actual experiment, we get two enantiomers as products!
- **Solvolytic** (reaction): A reaction in which the solvent and the reactant are the same.
- How can we explain the result in Figure 6.30c?

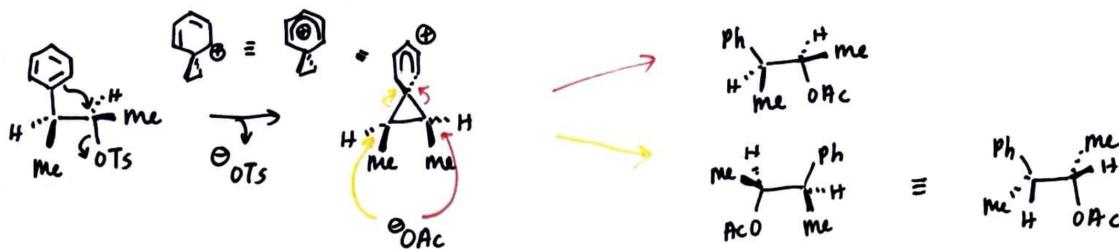


Figure 6.31: Neighboring group participation with aromatic rings.

- The phenyl group attacks the other carbon, pushing out tosylate and forming an intermediate.
 - The positive charge in this intermediate gets spread out over 5 carbons.
 - This intermediate also has a plane of symmetry.
- Because of the plane of symmetry, acetate can add to either the right or left sides, giving our enantiomeric products.
 - Indeed, we have destroyed our asymmetry by going through a symmetric intermediate.
 - Principle: Any reaction that goes through an achiral intermediate will *not* give an enantioenriched product (at least for the purposes of 5.13).
- We now move onto Subtopic C.4.b: Carbonyls as neighboring groups.
- Consider a single enantiomeric starting material, heated in acetic acid.

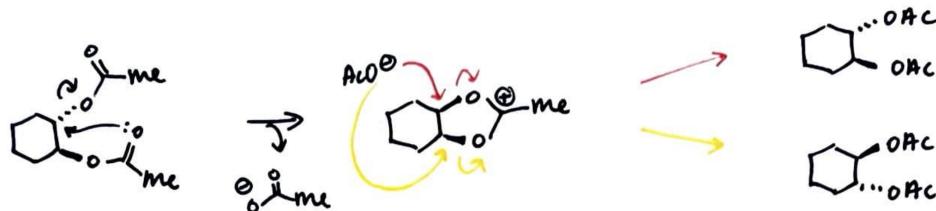


Figure 6.32: Neighboring group participation with carbonyls.

- The result is that we get a racemic mixture of products!
- Thus, we must be going through an achiral intermediate, which we can build with the displacement drawn in Figure 6.32.
- Note that the starting material is **chiral** and **enantiomerically pure**, while the product is chiral and racemic. This subtlety is often missed!
- **Chiral:** You have two hands that are not superimposable.
- **Enantiomerically pure:** You only have one of those hands.
- Recall our discussion of the Hock process (Figure 6.8) from couple of lectures ago.

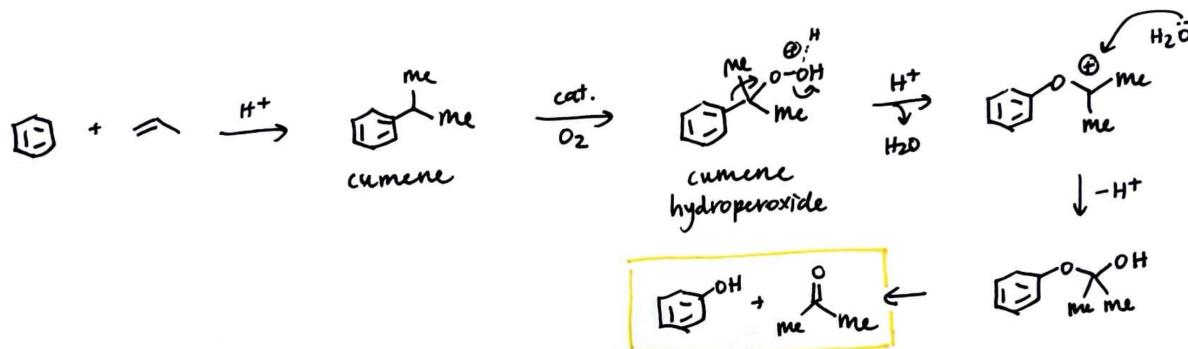


Figure 6.33: Hock process (stages 1-2).

- The Hock process produces phenol (the smell of paste when Prof. Buchwald was a child) and acetone (nail polish remover, and an industrial solvent).
- It does so on an unbelievable scale each year.
- The process works by forming **cumene** in the presence of an acid catalyst.

- We then form **cumene hydroperoxide**, an unstable intermediate, which rearranges and then fragments into the products.
- You would think that there is a simpler way to do this, but because it produces *two* value-added products at scale with cheap starting materials (benzene and propene are both products of petroleum cracking), it is more economical.