  - The Grignard reagent adds twice to carboxylic acid derivatives, yielding a tertiary alcohol.
    - This happens to acid chlorides, acid anhydrides, and esters.
    - Amides turn into the ketone (this is a special case!).
    - Carboxylates do not react.
  - Organolithium reagents (more potent than Grignards) react exactly the same as Grignards, except that they will *also* turn carboxylates into ketones!
    - This is a very surprising result, since we've talked about how unreactive carboxylates are.

- Where do ketones and aldehydes fit into the picture?
  - Ketones and aldehydes are between anhyrides and esters, and aldehydes are more reactive than ketones.
  - $NaBH_4$ will reduce ketones and aldehydes to the primary alcohol.
  - We'll talk about this more later.

- Next time: A mechanistic explanation for Table 4.2.

4.26 Acyl Transfer Reactions - 3 / Nitriles

11/6:

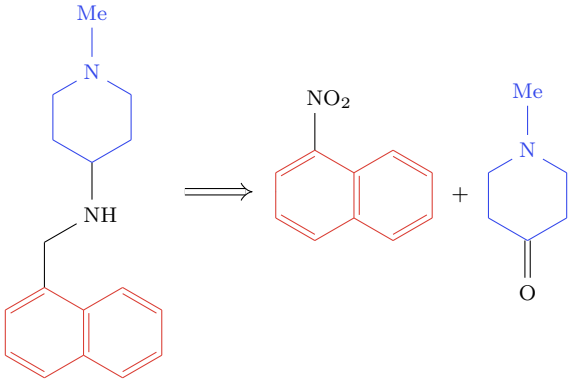
- Announcements.
  - Exam 3 is one week from today!
  - Lots of time today and Friday doing practice synthesis problems.
    - Friday's review will *not* involve a summary of the Unit 3-4 material; instead, Prof. Buchwald will send a synopsis in advance.
  - The more problems you work, the easier synthesis will become!!
  - Take advantage of the fact that we don't know *too* many reactions yet!

- Lecture 25 recap.
  - Evidence for a tetrahedral intermediate in acyl transfer reactions: Isotopic labeling studies.
  - Recall Table 4.2.
    - This gets back to what is key for synthesis: **Chemoselectivity**.
      - ➢ Example: Consider a molecule with an aldehyde and an amide. We can selectively reduce the aldehyde to the alcohol and not touch the amide if we reduce with $NaBH_4$.
      - ➢ This can be important in fancy molecules if we want to play with the **pharmacokinetics**.
    - Acid chlorides and anhydrides are *super* reactive.
    - Aldehydes and ketones get reduced by $NaBH_4$, too!
    - $NaBH_4$ is mild, while $LiAlH_4$ is *violent*. If you throw LAH into water, you'll get a *violent* reaction.
    - Similarly, Grignards are more mild than alkyllithium reagents.
      - ➢ Amides and carboxylates can become asymmetric ketones!

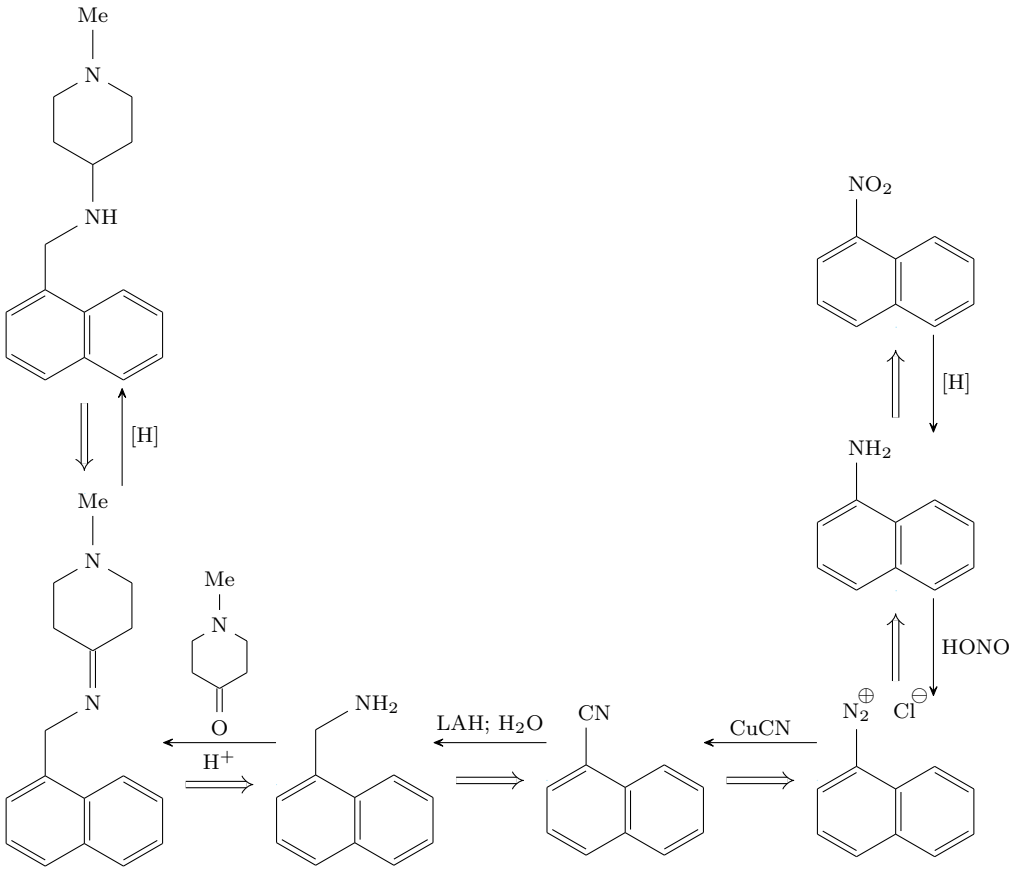
- **Chemoselectivity**: Selectivity for certain functional groups in the presence of other functional groups.

- **Pharmacokinetics**: The speed with which a drug moves into, through, and out of the body.
  - We don't want drugs to go straight through our bodies; we want them to hang around for a bit and do their thing (e.g., reduce our headache, soothe our cough, etc.).
  - We don't want to have to take it 5 times per day, so we modify functional groups with chemoselective reactions to slow the pharmacokinetics.

- TTQ: Synthesize the molecule at left in Figure 4.45a — a simplified version of a recently proposed candidate for treating epilepsy — from the provided starting materials.



(a) The desired molecule and starting materials.



(b) Retrosynthetic pathway.

Figure 4.45: TTQ: Synthesis of a drug molecule.

– Like last time (see Figure 4.42), let's start by mapping out the carbons.
  - Using color coding, we can identify which carbons in the starting materials become carbons in the products (Figure 4.45a).

  - It then becomes clear that what we need to add is a carbon-nitrogen linkage.
    - This could come from a cyano group!
    - Carbon-nitrogen doesn't *always* mean we need a cyano group, but it often does.
  - So thinking backwards, the desired molecule could have come from an imine.
    - In the forward direction, we'd use a reducing agent ($NaBH_4$ or $LiAlH_4$ and a water workup) to reduce the imine to the amine.
    - Next step: Transform the imine to an amine via reducitve amination.
    - Next step: Transform the amine to the nitrile via LAH and a water workup.
    - Next step: Transform the cyano group to an aryl diazonium salt via a **Sandmeyer reaction** (i.e., with CuCN).
    - Next step: Transform the aryl diazonium salt to the amine via HONO.
    - Final step: Transform the amine to the nitro group via reduction with H_2 / Pt, H_2 / Pd/C, or H_2 / Ni. LAH and H_2O are not ideal here.

- **Sandmeyer reaction**: Any method of displacing an aryl diazonium salt with a nucleophile in the presence of catalytic copper (I) salts.
- Takeaway: A general strategy for synthesis problems.
  1. Identify matching fragments (mostly carbon fragments).
  2. Look for functional groups and disconnections.
- This concludes today's synthesis example; we now return to the chemistry of carboxylic acid derivatives.
- Lecture outline.
  5. Reactions with $NaBH_4$, $LiAlH_4$, RMgBr, and RLi.
  6. Chemistry of nitriles.
     a. Formation.
     b. Reactions.
- We begin by resuming Topic 5: Reactions with $NaBH_4$, $LiAlH_4$, RMgBr, and RLi.
  - Specifically, we'll give the mechanistic explanation for Table 4.2 promised at the end of last lecture.
- Let's first consider why an acid chloride would react with hydride so quickly.

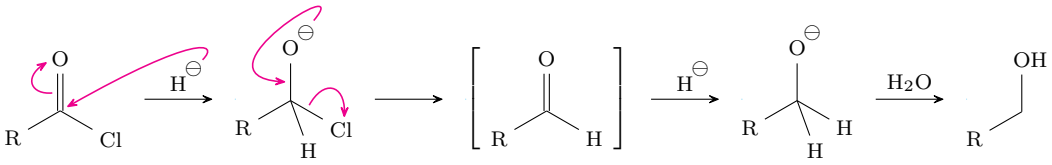


Figure 4.46: Reduction of acid chlorides mechanism.

  - For the same reasons as with Figure 4.23, both addition to and elimination from an acid chloride is fast — it makes no difference that our nucleophile is a hydride!
  - The first equivalent of hydride yields the aldehyde.
    - But we can't stop here!
    - Aldehydes are still reactive, so another equivalent of hydride will add in.
    - Then after a workup, we'll get the alcohol.
  - Aside: Reagents exist that *can* convert an acid chloride to an aldehyde and stop there.

- Let's now look at the addition of a Grignard to an acid anhydride.

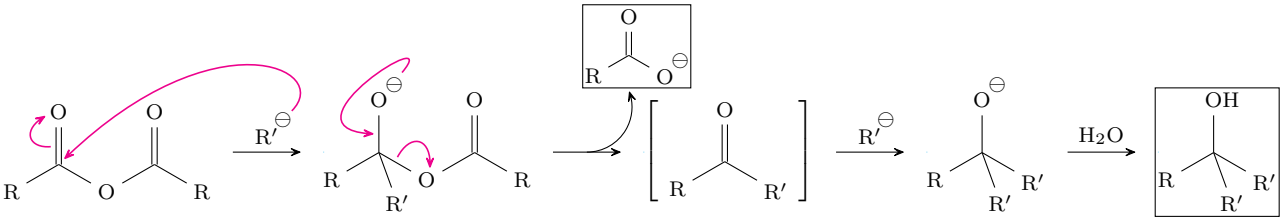


Figure 4.47: Grignard addition to acid anhydrides mechanism.

  - The Grignard (R′–MgBr) adds fast because acid anhydrides are not very resonance-stabilized either.
    - Then a good leaving group leaves to give a ketone.
    - Then the ketone reacts again to give us the tertiary alcohol.
  - But the carboxylate is still hanging around.
    - It will *not* react with a Grignard.
    - Thus, we get 50% of 3° alcohol and 50% carboxylate, so this is *not* an elegant reaction.

- If we use R′Li instead of R′MgBr, this gives us 100% of the 3° alcohol, so this *is* a good reaction.

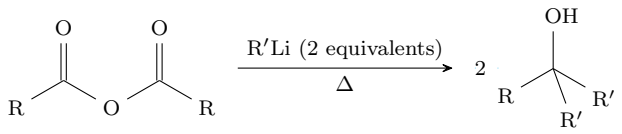


Figure 4.48: Alkyllithium addition to acid anhydrides.

  - R′Li is necessary because alkyllithium reagents are strong enough to reduce carboxylates, too (see Table 4.2).
  - Note that this reaction only proceeds with heating.
  - This reaction will *not* be tested!!

- With alkyllithium reagents, we can stop the reaction at the dianion and then quench.

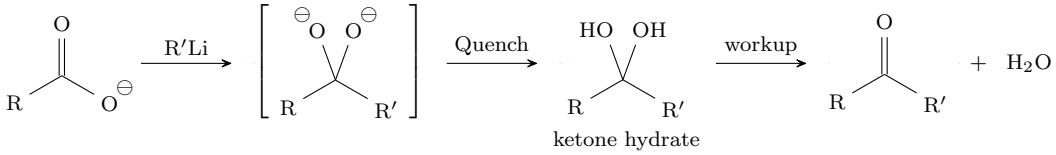


Figure 4.49: Alkyllithium addition to carboxylates.

  - To quench, use either water or H_3O^+.
    - You should write one of these two reagents above the arrow on a test, not "quench."
  - This gives us the ketone hydrate.
    - But ketone hydrates are not stable, so under workup, we'll lose H_2O and obtain the ketone.
  - This is the money reaction, and very much could be tested!!

- TTQ: How would you make a ketone from RLi and R′Li?

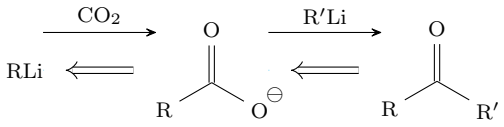


Figure 4.50: TTQ: Applying the addition of alkyllithium reagents to carboxylates.

  - First step: Transform the ketone into the carboxylate and R′Li via the reaction in Figure 4.49.
  - Second step: Transform the carboxylate into RLi via CO_2 carboxylation.

- Both LAH and R′M (M = MgBr, Li) can do add twice to esters.

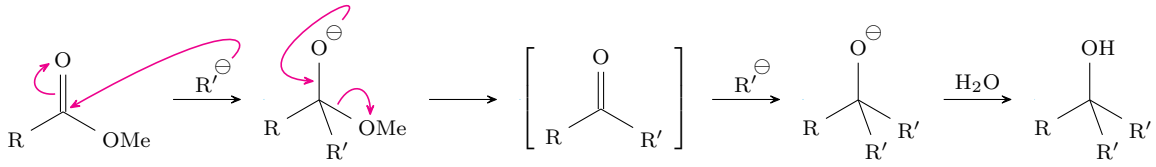


Figure 4.51: Organometallic addition to esters mechanism.

  - As we've seen before, the first step is addition to an electrophilic carbon center.
    - The resultant alkoxide anion is so powerful it can even push out a methoxide.
    - Then you get another addition to form the tertiary alcohol, after workup.
  - Takeaway: If you see a tertiary alcohol with two like substituents, get used to thinking that it might come from the reaction of two equivalents of a Grignard (or alkyllithium reagent) with an ester!

- We now discuss two other reactions to make ketones.
  - These take acyl derivatives — "acyl X" — to ketones.

- Reaction #1: Beginning with an acid chloride.

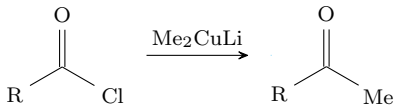


Figure 4.52: Monoaddition to acid chlorides with dimethylcopper lithium.

  - If we introduce a Grignard or alkyllithium reagent, the reaction will proceed all the way to the tertiary alcohol.
    - Thus, we need a gentler, more selective version of a Grignard or alkyllithium.
    - An example of such a reagent is **dimethylcopper lithium**.
  - TTQ: Given the reaction above (except for the starting material, reagent, or product), fill in the missing compound.

- **Dimethylcopper lithium**: A reagent composed of an anionic copper atom covalently bonded to two methyl groups and ionically bonded to a lithium cation. *Also known as* **Gilman reagent**, **organocuprate**. *Structure*

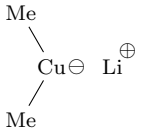


Figure 4.53: Dimethylcopper lithium.

  - History: Invented by Henry Gilman, an organic chemist at Iowa State University.
  - Aside: This compound is really good at 1,4-addition, also known as conjugate addition. We'll cover such this class of reactions in Unit 5.
  - Synthesis (not testable material): $2\,\mathrm{MeLi} + \mathrm{CuX} \longrightarrow \mathrm{Me_2CuLi}$

- Reaction #2: Beginning with a **Weinreb amide**.

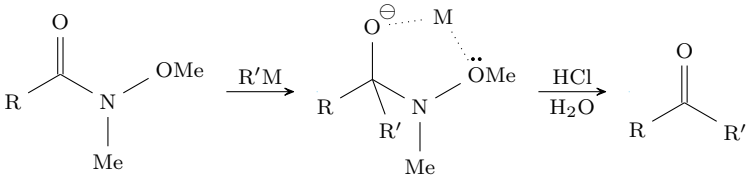


Figure 4.54: Weinreb ketone synthesis.

  - This reaction works with either Grignards or alkyllithium reagents.
  - After addition to the carbonyl, the metal coordinates to both the *N*-oxygen's lone pair and the alkoxy anion.
    - This is a quasi-stable species.
  - Water-workup then gets you the ketone.

- **Weinreb amide**: An amide with an *N*-methyl and *N*-methoxy group. *Structure*

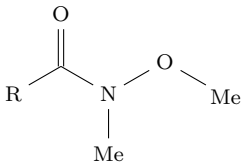
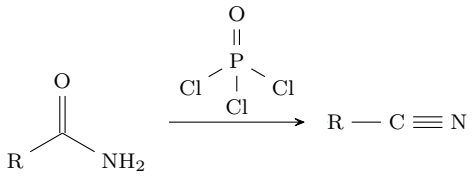


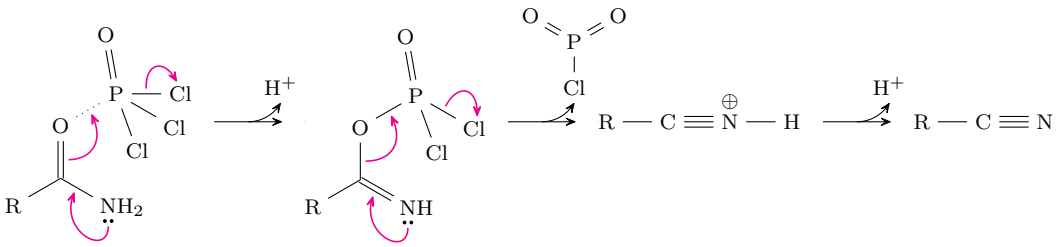
Figure 4.55: Weinreb amide.

- We now move onto Topic 6: The chemistry of nitriles.
- We'll begin with Subtopic 6.a: Formation of nitriles.
  - We'll start with three reactions you already know: S_N2 displacement, cyanohydrin formation, and the Sandmeyer reaction.
  - Then we'll cover one new method.
- S_N2 displacement (see Figure 3.21).
  - The X group can be Br, I, or OTs.

- Cyanohydrin formation (see Figure 3.22).
  - This reaction should be familiar from 5.12.
  - Note that the base catalyst usually has $pK_a \approx 9.5$.
- Sandmeyer reaction (see Figure 4.45b).
- One new method: Dehydration of amides.



(a) The reaction.



(b) A partial mechanism.

Figure 4.56: Nitrile synthesis: Dehydration of amides.

  - We add $POCl_3$ (the triacid chloride of phosphorous acid) to our amide (Figure 4.56).
    - $POCl_3$ is a very strong Lewis acid.
    - It rips out an equivalent of H_2O from our amide in a process known as dehydration.
  - Approximate mechanism (Figure 4.56b).
    - $POCl_3$ is a strong Lewis acid, so it will head straight for one of the carbonyl lone pairs. The amide lone pair can then kick up to allow proper O–P bond formation, and kick out a Cl^-.
    - Following deprotonation of the amide, we obtain an intermediate with a great leaving group. The new nitrogen lone pair can then kick out this leaving group, which will also lose another Cl^- to enable O=P bond formation.
    - A final deprotonation gives us our nitrile.
- We now move onto Subtopic 6.b: Reactions of nitriles.
- Nitrile hydrolysis (see Figure 4.8).
  - Adding a harsh acid or base gets you all the way to the carboxylic acid.
  - Adding a mild acid or base gets you the amide.
  - We will not ask you either set of conditions on an exam!!
- Converting nitriles to ketones.

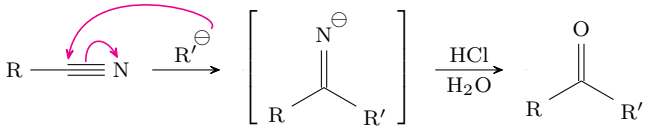
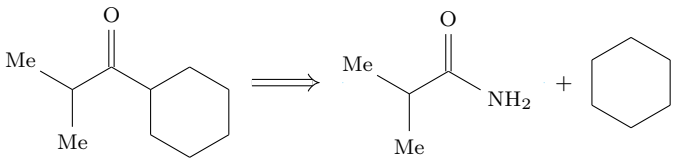


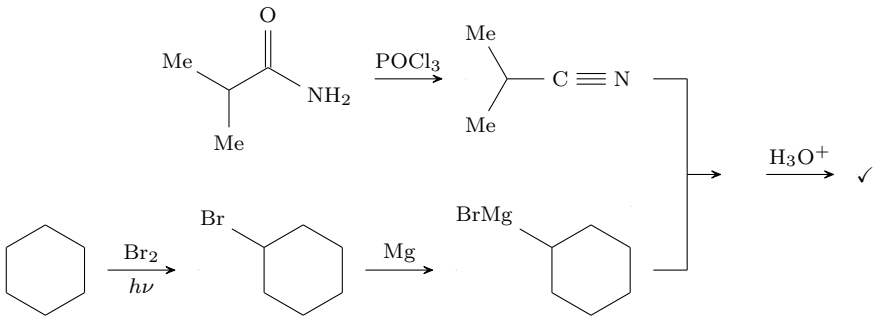
Figure 4.57: Organometallic addition to nitriles mechanism.

- Use an alkyllithium reagent or Grignard followed by an acidic workup.
- Implication: When you see a ketone in a molecule you're trying to synthesize, you can now think about whether it would be helpful if this retrosynthetically came from a nitrile and organometallic reagent, too!

- TTQ: Synthesize the molecule at left in Figure 4.58a from the provided starting materials.



(a) The desired molecule and starting materials.



(b) Solution.

Figure 4.58: TTQ: Applying nitrile addition chemistry.

- The cyclohexane to cyclohexyl bromide to Grignard reaction sequence in Figure 4.58b should be familiar from 5.12.
- Amide goes to nitrile with dehydration conditions ($POCl_3$).
- Then the nitrile plus the Grignard makes the product.