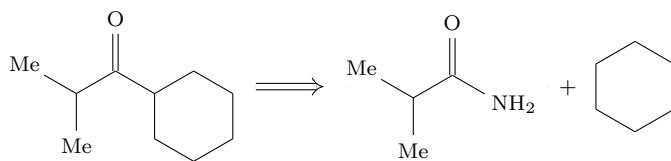
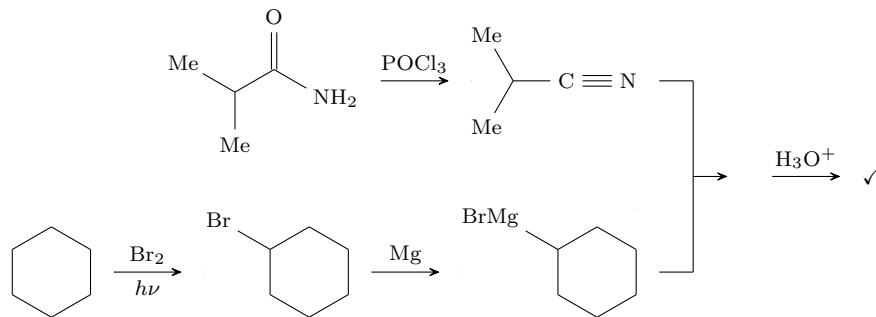


- Use an alkylolithium reagent or Grignard followed by an acidic workup.
- Implication: When you see a ketone in a molecule you're trying to synthesize, you can now think about whether it would be helpful if this retrosynthetically came from a nitrile and organometallic reagent, too!
- TTQ: Synthesize 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<sub>3</sub>).
- Then the nitrile plus the Grignard makes the product.

## 4.27 Review for Exam 3

11/8:

- Lecture 26 recap.
  - Cuprates take acyl chlorides to ketones (Figure 4.52).
  - Weinreb amides are another useful way of synthesizing ketones (Figure 4.54).
    - Note that Weinreb amides are synthesized from acyl chlorides and methylmethoxyamine (Me-NH-OMe) with Et<sub>3</sub>N as a secondary base to mop up the HCl generated (see Figure 4.25).
  - Nitriles.
    - Synthesize them with an S<sub>N</sub>2 displacement of a primary or secondary halide (Figure 3.21), cyanohydrin formation (Figure 3.22), the Sandmeyer reaction (Figure 4.45b), or the dehydration of amides (Figure 4.56).
    - Nitrile hydrolysis with harsh or mild acids (Figure 4.8).
    - Organometallic addition to nitriles (Figure 4.57).
- Prof. Buchwald sings an exam-based song to set everyone's mind at ease.

- Announcements.
  - Take the practice exam timed!
  - Go to the review sessions, and ask your questions there!
  - For synthesis questions, don't make compounds we already give you.
    - For example, if we give you an acid chloride, you don't need to prepare it from the carboxylic acid!
    - We won't take off, but it'll just waste your time.
  - Some of the exam will be fill in the reagent, some will be “what is wrong with this reaction,” some will be mechanism, some will be synthesis.
  - If you have questions during the exam, please ask!
- Today: Practice synthesis problems.
- TTQ: Identify the problem.

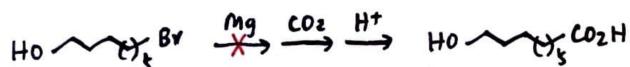
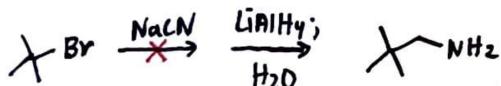


Figure 4.59: TTQ: Identify the problem (Grignard with acidic protons).

- We're trying to take an alkyl bromide with magnesium to make a Grignard reagent, which we can then carboxylate and work up into a carboxylic acid.
- This won't work because the Grignard intermediate will just deprotonate the acidic alcohol proton.
- Remember: Grignards aren't just very strong nucleophiles; they're very strong bases!
- TTQ: Fix the problem.

Figure 4.60: TTQ: Fix the problem ( $\text{S}_{\text{N}}2$  with  $3^\circ$ ).

- We do an  $\text{S}_{\text{N}}2$  displacement to form the nitrile, and then reduce to the homologated amine.
- Why will this not work?
  - Because  $\text{S}_{\text{N}}2$  doesn't happen with  $3^\circ$  alkyl halides.
- But what if we *have* to convert *tert*-butylbromide to neopentylamine (for example, because someone is holding Prof. Buchwald's cat for ransom)?
  - Bromide to Grignard to carboxylic acid to acid chloride to amide to product.
- TTQ: Fix the problem.

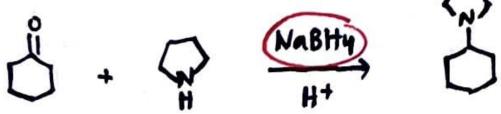


Figure 4.61: TTQ: Fix the problem (wrong reducing agent).

- Two reasons this doesn't work.
  - $\text{NaBH}_4$  will just reduce the ketone.
  - $\text{NaBH}_4$  will react with the acid in a nasty way.
- We can fix this by using  $\text{Na}(\text{CN})\text{BH}_3$ .
- TTQ: Fix the problem.



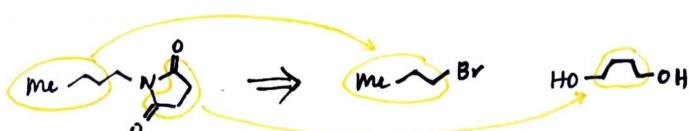
Figure 4.62: TTQ: Fix the problem (chemoselectivity).

- Suppose you want to reduce a cyanoaldehyde to an alcohol.
- Why will this not work?
  - $\text{LiAlH}_4$  will reduce both.
- We can fix this by using  $\text{NaBH}_4$ .
- TTQ: Fix the problem.

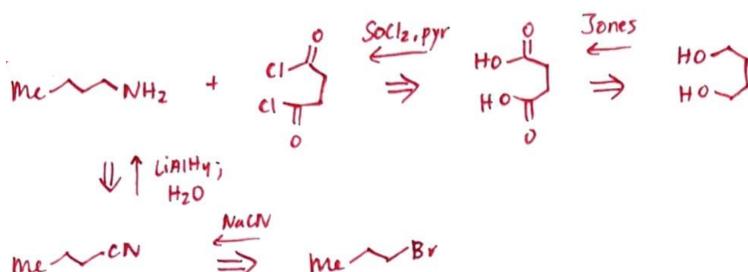


Figure 4.63: TTQ: Fix the problem (overreactivity).

- Treating an acid chloride with methyl magnesium bromide in water gives a methyl ketone.
- Why will this not work?
  - The Grignard will add twice to afford the tertiary alcohol.
- We can fix this with dimethylcopper lithium.
- TTQ: Two ways to synthesize a given compound from bromopropane and 1,4-butanediol.



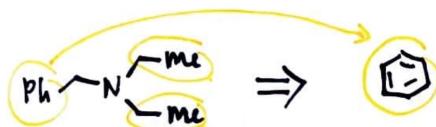
(a) The desired molecule and starting materials.



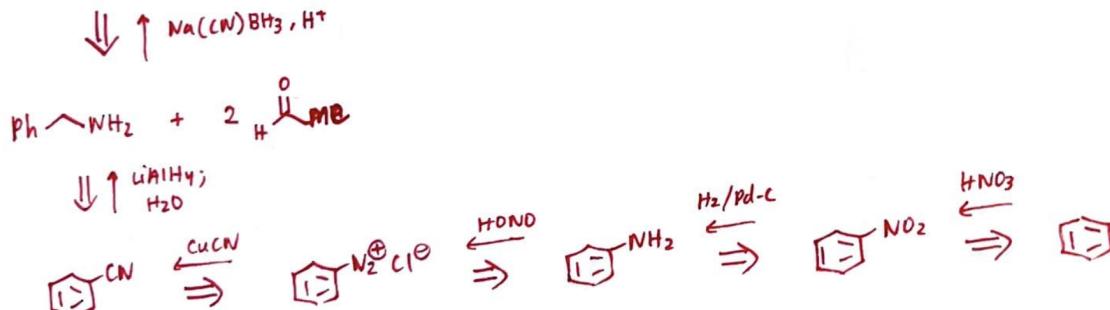
(b) Retrosynthetic pathway.

Figure 4.64: TTQ: Synthesis of a diamide.

- First, think about how the carbons might map onto the structure.
  - Thus, we need to adjust the oxidation state from alcohol to aldehyde.
  - We also need to input a  $\text{CH}_2\text{N}$ .
- Easiest way to do this disconnection: Split into a primary amide and a diacetyl chloride (specifically, succinyl chloride).
- Let's now retrosynthesize succinyl chloride.
  - Next step: Transform succinyl chloride into the dicarboxylic acid via  $\text{SOCl}_2$  and Py.
  - Next step: Transform the dicarboxylic acid into the original diol via Jones reagent.
- Let's now retrosynthesize the primary amine.
  - Next step: Transform the amine into the nitrile via  $\text{LiAlH}_4$  followed by  $\text{H}_2\text{O}$ .
  - Next step: Transform the nitrile into the original bromopropane via  $\text{NaCN}$ .
- Follow up question: Suppose we don't have access to cyanides (as we often don't since they're toxic). How could we go from bromopropane to the primary amine without the cyanide?
  - As we just did!
  - Bromide to Grignard to carboxylic acid to acid chloride to amide to amine.
- Could we go directly from the carboxylic acid to the diamide?
- Sure, there are reactions that do this (even though we have not covered them).
- But it will be more efficient anyway to go through the acid chloride.
- TTQ: Synthesize the given compound from benzene and any compound with less than two carbons.



(a) The desired molecule and starting materials.

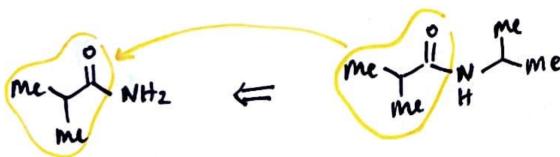


(b) Retrosynthetic pathway.

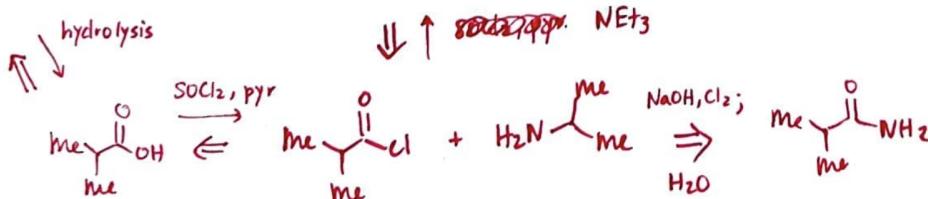
Figure 4.65: TTQ: Synthesis of a benzene derivative.

- First, think about how the carbons might map onto the structure.
  - Benzene becomes the phenyl ring.
  - Each other amine substituent has only two carbons!

- Transform the product into a primary amine and acetaldehyde (a two-carbon starting material!) via double reductive amination with  $\text{Na}(\text{CN})\text{BH}_3$  and  $\text{H}^+$ .
  - Next step: Transform the primary amine into a nitrile via LAH followed by  $\text{H}_2\text{O}$ .
  - Next step: Transform the nitrile into an aryl diazonium salt via the Sandmeyer reaction, i.e.,  $\text{CuCN}$ .
  - Next step: Transform the aryl diazonium salt into aniline via  $\text{HONO}$ .
  - Next step: Transform aniline into nitrobenzene via  $\text{H}_2 / \text{Pd/C}$ .
  - Next step: Transform nitrobenzene into benzene via  $\text{HNO}_3$ .
- Alternate pathway.
  - We could retrosynthesize the product to benzaldehyde and diethylamine, and then make both of those.
- TTQ: Synthesize the given compound from isobutyramide, a compound we saw last lecture!



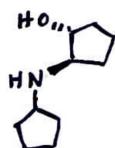
(a) The desired molecule and starting materials.



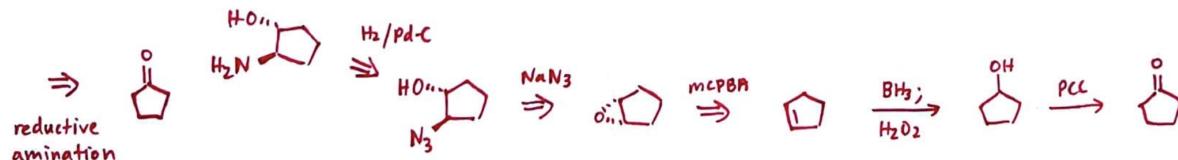
(b) Retrosynthetic pathway.

Figure 4.66: TTQ: Synthesis of a pseudodimer of isobutyramide.

- Transform the product into an acid chloride and a primary amine.
- Let's now retrosynthesize the acid chloride.
  - Next step: Transform the acid chloride into the carboxylic acid via  $\text{SOCl}_2$  and Py.
  - Next step: Transform the carboxylic acid into isobutyramide via amide hydrolysis, i.e.,  $\text{H}_3\text{O}^+$ .
- Let's now retrosynthesize the primary amine.
  - Next step: Transform the amine into the starting material via the Hofmann rearrangement, i.e.,  $\text{NaOH}$ ,  $\text{Cl}_2$ , and  $\text{H}_2\text{O}$ .
- Prof. Buchwald reviews the mechanism of the Hofmann rearrangement.
- TTQ: Synthesize the compound shown in Figure 4.67a.
  - Running out of time, so Prof. Buchwald gives an outline of the solution to this problem.
  - Transform the product into an imine via  $\text{NaBH}_4$ .
    - Next step: Transform the imine into cyclopentanone and an aminoalcohol.
    - Next step: Transform the *trans*-1,2-aminoalcohol into an epoxide as in the upper pathway of Figure 4.1.
  - Cyclohexanone could have come from cyclohexene via hydroboration followed by PCC.



(a) The desired molecule.



(b) Retrosynthetic pathway.

Figure 4.67: TTQ: Synthesis involving stereochemistry.

- Final pieces of advice.

- Do everything backwards slowly, step by step. Don't skip any! It will just confuse you.
- Take some time to study — that will help you on the exam!
- Take some time to relax — that will help you on the exam!
- Don't forget to write your review cards.