  - Not all fish smell to the same degree.
    - Ocean fish (like cod) smell worse than river fish (like catfish) after they die.
  - Ocean fish smell worse because of trimethylamine oxide.
    - There's a lot of salt in the ocean, so ocean fish use trimethylamine oxide to balance the salt levels in their cells.
    - This compound does not smell very much, but after they die, enzymes from the fish (and from bacteria in the fish) reduce trimethylamine oxide to trimethylamine (which smells horrible).
  - Second important thing: We put lemon juice on fish because the acidity of the lemon juice (coming from citric acid) protonates the trimethylamine, decreasing the smell (and the taste since smell is connected to taste) so that the fish tastes better.

- Resonance decreases the basicity of amines.

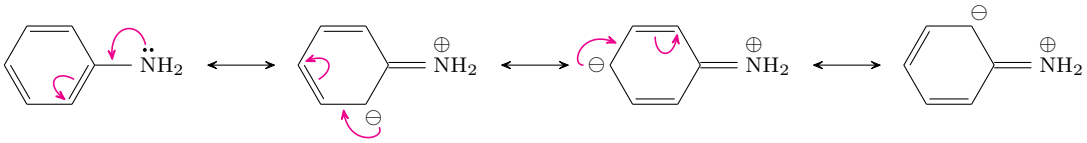


Figure 3.12: Basicity of aniline.

  - The conjugate base of aniline ($PhNH_3^+$) has $pK_a \approx 5$, indicating that aniline is much less basic than methylamine ($pK_a \approx 9 - 11$).
  - Why? Two reasons:
    1. The sp^2-carbon adjacent to the nitrogen in aniline is more electoron-donating than the sp^3-carbon adjacent to the nitrogen in methylamine.
    2. Resonance.
       - Just like in a phenol, we can push the heteroatom electrons into the benzene ring to get three other resonance forms (Figure 3.12).
       - Resonance decreases basicity, so aniline is much less basic than the any alkylamine.

3.22 Amines - 2

10/28:

- Lecture 21 recap.

  A. Amines are basic, nitrogen-containing compounds.
     - Their general form is R_3N, where $R = H, alkyl, aryl$.
     - Some other types will be discussed at the end of the semester.

  B. Types of amines: Ammonia (NH_3), 1°, 2°, or 3° depending on the number of hydrogens.

  C. Amines are often chiral, but rarely resolvable.

  D. Amines are Brønsted bases.
     - Substituents affect the acidities of the conjugate acids.
     - You can compare the basicity of methylamine and aniline by comparing the pK_a's of the conjugate acids.
     - Resonance makes amines less basic.

- Today: We'll cover Topic D.
  - The reading — Clayden et al. (2012, pp. 700–702) — covers snippets of amine synthesis.
- We'll begin with Subtopic D.1: Alkylation of amines.

- Specifically, let's look at how we might synthesize a primary amine.

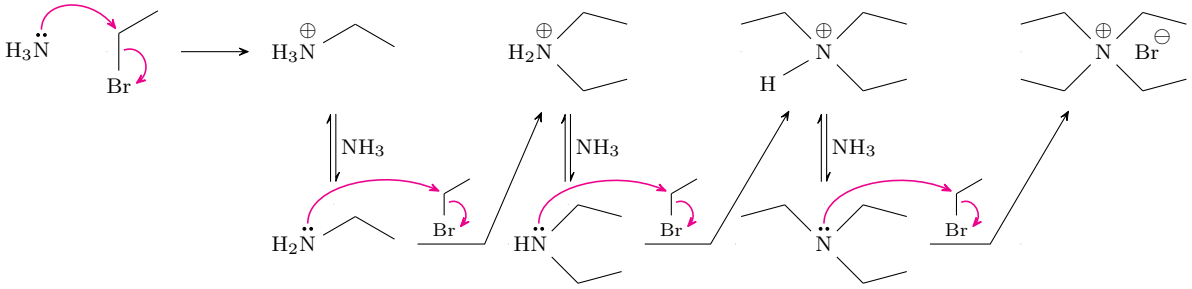


Figure 3.13: Alkylation of amines from ammonia and an alkyl halide.

  - If we wanted to synthesize ethylamine ($EtNH_2$), we might first think to react ammonia with bromoethane via an S_N2 mechanism.
  - Would this work? Sort of.
    - When we carry out this reaction, we obtain a primary ammonium cation that is easily (and reversibly) deprotonated to ethylamine by other basic ammonia molecules floating around.
    - This frees up the ethylamine product to react again! In fact, even though ethylamine is sterically more hindered, it is electronically more activated.
    - It follows that the ethylamine we've created will react *even faster* than ammonia, forming a secondary ammonium cation.
  - After a few more successive cycles of S_N2's and deprotonations — creating iteratively more substituted and hence more electronically activated amines — we obtain a quaternary ammonium salt[1] as our major product.
  - Therefore, the major product is tetraethylammonium, a quaternary ammonium salt.

- Aside: When we do synthesis, we do *not* want to form a mixture of products.
  - Mixtures decrease our efficiency and require separation.
  - We have all sorts ways to separate things, but separation techniques are inelegant, time consuming, and expensive.

- As such, if we do want to use ammonia and an alkyl halide, we must use a *large excess* of ammonia. However, this is not a great fix because...
  - Ammonia is toxic and smells horrible;
  - Ammonia is also a gas, and hence harder to control in the lab than a liquid.

- So we need an alternate method to synthesize primary amines. In fact, we'll discuss two!

- Alternative #1: Gabriel synthesis.

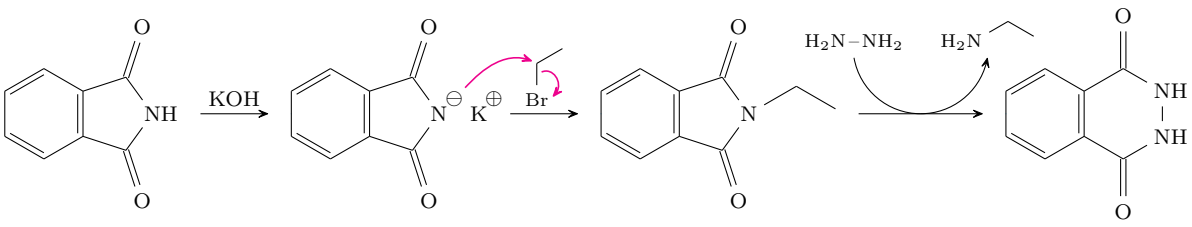


Figure 3.14: Gabriel synthesis.

[1] Note that at the board, Prof. Buchwald uses parentheses and numerical subscripts to indicate groups that are repeated multiple times.

  - This method can be used to synthesize primary amines.
  - The molecule we begin with is called phthalimide.
    - Phthalimide has $pK_a \approx 8$.
    - For comparison, NH_3 has $pK_a \approx 33 - 35$.
  - First step: Put phthalimide in the presence of KOH to yield the potassium salt.
  - Second step: The potassium salt can do an S_N2 reaction to monoalkylate.
    - Importantly, this monoalkylated intermediate cannot react further! This is because its nitrogen lone pair is tied up in conjugation with the carbonyls.
  - Third step: We need to release the product, which we can do by adding hydrazine.
    - This releases our desired ethylamine product and forms a byproduct.
    - Aside: Hydrazine is also used as rocket fuel! It's an extremely high energy molecule.

- Alternative #2: Reduction of azides.

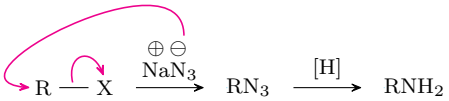


Figure 3.15: Reduction of azides.

  - This method can be used to synthesize primary *or* secondary amines.
  - We begin with an alkyl halide (RX), where R is primary or secondary.
    - Importantly, R *cannot* be tertiary because the first step proceeds through an S_N2 mechanism, and S_N2 cannot happen with tertiary alkyl halides.
  - First step: We react RX with sodium azide (NaN_3).
    - Sodium azide is a source of azide (N_3^-), a fantastic nucleophile.
    - This will give us an RN_3 intermediate.
  - Second step: We reduce the azide to the amine. There are two different ways to do this.[2]
    - Use lithium aluminum hydride ($LiAlH_4$ *or* LAH) followed by a water workup.
      - ➢ Note: Whenever we use LAH, we need a water workup.
    - Use hydrogen gas (H_2) and palladium on carbon (Pd/C).
      - ➢ Downside of these reagents: H_2 is explosive, and it's a gas (recall from our discussion of ammonia earlier today that gases are harder to control).
  - Downside of this method: RN_3 is explosive, so it is too dangerous to run this process industrially.
    - However, it's fine in small, controlled research settings when you know what you're doing.
  - Relevant reading: Clayden et al. (2012, p. 354).

- We now move onto Subtopic D.2: Reductive amination.
  - Reductive amination is super useful!
    - It is always in the *Journal of Medicinal Chemistry*'s decadal list of the top 5 most common reactions used in their papers.
    - Aside: Amide-bond formation is always (by far) the number 1 reaction, and a subject of Prof. Buchwald's research! It's not a perfectly solved problem, but we've gotten much better.
  - Relevant reading: Clayden et al. (2012, pp. 234–235).

[2] "[H]" is a general way of denoting a reduction. It is useful in Figure 3.15 because there are two possible reducing agents we can use, discussed next.

- Using reductive amination to convert secondary amines into tertiary amines.

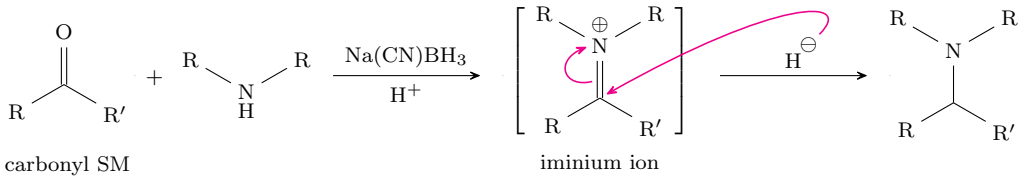
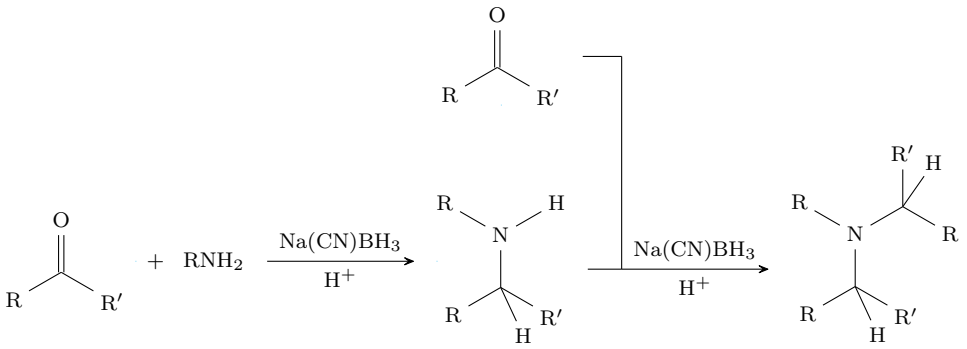


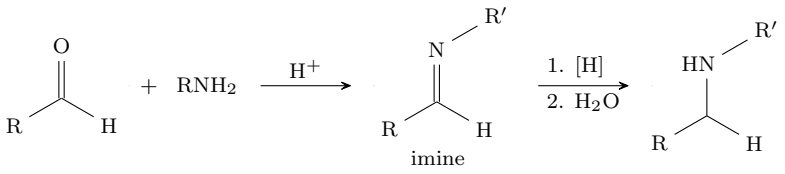
Figure 3.16: Reductive amination: $2° \rightarrow 3°$.

  - We begin with an aldehyde or a ketone (i.e., $R' = H, alkyl, aryl$).
  - Single step: Use sodium cyanoborohydride ($Na(CN)BH_3$) in acidic medium.
  - $Na(CN)BH_3$ is a much milder, nicer reducing agent than sodium borohydride ($NaBH_4$).
    - It selectively reduces **iminium ions** instead of the carbonyl starting material.
      - ➢ This is important because if the carbonyl gets reduced to an alkane, it can no longer react with the secondary amine!
    - It is also stable under moderately acidic conditions.
      - ➢ This is important because we don't want the acid to just neutralize our reducing agent.
  - After the iminium ion is formed, hydride from $Na(CN)BH_3$ attacks it. This yields the product.
  - To reiterate: This is an incredibly powerful transformation.

- Using reductive amination to convert primary amines into secondary amines.



(a) Concurrent iminium formation and reduction.



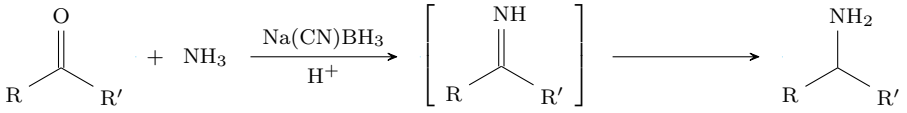
(b) Separate imine formation and reduction.

Figure 3.17: Reductive amination: $1° \rightarrow 2°$.

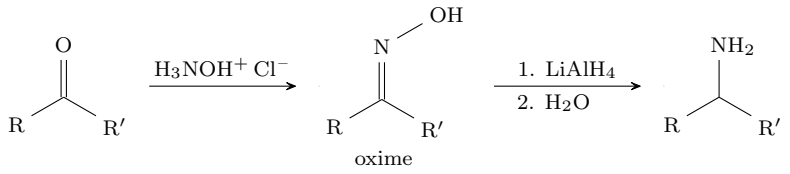
  - Let's first try using the same conditions as in Figure 3.16.
    - If we do this, we run into the same problem as in Figure 3.13.
    - In particular, the product of the first reductive amination in Figure 3.17a is a secondary amine and hence can react again to yield the rightmost product in Figure 3.17a.
    - Thus, if we did this, we'd have a mixture of products, and *we do not like mixtures*!

- Solution: Back off and run the reaction in two steps (Figure 3.17b).
  - First step: React an aldehyde with an amine to form an **imine**.
  - Second step: Reduce the imine with either $NaBH_4$ or $LiAlH_4$, followed by a water workup.
- Aside: $NaBH_4$ vs. $LiAlH_4$.
  - Since $NaBH_4$ is milder, we almost always prefer to use it over $LiAlH_4$ when we can.
- Aside: Why can't we use $Na(CN)BH_3$?
  - Worse at reducing imines.
  - More expensive than $NaBH_4$.
  - Toxic (cyanide exposure).

- Using reductive amination to make a branched primary amine.



(a) Concurrent iminium formation and reduction.



(b) Oxime formation and reduction.

Figure 3.18: Reductive amination: Forming 1°.

- Let's first try using the same conditions as in Figures 3.16 & 3.17a.
  - If we do this, the bracketed imine intermediate proposed in Figure 3.18a would be unstable.
  - As such, we would need to resort to using a large excess of ammonia if we really want to make this work, even though such volumes are not ideal.
- But what if you work in a place that doesn't allow you to handle gases?
- Solution: The two-step reaction in Figure 3.18b.
  - First step: Take your ketone or aldehyde and treat it with hydroxylamine hydrochloride ($H_3NOH^+\ Cl^-$) to form an **oxime**.
    - ➢ Unlike the proposed imine intermediate in Figure 3.18a, oximes are *really, really, really* stable.
  - Second step: Take the oxime and treat it with $LiAlH_4$ followed by a water workup.
    - ➢ Because oximes are so stable, we *need* a really strong reducing agent like $LiAlH_4$ to get the job done.
    - ➢ More ways to reduce oximes are listed on Clayden et al. (2012, pp. 702, 762, 902).
- Thus, we obtain a gas-free synthetic route to branched primary amines.

- We now move onto Subtopic D.3: Acylation and reduction.
- Acylation/reduction does monoalkylation, that is, the addition of one alkyl group to an amine.
  - This may be $NH_3 \rightarrow 1°$, $1° \rightarrow 2°$, or $2° \rightarrow 3°$!
- Reading on the acylation of amines, including the mechanism: Clayden et al. (2012, pp. 202–203).
- Reading on the reduction of amides: Clayden et al. (2012, p. 531).

- Example: Using acylation/reduction to convert primary amines to secondary amines.

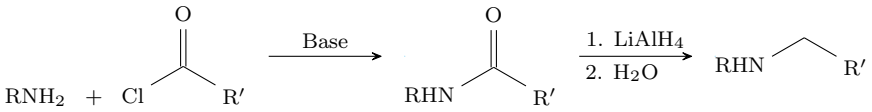


Figure 3.19: Monoalkylation by acylation and reduction.

  - We begin with an acid chloride and a primary amine.
  - First step: Mix the starting materials with a base (such as Et_3N).
    - This will form an amide.
    - As in the Gabriel synthesis (see Figure 3.14), this secondary amide does not react further because its nitrogen lone pair is tied up in conjugation with the carbonyl.
  - Second step: Reduce the amide with $LiAlH_4$, followed by a water workup.
    - This affords the secondary amine product.

- Aside: Why do we need so many methods of making amines?
  - Textbook chemistry (what we're doing) always works.
  - In the lab, molecules have many properties that might get in the way of one method working, so we need alternatives to try.
    - Example: Methods 1-26 might not work, but perhaps method 27 does.
  - This is the really exciting thing about Prof. Elkin's research: Prof. Elkin is using data science to avoid doing the first 26 bad reactions and make it so that the first time we try to do the reaction, it has a better chance of working.

- We now move onto Subtopic D.4: Reduction of nitriles.

- The general form of this reaction is as follows.

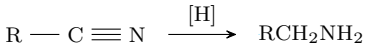


Figure 3.20: Reduction of nitriles.

  - The reducing agent can be $LiAlH_4$, or hydrogen and a nickel catalyst (H_2/Ni cat).

- This reaction is pretty straightforward, but where did we get the nitrile from?

Figure 3.21: Reduction of nitriles: Alkyl halide starting material.

  - Nitriles are often synthesized from (primary or secondary) alkyl halides through an S_N2 reaction in which CN^- is the nucleophile.
    - Once we have the nitrile, we can reduce it as in Figure 3.20.
  - Therefore, the overall reaction in Figure 3.21 takes an alkyl halide to an amine with one additional **methylene** (CH_2) interspersed.
    - This is called a **homologation** reaction, though you don't have to know that.

- Using the reduction of nitriles to synthesize 1,2-aminoalcohols.

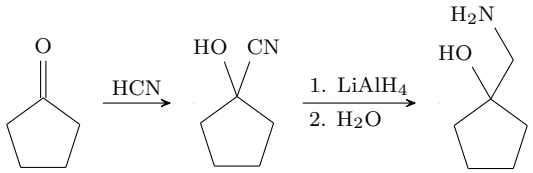
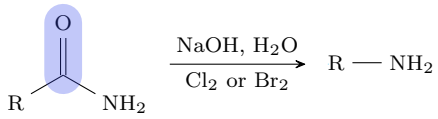


Figure 3.22: Reduction of nitriles: 1,2-aminoalcohol formation.

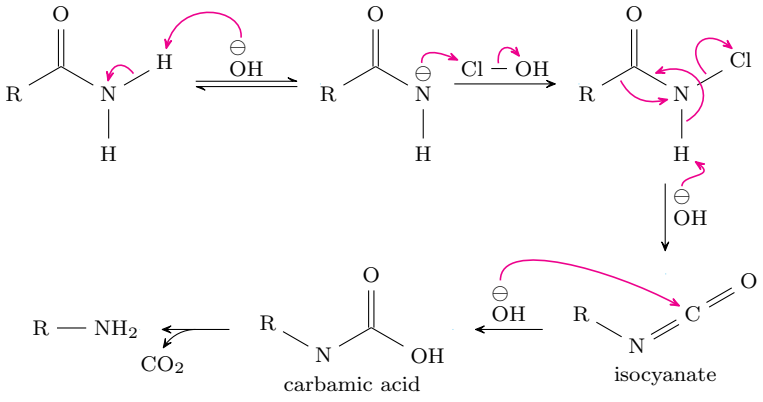
  - We begin with a ketone.
  - First step: Add HCN to reduce the ketone to a **cyanohydrin**, a quasi-stable intermediate..
  - Second step: Reduce the nitrile to afford the 1,2-aminoalcohol product.
  - Why do we care about 1,2-aminoalcohols?
    - Aside: Always ask why we care! Is it fundamentally interesting? Is there a practical application?
    - In this case, 1,2-aminoalcohols are critical to a number of pharmaceuticals, so that's why we care about being able to synthesize them.
  - Reading on cyanohydrin formation: Clayden et al. (2012, pp. 127–29).

- We now move onto Subtopic D.5: Miscellaneous reactions.

- The Hofmann rearrangement.



(a) General form.



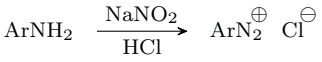
(b) Mechanism.

Figure 3.23: Hofmann rearrangement.

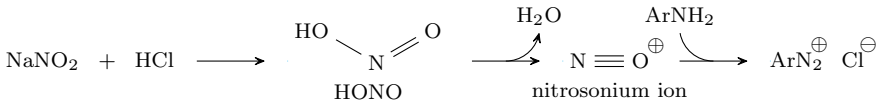
  - Figure 3.23a shows a very different kind of reaction from what we've seen.
    - This reaction starts with a primary amide and involves reduction to a primary amine, excising the CO highlighted in blue.
    - *Hint*: This reaction is related to the polymer problem on PSet 5!!
  - Reading: Clayden et al. (2012, p. 1022).

  - Let's now discuss the partial mechanism (Figure 3.23b).
  - First step: The base attacks an amide proton.
  - Second step: The amide anion grabs a halogen from a hypohalous acid.
    - Note that either hypochlorous acid (HOCl) or hypobromous acid (HOBr) will be formed *in situ* from the reaction of the hydroxide base with Cl_2 or Br_2, respectively.
    - The acid function as an X^+ equivalent, attracting the amide anion and leading to the formation of an *N*-chloroamide intermediate.
    - The amide halogen functions as an EWG, making the amide's remaining proton even more acidic than in the starting compound!
  - Third step: The extra-acidified *N*-chloroamide proton get attacked by an equivalent of base, leading to a significant rearrangement step.
    - This rearrangement produces an **isocyanate** intermediate.
  - Fourth step: The *sp*-hybridized carbon in the isocyanate reacts very rapidly to form a **carbamic acid** intermediate.
    - As with "homologation" reactions, we won't ask you to name "carbamic acids" on an exam!!
  - Fifth step: The carbamic acid spontaneously loses CO_2 to afford the amine.

- Forming an aryl diazonium salt ($ArN_2^+\ Cl^-$).



(a) General form.



(b) Mechanism.

Figure 3.24: Aryl diazonium salt formation.

  - Reading: Clayden et al. (2012, pp. 520–23).
  - First step: Sodium nitrite ($NaNO_2$) and HCl form **HONO** *in situ*.
  - Second step: HONO loses water and forms the **nitrosonium ion** *in situ*.
  - Third step: The nitrosonium ion then reacts with aniline to do the nitration.

- Next time (preview): A key reaction with aryl diazonium salts, related to the formation of an aryl diazonium salt from benzene.

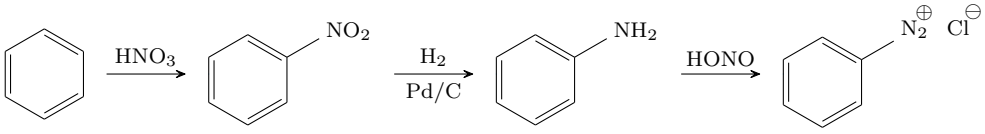


Figure 3.25: Synthesizing an aryl diazonium salt from benzene.