Unit 3

Amines

3.20 Special Topics

10/23:

- Grade cutoffs on Exam 2.
  - A-B cutoff: 80.
  - B-C cutoff: 60.
  - C-D cutoff: 45
  - Only F's were people who did not take the exam.
  - This was a significantly harder exam; y'all have been crushing it so far.
  - Remember that these grades are meant to give you a perspective for what you're on track for; they are *not* binding!
- Notes on Steve Buchwald.
  - He's a real big-name chemist: Has his name on a ton of reactions, can make a ton of pharmaceutical drugs, does a lot of consulting for chemical companies, etc.
  - But also super kind, humble, and nice.
  - Knows a ton, but is very down-to-earth and approachable.
- The rest of this course will be much more synthesis-heavy.
  - Feel free to continue to reach out to Prof. Elkin even though she's no longer at the blackboards!
- Today: We'll have fun and talk about machine learning.
  - Prof. Elkin will go through Beker et al. (2018), a paper about using machine learning to predict the outcome of Diels-Alder reactions.
- The basic idea of what the authors are saying is that if you encode the substituents, you get good prediction of the outputs!
  - Your computer doesn't know what a molecule is, so you have to encode your molecule in a way that is meaningful to a computer.
  - For example: You should not encode benzene with alternating single- and double bonds; benzene has six equivalent bonds due to resonance!
- Nowadays, computers can predict biological activities (doesn't work perfectly yet, though great progress), solubility and crystal structures (works fine), NMR spectra (works awesome), etc.
  - Predicting optimal reaction conditions works awesome.

- Predicting reaction outcomes or yields can be hit or miss.
- There have been maybe 1 000 000 chemical reactions ever catalogued, but most of them are not that useful.
- The low-data regime of predictive modeling is the final frontier, and the especially important one for chemistry.
- Taking high-level expertise and making it algorithmically applicable can be really difficult.
- "High accuracies are achieved only if the machine is provided some chemical 'insight' about the reaction (in particular, information about the reaction's core and key substituents)."
- While ML models cannot provide the generality of quantum mechanics, they work much faster.
- They trained the model with inverse electron-demand Diels-Alder reactions, Diels-Alder reactions that need to be site-selective, etc.
- The website to help you predict Diels-Alders is historical at this point, so don't worry if you can't access it in the paper.
- There are several classes on computational chemistry in both Course 5 and Course 10 if you're interested!
- A problem with Reaxys: All of the reactions in the database are data-scraped from old papers, so a significant number of them are wrong or incomplete (20-30%, and worse in other databases).
- Predictive modeling really reveals how difficult it is to predict reaction outcomes: Prof. Elkin has published papers where their model can predict yield far better than even chemistry experts.
- Conclusion: ML can be useful in predicting outcomes and can generalize to unseen reactions when descriptors carrying physically relevant information are used, and the machine gets appropriately formatted information.
- Note: None of this is testable material!

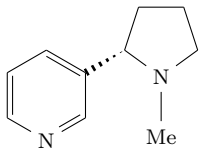
3.21 Amines - 1

10/25:

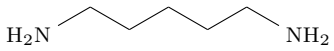
- New lecturer for the second half of the course: Prof. Steve Buchwald.
  - Born in Bloomington, Indiana.
  - Undergrad at Brown, PhD at Harvard, Postdoc at Caltech (with Bob Grubbs, a Nobel laureate).
  - At MIT for 40 years (since 1984).
  - Has two cats :)
  - Researches **organometallic chemistry**, with a focus on the synthesis of fine chemicals like pharmaceuticals.
    - Most organometallic chemistry is predicated on the development of ligands.
    - Many of Prof. Buchwald's ligands are named after his former cats!
    - Example: The RuPhos ligand is named after Prof. Buchwald's since-passed cat, Rufus.
- **Organometallic** (chemistry): A hybrid of organic and inorganic chemistry.
- Prof. Elkin is in Washington, D.C. today advising the federal government!

- Announcements.
  - The first half of this semester covered analytical techniques and physical chemistry; this half is more synthesis-focused.
  - Review your 5.12 reactions!! A list of what you need to know for PSet 5 will be posted on Canvas.
    - The teaching team will also keep a running list of reactions from this half of the course.
    - This will tell you what to know for the exams and PSets.
  - Prof. Buchwald will post "study guides" for each unit, containing all the unit's content.
    - Clayden et al. (2012) doesn't have a specific section on amines. Thus, the study guide lists all the pages spread throughout Clayden et al. (2012) where the different reactions can be found.
    - If you still have Smith (2023) — your 5.12 textbook — it's Chapter 23.
  - Plan: This lecture and the following one will cover amines.
    - Amines have a special place in Prof. Buchwald's heart because they're connected to a lot of his research!
  - Like Prof. Elkin, Prof. Buchwald will continue giving fun facts that relate these topics to the real world.
- Outline for the next two lectures.
  A. Intro.
  B. Chirality (or "handedness;" recall from 5.12).
  C. Brønsted basicity.
  D. Synthesis and reactivity (we'll spend the majority of our time on this topic).
     1. Alkylation of ammonia and alternatives.
     2. Reductive amination.
     3. Acylation and reduction.
     4. Reduction of nitriles (i.e., R–C≡N functional groups).
     5. Other miscellaneous methods.
- Today: We'll cover Topic A through most of Topic C.
- We now begin with Topic A: Introduction.
- **Amine**: An R_3N compound, where each R may be distinct and R is an H, alkyl, or aryl group.
- The simplest amine is ammonia (NH_3).
  - Notice that ammonia *is* an amine by the definition: All of its R groups are identically equal to H!
  - Fun fact: Ammonia is a necessary ingredient in fertilizer.
    - It is prepared industrially from N_2 using the Haber-Bosch process.
    - One could make a reasonable argument that the industrial production of ammonia is the most important technological advance in the history of the world.
      - ➢ This is because it enabled us to produce far more fertilizer, so that we could produce more food, so that we can feed a population of seven billion people.
    - Before Haber-Bosch, fertilizer came from an island covered in bird feces.
    - Two Nobel prizes were awarded in connection with the development of this process.
      - ➢ Haber won the Nobel Prize for his work on this process in 1918 (for the process).
      - ➢ Bosch won the Nobel Prize for his work on this process in 1931 (for high-pressure chemistry).

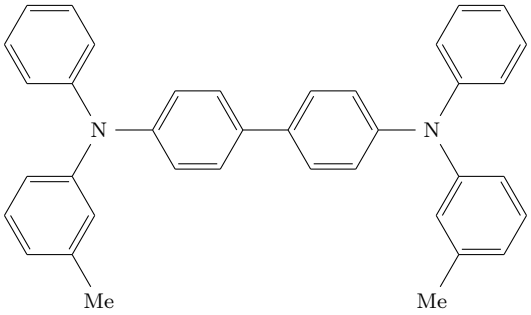
- Examples of amines.



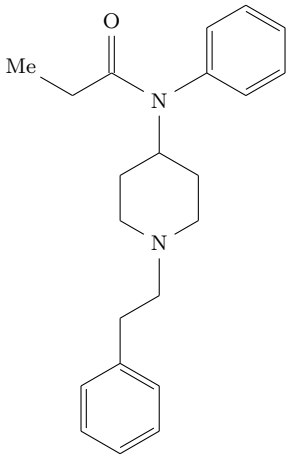
(a) Nicotine.



(b) Cadaverine.



(c) TPD.



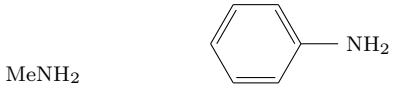
(d) Fentanyl.

Figure 3.1: Amine examples.

  - The top-selling pharmaceuticals in the world are all amines, at least in part.
    - Not all of these "pharmaceuticals" are fun, though! Some are illicit drugs.
  - Example: Nicotine (Figure 3.1a).
    - It's one of the most difficult habits to break.
    - There are drugs that mimic the structure of nicotine but bind to the receptor better and block nicotine from doing its job.
  - Example: Cadaverine (Figure 3.1b).
    - Does not smell good.
    - When animals die, their flesh putrifies/rots and this is what causes the smell.
  - Example: TPD (Figure 3.1c).
    - This is a hole transport agent commonly found in the toner cartriges of laser printers.
  - Example: Fentanyl (Figure 3.1d).
    - A synthetic opioid that has caused unbelievable amounts of societal problems.

- Classes of amines.
  - Ammonia (NH_3).
    - Good because it helps feed the world.
    - Bad because it's a toxic gas and smells horrible.
  - **Primary amines**.
  - **Secondary amines**.
  - **Tertiary amines**.
  - **Quaternary ammonium salts**: A related family of comounds.

- **Primary** (amine): An amine in which we've replaced one of the H's in ammonia with an (alkyl or aryl) R group. *Denoted by* **1°**. *General form* RNH_2.

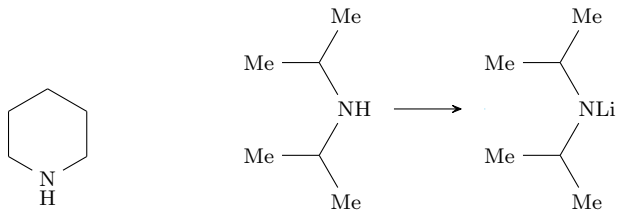


(a) Methylamine. (b) Aniline.

Figure 3.2: Primary amine examples.

  - Example: Methylamine (Figure 3.2a).
    - A gas like ammonia, but a liquid under pressure.
    - It's a controlled substance.
      - ➢ In *Breaking Bad*, this is what Walt, Jessie, and Todd heisted from the train!
  - Example: Aniline (Figure 3.2b).
    - Very important historically: Modern chemistry began in the 1800's with aniline-based dyes.
      - ➢ These companies are the precursor to modern-day pharmaceutical companies!

- **Secondary** (amine): An amine in which we've replaced two of the H's in ammonia with (alkyl or aryl) R groups. *Denoted by* **2°**. *General form* RR′NH.



(a) Piperidine. (b) Diisopropylamine and LDA.

Figure 3.3: Secondary amine examples.

  - The R groups can be separate, or they can be linked together.
  - Example of a cyclic secondary amine: Piperidine (Figure 3.3a).
    - Piperidine is important in a number of applications, including sequencing DNA.
  - Example of an acyclic secondary amine: Diisopropylamine (Figure 3.3b).
    - If you replace the amine hydrogen with lithium, you get lithium diisopropylamide (LDA).
      - ➢ This is a very strong base that we'll talk more about later in this course.

- **Tertiary** (amine): An amine in which we've replaced all three of the H's in ammonia with (alkyl or aryl) R groups. *Denoted by* **3°**. *General form* RR′R″N.

- **Quaternary ammonium salt**: A nitrogen covalently bonded to four R groups (and hence having a positive formal charge), coordinated to a negative counterion. *General form* $R_4N^+ X^-$.

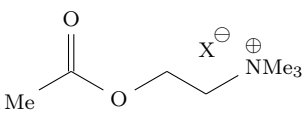


Figure 3.4: Quaternary ammonium salt example.

  - Example: Acetylcholine, an important neurotransmitter (Figure 3.4).

- This concludes our introduction to amines.
- Aside: Prof. Buchwald *strongly* recommends you show up for lecture the day before Halloween :)
- We now move onto Topic B: Chirality.
- Recall from 5.12 that some compounds are *chiral*, i.e., they can have enantiomers.

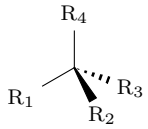


Figure 3.5: A chiral compound.

  - These enantiomers can often be separated.
  - They can also have different biological activities.
    - Fun fact: The FDA now requires all chiral molecules to be prepared in both enantiomers and independently tested, in part because of the thalidomide scandal.
- The structure of amines.

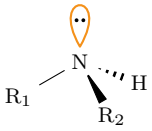


Figure 3.6: Amine structure.

  - Amines are sp^3-hybridized with a tetrahedral electron pair arrangement.
    - 3 bonding orbitals and 1 lone pair (lp).
  - The lp is responsible for the Brønsted basicity of amines.
  - If one of the R groups is hydrogen, then the amine can participate in hydrogen bonding (a very important interaction you should recall from Gen Chem).
- Is pyridine a tertiary amine?
  - Technically, yes; we'll discuss pyridine next lecture.
- Amines have two enantiomers as well.

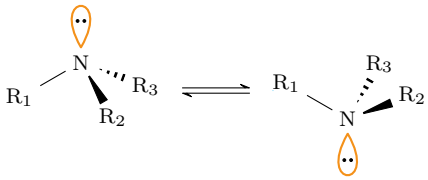


Figure 3.7: Amine enantiomer interconversion.

  - The energy barrier ($\Delta G^{\ddagger}$) between the two enantiomers is 5-6 kcal/mol.
  - Additionally, note that if $\Delta G^{\ddagger} \leq 20$ kcal/mol, the process is fast at room temperature.
  - Thus, amine enantiomers rapidly interconvert at room temperature, so we (usually) cannot resolve amines into individual enantiomers.
    - One time we can resolve amines into enantiomers is in the case of **aziridines**.

- **Aziridine**: A three-membered ring containing one nitrogen and two carbons. *Structure*

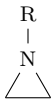


Figure 3.8: Aziridine.

  - These are the amine equivalent of an epoxide.
  - Like in any other amine, R can still be H, alkyl, or aryl.
  - The sp^3-hybridized atoms all want to have 109° bond angles but are strained to 60°.

- In order for aziridines to undergo **racemization**, the molecules must go through a transition state with an sp^2-nitrogen.

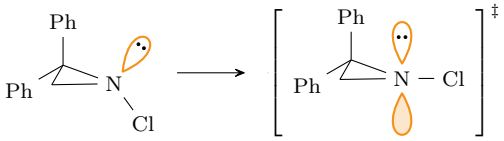


Figure 3.9: Aziridine enantiomer interconversion.

  - This sp^2-nitrogen wants to have 120° bond angles but is still strained down to 60°.
    - This is even worse than the strain in an sp^3-nitrogen!
  - Thus, the energy barrier to aziridine enantionmer interconversion is $\Delta G^\ddagger \approx 24\,\text{kcal/mol}$.
  - Therefore, (many) aziridines *do not* interconvert at room temperature because $24 > 20$.

- **Racemization**: The interconversion of enantiomers.
- This concludes our discussion of chirality.
- We now move onto Topic C: Brønsted basicity.
- Consider the following two protonation reactions.

(a) Methanol. (b) Methylamine.

Figure 3.10: Basicity of methanol vs. methylamine.

  - For $MeOH_2^+$, $pK_a \approx -2$.
    - This means that $MeOH_2^+$ is very acidic.
    - It follows that MeOH is only weakly basic.
  - For $MeNH_3^+$, $pK_a \approx 9 - 11$.
    - Thus, $MeNH_2$ is *much* more basic than MeOH.

- Something critical to everyday life: Why do fish smell so bad after they die?

Figure 3.11: Amines explain why fish smell, and how to season them!

  - 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.

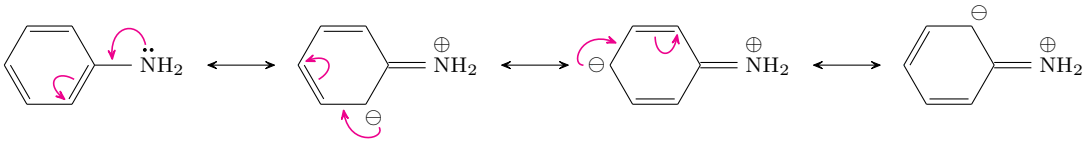


Figure 3.12: Basicity of aniline.

  - 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.

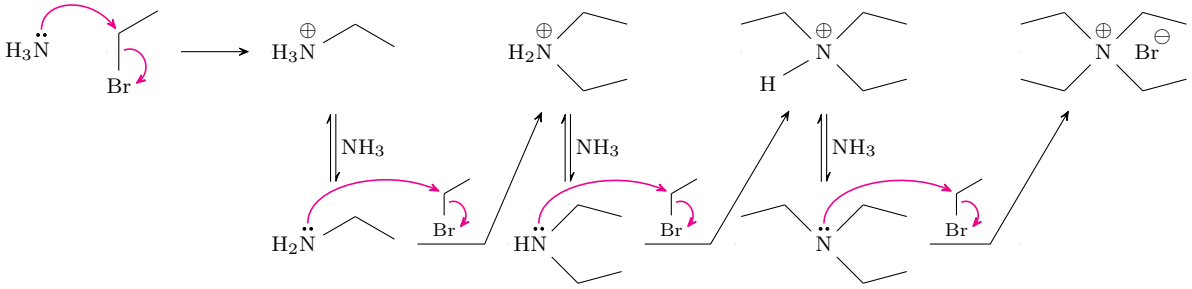


Figure 3.13: Alkylation of amines from ammonia and an alkyl halide.

  - 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.

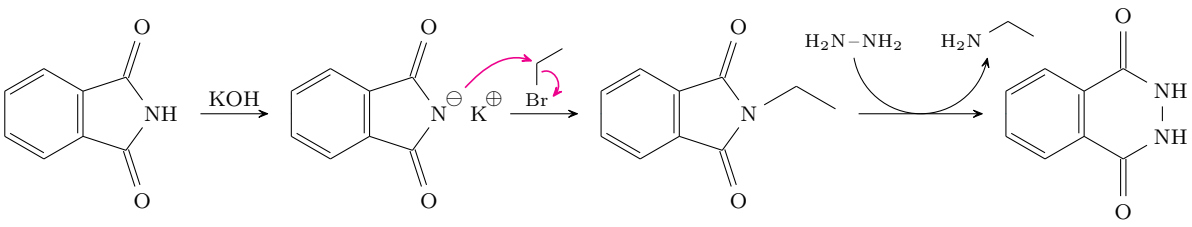


Figure 3.14: Gabriel synthesis.

[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.

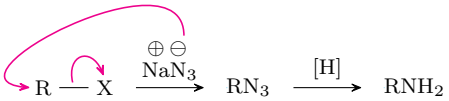


Figure 3.15: Reduction of azides.

  - 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.

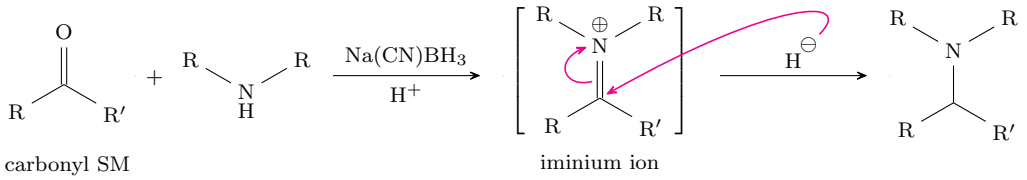
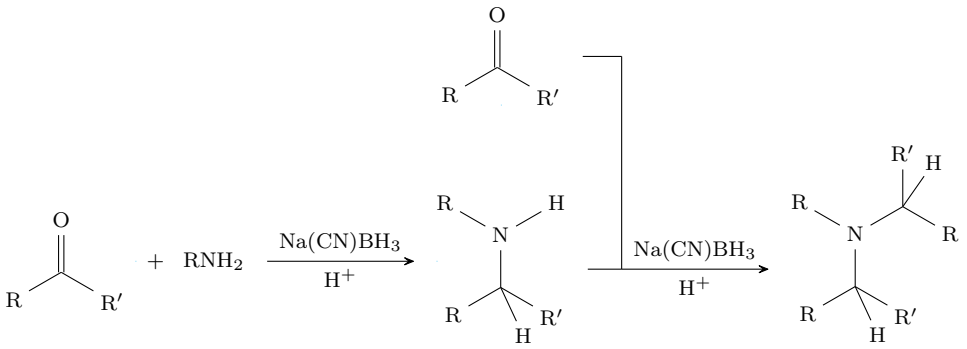


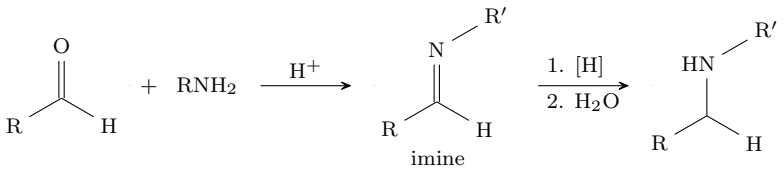
Figure 3.16: Reductive amination: $2° \rightarrow 3°$.

  - 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.



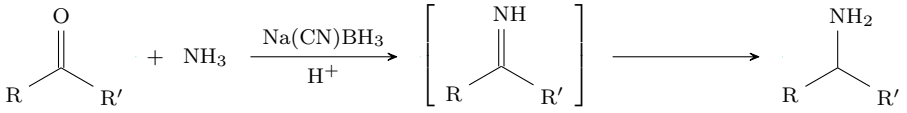
(b) Separate imine formation and reduction.

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

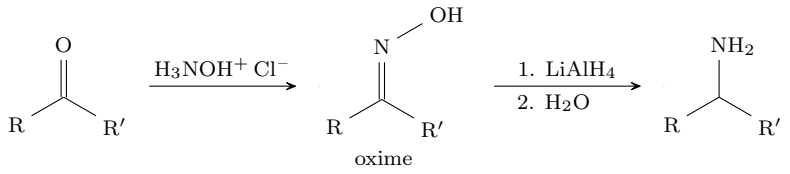
  - Let's first try using the same conditions as in Figure 3.16.
    - If we do this, we run into the same problem as in Figure 3.13.
    - In particular, the product of the first reductive amination in Figure 3.17a is a secondary amine and hence can react again to yield the rightmost product in Figure 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.

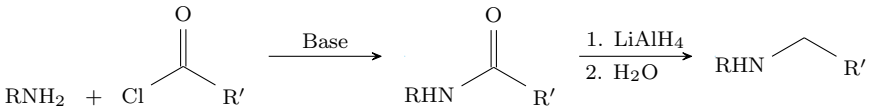


Figure 3.19: Monoalkylation by acylation and reduction.

  - 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.

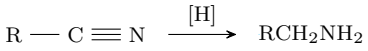


Figure 3.20: Reduction of nitriles.

  - 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.

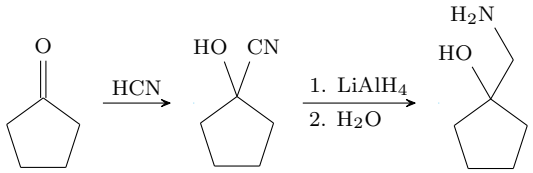
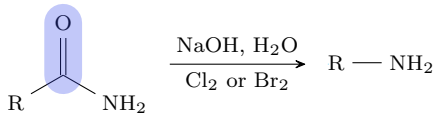


Figure 3.22: Reduction of nitriles: 1,2-aminoalcohol formation.

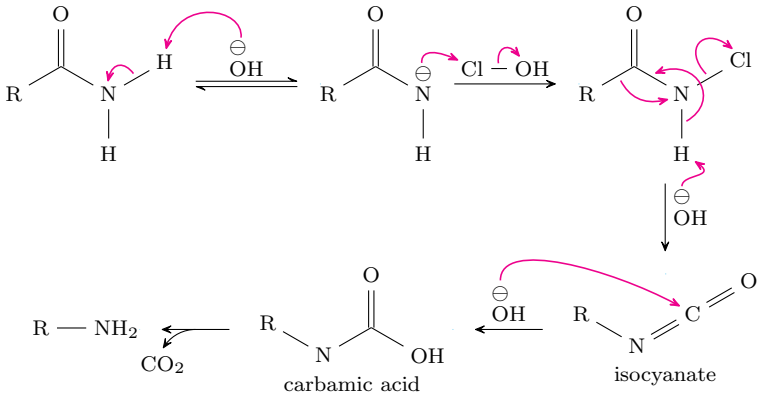
  - We begin with a ketone.
  - First step: Add HCN to reduce the ketone to a **cyanohydrin**, a quasi-stable intermediate..
  - Second step: Reduce the nitrile to afford the 1,2-aminoalcohol product.
  - Why do we care about 1,2-aminoalcohols?
    - Aside: Always ask why we care! Is it fundamentally interesting? 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.



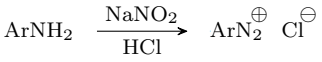
(b) Mechanism.

Figure 3.23: Hofmann rearrangement.

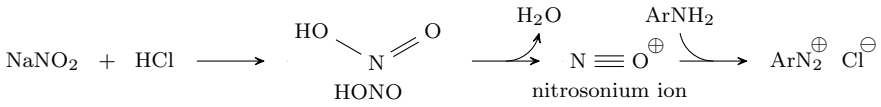
  - Figure 3.23a shows a very different kind of reaction from what we've seen.
    - This reaction starts with a primary amide and involves reduction to a primary amine, excising the CO highlighted in blue.
    - *Hint*: This reaction is related to the polymer problem on PSet 5!!
  - Reading: Clayden et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

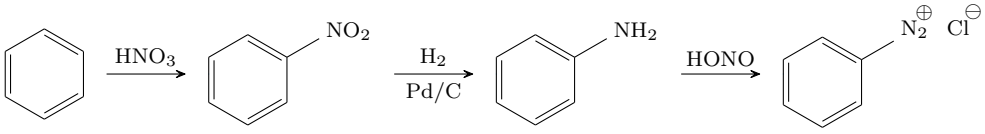


Figure 3.25: Synthesizing an aryl diazonium salt from benzene.