Topic 1

Pyridine Chemistry

1.1 Intro, Directed Metallation, and Organometallic Coupling

1/4:

- Announcements.
  - This class is a survey course; it is not comprehensive.
  - This class has a different philosophy from mainstream heterocyclic chemistry; we'll focus not on the "coolest" chemistry, but the chemistry that actually gets used.
    - Focus on *Journal of Medicinal Chemistry* and process chem journals.
    - Steve does not believe that academic research has to be useful, but...
    - Steve believes: Proof is in the pudding. If you're pretending what you're doing has some practical application, you should see it going after 5 years.
  - Grader: Dr. Dennis Kutateladze.
    - He grades the 2 exams; Steve writes both of them.
  - There are PSets (ungraded, but keys posted).
  - This is supposed to be a very low-key class; getting a good grade should be easy.
    - The goal is to expose you to a lot of different useful chemistry.
    - Don't look up PSets; goal is not to impress Steve, but to learn the material.
  - 2 exams + project; (project is graded for completion and effort).
    - With 20+ students, probably all of the last 3 classes will be dedicated to presentations.
  - Joule and Mills (2010) is somewhat dated.
    - "A lot of heterocyclic chemistry is ancient."
  - Organometallic methods come a bit more to the fore in this rendition because Allison isn't currently teaching 5.44 - Organometallic Chemistry.
  - The final project.
    - Most drugs come from the new FDA approvals from last year.
    - We should put together a 10-minute PowerPoint presentation in which we discuss the disease, how it was discovered, the MedChem synthesis, the process synthesis, the competitors, etc. Emphasis on medchem and process syntheses.
    - Look at patents, primary papers, etc. Do *not* find a review article and summarize it.
    - Goal: If we were interested in a compound for our research or job, how would we go about finding material on it?

- Mostly looking at aromatic heterocycles, e.g., not piperidines or tetrahydrofurans.

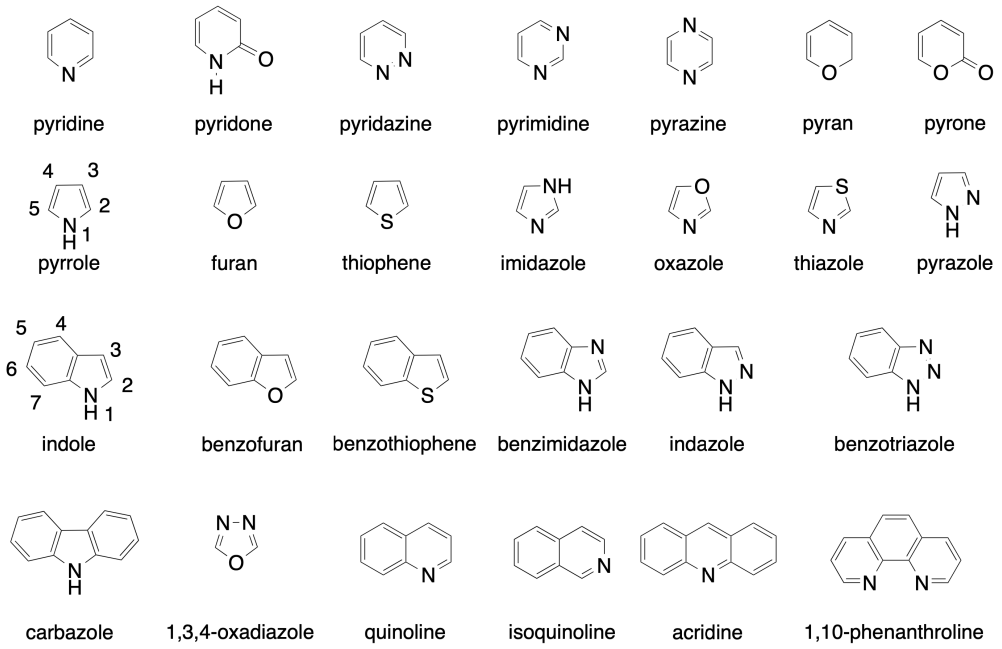


Figure 1.1: Heterocycles of interest.

  - We don't need to know the names of all the heterocycles, but we should learn the big ones!!
  - Interesting heterocycles often contain because it can be protonated, and it hydrogen bonds.
    - Hydrogen bonding is useful for receptors, salt bridges, etc.
  - Salts of these compounds usually imply some kind of water solubility.
  - **Pharmacokinetics** are often moderated by heterocycles.
    - Making the drug hang around for the right amount of time is super important, because the more times per day people have to take the drugs, the more that compliance goes down (especially among the elderly population).

- Blockbuster drugs.
  - Several examples given.
  - Imbruvica Janssen is a covalent drug, doing a Michael addition to DNA.

- Infamous drugs.
  - Lipitor.
    - A **statin**, i.e., a cholesterol-lowering agent.
    - One of the most important drugs in the last century in extending people's lifetimes.
    - Anyone over 50 either has taken one (or should take one, in Steve's opinion!).
  - Quinine.
    - Anti-malarial.
    - Also in gin and tonics!
  - Strychnine.
    - Rat poison.
    - Big target in synthetic chemistry, starting with Woodward.

  - β-lactam antibiotics.
    - Penicillin, and the ring-expanded cephalexins.
  - Thalidomide.
    - Caused the big push for the sale of single-enantiomer drugs!

- Pyridine.
  - Horrible-smelling, polar solvent.
  - Originally came from coal tar (precursor to petroleum).

- Current synthesis of pyridine.

$$CH_3CHO + H_2CO + NH_3 \xrightarrow[\text{Si/Al cat}]{\text{vapor phase}} \text{Py} + \text{3-MePy}$$

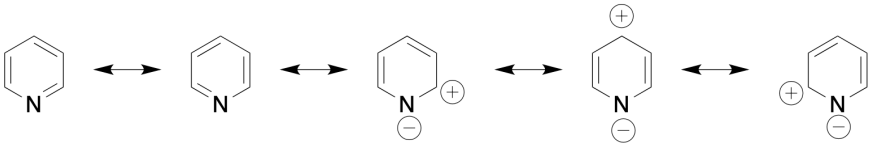
  - This synthesis is carried out with flow chemistry.
    - Before it was trendy in pharma, it is the only thing that was *ever* used in the production of commodity chemicals.
    - When you're making commodity chemicals, you can't afford solvents or separations.
  - It produces pyridine on a scale of 20,000 tons per year.

- Aside: Many chemicals are produced from such "magic reactions."
  - Example: Acrylonitrile.
    - Industrial synthesis: Mix propene and ammonia with a molybdenum/vanadium catalyst.
  - Example: THF.
    - Industrial synthesis: From butane!
  - "I mean, how?! Write a mechanism for that!"

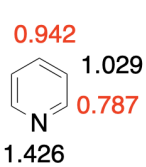
- Many drugs contain pyridine moieties. Here are some examples.
  - Muscopyridine: Perfumes.
  - Prevacid: Acid reflux.
  - Nexium: Sold as a single-enantiomer with a stereogenic sulfur atom!

- The pharmaceutical industry is largely focused on old people because it's a huge market share.
  - Pain, sleep, etc. are huge.
  - As you get older, your body starts to break down.
  - Alzheimers is a big target, but not much success so far.

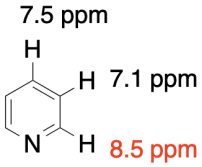
- The structure of pyridine.



(a) Important resonance forms.



(b) π-electron populations.



(c) ^{1}H NMR shifts.

Figure 1.2: Pyridine structure.

  - Analogous to benzene; slightly less aromatic, but very similar.
  - Insights from the ^{1}H NMR.
    - *ortho*-proton shifts significantly downfield, *meta*-proton is largely unaffected, and *para*-proton shifts downfield a bit.
    - This is because there are resonance structures where we put δ^+ on the 2,4,6-positions, while the *meta*-positions take a slight δ^-.
  - Strong dipole (2.2 D) toward the nitrogen atom.
  - More π-electron density on nitrogen than anything else.

- Reactivity of pyridine.
  - Can be reduced to piperidines, sometimes with selectivity, sometimes enantioselectively.
  - Minisci-type radical reactions.
  - As an electrophile.
  - As a Lewis base.
  - As a Brønsted base.
  - As a nucleophile.
  - As a reductant.
  - Very different electrophilic aromatic substitution (EAS) reactivity compared to benzene. You really need activating EDGs with pyridine!
  - Nucleophilicity is most likely to happen at the nitrogen atom.
  - S_NAr is most likely to happen at the electron-deficient 2,4,6-positions.
  - EAS is most likely to happen at the relatively electron-rich *meta*-positions.

- Pyridine as a base or nucleophile.
  - $pK_a \approx 5.5$; much less basic than piperidine.
  - Basicicity is modulated by EDGs/EWGs.
  - Pyridine can be transformed from a good to a great nucleophile with some EDGs, e.g., with DMAP.
    - DMAP provides rate enhancements of up to 10^4.

- Pyridine reactivity trends.
  - Much of pyridine reactivity is driven by...
    - Avoiding a δ^+ charge on N.
    - That pyridine is a π-deficient heterocycle (like pyrrole).
  - Brute force conditions can yield sulfonation.
    - The nitrogen would usually react with the electrophile first, and then the product is 10^8 times less reactive than pyridine, alone.

- Nucleophilic aromatic substitution (S_NAr) with pyridine.
  - Much better with pyridine than with benzene!
  - Charged intermediates (e.g., where the N has coordinated to E^+) react *exceptionally* fast.
  - 2,4-chloro is better because you can delocalize the negative charge onto the nitrogen.

- Example pyridine reactivity: Biological oxidation of alcohols to aldehydes.
  - Done with NAD^+ and a pyridine derivative!

- Pyridones.

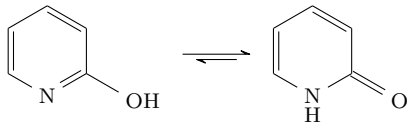
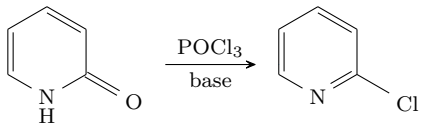


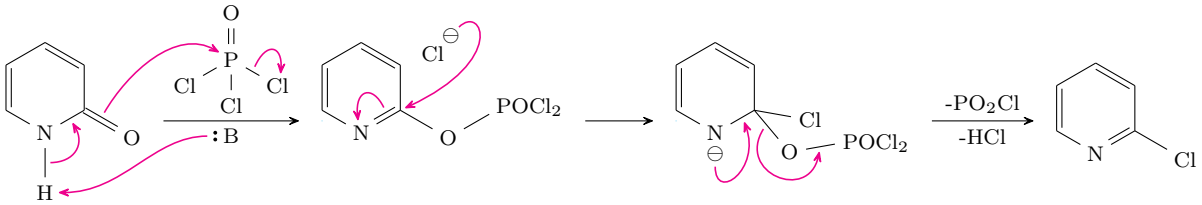
Figure 1.3: Pyridone tautomerization.

  - 2-pyridone (Figure 1.3): Both tautomers are aromatic, but pyridone has stronger BDEs.
  - 4-pyridone: Still the ketone form.
  - 3-pyridone: Forms the zwitterion.

- Pyridone reactivity.



(a) The reaction.



(b) The mechanism.

Figure 1.4: Pyridone chlorination.

  - $POCl_3$ is one of the most used species in heterocyclic chemistry.
  - It works so well because P=O bond formation is an *excellent* driving force.

- Directed metallation — see Labalme (2024).
  - Has been around for a while.
    - Sigma-Aldrich catalogs have thousands of monosubstituted aromatics, probably still thousands of disubstituted aromatics, but very few (very expensive) tri-substituted aromatics.
    - Example: Buy anisole, and then you can very easily upgrade it with directed metallation.
  - Pioneers: Victor Snieckus (Queen's University) and Peter Beak (UIUC).
  - Two mechanistic theories: Binding to the functional group, and an inductive effect of acidification.
    - An expert in lithium chemistry at Cornell has shown that the inductive effect is more important, at least in the case of anisole, contrary to 5.511!
  - Per Steve, this is one of the most important transformations in organic chemistry.
  - Common directing groups.
    - Aryl ethers, 3° amides, MOM ethers, 3° carbamates, and 3° sulfonamides.
    - For π-deficient heterocycles (e.g., pyridine), also: F, Cl, Br, CF_3, CO_2^-.
  - References: Snieckus (1990), Hartung and Snieckus (2002), El-Hiti et al. (2015).

- Pyridine preferably undergoes metallation *not* adjacent to the nitrogen.
  - N–Li binding kinetically favors lithiation at the *ortho*-positions.
  - However, having two lone pairs so close together is thermodynamically disfavored, presumably because of Coulombic repulsion between the electron pairs, i.e., the **α-effect**.
  - Indeed, lithiation actually prefers to happen at the more acidic *para*-position, which is still δ^+ but has less coulombic repulsion.
  - Remember that pK_a is a *thermodynamic* function.
- DMGs on pyridine.
  - Most *meta*-DMGs direct to the *para*-position: Cl, F, MOM ethers, siloxane ethers, bulky 3° amides (e.g., $C(O)N^iPr_2$), and bulky amides bonded through the nitrogen.
  - *meta*-OEt directs to the *ortho*-position.
  - Review some typical lithiation and functionalization reactions from 5.511.
    - LDA lithiates 3-chloropyridine at $-23\,^\circ C$ instead of eliminating to the benzyne derivative (as it would at a higher temperature).
  - References lithium halogen exchange.
- Lateral deprotonations.
  - *ortho*- and *para*-methylpyridine like to deprotonate "benzylically" much more than toluene because of additional nitrogen stabilization.
    - Indeed, the pK_a of the 2,3,4-positions is 29.5, 33.5, and 26, respectively.
    - In contrast, toluene's pK_a is 42.
  - Decarboxylation can be useful for substitution reactions.
    - Example: Mixing 2-pyridylacetic acid with a base leads to decarboxylation and the formation of 2-methylpyridine upon workup.
  - Thermodynamic vs. kinetic lateral deprotonations.
    - Consider 2,4-dimethylpyridine.
    - Bases of comparable strength (e.g., LDA) deprotonate thermodynamically at the 4-position.
    - Stronger bases with aggregates broken up by the directing nitrogen (e.g., ^{n}BuLi) deprotonate kinetically at the 2-position.
    - Interestingly, adding ^{n}BuLi and then an amine base allows for equilibration from the kinetic 2-lithiated to the thermodynamic 4-lithiated species!
    - Reference: Evans et al. (1999, p. 90).
- How could we convert 2-chloro to 2-methylpyridine?

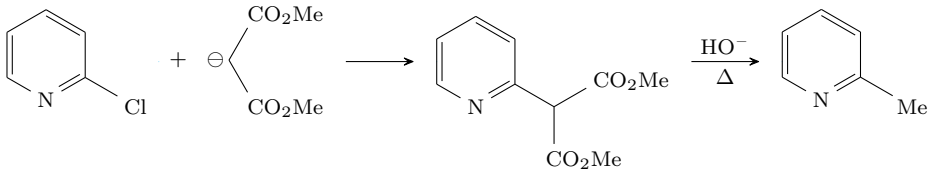
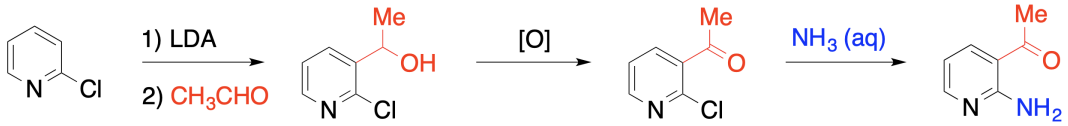


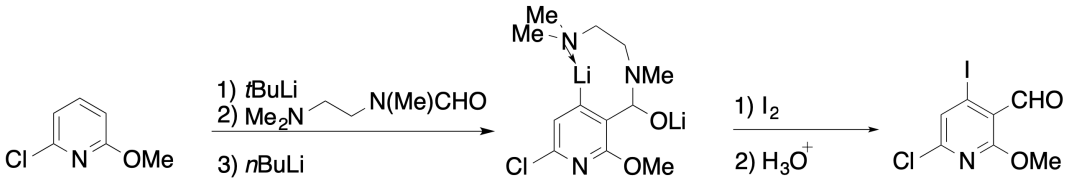
Figure 1.5: Lateral pyridine decarboxylation in robust synthesis.

  - General rule: If you can use chemistry from the 1920s, it will work better than chemistry from the 2020s.
  - Lab scale: Do cross-coupling with methyl boronic acid and a palladium catalyst.
  - 100 ton scale: Use a malonate anion and then double decarboxylation.

- Pyridines as ylide-like species.



(a) Preparation of pyridyne "ylides."



(b) 3,4-difunctionalization.

Figure 1.6: Multifunctionalization of pyridines.

  - You can form what is essentially a ylide between the 2- and 3-positions of the pyridyne by adding an EWG adjacent to a S_NAr position (Figure 1.6a).
    - Essentially, we begin with a species that has a DMG which can also (later on) do S_NAr.
    - We use it as a DMG to functionalize the adjacent position with an EWG of interest.
    - The EWG makes the ring even more activated toward S_NAr.
    - Thus, we've essentially added a nucleophile and electrophile to pyridine very quickly.
  - Can get fancier with 3,4-disubstitutions (Figure 1.6b).
    - The stronger methoxy DMG lithiates at the 3-position. We then add a TMEDA-like species and use it to lithiate at the 4-position.
    - An electrophile can then add at the 4-position, and we can cleave off TMEDA with an acid workup.
  - Steve skips the last reaction (using a *para*-carbamate to asymetrically functionalize both *meta*-positions).

- Aside on medchem.
  - *Yield* and *ee* are things we fixate on as academics, but medicinal chemists don't care.
  - "People who are unsuccessful spend a lot of time optimizing something that doesn't end up working out."
  - It's much more important to be able to get a mockup of the drug to test, and then they'll get a better working reaction later if need be.

- The **Chichibabin reaction**.

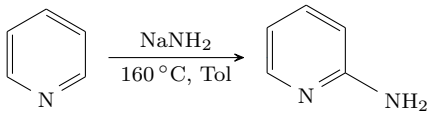


Figure 1.7: Chichibabin reaction.

  - Makes 2-aminopyridine from pyridine.

- Activating pyridine toward sp^2- and sp-Grignard reagents.
  - If we treat pyridine with an acid chloride or other EWG, it adds in to form an activated 'amide.'
  - We can then easily do S_NAr at the 2-position with ArMgX, ViMgX, or an alkynyl Grignard.
  - This reaction is *not* selective for alkyl Grignards.
- Pyridine isn't very good at EAS, but pyridine N-oxide can do it better.
- Synthesis of a pyridine N-oxide.

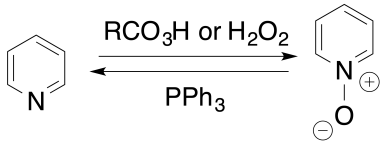


Figure 1.8: Synthesis of pyridine N-oxides.

  - Reversibly synthesize with peroxides, and PPh_3.
- The counterintuitive result of pyridine oxidation is that the ring becomes *more* electron-rich, because now the oxyanion's lone pairs donate in!
  - Thus, for example, pyridine N-oxide reacts under nitration conditions to yield 4-nitropyridine N-oxide.
  - As another example, **fuming sulfuric acid** and bromine lead to bromination at the 3-position.
    - This is because the reaction is thought to proceed via oxygen coordination to HSO_3^+.
  - $POCl_3$ can also covert pyridine N-oxide to 2-chloropyridine.
    - BMS and Phil Baran have somewhat supplanted this reaction (Wengryniuk et al., 2013).
- **Fuming sulfuric acid**: A mixture of H_2SO_4 and SO_3.
- We now move onto transition metal-catalyzed cross-coupling.
- TM-catalyzed cross-coupling has revolutionized the pharmaceutical industry, and somewhat distorted it.
  - New drugs have a lot of biaryls because they're easy to make, probably not because they're optimal.
  - Few reactions work with as much generality and substrate scope as cross-coupling.
- Steve reviews the typical catalytic cycle for cross-coupling.
- Top reactions in the pharmaceutical industry.
  - Amide-bond formation (huge!), and reductive amination.
- List of cross-coupling reactions.
  - Usually palladium- or nickel-catalyzed; some with copper.
  - Kumada and Corriu developed a nickel-catalyzed cross-coupling that would have won the Nobel prize except that Kumada died.
  - Negishi realized that a lot of magnesium reagents had functional group compatability issues.
    - He went through zirconium before he got to zinc.

  - Stille probably had the best coupling, but he died in a plane crash. Functional group compatability and ease of separation of products is ideal with this, but it's not used as much any more due to toxicity concerns.
  - Miyaura was an associate professor under Suzuki at Hokkaido who actually discovered this stuff.
    - Most widely used because of ease and low toxicity.
  - Heck probably understood the chemistry the best; he was a remarkable individual in Steve's estimation.
    - 7 single author back-to-back ($\times 7$) JACS publications.
      - ➢ References: Heck (1968a), Heck (1968e), Heck (1968c), Heck (1968f), Heck (1968d), Heck (1968b), and Heck (1968g).
    - Timing is everything, and he published it too early.
    - He was retired by the time he won the Nobel prize.
  - Ullmann was one of the first.
  - Carbonylation: Aryl palladium with CO forms the acyl palladium that reacts just like an acid halide.

- Ligands for CC.
  - $Pd(PPh_3)_4$ is classic.
  - Large bulky things turn out to be better.
  - Having a bottom second ring (as in Buchwald ligands) also turns out to be useful.
  - The principal: L_4Pd is unreactive; L_2Pd is quite good but hard to get to; L_1Pd is ideal. What the different ligands do is change the stability of the coordination environments. Buchwald ligands allow you to get down to L_1Pd species.
  - Cone angle and percent buried volume are what is modulated by diarylbialkylphosphines.
  - Trialkylphosphines and *N*-heterocyclic carbenes can also be useful.
  - References.
    - Walker et al. (2004) — Steve's original report of SPhos and XPhos for Suzuki-Miyaura coupling.
    - Martin and Buchwald (2008) — Review of Steve's dialkylphosphinobiaryl ligands.

- Suzuki-Miyaura couplings.
  - Hundreds of thousands of examples in the literature.
  - Pd/C leaches a bit and can do the chemistry.
  - You can also use ligands for more complicated stuff.