5.45 (Heterocyclic Chemistry) Notes

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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.

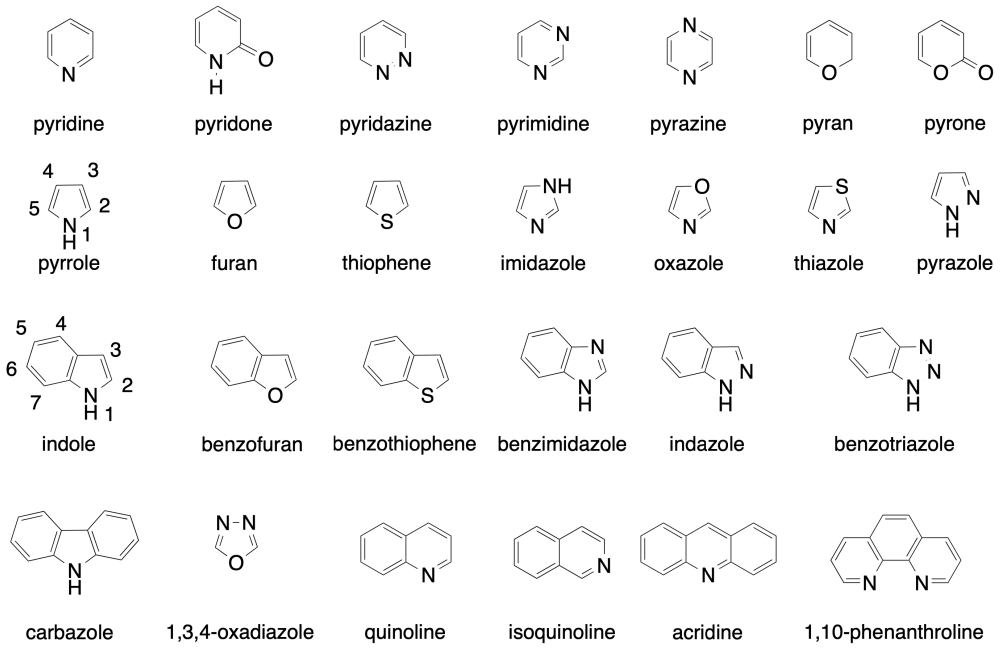


Figure 1.1: Heterocycles of interest.

  - 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.

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

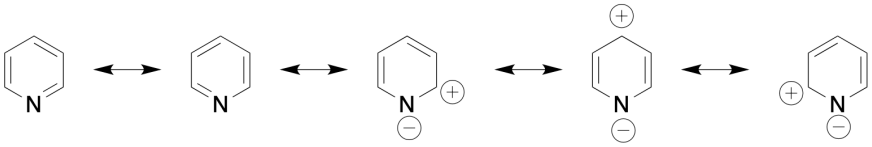
  - This synthesis is carried out with flow chemistry.
    - Before it was trendy in pharma, it is the only thing that was *ever* used in the production of commodity chemicals.
    - When you're making commodity chemicals, you can't afford solvents or separations.
  - It produces pyridine on a scale of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

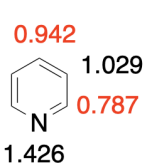
- Many drugs contain pyridine moieties. Here are some examples.
  - Muscopyridine: Perfumes.
  - Prevacid: Acid reflux.
  - Nexium: Sold as a single-enantiomer with a stereogenic sulfur atom!

- 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.

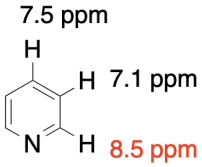
- The structure of pyridine.



(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.

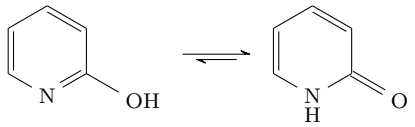
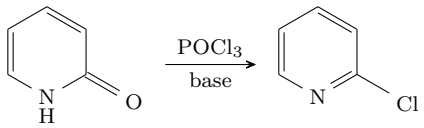


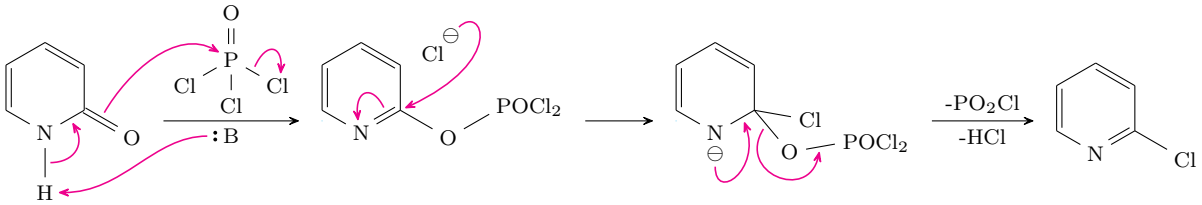
Figure 1.3: Pyridone tautomerization.

  - 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?

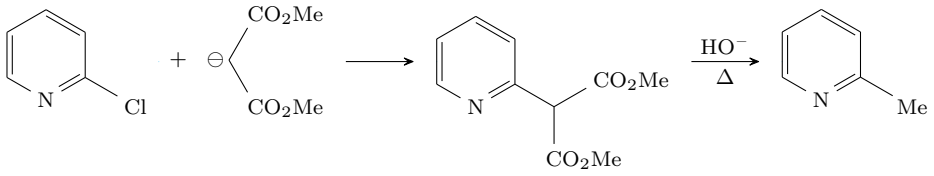
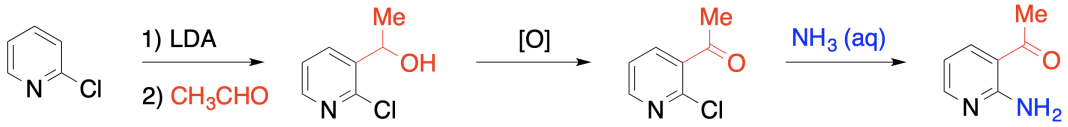


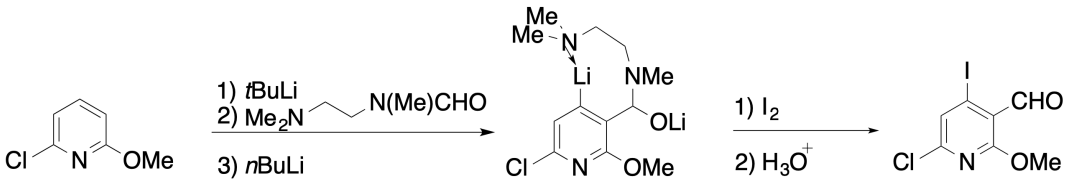
Figure 1.5: Lateral pyridine decarboxylation in robust synthesis.

  - 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).
  - Important note: Phenols are often hydrogenated with $POCl_3$ conversion to the chloride, and then $H_2 + Pd/C$, RaNi, transfer hydrogenation, etc!!

- 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**.

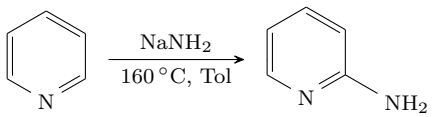


Figure 1.7: Chichibabin reaction.

  - 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.

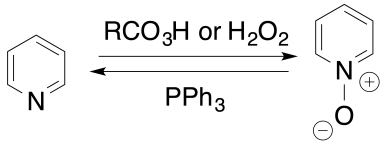


Figure 1.8: Synthesis of pyridine N-oxides.

  - 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.
    - R. 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.

1.2 Pyridine Cross-Coupling, Synthesis, and Derivatization

2/6:

- Announcements.
  - I am assigned compound No. 10 for the final project.
  - PSet 1 posted.
    - If you get stuck on a problem, don't do it!
    - Don't spend more than 3 hours on the PSet.
    - Spending 27 hours on this PSet demonstrates "a *decided* lack of judgment."

- Lecture begins: Back to cross-coupling.

- A major disadvantage of cross-coupling in synthesis: The amount of catalyst left behind.
  - Examples.
    - Pd, Rh, Ir: You can have 10 ppm residual in your **API**.
    - Ni: 20 ppm.
    - Cu: 300 ppm.
  - API: Active Pharmaceutical Ingredient.
  - There is a cottage industry of removing trace metals after reaction. Common methods include...
    - Adsorption onto surfaces;
    - Oxidation with swimming pool bleach;
    - Fancier solid-supported resins with ligands.
- We'll talk mostly about palladium-catalyzed cross-coupling.
  - Pd is used in 95% of applications.
    - Ni is the other 5%, since it has decided process benefits (cheaper, lower toxicity).
  - We add to solution a **precatalyst** (usually either Pd^0 or Pd^{II}).
    - If Pd^{II}, you need a reduction.
    - Contrary to some textbooks, phosphines *cannot* reduce Pd^{II}; phosphines *plus water* can.
  - After reduction (if needed), the precatalyst needs to lose a ligand or two.
  - d^8 metals follow a 16-electron rule, not an 18-electron one.
  - After oxidative addition to the *cis*-species, you get equilibration to the *trans*-species.
  - Rate of *oxidative addition* (not the overall catalytic cycle):

$$\mathrm{I} > \mathrm{CF_3SO_3} \approx \mathrm{Br} \gg \mathrm{Cl} > \mathrm{OTs} > \mathrm{OMs}$$

    - Cost runs in the opposite direction!
    - If you use a weak catalyst like palladium tetrakis, oxidative addition is rate-limiting. But with active, modern catalysts, ??oxidative addition to?? iodides can be rate limiting!
      - ➢ Is oxidative addition to iodides slower with modern catalysts, or is it transmetallation with iodides that makes the overall process slower??
  - Greg Fu (first at MIT, then at Caltech) really pioneered oxidative addition to sp^3-halides.
    - These substrates did not work previously due to competitive β-hydride elimination.
    - Reference: Kirchhoff et al. (2002).
- Transmetallation.
  - Transfer a group from boron, zinc, tin, etc.
  - Mechanism: σ-bond metathesis.
    - Note that "metathesis" has nothing to do with olefins; it just means "interchange."
  - Having an L_1Pd species means that you have lots of space for σ-bond metathesis to occur!
    - Bulky iodides take up space and can slow this down (with modern catalysts).
    - Steve has gathered experimental evidence for this effect! See Footnote 18 in Kinzel et al. (2010).
- Fu solves heteroaryl boronic acids.

$$\mathrm{Het_1B(OH)_2} + \mathrm{Het_2X} \xrightarrow[1,4-\mathrm{dioxane},\, \mathrm{H_2O},\, 100\,^\circ\mathrm{C}]{\mathrm{Pd_2(dba)_3}\ (1.0\,\mathrm{mol\%}),\, \mathrm{PCy_3}\ (2.4\,\mathrm{mol\%}),\, \mathrm{K_3PO_4}\ (1.7\,\mathrm{eq.})} \mathrm{Het_1{-}Het_2}$$

  - Very small differences have big impacts on reactivities.

- Look at what has been done and don't make assumptions, otherwise you can reinvent problems that have already been solved!
- They used $Pd_2(dba)_2$ (dibenzylideneacetone).
  - Good, cheap ligand.
  - Because it's good, it doesn't just say, "goodbye" in the flask; it hangs around and can slow reactivity.
- KF isn't extremely basic, but boron is very fluorophilic; the ate complex formed facilitates transmetallation.
- This is really good heterocycle-heterocycle chemistry!
- People have a love-hate relationship with boronic acids.
  - Often work but unstable, difficult to quantitate via NMR, etc.
  - This is why people like to use boronate esters or Molander salts (trifluoroborates), which are both *in situ* slow generators of boronic acids.
  - Proto-deboronation (replacement of boron with a hydrogen) is a problem, though.
- Reference: Kudo et al. (2006).

- Clever tricks with boron.

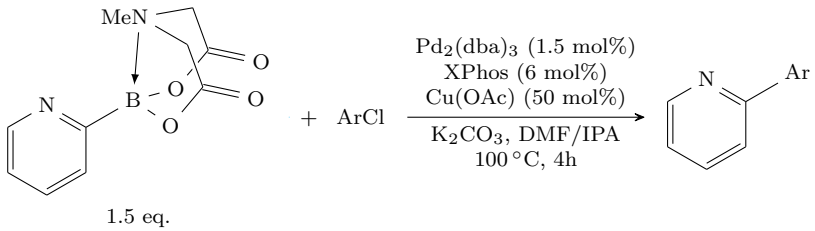


Figure 1.9: MIDA boronates for air-stable 2-pyridyl couplings.

- Marty Burke's (UIUC) slow-release strategy generates boronic acid *in situ* as needed.
  - Transfer of pyridyl group to copper and then transmetallation.
- 2-pyridylboronic acid is extremely unstable; you can buy it, but what you buy won't be it in Steve's opinion.
  - Steve believes you should *always* assay your starting materials.
- References.
  - Knapp et al. (2009) — original report of MIDA boronates.
  - Dick et al. (2012) — improved method with copper aminodiol additives.

- Negishi coupling of 2-pyridylzinc reagents is ideal!

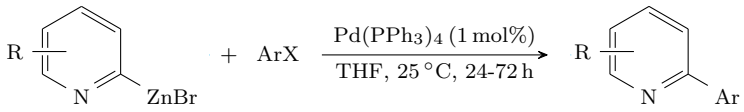


Figure 1.10: Negishi-type 2-pyridyl couplings.

- No protozincation unless you add water.
- Even with the simplest of catalysts, this works.
- But much fewer aryl zincs are commercially available.
- References: Rieke zinc, Milne and Buchwald (2004) — RuPhos optimizes Negishi.

- Steve's mantra in consulting: The best metal is none.
  - If you can do it without a metal, that's ideal.
  - If you're gonna use a metal, it had better confer a *major* advantage.
  - Metal catalysis might work on a discovery scale, but uncatalyzed heat will be preferred on a preparative scale.
- Dan Weix (Rochester → Wisconsin-Madison) has pioneered the area of combination catalysts.

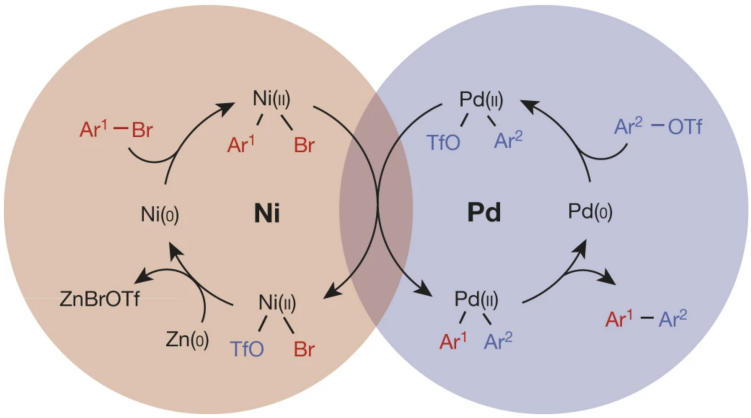


Figure 1.11: Tandem nickel-palladium catalyzed aryl halide cross-coupling.

  - Combination catalysis can achieve direct cross-coupling of two aryl halides.
    - This confers major advantages from a process chemistry perspective, as opposed to having to metallate one of them first.
  - Weix's tandem catalytic system uses nickel/palladium dual catalysis.
    - Nickel's ligand is dtbbpy.
      - ➢ ^{t}Butylation of bpy gives better solubility!
    - Palladium's ligand is dppp.
      - ➢ Because dppp has three carbons, the chelate effect is weakened to the point that one phosphine can pop off (as I suggested to Paul Chirik!).
    - Mixed-ligand square-planar species??
  - The advantage of this dual catalysis is that different metals do oxidative addition at different rates, so you can get transmetallation as if you'd used a different metal.
    - Ni prefers C−Br > C−Cl > C−OTf.
    - Pd prefers C−OTf > C−Br > C−Cl.
  - Although limited to a very narrow scope of pyridine derivatives, this is being used very widely!
  - References.
    - Ackerman et al. (2015) — original report.
    - Kang et al. (2021) — update for heterocycles.
    - Ehehalt et al. (2024) — review of cross-elecrophile couplings.
- Pyridine synthesis.
  - **Hantzsch pyridine synthesis** is particularly important.
  - **Cyclotrimerization** is most aesthetically pleasing, but not necessarily the most useful.
  - **Petrenko-Kritschenko** is a variation on a theme.

- Dicarbonyl approaches.
  - Scope-limiting factor is often how you get to the dicarbonyl.
  - Oxidation can be done with nitric acid or DDQ (particularly on a small scale).
- Asymmetric pyridines.
  - Do Hantzsch chemistry in two-steps.
  - First, make your preferred α,β-unsaturated ketone.
  - Then combine it with a **vinyligous urethane** (not an enamine) and oxidize.
  - Advantage: The presence of pyridinium eliminates the need to oxidize at the end.
- Kröhnke.
  - Make the α-halo species *in situ*, which reacts with pyridine.
  - Then enolization, addition, and condensation.
- $[2+2+2]$ pyridine synthesis.
  - Has been used in some contexts in very large scale, though not for pyridine synthesis.
  - Ramsay (aged 24) discovered this.
  - Chemistry in the 1800s was chemistry of "gentlemen," who did things in their home laboratories.
  - Original report: Acetylene (explosive) plus HCN (toxic) in a hot tube gives pyridine.
  - Bönnemann picks this up.
    - Two acetylenes combine with a cobalt catalyst.
    - Then Diels-Alder onto the nitrile.
  - Cyclotrimerizations are cyclotetramerizations have the regioisomer problem, though.
  - Wittig started the use of these to make aromatics.
  - If you have a regioisomer problem, cheat by either doing intramolecular stuff or a large excess of one reagent (e.g., as Vollhardt did).
- Zincke chemistry.
  - A chemist's hope in life is that you develop a reaction, somebody uses it to do something useful, and you get some of the credit or benefit of it. Sometimes this happens during your lifetime, and sometimes after.
  - Zincke's chemistry found utility 90 years after he died in an ingenious synthesis of strychnine (D. B. C. Martin & Vanderwal, 2011).
- Modern Zincke chemistry: *meta*-halogenation of pyridines via reversible ring-opening.

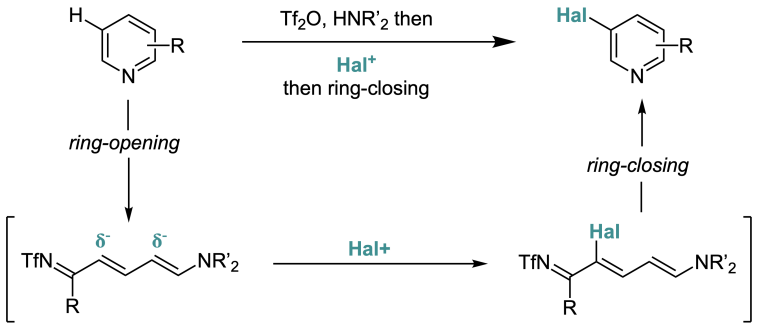


Figure 1.12: *meta*-halogenation of pyridines via Zinke chemistry.

  - After Vanderwal's efforts, Zincke chemistry once again lay fallow for a while. But then Andy McNally (Colorado State) used it for *meta*-CH activation.
  - Hal^+ is some kind of positive halogenating agent.
  - Mechanism.
    - Retrocyclization ring-opens pyridine following triflation.
    - This temporarily makes pyridines reactive with electrophiles!
  - Regiochemical ambiguity with NCS; very selective with NBS or NIS.
    - They had no clue why, so did DFT and Hammond-type arguments about early/late transition states.
  - Very elegant paper; eventually came up with good procedures for two types of compounds.
  - Reference: Boyle et al. (2022).
  - Takeaway: Heterocycles are not rocks; balance thinking of them as benzene analogs with thinking of them as normal molecules that can open, close, move around, come from different things, etc.

- *meta*-halogenation of pyridines via reversible dearomatization.

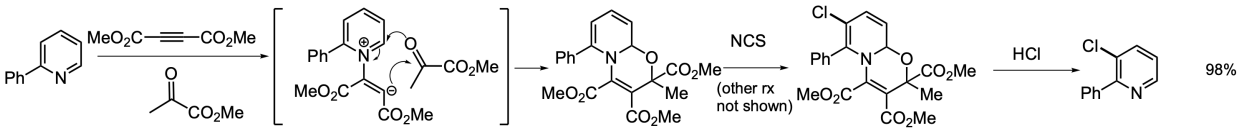


Figure 1.13: *meta*-halogenation of pyridines via temporary dearomatization.

  - Studer (Münster, top German school for OChem) develops this chemistry in the same time frame as McNally.
  - Again, different products for chlorination vs. bromination.
  - Take yields like 98% with a grain of salt, but it indicates that you're probably high-yielding.
  - Reference: Cao et al. (2022).

- Might do some problems on Monday!
- Steve covers the synthesis of Nexavar.
- Synthesis of a Chk1 Kinase inhibitor.
  - Starting material is a bromo/chloro/nitro-substituted 7-azaindole.
    - Steve wasn't quite sure how they got here, but his former postdoc is now the head of process chem at Genentech (lmao), so he was able to point Steve toward the route.
  - Strong acids protonate the pyridine, then add to the 3-position!
    - We'll talk more about this later in the course.
  - Piperidine's amine reacts much faster than the amide.
  - Amino-indoles are very prone to oxidation, but acylating it immediately gives a clean compound.
  - Lots of process chem involves what you can do in the same flask; this is **telescoping**.
  - But you don't want to do this so much that you have too many impurities to easily filter out.
  - At scale, you can do some extractions, but you mostly want to do crystallizations.
  - Different crystalline forms of the same compound can have different patents, different patent lifetimes, different pharmacokinetics, etc.

- Kinases are responsible for many different physiological functions
  - 700 in the body.
  - Steve thinks it's a miracle we can design molecules to hit 1 out of the 700!
- Another kinase synthesis.
  - Synthesis is done from commercial pyrazole using Claisen chemistry and then amide formation.
- Pharmaceuticals are also widely applied in agrochemistry.
  - If you work for Cortiva in Minneapolis, it's gonna be quite similar to Lilly in Indianapolis.
    - But when you do scale-up for agrochemicals, cost matters much more!
    - Though with the environmental push to use smaller quantities agrochemicals, cost is mattering less.
  - Selectfluor is an F^+ equivalent.
    - Very active and expensive.
  - You often put fluorine into molecules to block the site of oxidation; cytochrome enzymes do C–H oxidation as a first step in metabolic excretion, and you can block this with fluorination to slow the pharmacokinetics.
    - Very activated system, so probably can use a simple catalyst.
    - 2-halopyridines are *extremely* activated toward oxidative addition as with S_NAr; much worse for 3-halopyridines.
  - If there's a perfect SM but it's only available from one place, the company will raise the price to whatever they want now that they know their compound is important. Also, what if there's a supply chain interruption?
    - Companies like to have 3 sources as a general rule.
  - As it happens, the SM here is very cheap.
    - Most fluoridation reactions use the Halex reaction.
    - Often KF and a ton of heat; the fluoro compounds are more stable, so they come out with thermodynamic equilibration.
  - Each of these steps can be carried out on a large scale, and the most expensive thing anywhere here is CsF.
- Vinamidium salts are more stable 1,3-dialdehyde equivalents.
  - 1,3-dialdehydes do self-Claisen condensations and all kinds of nasty things.
  - Developed at Merck, then used on scale there.
  - Can be used to make tri-substituted pyridines!
  - 2-methyl group is perfectly setup for lateral deprotonation.
  - PPA (polyphosphoric acid) is a common strong acid. You isomerize the double bond and then do Friedel-Crafts on the aromatic ring.
    - Again, heat is better than a fancy catalyst.
- Process vs. medchem.
  - Mitsunobu, reduction of nitro (with stoichiometric iron and acetic acid as opposed to Ni, Pd, Pt + H_2).
  - Donating groups allow for mild halogenation.
  - Miyaura borylation.

  - This is an ugly synthesis; protecting groups are never great, and Pd at the end increases the chance of contamination.
  - Made better at process scale! Still has final Pd issue, though.

- Very non-activated NH requires Pd catalysis.
  - Xantphos, developed at Dutch Shell for hydroformylation but repurposed for C–N bond formation.

- Key synthetic transformations using pyridine.
  - S_NAr with heteroatom nucleophiles (O, N, S), or with malonate anions.
  - PPh_3 can remove an *N*-oxide because of strong P=O bond formation!
  - Alternative to R″MgX: Zincke chemistry!

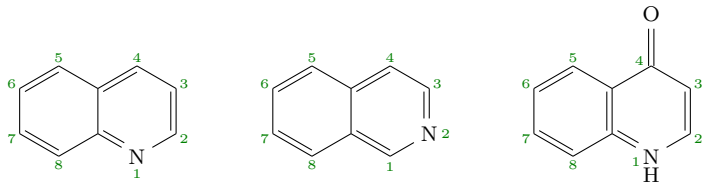
Topic 2

N-Doped Heterocycles

2.1 Benzannulated Pyridine Derivatives

1/11:

- Announcements.
  - Next week: Thursday lecture only.
  - Reiterates that we should try the problems, but don't fret.
- Today: An hour of lecture, and a half hour of problems.
- New heterocycles: **Quinoline** and **isoquinoline**.



(a) Quinoline. (b) Isoquinoline. (c) 4-quinolone.

Figure 2.1: Key quinoline derivatives.

  - Important subclass: Quinine- and **quinolone**-derived drugs.
  - Comparison with pyridine: Quinolines have two different aromatic regions.
- We'll now discuss some basic quinoline reactivity patterns.
- Relative EAS reactivity.

$$\text{Benzene} > \text{Isoquinolinium} > \text{Quinolinium} \gg \text{Pyridinium}$$

- Quinoline (dissolved in pyridine) can react to give the 3-bromoquinoline.

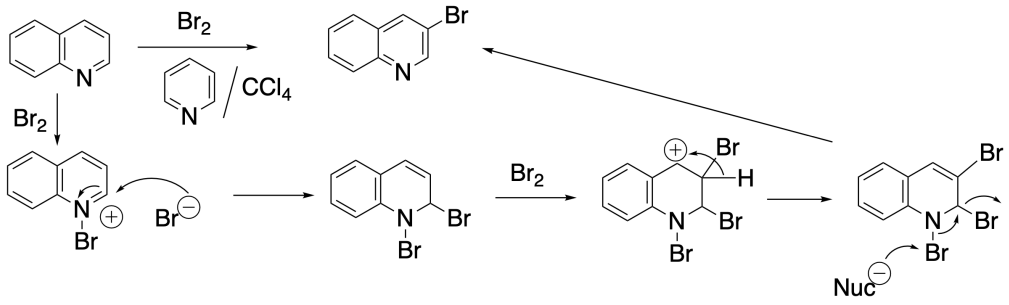
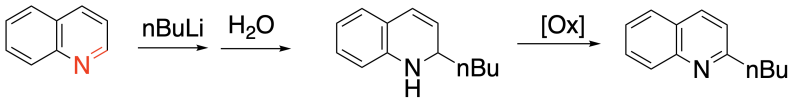


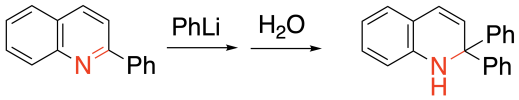
Figure 2.2: Quinoline 3-bromination mechanism.

  - However, the reaction mechanism is *not* EAS.
  - Indeed, this reaction is feasible only because a different mechanism is operational.

- Lithiates — followed by oxidation — add to quinoline at the 2-position.



(a) Monoaddition.



(b) Diaddition.

Figure 2.3: Lithiates add to quinoline.

  - We can also use analogous approaches to dearomatize the pyridine moiety by making a quaternary carbon.
  - Lithium-nitrogen coordination is critical to 2-addition; otherwise, we get 4-addition.

- Quinoline syntheses.
  - Many different ones, many from Germany.
  - Most common: **Skraup**, **Conrad-Limpach-Knorr**, and **Meth-Cohn** syntheses.
  - For most of these, you start with the aniline.
  - Common issues: Mixture of regioisomers.

- Meth-Cohn quinoline synthesis.
  - Proceeds via a mechanism analogous to the **Vilsmeier-Haack reaction**.
  - Driving force: P=O bond formation.
  - Amide $\rightarrow$ chloroimine, tautomerizes to enamine. Then an additional carbon comes from DMF.

- Quinoline hydrogenations.
  - You can get some interesting chemoselectivity, enabling you to reach basically whatever you want!
  - Reducing the benzene ring.
    - Completely counterintuitive result: In the presence of an acid, you reduce the non-heterocyclic part of the quinoline heterocycle.
  - Reducing the heterocyclic ring, or everything: Use Raney nickel (RaNi).
    - RaNi is a pyrophoric, extremely active form of nickel used for very difficult hydrogenations and desulfurizations.
    - Under 1 atm of H_2, you'll only hydrogenate the heterocyclic ring.
    - Under 70 atm of H_2, you'll hydrogenate everything (typically to the *cis*-decalin derivative, but you can get some isomers).

- Most famous quinoline synthesis: The Skraup quinoline synthesis.
  - Michael addition, Friedel-Crafts type cyclization, and oxidation.
  - A series of conditions for this reaction have been optimized over time.

  - Classic Skraup.
    - Reagents: Glycerol, sulfuric acid, and As_2O_5 (oxidizing agent).
    - Under acidic conditions, glycerol will lose 2 equivalents of H_2O to generate acrolein *in situ*.
      - ➢ Following protonation, the first step involves a hydride shift to β-hydroxyaldehyde.
      - ➢ Then we get E_1 via the electron conduit to acrolein.
    - Why don't we just add acrolein directly?
      - ➢ Glycerol is really safe and cheap, but acrolein will "polymerize if you look at it sideways."
      - ➢ Substituted acrolein derivatives (e.g., other Michael acceptors) can be added directly with sulfuric or tosylic acid, but acrolein, itself, needs these conditions.
    - Using Skraup methodology, we can synthesize 1,10-phenanthroline from 8-aminoquinoline.
    - But not super scalable: Reaction "often resulted in uncontrolled violence."
  - Scalable Skraup.
    - Alternative: Use glycerol in the presence of iron sulfate, a strong acid (e.g., methane sulfonic acid), and a strong oxidant (deprotonated sulfonic acid).
      - ➢ The use of this particular oxidant makes separation easier at the end.
      - ➢ This is an unusual use of a nitro group as an oxidizing agent; not often used, but was recently by Baran.
    - Once acrolein is generated *in situ*, it undergoes Michael addition. Then we get Friedel-Crafts reactivity, followed by oxidation.
    - This method was used to synthesize a PDE4 inhibitor.

- Misc. quinoline derivative syntheses.
  - **Combes** (quinoline synthesis): Aniline condenses with a β-diketone, followed by intramolecular acid-promoted Friedel-Crafts cyclization.
  - **Conrad-Limpach-Knorr** (quinolone synthesis): The mechanism involves a Combes-analogous condensation with a β-ketoester, followed by Friedel-Crafts cyclization.
    - Sulfuric acid gives the 2-quinolone product.
    - Heat gives the 4-quinolone product.
    - We'll discuss this difference later!
  - Used to make compounds that fight botulism, malaria, and ebola.
    - One important reagent used in some syntheses is **Eaton's reagent**.

- **Eaton's reagent**: $MeSO_3H + P_2O_5$.
  - This is a variation on PPA from last time. Easier to work with an quantitate.

- Making a KRAS inhibitor.
  - KRAS is a particularly virulent form of cancer for which inhibitors have not come on the market until recently.
  - The starting material is a trisubstituted anline that is probably not cheap.
  - Selectively (or selectively enough) chlorinate this SM.
    - On an exam, Steve will never ask us to think that we could do this selectively.
    - It's not obvious to him that we would chlorinate where we do, but we *should* be able to draw a mechanism!! (This is basically 5.12 chem.)
  - **Meldrum's acid** and a trimethyl orthoester condense into a new reagent.
    - This reagent is very prone to nucleophilic attack, so we get a Michael-type addition-elimination condensation with the aniline.

  - Then heating the mixture to boiling using Dowtherm as a solvent causes the substrate to collapse to the quinolone.
    - The mechanism for this is at the bottom in the box.
    - Note that at high temperatures, Meldrum's acid is known to undergo a pericyclic decomposition to a ketene, CO_2, and acetone; evidently, only acetone gets kicked out here, not CO_2.[1]
    - In fact, it appears that the whole mechanism in the box plausibly occurs via a sequence of pericyclic reactions.
  - Nitric acid then gives nitration.
  - $POCl_3$ chlorinates the ketone and aromatizes the system.
  - Pretty selective S_NAr occurs, even with a hindered piperazine.
  - A note of the mechanism of action: Acrylimides (top of the finished molecule) are thought to give Michael addition with DNA.

- **Friedlander** (quinoline synthesis).
  - Retrosynthetic disconnections: An alkene disconnects into a carbanion equivalent and a carbonyl, and an imine disconnects into an amine and a carbonyl.
    - Very rational.
  - Subject to regiocontrol issues.
    - McWilliams (at Pfizer) did a very careful study, and was able to use an organocatalyst to get 90% selectivity for one regioisomer.
  - Aside: Scalability.
    - 90% selectivity may not sound great to us.
    - But as long as we can reject the unwanted isomer via recrystallization or derivitization (not chromatography), this is much better than a 4-step synthesis that requires complicated/expensive reagents or conditions.
  - This chemistry is generalizable, as well; see the reaction at the bottom of the slide.
  - Anytime the symbol "OEi" appears in a slide, that means "Δ."

- Example synthesis: A MS drug by UCB (a Belgian pharmaceutical company).
  - Starting material: A nitro-phenylalanine derivative.
  - Condensation to the amide with a variant of Yamaguchi's reagent.
  - Reduction of the nitro group to the corresponding aniline.
  - Condensation with a dichlorobenzaldehyde to form the imine.
  - **Pavarov reaction** with a good leaving group.
    - Specifically, 2-pyrrolidone leave under oxidative conditions.
  - Lastly, we hydrolyze the ester to an acid.
  - Two solvent swaps.
    - These are supposed to purge impurities using washes; we rarely do this in academia.
    - Switching to ACN gets rid of water, and switching to heptane gets rid of the ACN because nonpolar molecules don't stick to polar molecules and can thus be removed well under vacuum.

- This concludes our discussion of quinolines for the time being.

- We now discuss isoquinolines.

[1] Wikipedia. Note also that Meldrum's acid is so strong because the conformational restriction caused by the ring forces the α-proton to undergo $\sigma_{CH} \to \pi^*_{CO}$ donation.

- Isoquinolines.
  - It's easier to do chemistry on their nonheterocyclic part.
    - For example, nitration and bromination most frequently occur at the 5- and 8-positions.
  - Unsurprisingly, the Chichibabin and lithiate/oxidation reactions work again.
    - Nucleophiles will *always* add at the position between the nitrogen and other aromatic ring.
    - With the dichloro species, you should be very confident you can do the addition to this position.
    - This may show up on an exam!!
- Isoquinoline syntheses.
  - **Pomeranz-Fritsch** (isoquinoline synthesis): A condensation/Friedel-Crafts between an aldehyde and the synthetic equivalent of 2-aminoacetaldehyde.
    - Like acrolein, we can't use 2-aminoacetaldehyde raw because it self-condenses.
    - Treatment with acid forms the heteroatom-stabilized carbocation that then does Friedel-Crafts chemistry.
  - We can also do C−N cross-coupling (which we'll discuss later).
  - **Bischler-Napieralski** (isoquinoline synthesis).
    - Make an amide.
    - Then use $POCl_3$ to access the nitrilium ion via a chloroimine-type mechanism.
    - The chloroimine is in no-bond resonance with the nitrilium ion, which is very active in Friedel-Crafts type chemistry.
  - **Pictet-Gams** variation of the Bischler-Napieralski reaction.
    - Start with a benylic alcohol.
    - Thus, you've pre-installed your oxidation! That's the advantage.
    - The disadvantage is getting the substrate.
- **Pictet-Spengler** reaction.
  - From early 20th century Germany.
  - Phenethyl amine and an aldehyde condense and cyclize.
  - Generalizable to other substrates.
  - Proposed mechanism: The iminium ion produced during condensation cyclizes.
    - This can occur via Friedel-Crafts type chemistry, or via a more complicated mechanism with shifts depending on the substrate.
    - In the example shown, it does make more sense that the more nucleophilic position would initially attack the iminium ion, before rearrangement!
- Example synthesis: Idorisia needed to make a pretty simple compound, but making it at scale was hard.
  - Process groups "compete" multiple routes for cost-efficiency, safety, and reliable access to reagents from multiple sources.
    - Because the bigshots will say, "we need 5 kilos in 3 months. If that goes well, 50 kilos 6 months after that. If that goes well, a tonne a year after that."
    - Then the process chemists will start with what they know works, and then they'll refine at cost, scale (e.g., issues with exotherms), issues with buying materials or catalysts, etc.
  - Route-scouting summary.
    - None of the routes use particularly fancy chemistry. Route A uses really old chemisty (**Balz-Schiemann** reaction).

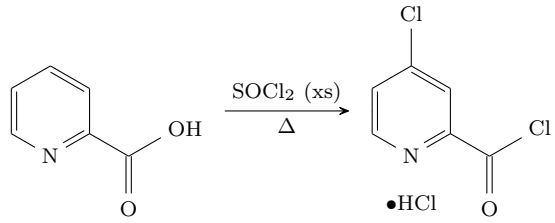
  - Route A overview.
    - $POCl_3$ probably gave a side product that was hard to reject, so they use $POCl(OPh)_2$.
    - Lots of energy put into optimizing this route, so Steve guesses it must have been a really desirable starting material.
    - Primary amide to Hofmann rearrangement.
    - Diazitized, then classic Balz-Schiemann.
  - Route B.
    - On small scale, we can do a Stille reaction.
      - ➢ We could also do tin/lithium exchange and something else (??) to get to a more scalable intermediate.
      - ➢ Then we can get to a desired α-fluoro reagent.
    - However, there's a better bucket chemistry approach.
      - ➢ Carboxylic acid to acyl malonate. Very acidic, hence easily able to fluorinate.
      - ➢ Then double hydrolysis/decarboxylation to form the α-fluoro intermediate.
    - We then use an amide acetal, a species analogous to an orthoester that is derived from DMF. This forms a **vinylogous**[2] amide, an enamine-type compound.
    - Then under hydrogenation conditions, a quinoline N-oxide is formed. This then gets hydrogenated down to form another intermediate.
    - At this point, we excise the alcohol OH with $POCl_3$ and reduction.
      - ➢ This is a **transfer hydrogenation**, with formate is a hydrogen source
    - Aside: Pharma companies have tight controls on hydrogen; you can't even use a balloon unless you go to a special room. Avoid until scale-up!
  - In the end, they chose to use Route C.
    - It's better to not use (very expensive) Selectfluor.

- We now move onto diazenes.
  - Key diazenes.
    - Benzene derivatives: Pyridazine, pyrimidine, pyrazine.
    - Quinoline derivatives: Cinnoline, phthalazine, quinazoline, quinoxaline.
    - The benzene derivatives aren't too common, but the benzanulated heterocycles are very common in pharmaceuticals.
  - Important characteristics.
    - All of the effects of adding one nitrogen to benzene to make pyridine are intensified.
    - Pyridazine, pyrimidine, and pyrazine are colorless liquids that are water soluble.
    - Nucleophilic addition is much easier.
    - Electrophilic addition is much harder.
    - The compounds are much less nucleophilic and basic.
  - The α-effect in pyridazine makes it easier to protonate than pyrimidine.

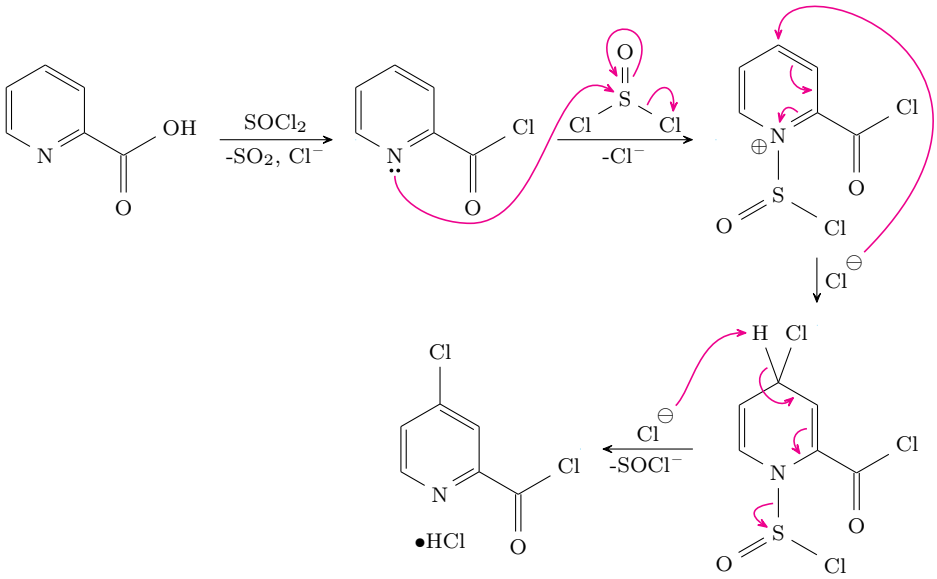
- Halo-diazenes.
  - For the purposes of this class, assume that 4-chloro will react faster than 2-chloro.
    - Sharon Neufeldt (Montana State) had a nice paper in JACS recently with an exception to this (Jackson et al., 2025).
  - These can be very fast S_NAr reactions.
  - Handwavey reason: Double α-effect is worse than one lone pair Coulombic problem.

[2] Wikipedia.

- Problem 1.



(a) The reaction.



(b) The mechanism.

Figure 2.4: TTQ: Pyridine 4-chlorination.

  - Convert to the acid chloride.
  - Activate the pyridine by reacting it with the best electrophile in solution; experimental studies show that it's not protonation here! Plus, protonation would make hydride your leaving group, which is much worse than $SOCl^-$.
  - Chloride may not be the base that does the final deprotonation, but we want the hydrochloride in the end so it's good to show that. If not chloride, subsequent proton exchange gives hydrochloride.
  - Fate of sulfur compound is unknown, so $SOCl^-$ is some kind of leaving group. That was our hint to use a sulfur electrophile to activate the ring.

- Problem 2.

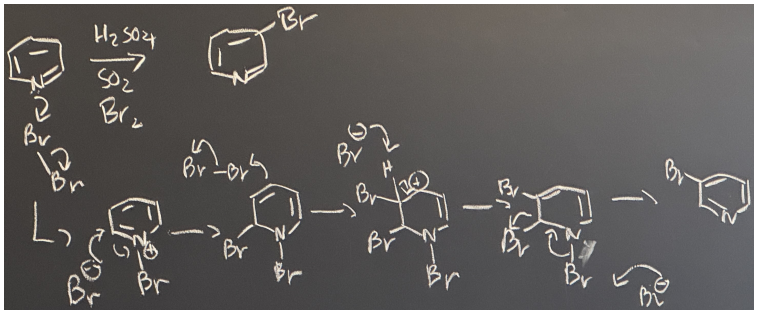


Figure 2.5: TTQ: Pyridine *meta*-bromination.

- Uses bromination mechanism from class (see Figure 2.2).
- Oleum could be SO_2 or SO_3.
- Br^- can remove either bromine in the last step.
- This gets full credit; it is great, but for the second bromination, it may make more sense to put the bromine on the other side of the compound; the 1,2-dibromide is unfavorable.
  - Principle: Large halides on contiguous carbons is just very challenging.
- Unclear what the SO_2 does.
- Electrophilic reaction $\rightarrow$ nucleophilic reaction with dearomatization.

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