

5.45 (Heterocyclic Chemistry) Notes

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Topic 1

Pyridine Chemistry

1.1 Intro, Directed Metallation, and Organometallic Coupling

2/4:

- 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.

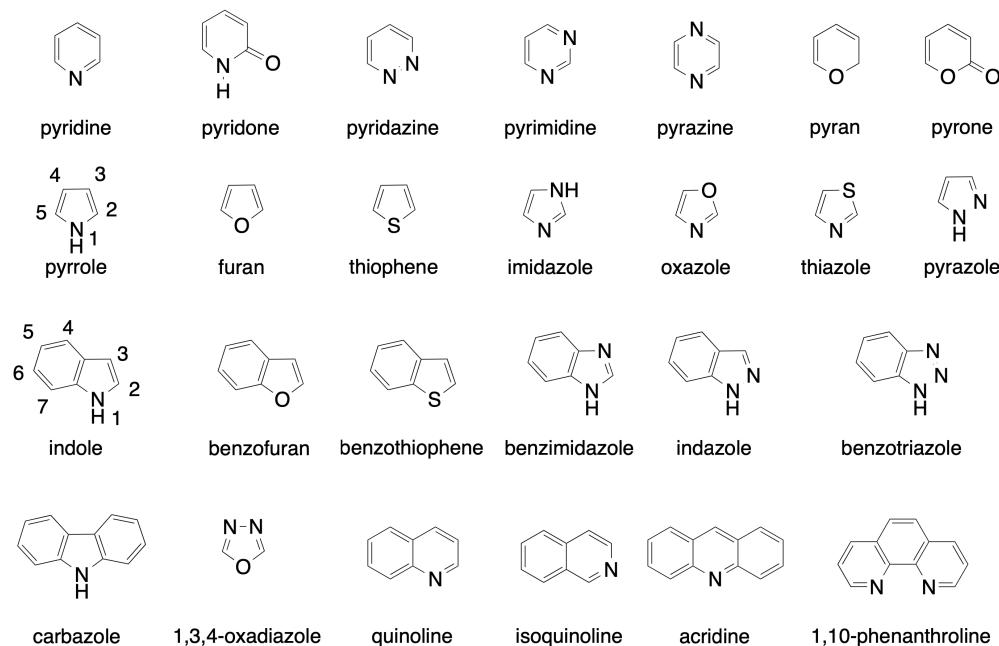


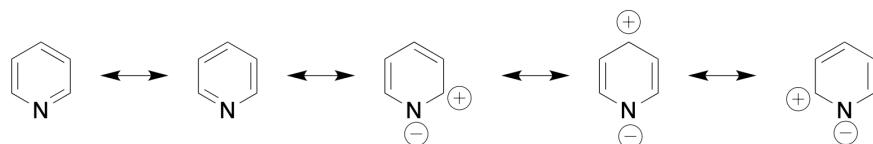
Figure 1.1: Heterocycles of interest.

- 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 cephalosporins.
- 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.

$$\text{CH}_3\text{CHO} + \text{H}_2\text{CO} + \text{NH}_3 \xrightarrow[\text{Si/Al cat}]{\text{vapor phase}} \text{Py} + 3\text{-MePy}$$

 - 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.
 - Muscropyridine: 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.

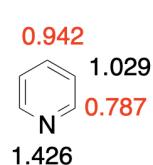
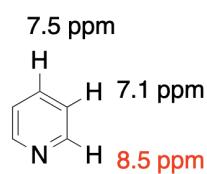
(b) π -electron populations.(c) ^1H NMR shifts.

Figure 1.2: Pyridine structure.

- Analogous to benzene; slightly less aromatic, but very similar.
 - Insights from the ^1H 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.
 - $\text{S}_{\text{N}}\text{Ar}$ 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.
 - $\text{pK}_a \approx 5.5$; much less basic than piperidine.
 - Basicity 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 ($\text{S}_{\text{N}}\text{Ar}$) 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.

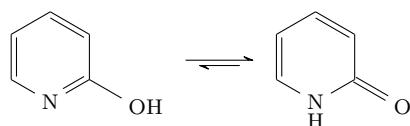
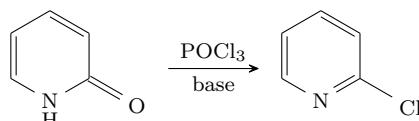


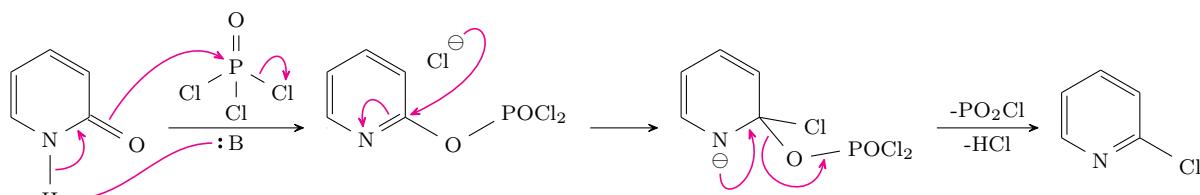
Figure 1.3: Pyridone tautomerization.

- 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., nBuLi) deprotonate kinetically at the 2-position.
 - Interestingly, adding nBuLi 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?

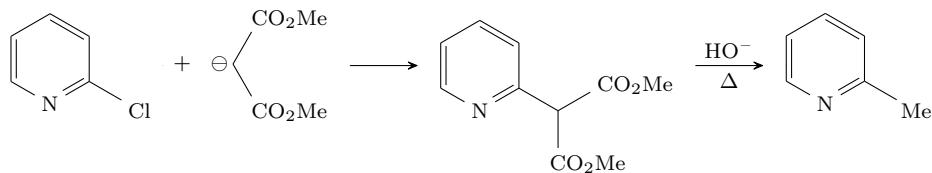
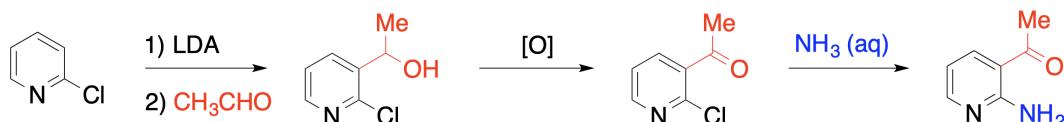


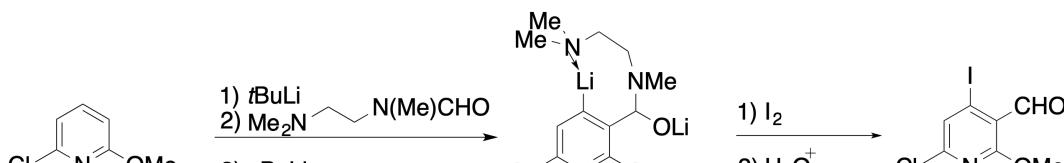
Figure 1.5: Lateral pyridine decarboxylation in robust synthesis.

- 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 asymmetrically functionalize both *meta*-positions).
- Important note: Phenols are often hydrogenated with POCl₃ conversion to the chloride, and then H₂ + 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.

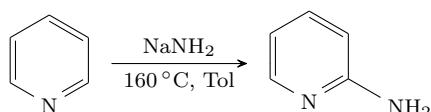


Figure 1.7: Chichibabin reaction.

- 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.

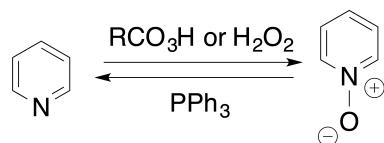


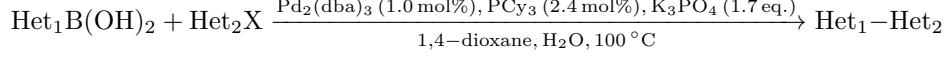
Figure 1.8: Synthesis of pyridine *N*-oxides.

- 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 convert 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 compatibility 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 compatibility 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.
 - $\text{Pd}(\text{PPh}_3)_4$ 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 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 Pd⁰ 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):

$$\text{I} > \text{CF}_3\text{SO}_3 \approx \text{Br} \gg \text{Cl} > \text{OTs} > \text{OMs}$$
 - 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 L₁Pd 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.



- 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 $\text{Pd}_2(\text{dba})_2$ (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 trans-metallation.
- 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.

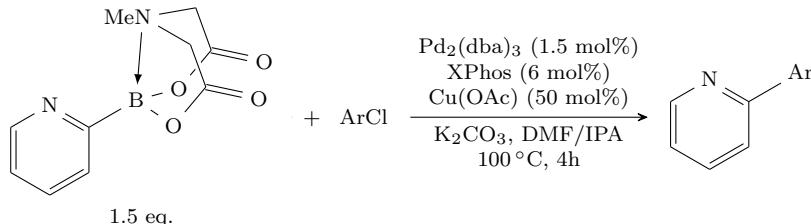


Figure 1.9: MIDA boronates for air-stable 2-pyridyl couplings.

- 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!

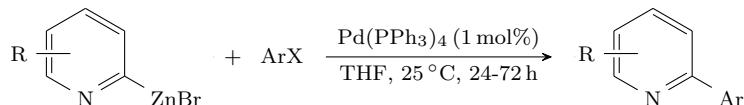


Figure 1.10: Negishi-type 2-pyridyl couplings.

- 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.

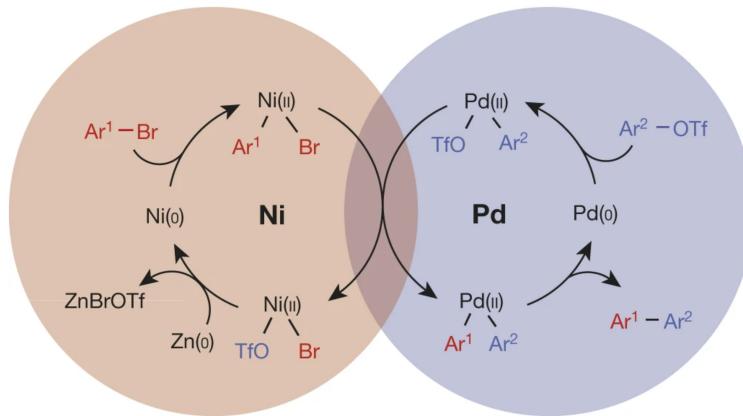


Figure 1.11: Tandem nickel-palladium catalyzed aryl halide cross-coupling.

- 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.
 - ^tButylation 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 transmetalation as if you'd used a different metal.
 - Ni prefers $\text{C}-\text{Br} > \text{C}-\text{Cl} > \text{C}-\text{OTf}$.
 - Pd prefers $\text{C}-\text{OTf} > \text{C}-\text{Br} > \text{C}-\text{Cl}$.
- 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-electrophile 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.

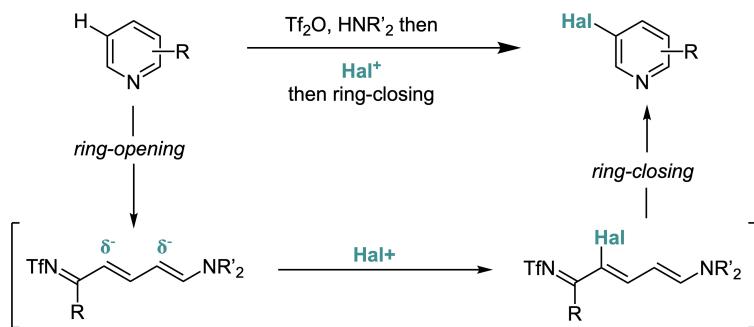


Figure 1.12: *meta*-halogenation of pyridines via Zincke chemistry.

- 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 **telescopin**.
 - 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 Corteva 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 + H₂).
 - 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.
 - PPh₃ 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

2/11:

- 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**.

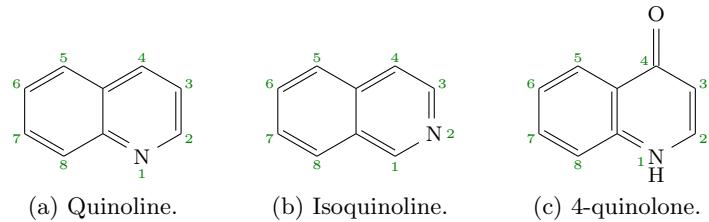
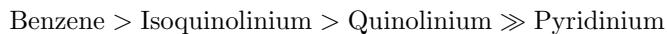


Figure 2.1: Key quinoline derivatives.

- 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.



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

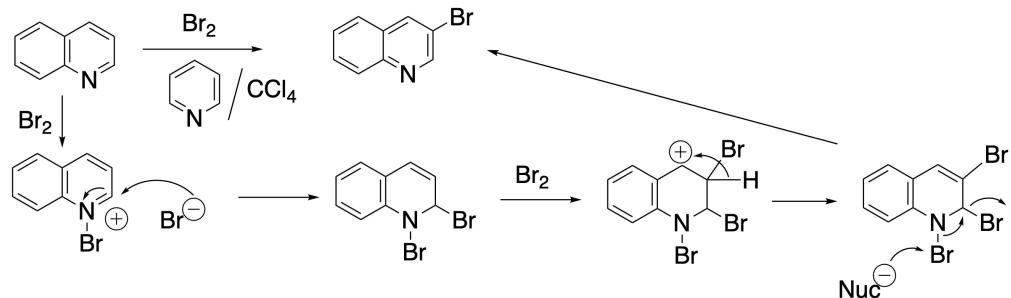


Figure 2.2: Quinoline 3-bromination mechanism.

- 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.

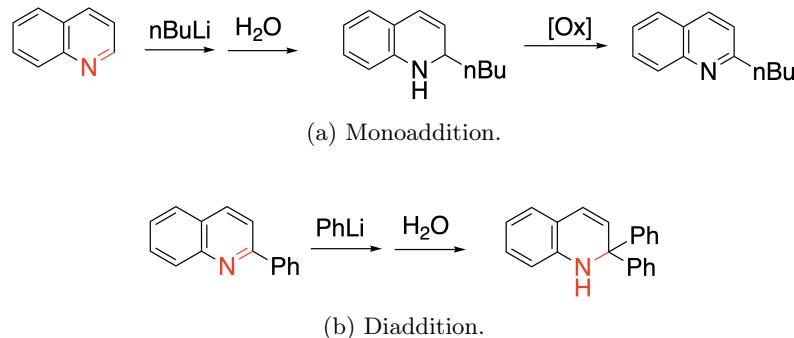


Figure 2.3: Lithiates add to quinoline.

- 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 → 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 H₂, you'll only hydrogenate the heterocyclic ring.
 - Under 70 atm of H₂, 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:** $\text{MeSO}_3\text{H} + \text{P}_2\text{O}_5$.
 - 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 aniline 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, CO₂, and acetone; evidently, only acetone gets kicked out here, not CO₂.^[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.
- POCl₃ 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 $\sigma_{\text{CH}} \rightarrow \pi_{\text{CO}}^*$ 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 chemistry (**Balz-Schiemann** reaction).

- Route A overview.
 - POCl_3 probably gave a side product that was hard to reject, so they use $\text{POCl}(\text{OPh})_2$.
 - 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 $S_N\text{Ar}$ reactions.
 - Handwavey reason: Double α -effect is worse than one lone pair Coulombic problem.

²[Wikipedia](#).

- Problem 1.

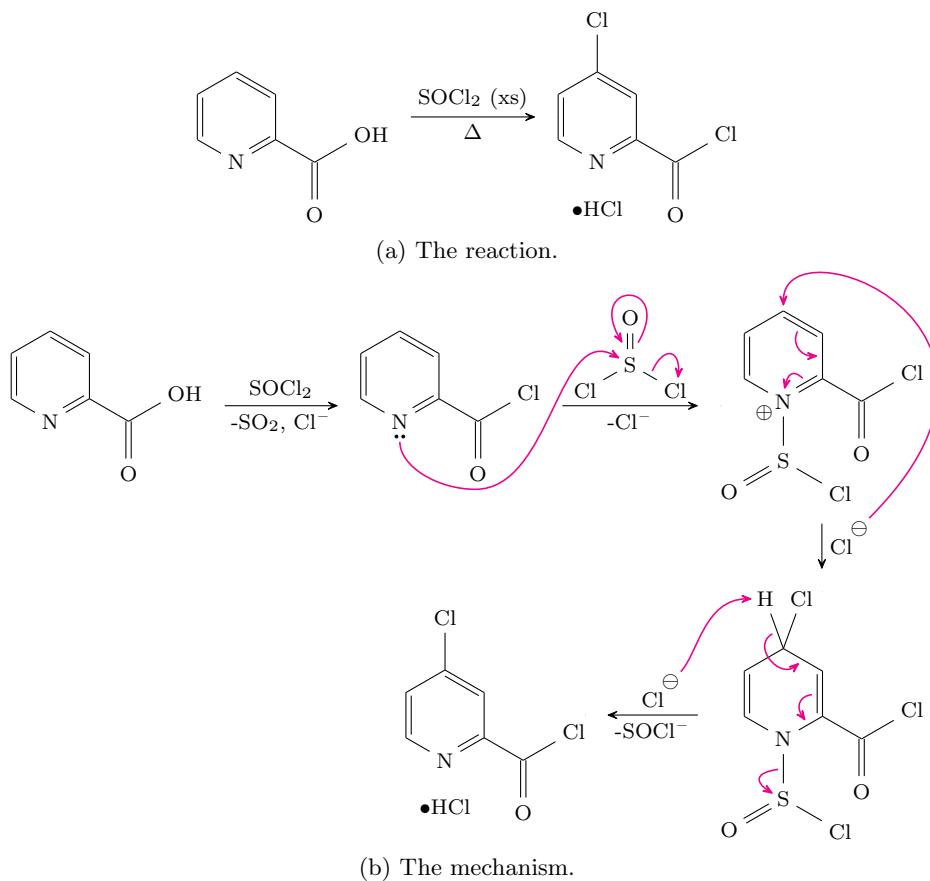
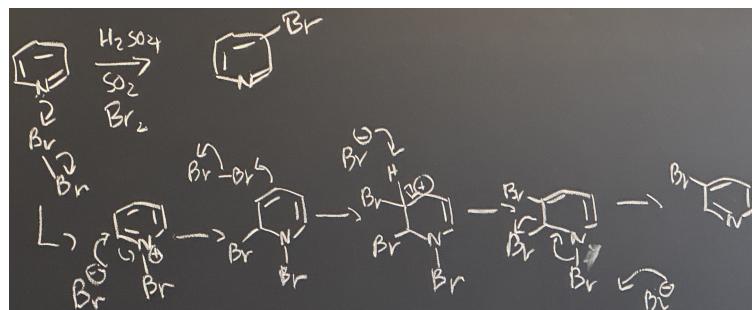


Figure 2.4: TTQ: Pyridine 4-chlorination.

- 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.

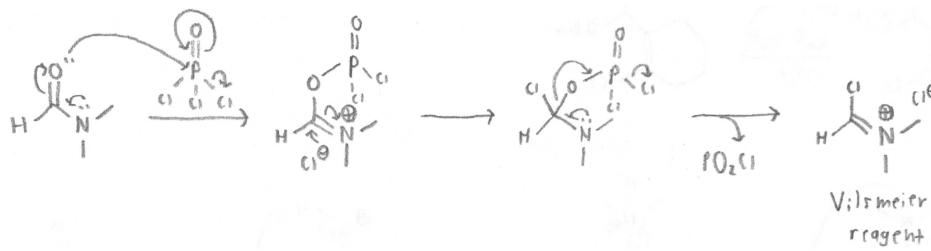
Figure 2.5: TTQ: Pyridine *meta*-bromination.

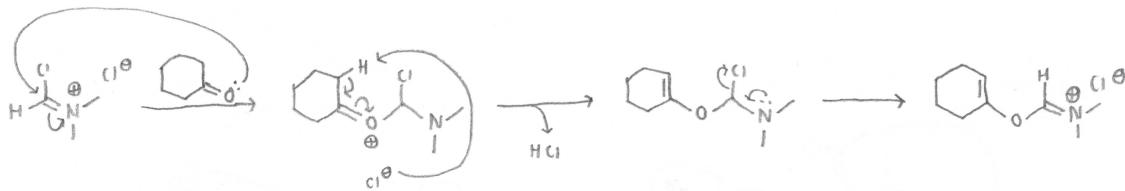
- Uses bromination mechanism from class (see Figure 2.2).
- Oleum could be SO_2 or SO_3 .
- Br^- can remove either bromine in the last step.
- This gets full credit; it is great, but for the second bromination, it may make more sense to put the bromine on the other side of the compound; the 1,2-dibromide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

2.2 Pyrimidines and Pyrroles

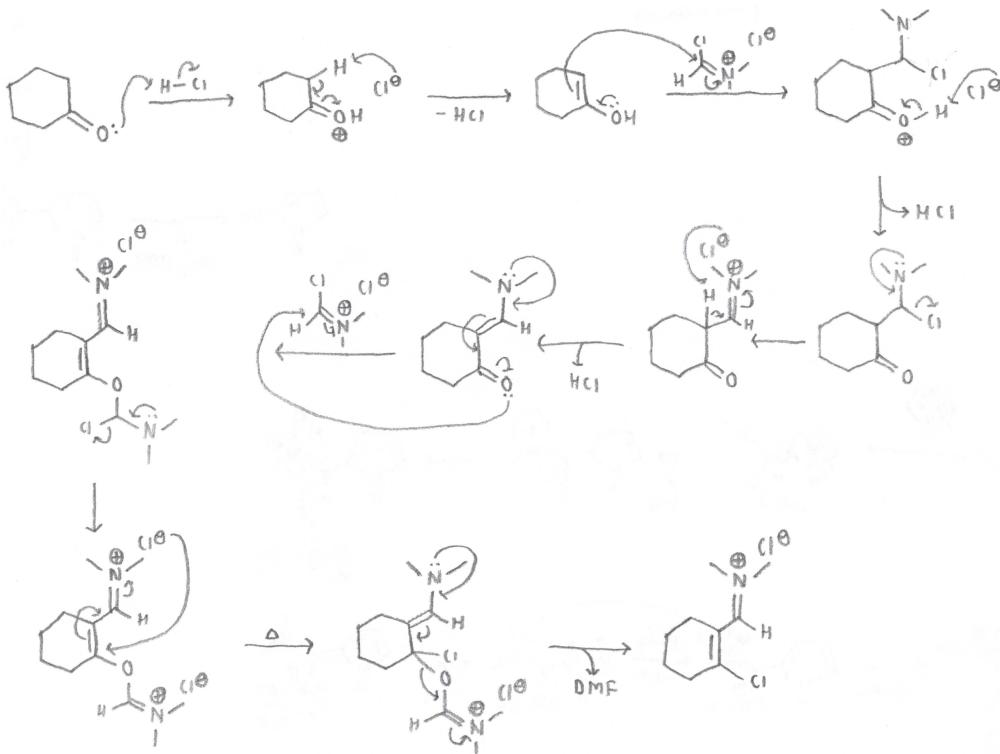
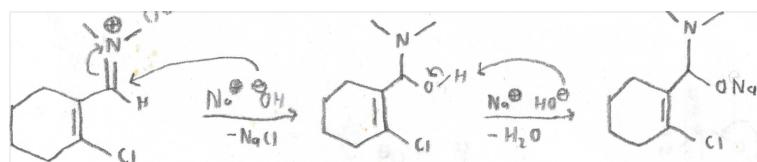
2/13:

- Syntheses of pyrimidines.
 - Several disconnections once again.
 - Most important ones: The [3 + 3] disconnections, especially the **Pinner reaction**.
 - Pinner reaction.
 - You make an **amidine**, typically by adding a sodamide (NH_2^-) to a nitrile.
 - **Grimaux** (pyrimidine synthesis).
 - Makes barbituric acid (part of barbituates).
 - Equivalent of a diacid chloride plus a urea.
 - Then can be converted into halides using reactions we've discussed such as POCl_3 .
 - **Biginelli** (pyrimidine synthesis).
 - Ignored for 125 years.
 - Became popular when people wanted libraries of heterocycles.
 - Popular because you can mix and match β -ketoesters, aldehydes, and ureas.
 - Mechanistically, you begin with a **Knoevenagel condensation** (aldol variant). This gives a species very activated toward Michael addition, so urea can add twice.
 - “Urea has the solubility of brick dust,” so you need a quite active solvent mixture to get at least some of it in solution.
 - **Ziegenbein-Franke** (pyrimidine synthesis).
 - Very young; about 60 years old.
 - Think about the mechanism of ketone to β -chloroaldehyde (once again, a 1,3-biselectrophile)!!
 - The β -chloroaldehyde is then pyrolyzed with formamide.
 - Mechanism: Michael addition, transitive imine formation, addition-elimination to lose H_2O .
 - **Pinner** (reaction).
 - Acidic reaction with a nitrile gives a **Pinner salt**.
 - Either hydrolyse or convert to the amidine.
 - Several 1,3-bisnucleophiles can be treated with 1,3-biselectrophiles (typically a β -dicarbonyl, but can be others) in this manner.
- Addendum: Vilsmeier-Haack type chloroformylation mechanism.

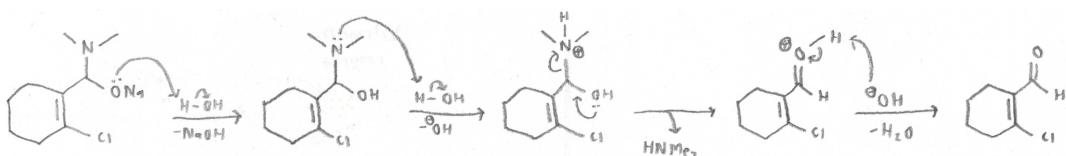




(b) Hydrochloric acid libration for autocatalysis of the keto-enol tautomerization.

(c) Formation of the β -chloroacryliminium chloride salt.

(d) Basic hydrolysis.



(e) Neutral/acidic hydrolysis.

Figure 2.6: Vilsmeier-Haack chloroformylation mechanism.

– **Vilsmeier reagent** prep (Figure 2.6a).

- To a solution of excess DMF, POCl_3 is added. Thus, POCl_3 will react completely with DMF to form the Vilsmeier reagent (and PO_2Cl byproduct). Said reagent will then be solubilized in the leftover DMF. This all occurs without competing reactivity with the ketone.
- Even if a ketone was present, POCl_3 would prefer to react with DMF over the ketone because DMF's carbonyl is more reactive than the ketone's owing to the conjugated nitrogen lone pair.
- DMF also reacts exclusively through its oxygen instead of its nitrogen because its nitrogen is dialkylated, so it cannot undergo amide-iminol tautomerization.

– Liberation of HCl (Figure 2.6b).

- When the ketone is added to solution, very little of it (about one molecule in a million) will be in the reactive enol form. Thus, the element most susceptible to immediate electrophilic attack by the Vilsmeier reagent is the ketone's lone pairs.
 - It is interesting that DMF does not attack the Vilsmeier reagent; or perhaps it only does so reversibly.
 - Perhaps this reaction is unfavorable because the resulting iminium ion would have DMF as a much better leaving group (entropically and enthalpically in a polar aprotic solvent) than chloride.
- Regardless, once the ketone attacks the Vilsmeier reagent, the resulting oxocarbenium ion's α -protons are greatly activated toward deprotonation, perhaps by the chloride formerly of the Vilsmeier reagent salt. This leads to HCl liberation.
- Now that there is no risk of forming an enthalpically unfavorable dication, the nitrogen lone pair is free to remove the chloride ion, reforming the more stable iminium salt (in a kind of no-bond resonance). The resultant species will not react further productively.

– However, the damage is done, and the liberated HCl can now catalyze the main sequence of steps.

– The main reaction (Figure 2.6c).

- HCl has $\text{pK}_a = -6.3$, comparable to a protonated ketone's -6 to -8 . Thus, HCl can now easily protonate a ketone in solution, accelerating keto-enol tautomerization.
 - HCl could surely protonate many other species, too, but this is the only productive reactivity so it will predominantly control experimental results.
- Keto-enol tautomerization yields an alkene that is sufficiently nucleophilic to attack another equivalent of the Vilsmeier reagent.
- The protonated ketone can then be deprotonated (liberating more HCl), and an iminium chloride salt reformed.
- The β -ketoiminium chloride has a *significantly* acidic α -proton, and a base in solution (shown as chloride, for the sake of balancing everything) can deprotonate it to yield another equivalent of HCl, as well as a conjugation-stabilized vinylgous amide.
 - The increasing concentration of HCl in solution results in an experimentally observable autocatalytic rate increase.
 - It is important to remember that conjugated alkenes are more stable than unconjugated ones, hence why the vinylgous amide is more thermodynamically stable than the β -ketoiminium ion.
 - This vinylgous amide intermediate can actually be isolated in some schemes!
- We now want to get rid of the ketone oxygen. To do so, another equivalent of the Vilsmeier reagent will be used to turn it into a better leaving group. This leads to the formation of a labile (unstable) bisiminium chloride.
 - Note that in much the same way that DMF's oxygen is activated toward nucleophilic attack by its nitrogen, the vinylgous amide's oxygen is activated by the further away, conjugated nitrogen.

- Under the heated conditions of the reaction, the bisiminium chloride is subject to attack at the β -position of the conjugated iminium ion, followed by a collapse that kicks out DMF as a great leaving group (strong C=O bond formation, amide-type conjugation, entropically favorable dissolution in the DMF solvent, etc.).
- We have now arrived at a species that is stable until workup.
- In most procedures, basic workup appears to be a prerequisite to neutralization (Figure 2.6d).
- Then, under acidic or neutral conditions, we get the collapse to the aldehyde (Figure 2.6e).
 - Note that this sequence of collapse to an aldehyde holding off until neutral or acidic conditions is reminiscent of Figure 3.7 in Labalme (2024).
 - Indeed, under basic conditions, an anion is more stable on oxygen than nitrogen; but under acidic conditions, a nitrogen is more easily protonated (and hence used as a leaving group) than an oxygen.
- It is worth noting that salt formation appears to be a driving force to be aware of, perhaps due to Coulombic attraction being more thermodynamically stable than covalent bond formation in some cases.
- References.
 - Marson (1992, pp. 3663–3665) — review with currently accepted reaction mechanism outline.
 - Virgilio and Heilweil (1981, pp. 12–13) — standard prep for Vilsmeier-type chloroformylation.
- Now some older chemistry.
 - Pyrimidines can be anti-asthma reagents.
 - **Dimroth rearrangement** is quite interesting, but we don't have to know it (it's pretty esoteric).
- Skipping Biginelli.
- Example synthesis: An α_1 -Adrenoceptor Antagonist.
 - Useful reagent, POCl_3 , $\text{S}_{\text{N}}\text{Ar}$, deprotection.
 - Aside: We should be saying in this class, “this again?!”
 - Lots of condensations, $\text{S}_{\text{N}}\text{Ar}$, dehydrations, etc.
- Example synthesis: GABA $\alpha 2/3$ agonist.
 - Europe is on the move to ban all fluorine-containing drugs.
 - But how do you make CF_3 -containing compounds?
 - CF_3^- equivalents are really expensive to use on a large scale.
 - Ideally, use TFA or anhydride; can also use CF_3H , but this is a greenhouse gas 500–2000 times worse than CO_2 .
 - They use the anhydride; Friedel-Crafts type reaction with ethyl vinyl ether.
 - Michael addition with guanidinium ion produces the core structure next.
 - Next reagent is the synthetic equivalent of α -bromoacetaldehyde.
- Example (medchem) synthesis: DNA-dependent kinase inhibitor.
 - Steve loves these compounds with high densities of nitrogens; this one has 8.
 - Strategy: Break into smaller heterocycles and use C–N cross-coupling.
 - The first reagent is an amide acetal (specifically, the dimethyl acetal of DMF, analogous to **Brederech's reagent**). It makes nitrogen into an electrophile; you acylate this, and then get intramolecular $\text{S}_{\text{N}}2$.
 - ??, Curtius rearrangement, C–N coupling with a Buchwald ligand (BrettPhos) on a palladium catalyst.

- Example synthesis: Fungicidal compound.
 - Key disconnection is a Suzuki-Miyaura cross-coupling.
 - 2-iodo-5-bromopyridine isn't too hard to access. Then you make the 2-metallocypyridine with **turbogrignard** (isopropyl magnesium chloride); negative charge attacks the halide (Br or I) to form the more stable anion.
 - This anion attacks PivCl.
 - Then lithiation and attack at the ketone.
 - Other route: Sequential alkylation to form the cyclobutane, even in the presence of a fairly weak base.
 - Then more turbogrignard (this time with the bromide) to generate the boronic acid. We can do this in the presence of a nitrile, presumably because the nitrile is so hindered.
- We now move onto 5-membered heterocycles.
 - Steve loves these, particular ones with multiple heteroatoms.
 - Their reactions are typically more challenging, so most people avoid them. They're also of great interest in many applications.
- **Pyrrole.** *Etymology* from Greek “bright red color which pyrrole imparts to pinewood shavings moistened with concentrated hydrochloric acid.”^[3]
 - Most chemistry started in Germany, because they had a huge coal industry and most heterocycles were originally isolated from coal tar.
 - PE and PP were invented (by accident) at the Max Planck institute, specifically the Ziegler-Natta polymerization; at Max Planck, they only call it the “Ziegler” polymerization.
 - Pyrrole is π -excessive; it's more electron-rich. Unlike in pyridine, the nitrogen lone pair is *part* of the aromatic system. This leads to anionic charges all throughout the ring.^[4]
 - pK_a of protonated pyrrole is -3.8 , and the proton actually resides on carbon (because the pyrrole nitrogen is so nonbasic).
 - Not quite as aromatic as benzene, but still pretty aromatic.
 - Tetramethylpyrrole has $pK_a = 3.7$ (methyl groups' hyperconjugation induces seven orders of magnitude difference). Also, now we protonate on the nitrogen (different in slides)??
- Very susceptible to EAS.
 - α -position is slightly more active than β -position (4 : 1 ratio in nitration).
 - So electrophilic that bromination (even under mild conditions) goes straight to tetrabrominated material.
 - Monobromination can be accomplished with an alternative electrophilic bromine equivalent to NBS, called **dibromodimethylhydantoin**.
 - Boc protection allows you to do mono- or di- α -brominated pyrrole.
 - TIPS protection allows you to do mono- or di- β -brominated pyrrole.
- When you do something to the nitrogen, you do not disrupt aromaticity.
- **Vilsmeier** is classic; this is the best way to make 2-pyrrolylaldehydes.
- Electrocyclic reactions.
 - Pyrrole is a very poor diene.

³Steve wonders, “How do you think to do that?!”

⁴If so electron rich, could help prevent thionolactonization tautomerization??

- Decarboxylation can be nice; can be much easier to synthesize carboxylated than decarboxylated version.
- Cross-coupling reactivity of pyrrole.
 - The choice of protecting group is key, and TIPS is usually best.
 - Protecting group-dependent coupling applies to the Miyaura borylation and everything else.
- Selected pyrrole syntheses.
 - Classic disconnections give unstable precursors (esp. the dialdehyde), so we need synthetic equivalents.
 - Pyrrole is no longer made from coal tar; it is today made commercially from furan.
 - Alternative big synthesis: Pyrolyzing the sugar derivative, **ammonium mucate**. This is entropically very favorable.
 - Classic way for an organic or medicinal chemist to do this: **Paal-Knorr synthesis**.
 - There are, in fact, lots of Knorr syntheses.
 - The issue is that you can't buy that many 1,4-dicarbonyl compounds.
 - Enamines (in mild acid) protonate at carbon (they protonate at nitrogen in strong acids). Pyrrole is essentially an enamine!
 - **Knorr** (pyrrole synthesis).
 - α -aminocarbonyl and β -ketoEWG (e.g., β -ketoester).
 - Imine formation, followed by aldol-like condensation.
 - Example: 2-aminoacetone and an activated system; activated because you don't want self-condensation.
 - Saponify the methyl ester selectively, distill to remove CO₂.
 - Write mechanisms for all transformations!!
 - **Hantzsch** (pyrrole synthesis).
 - α -halocarbonyl (no self-condensation!) and β -ketoEWG.
 - Alkylation followed by ammonia.
 - Example given.
 - **van Leusen** (pyrrole synthesis).
 - More unusual.
 - There are also several van Leusen syntheses of 5-membered heterocycles, all using TosMIC (an **isocyanide**, which is a type of heteroatom-stabilized carbene).
 - Mechanism: After deprotonation of the acidic TosMIC α -proton, Michael addition occurs. The resultant enolate adds at the isocyanide carbon to make the imino carbanion. Following protonation, the activated α -proton of the β -iminoketone gets deprotonated, generating an electron conduit through which to eject a tosyl leaving group. Finally, intramolecular proton transfer gives the desired pyrrole derivative.
 - Compatible with HWE to introduce functional groups at C3 and C4 from an aldehyde and phosphonate ester.
 - Pyrrole is a great nitrogen protecting group; what else doesn't have a free NH? This is a quite common protecting group, even in Steve's collaboration with BMS.
 - Example synthesis: Remdesivir (COVID-19 drug).
 - Required an efficient route to a certain heterocycle (on a 100 ton scale).
 - Has to be done efficiently, cheaply, reliable, no bad waste stream, and SMs are basically “air, earth, fire, and water;” things you can get very cheaply from a variety of sources.

- Chlorosulfonylisocyanate is a quite old reagent. Installs a nitrile (good to draw mechanism!!). Then Pinner-type reagent.
- This was ok for the first few tons (33% yield over 4 steps).
- Take pyrrole itself (write mechanism for Vilsmeier-type reaction!! Intermediacy of an oxime, followed by dehydration of the oxime).
- Then N–N bond from chloramine.
- Two telescoped transformations increases yield by about 50%!
- Addendum: CSI-type nitrile installation.

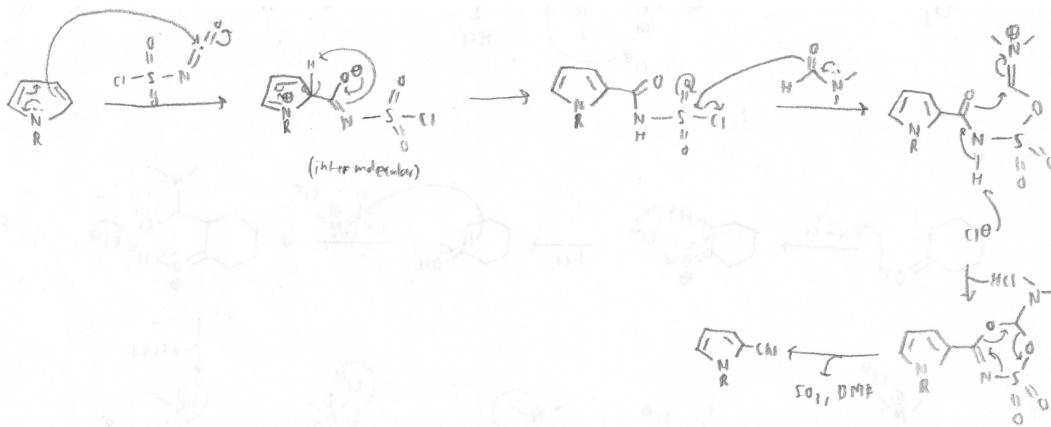
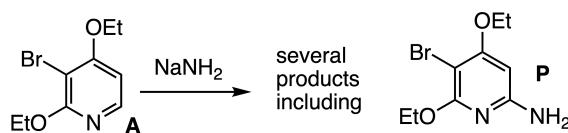


Figure 2.7: Chlorosulfonylisocyanate-induced nitrile installation.

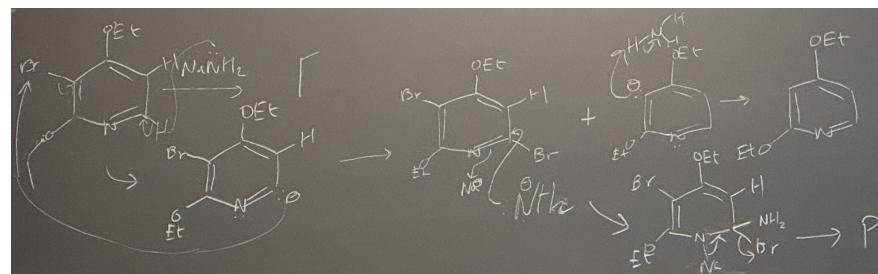
- CSI's electrophilic isocyanate induces EAS-type reactivity from the nucleophilic pyrrole.
- Then PT occurs to the more nucleophilic isocyanate nitrogen (most likely intermolecular, contrary to how it's drawn). This also has rearomatization as a favorable driving force.
- At this point, we're pretty stable, but the solvent DMF can get involved. A few pericyclic reactions later, we get DMF back, strong S=O bond formation in SO_3 , HCl catalyst formation, and our nitrile.
- Reference: Vorbrüggen and Krolikiewicz (1994, p. 6553).
- **Volumetric productivity:** How much material can you get through your reactors in a given day? The better you do, the less the cost of your reactor dilutes the cost of your pharmaceutical.
 - When you get to a certain scale, labor costs fall out of the equation.
- Academics should spend less time on the cost and more time on the novelty of the chemistry.
- Six steps for a practical synthesis of the fluoro/ethyl ester.
 - Aza-Michael addition.
 - Protect nitrogen as Boc.
 - Claisen to β -ketoester.
 - Treatment with DAST (not particularly nice or cheap, but is effective).
 - Pyrrolidine to dihydropyrrole, then a base as weak as Et_3N can form the shown product.
- Lipitor.
 - Largest-selling pharmaceutical (in terms of dollars) in the history of the world.

- Discovered at Park-Davis in Ann Arbor, a relatively small company. They partnered with Pfizer for the sales and marketing. They worked out a deal where they did well at low sales, but poorly at high sales; but this ended up being bad, and Pfizer acquired the company.
- Bruce Roth (the inventor) got laid off after 5 years, which kind of sucked.
- Classic example of a statin.
- Along with penicillin antibiotics, statins changed the world more than almost any other pharmaceutical class.
- Original synthesis: Paal-Knorr, enolate reduction, lactonization.
- β -ketoacids and esters are great substrates for asymmetric Noyori/Sharpless/Knowles chemistry.
- **Stetter** species reacts to form a carbon-carbon bond, then Michael addition.
- This material prepared from isoascorbic acid (available for 11 cents/gram).

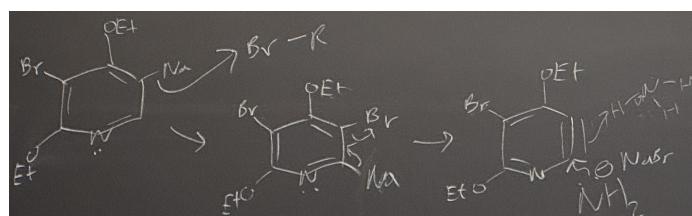
- Problem 3.



(a) The reaction.



(b) A defensible mechanism.



(c) Another defensible mechanism.

Figure 2.8: TTQ: Non-Chichibabin pyridine amination.

- Hint: This reaction does *not* proceed through a Chichibabin-type mechanism.
- Defensible mechanism 1 (Figure 2.8b).
 - If we're not starting with addition chemistry, then let's start with abstraction/deprotonation chemistry!
 - The *meta*-position is usually more acidic in pyridines, but the alkoxides both add electron density to it. Thus, the *ortho*-position is now more acidic.
 - Deprotonating there gives an anion; now we have a species that *cannot* be acted upon by a nucleophile.

- Additionally, this anion is destabilized by the α -effect.
 - So, in the spirit of turbogrignard, we react at the bromide (through an ate complex) to form a new, more stable anion.
- Then the new anion does intermolecular proton abstraction from the NH_3 we produced.
- But now the 2-bromoposition is activated in the molecule that abstracted a bromide, so we can do a more classic Chichibabin with our better leaving group.
 - Note that the second equivalent of NH_2 attacks C2 instead of C5 because we can delocalize the C2 charge onto the nitrogen but not a hypothetical C5 charge.
- Follow-up question: What happens if we deprotonate at the other pyridine hydrogen position?
- Defensible mechanism 2 (Figure 2.8c).
 - We start with the same type of bromine abstraction.
 - This is followed by benzyne-type formation. We're under brutal conditions, so sodamide can act as a base again!
 - From benzyne, the sodamide might attack it and then pick up a proton from the NH_3 .
- Differentiating the two mechanisms.
 - KIEs could work.
 - Selective deuteration of one position would also allow you to look at the product distribution and see whether the proton or deuteron got removed. In one, the deuteron will hang around; in the other, not.

Topic 3

π -Excessive Heterocycles

3.1 Imidazoles, Pyrazoles, and Indoles

2/20:

- Announcements.
 - PSet 2 will not be posted yet because most of the material won't be covered until next Tuesday.
 - We'll still have it a week before the exam, and the exam will not be so indole focused.
 - The practice exams are also still to come.
 - Lots of material and esoteric reactions in these slides; Steve will not discuss it all, nor expect that we remember it all.
- Imidazole and benzimidazole.
 - Important constituents in pharmaceuticals and biologically important substructures (e.g., histidine; nucleophile in salt bridges; constituent in DNA).
 - Proteins are often purified on nickel columns that act on histidines (see “HisTags”).
- Structure and reactivity.
 - Often put into structures to increase water solubility (can completely hydrogen-bond; both donor and acceptor)!
 - Combination of pyridine and pyrrole: One lone pair orthogonal to the π -system, and one pyrrole-like pair that does not typically react with electrophiles.
 - Imidazole is less nucleophilic than pyrrole at carbon.
 - Rapid tautomerization complicates reactivity; if you want to target a particular site, you might get a surprise. But there are ways to overcome this that we'll discuss.
 - Imidazole is amphoteric: One H is moderately acidic (not super, but not like C–H either), and then can protonate. Much less acidic than oxazole or thiazole because of resonance.
 - Alkylation at nitrogen occurs, followed by deprotonation, followed by more reactivity.
- Reactions of imidazole.
 - Deprotonation (with a strong base, e.g., NaH, LDA, NaHMDS) creates a strong base that monoalkylates.
 - Selective alkylation at nitrogen?
 - Target N² with protection (acylation), **ethyl Meerwein's reagent**, and deacylation.
 - Target N¹ with Buchwald amination (Steve: “I hate the amination, should've gotten rid of the amination”).
 - EAS.

- Better than benzene, worse than pyrrole.
- Nitration breaks the symmetry of the molecule. Easier to put nitrogen group next to non-positively charged nitrogen.
- Polybromination is also possible.
- Selective bromination occurs analogously to with pyridine (see Figure 2.5); attack at nitrogen, then carbon, then rearomatization.
- More “trivial” reactions.
 - S_NAr.
 - Moves the lone pair onto the nitrogen, as we've seen.
 - Directed metallation.
 - SEM (popularized by Bruce Lipschutz at UC-Santa Barbara) is the best protecting group. Can be removed by fluoride, which induces a loss of ethylene and formaldehyde.
 - Selective deprotonation between the two nitrogens (fairly standard, steric factors considered).
 - Can then do again.
 - Lithium-halogen exchange.
 - LiX exchange occurs faster than deprotonation, then deprotonation occurs.
 - To ensure that everything occurs in the right order, people will often add a strong base (e.g., LiHMDS) first; then add butyl lithium to do the LiX exchange.
 - Radical chemistry, e.g., the Minisci reaction.
 - Photochemistry as well, but that would be a whole other course; Steve won't discuss, take 5.44 with Alison if you want to hear more.
 - Minisci (radical decarboxylation) predates photoredox catalysis for generation of carbon-centered radicals.
 - Second example: Nucleophilic radical can add to electron-deficient (because of the aldehyde) carbon center.
 - Quaternary imidazolium salts.
 - Subsequent base yields ylide, i.e., the NHC (NHCs ubiquitous in catalysis).
- Selected imidazole disconnections.
 - Some should look familiar, and some may not.
 - The first one to talk about individually is the **Debus-Radziszewski** (imidazole synthesis).
 - From a long, long time ago. First reported synthesis of imidazole.
 - Combines a 1,2-diketone, aldehyde, and ammonia.
 - Proposed mechanism has zero evidence, but some variation is probably correct.
 - Aldehyde is probably converted to imine *before* formation of the diimine on the 1,2-diketone.
 - Then condensation.
 - Then tautomerization.
 - Synthesis 1: Analogous to the Pinner reaction; very common.
 - Van Leusen: Analogous to the pyrrole synthesis of the same name.
 - Synthesis 4.
 - Aminoacetal an acetal for stability reasons.
 - Attack to imine and then cyclization.
 - Synthesis 6: Paal-Knorr type.
- Example synthesis: Conivaptan.

- Pinner-type synthesis.
- Example synthesis: Estrogen receptor.
 - N⁻ adds to nitrile.
 - Workup to amidine.
 - Condense with α -bromoacetaldehyde to form the imidazole.
- Example synthesis: Obesity.
 - α -bromopyruvate.
- Van Leusen.
 - TosMIC: Stabilized isocyanide.
 - Easily deprotonated, add to the imine, attack at carbene, proton transfer, losing the sulfonate.
- COX-2 inhibitors.
 - Historically important chemistry.
 - Merck billion-dollar molecule.
 - Has to do with pain.
 - Aspirin (but disrupts stomach) → NSAIDs (ibuprofen, endoproxin) → tylenol (but dissolves liver) → opioids (but addictive).
 - Most things inhibit both pathways (COX-1 and COX-2), but this drug was selective for COX-2, specifically. But this (Vioxx) causes heart-valve problems (and Merck had to pull it from the market at great loss).
 - Celebrex as well, but the company died and had to be sold to Pfizer.
- Example synthesis: Like Lipitor, another statin compound.
 - Glycine benzyl ester is a fairly standard protected amino acid.
 - Treat it to form something, which after cleavage can be acylated.
 - Ester to benzylamine.
 - Cyclize with a primary amine to stitch in the nitrogen.
 - Cyclize (fairly typical with statins).
- Example synthesis: Debus-Radziszewski chemistry.
 - Microwave chemistry was huge, but the bubble has burst at this point. You still see it here and there, but not much.
 - Get to the asymmetric α -diketone with a SeO₂ oxidation.
 - What method you'll use commonly depends on what you have and what you have successfully been able to do previously.
 - Ester, cross-Claisen, hydrolysis/decarboxylation could also allow you to make a series of different imidazoles.
- Example synthesis: pan-JAK inhibitor.
 - Lab synthesis.
 - Buy the phenol and protect it as the SEM.
 - Miyaura borylation, Suzuki-Miyaura coupling, Pinner salt formation, convert to the imidium system.
 - Cleave with acid to liberate the carbonyl and do the intramolecular cyclization.

- Scale synthesis.
 - Removed Miyaura borylation with Grignard, etc.
 - Gets a byproduct, but it's inactive.
 - Many telescoped steps.
 - You need to worry about the form of the crystal that recrystallizes (there is a whole field of **crystal engineering**); is it too big, too small, etc.?
- Example synthesis: P13K β -Sparing.
 - No lateral deprotonation, despite intuition!
 - Weinreb amide (for adding carbanions to carbonyl derivatives).
 - Alkylate on nitrogen, do S_NAr (could also be benzyne).
 - Palladium catalyst for final Suzuki-Miyaura cross-coupling.
 - Can do it in the presence of *a lot* of basic functional groups.
 - More evidence why this chemistry won the Nobel prize.
- 1,2-azoles.
 - We'll talk mostly about pyrazole, but there's also isothiazole and isoxazole.
 - Dimeric structure in solution.
 - Also has tautomerization.
- A few reactions (similar again).
 - N lone pair in and out of the aromatic system.
 - Acylation → deprotonation again.
 - Selective halogenation can be rationalized based on arrow-pushing and charges.
 - Can acylate on carbon by sterically blocking the site that will typically react first; thus, more engineered and less useful.
 - Under neutral conditions, alkylation occurs at the lone pair.
 - Under basic conditions, we form the thermodynamic product.
 - Lots of companies have wanted to *N*-arylate at the thermodynamically unfavored nitrogen recently, and have needed catalysts to do that.
 - Lithiation.
- Pyrazole syntheses.
 - More condensation chemistry.
 - Always look for bisnucleophiles and biselectrophiles!
 - This is a very common disconnection.
 - Dipolar cycloadditions can also be employed (not as common, but occur on occasion).
 - Knorr gets his own synthesis.
 - This is good for symmetric pyrazoles.
 - Propynyl ketones act as the synthetic equivalent of a β -dicarbonyl.
 - Cyclopropane thing synthesis.
 - Take the diketone, halogenate in between, nucleophilic displacement. α -aryloxy ketone could feed into a cross-Claisen condensation.
 - Aside: Whenever you see a structure, think about whether you can get to it using chemistry that you learned in first-year organic; that's what people want to use.

- Diazomethane can be generated in flow now, so it can be used on scale.
 - Explosive and toxic; precursors are also nasty (mutagenic), so bad on lab scale, too.
- What if the condensation has 2 : 1 selectivity in the wrong direction?
 - Try a dipolar cycloaddition.
 - Treat a thing with base to do a 1,3-elimination. Then do this with an aryl acetylene (looks good, but hard to handle and explosive, so use an equivalent).
 - As an equivalent, use the enamine, which is an elimination away from the acetylene.
 - They did this chemistry on a huge scale, which is wild to Steve.
- In process chemistry, they will do almost anything (as long as its legal), even using brutal conditions, if necessary.
- DGAT-2.
 - Cyclopropanated benzimidazole derivative.
 - Reduce to the 1,2-diamino derivative. Then other piece for condensation.
 - Other piece: α -alkylation twice. Can't do S_N2 with cyclopropanes because the transition state wants to be 120° , but the cyclopropane is 60° .
 - GMP (General Manufacturing Procedure) synthesis (control access to the reactors, everyone is in clean suits, etc.). Very expensive, but makes sense if the compound is going into a person.
 - Got starting material from γ -bromocarboxylic acid via Hell-Volhard-Zelinsky reaction, in Steve's guess.
 - Cleave the ester under acidic conditions; in basic, you would have competitive $S_NAr??$ (easier to control the quality of acetyl chloride and methanol than gaseous chloride, so as to generate HCl *in situ*).
 - Do this in the presence of Boc-anhydride to form the Boc-amide.
 - Use T3P (a reagent to make amides).
 - Then cleave the Boc.
- Indoles.
 - Jeremy Knowles (Steve's doctoral advisor) used to make fun of people who made indoles, yet Steve ended up making them regardless.
 - Most widely occurring ones: (*S*)-tryptophan and serotonin (responsible for sleep, depression, anxiety, etc.).
 - SSRIs: Selective serotonin uptake inhibitors.
 - Triptans are antimigraine drugs, very structurally related to serotonin.
 - Migraines are financially huge to pharmaceutical companies. No generally successful solutions yet.
 - LSD.
- Reactions of indoles.
 - 5-membered ring is always the most reactive part.
 - 6 M sulfuric acid reveals that protonation at C3 is most favorable.
 - $pK_a = -3.5$, so does not protonate easily.
 - React with electrophiles at C3.
 - Example: Halogenation occurs at C3.
 - Acylation.
 - Acidic conditions: C3.

- Basic conditions: At the nitrogen.
- C3-blocking leads to C2 reactivity next.
- Excess of methyl iodide and heat leads to tetramethylated isoindole structure. Write how this forms!!
 - Skatole (one of the worst smelling compounds in the world) is the product; look it up!
- BF_3 -etherate.
 - Proceeds through spirocyclic intermediate (very common chemistry for indoles), as proven by isotopic labeling.
 - Aside: On mechanisms.
 - You used to have cumulative exams and 2 foreign languages as PhD requirements.
 - Frank Westheimer (famous guy who invented chemical biology) was one of Steve's "cumes." One question he gave was "cite the original experimental evidence for these 20 famous findings;" Steve had no idea.
- Mannich-type reactions.
 - pH = 6 is the Goldilocks range.
 - Pictet-Spengler type transformation, historically used in alkaloid synthesis.
- With base.
 - NaH is fine, but not great on scale (usually shipped as mineral oil dispersion).
 - EtMgI is shipped around in tank cars and it forms a base just fine.
- Directed metallation.
 - BOC is DMG, then deprotonate at C2, then electrophile.
 - Cooler way: Throw dry ice in (CO_2 source). Treat with more to form dianion, then deprotect.
- Reactions of gramine.
 - Tryptophan.
 - Put something on that isn't a great leaving group.
 - Put on an electron conduit that allows you to push out bad leaving groups.
 - This is a way to make racemic tryptophan.
 - N-methylation.
 - TIPS (big) allows for C4 lithiation.
 - This is important because the **Fischer indole synthesis** (typical) is not good at making 4-substituted indoles.
- We'll start with indole synthesis next time.
- Next Tuesday, after class: PSet 2 and previous years' exams.

3.2 Indoles, Indazoles, Thiophenes, and Furans

2/25:

- Announcements.
 - Exam 1: Next Tuesday, in class, same format as the two previous exams.
 - Purpose: Steve is required to give one.
 - Confirm what you know; have you paid attention, stayed awake, etc.? Some regurgitation.
 - What can you do with the material you know? Arrow pushing, etc. More like mechanistic problems.
 - A few synthesis problems.

- Some aspects of metal-catalyzed cross-coupling. You don't need to know this ligand vs. that, but you should know the basic features of C–C cross-coupling, basic steps of the reaction, what metal works, know some ligand, etc.
 - The exam will be *distinct* from the previous exams.
 - Current difficulty (before the TA edits it): Moderate.
 - Today's lecture material is the end of what will be covered on the exam.
- PSet 2 is much more indole-focused than the exam.
- Synthesis of indoles.
 - **Bartoli** (indole synthesis): Vinyl grignard plus nitroarene.
 - You have to believe it was discovered by accident, because it makes so little sense.
 - You need a relatively large R group (bromine counts as relatively large).
 - You can write a mechanism (this is plausible, but it may or may not have any basis in reality).
 - Plausible mechanism: Nucleophilic attack at oxygen, collapse to a nitroso intermediate, nucleophilic attack, sigmatropic rearrangement, intramolecular attack, deprotonation and rearomatization, and then workup.
 - Example: Propenyl grignard gives 3-methyl substituted.
 - Indole's 7-position is not trivial to functionalize, so having a starting material with that position activated that you can then Heck couple to later (or do something else to) is super useful.
 - Now some more historically important indole syntheses.
 - **Leimgruber-Batcho** (indole synthesis): Mix *ortho*-alkylated nitroarene with Brederech's reagent,^[1] and then heat it in DMF.
 - Mechanism: Spontaneously generates a bit of methoxide to do lateral deprotonation. Then addition to the compound formed by expulsion of the methoxide. This gives enamine. Now magic chemistry: Reduce nitro group to an amine, then addition-elimination to indole.
 - It's not been carefully elucidated what does the reduction, but the guess is that using "tickle 3" ($TiCl_3$) does inner sphere addition to nitroso, reduction of the nitroso, etc. Not yet published what actually happens.
 - **Bischler** (indole synthesis): Mix an aniline with an α -bromoacetaldehyde acetal.
 - A base deprotonates the aniline, which then engages in S_N2 bromide displacement.
 - Then, adding trifluoroacetic anhydride (TFAA) forms the *N*-trifluoromethylacetal.
 - Trifluoroacetyl groups are very labile. Acetamides are often the bane of synthetic chemists (very hard to cleave), but trifluoroacetamides are much easier to cleave (sometimes too easy).
 - Stabilized oxocarbenium then does Friedel-Crafts type chemistry.
 - Protecting groups in general tend to fall off of indoles (e.g., Boc_s, etc.). This is why you often have to resort to using a SEM, but those can be difficult to remove.
 - **Fischer** (indole synthesis): Mix an aryl hydrazine with a ketone.
 - Most important.
 - Also had to be discovered by accident. Here are Steve's thoughts on its origin.
 - Before NMR and IR, you had EA and melting point only. You determined molecular structure by making derivatives of certain functional groups and then taking melting points.
 - For example, **Tollens' reagent** (silver-based) was used to figure out if there was an aldehyde.

¹It appears that this is not actually "Brederech's reagent," but DMF-dimethylacetal.

- As another example, diphenylhydrazine was used to make a hydrazone. Hydrazones are super crystalline, so it's easy to get their melting point.
 - They were probably making a derivative, then realized that they made an indole!
 - Mechanism: Condensation to the aryl hydrazone, tautomerization to **ene-hydrazine**, [3,3]-sigmatropic rearrangement, rearomatization. Then ene or iminium formation.
 - They did not know what sigmatropics were back then, so that definitely just happened.
 - To make an aryl hydrazine, you make the aryl diazonium salt and then reduce it (typically with SnCl_2).
 - Limitations.
 - If R and R' are distinct, then the first intermediate can enolize two different ways, which leads to regioisomer formation.
 - Substituents at 4- or 6-positions on the aromatic ring lead to ambiguity in where the sigma-tropic rearrangement can occur.
 - Forcing conditions (strong acid and heating) can lead to issues with sensitive functional groups (esp. aldehydes).
 - You can manipulate the system, though.
 - Stronger vs. weaker acids modulate the direction of enolization. Kinetic vs. thermodynamic character; thermodynamic with the stronger acids.
 - Limitations are important to know because you want to know the pluses and minuses of each method.
- **Reissert** (indole synthesis): *ortho*-alkylated nitroarene, again, plus an oxalate.
 - Strong base leads to lateral deprotonation, addition to α -ketoester, then reduce to form the 2-ethylcarboxylate of indole.
 - Can then do addition at 3-position to form differentially substituted 2,3-disubstituted indole.
 - **Madelung** (indole synthesis): *N*-*ortho*-alkylarylamide collapses in strong base.
 - Deprotonation, probably via the dianion, which closes to form the indole and then can be further modified.
 - **Hemetsberger** (indole synthesis): Collapse of an α -azidoester on a styrene-type thing.
 - Fancier and less safe.
 - The starting material can be made from benzaldehyde and R-azidoacetate via Knoevenagel.
 - Mechanism: Photolysis to nitrene, which rearranges to azirine, which rearranges to the indole derivative.
 - Example synthesis: Applying the Leimgruber-Batcho indole synthesis.
 - Introduce two sulfonyl protecting groups so that you can put the nitro group at the desired position.
 - Superheated steam is a classic way to do desulfurization.
 - Benzyl-protect the phenol group.
 - Do Leimgruber-Batcho.
 - A pyrrolidine enamine is fairly common in this reaction.
 - Then convert to **semicarbazide**, to crystallize/isolate the intermediate before proceeding.
 - Now some 21st century chemistry: Reduce the nitro group and other functional group with iron under acidic conditions.
 - Then you add the aniline to the imine to form the aminal-type molecule, and collapse.

- Example synthesis: Applying the Hemetsberger synthesis.
 - Not often used because of “azidophobia.”
 - Reduce and oxidize to make the aldehyde.
 - Knoevenagel condensation to Hemetsberger starting material.
 - Reflux to complete the synthesis.
 - Hydrolyze the ester to the acid, make the primary amide, and then dehydrate to the nitrile.
 - Catalytic DMF with oxalyl chloride forms the Vilsmeier reagent, which can then chlorinate carboxylic acids before amidation.
 - Whereas POCl_3 forms the Vilsmeier reagent via the enthalpic driving force of strong $\text{P}=\text{O}$ bond formation, $(\text{COCl})_2$ forms the Vilsmeier reagent via the entropic driving force of $\text{CO}_2 + \text{CO}$ gas release.
 - Deprotonate with KH first because if you don’t, you might get reduction of the lithium/halogen-exchanged species.
 - Essentially, pre-deprotonation allows us to reliably and quantitatively form the dianion, whereas if we go straight through 2 eq. ${}^n\text{BuLi}$, we’ll do LiX exchange first (kinetically faster) and then the anion will deprotonate the N–H. The result is that we’ll have significant dehalogenated side product.
 - Then we add the anion into DMF, and warm/acidify to collapse.
- In industry, they do tons of safety evaluations (both for safety and because blowing up a reactor is expensive).
 - You want your calorimetry to give you 80°C between your reaction temperature and the exotherm.
 - That way, no part of the mixture is likely to get hot enough to induce a runaway reaction.
 - This is another example of the use of flow chemistry (it can control thermal runaways).
- Indazoles.
 - There exist 1- and 2-indazoles.
 - 1-indazoles are more common.
- Reactivity of indazoles.
 - N -substitution/protection.
 - Under basic conditions, bonding at either nitrogen is equally likely.
 - Under acidic conditions, N2-THP substitution occurs more quickly but N1-THP substitution is more thermodynamically favorable.^[2]
 - Thus, strong acid gives exclusively N1-THP substitution while weak acid is more likely to give N2-THP substitution (or a mixture at long reaction times).
 - Palladium catalyzed C–C or C–N coupling.
 - It’s often necessary to protect a nitrogen first.
- Syntheses of indazoles.
 - Route 1: Start with an *ortho*-alkylated aniline, acidify, form diazonium, do lateral deprotonation and collapse.
 - Route 2: Start with an **isatin**, and then use diazonium conditions again.
 - Isatins show up not infrequently in the literature.

²Mechanism.

- Isatins can be made from anilines and chloral,^[3] then hydroxylamine, then strong acid can also be good.
- Route 3: Start with bromofluorobenzaldehyde.
 - In S_NAr, it's the electron-withdrawing nature of the substituent that's important for selectivity (so F⁻ is a better leaving group!).
 - Hydrazone formation first, and then intramolecular S_NAr.
 - With nitrile or ester SM, you get different 3-substituted indazoles.
- Example synthesis: EGFR kinase inhibitor.
 - Protect with THP, use Xantphos (a great ligand for ??) to do C–N coupling.
 - Acrylamide inhibitor makes this another covalent inhibitor.
- Moving on back to something.
- Comparing π -excessive heterocycles: Structure.
 - Furan is least aromatic, then pyrrole, then thiophene is most aromatic.
 - All have one lone pair in aromatic system.
 - Furan is more reactive; lower cost to dearomatize.
 - Aromaticity trends are in accord with electronegativity of heteroatom (more electronegativity means less willing to delocalize).
- Comparing π -excessive heterocycles: Relative rates of acylation with TFAA.
 - Enormous reactivity difference: Pyrrole much more reactive than furan, more reactive than thiophene, and benzene doesn't react.
 - Selectivity.
 - β -addition is preferred because you get a more stable carbocation at the 2-position.
- Thiophenes.
 - Thiophene, benzothiophene = benzo[b]thiophene, and benzo[c]thiophene.
 - Derived from two Greek words: Sulfur and shining.
 - Discovered as a contaminant in benzene.
 - Benzene used to be sold as “thiophene-free.” If you were doing electrophilic reactions, thiophene was more reactive so you would get contaminants derived from it.
- Reactivity of thiophene.
 - Tetrabromothiophene can be made; tetraiodothiophene can't be made (iodines are too big).
 - Selective reduction can be done with palladium and NaBH₄: Oxidative addition is better at the α -position, and one α is much less hindered than the other.
- Syntheses: The usual suspects (Paal-Knorr), and then some other reactions (Hinsberg, Gewald [pretty useful], Fiessleman).
- Commercial synthesis of thiophene.
 - Butane and elemental sulfur, with a catalyst at 600 °C.
 - Another commercial route: Butanol and carbon disulfide.

³Mechanism.

- **Paal-Knorr** (thiophene synthesis): Heteroatom nucleophile and 1,4-diketone.
 - Example heteroatom nucleophiles: $H_2S + HCl$, P_4S_{10} , Lawesson's reagent.
 - Lawesson's reagent does sulfur Wittigs on a carbonyl: $C=O$ to $C=S$. Driving force is strong $P=O$ bond formation.
- **Fiesselmann** (thiophene synthesis).
 - β -chloroenal comes from Vilsmeier reaction; we should remember this chloroformylation!!
 - Deprotonate, add, and dehydrate.
- **Hinsberg** (thiophene synthesis).
 - Related to Debus-Radziszewski in some ways.
 - 1,2-dicarbonyl and 1,3-bisnucleophile. Deprotonate, add, eliminate twice sequentially. Then dehydrate.
 - Heating in base leads to decarboxylation.
- **Gewald** (thiophene synthesis).
 - Carbonyl (usually ketone) and α -EWG (usually cyano) cyanide.
 - This is bucket chemistry (large scale, inexpensive reagents).
 - Malononitrile forms dicyanoolefin, then reacts with amine to form compound shown there.
 - Knoevenagel condensation, deprotonate to form a sulfur species (you can go between S_1 to S_n , but S_1 will be reactive).
 - Then form an intermediate, followed by tautomerization.
 - Great if you don't have regiochemical ambiguity, but can give regioisomers.
 - To get around this, you cheat! Regiochemically pure alkyl bromide (raises cost), and then react.
- Example synthesis: Applying the Gewald reaction.
 - Target: A weak fungicide with a silicon atom in it.
 - Silicon atoms are becoming more and more common in pharmaceuticals and agrochemicals.
 - Discovery synthesis.
 - Sandmeyer-type.
 - nBuLi for LiX exchange, then $TMSCl$.
 - Acid chloride leads into amide.
 - This is a terrible scale synthesis, but it was "fit for purpose" (for discovery).
 - Yield is bad, Sandmeyer uses a hazardous reagent, silylation at $-70^\circ C$, preparation of acid chloride causes 20% protodesilylation.
 - Need to make rapid 20 kg and up to 200 kg batches.
 - Solution: Wash out the unused material (30-40% loss isn't environmentally good, but it can be good cost-wise).
 - To make even better, they went the cheating route: α -chloro material.
- Example synthesis: Ticlopidine (anti-platelet aggregation compound to lower blood pressure).
 - 1st synthesis: Selectively benzylate and reduce.
 - Problem: The thiophene-pyridine is not easy to access on scale.
 - Second synthesis: Start with thiophene-phenethyl amine, reductive amination on paraformaldehyde to cyclize, and reduce to the final product.

- Skipping one.
- Example synthesis: Tetrasubstituted thiophenes via directed metallation.
 - Cross-coupling can be good.
 - Turbogrignard forms anion (stable at 0 °C because it's thiophene; normal aromatic would eliminate to benzyne).
 - Then selective deprotonation via DMG and treatment with ethyl cyanoformate to form diester bromide.
 - Same base and S₈ form S⁻ that is then alkylated.
 - Then Miyaura borylation with Pd(^tBu₃P)₂ (not Pd(^tBu₂P)₂).
 - Then Suzuki-Miyaura cross-coupling.
- Furan.
 - Comes from Latin furfur (for bran), because furans come from agrochemical products; Quaker oats used to be the largest supplier of furan derivatives, esp. furfural.
 - Least aromatic of all 5-membered heterocycles.
 - In a variety of natural products and pharmaceuticals.
 - Before proton pump inhibitors, we had Zantac.
- Structure of furan.
 - One lone pair in aromatic system.
 - Quite acidic: pK_a < 36 at the α -position means we can deprotonate with ⁿBuLi.
 - Most electron density at oxygen; a lot, as well, at the α - and β -carbons.
 - Industrial source: Pentose-rich matter (known as bran), then acidic hydrolysis, then dehydrate to furfural, then catalytic decarbonylation.
- Reactivity of furan.
 - Electrophilic reactions.
 - 10¹¹ times more reactive than benzene. About 8 kcal/mol (??) difference.
 - Bromination: Steve did this as a student in a poor hood and then began “bleeding profusely from [his] nose.”
 - Cycloadditions.
 - Reduction and then thermolyzing (with Δ) is a cute way of making the diester.
 - Many cross-couplings.
 - Mannich substitution.
 - Dimethylamine and formaldehyde to form iminium ion, then reacts electrophilically at the 5-position.
 - Achmatowicz derivative.
 - Mechanism: Epoxidation of less-substituted double bond, ring-opening, then close.
 - Piancatelli: Don’t worry about.
 - Lithiation: Kinetic vs. thermodynamic control for 2- vs. 3-substitution.
- Synthesis of furans.
 - Paal-Knorr has same starting material (1,4-diketone), but is more of a rearrangement.
 - **Feist-Benary:** Only works on aldehydes; α -chloroketones have nucleophilic attack not at the aldehyde but at the carbon bearing chlorine.

- Benzofuran = benzo[b]furan.
 - First prep from Coumarin: Brominate and then treat with base to hydrolyze the lactone and decarboxylate with loss of bromine. Must have also been accidental.
- More on the exam.
 - You have to know stuff, but Steve also has to see that we can apply this stuff.

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