Topic 1

Pyridine Chemistry

1.1 Intro, Directed Metallation, and Organometallic Coupling

1/4:

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

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

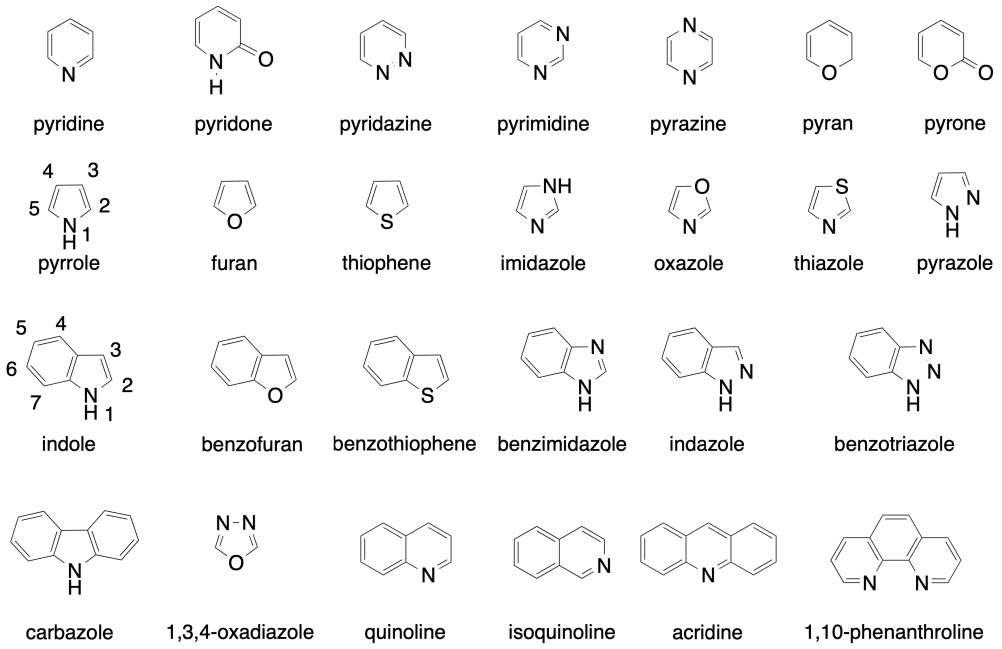


Figure 1.1: Heterocycles of interest.

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

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

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

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

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

- Current synthesis of pyridine.

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

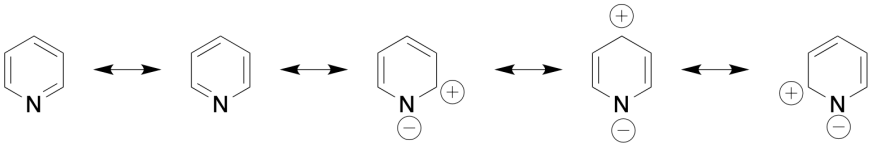
  - This synthesis is carried out with flow chemistry.
    - Before it was trendy in pharma, it is the only thing that was *ever* used in the production of commodity chemicals.
    - When you're making commodity chemicals, you can't afford solvents or separations.
  - It produces pyridine on a scale of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

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

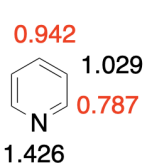
- Many drugs contain pyridine moieties. Here are some examples.
  - Muscopyridine: Perfumes.
  - Prevacid: Acid reflux.
  - Nexium: Sold as a single-enantiomer with a stereogenic sulfur atom!

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

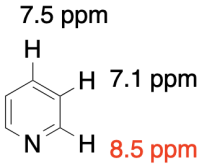
- The structure of pyridine.



(a) Important resonance forms.



(b) π-electron populations.



(c) ^{1}H NMR shifts.

Figure 1.2: Pyridine structure.

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

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

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

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

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

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

- Pyridones.

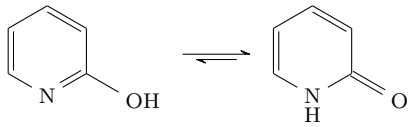
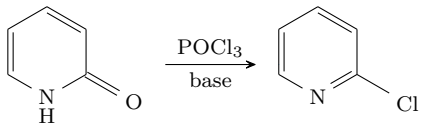


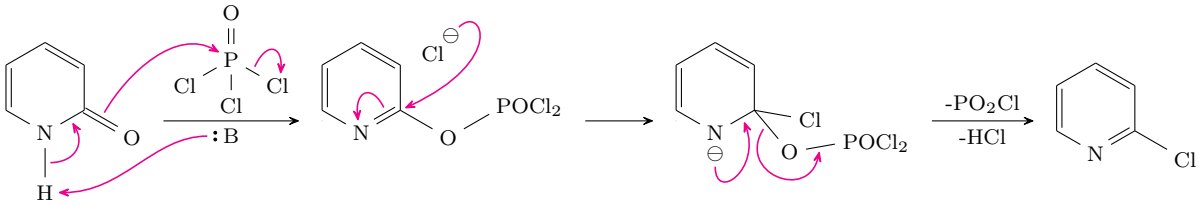
Figure 1.3: Pyridone tautomerization.

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

- Pyridone reactivity.



(a) The reaction.



(b) The mechanism.

Figure 1.4: Pyridone chlorination.

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

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

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

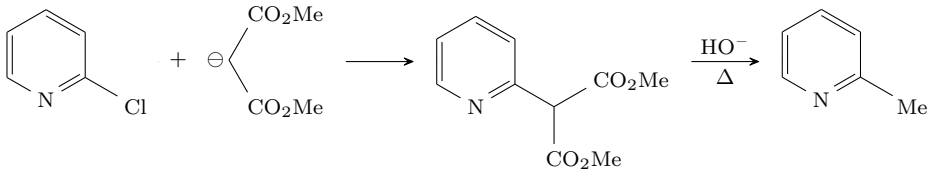
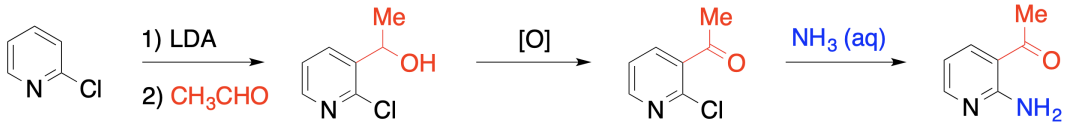


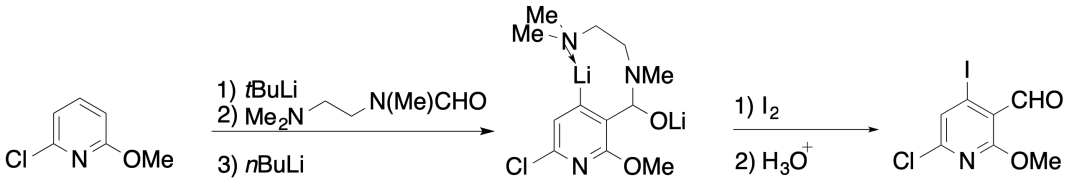
Figure 1.5: Lateral pyridine decarboxylation in robust synthesis.

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

- Pyridines as ylide-like species.



(a) Preparation of pyridyne "ylides."



(b) 3,4-difunctionalization.

Figure 1.6: Multifunctionalization of pyridines.

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

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

- The **Chichibabin reaction**.

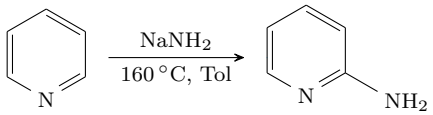


Figure 1.7: Chichibabin reaction.

  - Makes 2-aminopyridine from pyridine.

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

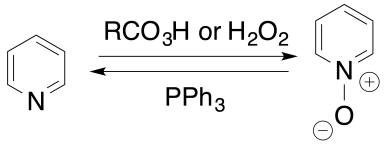


Figure 1.8: Synthesis of pyridine N-oxides.

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

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

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

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

1.2 Pyridine Cross-Coupling, Synthesis, and Derivatization

2/6:

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

- Lecture begins: Back to cross-coupling.

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

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

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

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

  - Very small differences have big impacts on reactivities.

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

- Clever tricks with boron.

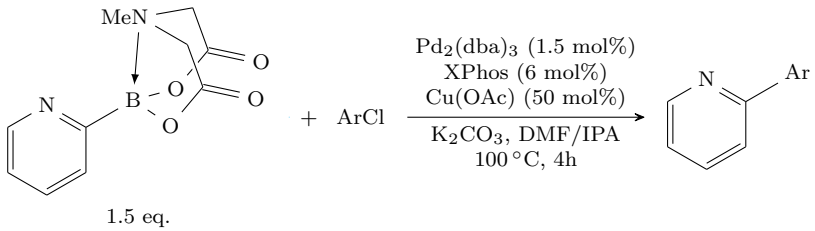


Figure 1.9: MIDA boronates for air-stable 2-pyridyl couplings.

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

- Negishi coupling of 2-pyridylzinc reagents is ideal!

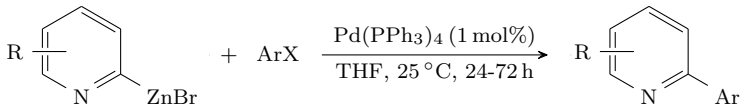


Figure 1.10: Negishi-type 2-pyridyl couplings.

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

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

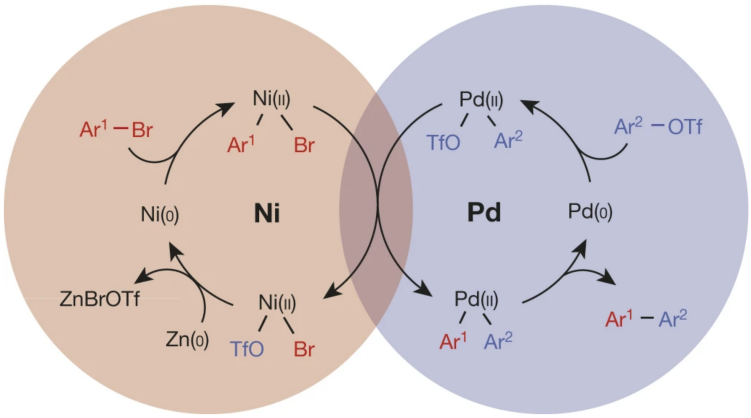


Figure 1.11: Tandem nickel-palladium catalyzed aryl halide cross-coupling.

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

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

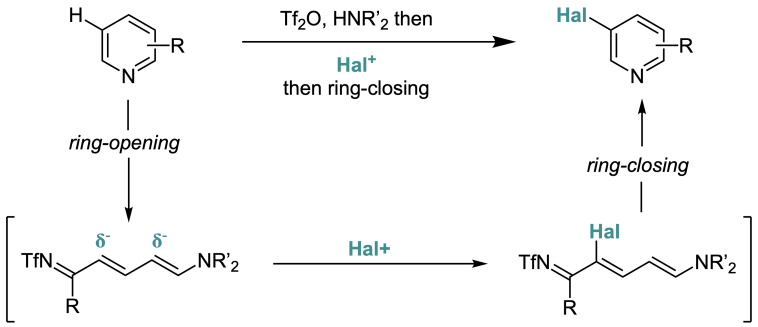


Figure 1.12: *meta*-halogenation of pyridines via Zinke chemistry.

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

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

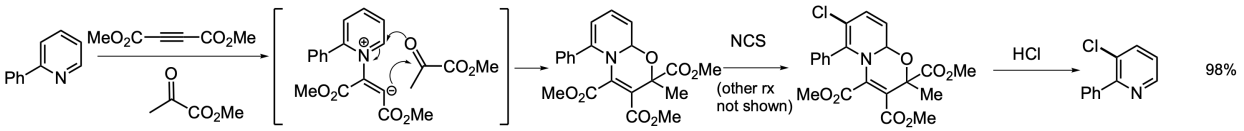


Figure 1.13: *meta*-halogenation of pyridines via temporary dearomatization.

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

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

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

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

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

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