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 reactivivity.
- Reactions of imidazole.
  - Deprotonation (with a strong base, e.g., NaH, LDA, NaHMDS) creates a strong base that monoalkylates.
  - Selective alkylation at nitrogen?
    - Target N^2 with protection (acylation), **ethyl Meerwein's reagent**, and deacylation.
    - Target N^1 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) $\rightarrow$ NSAIDs (ibuprofen, endoproxin) $\rightarrow$ tylenol (but dissolves liver) $\rightarrow$ 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 SeO_2 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/decarboxyliation 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 $\rightarrow$ 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 occuring ones: (*S*)-tryptophan and seratonin (responsible for sleep, depression, anxiety, etc.).
  - SSRIs: Selective seratonin uptake inhibitors.
    - Triptans are antimigrane drugs, very structurally related to seratonin.
    - 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 syntehsis** (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., Bocs, 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.

[1] It 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 sigmatropic 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 plusses 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: Photolyse 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 desulfonization.
  - 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 P=O bond formation, $(COCl)_2$ forms the Vilsmeier reagent via the entropic driving force of CO_2 + 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}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 thermodynaically 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.

[2] Mechanism.

        - 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.
        - α-addition is preferred because you get resonance delocalization through the π-system as well.

- 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 $NaBH_4$: 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], Fiesslemann).

- Commercial synthesis of thiophene.
    - Butane and elemental sulfur, with a catalyst at 600 °C.
    - Another commercial route: Butanol and carbon disulfide.

[3] Mechanism.

- **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.
  - Knovenagel 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.
    - ^{n}BuLi 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: Ticlopedine (anti-platelet aggreation 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 S_8 form S^- that is then alkylated.
  - Then Miyaura borylation with $Pd(^tBu_3P)_2$ (not $Pd(^tBu_2P)_2$).
  - 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 ^{n}BuLi.
  - 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.
    - 10^{11} 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.