Topic 4

Organometallic Coupling Reactions

4.1 Organometallic Coupling Reactions

2/27:

- Today: Organometallic transformations that are bread and butter for pharmaceutical chemists, both in discovery and at scale.
- **Heck** (reaction).
  - Many variants, but we'll focus on an aryl halide reacting with an olefin.
  - Feature: We regenerate the double bond, as opposed to most couplings which increase saturation.
  - Bio: Richard Heck.
    - Started in industry at Hercules Corporation.
    - Moved to University of Delaware.
    - Was told that what he was doing wasn't interesting, so he quit, moved to Florida to raise orchids, and then moved to the Phillipines.
    - A brilliant person who made contributions to a lot of fundamental mechanistic organometallic chemistry, as well. He was just ahead of his time, doing this stuff in the 60s-80s.
    - Larry Overman, ??Tommy Oganachi??, etc. total synthesis people resurrected cross-coupling in academia and industry.
  - Basic mechanism.
    - Oxidative addition.
      - ➢ Forms a 16 electron, square-planar palladium species.
      - ➢ Generally can't bind another ligand to go to an 18 electron species; that's high energy, so you dissociate a ligand.
    - Ligand exchange.
    - Migratory insertion.
    - β-hydride elimination.
      - ➢ Very common, but can be constrained (Fu chemistry).
    - Ligand exchange.
    - Reductive elimination.
      - ➢ Running the reaction in the presence of a base drives the reaction by precipitation of the acid.
  - Tri-*o*-tolylphosphine was the ligand of choice for a while, because it has ?? that makes it dissociate more easily during ligand exchange.
  - Small amounts of ?? can act as olefin isomerization catalysts and mess up reactions.
  - Regioselectivity: Aryl group typically goes to less-substituted carbon, and metal typically goes to the more-substituted carbon.

        - Rationalization: Steric factors and electronic factors.
        - More electropositive palladium wants to go to the δ^- carbon.
        - There is an added ionic component to Pd–C bonds with certain EWGs/EDGs. Steve had to keep this ionic character in mind during his early research on early transition metal catalysis.
        - Triflates can polarize palladium, and exaggerate this effect.

- Palladium-catalyzed carbon-nitrogen cross-coupling.
    - Much more challenging to generalize than C–C couplings.
        - With basic, nitrogen compounds, you have compounds that were previously used as ligands and compete for open coordination sites.
        - The balance is keeping palladium in solution ("you fear the precipitation of the dreaded palladium black") with ligands that don't let go.
    - Aryl halides and anilines are common.
    - Reagents.
        - $Pd(OAc)_2$ is relatively cheap, but it needs to be reduced before the chemistry starts.
        - $Pd_2(dba)_3$ is slightly more expensive, in the right oxidation state, but dba is hard to get rid of.
    - A history of ligands.
        - Instead of amines, use amido-stannanes. Tri-*o*-tolylphosphine ligands make this work (Migita, Kosugi). Amido-stannanes are terrible to work with, though.
        - Then the chemistry went to bidentate phosphines, then back to monodentate phosphines, then NHCs.
        - Most widely used ligands: Xantphos and racemic BINAP.
        - BippyPhos was developed to get around patents that MIT held; ironically developed by one of Steve's former postdocs.
    - Proposed catalytic cycle.
        - Particularly for C–N coupling, what's really going on is very messy. You want to keep stuff on-cycle, but there's all sorts of off-cycle equilibria.
        - Oxidative addition.
            - ➢ Used to be rate- and yield-determining, but no longer kinetically relevant.
            - ➢ Thus, it's better to not use aryl iodides now. Iodides are more expensive, their waste disposal is more expensive, and halogen loss is slower with sterically huge iodine.
        - There exists a sensitivity to aliphatic amines vs. anilines.
    - BINAP.
        - Racemic BINAP is very cheap. BINAP was developed as a ligand for asymmetric hydrogenation by Noyori.
        - Racemates typically have a ??higher?? melting point than individual enantiomers (because of **eutectic mixtures**; recall from PChem).
        - Triarylphosphine: Good electron donor, but not a fantastic one. Thus, very good for aryl bromides and triflates (which have relatively easy oxidative addition); not good for iodides due to the formation (presumably) of bridging compounds.
        - Many solvents good.
        - Strong bases and weak bases both good.

- Example synthesis: KRAS inhibitor.
    - Up to 300 kg scale with BINAP!

- Xantphos.

  - Invented by Pete Van Leeuwen when he was at Dutch Shell for hydroformylation (how all linear and branched alcohols are prepared, as well as butyraldehyde).
  - Billions of dollars were spent trying to change the ratio of linear to branched butyraldehyde, and this came out of that.
  - It's a good surrogate for BINAP in many reactions.
  - Only works with very activated heteroaryl chlorides.
    - Example: 2-chloropyridine is an honorary aryl bromide.
  - The slides list a good (albeit now a bit dated) review of the prior 10 years of cross-coupling.
- Tri-*t*-butylphosphine.
  - Used in many coupling reactions of heterocycles.
- Bulky mono-phosphines.
  - Air-stable.
  - Tons have been prepared and legally sold; "more tons have probably been prepared and... not legally sold."
  - Steve reviews the benefits of tetrakis vs. single-coordinate debate.
    - As the cone angle increases, the amount of L_1Pd increases.
  - It's only the interaction of the *ipso*-carbon (bound to upper ring) with the palladium that matters, not the whole bottom ring as is often incorrectly drawn.
  - At some point, the ligand gets too big and you reach an unstable situation.
- How do you form Pd^0?
  - It doesn't matter how active your catalyst is if you never form it!
    - Steve has often told his students to confirm that their catalyst is being formed if a reaction isn't working.
  - Out-of-the-bottle Pd^0 complexes come with extra-ligand baggage.
  - Kinetic studies by ?? have really shown that extra dba slows reations.
- Solution: Mechanism-based activation.
  - Put the middle of your catalytic cycle into your pre-catalyst! Then you get deprotonation, reductive elimination, etc.
  - Biscoe developed the first one, and it worked. Could make it on a 100 g scale. But if you put it in solution, it would decompose.
  - Yong could do multi-kilo synthesis, very simple preparation.
  - Carbazoles aren't cool in Europe (environmental concerns).
- Coupling of anilines and aryl chlorides.
  - Papers often get into JACS or *Science* with really active catalysts (0.01-0.05 mol%), but in Steve's opinion, there's no point to these catalysts if nobody wants any of the compounds they can be used to produce (i.e., if substrate scope is too small).
  - The vast majority of synthetic methods aren't useful in any real circumstances. What matters is if you can do the chemistry on complicated substrates.
  - The vast majority of people practicing the chemistry are in discovery chemistry, so you should target your work to them.
- Example synthesis: Gleevec.

  - This is great, even though you've got a free NH and tons of different nitrogens.
  - Common issue: Substrates and products can have poor solubility.

- Example synthesis: Amgen compound.
  - Optimized catalytic conditions.
  - Functionalized silica gel with thiourea stuff helps get rid of the palladium.

- Wacker oxidation.
  - Commerically makes acetaldehyde from ethylene.
  - Amazingly efficient: Low price difference between acetaldehyde and ethylene so it *has* to be super efficient.
  - Palladium, copper, air, and catalytic acid.
  - The palladium in this reaction *loves* terminal olefins.
  - You form a cationic Pd^{II} complex that binds the olefin. Water adds, enolization to the ketone.

- Lou Hegedus's chemistry.
  - Like Heck, he was too far ahead of his time for his own good. Avid fisherman. If he had invented it 20 years later, he would have been a superstar, but at the time, nobody thought it could be used.
  - This is ring-closing Wacker oxidation!!
  - Can be used for indole synthesis.
  - π-allyl (Tsuji-Trost) chemistry for the bottom left step.
  - Uses palladium for every step in this synthetic scheme! Like a competition to see how much palladium you can do.

- **Cacchi** (indole synthesis).
  - *ortho*-alkynyl aniline, with a protected N.
  - Net transformation: *trans*-addition of a nitrogen and an aryl group across an alkyne.
  - General principle: If you can do it once, it's good; if you can do it twice, it's better.
    - Thus, it's great that you can do it at two sites in the bottom example!

- **Larock** (indole synthesis).
  - Larock (now retired from ISU, interesting chemistry in the 70s).
  - Quite wide scope; can now be done with bromides and chlorides.
  - You essentialy annulate on the rest of the indole.

- **Mori-Ban** (indole synthesis).
  - Heck-type palladium coupling.
  - Used by Jim Cook to make substituted tryptophan derivatives.
  - **Schöllkopf's reagent** is an anionic amino acid equivalent.

- **Merck** (indole synthesis).
  - Highlights the limitations of the Larock indole synthesis.
  - DABCO is the ligand; a very common base used in pharmaceutical chemistry.
  - Condense to the enamine, oxidative addition, attack at Pd^{II}, then reductive elimination and aromatization.

- More on the Fischer indole synthesis.
  - Limitation: Requires aryl hydrazines.
    - Potent skin sensitizers, and have a multistep synthesis.
  - So...
    - Almost any palladium catalyst will form the desired aryl hydrazine *in situ*, and then we can do the Fischer indole synthesis.
    - This is the **Buchwald modification** (of the Fischer indole synthesis).
- Example: Non-nucleotide reverse transcriptase inhibitor.
  - Can do a second functionalization with the Fischer indole variant.
- Cu-catalyzed C–N bond formation.
  - History.
    - Started much earlier than palladium chemistry.
    - This is Ullmann and Goldberg chemistry.
    - Problem: They didn't have much mechanistic understanding, so they thought ligands were bad for the reaction.
    - Stoichiometric strong base and very polar solvents meant that high temperatures were required.
    - So the chemistry worked in some cases and not in others.
    - But in the 1990s, this chemistry was brought back to the fore and ligands were developed.
  - Aside/maxim: The most expensive thing you have in discovery chemistry is time, so you just want stuff to work as rapidly as possible.
  - Many ligands good.
    - Very different selectivities.
  - Amides is the **Irma Goldberg coupling**.
  - Ullmann discovered the original chemistry; Ullmann and Goldberg were married!
  - You want the ligands to be good enough that multiple nitrogen species won't bind.
  - Many different proposed mechanisms.
    - Oxidative addition/reductive elimination has the most support so far.
    - Caveat: Sensitivity of the reaction to the electronic nature of the aryl halide (think ρ and Hammett plots). For palladium-catalyzed oxidative addition, $\rho \approx 3.5$, so it's quite sensitive to the electronic environment. But in copper chemistry, $\rho \approx 0.3 - 0.5$.
    - Additionally, copper is much more sterically hindered at the substrates.
  - Ma's oxalamide ligands; Steve agrees with his interpretation.
  - Copper doesn't tend to work for aryl triflates. It probably is some kind of coupled electron transfer.
  - Primary amides and small-ring β-lactams are good to use.
  - People say that sulfur and nitrogen poison palladium, but there are exceptions.
  - Goldberg reaction.
    - Irma Goldberg broke the glass ceiling because her reactions were just that important.
- Applications with diamine ligands.
  - Doing the chemistry in the presence of added iodide does the copper chemistry more efficiently.