

Unit 3

???

3.1 Lecture 12: Intro to Catalysis

- 4/26:
- We're now moving from theoretical chemistry to some applications (namely catalysis) of the theory we've been learning.
 - History of defining catalysts:
 - Berzelius (in 1836) becomes interested in this behavior.
 - Ostwald (in 1894) defines a **catalyst**.
 - **Catalyst**: A substance that increases the rate of a chemical reaction without being consumed.
 - Energetically, this must happen by altering the transition state (this is a simplistic explanation).
 - The thermodynamics (ΔG , ΔS , and ΔH) are unaffected.
 - The kinetics (ΔG^\ddagger , ΔS^\ddagger , and ΔH^\ddagger) are reduced.
 - More realistically, a catalyst often substantially changes the reaction coordinate (one big hump in the energy diagram to many small humps).
 - The general set of intermediates during the reaction is the starting material plus the catalyst ($S + C$), the starting material-catalyst complex ($S \cdot C$), the product-catalyst complex ($P \cdot C$), and the product plus the catalyst ($P + C$).
 - Note that ΔG^\ddagger is the activation energy for the highest barrier step, as measured against the free energy of the reactants. This notably implies that ΔG^\ddagger is not necessarily the E_A of the *first* step; only the biggest. See Figure 3.2b.
 - Even though there are more steps, the rate increases because ΔG^\ddagger decreases.
 - If you get stuck at a low energy intermediate, this can reduce reaction rate, and the process is no longer being catalyzed.
 - Indeed, if your catalyst is a different structure at the end of the reaction, it's not a catalyst but a reagent.
 - Excessively stabilizing the starting materials can create a higher energy barrier to the products.
 - Example:

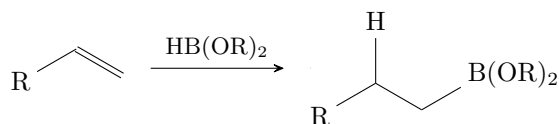


Figure 3.1: A process to be catalyzed.

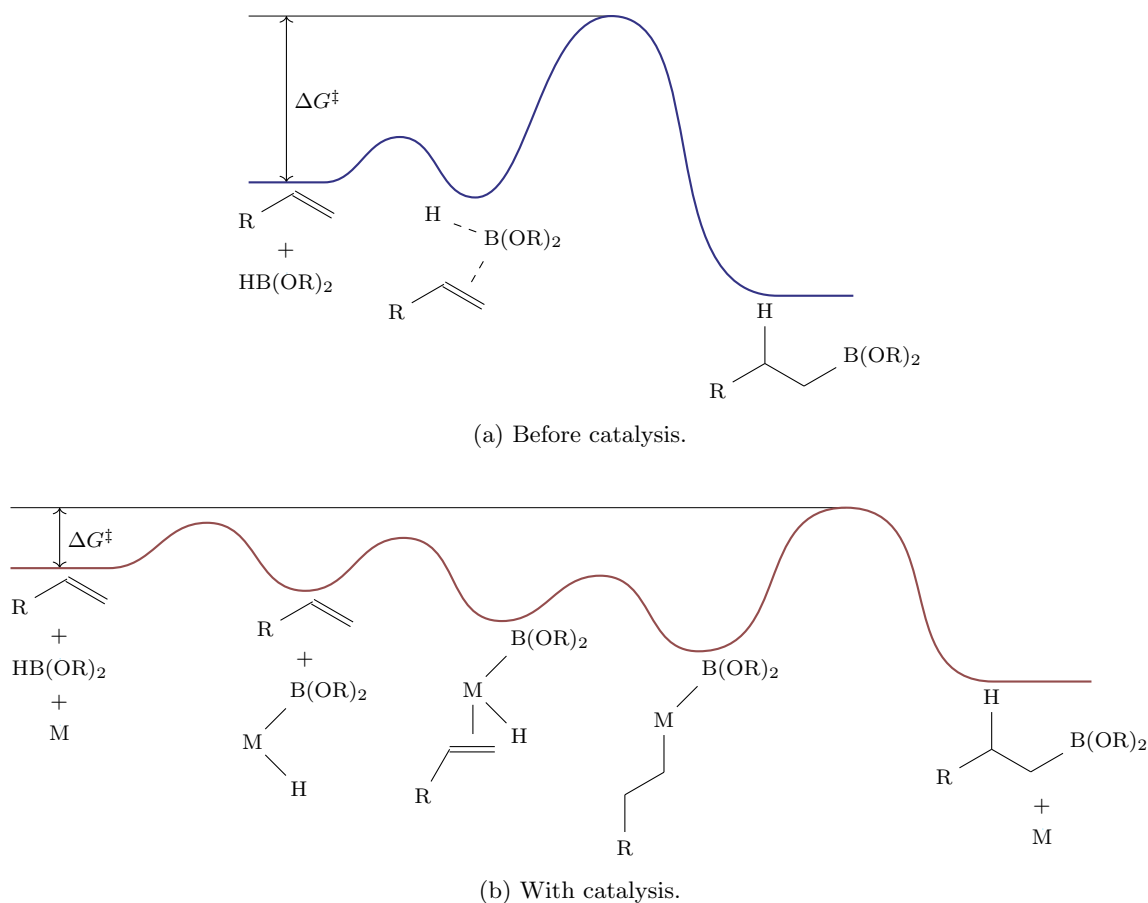


Figure 3.2: Catalysis energy diagrams.

- With transition metal catalysts, we have many more steps but potentially a lower ΔG^\ddagger .
- Anatomy/terminology of a catalytic cycle.

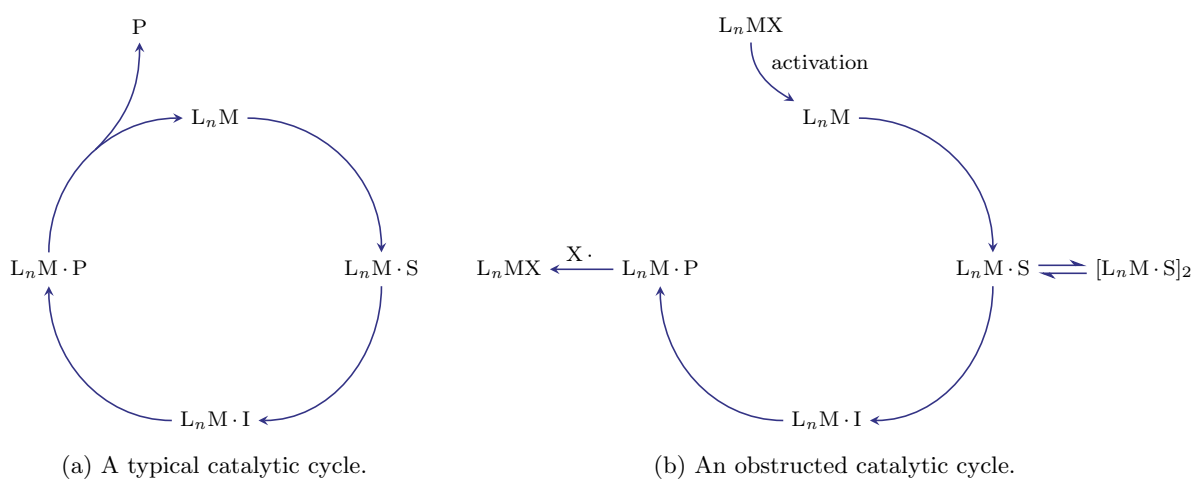


Figure 3.3: The anatomy of catalytic cycles.

- Simplistically, a catalytic cycle occurs as in Figure 3.3a.

- However, catalytic cycles can be complicated by **catalyst precursors**, **inactive off-cycles**, and **inactive poisoned states**.
- **Catalyst precursor:** A complex that must go through an activation step before it can be used as a catalyst.
 - See the reactant that becomes L_nM in Figure 3.3b.
- **Inactive off-cycle:** A reversible reaction that an intermediate participates in that is different from the intended reaction.
 - See the alternate pathway that $L_nM \cdot S$ participates in in Figure 3.3b.
- **Inactive poisoned state:** When an intermediate follows an alternate nonreversible reaction pathway.
 - See the alternate pathway that $L_nM \cdot P$ participates in in Figure 3.3b.
- Gives two examples of activating a catalyst (just a chemical reaction where one product is the catalyst).
 - A Pd^{2+} precursor must often be activated into a Pd^0 catalyst.
- **Turnover number:** The quotient of the moles of product and the moles of catalyst. *Also known as TON.*
- **Turnover frequency:** The quotient of the TON and time. *Also known as TOF.*
- Kinetics:
 - The rate constant for individual steps can vary, but at a steady state (where the catalyst is transforming the substrate as fast as possible), the rates must be identical.
- **Catalyst resting state:** The highest concentration form of the catalyst.
 - Can also be off-cycle or dormant.
 - The rate constant after it (i.e., the rate constant of the **turnover limiting step**) is the smallest among all rate constants for steps.
- **Turnover limiting step:** The step which proceeds from the catalyst resting state. *Also known as rate-determining step.*
- Heterogeneous vs. homogeneous catalysis:

Heterogeneous	Homogeneous
Solid state (2 phases).	Solution phase.
Robust (high pressures and temperatures are ok).	Selective.
Low-cost.	Tunable.
Easy separation.	Easy to study (comparatively).

- We distinguish between the two with **transmission-electron microscopy**, kinetics, a **filtration test**, a **mercury drop test**, and/or a **three-phase test**.
- **Transmission-electron microscopy:** Looks for nanoparticles. *Also known as TEM.*
- Kinetics: We need to observe soluble intermediates and show that they are **kinetically competent**.
- **Kinetically competent:** The step from the soluble intermediates to the products under another reagent must be at least as fast as the overall rate of catalysis.

- **Filtration test:** For heterogeneous catalysts. Do the reaction over the heterogeneous catalyst, filter out the solid heterogeneous catalyst, add in more substrate and see if the mother liquor or supernatant still catalyzes the reaction. If so, then something is leaching out of the catalyst.
- **Mercury drop test:** Mercury can typically block the pores of high-surface area catalysts or poison the cycle by forming TM alloys. *Also known as Hg-drop test.*
- **Three-phase test:** Attach a substrate to an insoluble support. If the catalyst is solid state, we see no reaction (poor phase mixing).
 - The gold standard.
- Asymmetric catalysis:
 - Propene is pro-chiral (it has a Re and a Si face) at the central carbon.
- **Dynamic kinetic resolution:** When a racemic mixture goes to an enantioenriched product.
 - Occurs when an achiral intermediate is accessed and selectively filtered into an enantioenriched product.
- **Kinetic resolution.** When a racemic mixture goes to an enantioenriched starting material and enantioenriched product.
 - Arises from selective reaction with one enantiomer over another.
- **Enantiomeric excess:** The quantity given by the following formula. *Also known as ee.*

$$\frac{[\text{major en.}] - [\text{minor en.}]}{[\text{major en.}] + [\text{minor en.}]} \times 100\%$$

- Enantiomeric ratio:

$$\frac{[\text{major en.}]}{[\text{minor en.}]} = e^{-\Delta\Delta G^\ddagger/RT}$$

- Note that $\Delta\Delta G^\ddagger$ is the difference in the ΔG^\ddagger values for the major and minor enantiomers.

- Ee is dependent on $\Delta\Delta G^\ddagger$ and T :

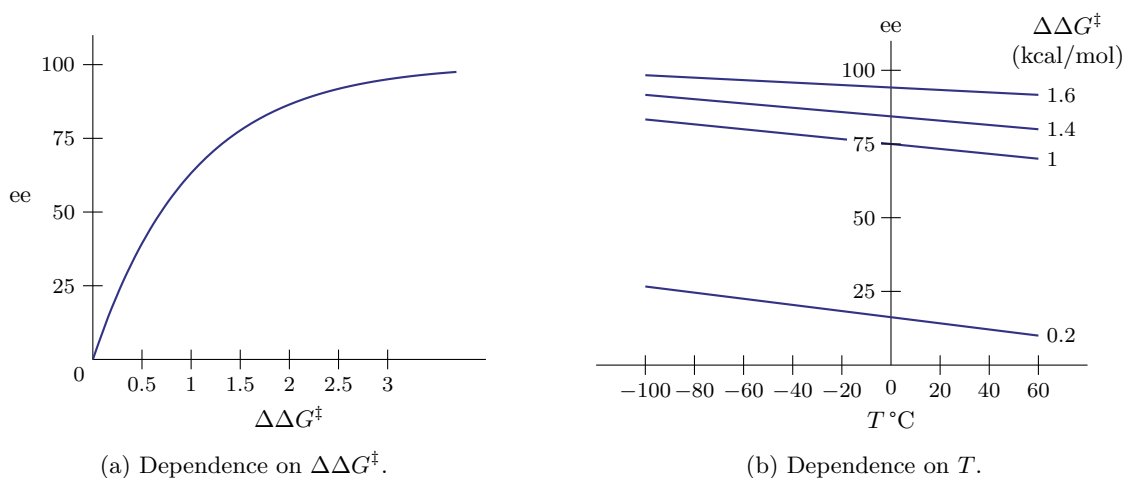


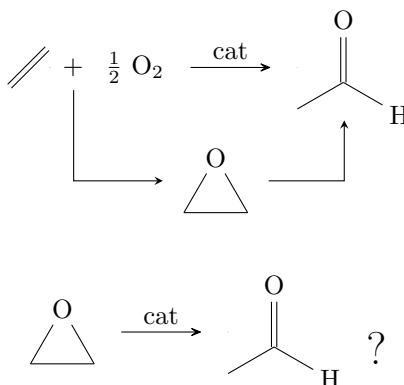
Figure 3.4: Dependence of ee on $\Delta\Delta G^\ddagger$ and T .

- Some enantiomers have differing catalytic properties.

- Furthermore, chirality is not necessarily set at the RDS.
- If A and B are two enantiomers, then it is possible that ΔG^\ddagger will differ for the formation of $M \cdot A + B$ vs. $M \cdot B + A$ (remember that this difference is $\Delta\Delta G^\ddagger$).
- If the activation energy required to form $M \cdot A + B$ (for example) is greater than that required to get from $M \cdot A + B$ to the products, formation of the $M \cdot A + B$ intermediate will be irreversible.
 - In this case, the kinetic product will be favored.
- If the activation energy required to form $M \cdot A + B$ (for example) is less than that required to get from $M \cdot A + B$ to the products, formation of the $M \cdot A + B$ intermediate will be reversible.
 - In this case, the thermodynamic product will be favored (we may see more of the intermediate that forms quickly, but in time, more of the other product will be formed because formation of the other product is irreversible^[1]).

3.2 Office Hours (Anderson)

- What does kinetically competent mean?



- Consider the reaction of ethylene and $\frac{1}{2} O_2$ with a catalyst to make acetaldehyde.
 - We propose that the intermediate is an epoxide.
 - To test this hypothesis, we take ethylene oxide and react it with the catalyst to see if it makes acetaldehyde.
 - If it does, that's a good first step. If it reacts with a rate at least as fast or faster than the overall catalyzed reaction, then we know that this intermediate *is* an intermediate in a catalytic cycle.
 - Essentially, this test confirms that an intermediate is one. If the rate of epoxide to product is at least as fast as the overall rate, then we're good.
- What do all of those tests test for? I.e., if we find nanoparticles with TEM, what does this mean?
 - We need all of these tests because none of them are definitive.
 - You can never prove a mechanism; you can only disprove it.
 - If you see nanoparticles with TEM, it might make you ask if a heterogeneous pathway is present.
 - You go through these experiments to try to determine that it's *not* homogeneous or *not* heterogeneous.
 - Resources for synthesis?
 - Inorganic is not like organic where we're pushing electrons and stuff.

¹Think the Mrs. Meer pens example.

- Don't worry about step efficiency.
- Don't worry about reactive fragments.
- For syntheses, completely ignore mechanism. Just balance the reaction.
 - Balance in terms of electrons and atoms.
 - Just focus on stoichiometry to start.
 - 99% of the time, this will get you to the right conclusion.
- If you have methyl iodide and you want to methylate the metal center, you want to make the metal nucleophilic and then react it.
- If you want to be really lazy, just show the reagents that will give you the products and be done.
 - You'll probs lose a few points for this, but that's ok.
 - Try and show the intermediates.
- Time crunch?
 - Skip a question.
 - Go through the easiest questions first.
 - You can probably get 80% of the points on the first question without writing a single synthesis.
 - Do the easy things fast and then move on.
 - View it as a scavenger hunt for points.

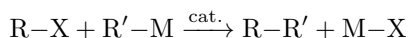
3.3 Discussion Section

- 4/27:
- There may be a midterm key.
 - HW3 will be due Monday 5/3/2021 at 5:00 PM; HW4 will be due Monday 5/10/2021 at 12:00 PM (the usual time, no changes).
 - Cross coupling mechanism (from lecture 13?):
 - Starts with a ligand substitution (or association/dissociation) to get to something lower coordinate.
 - Then there will be an oxidative addition.
 - ...
 - Alkyls (such as ethyl groups) are more electron-rich than aryls (such as phenyl groups).
 - Think Homework 2, Problem 12.
 - Goes over stuff that will be useful later in the week for HW3.

3.4 Lecture 13: Cross Coupling

- 4/28:
- Probably the single most-employed catalytic reaction in synthetic chemistry.
 - More important in pharmaceuticals and fine chemical synthesis, not industrial processes.
 - Nobel prize (2010) to Heck, Negishi, and Suzuki for aryl-type couplings.
 - Dominated by Pd^0 / Pd^{II} ("God's Metal" - John Bercaw).
 - There are also examples with Ni, Rh, Ir, and Cu.
 - These metals are so good because the reactivity is often based in oxidative addition and reductive elimination, but radical reactions are also useful (particularly with nickel).

- General form:



- Basically a nucleophilic attack.
 - But since substrates like ArI don't have very good reactivity for nucleophilic aromatic substitutions (despite the fact that iodide is a great leaving group), we need this mechanism.
- R, R' are typically carbon-based, but carbon-heteroatom (where the heteroatom is N, O, S, or something else) couplings are also advancing.
- History:
 - Kumada and Corriu report $\text{ArBr} + \text{RMgX} \xrightarrow[\text{substance}]{\text{Et}_2\text{O}, 25^\circ\text{C}} \text{Ph}-\text{C}=\text{C}-\text{R} + \text{R}'-\text{C}=\text{C}-\text{R}^{[2]}$.
 - The *substance* is Ni(acac)₂, dppe, NiCl₂, FeCl₃, CoCl₂, or CrCl₂.
 - Note that the aryl group can be phenyl, but it can also be vinylic or allylic (basically any *sp*²-hybridized carbon).
- There are many named reactions (usually defined by the nucleophile).
 - This is a con of this field.
 - Negishi: RZnX.
 - Stille: RSnR₃'.
 - Hiyama: RSiMe₂F.
 - Suzuki: RB(OH)₂ or RBF₃[−].
 - Mizoroki/Heck: $\text{Ph}-\text{Br} + \text{C}=\text{C}-\text{R} \xrightarrow[\text{base}]{\text{cat.}} \text{Ph}-\text{C}=\text{C}-\text{R}$.
- Alkynes can also be coupled.
- Enolates can also be used as nucleophiles.
- Most cross coupling reactions involve aryl nucleophiles, but we can also use aliphatic ones.
- Aliphatic couplings:
 - Alkyl electrophiles: $\text{CRR}'\text{X} + \text{Ar}-\text{M} \xrightarrow{\text{Ni or Pd}} \text{CRR}'\text{Ar}$.
 - These frequently go through a radical mechanism.
 - β-H can be a problem.
- Cyanide couplings:
 - $\text{Ph}-\text{X} + \text{M}(\text{CN})_n$ or $\text{CMe}_2(\text{CN})(\text{OH})$ can react with a palladium catalyst to form $\text{Ph}-\text{CN}$.
 - Note that M = K, Zn, K₄Fe(CN)₆.
- Enantioselective cross couplings:
 - The nucleophile racemizes quickly.
 - 93% ee with nickel.
 - 99% ee with palladium.
- Homo-couplings:
 - An alkyl/aryl halide plus that same substance but as a Grignard forming a “dimer” at the place where the Grignard is attached.
 - Use nickel as a catalyst here.

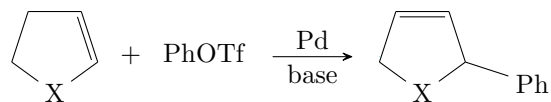


Figure 3.5: Heteroarene coupling partners.

- Heteroarene coupling partners:

- Note that TfO is triflate, an abbreviation of trifluoromethanesulfonate, which is an excellent leaving group.
- Also with enolates.

- Mechanism:

- Basic (see Figure 3.6a):

- We must first activate our palladium catalyst by causing it to lose a ligand, thus becoming lower-coordinate.
- Our aryl hydride will now oxidatively add to the activated catalyst.
- Next, we have transmetalation (the most complicated step of the cycle). There are two possible paths by which we can introduce our nucleophile into the system and remove an X (to make space for it). First, we can use a hydride of the nucleophile which will do what we want and then form an acid with X^- ; this acid can then be neutralized by the base. Alternatively, we can bond a metal to the nucleophile and simply have the metal swap Nu^- for X^- with the palladium center, forming a metal salt as a byproduct.
- The last step is reductive elimination, which yields our product and regenerates our starting material.

- Homocoupling (see Figure 3.6b):

- Once again, we first oxidatively add our aryl hydride.
- Then we transmetallate. Note that to regenerate our transmetallating nucleophile, we must treat it with some reductant (typically zinc metal); it can then oxidatively add $Ar-X$.
- Finally, we reductively eliminate again.

- Mizoroki-Heck (see Figure 3.6c):

- As in the basic cycle, we must activate our palladium catalyst.
- Next, we oxidatively add $Ar-X$ once again.
- This time, however, we use an olefin as our electrophile. Note that $R = H, CN$, a ketone, etc. Additionally, note that we show in Figure 3.6c that we dissociate a ligand L at this point, but we could also dissociate an X^- and carry that through. Overall, this step is a ligand substitution.
- A 1,2-migration follows. However, different types of migratory insertion can also occur as dictated by sterics.
- After this, we do a β -H elimination to kick out our product (note that the product doesn't have to be *trans* but it typically is) and bring us closer to regenerating the catalyst.
- Lastly, we can regenerate our initial catalyst with the reductive elimination of an acid (which will then be neutralized by an added base) as triggered by the addition of a ligand. Alternatively, the base can deprotonate the $L_{n-2}XH$ intermediate before pulling off the X^- group.
- Note that this reaction must be carried out in basic media.

- Oxidative addition:

- Occurs from a coordinatively and electronically unsaturated metal center

²Note that Anderson often uses \emptyset instead of Ph to denote a phenyl group.

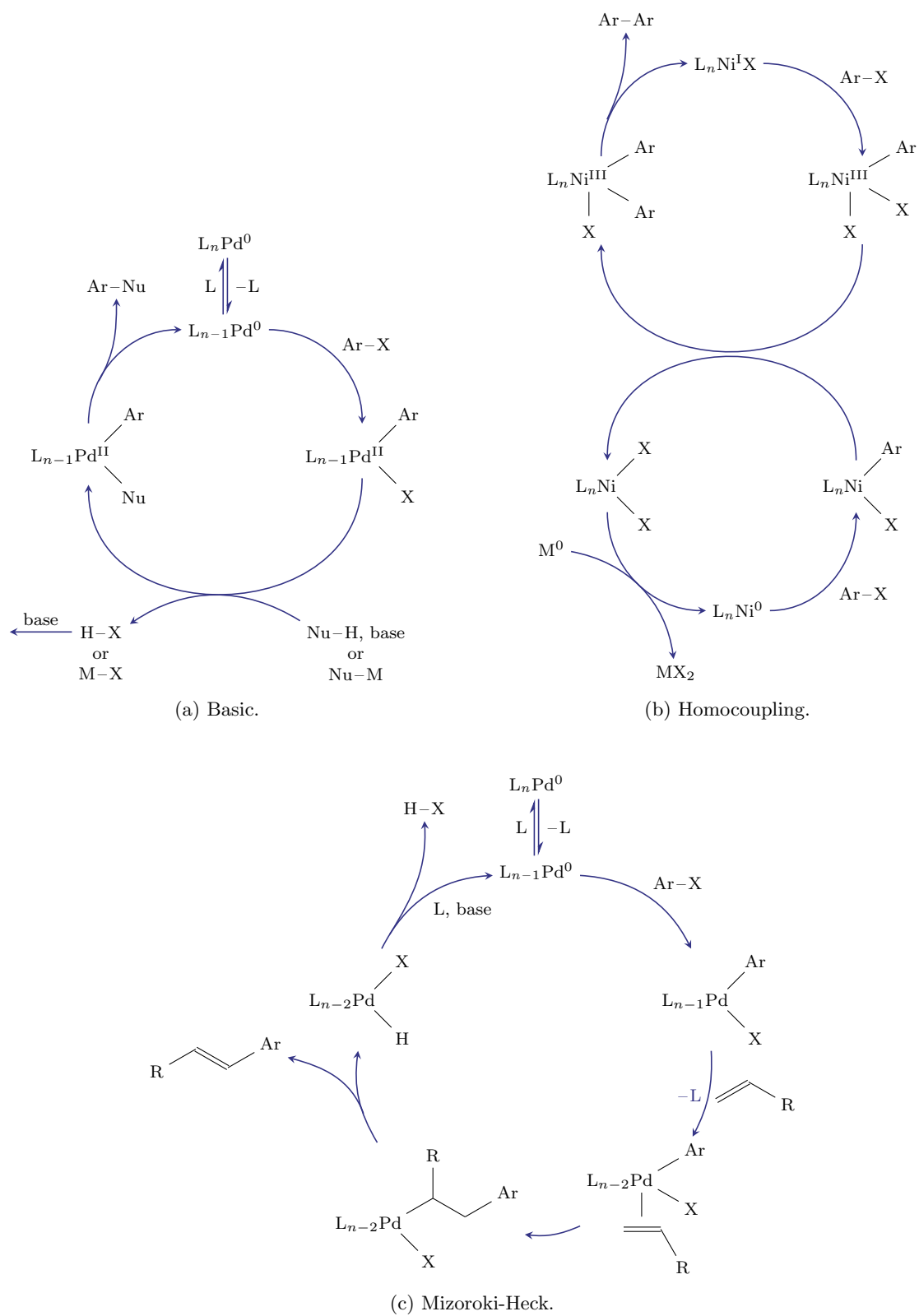
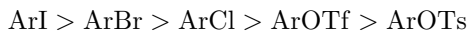


Figure 3.6: Cross coupling mechanisms.

- Thus, we usually use either a monoligated or diligated neutral palladium center.
- Large, bulky monodentate ligands (e.g., phosphines) are good.
 - More steric hindrance enhances oxidative addition because we need easy dissociation later.
- Influence of the electrophile on the speed of oxidative addition:



- This shows that electron poor substrates are faster.
 - Note that this makes sense because in an oxidative addition, the substrate is reduced, and more electron poor substrates will want to be reduced more.
- Ni is generally faster than Pd.

- Transmetallation:

- By far the most complicated step in cross coupling mechanisms. The least is known about it and it exhibits great variability. Thus, the following is just a couple notes; there's not necessarily anything definite that you should take away.
- General form:

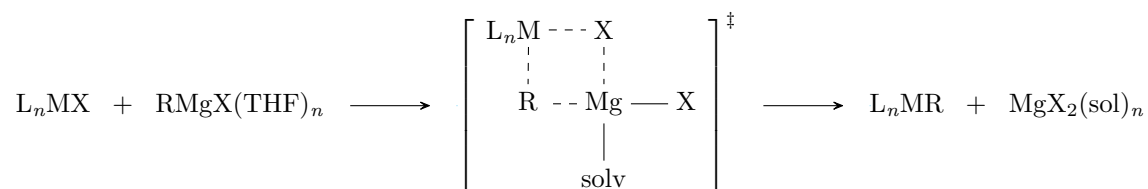


Figure 3.7: The general form of transmetallation.

- Some examples listed.
- On the subject of boronic acids, Negishi proposes the following: $\text{L}_2\text{PhPdBr} \xrightarrow{\text{KOH}} [\text{LPhPd}(\mu\text{-OH})]_2 \xrightarrow{\text{Ar(BOH)}_2} \text{Ar-Ph}$, 70%.
 - Negishi's conclusion: You typically need a base/nucleophile (such as hydroxide, water, or fluoride) to do the transfer of aryl boronic acids.
- Stille (Sn): Requires either a closed (such as in Figure 3.7) or open (as from a standard nucleophilic attack) transition state.

- Reductive elimination:

- Steric pressure favors reductive elimination, yet it typically occurs from a less stable 3-coordinate intermediate.
- Such an intermediate can be generated after ligand dissociation.
- The two groups that reductively eliminate must be *cis*.
- Aryl and vinyl groups are typically faster than alkyls.

- Ligands:

- A huge number.
 - These are typically phosphines, though.
- Tri(*tert*-butyl)phosphine is also known as tri(chicken foot)phosphine!
- Each ligand has very specific properties (better for one cross coupling than another).
- Very bulky phosphines tend to be good for these reactions, but chelating phosphines can be good, too.

- The reaction of a butyl Grignard in a cross coupling reaction gives us a couple of products (i.e., 1-Rbutane, 2-Rbutane).
 - Yields are poor with phosphines as L ligands.
 - Yields are much better with dppf.
- Dppf is ferrocene with a PPh_2 off of each Cp group. It's a chelating ligand (through the phosphines) with a very wide bite angle.
- Dppf is better because...
 - With phosphines, during the reductive elimination step of the basic cycle (Figure 3.6a), we have interference from β -H elimination (and sometimes ensuing migratory insertion of the eliminated hydride).
 - β -H elimination occurs with phosphine ligands because C.N. = 3, so there are open axial coordination sites to which the hydride can migrate.
 - However, with the bidentate dppf ligand, we essentially have a square-planar palladium species, which is very stable and will not easily form a 5-coordinate intermediate.
- Note that because dppf yields a 4-coordinate species, reductive elimination will be a bit slower, but we'll happily sacrifice speed for the much greater yield.
 - However, the large bite angle of dppf forces the aryl and R groups attached to the metal closer together, which promotes reductive elimination.
 - Thus, the decrease in speed is not that significant.
- Alternative schemes for cross coupling: Heteroatoms.
 - With nitrogen, we can do this with HNR_2 , H_2NR , NH_3 , imines, hydrosomes, etc.
 - Heterocycles, azoles, carbonates, sulfoximines, amides, etc.
 - Note that as N^- becomes less donating, reductive elimination slows down.
 - There's not really a transmetallation step here.
 - The issue is that these nucleophiles are not as basic as carbon-based ones.
 - We still need to worry about β -H elimination.
- Alternate mechanisms: Radicals.
 - Happens more with first-row transition metals (they're better at 1-electron redox chemistry).
 - Ullmann coupling (often with copper, but sometimes with nickel, too): $2 \text{Ph-X} \xrightarrow[\text{> } 200^\circ\text{C}]{\text{Cu}} \text{Ph}_2\text{Cu}$ salts, diamines, diols.
 - The temperature can be lowered with an appropriate ligand.
 - More flexibility in terms of the coupling partner.
 - We can do C-O, C-S, and C-N coupling in addition to C-C coupling.
 - Possible mechanisms (note that $\text{Y} = \text{Ar}, \text{R}$):
 - $\text{Ar-X} + \text{Cu}^{\text{I}}\text{Y} \longrightarrow \text{YCu}^{\text{III}}\text{XAr} \xrightarrow{\text{red. elim.}} \text{Ar-Y} + \text{CuX}$.
 - $\text{Ar-X} + \text{Cu}^{\text{I}}\text{Y} \longrightarrow \text{Cu}^{\text{II}}\text{Y}(\text{XAr}\cdot) \longrightarrow \text{Cu}^{\text{II}}\text{XY} + \text{Ar}\cdot \longrightarrow \text{Ar-Y} + \text{CuX}$ (most likely).
 - $\text{Ar-X} + \text{Cu}^{\text{I}}\text{Y} \longrightarrow \text{Cu}^{\text{II}}\text{Y}(\text{XAr}\cdot) \longrightarrow \text{Cu}^{\text{II}}\text{ArY}^- + \text{X}\cdot \longrightarrow \text{Ar-Y} + \text{CuX}$.
 - Ullmann couplings can be photoactivated (suggests a radical mechanism).
 - Cu^{III} is uncommon (suggests a radical mechanism).
 - Radical mechanisms can enable sp^3 - sp^3 couplings, even bulky ones (outer sphere radical attacks aren't as affected by steric bulk).