Unit 3

Intro to Catalysis

3.1 Lecture 12: Intro to Catalysis

- 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 ($\Delta G^{\ddagger}$, $\Delta S^{\ddagger}$, and $\Delta H^{\ddagger}$) 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 $\Delta G^{\ddagger}$ is the activation energy for the highest barrier step, as measured against the free energy of the reactants. This notably implies that $\Delta G^{\ddagger}$ 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 $\Delta G^{\ddagger}$ 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.
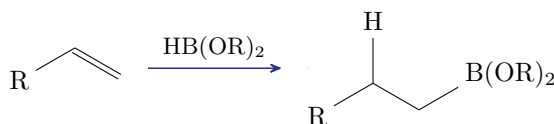
- Example:

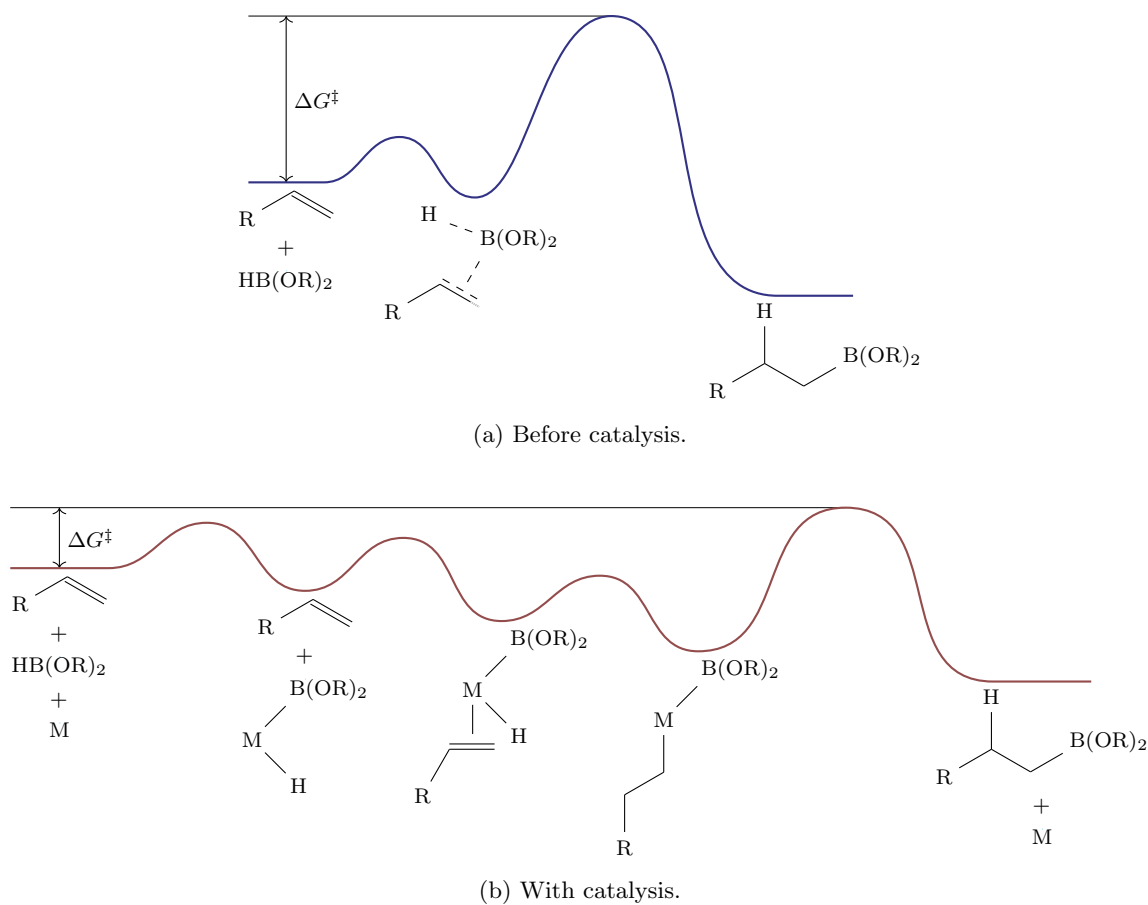Figure 3.1: A process to be catalyzed.

(a) Before catalysis.

(b) With catalysis.

Figure 3.2: Catalysis energy diagrams.

– With transition metal catalysts, we have many more steps but potentially a lower $\Delta G^{\ddagger}$.

• Anatomy/terminology of a catalytic cycle.

(a) A typical catalytic cycle.
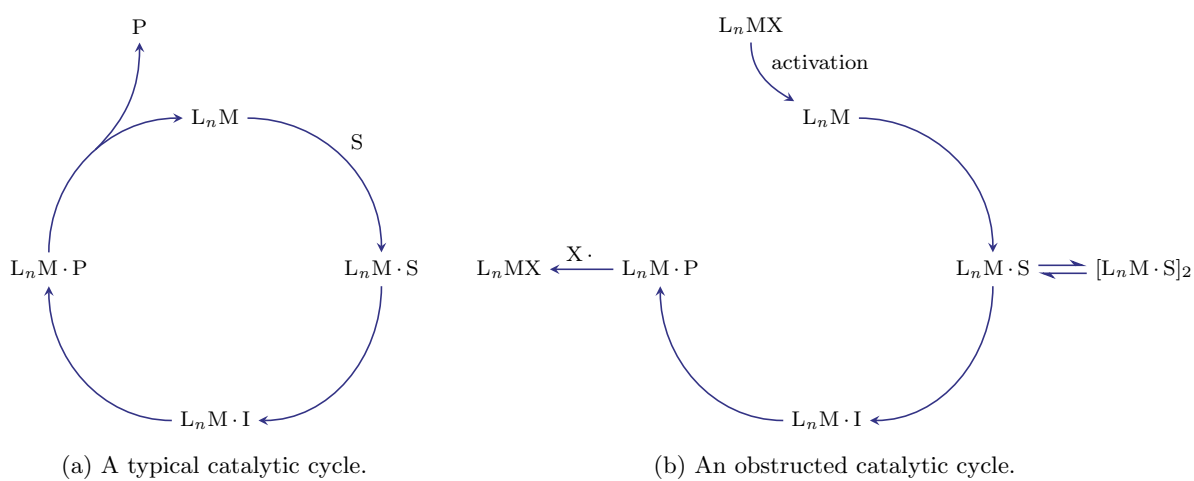

(b) An obstructed catalytic cycle.

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 $\Delta G^{\ddagger}$ values for the major and minor enantiomers.

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

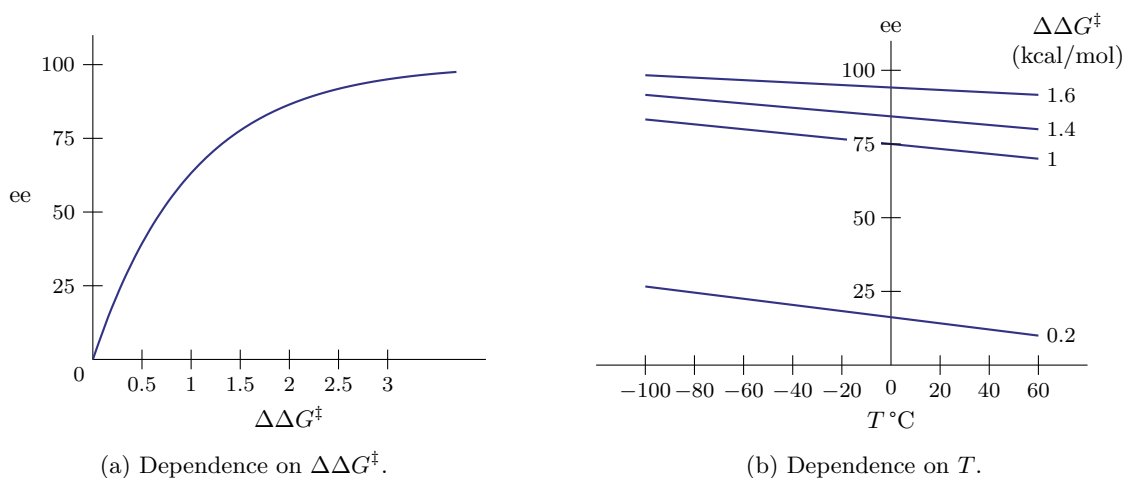(a) Dependence on $\Delta\Delta G^{\ddagger}$. (b) Dependence on T.

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 $\Delta G^{\ddagger}$ 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?
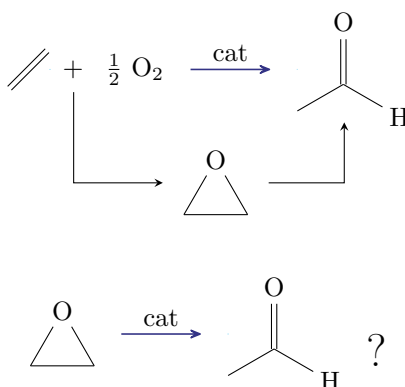
- Consider the reaction of ethylene and $\frac{1}{2}O_2$ with a catalyst to make acetaldehyde.
- We propose that the intermediate is an epoxide.
- To test this hypothesis, we take ethylene oxide and react it with the catalyst to see if it makes acetaldehyde.
- If it does, that's a good first step. If 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.

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[1]Think 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).

- Notes on cross coupling:

    - Mizoroki-Heck cross couplings are characterized by a migratory insertion into an olefin in place of transmetallation.
    - In transmetallation, we typically use Grignards, boronic acids (Negishi), tin reagents (Stille), or silylethers.
    - α- and β-elimination (commonly hydride) can give competing reactions with the β-hydrogens especially.

- Alkyls (such as ethyl groups) are more electron-rich than aryls (such as phenyl groups).

    - Think Homework 2, Problem 12.

- Goes over the arrow pushing from a ring-closing and ring-opening metathesis (very similar to Figure 3.19).

- Note the use of a Grignard in the basic cross coupling mechanism.

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:
$$R-X + R'-M \xrightarrow{\text{cat.}} R-R' + M-X$$

  - 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 $ArBr + RMgX \xrightarrow[\text{substance}]{Et_2O,\, 25\,°C} Ph-C{=}C-R + R'-C{=}C-R^{[2]}$.
    - The *substance* is $Ni(acac)_2$, dppe, $NiCl_2$, $FeCl_3$, $CoCl_2$, or $CrCl_2$.
    - 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: $RSnR_3'$.
  - Hiyama: $RSiMe_2F$.
  - Suzuki: $RB(OH)_2$ or $RBF_3{}^-$.
  - Mizoroki/Heck: $Ph-Br + C{=}C-R \xrightarrow[\text{base}]{\text{cat}} Ph-C{=}C-R$.

- 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: $CRR'X + Ar-M \xrightarrow{\text{Ni or Pd}} CRR'Ar$.
    - These frequently go through a radical mechanism.
    - β-H can be a problem.

- Cyanide couplings:

  - $Ph-X + M(CN)_n$ or $CMe_2(CN)(OH)$ can react with a palladium catalyst to form $Ph-CN$.
    - Note that $M = K, Zn, K_4Fe(CN)_6$.

- Enantioselective cross couplings:

  - The nucleophile racemizes quickly.
  - 93% ee with nickel.
  - 99% ee with palladium.

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

- 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.

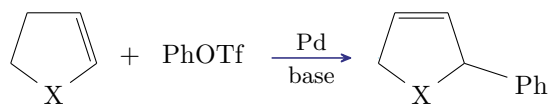- Heteroarene coupling partners[3]:

Figure 3.5: Heteroarene coupling partners.

  - 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 transmetallation (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 (re)generates our product and catalyst.
  - 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 agin.
  - 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^-.
    - Note that this reaction must be carried out in basic media.

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[3]Note that TfO is triflate, an abbreviation of trifluoromethanesulfonate, which is an excellent leaving group.

(a) Basic.
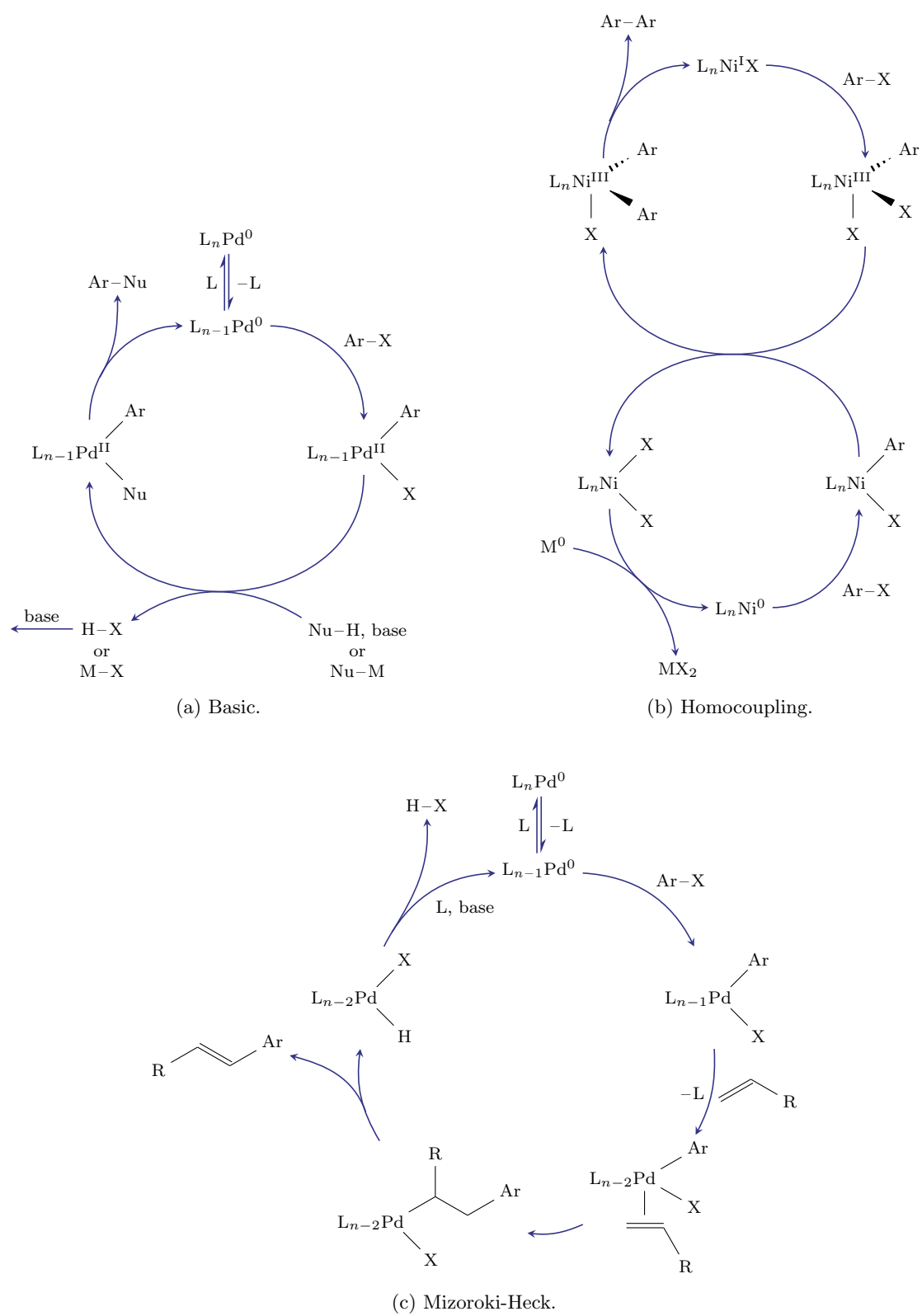

(b) Homocoupling.

(c) Mizoroki-Heck.

Figure 3.6: Cross coupling mechanisms.

- Oxidative addition:

  - Occurs from a coordinatively and electronically unsaturated metal center
  - 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:

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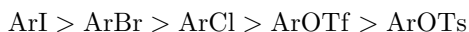
    - This shows that electron poor substrates are faster.
    - Note that this makes sense because in an oxidative addition, the substrate is reduced, and more electron poor substrates will want to be reduced more.
  - Ni is generally faster than Pd.

- 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.
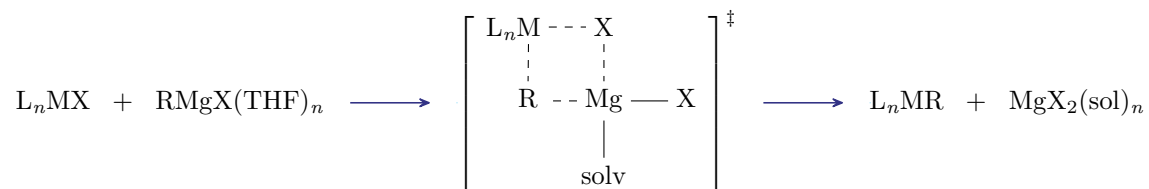 - General form:

$$\text{L}_n\text{MX} \; + \; \text{RMgX(THF)}_n \; \longrightarrow \; \left[\begin{array}{c} \text{L}_n\text{M} \text{ - - - } \text{X} \\ \vdots \quad\quad \vdots \\ \text{R} \text{ - - } \text{Mg} \text{ --- } \text{X} \\ | \\ \text{solv} \end{array} \right]^{\ddagger} \; \longrightarrow \; \text{L}_n\text{MR} \; + \; \text{MgX}_2(\text{sol})_n$$

Figure 3.7: The general form of transmetallation.

  - Some examples listed.
  - On the subject of boronic acids, Negishi proposes the following: $\text{L}_2\text{PdPhBr} \xrightarrow{\text{KOH}} [\text{LPhPd}(\mu\text{-OH})]_2 \xrightarrow{\text{Ar(BOH)}_2}$ 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-(R)butane, 2-(R)butane).
  - 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): $2\,Ph-X \xrightarrow[> 200\,°C]{Cu} Ph_2$, 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 $Y = Ar, R$):
    - $Ar-X + Cu^IY \longrightarrow YCu^{III}XAr \xrightarrow{red.\ elim.} Ar-Y + CuX$.
    - $Ar-X + Cu^IY \longrightarrow Cu^{II}Y(XAr\cdot) \longrightarrow Cu^{II}XY + Ar\cdot \longrightarrow Ar-Y + CuX$ (most likely).
    - $Ar-X + Cu^IY \longrightarrow Cu^{II}Y(XAr\cdot) \longrightarrow Cu^{II}ArY^- + X\cdot \longrightarrow Ar-Y + CuX$.
  - 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).

3.5   Lecture 14: Olefin Metathesis

4/30:
- Applies to both alkenes and alkynes.
    - Metal carbene, alkylidene, and alkylidyne complexes are also important for their catalytic applications to olefin metathesis.

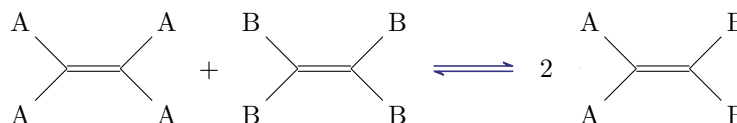- Nobel prize (2005) to Richard Schrock, Bob Grubbs, and Yves Chauvin.

- General form:

Figure 3.8: The general form of olefin metathesis.

- The olefins are not always tetrasubstituted, but we draw it as in Figure 3.8 to illustrate the point.
    - Alkyne metathesis is symmetric; just with disubstituted alkynes.
    - Equilibrium reaction (we need a thermodynamic driving force to favor specific products).
        - Can be limiting, but there are simple workarounds in the reaction types we are going to discuss.

- Not as widely used as cross coupling, but still important.

- Six basic classes of reactions:

    1. Distribution.
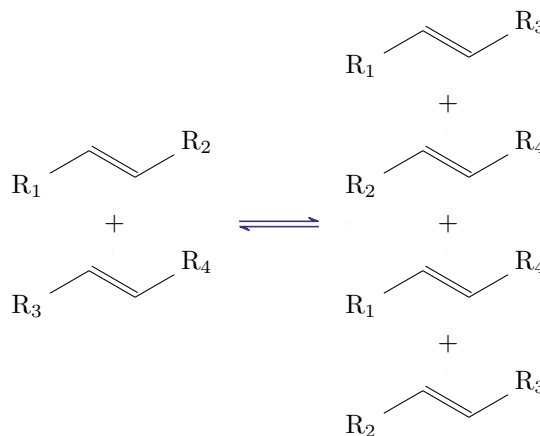
Figure 3.9: Olefin metathesis classes: Distribution.

- Two reactants form all possible permutations of the carbene fragments.
    - Not often useful, but...
    - Useful applications:
        - 2 propylenes make 2-butene and ethene, the latter of which is volatile and can be distilled off. Thus, distribution allows us to selectively make 2-butene from propylene, a widely available, mass-produced compound.
        - Shell higher olefin process (SHOP): Used to selectively make higher-mass olefins and distill off lighter ones.

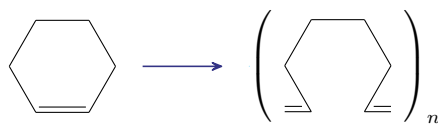2. Ring Opening Metathesis Polymerization (ROMP).

Figure 3.10: Olefin metathesis classes: ROMP.

– A ring with one double bond opens and polymerizes at the double bond.
– Note that this reaction can proceed with rings containing any number of carbons.
– Driving force: Release of ring strain.

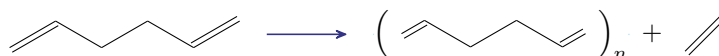3. Addition Metathesis Polymerization (ADMET).

Figure 3.11: Olefin metathesis classes: ADMET.

– A diolefin (under metathesis conditions) breaks off ethylene at both ends and polymerizes.
– Not as broadly useful as ROMP due to competitive ring-closing metathesis.
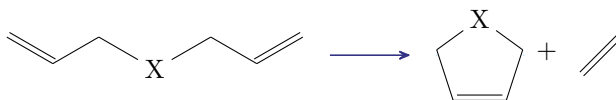
4. Ring-closing metathesis.

Figure 3.12: Olefin metathesis classes: Ring-closing metathesis.

– A diolefin (under metathesis conditions) makes a cyclic heterocycle and ethylene.
– Driving force: Release of a gas (ethene).
– Has utility in natural product synthesis (as a last step to close macrocyclic rings).

5. Cross metathesis.

Figure 3.13: Olefin metathesis classes: Cross metathesis.

– Two terminal olefins break of their end carbons (which combine to form ethene) and then combine, themselves, as carbene fragments to form an internal olefin.
– An equilibrium process; must compete with homometathesis (forming R–R and R'–R').
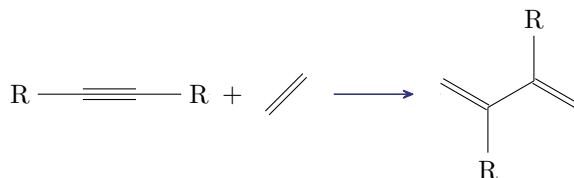– Driving force: Release of a gas (ethene).

6. Enyne metathesis.

Figure 3.14: Olefin metathesis classes: Enyne metathesis.

– An alkyne and ethylene makes a diene.
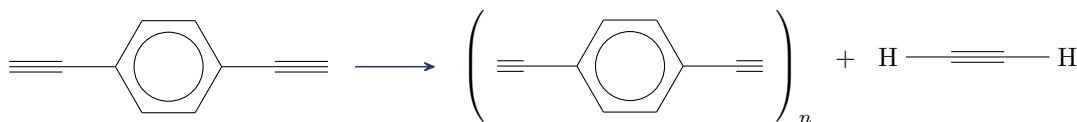
- Alkyne metathesis polymerization.

Figure 3.15: Alkyne metathesis polymerization.

  – A dialkyne makes a polymer and acetylene.
  – Very similar to ADMET.

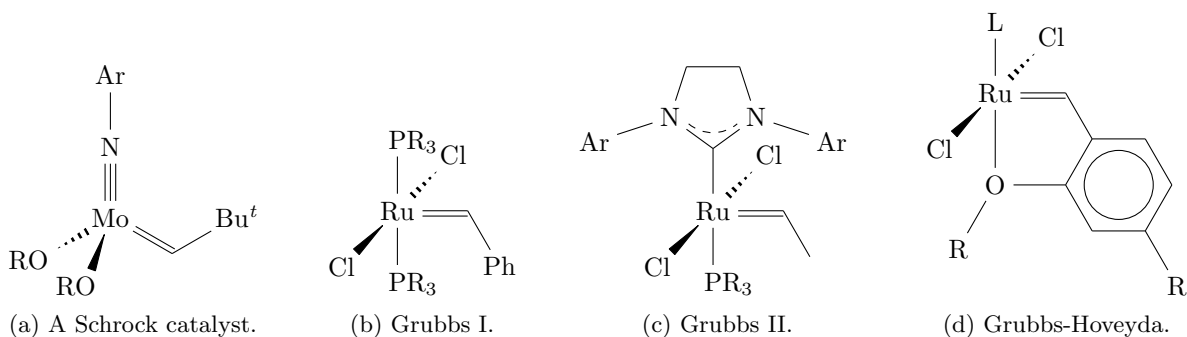- Ring-closing alkyne metathesis exists as well.

- Catalysts:

(a) A Schrock catalyst.   (b) Grubbs I.   (c) Grubbs II.   (d) Grubbs-Hoveyda.

Figure 3.16: Olefin metathesis catalysts.

1. Schrock catalysts (general form of Figure 3.16a).
   – Many of these exist.
     ■ The metal center, as well as the amido and alkoxide ligands can be varied.
     ■ Note that any X-type ligand can be substituted for the alkoxides.
   – Molybdenum or tungsten based (molybdenum is more active).
   – Since molybdenum is an early transition metal, the catalyst is very electropositive. Thus, it's an alkylidene with strong nucleophilic character at the carbon.
   – Extremely reactive. This is. . .
     ■ Good for hard reactions.
     ■ Bad because they're air sensitive and don't have a lot of functional group tolerance.

2. Grubbs catalysts (Figures 3.16b, 3.16c, and 3.16d).
   – Ruthenium based.
   – Less active, but more tolerant of air and water.
   – Note that the top ligand on Grubs II (Figure 3.16c) is called an NHC ligand, and that it is the same ligand that is typically present where "L" is written on Grubbs-Hoveyda (Figure 3.16d).
   – Note also that the big bidentate ligand on the the Grubbs-Hoveyda catalyst (Figure 3.16d) is a tethered alkylidene.
   – There has probably been a lot more utility in these since they're initially less reactive.

- General rule in inorganic chemistry: You can often make things more reactive (e.g., by heating them up), but rarely less (cooling things down can make the chemistry less reliable).

- Two mechanisms that were proposed early-on (related to Figure 3.18b):

  1. Metal-diolefin adduct to η^4-cyclobutadiene adducct, then refragmentation.
  2. Metal-diolefin adduct reductively couples into a 5-membered metallacycle, then to a metallacycle butane alkylidene, then rearrangement and separation.
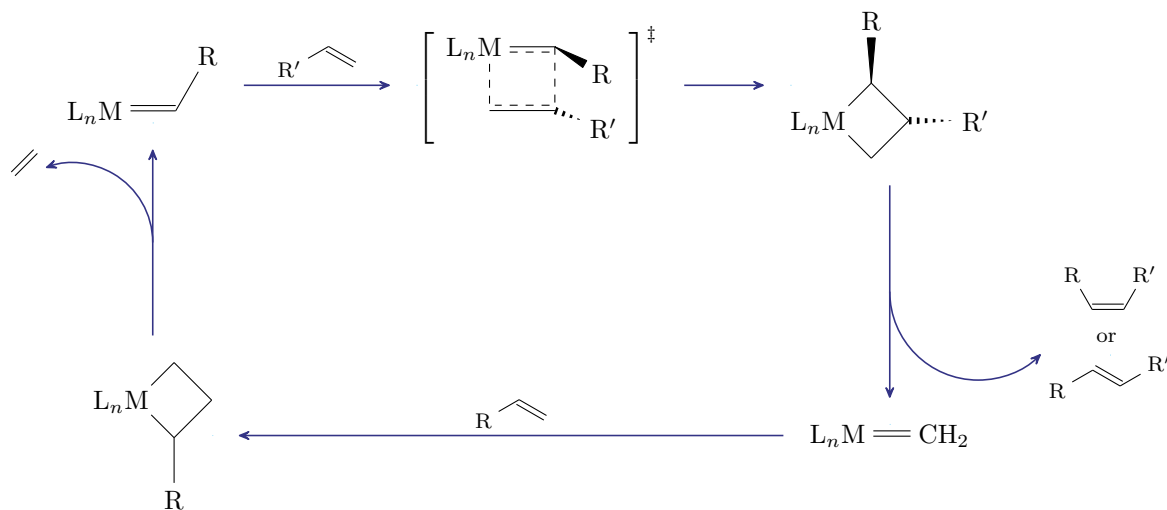
- Actual mechanism:

Figure 3.17: Olefin metathesis mechanism.

- Chauvin proposes this; Schrock and Grubbs prove it.
- Every step is an equilibrium reaction, but Figure 3.17 has monodirectional arrows for simplicity.
- On the transition state of the first step.
  - A $2 + 2$ cycloaddition.
  - Forbidden in organic chemistry, but allowed in inorganic because of the symmetry of the d orbitals.
- The first intermediate is a metallacyclobutane, which is a very important intermediate.
- The second intermediate is a terminal methylidene, which is highly reactive.
- Note that the mechanism drawn in Figure 3.17 is technically that of cross metathesis.
- There is frequently an activation step involving the loss of a ligand to free up a coordination site.
- There is also a degenerate pathway.
  - This starts with the formation of a *trans* metallacyclobutate in step 1. Thus, this pathway is actually favored sterically.
  - This metallacyclobutane can then collapse back down to an olefin and a metal alkylidene, possibly with R' on the metal alkylidene instead of R'.
  - This does indeed happen quite often, but it's clearly pretty harmless (also because this pathway is an equilibrium one, too).
  - If we have a means of siphoning off ethylene, we can favor the primary pathway.

- Mechanistic probes (things that indicated the actual mechanism over the other proposed ones):

  - Take a diphenyl compound with two styrenyl ligands (one with hydrogens; one with deuteriums).
  - The products are a cyclized olefin and distribution products.
  - A statistical mixture of CR_2 fragments is observed; this is only possible with the mechanism in Figure 3.17.

- Decomposition:

    - Where the catalysis can go wrong (and how to shut down these alternate pathways).

    - Primarily caused by the electrophilic methylidenes.

    - What happens is a nucleophylic attack by a phosphine on the electrophilic alkylidenes.

- Notes on stereochemistry.

    - Monoalkoxide pyridine (MAP) catalysts (recently reported by Schrock).

        - Chiral at Mo.

        - Can resolve enantiomers.

        - 100 times more active than bis-alkoxides (owing to the pyrilide ligand, which can coordinate face-on with a Cp and do some other odd things).

    - *trans* metallacyclobutanes (which lead to *trans* products) are preferred, but *cis* metallacyclobutanes can be favored with sterics.

        - For example, with respect to a Schrock catalyst (Figure 3.16a), making the alkoxides large and the nitrido small can force both R groups above the plane of the metallacyclobutane.

- Alkyne metathesis.

    - Again, largely developed by Schrock.

- RC≡Mo(OR)$_3$ is the active catalyst.

    - The method of generating this catalyst is shown.
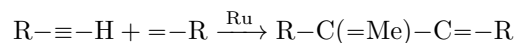
- Mechanisms:
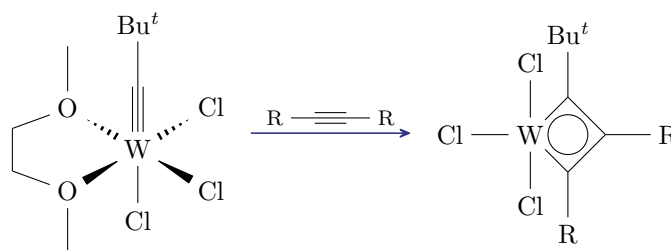
(a) The likely mechanism.
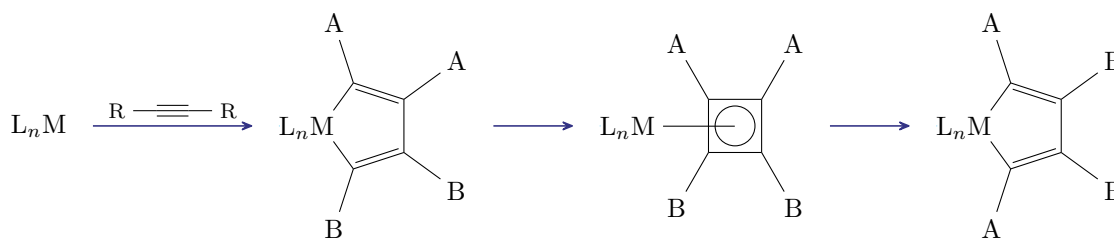
(b) A possible alternate mechanism.

Figure 3.18: Alkyne metathesis mechanisms.

- By Schrock.

- In Figure 3.18a, a tungsten alkylidyne reacts with an alkyne to generate an isolable metallacyclobutadiene in a pathway quite similar to Figure 3.17.

- However, the pathway in Figure 3.18b has also been observed, although not yet in a mechanistically, kinetically competent manner.

- Note that alkyne metathesis polymerization is a really interesting area being worked on by Adam Veige.

- Enyne metathesis.

- General form (related to Figure 3.14):

$$R-\equiv-H + =-R \xrightarrow{\text{Ru}} R-C(=Me)-C=-R$$

  – This chemistry is once again dominated by ruthenium.
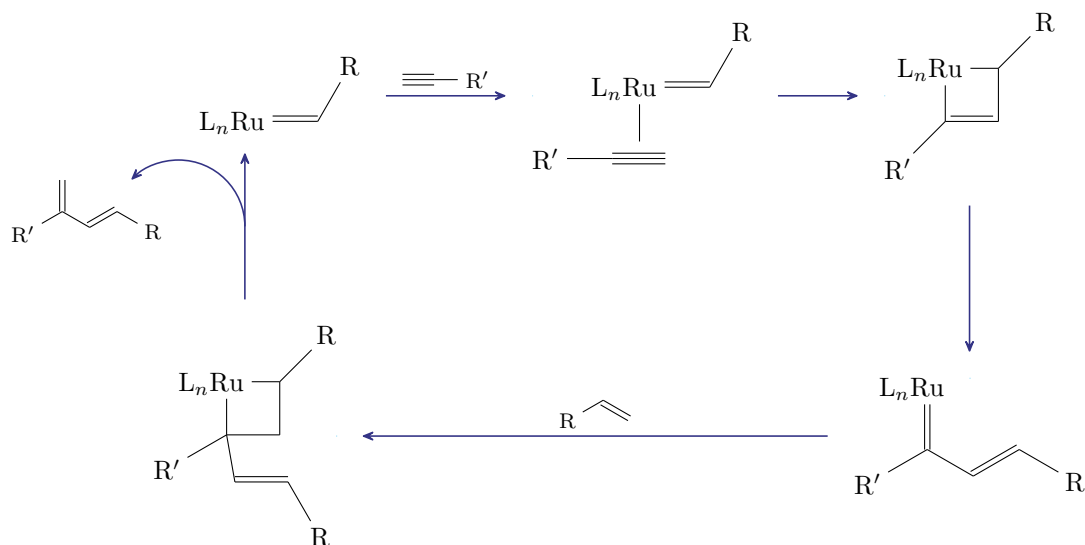
- Mechanism.

Figure 3.19: Enyne metathesis mechanism.

  – The second step is a $2 + 2$ cycloaddition, and yields a metallacyclobutene.

    ▪ For the reaction to proceed, we must have a 1,3-regioisomer, as shown.

  – The third step sees the double bond electrons push up and to the right, and the electrons from the top bond in the ring push down and to the left.

  – The final step occurs partially because of the instability of the tertiary carbon.

  – The product is often *trans* (as shown), but can be *cis*.