

5.44 Organometallic Chemistry

Notes from Spring 2020.

Last Updated: May 14, 2020.

Contents

1	Introduction	2
2	Transition Metals and Electron Counting	3
3	Bonding	5
4	Geometry	8
5	Ligand Substitution	10
6	Cross Coupling	15
7	Hydrogenation	20
8	Hydrofunctionalization	22
9	Hydroformylation	25
10	Oxygenases and Oxidases	27
11	Allylic Substitution	31
12	C-H Activation	33
13	Metathesis	36
14	Carbenoids	38

1 Introduction

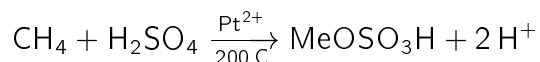
These notes were typeset from the online 5.44 lectures, taught by Alison Wendlandt. Special thanks to Andrew Lin for providing his LaTeX formatting template.

Question 1. *What is Organometallic Chemistry? Why study it?*

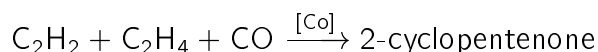
Organometallic Chemistry is very diverse - it is about transition metal complexes that actually perform chemical reactions, involving intermediates containing carbon-metal bonds. The diversity of the field is due to many factors, including the sheer number of metals there are, the range of oxidation states these metals have, and the diverse ligands that accompany the complexes themselves.

One of the primary uses of organometallics is in stabilizing reactive substrates - for example, benzyne and cyclobutadiene can be stabilized respectively by Zirconium and Cobalt (Buchwald, JACS, 1996, 118, 1028 and Maitlis, J. Organomet. Chem 1965, 4, 173).

Another reason is to promote otherwise unfeasible reactions - for example, the activation of methane in sulfuric acid (Periana, Science, 1998, 280, 560):



These unfeasible reactions can also generate complex molecular structures, for example, the Pauson-Khand reaction:



Finally, due to the wide variety of potential organometallic catalysts, they can also be used to tune reactivity, for example, with chiral ligands that favor formation of one enantiomer over another.

2 Transition Metals and Electron Counting

Definition 2

A **transition metal** is any element with an incomplete d-orbital shell, or which can give rise to cations with an incomplete d-orbital shell, typically those in groups 3-11. The early transition metals are those in earlier groups, and the late transition metals are those in later groups.

Some trends amongst these transition metals are as follows:

- As we move from early to late transition metals, more covalent bonds are created - the early transition metals are harder, more ionic, and more electrophilic. Thus, the early transition metals interact stronger with hard ligands - those with lower HOMOs, and these are mostly ionic interactions. On the other hand, the late transition metals interact stronger with soft ligands - those with higher HOMO energies, and these are mostly covalent interactions.
- Electronegativity trends follow the normal trend across a period - it increases from left to right. However, in transition metals, the electronegativity often increases from top to bottom, in contrast with the trend observed in the main group elements.
- As we go from top to bottom, the metals become less metallic, and thus form stronger bonds to carbon. This is because the metals become more electronegative, becoming closer to carbon's electronegativity, contributing to stabilization.

Not only does the identity of the metal matter, but its oxidation state does too. Even though the oxidation state is just a formality, it does help us count d-electrons.

Note 3

In general chemistry, we were taught that the electron configuration for, for example, Nickel, was $4s^2 3d^8$. However, this is for gas phase Nickel - in complexes, such as $\text{Ni}(\text{cod})_2 = \text{Ni}(\text{C}_8\text{H}_8)_2$, the electron configuration is $3d^{10}$. The group number thus directly correlates to the d electron count - the number of electrons that are not involved in principal bonding interactions.

By modifying the central d-electron count, we can change properties of the complexes themselves. d^0 is the maximum oxidation state, where the metal center itself has no electrons - thus it cannot do oxidative addition nor backbonding. d^{10} is the minimum oxidation state. An odd d-count leads to unpaired electrons, which leads to paramagnetism (though an even d-count does not necessarily lead to diamagnetism!)

To count the actual number of valence electrons in the metal center, we define **X type** and **L type** ligands. L type ligands are those that make a neutral ligand fragment upon disassociation, while X type ligands are those that create an anion upon disassociation. For example, CO is an L type ligand, and Cl is an X type ligand. L type ligands contribute 2 electrons to the metal center, while X type ligands contribute 1. These can also be combined - for example, Cp is a L₂X ligand. There are two main methods for counting them - either the ionic or the covalent method.

In general, a complex will have 18 electrons or less, with 18 electrons being the most stable (the **18-electron rule**.) This has its basis in the number of valence orbitals - 1 s orbital, 3 p orbitals, and 5 d orbitals combine to hold 18 electrons.

Remark 4. *Most complexes have a coordination number of 6 - an octahedral coordination. The highest transition metal coordination number observed has been 9 - in ReH₉²⁻ (though other complexes involving f-block elements have been found to have higher CN)*

The 18 electron rule, however, is just empirical, and it has been found that the p orbitals don't contribute much to the actual metal bonding. There are some important exceptions, such as the following:

- Notably, that d^8 complexes will very often be 16 electron square planar, due to the square planar d-orbital splittings.
- Bulky ligands will lead to fewer ligands being unfavorable (such as in Pt(PtBu₃)₂ being a 14 electron complex)
- Agostic interactions, where a metal orbital interacts with a C-H sigma bond in the ligand (such as in W(CO)₃[PCy₃]₂ being a 16 electron complex)
- π -donor interactions (such as in CrO₄²⁻ being a 16 electron complex)
- High-spin complexes, where spin-spin pairing interactions or negative spin-spin pairing interactions make it more favorable to have 17 electrons rather than 18 (such as Mn(H₂O)₆²⁺ having 17 electrons)
- Extra electrons residing in the ligand (resulting in more than 18 electrons)
- Different bonding modes (for example, Cp interacting with every carbon, 3 carbons, or one, corresponding to L₂X, LX, and X ligands). This property is called ligand fluxionality.

3 Bonding

To start off our discussion of bonding, let's go back to the basics of MO theory. Two atomic orbitals combine to form a more stable bonding orbital and a less stable antibonding orbital, and the net stabilization is proportional to the orbital overlap and the difference in the energy levels of the atomic orbitals. Based on this model, we can make two generalizations:

- 1) When electronegativities are similar between a metal and a ligand, then there is more covalent bonding. (recall from the previous lecture that going down a group increases electronegativity)
- 2) A larger electronegativity difference will lead to stronger ionic interactions.

The simplest molecular orbital diagram of a metal-ligand complex is far more complex than the simple diatomic bonding. For example, the PtH_6^{2-} octahedral complex's MO diagram is composed from metal valence orbitals - in order of energy (from lowest to highest), five d orbitals (splitting into a set of two e_g orbitals and three t_{2g} orbitals), one s orbital (labelled a_{1g}), then three p orbitals (labeled t_{1u}). The hydride ligands combine to form symmetry-adapted linear combinations (SALCs), composed of one a_{1g} orbital, three t_{1u} orbitals, and two e_g orbitals.

Since only orbitals of similar symmetry can interact, the s orbital interacts with the a_{1g} orbital, creating the lowest energy level (degeneracy = 1). The p orbitals likewise interact with the t_{1u} orbitals, creating the second lowest energy level (degeneracy = 3). The two d -orbitals with e_g symmetry interact with the SALC e_g orbitals, creating bonding and antibonding interactions, with the bonding interaction being the next energy level (degeneracy = 2). The t_{2g} orbitals remain nonbonding, being the fourth energy level and the HOMO (degeneracy = 3). The e_g antibonding orbital is then the LUMO.

Note 5

This orbital description actually provides an explanation of the 18 electron rule! The nonbonding and bonding energy levels provide enough degeneracies for exactly 18 electrons, and having more than 18 electrons means that the antibonding LUMO will have to be filled.

Now we'll see how metal-ligand interactions change the shape of the energy diagram. The simplest case is a σ -donor, where the interaction is just a covalent interaction, between an unfilled metal orbital and a ligand orbital, that lowers the overall energy of the metal.

Many ligands have both σ and π donation/accepting properties (or both)! CO is the archetypal π -acceptor ligand. The CO has an sp lone pair that will interact in a σ -donor interaction with an unfilled metal d orbital, and the empty σ^* antibonding orbital can also interact with a filled metal

orbital to its energy as well. Essentially, CO donates its lone pair to an unfilled orbital, and the metal donates electron density from its d orbital back to the ligand. This property is known as **metal-ligand backbonding** and results in a higher bond order for the M-C bond.

This also explains why CO is a bad Lewis acid, but a very strong binder to complexes. It also decreases the bond order of CO itself (since electron density is pushed into an antibonding orbital). This can be observed with IR spectroscopy - we see lower wavenumbers in complexes (2125-1850 cm^{-1}) as compared to free CO (2143 cm^{-1}). In fact, IR spectroscopy with metal carbonyls can be used as a metric for electron richness!

This technique is put into practice with the **Tolman Electronic Parameter**, which measures the frequency of the CO stretch of the $\text{Ni}(\text{CO})_3\text{L}$ complex. If the ligand is able to donate electron density into the metal, then the CO stretching frequency should decrease, since the effects of backbonding will be stronger. On the other hand, if the ligand accepts electron density, then the stretching frequency will be higher. (Tolman, CR, 1977, 77, 424).

Another class of π complexes is with alkenes, under the Chatt-Dewar-Duncanson model. Our alkene has a bonding orbital of σ symmetry and an antibonding orbital of π symmetry, which respectively interact with a filled and unfilled metal orbital. This differs from the CO interactions, since now both interactions come from the π bond itself. This means that alkenes can turn out to be both σ -donor and π -acceptor ligands, since we don't know if the metal donating to the alkene is more prominent than vice versa!

However, we can predict these properties. If the metal is in a high oxidation state, then there is not much productive orbital overlap between the filled metal orbital and the unfilled alkene orbital, so in this case the alkene would be a σ -donor, and the alkene bond length will be approximately that of the free alkene. If the metal instead is electron rich and has a low oxidation state, then the alkene will act as a π -acceptor and the C-C bond is then lengthened.

On one extreme, we have just a simple metal-alkene interaction being a σ -donor. On the other extreme, we have a π -acid (acceptor), consisting of a metal cyclopropane. This scale also manifests itself in terms of reactivity. The σ -donor alkene will become more electrophilic, and the π -acceptor will become more nucleophilic (due to lower and higher electron density, respectively). For example, Pd^{2+} can be used to activate alkenes towards hydration, similar to the Wacker process. On the other hand, a titanium-alkene complex can be used to make an alkene attack an aldehyde! (Bercaw, JACS, 1983, 105, 1136)

Note 6

This continuum is similar in σ -complex ligands, such as H_2 . On one extreme, the metal bonds directly to the sigma bond between the hydrogens, and on the other extreme, the two hydrogens are each separately bonded to the metal. The scale can similarly be measured via bond lengths, with free hydrogen being 0.74 \AA , and the hydrogen in metal complexes being anywhere from 0.82 \AA to 1.5 \AA , depending on the degree of electron density. If you think about this from a MO standpoint, the two situations are almost the same.

Not only does this happen with hydrogen, but it can also happen with any M-X bond. Then, a second equivalent of metal can bind to the M-X bond, and we commonly depict this as a bridging ligand, though this depiction is more accurate.

Our last class of interactors are π -donor ligands. This happens when the ligand itself has an extra lone pair - for example, halides, amides, etc. There is a σ -donor interaction between one lone pair and a metal d orbital, and a π -donor interaction from a p orbital into the d orbital. Since this ligand will only donate electron density into the metal, these ligands bind quite strongly to early transition metals to stabilize them, since they have unfilled orbitals and want more electron density. However, since the oxidation state formalism does not reflect the true electron density of a complex, the 18 electron rule often fails, as oxo and nitro ligands donate more electron density than would seem. For example, Jacobsen's epoxidation catalyst is a Mn^{3+} complex that only have 14 d electrons, but is stabilized by 2 N and 2 O ligands, making it relatively stable.

4 Geometry

The observed geometries for metal complexes are as follows:

- ML_3 : trigonal planar, T-shaped, trigonal pyramidal
- ML_4 : tetrahedral, square planar
- ML_5 : trigonal bipyramidal, square pyramidal
- ML_6 : octahedral, prismatic (having ligands at the vertices of a triangular prism)

VSEPR, as in general chemistry, provides a first approximation to transition metal complexes; however, its use is largely inadequate. This is emphasized by the fact that these complexes often do not adopt the sterically most favorable conformation. Instead, we can develop a model of geometry from the valence electrons and d electron count.

Recall from the earlier lecture that an octahedral complex shows a splitting into a set of two e_g orbitals and three t_{2g} orbitals, with the e_g orbitals being antibonding and t_{2g} being nonbonding. On the other hand, a tetrahedral complex also splits into these orbitals, but now the e orbitals become nonbonding and the t_2 orbitals become weakly antibonding. These qualitative MO diagrams can be constructed by assuming that the d -orbitals aligned with metal-ligand bonds will be increased in energy.

Now how do these considerations play into geometry? In octahedral complexes, we want to fill the nonbonding orbitals and none of the antibonding orbitals. The ligands contribute 12 electrons, and so we need 6 more to fulfill the 18 electron rule and fill the non-bonding electrons, making d^6 octahedral complexes highly favored.

Similarly, in a tetrahedral complex, we would need a d^4 complex to fill only the nonbonding orbitals, making that preferential. A completely filled d^{10} complex also prefers a tetrahedral configuration, due to spin-spin pairing that ultimately lowers the energy of the system (keeping in mind that the antibonding orbitals are only weakly antibonding). Half-filled orbitals also lower the energy of the system, so d^5 high spin complexes likewise prefer the tetrahedral geometry.

In a square planar complex, the orbitals become further split, with the d_{xy} orbital being slightly bonding, the d_{xz} and d_{yz} orbitals becoming nonbonding, the d_{z^2} orbital being significantly lowered in energy (still weakly antibonding), and the $d_{x^2-y^2}$ orbital increased in energy. Then, d^8 complexes will fill all the bonding, nonbonding and weakly antibonding orbitals, making them prefer the square planar complex.

If there are stronger metal-ligand bonds in octahedral complexes, then the bonding orbital becomes even lower in energy and the antibonding d-orbitals becomes higher in energy, ultimately increasing Δ , the "ligand field splitting parameter". This change can be quantified per ligand and put into a spectrochemical series, which states how much a ligand affects the splitting of a complex, and these orbital diagrams ultimately allow us to predict the spin states of octahedral complexes. This spin-state dependence on the ligand is most commonly observed in the 3d transition metals, since the metals in later periods will tend to have larger splittings just by themselves. However, these electronic properties can still have a profound influence on reactivity, even in the metals of later periods.

5 Ligand Substitution

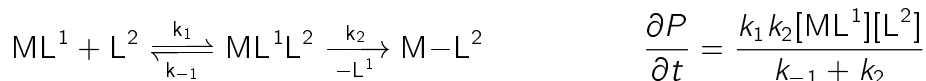
Now that we have an understanding of the fundamental structure of metal complexes, we can look at the fundamental elementary steps involved in actual organometallic mechanisms, as follows:

Name	Reaction	Δe^-	Δ Ox. State
Ligand exchange/substitution	$ML_n \xrightleftharpoons[\text{association}]{\text{disassociation}} ML_{n-1} + L$	-2	0
Red. elimination/Ox. addition	$L_nMXY \xrightleftharpoons[\text{oxidative addition}]{\text{reductive elimination}} L_nM + X-Y$	-2	-2
σ -bond metathesis/transmetallation	$XM^1L_n + M^2R \xrightleftharpoons{\text{metathesis}} L_nM^1R + M^2X$	0	0
Migratory Insertion/Deinsertion	$L_nMLR \xrightleftharpoons[\text{deinsertion}]{\text{migratory insertion}} L_nM-L-R$	-2	0

We'll examine all of these steps in greater detail in due time, but for now, we'll focus on ligand substitution. Though it seems like a basic reaction, it is often the first step in many catalytic reactions. Additionally, coordinatively unsaturated complexes can be made reactive towards OA or migration reactions. So, the presence of excess phosphine or CO can cause these metals to become saturated and essentially poisoned.

"A latent coordination site is perhaps the most important property of catalysts."

There are two major mechanisms for ligand substitution, the associative and dissociative mechanism. The associative mechanism has the following reaction equation and rate law:



which is derived from the steady state approximation. Here we have a second order dependence at all concentrations.

The dissociative mechanism has the following reaction equation and rate law:



which can likewise be derived from the steady state approximation. If the end step is the RDS, then $k_2 \ll k_{-1}$ and the rate law simplifies to $\frac{\partial P}{\partial t} = \frac{k_1 k_2 [ML^1][L^2]}{k_{-1}[L^1]}$. On the other hand, if the first step is the RDS, then $k_2 \gg k_{-1}$ and the rate law simplifies to $\frac{\partial P}{\partial t} = k_1 [ML^1]$.

These rate laws give us ideas on how to differentiate between the three possible cases (associative, dissociative with first step RDS, dissociative with second step RDS). If the rate is independent of $[L^2]$, then we have a dissociative mechanism with first step RDS. If running the reaction in the presence of added L^1 results in inhibition, then we have a dissociative mechanism with second step RDS, otherwise, it is an associative mechanism. The enthalpy and entropy of activation

also provides valuable data - the ΔS^\ddagger will be slightly negative and the ΔH^\ddagger will be positive for a dissociative mechanism with first step RDS, and vice versa otherwise.

We can also predict *a priori* which molecules are likely to undergo associative/dissociative mechanisms from the degree of unsaturation. If we have an 18-electron octahedral d^6 complex or a 18-electron d^{10} tetrahedral complex, then a dissociative pathway is preferred, since the intermediate is a stable 16-electron intermediate rather than a 20-electron intermediate.

Example 7

In the substitution reaction $\text{Ni}(\text{CO})_4 + \text{PPh}_3 \longrightarrow \text{CO} + \text{Ni}(\text{CO})_3\text{PPh}_3$, the rate law is unimolecular in the nickel complex, and has a negative entropy of activation and a positive enthalpy of activation (-8 eu and 24 kcal/mol). This data strongly points towards a dissociative mechanism with first step RDS, and is also supported by the fact that $\text{Ni}(\text{CO})_4$ is an 18 electron complex.

Remark 8. *The bond strength of the Ni-CO bond is on the order of 25 kcal/mol, so the enthalpy of activation tells us that the transition state is very product-like.*

Light, heat, bond strength, and steric properties can all influence the rate of ligand disassociation.

Example 9

Sterics can influence the disassociation equilibria heavily. For example, let us consider the disassociation of phosphine ligands from a nickel complex, $\text{NiL}_4 \xrightleftharpoons{K_d} \text{NiL}_3 + \text{L}$. The data is shown below:

ligand	$\text{P}(\text{OEt})_3$	$\text{P}(\text{OTol})_3$	$\text{P}(\text{OiPr})_3$	$\text{P}(\text{O}-o\text{-Tol})_3$	PPh_3
cone angle	109°	120°	130°	140°	145°
K_d (M)	$\leq 10^{-10}$	$6 \cdot 10^{-10}$	$3 \cdot 10^{-5}$	$4 \cdot 10^{-2}$	no NiL_4 detected

For a review of steric effects, see Chem. Rev. 1977, 77, 313.

Example 10

Another example is in the Buchwald-Hartwig reaction, between an aryl halide/pseudohalide with an amine, in the presence of palladium and diphosphine ligands. The mechanism is an oxidative addition of the aryl halide to the palladium (the rate limiting step), substitution of the halide with $-OtBu$, substitution of the $OtBu$ ligand with the amine, and then finally reductive elimination to regenerate the palladium catalyst and the product. Thus, to increase the rate of the reaction, we would attempt to speed up the oxidative addition step by using small electron-rich ligands.

However, one thing complicates this analysis is that the resting state of the palladium is tetra-coordinate, while only the dicoordinate ligand is catalytically active. Thus, replacement with the small ligands actually favors the tetracoordinate palladium, so the reaction is slower.

To fix this, we use instead even bulkier ligands to favor dicoordinate palladium, such as dialkylaryl or ferrocenium ligands. This leads to a faster and milder reaction, since the bulky ligands highly disfavor tetracoordinate palladium.

Ref: JACS 1998, 120, 24, 7369

What factors affect ligand association? Just as the 18-electron complexes favor dissociation to 16-electron intermediates rather than association to 20-electron intermediates, 16-electron square planar complexes favor association to 18-electron complexes. The nucleophile attacks the d_{z^2} orbital, creating a square pyramidal complex that then isomerizes through a trigonal bipyramidal intermediate to a square pyramidal complex that has the leaving group in the axial position, which then gets eliminated into the square planar complex.

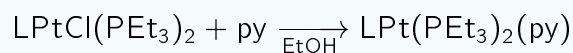
Interestingly, this reaction is relatively stereospecific, which can be explained by the principle of microscopic reversibility in where the leaving group should leave through the axial path. If the trigonal bipyramidal intermediate is long lived enough, however, **Berry pseudorotation**, an axial-equatorial isomerization, can take place, and the reaction no longer is stereospecific.

There are more factors governing ligand association than dissociation, which should be expected given that this is a bimolecular reaction. One factor is the metal itself, and the extent of interaction - namely, the hard/soft interactions, the size of the metal, and the strength of M-L bonds. For example, the rates of associative substitution of $X(CN)_4^{2-}$ decreases steadily as you go down group 10. Other properties include the steric/electronic properties of the departing ligand, and other ligands on the metal.

One specific consequence of other ligands is known as the **trans effect**, where the ligand trans to the departing ligand can have a large effect on the rate of substitution, in both kinetic and thermodynamic terms (i.e. the metal-ligand bond strength depends on the ligand trans to it.) In general, the rate of reaction is higher when the ligand is a good σ donor or π acceptor. The justification for this property is that the reaction undergoes a late pentacoordinate transition state, and the trans ligand is less destabilized there as compared to the square planar complex. This is because greater backbonding can be achieved from a pentacoordinate equatorial position (as compared to square planar), and the σ donation 'competes' for d -orbital overlap with the trans ligand.

Example 11

In the reaction below (L is trans to Cl), the rate of reaction is almost 10^4 greater if L=H rather than L=Cl:



Another consequence of reactivity is from ligand steric effects.

Example 12

In the substitution of $(\text{Et}_3\text{P})_2\text{PtClAr}$, where $\text{Ar}=\text{C}_6\text{H}_4\text{R}_2$, the rate of reaction is about 100000 times faster when $\text{R}=\text{H}$ as compared to $\text{R}=\text{Me}$.

A third example of influences of reactivity is from the 'ring slip,' where a Cp ligand changes its hapticity.

Example 13

In the substitution of PPh_3 in $\text{Cp}^*\text{Ir}(\text{NHPH})(\text{Me})(\text{PPh}_3)$, the rate law is proportional to the incoming ligand and the iridium complex, and there is a negative entropy of activation, implying the associative mechanism. However, this is an 18 electron complex, which contradicts our assumptions. What has been proposed to explain this is that the Cp ligand equilibrates from η^5 hapticity to η^3 hapticity, in which the latter 16-e complex actually participates in the substitution.

Example 14

Some interesting patterns are observed based on the nature of the Cp ligand. The Cp* ligand reacts about 100 times slower, while Cp–PPh₃⁺ reacts about 100 times faster, Cp–NO₂ reacts about 10⁴ faster, permethylated indene reacts about 10⁶ faster, and indene reacts about 10⁸. The indene ring systems have extremely high rate constants, since aromaticity is retained, thus also giving this effect the name the **indenyl effect**. The nitro and phosphonium substituted cyclopentadienes are also able to stabilize the system when the hapticity changes. On the other hand, the addition methyl groups destabilize the system formed, since the cyclopentadiene has somewhat of a negative charge, and carbanions favour less substitution.

Finally, we have one more example for the impact of sterics.

Example 15

In this study, a platinum-based polymerization catalyst was studied. It involved a platinum center coordinated to a diamine ligand, ethylene, and a methyl group, and it catalyzed the polymerization of ethylene. The mechanism was for intramolecular joining of the ethylene and methyl fragments, and then repeated addition of ethylene to the complex to create a growing alkyl chain. However, this suffered from problems in that the joined longer chain could undergo β -hydride elimination or chain transfer, before an equivalent of ethylene bound to it again.

To solve this, the group used bulkier diamine ligands to slow down the rate of the side reaction. This trick was simple, yet effective, increasing the average molecular weight about 4-fold. (JACS, 1995, 117, 6414).

6 Cross Coupling

Cross coupling reactions are essentially nucleophilic substitution reactions, that have emerged as “one of the most important catalytic processes in organic chemistry.” The general cross-coupling reaction is between an electrophile, typically an aryl halide, with a nucleophile, typically an alkyl metal, in the presence of a metal catalyst, resulting in formal nucleophilic substitution.

Note 16

These cross couplings have names associated with them, based on their discoverers, as follows:

- Kumada Coupling: Nuc = XMg-R , Cat = Ni/Pd
- Negishi Coupling: Nuc = XZn-R , Cat = Pd
- Stille Coupling: Nuc = $\text{R}_3\text{Sn-R}$, Cat = Pd
- Suzuki Coupling: Nuc = $(\text{RO})_2\text{B-R}$, Cat = Pd + base
- Hiyama Coupling: Nuc = $\text{R}_3\text{Si-R}$, Cat = Pd + F^-
- Sonagashira Coupling: Nuc = $[\text{Cu}]-\text{C}\equiv\text{C-R}$, Cat = Pd/Cu

Despite the variety of cross-coupling reactions, these all follow a similar mechanism. Specifically, we start with a $\text{L}_n\text{Pd}^{\text{II}}$ precatalyst, which gets activated (usually with loss of ligands) to generate a Pd^0 active catalyst that participates in a catalytic cycle. The aryl halide undergoes oxidative addition to the Pd^0 complex, turning it into $\text{L}_n\text{Pd}^{\text{II}}\text{ArX}$. Afterwards, transmetalation with the metal alkyl results in the formation of $\text{L}_n\text{Pd}^{\text{II}}\text{RAr}$, which then undergoes reductive elimination to generate the product and the active catalyst.

The first step of this process is oxidative addition, which is just a general term for the formal oxidation stage change. The process is favored by electron rich metals in low oxidation states (Pd^0) and a low coordination number, as well as electron rich ligands, and is also favored thermodynamically by the formation of strong bonds. It is observed that the rate of addition decreases in the order $\text{I} > \text{OTf} \sim \text{Br} \gg \text{Cl} > \text{OTs} > \text{OMs}$ and the reason for this is due to the lower bond strength of the C–X bond as one goes down this order.

However, new ligands have been developed to speed up the oxidative addition step, so even oxidative addition of aryl chlorides can occur at room temperature. Aryl iodides instead are not as good in these cycles, since they don't perform well in transmetalation. These ligands were developed by Buchwald (JACS 1998, 120, 9722) and Fu (ACIE, 1998, 37, 3387) to be used in the Suzuki coupling, with the conditions being 1.5% Pd_2dba_3 , 3.6% phosphine, 2.0% Cs_2CO_3 in dioxane. Buchwald's ligand ultimately became a diaryl phosphine amine, gave 96% yield, and Fu's PtBu_3 gave

86% yield. These bulkier ligands promote the formation of the activate catalyst (low coordination number) which promotes oxidative addition.

There are actually many mechanisms for oxidative addition itself, as follows:

- Concerted 3-center addition, which are generally seen in nonpolar substrates. A 3-membered 2-electron transition state is seen, and can be described as first generating an **encounter complex** consisting of a σ -interaction from the ligand σ -bond into the metal d orbital, which then proceeds to an actual transition state with an interaction between a metal d orbital and the antibonding orbital. As the backbonding character increases to be greater than the σ bonding character, then the transition state is favored.
- S_N2 -like addition, which is more commonly seen in polar substrates. Essentially, the metal L_nM adds to the nucleophile $A-B$ in a polar fashion, making $L_nM-A^+ + B^-$. For sp^3 electrophiles, this is truly S_N2 -like, and can be common for Pd/Pt. This mechanism can be distinguished with stereochemical studies, for example, with the reaction of $(Ph_3P)_4Pd$ and HDCCIPh, where we see inversion in the chiral center and have a trans stereochemistry of the alkyl group to the chloride. (Stille JACS, 1974, 96, 5956). This mechanism is also possible for sp^2 electrophiles, where we just have more of a S_NAr -like, highly charged transition state, shown with Hammett parameter data $\rho = 8.8!$ The order of reactivity is like the normal S_N2 addition, with the least sterically-hindered reagents and the ones with best leaving group quality reacting the fastest.
- Radical mechanism, which is generally seen with alkyl halides, and in Ni/Ir systems. The metal adds to the electrophile in a radical fashion, creating a radical which then adds back again to the metal. The order of reactivity is opposite that of the S_N2 , with it primarily determined by $R-X$ bond strength. The evidence for this mechanism comes from a halomethyl cyclopropyl radical clock, in where the generation of a radical results in ring opening and the formation of a propenyl moiety with the metal. This has also been observed with sp^2 substrates.
- Bimetallic mechanisms - not discussed

Reductive Elimination is the microscopic reverse of oxidative addition, so the factors which promote reductive elimination often disfavor oxidative addition - factors which include having metals in high oxidation states, those that are sterically hindered. Generally, sp^2 substrates react much faster than alkyl substrates, though electronic effects can also influence rate.

The other step in the catalytic cycle is transmetalation, which is now often the slow step. Its mechanism is highly dependent on nucleophile, and is much less well-understood. This step is often thermoneutral and reversible, so they are driven by subsequent reactivity of the intermediates.

The majority of studies have focused on the transfer from Sn to Pd. It is thought that the metal accepting the R group (Pd) is thought to be the electrophile, while the Sn-species is the nucleophile. The Hammett parameter is $\rho = 1.2$, indicating that the migrating group is experiencing a bit of a negative charge in the transition state. (Stille JACS 1983, 105, 6129), and explains why weakly nucleophilic transition metal reagents such as boron and silicon require activation (reacting with base and fluoride respectively to form negatively charged complexes, that increase the rate of addition).

There are two main mechanisms for transmetallation. The *closed transition state* is one of σ -bond metathesis, with a four membered ring. The other mechanism is known as the *open transition state*, where there is just a transfer of the R group to the metal with inversion of configuration. Which mechanism predominates is highly dependent on solvent and reaction conditions in general, and stereochemical probes can be used. In general, highly polar solvents favor an open transition state, while nonpolar solvents favor the closed transition state.

The rates of transmetallation have been experimentally determined to follow the order as follows: Alkynyl > Vinyl > Aryl > Benzyl \gg Me, Bu. This explains why we use SnBu_3 in the Stille Coupling - so that the transmetallation actually transfers the group we want! The rate is proportional to the electron richness (the s character), and the presence of coordinating functional groups also increases the rate. It is additionally also highly sensitive to sterics. Due to this sensitivity to sterics, the aryl chlorides and bromides react much faster than the iodide, and the bulky ligands still help with the rate by reducing the coordination number.

The final step in cross-coupling is in precatalyst activation. One method is to reduce it via transmetallation, making a dialkyl product after reductive elimination. Another method is with tertiary aliphatic amines, and an alcohol, where the amine displaces a halide from the palladium, then undergoes beta-hydride elimination to form an imine. Then reductive elimination of HX forms the Pd^0 species. A third method is to reduce the metal with phosphine - essentially, having the phosphine attack the metal, then having the displaced leaving group remove the phosphine, ultimately oxidizing the phosphine and reducing the metal. A fourth method (developed by Buchwald) is to use a sacrificial amine aryl ligand, whereupon treatment with base allows it to readily undergo reductive elimination. (Buchwald, 2008, 130, 6686) A method similarly based on these sacrificial ligands is based on the indene system seen in Hazari, Nova, ACS Cat, 2015, 5, 5596.

Now we're going to discuss the details of the cross-coupling reactions we discussed earlier - Kumada, Negishi, Stille, and Suzuki couplings.

The Kumada Coupling is normally beset with issues of low functional group compatibility, since it has a Grignard, though it is great if it works, since many other transmetallations proceed through

the grignard. The coupling is promoted usually by Ni/Pd, less commonly Fe, and $\text{NiCl}_2\text{dppp} = \text{NiCl}_2(\text{Ph}_2\text{PCH}_2\text{CH}_2\text{PPh}_2)$ is the catalyst system of choice due to the large bite angle that promotes reductive elimination. In this case, aryl chlorides generally react faster than Ar-Br/I systems. It's the most useful for constructing sp^2-sp^2 or sp^2-sp^3 linkages, and they are stereospecific with respect to the electrophile, but not necessarily stereospecific with respect to the nucleophile (dependent on conditions). Generally, the configurational stability of the nucleophile trends opposite to its nucleophilicity - lithium reagents are least stable and most nucleophilic, while boron reagents are most stable and least nucleophilic. This leads to fast racemization, which can be exploited in an enantioconvergent synthesis (for example, with (ppfa)PdCl₂ (Hayashi, J. Organomet Chem, 2002, 653, 41).

The Negishi coupling is between Al, Zr, Zn, etc, which are much milder and much more functional-group compatible. This is helpful in sp^2-sp^3 couplings where grignard decomposition is a problem. sp^3-sp^3 coupling also work (Knochel, ACIE, 1995, 34, 2723), but they are more challenging, since oxidative addition is much slower, and beta-hydride elimination competes with the transmetalation step. Thus, the presence of a tethered olefin or even alkene ligands can actually promote the reductive elimination step, by reducing electron density in the metal. (ACIE, 1998, 37, 2387). Secondary alkyl electrophiles can also be used with py-box ligands, which essentially occupy coordination sites to prevent beta-hydride elimination, and this discovery also led to the development of an enantioselective enantioconvergent Negishi reaction. (JACS 2003, 125, 14726)

The Stille coupling is between a trialkyltin nucleophile, and has a wide scope. The electrophile can be any sp^2 or sp group, and the electrophile can be any aryl or vinyl group. It is almost 100% functional group compatible, the organostannanes are easy to make, and are air and moisture stable, making it the coupling of choice by synthetic organic chemists. Mechanistic studies can be found in ACIE 2009, 43, 4704 and ACS Cat. 2015, 5, 3040, while a synthetic review can be found in J. Organomet. Chem. 2018, 869, 106.

Remark 17. *Lots of people believe that tin is toxic, due to SnMe_3 . However, most of the tin used is actually SnBu_3 , which is much less toxic.*

The Suzuki coupling is between boronic acids, with an additional base catalyst (that potentially generates the borane or can replace the halide with a hydroxy group after oxidative addition). The nucleophile can be sp^2 or sp^3 , including primary alkyl groups, and many types of boranes can be used. Alkyl-alkyl couplings are also possible (with Ni cat. and a diamine ligand). The advantage of Suzuki couplings are the large varieties of boronic acids commercially available, though they are not very stable, thus promoting their late-stage usage.

Question 18. *So which reaction should we use for our bond formation?*

- In a disubstituted alkene product, if we don't have many reactive functional groups, then we can simply use a Kumada coupling. Note that Pd often offers better stereoselectivity for cis-alkenes, otherwise, nickel is fine. Otherwise, Negishi or Stille couplings will work.
- For trisubstituted products, we may have problems with stereochemistry, but Kumada, Suzuki, Stille couplings are all fine.
- For aryl-alkyl couplings, Kumada couplings work great, but as usual, Suzuki/Negishi conditions are necessary for functional group tolerance. Also note that in Suzuki/Negishi conditions, either can be the nucleophile or the electrophile.
- For aryl-vinyl couplings, Suzuki and Stille couplings work fine, and if there are base-sensitive substrates, then using the Stille coupling is necessary.
- For alkene-alkene couplings, Negishi or Stille couplings work fine.
- For aryl-aryl couplings, essentially everything works.

Now we'll take a brief detour to look at the other types of nucleophiles that can be used in coupling reactions. One of these is with enolates, as seen in JACS 1999, 121, 1473. These can also be done enantioselectively, since the mechanism is very similar - the only difference being a substitution instead of a transmetallation. Many substitution modes are possible - either a η^3 or *O* coordination.

The most important non-metallic coupling is the Heck Coupling. It involves a similar mechanism as the standard cross-coupling reaction, and is the fastest with monodenate phosphine ligands. The mechanistic changes involve coordination of the alkene to the metal, syn-migratory insertion, molecular rotation, beta-hydride elimination (generating the product), and finally base-promoted reductive elimination. A cationic mechanism has also been proposed, in where bidentate ligands are used instead.

These mechanisms can influence regiochemistry. The neutral mechanism sees migration to the carbon that is least sterically hindered, while the cationic mechanism sees migration to the position with lowest electron density. (ACE, 1995, 28, 2 and TOC 1992, 57, 1480)

We can also do cross-couplings with non-carbon based nucleophiles - namely, making C-O and C-N bonds. The mechanism has been studied extensively (JACS, 2006, 128, 3584). Here, there is a precoordination of the amine to the metal, which then reacts with the base to deprotonate the amine. Now, we may produce beta-hydride elimination products, can dimerize, or actually produce our desired product. This reaction has been pretty well studied and its scope includes cyclic/acyclic, secondary, primary, and aromatic amines, as well as ammonia surrogates, amides, carbamates, and sulfonamides. These are summarized in the 'user guide' Buchwald Chem Sci, 2011, 2, 27.

Finally, Cu-catalyzed Ullman/Goldberg reactions are also possible - see Chem Rev 2008, 108, 3054.

7 Hydrogenation

Heterogeneous hydrogenations are very commonly used in industry, for example, in the Haber-Bosch and Fischer-Tropsch processes as well as the reduction of adiponitrile. These are often more advantageous due to the ease of product separation, recyclability of the catalyst, reactivity, and turnover number.

Homogeneous hydrogenations, which we will focus on, also have some advantages - namely, milder reaction conditions and ease of reactivity/selectivity control (for example, differentiation between alkene isomers, 1,2/1,4 addition, and ketone/imines.) Diastereoselective and enantioselective hydrogenations are also possible with homogeneous hydrogenations - in fact, enantioselective hydrogenations are the most important enantioselective catalytic reaction in industry. Finally, mechanistic studies are also more tractable.

The first use of hydrogenation catalysts was in Wilkinson's reduction of an alkene, which reacted much faster than the standard PtO_2 reduction, with the catalyst $\text{Rh}(\text{PPh}_3)_3\text{Cl}$. In the mechanism, named the **dihydride pathway**, one phosphine ligand is displaced with a solvent ligand, to which hydrogen is oxidatively added to the complex. (Alternatively, an associative mechanism can also take place, but is about 10^4 times slower, shown by subjecting an olefin to a 1:1 mixture of H_2 and D_2 , and noting that there were very few cross-products.) Then, the solvent is displaced by an alkene, to which the metal coordinates. The rate determining step is then the insertion of the hydride into the alkene (and the direct formation of a C-M bond), and afterwards, reductive elimination occurs to give the reduced product.

Since H_2 is a nonpolar substrate, the mechanism for oxidative addition is through the formation of the σ complex, which undergoes concerted addition to the cis-metal dihydride complex. Depending on the conditions, the σ complex may or may not be long lived. A certain tungsten complex (Kubas complex) actually has the σ complex as its most stable form!

After the hydride is added to the metal, then the substrate coordinates to the metal and then reversibly undergoes migratory insertion. In this process, there is no change in oxidation state, and the migrating group must be cis to the unsaturated ligand. Further, it is syn-selective (metal and hydrogen add to same side). Because insertion is very fast, there are very few hydride olefin complexes. Insertion of C-H bonds is often much faster than C-C bonds, due to better orbital overlap.

In general, terminal alkenes, cis alkenes, and unhindered alkenes react faster in hydrogenation reactions with a homogeneous catalyst - sterics determine selectivity (this is not necessarily true with solid-phase catalysts, where electron-rich alkenes react faster). Cationic catalysts can improve

this selectivity even more, for example in the Osborn-Schrock Rh catalysts or the Crabtree Ir catalysts. Wilkinson's catalyst works well for most types of alkenes, the Schrock does not work well with internal alkenes, and the Crabtree catalyst works for every type of alkene.

Using these catalysts, we can also perform directed hydrogenation. We can often get dr's of 99:1 when performing hydrogenation with directing groups (OMe, C=O, etc), even when sterics are unfavorable. In comparison, the standard Pd/C gives only about 4:1 dr. One thing to watch out for is that the catalysts can also act as Lewis acids promoting elimination of the products. This problem can be worked around with by using THF as solvent (not done often!)

These catalysts have a different mechanism than the Wilkinson's catalyst. Here, the alkene coordinates first to the metal, and the directing group coordinates as well (this is the resting state without hydrogen.) The hydrogenation of the metal is the rate limiting step, and the product is formed with a cis-migratory insertion and reductive elimination. (Halpern, Science 1982, 217, 401)

These catalysts can also be modified to be enantioselective. The classic example is the reduction by enamines by P-chiral C_2 symmetric (cod)Rh(DIPAMP), used in the Monsanto process of L-DOPA. Another more interesting example is with Ru(BINAP)(OAc)₂ complexes reported by Noyori, (JACS, 1986, 108, 7117), which offer greatly increased enantioselectivity, even with 0.01% catalyst!

The Noyori catalysts proceed through a different mechanism, called the monohydride mechanism (JACS 1991, 113, 589). Here, the alpha hydrogen comes from H₂, and the beta hydrogen comes from solvent. The mechanism proceeds first by loss of one acetate ligand and association by the carboxylic acid substrate moiety. The hydrogen binds to the metal in a sigma complex, and the other acetate ligand promotes heterolytic cleavage of the dihydrogen. This protonated acetate ligand then is replaced with the solvent, and hydride is inserted into the substrate. Reassociation of acetate and reductive elimination yields the product. Note that Ru stays in the +2 state through the whole cycle.

With Ru(BINAP)Cl₂, then ketones with close chelating groups can also be reduced. With a diamine ligand and base, then any ketones, even α, β unsaturated ketones, can be even favored over alkenes! (JACS 1995, 117, 10417) Now, if this is combined with chiral phosphine and chiral diamine ligands, then we can get enantioselective reduction of ketones!

The mechanism for the diamine-mediated reduction starts off by making the trans-dihydride complex with the loss of the two chlorine ligands. It's then proposed that the ketone doesn't directly interact with the metal, but rather a hydrogen-bond based activation by the diamine. The hydrogen atom that reduces the ketone then comes from the ruthenium, and the one that bonds to the oxygen comes from the nitrogen.

8 Hydrofunctionalization

Hydrofunctionalization has similar mechanisms to hydrogenation. For example, in hydrosilylation, organosilanes similarly undergo oxidative addition, then coordination of the alkene. If there is a C-H insertion this is known as the **Chalk-Harrod mechanism**, and reductive elimination creates the silane at the less substituted position. Alternatively, C-Si insertion can also occur (**modified Chalk-Harrod mechanism**) that reductively eliminates to give the same product (but can also eliminate on the other side to give rise to observed side products).

Typically, Rh, Ir, Pd, Pt, Cu, Au, Fe can be used, with Rh, Pd, Pt being the most common (specifically H_2PtCl_6). The reactions often use much milder conditions to affect reduction of carbonyl equivalents. (Org. Lett. 2007, 9, 1113)

Hydrosilylation can also be done to alkynes to add in a trans-fashion, once again with silicon adding to the less hindered side. This can also be done to internal alkynes. Treatment with fluoride after hydrosilylation allows for conversion of an alkyne to a trans-alkene. (Trost, JACS, 2002, 128, 9328)

Enantioselective hydrosilylation has also been developed. Using a Pd - MOP catalyst with HSiCl_3 , a SiCl_3 group is added to the more substituted position, upon which substitution with EtOH and a subsequent Tamao oxidation yields enantioselective hydroxylation.

Note 19

Classic chelating phosphines, such as DPPB, BINAP, etc don't work in these transformations.

We can also catalyze hydroboration, even though it is already pretty selective. We do this for better terminal selectivity or enantioselectivity, or even just for reaction speed-up. For example, hydroboration-oxidation of allylic alcohols will lead to the anti-product without a catalyst, but to the syn product with the catalyst.

The mechanism for one of these catalysts, for hydrogenation, is also a monohydride mechanism, but it is somewhat different. We start with $(\text{Ph}_3\text{P})_3\text{RuHCl}$, which undergoes standard loss of ligand to form $(\text{Ph}_3\text{P})_2\text{RuHCl}$. Then, coordination to the alkene, insertion of the hydride into the alkene happens as usual, and then a equivalent of hydrogen add to the metal to make an octahedral complex. Reductive elimination then results in regeneration of the four-coordinate metal and the hydrogenated product.

More specifically, we can investigate the hydride migration step. For highly charged early metals, such as Zr(IV), d^0 , the equilibria lies in favor of migratory insertion, since the alkene interaction is just a weak sigma donor interaction. This allows for the Schwartz reagent ZrCp_2ClH to be used

in a variety of transformations of alkenes, for example, with reaction with Br_2 , HCl , or H_2O_2 to respectively form the bromide, reduced product, or the hydroxy compounds. It can also be used for transmetallation purposes.

For late, low valent metals such as Pt(II) , we instead have stronger π -backbonding between the alkene and the metal, and hence the equilibria lies more towards the hydride complex. Thus, we can use these catalysts to affect isomerization between two olefins through addition then beta-elimination, or in polymerization. We can also use these low-valent metals to insert CO into the alkene as well.

We have one 'final' mechanism, seen in the reduction of anthracene to 9,10-dihydroanthracene, under H_2/CO and $\text{Co}_2(\text{CO})_8$ catalysis. This mechanism first sees formation of the $\text{HCo}(\text{CO})_4$ intermediate, which then reacts with the anthracene system to create an anthracene radical and $\text{Co}(\text{CO})_4$. Donation of another hydrogen and reformation of the dimer concludes the cycle.

In general, these reactions can proceed because metal-hydrogen bonds have low BDE's compared to C-H bonds, with the average being about 60-65 kcal and the first row metals having slightly lower BDEs.

Another reaction is in using a $\text{Mn}^{\text{III}}\text{TPPCl}$ catalyst in the presence of NaBH_4 and O_2 . There are both reductants and oxidants, since this reaction was designed to be a structural model for P450 (which uses O_2 and NADH .) In the oxidation of cyclohexene, what is found is that 20% of the allylic alcohol is made, and 80% of cyclohexanol is made. On the other hand, without NaBH_4 , 80% of the ketone is made, 18% of the allylic alcohol is made, and 2% of the epoxide is made.

This motif of oxidation-reduction hydration ultimately led to the **Mukaiyama hydration**, which adds water across a double bond with $\text{Co}(\text{acac})_2$, PhSiH_3 , and O_2 . These are much better chemoselectively and tolerating as compared to acid-catalyzed hydration, and adds to the more substituted position, as usual.

The mechanism for this reaction has not been fully understood, but is thought to involve oxidation of the Co(II) catalyst into a Co(III) hydride. Then, the alkene adds to the cobalt, and a radical is formed after cobalt leaves, which then reacts with the oxygen to form a peroxide radical, which reacts with the catalyst. Reduction with the silane results in regeneration of the active Co(III) hydride.

Since this reaction generates a radical, some applications have been developed, for example, in hydroazidation. With the reaction of an alkene, catalysts, and tosyl azide, then we can get azidation at the more substituted position. We can also perform hydroalkylation and alkene isomerizations with these systems as well. These radical-based reductions are often much more mild, and can even perform reductions on vinyl halides.

Note 20

Hartwig's first edition textbook (published in 2010) says that radical-based reactions are a thing of the past, but much work has been done in the last few years. For a review, see Shanvii *ACR* 2016, 116, 8912.

9 Hydroformylation

Hydroformylation is the addition of CO and H₂ across a double bond, generally making a linear and a branched isomer. It's catalyzed by platinum group metals, Pt, Ir, or Rh, and sees wide usage on an industrial scale (Oxo process). The first discovery was with a Co₂(CO)₈ catalyst, in a 1:1 H₂/CO mixture. Our modern rhodium catalysts operate at lower temperature and pressure, and also give better selectivity ratios. We can also use cationic co-catalysts: see Science 2020, 367, 542.

Note 21

The H₂/CO mixture is known as **syngas**, and is a waste product in petrochemistry, so it is available relatively cheaply.

In general, the active form of the catalyst is (Ph₃P)₂(CO)₂RhH, which can undergo equatorial-axial inversion. Without Ph₃P, the reaction actually proceeds much faster, but gives worse selectivity ratios. The general mechanism proceeds as follows:

First, a CO ligand is lost, and then the alkene coordinates to the Rh metal. Insertion of the hydride into the alkene, followed by binding of CO or a phosphine ligand, regenerates the Rh catalyst. Then, CO undergoes migratory insertion, upon which addition of H₂ regenerates the catalyst and produces the product through reductive elimination.

Originally, it was thought that the ratio of eq-ax isomers of the catalyst lead to the selectivity, and this inspired the development of diphosphines with large bite angles. This hypothesis is not true, but these ligands still offered improved selectivity (Buchwald JACS 1993, 115, 2066).

Since internal olefins can also undergo isomerization, then a mixture of internal and terminal alkenes can also be used in hydroformylation. This is important since these mixtures are produced from the industrial SHOP process.

Though hydroformylation commonly favors the linear product, branched-selective hydroformylation is also possible, and we can use chiral ligands, such as BINAPHOS in order to enforce enantioselectivity. (Takaya, JACS, 1993, 115, 7033). This has been used in syntheses, such as the one of ambraticin by Jacobsen.

Let's investigate the migratory insertion of the carbon monoxide. The question is - does the R group migrate to the CO, or does the CO migrate to the R group? Caldeazzo demonstrated that it was actually the R group that migrated, with stereochemical studies. (Caldeazzo J. Organomet. Chem. 1967, 10, 101.)

They investigated the insertion of CO in $\text{MeMn}(\text{CO})_5$. The first experiment was to run the reaction under a labelled CO atmosphere, and they saw that the resulting acyl group was always cis to the new CO ligand. Thus, CO-insertion is intramolecular, and isomerization is negligible.

The second experiment was to show that the principle of microscopic reversibility holds, by showing a labelled product (on the acyl) would result in cis-CO ligand to the methyl group in the starting material.

The third experiment was when one of the CO ligands cis to the acyl in the product was labelled. The isolated starting material were both the cis and trans isomers, and are observed in a ratio of 2:1. This shows that the methyl migrates, since otherwise we would only see cis starting materials.

The fourth experiment was when the starting material only had one of the cis-CO ligands labelled. The resulting products were the trans isomer, cis isomer, and the isomer where labelled CO was inserted, in a ratio of 1:2:1. Likewise, this is consistent only with the methyl migration.

Another example of hydroformylation is in Methanol carbonylation, which is used industrially to produce acetic acid. Rh/Ir are the common catalysts of choice, with $\text{Rh}(\text{CO})_2\text{I}_2^-$ being the catalyst.

The mechanism starts with the formation of hydrogen iodide, which reacts with methanol to make methyl iodide. This methyl iodide then reacts with the Rh catalyst to undergo a S_N2 -like oxidative addition (RLS for Rh). Insertion of CO (TOLS for Ir) followed by reductive elimination results in the production of acyl iodide and the rhodium catalyst, and the acyl iodide reacts with the water to form acetic acid and HI.

Since CO insertion/migration is known for every transition metal, then we can also use these methods in synthesis. For example, if we have a C-O coupling reaction, if we run it under CO, we can get an ester.

There are a few other reactions worth mentioning, for example, the insertion of CO into epoxides under Cr(salen) catalysis (JACS, 2002, 124, 1174), the Pauson-Khand reaction, and hydroesterification/hydroamidation with $(\text{Ph}_3\text{P})_2\text{PdCl}_2$, CO, and MeOH. The mechanism of hydroesterification involves insertion of CO to form an acyl chloride, then substitution of the chloride to form the ester by methanol, coordination by the alkene, and then migration to form the ester product which is reduced with reductive elimination.

10 Oxygenases and Oxidases

The next few lectures will focus on oxidative transformations affected by organometallic complexes. We'll first focus on biological enzymes **oxygenases** and **oxidases**, which differ depending on whether the oxidant (usually O_2) gets incorporated into the substrate or just serving as an electron acceptor.

Schematically, for an oxygenase, we can represent this as the formation of a metal-oxo complex, which then transfers the oxygen atom to the substrate. For an oxidase, the metal is also oxidized by oxygen without O transfer, which then goes on to oxidizes the substrate.

The archetypical oxygenase are the cytochromes, for example, **P450**, which has motivated the development of many catalysts. One example of the use of P450 is in the biosynthesis of Taxol, where an unactivated C-H bond is oxidized to a C-OH bond with retention of stereochemistry.

These cytochromes are based on a Fe(II)-heme complex. The general mechanism is for coordination of oxygen to make a hydroperoxyl radical Fe(III) complex, which then is reduced (by a coreductant, typically NADH) to the hydroperoxide Fe(III) complex. Then, addition of protons results in the loss of water and oxidation to the Fe(IV) complex, which then transfers the oxygen to a species of interest with concurrent reduction to Fe(III), which is then reduced back to Fe(II).

Note 22

Since the reduction of oxygen to water is a 4 electron reduction, but the incorporation of an oxygen atom is only a 2 electron oxidation, commonly coreductants are needed. A way to get around this is to use H_2O_2 as the oxidant instead.

We can use our own synthetic Fe(III) porphyrins for epoxidation/hydroxylation. For example, the reaction of 1,3-cyclohexadiene, with oxidant PhIO and 10% Fe(III)TPP-Cl, results in the formation of PhI and monoepoxidation. Chiral porphyrin catalysts are also possible, but enantioselectivities are not great since most porphyrins are mostly flat. One example is reported in Collman, Science, 1993, 261, 1404.

Salen-type ligands were also shown to be able to support high oxidation states. For example, use of 4% of Mn-salen complex and PhIO oxidizes cyclohexene to cyclohexene oxide (Kochi, JACS, 1986, 108, 2309), through an intermediate Mn-oxo species. The salen ligands can be made to be chiral, resulting in enantioenriched oxidation, known as the **Jacobsen/Katsuki epoxidation**. This reaction has wide scope, and performs best on cis alkenes (since trans alkenes may cause stereochemical scrambling). Sometimes, 4-phenylpyridine N-oxide is added to improve the reaction ee, where it acts as a coordinating ligand. A review can be found in CR 2005, 105, 1563.

It is thought that the enantioselectivity of this reaction derives from the side-on approach of the alkene to the Mn-oxo complex (from the alkene HOMO to the oxygen lone pair LUMO), and proceeds through stepwise radical intermediates. It is generally found that those ligands with electron-donating substituents give the highest ee's (JACS, 1991, 113, 6703).

Remark 23. *The Sharpless Ti-based enantioselective epoxidation is often complementary to the Jacobsen epoxidation.*

Aziridinations occur in a very similar way to epoxidations. For example, a $Mn\equiv N$ bond is formed from photolysis of a Mn-azide, and in the presence of trifluoroacetic anhydride, cyclohexene is oxidized to N-trifluoroacyl cycloaziridine. Another example is in the oxidation of a phenyl silyl enol ether, which then undergoes ring-opening to make N-trifluoroacyl 1-aminoacetophenone. A review can be found in Dubois, Carriera, ACR, 1997, 30, 372. The development of TFAA-free aziridation came when using copper catalysts with $PhI=NTs$ as oxidant to create tosylaziridines. (Jacobsen, JACS, 1993, 115, 5326).

Two mechanisms for the copper-catalyzed reaction have been proposed. The first mechanism involves a reduction of Cu(I) into a $Cu=NTs^+$ intermediate, which then oxidizes the alkene. The other proposed mechanism is one where the copper generates a nitrene-like species, $CuN(Ts)(IPh)$, which oxidizes alkenes without changes in copper oxidation state.

Remark 24. *The aziridination reaction has not been fully developed, and has limited scope (working only on styryl substrates and needing a protecting group). The state-of-the-art aziridations are based on rhodium systems.*

We also have some systems based on non-heme oxygenases. The biological system is the oxidation of methane to methanol with oxygen and NADPH as reductant, with a hydroxo-bridged Fe(II) dimer serving as catalyst. Addition of oxygen to this species makes a peroxo-bridged Fe(III) dimer, upon which protonation and loss of water creates a Fe(IV) oxo dimer (also represented as Fe(III)/Fe(IV-oxyl species). Abstraction of hydrogen generates a substrate radical, from which a radical rebound results in hydroxylation and generation of the Fe(III) hydroxy dimer, which is reduced back to Fe(II) with NADPH. (Lippard, CR, 2003, 103, 2385).

Non-heme ligands have been used in synthetic oxidation systems, which are often stereoretentive due to a radical rebound. These reactions often have yields that are moderate (51%) since the catalyst actively decomposes the hydrogen peroxide cocatalyst, and the catalyst system has to be recycled 3x. (White, Science, 2007, 318, 783). Another example of directed C-H hydroxylation is in the oxidation of a gibberilic acid, which uses a carboxylic acid-directed oxidation in 52% yield.

Now let's look at oxidases. One biological example is galactose oxidase, which converts galactose

into its aldehyde. The mechanism involves a Cu(II) catalyst with an organic tyrosyl radical cofactor. The alcohol coordinates to the Cu(II), and then there is a reaction in which the hydride transfers one electron to the tyrosyl radical and one to the Cu(I), forming an aldehyde in the process - a mechanism for a 2-electron oxidation with Cu. Coordination of oxygen makes the hydroperoxyl Cu(II) complex and releases the aldehyde product, then hydroxyl transfer regenerates the tyrosyl radical, and then substitution liberates hydrogen peroxide.

Remark 25. *In many of these biological reactions, the desired product is actually not the organic product, but rather H_2O_2 , which is useful cellularly.*

Oxidations based on this protocol have been developed using TEMPO instead of tyrosyl radical. The typical conditions are 5% Cu(OTf), 5% bpy, 5% TEMPO, 10% NMI, and air. (Stahl JACS, 2011, 133, 16901). The mechanism has been resolved (see JACS, 2013, 135, 6, 2357) and is very similar to biological oxidases. This protocol is useful for selectively oxidizing primary alcohols.

One of the most important organometallic oxidases is in the Wacker oxidation, which oxidizes alkenes to ketones and is used heavily industrially to oxidize ethylene. The catalysts are PdCl₂ and CuCl₂, and the reaction is done with O₂, H₂O, HCl. Note that this is an oxidase - the oxygen incorporated in the product comes from the water, not the oxygen.

The mechanism involves the coordination of the alkene, and then a nucleopalladation step that involves the outer-sphere attack of water onto the alkene to create a Pd-alkyl species with loss of HCl. Beta-hydride elimination makes a palladium hydride and our product that enolizes to the ketone. The palladium hydride reductively eliminates HCl and is reoxidized by copper chloride, which is oxidized by oxygen itself.

A cis-nucleopalladation step (where the hydroxyl is first bound to the palladium) has also been proposed, which was disproven by Stille. The key experiment was the stereocontrolled addition of cis-deuterated ethylene in the presence of CO. It ends up producing the trans-deutero product (a 4-membered lactone), showing that trans-nucleopalladation occurs.

Other oxidants such as benzoquinone (as seen in Tet, 1994, 35, 6481) can also be used. Enantioselective variants (based on sparteine) have also been developed. A cascade reaction has also been developed, using CO and MeOH to transform 5-hydroxy alkenes to tetrahydropyran moieties with a methyl ester (JACS, 1984, 106, 1496).

Finally, usage of other nucleophilicities has also been developed, for example, in the dihydroxyacetylation of indene with Pd(dppp)(H₂O)₂(OTf)₂ and PhI(OAc)₂, HOAc (JACS 2008, 130, 2964). The mechanism is thought to proceed via trans-attack of the acetic acid after alkene coordination, then oxidation to Pd(IV), from which a second attack by the incorporated acetic acid unit regenerates

Pd(II) and releases an acetoxyonium ion that can be ring-opened to give the dihydroxyacetylated product.

The usage of other nucleophilies has also led to oxidative annulation protocols (Stahl, JACS, 2007, 129, 6328), which undergoes cis-attack due to the intramolecular nature of annulations. Overall, cis/trans attack and regioselectivity itself depends on the catalyst system and solvent (JACS 2005, 127, 2868).

Hydroamination reactions (not oxidative) bear a similar mechanism to these Wacker-style oxidations. Instead of a beta-hydride elimination at the end, the alkyl substituent is simply protonated. A palladium hydride mechanism has also been proposed (Exercise for the reader). A review: Beller, ACIE, 2004, 43, 3368.

Finally, though this lecture has focused on palladium, rhodium catalysts have been developed (Hall, JACS 2019, 141, 739).

11 Allylic Substitution

Allylic substitution, like the Wacker oxidation, involves coordinated attack of a nucleophile from the outer-sphere. It is not an oxidation in itself, but has a similar mechanism. (For a review: CR 1996, 96, 395)

The general mechanism is a metal reacting with an allylic halide to generate the metal- η^3 allyl complex (through a alkene complex followed by an 'oxidative addition'), which then is subjected to nucleophilic attack (a 'reductive elimination') to generate a Pd-alkene complex, that ultimately disassociates to the product.

What are the stereochemical outcomes of this reaction? Trost found that if the nucleophilic is soft (enolates, amines, etc), then retention of stereochemistry occurred, through a double-substitution mechanism. On the other hand, when Grignards, organometallics, hydrides, or other hard nucleophiles are used, then inversion is seen. The mechanism of oxidative addition remains with inversion, but now the transmetalation occurs and cis-attack occurs for an inner-sphere cis-attack.

There is also a possibility for alkene isomerization, via η^3/η^1 slip, that can result in the formation of the trans-alkene from a cis allylic alcohol, through a Pd-alkyl intermediate. The rate of isomerization is slow for sterically hindered alkenes, but for unhindered alkenes, the syn-form (that leads to the trans-alkene) is favored. Thus we can exploit this to generate E alkenes selectively.

Additionally, linear products are preferred for steric reasons in the outer-sphere trans-attack mechanism. However, if there is a strong electronic bias, then internal substitution is instead preferred. Essentially, if a cation in the internal position is favored (or the outer group is an EWG), then sometimes the internal isomer is formed.

For an inner-sphere cis-attack mechanism, then the nucleophile will substitute at the more internal position, allowing the Pd to be less hindered.

The synthetic methodology that has been developed using allylic carbonates is known as the **Tsuji-Trost reaction** (Tsuji, TL, 1982, 23, 4809). Further, beta-ketoesters can also be used to mask the carbonate. This methodology has been used in many natural product syntheses. Further, allylic epoxides can also react, with concurrent ring opening (Trost, ACIE 1997, 36, 1486).

Rh and Ir-catalyzed allylic substitutions have higher regioselectivity for the more substituted position. This has been justified by proposing that the cationic site adjacent to the metal is more stable. An enyl complex (where the metal complexes to the alkene and has a sigma bond to the alkyl as well) is proposed instead, and this is slow to exchange to the other enyl complex. This was proposed since branched/linear allylic starting materials sometimes gave different product ra-

tios. Further, crystallography showed different bond lengths, that would not be present in the allyl complex.

Now let's look at how we can introduce asymmetry in these reactions. Supposing we have a symmetric allyl complex, attack at the two positions will generate two different enantiomers, and one can be selectively favored. Another method of introducing asymmetry is the creation of a new stereocenter from a prochiral molecule. A third method is substitution of diastereotopic leaving groups. Essentially, we have a symmetric alkene with two leaving groups, of which one selectively leaves to generate chirality. A fourth method is when we have an unsymmetric π -allyl complex, where one face of palladium coordination is favored. This depends on the rate of isomerization of the palladium coordinated complexes and the relative rates of reaction of each.

Examples can be seen in Stoltz, *ACIE*, 2006, 45, 3109 and Trost, *JACS*, 1999, 121, 3543, where a Bu_4NCl is used to facilitate isomerization of the two palladium diastereomers.

12 C-H Activation

C-H activation is the process of modifying C-H bonds to C-X or C-C bonds. It's been called the "holy grail" of chemistry - basically, how do we change something so inert (BDE 90-105 kcal/mol, pKa 45-50) into something reactive? Despite the relative stability of C-H bonds, they are actually pretty easy to break - just combust it in oxygen! The problem becomes how we just selectively activate one 1 C-H bond. (Review: ACR, 1995, 28, 3, 154.)

Some typical reactions we want to perform include the conversion of methane to methanol, or the cleavage of a CH₃ bond in the presence of a CH bond (which is easier to cleave). We also need to be wary of overoxidation, since the product C-H bonds are weaker than the starting material.

Recall that metal sigma complexes have two binding modes, on a continuum from backbonding to complete sigma-donation. The former is known as **Bergman-type** and is exemplified by Ir(I) complexes, while the latter is known as **Shilov-type** and is exemplified by Pt(II) complexes.

In Shilov complexes, C-H cleavage occurs in a heterolytic manner, and there is no oxidation state change of the metal. For example, this happens in the oxidation of methane to methanol in the presence of K₂PtCl₂, with K₂PtCl₆ as the stoichiometric oxidant.

The mechanism of this transformation starts with Cl₂Pt(OH₂)₂, where methane displaces water (!) [due to the softer nature of Pt] to make a sigma complex, which then becomes deprotonated by chloride to generate Cl₂Pt(OH₂)Me⁻. The oxidant oxidizes the Pt to Pt(IV) with the addition of two chloro ligands, and then water is lost, generating Cl₄PtMe⁻. Then, an S_N2-like pathway (shown by stereochemical studies) with water results in the loss of methanol and creation of PtCl₄²⁻, which then goes on to regenerate the catalyst. H/D exchange studies has shown that primary C-H bonds react faster than secondary and tertiary C-H bonds.

This method, however, is not very practical due to the use of K₂PtCl₆ stoichiometric oxidant, which has given hope that it could be replaced with another oxidant. Indeed, the Catalytica process using sulfuric acid as the oxidant has been developed. It involves the reaction of methane with H₂SO₄ (as the solvent) to generate methanesulfonic acid, in the presence of a PtCl₂(diamine) catalyst.

The mechanism for this process is very similar, with a starting (diamine)Pt(OSO₃H)₂ catalyst that has one of the sulfonic acids displaced by methane, which then generates the methyl complex. Sulfuric acid then oxidizes the Pt to a 6-coordinate complex, from which either reductive elimination or a S_N2-like pathway occurs to generate methanesulfonic acid.

A similar C-H activation of benzene has been developed by Crabtree, in where benzene (as the solvent as well) in the presence of Pd(OAc)₂, PhI(OAc)₂, AcOH becomes oxidized to acetoxyben-

zene. (J. Mol. Catal. 1996, 108, 35). The I(III) oxidants are decently mild (especially compared to the Catalytica process).

To avoid solvent-quantities of substrate and site-selectivity, directing group strategies have been used, with the I(III) catalysts. For example, in the acetyloxylation of 4-azaphenanthrene, the 5-position gets selectively acetyloxyated, due to the coordination of the nitrogen. Other groups such as Br, F, and OMe can also be incorporated. Further, other directing groups such as oximes and acids can also be used (Sanford, JACS, 2004, 126, 2300).

Using I(II) reagents, we can also make C-C bonds. For example, 3-methyl,2-phenylpyridine, under the action of $\text{Ph}_2\text{I}^+\text{BF}_4^-$ attaches a phenyl group to the 2' position of the phenyl group. The methyl group doesn't provide any selectivity, rather, it is just there to prevent overoxidation (restricting bond rotation). These I(II) reagents result in the transfer of the less hindered aryl group, so a $\text{MeIPh}^+\text{BF}_4^-$ reagent would result in the transfer of a phenyl group. (JACS, 2005, 127, 7330).

C-H activation can also be achieved with a Pd(0)/Pd(II) cycle, instead of the Pd(II)/Pd(IV) cycles discussed earlier. Benzoquinone and silver oxide is used, in the presence of a boronic acid, which ultimately gets incorporated in the same 2' position in the systems above. (Yu, 2006, 128, 73). We may also induce enantioselectivity with chiral amino acids (ACIE, 2008, 47, 4882).

Now, how do we get non-directed C-H activation? Electron-rich substrates like an indole will react with, for example, $\text{Pd}(\text{OAc})_2$ at the 2 position, which can further go on to react with I(II) to incorporate aryls. (JACS, 2000, 128, 4972). Electron-deficient arenes will also perform the same reaction. For example, the reaction of $\text{F}_5\text{C}_6\text{H}$ with 4-bromotoluene results in coupling of the H-Br bond. (Fagnou, JACS, 2006, 128, 16496)

The mechanism for concerted arylation involves first oxidative addition as usual, then a displacement of the halide with carbonate, creating a bidentate carbonate ligand. The relatively acidic perfluoroarene then is able to be deprotonated and concertedly attached to the palladium while the carbonate leaves, after which reductive elimination can take place. This mechanism is supported by higher reactivity or more acidic species, as well as large KIEs, and the fact that bromide or acetate ligands also worked.

If we use the substrate as a cosolvent, then electron-neutral arylation can also take place. We can then cause a dehydrogenative cross-coupling between an electron rich indole at the 3 position with *p*-difluorobenzene. (Science, 2007, 376, 117)

For allylic activation, Trost found that Pd(II) salts could also affect it, but in stoichiometric amounts (ACR, 1980, 13, 385). The challenge was to have both the electrophilic C-H activation and the nucleophilic formation of the π -allyl complex.

We can get around this by using benzoquinone and MnO_2 as oxidant, and AcOH as nucleophile, in order to impart allylic acetyloxylation. (Buckwall, Chem. Eur. J, 1998, 4, 1083). Wacker-type products can also result, depending on conditions. Specifically, the amount of Wacker-type products was much greater in pure AcOH as compared to a 1:1 AcOH/DMSO mixture. Thus, it was hypothesized that DMSO-like ligands could improve selectivity, and indeed it did (though to the branched isomer) (White, JACS, 2004, 126, 1346). An example is in the total synthesis of Hippolachnin A, which used a late stage acid-directed C-H cyclization (JACS 2016, 138, 7, 2437).

Now let's take a look at Bergman-like complexes, those with pi-backbonding character. These often involve Ir and Rh complexes, and were some of the first complexes discovered to induce C-H activation. Essentially, starting with a 3 or 4 coordinate ligand, treatment with heat and light causes the loss of ligand and formation of a 2-ligand 16 electron complex, which then can coordinate with a C-H bond either in a concerted or radical fashion (JACS, 1983, 105, 3929). Kinetic studies showed that there was a strong preference for activation of less hindered positions, with the difference being more profound for Rh rather than Ir. These catalysts can then be used to cause dehydrogenation (JACS 1979, 101, 7738)

Using similar systems, other methods such as selective C-H borylation have been developed. Mechanistically, the Iridium precatalyst (diamine)Ir(cod)(Bpin)₃ loses a cod ligand, and then oxidative addition/coordination of the aryl hydride results in a 7-coordinate Ir catalyst. Reductive elimination of PhBpin followed by addition of B₂pin₂ makes the product and regenerates the catalyst (Science 1997, 297, 211 and 2000, 207, 1995). Ortho-directed alkylation systems based on carbonyl and imine chelation (Murai, Nature 1993, 366, 529 and JACS 1996, 118, 493) have also been reported.

13 Metathesis

Metathesis is a catalyzed cleavage and reassembly of alkenes, essentially shifting substituents between alkenes. It is almost always under thermodynamic control just due to its reversible nature.

It was first discovered when looking at Ziegler-Natta polymerization catalysts, where ring-opened products were found in the polymerization under strong Lewis acids. Though these Lewis-acid based systems are sometimes used in industry, they often have low functional group compatibility and control. As a result, more mild homogeneous catalysts based on Mo, W, Ta, Ti, or Ru have been developed.

The mechanism for metathesis starts from a metal alkylidene, which first loses ligand and creates a metal-carbon double bond via reaction with an olefin. It then reacts with another olefin to create a 4-membered metallocycle via a [2+2] addition. A retro [2+2] provides for the product and another metal alkylidene. This can react with another equivalent of the alkene then loses ethylene under another retro [2+2], thus, the loss of ethylene can drive the reactions forward. This is why the reactions are sometimes done in slight vacuum.

The metathesis relies heavily on metal alkylidenes, which were first synthesized by Schrock starting from Cp_2TaMe_3 , which was reacted with $\text{CPh}_3^+\text{BF}_4^-$ and base to produce $\text{Cp}_2\text{Ta}(=\text{CH}_2)\text{Me}$ (Schrock, JACS, 1975, 97, 6577).

These carbenes are electrophilic at the metal and nucleophilic at the carbon. As a result, they are highly reactive towards polarized π systems like carbonyls and can act as olefinating reagents, for example, in the Tebbe reagent and the Petathesis reagent that have $\text{Cp}_2\text{Ti}=\text{CH}_2$ as its active catalyst (Tebbe, JACS 1978, 100, 3611). These reagents are more nucleophilic and less basic than Wittig reagents, and hence provide a method for the reaction of less reactive functional groups.

Grubbs was able to show that the Tebbe reagent was able to act as a metathesis catalyst in the polymerization of norbornene, through a metallocyclobutane. (Grubbs, JACS, 1980, 102, 6876). From this, metathesis catalysts such as "Schrock's catalyst" (based on Mo) and "Grubbs' catalyst" (based on Ru) were developed.

In general, as we move further to the right of the periodic table and metals become less oxophilic, we get higher olefin/carbonyl selectivity. Thus, Ti/W catalysts are generally unusable, Mo catalysts are usable but react with air and water and have low functional group tolerance, and Ru catalysts work fine.

The active catalyst can be generated from the precatalyst through the disassociation of the phosphine ligand. In the second generation catalysts the carbenes slows both the disassociation, but

slows the association even more, thus shifting the equilibrium to the active form of the catalyst. The 3rd generation catalyst is also slow to initiate but more stable. There are also fast-activating catalysts, for example, by using pyridine as ligand in ROMP.

Since metathesis is often based on equilibrating mixtures, how do we predict which products get formed? Grubbs proposed a classification of olefins into four types:

- Type 1: rapid homodimerization, which can react further.
- Type 2: slow homodimerization, which cannot react further.
- Type 3: no homodimerization.
- Type 4: spectator olefin that does not deactivate the catalyst.

These classifications differ based on catalysts. Terminal olefins, and allyl silyl olefins are type 1, while allyl alcohols and styrenes are either type 1 or 2. 1,1-disubstituted olefins are often type 3 or 4, while vinyl nitro olefins are almost exclusively type 4. (JACS, 2003, 125, 11360)

Now based on these classifications, we have some rules for cross-metathesis:

1. Two type 1 olefins reacting will lead to statistical mixtures. To achieve selectivity, we need a large excess (about 10-fold) of one of the alkenes.
2. Reactions between two non-type 1 olefins will lead to non-selective outcomes (bad!)
3. Reactions between two different types of olefins are generally good. Even though they initially may be poorly selective, the homodimers could still react and form the desired product when ethylene is removed from the system.

We can use metathesis catalysts to affect ring-opening, as well as enantioselectivity (resulting from ring-closing). In general, medium sized rings (5, 6, 7) are the most reactive, while macrocyclizations can be more challenging, but still possible.

A technique known as *Relay ring-closing metathesis* is also possible for hard macrocyclizations. Essentially, you append on a $(\text{CH}_2)_3-\text{CH}=\text{CH}_2$ unit to the terminal olefin, which the ruthenium reacts with. Loss of cyclopentadiene then makes the ruthenium bind to the original olefin, improving reactivity. (Porco, ACIE, 2004, 43, 3601).

A modification is in ene-yne metathesis, in where we essentially have metathesis with an alkene and an alkyne. The ruthenium catalyst can react with either component and join them together, leading to the same product.

14 Carbenoids

Note: This is the final lecture of the class.

Carbenes are classified into two types based on electronic structure - **Fischer carbenes** and **Schrock carbenes**. Fischer carbenes often are nucleophilic at the metal and electrophilic at the carbon, and have EDG substituents on the carbene and π -acceptor ligands on the metal. Additionally they often have low oxidation state metals. In essence, Fischer carbenes are carbenes that favor a negatively-charged metal.

Schrock carbenes are the opposite - they are nucleophilic at carbon instead and often have H and R groups on the carbene. They have π -donor ligands instead and are often in a high oxidation state.

We actually have a third type of carbenes, known as **carbenoids**. These carbenoids have an EWG acceptor such as a carbonyl, and have never been isolated. Their reactivity instead resembles that of singlet carbenes. This is because the carbene essentially interacts only through a weak π -backbonding interaction and a strong σ donor interaction. Since the backbonding interaction is weak, the carbene is still quite electrophilic.

The discovery of these carbenes was accidental - when a Wolff rearrangement was attempted to be performed on an α -diazoketone with a copper catalyst and ethanol, the copper instead was able to make a carbene and insert itself into ethanol, making unexpected products. (JACS 1952, 74, 5376).

In general, copper and rhodium are used for the generation of carbenes. Cu(I) is often used for the addition of carbenes to π -bonds, and can do this enantioselectively. We have a few types of precursors such as α -diazoketones (acceptor), α -diazo-1,3-diketones (acceptor/acceptor), and α -diazoarylketones (acceptor/donor).

The mechanism starts with Cu coordinating to one of the olefins, then to the diazo reactant (through the nitrogen). Loss of N_2 then generates the Cu carbenoid, which then can react to form a cyclopropane. Coordination of another alkene then regenerates the catalyst.

Rh(II) dimers are instead more effective in C-H insertion reactions, in addition to cyclopropanation. The carbene interacts with the σ^* orbital of the rhodium dimer and the rhodium interacts with the π^* orbital of the carbene. Though the basic C-H insertion (for example, with decomposition of a diazoketone with Ag_2O) is feasible without catalyst, using rhodium improves the selectivity much more. Rhodium often forms 5-membered rings, with the more electronically activated position reacting with the carbenoid species. The C-H insertion is stereoretentive (JACS, 1985, 107, 196).

Two mechanisms have been proposed. The first involves coordination of the rhodium to the carbon bonded to the diazo group, which then has a rate-determining loss of N_2 to form the carbenoid. Now, the path to form the product can proceed through a 3-center-2-electron pathway, or instead by breaking the Rh-Rh bond (forming a Rh(III)/Rh(I) pair) and causing subsequent oxidative addition and reductive elimination to form the product. The first mechanism is generally favored.

These carbenoids can take on a few forms, based on many heterocycles such as proline-derived and phthalimido-derived substituents replacing the acetates from $Rh_2(OAc)_4$. These catalysts can improve selectivity and induce enantioselectivity.

Intermolecular carbenoid C-H insertion is much harder, but possible. There may be issues with chemoselectivity, functional group tolerance, or carbene dimerization. These carbenoids are often donor/acceptor carbenes, and can insert into substrates such as Boc-piperidine or cyclohexane. These insertions can create structures that resemble products from Aldol addition, Michael addition, or Mannich reactions, just to give a few examples. O-H and N-H bond intermolecular insertions are often possible, with Fu ligands.

Rh dimers have also been seen to induce nitrene insertions, for example. We can use carbamates to insert and form 5-membered rings, while using sulfamides favors forming 6-membered rings. This allows for syn-selective 1,2 and 1,3 amination from the alcohol (JACS, 2001, 123, 6955). Using $Rh_2(esp)_2$ catalysts on, 1,3 diamidosulfamates can also be formed. This catalyst can also promote intermolecular stereoretentive insertion. Other catalyst systems can also be used to induce enantiospecificity.