Organometallic Chemistry of the Transition Metals: Mechanisms and Applications to Catalysis

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Updated fall 2019

These notes have been prepared by Dr. Kevin Shaughnessy, Professor of Chemistry & Biochemistry at The University of Alabama for use in CH 409/609, Organometallic Chemistry. These notes are designed to be stand alone, but can be supplemented with any organometallic textbook, such as those by Hartwig, Crabtree, or Spessard. These materials may be freely used without permission provided that credit to the author is given and they are not altered or incorporated into other materials without permission from the author.

Updated versions of these notes can be found at: http://kshaughnessy.people.ua.edu/resources.html

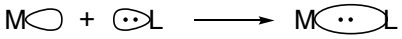
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1. Structure and Bonding

Basic Picture of Metal-Ligand Bonds

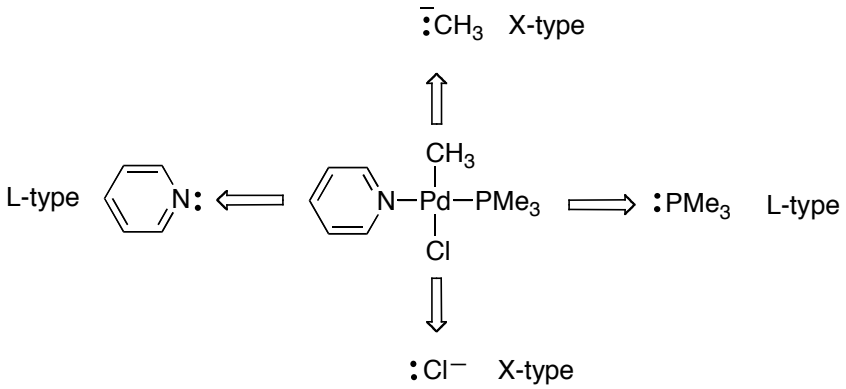
As we'll discuss, there are a wide variety of metal-ligand bonding interactions. They can nearly all be described as a Lewis acid-Lewis base interaction, however. The ligand will generally act as an electron pair donor (Lewis base) with the metal acting as an electron pair acceptor (Lewis acid). The resulting bond will have significant covalent character, but is unique from the covalent bonds described for main group elements like carbon. When we think about bond dissociation of a C-H bond, for example, we mean hemolysis to a carbon and hydrogen radical. When discussing metal-ligand bond energies, we are referring to cleavage in which the ligand retains the electron pair.



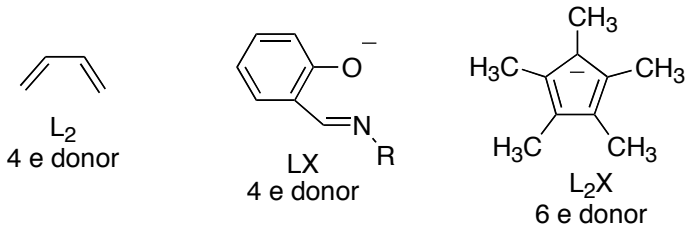
Types of Ligand Coordination

Three generic classes of ligands:
L: a neutral electron pair donor (i.e., CO, PR_3)
X: an anionic electron pair donor (i.e., X^-, H^-)
Z: electron pair acceptor (Lewis acid)
M-M: neutral 1 electron donor

Distinguishing L-type ligands from X-type ligands: To distinguish between X and L type ligands, consider removing ligand from metal center with the ligand taking the electron pair in the M-L bond. If the ligand in it's free state is neutral, it is an L-type ligand. If it would be anionic, it is X-type.

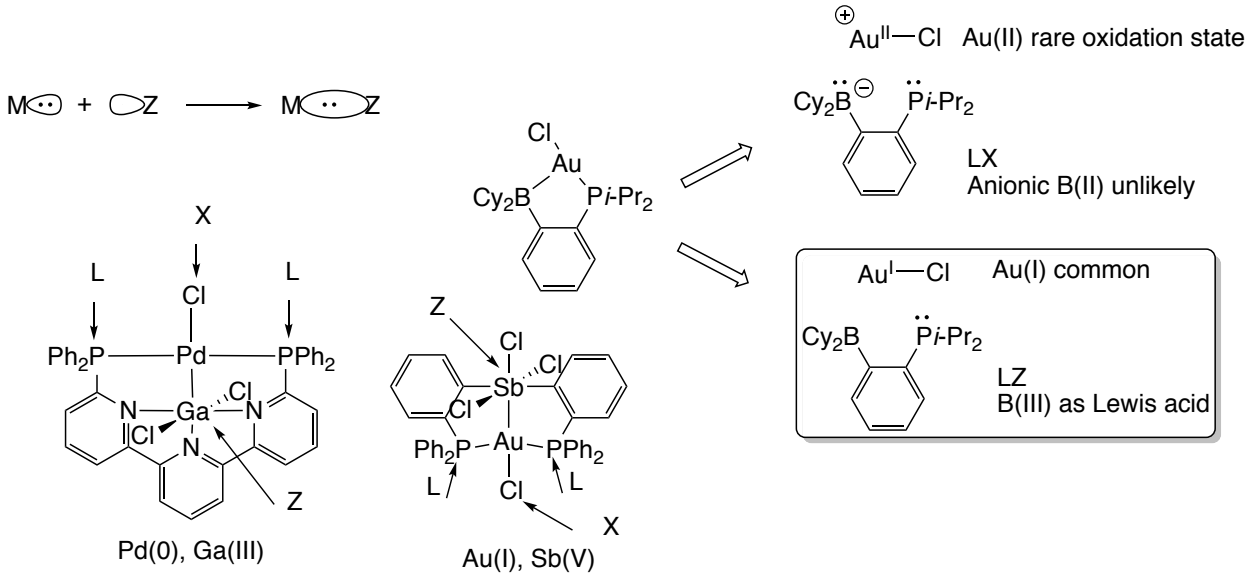


Ligands that can donate more than one pair of electrons can be classified using L and X designations:



Z-type ligands are less common, but have attracted increasing attention. In the case of a Z-type ligand, the metal is the electron pair donor and the ligand is an electron acceptor. These can be more difficult to recognize. Typical Z-type coordinating atoms will be typical Lewis acidic elements (B, Al, Ga, In, Si, Sn,

Sb, etc) where location of a lone pair on the coordinating atom does not make sense. Z-type ligands are generally weakly coordinating, so the known examples are part of chelating ligand systems. The metals are typically low valent, late transition metals (Pd(0), Pt(0), Au(I)).

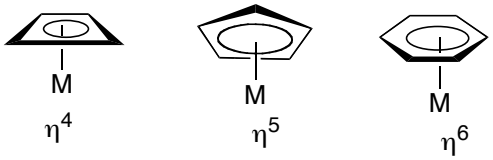


Types of ligand coordination:

Terminal: Ligand is bound to only one metal center (L-M or X-M)

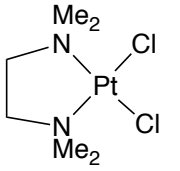
Bridging (μ): Ligand is attached to two different metal centers (M-L-M' or M-X-M'). For L-type ligands, the lone pair is usually shared between the two metals (count 1 electron for each metal). For X ligands, the lone pair can also be shared. If the X ligand has additional lone pairs (i.e., halide, alkoxide), then the additional lone pairs can be used to coordinate to the second metal center.

Hapticity (η): Ligand attached to a metal center through more than one atom without non-coordinating atoms in between. Most commonly seen with conjugated π-systems

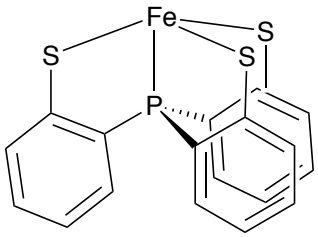


Hapticity for ligands such as Cp can be variable depending on how it is coordinated. Usually Cp is a η^5-L_2X ligand, but it can also coordinate as an η^3-LX, or even an η^1-X. The process of going from η^5 to η^3 is called *ring slippage.*

Chelation: Ligand attached through more than one atom usually separated by one or more atoms. Chelating ligands are sometimes classified as being bidentate (2 points of attachment), tridentate (three points of attachment), or tetradentate (4 points of attachment).

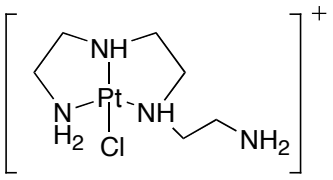


κ^2*N,N*-coordination
bidentate ligand



κ^4*P,S,S,S*-coordination
tetradentate ligand

Kappa convention (κ): The kappa convention is sometimes used to indicate the coordinating atoms of a polydentate ligand. If only some of the possible coordination sites are bonded to the metal, the coordinating atoms are indicated with a kappa. Some authors use kappa to indicate how many of the coordinating atoms are attached in a polydentate ligand.



κ^3-[*N,N'*-di(2-aminoethyl)ethane 1,2-diamine]chloroplatinum ion
or
[*N*-(2-amino-κ*N*-ethyl)-*N'*-(2-aminoethyl)ethane 1,2-diamine-κ^2*N,N'*]chloroplatinum ion

The 18-Electron Rule

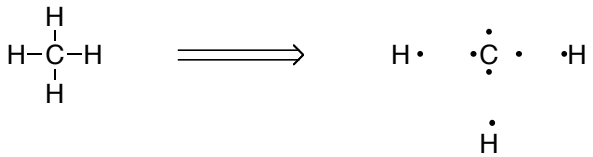
Recall: Second row elements (B, C, N, O, F) have 4 valence orbitals (1 *s* + 3 *p*) so they can accommodate up to 8 valence electrons--*the octet rule*.

Transition metals have 9 valence orbitals (1 *s* + 3 *p* + 5 *d*). Upon bonding to a ligand set, there will be a total of 9 low lying orbitals (see MO theory discussion below). Therefore, we can expect that the low lying MOs can accommodate up to 18 valence electrons--*The 18-Electron Rule*. Organometallic complexes with 18 electrons are predicted to be particularly stable because they will have a closed shell of electrons. Complexes with 18 electrons are often referred to as being *coordinatively saturated*.

Counting electrons: There are two models for counting electrons. Both give the same answer, but offer different advantages and disadvantages.

Example: CH_4

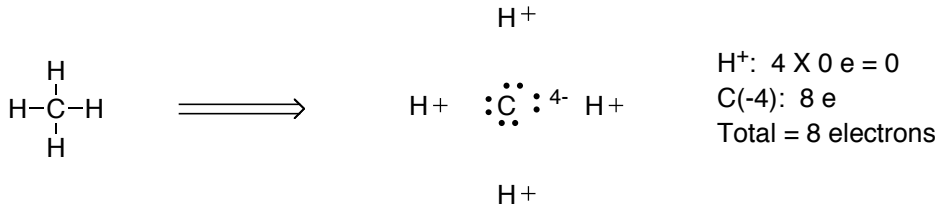
Covalent model: Since C-H bonds are covalent, assume that the electrons are shared equally between carbon and hydrogen. To count the electrons, we dissect the molecule giving each atom 1 electron of the bonding pair.



H: 4 X 1 e = 4
C: 4e
Total = 8 electrons

Ionic model: Alternatively, we can treat the bonds as being ionic. This allows us to assign a formal oxidation state to the carbon atom. This can be useful to determine whether a particular transformation is an oxidation or a reduction. In this model, both electrons are given to the atom with the higher electronegativity. For a C-H bond, this is the carbon.

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Similarly for a transition metal complex, the electron count is the sum of the metal valence electrons + the ligand centered electrons.

Covalent Model: # e = # metal electrons (zero valent) + # ligand electrons - complex charge

Metal: The number of metal electrons equals its column number (i.e., Ti = 4e, Cr = 6 e, Ni = 10 e)
Ligands: In general L donates 2 electrons, X donates 1 electron. See the table below.

Ionic Model: # e = # metal electrons (d^n) + # ligand electrons

Metal: Determined based on the number of valence electrons for a metal at the oxidation state present in the complex
Ligands: In general and L and X are both 2 e donors. See the table below.

In my opinion, the ionic model is easier and gives a clearer picture of the actual chemistry, since the formal oxidation state is part of the calculation. All discussions in this class will use the ionic model, so I would encourage you to learn that one. You should also be aware of the covalent method, since you will encounter it from time to time.

Metal oxidation states: The oxidation state of a metal can be simply determined by adding up the total charge for the free ligands (each X ligand is -1). If the complex is neutral, the metal must have a positive charge to match the total negative charge of the ligands. If the complex has an overall charge, this must be considered.

$Ti(CH_3)_4$: The methyl groups have -1 charges, so the total ligand charge is -4. Therefore the titanium center must match that and be +4.
$[Pd(NH_3)Cl_3]^-$: There is a total -3 charge on the ligands ($3XCl^-$), but the complex has an overall negative charge. Therefore, the metal is Pd(+2).

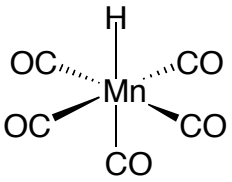
d electron count: Chemists often refer the d-electron count of a metal. This indicates the number of valence electrons. For an isolated, zero-valent transition metal the s orbitals of the next row are lower in energy than the d orbitals. Thus, the configuration of Ni(0) could be written as $[Ar]4s^23e^8$. In reality, the 4s and 3d (or 5s/4d or 6s/5d) orbitals are very close in energy. When a metal interacts with other ligands, the d orbitals are almost always lower in energy than the s orbitals of the next row, which is a M-L σ* orbital. Thus, for our purposes the d electron count for a zero-valent metal will always just be its column number. For a metal ion, it will be the column number minus the formal oxidation state. Thus Ni(0) would be d^{10} and Ni(II) would be d^8.

Examples:

$HMn(CO)_5$

Covalent Model

•H = 1 e
5 X CO = 10 e
Mn = 7 e
Total = 18 e



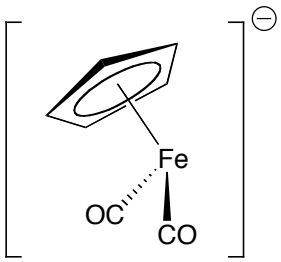
Ionic Model

H^- = 2 e
5 X CO = 10 e
Mn(I) d^6 = 6 e
Total = 18 e

$[CpFe(CO)]^-$

Covalent Model

Cp• =
2 X CO =
Fe =
Charge (-1) =
Total =



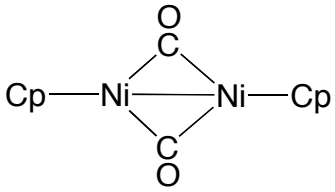
Ionic Model

Cp^- =
2 X CO =
Fe(0) d^8 =
Total =

$[CpNi(\mu\text{-}CO)]_2$

Covalent Model

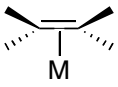
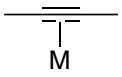
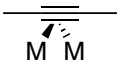
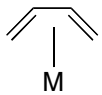
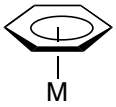
Cp• =
2 X 1/2 CO =
Ni-Ni =
Ni =
Total =



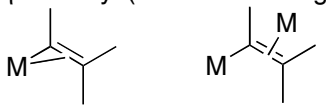
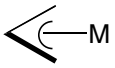
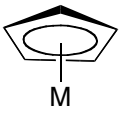
Ionic Model

Cp^- =
2 X 1/2 CO =
Ni-Ni =
Ni(I) d^9 =
Total =

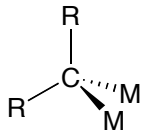
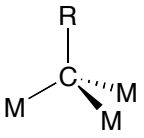
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Ligand Name	**Covalent Model**	**Ionic Model**	
	Electron Count	Charge	Electron Count
Nitrosyl (linear, NO^+), terminal or bridging)	3	+1	2
Carbene (CYR, where Y = substituent with π interaction with carbene, i.e., OR, NR_2, Ph, X 	2	0	2
CO, CNR (bridging or terminal)	2	0	2
PR_3, AsR_3, SbR_3, NR_3, imines, nitriles, ethers, sulfides, etc.	2	0	2
Terminal dinitrogren (N_2)	2	0	2
$\eta^2(\pi)$-Alkene 	2	0	2
$\eta^2(\pi)$-Alkyne 	2	0	2
$\eta^2(\pi)$-Carbonyl 	2	0	2
$\eta^2(\sigma)$-Dihydrogen 	2	0	2
μ-η^2-Alkyne 	4	0	4
η^4-acyclic diene 	4	0	4
η^6-Arene 	6	0	6
Hydride (H^-)	1	-1	2

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Terminal or bridging Alkyl ($^-CR_3$)	1	-1	2
η^1-Acyl 	1	-1	2
η^1-Aryl, alkenyl, or alkynyl	1	-1	2
ER_3 or EX_3 (E = Si, Ge, Sn)	1	-1	2
Alkoxide (^-OR), thiolate (^-SR), amide ($^-NR_2$), or phosphide ($^-PR_2$)	1	-1	2
Superoxide 	1	-1	2
Halide (F^-, Cl^-, Br^-, I^-) or pseudohalide (^-CN, ^-OTs, etc)	1	-1	2
Bridging alkoxide, thiolate, amide, or phosphide	3	-1	4
Bridging Halide (μ-X) M-X-M	3	-1	4
η^2-Acyl 	3	-1	4
η^2-Alkenyl (terminal or bridging)  Terminal Bridging	3	-1	4
η^3-Allyl 	3	-1	4
η^5-Cyclopentadienyl (Cp^-) 	5	-1	6
Carbene (CR_2 where R = substituent with no π interactions with the carbene carbon) 	2	-2	4

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μ-CYR or CR_2 	2	-2	4
Imide (M=NR)	2	-2	4
Oxide (M=O)	2	-2	4
Peroxide (terminal or bridging) 	2	-2	4
Alkylidine or carbyne, terminal M≡C−R	3	-3	6
μ-Alkylidine 	3	-3	6
Nitride M≡N	3	-3	6

Application of the 18-electron rule:

The 18-electron rule can be used as predictor for the number of ligands a particular metal will coordinate.

$V(CO)_6$	$Cr(CO)_6$	$(CO)_5Mn\text{-}Mn(CO_5$	$Fe(CO)_5$	$(CO)_3Co(\mu\text{-}CO)_2Co(CO)_3$	$Ni(CO)_4$
d^5	d^6	d^7	d^8	d^9	d^{10}
17 e	18 e	18 e	18 e	18 e	18 e

The 18 electron rule works best for low-valent metals with small ligands that are strong σ donors and/or π acceptors (i.e., H^- and CO). The types of ligands are strongly coordinating and are small enough to allow the metal to be coordinatively saturated.

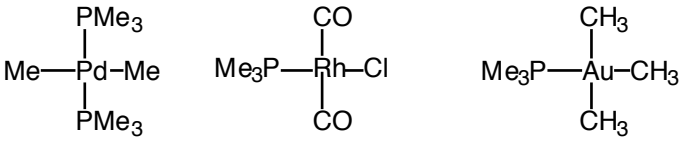
For complexes that follow the 18 electron rule, it can be used to predict reactivity as we will see throughout the semester.

Note, that just like the octet rule, the 18-electron rule is not an absolute requirement. There are many exceptions, particularly for metals that have fewer than 18 electrons. Exceeding the 18 electron rule is rare and often involves changes that bring the electron count to 18 or below.

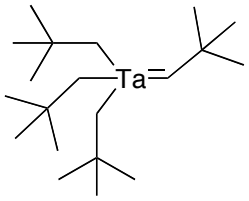
Common exceptions to the 18 electron rule:

> <u>d^8 metals:</u> The d^8 metals (groups 8 - 11) have a tendency to form square-planar 16 electron complexes. This tendency is weakest for group 8 (Fe(0), Ru(0), and Os(0)) and is very strong for groups 10 and 11 (Pd(II), Au(III)). Square planar, 16 electron complexes of d^8 metals have 4 low lying d orbitals that can be filled by the 8 d-electrons.

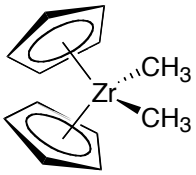
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d^0 metals: The high-valent *d*^{0} complexes often have lower electron counts than 18. It is difficult for these metals to coordinate enough ligands to get to 18 electrons. An exception is $[ReH_9]^{2-}$.

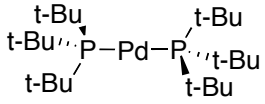


3 X Np^- = 6
carbene = 4
Ta(V) *d*^{0} = 0
Total = 10 e

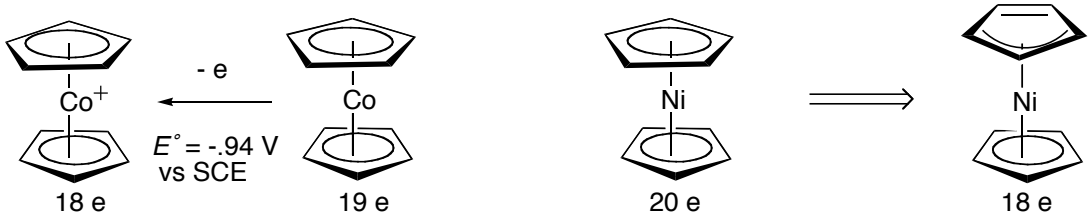


2 X Cp^- = 12 e
2 X CH_3^- = 4 e
Zr(IV) *d*^{4} = 0 e
Total = 16 e

Bulky Ligands: Sterically demanding ligands will often result in lower than expected electron counts.



> 18 electron complexes: Complexes with formally 19 or 20 electrons are known, but they are usually unstable, or adopt alternate configurations.



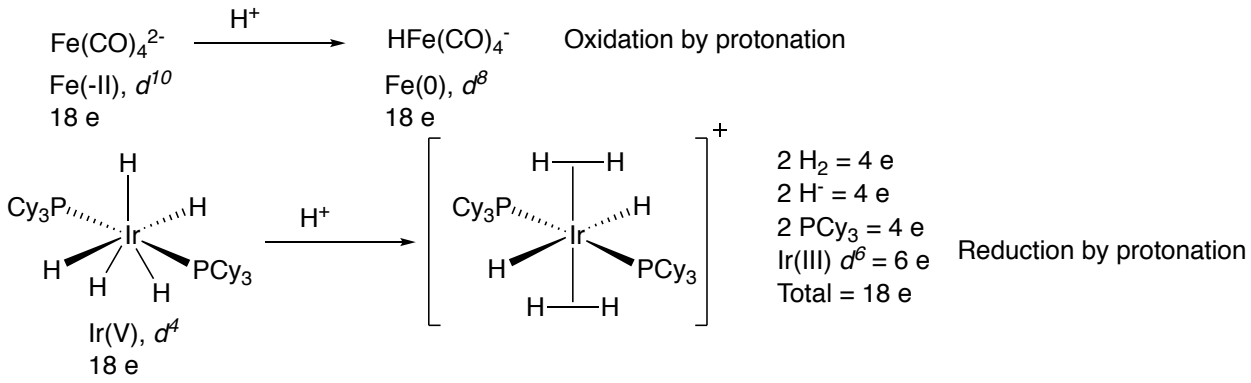
Formal Oxidation State and *d* electron configuration

Oxidation states in organometallic complexes are merely formalisms that may bear little resemblance to the actual positive charge on the metal.

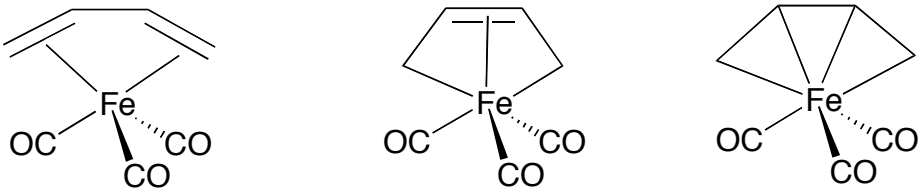
> *"Formalisms are convenient fictions which contain a piece of the truth--and it is so sad that people spend a lot of time arguing about the deductions they draw, often ingeniously and artfully, from formalisms, without worrying about their underlying assumptions."*
> (Roald Hoffman, *JACS*, **1984**, *106*, 2006)

Consider the range of possible formal charges on metal centers:
$[Fe(CO)_4]^{2-}$ (Collman's reagent): Fe(-II), although the metal likely has little if any negative charge
$[ReH_9]^{2-}$: Re(VII), although it is made by reduction of ReO_4^- (also Re(VII)) with sodium in ethanol

Therefore, formal oxidations and reductions do not necessarily result in a decrease or increase in electron density at the metal center. Conversely, reactions where the oxidation state does not change can greatly affect the electron density of the metal center.



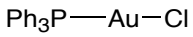
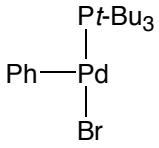
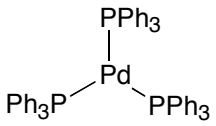
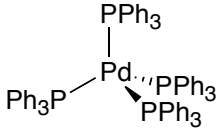
For π-coordinated ligands (i.e., alkenes, dienes, etc.) a number of different formal oxidation states can be determined. In the butadiene complex below, the ligand can either be considered an L_2 ligand donating 4 electrons, an LX_2 donating 6 electrons, or an X_4 ligand donating 8 electrons. Therefore, the iron center can be Fe(0), Fe(II), or Fe(IV). In each case the complex has 18 electrons. These forms can be considered a type of resonance. All that is changing is where the electrons are formally being assigned.



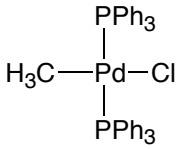
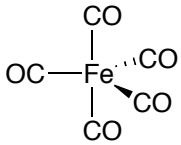
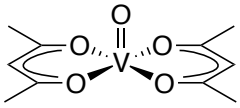
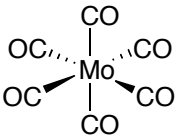
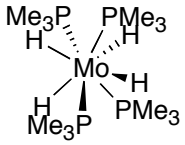
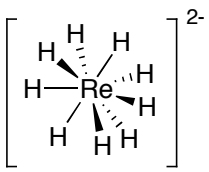
Fe(0), d^8 Fe(II), d^6 Fe(IV), d^4

Coordination geometry:

Metal coordination geometries can often be predicted based on the number of ligands and VSEPR theory. Metals with d electron counts resulting in unfilled, half-filled, or fully filled d orbitals will always follow the VSEPR rules. Metals with d^8 electron counts tend to favor lower symmetry structures as we'll discuss later.

Coordination Number	**Geometry**	**Preferred d^n**	**Example**
2	Linear		
3	T-Shaped	d^8	
3	Trigonal	d^0, d^5, d^{10}	
4	Tetrahedral	d^0, d^5, d^{10}	

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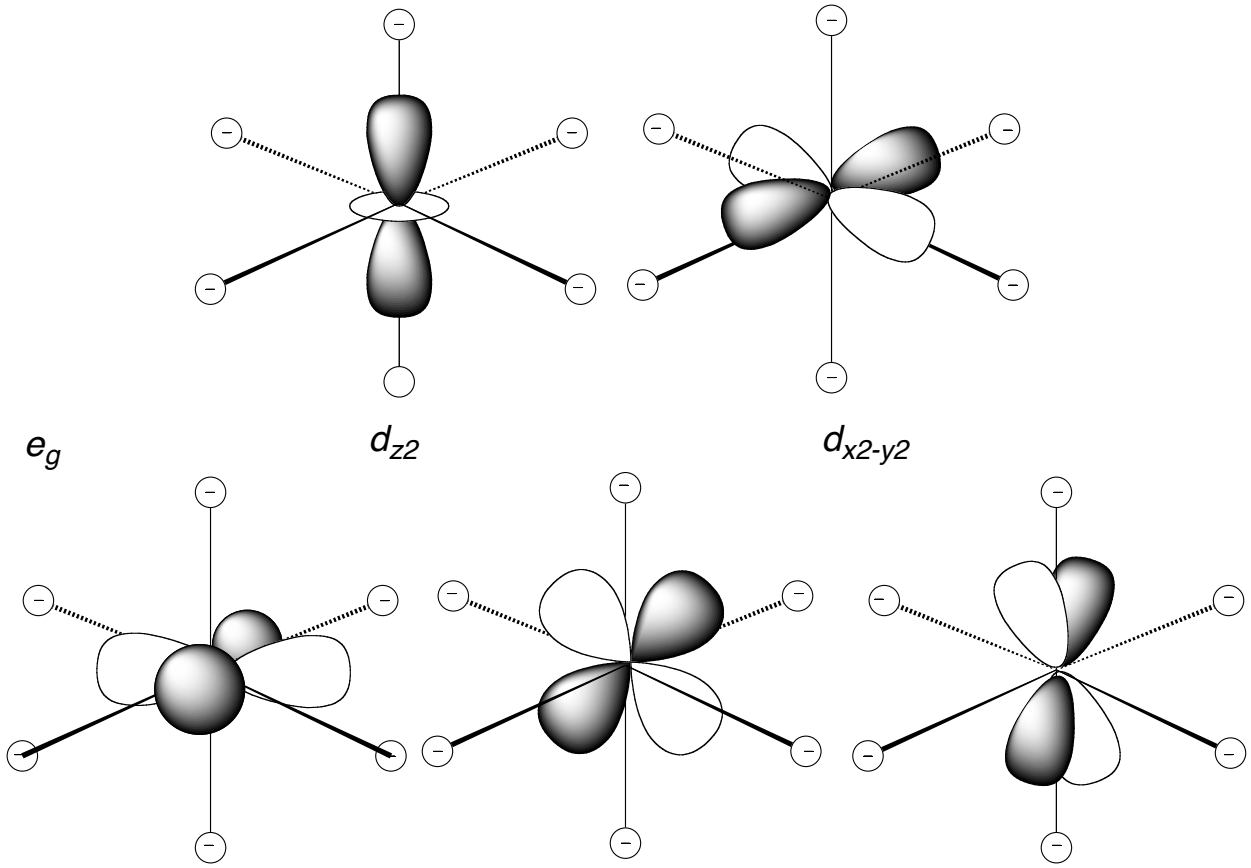
4	Square Planar	d^8	
5	Trigonal Bipyramidyl	d^8, d^6 (distorted)	
5	Square Pyramidal		
6	Octahedral	d^0, d^3, d^5, d^6	
8	Dodecahedral	d^1	
9	Tricapped Trigonal Prism	d^0	

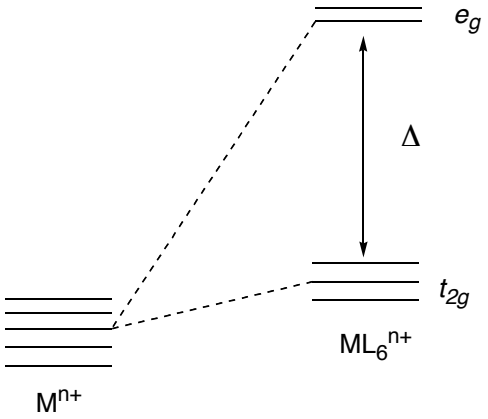
To explain the bonding of ligands to metals, we have to consider the molecular orbitals involved metal-ligand bonding. Before the development of molecular orbital theory, the interaction of ligands with metals was described using crystal field theory. We'll discuss this briefly and then consider the true orbital interactions.

Crystal Field Theory

Assumption: Ligands act as points of negative charge surrounding the metal center

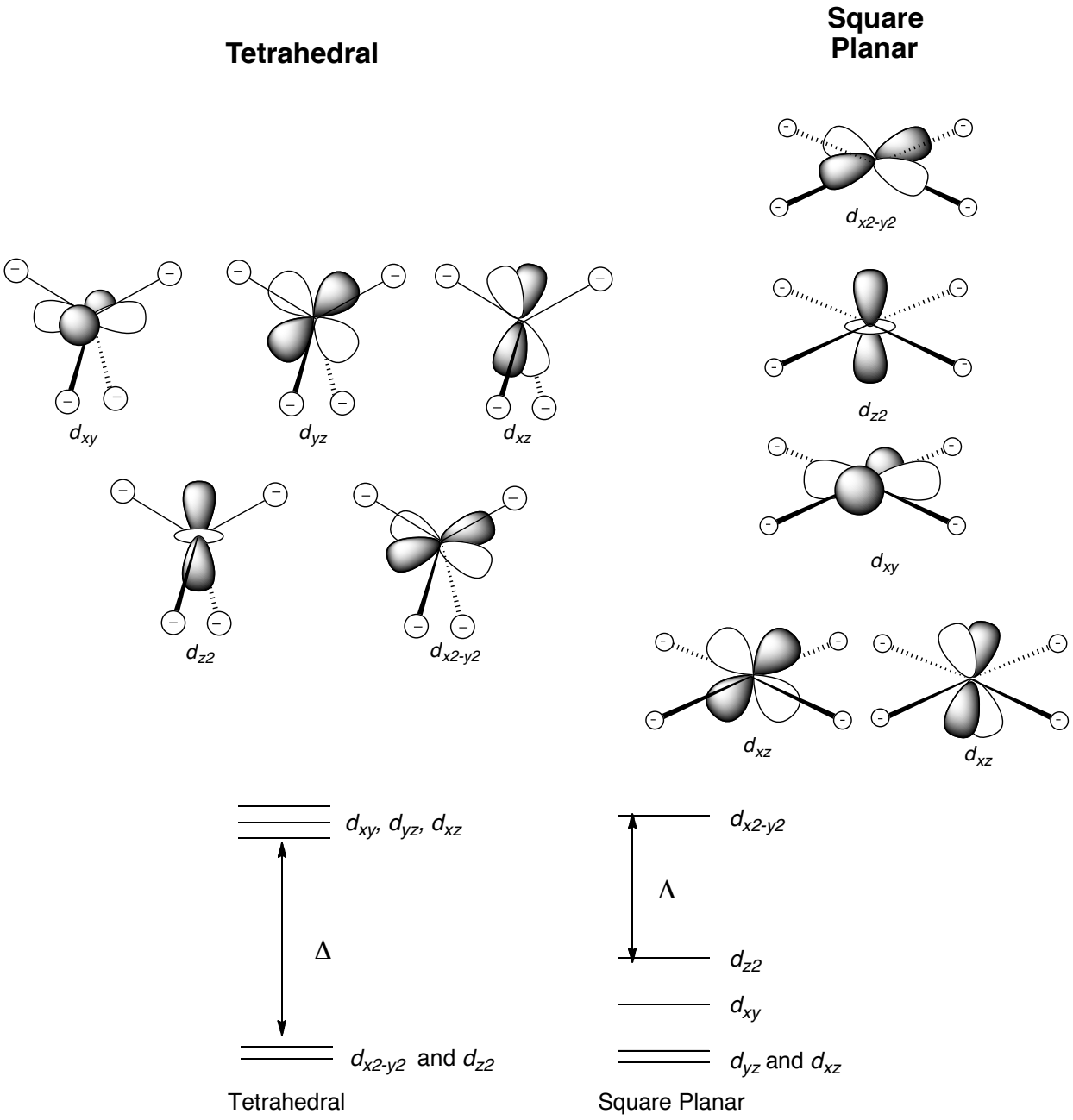
For an isolated metal ion, the 5 *d* orbitals are degenerate. As an octahedral set of ligands approach, the *d* orbitals pointing along the *x*, *y*, and *z* axes (d_{z^2}, $d_{x^2-y^2}$) are destabilized. The other orbitals (d_{xy}, d_{yz}, and d_{xz}) are less destabilized.





e_g orbitals (d_σ) can form σ bonds with the ligands
t_{2g} orbitals (d_π) can form π bonds with the ligands

Crystal field splitting of other common geometries:



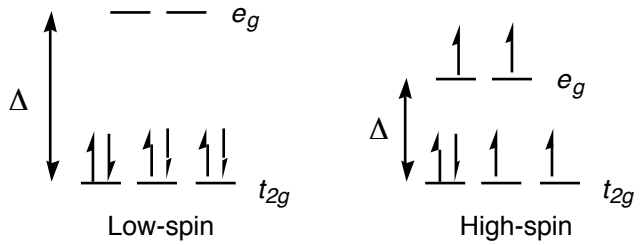
High spin and Low spin complexes

Co(III) has the electron configuration [Ar]4$s^2$3d^4 as a free atom. Upon coordination, the 3*d* orbitals are stabilized relative to the 4*s* and the metal takes on a [Ar]3$d^6$4s^0 electronic configuration. This configuration is usually shortened to d^6.

A d^6 electronic configuration would be expected to strongly favor an octahedral ligand arrangement, since this would result in the a completely filled set of the low-lying d_π (t_{2g}) orbitals. This electronic configuration is called the *low-spin* form, since all electron spins are paired.

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If Δ is small enough, though, a *high-spin* form with a $t_{2g}^4 e_g^2$ configuration is possible. In this configuration there are 4 unpaired electrons.

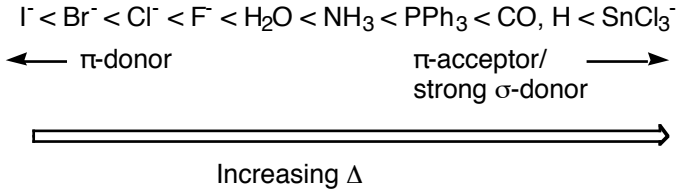


The size of the ligand field splitting (Δ) is dependent on the ligands as well as the metal center.

– 2nd and 3rd row transition metals tend to have higher Δ

– Higher oxidation state metals have higher Δ

– π-acceptor and strong σ-donor ligands give high Δ, while π-donor ligands give low Δ

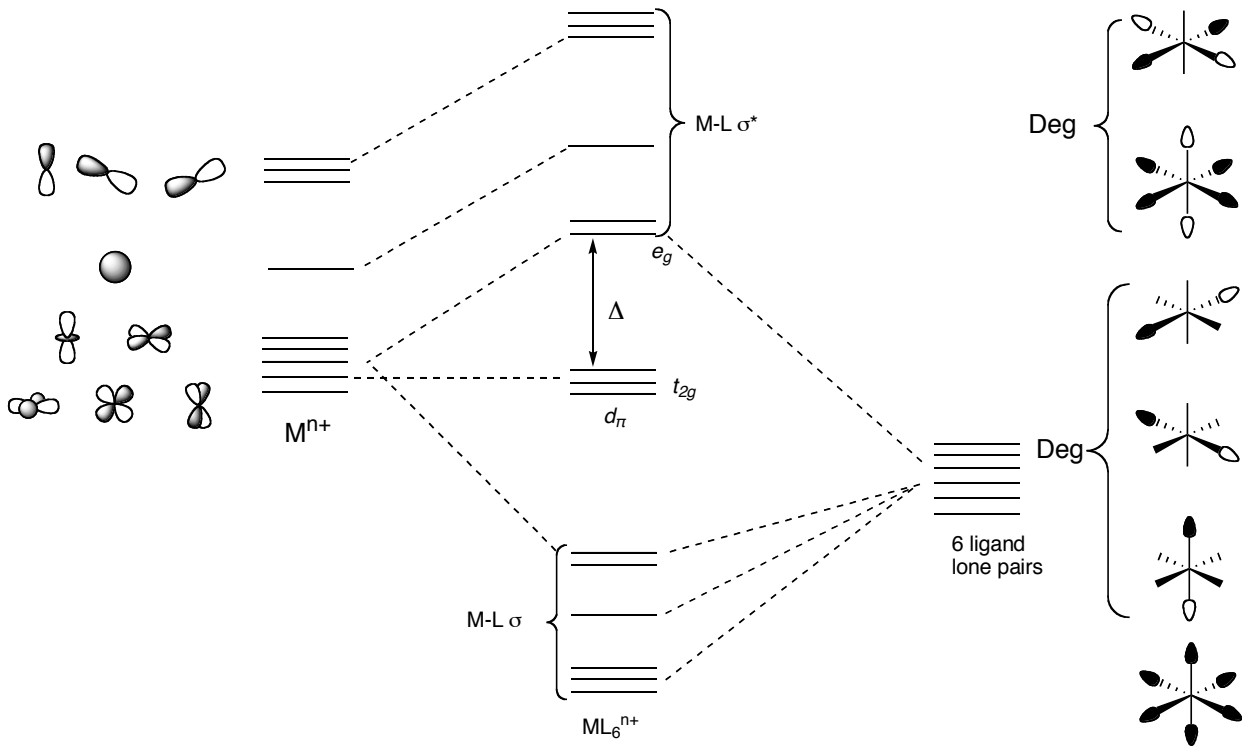


Ligand Field Theory

Crystal Field Theory is qualitative. To get a better understanding we can turn to a MO picture of bonding in coordination complexes.

For an octahedral complex of pure σ donor ligands, the *s*, three *p*, and five *d* orbitals of the metal interact with the lone pair orbitals of the ligand.
– 6 of the metal orbitals (*s*, three *p*, and 2 d_σ) are of the appropriate symmetry to interact with the ligand orbital set.
– Therefore, a set of 6 bonding M-L σ MO's and 6 anti-bonding M-L σ * MO's are formed. The three d_π do not find a symmetry match and remain as non-bonding orbitals.
– As a result, an octahedral complex can accommodate 18 electrons in the bonding and non-bonding orbitals. We will see that this maximum is similar to the octet rule in the first row elements.

An octahedral d^6 metal complex will have 18 valence electrons. The 6 ligands will each contribute 2 electrons (12 total) and the metal will contribute 6. These 18 electrons will fill all of the bonding orbitals (6 bonds) plus the three non-bonding d_π orbitals (assuming a low spin complex). Note that in a high-spin complex the filled e_{2g} orbitals are actually M-L antibonding orbitals.



Types of Ligands

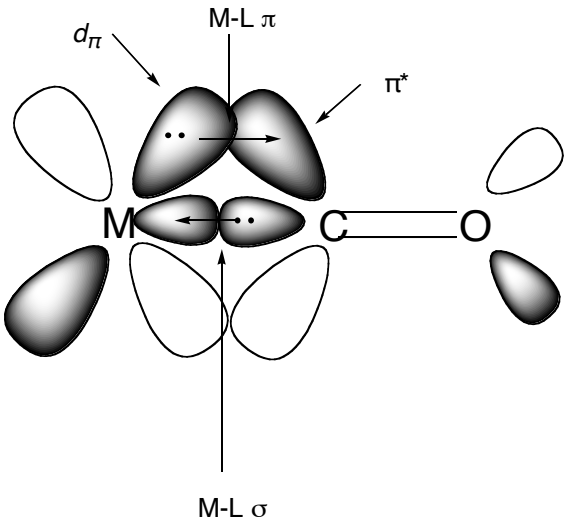
σ-donors: Typical M-L bonding arrangement. Lone pair orbital of ligand interacts with metal orbitals.

σ-acceptors: M-Z bonding arrangement with the metal as electron pair donor to an empty ligand orbital.

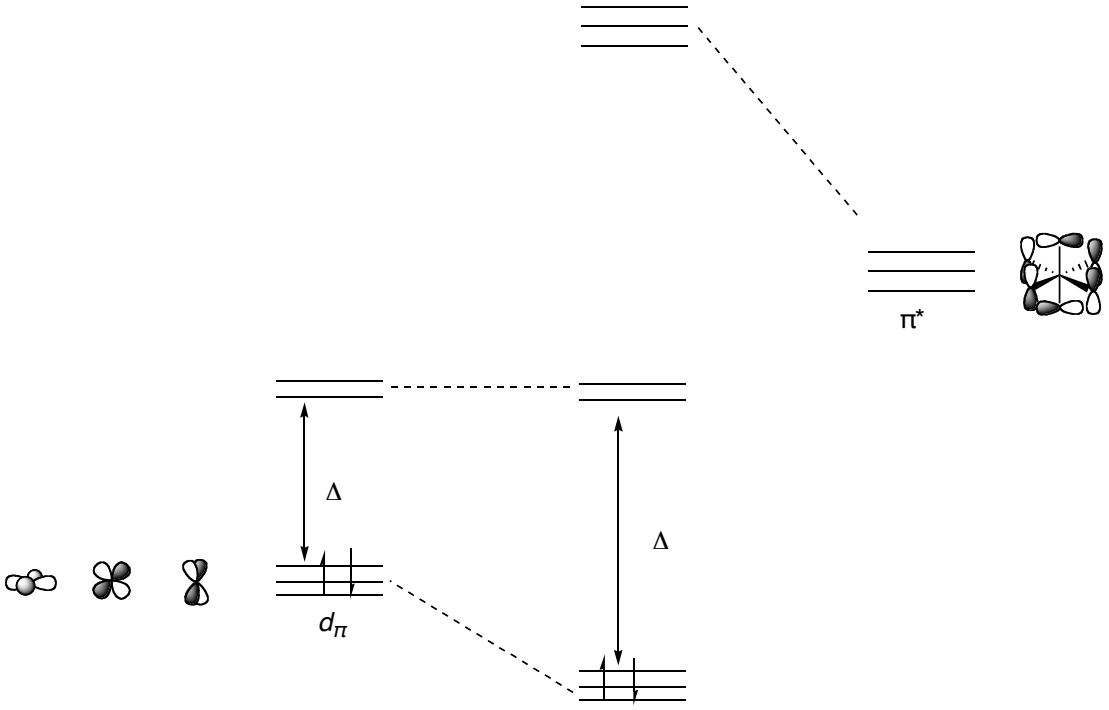
π-acceptors:

Ligands such as CO have empty MO's of proper symmetry to overlap with the filled d_π orbitals of the metal center. CO is an example of a *π-acceptor ligand* (often called a π-acid). In the case of CO, the π* MO of CO is the orbital that interacts with the metal d_π.

In the MO description above, the CO π* orbitals will interact with the Md_π orbitals. This interaction stabilizes the filled Md_π orbitals. As a result of this bonding interaction, the metal is donating electron density back to the ligands in a process called *back bonding*.
– π acceptors form very strong M-L bonds due to this back bonding
– π-acceptors increase the ligand splitting by stabilizing the t_{2g} set of orbitals increasing Δ
- back bonding allows electron density to be donated back to the ligand. This allows low-valent metals with filled *d* orbitals to form complexes with ligands



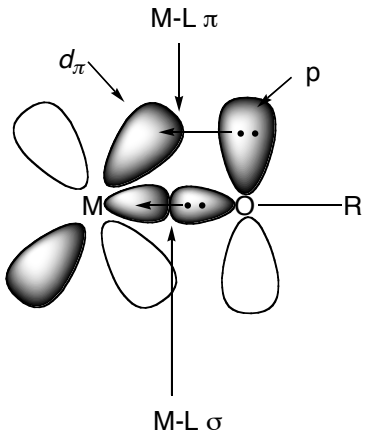
Other π-acceptor ligands: NO, N_2, CN-R, PF_3



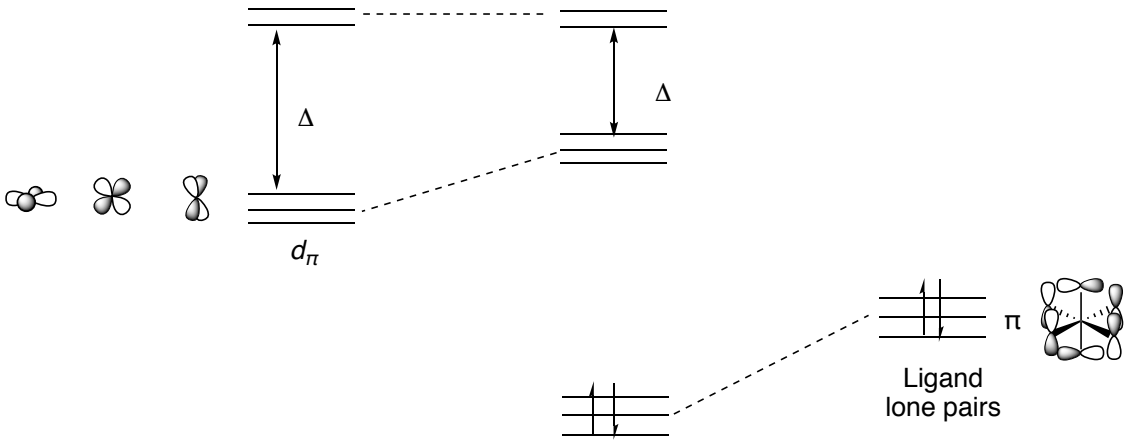
<u>π-donors:</u>

Ligands with lone pairs on the coordinating atom (i.e., ^-OR, ^-X, $^-NR_2$) can act as π-donor ligands. The atom can rehybridize to place the lone pairs in orbitals with π symmetry that can overlap with the metal d_π orbitals.

As a result, the number of electrons that can be donated by these ligands will depend on how electron deficient the metal is. For example, oxygen could donate 2, 4, or 6 electrons. This concept will be further developed in the next chapter of notes.



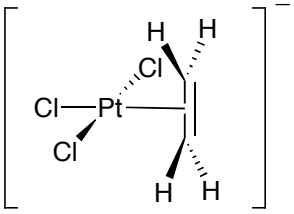
For a metal with filled d_π orbitals, π-donation will result in a destabilization of these orbitals due to repulsion between the lone pair electrons and the d_π electrons. This results in a smaller Δ and a weaker M-L bond.



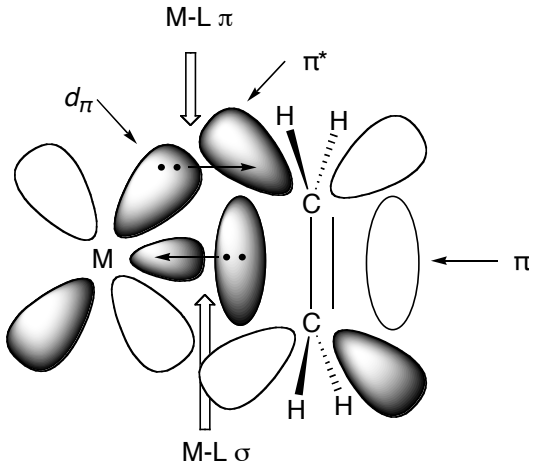
For d^0 metals, such as W^{6+}, π-donation is a favorable interaction and leads to stronger M-L bonds.

π-complexes:

Unsaturated molecules can donate π electrons to form M-L bonds rather than non-bonding lone pairs. Ethylene is a classic example.



Zeise's Salt--1825
Organometallics, **2001**, *20*, 2-6

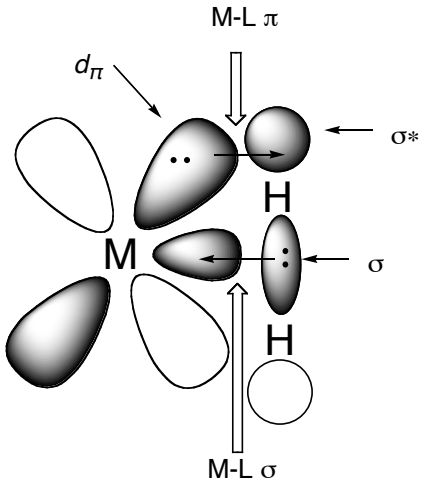


The π orbital of ethylene acts as a σ donor. The π* orbital of ethylene is of the proper symmetry to act as a π-acceptor (back bonding). As a result, the bonding picture is very similar to that of CO. The π-accepting alkene will lower the energy of the d_π orbitals, resulting in a larger Δ splitting. As a result, the complexes will typically be low spin.

Any compound with a π bond can potentially form a π complex with a metal center (alkynes, arenes, ketones, etc.)

σ-complexes:

Dihydrogen can bind to metal centers as an intact molecule. H_2 has neither lone pairs nor π electrons. The electron pair that interacts with the metal center is the σ-bonding electrons of the H-H bond. The σ*-orbital can act as a π-acceptor allowing back bonding to occur in the same way as for π-complexes or CO.



Other σ-complexes that have been identified include: C-H, Si-H, Sn-H, P-H, S-H, B-H, M-H

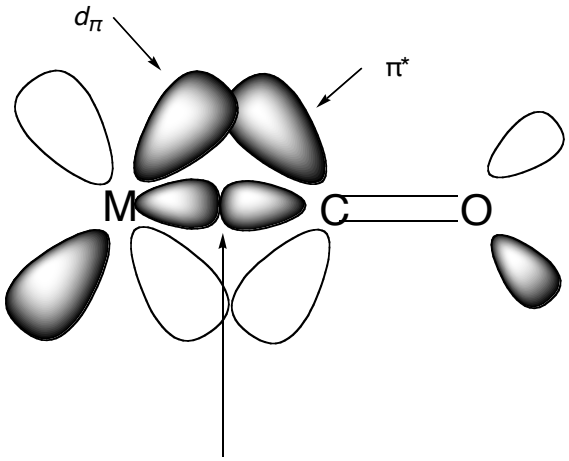
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2: Survey of Ligand Types--Part 1 (L-type ligands)

A. Neutral σ-donor/π acceptors: CO, phosphines, and carbenes

1. Carbonyls

Bonding:

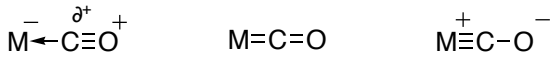


M-L σ

σ-Donor: The HOMO of CO is a non-bonding lone pair on the C. CO is a strong σ-donor.

π-Acceptor: The LUMO of CO is polarized towards the C, as well. This orbital overlaps with the d_π orbitals of the metal.

Depending on the metal and other ligands, the nature of the CO ligand in L_nM-CO can vary.
- If L are good π acids or the complex is cationic, then σ-donation will be more important while the metal will be a weaker π-base. (**A**)
- If the L are σ-donors or the complex is anionic, then the metal will be a strong π-donor. (**C**)

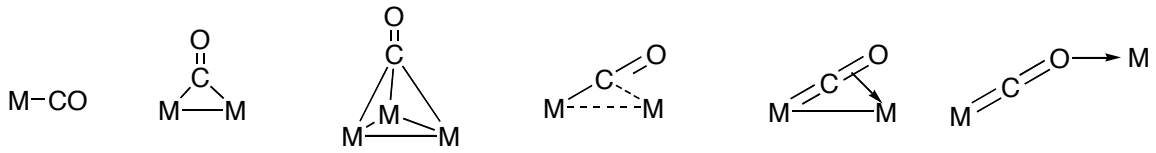


A **B** **C**

The degree of back bonding can readily be determined by IR spectroscopy.

$V(CO)_6$	$Cr(CO)_6$	$Mn_2(CO)_{10}$	$Fe(CO)_5$	$Co_2(CO)_8$	$Ni(CO)_4$
1976 cm^{-1}	2000 cm^{-1}	2013 cm^{-1}	2023 cm^{-1}	2044 cm^{-1}	2057 cm^{-1}
$[Ti(CO)_6]^{2-}$	$[V(CO)_6]^-$	$Cr(CO)_6$	$[Mn(CO)_6]^+$	$[Fe(CO)_6]^{2+}$	CO
1747 cm^{-1}	1860 cm^{-1}	2000 cm^{-1}	2090 cm^{-1}	2204 cm^{-1}	2143 cm^{-1}

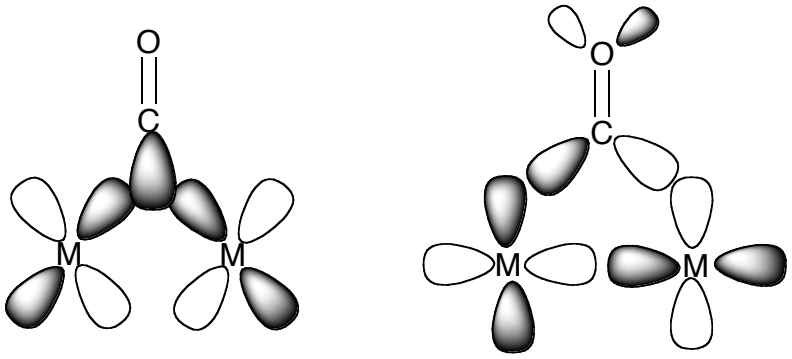
Bridging CO: CO is able to bridge 2 or more metals in a variety of ways. Type II CO is a 1 e donor to each metal. Type III would donate 2/3 e to each metal. In type IV-VI complexes, the CO is an 2e donor to one metal and a 2e donor to the second metal via a second pair of electrons.



Type I Type II Type III Type IV Type V Type VI

Bridging carbonyls tend to have lower stretching frequencies. Type II = 1850 1700 cm^{-1}; Type III = 1675 - 1600 cm^{-1}.

Type II bridging carbonyls are not metalloketones. The M-C-M angle is between 77 - 90 °. The bonding is delocalized and involves the σ and π* MOs of CO.



Other unsaturated molecules capable of binding in a similar fashion: CS, CN-R, electrophilic carbenes, N_2, linear NO ($^+$NO)

2. Phosphines

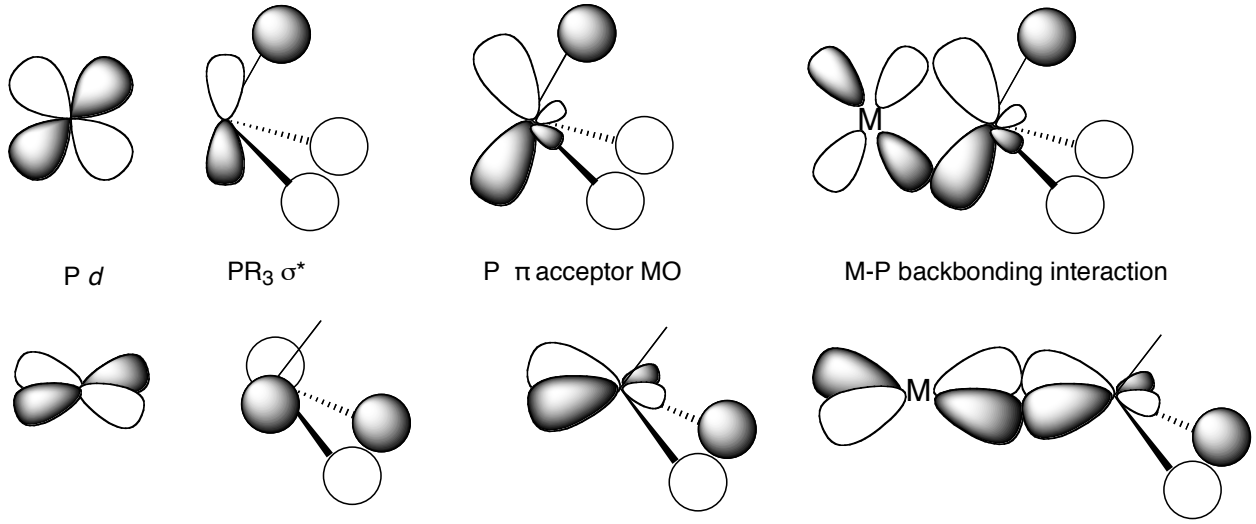
Phosphines are probably the most important organometallic ligands because their steric and electronic properties can be easily modified.

Bonding: Phosphines, like amines, are strong σ-donors. Unlike amines, they are also π-acceptors. Phosphines are softer Lewis bases than amines, so they tend to coordinate strongly to softer Lewis acids, such as the later transition metals.

π acceptor ability

$PR_3 \approx P(NR_2)_3 < PAr_3 < P(OR)_3 < P(OAr)_3 < PCl_3 < CO \approx PF_3$

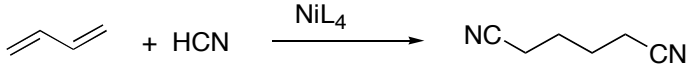
For PR_3, the σ* orbital of the P-R interacts with the P *d* orbital to give a π-acceptor orbital. (*Chem. Commun.* **1985**, 1810; *Inorg. Chem.*, **1992**, *31*, 4391)



P *d* PR_3 σ* P π acceptor MO M-P backbonding interaction

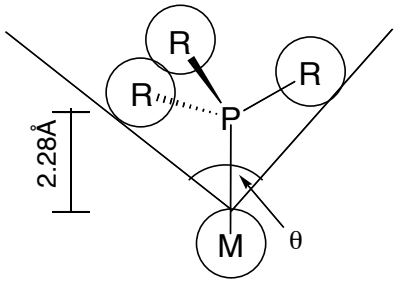
Phosphines tend to be sterically demanding, and thus steric effects dominate coordination
- Bulky phosphines will tend to bind trans to one another
- The presence of several bulky phosphines will result in deviations from ideal geometries.

Steric and electronic parameters have been developed to account for variations in ligand structure on the reactivity of metal complexes. Chadwick Tollman, working at DuPont, developed electronic and steric parameters for phosphines to explain ligand effects on the L_4Ni-catalyzed hydrocyanation of butadiene.



The steric parameter--θ--The Cone Angle:

Tolman developed the cone angle to describe the steric demand of a phosphine ligand. (Tolman, *Chem. Rev.*, **1977**, *77*, 313, *Adv. Organomet. Chem.*, **1994**, *36*, 95-158). Tolman made his measurements using space filling models (CPK) of the ligands with a fixed M-P bond length (2.28 Å). In cases where the ligand could have more than one conformation, he chose the conformation giving the smallest cone angle.



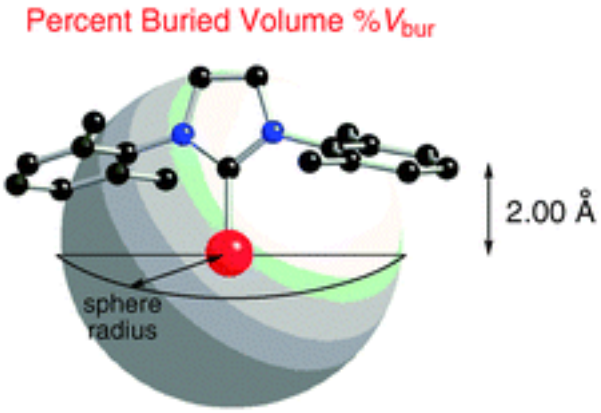
Solid cone angles: The solid cone angle imagines that the metal is a light source. The shadow projected by the ligands on a sphere at an arbitrary radius (outside the ligands) is then determined. The challenge is to deal with the numerous areas of overlapping shadows. The are of the sphere that is in shadow is then mathematically converted to an "cone angle". This method can deal more effectively with non-symmetrical ligands than Tolman's original method. The STERIC program

provides a method to calculate cone angles from these computed structures (Taverner, *J. Comput. Chem.,* **1996**, *17*, 1612-1623).

Exact Cone Angle: Wesley Allen has developed an approach that uses high level theory to determine the optimal structure of a metal complex. He then uses this geometry to generate a cone angle using the Tolman definition rather than a solid cone angle. He calls this method the exact cone angle (*J. Comput. Chem.*, **2013**, *34*, 1189-1197).

X-ray cone angles: Cone angles can also be obtained from solid-state structures using any of these computational methods. These values show true solid state structure, but the solid state structure may not match the solution structure. (Mingos, *Transition Met. Chem.*, **1995**, *20*, 533-539)

Percent buried volume: The cone angle concept works well for symmetrical phosphine ligands, but is less useful for other ligand types, such as non-symmetrical phosphines, *N*-heterocyclic carbenes, or chelating ligands. An alternate approach is the percent buried volume ($\%V_{bur}$), which uses X-ray structures to determine how much of a hypothetical metal sphere is buried by the ligands. The larger the $\%V_{bur}$, the more sterically hindered the ligand. (Cavallo, *Organometallics*, **2016**, 35, 2286). A simple online tool (SambVca 2.0) can be used to calculate $\%V_{bur}$ from structural data (X-ray or calculated structures). https://www.molnac.unisa.it/OMtools/sambvca2.0/index.html



Steric parameters for palladium complexes of different ligands

Method	$P(OMe)_3$	PMe_3	PPh_3	PCy_3	$Pt\text{-}Bu_3$	$P(o\text{-tol})_3$
Tolman	107	118	145	170	182	194
Solid Cone Angle		124	172		194	214
Exact Cone Angle		120	170		188	176
Cone Angle (X-ray)		111	148	160		
$\%V_{bur}$		22%	39%	32%	27%	41%

The electronic parameter--χ

The electron donating or withdrawing ability of phosphines can be correlated with the CO stretching frequency of monophosphine metal carbonyls. While any metal carbonyl can be used, $LNi(CO)_3$ is used most commonly. (*J. Organomet. Chem.*, **1984**, *272*, 29-41).

L	P(*t*-Bu)$_3$	PMe_3	PPh_3	P(*p*-C_6H_5F)$_3$	$P(OMe)_3$	PF_3
CO ν (cm^{-1})	2056.1	2064.1	2068.9	2071.3	2079.5	2110.8
χ (cm^{-1})	0.0	8.0	12.8	15.2	23.2	54.7

It had been shown that ligand dissociation from L_4Ni was the key step in the hydrocyanation process. Therefore, Tollman compared his steric and electronic parameters with the K_D of the following reaction.

$$NiL_4 \overset{K_D}{\rightleftharpoons} NiL_3 + L$$

The steric parameter gave a good correlation with the dissociation rate of NL_4 complexes. It also correlated with catalyst activity for hydrocyanation of alkenes.

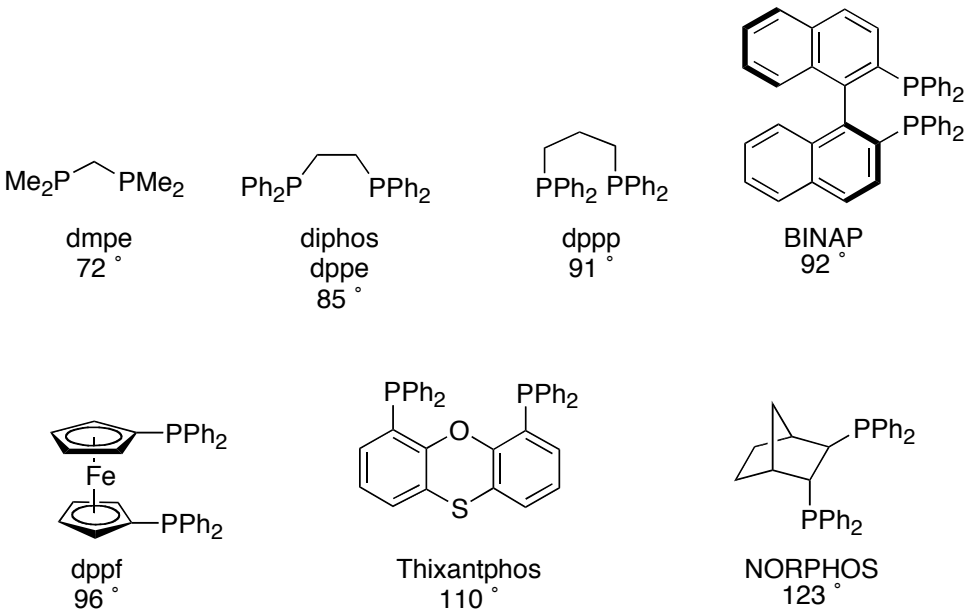
Ligand	θ	K_D (M)
$P(OEt)_3$	109	$<10^{-10}$
PMe_3	118	$<10^{-9}$
P(O-*p*-C_6H_4Cl)$_3$	128	2×10^{-10}
P(O-*p*-$C_6H_4CH_3$)$_3$	128	6×10^{-10}
P(O-*i*Pr)$_3$	130	2.7×10^{-5}
PEt_3	132	1.2×10^{-2}
$PMePh_2$	136	5×10^{-2}
PPh_3	145	No NiL_4 detected

It was found that the electronic parameter did not correlate well with k_d of NiL_4, or with the hydrocyanation reaction that Tollman was studying.

Chelating phosphines

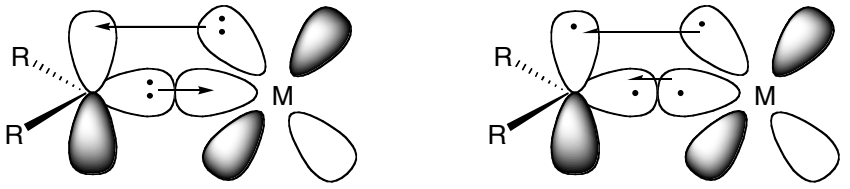
Chelating phosphines are widely used to control structure and reactivity. Chelating diphosphines preferentially coordinate in cis fashion, while 2 monophosphines would adopt a trans geometry.

Natural Ligand Bite Angle (β_n): The ligand preferred P-M-P angle for a chelating diphosphine. This can be determined from x-ray structures or by molecular modeling. (*Chem. Rev.*, **2000**, *100*, 2741-2769)



3. Carbenes

There are two limiting classes of carbenes: electrophilic (Fischer) carbenes and nucleophilic (Schrock) carbenes.



Electrophilic (Fischer) carbene Nucleophilic (Schrock) carbene

<u>Fischer carbenes</u>

- Low oxidation state, late transition metals
- π-acceptor ligands on M
- π-donor substituents (R) on the carbene

Fischer carbenes can be considered as neutral 2 e ligands (L-type) derived from singlet carbenes.

Since the carbene is acting as a σ-donor, it has a ∂+ charge and acts as an electrophilic center.

Schrock carbenes

- High oxidation state, early transition metals
- non-π-acceptor ligands on M

- non-π-donor substituents (R) on the carbene

  Schrock carbenes are formally considered as X_2-type ligands derived from triplet carbenes.

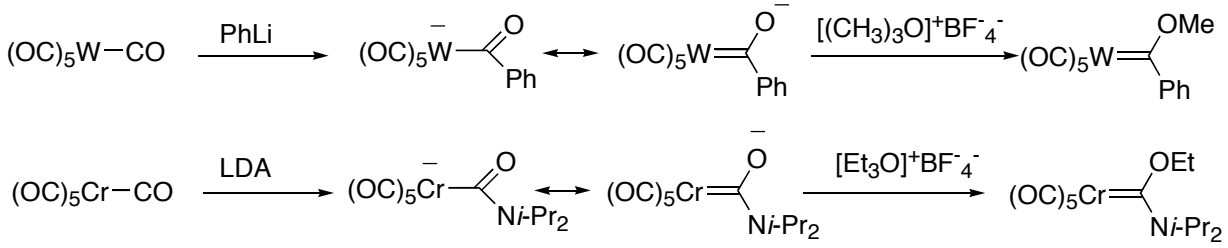
  The carbene carbon has a partial negative charge and acts as a nucleophile.

Fischer Carbenes

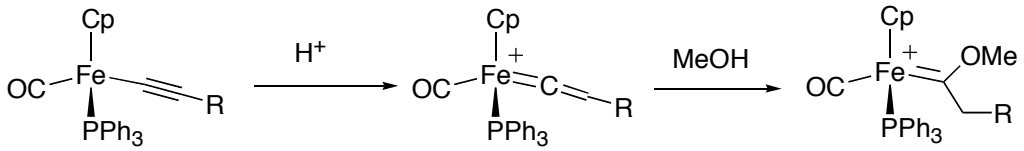
E. O. Fischer first reported carbene complexes in 1964. (*Angew. Chem. Int. Ed.*, **1964**, *3*, 580)

Preparation

A. Nucleophilic attack on coordinated ligand

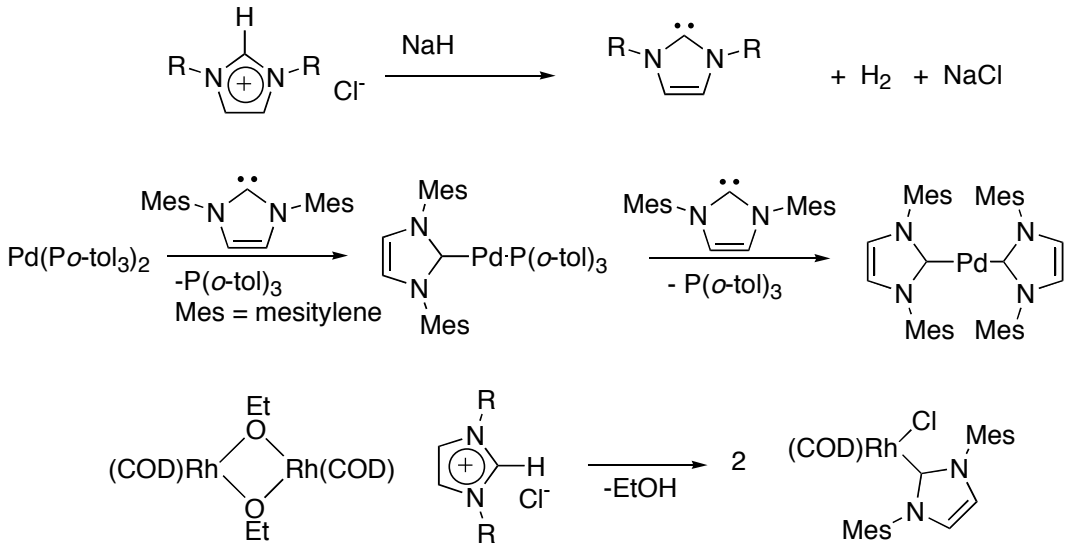


B. From acetylides (Chugaev, *J. Russ. Chem. Soc.*, **1915**, *47*, 776; *Inorg. Chem.* , **1971**, *10*, 1711)



C. From stable carbenes (*Angew. Chem. Int. Ed.* **1997**, *36*, 2162-2187; *J. Organomet. Chem.*, **2000**, *600*, 12-22)

Stable carbenes developed by Arduengo (*Acc. Chem. Res.* **1999**, *32*, 913) can be used as neutral 2 e ligands in place of CO or phosphines. The carbene can either be preformed or prepared *in situ*.

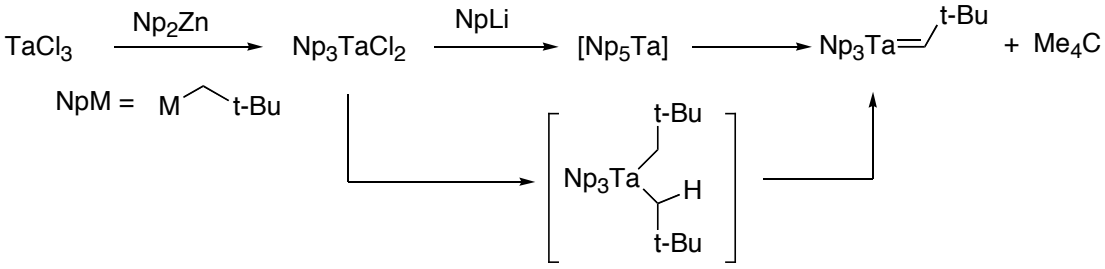


Unlike the Fischer-type carbenes, imidazolylidenes (N-heterocyclic carbenes, NHCs) tend be strong sigma donors, but weak π-acids. Originally it was thought that backbonding played little or no role in the bonding of NHCs to metals. More recent analysis show that backbonding does contribute to the M-L bond. Nolan determined that backbonding accounted for 13% of the bonding in Pt-NHC complexes (*Orgnaometallics*, **2007,** *26*, 5880).

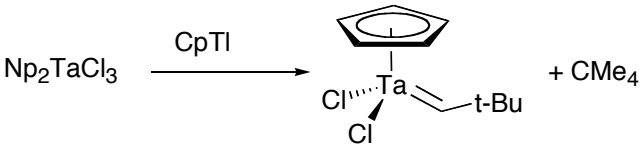
Schrock Carbenes

Synthesis

The first nucleophilic carbenes were prepared by Schrock in an effort to prepare a homoleptic tantalum(V) alkyl. (*Acc. Chem. Res.*, **1979**, *12*, 98)

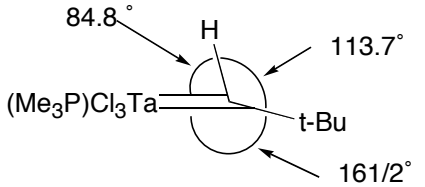


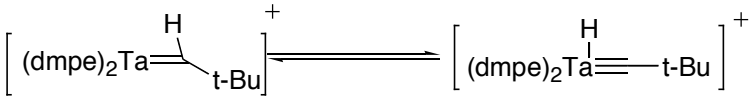
Sterically crowded early transition metal alkyls undergo α-elimination readily to give nucleophilic carbenes and alkanes. Carbene formation can be promoted by increasing the steric strain in a metal complex.



Structure

Schrock carbenes tend to have strong α-agostic interactions that result in significant distortions from idealized bond angles. In some cases, the carbene complex will be in equilibrium with a tautomeric carbyne-hydride.

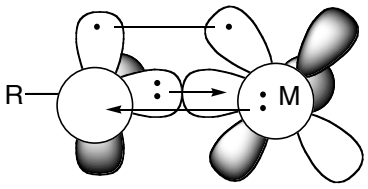




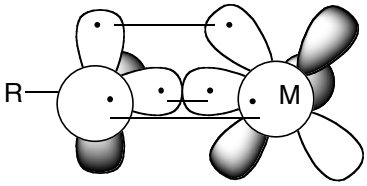
J. Am. Chem. Soc., **1982**, *104*, 1710

Carbynes and Carbides

Compounds with formal metal-carbon triple bonds are also known. Like carbenes, electrophilic (Fischer) and nucleophilic (Schrock) extremes can be envisioned for the bonding model. The electrophilic carbyne complex is derived from a doublet carbine (4e LX-type ligand), while the nucleophilic complex is derived from a quartet carbine (6e X_3-type ligand). The distinction between Fischer and Schrock carbynes is not nearly as distinct as in the case of carbenes.



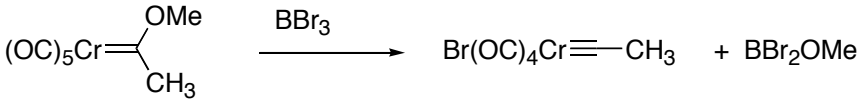
Electrophilic (Fischer) carbyne



Nucleophilic (Schrock) carbyne

<u>Synthesis of Fischer carbynes:</u>

Fisher carbynes can be made by Lewis acid abstraction of alkoxide from alkoxy carbene complexes.



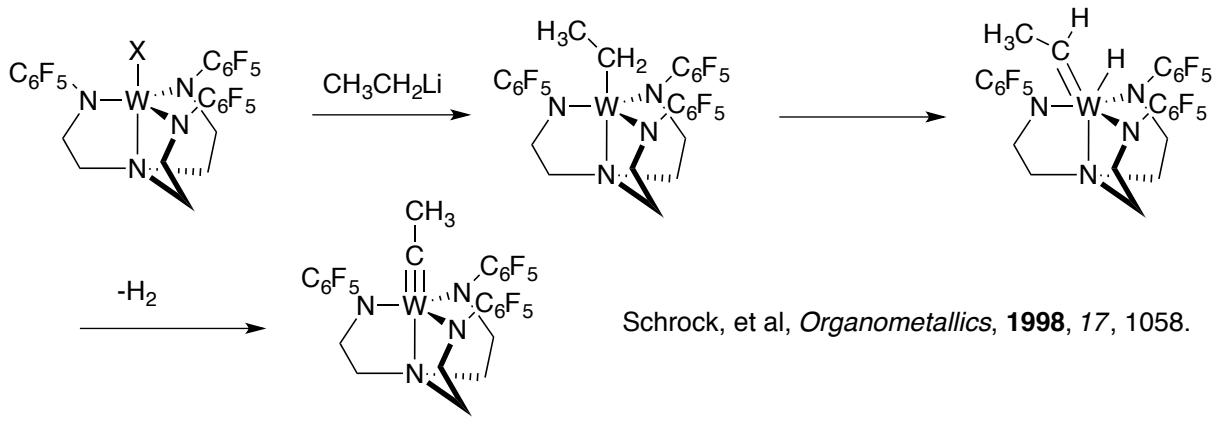
<u>Synthesis of Schrock carbynes</u>

Schrock carbynes can be prepared by deprotonation or α-elimination of Schrock carbenes.



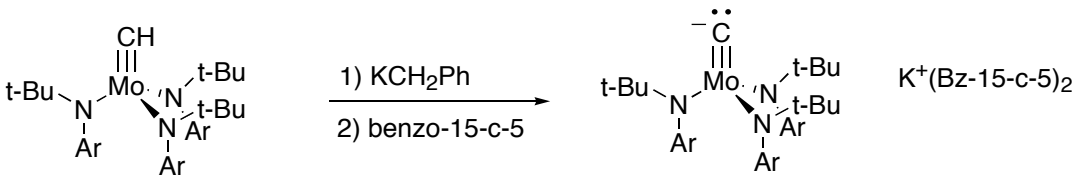
Kevin Shaughnessy
The University of Alabama, 2019

Group VI complexes of tetradentate nitrogen ligands undergo double dehydrogenation to give carbynes starting from metal alkyl complexes.



Schrock, et al, *Organometallics*, **1998**, *17*, 1058.

Like alkynes, terminal carbynes can be deprotonated. For example, Cummins showed that the Mo carbyne complex below could be deprotonated with benzyl potassium. The initial product is a dimer with the potassium ions bridging two carbide anions. Treatment with cryptands or crown ethers gave the free carbide complex. (*Chem. Commun.*, **1997**, 1995-1996)

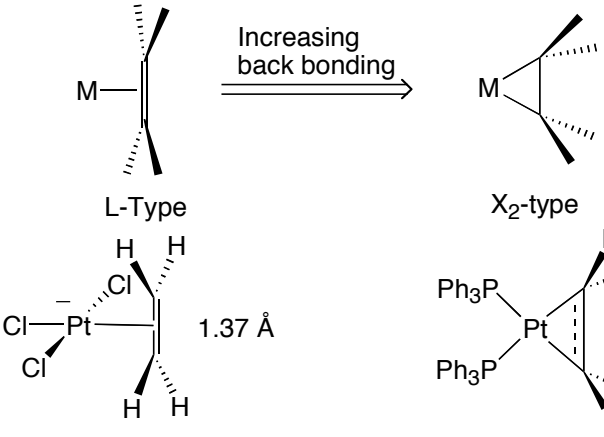


B. π-electron donor ligands

1. alkenes, alkynes, polyenes, and arenes

A. Alkene complexes: π-bonds can act as σ-donor/π-acceptor ligands similar to CO.

As the metal becomes more π-basic, the π* orbital of the ligand becomes more populated. Therefore, the unsaturated C-C bond is weakened.



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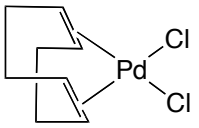
Factors favoring X_2-type binding
- strong donor ligands
- a net negative charge on the complex
- low-oxidation state metals

Reactivity difference between the bonding types:
L-type: the alkene is electron deficient and prone to attack by nucleophiles
X_2-type: the carbons are carbanion-like and prone to attack by electrophiles

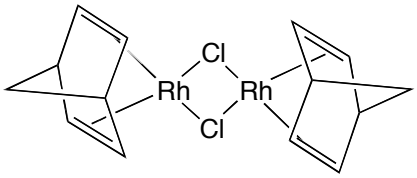
Olefin binding strengths:

- Olefin coordination is very sensitive to steric changes: ethylene > propylene > *cis*-2-butene > *trans*-2-butene

- Chelating dienes form more stable complexes than simple alkenes.

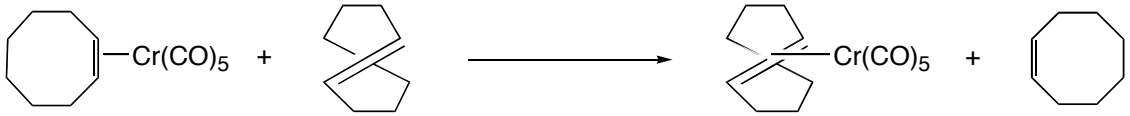


(η^4-cyclooctadiene)palladium dichloride
$(COD)PdCl_2$



(η^4-norbornadiene)rhodium(I) chloride dimer
$[(nbd)RhCl]_2$

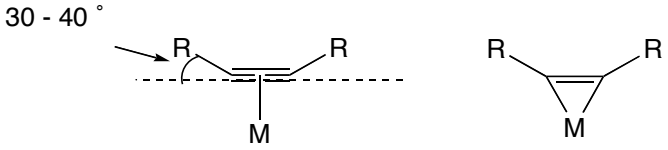
- Due to the shift to sp^3 hybridization upon binding, strained olefins bind more strongly than unstrained ones



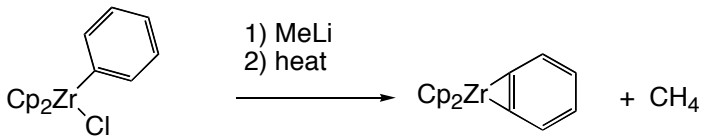
(coe)

B. Alkyne complexes: Alkynes can bind to metal centers in the same way as alkenes

Alkynes are more electronegative, therefore are better π-acceptors

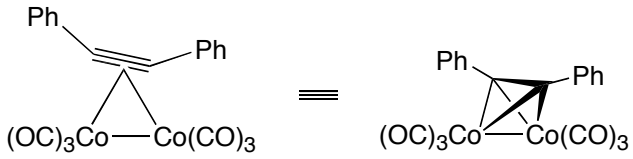


Metals can stabilize alkynes that cannot be observed as free compounds

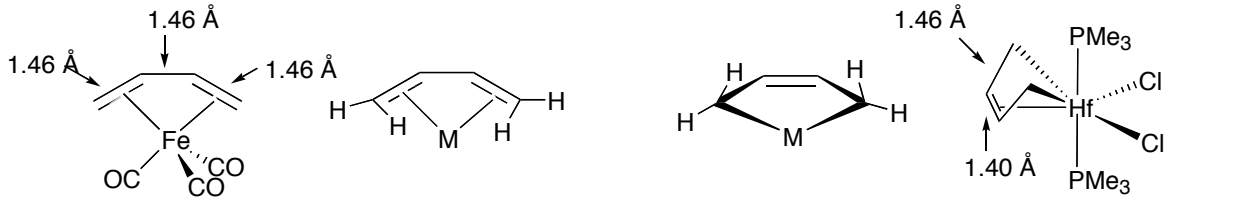


Chem. Rev., **1988**, *88*, 1047-1058

Alkynes can bridge M-M bonds. The alkyne acts as a 2e donor to each metal center

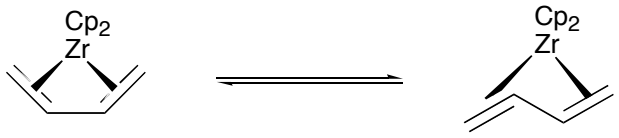


C. η^4-Diene Complexes: 1,3-Dienes can act as L_2-type (4 e) or LX_2-type (6 e) ligands



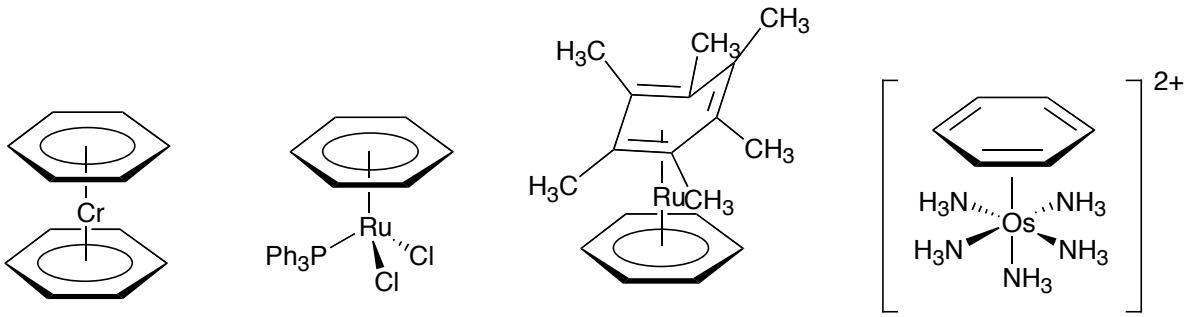
J. Chem. Soc., Dalton, **1992**, 2641

Although *cis*-diene coordination is much more common, *trans*-diene coordination is observed occasionally. (*J. Am. Chem. Soc.*, **1980**, *102*, 6344)



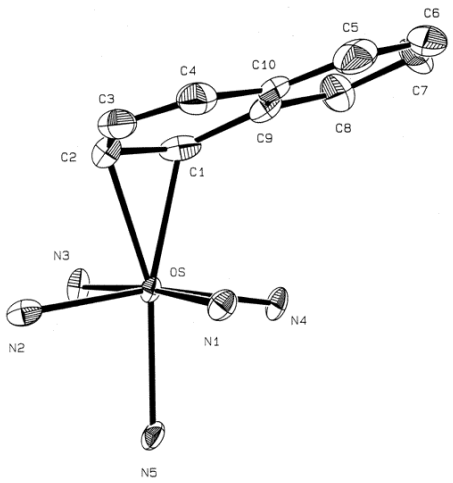
Thermodynamic: 1:1 *cis*:*trans*
Photochemical: all *trans*

D. Arene complexes: Arenes usually will bind η^6-fashion, but η^4- and η^2-complexes are known in cases where η^6-coordination would exceed 18 electrons at the metal



η^6-arene η^4-arene η^2-arene

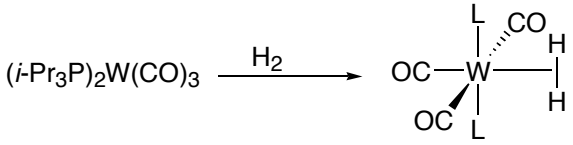
Prof. Dean Harman (UVa) has developed very rich chemistry based on the η^2-coordination of $Os(NH_3)_5^{2+}$ to arenes. (*Chem. Rev.*, **1997**, *97*, 1953-1978)



Crystal structure of (η^2-naphthalene)Os(NH_3)$_5^{2+}$: *Organometallics*, **1997**, *16*, 3672-3678

2. σ-Complexes: Dihydrogen, Silanes, Boranes, Alkanes, etc. (Review: Crabtree, *Angew. Chem. Int. Ed.*, **1993**, *32*, 789)

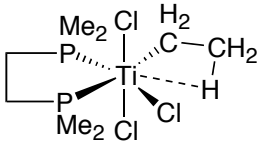
A. Dihydrogen complexes: First reported in 1984 by Kubas (*JACS*, **1984**, *96*, 480)

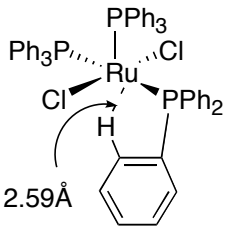


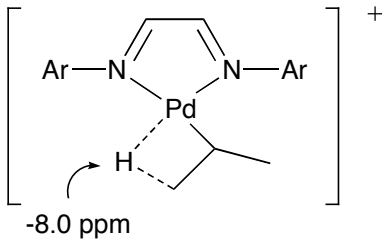
Transient dihydrogen complexes are believed to be intermediates in the oxidative addition of H_2 to give metal dihydride complexes.

B. Alkane complexes:

1. Agostic C-H complexes: Coordination of a C-H bond that is present in a bound ligand. (Original description: Brookhart and Green, *J. Organomet. Chem.*, **1983**, *350*, 395-408)







Characterization of agostic complexes

Crystallography: Characterized by close M-H contacts. C-H bonds are lengthened. M-H distance is longer than for a metal-hydride

NMR: Both ^{1}H and ^{13}C appear upfield compared to normal alkyl chemical shifts. $J(^{13}C\text{-}^1H)$ is typically lower than for a non-bridged species (75 - 120 Hz vs. 100 - 150 Hz). Agostic interactions are often fluxional.

Kevin Shaughnessy
The University of Alabama, 2019

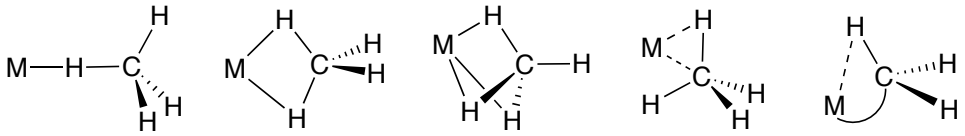
IR: Lower C-H stretching frequencies are sometimes observed (2700 - 2350 cm^{-1})

Agostic interactions are often fluctional, so they can be hard to observe.

Agostic interactions help to stabilize metal alkyls. They also can be considered as "stable intermediates" of migratory insertion/ß-hydride elimination. Agostic complexes play important roles in olefin polymerization catalysts.

2. Alkane complexes: Alkanes can act as ligands to metal centers, but bind very weakly. Direct observation of alkane complexes is difficult. Alkane complexes are thought to be key intermediates in oxidative addition/reductive elimination of alkanes. Review: Young, *Chem—Eur. J.* **2014**, *20*, 12704-12718

Alkane bonding modes:



κ^1-H κ^2-H,H κ^3-H,H,H κ^2-H,C agostic

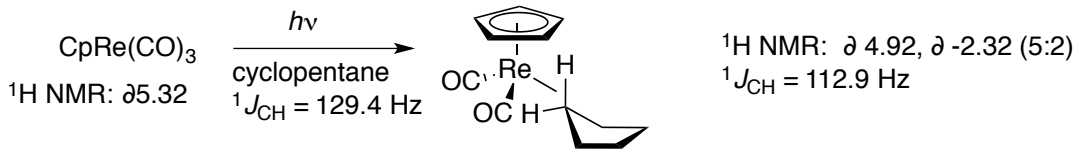
<u>Observation by time resolved IR:</u> Many examples of 16 e metal carbonyls coordinating to alkanes have been observed, although lifetimes of these complexes are very short (300 ns - 200 μs)

$$CpRe(CO)_3 \xrightarrow[\text{heptane}]{h\nu\ 266\ nm} CpRe(CO)_2(\text{heptane}) + CO \longrightarrow CpRe(CO)_3 + \text{heptane}$$

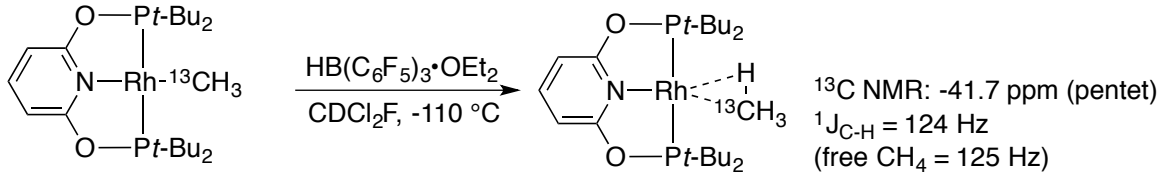
IR: 2032, 1940 IR:1951, 1866 k = 2.1 X 10^3 l/mol s

JACS, **1997**, *119*, 7521-7525; *JACS*, **2012**, *133*, 2303

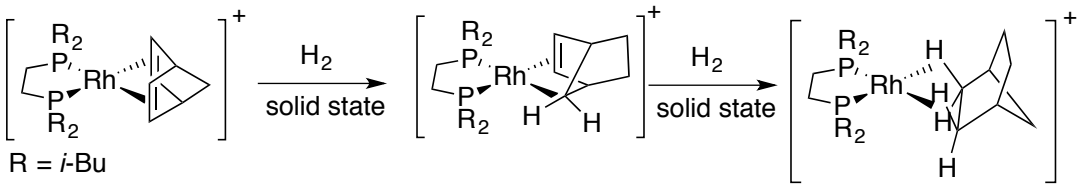
Observation by NMR: *JACS*, **1998**, *120*, 9953-9954; *Chem. Commun.* **2009**, 1401-1403

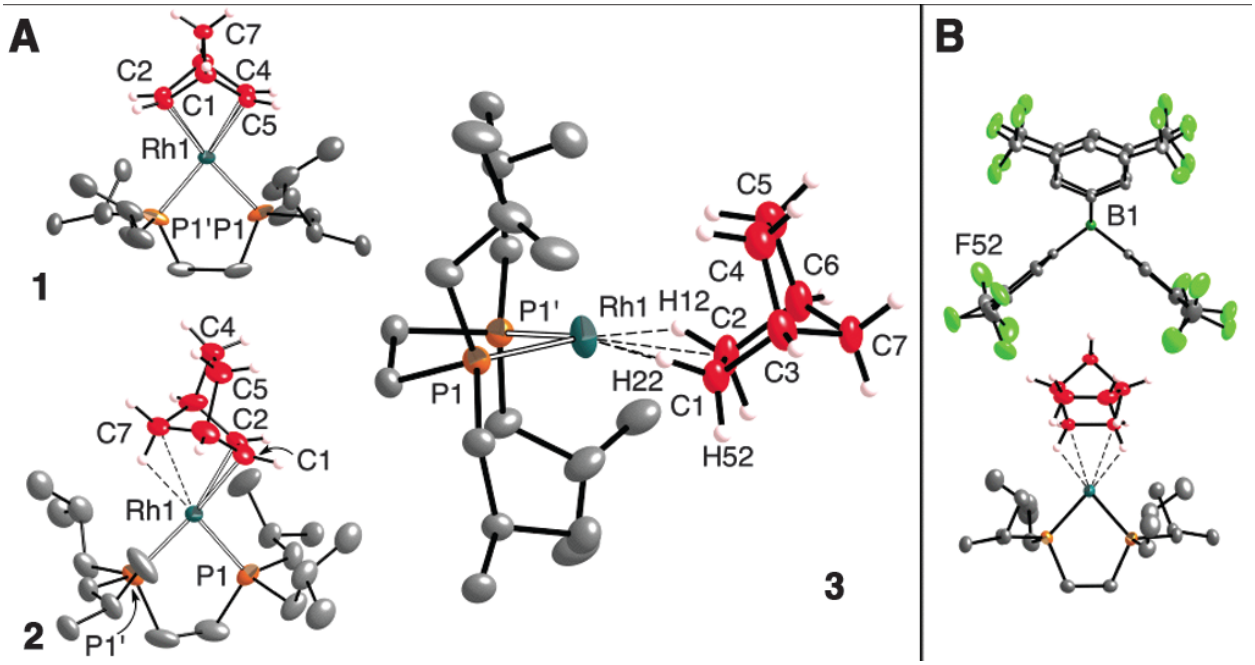


A methane adduct of a Rh(I) pincer complex has been characterized by NMR. The methane ligand is fluxional at -110 °C, so that all 4 H's are equivalent. *Science,* **2009**, *326*, 553-556



Crystallographic characterization: Alkane complexes are generally not stable enough to be characterized crystallographically. The first example of an unambiguous examples of an alkane complex was reported by Macgregor. (*Science*, **2012**, *337*, 1648-1651). To avoid loss of the alkane, the alkane complex was generated by reduction of a coordinated norbornadiene ligand in a single crystal, solid-state reaction.

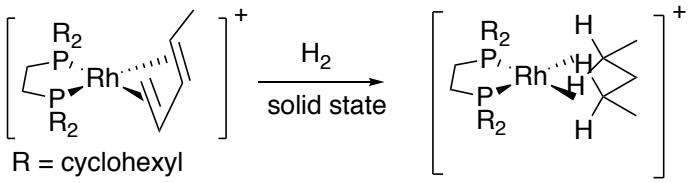


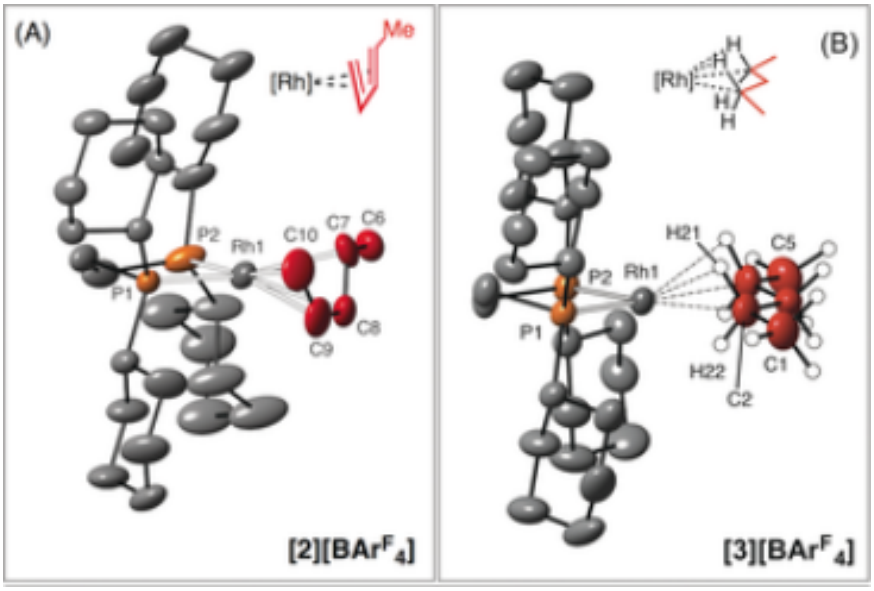


Rh1-C1, 2.214(13) Å; Rh1-C2, 2.169(12) Å

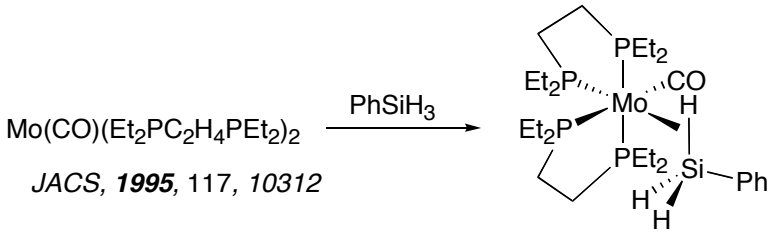
Kevin Shaughnessy
The University of Alabama, 2019

Macgregor has extended this to a linear alkane complex by solid-state reduction of a Rh 1,3-pentadiene complex to a Rh pentane complex with a chelating interaction with the two methylene units. *Angew. Chem. Int. Ed.* **2016**, *55*, 3677

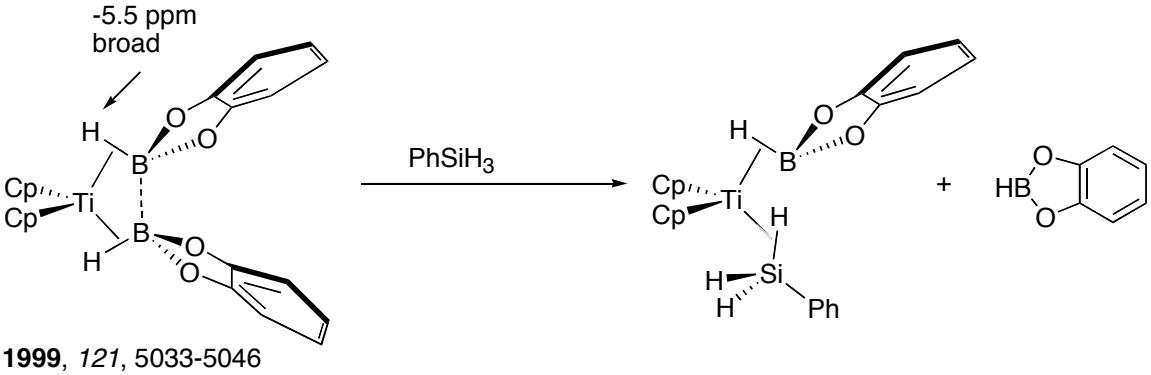




2. Silanes and boranes



*JACS, **1995**,* 117*, 10312*



JACS, **1999**, *121*, 5033-5046

2: Survey of Ligand Types--Part 2 (X-type ligands)

1. Hydrides

History
1931: $H_2Fe(CO)_4$ prepared by Hieber, although the hydride structure was not accepted initially
1955-1964: Cp_2ReH, $(PR_3)_2PtHCl$, and $K_2[ReH_9]$ prepared showing that M-H bonds do exist
1984: Dihydrogen complexes discovered ($M\text{-}H_2$)

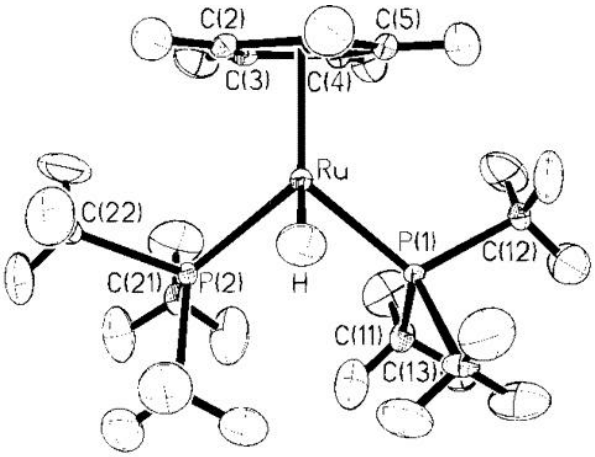
Bond strength

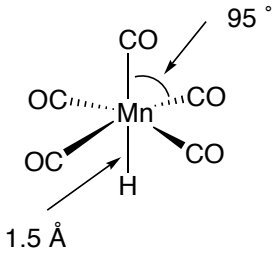
M-H BDE energies are typically between 60 and 70 kJ/mol. M-H bond strengths increase moving down columns (1st row < 2nd row < 3rd row)

Structure of hydride complexes:

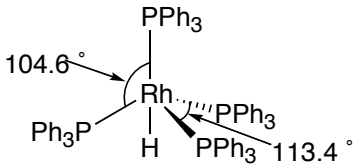
Terminal Hydrides

Hydrides are stereochemically active: the hydride generally occupies a normal coordination site in the complex. Due to its small size, the complex's geometry can be perturbed if there are other large ligands present.





Inorg. Chem. **1969**, *8*, 1928



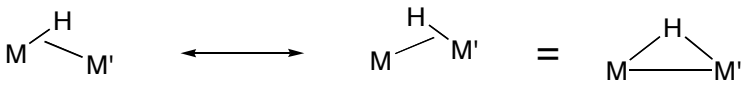
Inorg. Chim. Acta., **1989**, *166* , 173

Organometallics, **1996**, *15*, 1721

Bridging Hydrides

Bridging hydrides always adopt a bent M-H-M conformation. The bonding is similar to the 3 center/2 electron bonding B-H-B bridge in boranes.

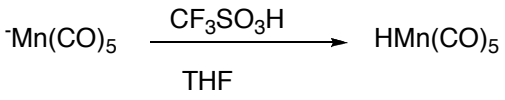
The bonding can be thought of as a σ-bond complex of an M-H bond to the other metal center. Thus, there would be two resonance structures for a bridging hydride. Often this is drawn showing a M-M bond as well as the M-H bonds.

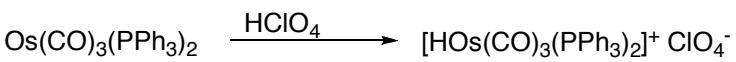


In the ionic model, the hydride is a 1 electron donor to each metal. The M-M' bond donates 1 electron to each metal as well.

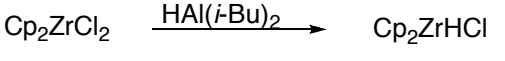
Synthesis of metal hydrides:

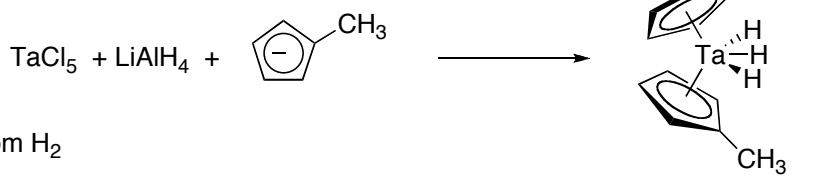
1) Protonation



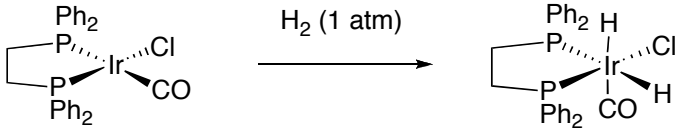


2) Hydride donors

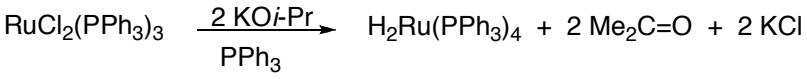


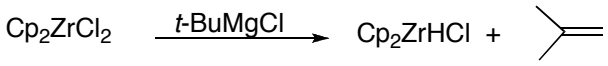


3) From H_2



4) Elimination





Characterization

NMR: Hydrides usually appear very far upfield (0 - -60 ppm). For example:

$HCo(CO)_4$ (-10.7 ppm) $HMn(CO)_5$ (-7.5 ppm) $(Cy_3P)_2Pt(H)OPh$ (-17.5 ppm)

These upfield shifts do not necessarily imply strong hydridic character. The upfield chemical shift is largely due to mixing of low-lying excited states with the ground state when the magnetic field is applied. (*J. Chem. Soc.* **1964**, 2747 and 4583). This tendency is strongest for d^1 - d^9 metals, while d^0 and d^{10} metals, which do not have low lying excited states, generally give hydride shifts downfield of TMS.

Cp_2ZrH_2 (7.46 ppm) $[HCuP(p\text{-tol})_3]_6$ (3.5 ppm)

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IR: Terminal M-H stretching frequency are usually between 1500 - 2200 cm^{-1}. Bridging hydrides generally have lower energy vibrations (800 - 1600 cm^{-1}). The intensities are usually weak for metal hydrides. Raman often gives more intense absorptions.

Crystallography: The hydrogenhas little electron density and does not scatter X-rays well, so hydride ligands can be difficult to find. Since X-rays are scattered by electron density, which is between the M and H nuclei, M-H bond distances are usually underestimated by 0.1 Å.

Neutrons diffraction detects the hydrogen nucleus, so these experiments tend to give more accurate M-H distances. Neutron structures usually require very large crystals and synchrotron neutron sources.

Acidity

Many hydrides are appreciably acidic.

General trends:
- pK_a generally increases as you move down a column—stronger M-H bond
- electron donating ligands increase pK_a values

Hydride	pK_a (CH_3CN)
$HMn(CO)_5$	14.1
$HMn(CO)_5PPh_3$	20.4
$HRe(CO)_5$	21
$HFe(CO)_2Cp$	19.4
$HFe(CO)_2Cp^*$	26.3
$CpCr(CO)_3H$	13.3
$CpMo(CO)_3H$	13.9
$CpW(CO)_3H$	16.1

From Hartwig, *Organotransition Metal Chemistry*, University Science Books, 2010, pg. 129.

- **Alkyls, Vinyls, and Aryls**

Metal alkyls: stabilized carbanions
- As the metal electronegativity increases, the nucleophilic reactivity of the M-C bond decreases.
- Nucleophilic reactivity decreases with more stable carbanions (i.e. $^-CH_3 < ^-C_6H_5 < ^-CCR$).

- M-C bond strength increases moving down columns. M-C BDE typically are weaker than M-H bonds. Most fall in the range of 30-60 kcal/mol

Early transition metal alkyls are very sensitive to water and oxygen.

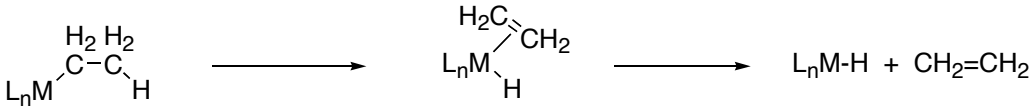
Late transition metal alkyls are more stable to water and oxygen.

Stability of Transition metal alkyls: Originally it was thought that the transition metal-carbon bond was too weak to give stable products.

Actually lack of kinetic stability rather than thermodynamic stability was the problem

Decomposition pathways:

– ß-hydride elimination:



ß-Hydride elimination occurs for nearly all transition metal-alkyls that meet the following requirements:

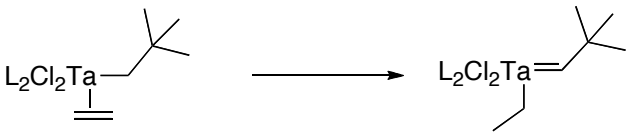
1. The β carbon must have hydrogen substituents
2. The M-C-C-H unit can adopt a roughly syn-coplanar conformation that brings the ß-hydrogen close to the metal center.
3. There is a vacant coordination site (orbital) *cis* to the alkyl substituent

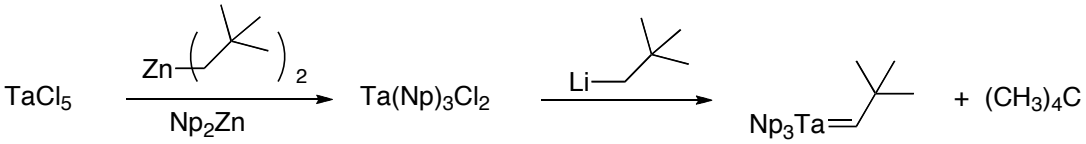
Metal-alkyls that are stable to β-hydride elimination

1. Alkyls that do not have β-hydrogens
2. Alkyls for which the ß-hydrogen cannot approach the metal center
3. Alkyls in which the M-C-C-H unit cannot become coplanar
4. 18-electron species that cannot dissociate a ligand
5. Some d^0- alkyls

– α-hydride elimination:

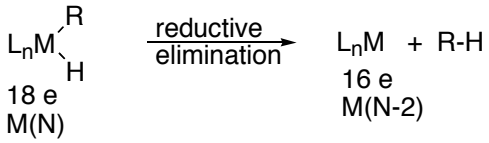
For early transition metal alkyls, α-hydride elimination can be an important decomposition pathway.





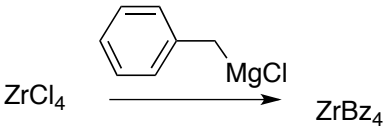
J. Am. Chem. Soc. **1978**, *100*, 3359

– Reductive Elimination:

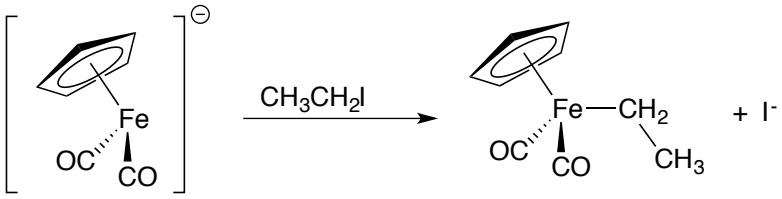


Synthesis of Transition Metal Alkyls

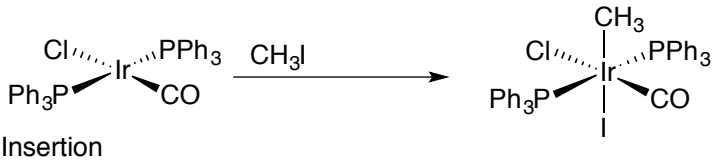
1) Alkylation with a nucleophilic organometallic species



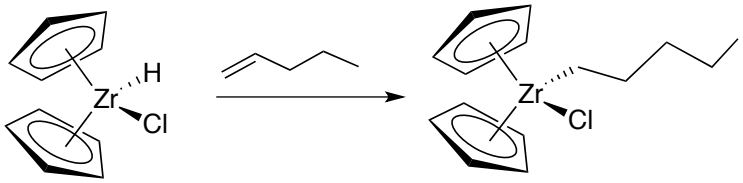
2) Nucleophilic addition to an electrophilic alkyl



3) Oxidative Addition

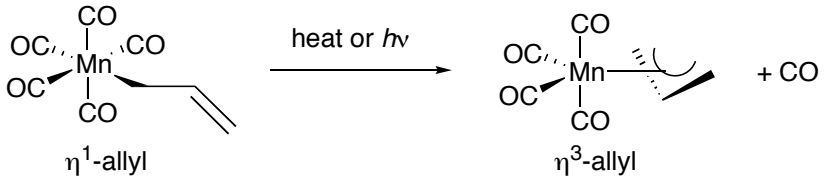


4) Insertion

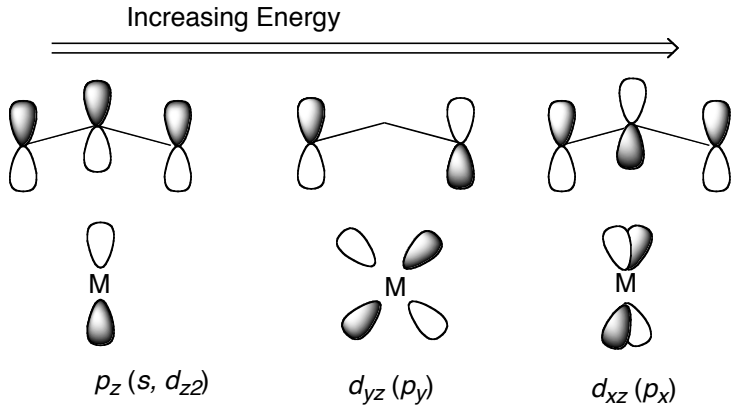


3. L_nX carbon ligands

A. π-Allyl complexes: The allyl group ($C_3H_6^-$) can act as an η^1-X or η^3-LX ligand.



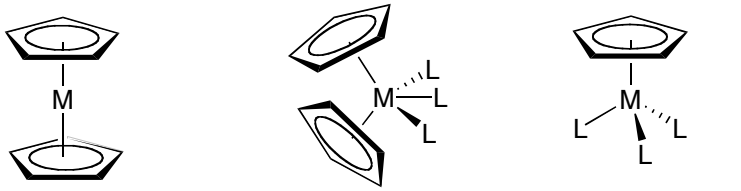
Orbital interactions



B. Cyclopentadienyl (Cp) complexes

Cp complexes of all transition metals are known. The Cp ligand binds strongly and is resistant to attacks by nucleophiles and electrophiles, so it makes a good spectator ligand in many cases.

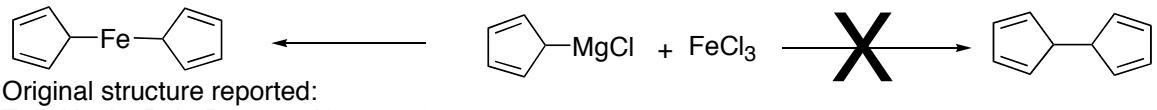
Types of Cp complexes:



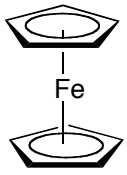
Metallocenes Bent Metallocenes Half-Sandwich

i. Metallocenes

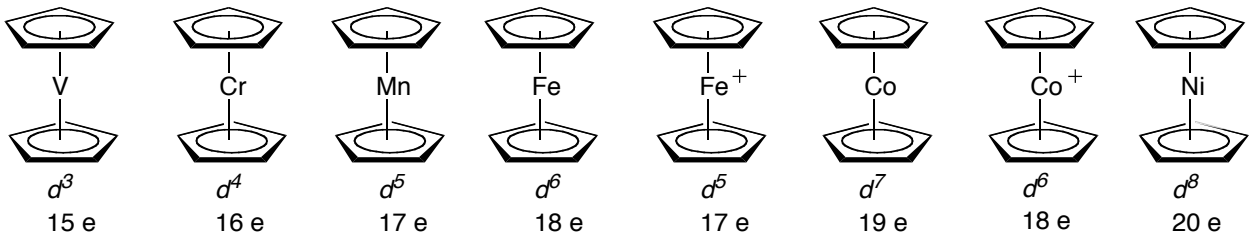
Ferrocene



Original structure reported:
T. J. Kealy, P. L. Pauson, *Nature*, **1951**,*168*, 1039
J. A. Tebboth, J. F. Tremaine, *J. Chem. Soc.*, **1952** , 632-635 (by another route)

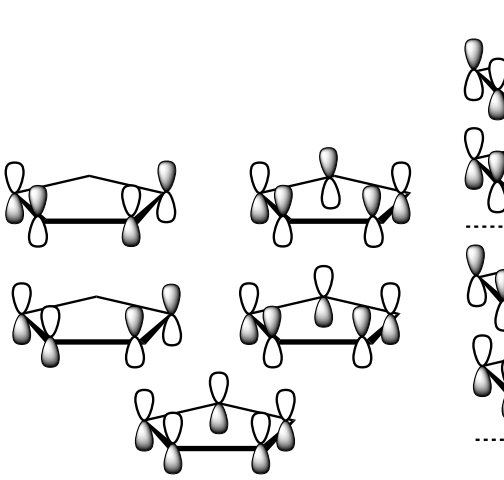


Correct structure originally proposed in 1952:
G. Wilkinson, R.B. Woodward, et al, *J. Am. Chem. Soc.*, **1952**, *74*, 2125-2126
E. O. Fischer, W. Pfab, *Z. Naturforsch. B*, **1952***, 7*, 377-379
Crystal structure:
P. F. eilan, R. Pepinsky, *J. Am. Chem. Soc.*, **1952**, *74*, 4971
L. E. Orgel, J. D. Dumitz, *Nature*, **1953**, *171*, 121-122

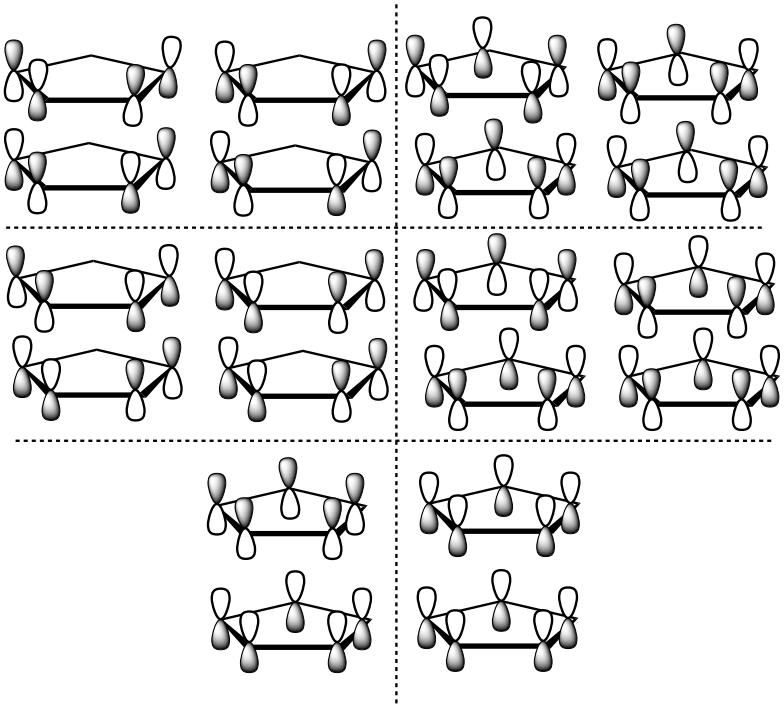


MO diagram for metal-Cp bonding

Cp and Cp_2 π-molecular orbitals: The Cp molecular orbitals have three energy levels. One that his fully symmetric, two degenerate orbitals with a single node (p-symmetry), and two degenerate orbitals with two nodes (d-symmetry). These can be combined to give a set of orbitals for the Cp_2 environmental of a metallocene.

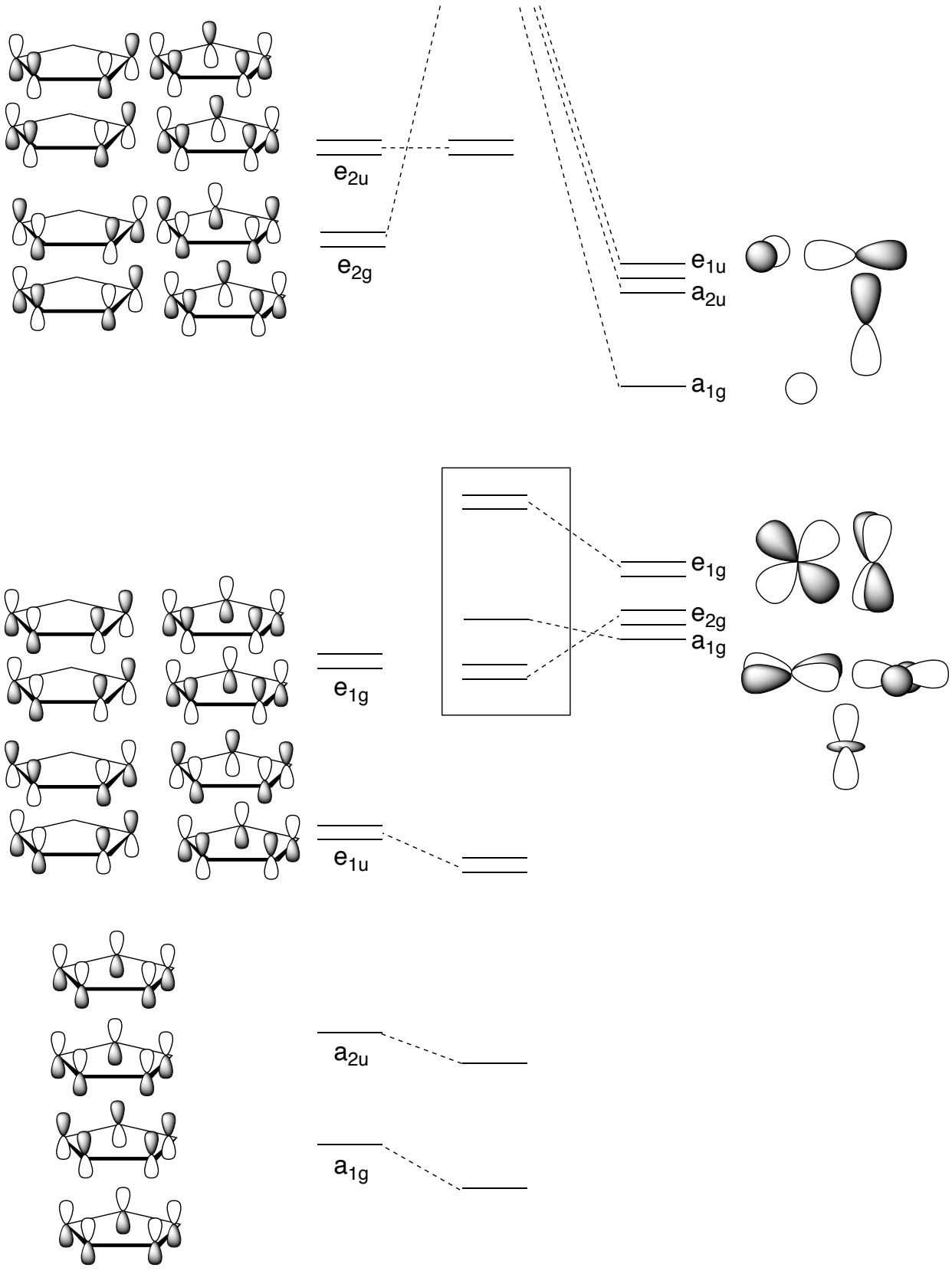


Cp MO diagram



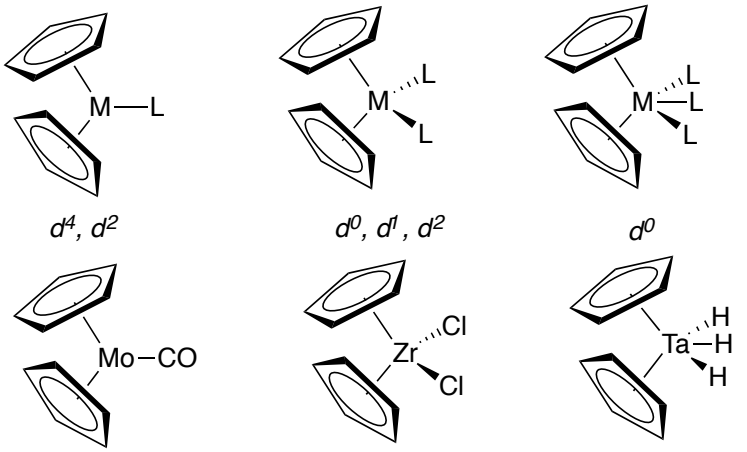
Cp_2 MO diagram

Combining the Cp_2 orbitals with the metal orbitals give the following interactions.



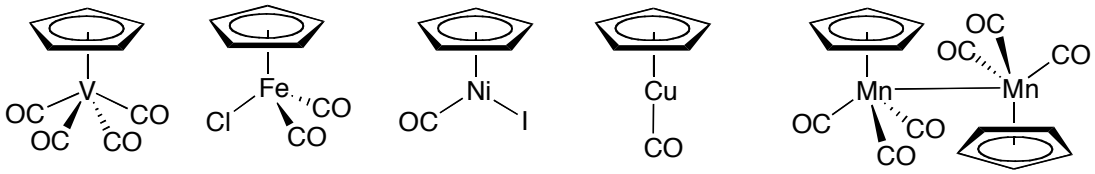
Kevin Shaughnessy
The University of Alabama, 2019

ii. Bent Metallocenes: Metals of group 4 and the 2nd and 3rd rows of groups 5-7 do not form stable Cp_2M complexes. However they do form stable metallocenes with additional ligands attached to the metal center.

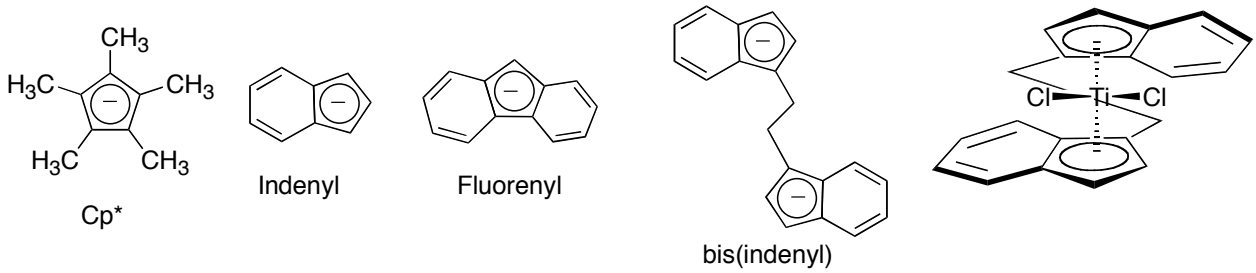


iii. Half-Sandwich Complexes (Piano Stool Complexes): Metallocenes have limited reactivity because they are typically coordinatively saturated. Bent-metallocenes offer more interesting chemistry (olefin polymerization), but half-sandwich complexes offer the most diverse reactivity.

Some examples:



iv. Other important Cp-type ligands:



4. Halides, Alkoxides, Amides, etc.

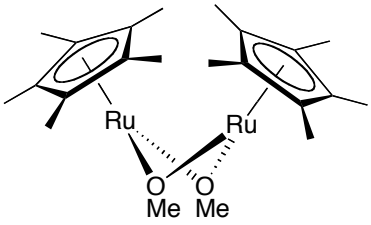
This class of ligands contain additional lone pairs that can be donated to the same metal (π-donors) or to another metal center (bridging species).

A. π-donors: amide, alkoxide, and fluoride are strong π-donors.

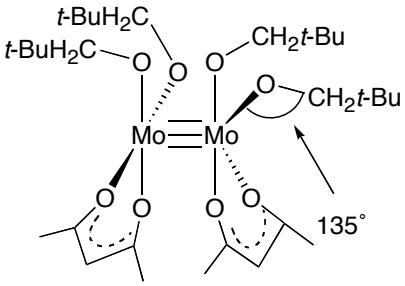
In late, 18 e transition metal complexes, π donation weakens the M-X bond due to repulsion between filled orbitals.

In early transition metals π-donation is a favorable interaction between the filled ligand orbital and empty d_π orbitals on the metal center. Early transition metals are often referred to as being *oxophilic* or *fluorophilic*.

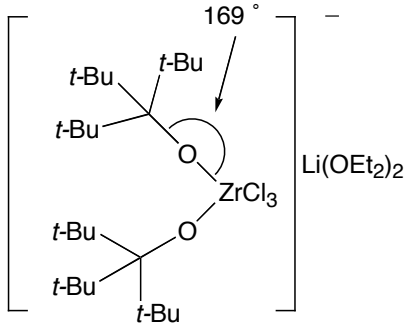
Alkoxides: Alkoxides commonly act as bridging ligands for electropositive metals. To avoid formation of bridges, bulky alkoxides must be used. With high valent transition metals, π-donation becomes important. M-O-C angles approaching 120 ˚ or even 180 ˚ are common.



J. Am. Chem. Soc, **1989** *111*, 4712-4718



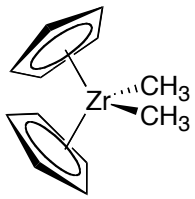
Inorg. Chem., **1984**, *5*, 613-618

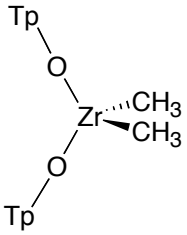


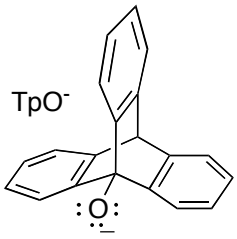
Organometallics, **1984**, *3*, 977-83

An angle near 120 ˚ suggests that the O is sp^2 hybridized and acting as a 4 electron donor (LX).

An angle near 180 ˚ suggests that the O is sp hybridized and acting as a 6 electron donor (LX_2). In this case the alkoxide can be considered to be isoelectronic with the Cp ligand.



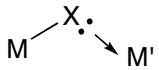




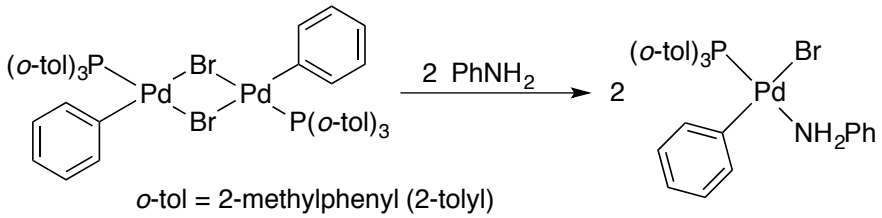
Dialkylamido ligands ($-NR_2$) often act as 4 electron LX donors to high valent metals. The nitrogen adopts a planar configuration suggesting sp^2 hybridization.

B. Bridging:

Halides other than fluoride, non-bulky alkoxides, thiolates and phosphides have a strong tendency to act as bridging ligands.



Coordinatively unsaturated metal halides often dimerize to give halide bridged species. These species can be cleaved by reaction with an additional coordinating ligand.



o-tol = 2-methylphenyl (2-tolyl)

3-Ligand Substitution

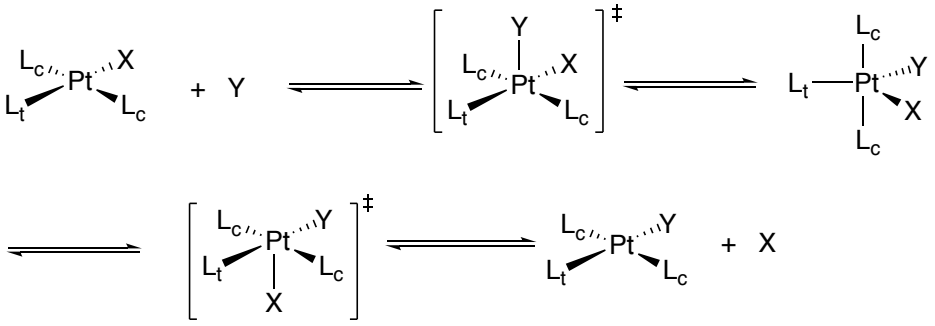
Limiting mechanisms for ligand substitution:

Associative Mechanism (A): Bond making occurs before bond breaking.

Dissociative Mechanism (B): Bond breaking occurs before bond making.

Mechanisms between these two extremes are called **Interchange (I)** mechanisms. These can be associatively activated ($\mathbf{I_a}$) or dissociatively activated ($\mathbf{I_d}$).

Associative Mechanism: This is the most common mechanism for coordinatively unsaturated metal complexes. The d^8 square planar complexes are prototypical examples. Square planar complexes of Pt(II), Pd(II), Ir(I), and Rh(I) have been extensively studied.

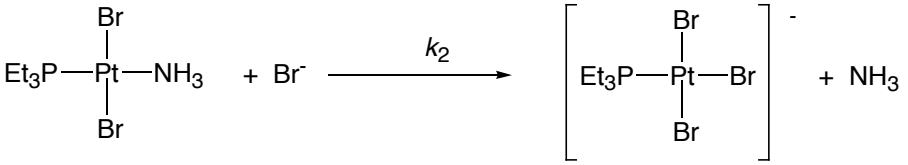


Characteristics of this reaction:

1. Stereochemistry at the metal center is *usually* retained
2. Kinetics are second order, although the rate law usually has two terms: rate = k_1[Pt] + k_2[Pt][Y]
3. Negative entropy of activation ($\Delta S^{\ddagger}$ = -40 to - 60 J/mol•K)
4. The reaction rate is dependent on:
    5. the incoming ligand: PR_3 > pyridine > NH_3, Cl^- > H_2O > ^-OH--range = 10^5
    6. the leaving ligand: NO_3^- > H_2O > Cl^- > Br^- > I^- > N_3^- > CN^-
    7. the metal: M^{2+} = Ni > Pd >> Pt--range = 10^6
    8. ligands cis and trans to the leaving ligand

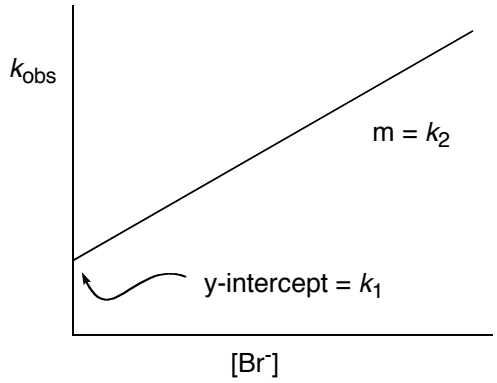
Kinetics of Associative Ligand Substitution:

The simple associative substitution follows a second order rate law: rate = k_2[M][Nu]. Kinetics studies of associative substitution, however, often give more complex rate laws. Ligand substitution of square planar Pt(II) complexes are a classic example.



Inorg. Chem. **1970**, *9*, 258-261

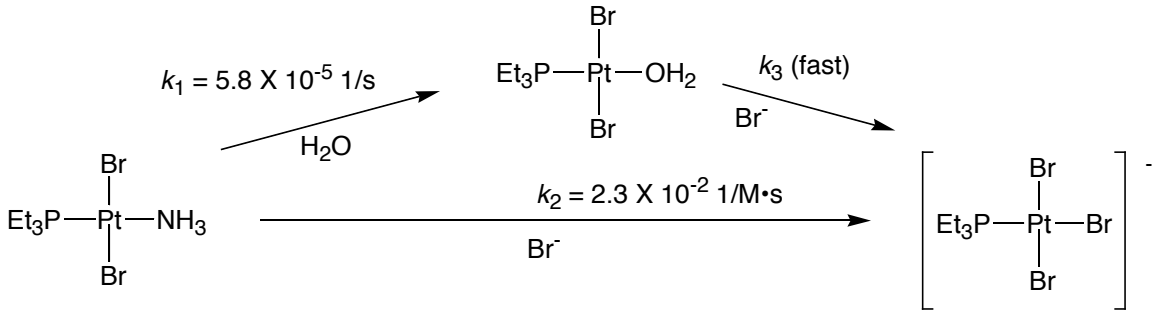
Pseudo-first order rate constants (k_{obs}) were determined at various [Br^-] values. A plot of k_{obs} vs. [Br^-] will give the k_2 second order rate constant for the reaction. If the reaction followed clean second order kinetics, the y-intercept would be zero. In fact, the y-intercept is not zero.



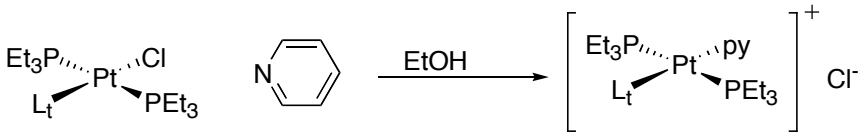
The nonzero y-intercept indicates that there is a second process that is not dependent on [Br^-].

$$\text{Rate} = (k_1 + k_2[\text{Br}^-])[(\text{Et}_3\text{P})\text{PtBr}_2(\text{NH}_3)]$$

The [Br^-] independent term is due to a mechanism where ligand substitution by solvent occurs, followed by displacement of solvent by the nucleophile in a fast step.



<u>The *trans*-effect and -influence:</u>
Trans-influence: Extent to which a ligand weakens the bond *trans* to itself.
Trans-effect: The effect of a ligand upon the <u>rate</u> of ligand replacement of the group *trans* to itself.



L_t	H	CH_3	C_6H_5	Cl
Rel. Rate	10^4	1.7 X 10^3	400	1

J. Chem. Soc. **1961**, 2207.

Trans effect/influence series:

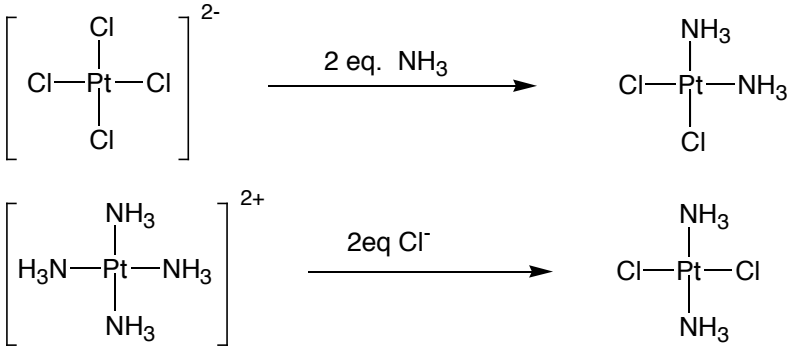
H^- , CH_3^-, olefins, CO > PR_3, I^- > Br^- > Cl^- > NH_3 > OH^- > H_2O

Why??:

σ-donors: Strong σ-donors increase the electron density of the orbital that points towards the *trans* ligand

π-acceptors: Strong π acids stabilize the trigonal bipyramidal intermediate (withdraws electron density away from ligands Y and X in the intermediate.

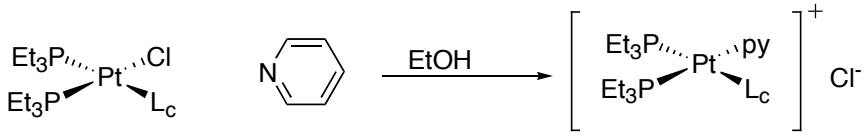
The trans influence/effect can be used to predict substitution stereochemistry.



For a more extensive listing of the trans influence of ligands see, *Coord. Chem. Rev.* **1973**, *10*, 335.

Cis influence/effect

Cis ligands also affect substitution rates, but to a much smaller extent.



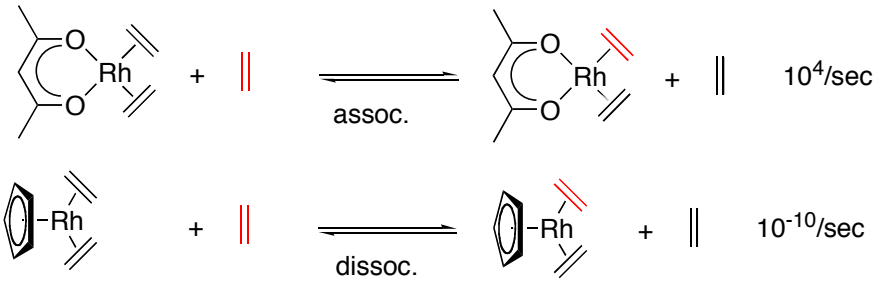
L_t	CH_3	C_6H_5	Cl
Rel. Rate	3.6	2.3	1

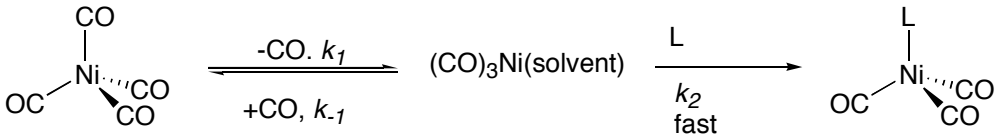
J. Chem. Soc. **1961**, 2207.

Dissociative Substitution

Dissociative substitution is normally the preferred mechanism for coordinatively saturated 18 e complexes, since they can more readily form a 16 electron complex than one with 20 electrons. The

rates of ligand substitution for coordinatively saturated complexes are usually significantly slower than those for coordinatively unsaturated complexes.



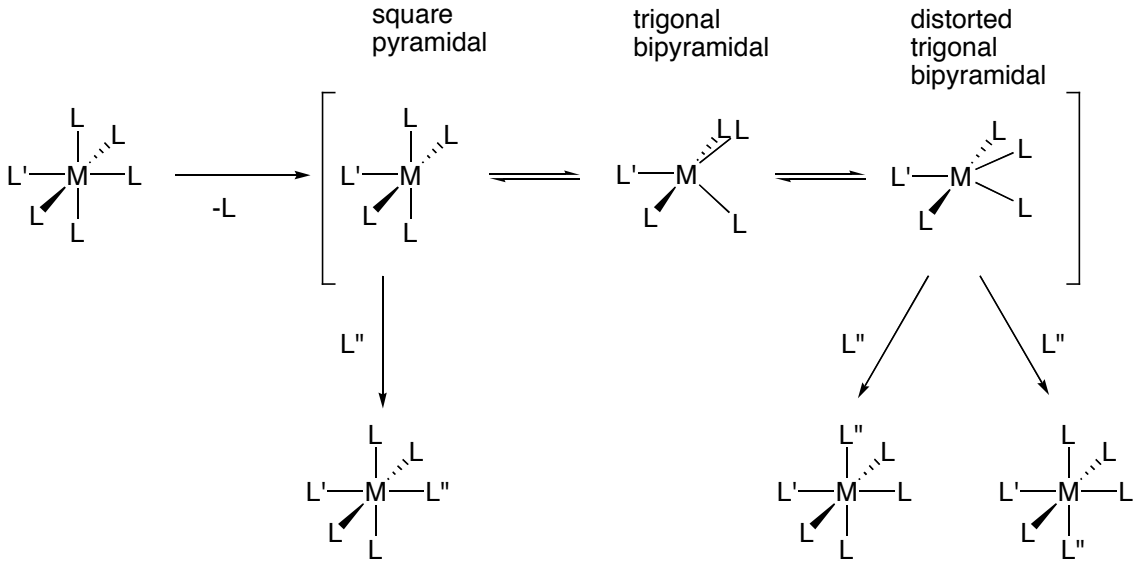


6. $\text{rate}=\frac{k_1 k_2[L][Ni(CO)_4]}{k_{-1}[CO]+k_2[L]}$ If $k_2 >> k_{-1}$ then the rate law is simplified to rate = $k_1[Ni(CO)_4]$

7. $\Delta H^{\ddagger}$ = 105 kJ/mol, which is close to the Ni-CO BDE

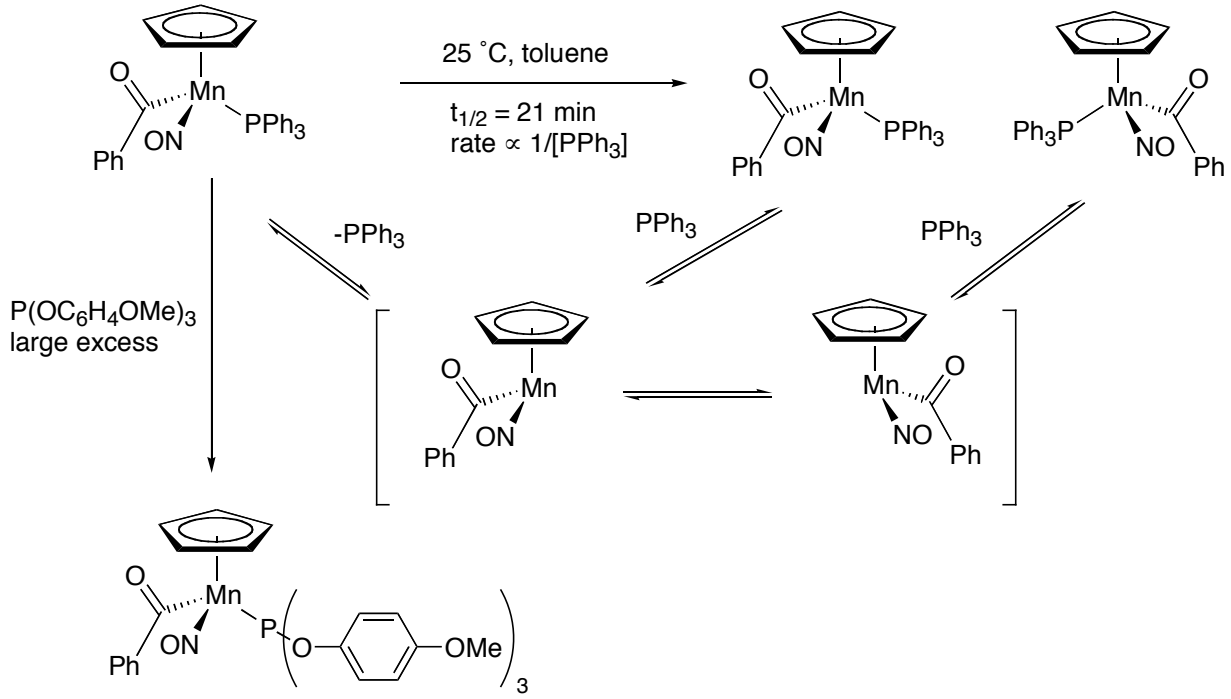
8. $\Delta S^{\ddagger}$ = 33 J/mol•K

<u>Stereochemistry of Substitution:</u> Both retention and inversion are observed for dissociative ligand substitutions.



Dissociation of a ligand from an octahedral complex gives a square pyramidal ML_5 complex. If L' is a strong trans effect ligand, this geometry is stable and substitution will occur with retention. For d^6 metals, the trigonal bipyramidal structure is not stable and retention is preferred. A distorted trigonal bipyramid is preferred when L' is a π-donor ligand, which can result in a mixture of stereoisomers.

Pseudo-four-coordinate, 18 electron metal complexes can be chiral at the metal center. In many cases these complexes can be resolved. Racemization of these complexes occurs by a dissociative mechanism. Loss of phosphine gives a fluxional intermediate. Recoordination of phosphine can give either enantiomer of the metal complex. Substitution with a large excess of a phosphite gives substitution with retention of stereochemistry.



<u>Dependence of Dissociative Substitution on the Metal Center:</u>

Electronic configuration: $d^8 > d^{10} >> d^6$

d^6 metals are often referred to as being substitutionally inert.

<u>17 electron complexes:</u>

17 electron complexes undergo ligand dissociation much faster than 18 electron complexes (10^3 to 10^7 times faster).

$$V(CO)_6 \xrightarrow[\text{-70 °C}\\ \text{90 minutes}]{PPh_3} (PPh_3)V(CO)_5 + CO$$

$$[V(CO)_6]^- \xrightarrow[PPh_3]{\text{molten}} \text{No reaction}$$

<u>Do 17 electron complexes undergo associative or dissociative ligand substitution?</u>

$$V(CO)_6 + L \xrightarrow{\leq 25\ °C} (PPh_3)V(CO)_5 + CO$$

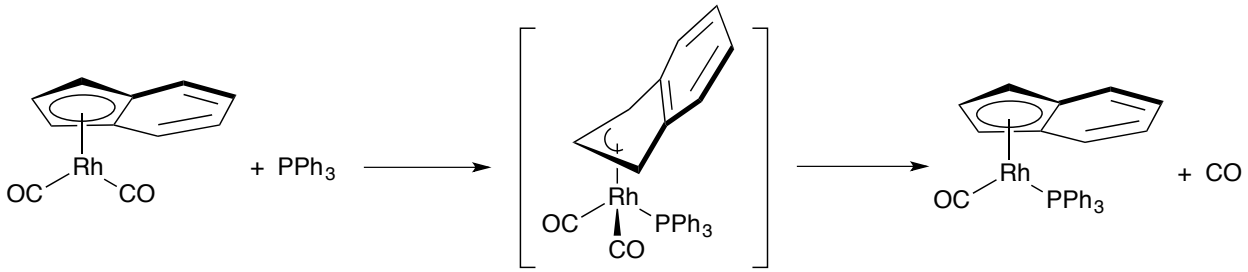
J. Am. Chem. Soc., **1984**, *106*, 71

- rate $\propto$ [L]
- rate is unaffected by [CO]
- $\Delta S^{\ddagger}$ = -118 J/mol•K (L = PPh_3)

The rate of the reaction was largely unaffected by the size of the incoming ligand. Only $P(i\text{-}Pr)_3$ showed a significantly slower rate than less sterically demanding ligands.

Do 18 electron complexes ever undergo ligand substitution by an associative mechanism?

Yes, but usually only when a poly-hapto ligand or chelating ligand can adopt a lower hapticity coordination. This is necessary to avoid a 20 e intermediate.



JCS, Chem. Commun. **1983**, 1208

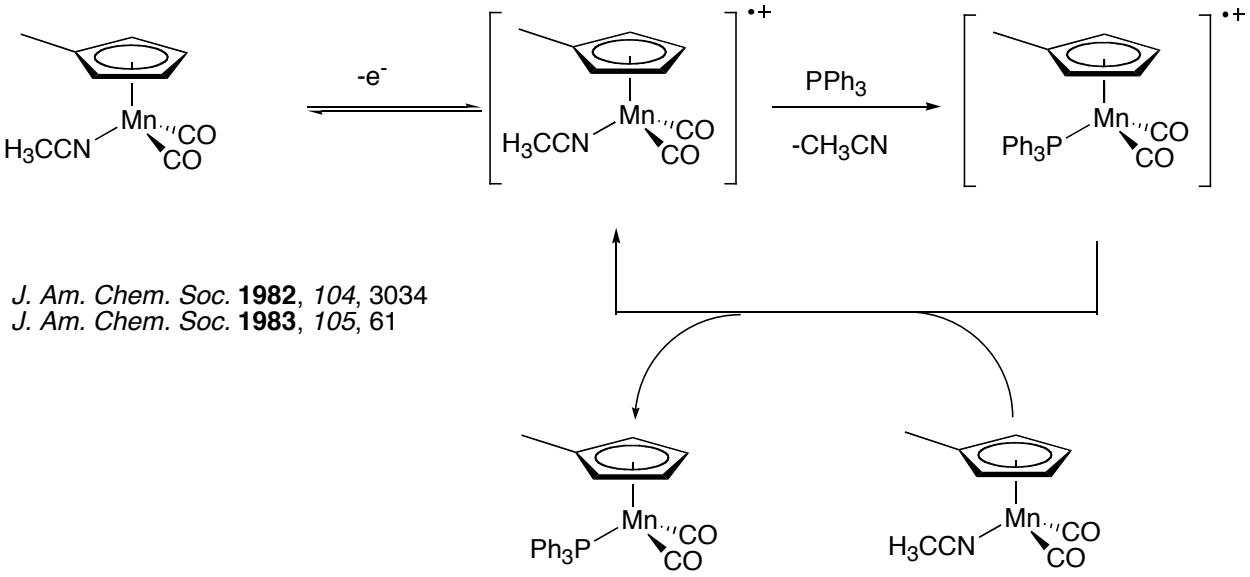
Catalyzed or Assisted Ligand Substitution

Electron-Transfer Catalysis:

Odd number (17 or 19 e) species typically undergo ligand substitution at much higher rates than 18 e complexes. This fact can be used to accelerate ligand substitution reactions.

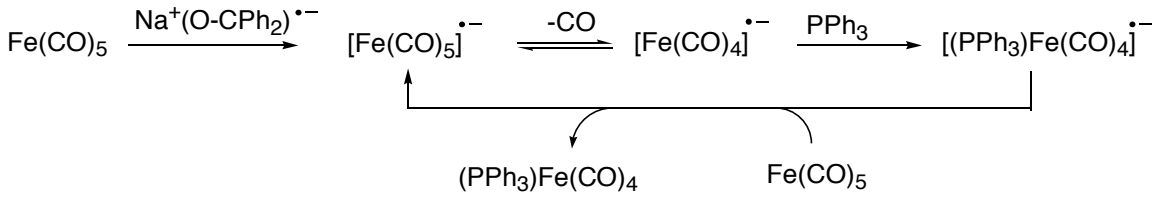
Catalysis by oxidation:

Oxidation of 18 e electron complexes will give substitutionally labile 17 e complexes. Rapid ligand substitution follows the oxidation. In many cases these reactions are electrocatalytic. For this reaction to be catalytic, it is necessary that the oxidation potential of the product be more positive than that of the starting complex. In the case below the oxidation potential of the starting complex is 0.22 V (vs. ferrocene/ferrocenium) and the E° of the product is 0.55 V.



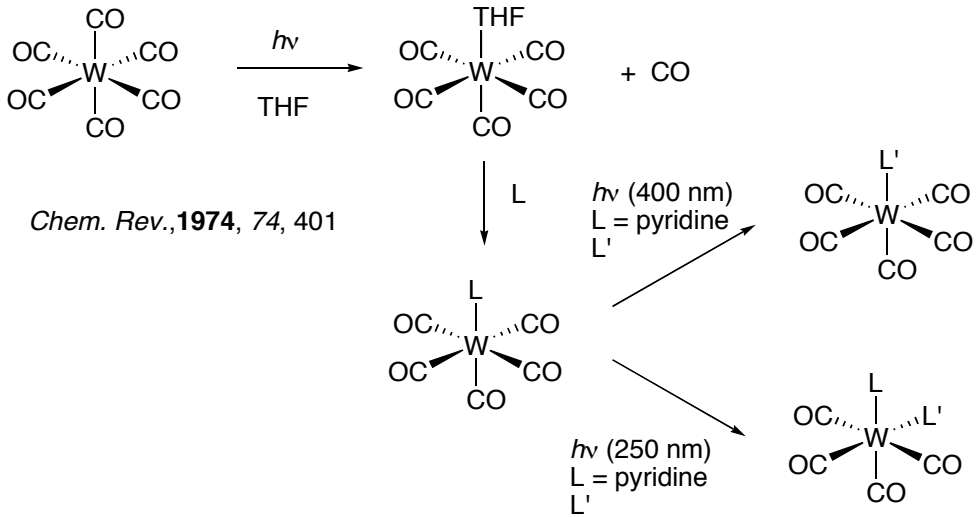
J. Am. Chem. Soc. **1982**, *104*, 3034
J. Am. Chem. Soc. **1983**, *105*, 61

Catalysis by reduction: Reduction to 19 e species can also accelerate ligand substitution. This is commonly used for metal carbonyls.



Photochemical Ligand Substitution:

Photolysis of metal complexes can lead to ligand dissociation, which will accelerate ligand substitution.



Chem. Rev.,**1974**, *74*, 401

Carbonyls: Substitution of substitutionally inert octahedral metal complexes can be accelerated by UV or in some cases visible light. Absorption of light by an octahedral results in promotion of an electron from the t_{2g} (d_π) to the e_g (d_σ), which is an anti-bonding M-L orbital.

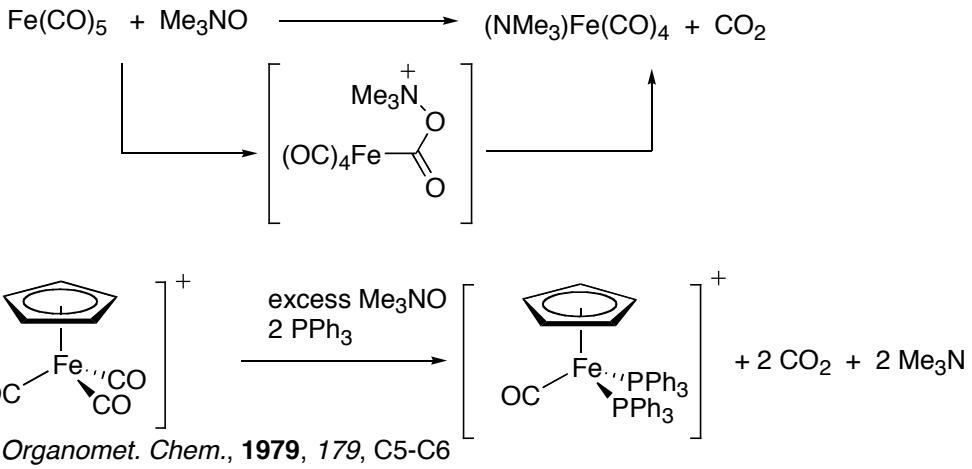
M-M bonds: Weak M-M bonds can be homolyzed photochemically. Homolysis of $Mn_2(CO)_5$ gives the 17 electron $Mn(CO)_5$ species that undergoes rapid substitution. Recombination of the 17 electron species gives $Mn_2(CO)_9PPh_3$.

$$(OC)_5Mn{-}Mn(CO)_5 \xrightarrow{h\nu} 2\ Mn(CO)_5$$

$$Mn(CO)_5 + PPh_3 \longrightarrow Mn(CO)_4PPh_3 + CO$$

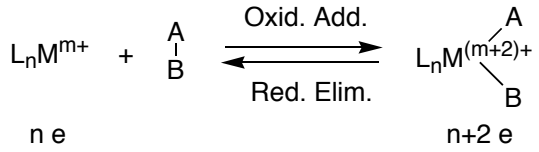
$$Mn(CO)_4PPh_3 + Mn(CO)_5 \longrightarrow (OC)_5Mn{-}Mn(CO)_4PPh_3$$

Nucleophile Assisted Substitution: Oxygen transfer reagents (i.e., R_3NO, R_3PO, DMSO) can induce decarbonylation of metal carbonyls by an oxidative mechanism. (*Coord. Chem. Rev.*, **1984**, *53*, 227-259)



J. Organomet. Chem., **1979**, *179*, C5-C6

4-Oxidative Addition/Reductive Elimination



Oxidative Addition: Addition of A-B to a metal center resulting in an increase in coordination number by two, an increase of oxidation state by 2 units, and an increase in the electron count by 2.
Reductive Elimination: Elimination of two ligands from a metal center to give a new A-B bond. The metal center is reduced by 2 units and has 2 fewer coordinated ligands. The complex has 2 less electrons.

Oxidative addition and reductive elimination are the microscopic reverse of each other. They represent the forward and reverse reaction of an equilibrium. The position of the equilibrium depends on the thermodynamics of the oxidative addition (or reductive elimination process). For example many metal complexes will oxidatively add CH_3I, but few will reductively eliminate this compound. In contrast M(H)R usually undergo rapid reductive elimination, but oxidative addition of alkanes is much less common.

General features of oxidative addition:

- Oxidative addition favored at more electron-rich metal centers.
- Oxidative addition favored at less sterically demanding metal centers
- Oxidative addition generally requires an electron count of 16 or less (17 electrons for bimolecular oxidative addition). There must be at least 2 d electrons for oxidative addition to occur. Oxidative addition of polar reagents in which the anionic leaving group does not coordinate to the metal center can occur at 18 e complexes.
- Oxidative addition of non-polar reagents (see below) requires an open coordination site. This is not always true for polar reagents.
- Ligand dissociation is often required prior to oxidative addition, thus the coordinating ability of the ligands can affect the rate.

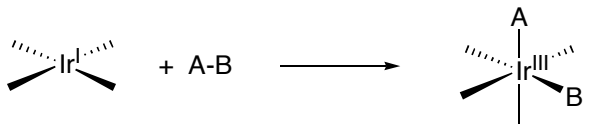
Oxidative Addition: There are three major classes of substrates that undergo oxidative addition. We will consider their mechanisms separately.

- Non-polar bonds: (H-H, H-CR_3, H-SiR_3, etc)

- Polar bonds: (R-X, H-X, RCOX)

- π-systems: (O_2, $MeO_2CC{\equiv}CCO_2Me$)

Thermochemistry of Oxidative Addition



A-B	A-B BDE (kcal/mol)	Ir-A BDE (kcal/mol)	Ir-B BDE (kcal/mol)	ΔH (kcal/mol)	ΔG (kcal/mol)
H-H	104	Ir-H: 60	Ir-H: 60	-16	-6
CH_3-H	104	Ir-CH_3: 46	Ir-H: 60	-2	+8
CH_3-CH_3	88	Ir-CH_3: 46	Ir-CH_3: 46	-4	+6
CH_3-I	56	Ir-CH_3: 46	Ir-I: 45	-35	-25

Although C-H and C-C oxidative addition is unfavorable in this system, changing the ligands can make these processes thermodynamically favored as we'll see.

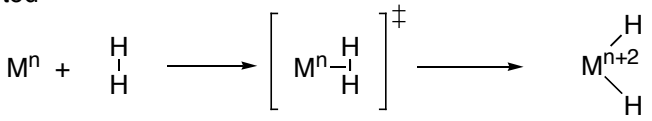
1) Oxidative addition of non-polar compounds

A. Dihydrogen (H_2)

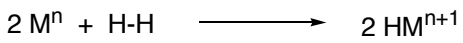
Oxidative addition of H_2 is a key step in the hydrogenation of alkenes and other related reactions. It is the best understood oxidative addition of non-polar reagents. There are three major mechanisms by which dihydrogen can undergo oxidative addition. We will see that these also apply to other non-polar compounds.

Mechanisms of H_2 Activation

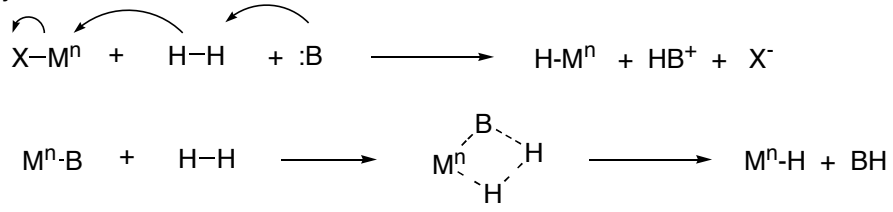
Concerted



Homolytic

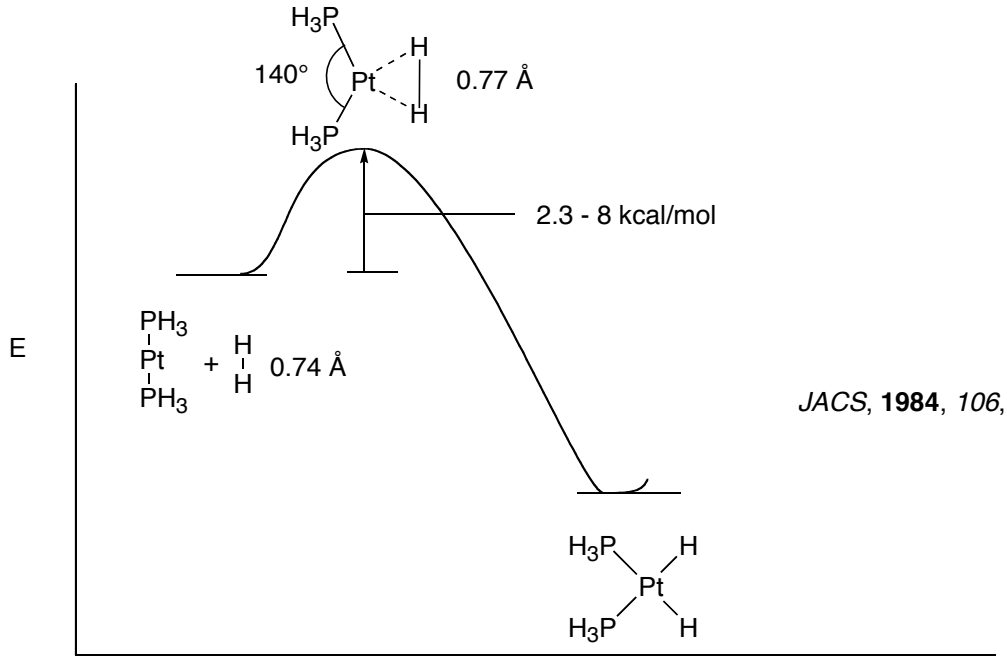


Heterolytic



1. Concerted Addition of H_2

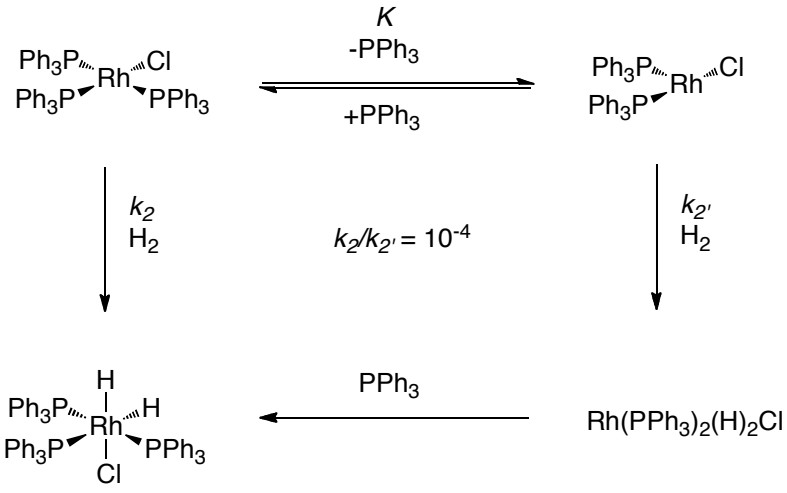
Theoretical treatment of the gas-phase oxidative addition of H_2 to $(H_3P)_2Pt$:



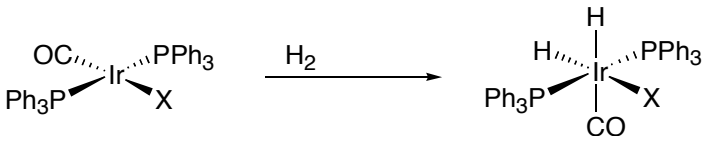
JACS, **1984**, *106*, 6928 and 8321

H_2 approaches side on rather than end on.
cis addition of H_2 occurs with a low barrier, while trans addition is forbidden.
The transition state occurs early as expected for an exothermic reaction.
The transition state is similar to our discussion of the bonding of dihydrogen to metal centers.

Dihydrogen addition to Wilkinson's catalyst



cis-dihydrogen addition to Vaska's complex (*JACS*, **1985**, *107*, 8049):



Kevin Shaughnessy
The University of Alabama, 2019

9. Rate = k_{obs}[Ir][H_2]

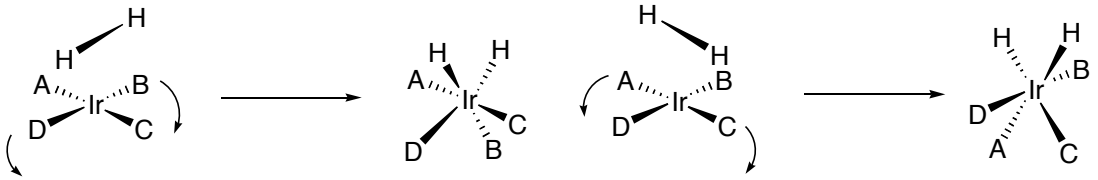
10. $\Delta H^{\ddagger}$ = 11 kcal/mol

11. $\Delta S^{\ddagger}$ = -21 eu

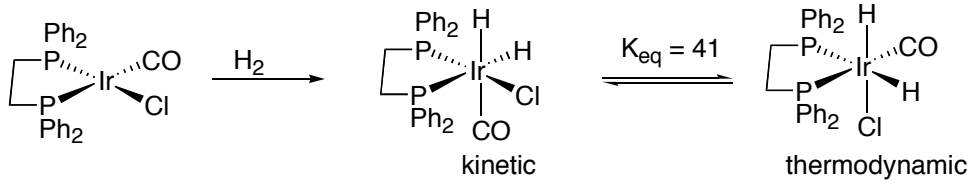
12. Rate: I > Br > Cl (100:14.3:0.93)

13. k_H/k_D = 1.09

Stereochemistry of oxidative addition: When H_2 adds to a square planar complex, it can add along two different L-M-L' axes.

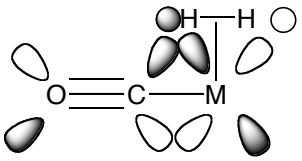


In the case of a chelated version of Vaska's complex, a stereospecific addition is seen. The H_2 approaches along the P-M-CO axis.



kinetic thermodynamic

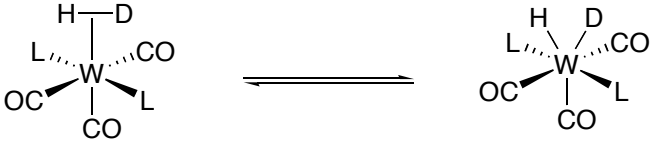
Why does CO move initially?



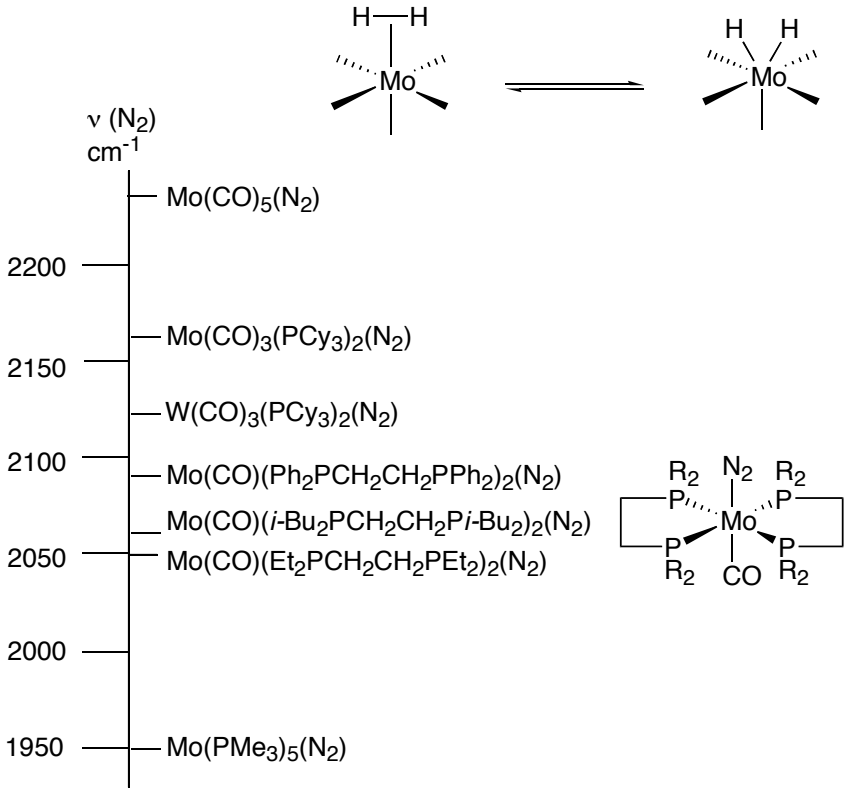
The π-acceptor orbital of CO helps to stabilize the H_2 complex promoting oxidative addition along that axis.

Dihydrogen complexes as intermediates:

The Kubas dihydrogen complex undergoes reversible oxidative addition to give the dihydride (*JACS*, **1986**, *133*, 9). A variable temperature NMR study showed that at 50 °C, the $^1J_{H\text{-}D}$ disappears reversibly.

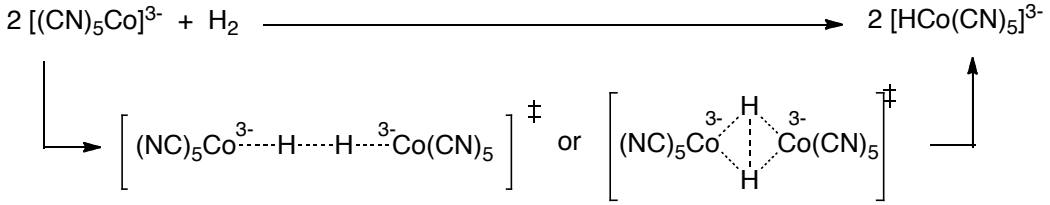


Since population of the σ* orbital is required for oxidative addition, predictions can be made about whether a metal complex will oxidatively add H_2, form an H_2 complex, or fail to react with H_2 based on the π-basicity of the metal center.



2. Homolytic Cleavage of Hydrogen:

Although less common, there are examples of 17 e metal complexes oxidatively adding H_2 by a homolytic mechanism.



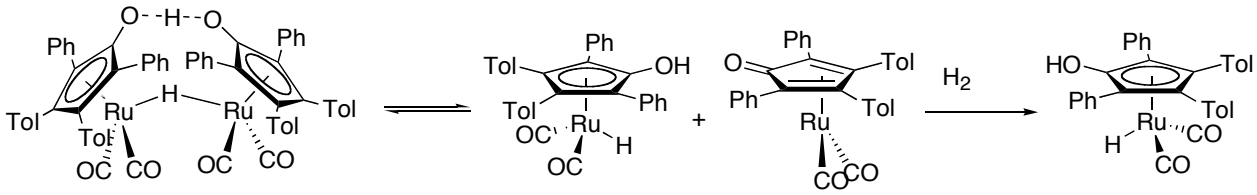
- rate = $k_{obs}[(CN)_5Co^{3-}]^2[H_2]$
- $\Delta H^{‡}$ = -0.7 kcal/mol
- $\Delta S^{‡}$ = -55 eu

Halpern, *Inorg. Chem.* **1970**, *9*, 2616; *Inorg. Chim. Act.* **1983**, *77*, L105-L106

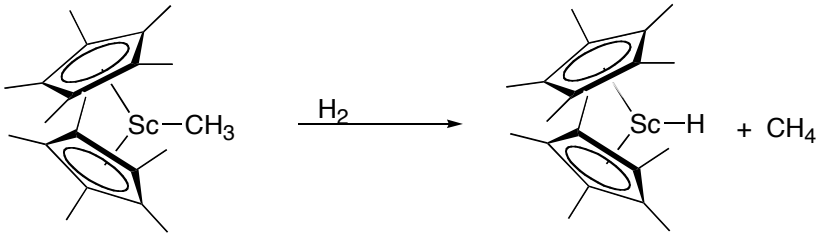
3. Heterolytic Cleavage:

Activation of H_2 by heterolytic cleavage is not formally an oxidative addition. The metal retains the same oxidation state and coordination number in the product. A base, either external or one of the ligands, promotes the heterolytic cleavage by deprotonating the bound H_2 ligand.

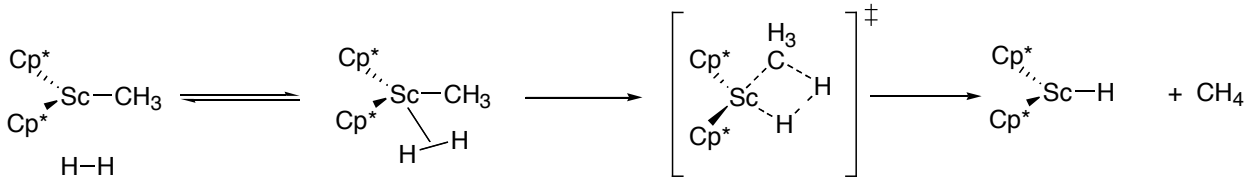
Heterolytic oxidative addition of H_2 promoted by a base is a key step in many ionic hydrogenation catalysts. An example is this hydride bridged Ru dimer, where the oxygen acts as a base to promote H_2 addition to give the hydroxy Ru-H. C.P. Casey, *JACS*, **2001**, *123*, 1092.



Participation by an internal ligand is very common for early transition metals, activation by an external base is less commonly observed.



Sc(III) is d^0 metal, so this reaction cannot involve oxidative addition of dihydrogen. Instead the reaction occurs by a process called *σ-bond metathesis*. The reaction likely proceeds through initial coordination of H_2 to the metal center, followed by a 4-center transition state, in which methane is released and a Sc-H bond is formed.



We will see that σ-bond metathesis plays an important role in the activation of C-H bonds by early transition metals as well.

B. Oxidative addition of Alkanes (C-H)

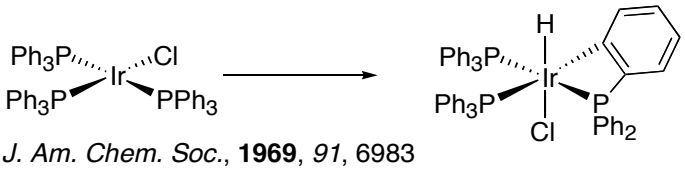
Same mechanisms as H_2 oxidative addition:
1. Concerted: $M^{n-} + H\text{-}CR_3 \rightarrow$ (alkane complex) $\rightarrow H\text{-}M^{n+2}\text{-}CR_3$
2. Homolytic: $2\ M^n + H\text{-}CR_3 \rightarrow M^{n+1}\text{-}CR_3 + M^{n+1}\text{-}H$
3. Heterolytic: $M\text{-}Z + H\text{-}CR_3 \rightarrow M\text{-}CR_3 + HZ$

General trend: sp^2 C-H bonds are usually activated more readily than sp^3 C-H bonds.

1. Concerted Oxidative Addition

a. Intramolecular C-H oxidative addition

Intramolecular oxidative addition, which is often called cyclometallation is very common.

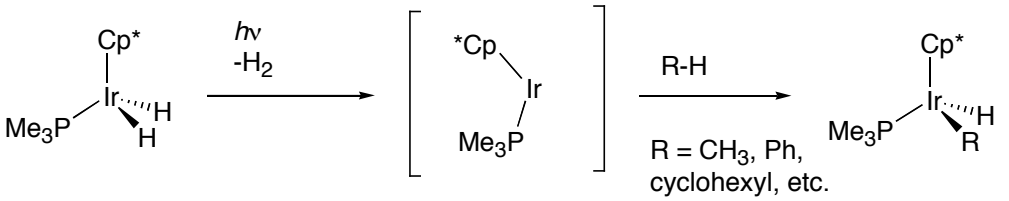


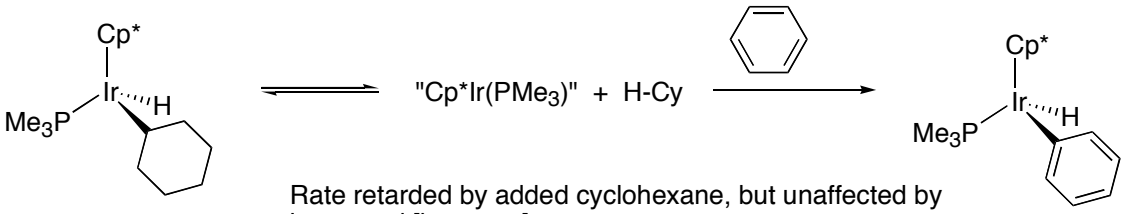
J. Am. Chem. Soc., **1969**, *91*, 6983

Prior coordination (agostic) allows the weakly binding C-H species to be held in close proximity to the metal center facilitating oxidative addition.

b. Intermolecular C-H oxidative addition

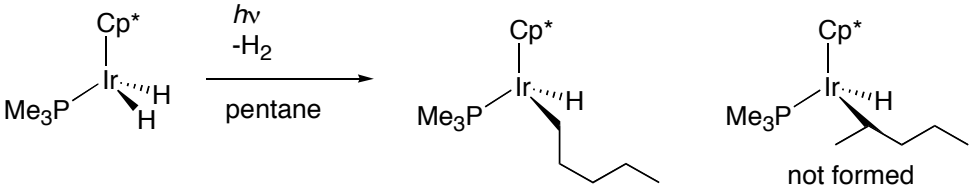
The first examples of intermolecular oxidative addition of alkanes was reported by Bergman (*J. Am. Chem. Soc.*, **1982**, *104*, 352 and **1983**, *105*, 7190) using coordinatively unsaturated iridium(I) complexes formed by expulsion of H_2.



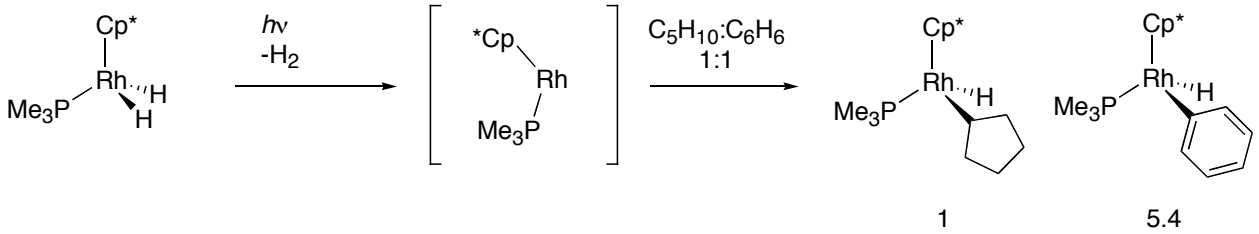


Rate retarded by added cyclohexane, but unaffected by increased [benzene].

For alkanes, less sterically hindered C-H bonds add at faster rate. This presumably is due to the greater stability of less sterically demanding alkane complexes.



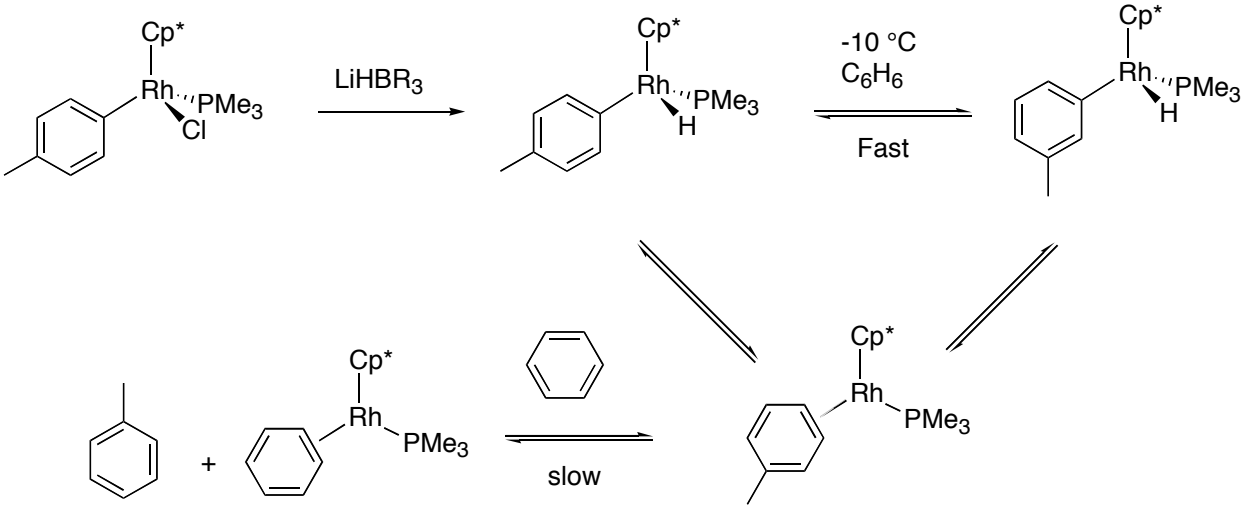
Oxidative addition of arenes is generally preferred over oxidative addition of alkanes.
Arene C-H: 110 kcal/mol
Alkane C-H: 95 kcal/mol



1 5.4

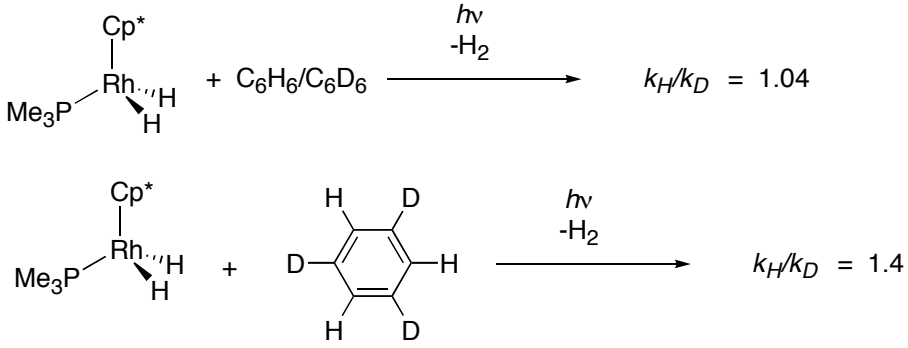
The preference must be kinetic rather than thermodynamic. Why would arene oxidative addition be kinetically preferred?

The importance of prior coordination has been studied by various authors for systems similar to Bergman's Ir complex.

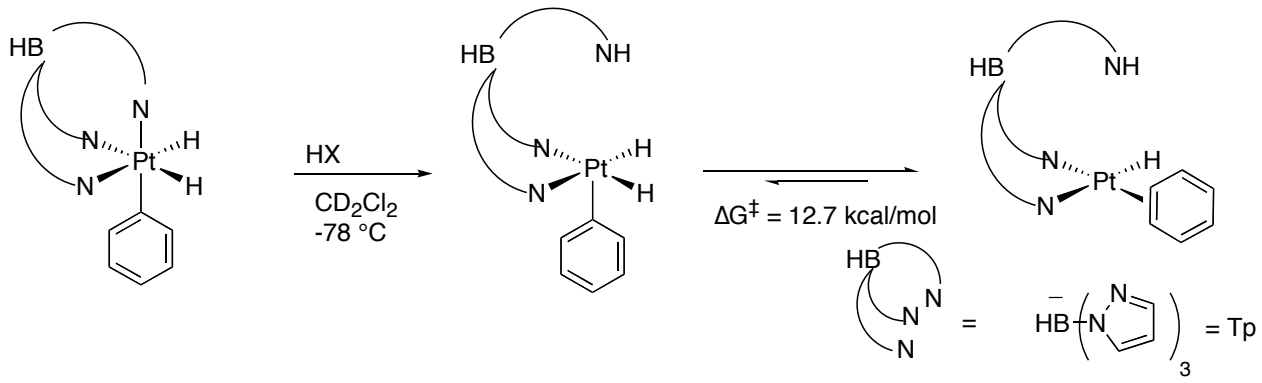


J. Amer. Chem. Soc. **1982**, *104* 4240.

Kinetic studies appear to confirm the intermediacy of an arene complex.



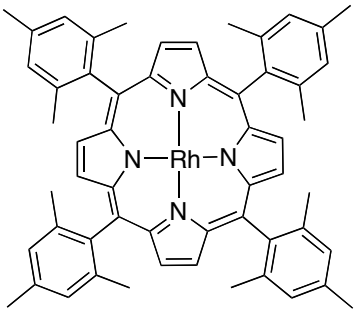
In a platinum system, the η^2–arene adduct is stable relative to the oxidative addition product and can be isolated and characterized. Exchange of arene protons and the Pt-H show that oxidative addition/reductive elimination occurs reversibly. (*J. Am. Chem. Soc.*, **2001**, *123*, 12724-5)



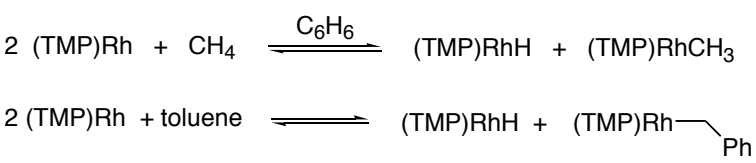
Oxidative addition often requires the presence of an open coordination site. Since alkanes are very weak ligands, they cannot displace other ligands readily. A recent example shows the first example of a stable product of oxidative addition of an alkane to a Pt(II) center.

2. Homolytic Activation

J. Am. Chem. Soc. **1991**, *113*, 5305

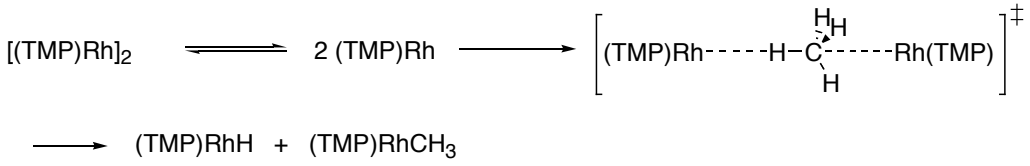


(TMP)Rh



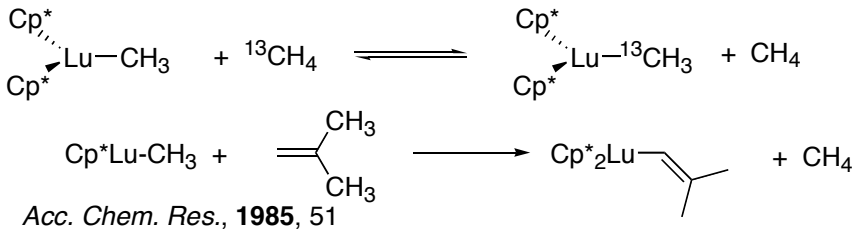
rate = $k_{obs}[(TMP)Rh]^2[R\text{-}H]$
$\Delta H^{\ddagger}$ = 7.1 kcal/mole
$\Delta S^{\ddagger}$ = -39 eu

Proposed mechanism



3. Heterolytic cleavage: σ-bond metathesis

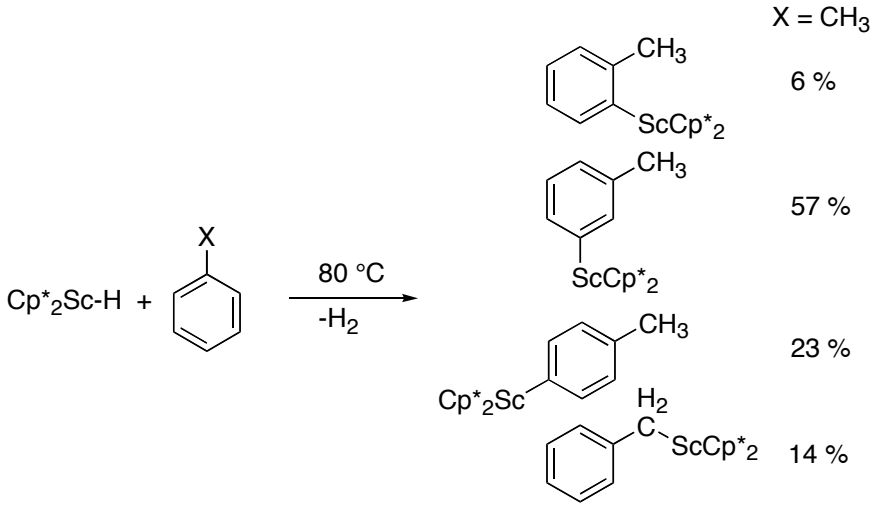
Early transition metals (usually d^0) with basic ligands (H^-, R^-) will heterolytically activate C-H bonds. There are now numerous examples of this type of reactivity. For d^0 metals, oxidative addition is not possible, so the reaction must proceed by σ-bond metathesis.



Acc. Chem. Res., **1985**, 51

Kevin Shaughnessy
The University of Alabama, 2019

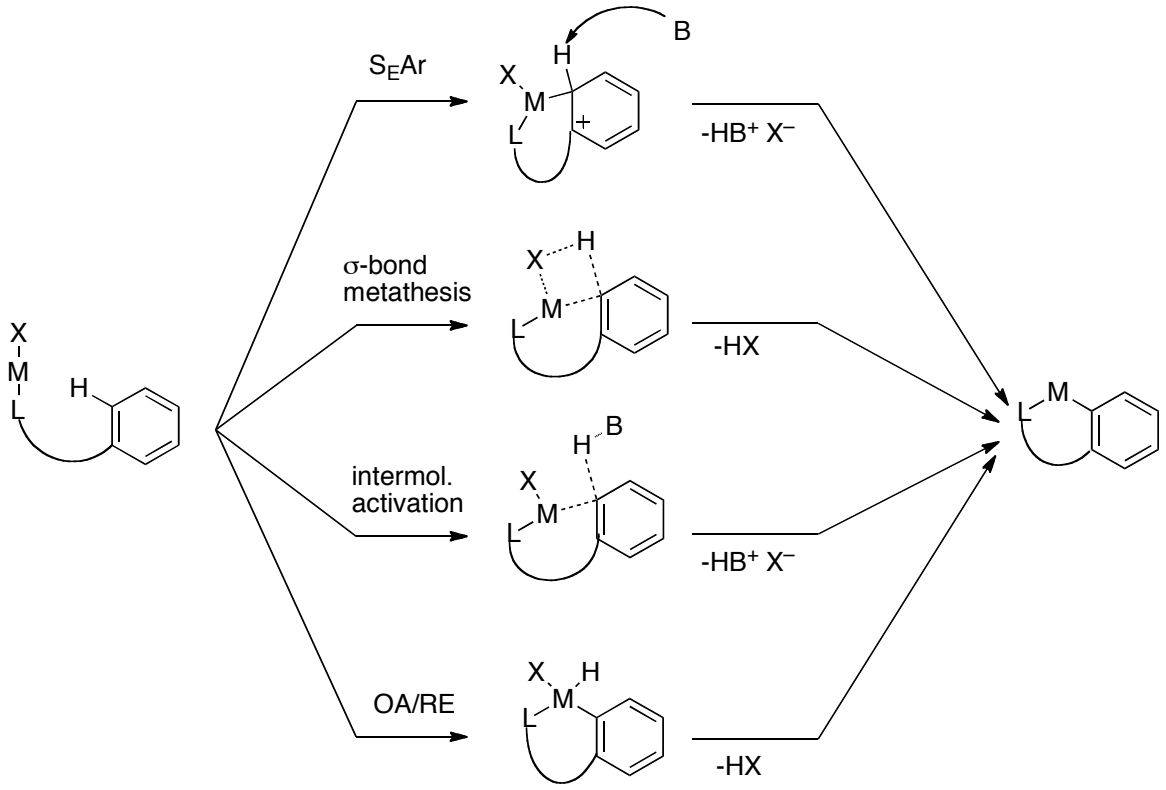
Is the mechanism simply electrophilic aromatic substitution?



X	k (X 10^5 $M^{-1}s^{-1}$)
H	3.3
CH_3	3.4
NMe_2	3.2

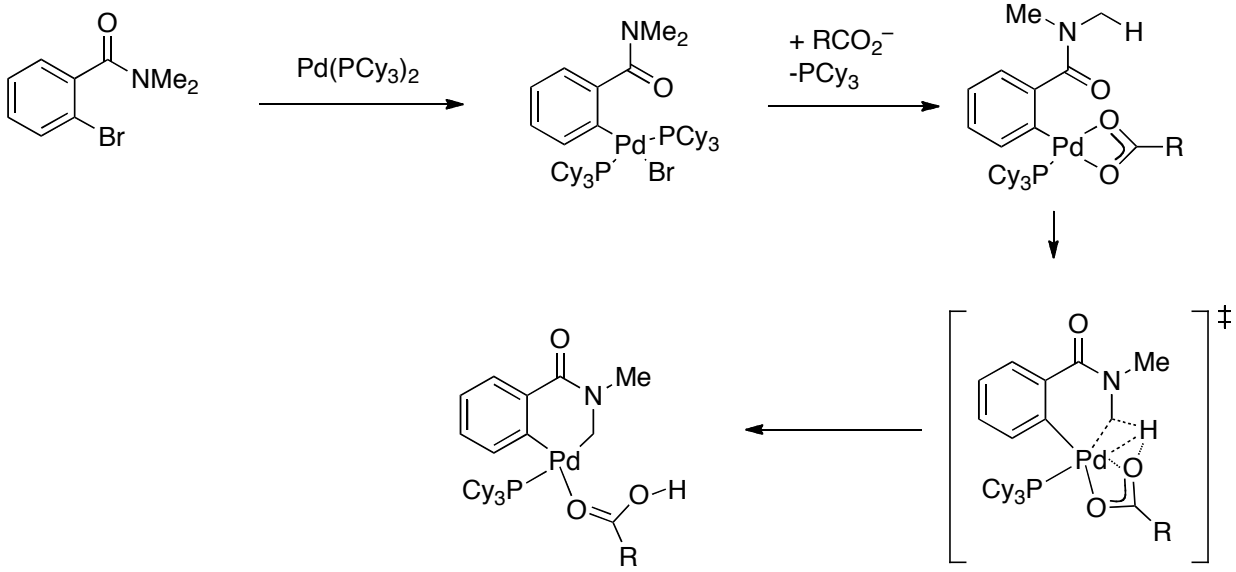
Late transition metals often undergo ligand-directed metallation. This is a key step in direct functionalization of sp^2 and sp^3 bonds by late transition metal catalysts. These processes are generally thought to follow a heterolytic mechanism. In some cases, C-H activation of arenes can be achieved without prior coordination. The mechanism is thought to be similar to the ligand-assisted routes.

Possible mechanisms include electrophilic aromatic substitution (S_EAr), σ-bond metathesis (intramolecalur heterolytic cleavage), intermolecular heterolytic cleavage, or oxidative addition/reductive elimination. The heterolytic mechanisms are most common. Review: Kapdi, A, *Dalton Trans*, **2014**, *43*, 3021.



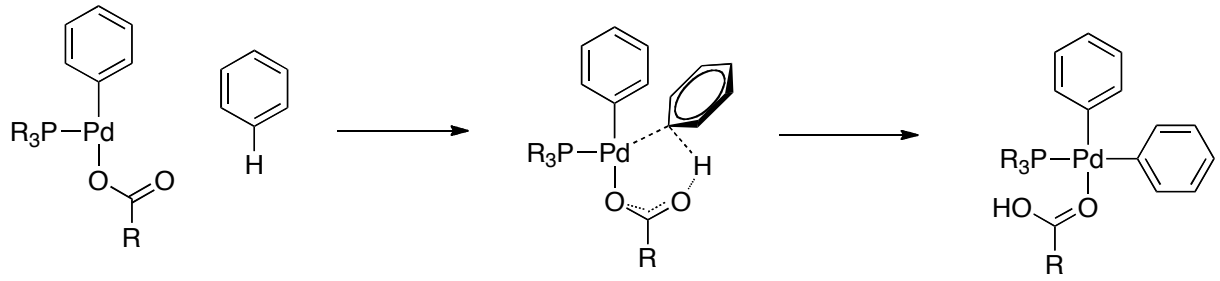
For C-H bond activation by palladium catalysts in the presence of carboxylate anions, a σ-bond metathesis mechanism has been implicated for both sp^3 (Rousseaux, and Fagnou, *J. Am. Chem. Soc.* **2010**, *132*, 10692-10705.and sp^2 (Fagnou. *J. Am. Chem. Soc.* **2008**, *130*, 10848-10849) C-H activation. This type of mechanism is often called concerted metalation/deprotonation (CMD) and is typical for lower-valent late transitions metals, particularly d^8 square planar complexes (Pd(II), Rh(I))

sp^3



Kevin Shaughnessy
The University of Alabama, 2019

sp^2



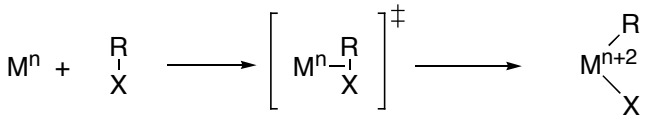
4-Oxidative Addition/Reductive Elimination: Part 2

2. Oxidative addition of polar reagents

Major mechanisms:

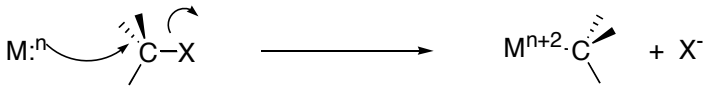
A. Two-electron Processes

1. Concerted



- Requires coordinative unsaturation
- Retention of configuration at carbon
- cis stereochemistry at the metal
- Mostly observed for oxidative addition of aryl halides

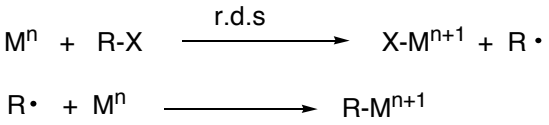
2. S_N2 Oxidative Addition



- inversion at carbon
- cationic (interceptable?) intermediate
- second order kinetics
- typical S_N2 reactivity patterns
- Most commonly seen with 1° and 2° alkyl halides

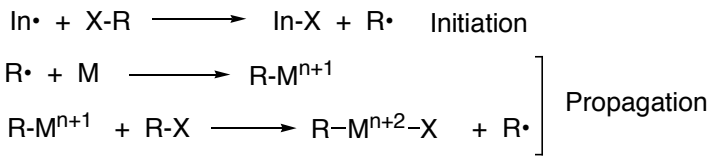
B. One-electron mechanisms

1. Atom Abstraction and Combination with a Second Metal



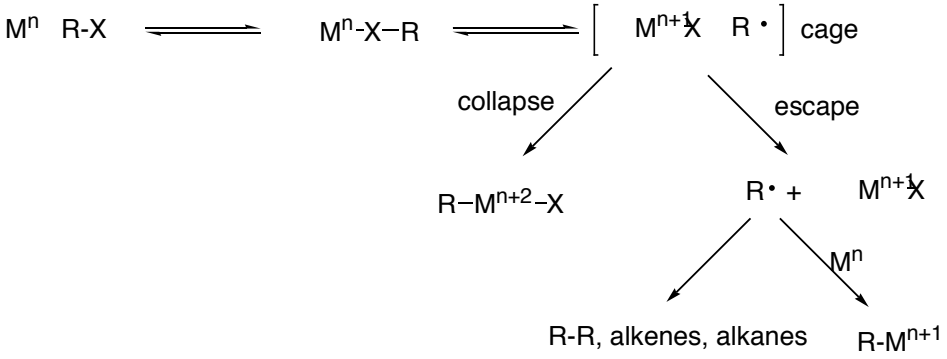
- Typical for metals with odd electron counts
- 2:1 M:RX stoichiometry
- racemization at carbon
- rate = k_{obs}[M][RX]
- tertiary > secondary > primary > methyl typical of free radical
- Evidence for R• (EPR, trapping, etc)

2. Radical Chain Pathway



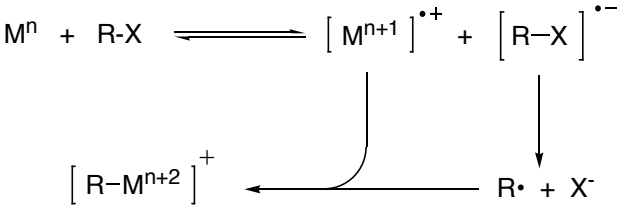
- Evidence for R• (racemization, homocoupling, disproportionation, trapping, radical clocks)
- Initiation or inhibition

3. Inner-Sphere Electron Transfer/Caged Radical-Pair Mechanism



- Similar to S_N2, but could give racemization at carbon

4. Outer-Sphere Electron Transfer Mechanism



- Occurs with high barrier
- Only occurs when RX coordination (inner-sphere) is inhibited (i.e., coordinatively saturated metals with strongly bound ligands) and S_N2 pathways are relatively slow.

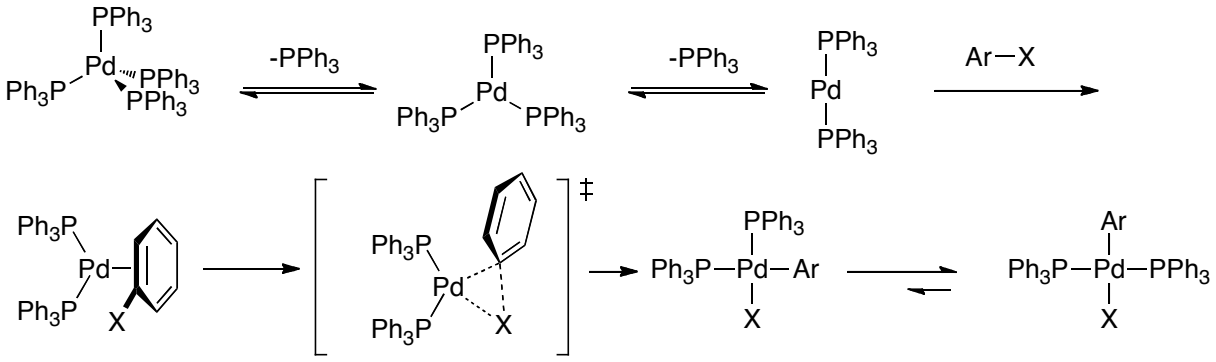
Ways to study mechanisms:

- Stereochemistry at metal and/or carbon
- Kinetics and thermodynamics
- Probes: radical traps, radical clocks, etc.

2-electron Processes

1: Concerted Oxidative Addition: Oxidative addition of aryl halides to Pd(0)

$Pd(PPh_3)_4$ mechanism: Kinetic studies have shown that the 14-electron $Pd(PPh_3)_2$ species formed by loss of two equivalents of PPh_3 is the species that reacts with the aryl halide. Initial coordination as a π-complex is believed to occur, followed by insertion into the C-X bond through a 3-centered transition state.



J. Organomet. Chem. **1971**, *28,* 287-291

Halide Effect: PhI (room temp) > PhBr (80 °C) > PhCl (no reaction at 135 °C). solvent = benzene ArF are generally inert

Electronic Effects (Aryl Halide): Electron donating groups slow down the rate of oxidative addition, while electron withdrawing groups accelerate the reaction: PhCl (no reaction at 135 °C) < *p*-Cl-benzophenone (89%, 135 °C), < *p*-chlorobenzonitrile (97%, 100 °C) < 4-chloronitrobenzene (86%, 80 °C).

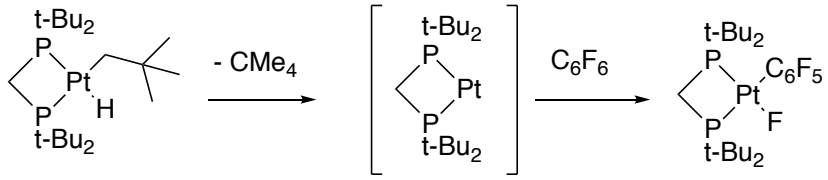
Stereochemistry: The initial product is presumably the cis-diphosphine complex, but the isolated product is usually the trans-diphosphine product. In most cases, the cis intermediate cannot be observed.

Ligand Effects: Changing the steric, electronic, and chelating properties of the ligands can significantly affect the rate and mechanism of the oxidative addition reaction.

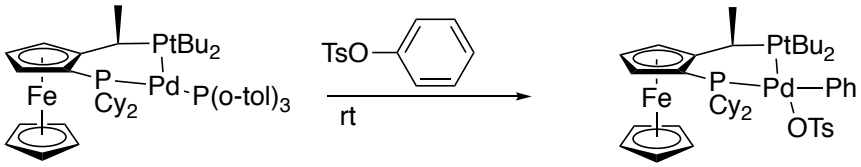
Ligand Size: Larger ligands can accelerate oxidative addition. They promote formation of coordinatively unsaturated LPd(0) complexes, which are highly reactive towards aryl halides.

Electron Donating Ability: Increased electron donating ability of the ligand accelerates oxidative addition. With P(*t*-Bu_3), oxidative addition can occur efficiently at, or below, room temperature. ArCl oxidative addition occurs efficiently at 25-60 °C.

Chelating Ligands: Small bite angles can accelerate oxidative addition. The (L-L)Pd(0) intermediate is highly strained resulting in very high reactivity. For example, photochemically generated (CH_2(P*t*-Bu_2)$_2$)Pt(0) will oxidatively add aryl fluorides (*Chem. Ber.* **1992**, *125*, 629). These strained complexes are usually not good catalysts, because the resulting oxidative addition product is too stable.

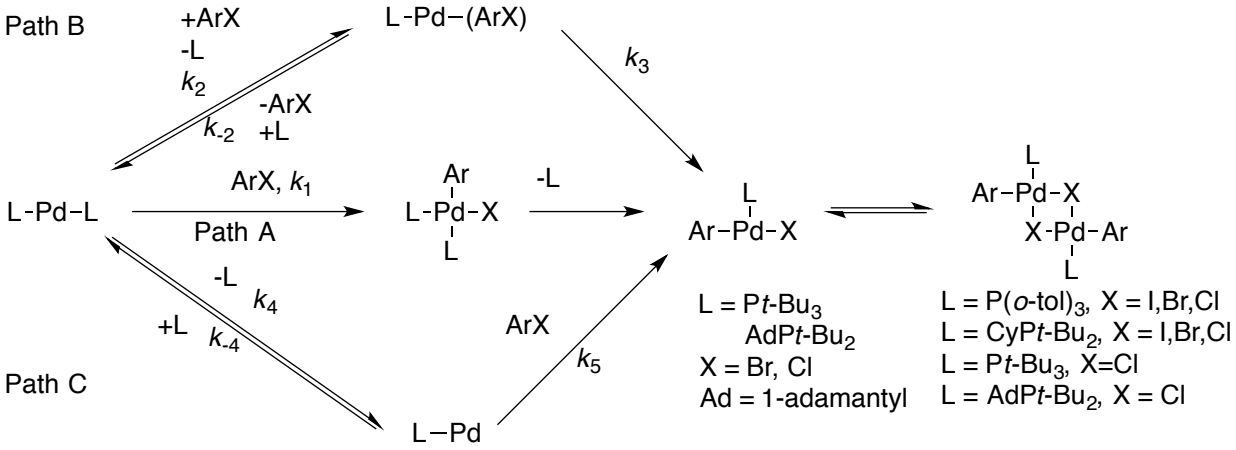


In other cases, larger bite angle complexes, such as the Josiphos ligands, can promote difficult oxidative additions of aryl tosylates (*JACS*, **2003**, *125*, 8704).



Mechanisms with sterically-hindered phosphines: For large cone angle ligands (i.e., P(*o*-tol)$_3$, P*t*-Bu$_3$), the stable Pd(0) complex is a 14-electron L$_2$Pd species. Ligand dissociation occurs prior to oxidative addition and the resulting products are either 3-coordinate LPd(Ar)X complexes or dimeric [LPd(ArX)]$_2$ species (Hartwig, *JACS*, **2009**, *131*, 8141-8154). Depending on the ligand and ArX, several different mechanisms can be considered. Possible mechanisms include:

- Path A: Direct oxidative addition to L$_2$Pd followed by ligand dissociation: This mechanism does not occur for large cone angle ligands. With the smaller dicyclohexylphosphine ligand, this mechanism may occur.
- Path B: Reversible associative ligand substitution of the aryl halide for phosphine followed by rate limiting oxidative addition
- Path B': Irreversible associative ligand substitution followed by fast oxidative addition. Oxidative addition faster than associative displacement of ArX by L.
- Path C: Reversible ligand dissociation followed by oxidative addition to the 12-electron LPd species. Could also consider this a dissociative substitution of ArX for L, followed by oxidative addition.
- Path C': Irreversible ligand dissociation followed by oxidative addition (oxidative addition faster than recoordination of L).



Path A:

$rate = k_{obs}[L_2Pd] \quad k_{obs} = k_1[ArX]$

Path B

$$rate = k_{obs}[L_2Pd]$$

$$k_{obs} = \frac{k_2 k_3[ArX]}{k_3 + k_{-2}[L]}$$

$$\frac{1}{k_{obs}} = \left(\frac{1}{k_2} + \frac{k_{-2}[L]}{k_2 k_3}\right)\frac{1}{[ArX]}$$

Path B': $k_3 \gg k_{-2}[L]$

$$rate = k_{obs}[L_2Pd] \quad k_{obs} = k_2[ArX]$$

Path C:

$$rate = k_{obs}[L_2Pd]$$

$$k_{obs} = \frac{k_4 k_5[ArX]}{k_5[ArX] + k_{-4}[L]}$$

$$\frac{1}{k_{obs}} = \frac{1}{k_4} + \frac{k_{-4}[L]}{k_4 k_5[ArX]}$$

Path C': $k_5[ArX] \gg k_{-4}[L]$

$$rate = k_{obs}[L_2Pd] \quad k_{obs} = k_4$$

Experimental Data

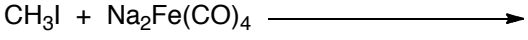
ArI: Kinetic data shows first order dependence on [ArI] and zero order dependence on [L].

ArBr: Kinetic data shows a first order dependence on [ArBr]. A plot of observed rate constant (k_{obs}) vs. [ArBr] was linear, but had a non-zero intercept. There was no dependence on [L].

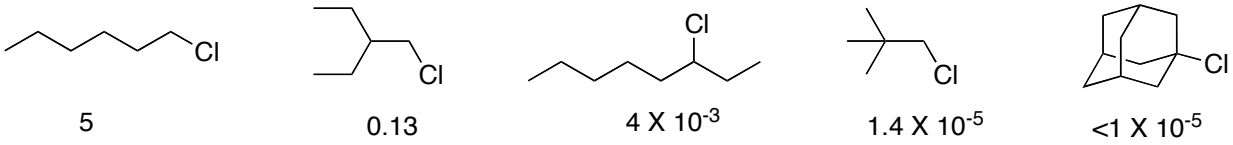
ArCl: Kinetic data shows a first order dependence on [ArCl] and inverse first order dependence on [L]. A plot of $1/k_{obs}$ vs. 1/[ArCl] was linear with a non-zero y-intercept.

2: S_N2-type oxidative addition:

General Features: Oxidative addition to $Na_2Fe(CO)_4$ (Collman, *JACS*, **1977**, *99*, 2515)

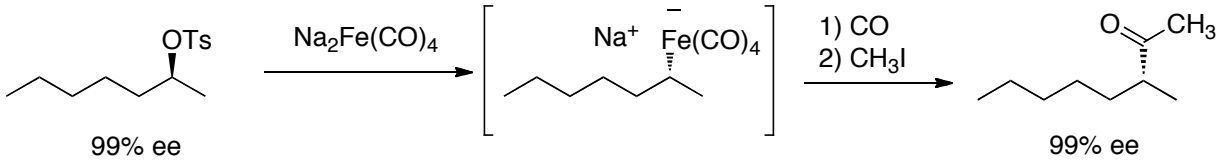


Substrate reactivity

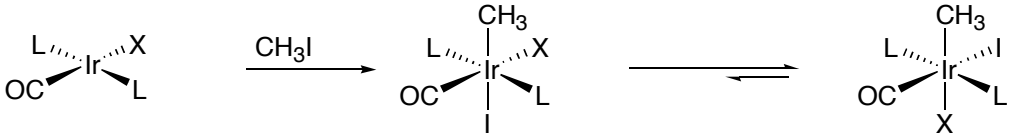


$C_{10}H_{21}X$ X = I > Br > OTs > Cl
51 1 0.58 2.3 X 10^{-3}

Stereochemistry

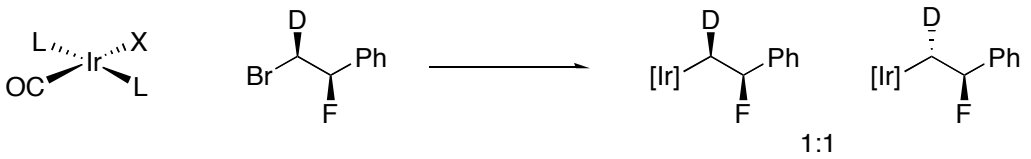


Oxidative addition to Vaska's complex:



Halpern, *J. Am. Chem. Soc.* **1966**, *88*, 3511

- Rate = k_{obs}[Ir][CH_3I]
- $\Delta H^{\ddagger}$ = 5-9 kcal/mol
- $\Delta S^{\ddagger}$ = -50 eu
- Faster in polar solvents (reaction 10X faster in DMF than in toluene, *J. Phys. Chem.* **1973**, *77*, 290)
- Faster with more basic phosphines
- rate RX: I > Br > Cl. CH_3I >> CH_3CH_2I >> R_2CHI >> R_3CI
- unaffected by radical traps or initiators

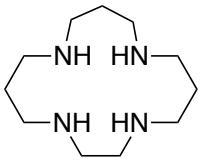


- ROTs slower than RBr
- Initiated by O_2, AIBN, benzoyl peroxide
- Inhibited by radical traps

<u>1-electron Processes</u>

1. Atom Abstraction:

Reaction of Cr(II) with alkyl halides

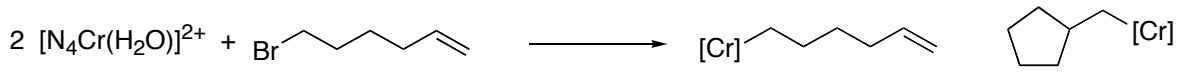


= N_4

2 $[N_4Cr(H_2O)]^{2+}$ + RX $\xrightarrow{H_2O}$ $[N_4CrR(H_2O)]^{2+}$ + $[N_4CrX(H_2O)]^{2+}$

Espenson, *Inorg. Chem.*, **1979**, *18*, 2587.

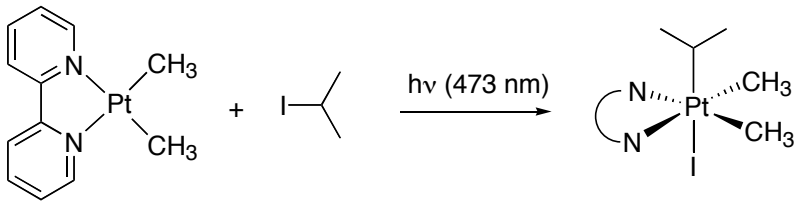
- rate = k_{obs}[Cr][RX]
- relative rates: MeI (1) < EtI (9) < *i*-PrI (107) < BnBr (4.15×10^5)
- reaction with 6-bromo-1-hexene



0.022 M Cr, 0.0029 M RX: 1.6 : 1
0.044 M Cr, 0.0048 M RX: 4.9 : 1

2. Radical Chain

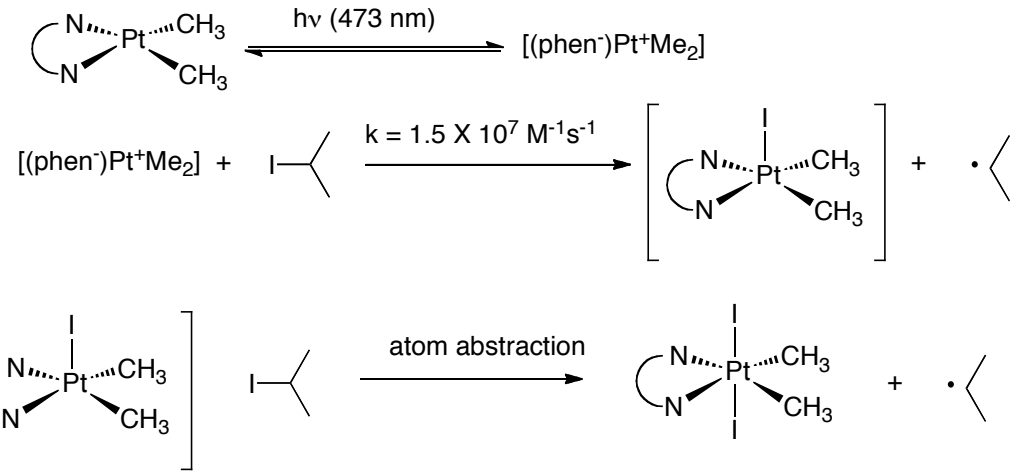
Radical Chain Oxidative addition of alkyl halides to Pt(II)



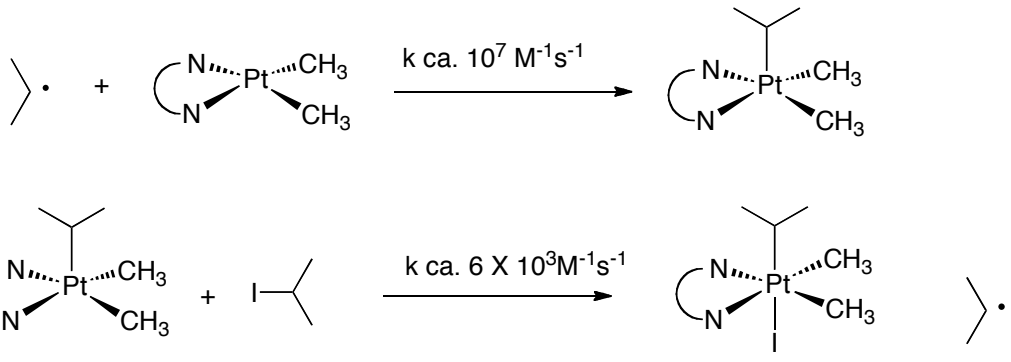
J. Am. Chem. Soc. **1985**, *107*, 1218-1225

- Reaction does not occur in the dark
- Reaction inhibited by pyrene and activated by benzophenone
- Quantum efficiency dependent on [Pr•]
- Only Pr• was trapped by a radical trap
- Free radical scavenger reduced the quantum yield by 2000 X

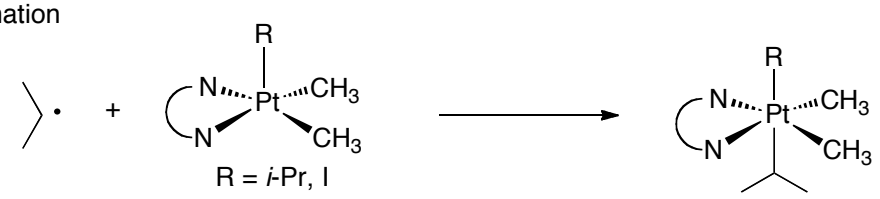
Initiation



Propagation

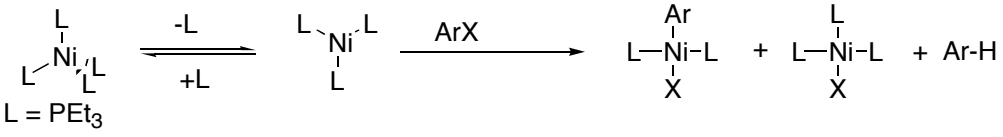


Termination

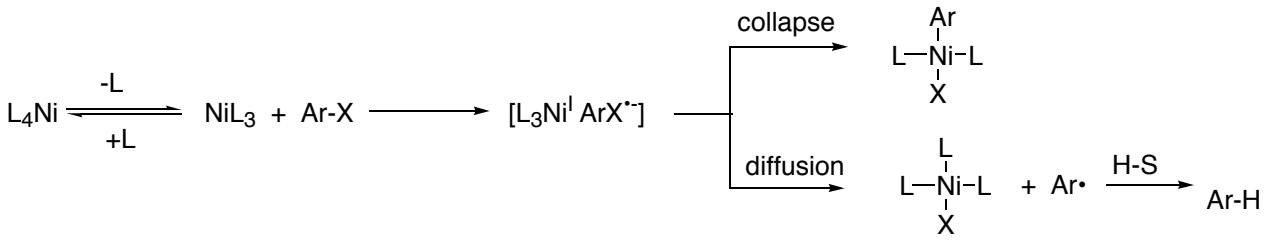


5. Inner-Sphere Electron Transfer

Oxidative addition of aryl halides to $L_4Ni(0)$



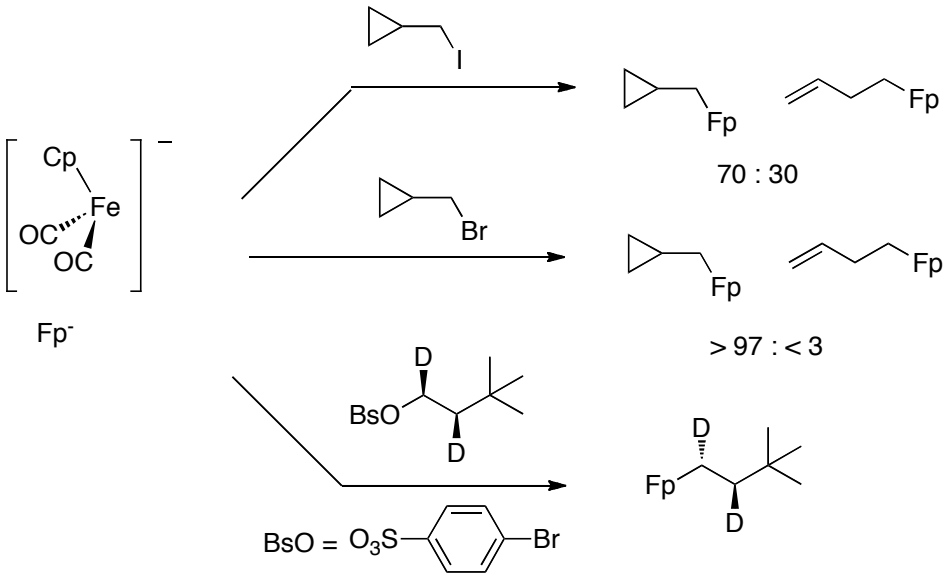
- Yield of ArNiX is highest for ArCl and lowest for ArI
- ArNiX:XNi(I) ratio is largely unaffected by degree of coordination
- The reaction is not inhibited by free radical scavengers
- All aryl halides show a similar Hammet plot dependence



Kochi, *J. Am. Chem.Soc.*, **1979**, *101*, 6319

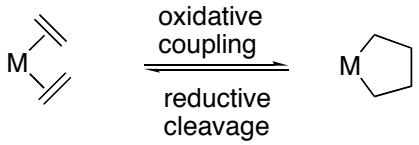
6. Outersphere Electron Transfer

Alkylation of Fp^-

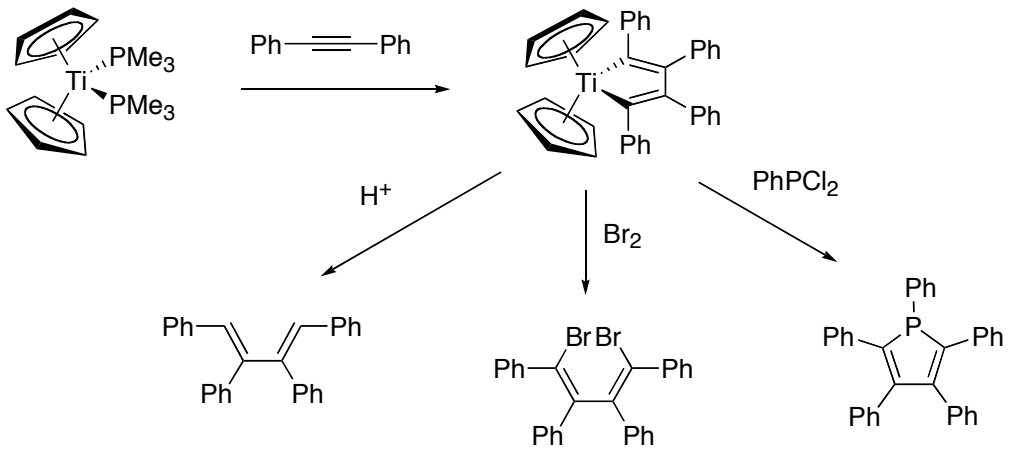


3. Oxidative Coupling

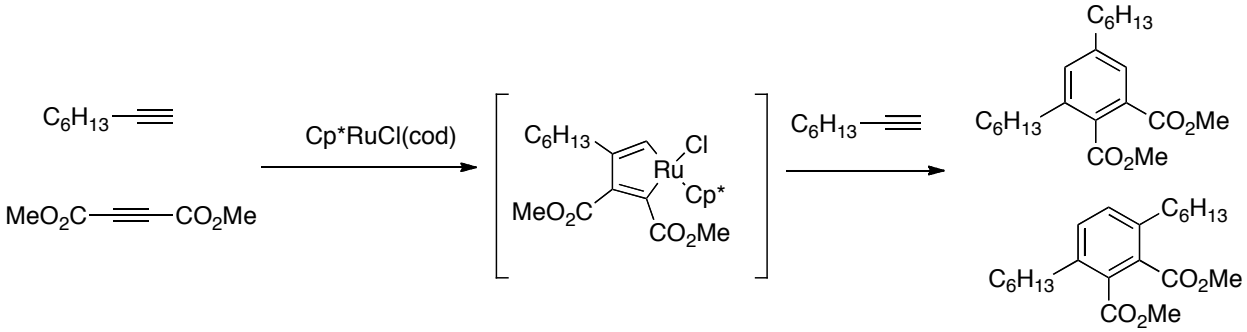
π-bound ligands can be coupled at transition metal centers in a formal oxidative coupling. Often this is referred to as reductive coupling because the organic fragments are reduced. It all depends on your point of view.



This process can be applied to the stoichiometric, or in some cases catalytic, coupling of unsaturated molecules. A stoichiometric example is the coupling of alkynes to give a metallacyclopentadiene. This species can be reacted with various electrophiles to give dienes or heterocycles.



Metallacyclobutadienes are believed to be key intermediates in the [2+2+2] cyclotrimerization of alkynes to give arenes and heterocycles. (Mitsudo, *J. Mol. Cat. A.* **2004**, *205*, 35).



4. Reductive Elimination

Reductive elimination is the microscopic reverse of oxidative addition. Therefore the observed mechanisms are the reverse of those we've discussed. Those that are of the most are interest are the concerted reductive eliminations that produce C-H, C-C, or C-X bonds.

General observations (H-H, C-H, C-C):

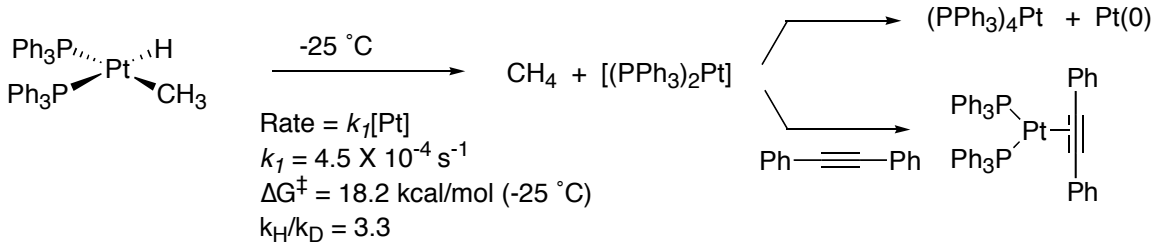
2. rate of reductive elimination: H-C > H-H > C-C, although -ΔG increases as H-H < C-H < C-C

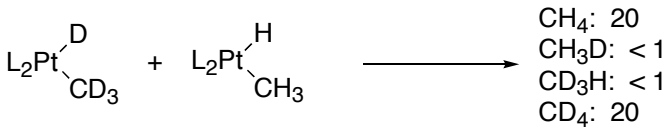
3. The low valent ML_n fragment formed upon reductive elimination must be stable

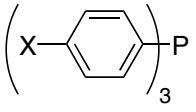
4. π-accepting ligands generally accelerate reductive elimination

5. Reductive elimination of non-polar bonds (H-H, C-H, C-C) is common, while reductive elimination of polar bonds is less common

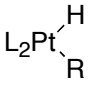
Halpern and Sen, *J. Am. Chem. Soc.*, **1978**, *100*, 2915





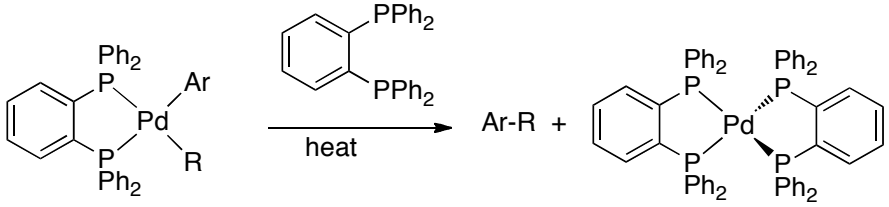


X	k_1 (10^4)
Cl	9.2
H	4.5
CH_3	1.4
OCH_3	0.47



Ph > Et > CH_3

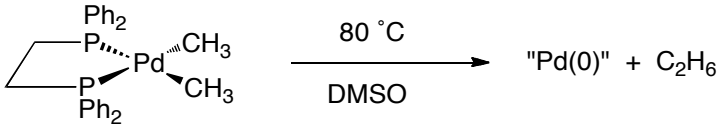
Reductive elimination is favored with more electron-donating alkyl groups (Hartwig, *Organometallics*, **2004**, *23*, 3398).

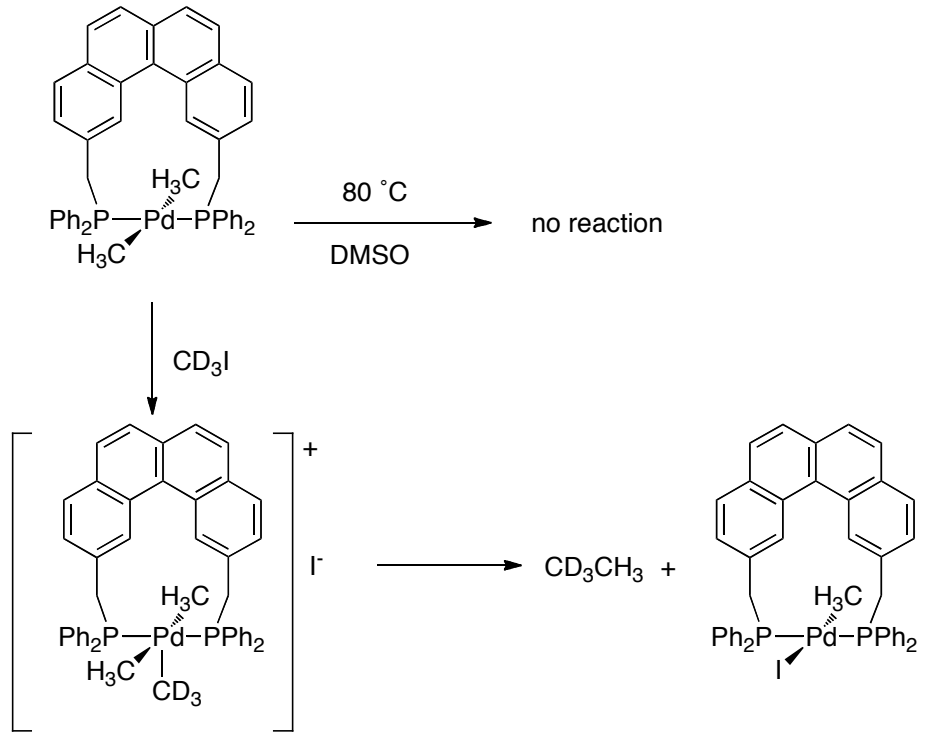


R	k_{rel}
CH_3	600
Bn	250
CH_2CF_3	1.7
CH_2CN	1
CF_3	No Rxn

A. Geometric requirement

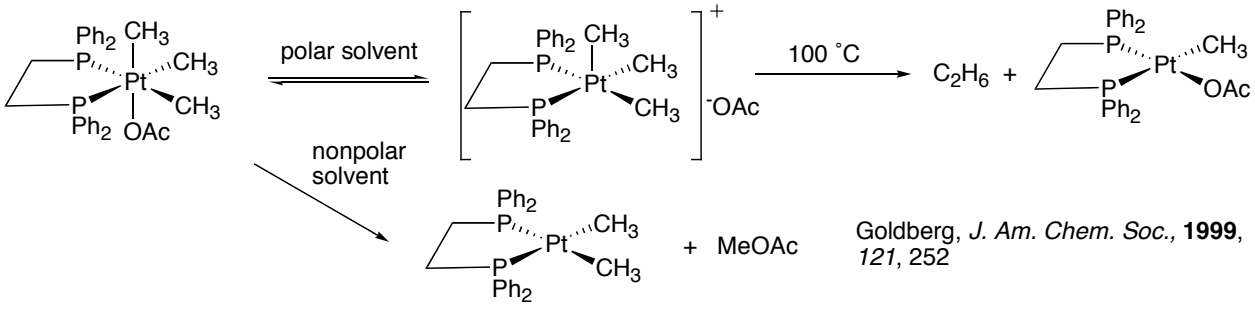
Concerted reductive elimination requires cis coordination of the ligands to be eliminated.



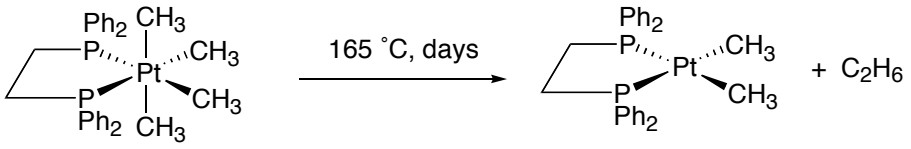


B. Ligand dissociation (dissociative)

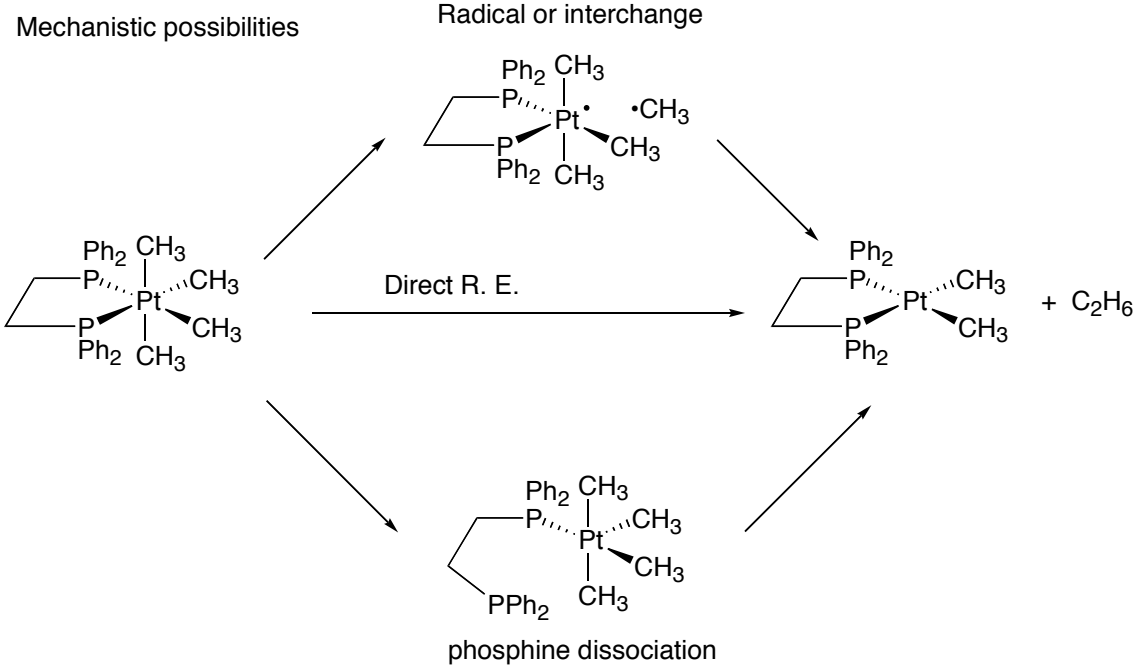
Except for particularly facile reductive elimination (H-H or H-CR_3), prior ligand dissociation is often required.

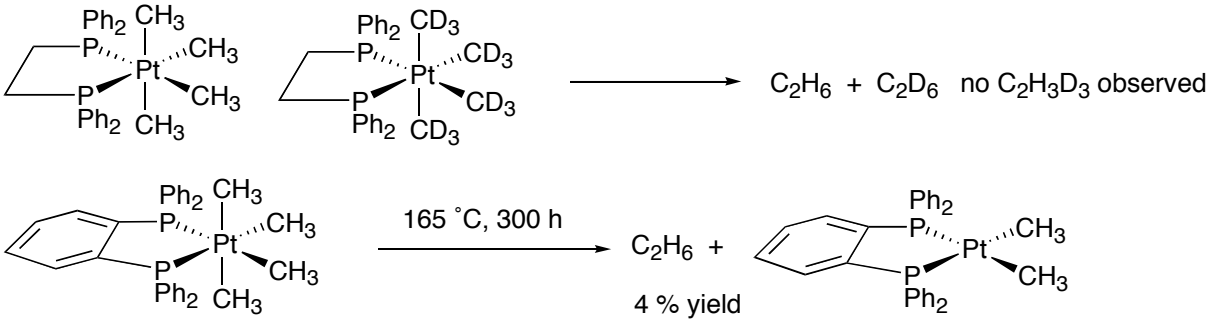


Goldberg, *J. Am. Chem. Soc.,* **1999**, *121*, 252



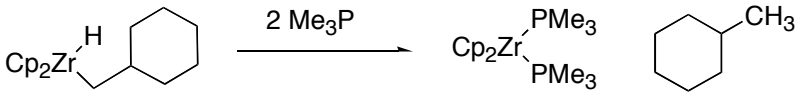
Golberg, *J. Am. Chem. Soc.*, **2000**. *122*, 962-3



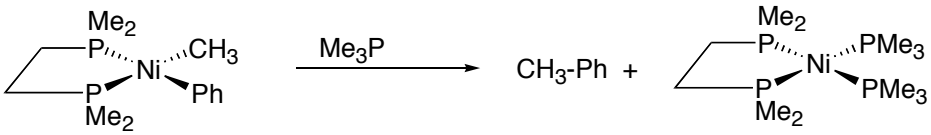


C. Ligand assisted (associative)

Less commonly prior ligand association will accelerate reductive elimination. Normally we would expect that coordination of electron rich ligands would make reductive elimination less favorable, however the increased steric strain promotes the reductive elimination.

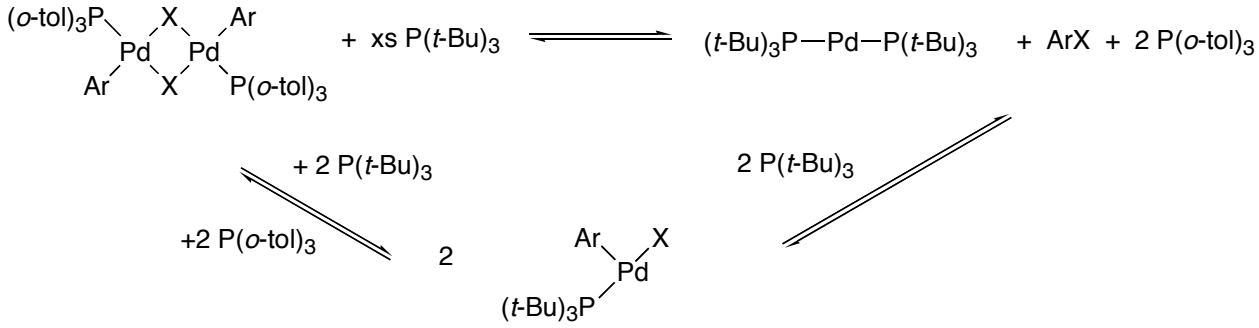


Schwartz, *J. Am. Chem. Soc.* **1981**, *103*, 2687-2695



Tatsumi, *J. Am. Chem. Soc.*, **1984**, *106*, 8181 (theoretical treatment)

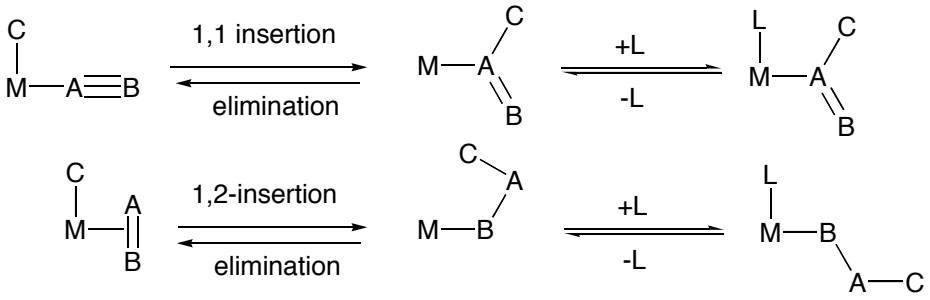
Very sterically demanding ligands, such as $(t\text{-Bu})_3P$, can even induce reductive elimination of aryl halides from Pd(II) complexes. Normally oxidative addition is an exothermic process, so the observation of thermodynamically preferred reductive elimination is rather unusual.



Hartwig, *Organometallics*, **2004**, *23*, 1533-1541.

5-Migratory Insertion and Elimination

The third fundamental transformation involved in organometallic transformations (ligand substitution and oxidative addition/reductive elimination being the others we've discussed) is migratory insertion/elimination.



General Features:

- There is no change in the formal oxidation state of the metal unless AB is an alkylidene or alkylidyne.

- The groups undergoing migratory insertion must be cis to one another. In complexes where the cis coordination sites are blocked by strongly coordinated ligands insertion or elimination processes are not possible.

- An open coordination site is created during migratory insertion. Therefore, for the reverse reaction--elimination--to occur, an open coordination site must be generated by ligand dissociation.

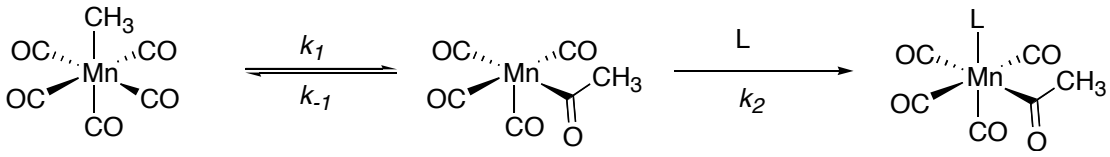
- In cases where C is a chiral carbon center, the reaction usually occurs with retention of configuration.

- Cases where C migrates to AB followed by coordination of L in place of C, and where AB migrates to C followed by coordination of L in place of AB are both known.

1,1-Migratory Insertion: Insertion of CO:

Most of the early mechanistic work has been carried out on iron and manganese alkyls.

A. Kinetics and Mechanism:



$$\text{rate} = \frac{-d[\text{MeMnCO}_5]}{dt} = \frac{k_1 k_2[\text{L}][\text{MeMnCO}_5]}{k_{-1} + k_2[\text{L}]}$$

i. If k_{-1} is very small relative to k_2[L], then the rate expression is simplified to:

$$\text{rate} = \frac{-d[\text{MeMnCO}_5]}{dt} = k_1[\text{MeMnCO}_5]$$

ii. If k_{-1} is large relative to k_2[L], then the equation becomes:

$$\text{rate} = \frac{-d[\text{MeMnCO}_5]}{dt} = \frac{k_1 k_2[\text{L}][\text{MeMnCO}_5]}{k_{-1}}$$

iii. If k_{-1} and k_2[L], have similar magnitudes, then a complex rate expression is observed that displays saturation in the ligand concentration dependence..

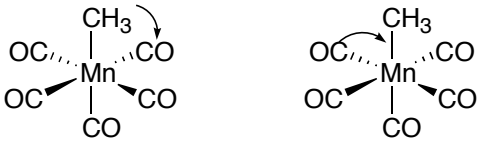
$$\text{rate} = \frac{-d[\text{MeMnCO}_5]}{dt} = \frac{k_1 k_2[\text{L}][\text{MeMnCO}_5]}{k_{-1} + k_2[\text{L}]} = k_{obs}[\text{MeMnCO}_5]$$

$$k_{obs} = \frac{k_1 k_2[\text{L}]}{k_{-1} + k_2[\text{L}]}$$

Under pseudo-first order conditions ([L] >> [MeMn(CO)$_5$], a plot of $1/k_{obs}$ vs. $1/[L]$ will have slope = k_{-1}/k_1k_2 and y intercept = $1/k_1$.

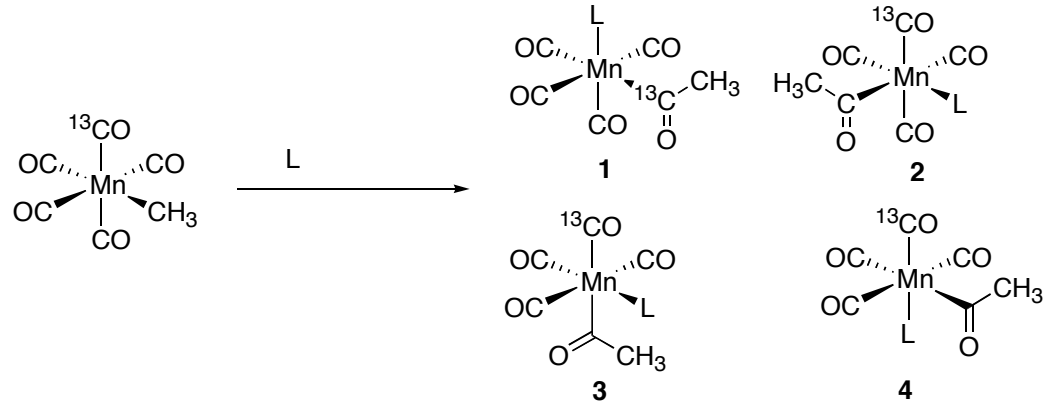
B. Stereochemistry at the Metal:

For the migratory insertion of CO into a Mn-Me bond, two limiting mechanisms could be envisioned. Methyl migration to a bound CO (A), or CO migration to the Mn-Me bond (B).



A **B**

To address this issue, Calderazzo looked at the migratory insertion of $CH_3Mn(CO)_5$ labeled with ^{13}CO *cis* to the methyl substituent. There are 4 possible stereochemical outcomes considering both mechanisms. (*J. Organomet. Chem.*, **1967**, *10*, 101; *Angew. Chem. Int Ed. Engl.* **1977**, *16*, 299)

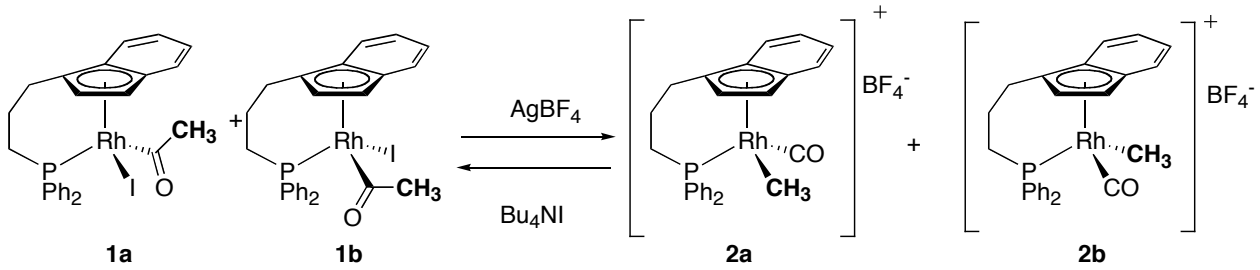


1 **2** **3** **4**

When the reaction is performed, a 1:2:1 mixture of **1**, **2**, and **3** was formed. Which mechanism is responsible for this product distribution?.

Kevin Shaughnessy
The University of Alabama, 2019

A more recent example used a chiral rhodium complex (*Organometallics*, **2001**, *20*, 2431). The presence or absence of iodide determined whether the compound existed as an acyl iodide complex or a methyl carbonyl complex. By looking at the stereochemistry of the migratory insertion/deinsertion using the chemical shift of the methyl groups, the nature of the migration could be determined..



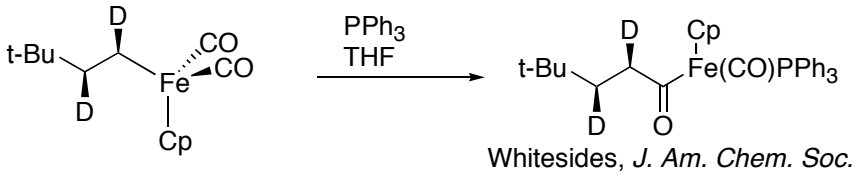
1a **1b** **2a** **2b**

Major: δ 2.22
MInor: δ 2.85

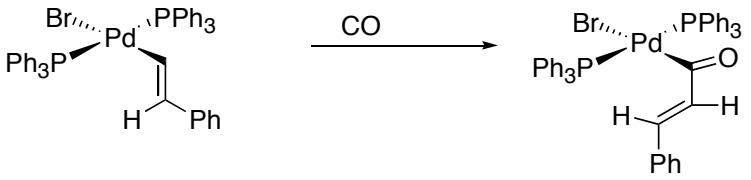
Major: δ 1.10
Minor: δ -0.26

C. Stereochemistry at Carbon

For concerted migratory insertion or elimination, carbon stereochemistry is nearly always retained.



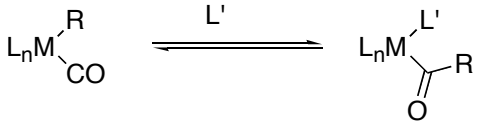
Whitesides, *J. Am. Chem. Soc.*, **1974**, *96*, 2814



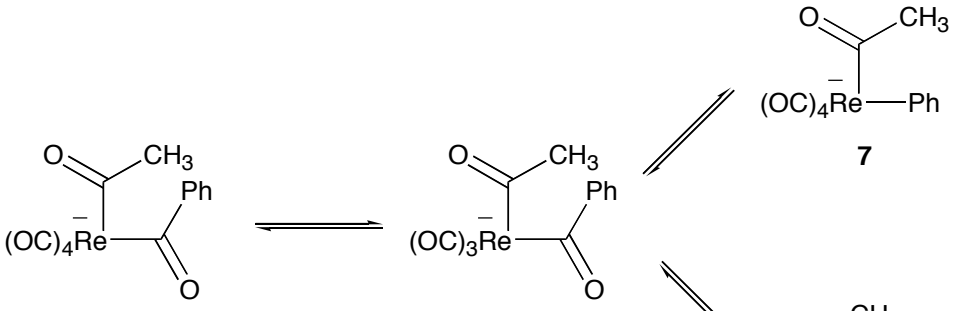
Gazz. Chim. Ital, **1973**, *103*, 793

D. Aptitude for Migration:

The identity of R has a significant effect on the aptitude to undergo migratory insertion to form an metal acyl. Migratory insertion ability cannot be easily correlated to M-R bond strength.



R	M-L BDE	Insertion/Elimination
$PhCH_2$	29	Slower insertion than CH_3
CH_3CO-	39	Elimination
CH_3	44	Fast insertion
CF_3	49	Elimination
Ph	49	Slower insertion than CH_3, but the product is more stable
H	59	Elimination



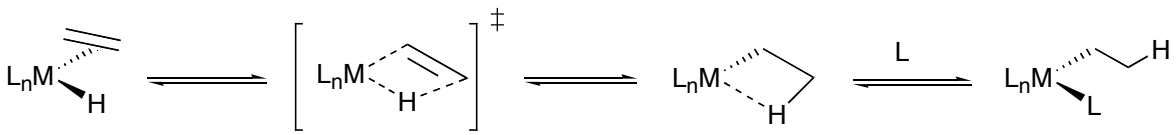
J. Am. Chem. Soc., **1980**, *102*, 2723

E. Accelerating Insertion:

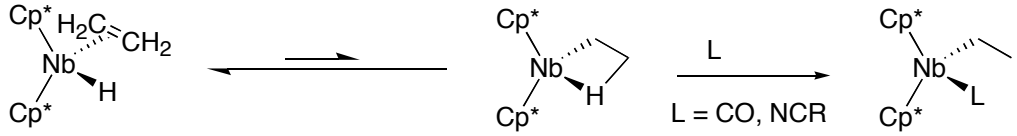
- Sterically bulky ligands: Insertion reduces the steric strain in the metal complex.
- Lewis acids: Coordinate to the oxygen of CO increasing the δ^+ on C. Also coordinates strongly to the acyl oxygen accelerating ligand trapping.
- Increased electrophilicity of the metal center (π-acid ligands, cationic complexes). Makes the carbonyl more electrophilic towards attack by the migrating nucleophile.
- Oxidation of the metal center: Increased lability of 17 electron complexes may play a role in addition to the increased electrophilicity of the metal center.

1,2-Migratory Insertion of Alkenes or Alkynes

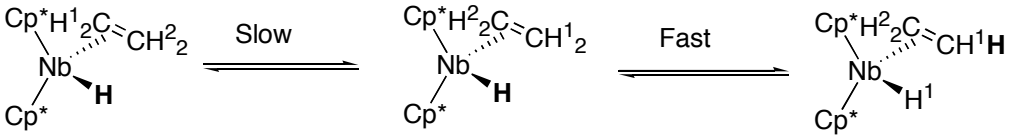
Important catalytic processes such as alkene hydrogenation and olefin polymerization involved migratory insertion of alkenes.



John Bercaw (Cal Tech) has carried out a detailed study of the reversible migratory insertion of a stable Nb(III) olefin hydride complex. *JACS*, **1985**, *107*, 2670.



- The Nb olefin complex has a planar cis-olefin hydride geometry.
- The Nb-Ethyl complex cannot be observed directly. It can be inferred by exchange of the hydride into the ethylene ligand and by trapping with external ligands.
- Rate of formation of the NbEt(L) complex has a first order dependence on L, consistent with a fast preequilibrium migratory insertion and slow trapping by L. The rate law is identical to that discussed above for CO insertion.
- VT-NMR studies of this system by magnetization transfer shows two dynamic processes.
    - A relatively fast process that exchanges the hydride with the terminal ethylene protons.
    - A slower rotation of the ethylene ligand.



H = -3.1 ppm
H^1 = 0.5 ppm
H^2 = -0.4 ppm

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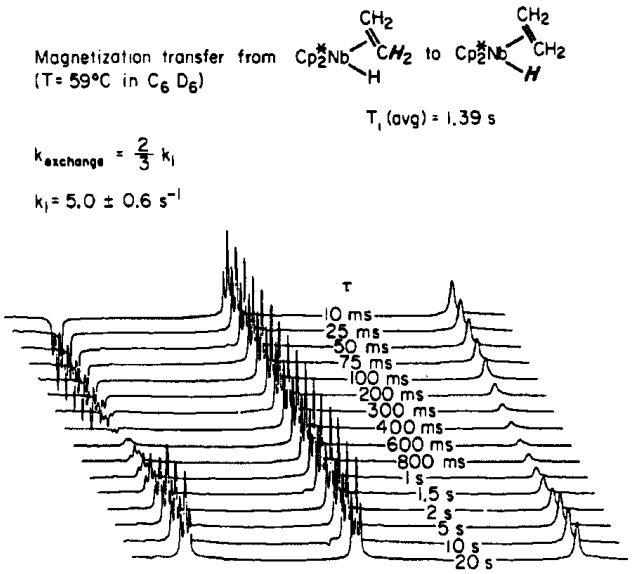
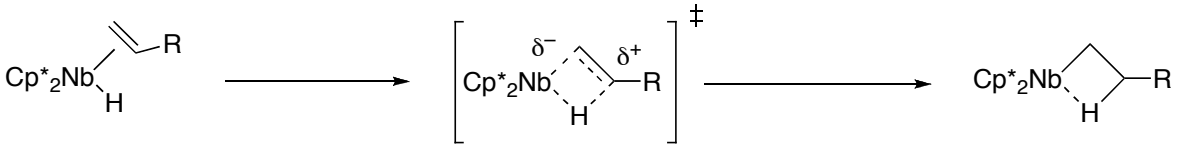


Figure 2. Magnetization transfer experiment for $Cp^*_2Nb(CH_2{=}CH_2)(H)$.

- Migratory insertion rate for substituted styrenes showed that more electron rich styrenes gave slightly faster insertion rates, consistent with a small positive charge developing on the alkene carbon next to the aromatic ring.

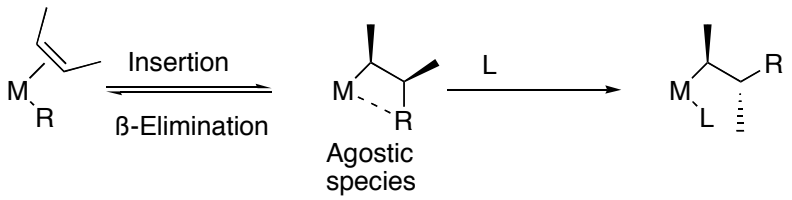
- In comparing alkenes a combination of steric and electronic factors contribute: propylene >> styrene ≥ ethylene. (Note that this is not the universal trend. Often ethylene inserts fastest). Again, these results are consistent with a small positive charge developing on the substituted alkene carbon.

- Although there are some electronic effects, they are small. The reaction is essentially concerted, but the M-C bond forms slightly before the C-H bond, which results in the development of some charge.



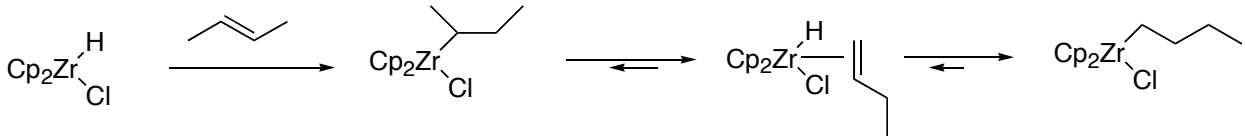
General features of migratory insertion of alkenes:

A. Stereoselectivity of Insertion: Migratory insertion results in syn-addition across the alkene, although other processes may cause isomerization after migratory insertion.

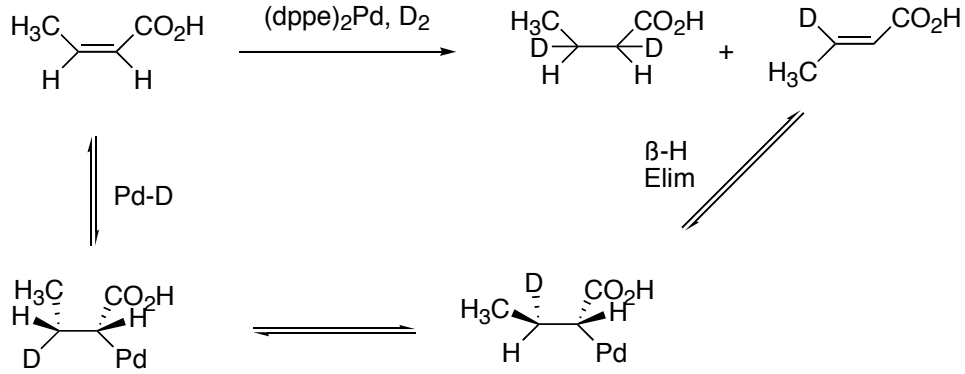


B. Regioselectivity of Insertion: The regioselectivity of the insertion depends on the steric and electronic properties of the alkene/alkyne and the metal species.

Typically steric factors will result in a thermodynamic preference for the sterically less hindered carbon to be bonded to the metal center. Hydrozirconation of alkenes with the Schwartz reagent is a good example of this thermodynamic preference. (*Pure Appl. Chem.*, **1980**, *52*, 733)



For alkenes with strong electron withdrawing or donating groups, electronic factors often become more important than steric ones. (*J. Am. Chem. Soc.*, **1997**, *119*, 5257)

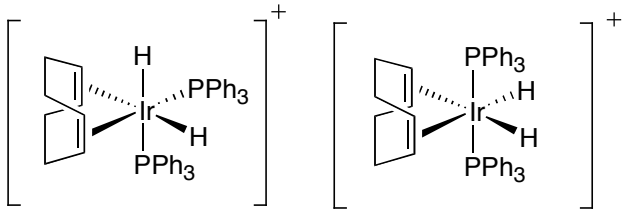


Styrene usually undergoes insertion to place the metal in the benzylic position, where it is stabilized by coordination to the arene. The opposite regioisomer can sometimes be obtained when the metal is very sterically hindered.

C. Geometric Requirement:

The M-R bond and the alkene must be able to adopt a coplanar geometry for insertion (or elimination).

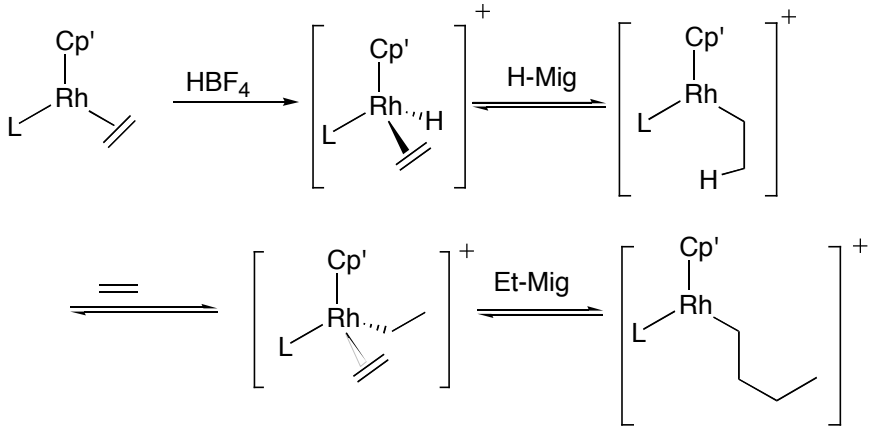
For the COD iridium complexes below, **9** undergoes insertion 40 times faster than **10**, although both have the alkene and H in *cis*-coordination sites.



9 **10**

D. Insertion into M-H versus M-R:

Migratory insertion into M-H bonds occurs at much higher rates than insertion into M-R bonds. As in CO migratory insertion, alkene insertion into M-R is thermodynamically favored over M-H insertion. Therefore, the preference for M-H insertion must be due to kinetic factors, not thermodynamic factors. One example of the difference in activation energies was reported by Brookhart (*J. Am. Chem. Soc.*, **1992**, *114*, 10394)



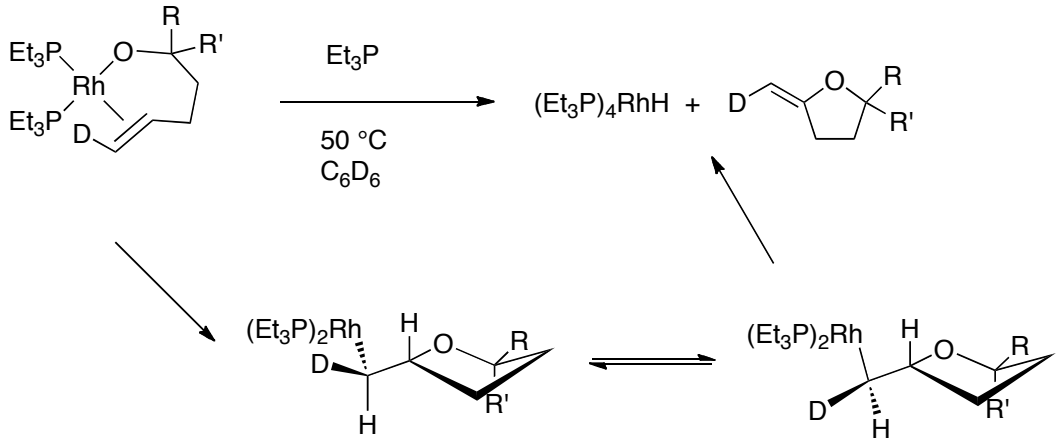
Cp'	L	ΔG‡ H-Mig (kcal/mol)	ΔG‡ Et-Mig (kcal/mol)
Cp*	$P(OMe)_3$	12.2	22.4
Cp*	PMe_3	12.1	23.4
Cp	$P(OMe)_3$	15.0	23.4
Cp	PMe_3	15	24.7

The difference in activation energies suggests $k_H/k_{Et} = 10^6 - 10^8$.

Migratory Insertion to M-heteroatom bonds

Although less common, metal alkoxides and amido complexes can undergo migratory insertion of olefins to give C-O/N bond formation. Most commonly this is seen for intramolecular reactions. In intermolecular reactions, another possible mechanism is nucleophilic attack by the O or N on the bound alkene. We will discuss this in chapter 14.

The mechanism for migratory insertion is generally a syn-addition as seen with H or C.

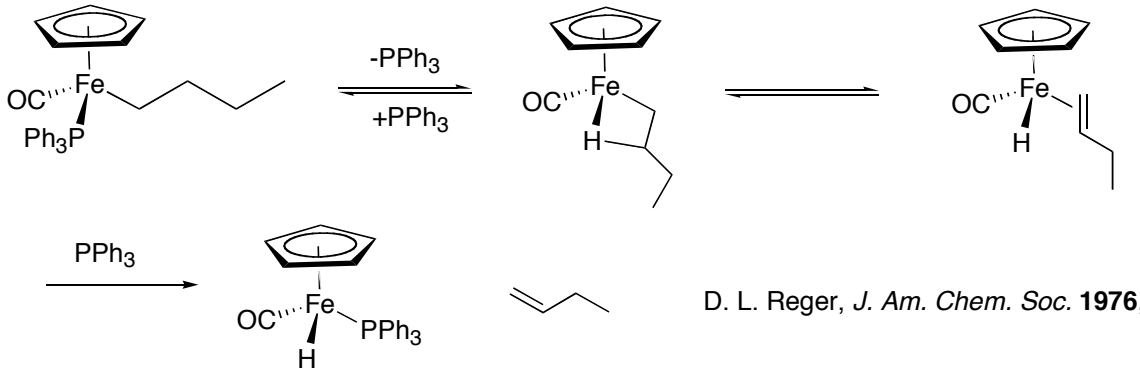


JACS **2006**, *128*, 9642

Migratory Elimination

A. ß-Hydride Elimination: Elimination is the microscopic reverse of 1,2-insertion, therefore the mechanisms must be the same. In particular, ß-H elimination requires an open coordination site, and that the M-C-C-H group can become coplanar.

For 18 electron complexes, a ligand must always dissociate to form an open coordination site cis to the alkyl group undergoing ß-H elimination. Ligand dissociation may, or may not, be rate limiting.



D. L. Reger, *J. Am. Chem. Soc.* **1976**, *98*, 2789

Experimental observations

1. Only alkene products were isolated.

2. Decompositions of 1,1-d_2 or 2,2-d_2 butyl complexes resulted in complete scrambling of deuterium in the 1-butene product.

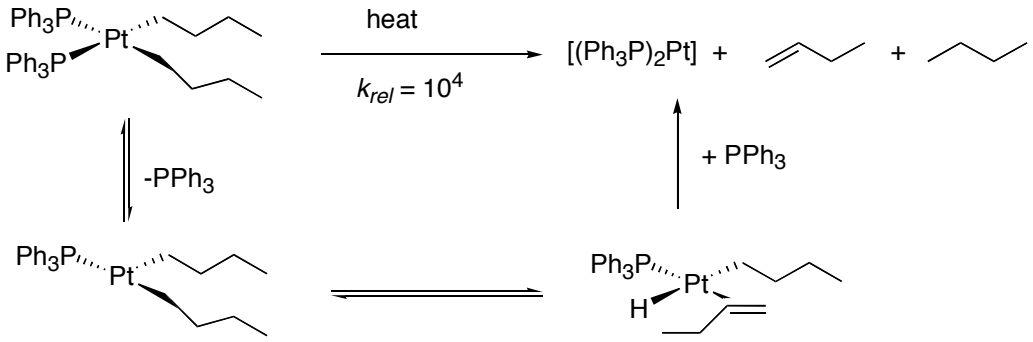
3. First order kinetics with a very small kinetic isotope effect for 1,1-d_2 or 2,2-d_2 butyl complexes.

4. Reaction is completely retarded in the presence of excess PPh_3. Other Lewis bases (THF or dioxane) also slow down the reaction, but to a lesser extent.

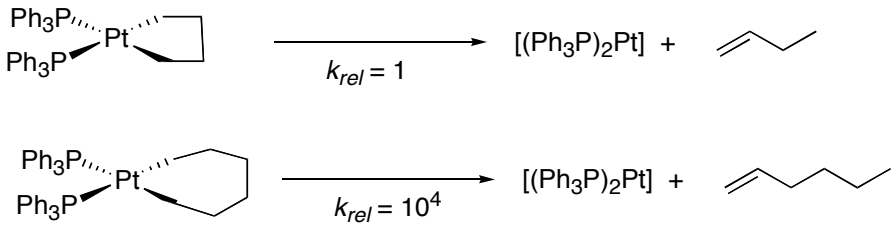
5. Starting material recovered from reactions stopped after less than one half-life showed extensive scrambling of deuterium throughout the alkyl chain.

For 16 electron complexes, prior ligand dissociation is not required with the exception of Pd(II) and particularly Pt(II), which do not like to become 18e complexes.

Whitesides has studied the thermal decomposition of Pt dialkyls. Decomposition of $(Ph_3P)_2PtBu_2$ gives butane and butene. The rate of decomposition is inversely dependent upon $[PPh_3]$. (*J. Am. Chem. Soc.*, **1972**, *94*, 5258; *ibid.*, **1973**, *95*, 4491, *ibid*, **1976**, *98*, 6521; *Organometallics*, **1986**, *5*, 1473)

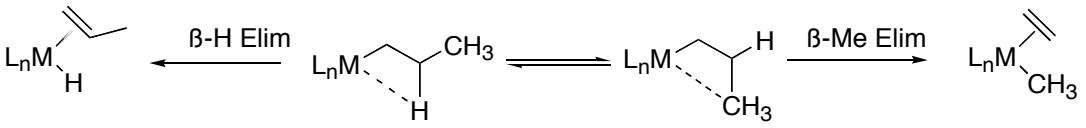


The platinacyclopentane analog undergoes decomposition 10,000 times more slowly. This reaction most likely goes by a radical mechanism. However larger platinacycles undergo decomposition at a similar rate to the dibutyl complex and by the same mechanism.



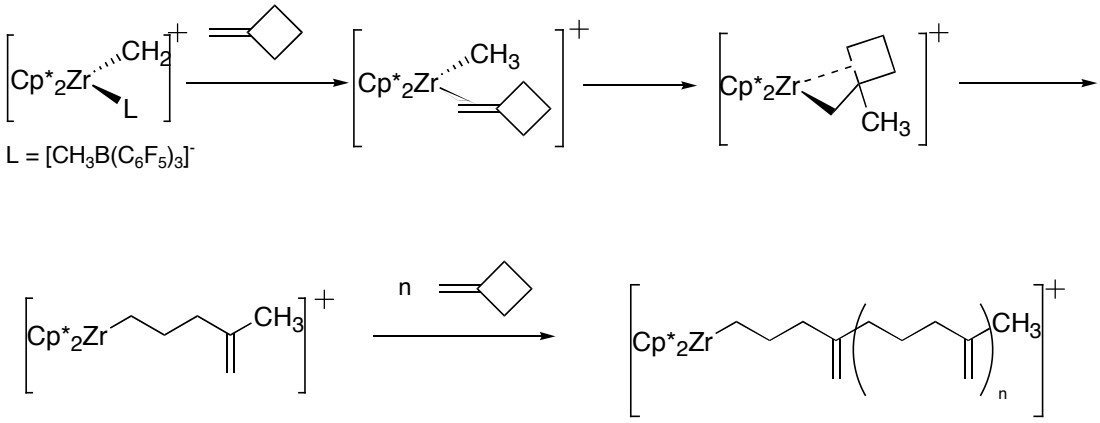
B. β-Carbon Elimination

As discussed above, there is a much higher barrier to hydride migration compared to alkyl migration, thus a strong kinetic preference for hydride migration. These results suggest a similar preference for ß-H elimination over ß-alkyl elimination.

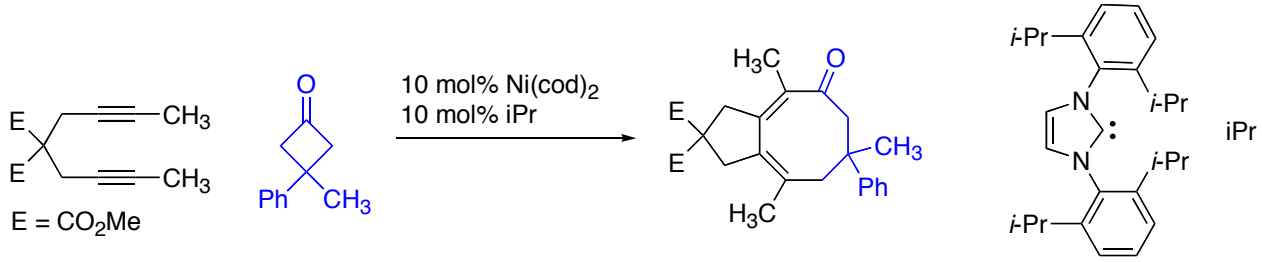


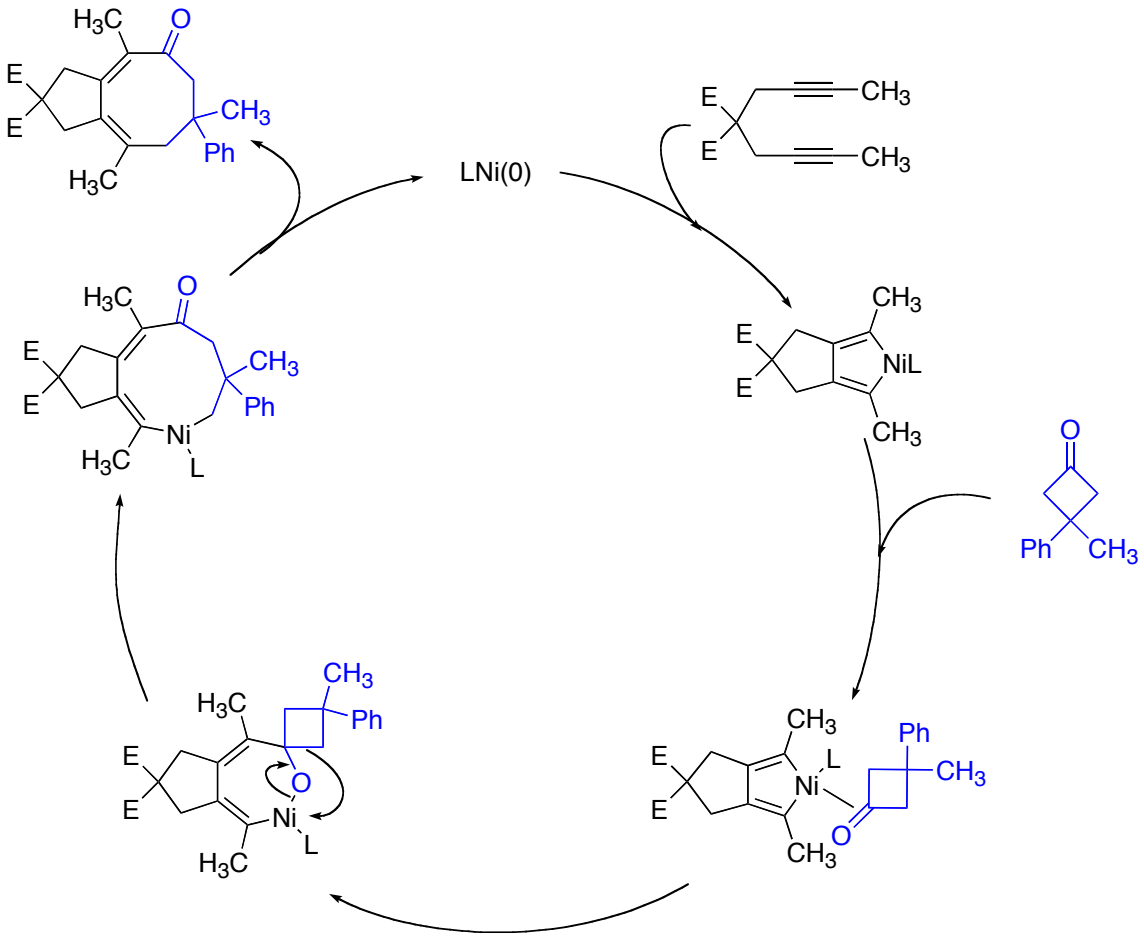
Typically ß-alkyl elimination is only observed where there is a large amount of strain in the C-C bond, or where there is no ß-H to undergo elimination. ß-Alkyl elimination is more common with highly electrophilic d^0 metal complexes.

Tobin Marks, *J. Am. Che.m Soc.*, **1993**, *115*, 3392



Murakami, *J. Am. Chem. Soc.* **2006**, *128*, 2166-2167

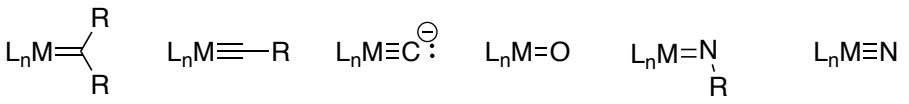




Kevin Shaughnessy
The University of Alabama, 2019

6-Metal-Ligand Multiple Bonds

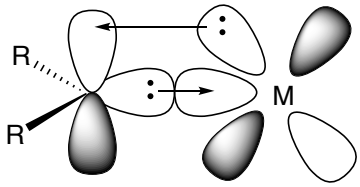
Nomenclature



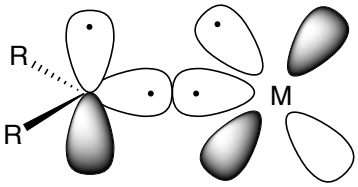
name	carbene alkylidene	carbyne alkylidyne	carbide	oxo	imido	nitride nitrido
Type	L or X_2	LX_2 or X_3	X_4	X_2	X_2	X_3
#e	2 or 4e	6e	6e	4 or 6e	4 or 6e	6e

Bonding in Carbenes

Recall from Chapter 2 of the notes that there are two limiting classes of carbenes: electrophilic (Fischer) carbenes and nucleophilic (Schrock) carbenes.



Electrophilic (Fischer) carbene



Nucleophilic (Schrock) carbene

<u>Fischer carbenes</u>

- Low oxidation state, late transition metals
- π-acceptor ligands on M
- π-donor substituents (R) on the carbene

Fischer carbenes can be considered as neutral 2 e ligands (L-type) derived from singlet carbenes.

Since the carbene is acting as a σ-donor, it has a ∂+ charge and acts as an electrophilic center.

Schrock carbenes

- High oxidation state, early transition metals
- non-π-acceptor ligands on M
- non-π-donor substituents (R) on the carbene

Schrock carbenes are formally considered as X_2-type ligands derived from triplet carbenes.

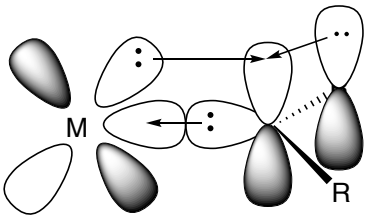
The carbene carbon has a partial negative charge and acts as a nucleophile.

Fischer Carbenes

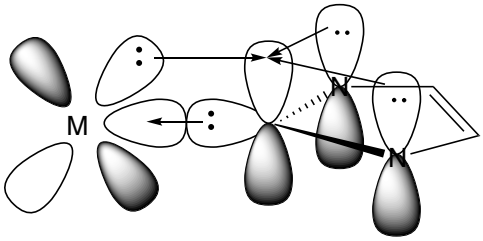
E. O. Fischer first reported carbene complexes in 1964. (*Angew. Chem. Int. Ed.*, **1964**, *3*, 580). See Chapter 2 of the notes for methods of preparing Fischer carbenes.

Metal-Ligand Interactions

Fischer carbenes are considered L-type 2-electron donors. The metal-carbon double bond is considered to derive from σ-donation of the carbon lone pair to the metal and significant π-back donation from the metal. Note that for Fischer carbenes, there is usually one, or two, π-donor substituents attached to the carbene carbon that also compete for the empty p-orbital. Arduengo-type NHC ligands have two N-donors as part of a heterocyclic ligand that significantly occupy the carbene p-orbital. Initially, it was thought that there was little if any π-back donation. Recent results show that there is significant π-back donation. Approximately 15-25% of the metal-carbene interaction is calculated to be due to π-back bonding, which is similar to more typical Fischer carbenes (*Organometallics*, **2018**, *37*, 275). Despite this, the metal-NHC interaction is typically drawn with a single bond, based on the earlier understanding.



Typical Fischer Carbene



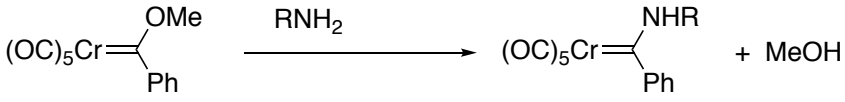
Metal-NHC complex

Electrophilic Reactivity

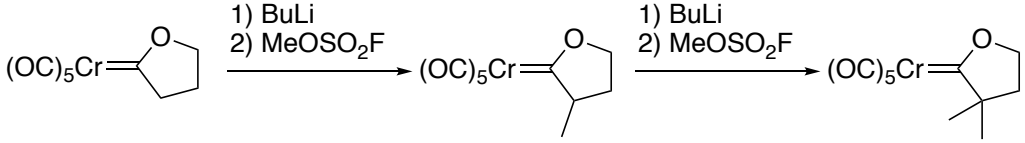


Much of the reactivity of Fischer carbenes is directly analogous to the reactivity of carboxylic acid derivatives. Both have electrophilic carbon centers with leaving groups.

A. Nucleophilic attack



B. "Enolate" reactivity



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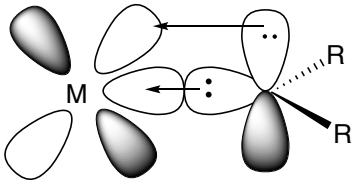
Note that the NHC-type carbenes typically do not show these types of reactivity.

Schrock Carbenes

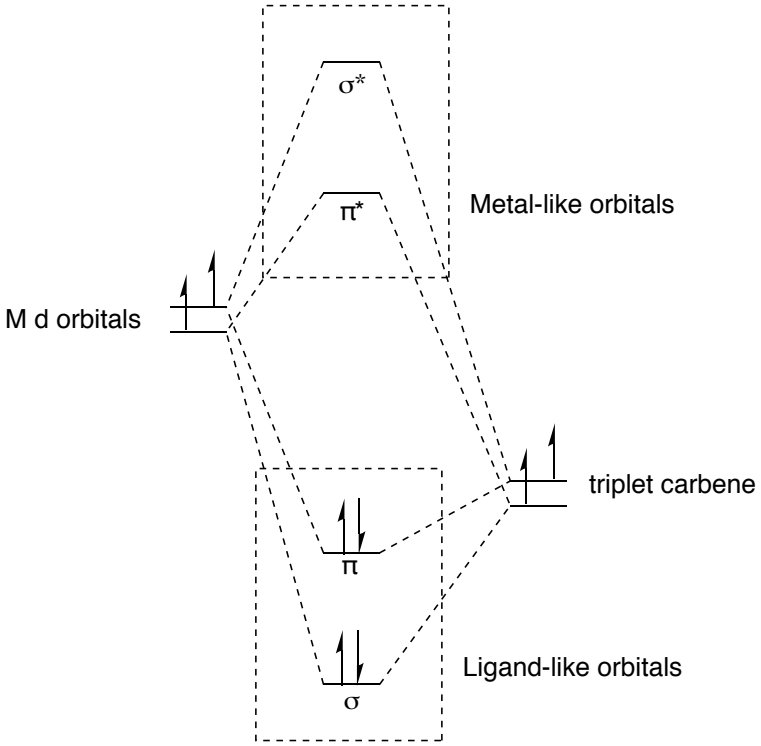
The first nucleophilic carbenes were prepared by Schrock in an effort to prepare a homoleptic tantalum(V) alkyl. (*Acc. Chem. Res.*, **1979**, *12*, 98) See notes Chapter 2 for details.

Metal-Ligand Interaction

In the case of Schrock-type carbenes, the metal carbon double bond is considered to be two covalent bonds. All four electrons in the metal-ligand interaction are in "ligand-like" orbitals, so the Schrock carbene ligand is considered to be an X_2-type ligand (R_2C^{2-}) that acts as a 4-electron donor. It thus acts as a σ-donor and a π-donor to the metal center. Because of the significant electron density on the carbene carbon, it tends to behave as a base or nucleophile.

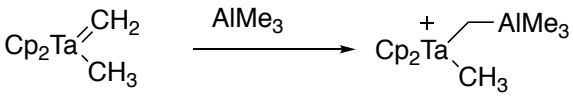


Typical Schrock Carbene

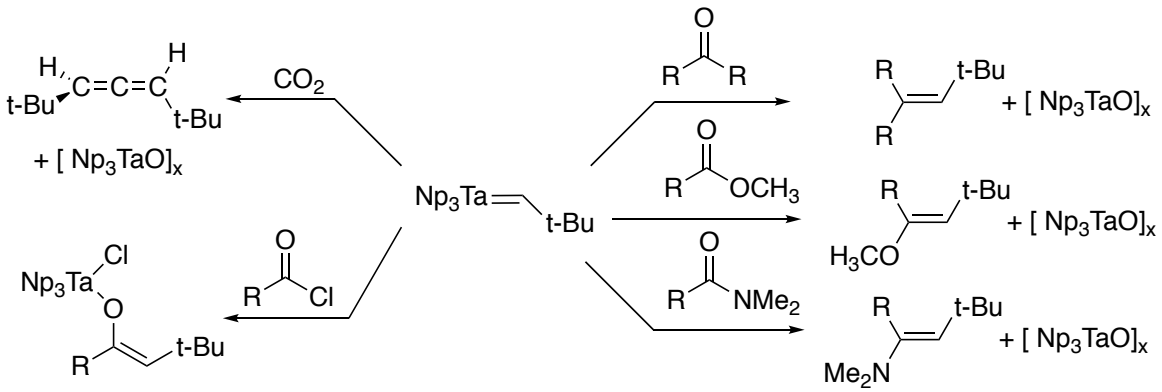


Nucleophilic reactivity

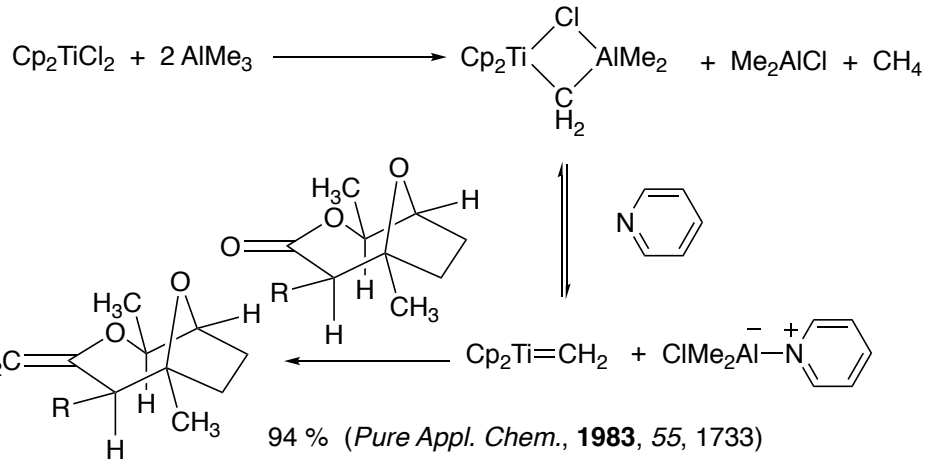
A. Lewis acid adducts



B. Addition to carbonyls



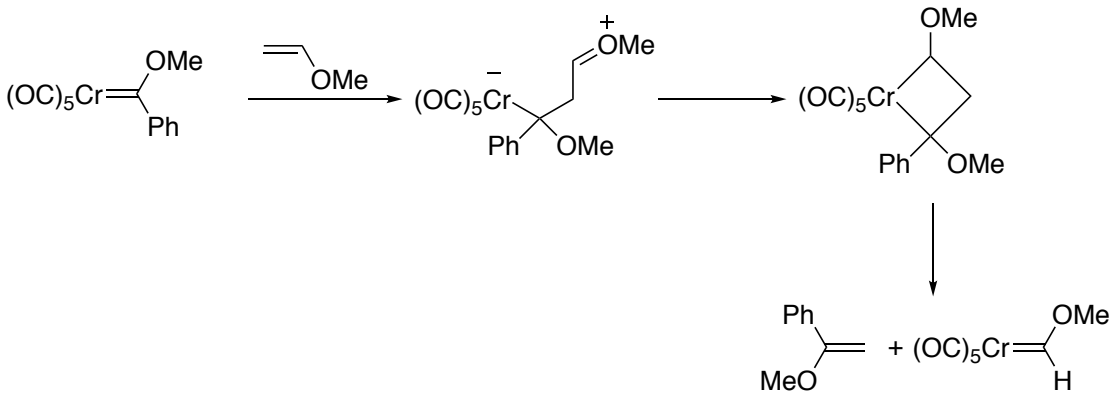
The Tebbe reagent is particularly useful for the conversion of esters to vinyl ethers. It will olefinate carbonyls without enolizing α–stereocenters.



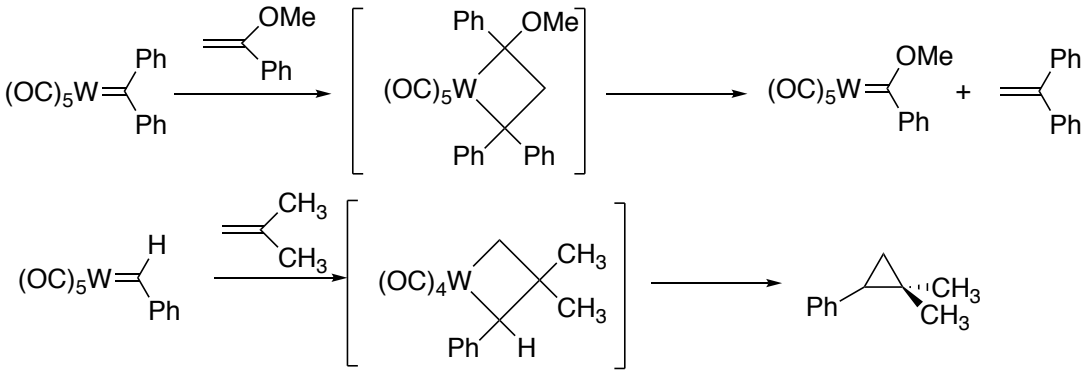
Reaction of carbenes with unsaturated alkenes and alkynes

Fischer Carbenes

Reaction with alkenes to give metalacyclobutanes. The metalacyclobutane can decompose either by release of an alkene or by reductive elimination to give a cyclopropane.

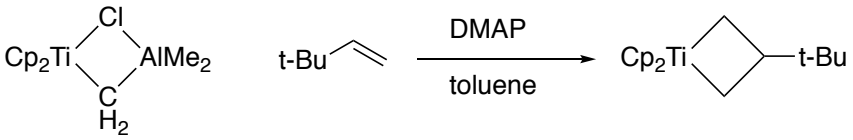


Olefin Methathesis

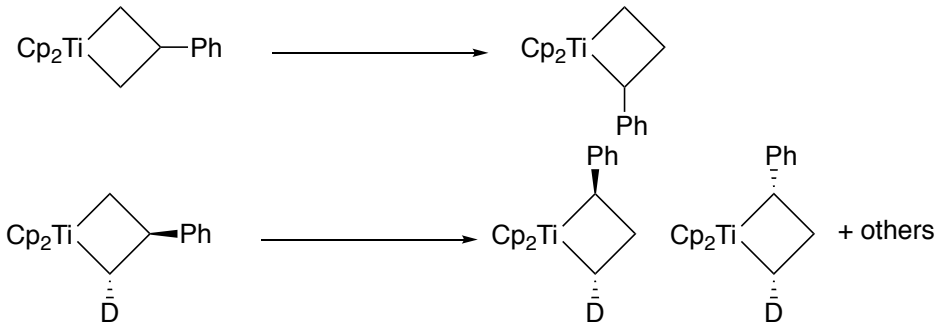


Schrock Carbenes

Nucleophilic carbenes react with alkenes to form metalacyclobutanes, which can undergo a variety of rearrangement processes.

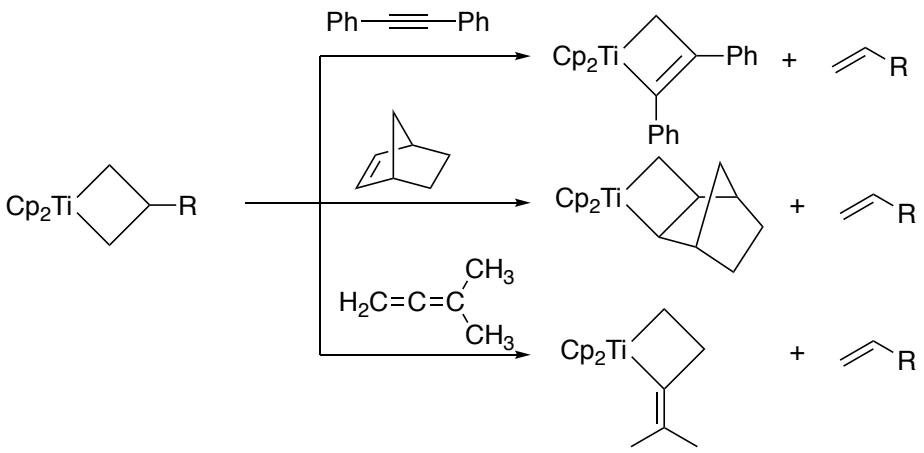


These titanacyclobutanes undergo rearrangements to the more stable 2-phenyl substituted products.



The titanacyclobutanes undergo exchange with free olefins to give new metallacycles. This transformation will play an important role in our discussion of metathesis.

Kevin Shaughnessy
The University of Alabama, 2019



Metal-heteroatom multiple bonds

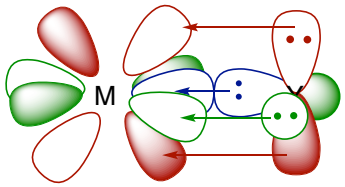
Metal-oxo and –imido complexes

Bonding

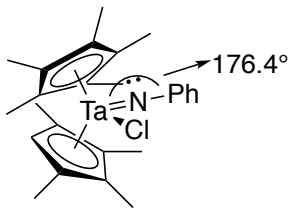
Oxo and nitrido ligands are considered to be X_2-type ligands with a -2 charge. They are typically drawn as M-L double bonds. For both O and N, there is an additional lone pair in a p-orbital that can potentially bond with the metal in a dative bond. Considering this bonding, the oxo or nitriido would be considered an LX_2 ligand and a 6 electron donor. Oxo and nitrido ligands are most commonly found on metals with low d-electron counts (d^0–d^2), so the extra electron donation is favorable.

potenial dative bond

$L_nM \leftarrow :Y$ Y = O, NR

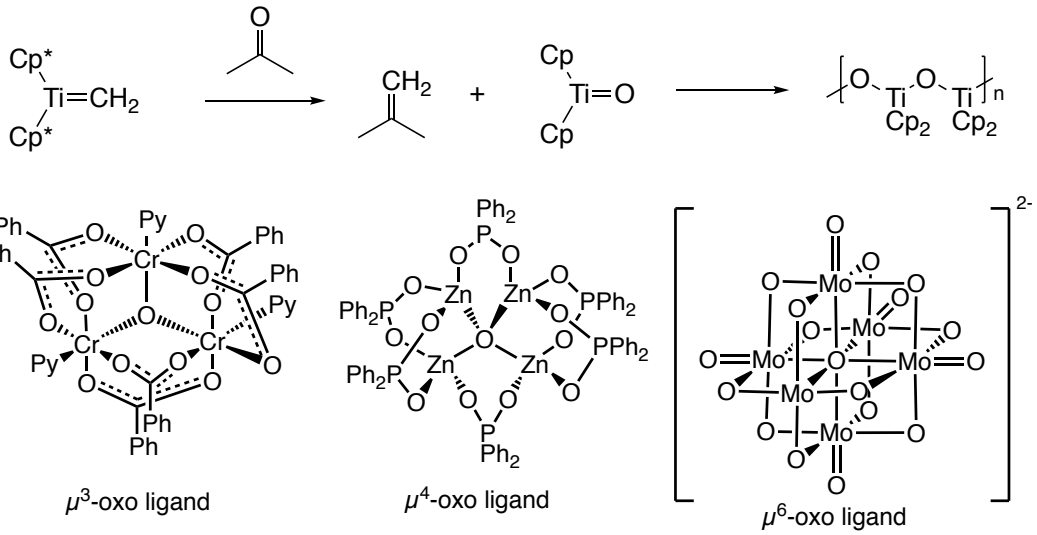


In the case of imido complexes, this additional bonding could potentially be determined based on the M-N-R bond angle. Angles near 180° might suggest an sp-hybridized atom. In fact, most metal-nitrido complexes have linear structures, even in cases where the additional bond would formally result in exceeding the 18 electron count. It appears that there is little energy difference between the sp^2 and sp-hybridized nitrogen and that steric factors favor the linear structure.



4e imido: 18 e
6e imido: 20 e

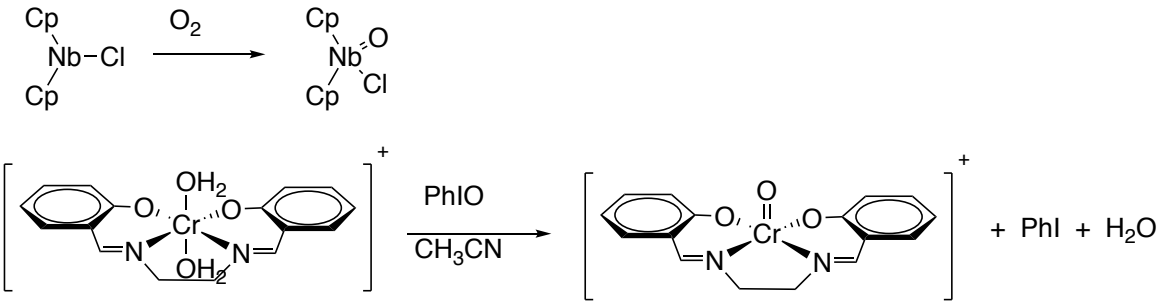
Oxo ligands more typically act as bridging ligands between metals than as terminal ligands. MnO_4^-, OsO_4, and $RReO_3$ are examples of stable complexes with terminal oxo ligands. A more typical example is TiO_2 (titania), which is a networked solid that is insoluble in all solvents. Non-homoleptic metal oxo complexes are also typically polymeric. Titanocene oxo exists as a polymeric structure with an O-Ti-O-Ti repeat unit. These types of structures are generally completely insoluble and cannot be fully characterized. Oxo ligands can be associated with up to 6 metal centers.



μ^3-oxo ligand μ^4-oxo ligand μ^6-oxo ligand

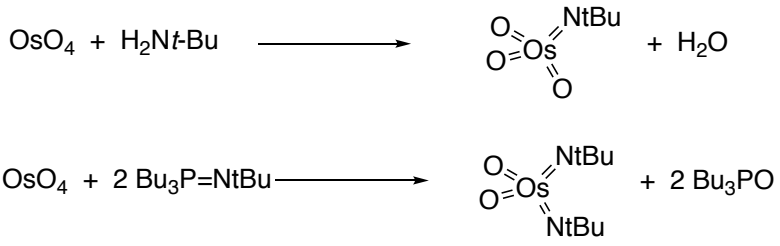
Synthesis of metal-oxo and –imido complexes

Metal-oxo complexes: Metal oxo complexes are typically prepared by oxidation resulting in delivery of an oxygen atom from various oxidants (O_2, NaOCl, PhIO).

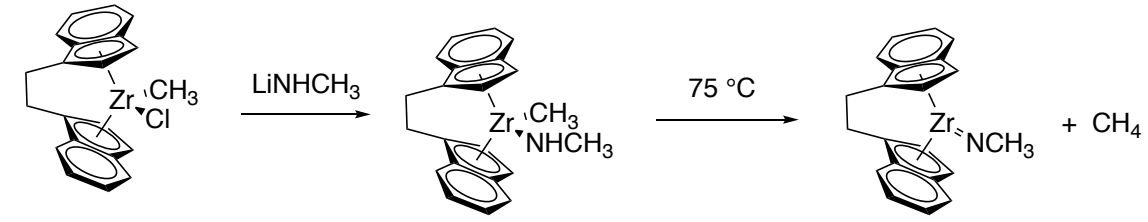


Metal-imido complexes: Metal-imido complexes can be prepared in a number of ways. Metal-oxo ligands can be converted to imido ligands either by direct reaction with amines and release of water or using nitrene transfer reagents, such as $Ph_3P{=}NR$. α-Elimination from amido complexes using a basic ligand, such as a carbanion ligand or another amine, is another common route to imido complexes.

Oxo replacement



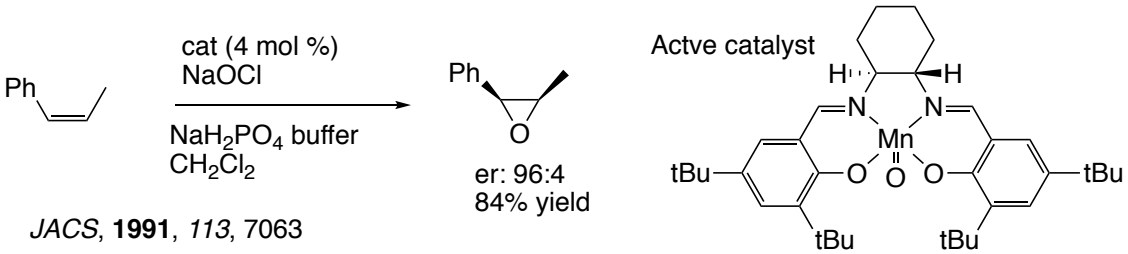
Elimination



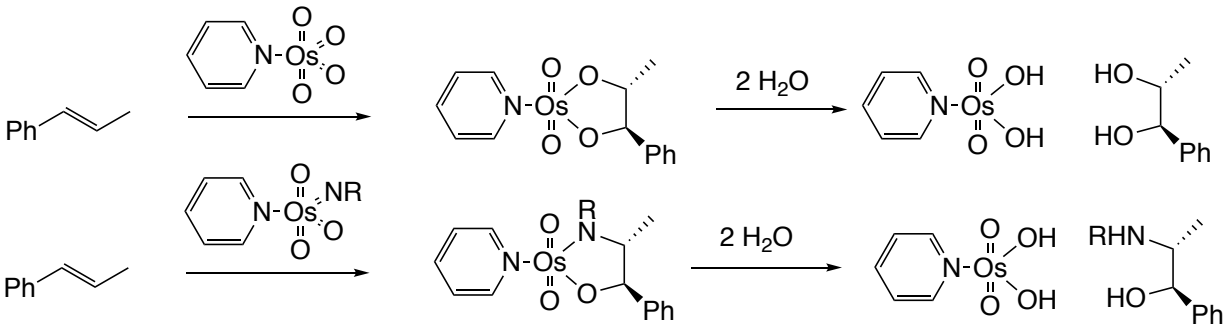
Bergman, R. G., *JACS*, **2004**, *126*, 1018

Reactivity

Atom transfer reactions: Metal-oxo complexes are common intermediates in the catalytic oxidation of alkenes to expoxides or vicinal diols. Metal-imido compounds can do similar reactions to give aziridines or amimoalcahol products.



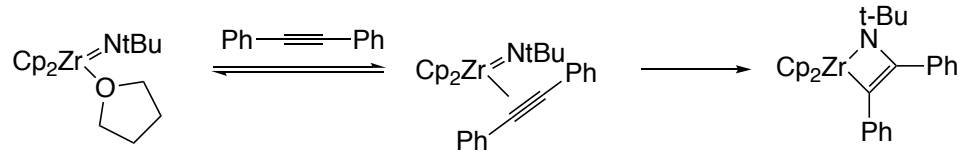
JACS, **1991**, *113*, 7063



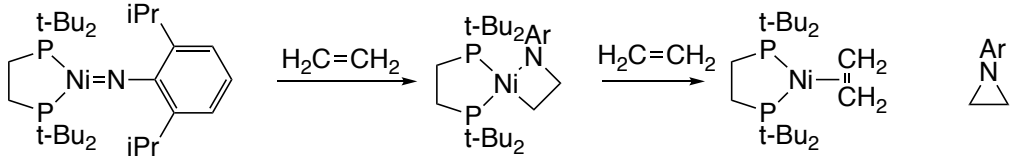
L = chiral quinine or quinidine derivative in place of pyridine gives asymmetric dihydroxylation developed by K. B. Sharpless.

[2+2] cycloadditions: Metal-heteroatom π bonds undergo [2+2] cycloadditions with unsaturated species to give metallocyclobutane/ene species. In the case of early transition metals, this species is typically stable. With later transition metals, the azametallacycle will often undergo reductive elimination to give an aziridene.

Kevin Shaughnessy
The University of Alabama, 2019

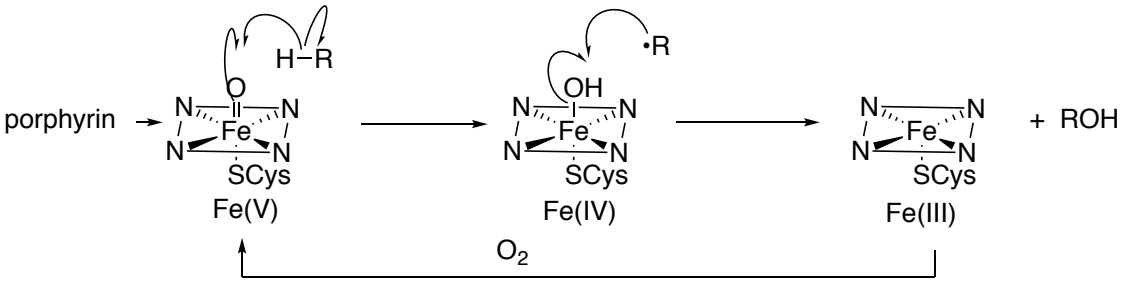


Bergman, R. G. *JACS*, **1988**, *110*, 8731

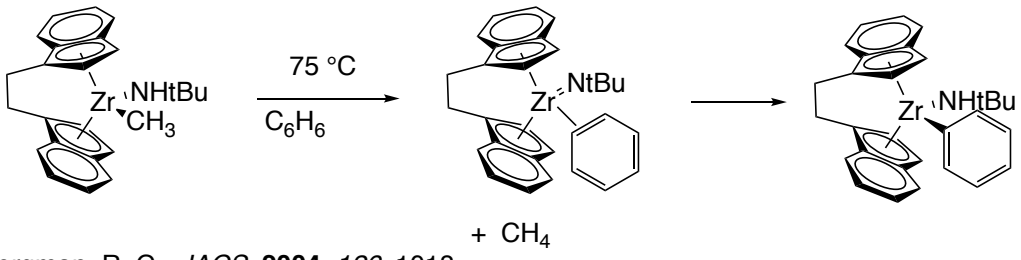


Che, C.-M., *JACS*, **1999**, *121*, 7164

Reactions with C-H bonds: Metal-oxo and –imido complexes will often activate C-H bonds in alkanes and arenes. Cytochrome P450 uses an Fe(V)-oxo porphyrin complex to oxidize organic compounds in order to make them more water soluble so they can be eliminated from the body. A common mechanism is H-atom abstraction by a Fe(V) oxo to give a carbon radical and an Fe(IV) hydroxide. The carbon radical can then abstract hydroxyl radical to give Fe(III) and an alcohol product.



Metal-imido complexes of early transition metals will react with C-H bonds to reversibly give metal alkyl amido complexes.



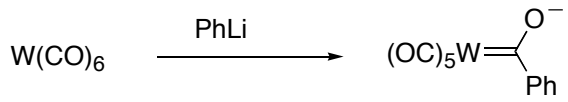
Bergman, R. G., *JACS*, **2004**, *126*, 1018

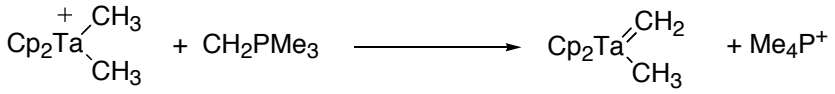
7-Nucleophilic and Electrophilic Attack on Ligands

Ligands bound to metal centers often have quite different reactivity from the free compound. Many bound ligands can be modified or removed from the metal center by nucleophilic or electrophilic reactions. Often these reactions involve direct attack on the bound ligand.

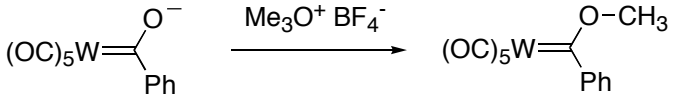
Types of Reactions:

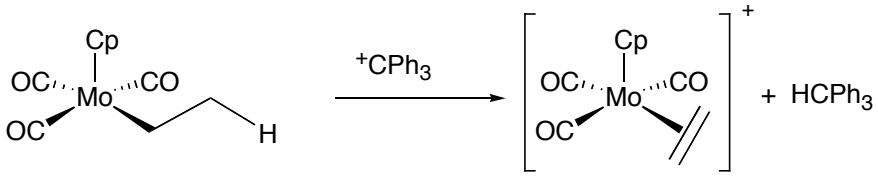
- Nucleophilic attack: Favored for metals that are weak π-bases and good σ-acids (i.e., complexes with net positive charges or π-acidic ligands). Ligands bound to electrophilic metals will tend to be electrophilic themselves.





- Electrophilic attack: Favored for electron rich metals that act as weak σ-acids, but strong π-bases (i.e. low valent metals, or those with net negative charges and/or electron donating ligands). Ligands bound to π-basic metals tend to be electron rich, and act as nucleophiles.





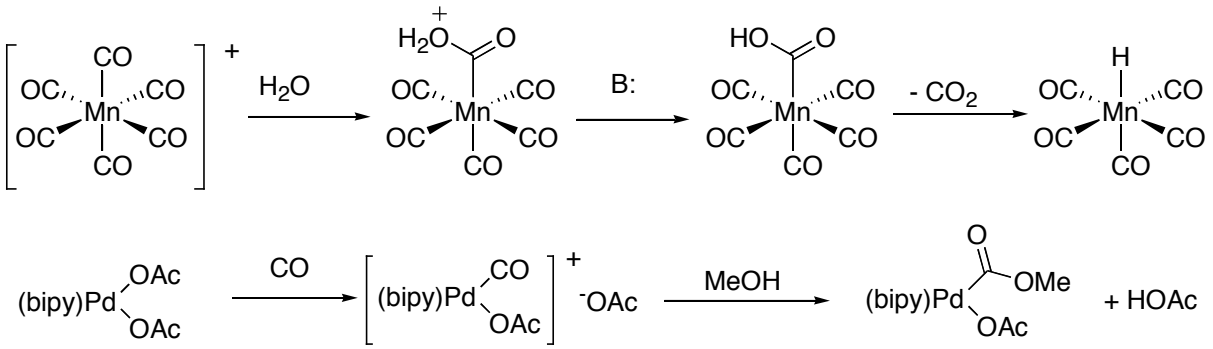
- Addition reactions: When a ligand is attacked by a nucleophile to give a new ligand that remains bound to the metal, it is called an addition reaction.

- Abstraction: If attack on the ligand results in the ligand, or part of it leaving the metal center, it is referred to as an abstraction.

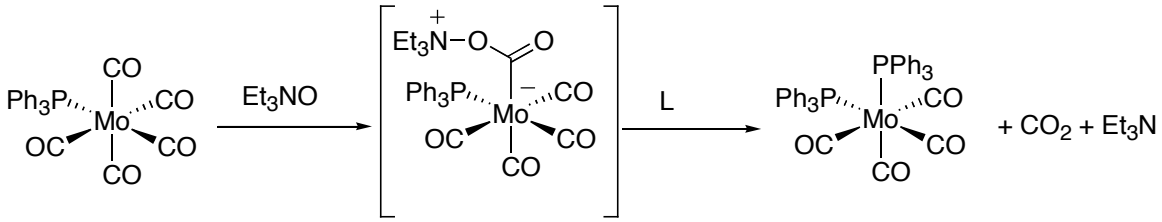
Nucleophilic Attack

Nucleophilic Attack on CO

CO is prone to attack by nucleophiles when coordinated to weakly π-basic metals. We have already seen that alkyl lithium reagents will alkylate CO. Increasing the electrophilicity of the metal center allows weaker nucleophiles like water or alcohols to attack.

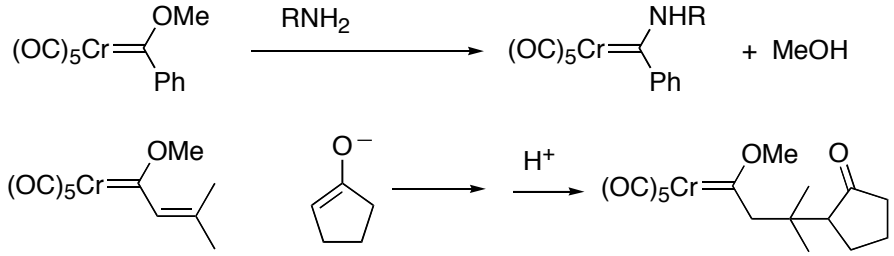


As we've discussed before, N-oxides are strongly nucleophilic reagents that can be used to abstract CO ligands. (*J. Organomet. Chem.* **1979**, *173*, 1-76) The ligand substitution occurs exclusively *cis* to the phosphine.



Nucleophilic Attack on Electrophilic Carbenes:

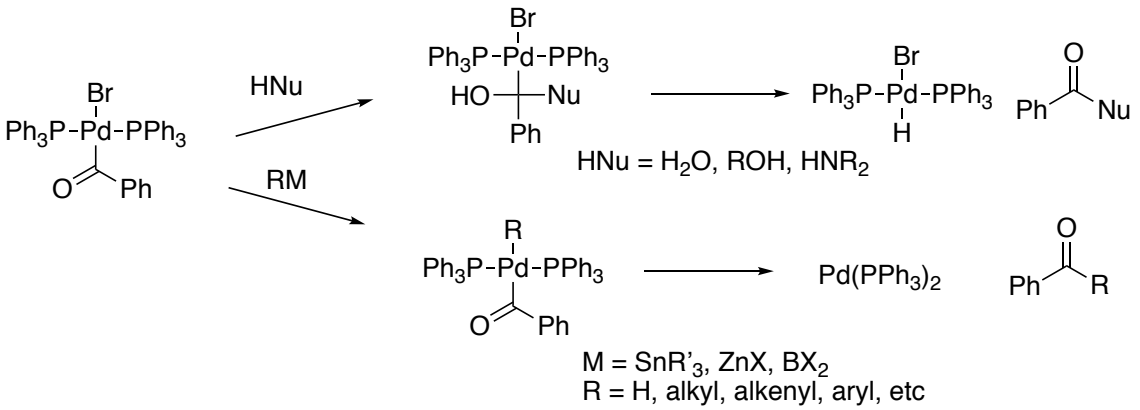
Electrophilic carbenes are prone to nucleophilic attack as we've previously seen. The reactivity is similar to that of carbonyl derivatives in organic chemistry. This includes Michael-type additions to conjugated carbenes.



J. Organomet. Chem., **1974**, *77*, 345

Nucleophilic attack on metal acyls:

Nucleophilic attack on metal acyls to give carboxylic acid derivatives, aldehydes, and ketones is well precedented. Depending on the type of nucleophile, two different mechanisms can occur. With weaker protic nucleophiles (H_2O, ROH, R_2NH, etc), nucleophilic attack occurs directly on the acyl carbon in a nucleophilic acyl substitution-type mechanism. The palladium ends up as a palladium hydride, that can be deprotonated to return to Pd(0). Strong hydride or organometallic reagents tend to add to the metal followed by reductive elimination.



Nucleophilic Attack on Polyene and Polyenyl Ligands:

Polyenes such as benzene and butadiene typically react with electrophiles rather than nucleophiles. Coordination to an electron deficient metal center reverses this normal reactivity (umpoulong). Coordinated polyenes and polyenyls tend to react with nucleophiles.

The reactivity of polyenes can be predicted based on their structures. Qualitative rules were first developed by Green, Davies, and Mingo (*Tetrahedron*, **1978**, *34*, 3047). The Green-Davies-Mingo rules were developed for 18 electron complexes reacting under kinetic control, and only apply directly to those systems.

Green-Davies-Mingo Rules:

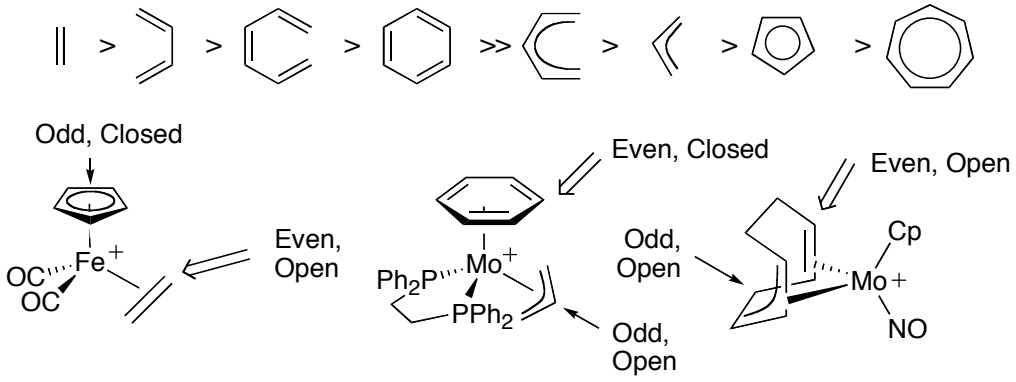
1. Polyenes (even hapticity or L_n ligands) react before polyenyls (odd hapticity or L_nX ligands)

2. Open ligands react before closed ligands

3. Open polyenes react exclusively by terminal addition. Open polyenyls usually react by terminal addition unless the metal is π-basic.

When in conflict, rule 1 takes precedence over rule 2.

Based on these rules, the order of polyene and polyenyl reactivity can be predicted.

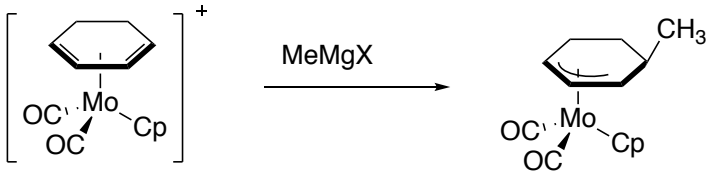


Although the Green-Davis-Mingo rules are qualitative, these rules often predict the atom(s) with the highest coefficient of the LUMO. Since the reactions are under kinetic control, attack of the atom with

the largest coefficient will be favored. For non-cyclic polyenes, this is generally the terminus of the polyene.

Nucleophilic attack on a polyene:

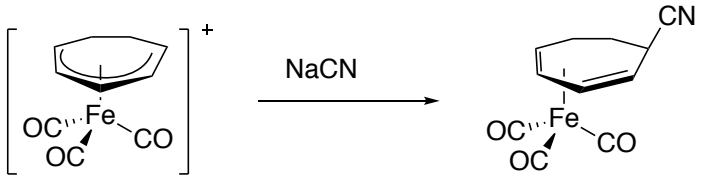
- Decreases the hapticity by 1
- Results in formation of an anionic polyenyl ligand
- Does not change the metal oxidation state
- Nucleophilic attack is always on the terminus of the polyene



Mo(II) Mo(II)

Nucleophilic attack on a polyenyl:

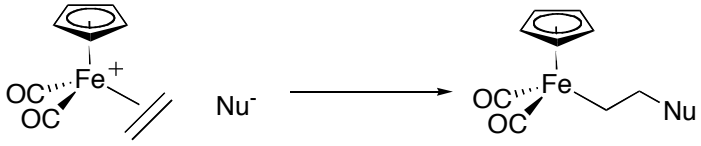
- Decreases the hapticity by 1
- Results in formation of a neutral polyene ligand
- Reduces the metal by 2 oxidation states (reductive elimination)
- Nucleophilic attack is usually on the terminus, unless the metal is strong π-donating. Then it may be in the center of the polyene (allyls).



Fe(II) Fe(0)

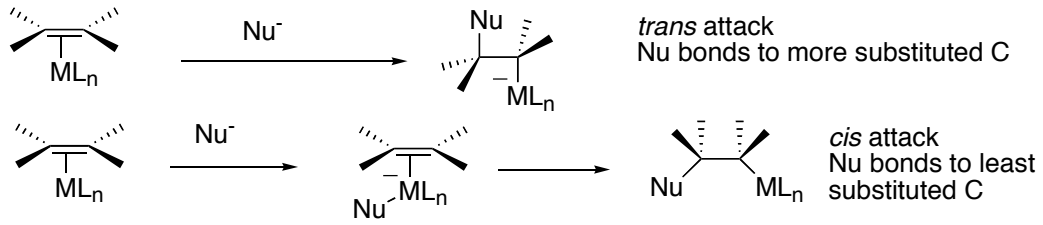
<u>η^2-Olefin complexes:</u>

Alkenes bound to electrophilic metals, particularly Pd(II), Pt(II), Fe(II) are prone to attack by a wide range of nucleophiles.



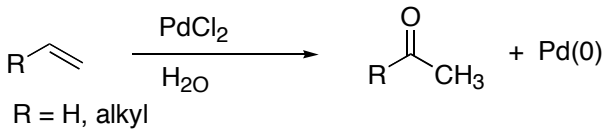
Nu^- = ^-OR, ^-SR, R_2NH, enolates, enamines, cuptrates

There are two mechanisms by which nucleophilic attack on a bound alkene can occur. Direct attack on the bound ligand, or initial coordination to the metal followed by migratory insertion.

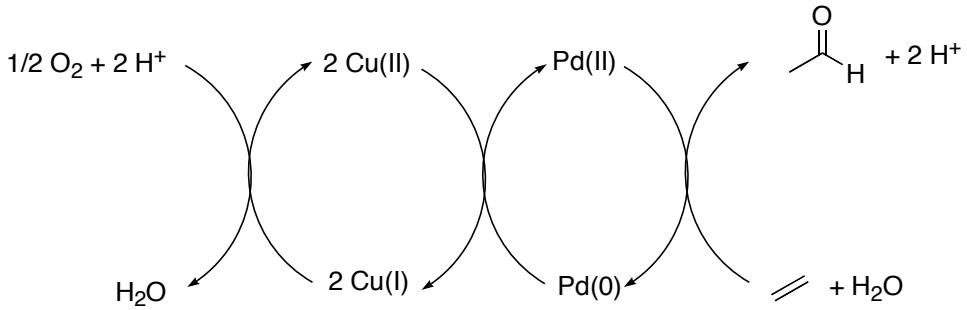


The Wacker oxidation

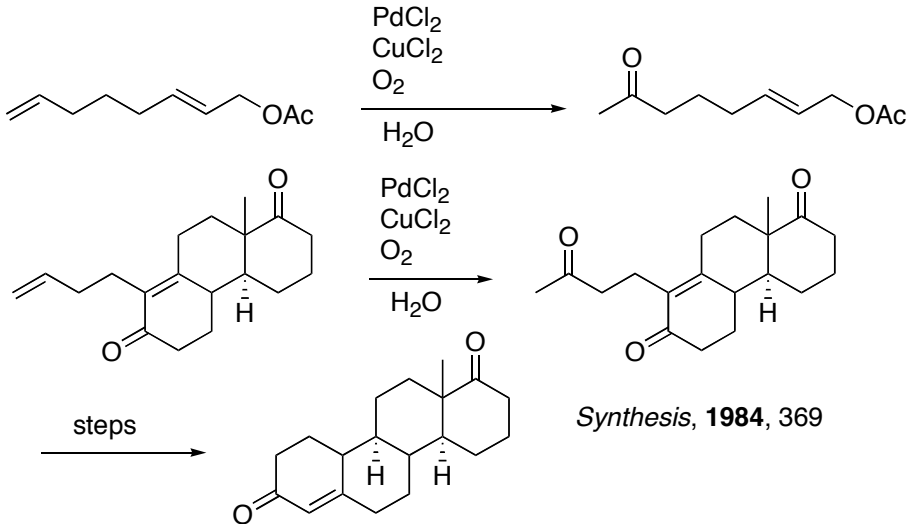
The most important application of nucleophilic attack on alkenes is the "oxidation" of alkenes to ketones or aldehydes with water in the presence of Pd(II). Stoichiometric versions of this reaction have been known for more than a century. (*Am. Chem. J.*, **1894**, *16* , 255)



It was not until the 50's that researchers at Wacker Chemie developed a system to reoxidize Pd(0) allowing the reaction to be catalytic. In fact a cascade of reactions is used to convert ethylene to acetaldehyde using oxygen as the stoichiometric oxidant. This process is the major industrial route to acetaldehyde, and can be used to make methyl ketones of higher alkenes.



This reaction depends on the coordination of alkenes to the Pd center, so it is very sensitive to the structure of the alkene. Ethylene works very well as do 1-alkenes. Internal alkenes are less effective, and tri- and tetra-substituted alkenes generally to not bind strongly enough to react.

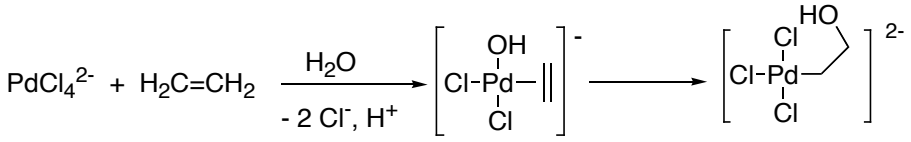


Synthesis, **1984**, 369

The original mechanism proposed for the Wacker oxidation was based on the rate expression determined for the reaction.

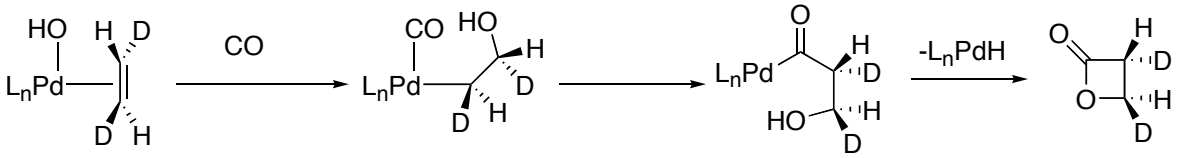
$$\text{Rate} = \frac{k[PdCl_4^{2-}][C_2H_4]}{[Cl^-]^2[H^+]}$$

The rate expression implies that two chlorides and a proton are lost in the coordination of ethylene to the Pd center. Based on the rate expression, it was proposed that coordinated water lost a proton to give a hydroxy Pd-alkene intermediate.

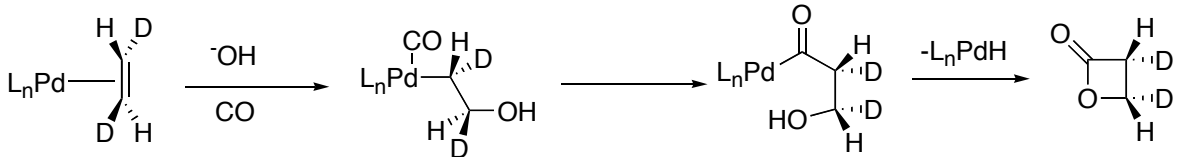


This process would proceed with retention of stereochemistry at the alkene carbons. In contrast, if coordinated ethylene was attacked by an external nucleophile, the stereochemistry of the carbon attacked by water would be inverted. Only in the late 70's was the mechanistic question resolved.

Internal Attack

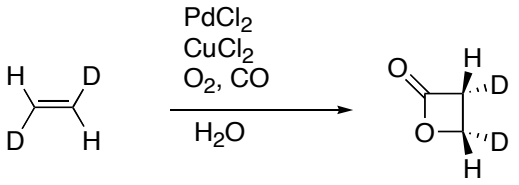


External attack

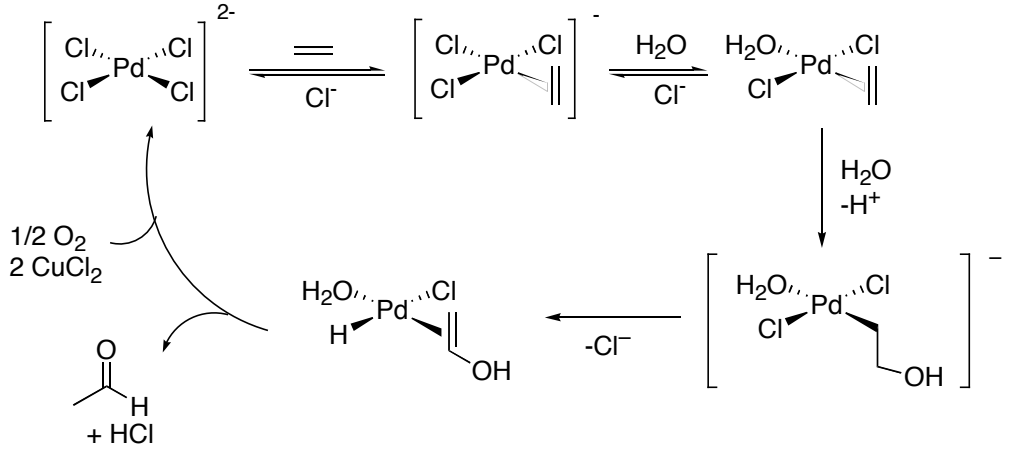


Bäckvall, *J. Am. Chem. Soc.*, **1979**, *101*, 2411; Stille, *J. Organomet. Chem.*, **1979**, *169*, 239

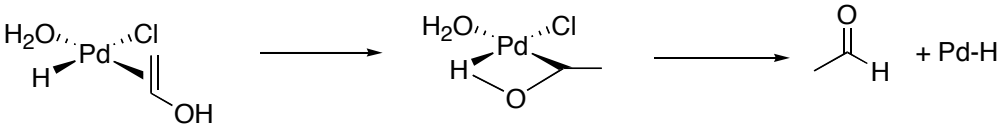
Kevin Shaughnessy
The University of Alabama, 2019



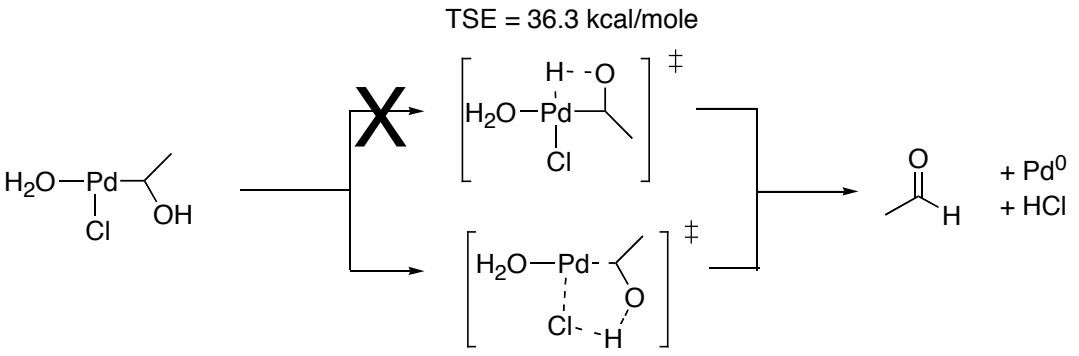
The currently accepted mechanism involves external nucleophilic attack of water on a bound alkene. The Pd species is actually an aquo complex, so there should be a $[H_2O]^2$ term in the rate expression, but since water is the solvent it is not observed.

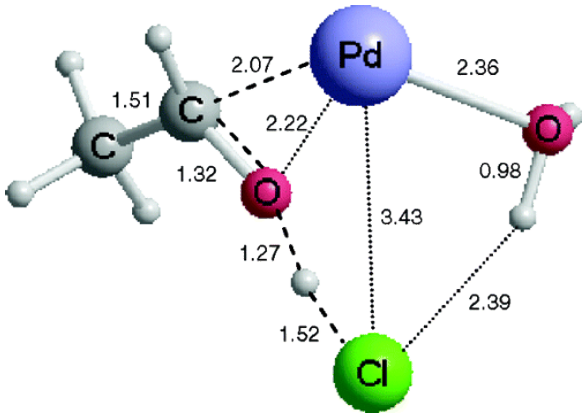


It was originally assumed that vinyl alcohol was dissociated followed by tautomerization to acetaldehyde. However, carrying out the reaction in D_2O resulted in no deuterium incorporation on the methyl group. Therefore, it was assumed that the coordinated vinyl alcohol underwent insertion to give a secondary Pd-C bond. β-H elimination of the OH hydrogen then resulted in formation of the aldehyde.



A recent computational paper (*J. Am. Chem. Soc.* **2006**, *128*, 3132) shows that this β-H elimination has a very high activation barrier (36 kcal/mol). This value is nearly double the 19.8 kcal/mole that has been measured for the overall Wacker cycle. Since this transition state was unreasonable, they looked for lower energy ones. The one they identified involved a Cl mediated proton abstraction. This transition state leads to the loss of both HCl and acetaldehyde from the Pd center in the same step. As a result, this reaction can be considered more similar to a heterolytic reductive elimination, rather than a β-H elimination.

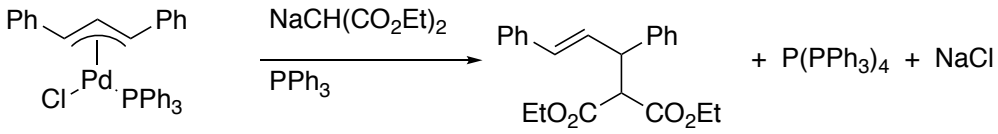




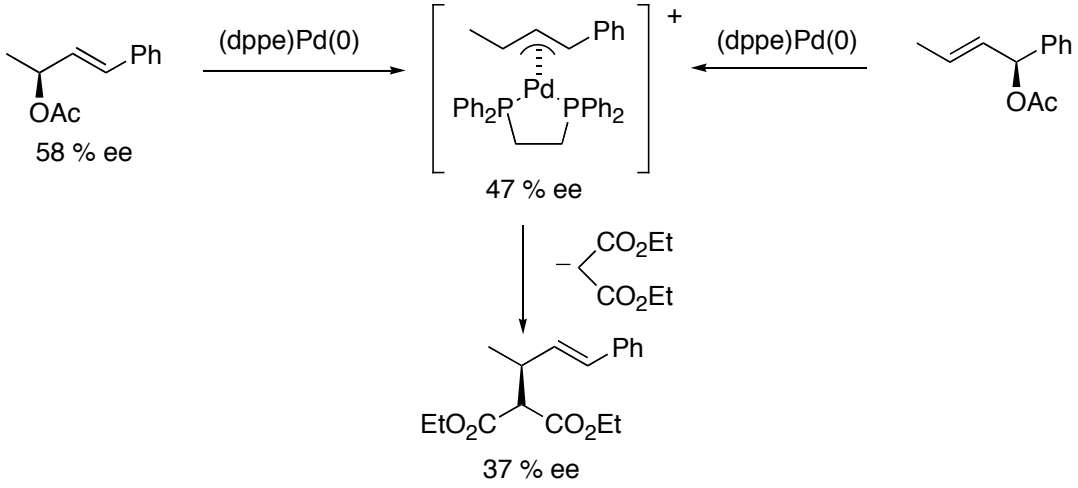
<u>η³-Allylic substitution:</u>

Nucleophilic attack on η³-allyl species, particularly those of palladium(II), are widely used to form new C-C and C-heteroatom bonds. In many cases these reactions can be accomplished in high enantioselectivity.

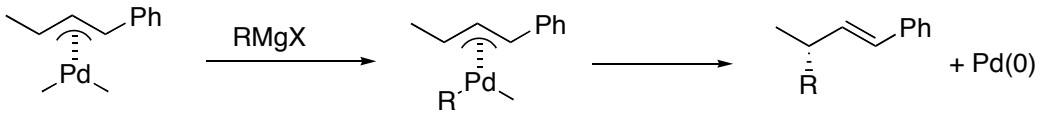
Nucleophilic attack on metal allyl complexes generally occurs at the terminus of the allyl unit, often at the less-substituted end.



η³-Allyl species can be formed by allylic C-H activation, but the most common route to Pd-allyl species is by oxidative addition of allylic halides or acetates. This reaction goes with clean inversion. The regioisomeric allylic acetate gives the identical Pd-allyl. Soft nucleophiles (pKa < 25) attack the face opposite the metal center to give clean inversion. Therefore, the overall reaction occurs with retention of stereochemistry. Attack generally comes at the less hindered terminus of the allyl group. (*J. Am. Chem. Soc.* **1983**, *105*, 7767)

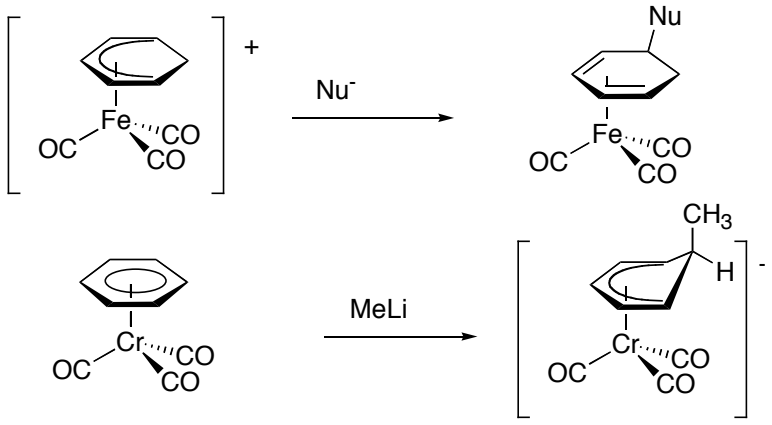


In contrast, hard nucleophiles (pKa > 25) tend to add to the metal first. Bond formation is by reductive elimination, which occurs with retention. Therefore, the overall substitution reaction occurs with inversion. (*Chem. Comm.* **1984**, 107).



Other polyene and polyenyl systems:

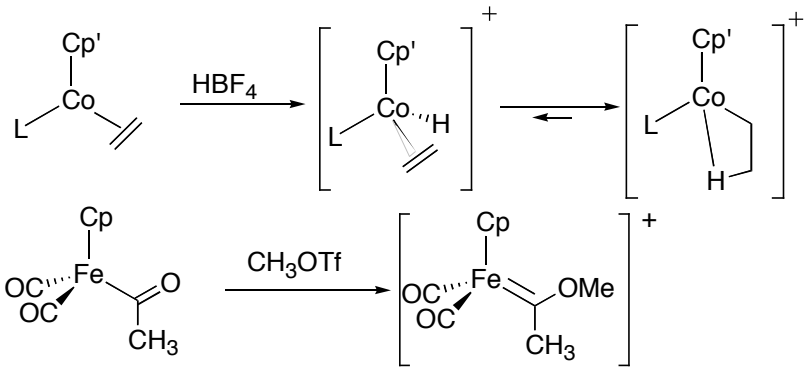
Other polyene and polyenyl systems undergo attack similarly to allyl systems. Attack is exclusively from the face opposite the metal.



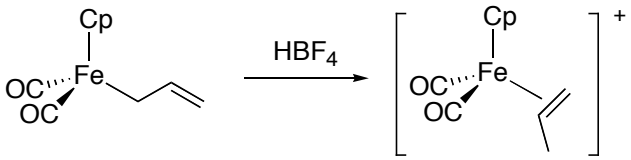
Electrophilic Substitution and Abstraction

Electrophilic addition:

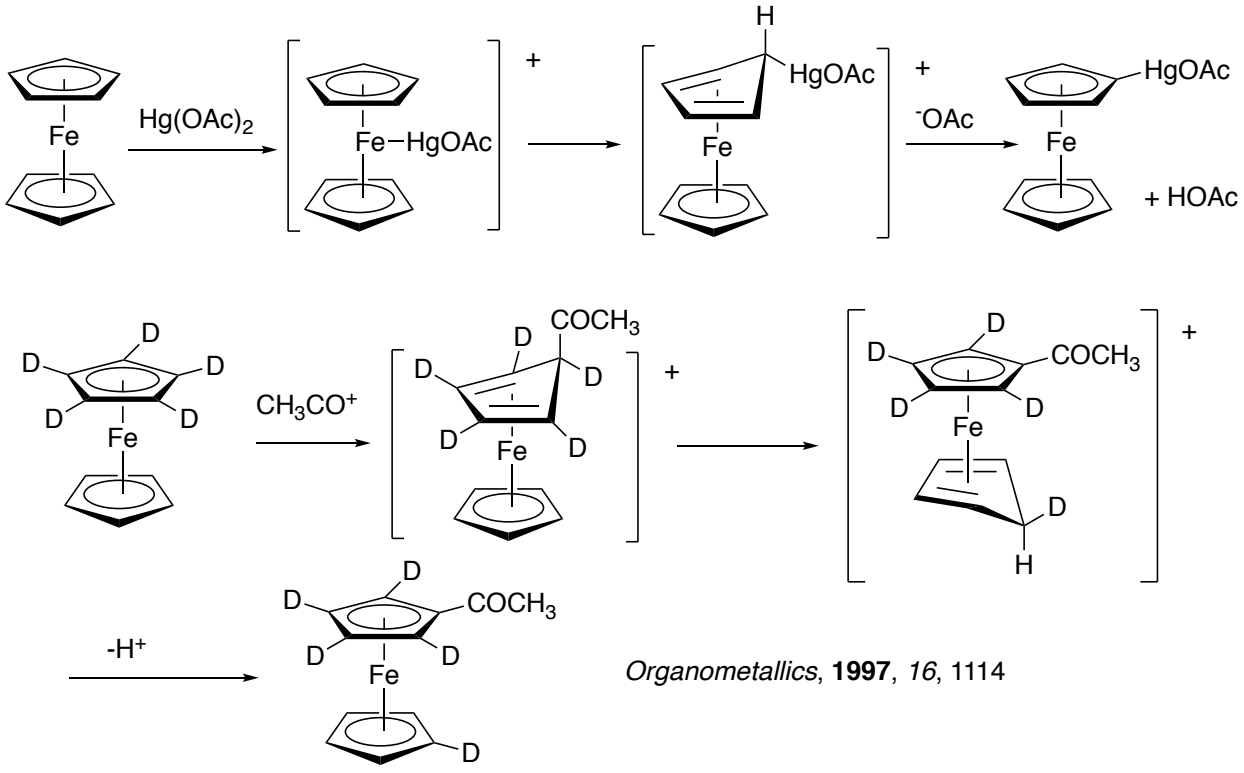
We have already discussed some examples of electrophilic addition reactions. Typically these reactions require a relatively electron rich metal center to act as a base. The electrophile can either add first to the metal center, or directly to the ligand. The order of addition will depend on the relative basicity of the metal and the ligand.



Other important examples of electrophilic addition include addition to electron rich metal allyls. This provides a convenient synthesis of cationic metal olefin complexes. In this case, the allylic group is introduced by an S_N2 oxidative addition to Fp^-.



Cp is usually not susceptible to nucleophilic attack, but electron rich metallocenes are prone to electrophilic attack. Ferrocene undergoes electrophilic substitution reactions similar to benzene. Depending on the electrophile, addition to a Cp ring of ferrocene can either occur directly or by initial attack at iron. Mercuric acetate adds initially to the iron center followed by an endo attack on the Cp ring. Exo deprotonation completes the electrophilic substitution. For a hard electrophile, such as CH_3CO^+, exo attack on the Cp ring occurs directly. There is a strong preference for exo deprotonation, so the proton is transferred to the other Cp ring followed by exo deprotonation. This can be seen in the acetylation of d_5-ferrocene.

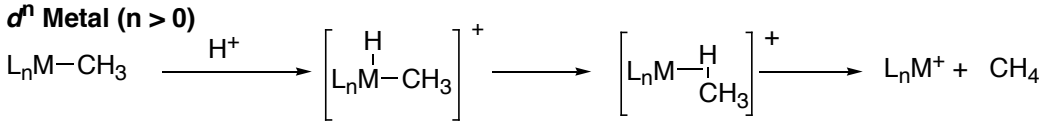


Organometallics, **1997**, *16*, 1114

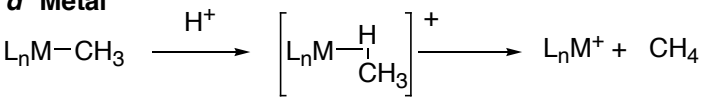
Electrophilic abstraction of metal alkyls:

The most common electrophilic attack is by proton. Early transition metals are very reactive towards even weak acids such as water, but later transition metals require more vigorous conditions. For metals with d electrons, protonation at the metal followed by reductive elimination is thought to occur. Since d^0 metals cannot be protonated, attack must occur at the ligand.

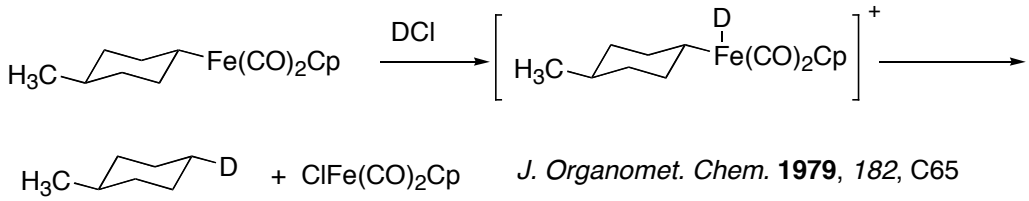
d^n Metal (n > 0)



d^0 Metal



In cases where attack at the metal center occurs first, we would expect to see retention of configuration.



J. Organomet. Chem. **1979**, *182*, C65

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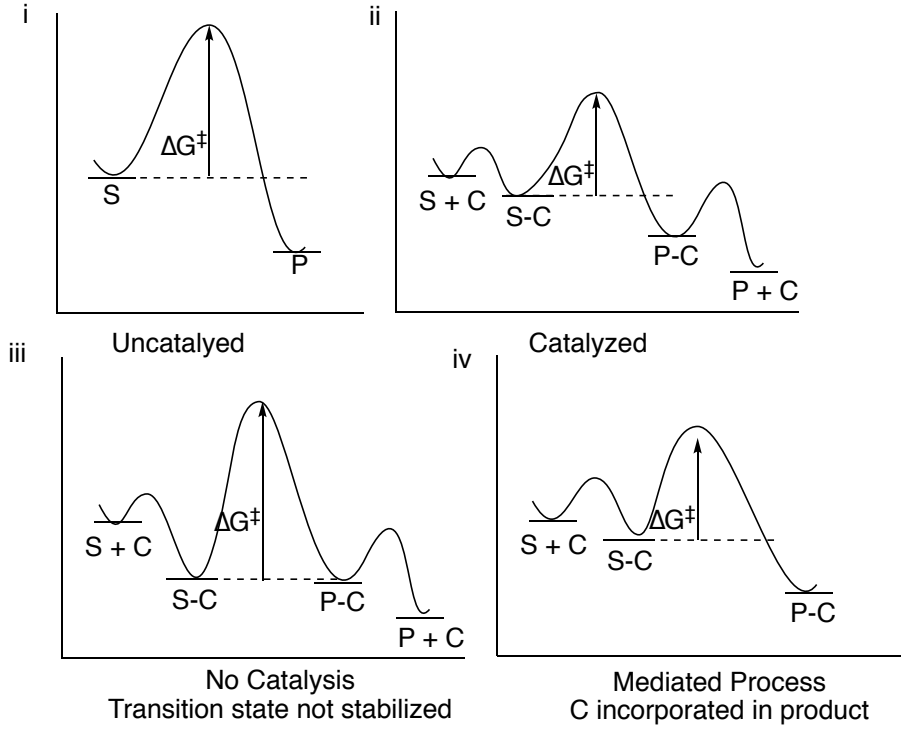
8-Catalysis General Principles

One of the most important applications of organometallic compounds has been in catalysis, primarily directed towards organic synthesis. Catalytic applications range from large scale industrial processes, such as olefin polymerization, hydroformylation, and hydrogenation processes to complex transformations used in academic synthesis and the pharmaceutical industry.

Catalysis Defined:

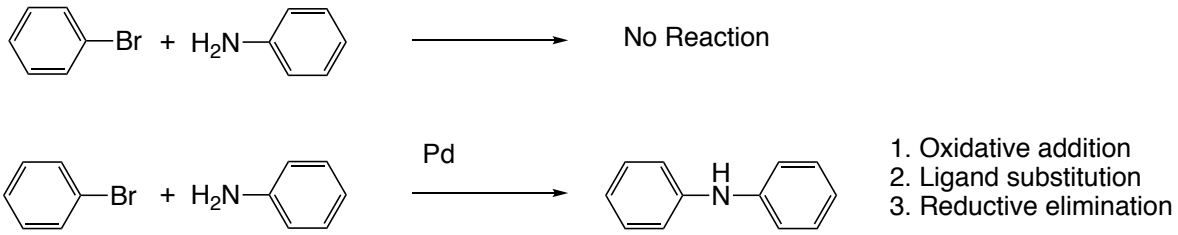
A catalyst is defined as a substance that increases the rate of a chemical reaction without being consumed. This is achieved by lowering the activation barrier compared to the uncatalyzed reaction. Note that the thermodynamics of the reaction are unaffected.

Typically, the catalyst (C) will first bind to the substrate (S) and then promote the reaction by a lower barrier pathway, thus lowering $\Delta G^{\ddagger}$ (ii). The catalyst will then release the product to restart the cycle. If the substrate-catalyst complex is too stable, and the transition state energy not lowered enough, then there is no catalysis. The barrier is actually higher (iii). If the C reagent is incorporated into the product, or otherwise irreversibly altered, then it is not a catalyst (iv). In this case, C would be a reagent (if incorporated) or would mediate the process if it is converted into a species that will not promote the reaction, but is not part of the product.



Enzymes catalyze reactions by binding the reactants in the proper orientation for the reaction and stabilizing the transition state species. Organometallic complexes typically catalyze reactions by providing alternate, lower energy pathways. Consider the reaction of aniline with bromobenzene. The direct reaction will not occur, because there is no low energy pathway for this reaction. An S_N2 reaction is not possible because the back side of the C-Br is inaccessible. S_NAr is unlikely because the carbanion intermediate would be very unstable. A benzyne process is unlikely because aniline is not a strong base. This reaction can be accomplished at low temperature using a palladium catalyst, however. In this case,

the C-Br bond is broken in an oxidative addition step, that occurs readily. The amine is then coordinated to palladium, deprotonated, and then reductive elimination occurs (details in Chapter 8).



Classes of catalysts

One way that catalysts are classified is by whether they are in the same phase as the reagents or not.

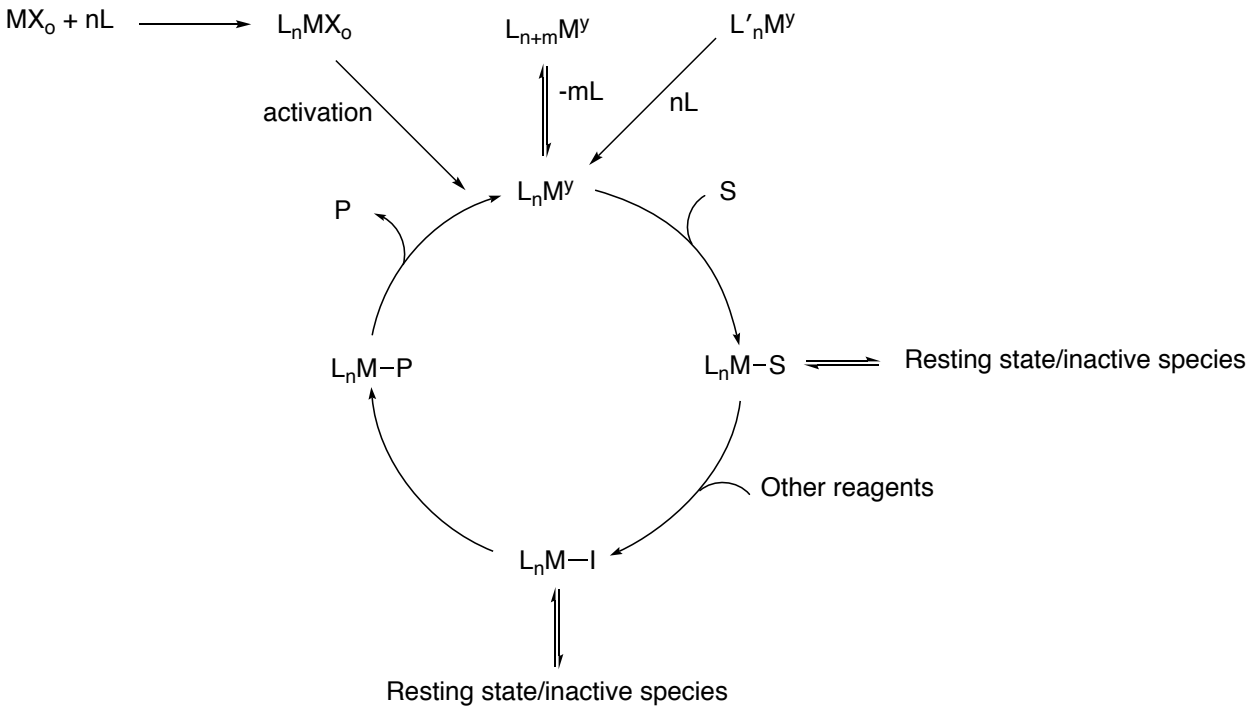
Heterogeneous catalyst: A heterogeneous catalyst is not soluble in the reaction phase. Often the catalyst is a solid and the reactants are liquids and/or gases. Heterogeneous catalysts are often metals supported on a solid substrate, such as a metal oxide (alumina, silica) or carbon. These types of catalysts are preferred for large scale industrial processes because product separation from the catalyst is simple. There is often limited ability to rationally modify the catalyst species, which will often be a distribution of metal particles.

Homogeneous catalyst: A homogeneous catalyst is by definition soluble in the reaction mixture. Most typically it is a molecular organometallic complex, although soluble metal nanoparticles can also be considered homogeneous. We will primarily focus on these types of processes. Because ligands are involved, it is possible to infinitely tune the reactivity and selectivity of the metal center. The challenge with these processes is separating the catalyst from the product. This is necessary to recover high value metals and to avoid metal contamination products, such as drugs.

Asymmetric catalysts: A special case of catalysts that can convert achiral starting materials into a chiral product. They are usually homogeneous catalysts, although some heterogeneous versions are known. Typically, a chiral ligand is used to promote the asymmetric reaction. Asymmetric catalysis is very important in modern organic chemistry as it allows a small amount of a chiral compound to produce large amounts of chiral products from relatively cheap achiral starting materials.

The catalytic cycle

Catalytic mechanisms are typically written as a catalytic cycle to emphasize the fact that the catalyst returns to a common active species. Note that the active species may not be the organometallic complex that is put into the reaction. Often a **precatalyst** is used that is converted to the **active species**, which is what actually catalyzes the reaction. In many cases the active catalyst is formed in situ by the processes that could include: dissociation of ligands, coordination of new ligands, and/or oxidation or reduction of the metal center. Reagents that enter the cycle and products or by products formed are shown as entering or leaving the cycle. The metal complexes involved in the cycle are shown on the catalytic cycle.



The productive steps on the catalytic cycle are the key to product formation. There may be processes that take the catalyst out of the active cycle. These could be steps that revert the precatalyst to an inactive form, such as ligand coordination. Alternatively, they could be steps that convert an intermediate into a non-catalytic species either reversibly or irreversible. If irreversibly, then this is a catalyst deactivation process. If reversibly, then this may be a resting state for the catalyst.

Catalyst resting state: The species at highest concentration during the catalytic cycle. Typically would be the species prior to the rate limiting step of the catalytic cycle.

Rate limiting step: The slowest step in the catalytic cycle. Therefore, the step with the highest activation barrier. Improving the rate of a catalytic reaction requires speeding up this step.

Quantifying the efficiency of a catalytic reaction

Typically organic chemists define reaction efficiency as the yield of a chemical process. This is not very informative, as it does not indicate anything about the rate of a process. Only how much product is formed at some indeterminate time. For catalytic systems there are a number of metrics that provide information on how efficient the catalyst is.

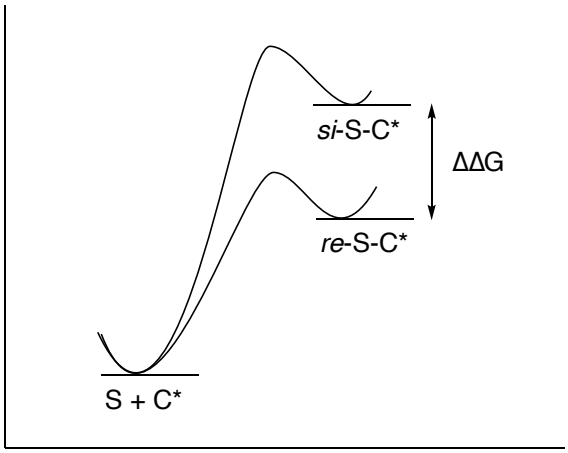
Turnover number (TON): This is simply the number of moles of product formed divided by the moles of catalyst used (mol/mol cat). There is no time component to this value, so it does not indicate rate. It is an indication of the stability of the catalyst. A higher TON means the catalyst can survive for a long time, relative to the reaction rate. For industrial processes, a TON of 1000 is typically a minimally acceptable value for high value products, such as pharmaceuticals. The goal is to have this value as high as possible. Catalysts with TON in the $10^{4\text{-}6}$ range are common.

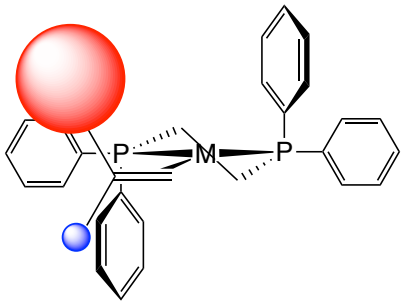
Turnover frequency (TOF): The turnover frequency is the TON divided by time (mol/mol cat•time). The time unit can be in seconds, minute, or hours. For reactions involving gases, there may also be a pressure term associated (mol/mol cat•h•bar). This value provides kinetic information about a reaction. To get true kinetics, the TOF would need to be measured as a function of time.

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Chiral Catalysis

An asymmetric catalyst typically has a chiral ligand environment. A common situation is that the chiral catalyst will bind selectively to one face of a prochiral compound, such as an alkene. This is controlled through steric interactions most commonly. Since the catalyst is chiral, it forms diastereotopic complexes with a prochiral substrate. The enantioselectivity of the catalyst will be determined by the energy difference between these two diastereotopic intermediates. The energy difference required is relatively small. A 1.37 kcal/mol difference in energy (assuming room temperature) results in a 9:1 selectivity. A 99:1 selectivity is achieved with a 2.74 kcal/mol difference.

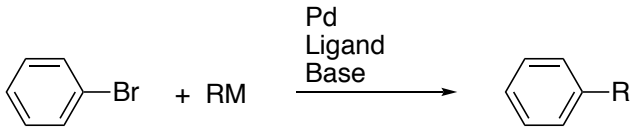




9 Cross-Coupling Reactions

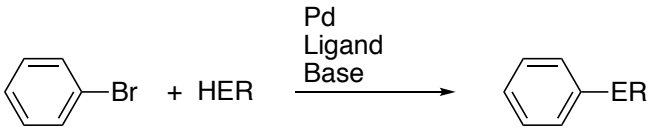
Over the past 20-30 years an extensive collection of metal catalyzed cross-coupling reactions of organic halides and nucleophiles has been developed. These reactions have become powerful synthetic methods because they allow C-C and C-heteroatom bonds to be formed under very mild conditions with excellent functional group tolerance. Their influence was recognized with the 2010 Nobel Prize, which went to Richard Heck, Akira Suzuki, and Ei-ichi Negishi for their role in the development of these reactions.

Coupling with organometallic reagents



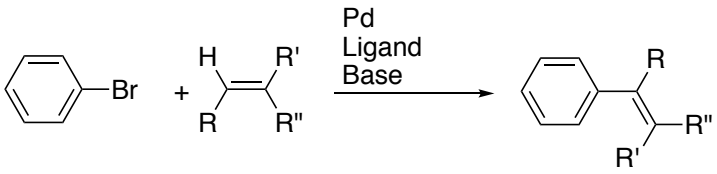
RM
R'MgX - Kumada
R'ZnX - Negishi
R'Zr - Negishi
$R'BX_2$ - Suzuki-Miyaura
$RSi(OR)_3$ - Hiyama, Denmark
$R'SnR''_3$ - Stille
R—≡—Cu - Sonogarshira

Hartwig-Buchwald heteroatom cross-couplings

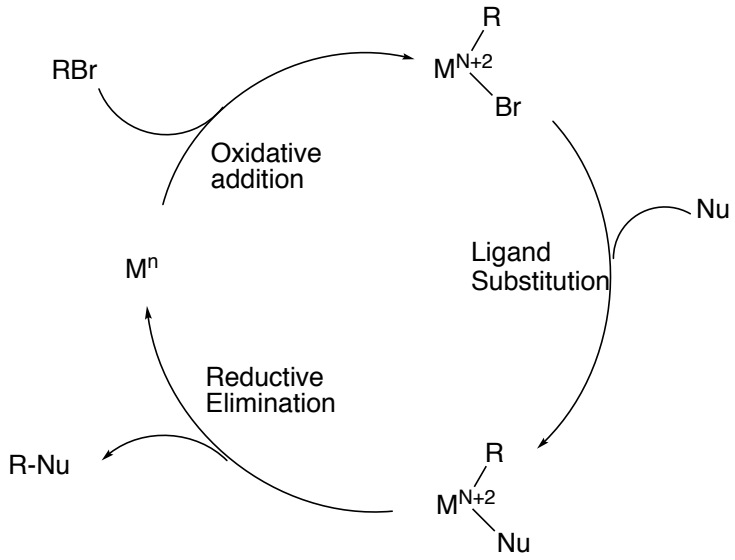


HER = amine, amide, thiol, ether, ketone, etc.

Heck Coupling



With the exception of the Heck reaction, all of these coupling reactions follow the same general catalytic cycle: 1) oxidative addition of the organic halide; 2) ligand substitution of the nucleophile for the halide; 3) reductive elimination of the new organic product.



Nu
R'MgX - Kumada
R'ZnX - Negishi
R'Zr - Negishi
$R'BX_2$ - Suzuki-Miyaura
$RSi(OR)_3$ - Hiyama, Denmark
$R'SnR''_3$ - Stille
R—≡—Cu - Sonogarshira
R_2NH - Buchwald-Hartwig
ROH - Buchwald-Hartwig
RSH - Buchwald-Hartwig
enolate - Buchwald-Hartwig

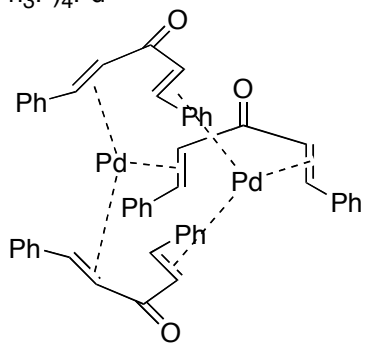
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The Heck reaction follows a similar mechanism that we will focus on later, which involves: 1) oxidative addition; 2) ligand substitution by the alkene; 3) migratory insertion; 4) ß-hydride elimination; 5) reductive elimination.

General Trends in Pd-Catalyzed Cross-Coupling: Apply with minor variations to all cross-coupling reactions

1. Catalyst Precursors:

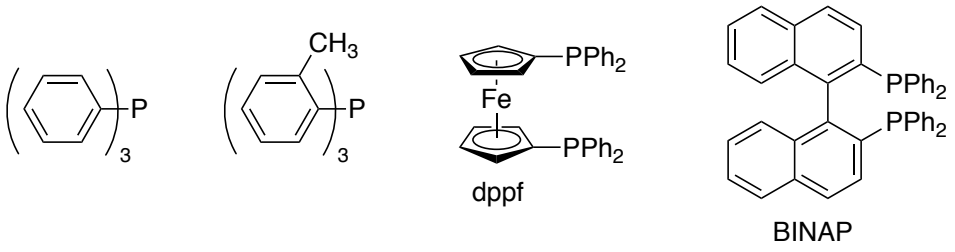
Metal Sources: Palladium is the most widely used metal for cross-coupling followed by copper, although there are examples of nickel, cobalt, rhodium, and iron(?) catalyzed coupling reactions as well. Generally the palladium is supported by a ligand. The catalyst can be derived from a preformed complex (i.e., $(Ph_3P)_4Pd$, $(Ph_3P)_2PdCl_2$, etc.) or formed *in situ* from combinations of Pd sources ($PdCl_2$, $Pd(OAc)_2$, $Pd(dba)_2$, etc) and a ligand. Both Pd(0) and Pd(II) sources can be used, although the active species is Pd(0) in all cases.

Pd^0	Pd^{II}
$(Ph_3P)_4Pd$	$(Ph_3P)_2PdCl_2$
	$Pd(OAc)_2$
$Pd_2(dba)_3$ $Pd(dba)_2$	$PdCl_2$
	$(CH_3CN)_2PdCl_2$
Pd/C	

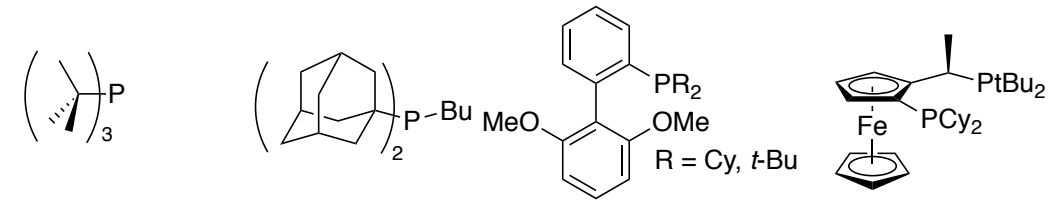
Nickel can catalyze many of the same reactions as palladium. Nickel is attractive because it is much less expensive than palladium. Nickel-based catalysts tend to be less active and general, however. Nickel is better at activating aryl chlorides and C-O bonds than palladium, however. Platinum has shown no activity in cross-coupling chemistry. Copper(I) is also a useful catalyst for cross-coupling. In fact, copper-promoted systems developed by Ullmann and Goldberg in the early 1900s were the first examples of metal-catalyzed cross-coupling.

Ligands: Palladium alone can catalyze cross-coupling reactions without additional supporting ligands, but usually only with reactive substrates (ArI) and/or high temperatures. Ligands are usually necessary to give more active catalyst systems. The ligand serves to stabilize the Pd^0 intermediate, solubilize the catalyst, and increase the rate of oxidative addition.

Phosphines: Phosphines remain the most widely used ligands. The most commonly used phosphine is triphenylphosphine. In general, arylphosphines remain the most widely used. Monodentate phosphines are usually the most effective ligands, but some chelating ligands like dppf and binap have proven useful in certain reactions.



Sterically demanding, electron rich phosphines have received increasing attention recently as they provide more effective catalysts for less reactive substrates, such as aryl chlorides. The key features of these ligands is that their steric bulk promotes low coordination LPd(0) complexes and their strong electron-donating ability makes the palladium highly reactive towards oxidative addition.



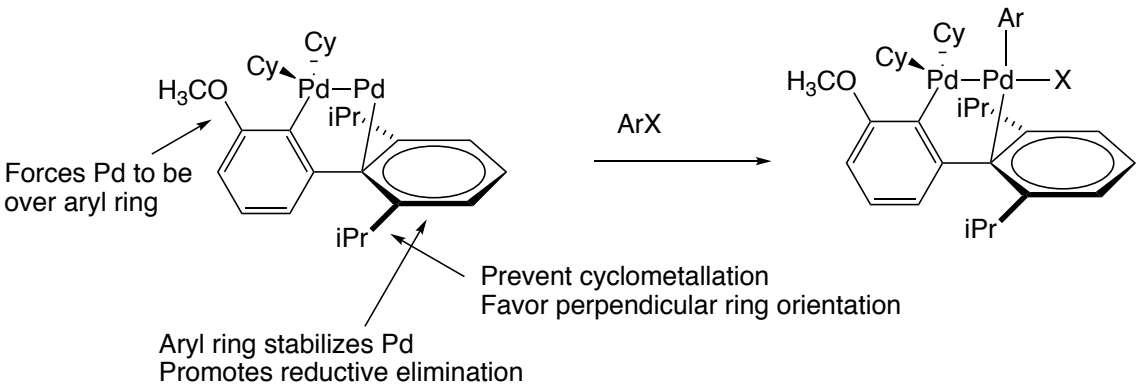
G. C. Fu
J. F. Hartwig

M. Beller

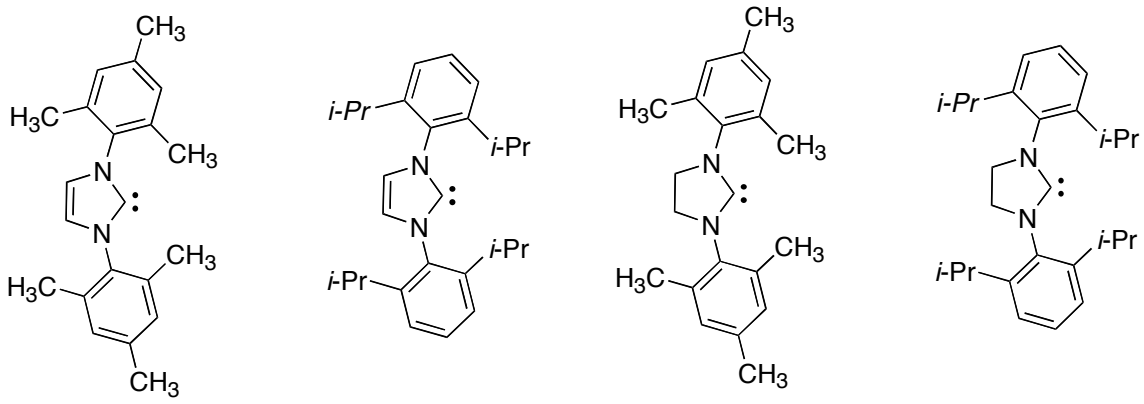
S-Phos
S. L. Buchwald

Josiphos
J. F. Hartwig

The Buchwald ligands, such S-Phos, have been designed to provide high catalyst activity (*Angew. Chem. Int. Ed.* **2008**, *47*, 6338). The biaryl structure stabilizes the monodentate Pd(0) species through coordination to the second aromatic ring. Substituents on the ortho position prevent cyclometallation. Additional substituents ortho to the phosphine favor the conformation in which the palladium is oriented over the bottom aryl ring.



<u>*N*-Heterocyclic Carbenes:</u> *N*-heterocyclic carbenes (NHCs, Arduengo carbenes) have attracted significant attention as ligands for cross-coupling reactions. NHCs are stronger electron donors than phosphines and they tend to have stronger M-L bonds, thus they may give more stable catalysts. Major players in the application of carbene ligands to cross-coupling are Wolfgang Herrmann, Steve Nolan, and John Hartwig

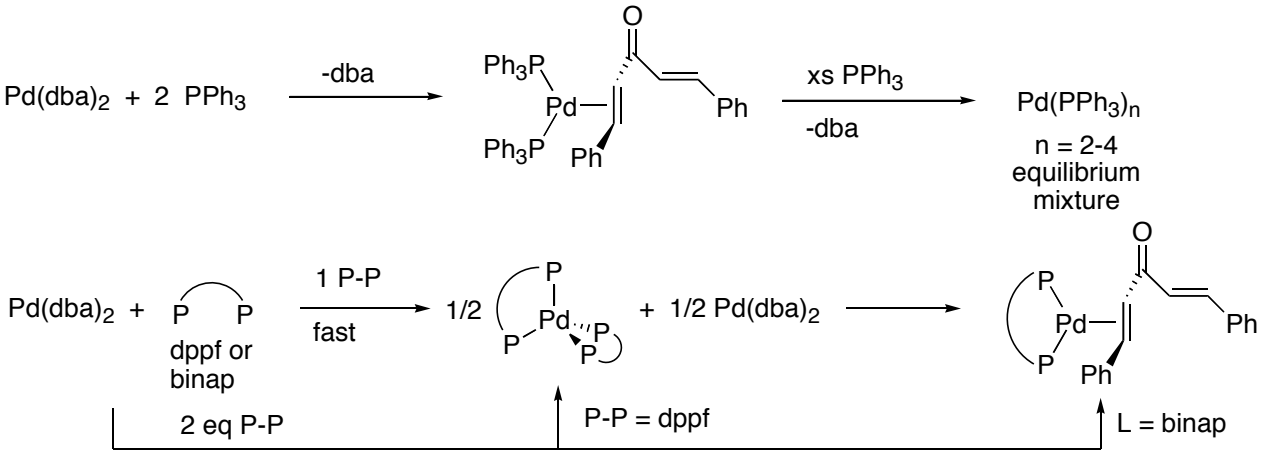


2. Generation of Catalytically Active Species

In almost every case, the metal/ligand combination added to the reaction is not the true catalytically active species. $(Ph_3P)_4Pd$ may be the closest example of the active catalyst resembling what was added to the reaction, although two phosphines must dissociate to give the true active species. Many catalysts are generated *in situ* from a Pd source and an appropriate ligand. At a minimum, a ligand exchange must occur for the desired ligand to coordinate to the Pd(0) precatalyst. If a Pd(II) source is used, then there must be some mechanism for the Pd(II) precursor to be reduced. In many cases, it has been shown that the presumed catalyst actually decomposes to highly active palladium colloids, which are the true active catalysts.

Ligand Substitution: Catalysts derived from $Pd(dba)_2$.

$Pd(dba)_2$ ($Pd_2(dba)_3$ and $Pd_2(dba)_3{\cdot}CHCl_3$ serve the same purpose) is the most common Pd(0) catalyst precursor. The dba ligands can be easily displaced with phosphines to give Pd(0)-phosphine complexes. The dba ligand is not completely uninvolved, however. When 2 equivalents of P/Pd are used, mixed phosphine/dba complexes are formed. The dba acts as a weakly coordinating ligand that can be displaced by ArX.



C. Amatore and A. Jutand, *Coord. Chem. Rev.* **1998**, *178-180*, 511-528.

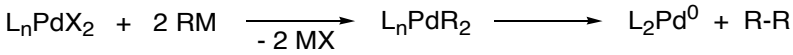
Preferred Ligand:Pd ratios: Depending on the size of the ligand, there will be a preferred ligand to Pd ratio for the stable homoleptic ligand (phosphine or carbene) complex. The true active species will have a lower coordination number due to the need for an open site for oxidative addition to occur (Notes,

Chapter 4.2). Chelating diphosphines will generally behave like small phosphines as in the Amatore example above.

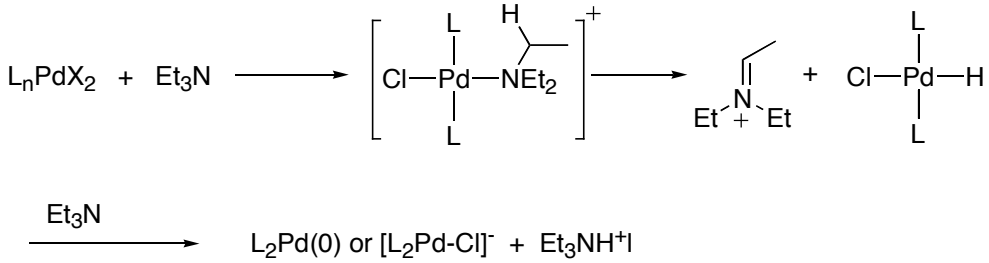
	Small R_3P ($\theta < 170$, i.e. PPh_3)	Large R_3P ($\theta > 180$, i.e. P*t*-Bu_3)	IMes, IPr, etc.
Stable $L_nPd(0)$	L_4Pd	L_2Pd	L_2Pd
$L_nPd(dba)$	$L_2Pd(dba)$	LPd(dba)	LPd(dba)
Active species	L_2Pd	LPd	LPd

Reduction of Pd(II) to Pd(0): Pd(II) sources are popular as they are less expensive than $Pd(dba)_2$. There are several mechanisms by which the Pd(II) precursor can be reduced under the reaction conditions.

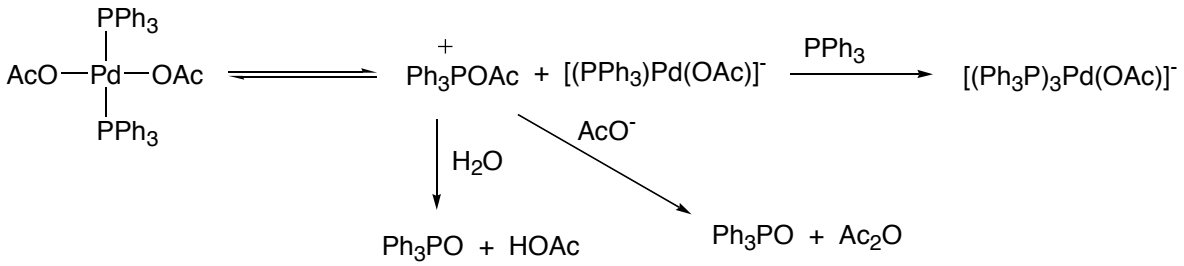
Reduction by an organometallic species: The organometallic coupling partner can reduce the Pd(II) precursor by displacing the two anionic ligands to give a PdR_2 complex that undergoes reductive elimination. This is the major mechanism of reduction for couplings involving organometallic nucleophiles.



Reduction by an amine or alcohol: Amines or alcohols with β-hydrogens can coordinate to Pd(II) centers and then undergo β-hydrogen elimination. Deprotonation of the Pd(II)-hydride (reductive elimination) gives the Pd(0) active species. This reduction pathway is most important in Heck and Hartwig-Buchwald couplings.

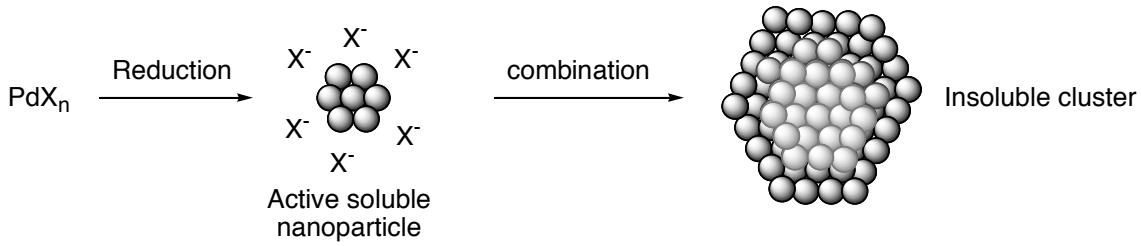


Reductive elimination of P-O: Triarylphosphines can reduce Pd(II) species in the presence of hard oxygen anions, such as acetate or hydroxide. The reduction involves reductive elimination of a P-O species. Jutand and Amatore have shown that $Pd(OAc)_2$ is reduced by PPh_3 to give anionic Pd(0)-acetate complexes, which appear to be the true active species. The P-O species ultimately ends up as a phosphine-oxide. (C Amatore and A. Jutand, *Acc. Chem. Res.* **2000**, *33*, 314-321).



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Generation of Pd(0) colloids or nanoparticles: "Ligand free" catalyst systems are believed to be catalyzed by soluble Pd(0) clusters. These clusters can be highly active, but tend to grow until they precipitate as unreactive Pd metal precipitate (Pd black). Halide salts, surfactants, polymers, and other weakly coordinating ligands have been shown to stabilize these nanoparticles. The formation of insoluble Pd particles is also the main deactivation mechanism for ligand supported catalyst systems.

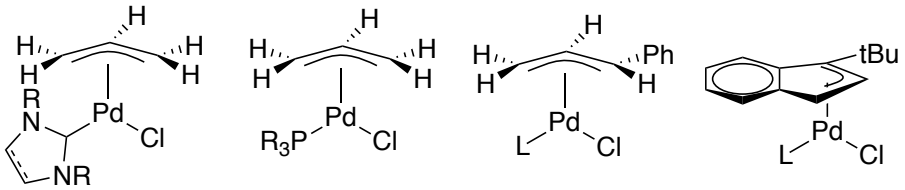


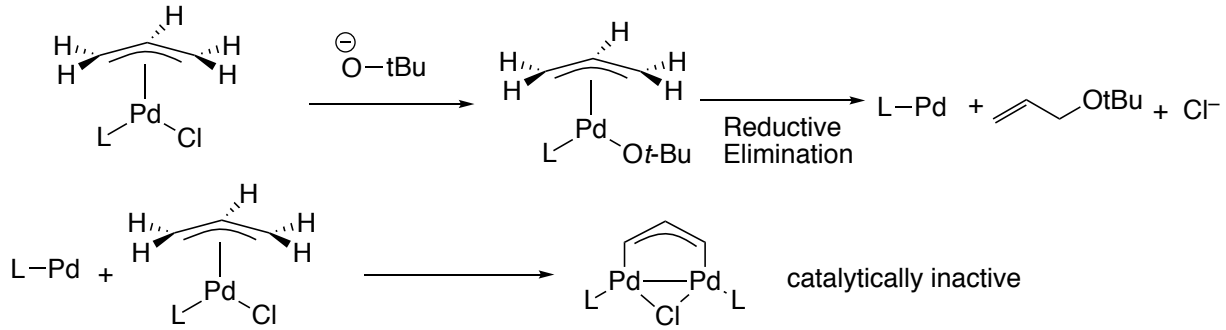
Heterogeneous catalysts: There has been some work on the use of heterogeneous palladium sources. The most common is Pd/C. Often these heterogeneous catalysts leach soluble nanoparticles into solution that do the catalysis. If the particles redeposit on the support in a usable form, the catalyst can be recycled. Review: *Chem. Rev.* **2018**, *118*, 2249

Generation of LPd(0) from precatalyst species

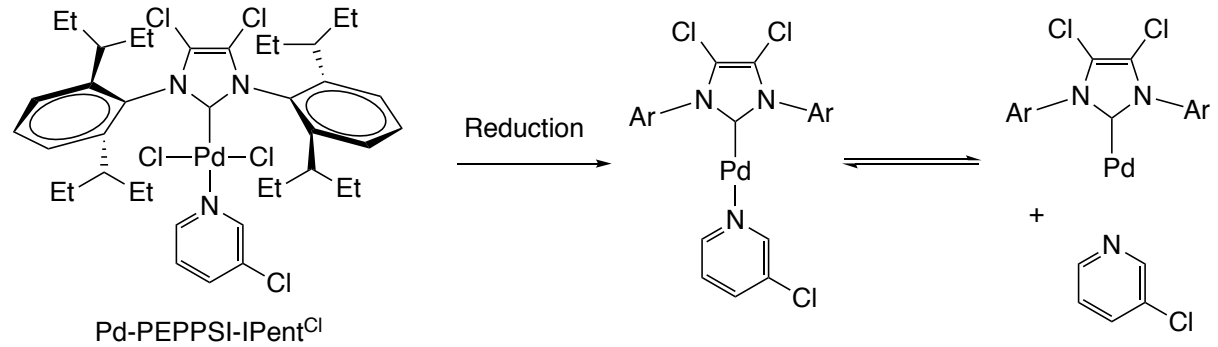
Most cross coupling reactions are performed by the in situ generation of the active catalyst from a ligand and a palladium precursor. There is growing interest in the development of stable palladium-ligand complexes that will readily form the active species under the reaction conditions. In particular, systems that will generate an LPd(0) species rapidly from a stable precursor are desired (*Isr. J. Chem.* **2019**, online, DOI: 10.1002/ijch.201900067)

Palladium-allyl complexes: Allyl palladium phosphine and carbene complexes are effective sources of LPd(0) active species (*Acc. Chem. Res.* **2008**, *41*, 1440; *J. Org. Chem.* **2010**, *75*, 6477). The mechanism of activation involves nucleophilic attack on the allyl, resulting in reductive elimination to give a LPd(0) active species. Unsubstituted allyl complexes are prone to formation of dipalladium(I) μ-allyl dimers that are catalytically inactive. This process occurs thermally upon storage and more rapidly during activation. This problem can be reduced by using the cinnamyl complex. An indenyl complex reported by Hazari completely avoids the Pd(I) dimer formation.



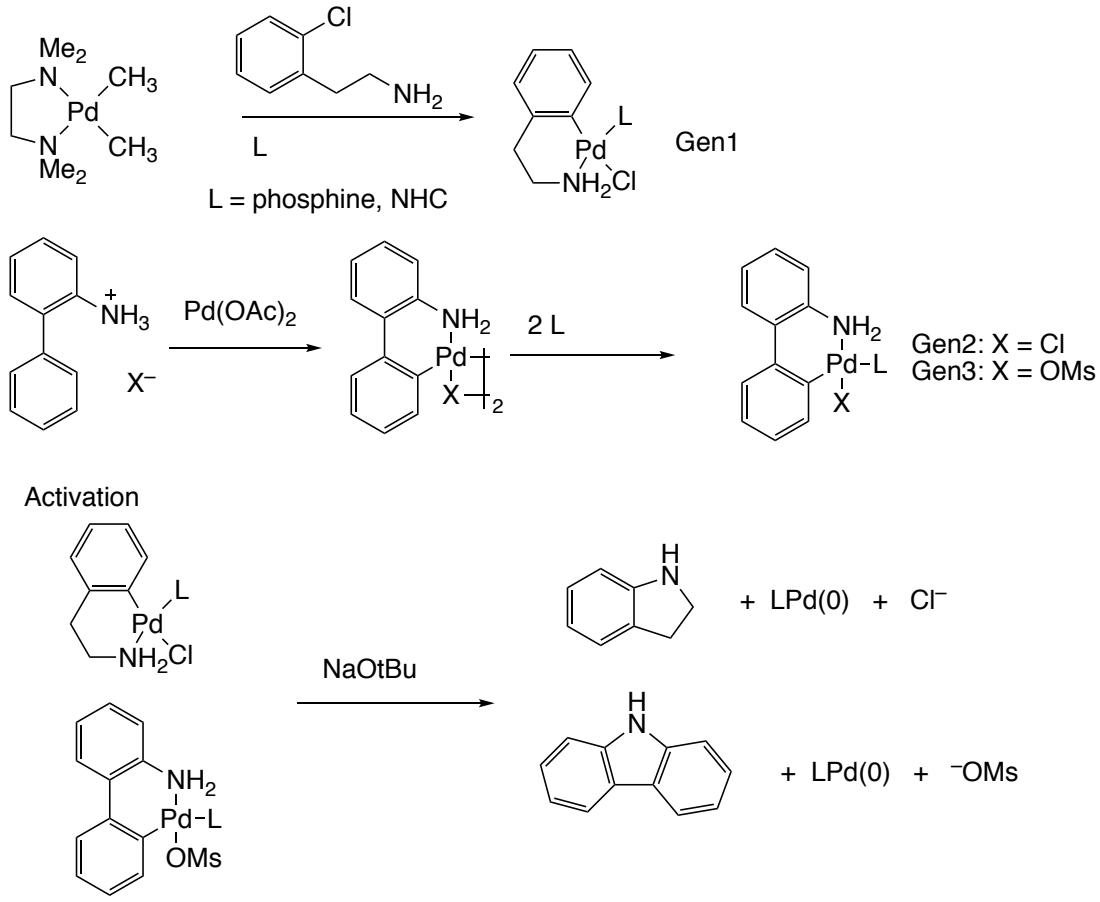


PEPPSI Catalysts: Prof. Michael Organ at York University in Canada has developed what he calls the PEPPSI family of catalysts (PEPPSI = pyridine-enhanced precatalyst preparation, stabilization, and initiation) (*Org. Proc. Res. Dev.* **2014**, *18*, 180). The PEPPSI catalysts have a single NHC carbene ligand and a labile 3-chloropyridine ligand. The chloropyridine ligand can be readily displaced to give the low-valent Pd(0) complex, but can recoordinate to stabilize the Pd(0) active species allowing for long catalyst lifetimes. The complex is a Pd(II) species, so must still undergo reduction to Pd(0) under the reaction conditions.



Buchwald Palladacycles: Buchwald has developed air-stable palladacycle complexes that undergo rapid reductive elimination to form nitrogen heterocycles and LPd(0) active species (*Chem. Sci*, **2013**, *4*, 916; *J. Am. Chem. Soc.*, **2008**, *130,* 6886). The ligands in these complexes are typically 2-biarylphosphines (i.e. S-phos) developed by Buchwald.

Synthesis



3. Oxidative Addition:

Oxidative addition is the rate limiting step in many cross-coupling reactions, particularly with less reactive bromide and chloride substrates.

All classes of organic halides have been successfully used in cross-coupling reactions, although sp^2-organohalides are the most commonly used substrates. In addition, a variety of other leaving groups, such as triflates, tosylates, diazonium ions, phenyl iodonium ions, etc. have been explored in these reactions. Halides remain the most common class of substrate.

General reactivity trends

Aryl Halides: As discussed in chapter 4, the rate of oxidative addition is: ArI > ArBr > ArCl. Aryl triflates generally fall between iodides and bromides. Tosylates and mesylates are generally similar to chlorides, but not all catalyst systems are effective for sulfonate leaving groups. Electron-withdrawing groups make the aryl halide more reactive, while electron-donating groups deactivate the aryl halide.

Ligand Choice: Although the exact conditions will depend on the substrates, ligand structure, and other reaction conditions, a general idea of the ability of various catalyst types to couple aryl halides is shown below. Activated (EWG) aryl halides will be at the low temperature end, while deactivated (EDG) aryl halides will be at the high end, or possibly completely unreactive.

	ArI	ArBr	ArCl
Ligand Free, N, O, and S ligands	rt – 80 °C	80 – 150 °C	usually not possible
Triarylphosphines	room temp	50 – 120 °C	>150 °C, if at all
Trialkylphosphines and NHCs	room temp, very fast	room temp	room temp – 100 °C

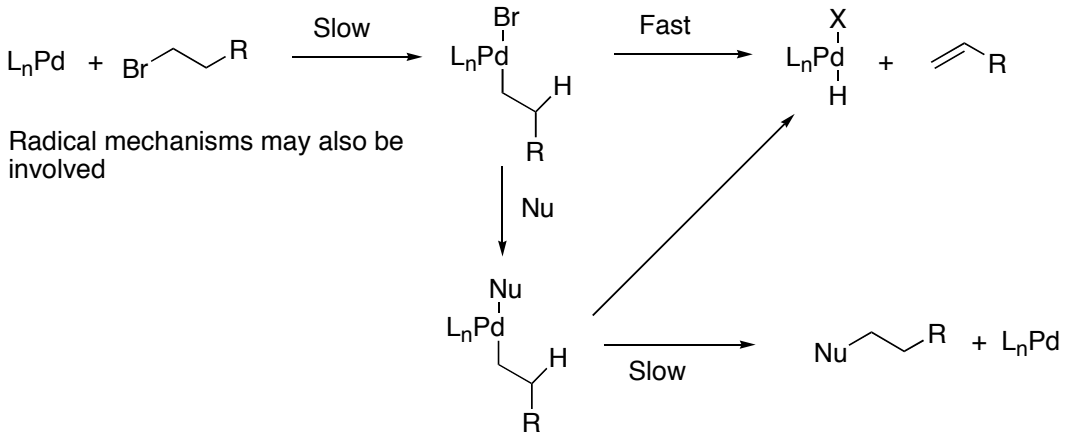
Bulky alkylphosphines give stable 3-coordinate species, rather than either 4-coordinate $L_2Pd(Ar)X$ (PPh_3) or dimeric $[LPd(Ar)X]_2$ complexes (P(*o*-tol)$_3$) (Hartwig, *JACS*, **2004**, *126*, 1184-1194)). In the presence of an excess of bulky alkylphosphine, the aryl halide complex reductively eliminates Ar-X (Hartwig, *Organometallics*, **2004**, *23*, 1533-1541).

With bulky alkylphosphines, the mechanism of oxidative addition to L_2Pd is different, depending on the halide (Notes, Chapter 4.2; Hartwig, *JACS*, **2009**, *127*, 8141-8154).

- ArI: rate limiting associative substitution of ArI for L followed by fast oxidative addition.
- ArBr: rate limiting dissociation of phosphine, followed by fast oxidative addition to LPd
- ArCl: reversible dissociation of phosphine, followed by rate limiting oxidative addition to LPd

Alkenyl Halides: Alkenyl halides have similar reactivity trends to aryl halides. Oxidative addition/reductive elimination almost always occurs with retention of olefin geometry.

Alkyl Halides: As discussed in chapter 4, alkyl halides oxidatively add by S_N2 or radical mechanisms. Benzyl and allyl halides are the most reactive (S_N2). Simple alkyl halides typically undergo oxidative addition slowly (mostly radical). Reductive elimination is also slow, generally If ß-H are present, elimination is usually an important side reaction. Generally alkyl halides are not good substrates for cross-coupling.



Greg Fu (MIT) has shown examples of Suzuki, Sonogashira, and Stille couplings of alkyl halides can be achieved by proper choice of ligand (*J. Am. Chem. Soc.* **2003**, *125*, 13632; *ibid*, 3718; *Angew. Chem. Int. Ed.* **2002**, *41*, 1945, *J. Am. Chem. Soc.,* **2001**, *123*, 10099, review *Science*, **2017**, *356*, eaaf7230).

The reactions are typically limited to primary and secondary alkyl halides. Some examples of tertiary halides have been reported (*ACS Cent. Sci*, **2016**, *2*, 647). Alkyl-alkyl couplings are largely limited to coupling of alkyl halides with Grignard reagents, organoboron, and organozinc compounds.

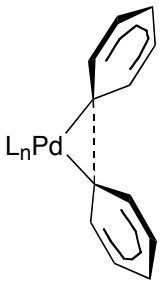
4. Reductive Elimination: Reductive elimination is usually a fast step in the catalytic cycle, so there is less focus on designing ligands to promote it. Reductive elimination is favored by electron deficient ligands (opposite of oxidative addition) and sterically demanding ligands (same as oxidative addition).

Occurs only from *cis* L_nPdRR'

aryl-aryl ≈ vinyl-vinyl/aryl > alkyl-aryl/vinyl > alkyl-alkyl > Me-Me

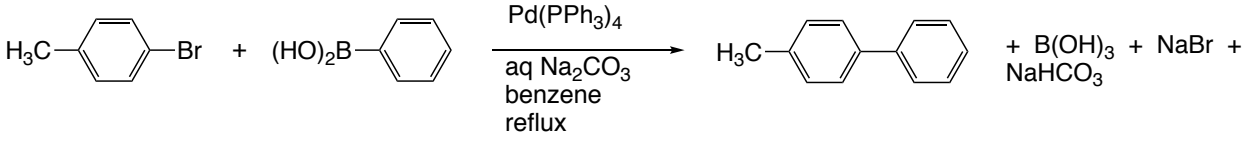
For $(Ph_3P)_2PdMe_2$, rate of R.E. is ∝ to 1/[PPh_3]

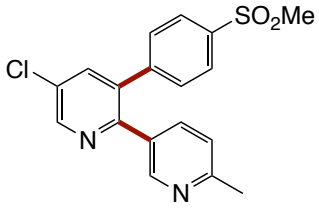
For $(Ph_3P)_2PdPh_2$, R.E. occurs directly from the 4-coordinate species.



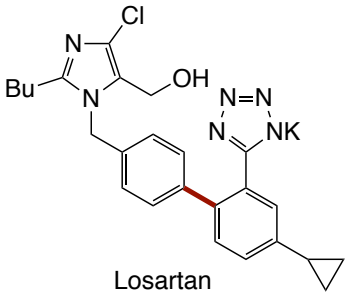
Miyaura-Suzuki Coupling

The Suzuki coupling involves the cross-coupling of an organohalide and an organoboron species. This reaction is widely used in organic synthesis because organoboron compounds are generally air and water stable and the products are non-toxic (borax). For reviews see: *Chem. Rev.* **1995,** *95*, 2457; *J. Organomet. Chem.* **1999**, *576*, 147; *Chem. Commun.* **2005**, 4759. This methodology is widely used and has been incorporated into a large number of industrial scale syntheses, particularly in the pharmaceutical industry.

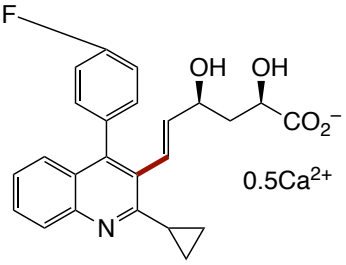




Etoricoxib
Arcoxia
pain and inflamation



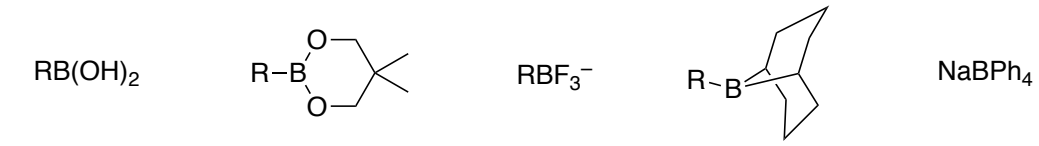
Losartan
Cosaar
anti-hypertensive



Pitavastatin
Livalo
high cholesterol treatment

General Features

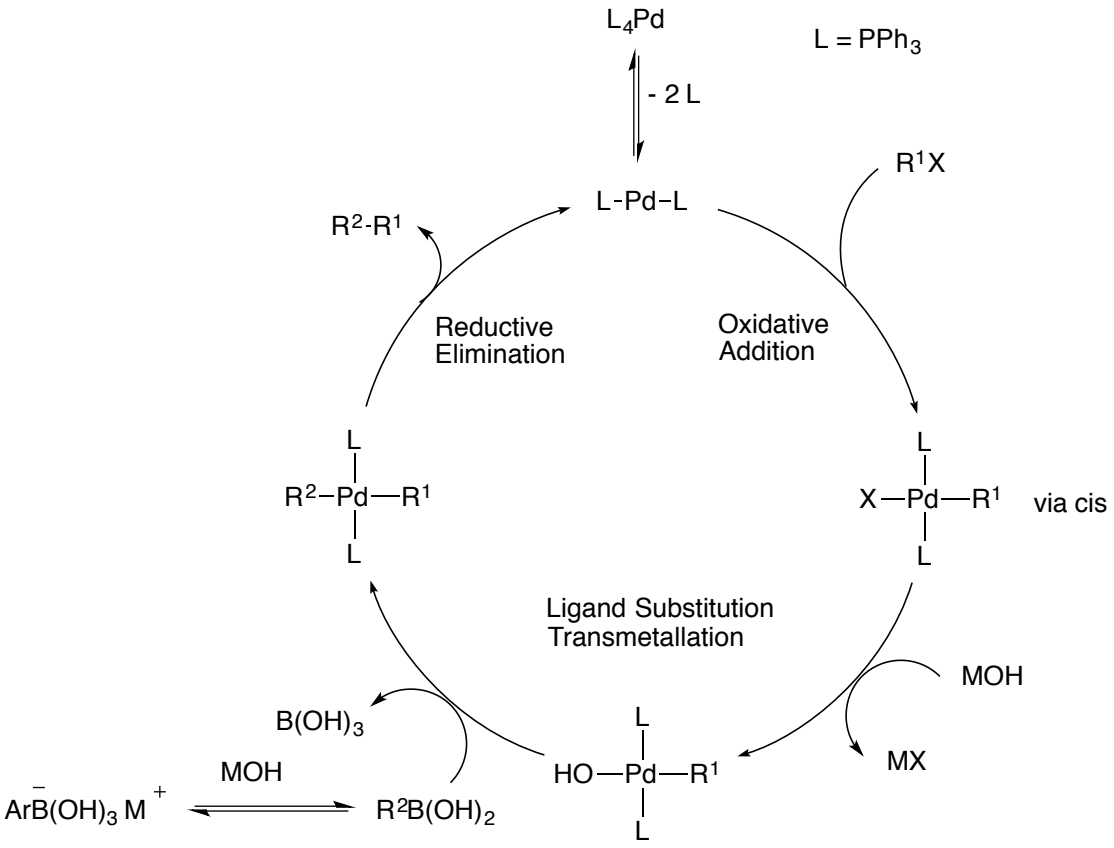
- RX: The organic halide can be aryl, alkenyl, alkyl. The leaving group is typically a halide (I, Br, Cl), but examples with sulfonates are also known.
- Organoboron: Boronic acids are most common followed by trifluoroborates. Boronate esters, triorganoboron, and tetraorganoborate nucleophiles are also used. The R group on boron can be sp, sp^2, or sp^3.



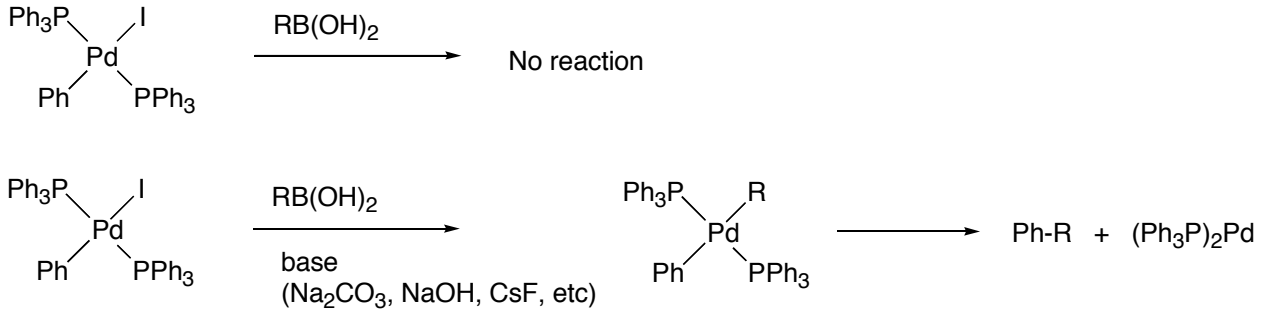
- Base: The reaction requires a base. The most common base is aqueous sodium carbonate. Anhydrous conditions are also common using heterogeneous bases, such as CsOH, Na_2CO_3, or K_3PO_4.
- Organic solvent: Organic cosolvents can range widely. Most common are relatively non-polar solvents, such as toluene or THF. Aqueous conditions are also commonly done with ethanol or acetone as the organic cosolvent.

Catalytic Cycle:

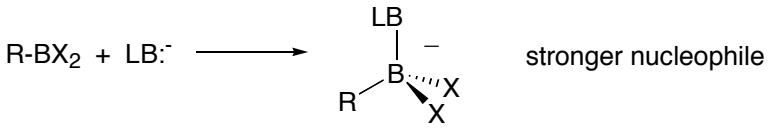
Triphenylphosphine:



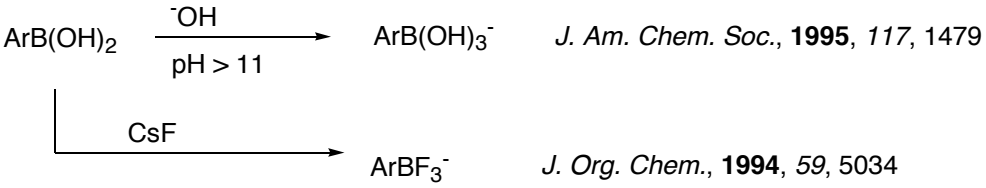
Transmetallation: Organoboranes or boronates are only weakly nucleophilic, which is why they are stable to water and oxygen (organoboronates, boronic acids only). This low nucleophilicity means that they do not undergo transmetallation with palladium halides, except in the presence of oxygen or fluoride Lewis bases. Therefore, typical Suzuki coupling conditions either involve aqueous hydroxide or fluoride salts in organic solvents.



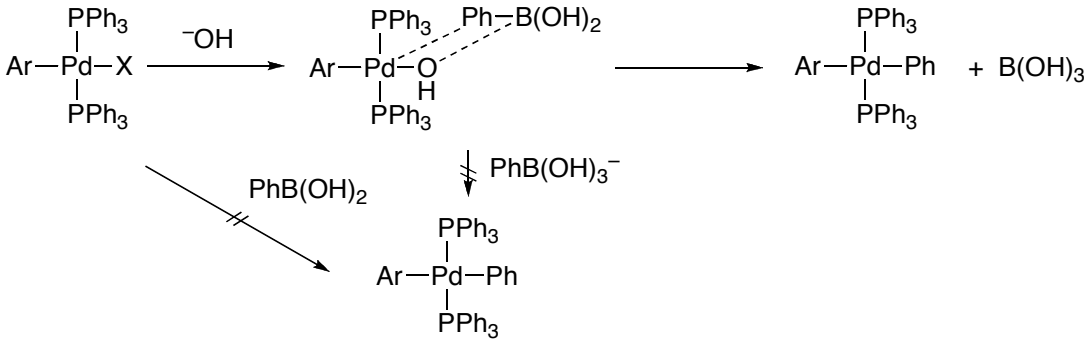
One explanation for the base accelerating effect is that tetrahedral boron-ate complexes are formed.



In fact it has been shown that in the presence of hydroxide or fluoride, that boronate species are formed from boronic acids typically used in the Suzuki coupling.



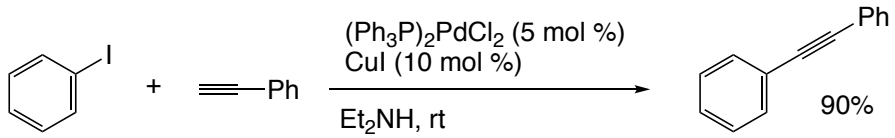
The other possible role for hydroxide is formation of a Pd-hydroxide complex. Results by Jutand and Amatore show that Pd-hydroxide complexes play a key role in the Suzuki coupling and that trihydroxyborate salts are not reactive (*Chem. Eur. J.*, **2011**, *17*, 2492-2503).



Other Organometallic Cross-Couplings: A wide range of organometallic species can be used in cross-couplings that are analogous to the Suzuki coupling. The most common examples include: RLi, RMgX (Kumada), $RSi(OR)_3$ (Hiyama-Denmark), $RSnBu_3$ (Stille), RZnX (Negishi). In principle, any metal that is more electropositive than palladium will undergo transmetalation, and thus can be used in a cross-coupling reaction. The list includes all main group metals and metalloids, as well as many transition metals. The choice of reagent primarily comes down to what type of organometallic species can be most readily accessed.

Sonogashira Coupling

The Sonogashira coupling involves the arylation of a terminal alkyne. Copper is often used as a co-catalyst to promote the formation of a copper acetylide in these reactions. Heck and others had reported the palladium catalyzed coupling of aryl halides and alkynes (*J. Organomet. Chem.* **1975**, *93*, 259). Sonogashira reported that catalytic Cu(I) salts accelerated the reaction and improved yields (*Tetrahedron Lett.* **1975**, *16*, 4467). Review (*Chem. Rev.* **2007**, *107*, 874).

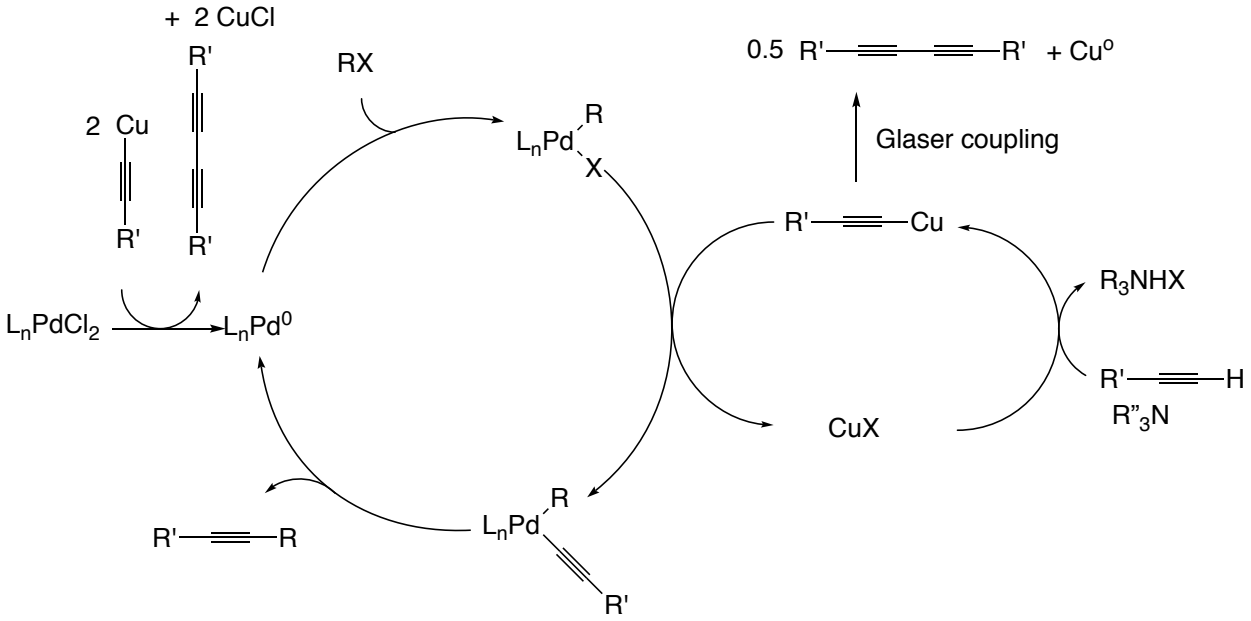


General features:

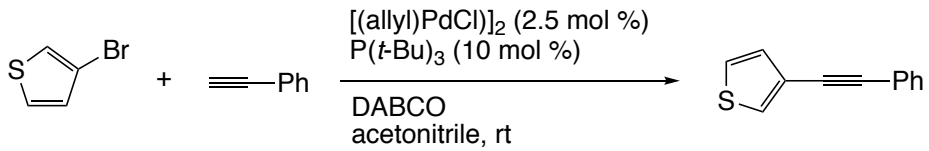
- Organic halide: Aryl and alkenyl halides are most common. Examples with alkynyl halides are known. Alkyl halides (1°) don't require a catalyst. The halide can be I, Br, Cl, OTf, OTs with similar activity trends to the Suzuki coupling.
- Alkyne: Typically terminal alkynes. Examples with protected terminal alkynes, such as silyl alkynes or propiolic acids ($RCCCO_2H$) are also known.
- Catalyst: Earlier examples generally used triphenyl phosphine complexes. Modern versions use bulky alkylphosphines, such as $P(t\text{-}Bu)_3$. Wide range of ligands are useful. Unlike Suzuki coupling, palladium chloride precursors tend to work best. CuI is typically used as the copper source. Copper-free systems are known (see below).
- Base: The reaction requires a base. Most commonly this is an alkyl amine base, which may also be the solvent. Examples with hydroxide or other oxygen bases are known.
- Solvent: Often the amine base. If not, it is typically a polar aprotic solvent, such as DMF.

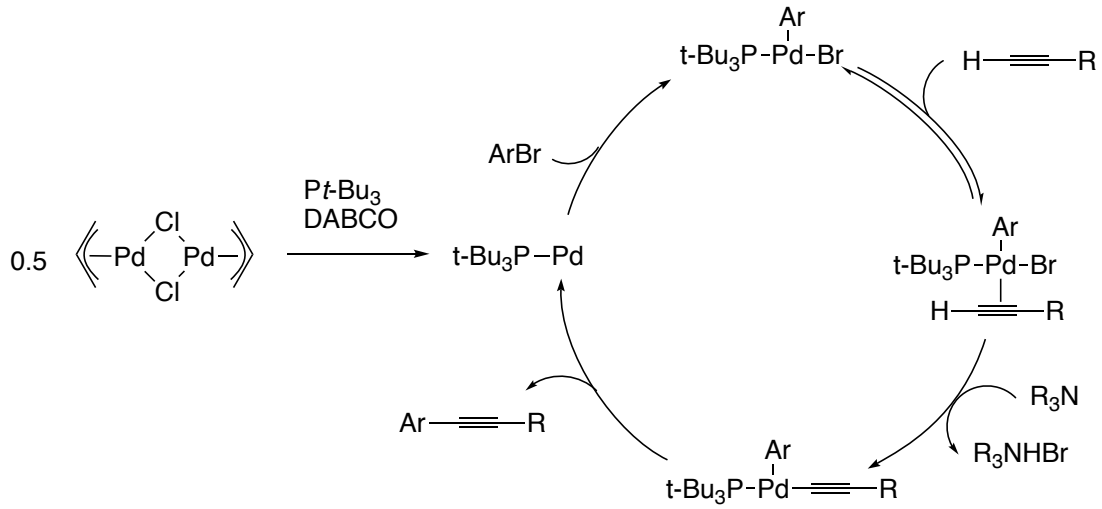
Mechanism:

The mechanism follows the same general sequence as other cross-couplings. Oxidative addition is followed by transmetalation from a copper-acetylide. The resulting complex undergoes reductive elimination. There is also a copper catalytic cycle in which the copper coordinates the alkyne, which is deprotonated to give the copper acetylide. A downside of the addition of copper, is that it can also promote the homocoupling of the alkyne to give a conjugated diyne and Cu^0. If there is trace oxygen, the Cu^0 can be recycled to Cu^I.



Because of the potential for Glaser coupling, copper-free catalyst systems have been sought. These are generally possible with appropriate choice of base and ligand. For example, a P(*t*-Bu)$_3$ catalyst system using either piperidine or DABCO effectively couples aryl bromides and alkynes without copper. In this case, the alkyne is thought to coordinate to the palladium, increasing its pKa, so that it can be deprotonated. Example (*Org. Lett*. **2003**, *5*, 4191).

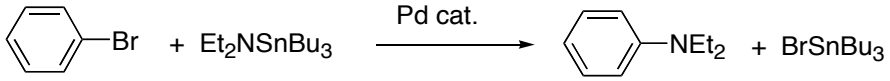




Buchwald-Hartwig Amination (and other couplings to moderately acidic nucleophiles)

Beginning in the 90's, John Hartwig (Yale) and Stephen Buchwald (MIT) independently developed catalyst systems that promote the cross-coupling of aryl halides and amines to give aryl amines. This methodology has become widely used because there were few mild methods to prepare aryl amines. For reviews of this methodology, see: Buchwald et al, *Acc. Chem. Res.*, **1998**, *31,* 805-818; Hartwig, *Acc. Chem. Res.*, **1998**, *31*, 852-860; Hartwig, *Angew. Chem. Int. Ed.*, **1998**, *37*, 2046-2067, Hartwig, *Acc. Chem. Res.* **2008**, *41*, 1534, Buchwald, et al, *Chem. Sci*, **2011**, *2*, 27.

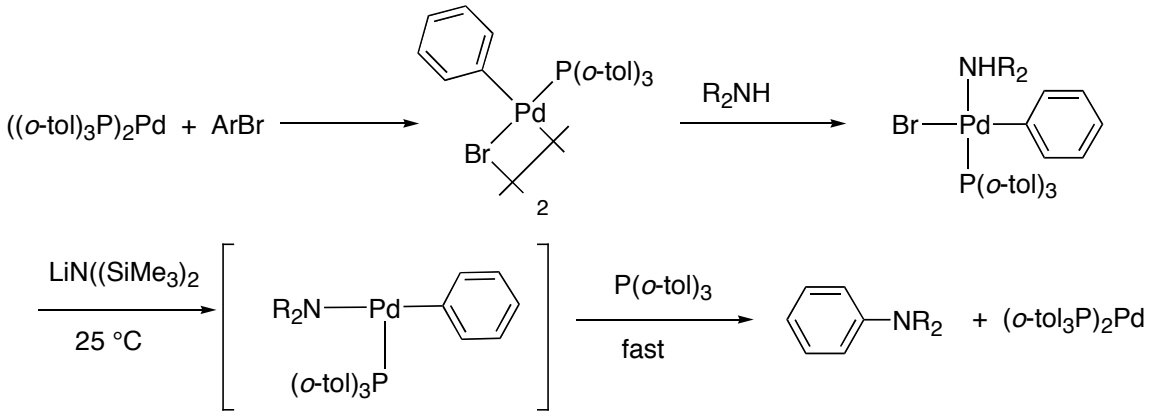
In 1983, Kosugi showed that palladium could catalyze the amination of aryl halides with stannyl amines.



Chem. Lett., **1983**, 927-928

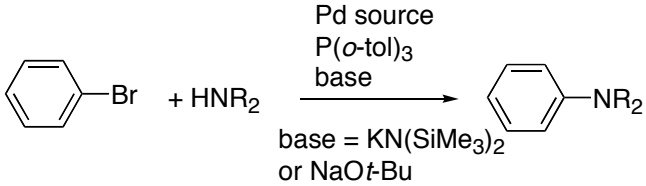
Although synthetically unattractive, it represented a useful transformation that appears to proceed through an unusual C-N reductive elimination.

Hartwig showed that in the presence of base, bound amines could be deprotonated to Pd-amide complexes. These would undergo fast reductive elimination for C-N bonds.



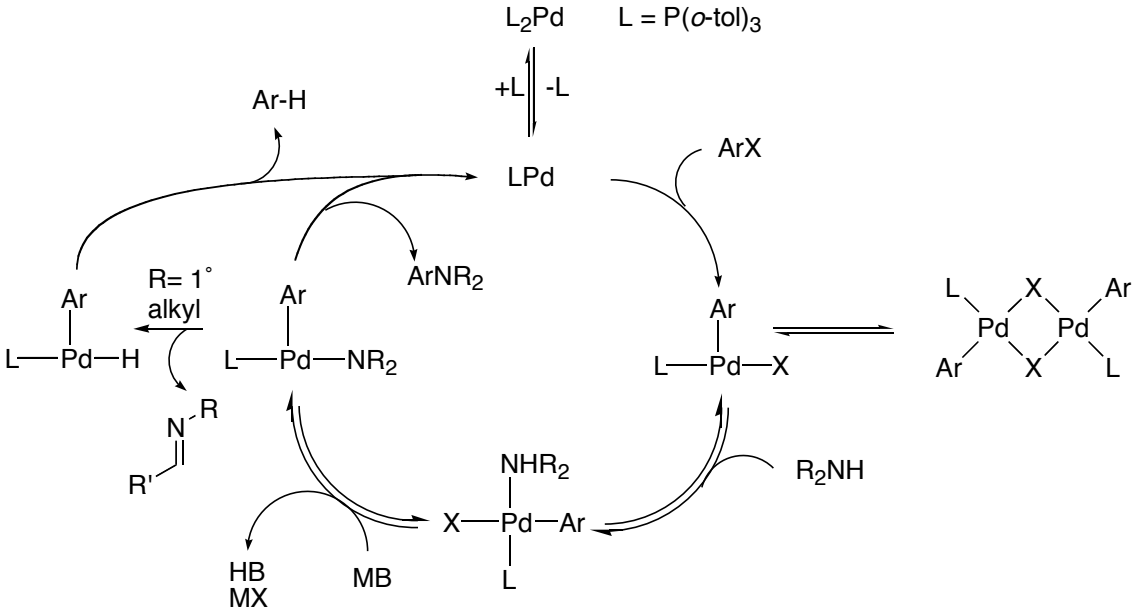
Organometallics, **1996**, *15,* 2794-2805

This mechanistic work showed the viability of using strong base to promote the coupling of amines and aryl bromides. The Hartwig and Buchwald groups published this catalytic result nearly simultaneously.



Hartwig, *Tetrahedron Lett.* **1995**, *36*, 3609
Buchwald, *Angew. Chem. Int. Ed.* **1995**, *34*, 1348

Based on a series of detailed mechanistic studies, it is possible to propose a mechanism in which all of the steps are supported experimentally. For review see: *Angew. Chem. Int. Ed.*, **1998**, *37*, 2046-2067.



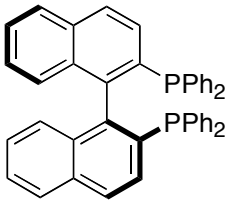
Supporting mechanistic data:

- Oxidative Addition: Inverse [P(*o*-tol)$_3$] dependence, formation of dimer product
- Ligand substitution: Pd dimer readily split by amines to give square planar amine complex
- Deprotonation/Reductive elimination: Treatment of amine complex with base leads to rapid reductive elimination, presumably through 3 coordinate species.
- ß-H elimination: When amines with primary alkyl substituents are used, arene formation becomes a major side process.

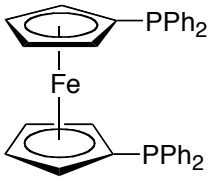
Problems with this system:

- Required high temperatures (80-100 ˚C for aryl bromides)
- Secondary amines gave good yields, but primary amines gave low yields in most cases.
- Acyclic secondary alkyl amines often gave reduction of aryl halides.

β-Hydride elimination is facile in the three-coordinate intermediate prior to reductive elimination. Both Hartwig and Buchwald reasoned that a chelating phosphine, which would necessarily give a 4-coordinate species at this point, would hinder β-hydride elimination, since there would be no open coordination site for the hydride (we will discuss this in the migratory insertion/reductive elimination chapter).

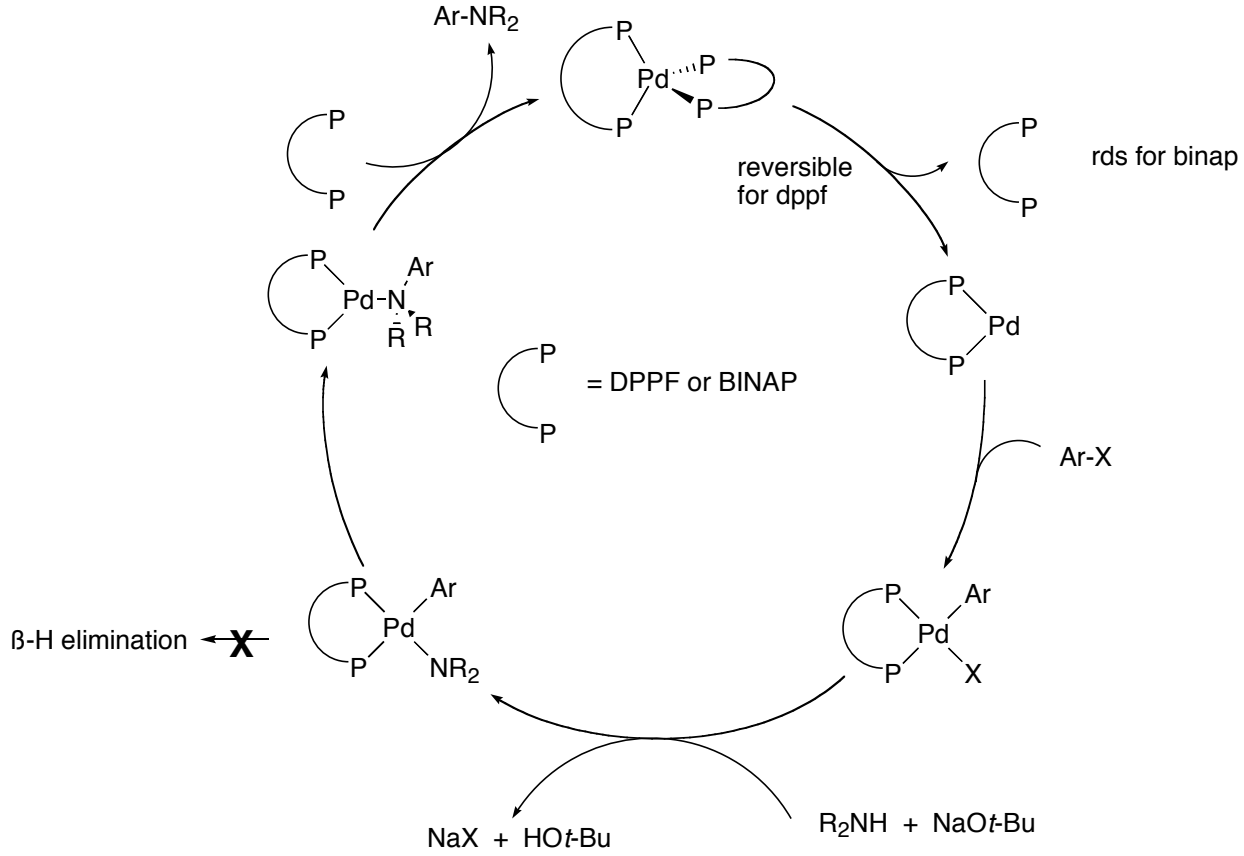


BINAP
Buchwald
JACS, **1996**, *118*, 7215

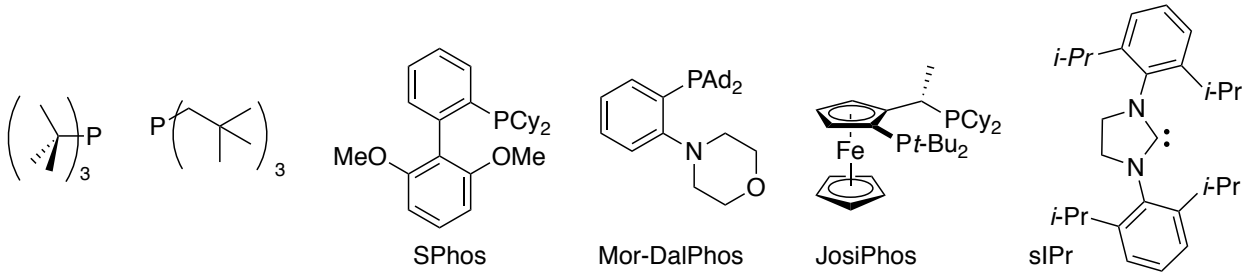


DPPF
Hartwig
JACS, **1996**, *118*, 7217

The mechanism for the chelating case has also been studied in some detail by Hartwig (*JACS*, **2000**, *122*, 4618-4630). The mechanism is similar to that proposed for the monophosphine. The main differences are that oxidative addition gives a 4-coordinate species. In addition, the coordinatively saturated species is part of the catalytic cycle, unlike in the P(*o*-tol)$_3$ case. In the case of binap, ligand dissociation is the rate limiting step. For dppf, ligand dissociation is reversible. Hartwig could not determine whether ligand dissociation or oxidative addition was the rate limiting step for dppf.



The next generation of ligands focused on sterically demanding alkylphosphines. Hartwig has applied sterically demanding alkylphoshines (*t*-Bu$_3$P, (1-adamantyl)$_2$P*t*-Bu) and *N*-heterocyclic carbenes. Buchwald has developed a family of 2-phosphinobiphenyl ligands. Catalysts derived from these ligands promote amination of aryl bromides at room temperature and were the first systems to couple aryl chlorides with amines.



The mechanistic details have not been fully worked out for these catalyst systems, but are likely similar to the catalytic cycle for P(*o*-tol)$_3$. Based on Hartwig's work with aryl halide oxidative addition, the rate limiting step is likely ligand dissociation for coupling of aryl bromides and oxidative addition for coupling of aryl chlorides.

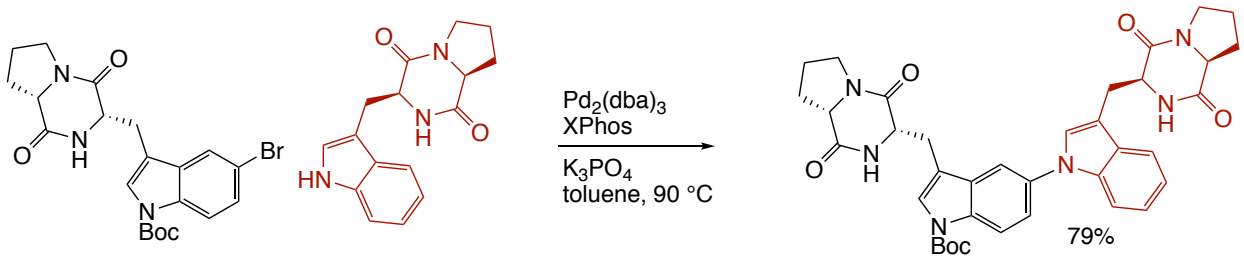
Kevin Shaughnessy
The University of Alabama, 2019

General reaction features:

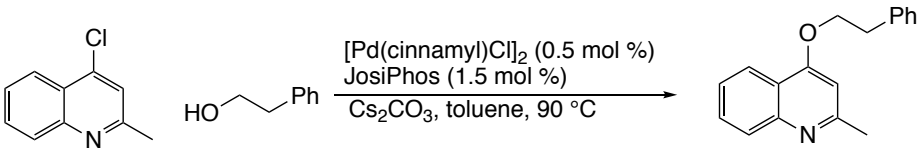
- RX: Aryl halides are most common, triflates and tosylates can be used in some cases. Vinyl halides also work to give enamine products.
- Nitrogen nucleophile: Aryl amines work best, but primary and secondary alkyl amines can be good substrates. Ammonia is a challenging substrate, but JosiPhos and some other ligand classes work well. More acidic nitrogen compounds, such as azoles and amides have also been successfully arylated. Examples with nearly all N-H bond systems are known.
- Ligand: Most active ligands are those listed above including bulky trialkylphosphines, 2-phosphinobiaryls, and NHC ligands. The JosiPhos family are useful for ammonia. Chelating ligands are effective for primary alkyl amines.

Related classes of reactions:

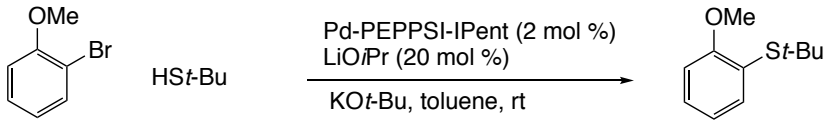
N-heterocycle arylation



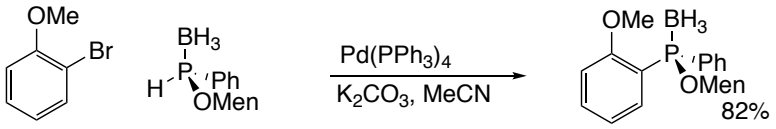
Etherification



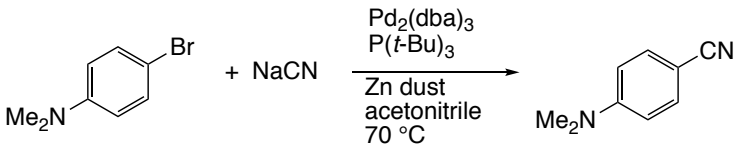
Sulfination



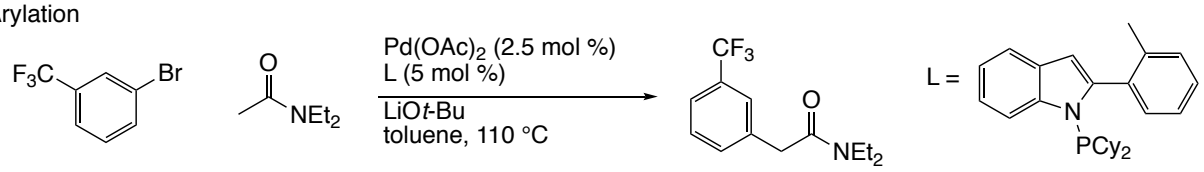
Phosphination



Cyanation



α-Arylation



Heck Coupling

The Heck coupling was one of the first Pd-catalyzed cross-coupling reactions to be developed. It still remains widely used and studied. Although similar to the coupling reactions we have discussed, the Heck reaction is unique, in that the C-C bond forming reaction is a migratory insertion, not a reductive elimination. For reviews on the Heck reaction see: Heck, R. F, *Acc. Chem. Res.* **1979**, *12*, 146; *Angew. Chem. Int. Ed.,* **1995**, *33*, 2379; *Chem. Rev.* **2000**, *100*, 3009 (excellent discussion of the mechanism).

General features:

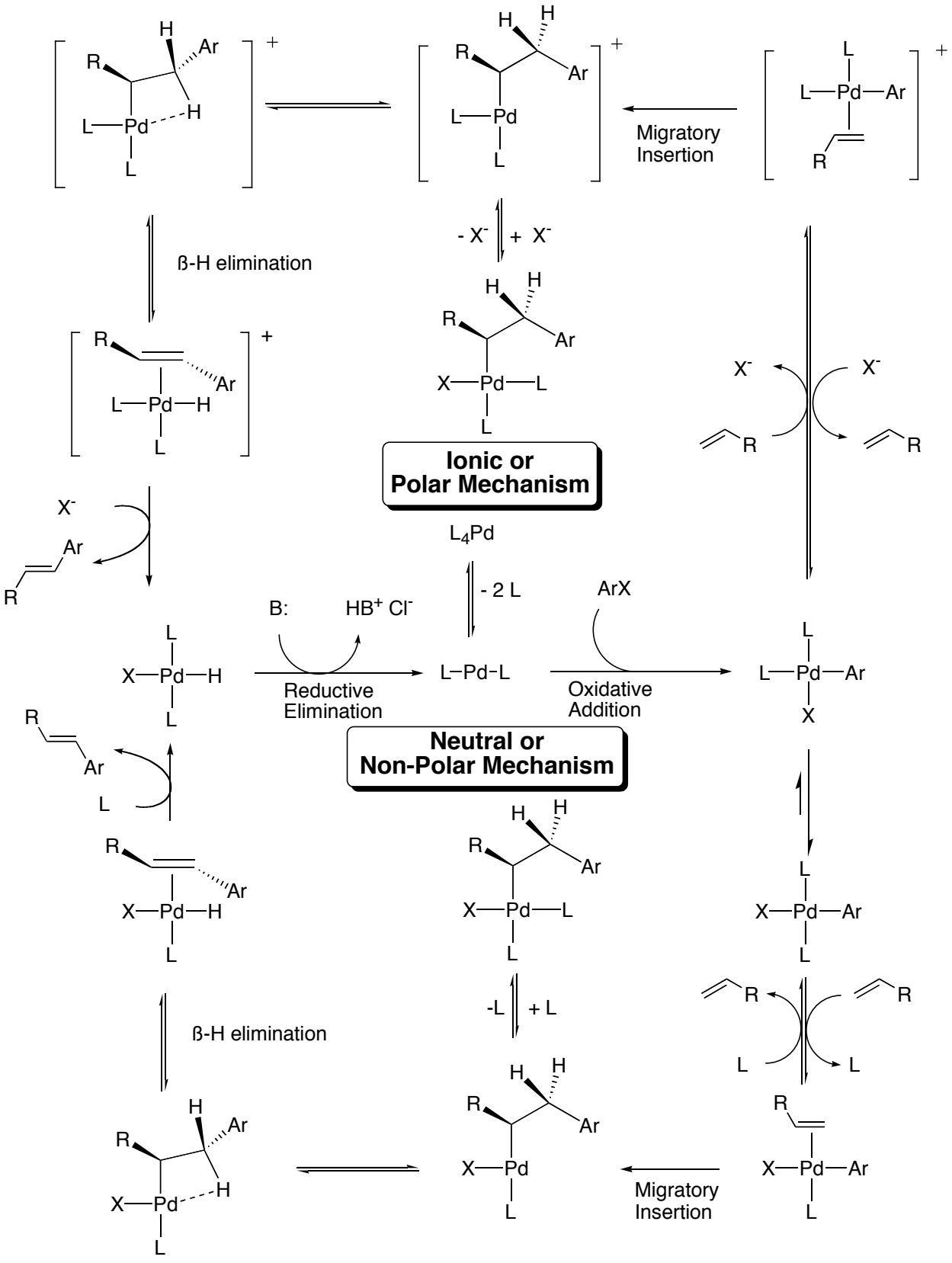
- RX: Usually an aryl or alkenyl halide. Alkyl halides have also been reported (*Chem. Commun.* **2014**, *50*, 3725).
- Alkene: Generally works best with conjugated, electron deficient alkenes such as styrenes or unsaturated carbonyls. Electron-rich alkenes are also effective, but give opposite regiochemistry. Simple alkenes often give mixtures of products.
- Ligands: Phosphines are most common (PPh_3, P*t*-Bu_3, etc.). There are a lot of examples of ligand-free catalyst systems that likely proceed through palladium nanoparticles.
- Reaction conditions: Typical bases include amines and inorganic bases (carbonate, phosphate). Solvents are often polar aprotic. Reaction generally requires high temperatures (80-150 °C).

The neutral mechanism is favored in less polar solvents and when the leaving group is a halide. The ionic mechanism is more likely in highly polar solvents, when a halide abstracting reagent (Ag(I) salts) are used, and in dipolar aprotic solvents (DMF).

Ligand Substitution: The key step is coordination of the alkene to the Pd complex via an associative (usually) ligand substitution mechanism. Either a neutral ligand (usually phosphine) or an anionic ligand may be the leaving group, resulting in two pathways (next page): neutral or non-polar and ionic or polar. The polar mechanism becomes more important when X is a good leaving group (I^- or ^-OTf), when chelating phosphines are used, or in polar solvents (DMF, water, ionic liquids).

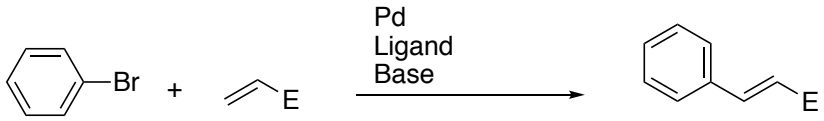
Migratory Insertion: The majority of the evidence shows that the migratory insertion is largely concerted. With more electrophilic Pd centers and electron rich alkenes, a cationic mechanism is also possible, in which the Pd adds to the alkene electrophilically before delivering the aryl nucleophile.

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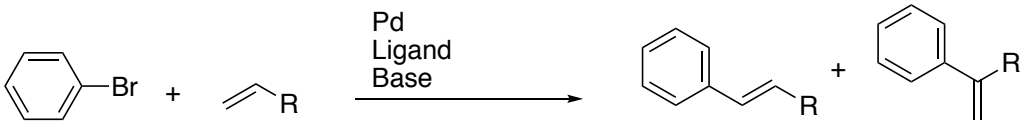


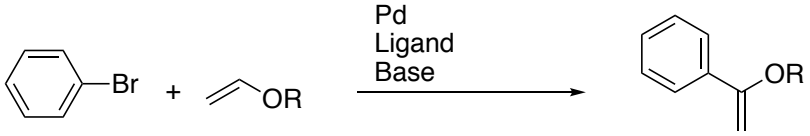
Kevin Shaughnessy
The University of Alabama, 2019

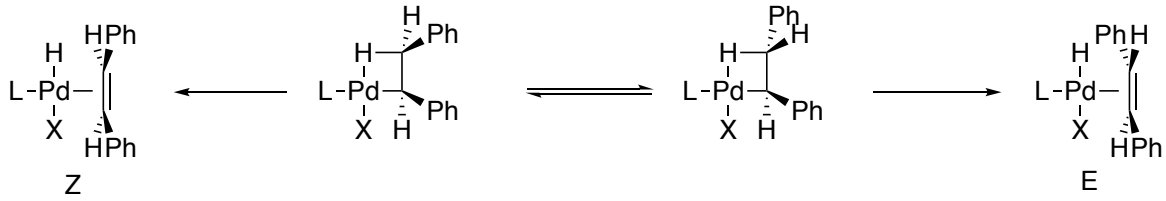
Regio- and Stereoselectivity: Migratory insertion can place the aryl group on either carbon of the alkene. The placement can be controlled electronically. With electron deficient alkenes and styrene derivatives, the aryl group is generally placed β to the Ph or EWG, thus placing the aryl group on the most electrophilic carbon. For vinyl ethers, the opposite regiochemistry is seen to again place the aryl group on the electrophilic carbon. With simple alkenes, a mixture of products is usually obtained that will be governed by steric factors of the alkene and catalyst species. β-Hydride elimination must occur through a *syn*-coplanar conformation. When possible, the elimination will occur to give the more stable *trans*-alkene.



E = Ph, EWG (CN, C(=O)R, NO_2)

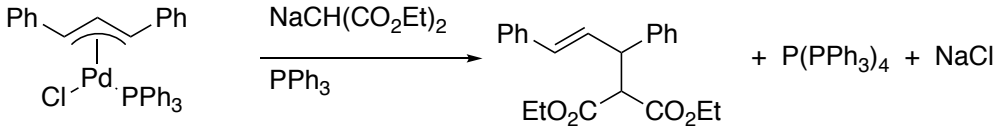




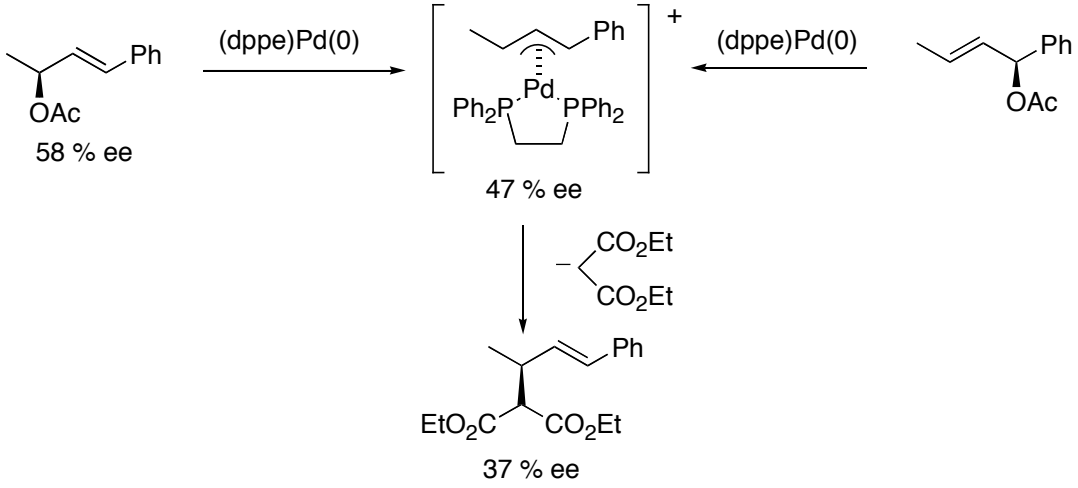


Trost-Tsuji couplings:

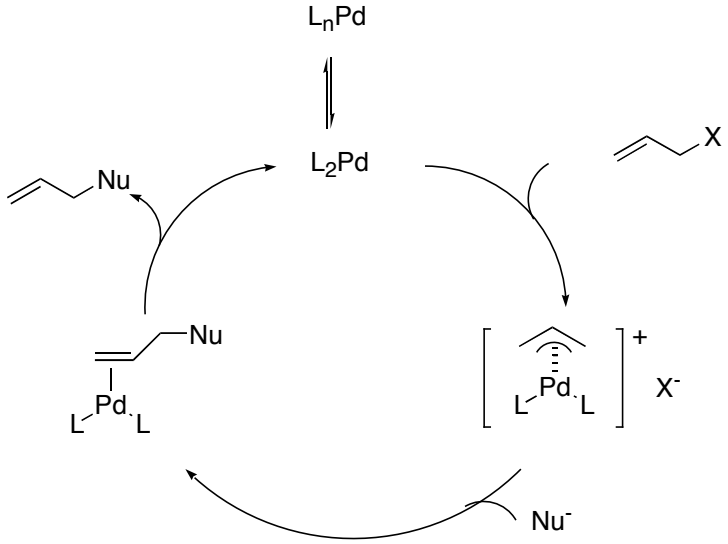
As discussed in section 7, nucleophilic attack on η^3-allyl species results in formation of a new C-C or C-heteroatom bond.



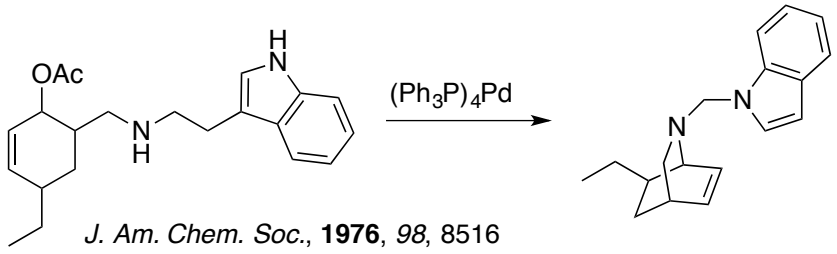
The process involves oxidative addition into an allyl-leaving group species followed by nucleophilic attack on the resulting palladium allyl. This process gives the product and regenerates palladium(0).



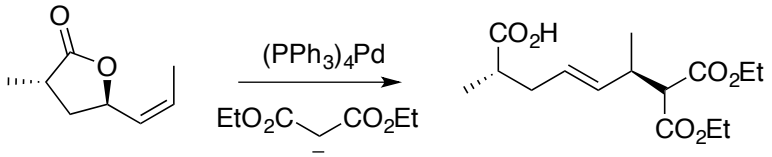
Because a Pd(0) reagent is regenerated, the reaction can be catalytic.



Typical nucleophiles for these reactions are amines and stabilized carbanions. The leaving group on the allylic group can be a halide, ester, or in some cases phosphonate. Esters, particularly acetate, are most widely used since allylic alcohols are readily prepared. The methodology has been applied to a wide range of synthetic problems.

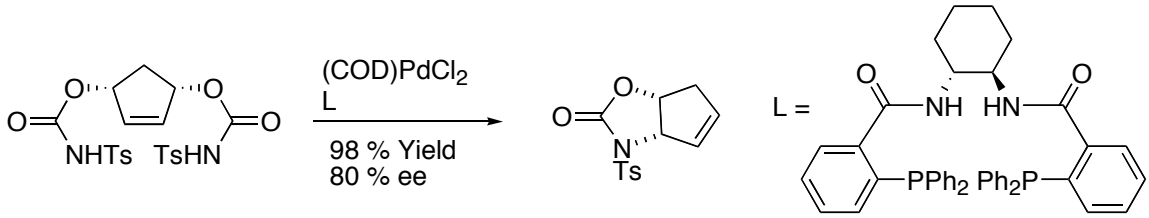


J. Am. Chem. Soc., **1976**, *98*, 8516

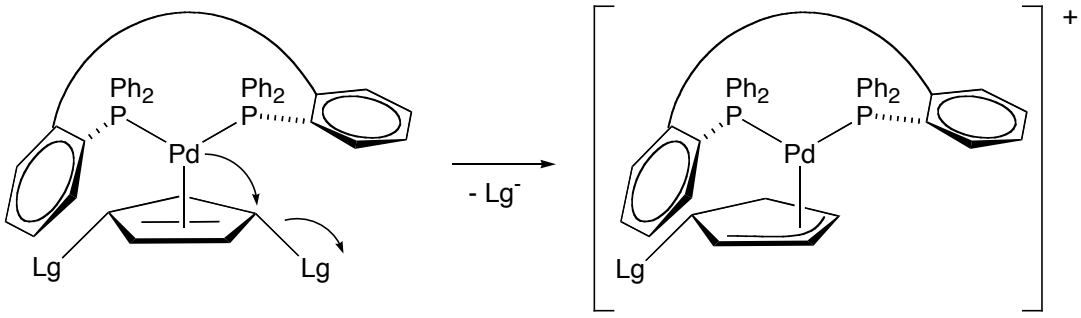


Chem. Rev., **1989**, *89*, 1513

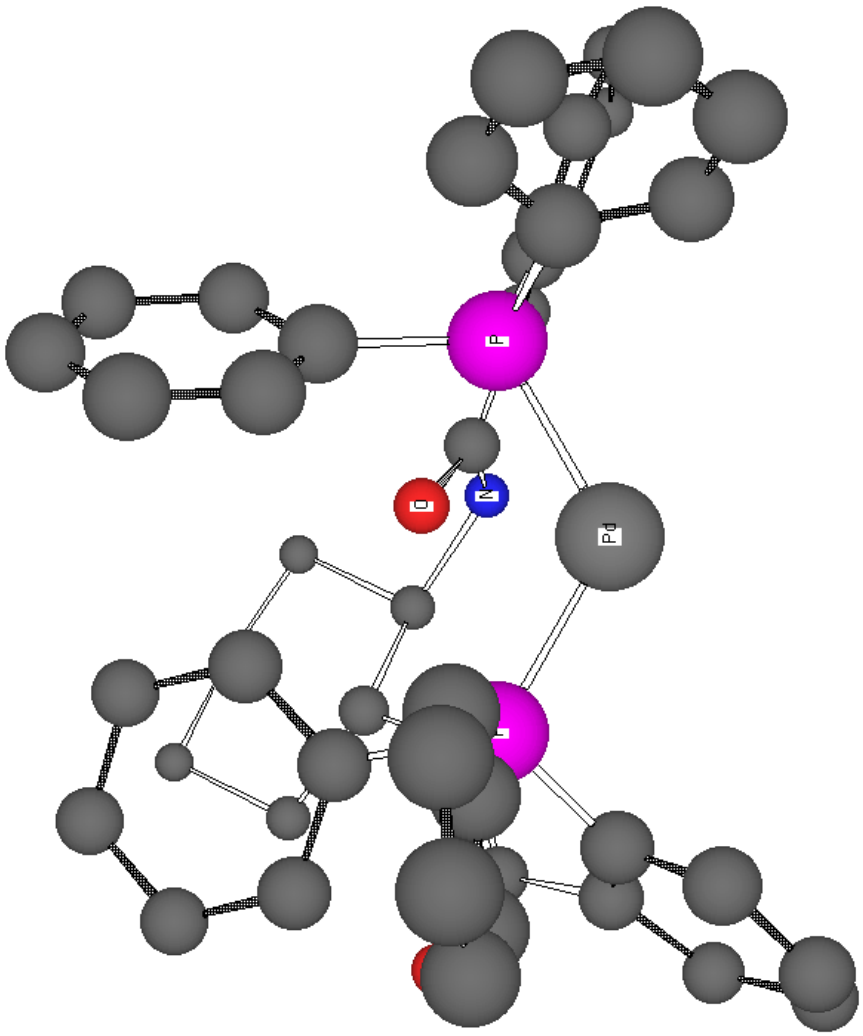
The most significant advance in this reaction has been the development of efficient asymmetric versions of this catalytic cycle (*Chem. Rev.*, **1996**, *96*, 395). This work was originated by Trost, but today numerous researchers are working to develop ligands to allow for general, highly selective allylic substitution reactions.



In this case the mode of enantioselection probably involves coordination to the alkene and then selective attack on one of the meso leaving groups. The ligand only allows attack at one of the leaving groups, resulting in selective formation of a single Pd-allyl species. Rapid intramolecular trapping of the allyl prevents racemization.



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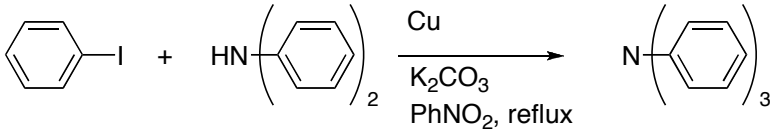
Molecular model of a Pd complex of Trost's ligand.

Cu-Catalyzed Coupling

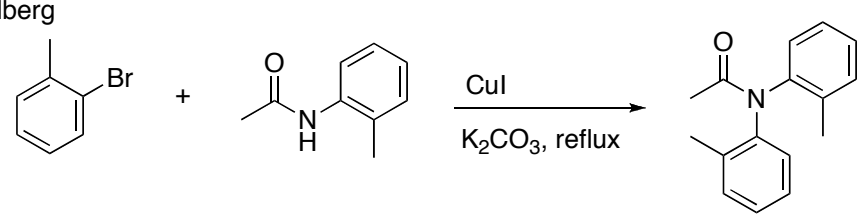
Ullman (*Ber. Dtsch. Chem. Ges.* **1903,** *36*, 2382) and Goldberg (*Ber. Dtsch. Chem. Ges.* **1906,** *39*, 1691) reported the coupling of aryl halides with anilines and amides, respectively. These reactions used stoichiometric amounts of copper metal and/or copper salts and generally required high temperatures

(150-200 °C). This reaction represented the state of the art for arylation of N, O, and S until the development of Pd-catalyzed reactions by Buchwald and Hartwig.

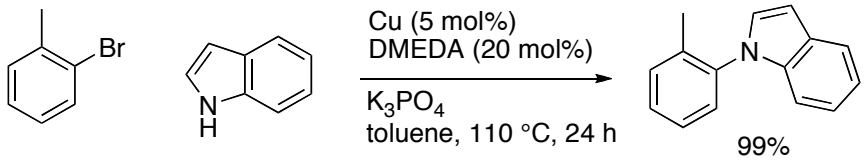
Ullmann



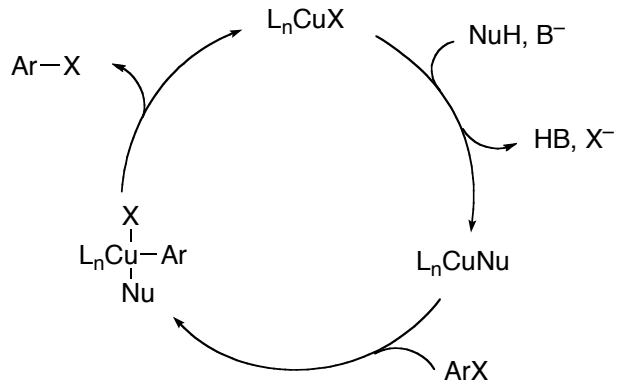
Goldberg



In recent years, copper-catalyzed couplings have seen a resurgence with the development of ligand-promoted versions of the Ullmann and Goldberg reactions.Diamines, amino acids, and diketonate ligands are the most commonly used ligands, although a wide range of N and O chelating ligands can be used successfully (Review: *Chem. Sci*, **2010**, *1*, 13; *Angew. Chem. Int. Ed.*, **2009**, *48*, 6954; *Acc. Chem. Res*, **2008**, *41*, 1450). Cu-catalyzed reactions tend to work better than Pd-catalyzed versions for arylation of amides and azoles. In addition, copper is significantly cheaper than Pd.

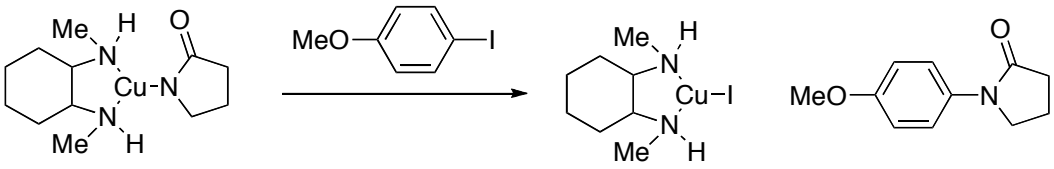


The mechanism for the Cu-catalyzed couplings is not as well understood as for Pd-catalyzed reactions (*Dalton Trans.* **2010**, *39*, 10338). Both radical and concerted mechanisms have been proposed for the aryl halide activation step. The most commonly accepted mechanism involves coordination of the nucleophile to the copper center followed by oxidative addition of the aryl halide to give a Cu(III) intermediate and reductive elimination to form the bond. The Cu(III) intermediate has not been observed.



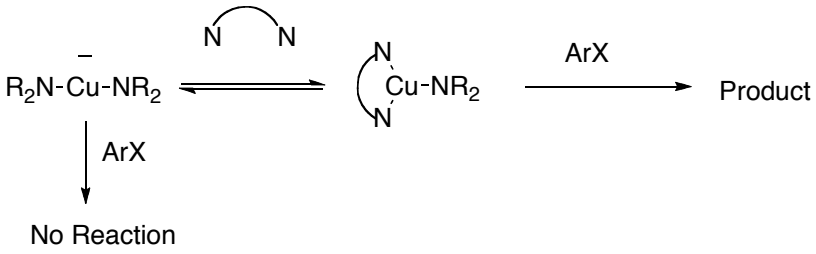
Note that the order of steps is reversed from that in Pd-catalyzed coupling. Evidence for the nucleophile coordinate occurring first is based on the fact that L_nCuX species do not react with aryl halides, while L_nCu-Nu complexes do (see reaction below). Computational studies show that L_nCu-Nu undergoes oxidative addition with lower barrier than L_NCuX (*Organometallics*, **2007**, *26*, 4546).

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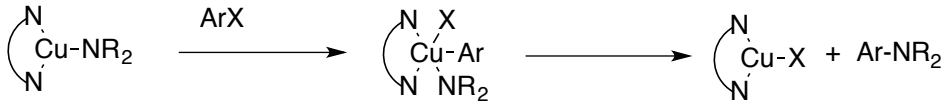
Buchwald, *J. Amer. Chem. Soc*, **2009**, *131*, 78

One important role of the ligand appears to be to prevent formation of $[Cu(NR_2)_n]^{(n-1)-}$ complexes, which are catalytically inactive. (*JACS*, **2005**, *127*, 4120).

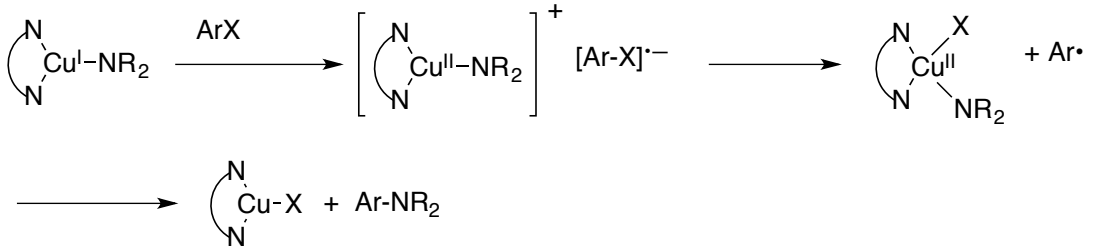


The mechanism of the Ar-X activation step is still a matter of debate. Both 2 e oxidative addition/reductive elimination and radical pathways have been proposed.

Oxidative Addition/Reductive Elimination

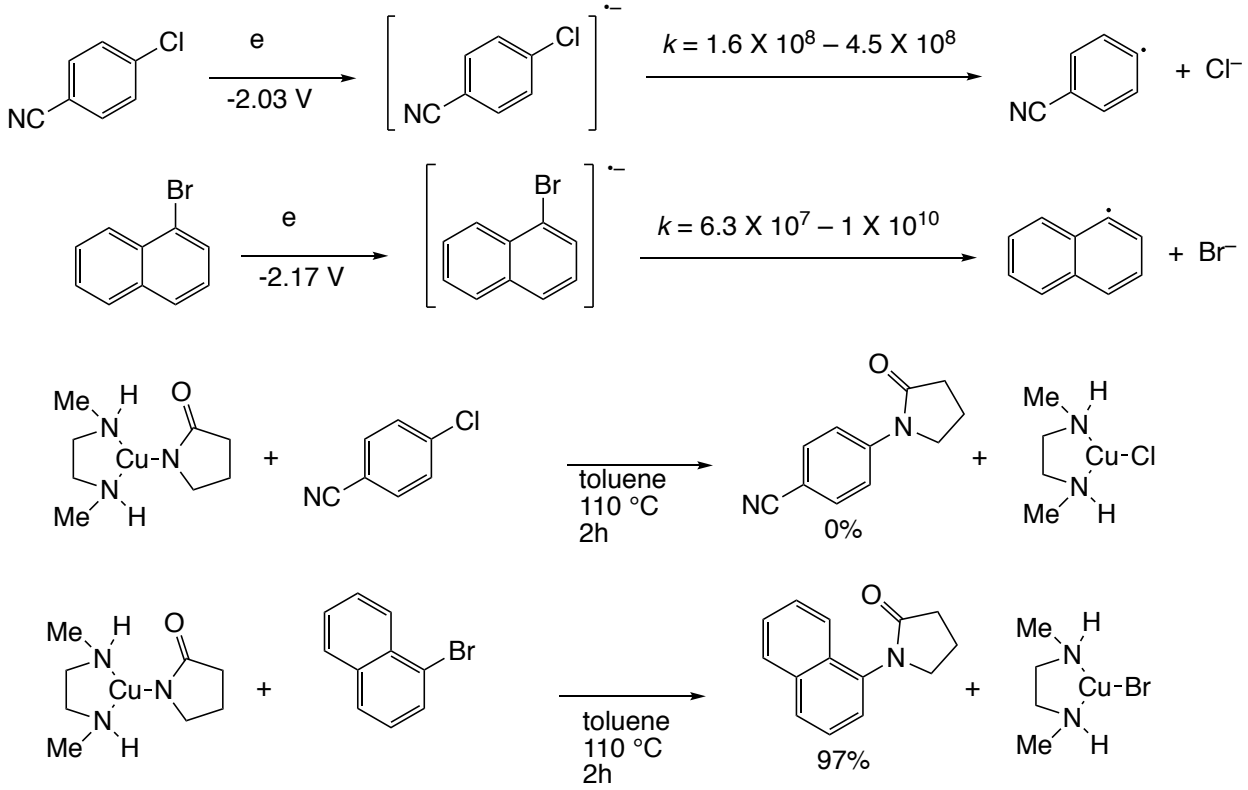


Single Electron Transfer (SET)

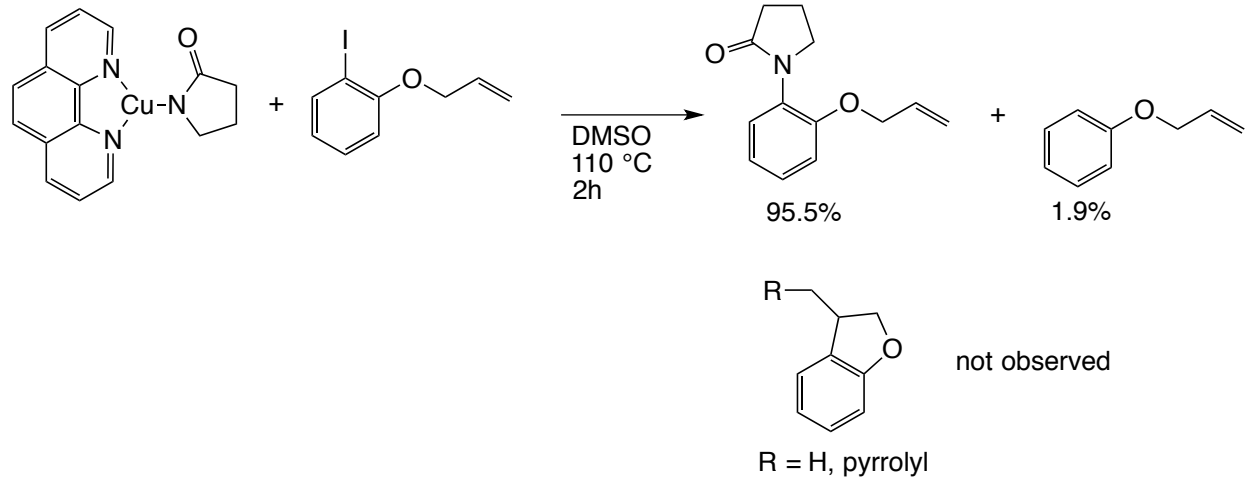


Hartwig used a number of experiments to conclude that the step is likely an oxidative addition/reductive elimination sequence (*JACS*, **2008**, *130*, 9971). How do these results support a non-radical pathway?

1. Comparison of reactivity of aryl halides having similar reduction potentials and halide dissociation rates.

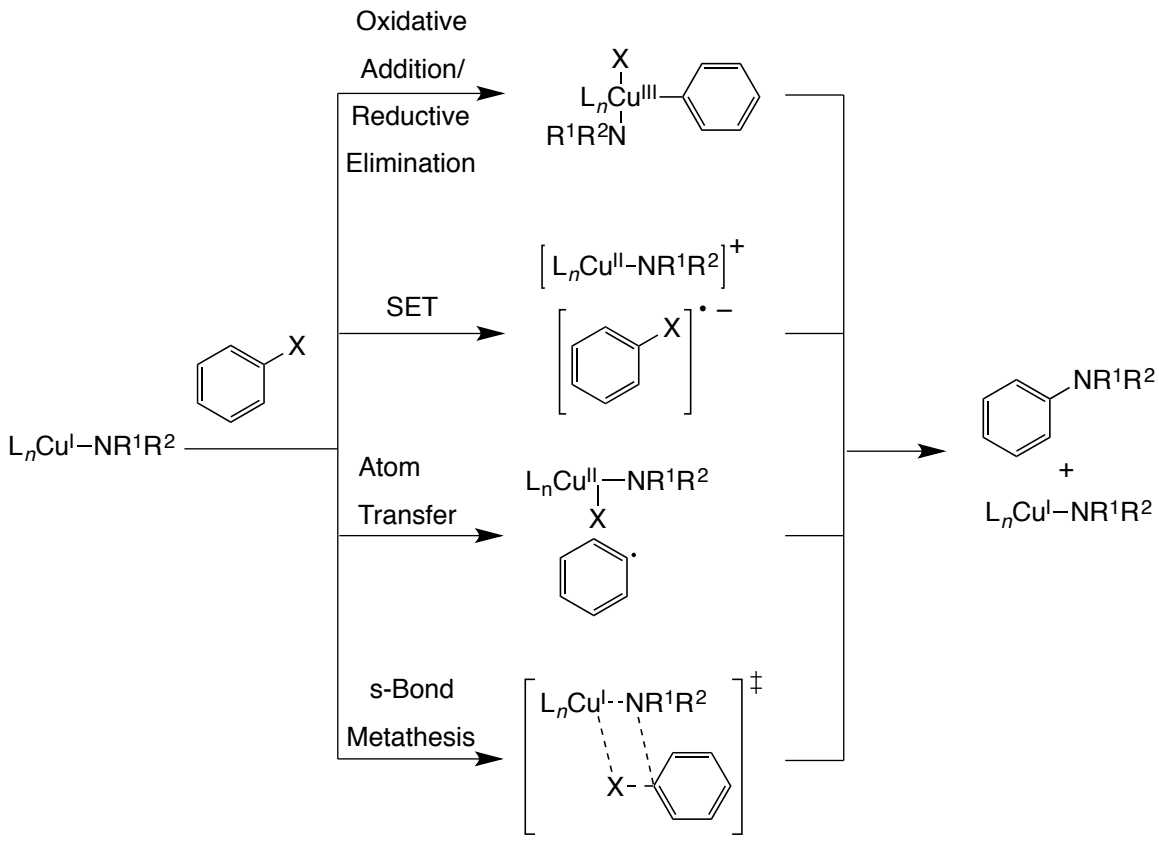


2. Use of a radical clock



A computational study by Buchwald and Houk suggested that a SET or atom transfer pathway had the lowest energy barrier, depending on the ligand and nucleophile, however. *JACS*, **2010**, *132*, 6205. The computation study could be consistent with Hartwig's experimental results if the free radical intermediate has a very short lifetime.

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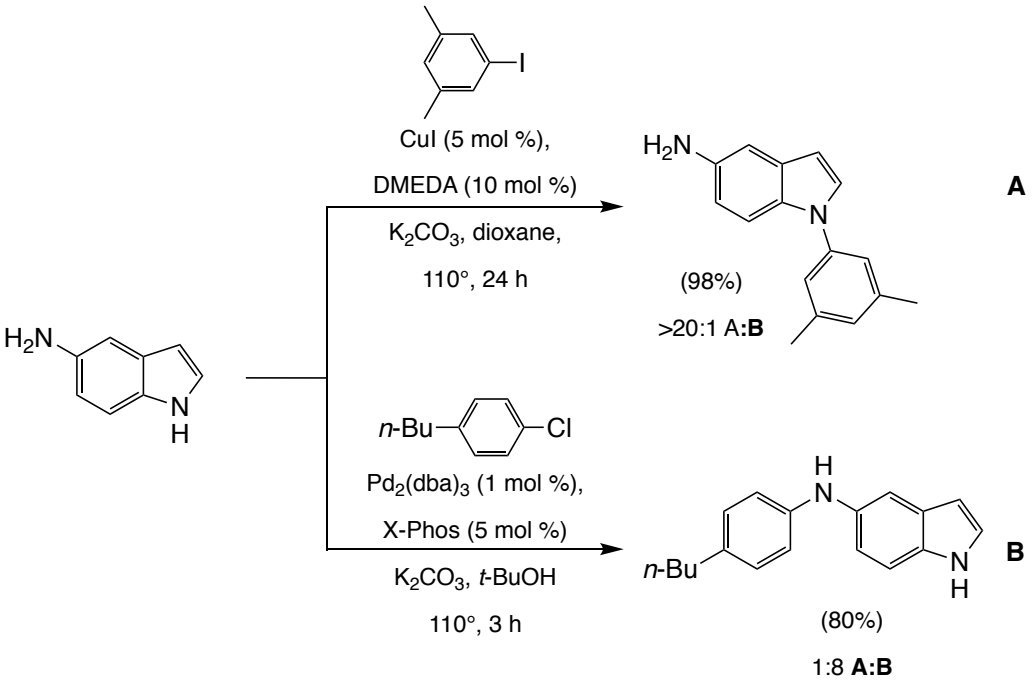


Comparison of Pd- and Cu-catalyzed coupling

Parameter	Pd	Cu
Metal cost	ca. $3,000/mol	ca. $0.6/mol
Loading	≤ 1 mol %	5-10 mol %
Ligands	Phosphines, NHC	Amines
ArX Scope	ArI, ArBr, ArCl, $ArOSO_3R$	ArI, ArBr (ArCl rare)
N Scope	Amines Amides, azoles known but limited	Best with amides, azoles. Amines also work
Temperature	rt-100 °C	80-150 °C

The Pd- and Cu-catalyzed carbon-heteroatom bond-forming reactions are often complementary to each other. The example below was reported by Buchwald (*JACS*, 2003, *125*, 6653). Using copper, the indole nitrogen is exclusively arylated. In contrast, Pd primarily gives arylation at the amino nitrogen. Copper-catalyzed reactions tend to favor more acidic and softer nitrogen nucleophiles. Palladium generally gives better results with more nucleophilic amine nitrogens.

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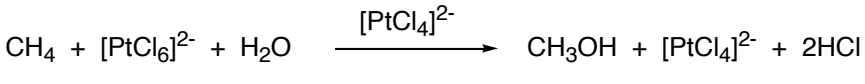

I
CuI (5 mol %),
DMEDA (10 mol %)
K2CO3, dioxane,
110°, 24 h
H2N
N
H
H2N
N
(98%)
>20:1 A:B
A
n-Bu
Cl
Pd2(dba)3 (1 mol %),
X-Phos (5 mol %)
K2CO3, t-BuOH
110°, 3 h
H
N
n-Bu
N
H
(80%)
1:8 A:B
B

10-Hydrocarbon Functionalization by C-H Activation

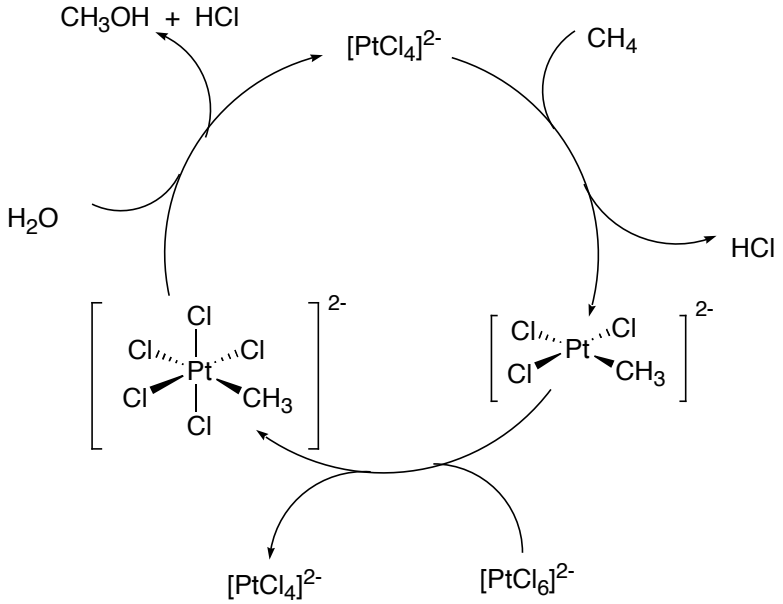
Organic chemistry has historically been based on the conversion of functional groups into desired functional groups. For example, cross-coupling reactions require a preexisting halide. Often these functional groups had to be introduced from the original hydrocarbon starting material. Directly functionalizing C-H bounds would allow chemists to avoid this prefunctionalization. In contrast, there are relatively few approaches to directly converting alkanes or arenes into functionalized derivatives. Alkanes can be radically halogenated and arene C-H bonds can undergo electrophilic aromatic substitution, for example. We have discussed that metals can insert into C-H bonds. If these intermediates can be functionalized, a catalytic process is possible. Challenges with this approach are first activating the strong and relatively unreactive C-H bond. If this can be achieved, the question is how to do this selectively.

Non-Directed C-H Activation—A long standing goal has been identifying methods to selectively oxidize alkane or arene C-H bonds in a selective manner. Alkanes are particularly challenging substrates as they are poor ligands. Review, *ACS Central Sci.*, **2016**, *2*, 281.

Selective Oxidation of Alkanes: Shilov-type oxidation of methane



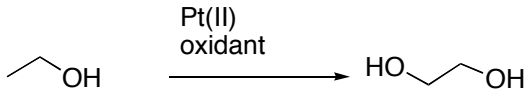
Zh. Fiz. Khim., **1969**, *43*, 2174



While impractical (stoichiometric in Pt), the Shilov system represented a very selective method for alkane oxidation.

Reactivity of H-CH_3 100 X higher than that of H-CH_2OH

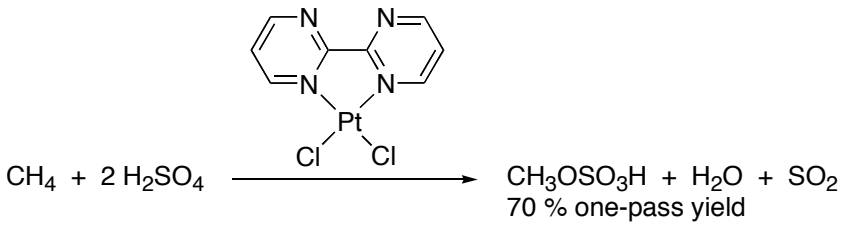
Very strong preference for oxidation of C-H bonds on sterically unhindered methyl groups.

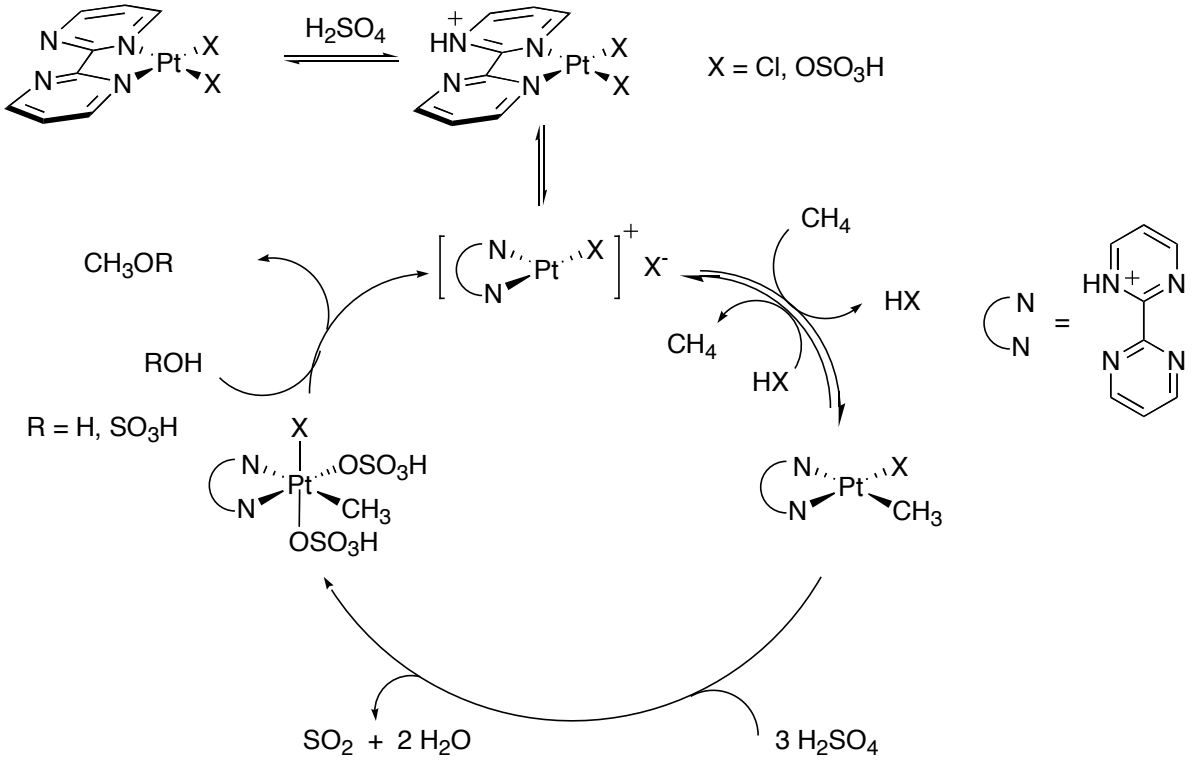


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For original Shilov chemistry, the Pt(0)/Pt(II) and Pt(II)/Pt(IV) redox couples have similar potentials. Thus Pt(II) can also disproportionate into Pt(0) and Pt(IV). This leads to precipitation of Pt metal and undesired side reactions.

Catalytica System (Roy Periana, now at USC): *Science*, **1998**, *280*, 560





In principle an industrially viable series of processes can be envisioned:

$$CH_4 + 2\,H_2SO_4 \longrightarrow CH_3OSO_3H + H_2O + SO_2$$

$$H_2O + SO_2 + 0.5\,O_2 \longrightarrow H_2SO_4$$

$$CH_3OSO_3H + H_2O \longrightarrow CH_3OH + H_2SO_4$$

$$\text{Net: } CH_4 + 0.5\,O_2 \longrightarrow CH_3OH$$

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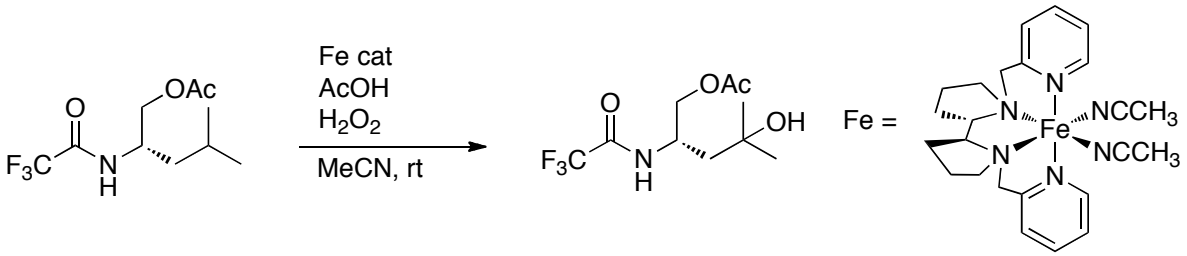
Problems limiting commercial application:

9. Turnover frequencies are 2 orders of magnitude too low

10. MeOH recovery from concentrated sulfuric acid is too costly

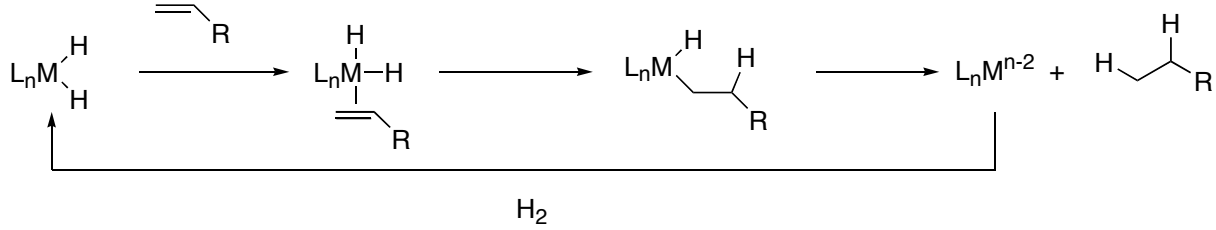
11. SO_2 reoxidation to sulfuric acid is impractical

Most alkane C-H activation occurs at the least hindered C-H bond (1°>>2°>>3°). Catalysts selective for secondary or tertiary C-H bonds would be desirable. Christina White (Illinois) has developed such a system (*Science*, **2007**, *318*, 783; *Science*, **2010**, *327*, 566).



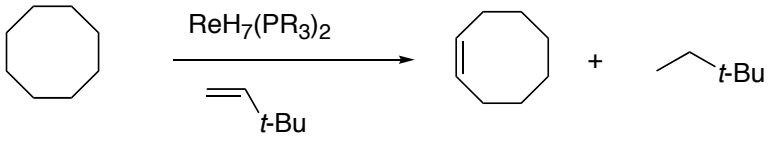
Alkane Dehydrogenation:

Alkene hydrogenation is well precedented. Would it be possible to identify systems where the reverse reaction (alkane dehydrogenation) would be favored?

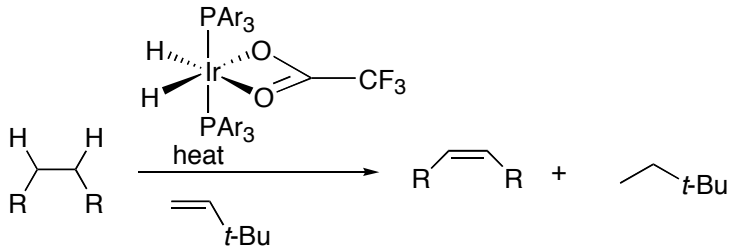


The first catalytic system:

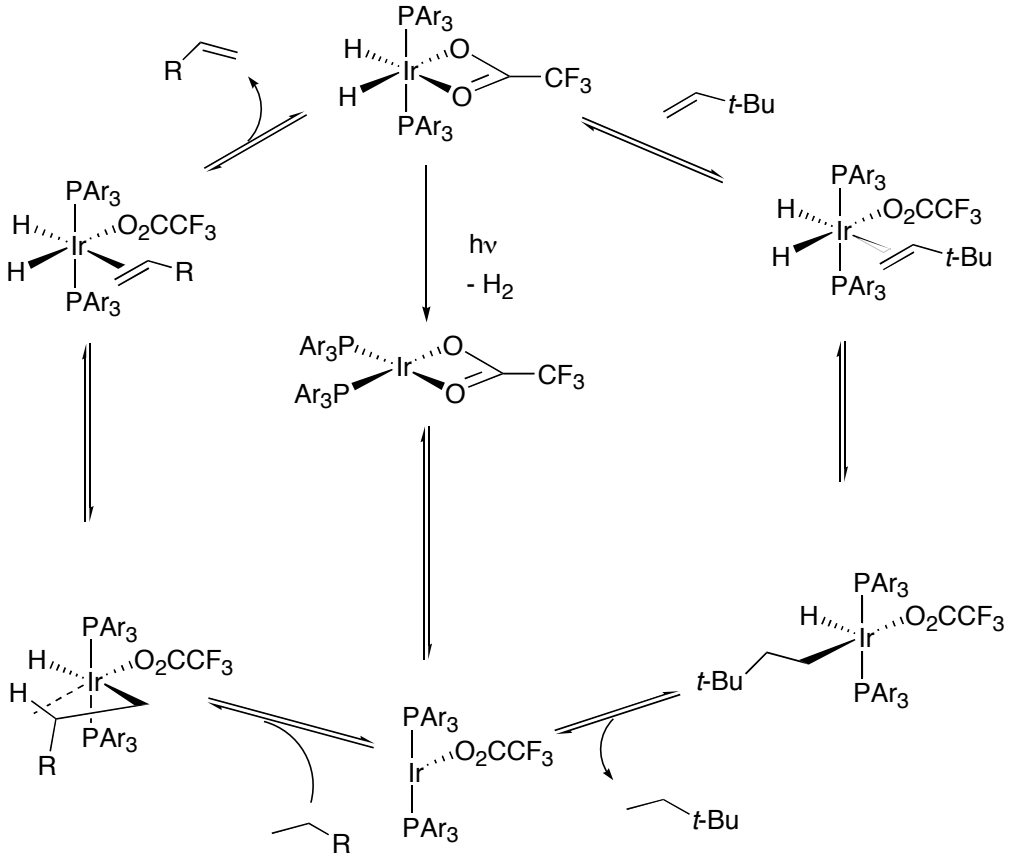
In order to drive the reaction towards dehydrogenation, it is usually necessary to remove H_2 from the reaction system. Often a reactive alkene is used as a hydrogen acceptor. 3,3-Dimethyl-1-butene is used as a hydrogen acceptor because of its high heat of hydrogenation.



J. Chem. Soc., Chem. Comm. **1982**, 1235



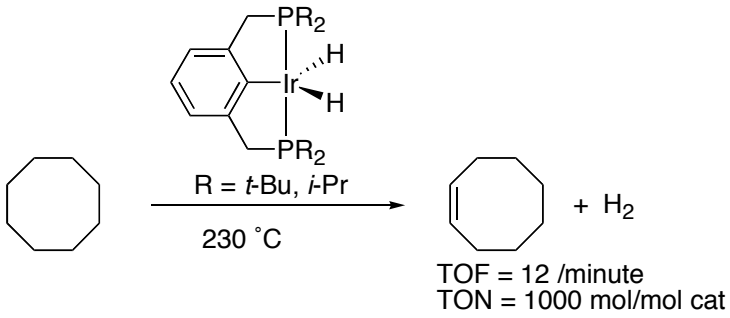
J. Amer. Chem. Soc. **1987**, *109*, 8025



t-BuCH=CH_2 converts the Ir dihydride to a coordinatively unsaturated Ir(I) complex. The driving force for this reaction is the very exothermic hydrogenation of *t*-BuCH=CH_2. The unsaturated Ir(I) species can then oxidatively add the substrate.

The need for *t*-BuCH=CH_2 can be eliminated by using light to remove H_2 from the Ir(III) dihydride. Thus the driving force is provided by the incoming photon.

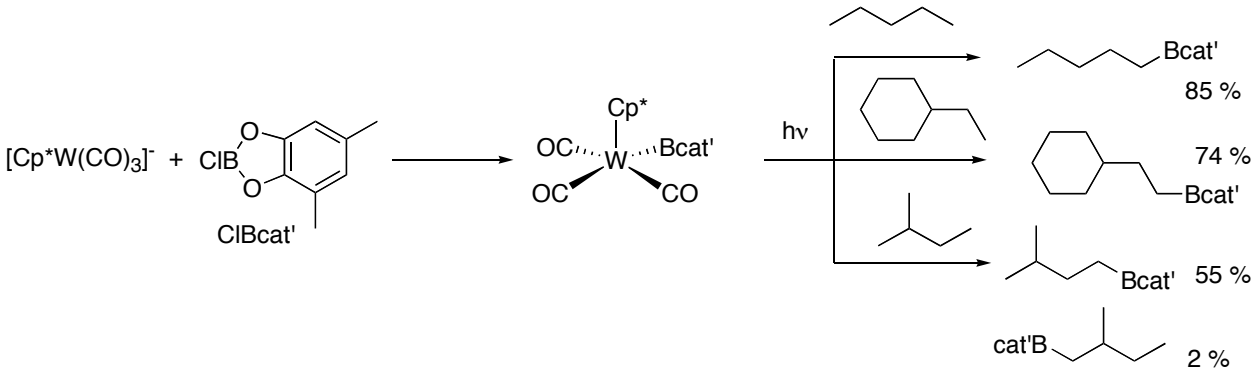
The dehydration can also be carried out thermally without an H_2 acceptor if hydrogen can be purged from the reaction system. Catalyst stability becomes an important issue under these conditions (150 - 230 ˚C). In particular, ligand metallation and other decomposition pathways become important.



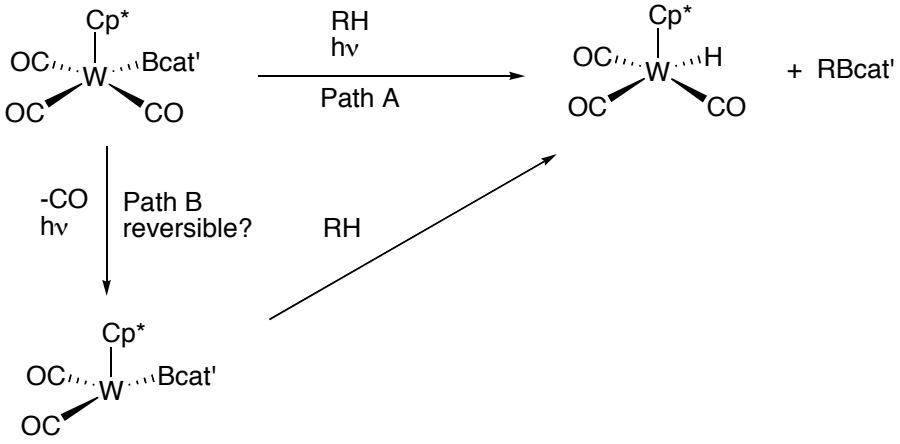
Angew. Chem. Int. Ed. **2001**, *40*, 3596-3600

Borylation of Alkanes:

1. Stoichiometric Functionalization (*Science*, **1997**, *277*, 211)



Possible Mechanisms:



Observations:

- The reaction is not inhibited by CO
- Photolysis under ^{13}CO does not result in incorporation of ^{13}CO into the complex
- Reaction in pentane and pentane-d_{12} showed indistinguishable conversion rates, but a large isotope effect was observed in a 1:1 mixture of C_5H_{12} and C_5D_{12}

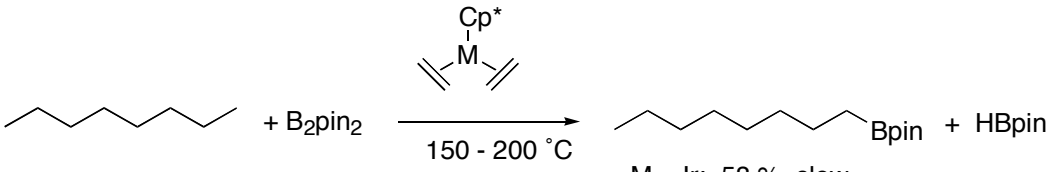
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- Photolysis of the W-Bcat' complex in the presence of PMe_3 in pentane led to formation of the PMe_3 adduct in addition to pentyl-Bcat'. The ratio of PMe_3 complex:pentylBcat' was dependent [PMe_3]

Formation of a strong B-C bond drives this reaction (B-C is 10-15 kcal/mol stronger than C-H, while M-B and M-H have similar bond strengths).

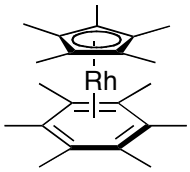
2. Thermal, metal catalyzed alkane and arene borylation (Science, **2000**, 287, 1995, J. *Am. Chem. Soc.*, **2002**, *124*, 390-391, *Science*, **2002**, *295,* 305)

To carry out the reaction thermally, need a complex where the ligands can be extruded upon heating (H_2 or alkenes).

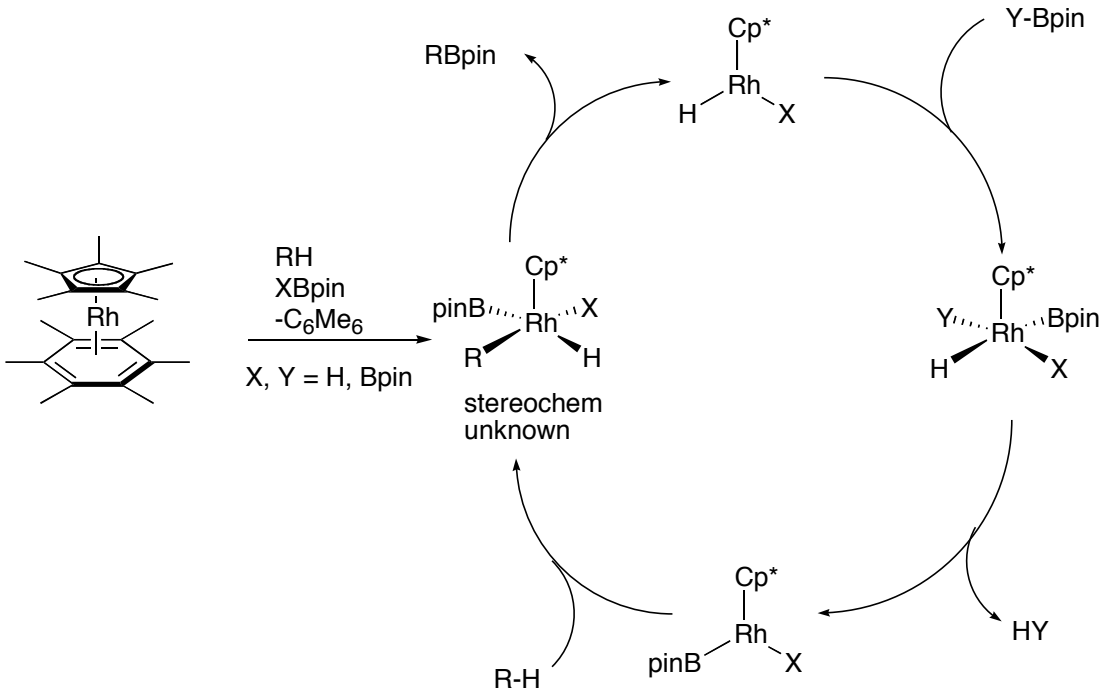


M = Ir: 58 %, slow
M = Rh: octylBpin > B_2pin_2 consumed
Overall yield 84 % based on boron

A variety of ethylene derived borane products were observed. Therefore, a catalyst that would release an unreactive fragment was required.

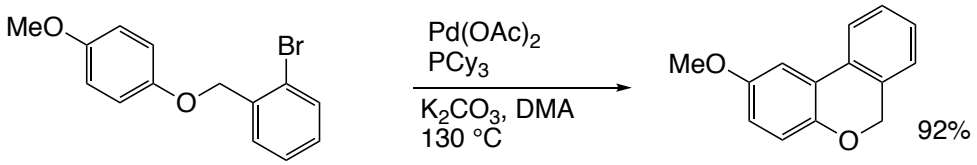


Proposed Mechanism: *JACS*, **2005**, *127*, 2538

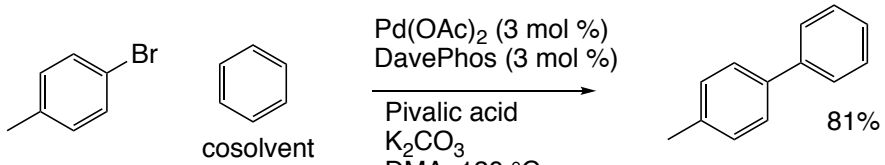


C-C Bond Formation

In addition to C-heteroatom bond formation, a large number of C-C bond-forming reactions have been reported. Often these involve the coupling of an aryl halide with an arene. The C-X bond is activated by a normal oxidative addition process. The C-H bond is activated by a heterolytic C-H bond activation (see below).

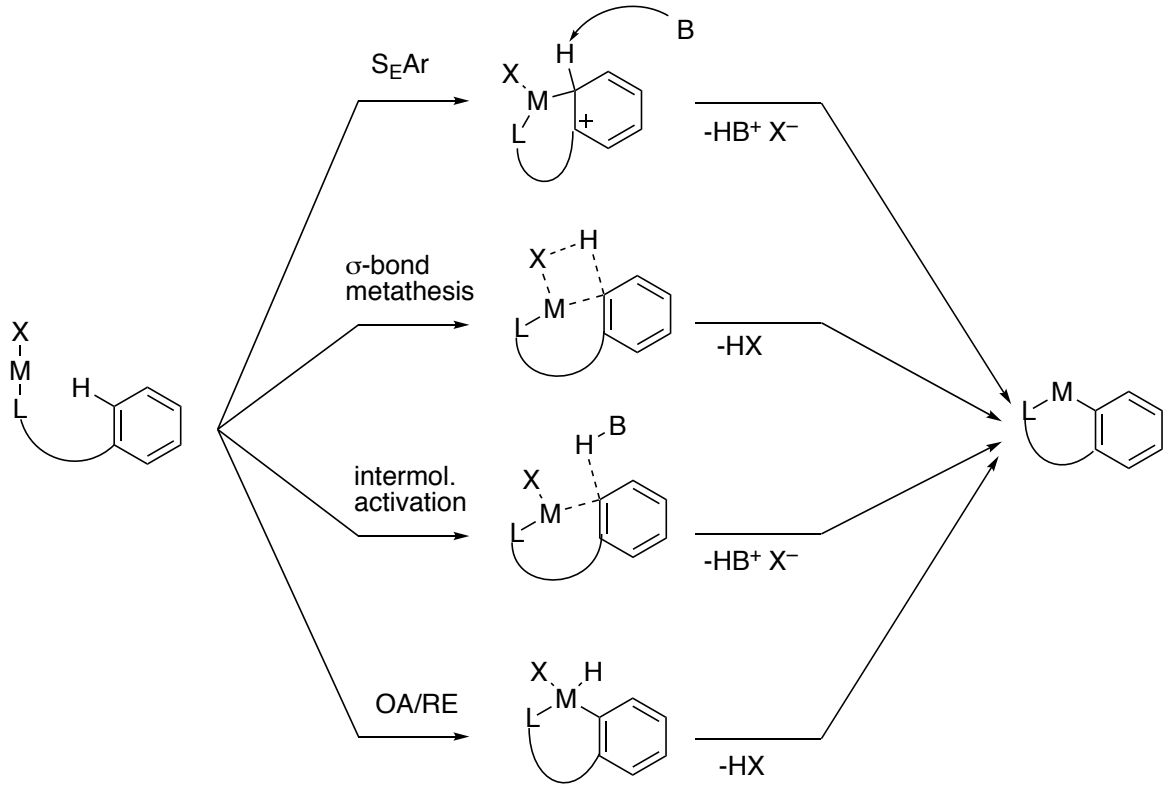


Fagnou*, JACS*, **2006**, *128*, 581

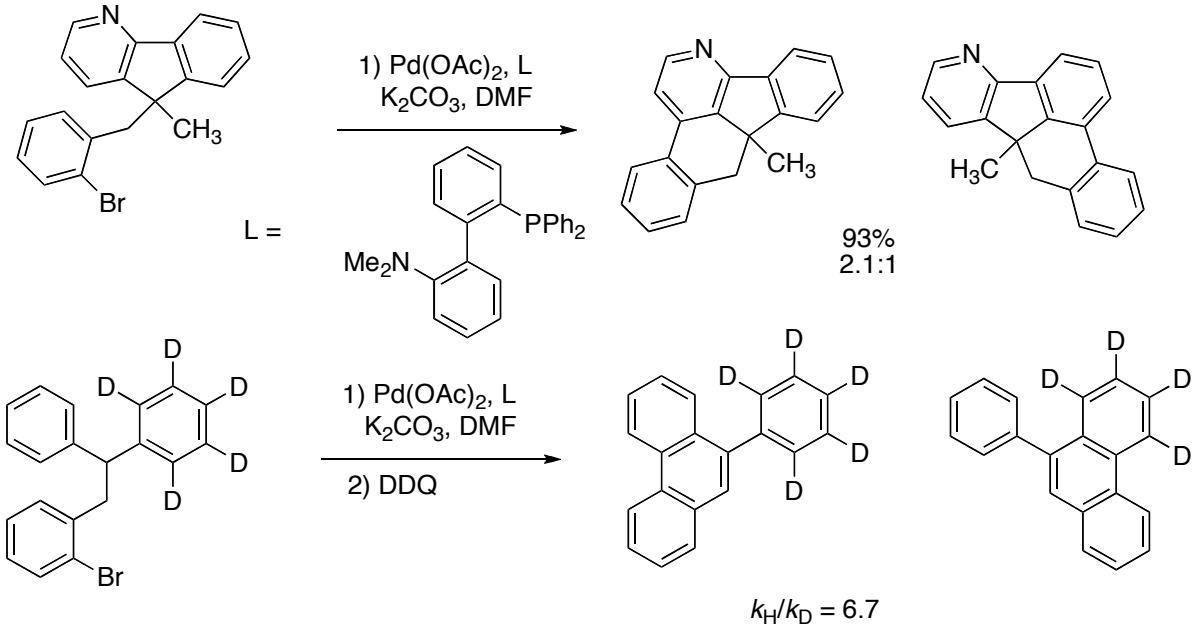


Fagnou, *JACS*, **2006**, *128,* 16496

Several mechanisms have been proposed for these types of transformations. Electrophilic aromatic substitution-type reactions were commonly invoked. Echevarren proposed a heterolyic mechanism. For Pd(II), OA/RE was expected to be less likely. (*J. Am. Chem. Soc.* **2007**, *129*, 6880-6886).



In an effort to distinguish between these mechanisms, Echevarren performed two competition experiments. In the first, the substrate had two electronically different ring systems. In the second, a KIE was measured.

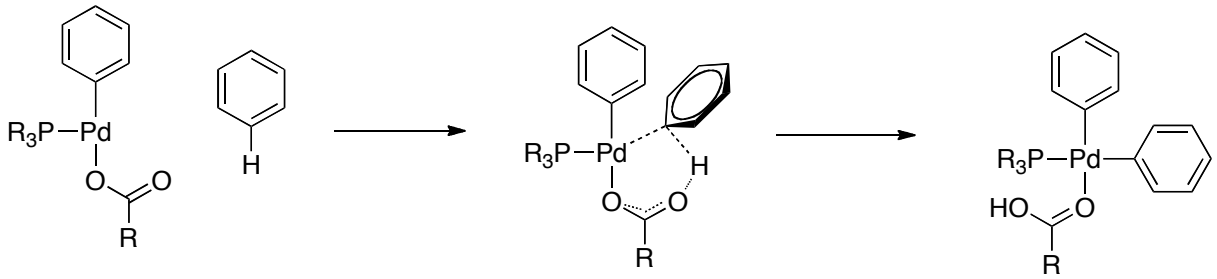


For C-H bond activation by palladium catalysts in the presence of carboxylate anions, a σ-bond metathesis mechanism using the carboxylate as an intenral base has been implicated for both sp^3

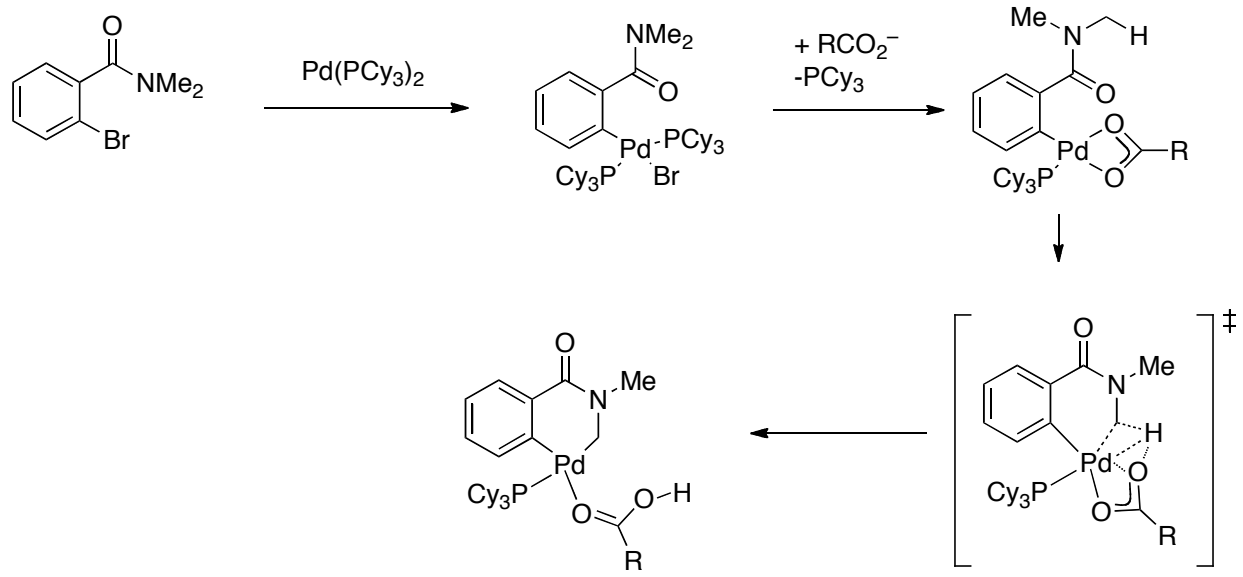
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(Rousseaux, and Fagnou, *J. Am. Chem. Soc.* **2010**, *132*, 10692-10705.and sp^2 (Fagnou. *J. Am. Chem. Soc.* **2008**, *130*, 10848-10849) C-H activation. This type of mechanism is often called concerted metalation/deprotonation (CMD) and is typical for lower-valent late transitions metals, particularly d^8 square planar complexes (Pd(II), Rh(I))

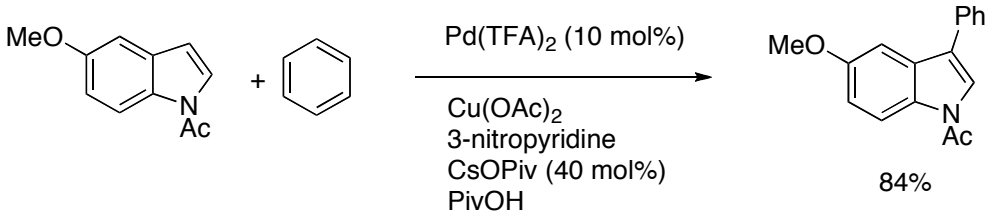
sp^2



sp^3

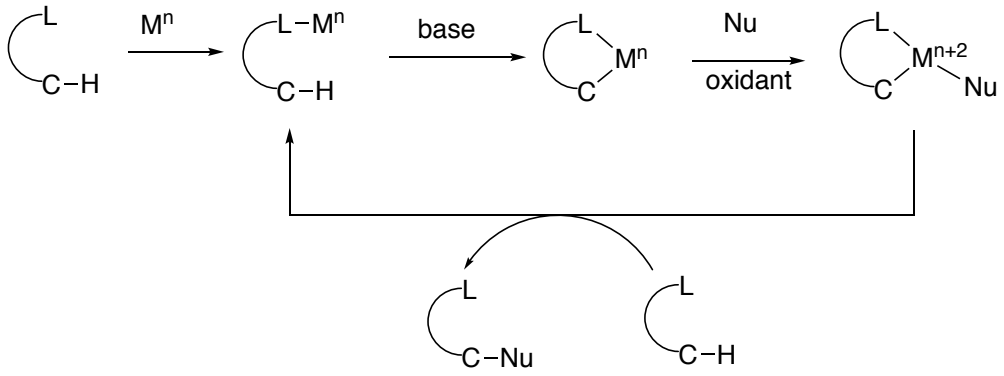


It is even possible to have both reaction partners involve C-H activation. Fagnou reported the cross coupling of electron rich azoles with arenes. This type of reaction requires an oxidant to convert the Pd(0) species formed upon reductive elimination back to Pd(II). Good yields of cross-coupled products were obtained, although a large excess of the arene had to be used. *Science*, **2007**, *316*, 1172-1175

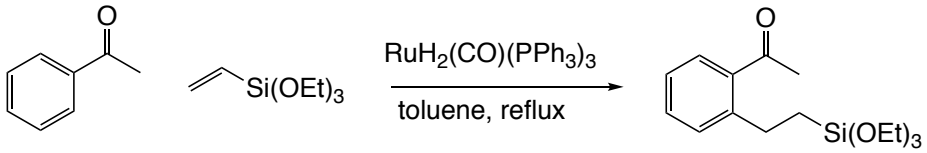


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Directed C-H functionalization: A way to overcome the selectivity issue is to use a coordinating group in the substrate to direct the metal to a particular C-H bond. Examples where the C-H activation is promoted by coordination to a Lewis-basic functional group are very common. (*Chem Rev*, **2010**, *110*, 1147) The coordinating group directs C-H activation to a nearby C-H bond. The resulting metal-carbon can then be functionalized.

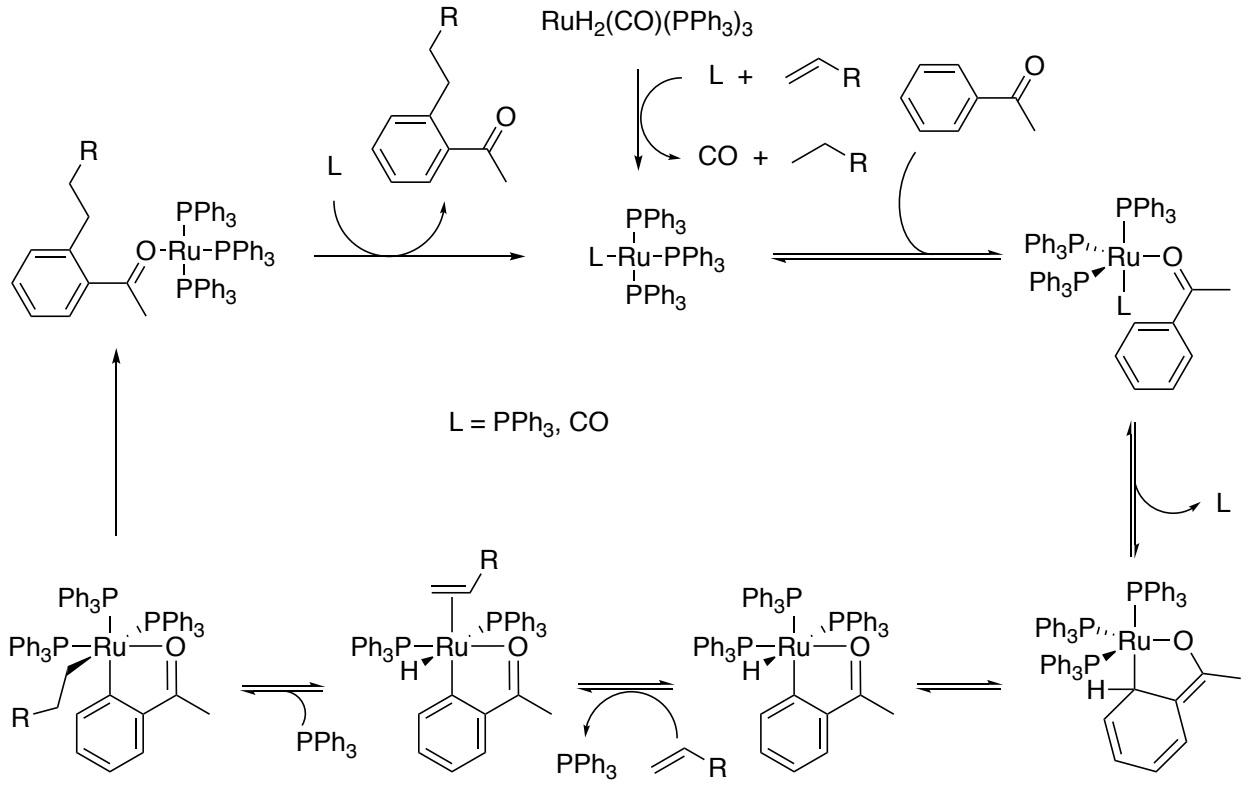


The first examples of this type of reaction reported by Murai in the early 1990s. He showed that a Ru catalyst would promote an ortho alkylation of aryl ketones. The ketone served as a directing group to promote C-H activation in the ortho position.

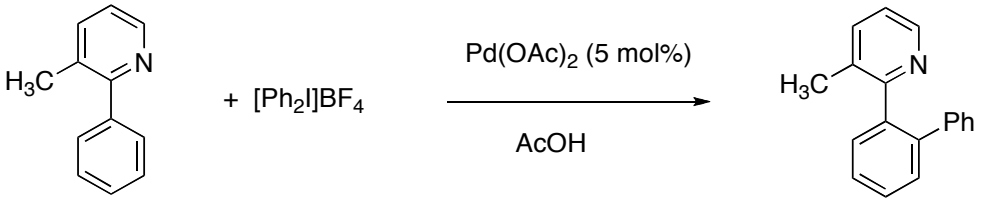


Nature, **1993**, *366*, 529

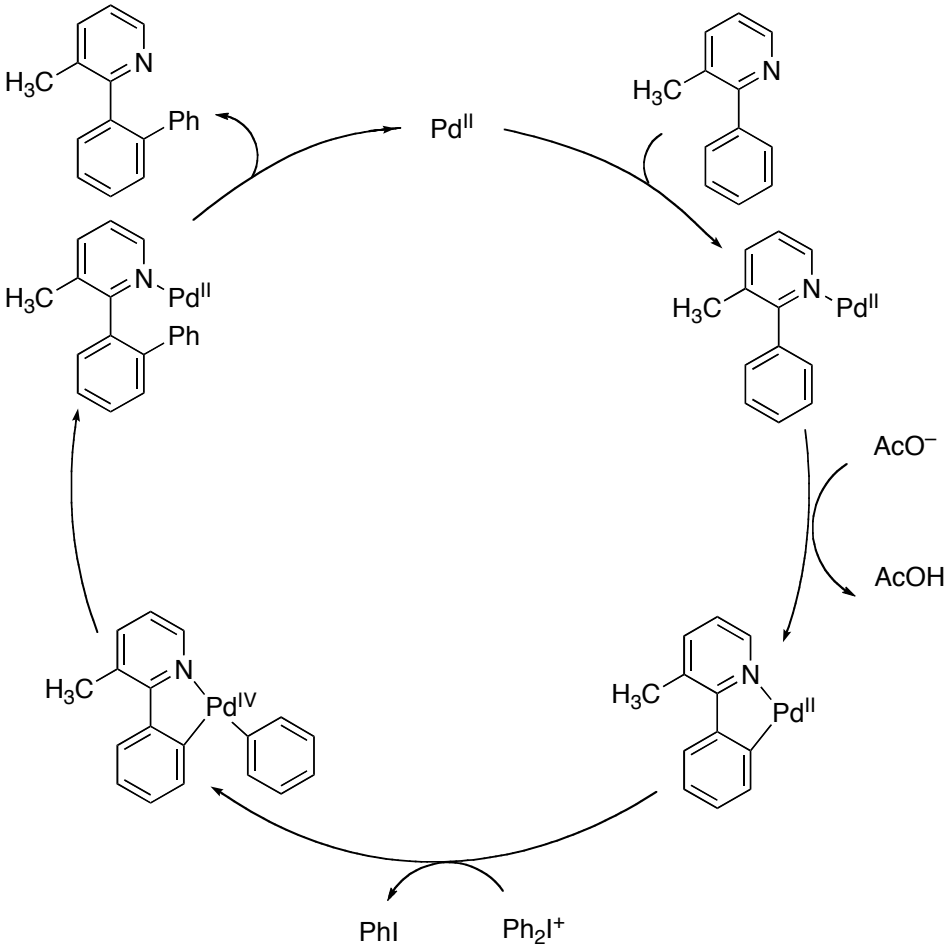
The mechanism has been shown to involve the directed oxidative addition of an ortho C-H bond by Ru. Alkene insertion into the Ru-H gives a alkyl group that undergoes reductive elimination. Since there is a closed redox loop, no oxidant is needed.



This type of reaction received little attention for almost a decade. People then began exploring palladium-catalyzed arylation of C-H bonds using directing groups. For these types of reactions, an oxidant is often needed. In the example below from Sanford, the Ph_2I^+ species is able to oxidatively add to the Pd(II) palladacycle. The bond is formed by reductive elimination.

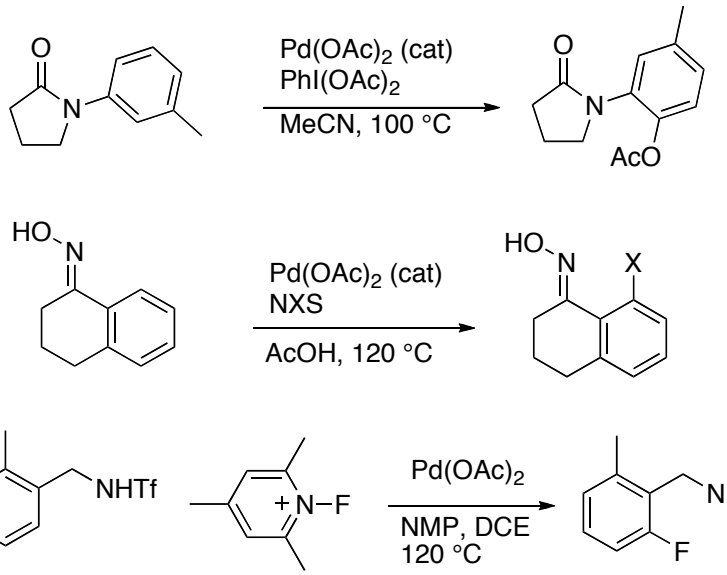


Sanford, M. S.; et al. *J. Amer. Chem. Soc.* **2005**, *127*, 7330-7331.

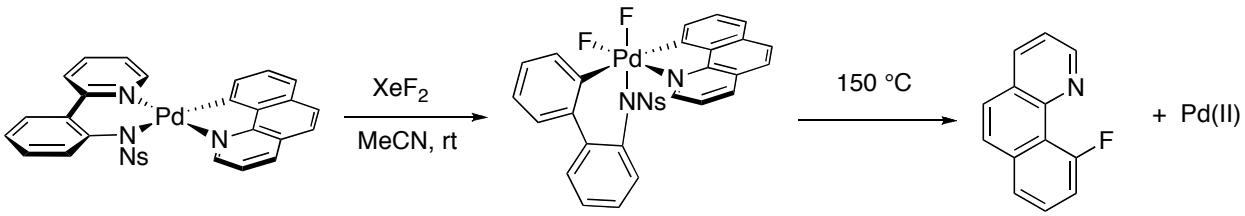


C-heteroatom bond formation:

C-H activation is an effective method to introduce heteroatoms, such as halogens, O, or N into aromatic systems.



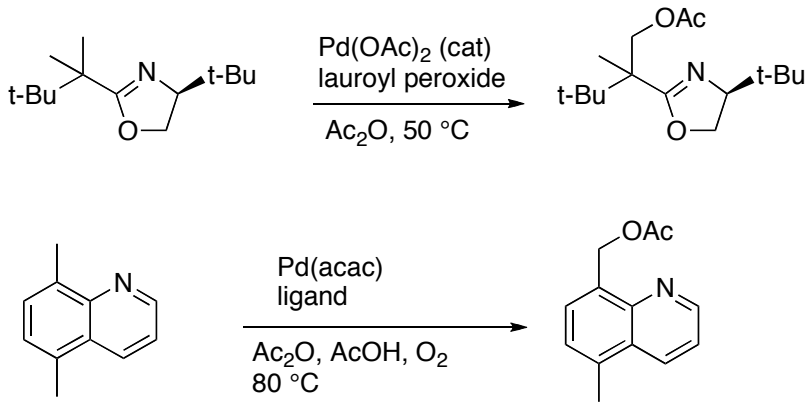
The mechanism is believed to proceed through a Pd(IV) intermediate. Pd(IV) undergoes reductive elimination of C-X bonds much easier than Pd(II). The intermediacy of Pd(IV) has been shown in stoichiometric studies.



Ritter, *JACS*, **2008**, *130*, 10060
Sanford, *JACS*, **2009**, *131*, 3796

Alkane Functionalization

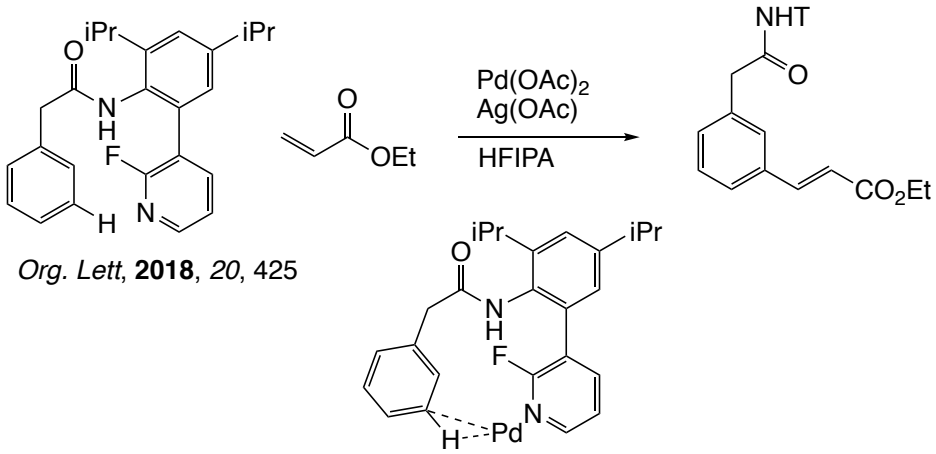
In addition to arene C-H activation, ligand directed activation of sp^3 bonds is common.



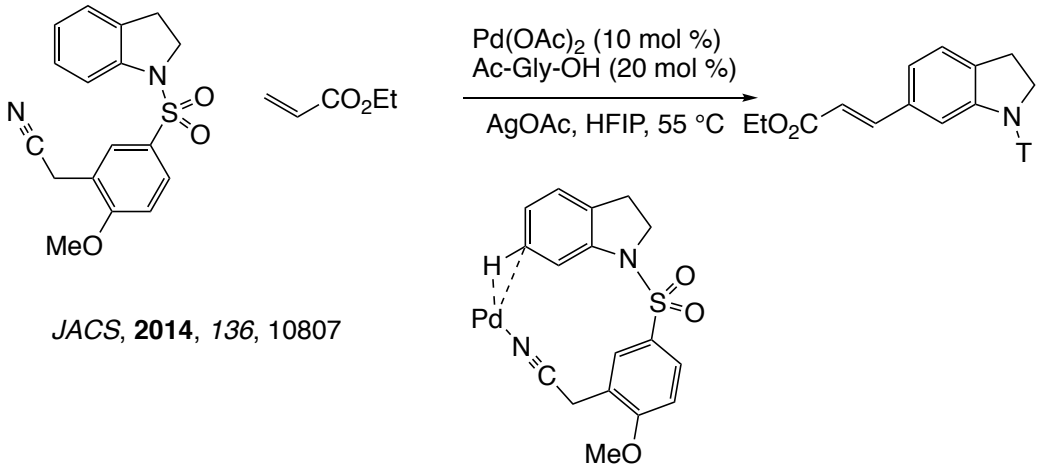
Remote Functionalization

Disadvantages of using a directing group are: 1) the directing group must be introduced using a preexisting functional group. This group, or its derivatives, must be tolerated in the final product. 2) The directing group can typically only direct the metal to a nearby bond, such as the ortho position of a substituted arene.

Jin-Quan Yu and his group have demonstrated that more remote functionalization is possible using cleverly designed templates that direct the metal to a desired bond.

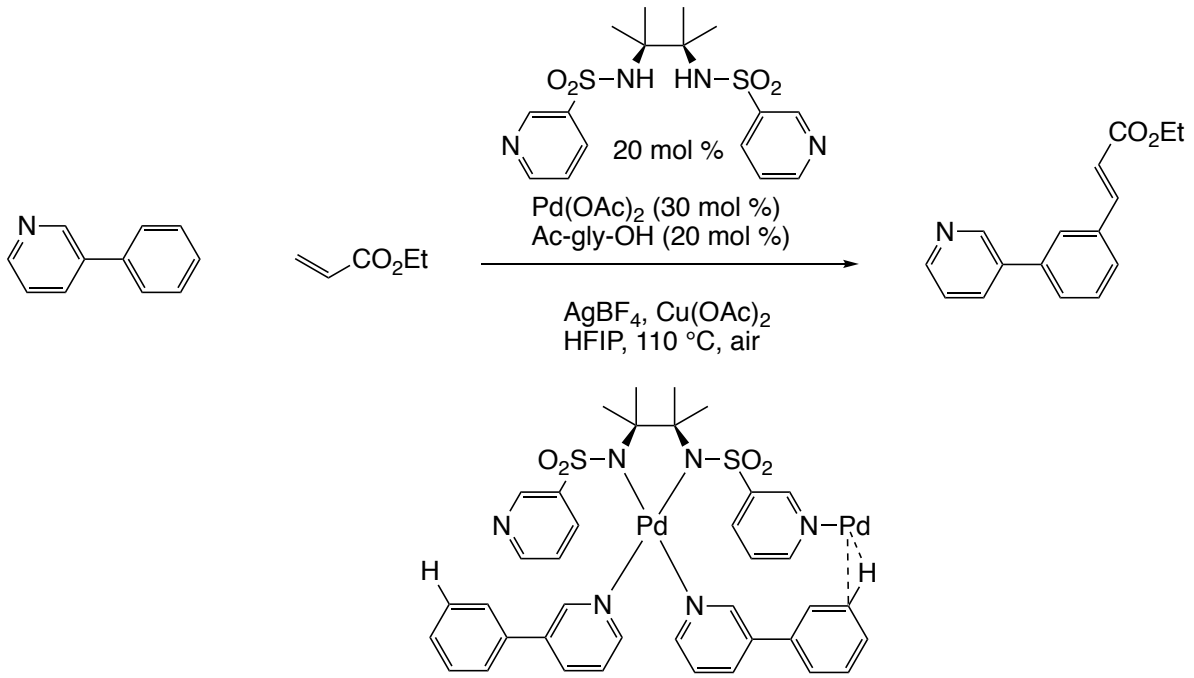


Org. Lett, **2018**, *20*, 425



JACS, **2014**, *136*, 10807

Recently, Yu has reported an example where the directing group is not covalently bonded to the substrate. Rather a metal-coordination interaction is used to bind the substrate to the directing ligand. *Nature,* **2017**, *543*, 538

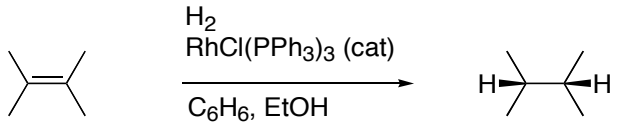

O2S–NH HN–SO2
N
20 mol %
N
Pd(OAc)2 (30 mol %)
Ac-gly-OH (20 mol %)
N
CO2Et
CO2Et
N
AgBF4, Cu(OAc)2
HFIP, 110 °C, air
O2S–N N–SO2
N
Pd
N–Pd
H
H
N
N

11-Hydrogenation of Unsaturated Compounds

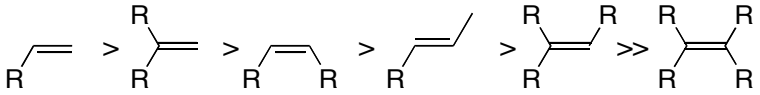
Alkene hydrogenation is one of the oldest metal catalyzed reactions (Pd/C) and one of the first homogeneous catalytic cycles to be carefully studied mechanistically. There are three steps involved in nearly all hydrogenation reactions.

- Hydrogen activation: oxidative addition, heterolytic, or homolytic
- Migratory insertion
- Elimination of alkane: Reductive elimination, σ-bond metathesis or homolytically

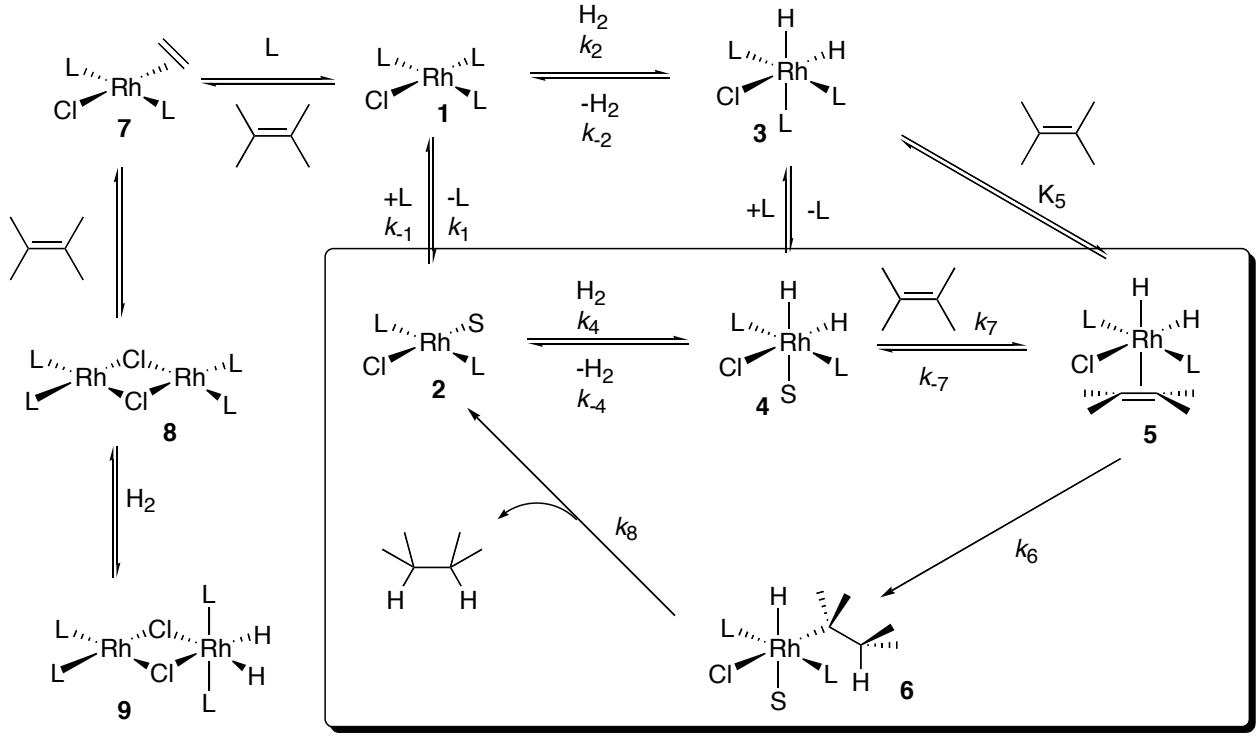
Wilkinson's Catalyst: $RhCl(PPh_3)_3$



The rates of hydrogenation of alkenes by Wilkinson's catalyst mirror their relative binding affinity to the metal center. Differences in rate between the alkenes is about 50X. Alkenes that bind very tightly (i.e., ethylene) give slow hydrogenation rates, though.



Proposed mechanism as elucidated by Halpern: (*J. Mol. Cat.*, **1976**, *2*, 65; *J. Am. Chem. Soc.*, **1977**, *99*, 8055; *J. Am. Chem. Soc.*, **1980**, *102*, 838; *Science*, **1982**, *217*, 401)



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The Rh complexes outside of the box have been observed under the catalytic conditions. None of the compounds inside the box have been observed, but based on the evidence are believed to be the actual species involved in the catalytic cycle.

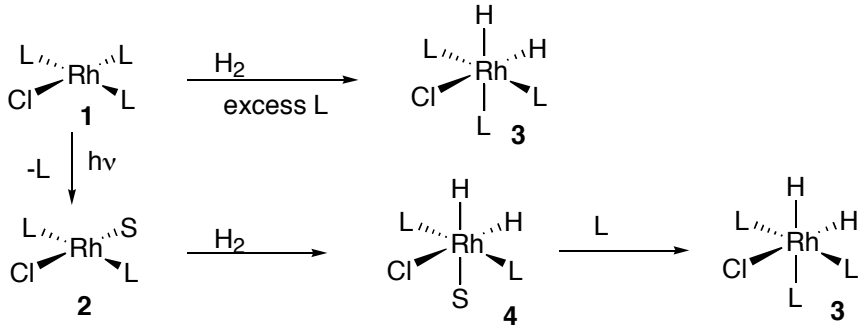
The hydrogenation reaction occurs in two steps:

- Dihydrogen activation
- Alkene hydrogenation

Since H_2 is activated first, this is often called the hydride path.

Dihydrogen activation:

Halpern's evidence supports an initial dissociation of PPh_3 prior to oxidative addition of H_2. The rate of oxidative addition is inhibited by increased [PPh_3]. In fact the direct addition of H_2 to **1** to give **3** in the presence of excess PPh_3 occurs very slowly. (*J. Mol. Cat.*, **1976**, *2*, 65; *Inorg. Chim. Act.* **1981**, *50*, 11). Oxidative addition of H_2 to **2** was estimated by Halpern to occur 10^4 X faster than to **1**, which was later confirmed by generating **2** by flash photolysis. (*J. Am. Chem. Soc.*, **1985**, *107*, 1794 and **1986**, *108*, 4838).

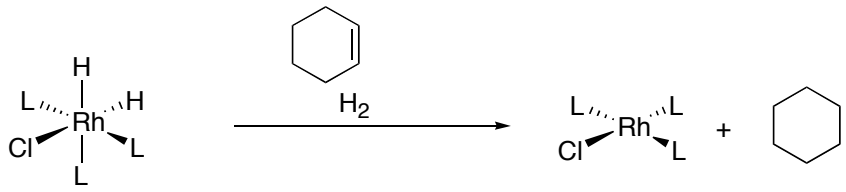


Wilkinson originally proposed a similar mechanism based on his assumption that k_1/k_{-1} would be large. In fact the equilibrium constant is approximately 10^{-5}. Wilkinson's error was due to the oxygen sensitivity of $RhCl(PPh_3)_3$, which reacts with oxygen to give Ph_3PO as a weakly bonded ligand.

2 has a strong tendency to dimerize to **8**, although this is not a significant process under higher H_2 pressures. The alkene complex **7** also does not represent a significant trap for the Rh species, except in the case of tightly binding alkenes such as ethylene.

Olefin Hydrogenation:

Kinetic studies were carried out on the reaction of **3** with a large excess of alkene.



Treating the conversion of **3** to **5** as a rapid pre-equilibrium (K_5) and the conversion of **5** to **6** as the rate determining step results in the following rate expression.

$$\frac{-d[3]}{dt} = \left(\frac{K_5 k_6[\text{alkene}]}{[L] - K_5[\text{alkene}]}\right)[3] = k_{obs}[3]$$

$$k_{obs} = \frac{K_5 k_6[\text{alkene}]}{[L] - K_5[\text{alkene}]}$$

This rate expression predicts that a plot of $1/k_{obs}$ versus [L]/[alkene] should be linear with slope = $1/K_5k_6$ and an intercept of $-1/k_6$.

$$\frac{1}{k_{obs}} = \left(\frac{1}{K_5 k_6}\right)\left(\frac{[L]}{[\text{alkene}]}\right) - \frac{1}{k_6}$$

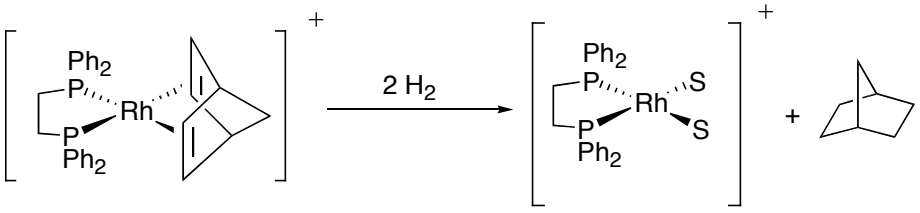
Plotting data from experiments where [L]/[alkene] was varied over a wide range were linear and gave values for K_5 (3.4 X 10^{-4}) and k_6 (0.2 s^{-1}). Kinetic results suggest that k_8 (reductive elimination) is sufficiently fast that the reverse of hydride migration (ß-hydride elimination) is not observed. These results account for the lack of isotopic exchange when the reaction is carried out with D_2.

The fact that **6** is not trapped by phosphine can be inferred from the lack of [PPh_3] dependence on the migratory insertion step.

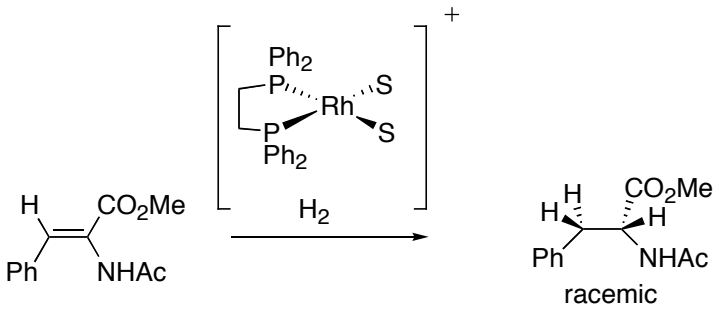
Although this mechanism has been carefully worked out, variation of the ligand or the substrate can drastically alter the observed mechanism and rate expressions.

- Alkenes that bind more strongly than cyclohexene (i.e., styrene) indicate a parallel mechanistic path where two equivalents of styrene bind to the metal center.
- Ethylene which binds very strongly to the metal center appear to follow path where the alkene binds prior to H_2 oxidative addition.
- Use of more electron rich trialkylphosphines can strongly affect the dissociative equilibria altering the mechanism.

Cationic Rhodium catalysts [RhL_2S_2]$^+$

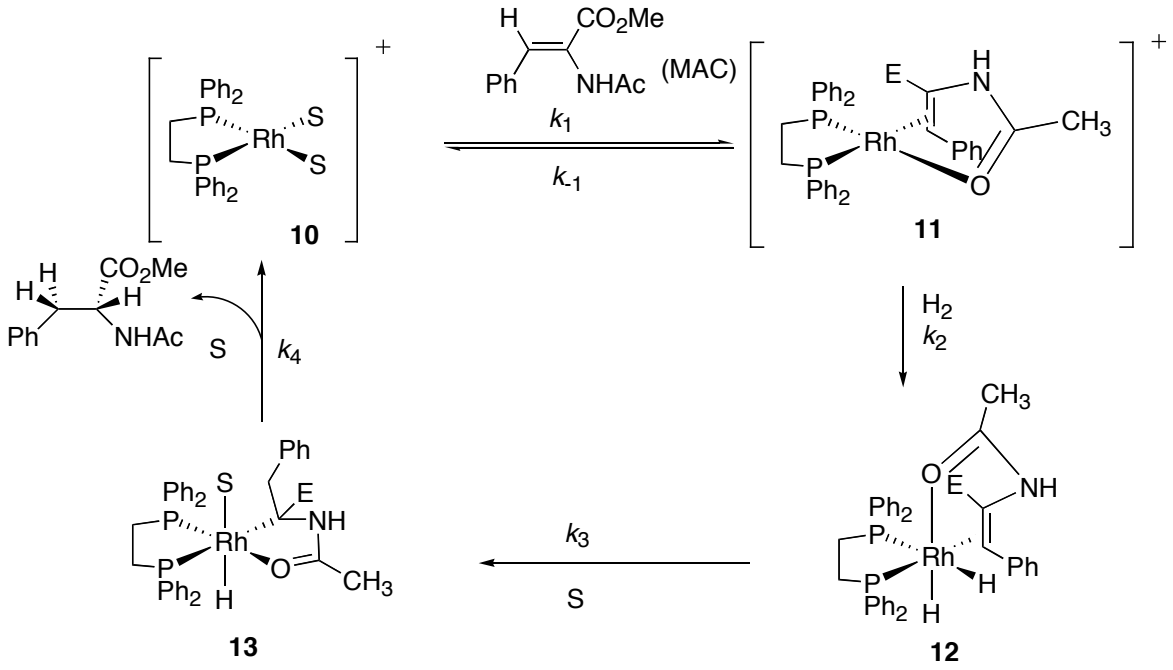


These systems work particularly well for alkenes with other functionality that can coordinate to the electrophilic rhodium center.



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For these cationic metal complexes, the mechanism proceeds by initial alkene coordination followed by H_2 oxidative addition, hydride migration, and reductive elimination. Halpern has also studied the mechanism of this catalytic cycle in detail. (*J. Am. chem. Soc.* **1977**, *99*, 8055, and **1980**, *102*, 838; *Science*, **1982**, *217*, 401)



Complexes **10**, **11**, and **13** can be observed in the catalytic cycle. In this case the observed species are part of the actual catalytic cycle.

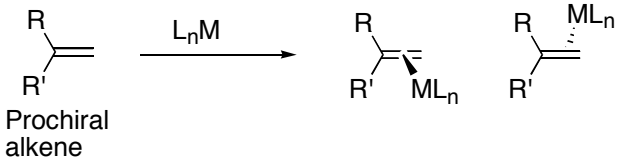
Complex **10** is in equilibrium with the alkene complex **11**. Even relatively weak π-ligands like benzene coordinate strongly to the electrophilic Rh center. Since benzene is not reduced by this catalyst, it acts as a competitive inhibitor. For alkenes such as MAC, the equilibrium is rapidly established and lies far towards the alkene complex. Complex **11** has been characterized by X-ray crystallography.

At 25 ˚C, oxidative addition of H_2 to **11** is the rate limiting step, but at -40 ˚C reductive elimination becomes rate limiting. Hydride migration to the alkene occurs very rapidly in contrast to Wilkinson's catalyst.

These systems are of particular interest because they allowed the first *enantioselective* hydrogenations of prochiral alkenes.

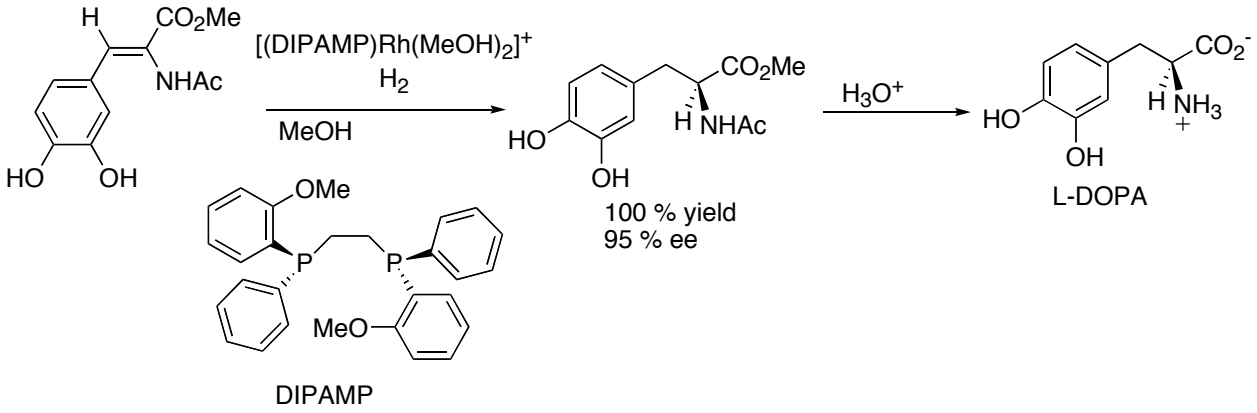
Asymmetric Hydrogenation:

Coordination of a prochiral alkene to a transition metal center produces a pair of enantiomeric alkene complexes that are converted to enantiomeric hydrogenation products. If the starting organometallic complex is chiral, though, the alkene complexes are diastereomers of each other.

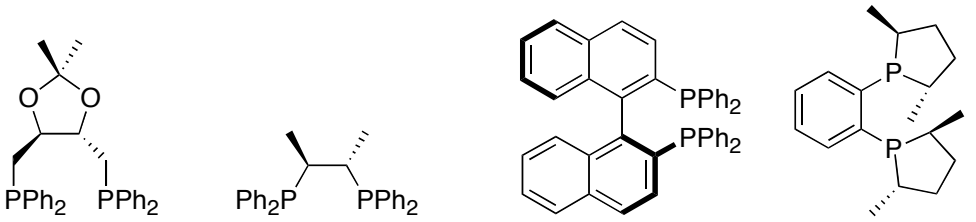


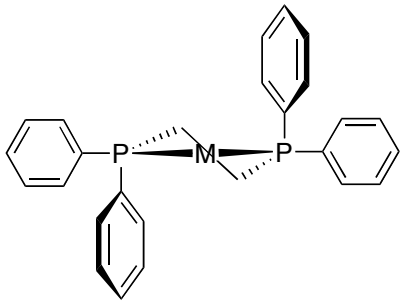
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The first commercial application of this idea was the synthesis of L-Dopa commercialized by Monsanto. This seminal work by William Knowles was recognized with the Nobel prize in 2001.



DIPAMP is chiral at phosphorous. Other ligands, which have chiral backbones have become more popular because of their ease of synthesis from optically pure organic precursors.

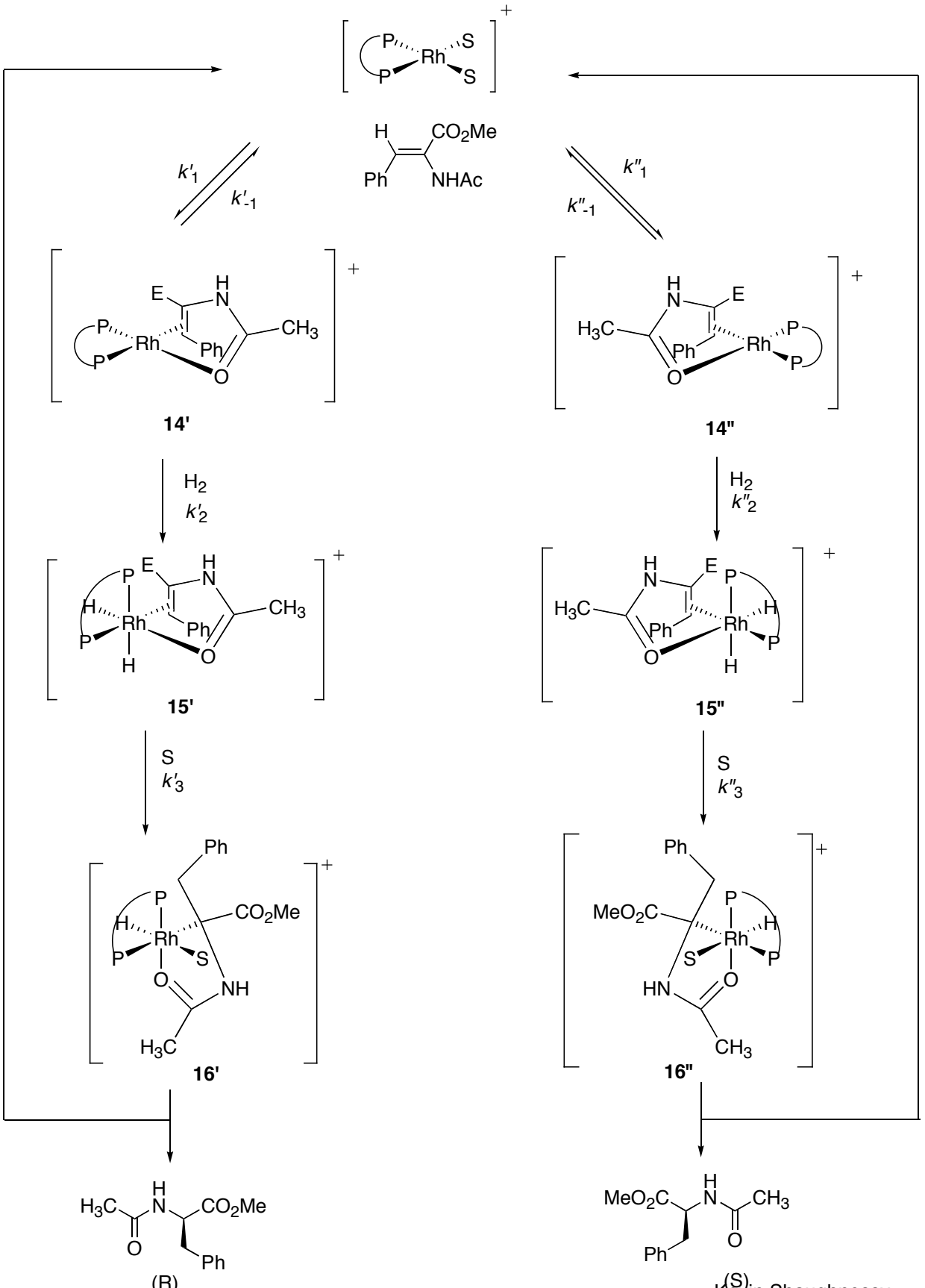




Early studies by multinuclear NMR showed only a single diastereomer was produced upon coordination of MAC to Rh((*S,S*,)-CHIRAPHOS)+ (**14'** or **14"**). It was originally assumed that the major isomer observed by NMR would be the one that led to the observed product enantiomer. When the alkene adduct was characterized crystallographically, the structure was determined to be **14"** (re face). This would predict formation of the *S*-product, but in fact the (*S,S*,)-CHIRAPHOS ligand gives predominately the *R*-isomer.

With the ligand (*R,R*)-DIPAMP, both **14'** and **14"** are observed in unequal amounts, although their absolute configuration was not determined. At low temperatures, where the diastereomers do not interconvert, the minor diastereomer reacts with H_2 much more rapidly. The results suggested that the minor diastereomer of **14** reacts with H_2 ca. 1000 times faster than the major diastereomer. (*J. Chem Soc., Chem. Comm.* **1980**, 344; **1983**, 664; and **1985**, 575)

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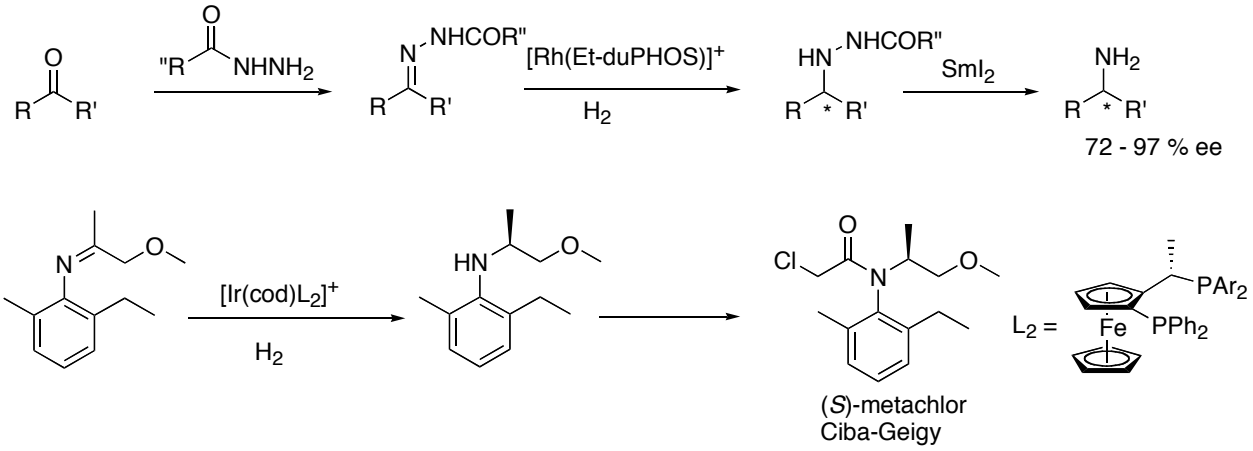
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Mechanisms in which an initial rapid equilibrium is formed between reaction intermediates followed by slow product forming steps are known as Curtin-Hammett-type mechanisms. This type of mechanism turns out to be fairly common for these types of asymmetric hydrogenations. Two useful experiments that can be used to probe for this type of mechanism are:

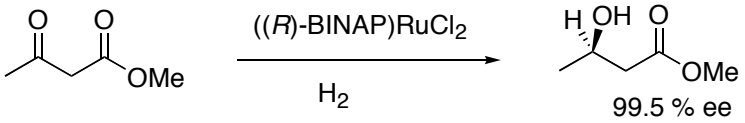
- Effect of changing H_2 pressure
- Temperature effect on the enantioselectivity of the reaction

Hydrogenation of other unsaturated compounds

Burk developed the duPHOS family of ligands while working at DuPont. In addition to giving highly enantioselective reduction of enamides, Rh complexes of duPHOS also give high ee's in the reduction of hydrazones. (*J. Am. Chem. Soc.*, **1991**, *113*, 8518; **1992**, *114*, 6266)



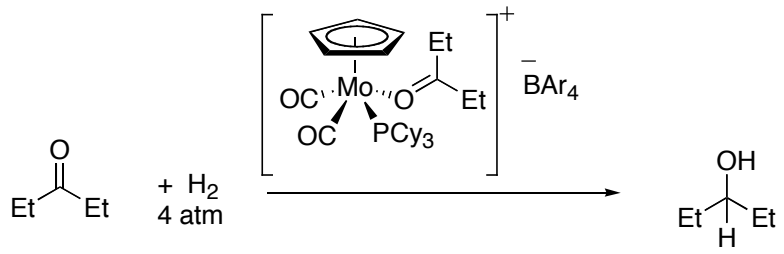
Ryori Noyori was also a recipient of the 2001 Nobel Prize for his development and application of the BINAP ligand. Using Ru(II) in place of Rh(I) resulted in a more general catalyst that could hydrogenate ketones and imines as well as alkenes.

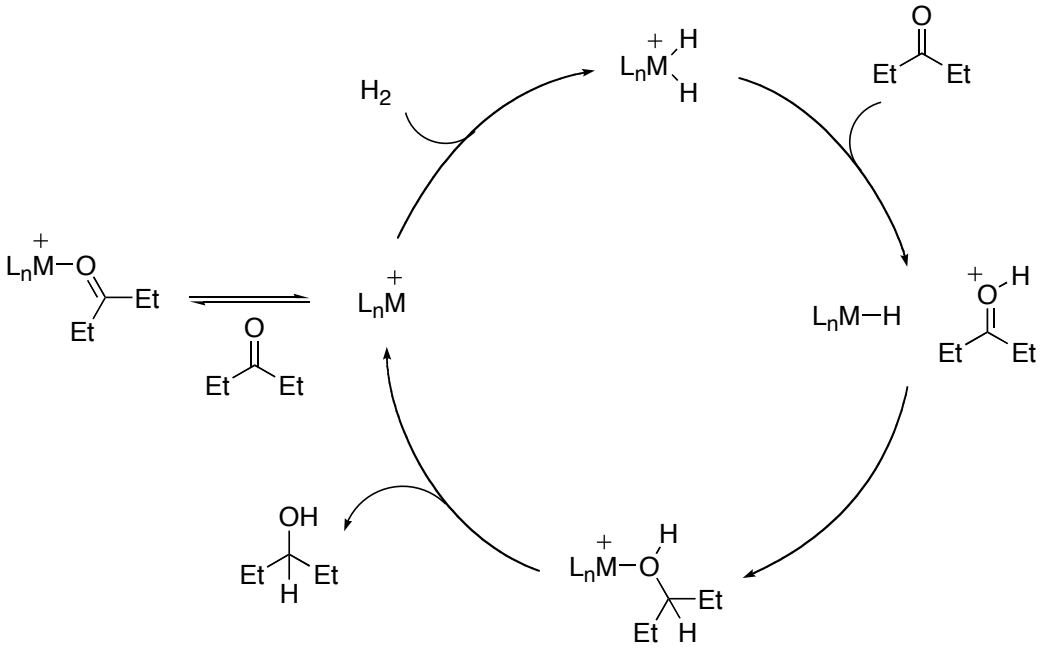


This catalyst system has been commercialized for the synthesis of (*R*)-1,2-propanediol, which is used as a precursor for the synthesis of the antibiotic levofloxacin.

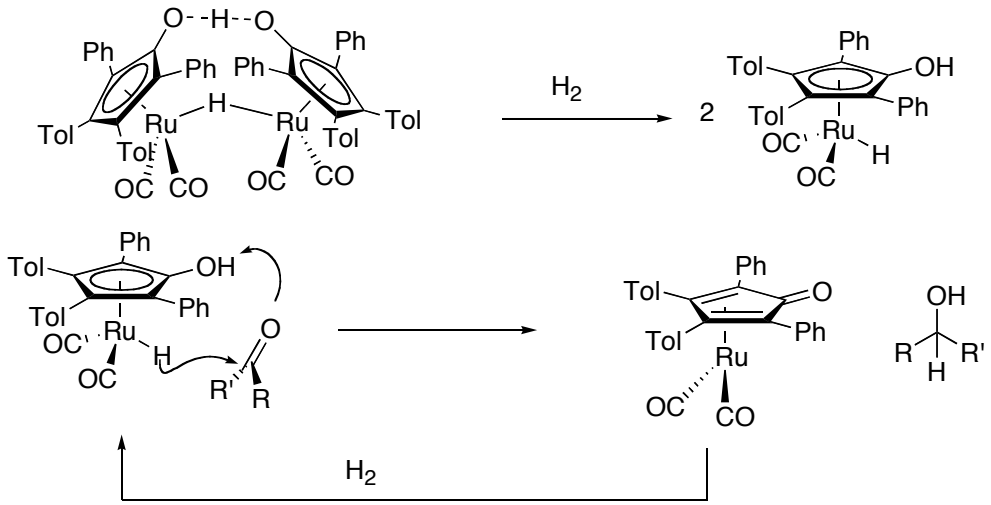
Ionic Hydrogenation

The Noyori catalyst is believed to follow ionic mechanism in the reduction of carbonyls and imines. In an ionic mechanism H_2 is added as H^+ and H^-, rather than by a migratory insertion process. This mechanism is particularly prevalent in the reduction of ketones and imines that can serve as proton acceptors. *Chem. Eur. J.* **2004**, 2366-2374.



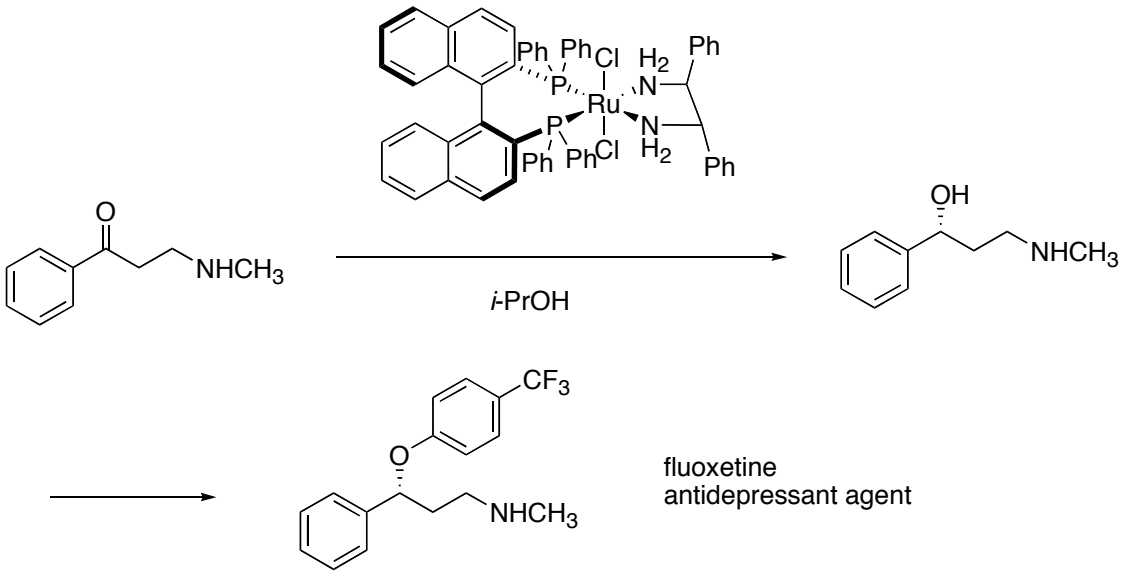


A number of systems have been developed in which a Lewis basic site in the ligand environment serves as the proton donor, while the metal provides the hydride. Shvo developed a system based on a Ru complex of cyclopentadienone. Heterolytic oxidative addition of H_2 gives a cyclopentadienol-ruthenium hydride. *Organometallics*, **1997**, *17*, 133-138.

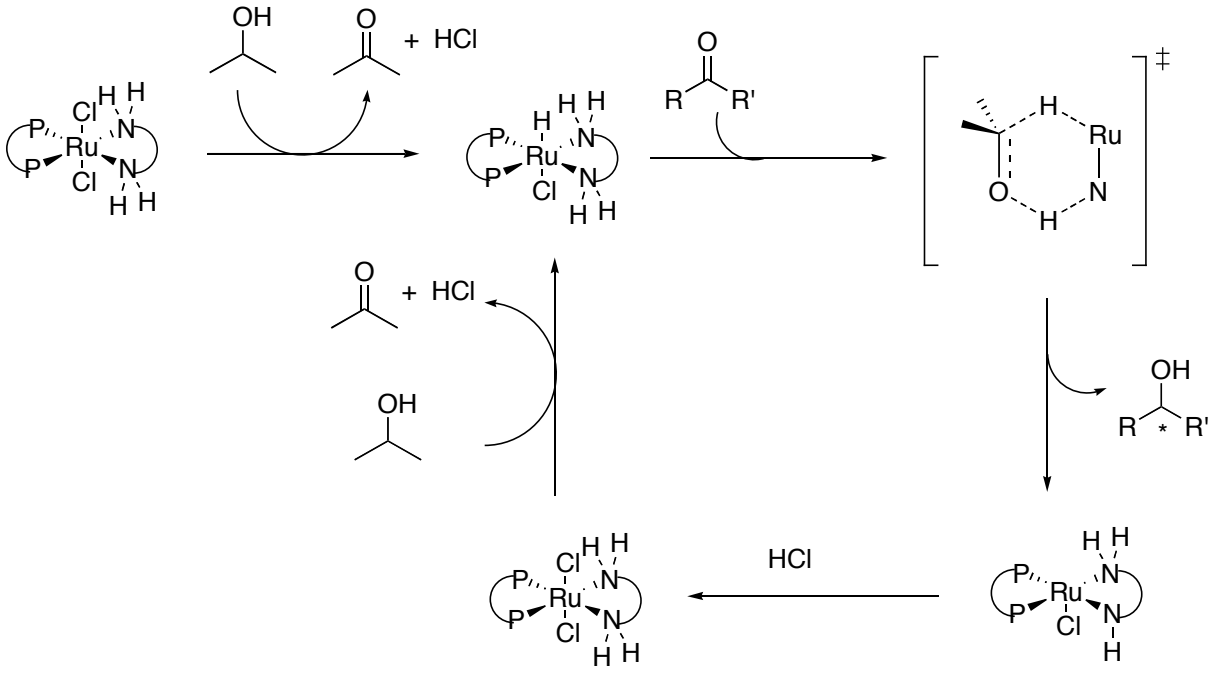


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Noyori has developed a highly successful catalyst system based on ruthenium amine complexes. The amine serves as the proton donor, while the ruthenium delivers hydride. These systems are highly enantioselective catalysts for reduction of carbonyls and imines. *Angew. Chem. Int. Ed.* **2002**, *41*, 2008 and 2108.



This hydrogenation is an example of a transfer hydrogenation. Isopropanol serves as the source of hydrogen. The isopropanol adds to the Ru center, followed by β-hydride elimination. The hydrogen transfer step is believed to involved a 6-membered transition state in which the N-H and Ru-H both deliver H at the same time. The transition state has been computationally modeled.



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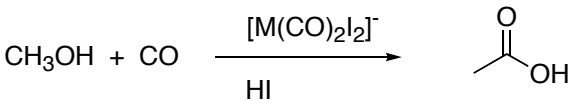
12-Carbonylation Reactions

CO is an important building block in industrial and academic synthesis. Incorporation of CO allows a carbon to be added and usually results in the formation of a carbonyl product. CO is produced industrially from the water-gas shift reaction in which CO_2 and H_2 can be reacted to form CO and water.

I. Carbonylation of alcohols and organic halides

The Acetic Acid process

Approximately 60 % of the 6.5 million metric tons (1,000 kg) of acetic acid made each year is produced by the carbonylation of methanol.



1960: Original system developed by BASF

M = Co, 250 ˚C, 680 bar CO, 90 % acetic acid based on MeOH

1966: Monsanto Acetic Acid process

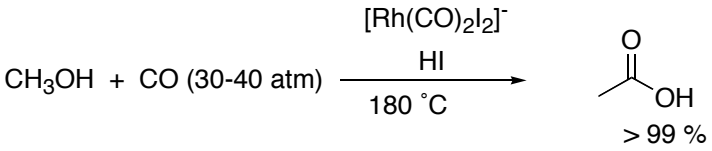
M = Rh, 150 - 200 ˚C, 20 - 60 bar CO, > 99 % acetic acid from MeOH, lower yield relative to CO

1996: BP Cativa™ process

M = Ir, improved catalyst stability, very high rates, and good product selectivity relative to both MeOH and CO

Rhodium: The Monsanto Acetic Acid Process:

Adv. Organomet. Chem., **1979**, *17*, 255
Chemtech, **1971**, *1*, 600
U.S. Patent 3,769,329, 1973



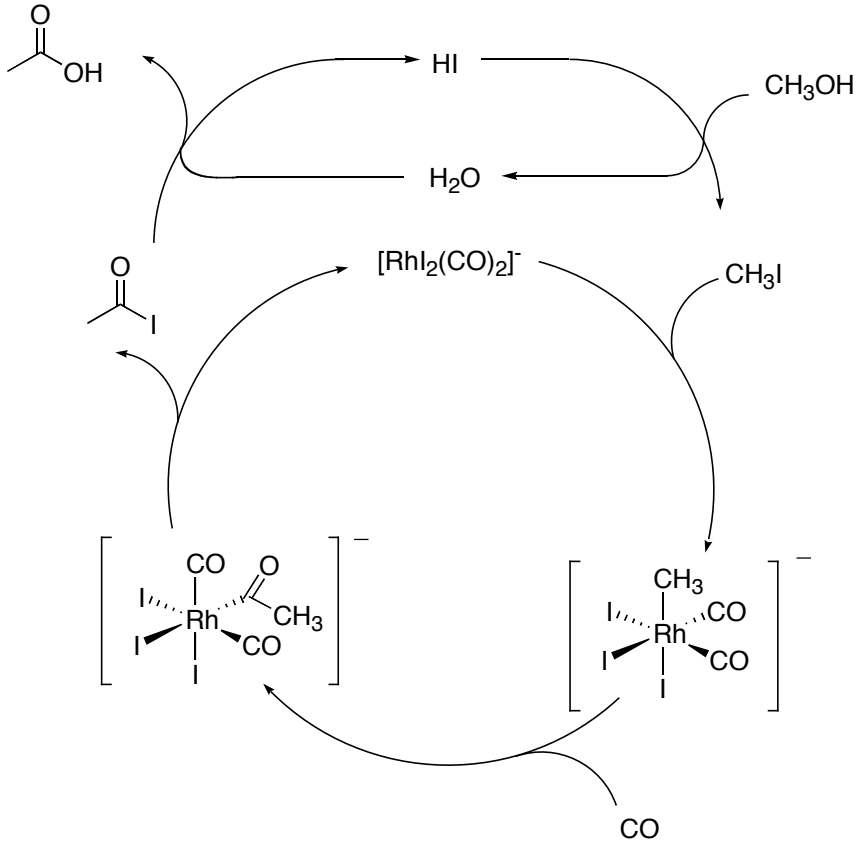
Virtually any source of Rh(I) and iodide catalysts can be used. These are converted under the reaction conditions to $[RhI_2(CO)_2]^-$ and CH_3I

The key steps in the catalytic cycle are: 1) anion assisted oxidative addition of MeI; 2) migratory insertion of CO; 3) reductive elimination of acetyl iodide.

The use of I^- is critical. Bromide gives rates that are 10X slower than iodide.

- Iodide is a good nucleophile
- Iodide is a weak Brønsted base
- Iodide is a good ligand for Rh

Rate = $k[Rh]^1[I^-]^1[CO]^0[CH_3OH]^0$



The Me-Rh species can only be observed spectroscopically (*J. Am. Chem. Soc.*, **1993**, *115*, 4093), while the acyl rhodium species has not been observed.

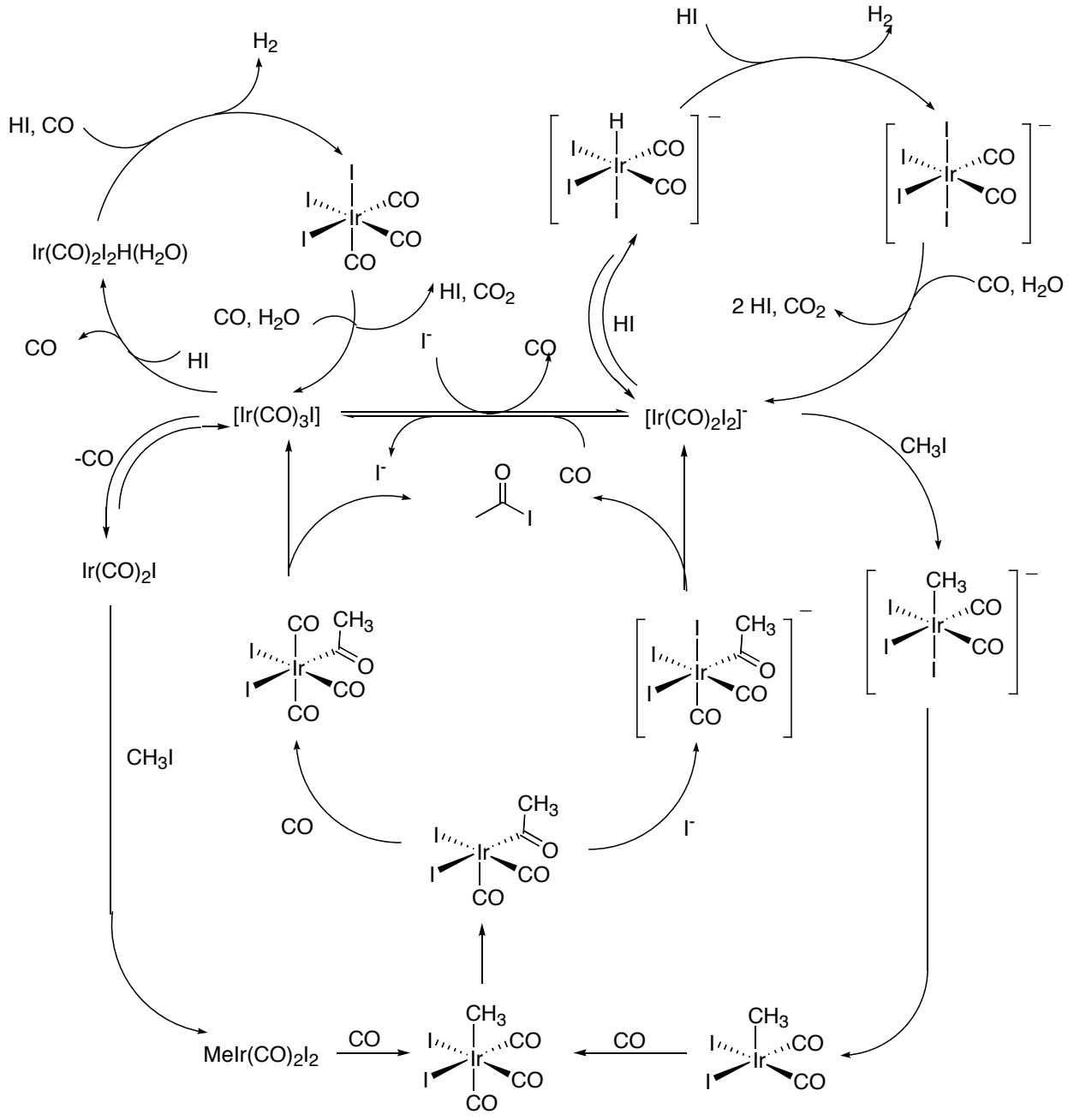
Disadvantages of this system:

- Iodide is corrosive
- The rhodium catalyst is only stable under certain conditions (high CO pressure), so catalyst recycling is difficult
- A heterogeneous version is unlikely

Iridium: The BP Cativa™ Process

Iridium catalysts have very high rates, but can have low selectivity.

The mechanism as determined by Forster (*J. Chem. Soc., Dalton Trans.*, **1979**, 1639; *Adv. Catal.*, **1986**, *34*, 81; *J. Mol. Cat.*, **1982**, *17*, 299) showed that the iridium system is more complex mechanistically than the rhodium system. There appear to be two catalytic cycles involving both anionic and neutral iridium complexes.



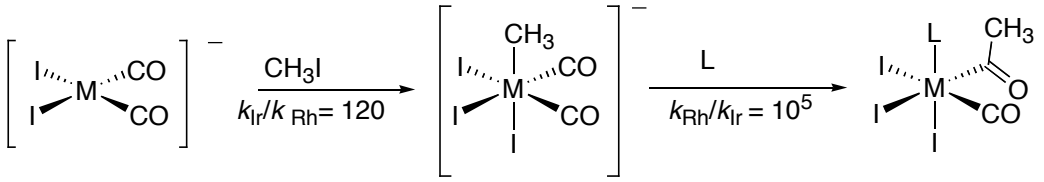
Reproduced from *Catal. Today*, **2000**, *58*, 293-307

Regime 1: Favored at low ratios of MeI to Ir and at low [H_20] and [I^-].
Reaction rate is inversely proportional to P_{CO}.
Major from of Ir is $Ir(CO)_3I$

Regime 2: Observed at high [I^-]
Major Ir species is $[Ir(CO)_2I_2]^-$
Rate increases with increasing P_{CO} and decreases with increasing [I^-]

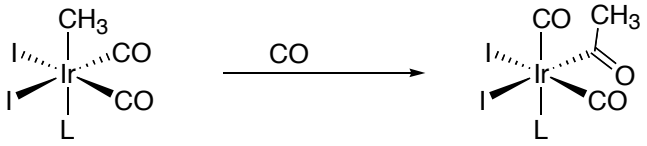
Regime 3: Observed under a variety of conditions, particularly at high [H_2O] or [MeOH]
Major species is [$HIr(CO)_2I_2]^-$ which catalyzes both methanol carbonylation and the water-gas shift reaction.

Comparison of the Rh and Ir systems: Model studies in aprotic solvents (*J. Chem. Soc., Dalton Trans.* **1996**, 2187):
- The Ir-CH_3 bond is stronger than the Rh-CH_3 bond due to relativistic effects of the heavier Ir center. (Theoretical study: *Organometallics,* **2000**, *19*, 1973-1982)



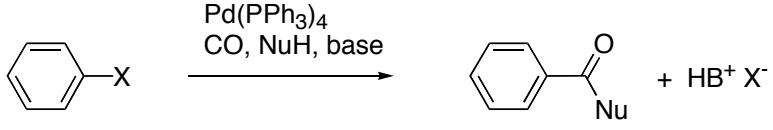
While oxidative addition to Ir is faster by 2 orders of magnitude than for Rh, the situation is reversed for the migratory insertion step. For Rh, oxidative addition is rate limiting followed by very fast migratory insertion. For Ir, the methyl complex can be isolated and only undergoes migratory insertion upon heating under CO pressure. Under protic conditions, migratory insertion is greatly accelerated for the Ir complex (*Chem. Commun.* **1995**, 1045). Protic solvents facilitate dissociation of iodide from [$MeIr(CO)_2I_3]^-$, which occurs prior to migratory insertion.

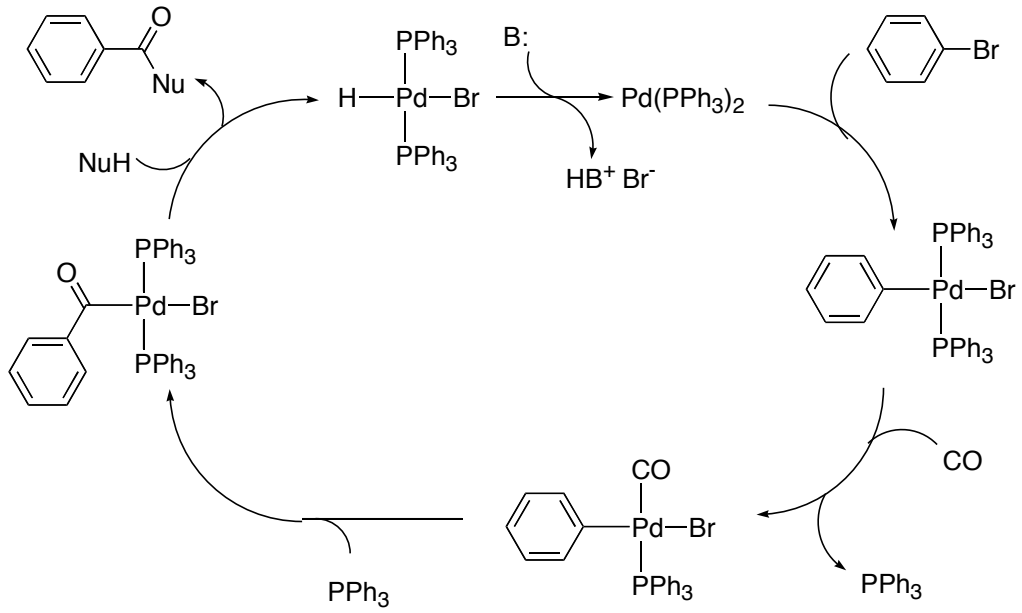
Recent studies of the catalytic cycle have shown the key intermediate to be [$MeIr(CO)_3I_2$], which undergoes migratory insertion much faster than [$MeIr(CO)_2I_3]^-$. (*Chem. Comm.* **1998**, 1023-1024)



L = CO is 800 times faster than L = I at 85 ˚C under 400 psi CO in chlorobenzene.
L = CO: $\Delta H^{\ddagger}$ = 89 kJ/mol, $\Delta S^{\ddagger}$ = -36 J/mol•K
L = I^-: $\Delta H^{\ddagger}$ = 109 kJ/mol
Extrapolation of these results to 185 ˚C would predict that the neutral species would undergo migratory insertion 9 times faster than the anionic species.

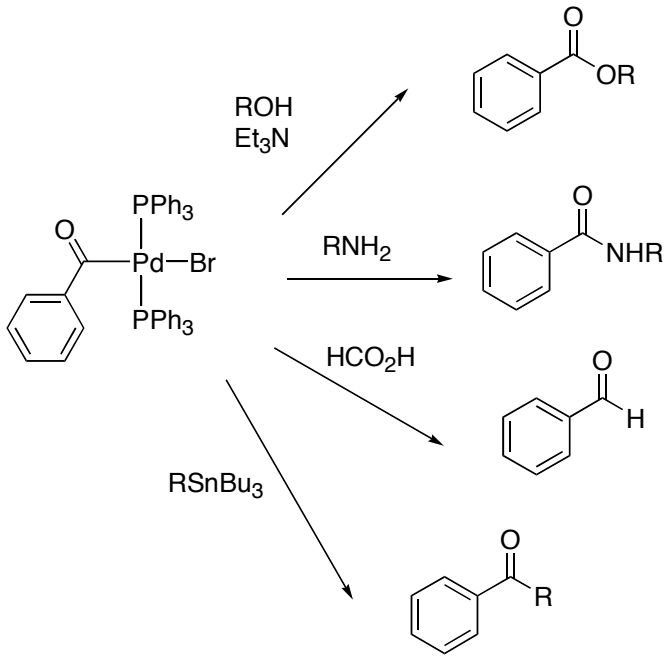
Pd-catalyzed carbonylation of aryl and vinyl halides
J. Tsuji, *Palladium Reagents and Catalysts*, Wiley & Sons, Chichester, 1995, Ch. 4





Oxidative addition is followed by migratory insertion to give a palladium-acyl. Nucleophilic attack by alcohols or amines on the carbonyl carbon results in formation of the organic product and a Pd-H that rapidly decomposes. The mechanism for the nucleophilic attack is analogous to the mechanism for nucleophilic attack on simple carboxylic acid derivatives.

This reaction is most commonly applied to the synthesis of esters and amides, but aldehydes and ketones can be made in this way as well.

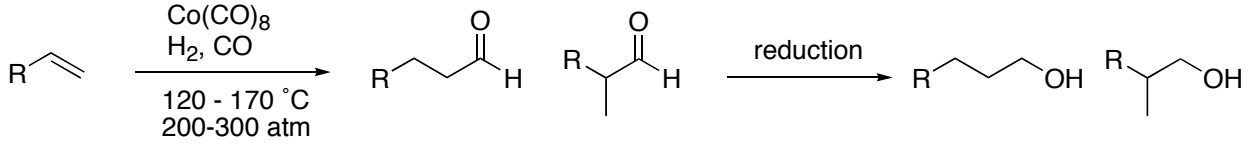


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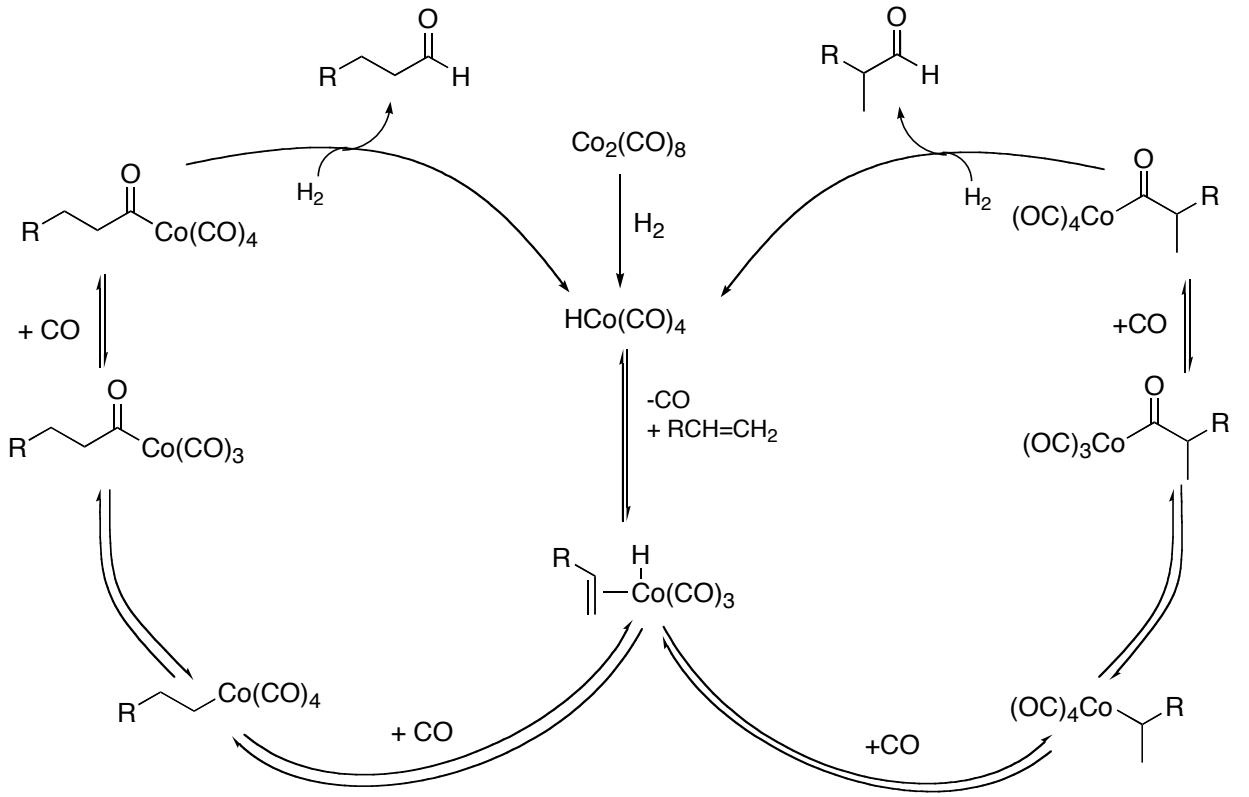
2. Hydroformylation

Cobalt-based hydroformylation catalysts

Hydroformylation or the oxo process was originally developed by Roelen in the late 1930's while working for Ruhrchemie. The original catalyst was $Co_2(CO)_8$, which is still widely used. In the hydroformylation reaction, the elements of formaldehyde (H and CHO) are added across a double bond to give an aldehyde. Both linear and branched products can be produced, although the more desirable linear aldehydes are usually the major products when using aliphatic olefins. Depending on the catalyst and conditions, the aldehydes can be directly reduced to alcohols during the reaction.



Catalytic cycle: Although the exact nature of some steps have not been conclusively determined, the catalytic cycle is as follows.



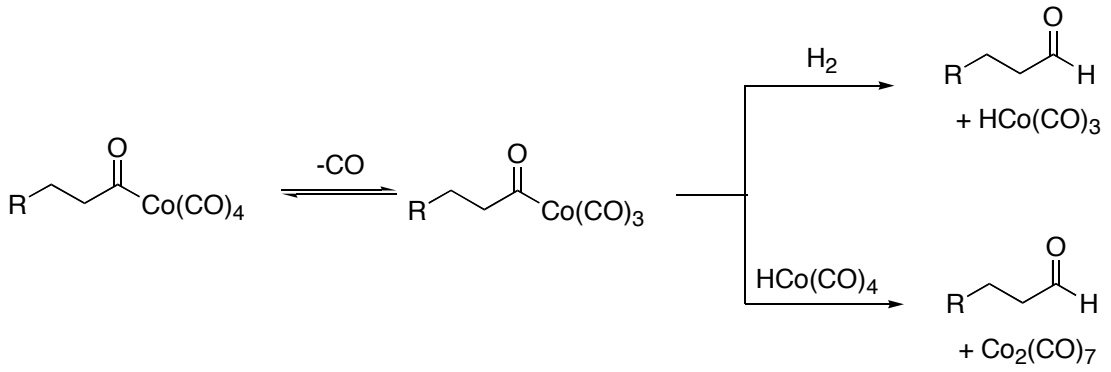
$Co_2(CO)_8$ undergoes hydrogenation to give the acidic "hydride" complex $HCo(CO)_8$, which can also be prepared directly and used as the catalyst.

The first step is a dissociative substitution of alkene for CO. Migratory insertion can result in either a primary or secondary metal alkyl. Although this is the step that sets the regiochemistry of the products, it

is rapidly reversible. This rapid reversibility results in alkene isomerization and H/D exchange. Since ß-H elimination requires an open coordination site, isomerization and isotope exchange are inhibited by increased CO pressures.

The next step is a second migratory insertion to form the coordinatively unsaturated acyl that can coordinate another CO to give the 18 electron acyl complex. Under standard catalytic conditions with 1-octene, this is the only species observed by IR.

The mechanism of the hydrogenolysis step is less clear. One possible mechanism is the reaction with H_2 to give the aldehyde and $HCo(CO)_4$, which could occur by oxidative addition/reductive elimination (unlikely due to the expected high activation barrier) or heterolytic H_2 activation (σ-bond metathesis). A second possible mechanism would involve a dinuclear reaction with $HCo(CO)_4$.



Evidence for both mechanisms has been observed. $HCo(CO)_4$ reacts 20-30 X faster with the Co-acyl than H_2 does at room temperature (*Organometallics*, **1986**, *5*, 209-215). Under the catalytic conditions, the H_2 concentration is about 2 orders of magnitude larger than that of $HCo(CO)_4$. At the typical reaction temperature (> 100 ˚C), the higher activation enthalpy of H_2 cleavage than $HCo(CO)_4$ cleavage will become less significant. Therefore, it is accepted that under industrially relevant conditions, cleavage occurs by H_2 addition.

Regioselectivity: Generally the linear isomer is more valuable industrially than the branched isomer. Since the catalytic cycle is irreversible, the observed regioselectivity represents the kinetic product ratio rather than the thermodynamic preference. Generally the regioselectivity is not determined by the rate at which alkene insertion occurs to give primary and secondary Co-alkyls. Rather the regioselectivity is determined by the relative rate of migratory insertion of the primary and secondary alkyls to CO. Less hindered alkyl groups migrate more rapidly than larger groups.

The regioselectivity can be modified by adding phosphine to the Co-catalyzed hydroformylation system. This advance was discovered at Shell chemical. Using $HCo(CO)_3PBu_3$ as catalyst, higher linear:branched ratios are achieved. This appears to be due to a greater degree of regiocontrol in the initial migratory insertion of the alkene into the Co-H.

- Steric: Substituting PBu_3 for CO increases the steric bulk of the metal center, which would be expected to favor formation of a primary Co-alkyl.

- Electronic: Substituting PBu_3 for CO significantly decreases the acidity of the cobalt-hydride. Therefore, there is a lower preference for Markovnikov-type addition of H-Co to the alkene.

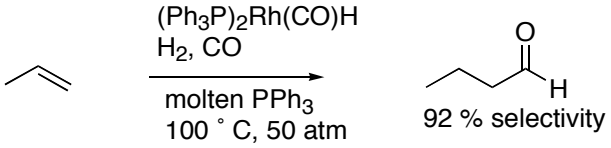
The Shell phosphine-modified catalyst is slower than $HCo(CO)_4$, so higher temperatures are required for acceptable rates. The phosphine-modified catalyst is more stable though, so it can run at lower CO pressures.

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Rhodium-based hydroformylation catalysts

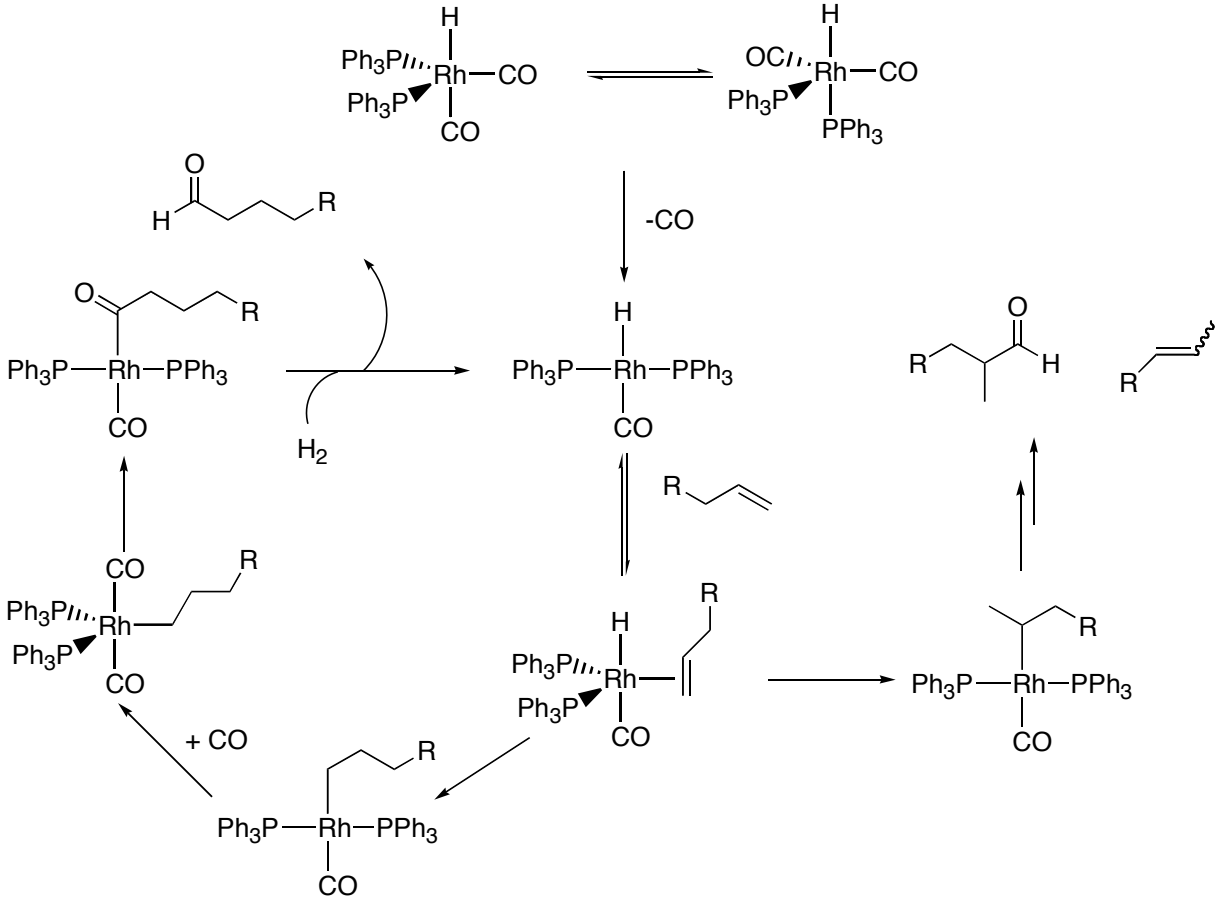
Simple rhodium carbonyls are inactive for the hydroformylation reaction due to the formation of stable, catalytically inactive Rh-carbonyl clusters occurs. $HRh(CO)_4$ can be formed under high H_2 and CO pressures to give a very active catalyst, but it also isomerizes alkenes and gives low linear:branched ratios.

Addition of phosphines to these rhodium systems dramatically improves both the chemo- and regioselectivity, while maintaining high reaction rates of the initial Rh-carbonyls. This system has been commercialized by Union Carbide.



The Rh-system is sufficiently more reactive than the Co-systems to offset the dramatic price difference ($Rh:$Co = ca. 300:1).

The generally accepted mechanism for the Rh systems is similar to that for the Co catalysts. It was first proposed by Sir Geoffrey Wilkinson in 1968. (*J. Chem. Soc. (A)* **1968**, 3133-3142)

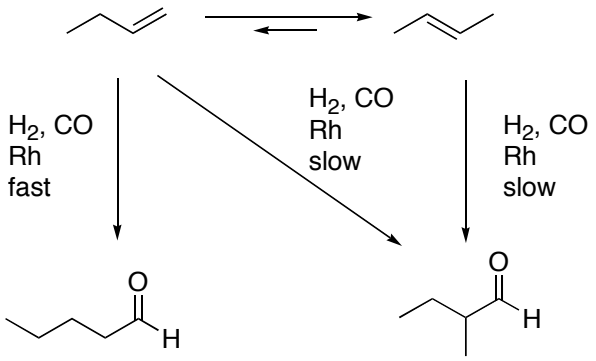


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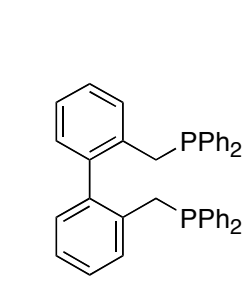
The key Rh complex is a 5-coordinate 18 electron species. Due to the high trans-effect ligands (CO, H), the large phosphines occupy cis coordination sites. Both phosphines can be equatorial, or one can occupy an axial position.

Dissociative substitution of alkene for CO proceeds through a 4-coordinate, square planar intermediate. These catalyst have very high linear:branched ratios. Alkene migratory insertion largely determines the regioisomeric ratio, because the square planar Rh-alkyl is rapidly trapped by CO in an irreversible reaction under the reaction conditions. For a primary Rh-alkyl this is followed by CO migratory insertion and then hydrogen cleavage. Secondary Rh-alkyls undergo CO insertion slowly, so alkene isomerization products are also observed.

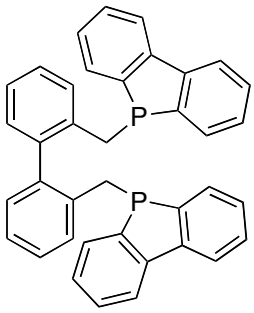
The strong kinetic preference for CO insertion to occur for primary Rh-alkyls can be very useful. Industrially, alkenes can be prepared most economically as a thermodynamic mixture of alkene isomers. These rhodium catalysts will hydroformylate both terminal and internal alkenes to predominately linear aldehydes.



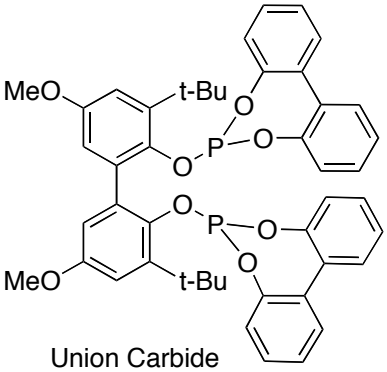
Improved linear to branched ratios are obtained using chelating phosphines with large bite angles. Texas-Eastman has commercialized hydroformylation processes using ligands such as BISBI that give linear:branched ratios of 96:4 under mild conditions and low L:Rh ratios. (U.S. patents 4,694,109 (1987) and 4,879,416 (1989)) BISBI ($ß_N$ = 113˚) gives a much more regioselective catalyst than dppe ($ß_N$ = 86 ˚). Substituting the diphenylphosphino group for a dibenzophosphole increases the regioselectivity to 99.4:0.6, although catalyst stability is a problem (U.S. Patent 5,332,846 (1994). Union carbide has developed bis(phosphite) ligands that also show very high linear:branched ratios (96:4) even when starting with 2-butene.



BISBI
Eastman Kodak



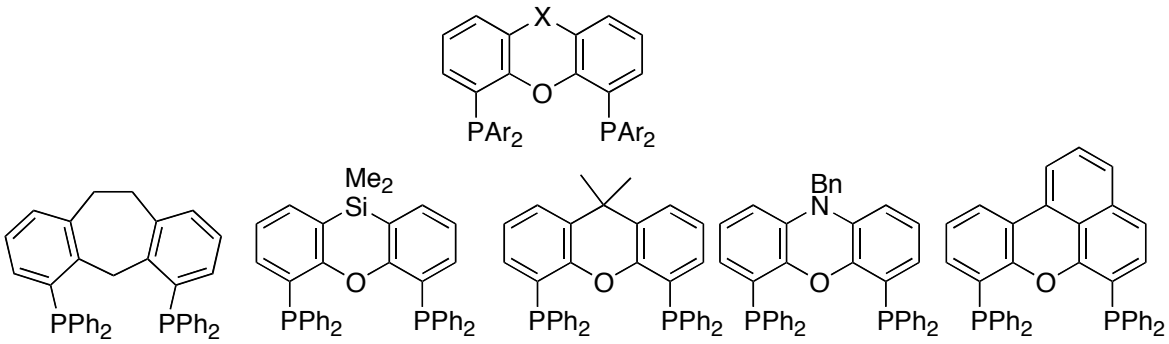
Eastman Kodak



Union Carbide

To what degree does the bite angle affect the linear:branched ratio as well as the catalytic activity in these systems? Piet van Leeuwen has developed a class of ligands that provide highly active

hydroformylation catalysts. They can also be easily modified to adjust either the bite angle or the electron donating ability of the ligand. (*Organometallics*, **2000**, *19*, 872-883)



1 102.0˚ **2** 108.5˚ **3** 111.4˚ **4** 114.1˚ **5** 120.6˚

Hydroformylation of 1-octene at 80 ˚C

Ligand	l:b ratio	% linear aldehyde	TOF (mol/mol Rh•h)
1	8.5	88.2	36.9
2	24.2	94.4	76.5
3	52.2	94.5	187
4	50.6	94.3	154
5	50.2	96.5	343

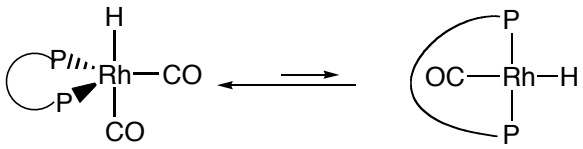
Increasing bite angle improves the linear:branched ratio and has an even more significant improvement on the TOF of the catalyst. How does the bite angle affect both regioselectivity and TOF?

It has been hypothesized that bite angle might affect the equilibrium between the diequatorial (ee) and equatorial-axial (ea) $L_2Rh(CO)_2H$ complexes, but van Leeuwen sees no correlation between bite angle and the ee:ea ratio. There also does not seem to be any relationship between bite angle and the rate of CO dissociation from $L_2Rh(CO)_2H$.

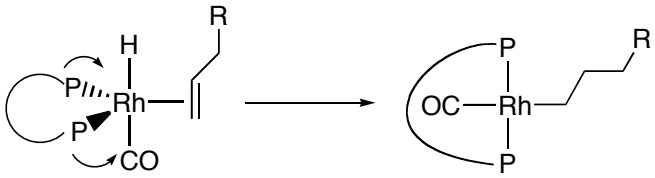
The increase in the linear to branched ratio is likely a steric effect. As the bite angle increases, the chelating phosphine should crowd the neighboring ligands. This would result in an increased preference for alkene insertion to give a less sterically demanding primary Rh-alkyl.

The effect of bite angle on the TOF is less clear. Numerous steps in the cycle could be affected by changes in the bite angle. Based on their data, van Leeuwen offers two possible explanations.

1) Increased stability of the square-planar $L_2Rh(CO)H$ intermediate with increasing bite angle. Due to steric strain, the trans square-planar complex should be more stable than the cis-isomer. Therefore, ligands with large bite angles may be able to better accommodate the more stable trans-chelate. Stabilization of the square-planar intermediate will increase it's equilibrium concentration. Since the reaction rate (TOF) is directly related to the concentration of this species, increasing it's equilibrium concentration should result in higher TOF values.

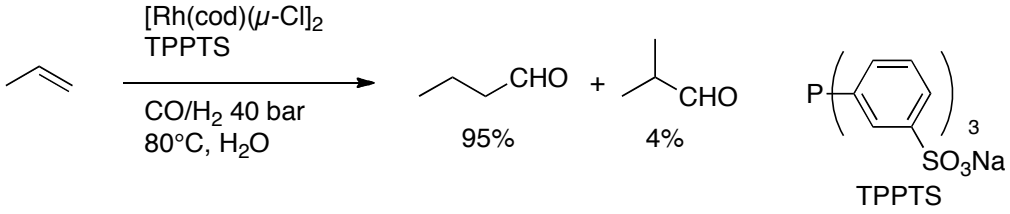


2) Increasing the bite angle is expected to accelerate migratory insertion of the alkene, as well as the subsequent insertion of CO. As the bite angle gets larger, the chelating ligand becomes more sterically demanding. Migratory insertion lowers the coordination number at the metal, so it reduces the steric strain.

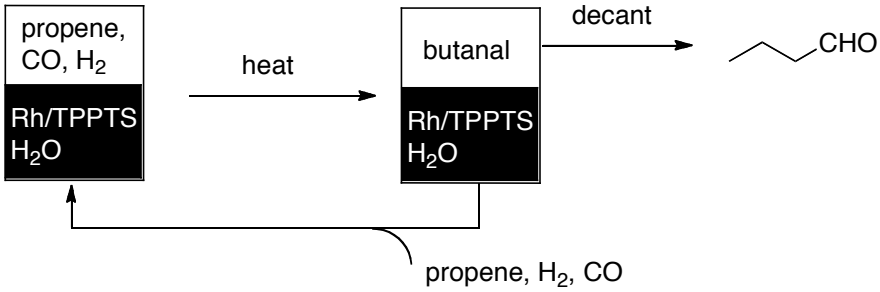


Aqueous-Phase Hydroformylation

Because of the very high price of Rh, a way to efficiently recycle the catalyst was desired. In the 1970s, Rhône-Poulenc commercialized an aqueous-phase process based on a catalyst derived from Rh/TPPTS (TPPTS = triphenylphosphine trisulfonate).



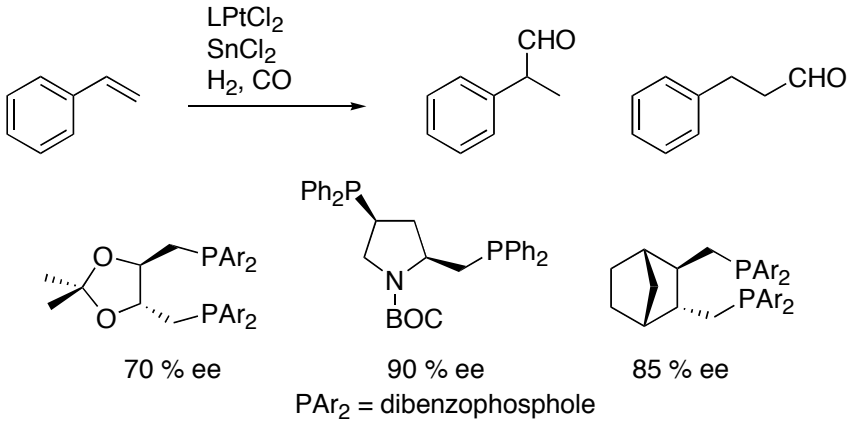
Propene has low solubility in water, but is sufficiently soluble to give good rates of conversion. The butanal product has low solubility in water and forms an immiscible phase. The butanal can be decanted off and the aqueous Rh solution reused. Industrial systems can be used for months before requiring a new charge of catalyst. Because of the low solubility of higher alkenes (i.e., 1-octene) in water, this system gives very low conversion. The use of surfactants or ligands that are surface active can improve the reactivity of these higher olefins. (*Chem. Rev*, **2009**, *109*, 643).



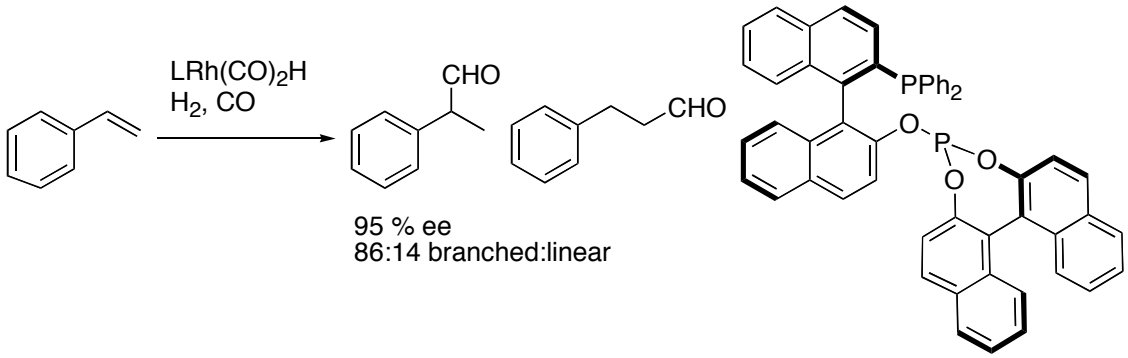
Asymmetric Hydroformylation

Asymmetric hydroformylation requires that the catalyst exhibit both high regioselectivity and enantioselectivity. Moreover, the necessary regioselectivity is opposite to that typically desired. As such, generally, the systems are only useful in hydroformylation of styrene derivatives.

Initial work focused on Pt based catalysts modified with $SnCl_2$ in the presence of chiral diphosphines. Although these systems offer high enantioselectivity, they suffer from poor regio- and chemoselectivity.



Rh-based systems have been reported with high enantioselectivity and improved regioselectivity. (*J. Am. Chem. Soc.* **1993**, *115*, 7033; *Chem. Comm*, **1994**, 395; *Tetr. Lett.* **1994**, *35*, 2023) Similar ligands have been developed by Union Carbide (WO 93/03839 (1993)).



13-Insertion Polymerization and Oligomerization of Alkenes, Part 1: Early Transition Metals

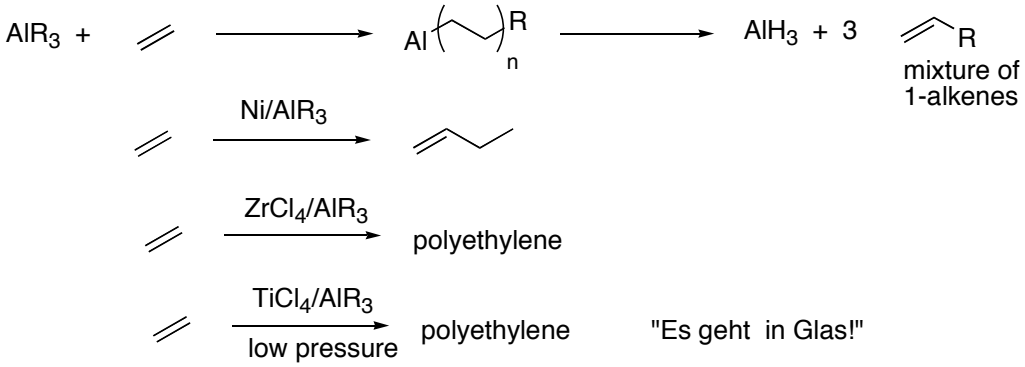
Metal-catalyzed (insertion) polymerization of alkenes has become a massive business, supplying plastics for a wide variety of uses. Global polyolefin production (polyethylene and polypropylene) was 113 million tons in 2009

Material	Production in 2009 (millions of tons)	Applications
Polyethylene		
Low Density (LDPE): Radical polymerization, highly branched	18.1	Flexible, resilient material: plastic bags, bottles, tubing, lab equipment
Linear Low Density (LLDPE) : Ziegler Natta catalysts	19.2	Very flexible, stretchable: plastic wrap (saran), plastic bags/sheets
High Density (HDPE) : Ziegler Natta catalysts, often ethylene/1-alkene copolymer	30.5	Strong, rigid material: fuel tanks, folding tables/chairs, water pipes, plastic lumber, hard hats
Polypropylene: Ziegler Natta catalysts	45.2	Tough, flexible, colorfast: engineering plastic, Rubbermaid containers, carpets/rugs

Heterogeneous Olefin Polymerization Catalysts: The Ziegler-Natta systems.

History of insertion polymerization: Frank McMillan, "*The Chain Straighteners: The Discovery of Linear and Stereoregular Polymers,* MacMillan Press, London, 1967.

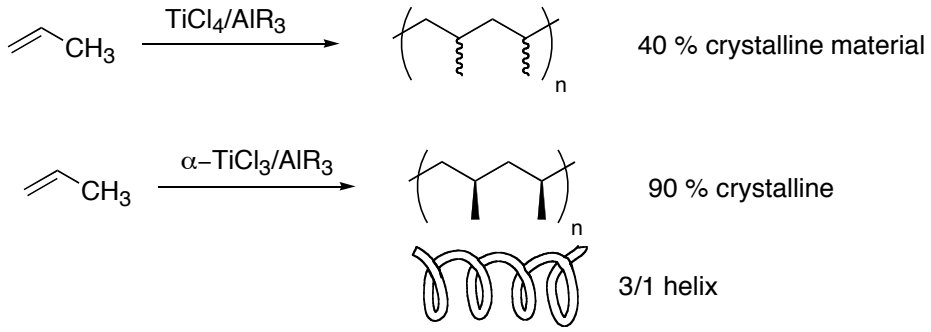
K. Ziegler (*Angew. Chem.*, **1952**, *64*, 233): Ziegler was originally studying the Aufbau reaction, which uses trialkyl aluminum compounds to make oligomers from ethylene. Ziegler found that adding transition metals salts resulted in significant changes in the reactivity.



This was a heterogeneous process. Insoluble metal salts and trialkylaluminum species were mixed in a hydrocarbon solvent under ethylene pressure.

G. Natta (*J. Am. Chem. Soc.*, **1955**, *77*, 1708): Soon after, Natta showed that the Ziegler catalyst would polymerize propylene to give polypropylene.

Kevin Shaughnessy
The University of Alabama, 2019

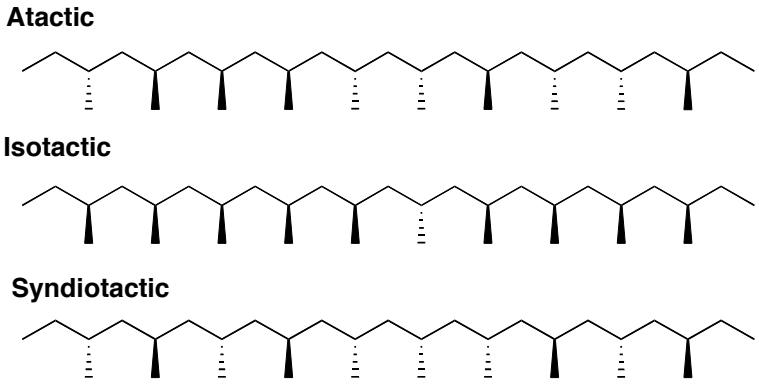


X-ray and IR studies showed that the crystalline material had the same configuration at each chiral center. The polymer was isotactic, (*vide infra*) and existed as a 3/1 helix in the solid-state.

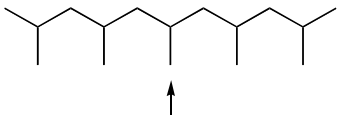
Ziegler and Natta shared the 1963 Nobel Prize in chemistry for their contributions.

Aside: Polymer Stereochemistry

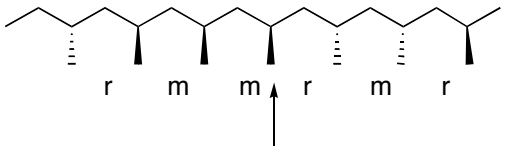
Polymers, such as polypropylene, are often classified by the relative stereochemistry of the side-chains along the polymer backbone. The major classes of stereochemistry are: atactic, isotactic, and syndiotactic



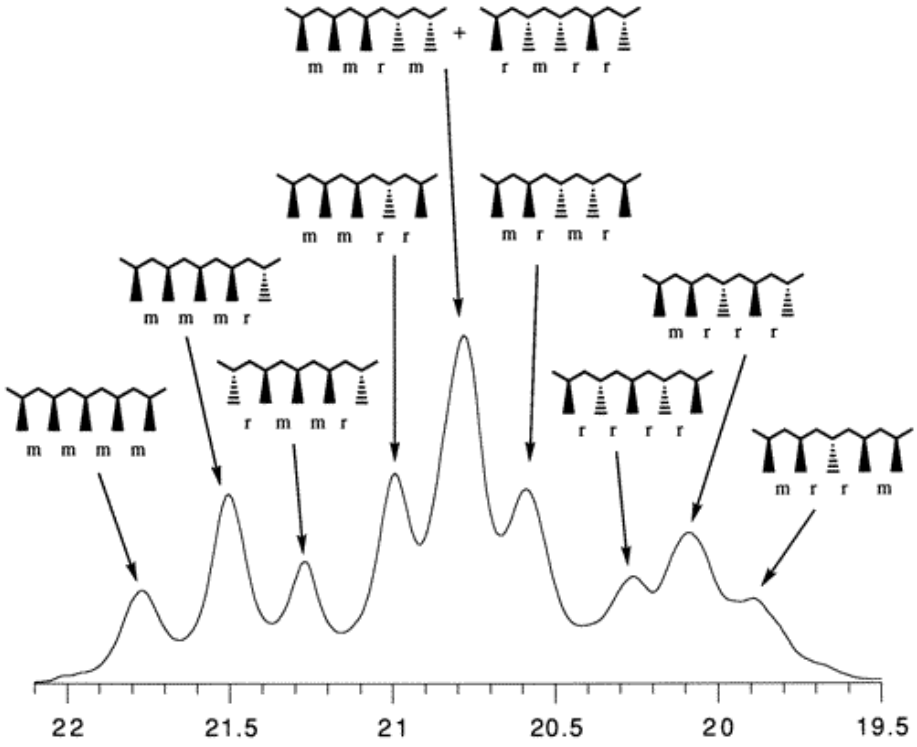
The microstructure of polypropylene is most conveniently analyzed using ^{13}C NMR.



^{13}C NMR shift is sensitive to the two stereocenters on either side on spectrometers > 300 MHz. This is called pentad resolution.



mmrm pentad



Heterogeneous Ziegler-Natta systems are still widely used in industry, but from the beginning there was interest in developing *homogenous*, single-site catalysts for olefin polymerization. These were desired both as model compounds for mechanistic studies and to provide more consistent and tunable catalysts. We will discuss this in detail later.

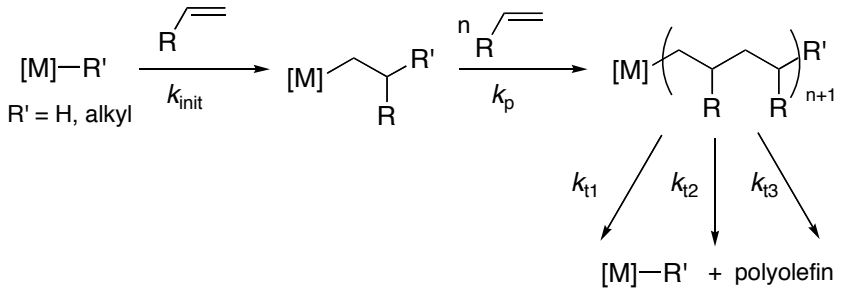
The major problems with heterogeneous systems are:

- There are a variety of different catalytic sites with different activity producing polymers with different molecular weights and tacticities. The polymers produced are always blends.

- Heterogeneous systems are difficult to tune, because there is not much that can be varied and they are generally poorly understood. Although fairly selective systems have been developed, the work is largely empirical.

The major advantage is that they are heterogeneous and can be used under industrially desirable conditions either in the gas phase or as suspensions.

Mechanism of Alkene Polymerization:

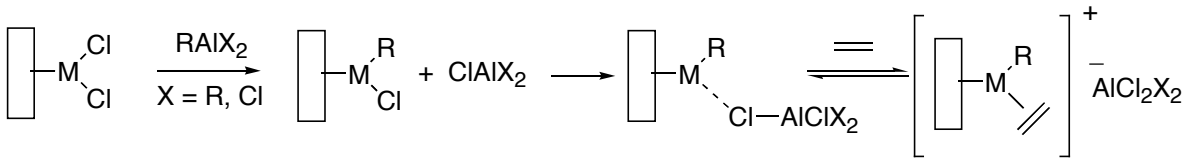


Molecular weight is determined by the ratio of the rate of propagation vs. the rate of chain transfer.

$$M_w = \frac{k_p}{\sum k_{tn}}$$

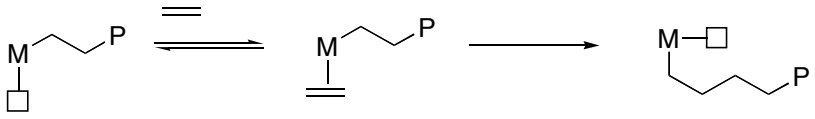
Initiation:

The active species is believed to be a coordinatively unsaturated metal alkyl formed by reaction of the metal halide salt with the alkyl aluminum species.



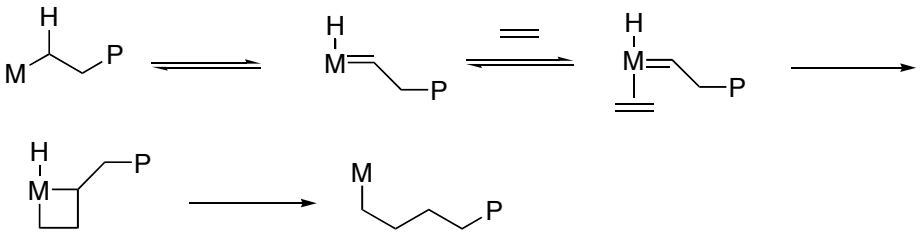
Propagation:

The exact nature of the propagation step was controversial for some time. Cossee proposed a mechanism involving simple migratory insertion of an alkene into a metal alkyl (*Tetrahedron Lett.*, **1960**, *1*(38) 12-16).



□ = open coordination site

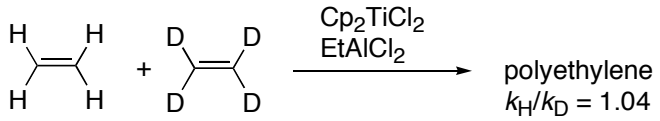
Green, and Rooney proposed an alternative mechanism based on an α-elimination to give a carbene. Since there were few examples of isolated alkene alkyl complexes that undergo migratory insertion, they felt that an alternative mechanism was necessary. Formation of a metalacycle followed by reductive elimination gives a new metal-alkyl. (*J. Chem. Soc., Chem. Comm.*, **1978**, 604)



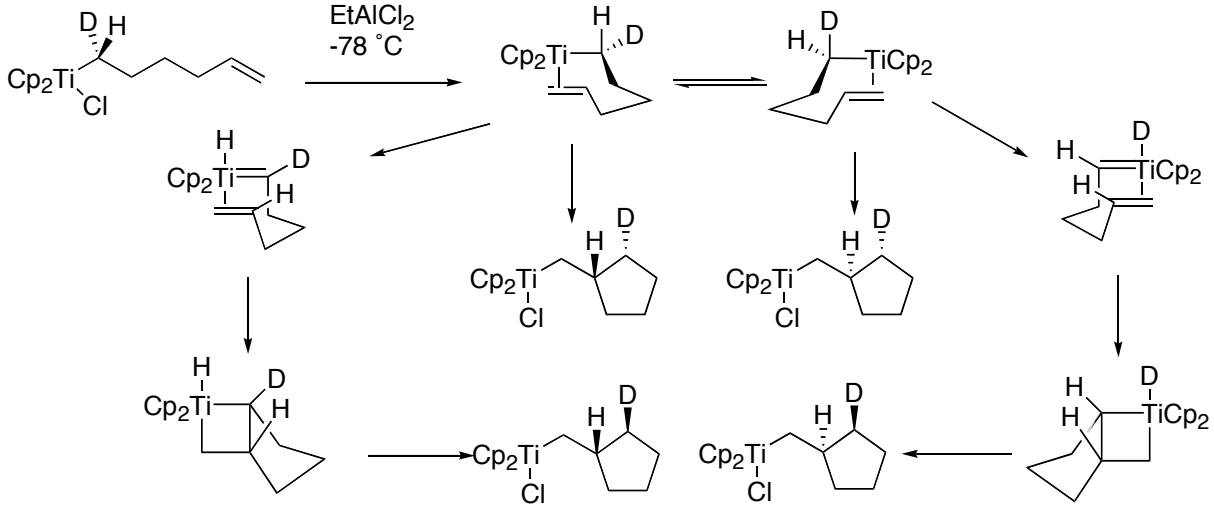
The major difference between the two mechanisms, should be in the kinetic isotope effect. The Green Rooney mechanism would require a large kinetic isotope effect (ca. 3).

Grubbs carried out two sets of experiments to probe the isotope effect in models for the Z-N systems.

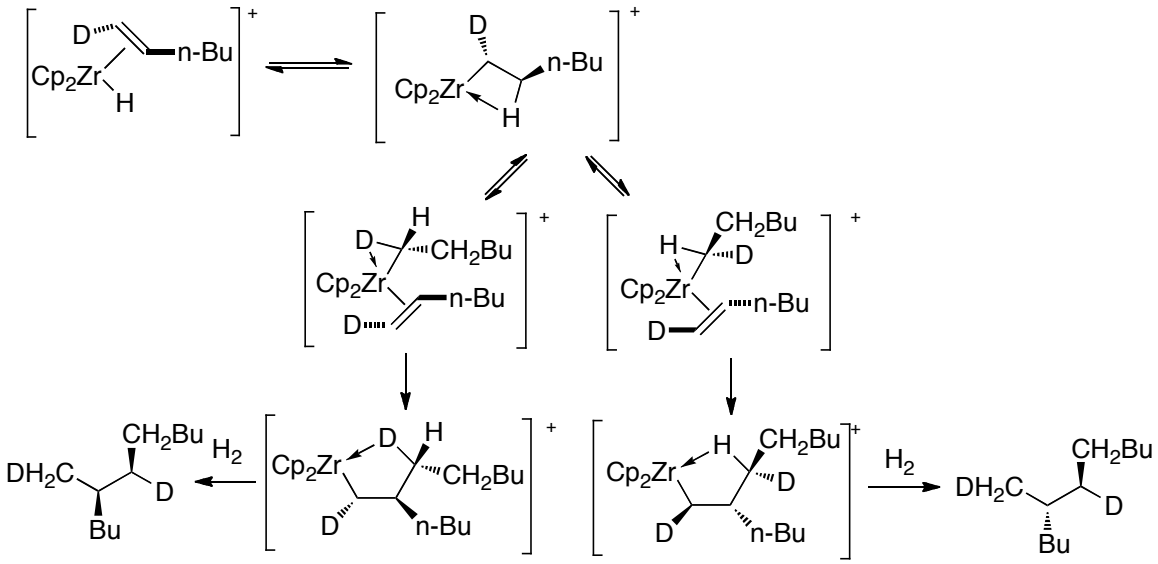
Grubbs first carried out the polymerization of a mixture of ethylene and ethylene-d_4. (*J. Am. Chem. Soc.*, **1982**, *104*, 4479) No isotope effect was observed, however this result did not definitively rule out an α-elimination mechanism.



Since this experiment was inconclusive, Grubbs designed a stereochemical probe to determine if an α-H/D agostic interaction affected the insertion process. The Cossee mechanism should give a nearly 1:1 mixture of diastereomers, since there is no primary isotope effect in this mechanism. The Rooney-Green mechanism would be expected to give a unequal product distribution. A 50:50 diastereomeric ratio of products was produced in the reaction. (*J. Am. Chem. Soc.*, **1985**, *107*, 3377)

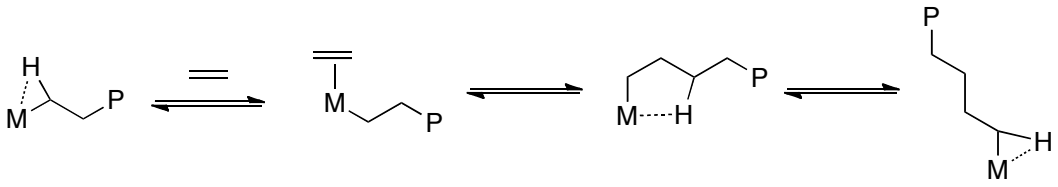


Other systems have shown that there is a KIE (*Angew. Chem. Int. Ed.* **1990**, *29*, 1412).



1:1.30

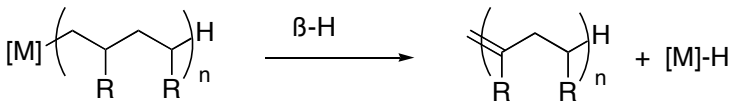
These observations have led to the modified Green-Rooney mechanism that involves an α-agostic interactions rather than α-elimination (*Organomet.* **1992**, *11*, 4036; *Angew. Chem. Int. Ed.* **1990**, *29*, 279). Grubbs and Coates suggest that high activity catalysts do not need the α-agostic assistance, while less reactive complexes do and show a isotope effect (*Acc. Chem. Res.* **1996**, *29*, 85).



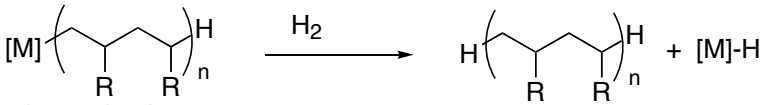
Chain Transfer:

A variety of chain transfer mechanisms have been identified by modeling studies.

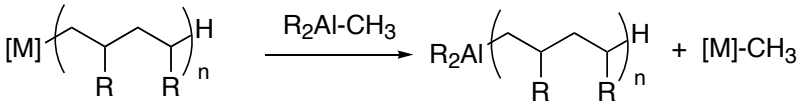
ß-H elimination



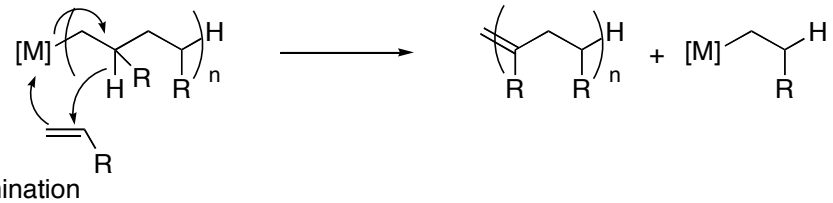
Hydrogenation



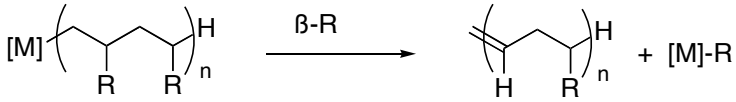
Chain transfer to aluminum



Chain transfer to monomer

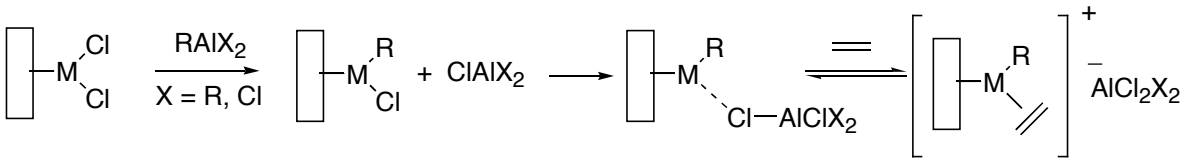


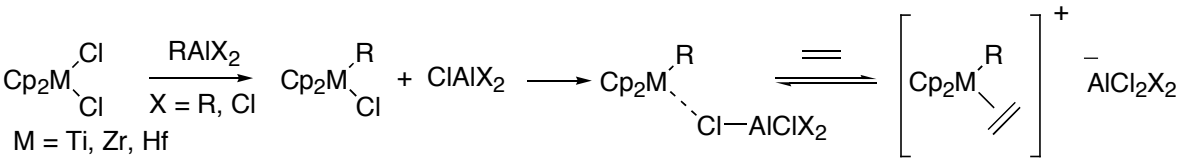
ß-R elimination



Homogeneous Ziegler-Natta-type polymerization catalysts

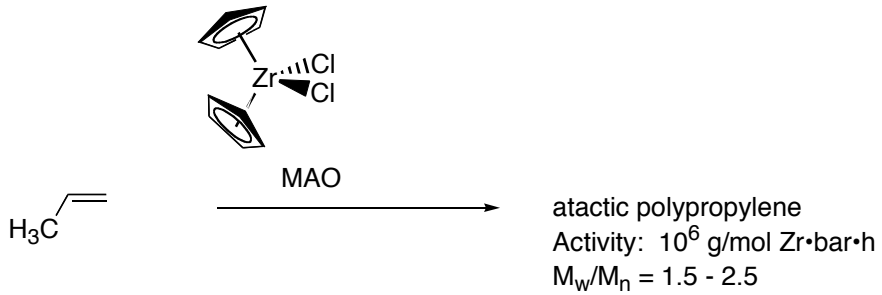
The first homogeneous systems were based on metallocene dichlorides, and were designed to mimic the activation process believed to occur in the heterogeneous systems.



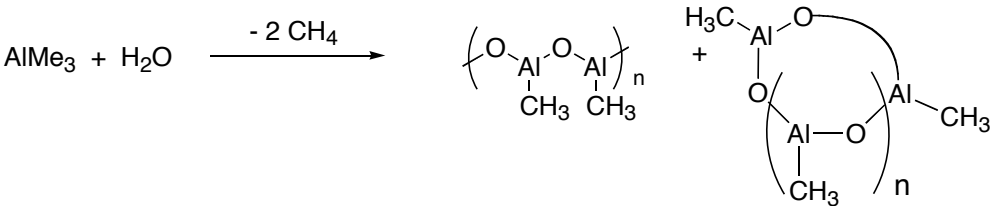


M = Ti, Zr, Hf

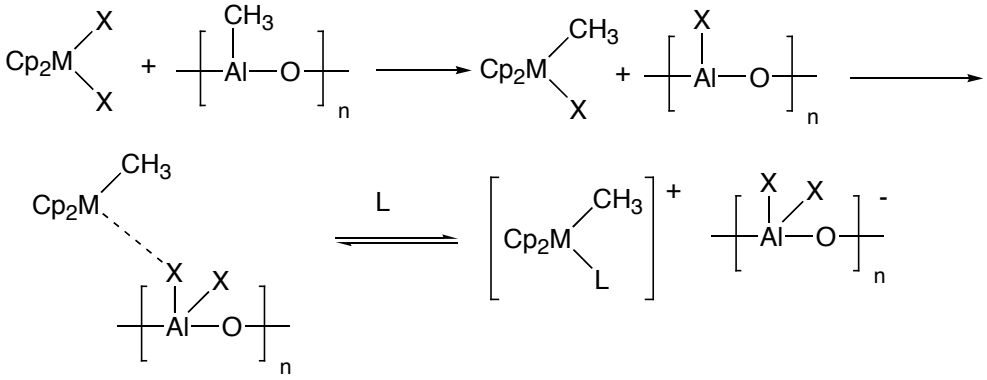
These systems would polymerize ethylene, but slowly. Propylene and other higher alkenes could not be polymerized. The major advance was the introduction of the activator methylaluminoxane (MAO) by Kaminsky (*Macromol. Chem. Rapid. Comm.*, **1983**, *4*, 417)



MAO was the magic ingredient that provided much more active catalysts than were obtained with typical alkylaluminum Lewis acids. MAO is a poorly defined mixture of linear and cyclic oligomers produced by the controlled hydrolysis of trimethylaluminum.



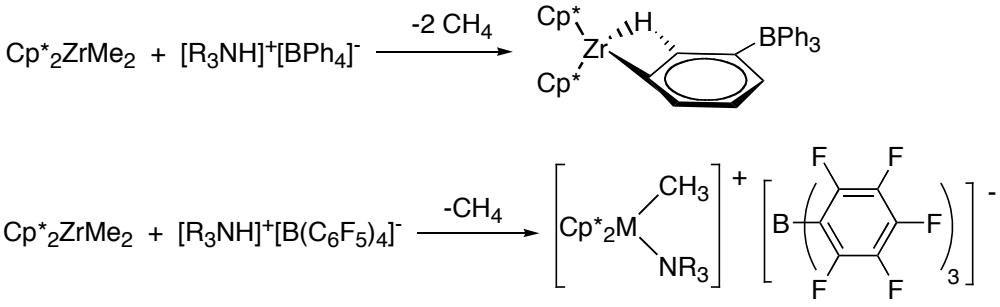
MAO acts as both an alkylating agent and a Lewis acid to form the catalytically active, 14 electron zirconocene-methyl cation.



MAO is typically used in large excess (1000 – 10000:1 Al:Zr) to ensure activation of the catalyst and destruction of catalyst poisons (water, oxygen, etc). Although widely used, it's complex nature and the need to use a large excess led to the development of monomeric reagents that could produce the necessary cationic complexes.

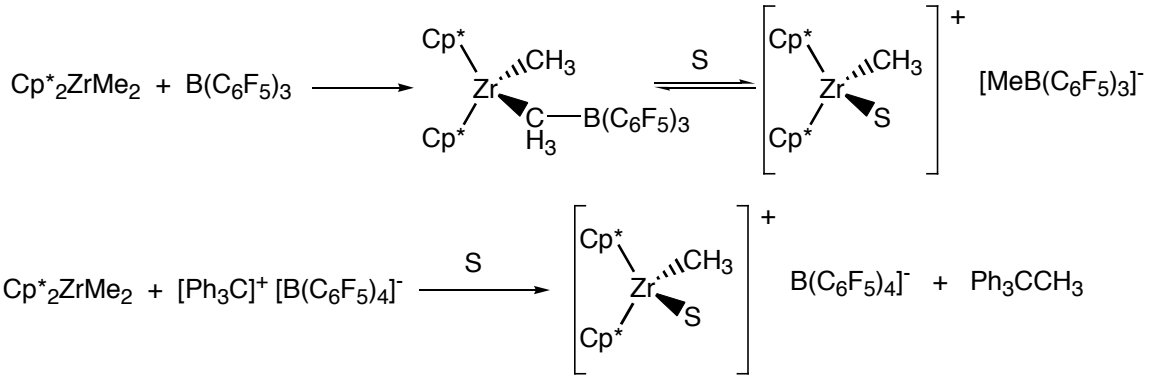
The cationic metallocene-alkyls are extremely strong Lewis acids. Very weakly coordinating anions must be used to ensure that they exist as separated ion pairs. Common "non-coordinating anions" such as BF_4^-, PF_6^-, or SbF_6^- form fluoride bridged adducts and/or lose F^-. The best systems are based on fluorinated triarylboranes or tetraarylborates. (Review: Marks, *Chem. Rev.*, **2000**, *100*, 1391-1434)

Protonation: Turner and Hlatky, US Patent 4,752,597 (1988); Turner, *J. Am. Chem. Soc*, **1989**, *111*, 2728; Bochmann, *Angew. Chem. Int. Ed.*, **1990**, 780; Bochmann, *J. Organmet. Chem.*, **1992**, C5

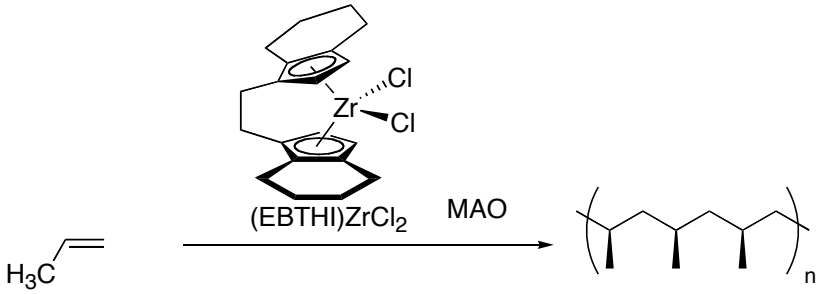


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The University of Alabama, 2019

Alkyl Abstraction: Marks, *J. Am. Chem. Soc.*, **1991**, *113*, 3623; Ewen, Eur. Pat. 0427697 (1991); Chien, *J. Am. Chem. Soc.*, **1991**, *113*, 8570.

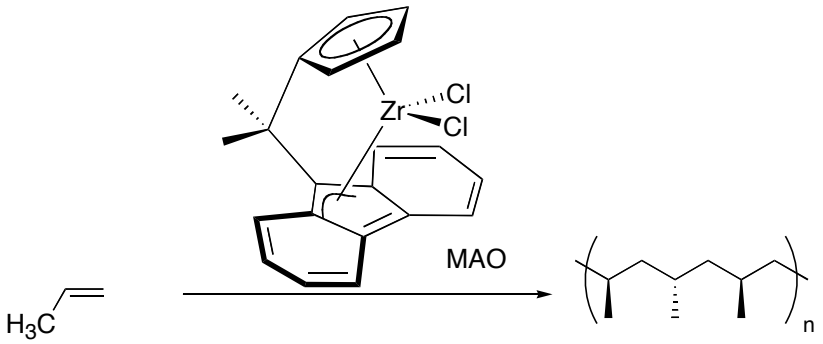


With the development of active homogenous catalysts that could polymerize 1-alkenes (i.e., propylene), efforts were made to rationally design catalysts that would give specific tacticities. (Reviews: *Chem. Rev.* **2000**, *100*, 1223; *ibid*, 1253)



Isotactic polypropylene
> 95% isosteric sequences

Ewen, *J. Am. Chem. Soc.*, **1984**, *106*, 6355; Kaminsky and Brintzinger, *Angew. Chem. Int. Ed. Engl.*, **1985**, *24*, 507.



Syndiotactic polypropylene
> 95%heterosteric sequences

Ewen, *J. Am. Chem. Soc.*, **1988**, *110*, 6255

<u>Origin of Stereocontrol:</u>

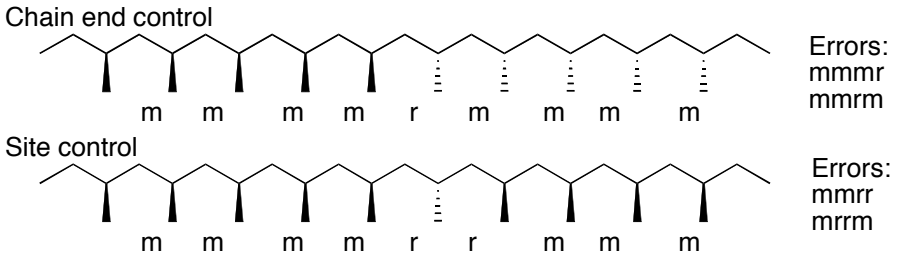
Mechanisms for stereocontrol in polymerization reactions:

1) Chain-End control: The last monomer inserted (or sometimes the penultimate one) controls the stereochemistry of the next insertion
2) Enantiomorphic Site Control: Topology of the catalyst determines the stereochemistry

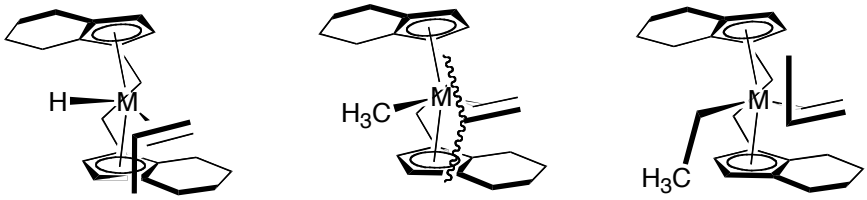
Purely isotactic polypropylene would give only the mmmm pentad, but there are always errors. The types of errors can determine what the mechanism of stereocontrol is.

Kevin Shaughnessy
The University of Alabama, 2019

These two mechanisms can be differentiated by analyzing the *microstructure* of the polymer.

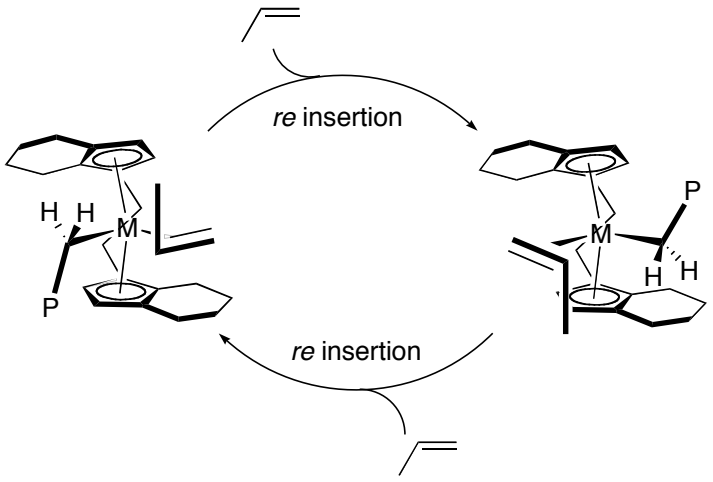


Metallocenes typically operate under enantiomorphic site control. This raises the question of how the chiral ligand set controls enantioselectivity. Unfortunately, polypropylene is not optically active, so model studies must be carried out. Zambelli (*Macromolecules*, **1987**, *20*, 1015-1018) and Pino (*J. Am. Chem. Soc.*, **1990**, *112*, 4911-4914) looked at the insertion of alkenes into chiral, resolved Zr-alkyl and Zr-H species.

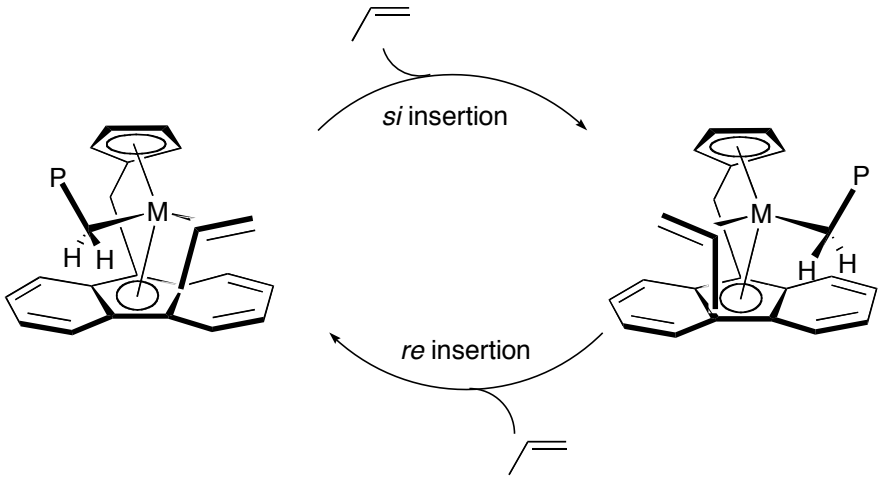


Predominant *si* insertion | ***re* and *si* insertion** | **Predominant *re* insertion**

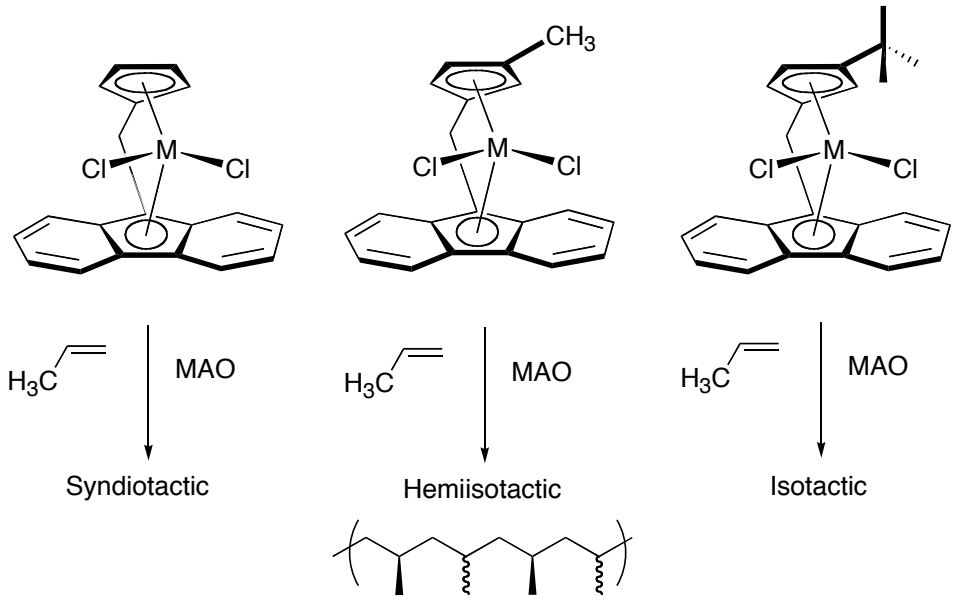
Thus, the chiral ligand appears to control the conformation of the alkyl chain. The incoming alkene orients itself opposite the alkyl chain. Since the catalyst has C_2-symmetry, insertion from either side should give the same *re* insertion (i.e., the coordination sites are homotopic).



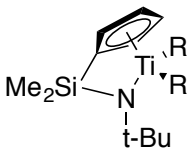
The syndiotactic selectivity of Ewen's C_s-symmetry catalyst can be explained in the same way. Since this complex has a mirror plane of symmetry, the two coordination sites are enantiotopic.



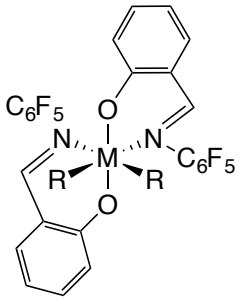
C_1-symmetry can give a range of tacticities depending on the exact structure.



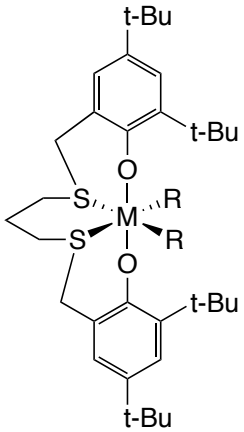
Recent research has looked to move beyond metallocenes to other ligand architectures that are easier to make and modify and that offer unique activity or selectivity. (review of phenoxy-imine and related catalysts). *Chem. Rev.* **2011**, *111*, 2363)



Constrained Geometry
Dow



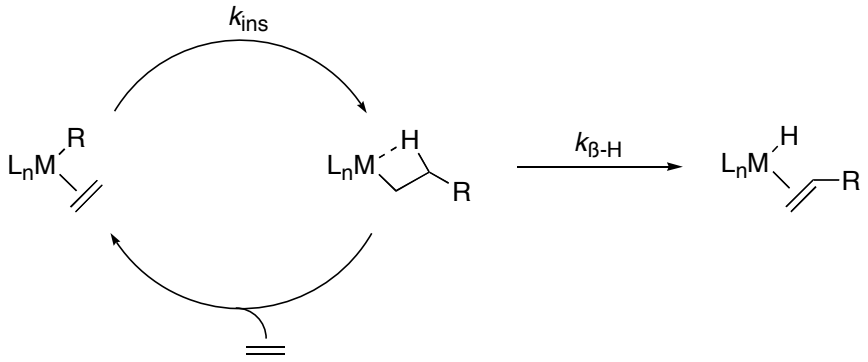
M = Ti, Zr, Hf
Phenoxy-Imine catalysts
Coates, Fujita



Symyx

13-Insertion Polymerization and Oligomerization of Alkenes, Part 2: Late Transition Metals

It had long been thought that late transition metals could not polymerize simple alkenes, such as ethylene.

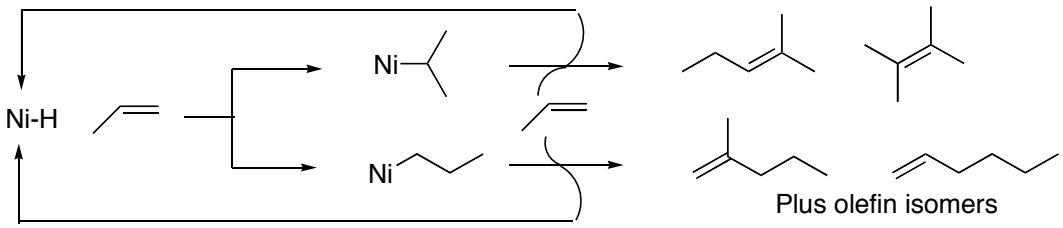


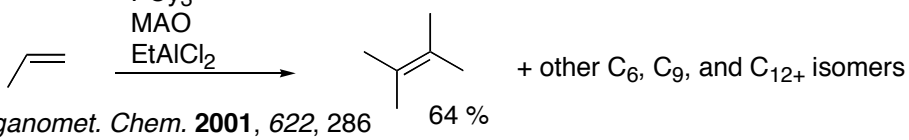
Most late transition metal complexes undergo migratory insertion (k_{ins}) slowly and ß-H elimination rapidly ($k_{ß\text{-}H}$). In contrast highly electrophilic early transition metals have fast insertion rates and relatively slow ß-H elimination rates. The ratio of the rates largely determines whether dimers, oligomers, or polymers are produced.

- $K_{ins} << k_{ß\text{-}H}$: Dimerization
- $K_{ins} \approx k_{ß\text{-}H}$: Oligomerization
- $K_{ins} >> k_{ß\text{-}H}$: Polymerization

Dimerization

Many late transition metal complexes, particularly d^8 metals, will dimerize ethylene or 1-alkenes. Ethylene dimerization is not industrially useful, but dimerization of higher alkenes can be. Dimerization of propylene can give a multitude of products. 2,3-Dimethyl-2-butene is useful as an anti-knock additive to gasoline.





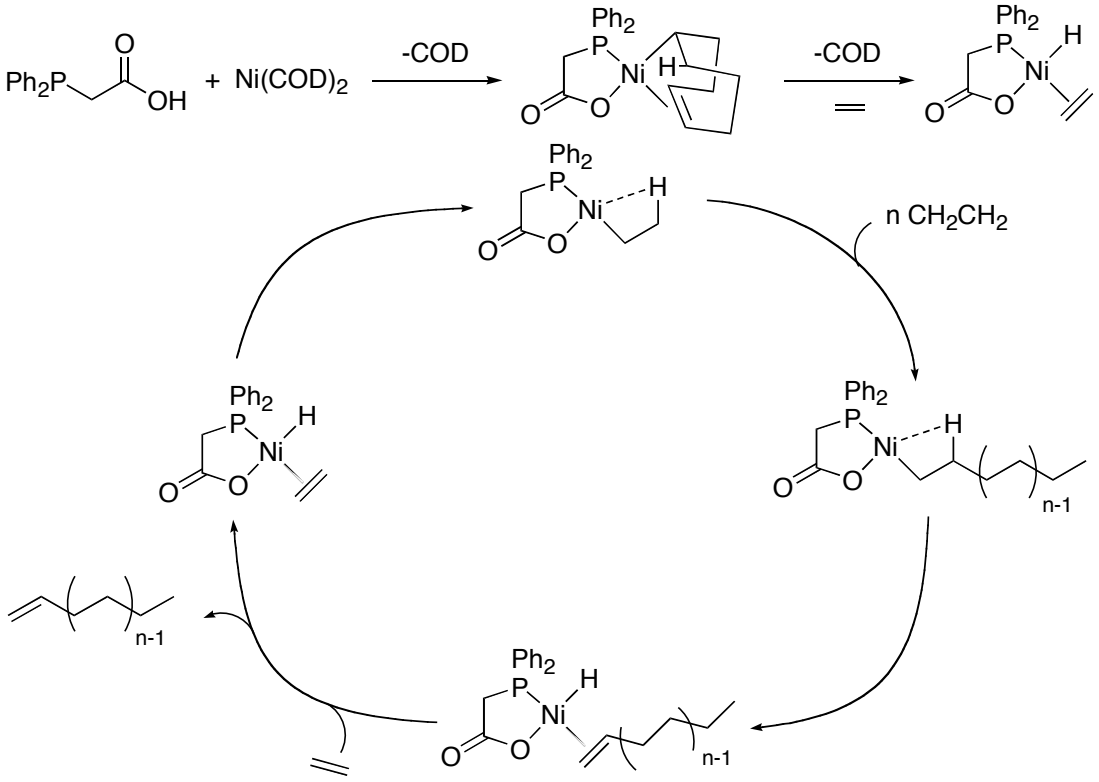
J. Organomet. Chem. **2001**, *622*, 286

Oligomerization of Ethylene:

A variety of Nickel catalysts can be used to oligomerize ethylene into mixtures of higher alkenes. This chemistry is part of the Shell Higher Olefin Process (SHOP), which converts ethylene to alkenes, which can be sold or converted to long chain aldehydes or alcohols by hydroformylation.

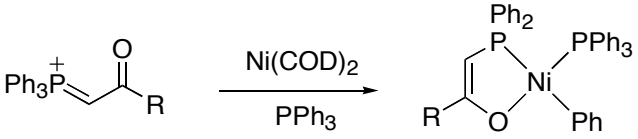
Kevin Shaughnessy
The University of Alabama, 2019

The Ni complex used in the SHOP process is a P-O anionic chelate that can be prepared *in situ* from the ligand and $(COD)_2Ni$.

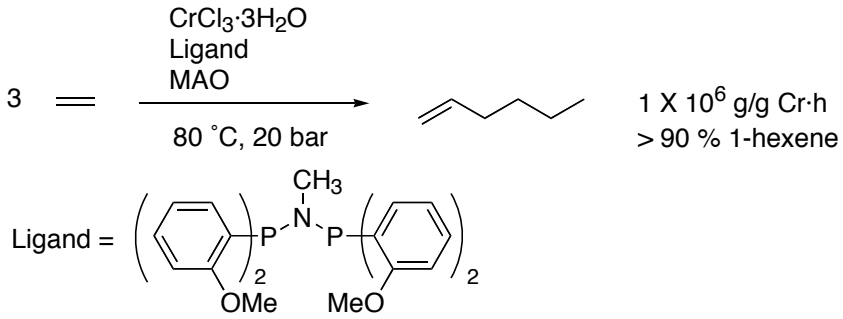


This catalyst is very selective for the production of linear 1-alkenes (> 98 %). A Schulz-Flory distribution of alkene oligomers is produced.

A related class of Ni complexes are formed starting from a phosphorous ylide. These catalyst typically give higher molecular weight products, and in some cases can give polyethylene.

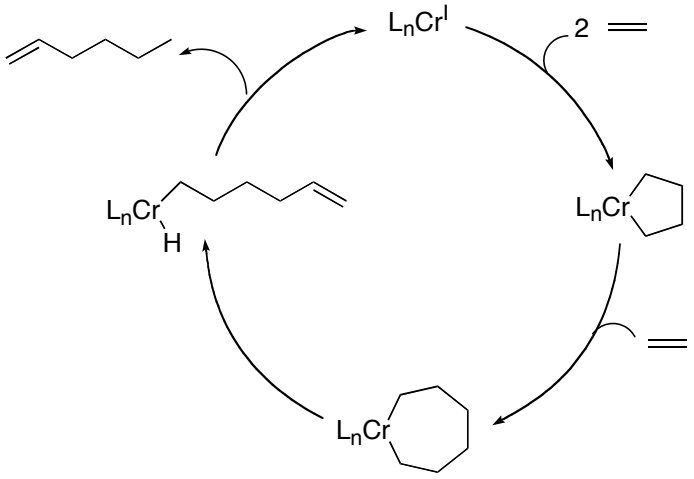


Chromium-based catalysts are able to produce 1-hexene with very high selectivity, rather than the statistical distribution seen with the nickel-based systems (i.e. *Chem. Commun.* **2002**, 858).



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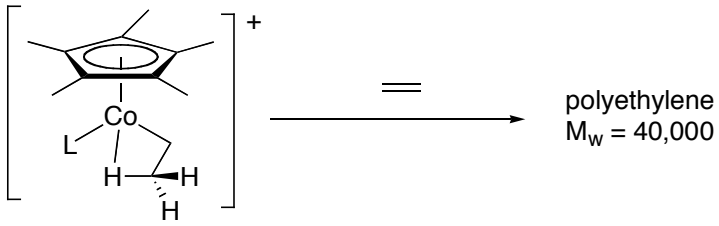
The mechanism of this oligomerization is different from the nickel case, in that it proceeds through a Cr(III) metallacycle (Bercaw, *JACS*, 2004, *126*, 1305). This mechanism is the key to the selectivity. The metallacyclopentane cannot easily undergo β-hydride elimination to give 1-butene. In contrast, the chromocycloheptane undergoes β-hydride elimination faster than insertion of another ethylene.



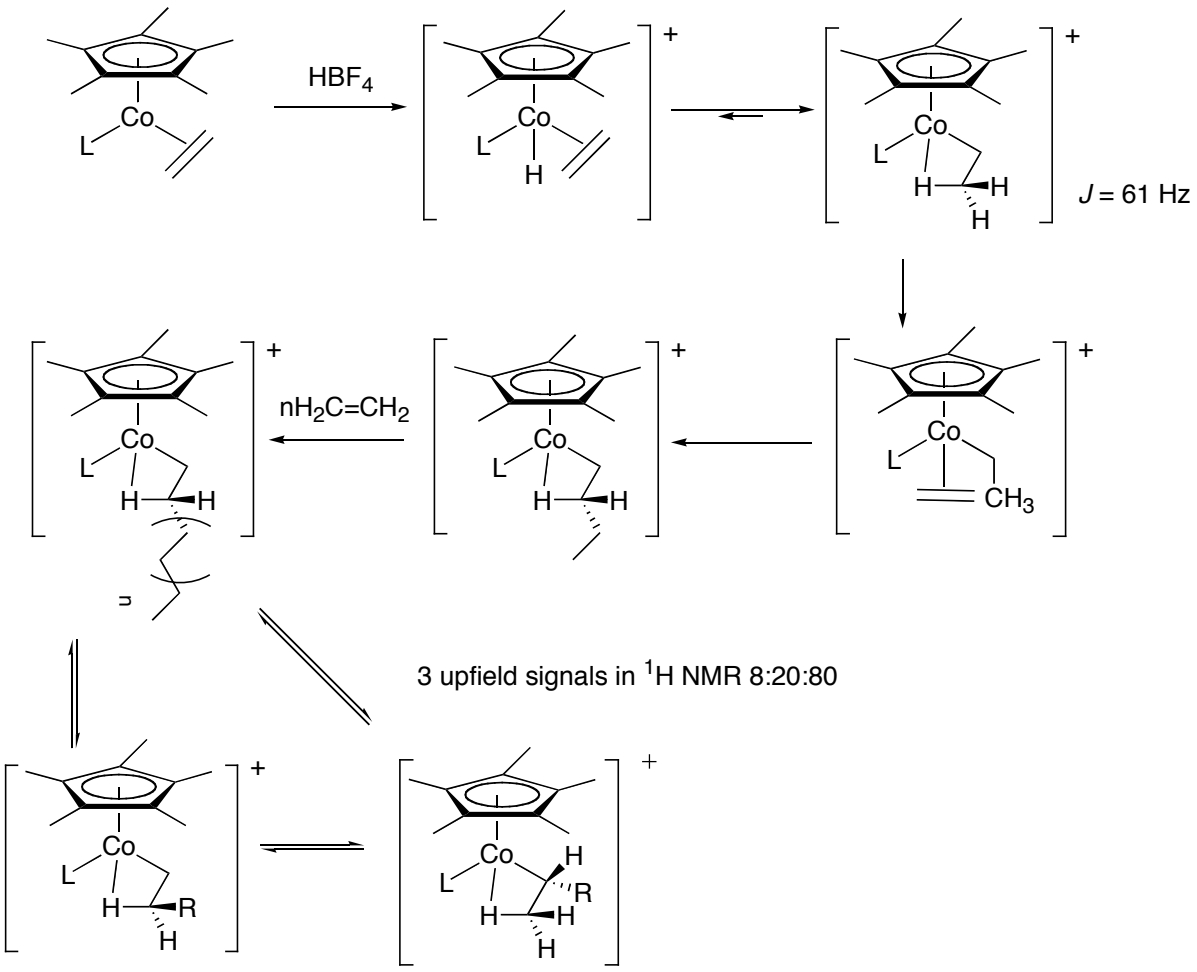
A group at Sasol has shown that by changing the ligand to $(Ph_2P)_2N$*i*-Pr that the catalyst can be made to selectively make 1-octene (> 70% selectivity).

Ethylene Polymerization

Because of the slow rates of alkyl migration for most late-transition metal complexes, it was long thought that high molecular weight polymer could not be produced. Maurice Brookhart (UNC) has shown that this is not the case as long as electrophilic late transition metal complexes are used as the catalysts. Review: *Chem. Rev.*, **2000**, *100*, 1199-1203



At low temperature (-70 ˚C) the polymerization reaction can be observed by ^{1}H NMR (*J. Am. Chem. Soc.*, **1985**, *107*, 1443-1444). The ethylene alkyl species cannot be observed, but the growing polymer chain is observed as an equilibrating mixture of ß-agostic species.

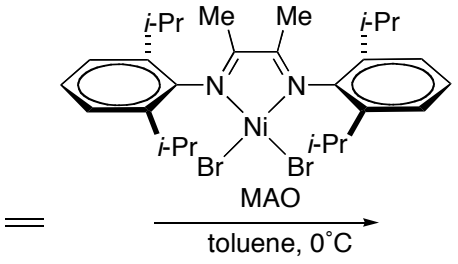


Although this system is much slower than Ziegler-Natta-type catalysts, it showed that under certain circumstances late transition metals could polymerize alkenes.

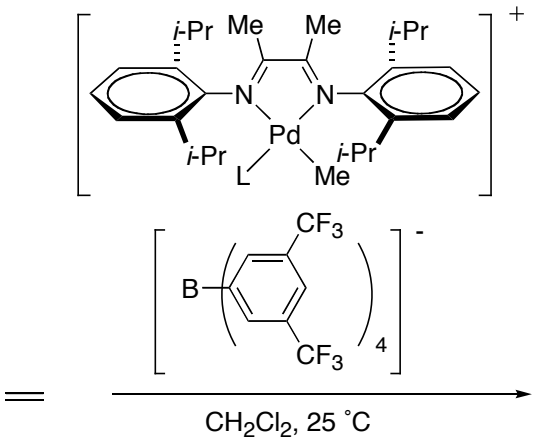
- Requires highly electrophilic metal center (cationic metal with “non-coordinating anion”)
- π-acidic ligands help to give an electrophilic metal center.

Pd and Ni diimine based systems:

In the late 90’s Brookhart and collaborators at DuPont developed a class of nickel and palladium catalysts that would polymerize ethylene to high molecular weight polyethylene. (*JACS*, **1995**, *117*, 6414)



branched polyethylene (50 branches/1000 C's)
M_w =80,000
3 X10^6 g/mol Ni•h



CH_2Cl_2, 25 ˚C

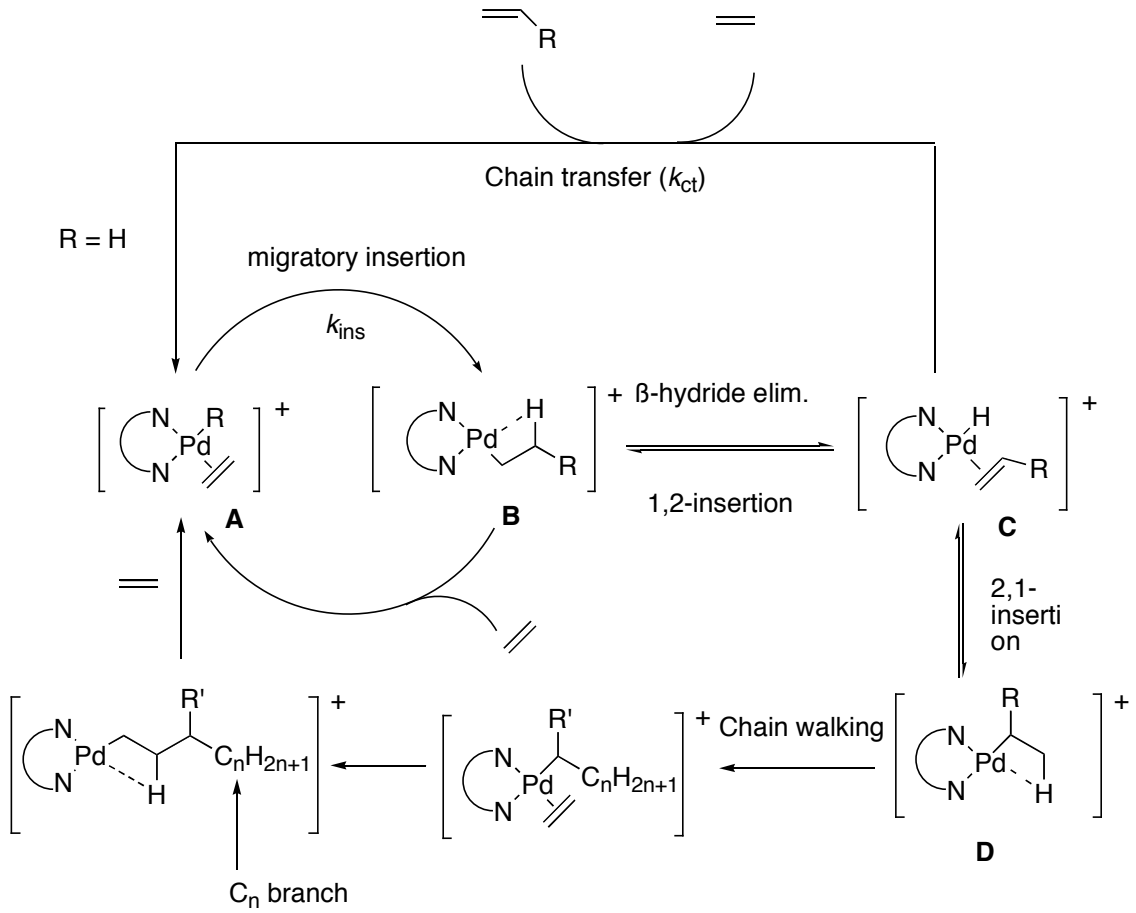
highly branched polyethylene (100/1000 C's)
M_w =10,000
20 kg/mol Pd•h

Catalyst activity and polymer molecular weight were strongly dependent on the steric bulk of the ortho substituents on the aromatic rings. When the substituent was methyl instead of isopropyl, the molecular weight of the polymer dropped by an order of magnitude. The productivity was also an order of magnitude lower with the methyl substituent.

These catalysts were unique because they produced highly branched polyethylene rather than linear polyethylene, particularly for Pd. Interestingly, use of hexane as the monomer gave a very similar polymer as ethylene. Nickel gave lower branching ratios, although the amount of branching could be greatly varied.

The high degree of branched suggested a “chain walking” mechanism. Thus, ß-hydride elimination is competitive with, if not faster than, migratory insertion, yet high molecular weight polymer is produced. Therefore, displacement of the polymer chain by ethylene (**C** to **A**) must be slow.

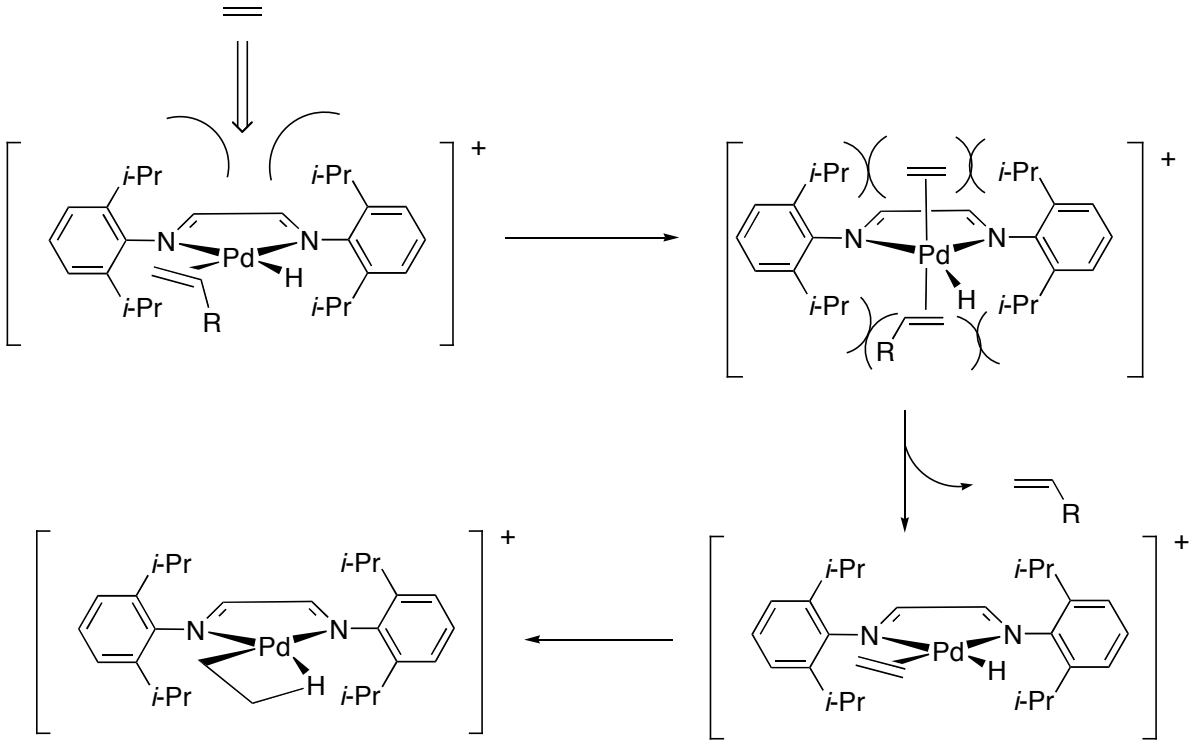
Unlike early transition metal, Ziegler-Natta polymerization catalysts, the alkyl olefin complex can be observed. For both the Ni and Pd systems, this is the resting state. The rate determining step is migratory insertion. Therefore the reaction rate is independent of [ethylene]. At low temperature, Ni and Pd alkyl ethylene complexes can be prepared and the rate of migratory insertion measured using NMR. (Pd: *J. Am. Chem. Soc.*, **1995**, *117*, 6414-6415. Ni: *J. Am. Chem. Soc.*, **1999**, *121*, 10634-10635)



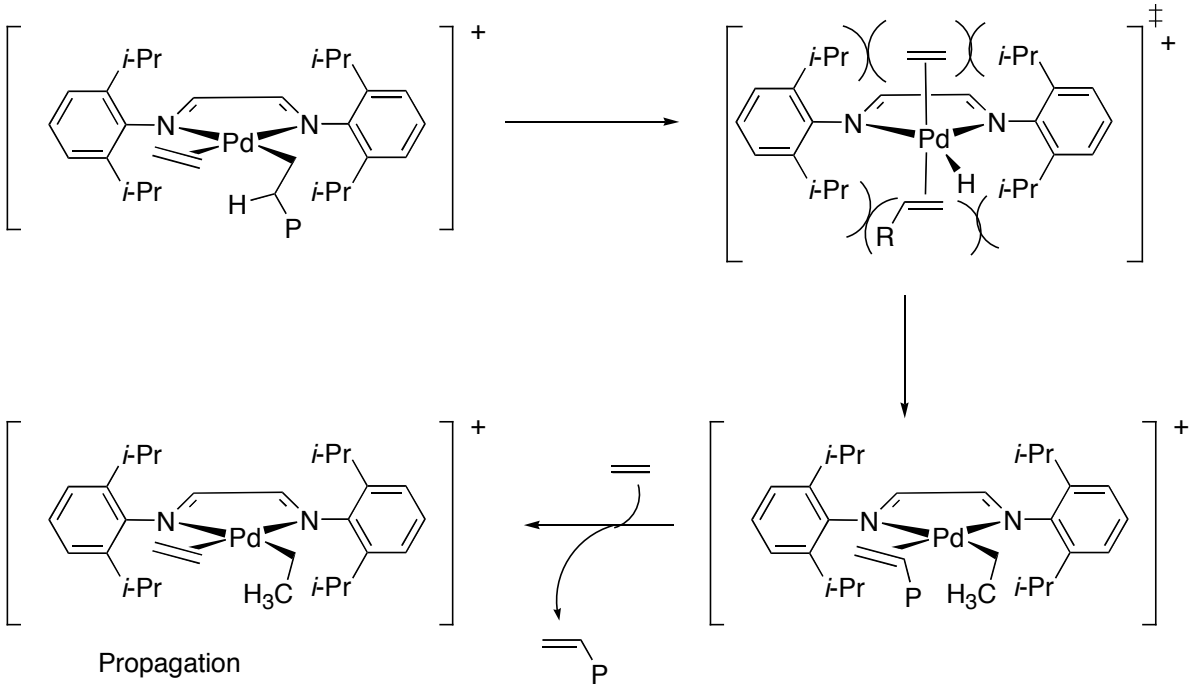
Theory gives good agreement with the experimental values. The theoretical analysis of the Ni systems suggests that bulky ligands lower the migratory insertion barrier by destabilizing the resting state complex. Bulky ligands also greatly increase the barrier to chain transfer by destabilizing the transition state for this process. The barrier is approximately double to that determined computationally for a sterically unhindered complex. (Ziegler, *J. Am. Chem. Soc.* **1997**, *119*, 1094-1100 and 6177-6186)

Complex	Propagation	Branching	Termination
2,6-di-*i*-Pr	13.2	15.6	18.2
no aryl	16.8	12.8	9.7

Brookhart initially proposed that the large steric bulk of the *ortho*-substituents on the aromatic rings inhibited associative displacement of the polymer chain from **C**.



Ziegler has suggested a variation on this mechanism in which hydride is directly transferred from the ß-carbon of the polymer chain to coordinated ethylene. This mechanism was proposed since no stable olefin hydride species could be identified.

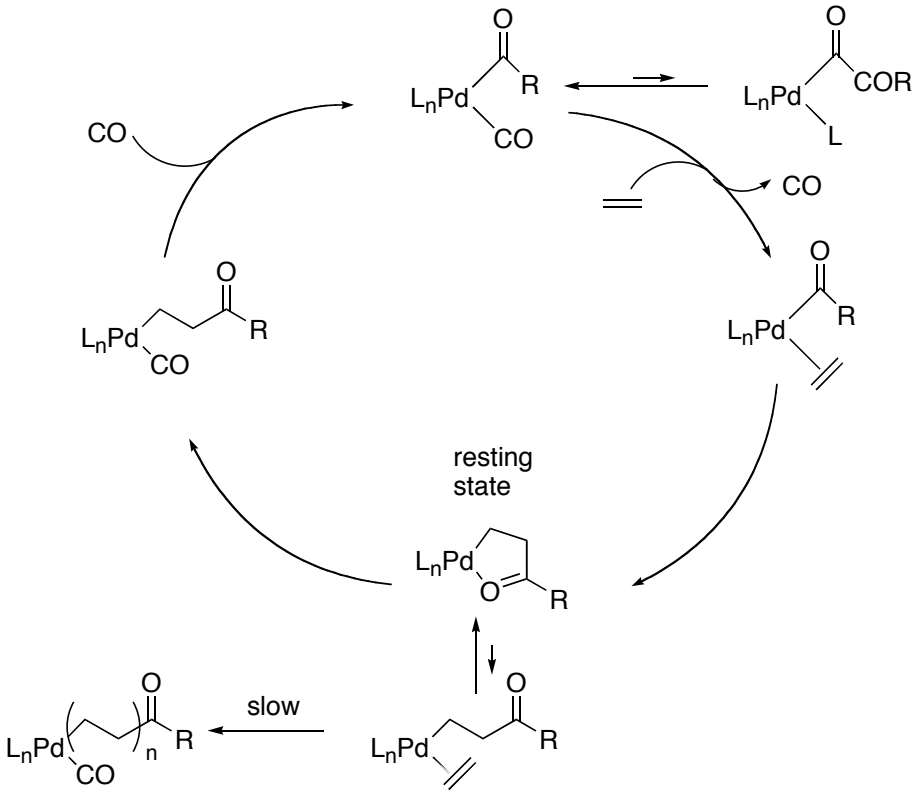


Propagation

Olefin/CO Alternating Polymerization

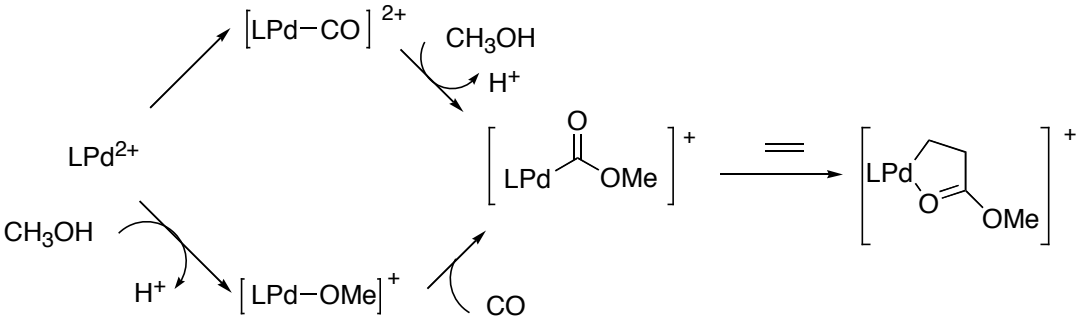
Palladium complexes catalyze the perfectly alternating polymerization of CO and alkenes. (Review: *Chem. Rev.* **1996**, *96*, 663-681).

The polymer is produced by sequential migratory insertion of CO and alkene. The perfect selectivity is due to the unfavorable thermodynamics of sequential CO insertion and the slow insertion of alkene into a Pd-alkyl species.

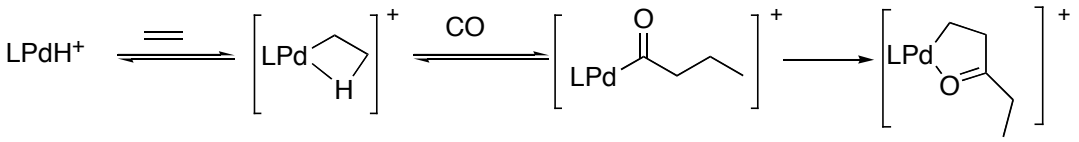


Initiation: Analysis of polymer end groups suggest that there are two initiation pathways involved under normal conditions. 1) Formation of a Pd-acyl species. 2) Insertion of an alkene into a Pd-hydride.

Pd-Carbomethoxy Initiation

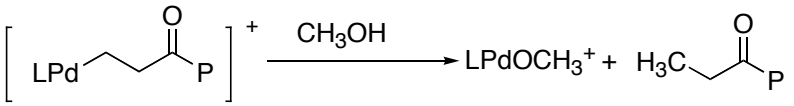


Pd-H Initiation

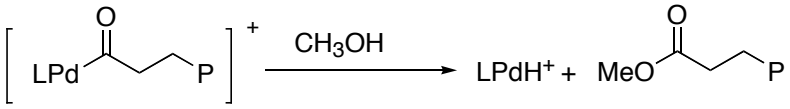


Termination: Similarly, there are two likely chain transfer mechanisms involved.

Protonolysis



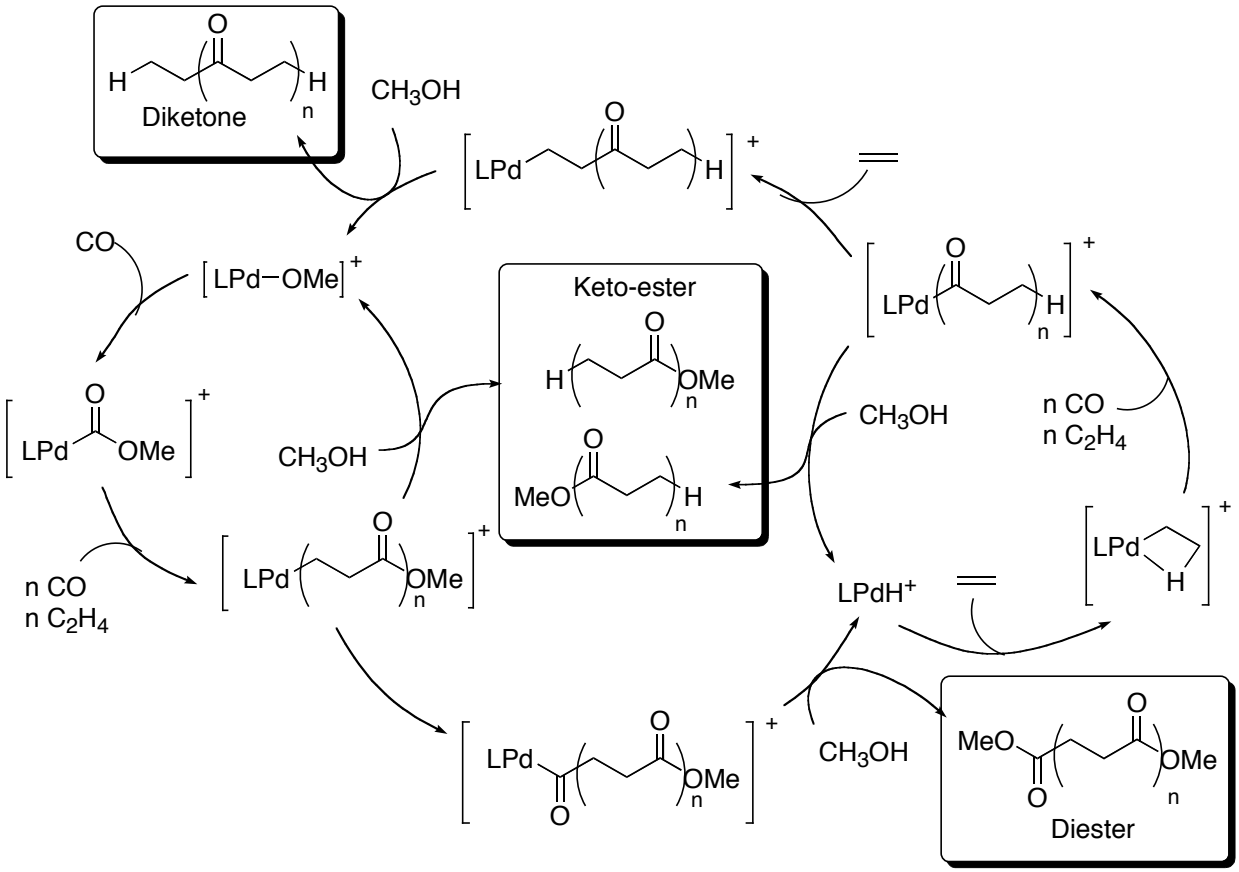
Methanolysis



Thus three different polymeric products can be produced:

1. A diester: Pd-CO_2Me initiation and methanolysis chain transfer
2. A diketone: Pd-H initiation and protonolysis chain transfer
3. A keto-ester: Can be produced either by Pd-CO_2Me initiation and protonolysis chain transfer or Pd-H initiation and methanolysis termination

At higher temperatures a mixture of all three types of products are produced, suggesting that both pathways are viable and that crossover can occur. At lower temperature, only keto-esters are formed.

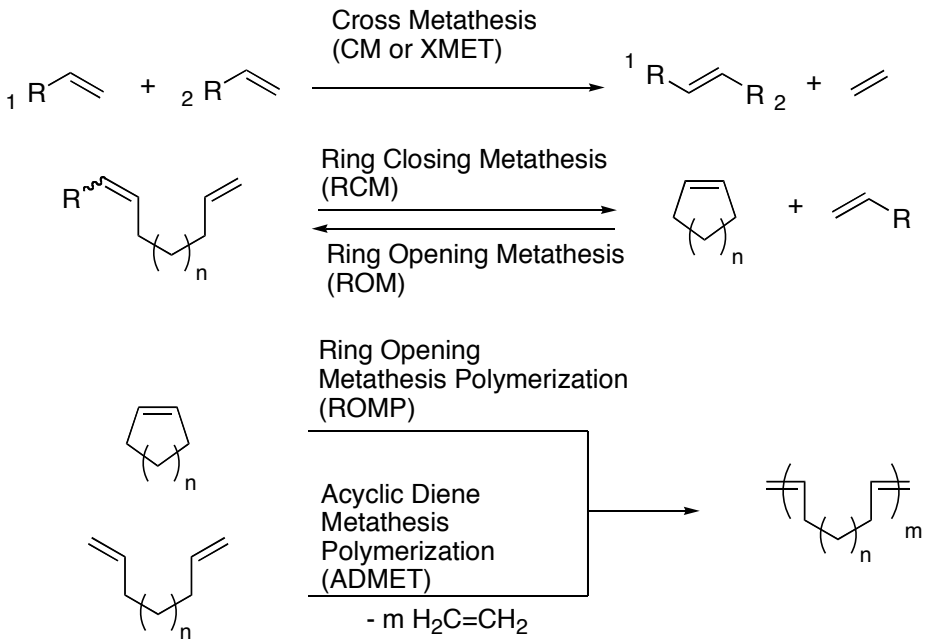


Kevin Shaughnessy
The University of Alabama, 2019

14-Alkene and Alkyne Metathesis

Alkene metathesis is the metal-catalyzed disproportion of alkenes. This reaction has been known for nearly 60 years, but only in the past 15-20 years has it become widely used in both industrial and academic labs for the synthesis of polymers and complex organic compounds. The 2005 Nobel prize was award to Yves Chauvin, Richard Schrock, and Robert Grubbs for their work in developing olefin metathesis into a widely used process.

There are several classes of olefin metathesis reactions.



All of the above reactions are reversible, so equilibrium mixtures are obtained. To produce high yields of a given product a suitable driving force must be present.

- Cross metathesis: Mixtures of products are produced unless a volatile byproduct (ethylene) is produced that can be removed from the reaction mixture. The alkenes must also have different reactivity in order to get selective cross-metathesis (*J. Am. Chem. Soc*, **2003**, *125*, 11360).

Olefin Type	Grubbs Gen 2	Grubbs Gen 1	Schrock
Type I fast homodimerization	terminal alkenes, wide range of allylic species, styrenes	terminal alkenes, allyl silanes, allylic alcohols ethers and esters, allyl halides	terminal alkenes, allyl silanes
Type II slow homodimerization	styrenes with large *o*-subst., electron deficient alkenes, 2° and 3° allylic alcohols	styrene, 2° allylic alcohols, vinyl dioxolanes, vinyl boronates	styrene, allyl stannanes

Type III no homodimerization	1,1-disubstituted alkenes, non-bulky trisubst. alkenes, vinyl phosphonates, 4° allylic carbons, protected 3° allylic alcohols	vinyl siloxanes	3° allyl amines, acrylonitrile
Type IV spectators to CM	nitro alkenes, trisubstituted protected allylic alcohols	1,1-disubstituted alkenes, disubst. enones, 4° allylic carbons, perfluorinated alkyl alkenes, 3° protected allyl amines	1,1-disubstituted alkenes

Reactions between two Type I alkenes: statistical mixture

Reactions between two alkenes of the same type (not Type I): non-statistical mixture

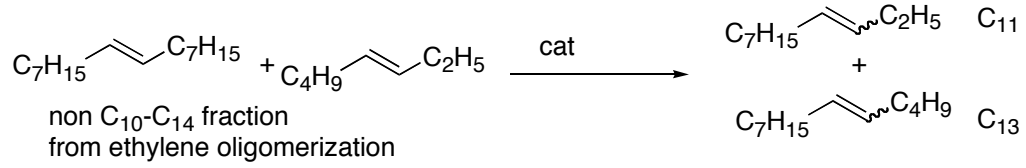
Reactions between alkenes of different types: selective CM

- RCM is favored for the production of unstrained rings and is driven both entropically and by the elimination of a volatile alkene.
- ROM is only favored at very high olefin concentrations, or more commonly with strained olefins.

The same general features will hold true for the polymerization reactions.

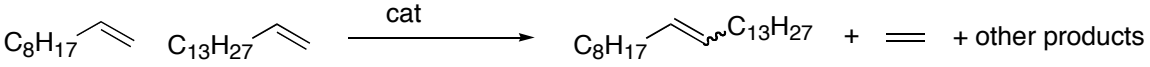
Olefin metathesis was discovered in the 1950's about the same time as Ziegler-Natta olefin polymerization. The catalysts used from this time through the 80's were poorly defined combinations of a metal salt and main-group organometallic species. (i.e., WCl_5/Bu_4Sn or $MoCl_2(NO)_2(PPh_3)_2/Al_2Me_3Cl_3$. These types of catalysts are still used industrially.

Metathesis in the Shell Higher Olefin Process (SHOP)



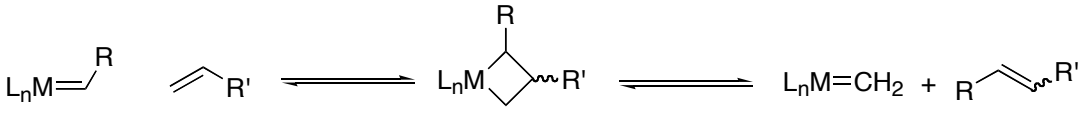
non C_{10}-C_{14} fraction
from ethylene oligomerization

Commercial synthesis of house fly pheromone



Mechanism:

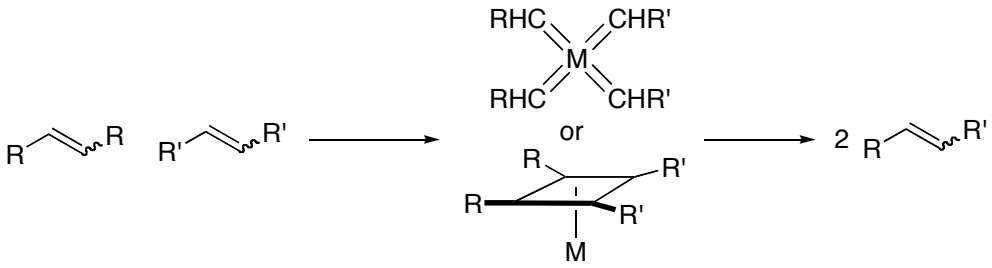
The mechanism of the reaction was disputed for a long time. One of the early proposals by Chauvin turned out to be correct, but was not accepted for some time. He proposed a [2+2] reaction between a metal carbene and the alkene to give a metalacyclobutane. Retro [2+2] would give the metathesis products. (*Makromol. Chem.*, **1970**, *141*, 161) His early contribution was the reason he was awarded the Nobel prize.



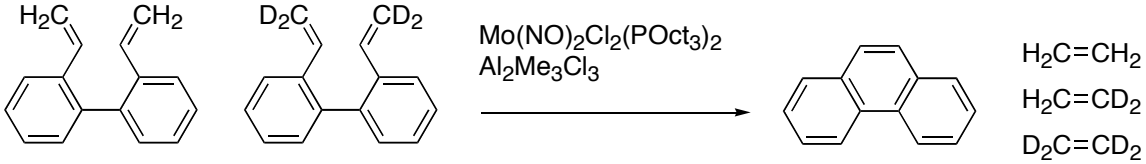
Kevin Shaughnessy
The University of Alabama, 2019

When this mechanism was proposed there was no precedent in the organometallic literature to support it. Metal-carbenes without π-donor substituents (Schrock-type) had not been observed, and there was no precedent for a [2+2] cyclization to give a metalacyclobutane. Pericyclic reaction theory tells us that a concerted [2+2] reaction is not thermally allowed, although this applies for atoms with s and p orbitals only.

An alternative mechanism, the pair-wise mechanism, was supported by many researchers.



Crossover experiments have been used in an effort to distinguish between these mechanisms. Since a metathesis catalyst continues to scramble olefins through the reaction, it is important to design an experiment that will let you look at the initial products.

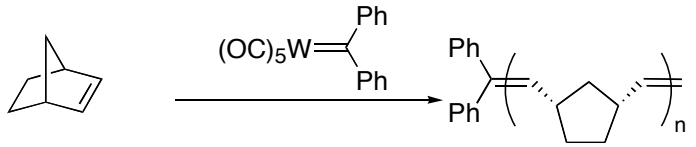


J. Am. Chem. Soc., **1976**, *98*, 2519

Well-defined catalysts

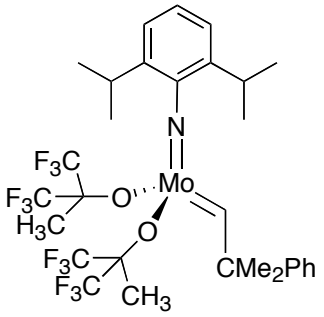
With the acceptance of the Chauvin mechanism, metal-carbene complexes were explored for their ability to catalyze olefin metathesis.

The first active, well-defined system was $(OC)_5W{=}CPh_2$ (*Tetr. Lett.*, **1976**, *17*, 4247). This complex would polymerize cyclic olefins with modest activity and high selectivity for cis-alkene polymers.

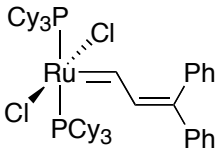


M_W = 440,000
95 % cis alkenes

Today there are two major classes of metathesis catalysts that are widely used. A molybdenum carbene developed by Schrock (*Tetrahedron*, **1999**, *55*, 8141-8153) and a ruthenium carbene developed by Grubbs (*Acc. Chem. Res.*, **2001**, *34*, 18-29). Both compounds are now commercially available and have been applied to a wide range of synthetic problems.



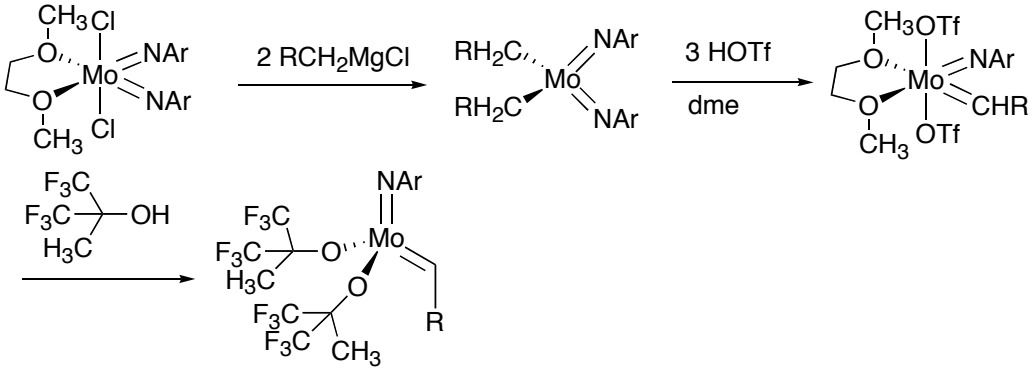
Schrock



Grubbs

The Schrock metathesis catalyst

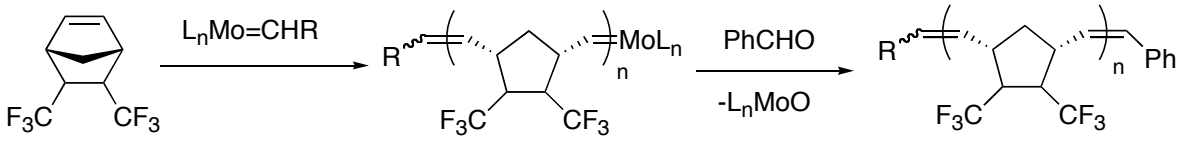
Synthesis:



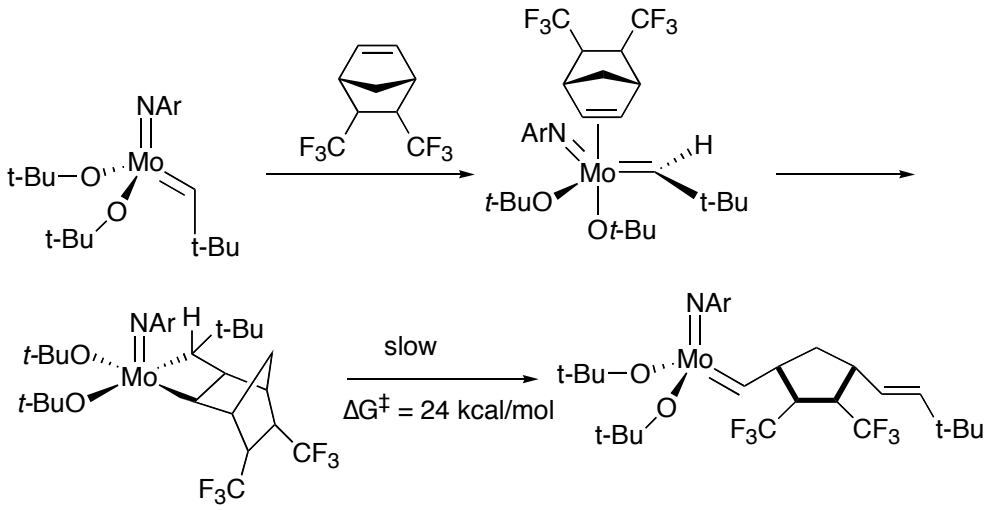
The molybdenum carbene is very sensitive to oxygen and moisture as well as protic compounds (alcohols, ketones, aldehydes, etc.), but is stable for long periods in an inert atmosphere.

Reactivity and mechanism:

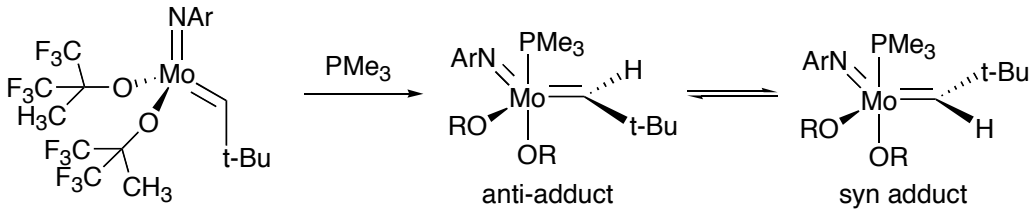
The Schrock metathesis catalysts carry out the living ring opening metathesis polymerization of cyclic olefins.



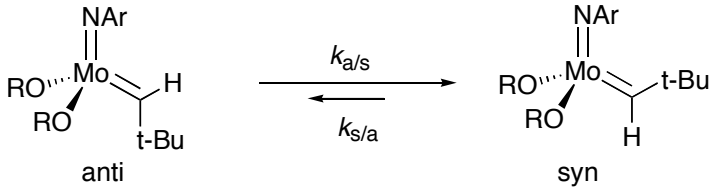
Electron withdrawing alkoxide groups give higher reaction rates in metathesis reactions. The *t*-BuO complex forms stable metallacycles that only slowly decompose to give the ring opened product.



The increased reactivity towards coordinating ligands of the $-O(CF_3)_2CH_3$ complexes is seen in the reaction with PMe_3. This complex forms a stable adduct, while the *t*-BuO- complex does not. (*Organometallics,* **1991**, *10*, 1832-1843)

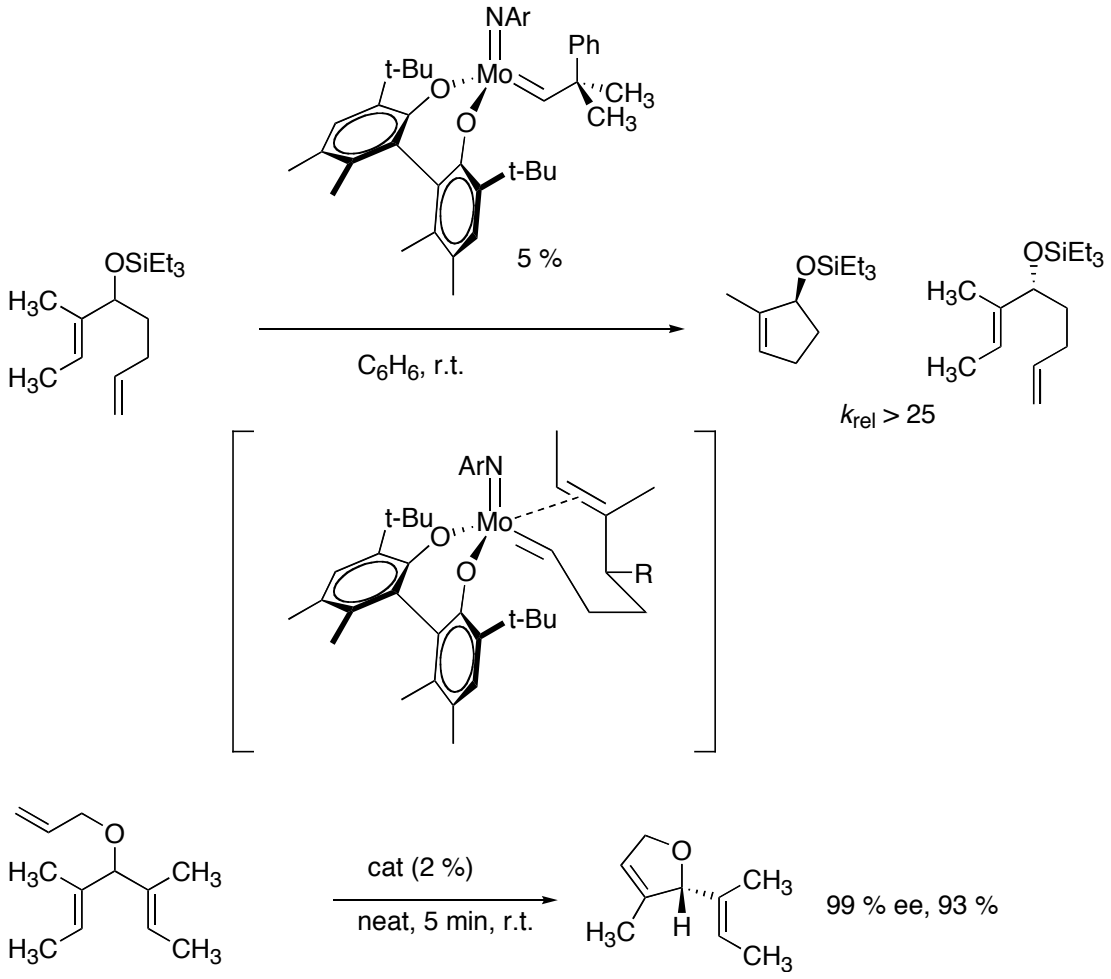


The alkylidene can exist in two rotameric forms, but in solution only the *syn* rotomer is observed by NMR. The rate of interconversion between these forms is dependent upon the alkoxide ligand. The *t*-BuO- complex interconverts 10^8 times faster than the $-O(CF_3)_2CH_3$ complex. The *anti* form reacts faster with alkenes to give ROMP.



Asymmetric Ring Closing Metathesis

Schrock in collaboration with Hoveyda have applied the molybdenum alkylidenes to asymmetric synthesis (*Chem. Eur. J.*, **2001**, *7*, 945-950). By replacing the alkoxide ligands with chiral diols, enantioselective RCM reactions are possible. This methodology can be applied to the resolution of racemic dienes or enantioselective ring closing of meso-dienes.



Advantages of the Schrock catalyst:

- Very high activity
- Allows synthesis of tri- and tetra-substituted alkenes
- Efficient asymmetric ring closing metathesis.

Disadvantages of the Schrock catalyst:

- Requires rigorous exclusion of air and moisture
- Limited functional group tolerance

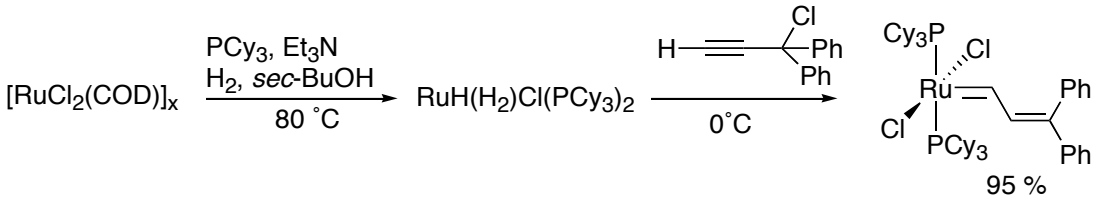
The Grubbs Metathesis Catalyst

The Schrock catalyst and related complexes based on electrophilic metal centers suffered from limited tolerance of functional groups. While the Schrock catalyst would tolerate ketones, esters, and amides, function groups such as aldehydes, alcohols, and acids were not tolerated, nor was water. It would be expected that lower-valent , late transition metal complexes would be more tolerant of electrophilic and protic functional groups. This is because the carbene would be less nucleophilic (more Fischer character).

Grubbs has developed an excellent family of catalysts based on Ru alkylidienes (*Acc. Chem. Res.* **2001**, *34*, 18-29).

Synthesis:

The synthesis of the first generation catalyst occurs in high yield and has been carried out in 10 kg batches.

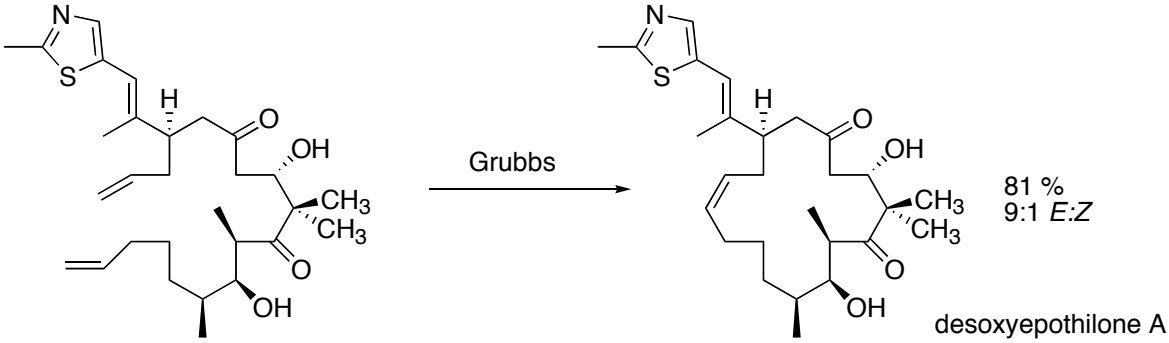


Reactivity and Mechanism:

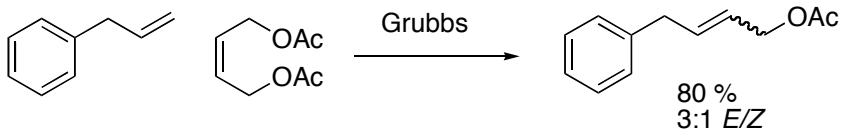
The Grubbs catalyst carries out living ROMP polymerization similar to the Schrock catalyst, but with lower activity. The Grubbs catalyst shows improved functional group compatibility, though. In fact, aqueous phase ROMP polymerizations are possible with water-soluble versions of the Grubbs catalyst.

The Grubbs catalyst has been most widely used in organic synthesis for RCM and CM reactions, due to it's stability and good functional group compatibility.

RCM (*J. Am. Chem. Soc.*, **1997**, *119*, 2733)



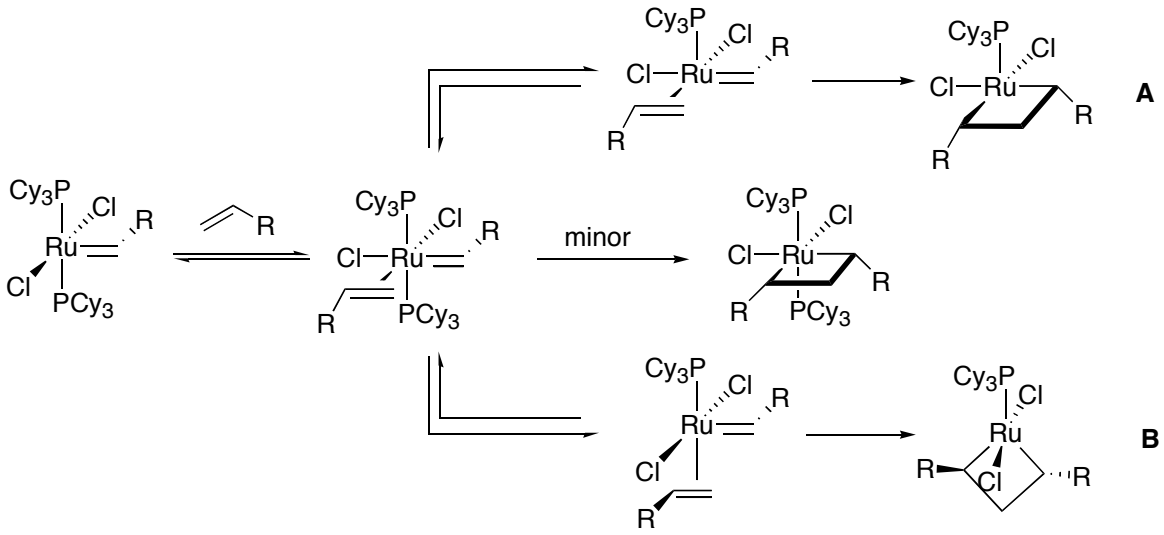
Heterocross Metathesis (*J. Am. Chem. Soc.*, **2000**, *122*, 58-71



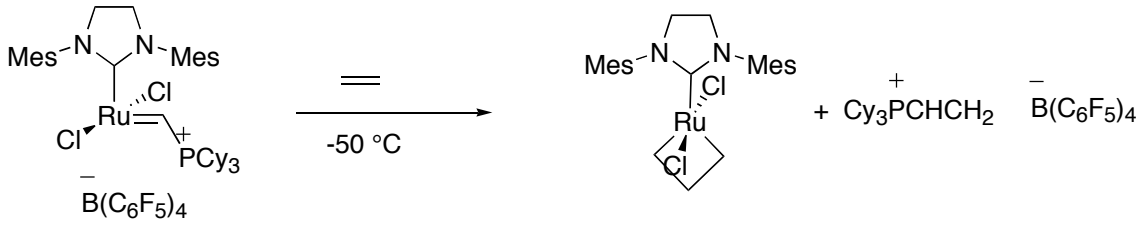
Two main pathways have been suggested for the metathesis propagation step. There are several pieces of data suggesting that phosphine dissociation is required for metalacycle formation. (*J. Am. Chem. Soc.*, **1997**, *119*, 3887)

- Inverse rate dependence on [PCy_3]
- Observation of a monophosphine olefin complex in the reaction (*J. Am. Chem. Soc*, **1997**, *119*, 7157)
- Observation of chelated metalacyclobutane species.
- Quantum chemical calculations.

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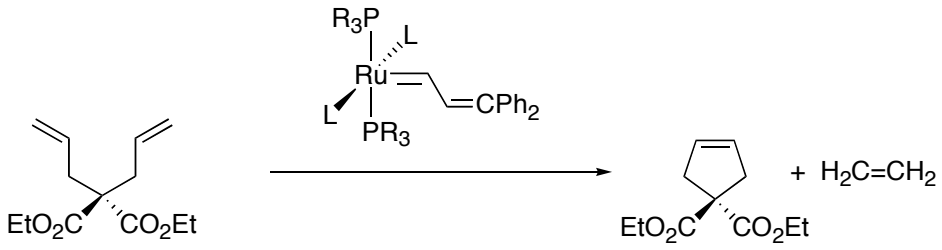
While the dissociation was well established early on, there is a great deal of debate about the nature of the metallacyclobutane intermediate. Two likely structures are **A** and **B**. Recently Piers was able to generate and observe the metallacyclobutane and showed that it is in fact the symmetric structure **B**. (*JACS*, **2005**, *127*, 5032).



The activity of the Grubbs system is dependent on both the phosphine and the halide ligands.

Larger more electron donating phosphines give higher rates

Smaller less electron donating halides give higher rates.



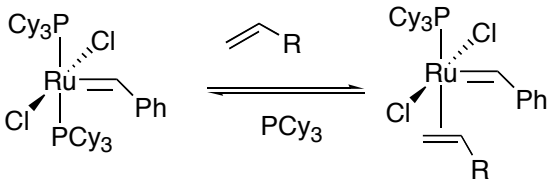
Cl > Br > I
$PCy_3 > P\textit{i}\text{-}Pr_3 > PhPCy_2 > PhP\textit{i}\text{-}Pr_2$

Design of the next generation of Grubbs catalysts

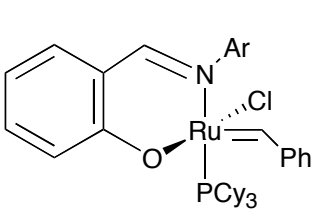
The mechanistic results suggested that the active species was a monophosphine ruthenium alkylidene. Therefore, stable monophosphine complexes were sought. The ideal catalyst would have high activity

and stability. This requires easy formation of the 14 electron monophosphine complex without decomposition.

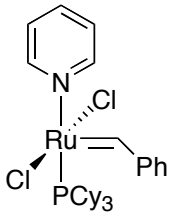
- A chelated complex was stable at high temperatures, but had low activity
- Replacement of a phosphine with a weakly coordinating ligand, gave a very active catalyst with a short lifetime.
- *N*-Heterocyclic carbenes are stronger σ-donors than phosphines, but also have stronger M-L bonds.
    - The bis carbene complex had low activity because carbene dissociation is slow.
    - The mixed carbene/phosphine complex is both highly active and very stable.



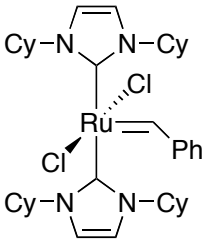
Need system that favors formation of alkene complex, but is stable.



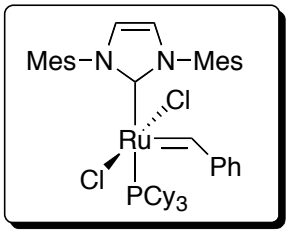
Stable, but low activity



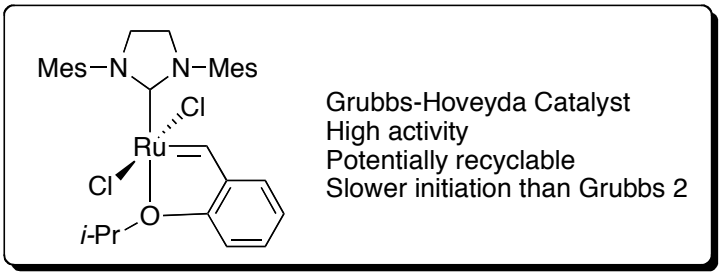
High activity, but unstable



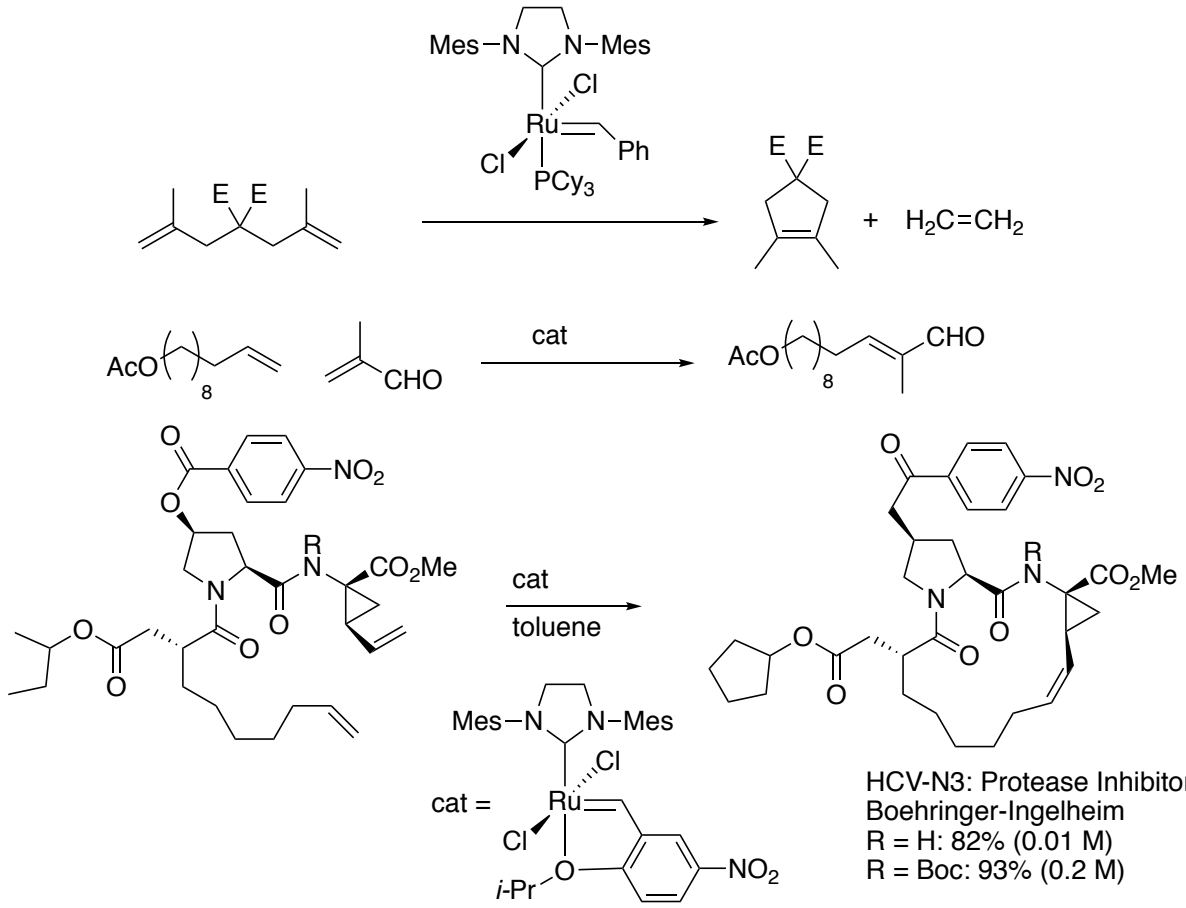
Low activity



High actvity and Stability



The monocarbene complex and the saturated carbene analog allow reactions that were previously only possible with the Schrock catalyst.

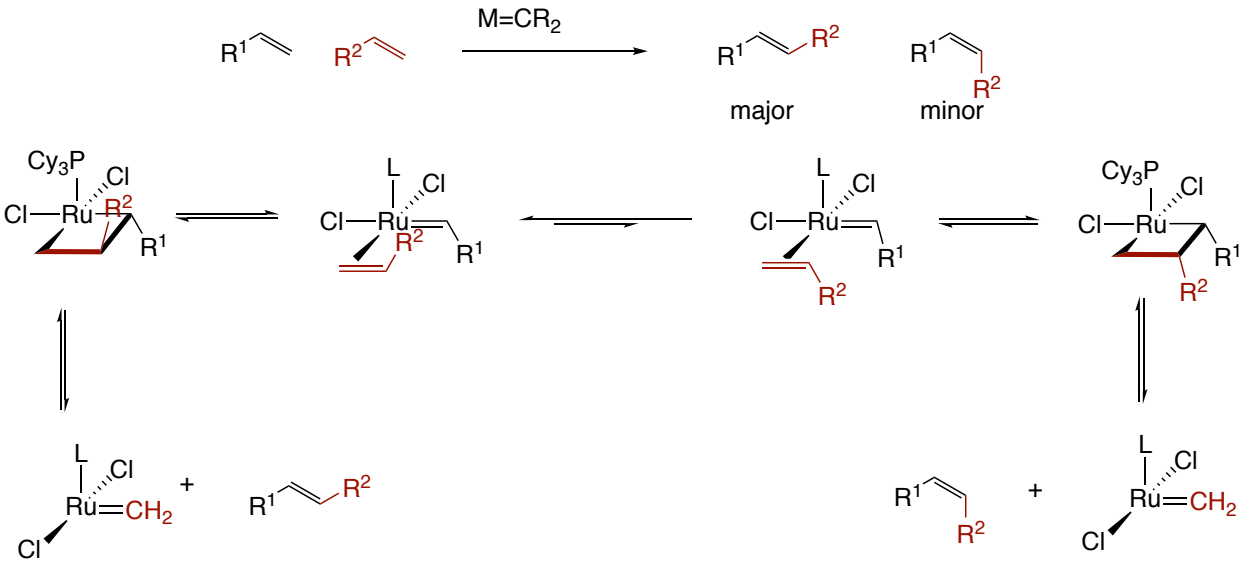


The second generation of Grubbs catalysts combine the high activity of the Schrock catalysts with good stability and functional group tolerance. The only application where the Schrock catalyst is still superior is in the asymmetric RCM reactions.

Stereoselectivity in Olefin Metathesis

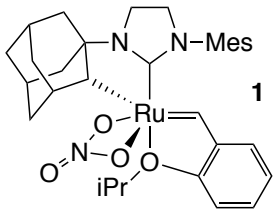
Alkene metathesis is typically an equilibrium process that is under thermodynamic control. For cross-metathesis to form acyclic alkenes, the *E*-isomer is generally favored, but a mixture of *E* and *Z* is usually formed. In RCM reactions, there is generally a preference for the Z-isomer, unless the ring is large enough to accommodate a trans-alkene. Significant efforts have been made to develop stereoselective catalysts for CM.

Stereoselectivity in CM depends on the orientation of the alkylidene substituent and the substituents on the coordinated alkene as the metallacyclobutane is formed. The preferred structure would place the substituents trans, leading to an *E* alkene.

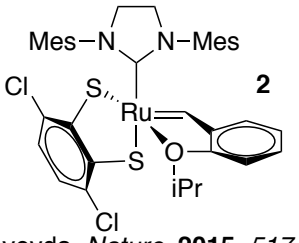


Z-selective CM:

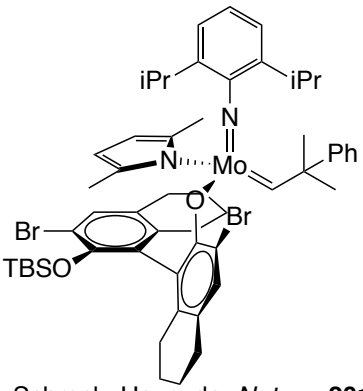
The *Z*-alkene is generally thermodynamically less stable, so it usually the minor product. A number of research groups have worked to develop *Z*-selective catalyst systems. Grubbs, Hoveyda, and Schrock have all developed systems with high *Z*-selectivity. The proposed mechanism for stereocontrol is that a large ligand favors placing the alkene substituents away from this ligand, resulting in them being syn in the metallacyclobutane. This results in a *Z*-alkene. The alternative results in a steric clash with the ligand.



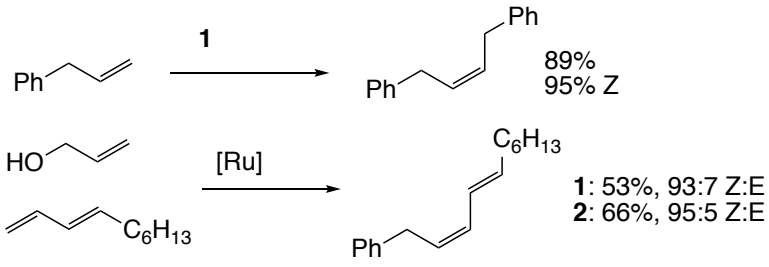
Grubbs, *JACS*, **2012**, 693

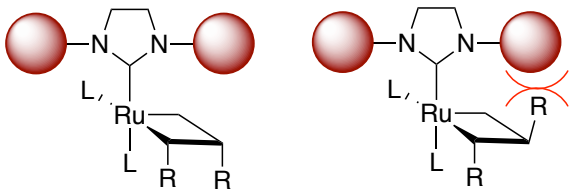


Hoveyda, *Nature*, **2015**, *517*, 181



Schrock, Hoveyda, *Nature*, **2011**, *471*, 461

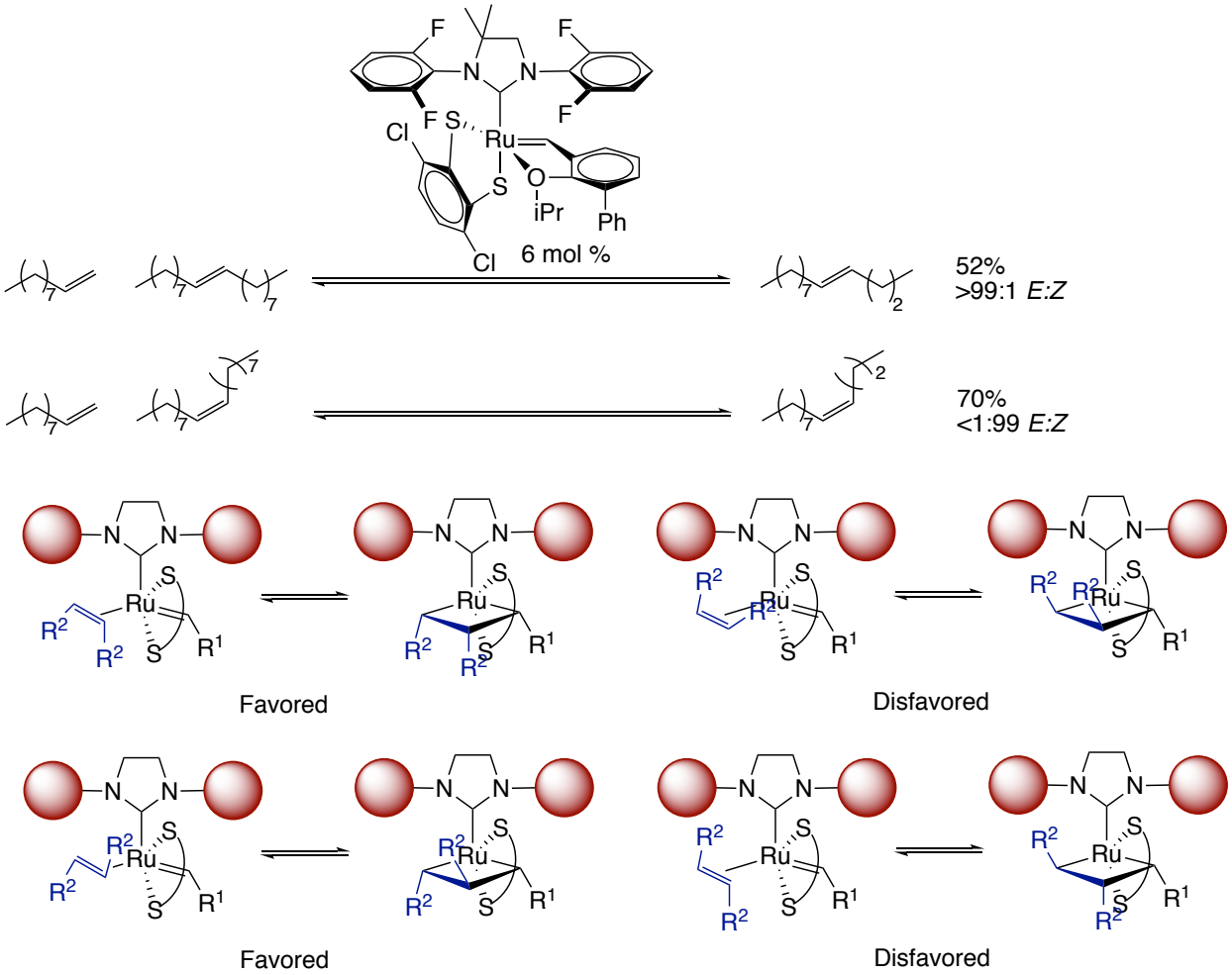




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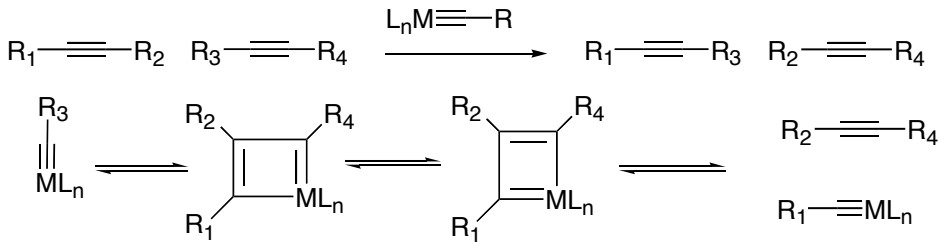
E-Selective CM

Although *E*-alkenes are generally favored, there are no catalyst systems that give a high preference for *E*-alkenes. Grubbs has developed a system that is capable of stereospecific cross-metathesis of internal alkenes. Using this catalyst, *Z*-alkene starting materials are exclusively converted to *Z*-alkene products. Similarly, *E*-alkenes are converted to *E*-alkene products. *E*-Alkenes are poor substrates, however and generally give slow reactions and low yields. Grubbs found that using smaller fluorine substituents and the N-aryl groups gave a catalyst with low *E/Z* selectivity for terminal alkenes. As a result, the starting alkene geometry determines the product stereochemistry. A similar mechanism is proposed with the large substituents on the NHC ring exerting control over the alkylidene and coordinated alkene. With *Z*-alkenes, all substituents want to be away from the NHC ligand. In the case of *E*-alkenes, the alkene will coordinate with one R group pointing into the open space in front of the NHC ring. This leads to an *E*-product.

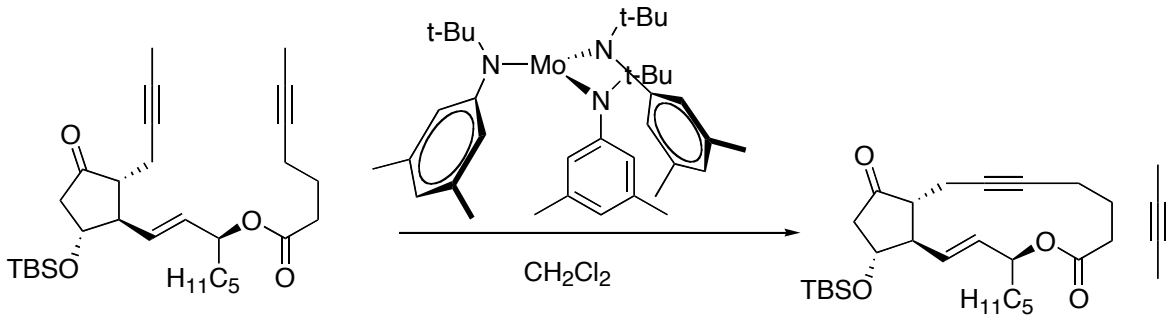


Alkyne Metathesis

Although alkene methathesis is well established as a synthetic methodology, particularly with the Grubbs catalysts, the analogous alkyne metathesis is much less well developed.



Fürstner (*JACS,* **2000**, *122*, 11799 and references therein, *Angew. Chem. Int. Ed.* **2013**, *52*, 2794, review) was one of the first to adopt alkyne metathesis for organic synthesis. He showed that a Mo(III) tris(amide) could be used as a catalyst precursor for the diyne ring closing metathesis as part of the synthesis of prostaglandins.



The active catalyst was formed from the reaction of the Mo precursor and the reaction solvent (CH_2Cl_2) to give a mixture of chloride complex and alkylidyne. Moore (*JACS* **2004**, *126*, 329-335) showed that the alkylidyne could be made in high yield by recycling the Mo-Cl complex. Mg was used to reduce the chloride complex back to the starting Mo-amide complex. In this way nearly all of the Mo would eventually be converted to the desired alkylidyne.

