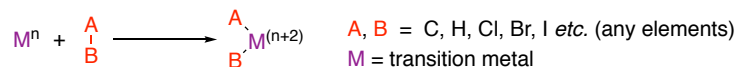# 2. Reactions of organic molecule with transition-metal complex

(1) Oxidative addition
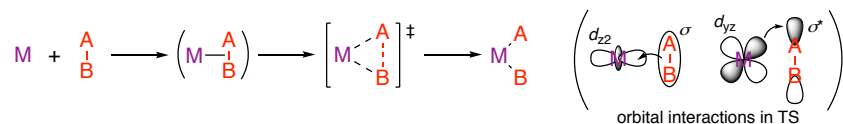
General   J. A. Labinger, *Organometallics*, **34**, 4784 (2015).

$$M^n + \overset{A}{\underset{B}{|}} \longrightarrow \overset{A}{\underset{B}{\diagdown}}M^{(n+2)}$$

A, B = C, H, Cl, Br, I *etc.* (any elements)
M = transition metal
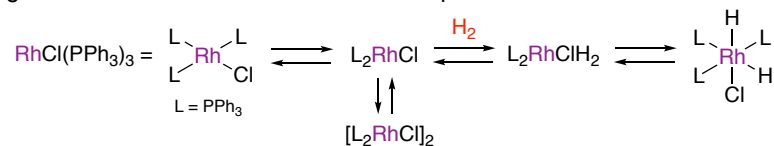
- Oxidative addition is the addition of a covalent bond A–B to a low-valent metal atom.
- In the oxidative addition, two electrons are apparently transferred from the metal to the covalent bond. As a result of the electron transfer, the cleavage of A–B gives two anionic ligands, A⁻ and B⁻, which bond to the metal atom.
- The oxidation number of the metal increases by two through the oxidative addition.
- In general, higher electron density on the metal atom accelerates the oxidative addition. Electron-donating spectator ligands facilitates the oxidative addition.
- Less steric hindrance and vacant coordination site around the metal is favorable for the oxidative addition.
- Three types of mechanism are conceivable for the oxidative addition.

(a) Three-centered mechanism

$$M + \overset{A}{\underset{B}{|}} \longrightarrow \left(M\text{–}\overset{A}{\underset{B}{|}}\right) \longrightarrow \left[M\diagdown\!\!\!\overset{A}{\underset{B}{\vdots}}\right]^{\ddagger} \longrightarrow M\diagup\!\!\!\overset{A}{\underset{B}{}}$$

orbital interactions in TS

- Oxidative addition of non- or less-polar covalent bond, *e.g.* H–H, C–H, C–C, Si–H, commonly proceeds through a concerted three-centered transition state.
- LUMO on the metal atom interacts with the σ-orbital of A–B. The interaction leads to the bond cleavage between A and B.
- HOMO on the metal atom interacts with the σ*-orbital of A–B. The interaction results in the formation of metal–ligand bonds, M–A and M–B.
- The stereochemistry on A or B is retained during this process.
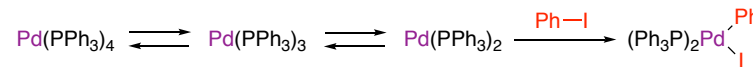- Ligands A and B on the metal locate in cis-position each other.

RhCl(PPh₃)₃ =

L = PPh₃

[L₂RhCl]₂

C. A. Tolman, *J. Am. Chem. Soc.*, **96**, 2762 (1974).
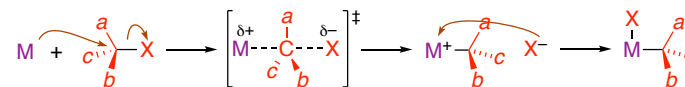
Oxidative addition of haloarenes

X = I, Br, Cl, OTf
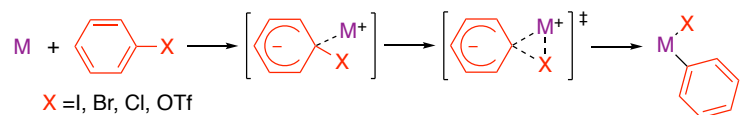
- C–X bonds in aryl and vinyl halides are polar. However, their oxidative additions proceed through the three-centered pathway, because nucleophilic low-valent transition metal is hard to access behind the C–X bond.

- The oxidative addition of C–X bond may proceed through a pathway similar to aromatic nucleophilic substitution.
- Reactivity of the leaving groups: I > Br, OTf > Cl ≫ F.
- Vacant coordination site on the metal is required for the efficient oxidative addition.

$$Pd(PPh_3)_4 \rightleftharpoons Pd(PPh_3)_3 \rightleftharpoons Pd(PPh_3)_2 \xrightarrow{Ph\text{–}I} (Ph_3P)_2Pd\diagdown\!\!\!\overset{Ph}{\underset{I}{}}$$

J.-F. Fauvarque, *J. Organomet. Chem.*, **208**, 419 (1981); C. Amatore, *Organometallics*, **9**, 2276 (1990).

(b) Sₙ2-type mechanism

- Oxidative addition of polar covalent bond, *e.g.* C–X, C–O, H–X, commonly proceeds through the backside attack of nucleophile.
- As with Sₙ2 reaction, the HOMO on the metal atom provides its electrons to the vacant σ*-orbital of C–X bond.
- The stereogenic center of the chiral alkyl halide is inverted through this type of oxidative addition.

88% ee   63% ee
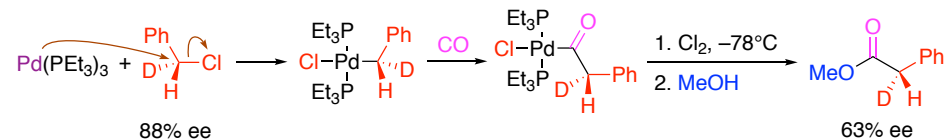
J. K. Stille, *J. Am. Chem. Soc.*, **98**, 5832 (1976); *ibid*, **100**, 838 (1978).

(c) Sₙ2'-like mechanism for allylic substrate
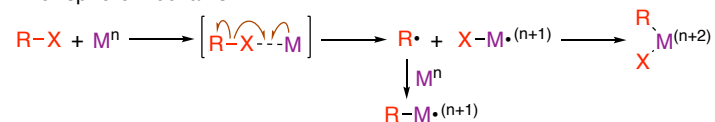
π-allyl metal complex
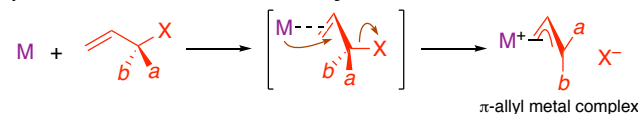
- Allylic electrophiles, *e.g.* allyl chloride and acetate, also undergo the nucleophilic attack of low-valent transition metal.
- The oxidative addition of allylic electrophiles starts from the coordination of the C–C double bond to the low-valent metal atom. The coordination induces the elimination of leaving group X to form allylmetal complex, in which the allyl ligand coordinates on the metal through its π-orbital.
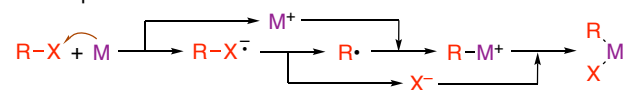- The stereochemistry of the oxidative addition is also inversion.

58% ee   1. PdCl₂(dppe), PPh₃, *i*-Bu₂AlH   2. NaBF₄   47% ee   DPPE =
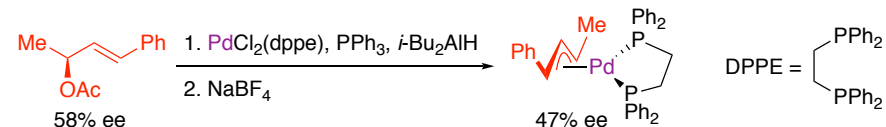
T. Hayashi, *J. Am. Chem. Soc.*, **105**, 7767 (1983); *J. Org. Chem*, **61**, 5391 (1986).

(d) One-electron transfer mechanism

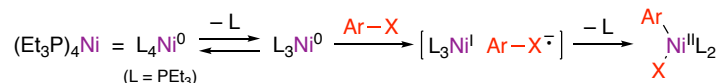**Inner-sphere mechanism**

$$R-X + M^n \longrightarrow [R-X---M] \longrightarrow R\bullet + X-M\bullet^{(n+1)} \longrightarrow \overset{R}{\underset{X}{\diagdown}}M^{(n+2)}$$

$$\downarrow M^n$$

$$R-M\bullet^{(n+1)}$$

Outer-sphere mechanism

$$R-X + M \longrightarrow R-X\overset{\bullet}{^-} \longrightarrow R\bullet \longrightarrow R-M^+ \longrightarrow \overset{R}{\underset{X}{\diagdown}}M$$
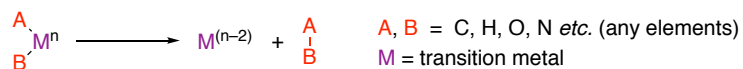$$M^+ \qquad\qquad X^-$$

- Some oxidative additions involve radical species, which is generated from one-electron transfer from metal to organic halide.
- This radical pathway is the most plausible for the oxidative addition of alkyl halides.
- With the coordinatively unsaturated metal complex, the reaction commonly proceeds through inner-sphere mechanism, which starts from coordination of the substrate to the metal. The electron transfer directly induces the homolytic C–X bond cleavage to yield carboradical species.
- The oxidative addition proceeds through the outer-sphere mechanism, when the metal species is an 18-electon complex.
- The radical pathway mostly accompanies with racemization, when the leaving group bonds to stereogenic center in the substrate.
- The pathway is most common with transition metal complex of the first row.

$$(Et_3P)_4Ni = L_4Ni^0 \underset{-L}{\overset{-L}{\rightleftharpoons}} L_3Ni^0 \overset{Ar-X}{\longrightarrow} [L_3Ni^I \ Ar-X\overset{\bullet}{^-}] \overset{-L}{\longrightarrow} \overset{Ar}{\underset{X}{\diagdown}}Ni^{II}L_2$$

$$(L = PEt_3)$$

J. K. Kochi, *J. Am. Chem. Soc.*, **101**, 6319 (1979).

- Mechanism of oxidative addition is affected by the substrate, spectator ligand on metal, and other reaction parameters. For example, Ni(PPh$_3$)$_4$ would react with iodoarenes through the three-centered mechanism, although radical species is involved with the oxidative addition of Ar–I to Ni(PEt$_3$)$_4$.
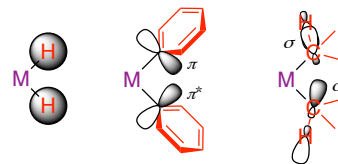
(2) Reductive elimination

$$\overset{A}{\underset{B}{\diagdown}}M^n \longrightarrow M^{(n-2)} + \overset{A}{\underset{B}{|}}$$
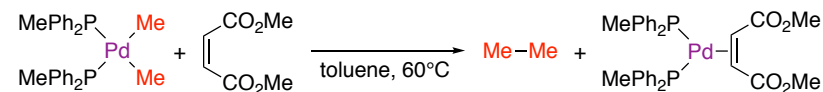
A, B = C, H, O, N *etc.* (any elements)
M = transition metal

- Reductive elimination is the reverse of oxidative addition through the three-centered mechanism.
- The anionic ligands A and B are eliminated from the metal to form the covalent bond between A and B.
- In this process, two electrons are apparently transferred from the ligands to the metal atom. As a result of the electron transfer, the cleavage of A–B gives two radical species, A• and B•, which coupled with each other.
- The oxidation number of the metal decreases by two through the reductive elimination.
- The reductive elimination requires cis-geometry of the eliminating ligands, A and B, on the metal atom.

- In general, lower electron density and larger steric hindrance of the spectator ligand accelerates the reductive elimination. Electron-withdrawing ligands are preferable for the reductive elimination to electron-donating ones.
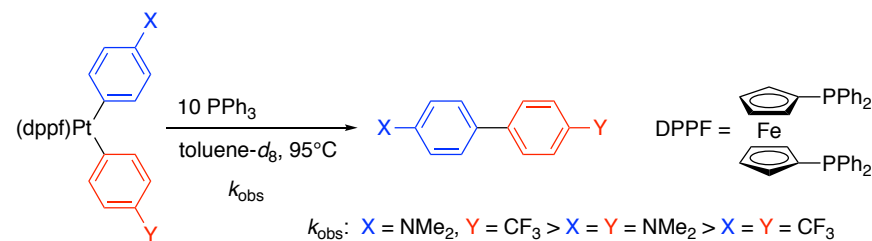- Reactivity of the eliminating ligand: alkyl [C(sp^3)] < aryl, alkenyl [C(sp^2)] < H

- The reductive elimination is often promoted in the presence of additional neutral donor ligand, such as PR$_3$, alkene. The donor ligand stabilizes the coordinatively unsaturated metal product and makes the reaction thermodynamically favorable. Alternatively, the coordination of the additional ligands may accelerate the reductive elimination.

$$\underset{MePh_2P}{\overset{MePh_2P}{\diagdown}}\underset{Me}{\overset{Me}{Pd}} + \text{(dimethyl maleate)} \xrightarrow{\text{toluene, 60°C}} Me-Me + \underset{MePh_2P}{\overset{MePh_2P}{\diagdown}}Pd\text{(=alkene)}$$

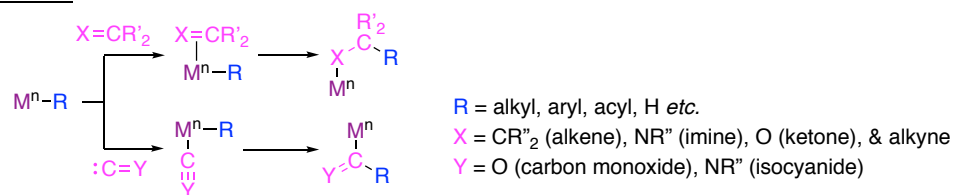A. Yamamoto, *Bull. Chem. Soc. Jpn.*, **54**, 1868 (1981).

- For the reductive elimination from symmetrical di(*p*-substituted aryl)platinum complex, the electron-donating substituents are preferable to the electron-withdrawing one. However, unsymmetrical complex bearing electron-rich and deficient aryl groups is more reactive than the symmetrical ones.

(dppf)Pt $\xrightarrow[\text{toluene-}d_8, 95°C]{10 \ PPh_3}$ X—(aryl)—(aryl)—Y $\qquad k_{obs}$

DPPF = (ferrocene with two PPh$_2$)

k_{obs}: X = NMe$_2$, Y = CF$_3$ > X = Y = NMe$_2$ > X = Y = CF$_3$

J. F. Hartwig, *J. Am. Chem. Soc.*, **126**, 13016 (2004).

(3) Migratory insertion

General

R = alkyl, aryl, acyl, H *etc.*
X = CR"$_2$ (alkene), NR" (imine), O (ketone), & alkyne
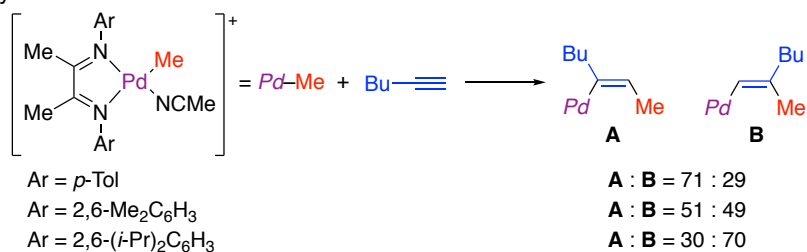Y = O (carbon monoxide), NR" (isocyanide)

- Various unsaturated compounds apparently insert into the transition-metal–carbon bond.
- R group on the metal migrates to the unsaturated substrates to form a new organometallic species, in which the original position of R is a vacant coordination site.
- The oxidation number of the metal remains unchanged during the process.
- Multiple unsaturated substrates can be successively inserted into the M–R bond.   This multiple insertion leads to polymerization.
- The insertion process is commonly reversible (see, (4) β-Elimination).

(a) 1,2-Insertions of alkene, alkyne, and others
- The migratory insertions of alkene, ketone, imine, alkyne, and other multiple bonds are equivalent to the 1,2-addition of M–R to the X–C multiple bond.
- Commonly, the 1,2-insertion proceeds with *syn*-stereochemistry.
- The regioselectivity of the 1,2-insertion is controlled by reaction conditions as well as the structure of ligand.
- It is not easy to study the 1,2-insertion of alkenes, because the resulting alkyl–metal species rapidly decomposes into the corresponding alkene and hydridometal through β-hydride elimination.


Ar = *p*-Tol
Ar = 2,6-Me$_2$C$_6$H$_3$
Ar = 2,6-(*i*-Pr)$_2$C$_6$H$_3$

A : **B** = 71 : 29
A : **B** = 51 : 49
A : **B** = 30 : 70

M. Brookhart, *Organometallics*, **17**, 1530 (1998).

### (b) 1,1-Insertions of carbon monoxide and isocyanides
- The M–R bond is added to the carbon atom in carbon monoxide (or isocyanide) to give acylmetal species.   The terminal carbon of CO (or CNR) behaves as a carbene in the 1,1-insertion.
- Commonly, the stereochemistry of R is retained during the 1,1-insertion.
- Isocyanides successively inserts into the M–R bond to form poly(imine).   Meanwhile, the double insertion of carbon monoxide is not easy.
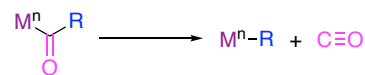
(4) Elimination

(a) β-Elimination

X = CR'$_2$, NR', O, *etc.*
Y = H, halogen, OR", (CR"$_3$), *etc.*
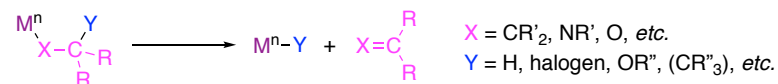
- When an organometal has a good leaving group Y on its β-carbon, the metal substituent M and Y are readily eliminated to form M–Y bond and alkenes.   The β-elimination is observed in metal alkoxides and amides as well as organometals.
- This β-elimination is the reverse of migratory insertion of alkenes, ketones, and imines.
- The hydrogen atom also works as the good leaving group in the β-elimination.   The β-elimination of M–H from organometal is 'β-hydride elimination.'
- The oxidation number of the metal remains unchanged during the process.
- The stereochemistry of the β-elimination is commonly *syn*.

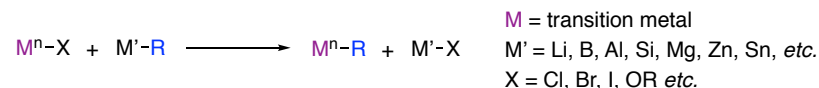R. Heck, *J. Am. Chem. Soc.*, **91**, 6707 (1969).
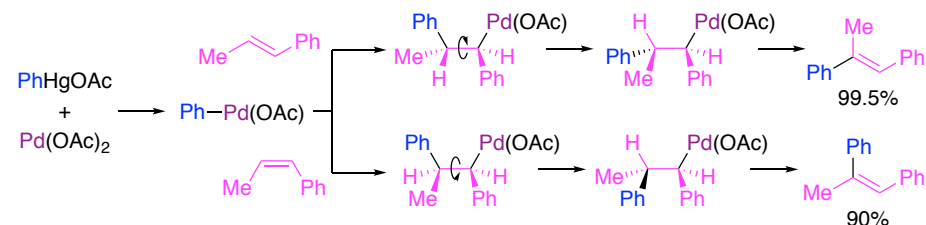
(b) Decarbonylation

- Carbon monoxide is also eliminated from acylmetal complex.   The decarbonylation is the reverse of migratory insertion of carbon monoxide.

(5) Transmetalation

M = transition metal
M' = Li, B, Al, Si, Mg, Zn, Sn, *etc.*
X = Cl, Br, I, OR *etc.*

- Transition metal complex bearing X ligand (halogen, alkoxide *etc.*) reacts with various reactive organometals, M'–R.   Through the reaction, the X ligand is replaced by R.
- The substituent R on the metal having lower electronegativity transfers to the metal with higher electronegativity as with the main group organometallic chemistry.
- The oxidation number of the metal remains unchanged during the process.

(6) Nucleophilic attack on the π-ligand on metal

General

- Various nucleophiles can attack on the unsaturated bond interacting with a transition-metal through π-coordination.
- The Lewis acidic metal atom withdraws the π-electron to enhance the electrophilicity of the π-ligand.
- The nucleophile commonly accesses the π-face that is opposite from the metal. As the result of the reaction pathway, the metal and nucleophile adds across the π-bond with anti-stereochemistry.

(a) Nucleophilic attack on neutral π-ligand

Nu = nucleophile
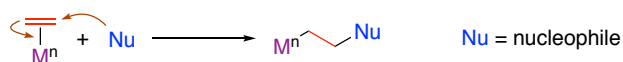
- Many transition metal atoms strongly interacts with alkene or alkyne through the donation and back donation of electrons.

donation $d_{x^2-y^2}$ (LUMO) π (HOMO)   back-donation d_{xy} (HOMO) π* (LUMO)
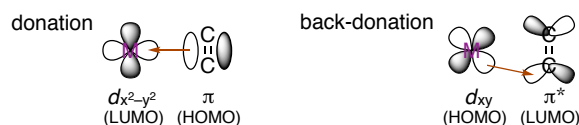
- The electron donation from the ligand to metal occurs through the interaction between the ligand π-orbital and the metal LUMO (d-π interaction). The interaction enhances the electrophilicity of the ligand.
- Meanwhile, the metal provides its electrons to the ligand through the interaction between the metal HOMO and the ligand π*-orbital (back donation).
- Cationic metal giving weak back donation is preferable for the activation of alkenes and alkynes.
- The oxidation number of the metal remains unchanged during the process.
- In this pathway, the nucleophiles attack the π-bond from the opposite side from the metal to give the *anti*-addition product.
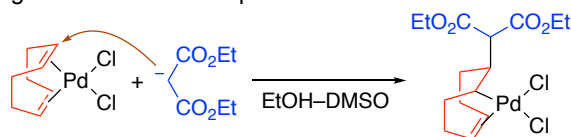

J. Tsuji, *J. Am. Chem. Soc.*, **90**, 2387 (1968); G. K. Anderson, Organometallics, 17, 1155 (1998).

- Sometimes, selective formation of the syn-adduct may be observed in the reaction of alkene–metal complex with nucleophile. The syn-product will be generated through the nucleophilic attack on the metal followed by the migrate insertion of the alkene into the C–Nu bond.

(b) Nucleophilic attack on anionic π-ligand (π-allyl, cyclopentadienyl)

Nu = nucleophile
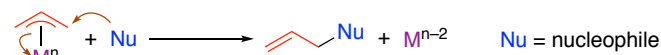
- In transition-metal–allyl species, its C–C double bond interacts to the metal atom as well as its allylic sp^3 carbon. As a result of the unique interaction, two allylic termini are equivalent to each other. The metal atom bonds to the delocalized allyl anion through its π-orbital to form η^3-allylmetal (π-allylmetal) complex.
- The π-allyl ligand is usually electrophilic rather than nucleophilic although it is anionic. The π-allylmetal species readily reacts with various soft nucleophlies, such as stabilized carbanions, amines, and phenoxides, to give the corresponding products.
- The oxidation number of the metal decreases by two through the process.
- In most cases, the nucleophilic attack is accompanied with the inversion of the stereogenic center on the allylic ligands.

82% ee   79% ee
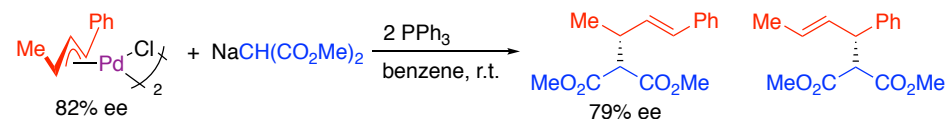
T. Hayashi, *J. Am. Chem. Soc.*, **105**, 7767 (1983); *Chem. Commun.*, 107 (1984).

## (7) Oxidative cyclization

General

- A low-valent transition-metal complex provides two electrons to multiple bond(s) to form 3-, 5-, or 7-membered ring containing the metal atom (metallacycle). This cyclization is called 'oxidative cyclization'.
- The electron transfer leads to the formation of two M–C bonds with each terminus of the unsaturated bond(s).
- The oxidation number of the metal increases by two through the oxidative cyclization.
- Two or more multiple bonds can participate in the oxidative cyclization. In this case, the remaining termini forms a new C–C bond to form a 5-membered or larger metallacycle.
- Various unsaturated bonds, such as alkene, alkyne, diene, ketone, and nitriles, undergo the oxidative cyclization.

## (8) Concerted metalation–deprotonation mechanism

General
D. Lapointe, *Chem. Lett.*, **39**, 4784 (2010).

B = anionic ligand bearing Lewis basic site
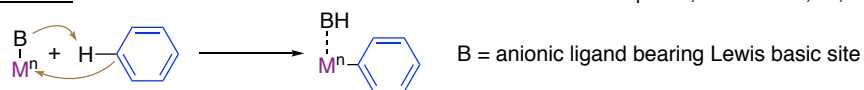
- The C–H bond in organic molecules is often cleaved with an electron-deficient transition-metal through a simultaneous metalation and deprotonation. The mechanism of C–H bond cleavage is named 'CMD (concerted metalation–deprotonation) mechanism.'
- In this process, a base removes the H atom as proton from the substrate and the remaining carbon atom bearing lone pair concurrently reacts with the electron-deficient metal atom to form the M–C bond.
- When the anionic ligand on metal has a Lewis basic site such as acetate, the ligand works as the base for the intramolecular deprotonation.
- Commonly, the oxidation number of the metal remains unchanged during the process.
- The CMD process may be a variant of transmetalation if the H atom (H$^+$?) is regarded as an equivalent of metal cation.

(9) Metathesis

General
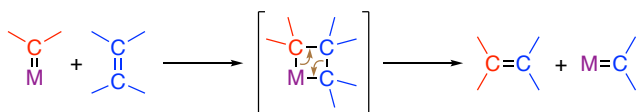
- Metathesis means the redistribution of fragments resulting from bond cleavage.
- In the case of olefin metathesis, the metal–carbon double bond in metal–carbene complex undergoes the concerted [2+2] cycloaddition with an olefinic substrate to form the metallacyclobutane. The 4-membered ring decomposes into other alkene and metal–carbene complex through the retro [2+2] cycloaddition.
- The metathesis is commonly reversible.
- Alkynes and carbonyl groups also undergo metathesis with metal–carbene complex.

- Metathesis is often observed in the reaction between M–E σ-bond and the E–E σ-bond, in which E represents main group element. The reaction is called 'σ-bond metathesis'.

E = H, B, Si *etc.*