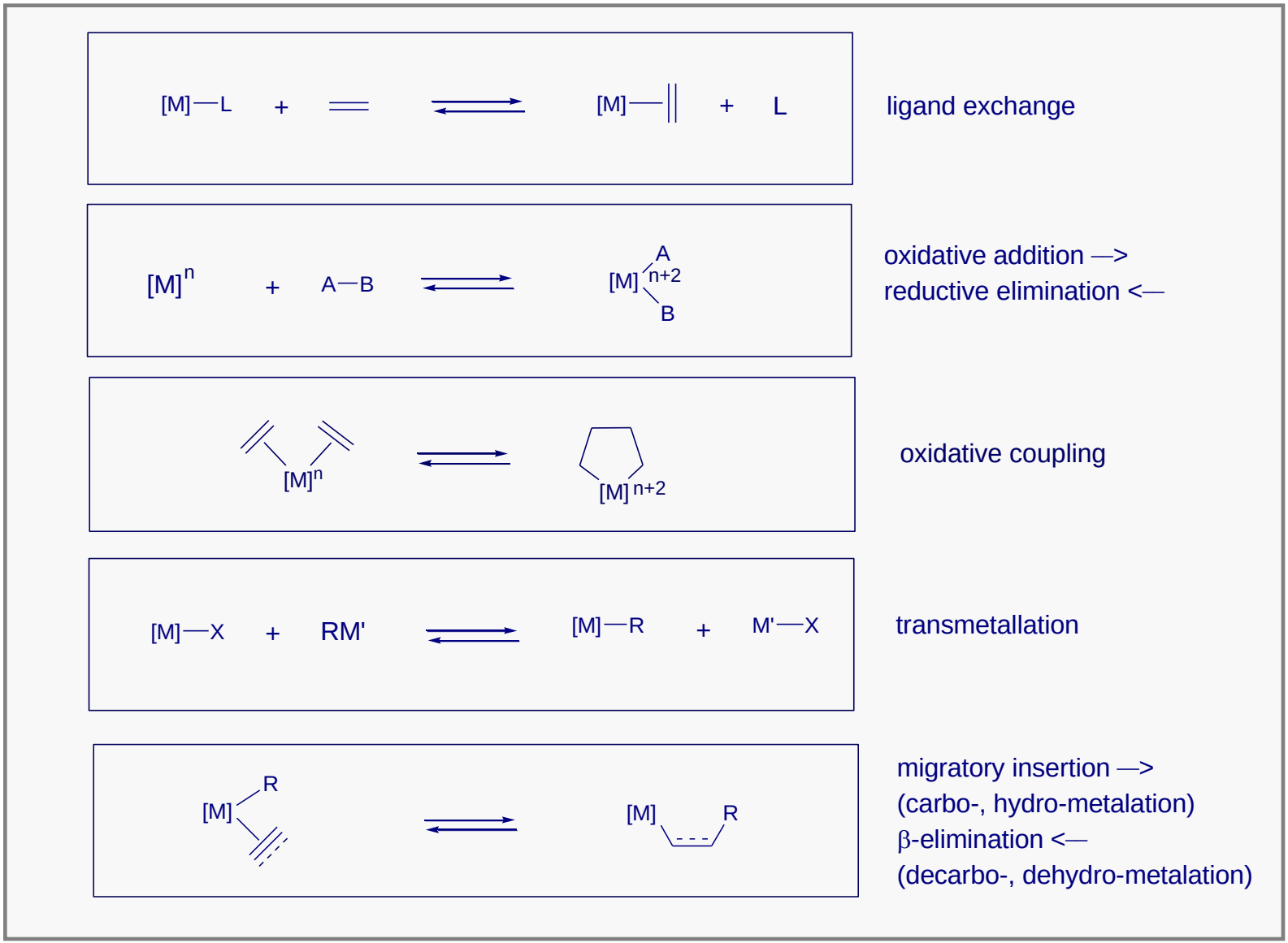
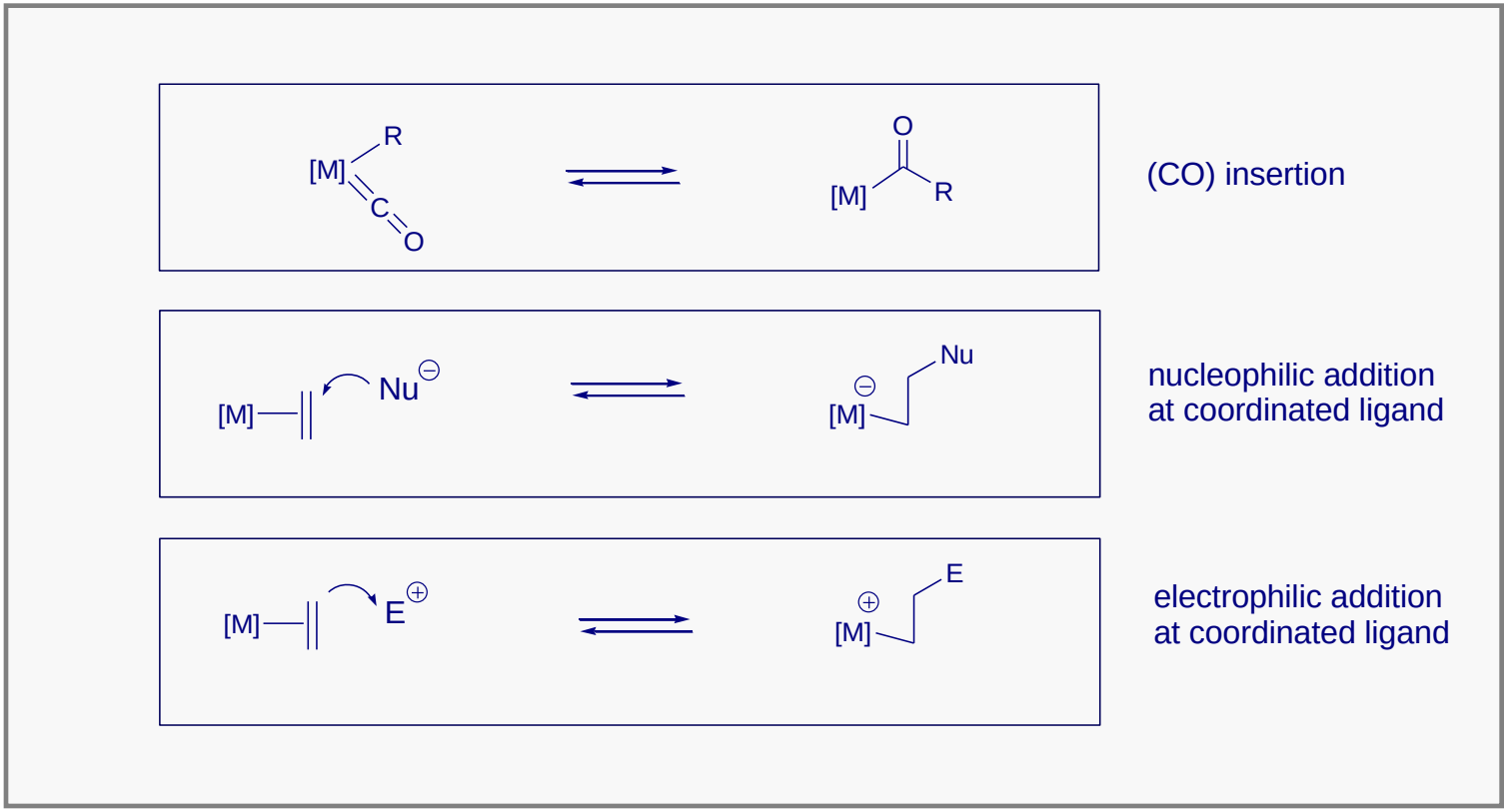
The Elementary Steps in TM Catalysis

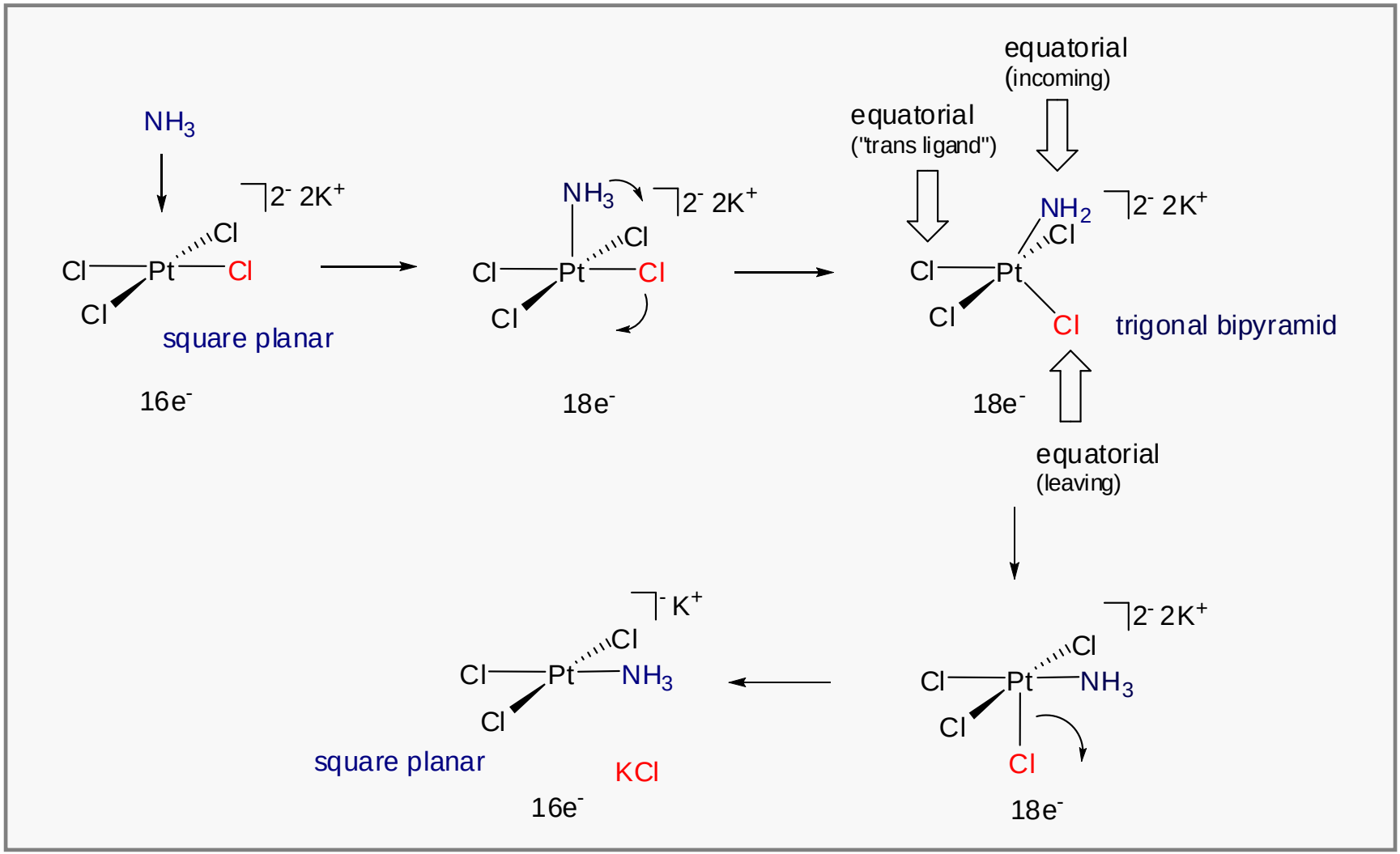


The Elementary Steps in TM Catalysis



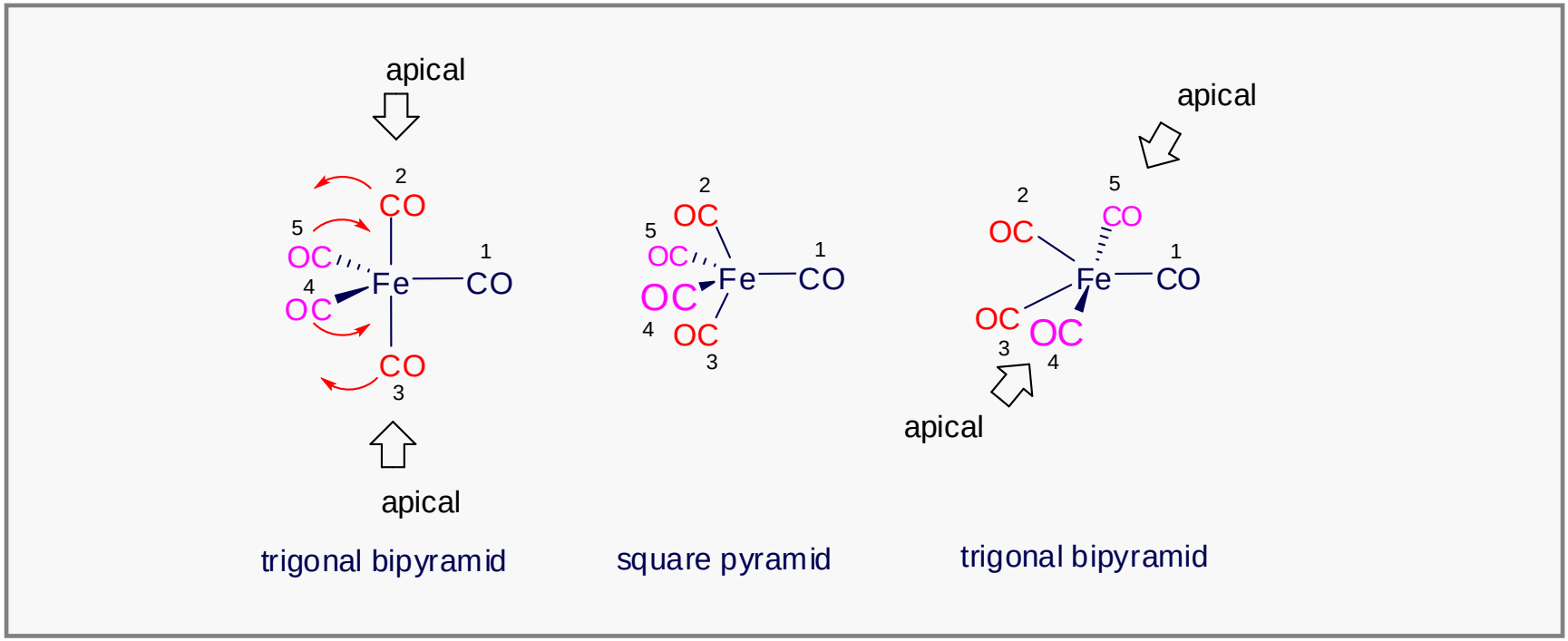
Associative Ligand Substitution

It usually takes place on square planar d^8 $16e^-$ complexes.



The Vibration of Pentacordinated Complexes

The **Berry pseudorotation** is a type of vibration causing molecules to isomerize by exchanging the two axial ligands .For examlpe, it occurs in trigonal bipyramidal molecules, such as $Fe(CO)_5$, due to rapid interchange of the CO ligands.



Trans Influence and Trans Effect

Trans Influence: the extent to which a ligand weakens the bond trans to itself. The stronger the σ-donor, the stronger its trans influence. ***This is a thermodynamic consequence.***

Trans effect : the power of a ligand to activate the substitution of the ligand located trans to itself. ***This is a kinetic effect***

Trans effect is favored by strong σ-donor ligands (R_3Si, H, Alk…) (which feature trans influence, too) as well as by strong π-acceptor ligands (olefins, CO) (which do not show trans influence).

The Trans Effect

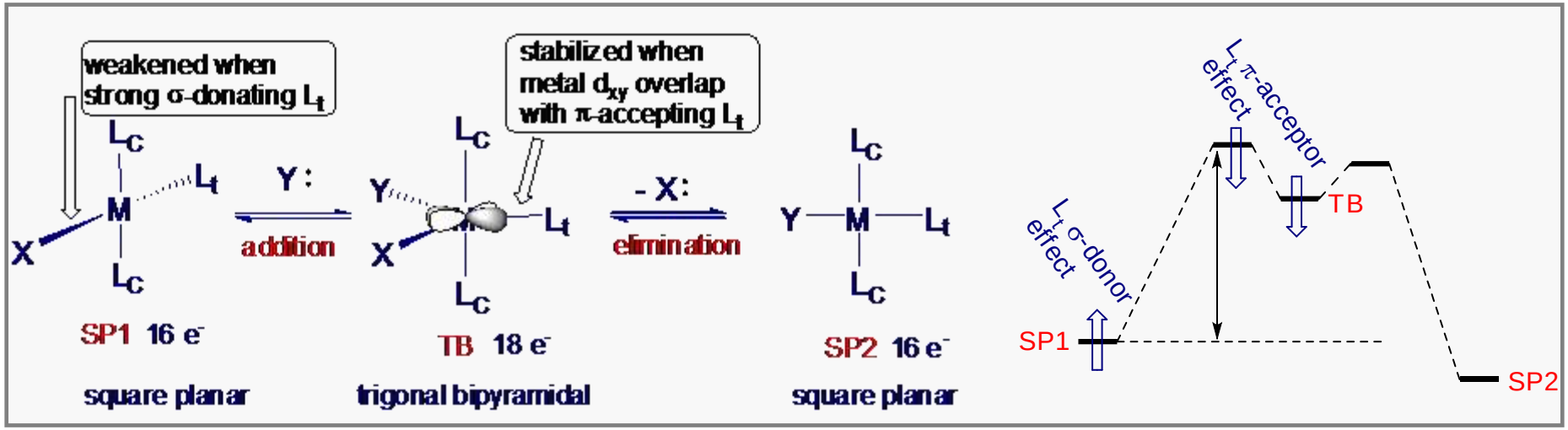
Let us consider an associative ligand substitution on a d^8 square planar complex. Association of the incoming ligand generates a five-coordinated intermediate with the original trans ligand L_t in the equatorial plane. The incoming ligand (Y) will approach the metal occupying an equatorial position of the five-coordinated intermediate, and, due to the principle of microscopic reversibility, the departing ligand (X) will also leave from the remaining equatorial position.

Both **strong σ-donor** and **strong π-acceptor ligands** favor formation of the trigonal bipyramidal intermediate, though, for different reasons. Indeed, the former ligands **destabilize the initial square planar** complex weakening the M-X bond, whereas the latter ones **stabilize the trigonal bipyramidal** intermediate (hence its transition state, too; see Hammond's postulate). The net result is departure of the ligand trans to L_t.

The trans effect has important implications in the mechanism of several catalytic processes such as hydrogenations or asymmetric Pd-catalyzed allylations.

The Trans Effect

Let us consider an associative ligand substitution on a d^8 square planar complex:



2nd order rate depending on :

Incoming ligand Y : $R_3P > Py > NH_3$, Cl- > H_2O > OH-

Leaving ligand X : $NO_3^- > H_2O > Cl^- > Br^- > I^- > N_3^- > SCN^- > NO_2^- > CN^-$

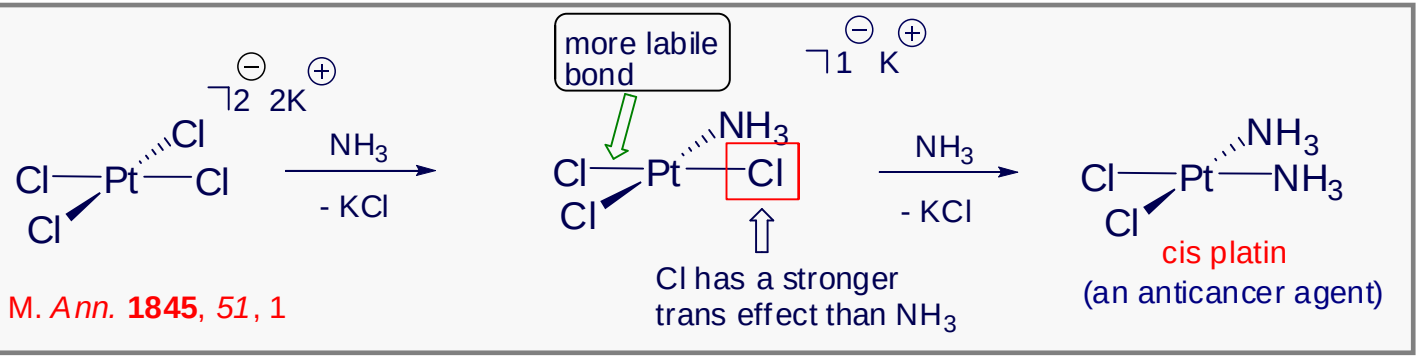
Trans ligand* : $R_3Si- > H- \sim CH_3^- \sim CN- \sim$ olefins ~ CO > $PR_3 \sim NO_2^- \sim I^- \sim > Br^-$ Cl^- > $RNH_2 \sim NH_3 > OH^- > NO_3^- \sim H_2O$

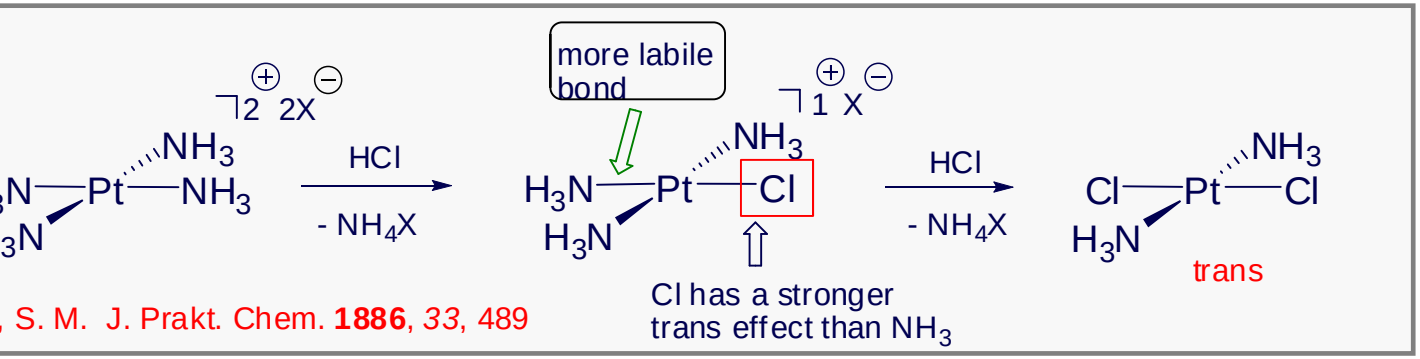
* Ligand trans with respect to the one being displaced

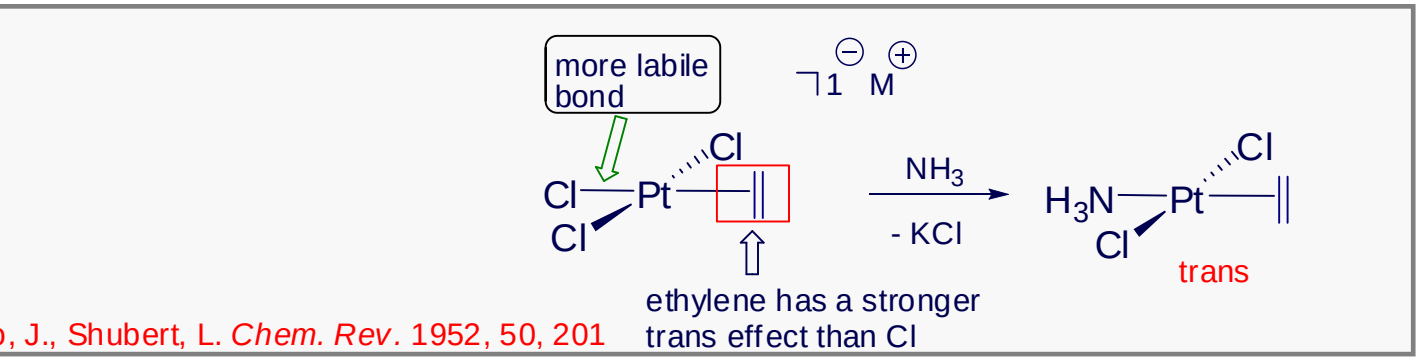
Frankcombe, K. E.; Cavell, K. J.; Yates, B. F.; Knott, R. B. *Organometallics,* **1997**, *16*, 3199.

The Trans Effect

Some well-know examples of the trans effect



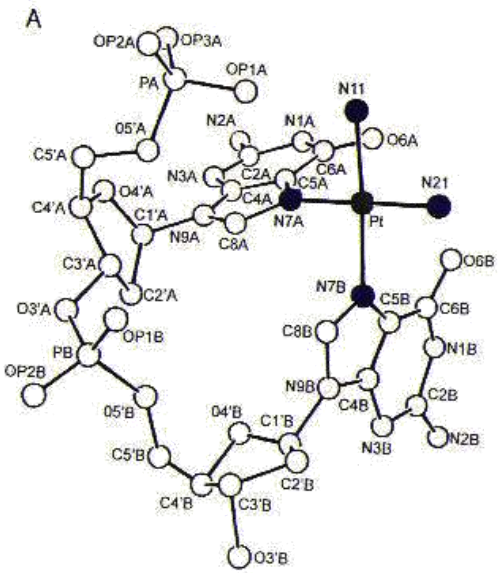




About cis-platin

After administration of cis-platin, a chloride ligand is displaced by water, then by a guanine base of DNA to give $[PtCl(guanine\text{-}DNA)(NH_3)_2]^+$. Crosslinking then occurs via displacement of the other chloride ligand, usually, by another guanine of DNA.

This event interferes with cell division by mitosis. The damaged DNA first elicits DNA repair mechanisms, then, activates apoptosis when repair proves impossible.



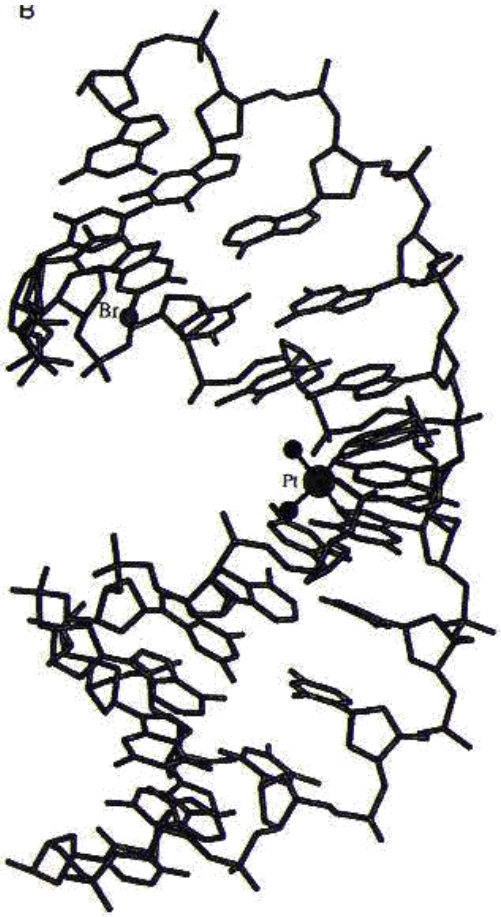
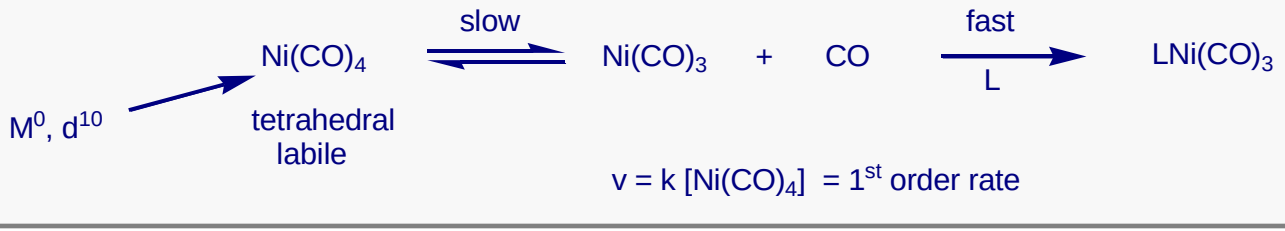


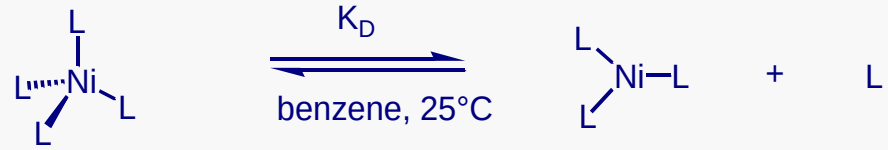
Image taken from: http://chemcases.com/cisplat/cisplat12.htm Left: the structure of cisplatin coordinated to a dinucleotide containing two guanines. Notice the destacking of guanine bases, which would normally be parallel to one another. Right: the structure of cisplatin coordinated to two guanines in a DNA duplex.

Pil, P., Lippard, S. J. *In Encyclopedia of Cancer,* J. R. Bertino, Ed. Academic Press: San Diego, CA, 1997, Vol. 1, pp. 392-410.

Dissociative Ligand Substitutions

The rate of the ligand exchange can be accelerated by bulky ligands , since loss of one ligand leads to release of steric strain

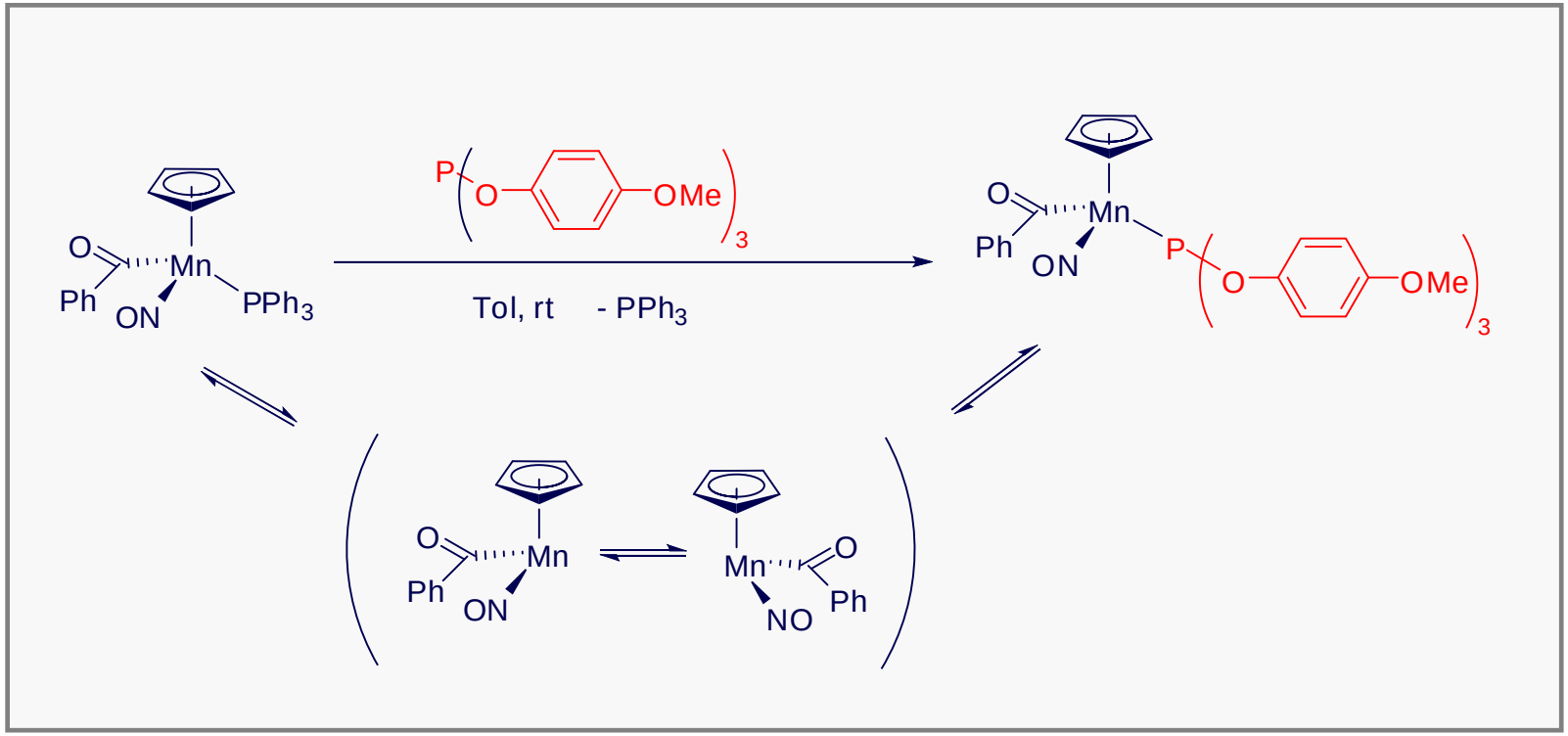




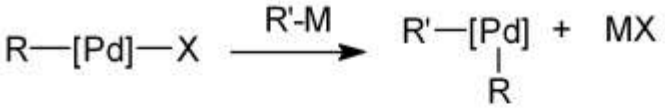
Ligand	$P(OEt)_3$	$P(O\text{-}p\text{-}Tol)_3$	$P(O\text{-}i\text{Pr})_3$	$P(O\text{-}o\text{-}Tol)_3$	PPh_3
Cone Angle	109°	128°	130°	141°	145°
K_D	$< 10^{-10}$	6×10^{-10}	2.7×10^{-5}	4×10^{-2}	No NiL_4

The ability to control the bulk of the ligand permits to tune the reactivity of the metal complex. For example, if the dissociation of the phosphine ligand is the first step in a reaction, the reaction can be accelerated by utilizing a larger phosphine ligand. Likewise, if dissociation is a problem, then a smaller phosphine can be used.

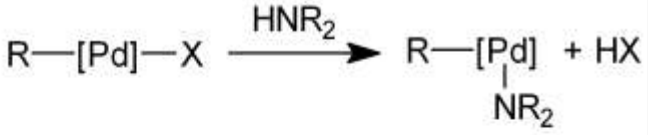
Dissociative Ligand Substitutions



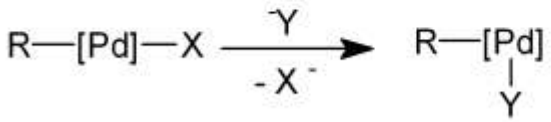
Some Examples of Ligand Substitution



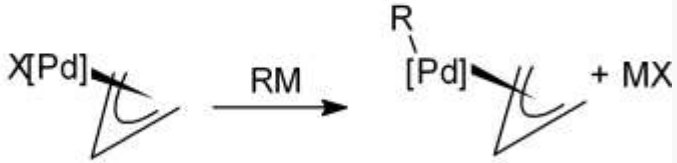
Nucleophilic addition of main group organometallic reagents. Especially useful with M = Zn, Sn, B



Nucleophilic addition of amines



Nucleophilic addition of anionic nucleophiles Y^-: H^-, NC^-

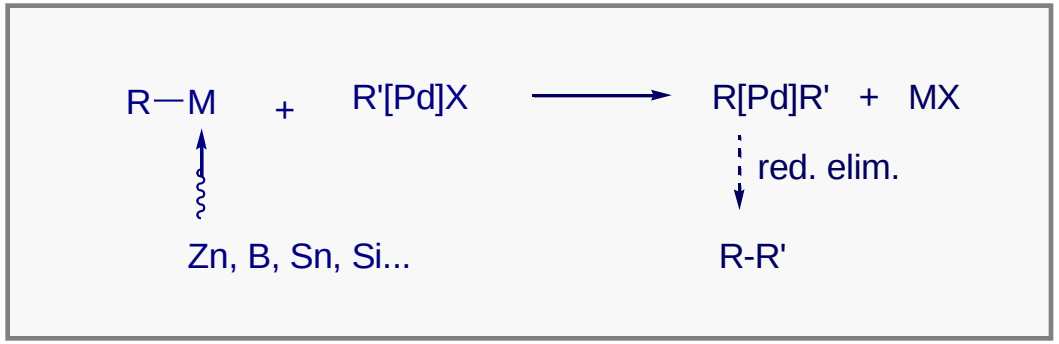


Nucleophilic addition of organometallic reagents (Sn) and hydrides to a π-allyl-Pd(II) complex

Transmetalation

Transfer of an R group from a main group organometallic compound to a TM complex.

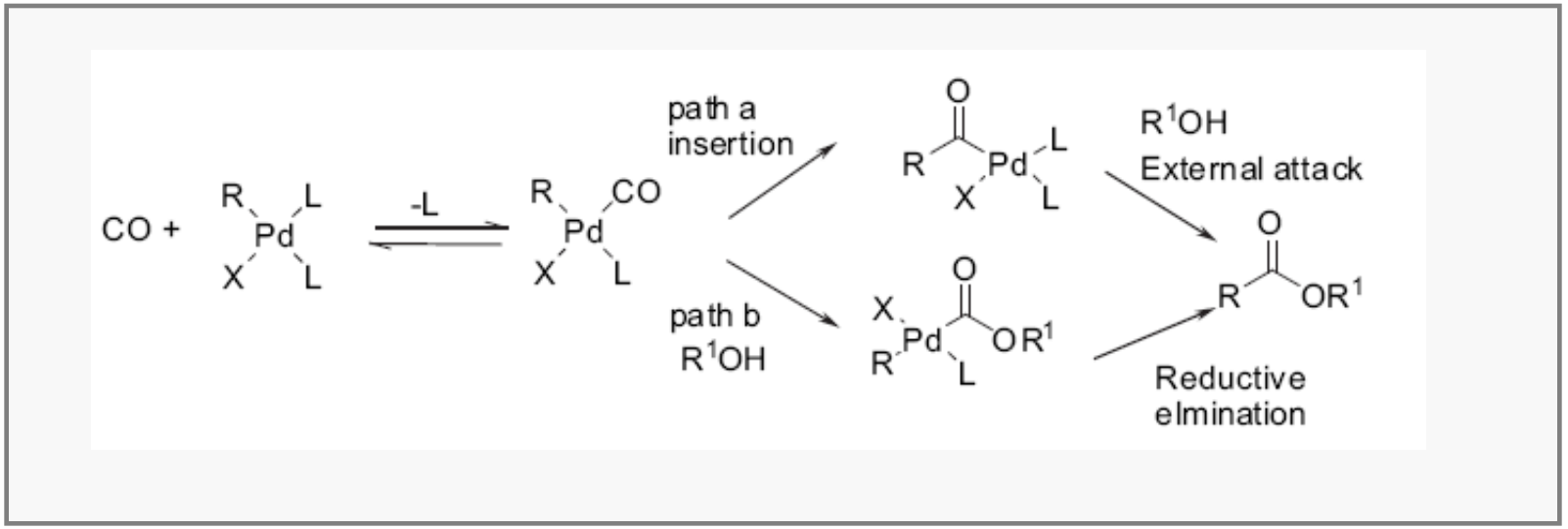
When combined with reactions which introduce an R group into the Pd complex such as oxidative additions or nucleophilic attack on alkenes, efficient C-C bond forming reactions ensue: cross-coupling (Zn: Negishi-Baba, B: Suzuki-Miyaura, Sn: Migita-Kosugi-Stille, Si: Hiyama,…)



The main group organometallic must be more electropositive than Pd.
The nature of X is also important.

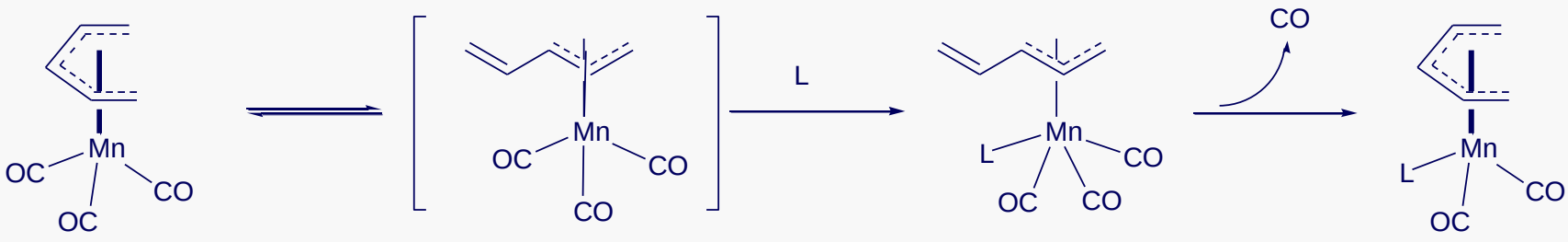
Anion Capture

The nucleophilic addition at palladium is usually followed by the reductive elimination, and the combination of these two elementary steps is known as the *anion capture*. The transiently generated σ-alkylpalladium complexes can be alkoxycarbonylated, with concomitant regeneration of Pd(0), by treatment with carbon monoxide in the presence of an alcohol (usually methanol) or amines.



Stille, J. K. in *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I. Eds.; Pergamon Press, **1991**, vol. 4, p. 932.
Copéret, C.; Sugihara, T.; Negishi, E. *Tetrahedron Lett.*, **1995**, *36*, 1771.

Ligand Exchange via Slippage



Mn^{I} ; d^{6} ; 18 e^{-}
saturated

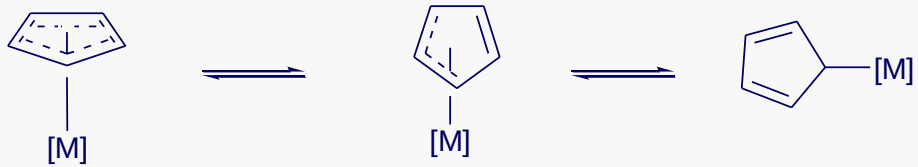
Mn^{I} ; d^{6} ; 16 e^{-}
unsaturated

Mn^{I} ; d^{6} ; 18 e^{-}
saturated (isolated)

Mn^{I} ; d^{6} ; 18 e^{-}
saturated

η^{3}- allyl
(2 sites)

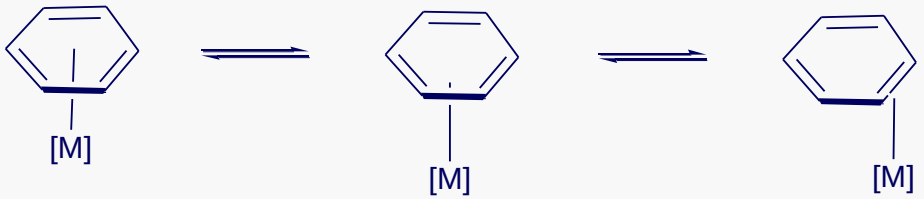
η^{1}- allyl
(1 site)



η^{5}- Cp
(3 sites)

η^{3}- Cp
(2 sites)

η^{1}- Cp
(1 site)



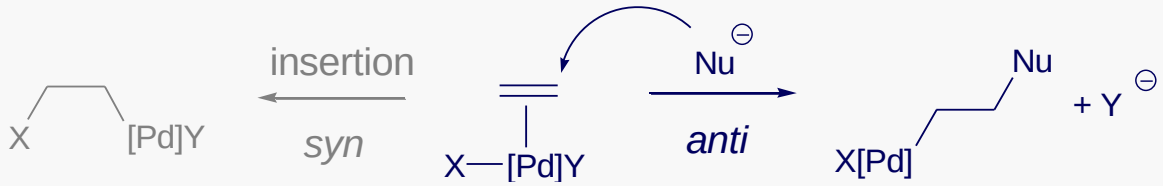
η^{6}-arene
(3 sites)

η^{4}-arene
(2 sites)

η^{2}-arene
(1 site)

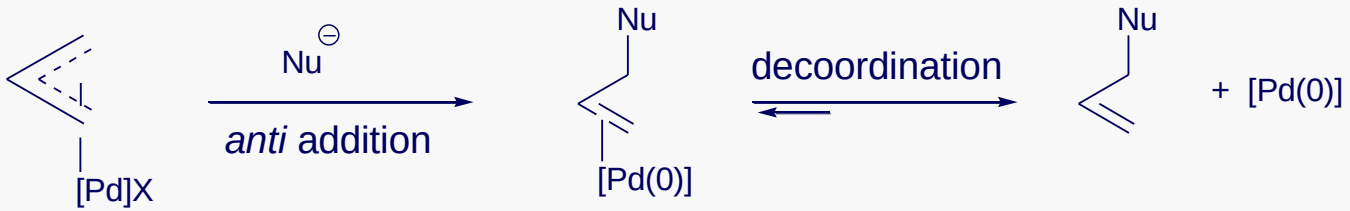
Nucleophilic Attack on Coordinated Ligands

Alkenes: direct attack at the ligand, anti to the metal, usually at the most substituted carbon atom



Nu: Cl^-, AcO^-, ROH, RNH_2, RLi

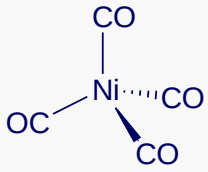
Allyles: stabilized nucleophiles attack the ligand, anti to the metal. Regioselectivity depends on the nature of the nucleophile and of the ancillary ligands



η3-allyl complex

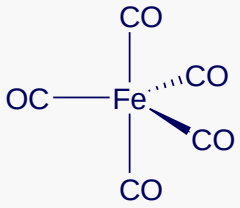
η^2–complex

Chemically Promoted Substitution

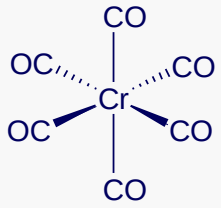


tetrahedral

easy dissociation



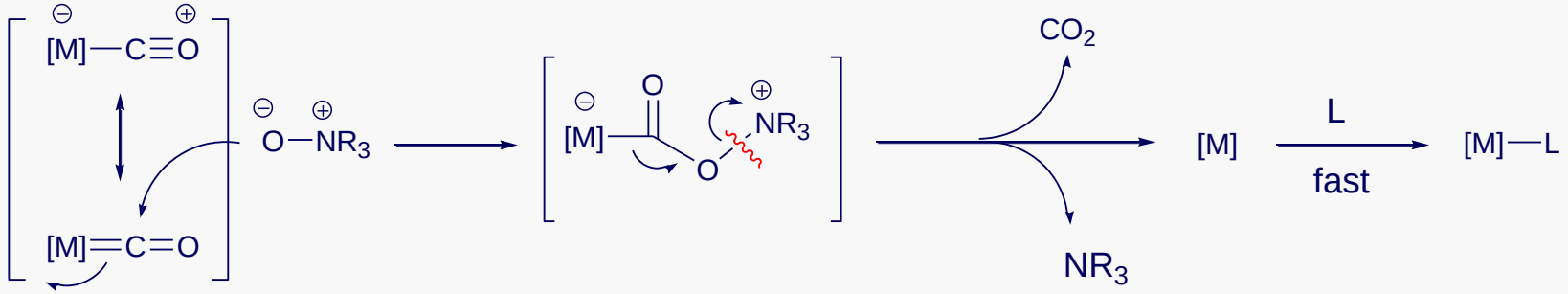
trigonal bipyramidal



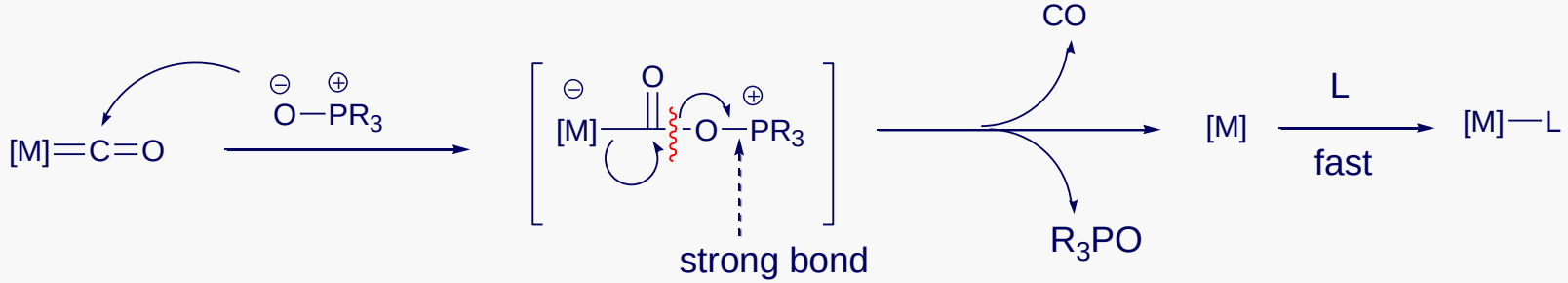
octahedral

these complexes undergo only promoted ligand substitution

Amine N-oxide promoted ligand dissociation



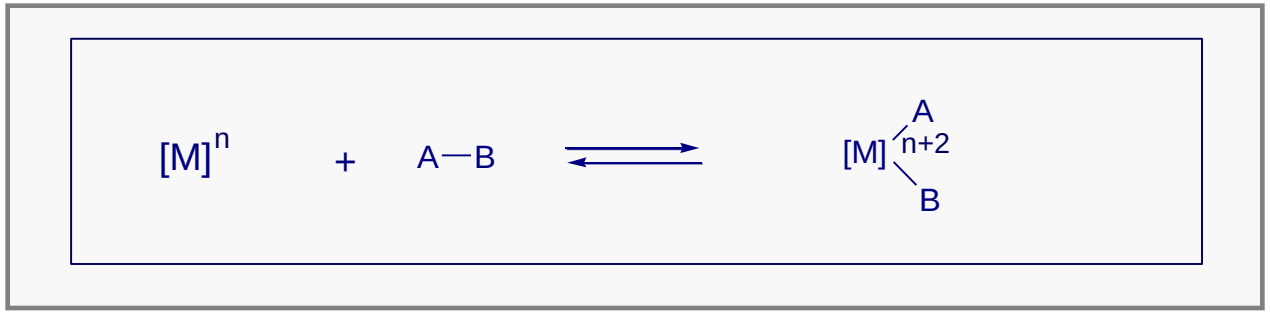
Phosphine-oxide promoted ligand dissociation



Oxidative Addition

Oxidative Addition

Pd(0) is electron rich and has a nucleophilic character. This transformation often represents the first step of a catalytic cycle and its mechanism depends on the nature of the metal as well as on the substrate involved. An increase of 2 in the formal oxidation state of the metal and of the coordination number is observed.



The most commonly encountered systems:

(d^{10} / d^{8}): Ni(0) / Ni(II), **Pd(0) / Pd(II)**

(d^{8} / d^{6}): Co(I) / Co(III), Rh(I) / Rh(III), Ir(I) / Ir(III)

Homogeneous Pd(0): The Seminal Paper

231. *Palladium(0) Compounds. Part II.*[1] *Compounds with Triarylphosphines, Triaryl Phosphites, and Triarylarsines.*

By L. Malatesta and (Miss) M. Angoletta.

The preparation of a number of complex compounds of zero-valent palladium with phosphorus donors is described. They can be prepared from $Pd(R{\cdot}NC)_2$ and donor, or by reduction of palladium(II) compounds in the presence of excess of donor.

Three types of complexes have been isolated : $(R{\cdot}NC)(L)_3Pd$, PdL_4, and PdL_3 (L = triarylphosphines and triaryl phosphites). The compounds PdL_4 are largely dissociated in solution.

The triphenylarsine complex $(Ph_3As)_4Pd$ has also been obtained.

Previously we mentioned [1] the reaction between di*iso*cyanopalladium(0) and tri-*p*-chloro phenyl phosphite which yielded a mixed phosphite–*iso*cyanide complex. This is a genera reaction, and is shown by triaryl phosphites, triarylphosphines, and triarylarsines. Its course however, varies with the *iso*cyanide which forms complexes with palladium(0) and the sub stituting ligand (*e.g.*, phosphines, arsines, and various *para*-substituted triphenyl phosphites)

Oxidative Addition: The Seminal Paper

CHEMICAL COMMUNICATIONS, 1968

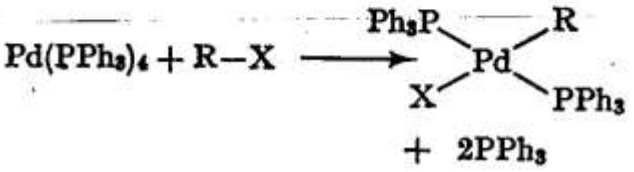
Oxidative Additions to Palladium(0)

By P. FITTON,* M. P. JOHNSON, and J. E. MCKEON

(*Research and Development Department, Union Carbide Corporation, Chemicals and Plastics, South Charleston, West Virginia* 25303)

THE oxidative addition of chloro-olefins to palladium(0)–phosphine complexes, described in the preceding Communication, has now been extended to other organic compounds which contain a carbon–halogen bond, and has been found to be a general method for the preparation of palladium(II) complexes, difficult to prepare by other methods.

The products were obtained in good yield by the addition of the halogenocarbon to a suspension of $Pd(PPh_3)_4$ in benzene at room temperature. Removal of benzene *in vacuo* gave a solid which was triturated with ether to remove triphenylphosphine. Recrystallization of the residue from methylene chloride–hexane gave the pure complexes.†

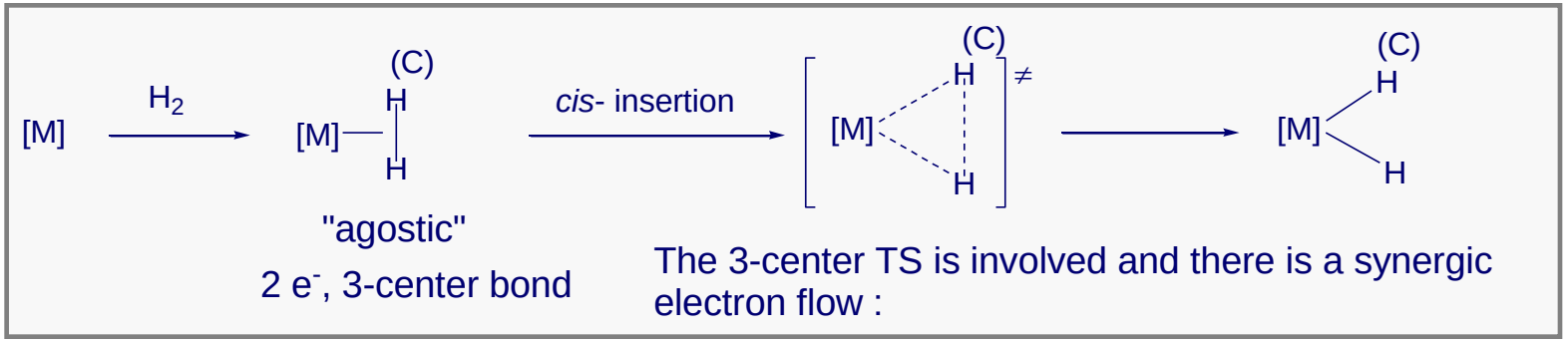


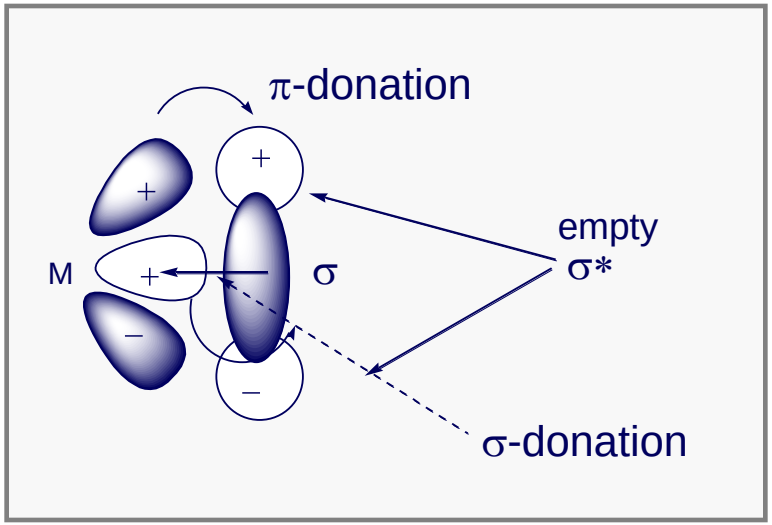
variation of ν(Pd–Cl) was noted in the complexes derived from chloro-olefins.[2] The *trans*-configuration of the products does not illuminate the stereochemistry of the oxidative addition. The *cis*-isomers are generally the less stable forms in the palladium series and isomerization is easy, particularly in the presence of excess triphenylphosphine.[3]

When methyl iodide was added to bis(triphenylphosphine)palladium(0)[2] the product after recrystallization was identical with that obtained when $Pd(PPh_3)_4$ was used. This complex (I) gave an n.m.r. spectrum consistent with the proposed structure; the methyl protons appear at 0·18 p.p.m., split into a 1 : 2 : 1 triplet by coupling to two phosphorus nuclei (J = 5·0 c./sec.). Occasionally the reaction of methyl iodide and $[Pd(PPh_3)_2]_x$ gave an adduct, the n.m.r. spectrum of which contained, in addition to the usual triplet at 0·18, a second 1 : 2 : 1 triplet of comparable intensity at −0·10 p.p.m. (J = 5·0 c./sec.). This was at first attributed to the presence of some

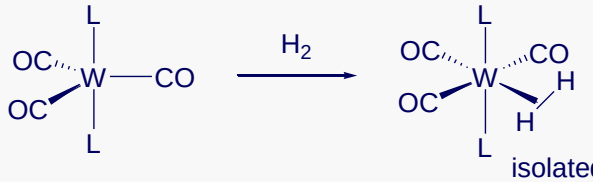
Non-polar Substrates

Oxidative addition of H_2 takes place via a 3-center mechanism (central to catalytic hydrogenation and related to C-H bond activation).

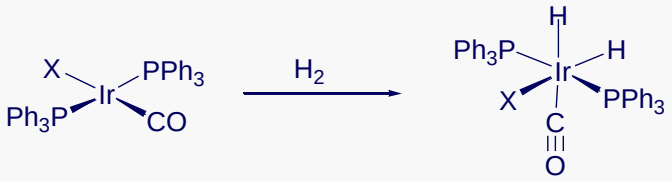




Proof of the mechanism :



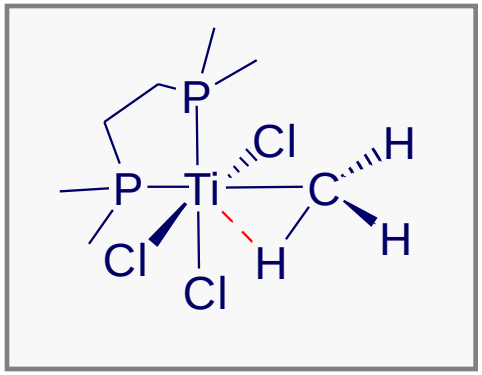
Proof of the structure :

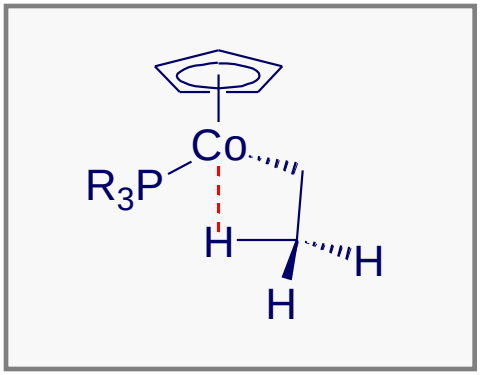


IR: 2 M-H stretching bands (symm and asymm). If trans, only asymm. is expected

By the Way: Agostic

Agostic interactions :



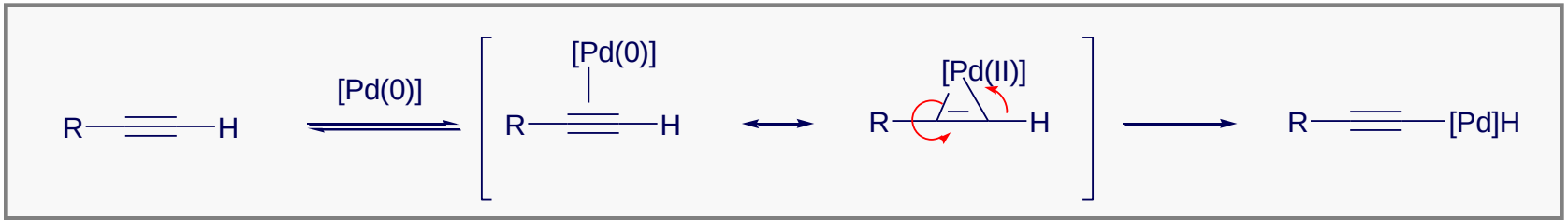


From the Greek :

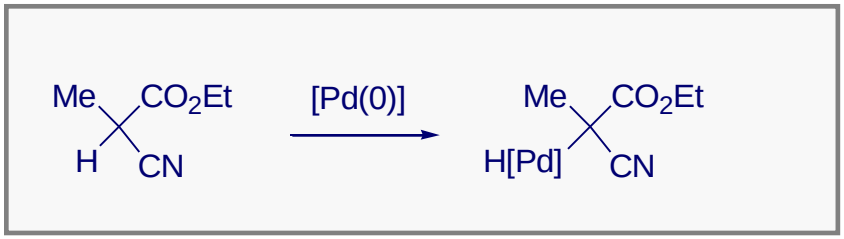
to hold one to oneself. It refers to a C-H bond on a ligand that undergoes an interaction with the metal complex.

Oxidative Addition of CH or OH Bonds

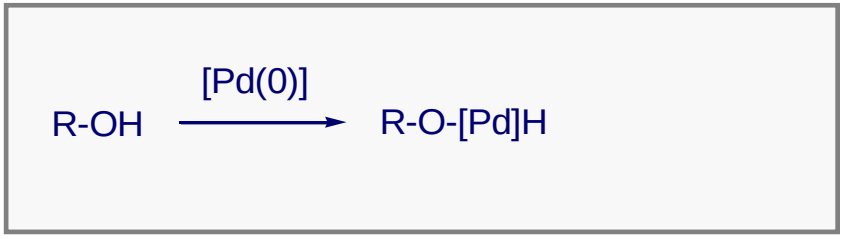
terminal alkynes



active methylenes



alcohols



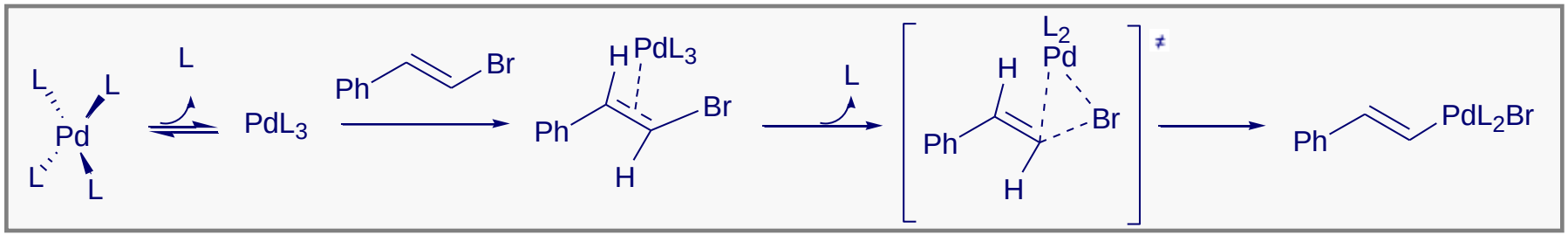
Oxidative Addition of Vinyl and Aryl Halides

Halides: If the halide carries a β-H, dehydropalladation (β -H elimination) may be a facile, and normally undesired, process, thereby generating an alkene. Accordingly, the most widely used substrates are vinyl-, aryl or benzyl-halides, whose corresponding σ-alkyl Pd complexes have no β-H.

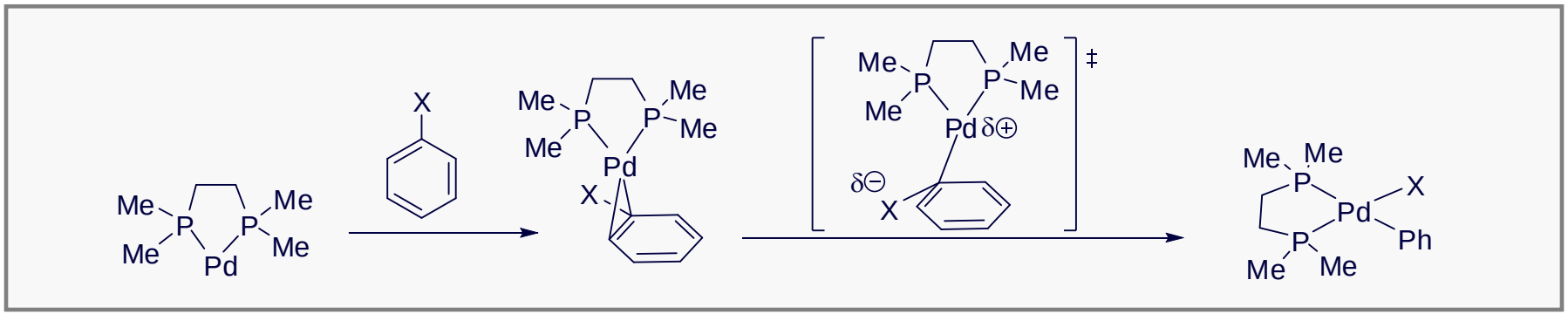
The better the leaving group, the faster the oxidative addition: N_2^+ >> TfO > I > Br > OTs > Cl

Jutand, A.; Négri, S. *Organometallics*, **2003**, *22*, 4229

vinyl halides: clean retention mechanism is observed

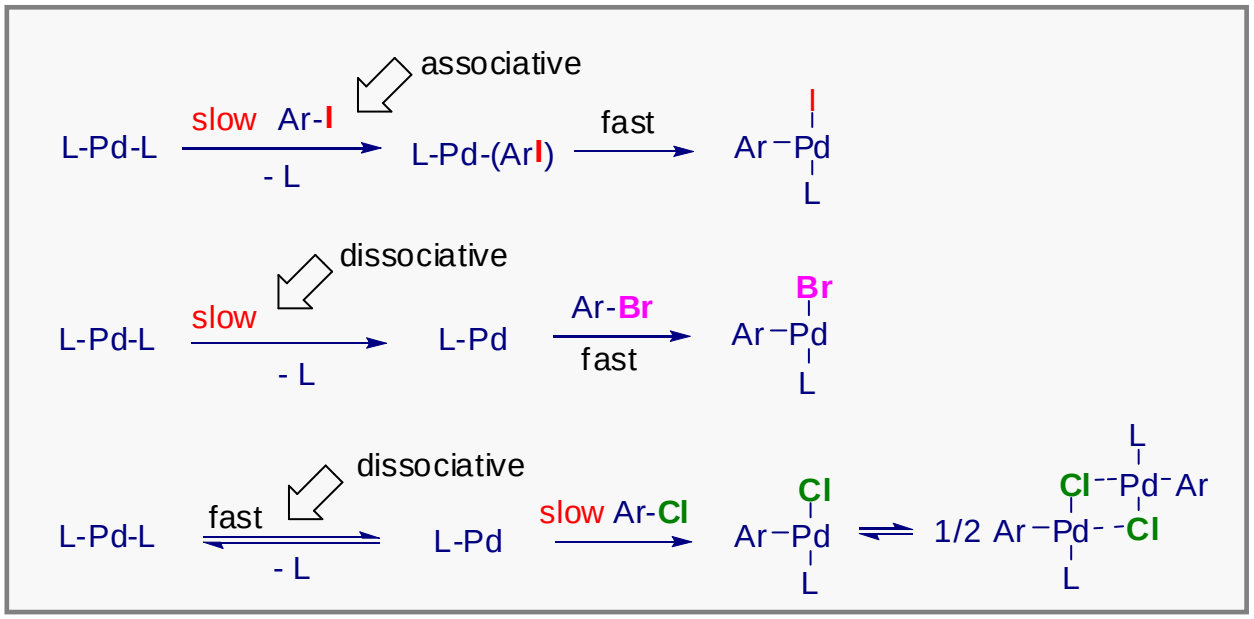


aryl halides: via an η^2-arene pre-reaction complex



Senn, H. M.; Ziegler, T. *Organometallics* **2004**, *23*, 2980

Rates of Oxidative Addition of Aryl Halides

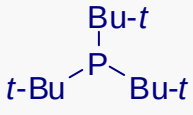


Oxidative addition of chloro-, bromo-, and iodoarenes to sterically hindered (QPhos-tol)$_2$Pd occurs through three different mechanisms. Addition of PhI occurs by associative displacement of a phosphine. Addition of PhBr occurs by rate-limiting dissociation of phosphine. Addition of PhCl occurs by reversible dissociation of phosphine, followed by rate-limiting oxidative addition.

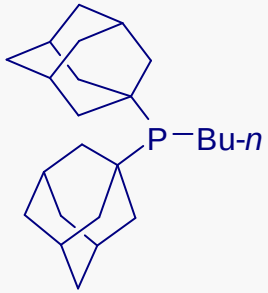
Barrios-Landeros, F.; Hartwig, J. F. *J. Am; Chem. Soc.* **2005**, *127*, 6944

Barrios-Landeros, F.; Carrow, B. P.; Hartwig, J. F.. *J. Am. Chem. Soc*. **2009**, *131*, 8141

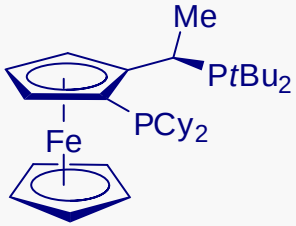
“Special” Phosphines for Suzuki and Other Couplings



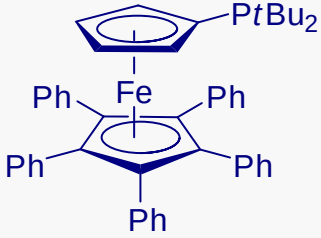
PBu-t_3
(Fu)



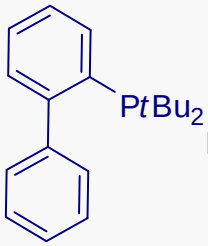
CataCXium A
(Beller)



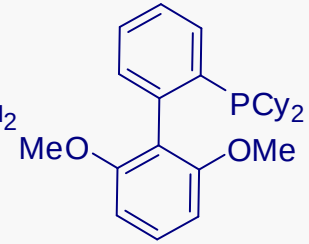
Josiphos
(Hartwig)



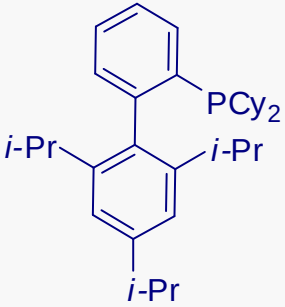
QPhos
(Hartwig)



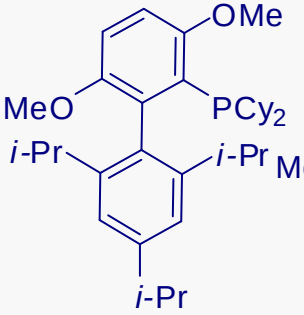
JohnPhos
(Buchwald)



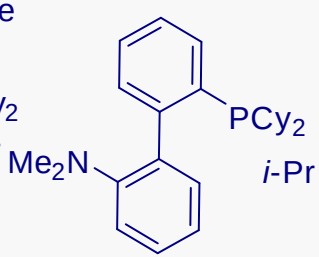
SPhos
(Buchwald)



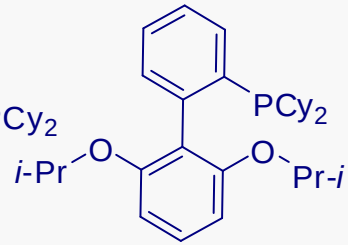
XPhos
(Buchwald)



Brettphos
(Buchwald)



DavePhos
(Buchwald)



RuPhos
(Buchwald)

The first hint: “…significant catalytic activity is found only with phosphines which are both strongly basic (pKa 4 6.5) and with well defined steric volume, i.e. the cone angle theta must exceed ca. 160°.”
M. Huser, M.-T. Youinou and J. A. Osborn, *Angew. Chem., Int. Ed. Engl.*, **1989**, *28*, 1386.

Some References About These Special Ligands

Fleckenstein, C. A. Plenio H. *Chem. Soc. Rev.,* **2010**, *39*, 694

Martin, R.; Buchwald, S.L. *Acc. Chem. Res.* **2008**, *41*, 1461

Zapf A., Beller, M. *Chem. Commun*., **2005**, 431

Zapf, A.; Ehrentraut, A.; Beller, M. *Angew*. *Chem*., *Int*. *Ed*. **2000**, 39, *4153*

Hartwig, J.F., *Acc. Chem. Res.* 2008, **41**, 534.

Fu, G. C. *Acc. Chem. Res.* **2008**, *41*, 1555

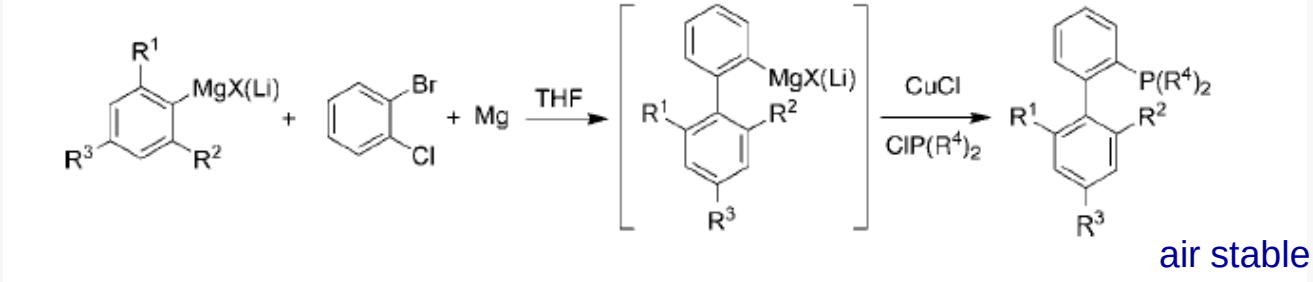
Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011** *111*, 1417-1492.

Wasa, M.; Engle, K. M.; Yu, J. Q. *Isr. J. Chem*. **2010**, *50*, 605-616

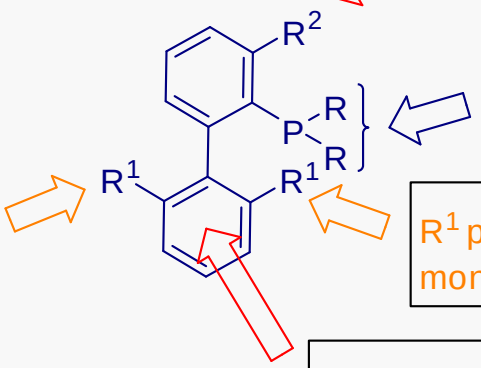
These specially designed phospines have been mainly developed to run difficult cross-coupling reactions (Suzuki coupling, Buchwald-Hartwig aromatic amination, etc.), see later. As we will see, they not only favor oxidative addition step, but may also facilitate other steps of the catalytic cycle.

Features of Buchwald Dialkyl *ortho*-biarylphosphines

General synthesis



air stable



R^2 fixes conformation of R_2P over the bottom ring enhancing rate of reductive elimination

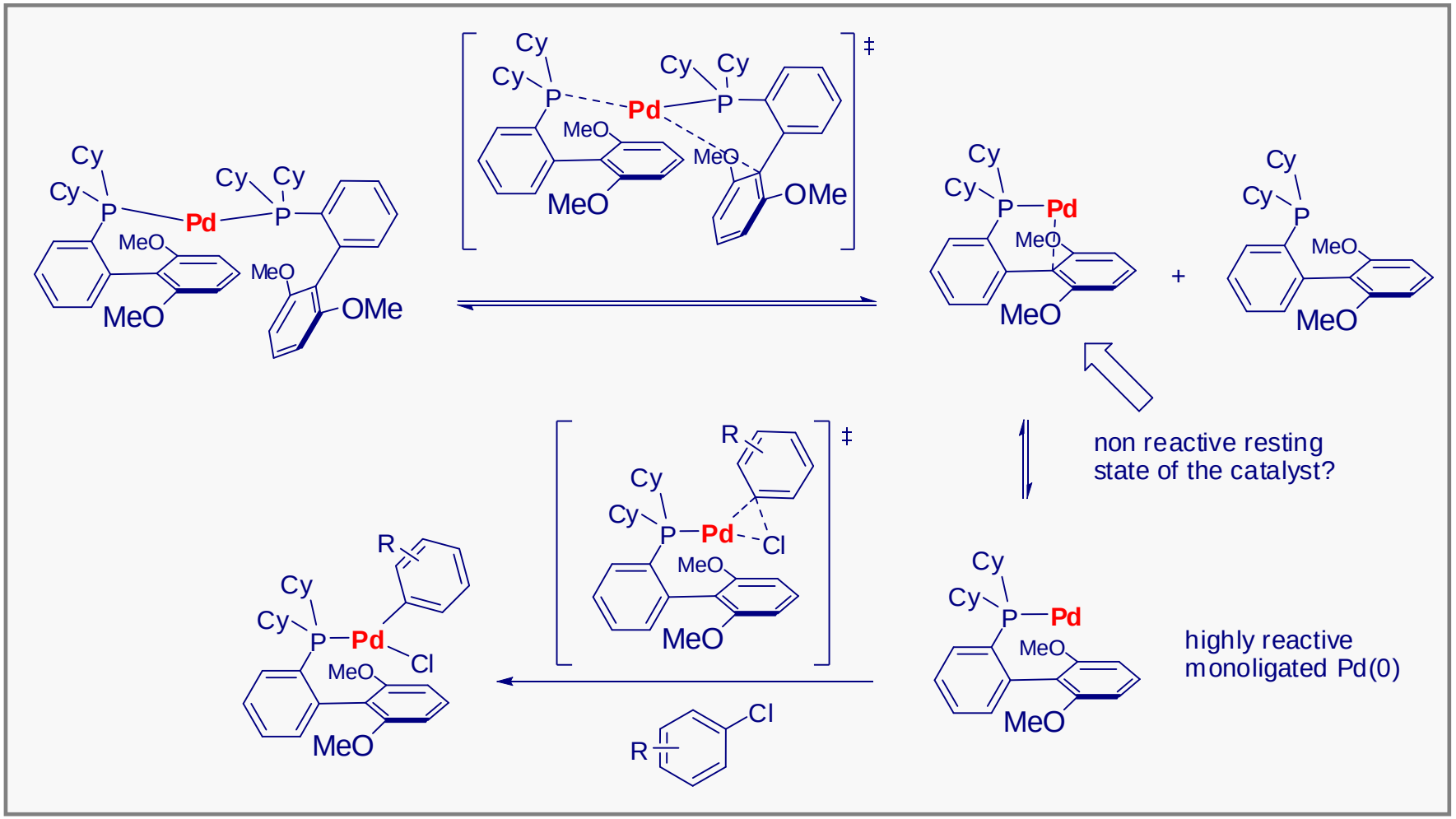
electron-rich alkyl substituents R increase oxidative addition rate large R substituents enhance the rate of reductive elimination and large R substituents favor monoligand complexation [L_1Pd(0)]

R^1 prevent cyclometalation. If bulky favor monoligand complexation [L_1Pd(0)]

The *o*-substituted aromatic ring slows rate of oxidation by oxygen and stabilizes Pd via Pd-Ar π-interaction

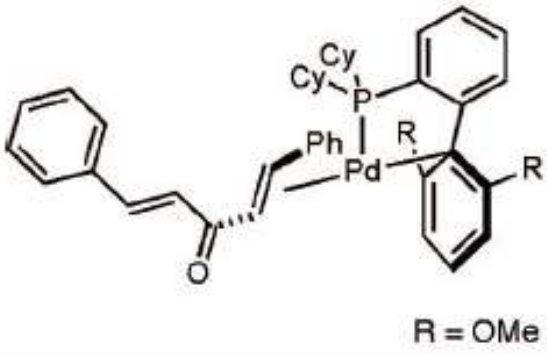
Adapted from:
Martin, R.; Buchwald, S.L. *Acc. Chem. Res.* **2008**, *41*, 1461

Mechanistic Hypothesis for Oxid. Add. of Sphos-Pd

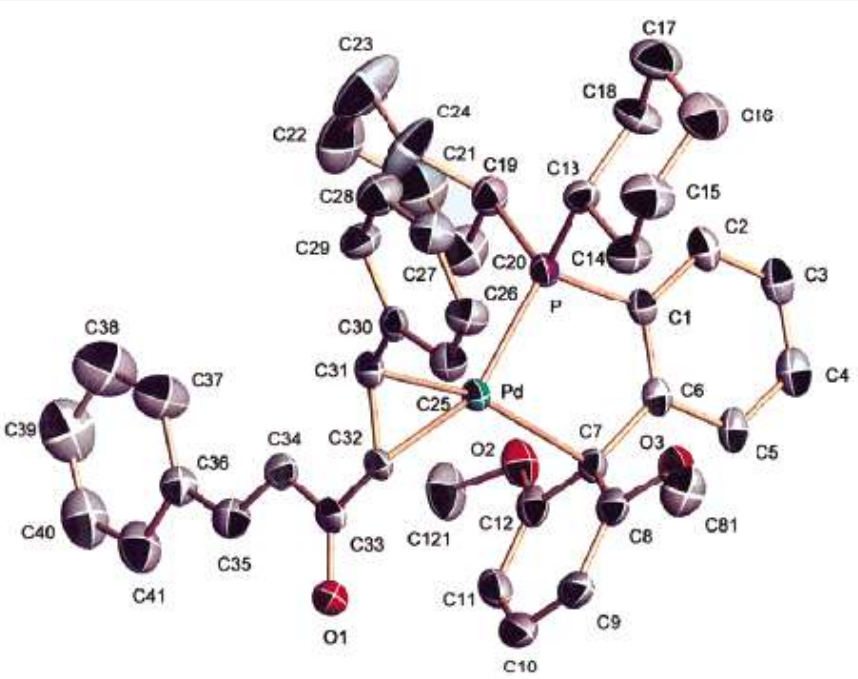


Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685.

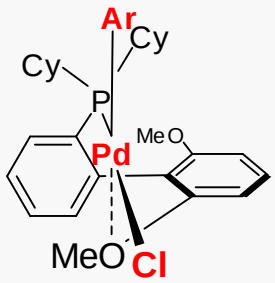
X-Ray Structure Sphos-dba and Oxid. Add. Computations



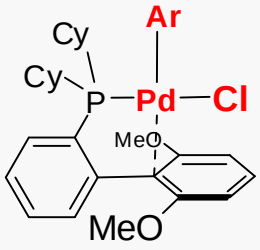
X-Ray crystal structure of dba-SPhos



Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685.



E_{rel} 0.0 kca/mol
O-Pd coordination



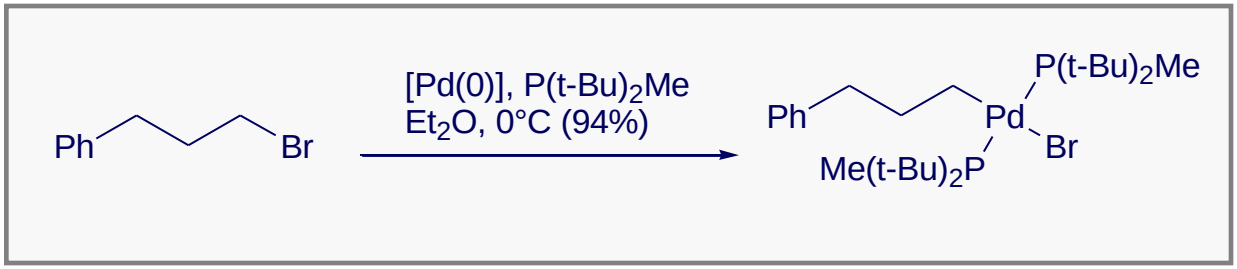
E_{rel} 0.8 kca/mol
η^1-aryl-Pd coordination

DFT

Barder, T. E.; Biscoe, M. R.; Buchwald, S. L. *Organometallics* **2007**, *26,* 2183.

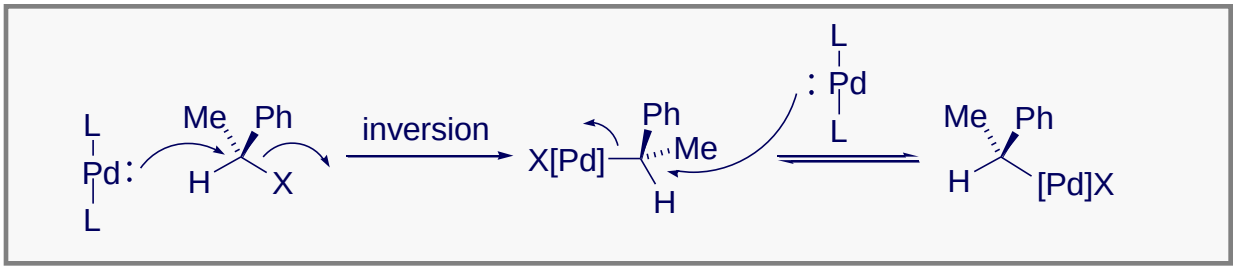
Alkyl and Benzyl Halides

However, in the presence of suitable electron rich bulky phosphines, or heterocyclic carbenes, oxidative addition to Pd(0) becomes so facile that alkyl halides having β-hydrogens can afford the corresponding σ-alkyl complexes under very mild conditions and without subsequent dehydropalladation.



Kirchhoff, J.H.; Netherton, M. R.; Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.,* **2002**, *124*, 13662

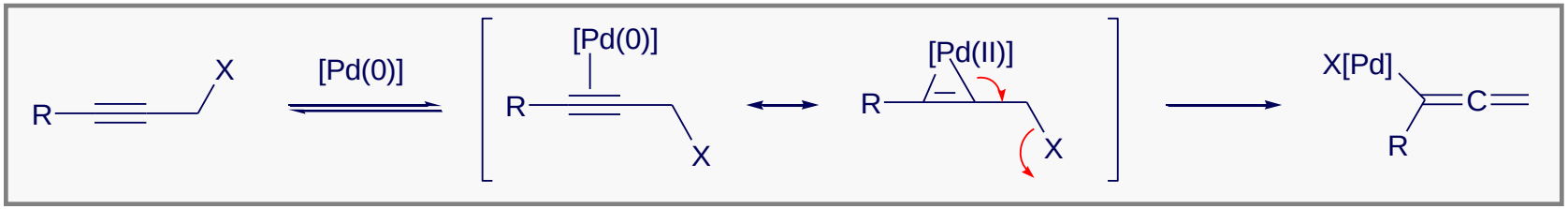
Alkyl halides oxidatively add to Pd(0) via a SN2 like process. Inversion mechanism is observed……but sometimes racemisation via double inversion takes place



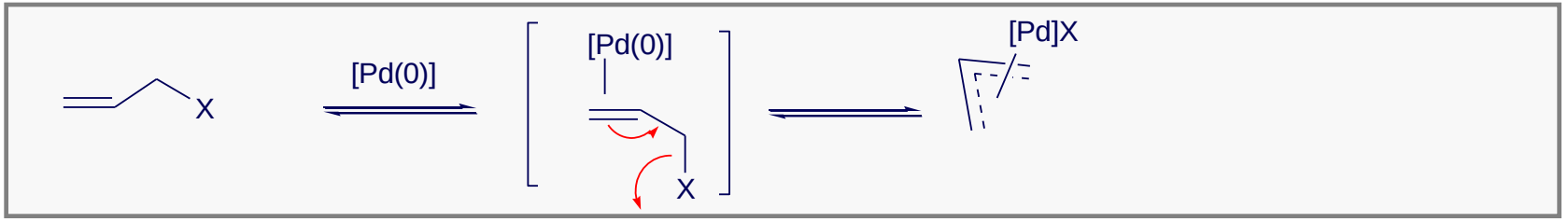
Stille, J. K.; Patai, S. Ed. *The chemistry of the metal-carbon bond*, vol. 2, Wiley, **1985**, chap 9.
Netherton, M.R.; Fu, G. C. *Angew. Chem. Int. Ed.* , **2002**, *41*, 3910

Allyl and Propargyl Systems

propargylic systems (X = leaving group)

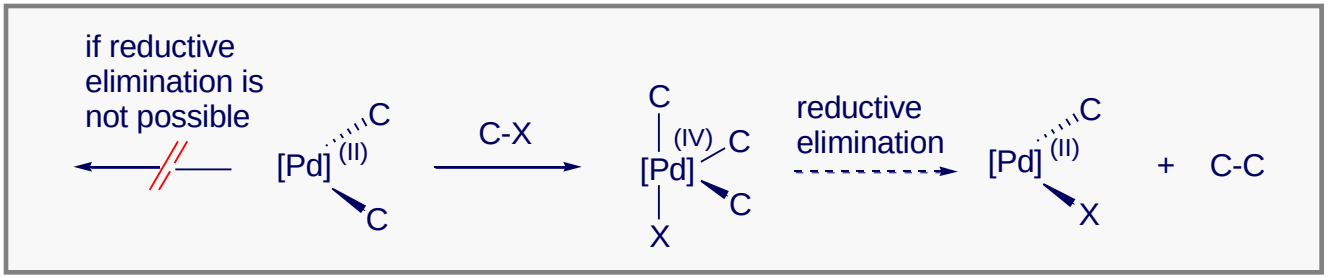


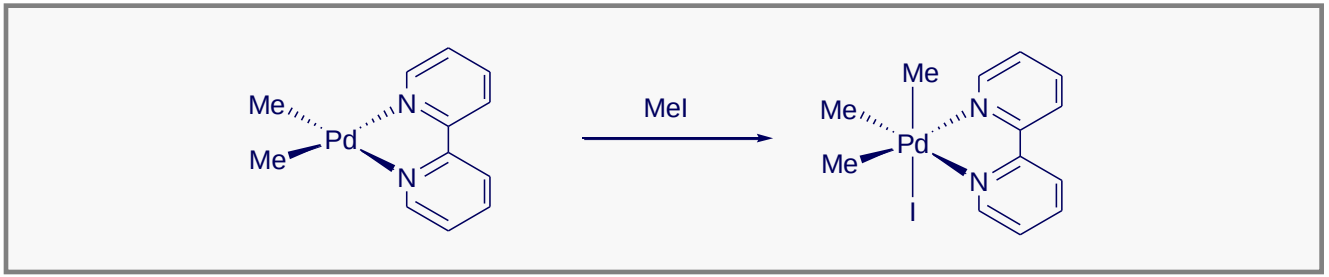
allylic systems (X = leaving group)



From Pd(II) to Pd(IV)

Alkyl halides may also oxidatively add to R-Pd(II)-R complexes to give a usually unstable Pd(IV) complex.

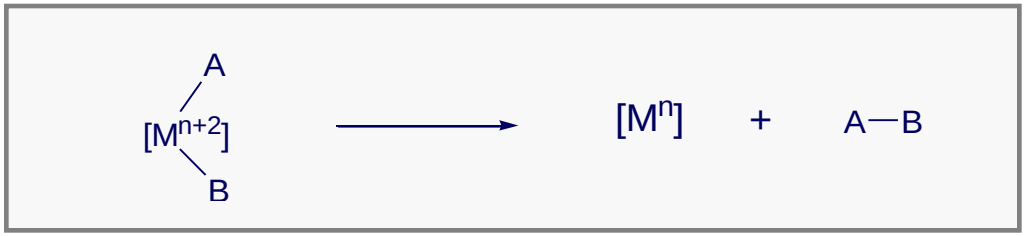




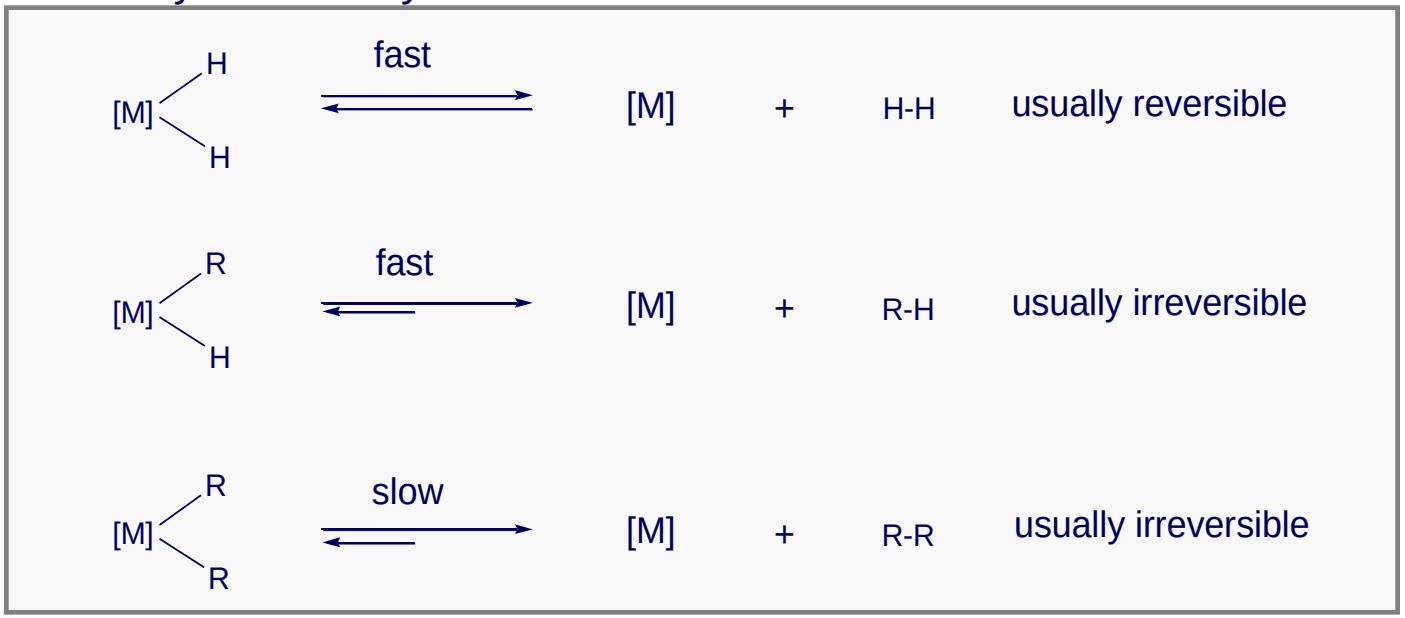
Canty, A.J., *Acc. Chem. Res.* **1992,** *25*, 83-90

Reductive Elimination

The reverse of oxidation addition
Reductive elimination produces coordinatively unsaturated metal centers



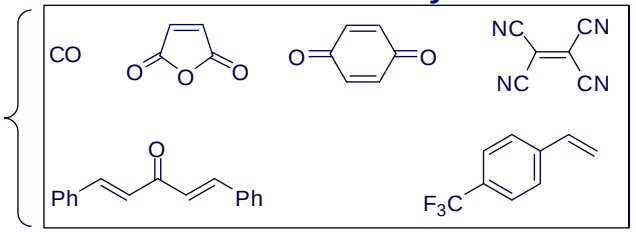
Thermodynamics may be different :



D_{M-R} = ~145 kJ/mol, D_{R-H} = ~ 420 kJ/mol, D_{M-H} = ~230 kJ/mol, D_{H-H} = ~435 kJ/mol, D_{R-R} = ~375 kJ/mol

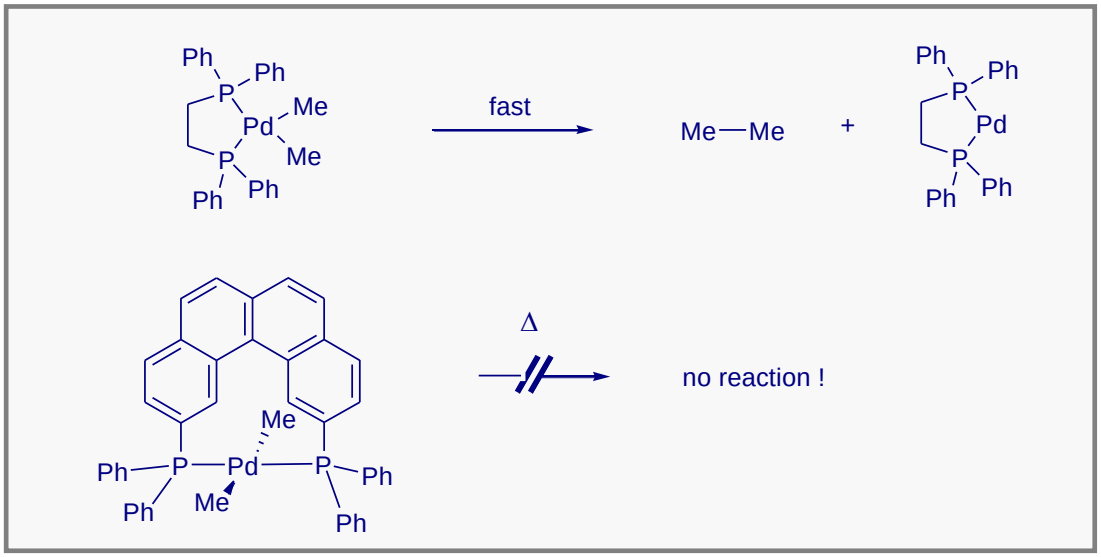
Reductive Elimination

Reductive elimination is favored by methods that reduce electron density on the metal
oxidation of the metal
addition of strong π-acceptor ligands* such as:
-Bulky monodentate ligands (Buchwald)



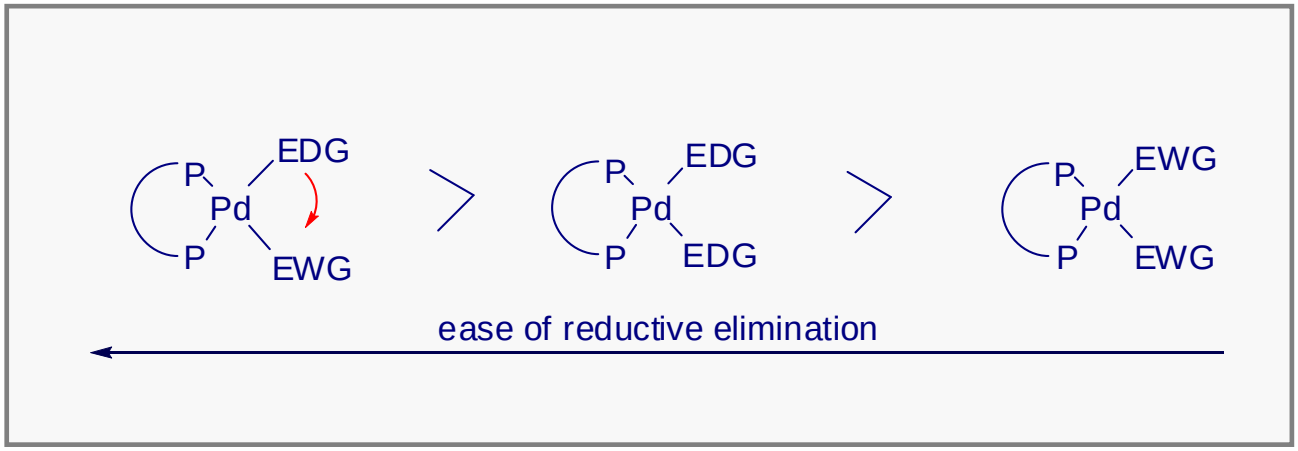
Reductive elimination is inhibited by excess phosphine

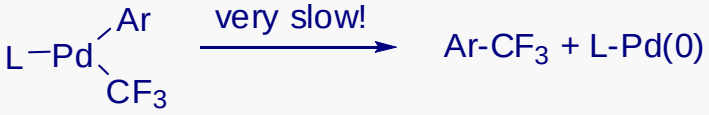
The fragments to be eliminated must occupy *cis* position on the metal or must rearrange from *trans* to *cis* prior to the reductive elimination. This is why ***chelating phosphines with large bite angles*** are best to favor RE.

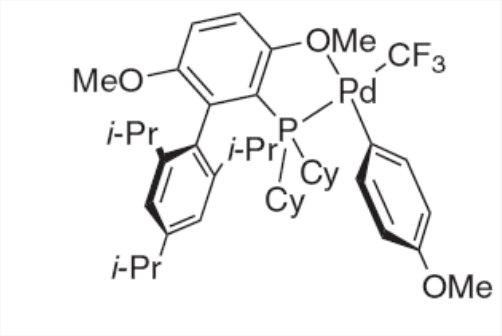


(*) Knochel, P. et al. *Angew. Chem. Int.* **1998**, *32*, 2387

Reductive Elimination



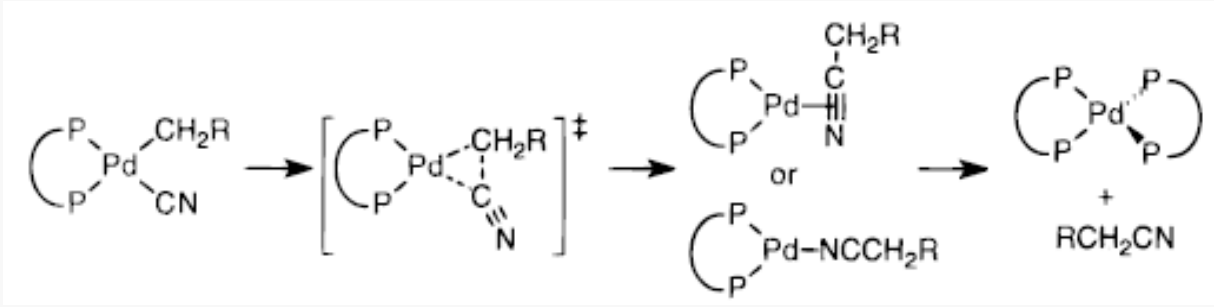




from BrettPhos

Watson, D.A, Buchwald, S.L. *et al. Science*, **2010**, *328*, 1679

Reductive Elimination

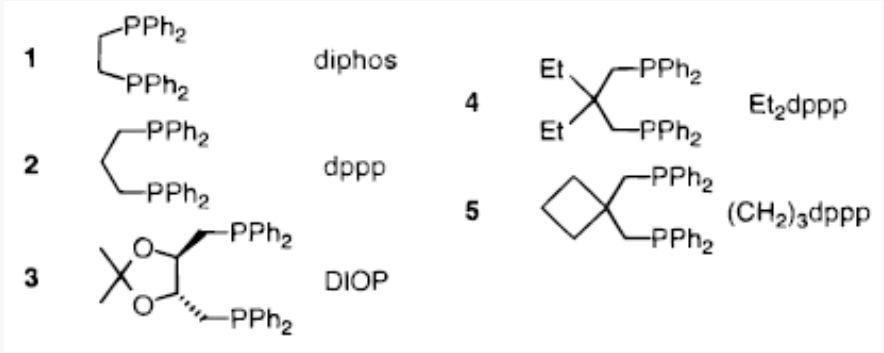


bite angle

slowest ~85°

~90°

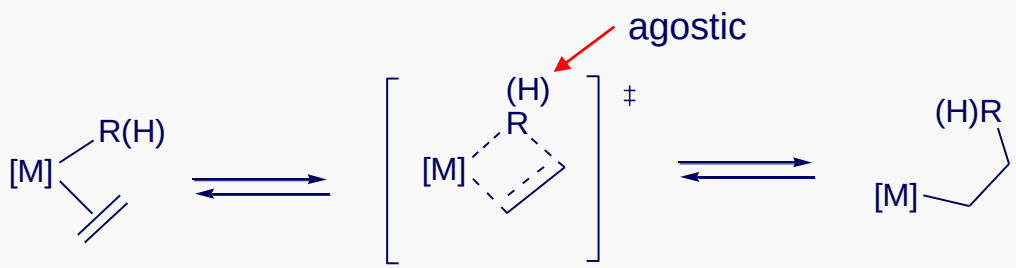
fastest ~100°



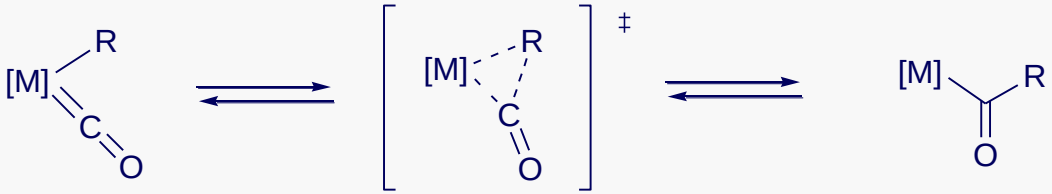
Complex	k at 80 °C (s^{-1})[a,b]	$\Delta H^{\ddagger}$ (kcal mol^{-1})[c]	$\Delta S^{\ddagger}$ (e.u.)[c]	temp range (°C)
1	2.1(0.2)e-6	30.8(3)	2.3(8)	85−119
2	5.0(0.7)e-5	27.3(1.2)	−1(3)	60−98
3	1.0(0.2)e-2	28.2(0.4)	12(1)	36−60
4	2.1(0.1)e-5	32.9(0.6)	13(2)	65−94
5	7.4(0.7)e-5	32.5(0.9)	14(3)	60−94
diphosPd (CH_2CMe_3)(CN)	2.6(0.1)e-5	28.7(0.5)	1(2)	66−87

J. E. Marcone, K. G. Moloy, *J. Am. Chem. Soc.* **1998**, *120,* 8527

Migratory Insertion / Dehydrometalation



migratory insertion —>
(carbo-, hydro-metalation)
β-elimination <—
(decarbo-, dehydro-metalation)



(CO) insertion

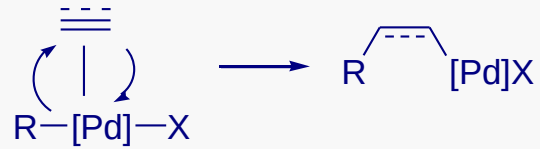
Usually a reversible process, no variation in the oxidation state

Both the metal and the migrating group add to the same face of the olefin (syn addition)

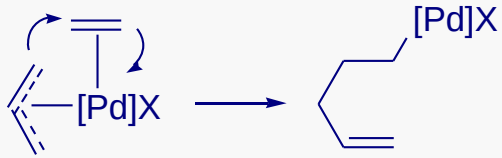
Migratory insertion generates a vacant site. Conversely, dehydrometalation (β-H elimination) requires a vacant *cis* site on the metal.

When an alkyl group migrates, its stereochemistry is maintained.

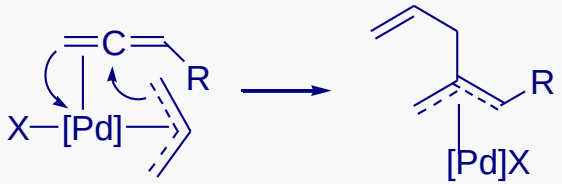
Migratory Insertion: Some Examples



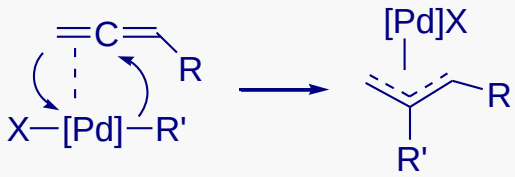
alkene or alkyne insertion into RPdX
R = H: hydropalladation; R = C: carbopalladation



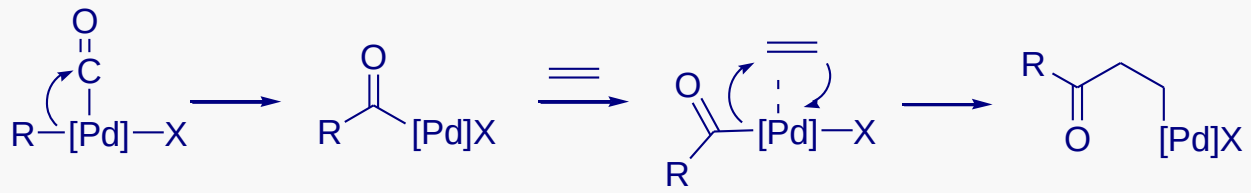
alkene insertion into π-allyl-PdX



allene insertion into π-allyl-PdX (R = C, H)



allene insertion into RPdX (R' = C, H)



CO insertion (carbonylation) into RPdX (R = C, H)

alkene insertion into acyl-PdX