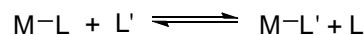


Elementary Organometallic Reactions

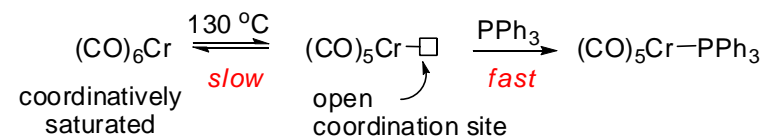
All mechanisms are simply a combination of elementary reactions.

- 1) Coordination -- Dissociation
- 2) Oxidative Addition -- Reductive Elimination
- 3) σ -bond metathesis
- 4) Atom abstraction
- 5) Addition -- Elimination
- 6) Alkyl-Acyl Intercoversion (CO migratory insertion)

Ligand Substitution Reactions



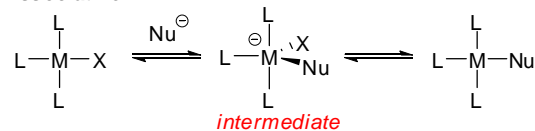
Dissociative (like S_N1)



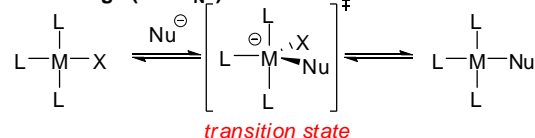
Associative Mechanisms

Very common for square planar complexes!

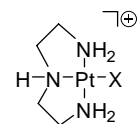
Associative



Interchange (like S_N2)



Relative rates of substitution at 25°C in H₂O



X	Nu	rel rate
Br	pyr	1
Br	N ₃ ⁻	2.3
Br	I ⁻	69
H ₂ O	pyr	57
I	pyr	0.5

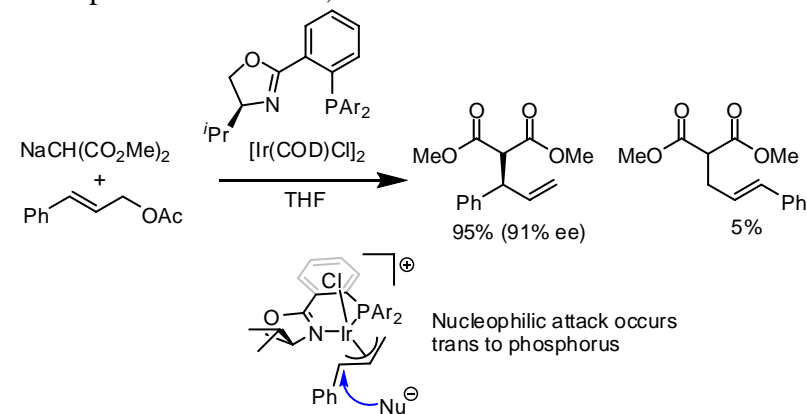
Trans effect: (kinetic) strong σ -donors or π -acceptors accelerate substitution of substituents that are trans to themselves.

Relative rates of substitution of chloride

L	rel rate
Cl	1
Ph	40
CH ₃	167
PEt ₃	9500
H	10,500

General order: R, H, alkene, CO \gg PR₃ > I > Cl > pyr > NH₃ > OH

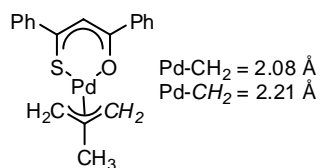
Example: Helmchen G.; *TL* 1997 8025.



Trans influence: (thermodynamic) strong σ -donors weaken the bonds to atoms that are trans to themselves.

General order: R, H > PR₃ > P(OR)₃, HNR₂ > pyr > CO, olefin, Cl

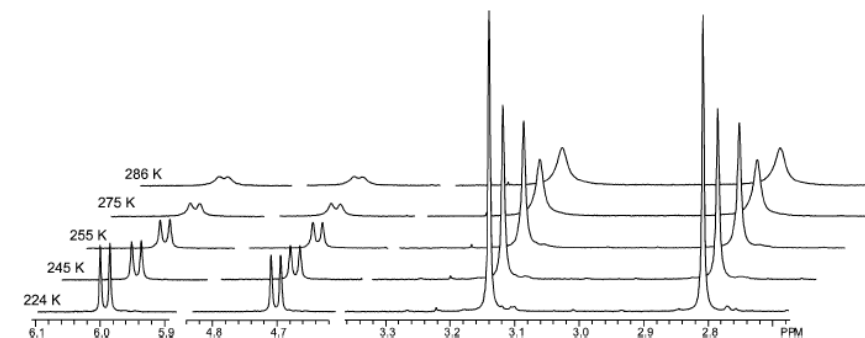
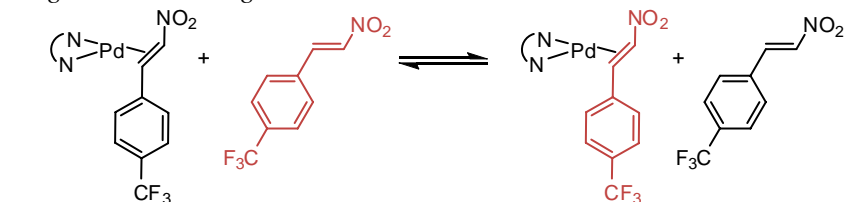
Example: Lippard, S. J. *JACS* **1969** 2504.



“Inverse electron demand” associative substitution

Stahl, S. S. *JACS* **2003** 12; Stahl, S. S.; Landis, C. L. *JACS* **2004** 14832.

Degenerate exchange



^1H NMR line-broadening measures rates from $0.1\text{-}100 \text{ s}^{-1}$

Exchange rate gives: $\Delta H^\ddagger = 7.3 \text{ kcal/mol}$ $\Delta S^\ddagger = -24 \text{ eu}$.

so $k(25^\circ\text{C}) = 749 \text{ M}^{-1}\text{s}^{-1}$

exchange rate = $k = \pi(W_{\text{obs}} - W_{\text{nat}})$ W = peak width at $1/2$ height.

Coalescence of peaks occurs when $k = \pi(\Delta\nu)/1.414$ where $\Delta\nu$ is the peak separation in Hz.

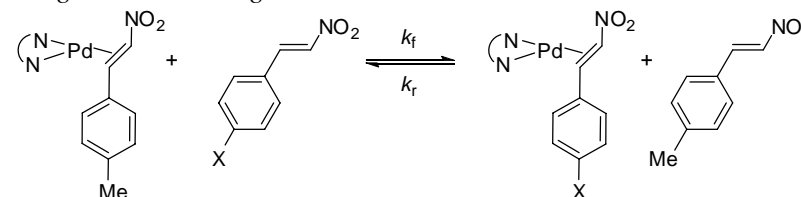
Eyring equation: $k = \frac{k_B T}{h} e^{-\frac{\Delta G^\ddagger}{RT}} = \frac{k_B T}{h} e^{-\frac{\Delta H^\ddagger}{RT}} e^{-\frac{\Delta S^\ddagger}{R}}$

$$\ln \frac{k}{T} = \frac{-\Delta H^\ddagger}{RT} + \ln \frac{k_B}{h} + \frac{\Delta S^\ddagger}{R}$$

slope
intercept

To determine activation parameters

Nondegenerate exchange



Monitor the rate of approach to equilibrium.

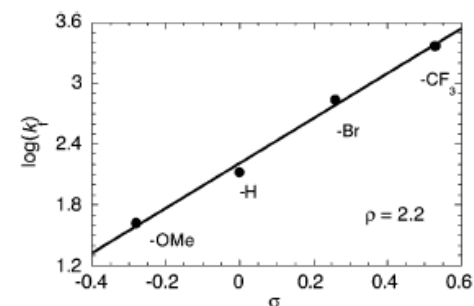
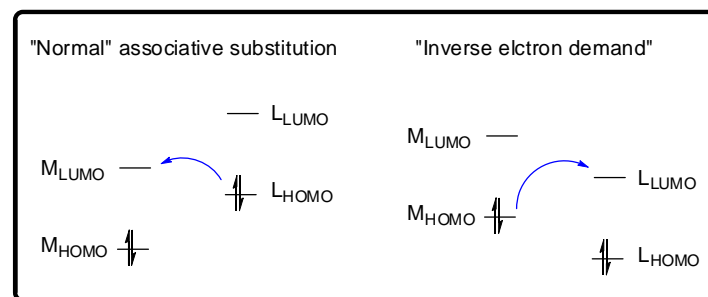
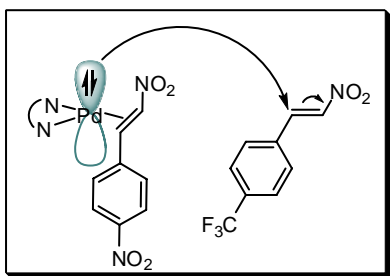


Figure 4. Hammett plot reflecting electronic effects on ligand substitution of ns^{CH_3} from $(\text{bc})\text{Pd}(\text{ns}^{\text{CH}_3})$ by p -substituted nitrostyrene derivatives.

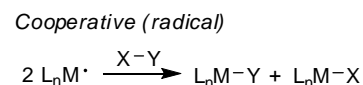
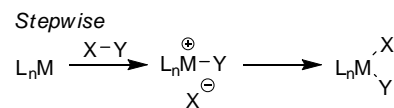
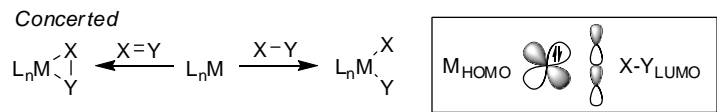
$\rho = +2.2$ (exchange is faster with electron deficient alkenes)



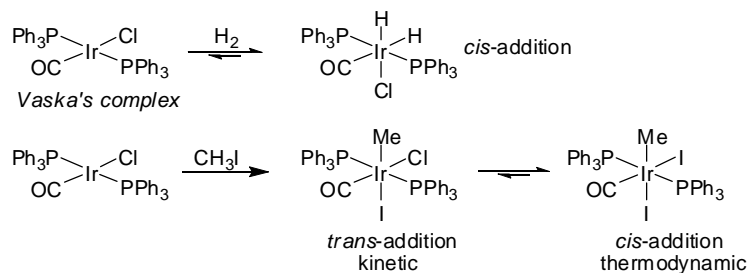


Note: Substitutions are also possible via a radical chain mechanism, but these processes are not as prevalent in catalysis.

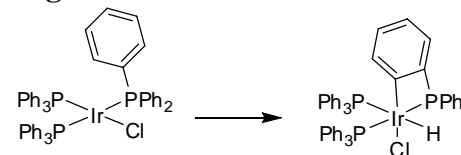
Oxidative addition



Concerted (*cis*) – Stepwise (*trans*)

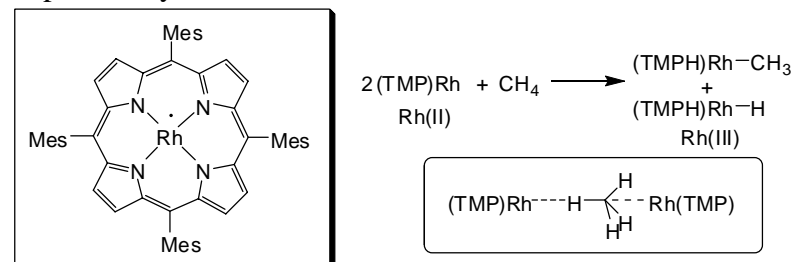


Intramolecular ligand/substrate activation is common



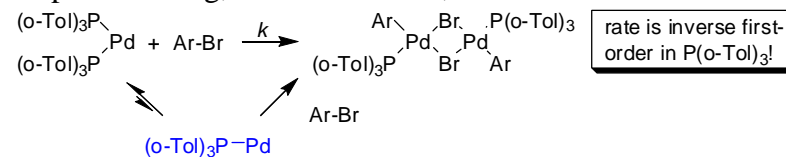
Oxidative addition to radicals

Example: Wayland, B. B. *JACS* **1991** 5305.



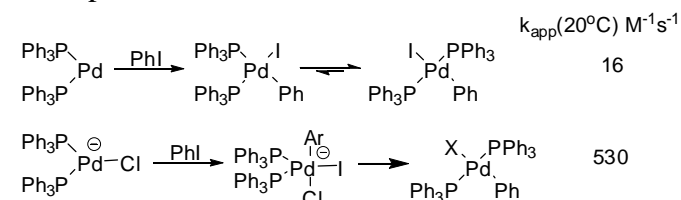
Oxidative addition can be accelerated by ligand dissociation...

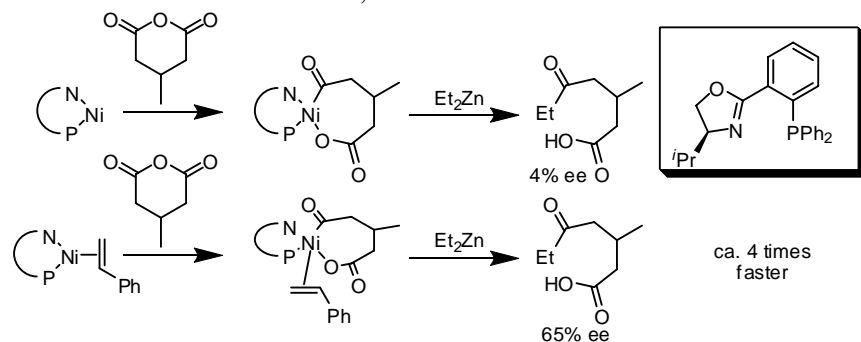
Example: Hartwig, J. F. *JACS* **1995**, 5373.



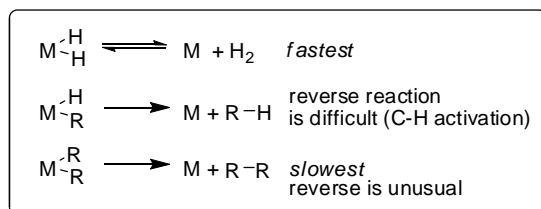
...or ligand association

Pd "ate" complexes: Amatore, C. *Acc. Chem. Res.* **2000**, 314.



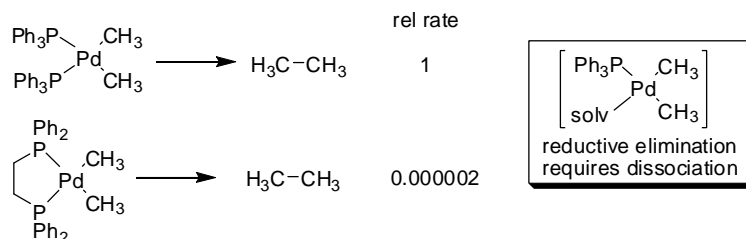
Olefin coordination: Rovis, T. *JACS* 2007 2718.

Reductive Elimination: the microscopic reverse of oxidative addition.

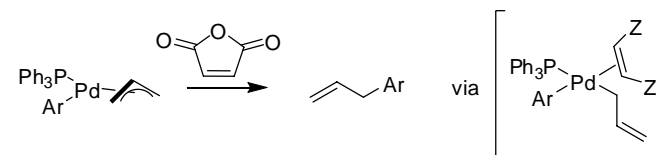


Ligand dissociation can induce reductive elimination

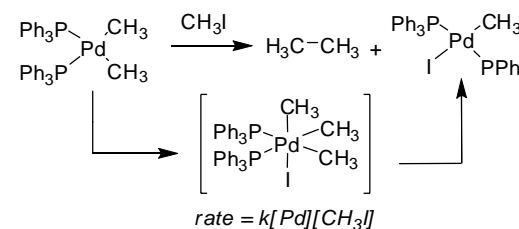
Stille, J. K. *JACS* 1980 4933.



Ligand association can induce reductive elimination

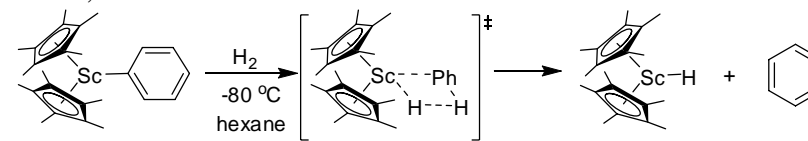


Reductive elimination can be stimulated by oxidation.



σ -Bond Metathesis: Very common for early transition metals

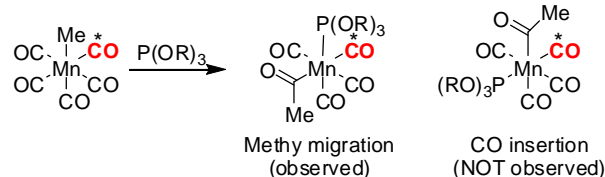
Bercaw, J. E. *JACS* 1987 203.



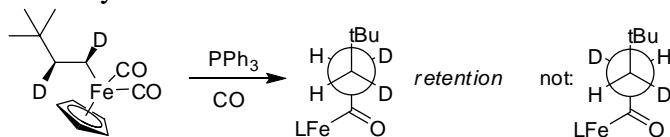
It is often difficult to tell whether late transition metals undergo σ -bond metathesis or oxidative addition/reductive elimination, but generally the latter is favored.

Migratory Insertion

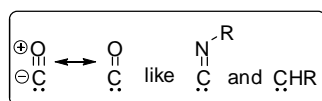
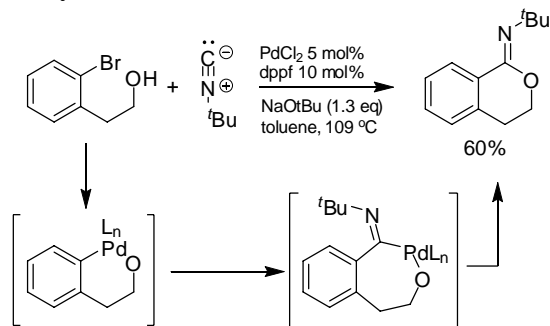
Alkyl-acyl interconversion (a 1,1-insertion)

Does methyl migrate or CO insert? (Flood, T. C. *JACS* **1981** 4410)

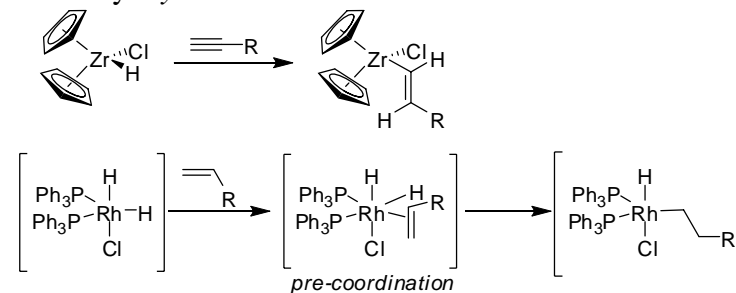
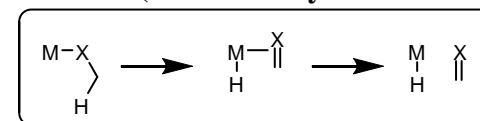
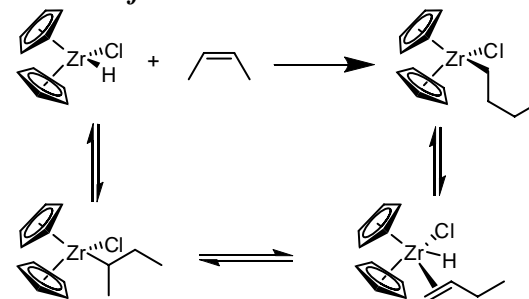
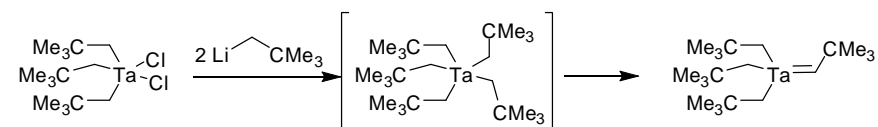
Stereochemistry - retention

Whitesides G. M. *JACS* **1974** 2814.

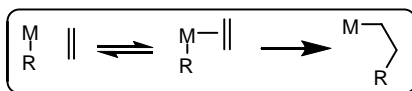
Isonitriles and carbenes are isoelectronic with CO.

Example: Whitby, R. J. *TL* **2004** 6995.

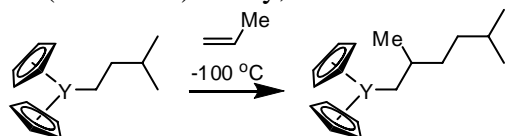
Hydrometallation (a 1,2-insertion, very common)

Almost always *syn*-addition β -Hydride elimination (reverse of hydrometallation)*Hydrometallation is often reversible.*See: Gibson, T. *TL* **1982**, 157. α -Hydride elimination (reverse of migratory insertion)much more rare than β -Hydride elimination

Carbometallation

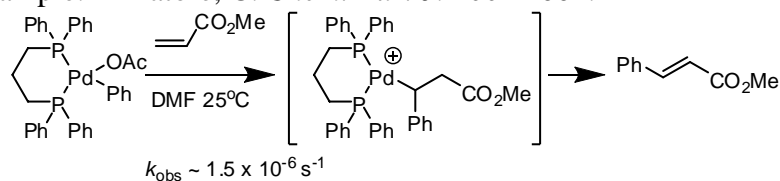


Slower than hydrometallation but still very facile for early transition metals (and Y too) Casey, C. P. *JACS* **2003**, 2641.



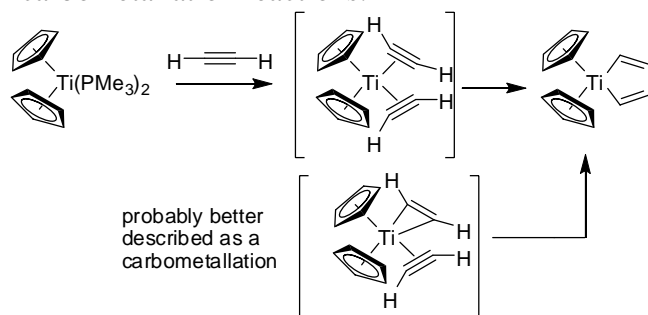
Carbometallation with late transition metals is normally slower

Example: Amatore, C. *Chem. Eur. J.* **2007** 2002.



Reductive coupling of ligands.

The reductive coupling of alkenes and alkynes to form metallacycles is a common theme in catalysis. It is a specific subset of carbometallation reactions.



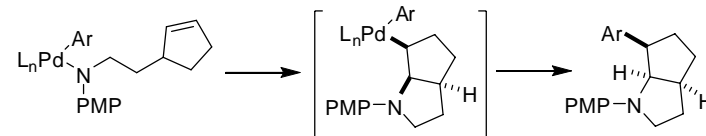
Intramolecular bicyclization: see Nugent, W. A. *JACS* **1984** 6422.

9/11/2007

Heterometalation

Similar to carbometallation, but often thought to be more difficult.

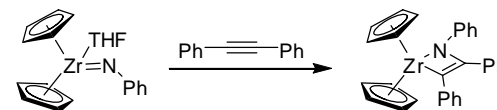
Reactions that proceed by aminopalladation have been the subject of much recent investigation. See: Wolfe, J. P. *JACS* **2005** 8644. Review: Muniz, K. *Chem. Soc. Rev.* **2007** 1142.



Cycloaddition is a common way for aminometalation.

Note: [2+2] is thermally allowed.

Bergman, R. G. *JACS* **1988** 8729.

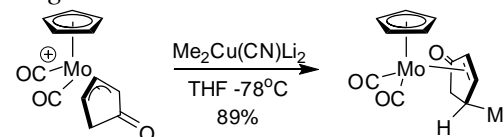


Nucleophilic attack on coordinated ligands.

Very common: Lewis acids promote nucleophilic attack of most π -electrophiles.

Attack on cationic π -complexes is very common.

Libeskind, L. *Orgmet* **1994** 1476.

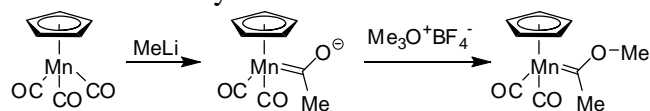


Davies-Green-Mingos Rules:

- 1) Nucleophilic attack at even polyenes is preferred
- 2) Nucleophilic attack at open polyenes is preferred
- 3) Even-open polyenes attacked at terminal C

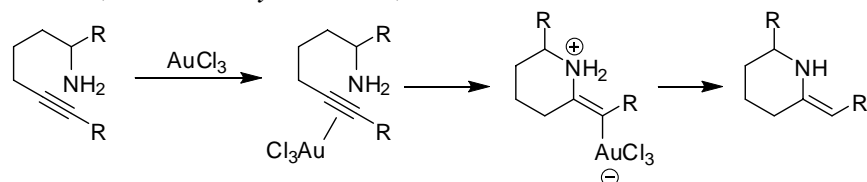
- 4) Odd-open attacked at terminal C if M^+ is very electrophilic

Attack on CO: a useful synthesis of Fischer carbenes



Electrophilic “soft” metals activate alkynes.

Nozaki, H. *Heterocycles* **1987**, 297.



Transmetalation

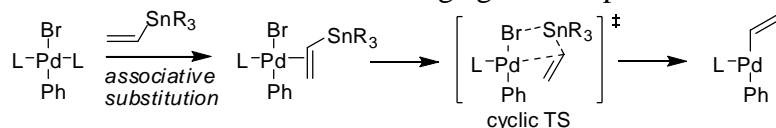
Transmetalation is likely not a unique class of elementary reactions. Such processes most likely occur by standard ligand substitution sequences or by σ -bond metathesis. Nonetheless, transmetalation is extremely important in catalysis and it requires some unique considerations.

Many transmetalations exploit the transfer of C to “softer” less electrophilic metals. Thus, a wide variety of organometallics can be prepared by treatment of metal halides with LiR or RMgX.

Examples: Transmetalation in Stille couplings

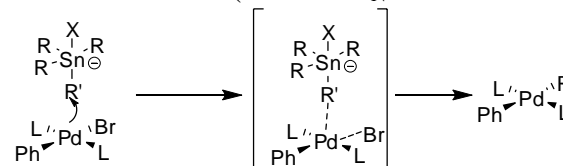
Espinet, P. *JACS* **1998**, 8978; *JACS* **2006** 14571.

Precoordination of the transmetalating agent is important.



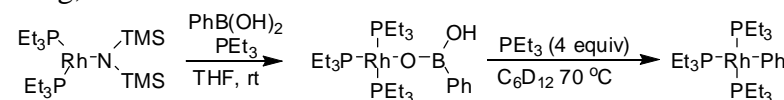
The cyclic transition state gives retention of configuration at C.

An alternative open transition state explains cases where inversion of configuration is observed (i.e. with S_N2 -activated alkyl halides)



Direct observation of transmetalation.

Hartwig, J. F. *JACS* **2007** 1876.



Catalysis

Catalysis is a wholly kinetic phenomenon.

Stability is often inversely proportional to activity.

Other important concepts

- 1) Precatalyst vs. Catalyst
- 2) Resting State
- 3) Rate-limiting step

Calibrations

Rates always increase with temperature but...

What activation energy does a given temperature supply?

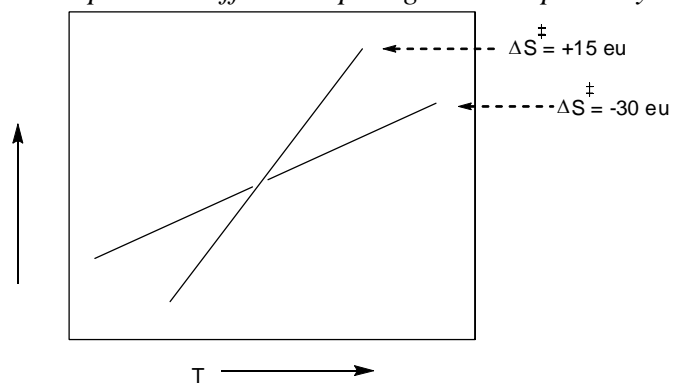
(Assume a reaction that is completed in 4 hours – $t_{1/2} = 1$ h; $k = 1.9 \times 10^{-4} s^{-1}$) What is the activation energy of that reaction?

-78 °C	16.5 kcal/mol
-50 °C	18.6 kcal/mol
0 °C	20.6 kcal/mol
25 °C	22.5 kcal/mol
100 °C	29.1 kcal/mol

What is the effect of temperature on a reaction with a free energy of activation of 25 kcal/mol? (Assuming the activation energy is T independent)

T	k_{obs}	rxn time
0 °C	$5.5 \times 10^{-8} \text{ s}^{-1}$	583 d
25 °C	$2.9 \times 10^{-6} \text{ s}^{-1}$	11 d
35 °C	$1.2 \times 10^{-5} \text{ s}^{-1}$	2.7 d
45 °C	$4.3 \times 10^{-5} \text{ s}^{-1}$	18 h
55 °C	$1.5 \times 10^{-4} \text{ s}^{-1}$	5.2 h
65 °C	$4.8 \times 10^{-4} \text{ s}^{-1}$	1.6 h

How does temperature affect competing reaction pathways?



Higher temps disfavor bimolecular reaction paths.