



ELEMENTARY REACTIONS

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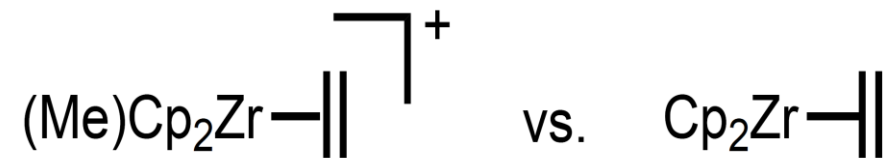
Biomolecular Systems

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POD #1

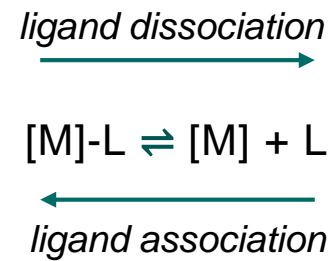
Consider the following two complexes and the ability of the metal in both cases to participate in back-bonding. **Provide an explanation for why one of the species results in a more stable complex than the other.**



*No back-bonding
possible from a d^0 !*



2.1 LIGAND SUBSTITUTION



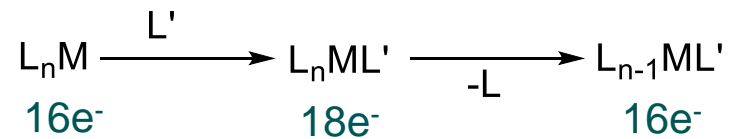
Valence electron	$\Delta = -2$
Coordination number	$\Delta = -1$
Oxidation number	$\Delta = 0$



2.1.1 LIGAND SUBSTITUTION - MECHANISM

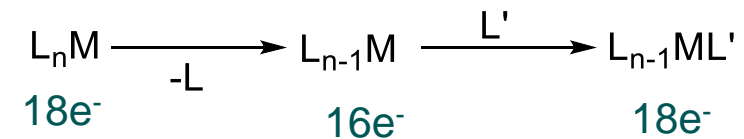
Associative Substitution

e.g. $\text{Pt}(\text{PR}_3)_2\text{Cl}_2$



Dissociative Substitution

e.g. $\text{Ni}(\text{CO})_4$



Rate law

1st order in entering ligand

Rate law

0 order in entering ligand

Activation parameters

large negative ΔS

large negative ΔV

Activation parameters

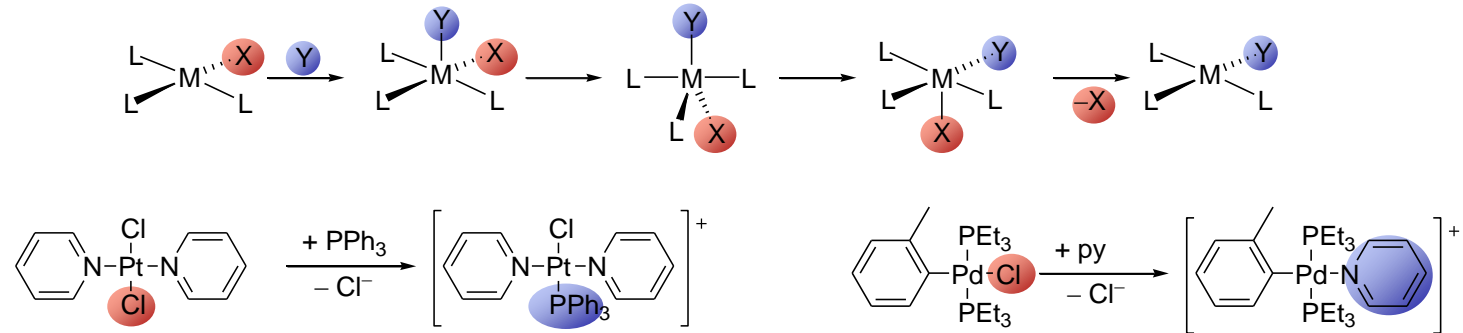
small positive ΔS

small positive ΔV

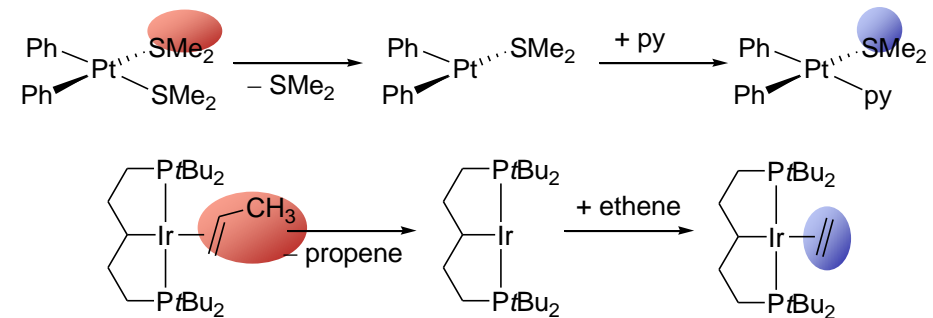


2.1.1 LIGAND SUBSTITUTION – EXAMPLES

Associative:



Dissociative:

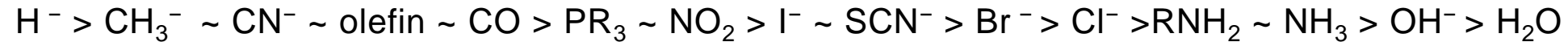




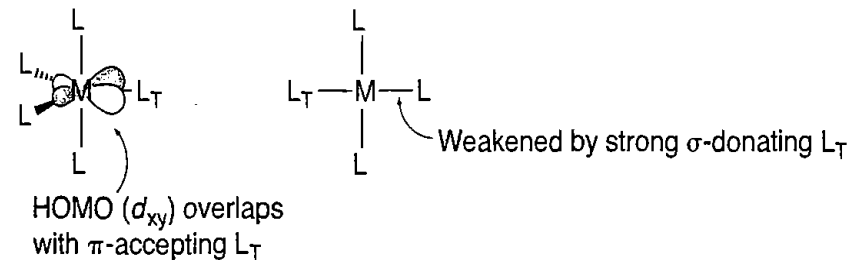
2.1.2 LIGAND SUBSTITUTION - TRANS EFFECT

Ancillary ligands that are more effective at labilizing a ligand trans to themselves, usually observed in a d^8 square planar complex.

Trend:



Can be rationalized with the relative stabilization of the trigonal bipyramidal intermediate (vs. sq. pl.), two factors:



Trans effect – kinetic i.e. impact on rate of ligand substitution

Trans influence – thermodynamic i.e. effect on the bond strength (P-NMR, XRD length)

Coord Chem Rev, **1973**, 10, 335. DOI: [10.1016/S0010-8545\(00\)80238-6](https://doi.org/10.1016/S0010-8545(00)80238-6)



2.1.2 LIGAND SUBSTITUTION - TRANS EFFECT VS. CIS EFFECT

Table 5.7. Example of the trans effect on the rate of ligand substitution on organometallic platinum complexes.^a

$trans\text{-Pt}(\text{PEt}_3)_2(\text{X})\text{Cl} + \text{py} \xrightarrow{\text{EtOH}} trans\text{-Pt}(\text{PEt}_3)_2(\text{X})(\text{py})^\ominus + \text{Cl}^\ominus$		
X	$k_{\text{obs}}(\text{s}^{-1})^b$	t (°C)
H ⁻	4.7×10^{-2}	0
Me ⁻	6.0×10^{-4}	25
C ₆ H ₅ ⁻	1.2×10^{-4}	25
Cl ⁻	3.5×10^{-6}	25

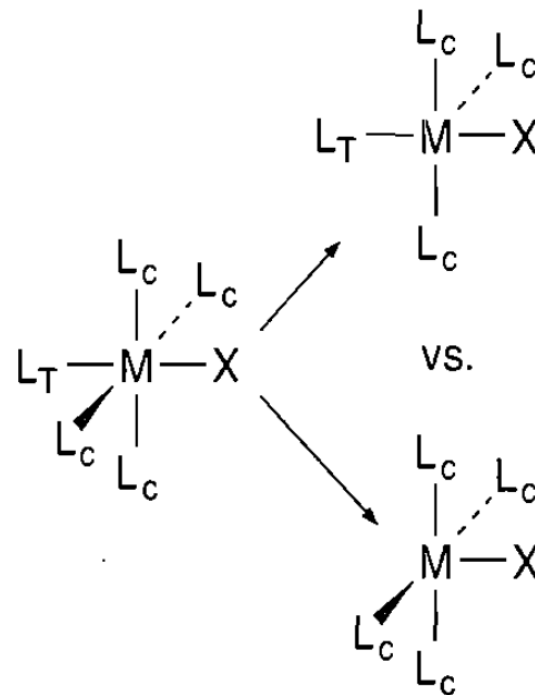
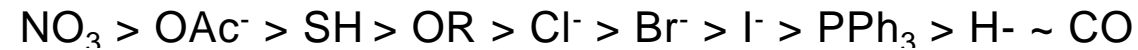
Table 5.8. Example of the cis effect on the rate of ligand substitution on organometallic platinum complexes.^a

$cis\text{-Pt}(\text{PEt}_3)_2(\text{X})\text{Cl} + \text{py} \xrightarrow{\text{MeOH}} cis\text{-Pt}(\text{PEt}_3)_2(\text{X})(\text{py})^\ominus + \text{Cl}^\ominus$		
X	$k_{\text{obs}}(\text{s}^{-1})^b$	t (°C)
Me ⁻	11.4	25
C ₆ H ₅ ⁻	7.92	25
Cl ⁻	4.17	25



2.1.2 LIGAND SUBSTITUTION - CIS EFFECT

Cis effect for octahedral compounds comparable to trans effect in square planar (trend reverse)

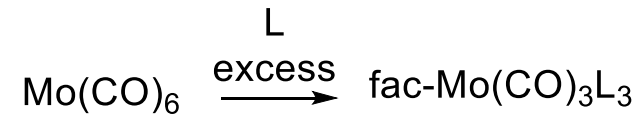


Stabilized by bidentate binding of X
Destabilized by strong σ -donation by X
Destabilized by strong π -acceptance by X



2.1.2 HOW TO ENCOURAGE LIGAND EXCHANGE

Ligand substitution can be incomplete:



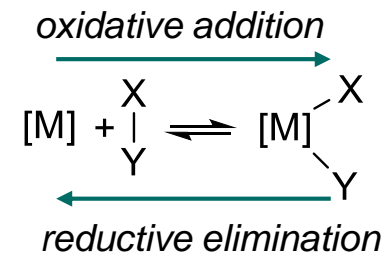
Can be forced:

- Photolysis M-CO
- Affecting equilibrium via phase change (precipitation AgCl, H₂ evolution)
- Forcing conditions (Grignard reagents to remove halide and introduce new L)

Spectator / ancillary ligand do not participate in reactions of the metal
Actor / reactive ligand a ligand that engages in chemical change



2.2 OXIDATIVE ADDITION



Valence electron	$\Delta = +2$
Coordination number	$\Delta = +2$
Oxidation number	$\Delta = +2$



2.2 OXIDATIVE ADDITION - INTRODUCTION

- Metal-mediated cleavage of a bond of an organic/main group reagent and formation of 2 new M-L σ -bonds
- Metal must have d-electrons
- Metal must have at least vacant coordination site
- Electron-rich, sterically accessible M centers are more reactive
- Increases oxidation state and coordination number
- Decreases d-electron count
- Good ligands: strong σ -donors, sterically small

Acc. Chem. Res. **1968**, 1, 136. DOI: [10.1021/ar50005a002](https://doi.org/10.1021/ar50005a002)



2.2.1 OXIDATIVE ADDITION – SUBSTRATE CLASSES

1. NON-POLAR – A/B non highly electronegative / not good oxidant

e.g. H₂, C-H, S-H, N-H, S-S

- require vacant orbital

2. POLAR – A/B electronegative or good oxidant

e.g. Cl₂, Br₂, RX, ArX, HX

- does not require vacant orbital

- L_nM is 16 e⁻, both coordinates

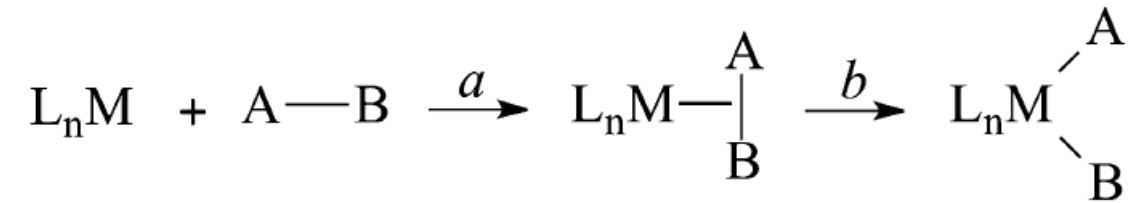
- L_nM is 18 e⁻, only one coordinates

3. INTACT – A-B BOND RETAINED

e.g. O₂, R-≡-R



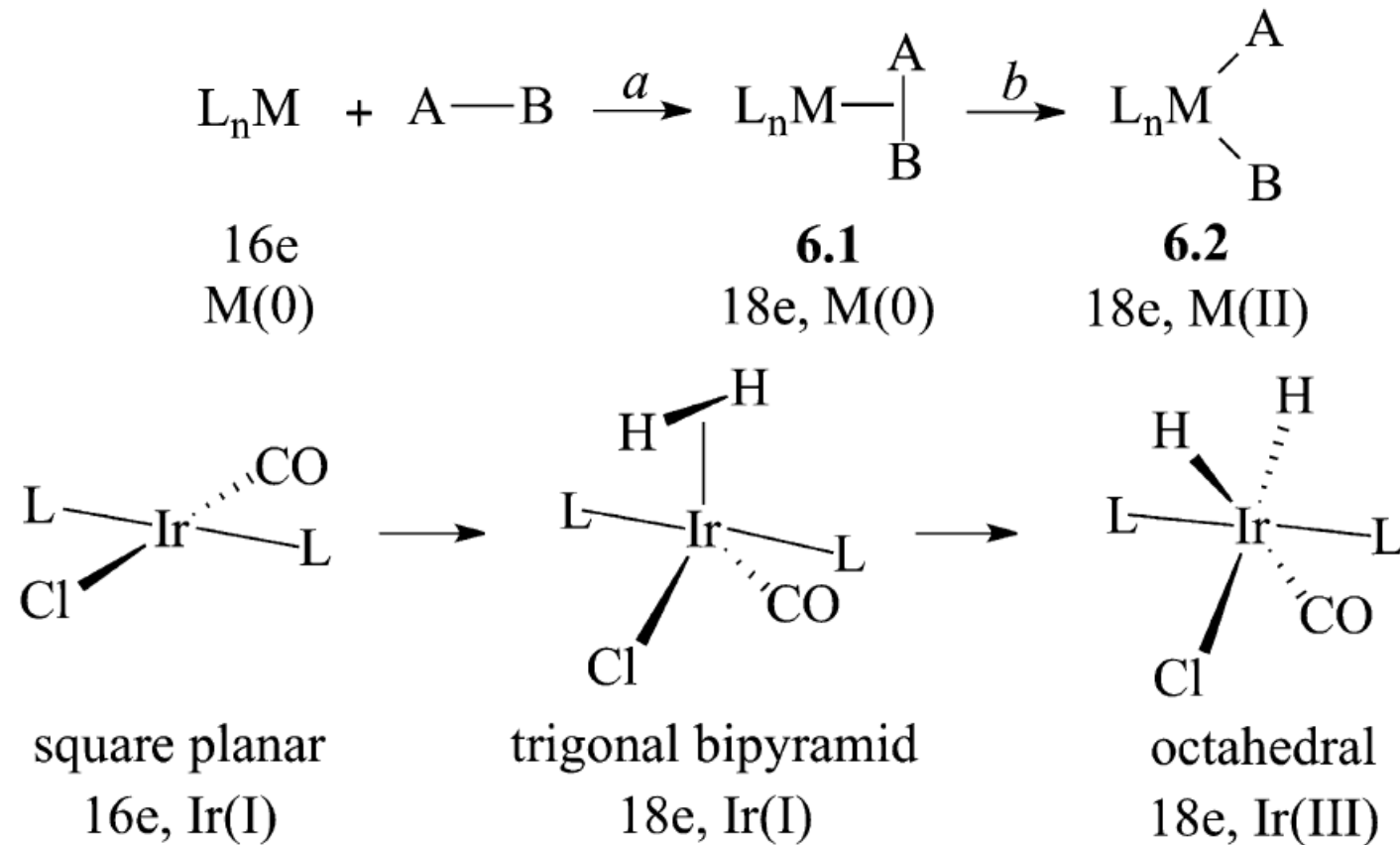
2.2.2 OXIDATIVE ADDITION – CONCERTED MECHANISM



- **Common for non-polar substrates**
- 3c2e⁻ TS
- Stereospecific (cis)
- Stereoretentive
- Coordinatively unsaturated metal
- Generally second order kinetics
- Generally solvent insensitive, TS not charged



2.2.2 OXIDATIVE ADDITION – CONCERTED MECHANISM





2.2.2 OXIDATIVE ADDITION – CONCERTED MECHANISM

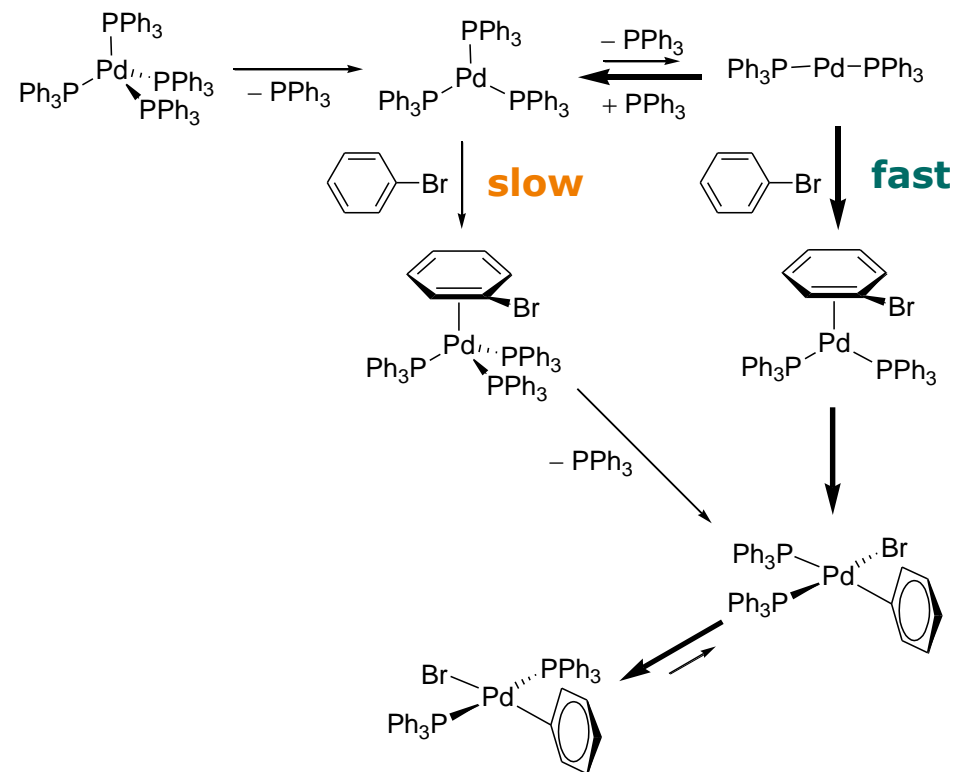
Rate depends on ...

... halide

... ligand

... aryl

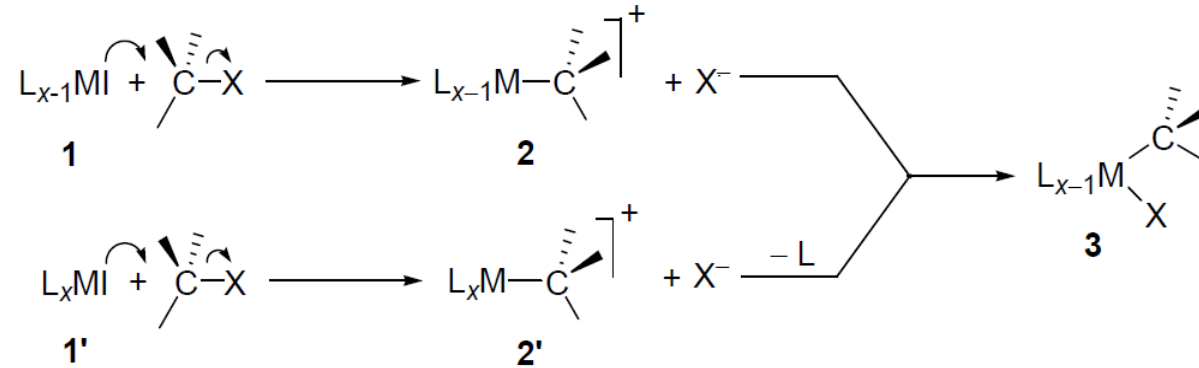
... metal



J. Organomet. Chem. **1971**, 28, 287. DOI: [10.1016/S0022-328X\(00\)84578-7](https://doi.org/10.1016/S0022-328X(00)84578-7)



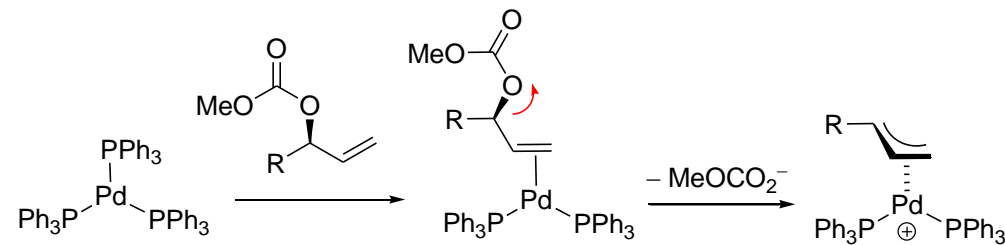
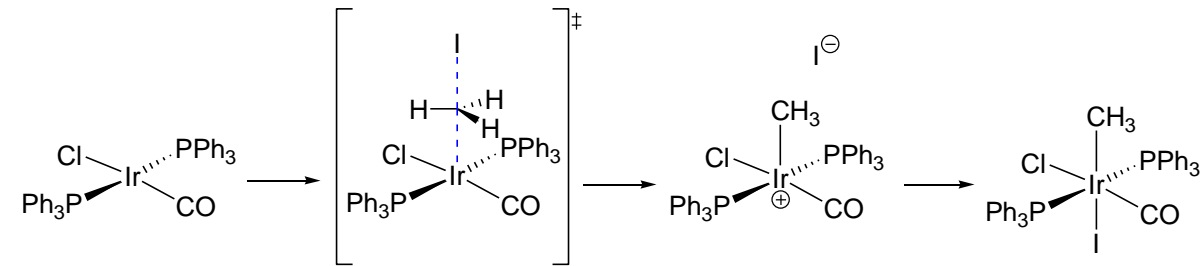
2.2.3 OXIDATIVE ADDITION – NUCLEOPHILIC MECHANISM



- **Common for polar substrates**
- Resembles S_N2
- A and B often trans
- Stereoinvertive
- Dipolar TS
- Reaction rate sensitive to ligand environment
Ni(PR₃)₄ > Ni(PAr₃)₄ > Ni(PR₃)₂alkene > Ni(PAr₃)₂alkene > Ni(cod)₂
- Better LG accelerates reaction
R-OTs > R-I > R-Br > R-Cl
- Steric hindrance slows reaction
Me-I > Et-I > *i*Pr-I

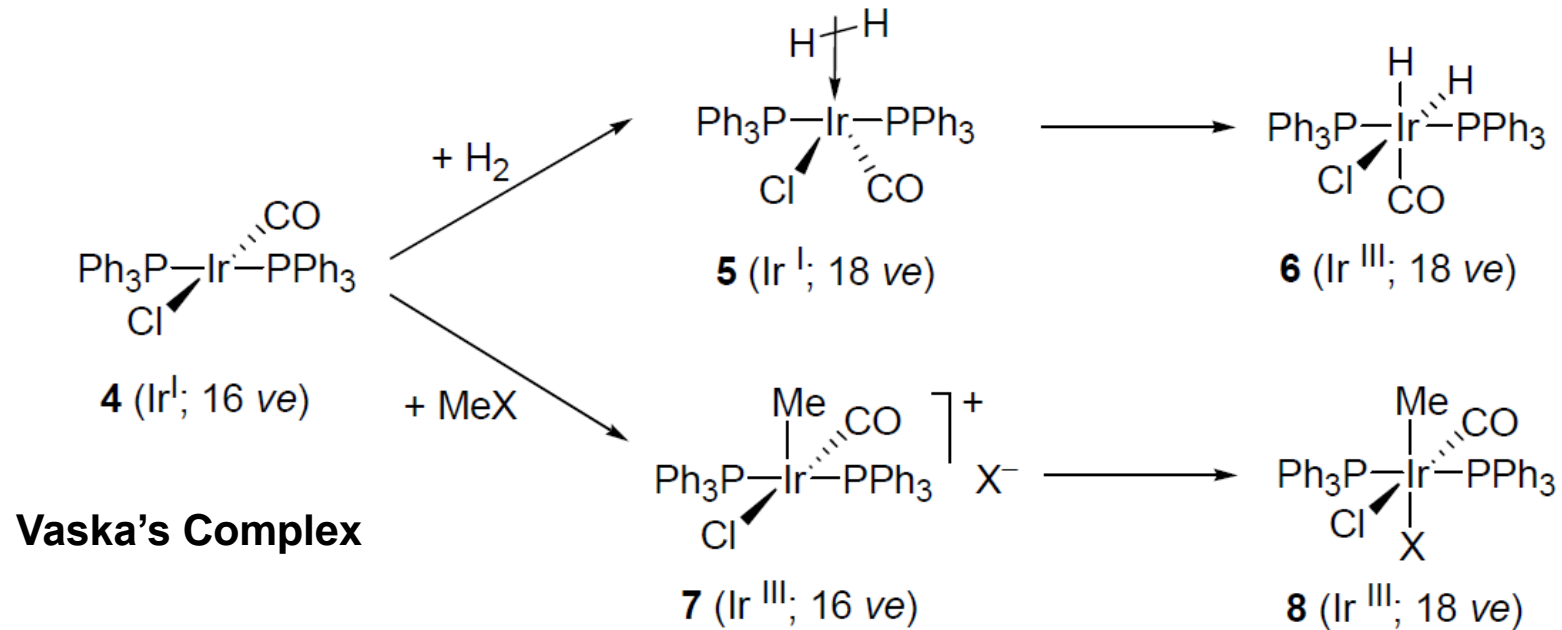


2.2.3 OXIDATIVE ADDITION – NUCLEOPHILIC MECHANISM





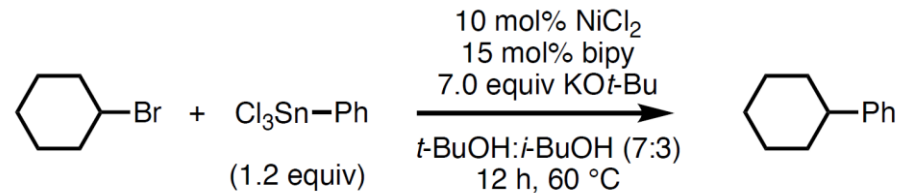
2.2.3 OXIDATIVE ADDITION – CONCERTED VS. NUCLEOPHILIC





POD #4

- Consider the cross-coupling reaction below, which is proposed to involve an oxidative addition step. **Propose experiments to determine the mechanism of oxidative addition.**

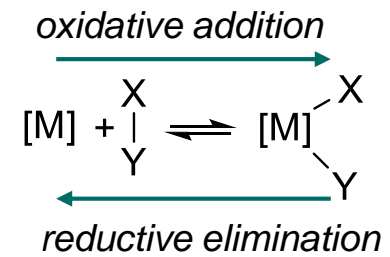


- Chiral substrate, kinetics (solvent effect), reactivity trend substrate, radical traps...

Fu and co-workers, *JACS*, **2005**, 127, 2, 51. DOI: [10.1021/ja0436300](https://doi.org/10.1021/ja0436300)



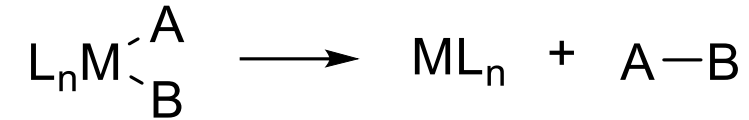
2.3 REDUCTIVE ELIMINATION



Valence electron	$\Delta = -2$
Coordination number	$\Delta = -2$
Oxidation number	$\Delta = -2$



2.3.1 REDUCTIVE ELIMINATION – INTRODUCTION

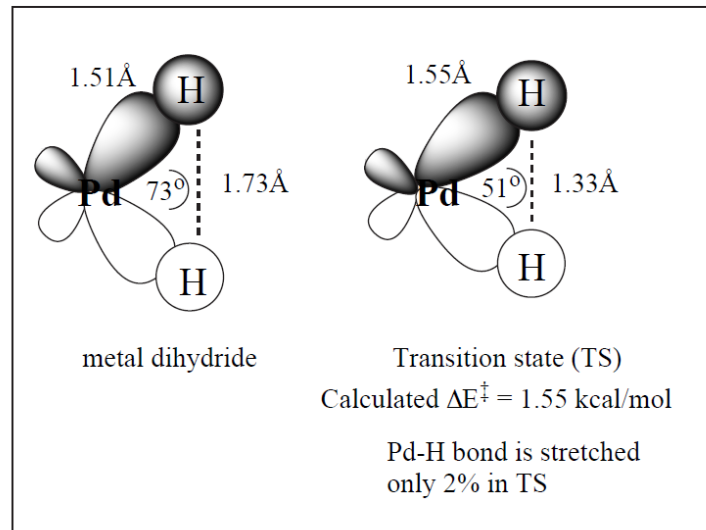


- Microscopic reverse of OA. Same concerted, nucleophilic and radical mechanisms, reversed.
- Forms products from coupling of two covalent ligands at a single (or two) transition metal center
- Electron-poor, sterically hindered complexes are more reactive
- Decreases oxidation state and coordination number
- Increases d-electron count
- Complexes with n=1,3 ligands react faster than complexes n=2,4
- For A and B: H reacts faster than R (i.e. C–H > C–C and sp > sp² > sp³)
- Historically C-N, C-O, C-F harder than C-C
- 1st row > 2nd row > 3rd row

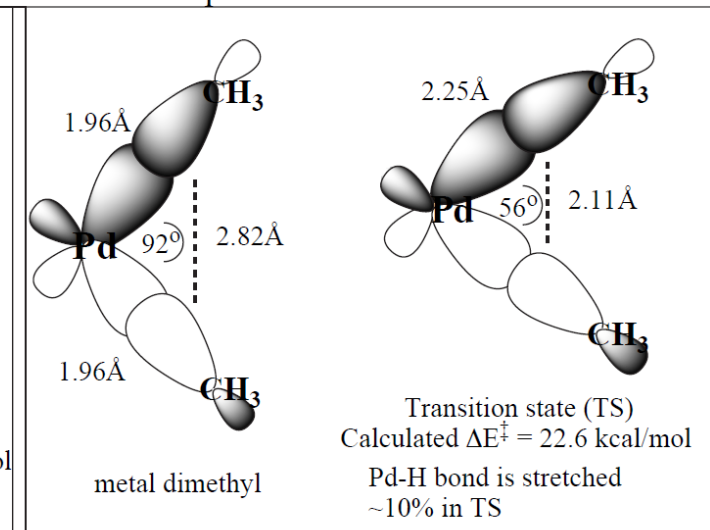
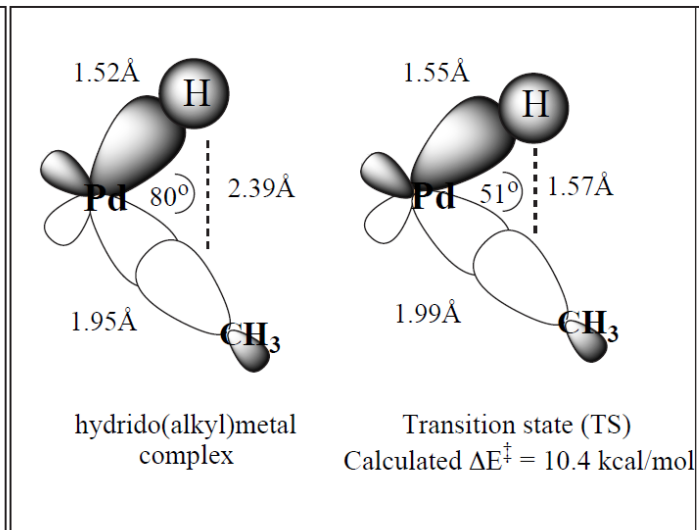


2.3.2 REDUCTIVE ELIMINATION – H-H VS. C-H VS. C-C

Best overlap



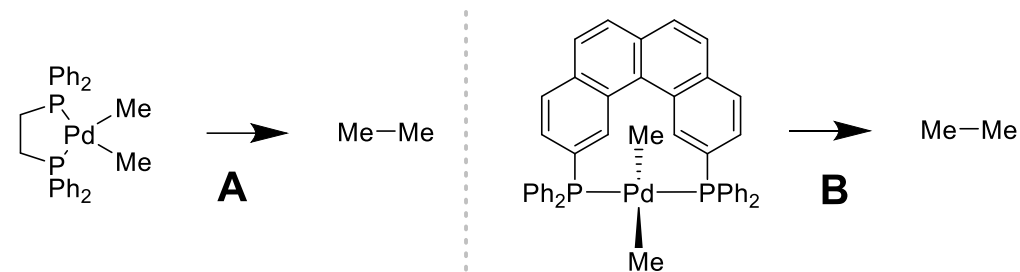
Worst overlap





2.3.1 POD #1

Consider the two reductive elimination processes shown below:



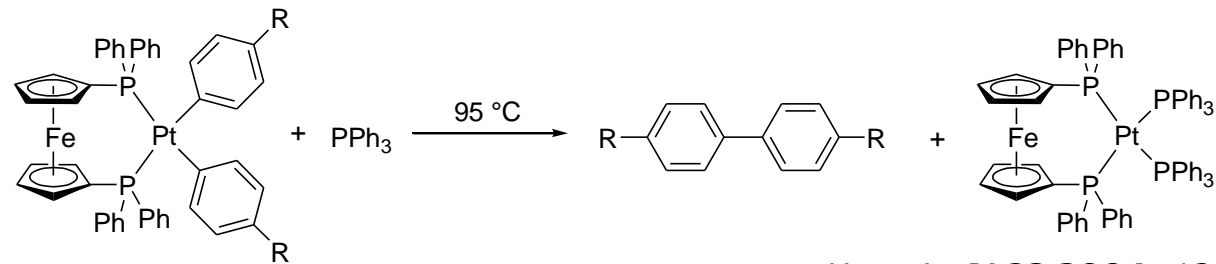
- Predict which reaction is faster and explain why.**
- The slow-reacting complex A forms ethane immediately upon methyl iodide addition at room temperature. **Provide one or more mechanistic hypothesis that would explain this observation.**
- Design experiments to distinguish between the possibilities listed in b).

Stille *JACS* **1981** 103, 14, 4182. DOI: [10.1021/ja00404a034](https://doi.org/10.1021/ja00404a034)



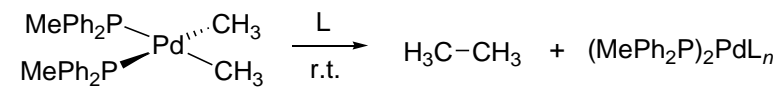
2.3.2 REDUCTIVE ELIMINATION – C-C BOND FORMATION

- Directly from tetra-coordinated biaryl complex:



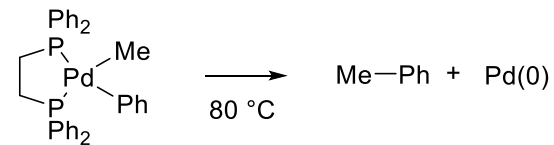
Hartwig *JACS* **2004**, *126*, 13016. DOI: [10.1021/ja0480365](https://doi.org/10.1021/ja0480365)

- After ligand dissociation



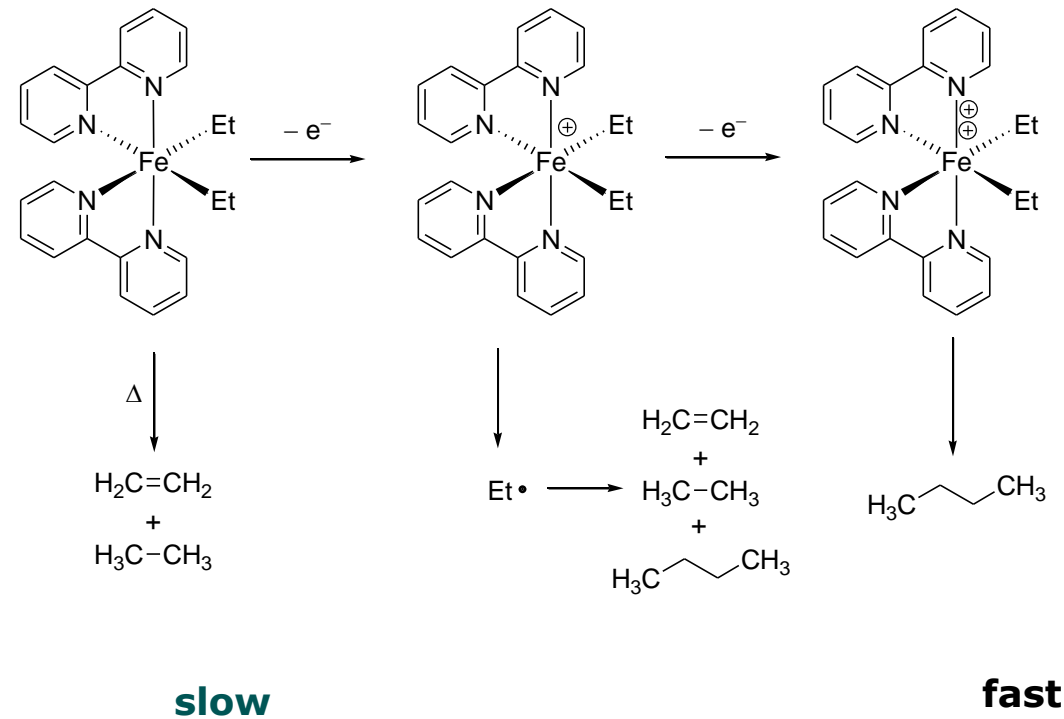
Stille *JACS* **1980**, *102*, 4933. DOI: [10.1021/ja00535a018](https://doi.org/10.1021/ja00535a018)

VS.



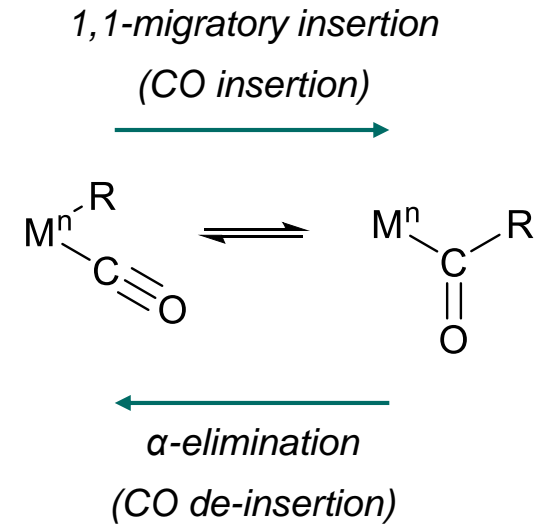


2.3.2 REDUCTIVE ELIMINATION – C-C BOND FORMATION





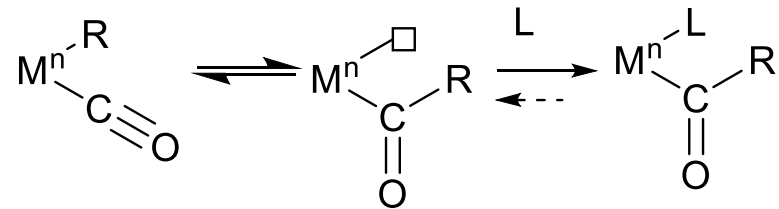
2.4 1,1-MIGRATORY INSERTION



Valence electron	$\Delta = -2$
Coordination number	$\Delta = -1$
Oxidation number	$\Delta = 0$



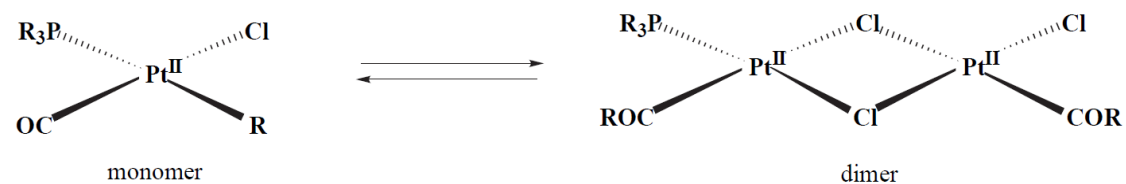
2.4.1 1,1-MIGRATORY INSERTION – INTRODUCTION



- No change in ox. state
- Two reacting ligands must be cisoid
- Trapping ligand often needed to coordinate the empty site
- Stereochemistry of migrating group is preserved (concerted mechanism)
- To accelerate:
 - More electron-poor M
 - Bulkier ligands
 - More polarized M-CO (e.g. w/ LA)
 - SET oxidation



2.4.2 1,1-MIGRATORY INSERTION – MIGRATORY APTITUDE



R	Monomer	Dimer
	0%	100%
	12%	88%
	24%	76%
	46%	54%
	73%	27%
	100%	0%

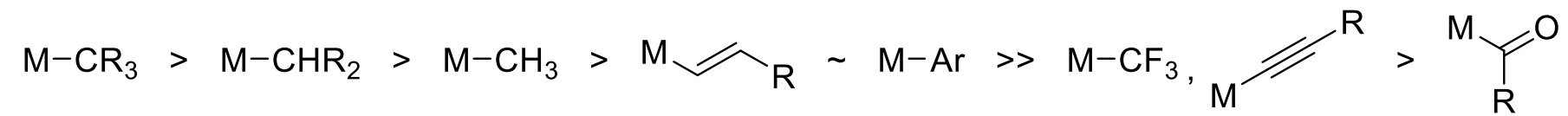
Anderson *Acc. Chem. Res.* **1984** (17) 67. DOI: [10.1021/ar00098a005](https://doi.org/10.1021/ar00098a005)

Cross *J. Chem. Soc., Dalton Trans.* **1981**, 2317. DOI: [10.1039/DT9810002317](https://doi.org/10.1039/DT9810002317)



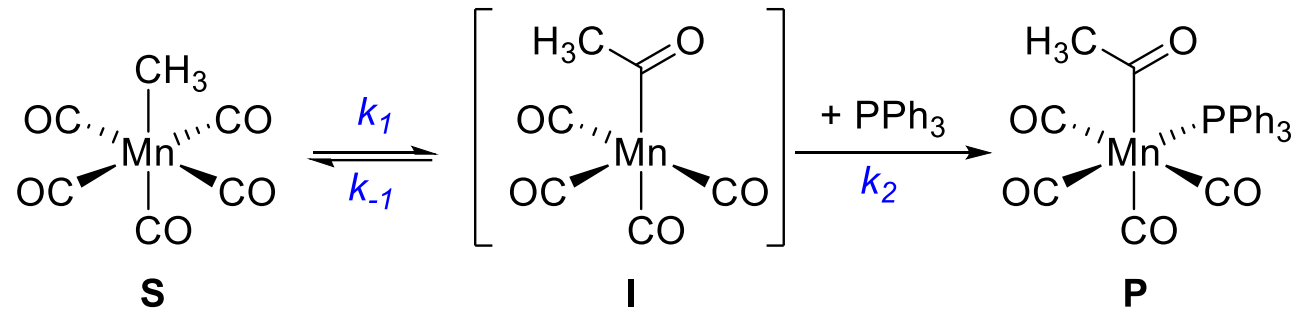
2.4.2 1,1-MIGRATORY INSERTION – MIGRATORY APTITUDE

1. consider **thermodynamics** (e.g. not thermodynamically favored M-H, M-OR, M-NR₂...)
2. **kinetic** considerations





2.4.2 1,1-MIGRATORY INSERTION – KINETICS



$$rate = \frac{d[P]}{dt} = -\frac{d[S]}{dt}$$

Steady state assumption, i.e. $\frac{d[I]}{dt} = 0 = k_1[S] - k_{-1}[I] - k_2[I][L]$

$$k_1[S] = [I](k_{-1} + k_2[L])$$

$$[I] = \frac{k_1[S]}{k_{-1} + k_2[L]}$$

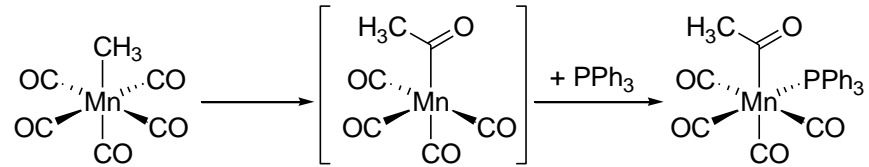
$$rate = k_2[L][I] = \frac{k_1 k_2 [S][L]}{k_{-1} + k_2[L]}$$

- $k_{-1} \ll k_1, k_2$ then $rate = k_1[S]$, 1st order in $[S]$, “L” always traps
- $k_{-1} \gg k_2[L]$ then $rate = \frac{k_1 k_2 [S][L]}{k_{-1}}$, overall 2nd order, almost always goes back
- Intermediate between the two



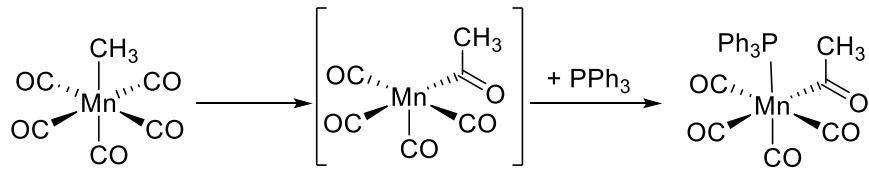
2.4.3 INSERTION VS. MIGRATION

Carbonyl Insertion



or

Methyl Migration

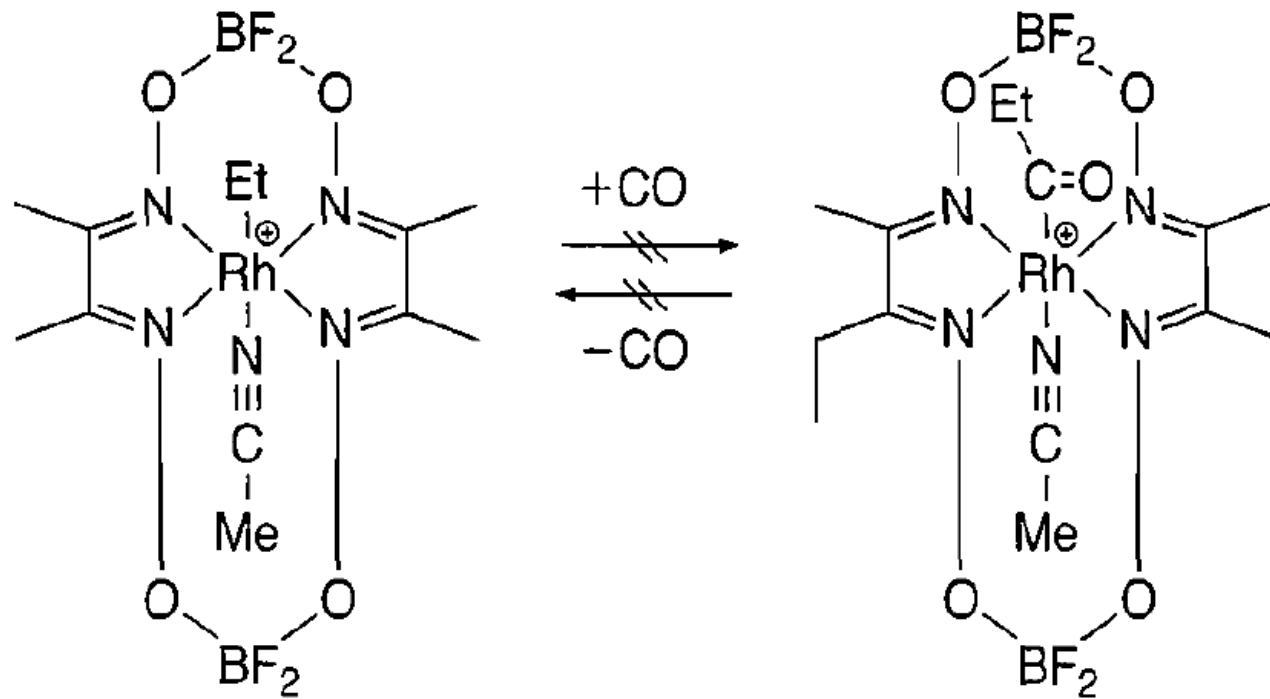


?



2.4.3 INSERTION VS. MIGRATION

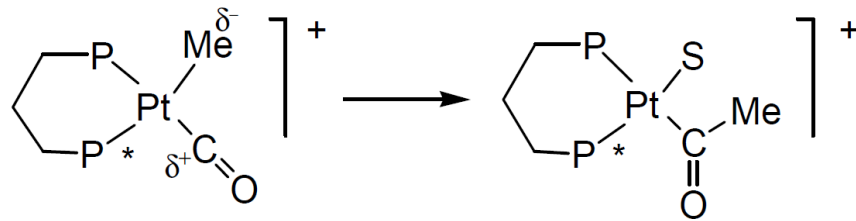
CO and Alkyl must be cis...





2.4.3 INSERTION VS. MIGRATION

P-NMR studies with slightly different phosphines
(that can be distinguished by NMR)



Rh “piano-stool” complex



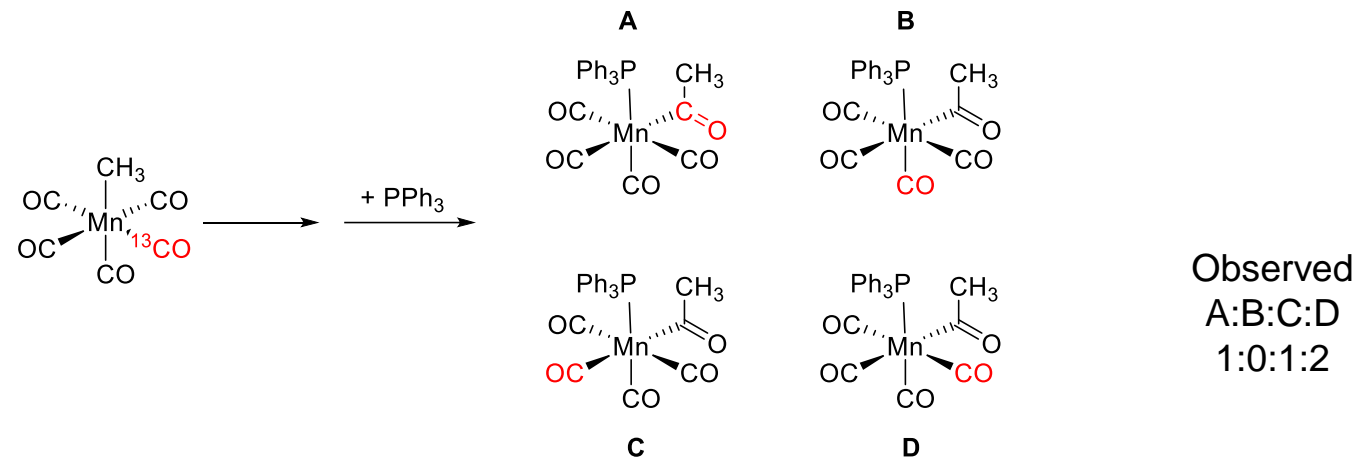
Van Leeuwen *et al.*, *JACS*, **1994**, 116, 24. DOI: [10.1021/ja00105a088](https://doi.org/10.1021/ja00105a088)

Organometallics **2001**, 20, 12, 2431. DOI: [10.1021/om010143+](https://doi.org/10.1021/om010143+)



2.4.3 POD #2

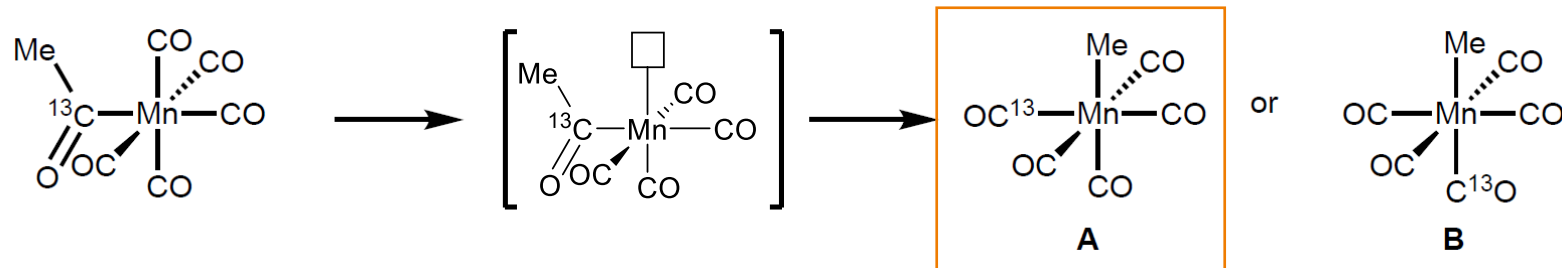
- Consider the following reaction. **Draw all possible stereoisomers of the product and predict their ratio.**





2.4.3 POD #3

Consider the following manganese complex. **Propose the intermediate and product (A or B).**

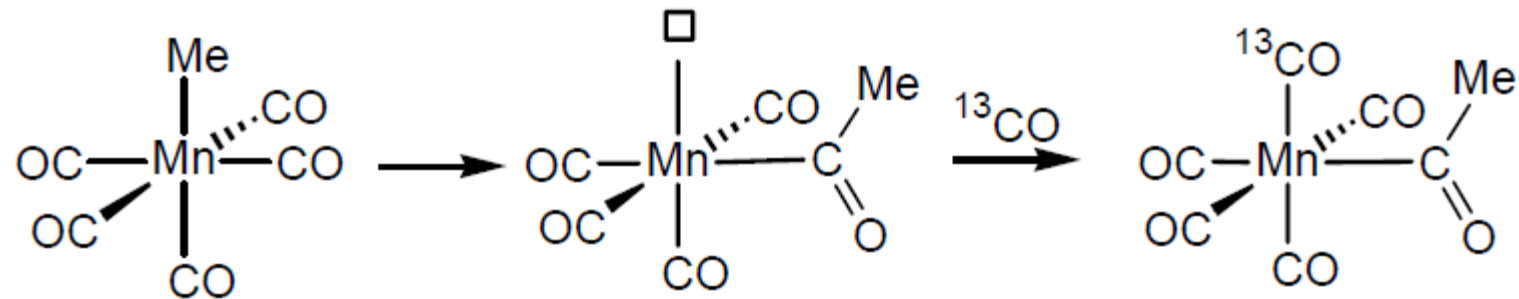


Calderazzo *J Organomet Chem.* **1967**, *10*, 101. DOI: [10.1016/S0022-328X\(00\)81721-0](https://doi.org/10.1016/S0022-328X(00)81721-0)
Angew. Chem. Int. Ed. Engl. **1977**, *16*, 299. DOI: [10.1002/anie.197702991](https://doi.org/10.1002/anie.197702991)



2.4.3 DISPROVAL OF “OUTERSPHERE” INSERTION

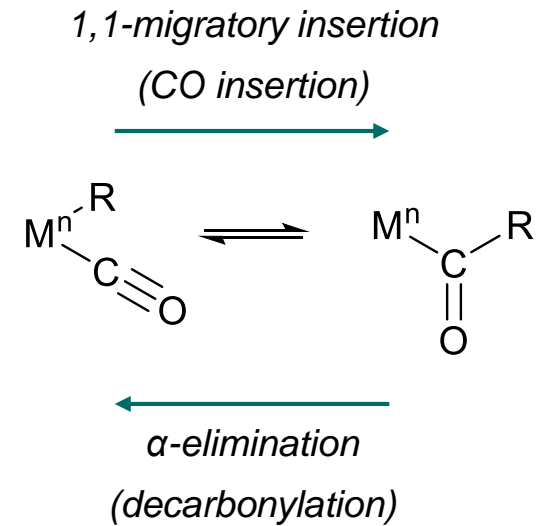
$\text{CH}_3\text{Mn}(\text{CO})_5$ exchanges CO slowly.



No proven example of insertion from uncomplexed unsaturated substrates into metal-carbon bonds.



2.5 α -ELIMINATION



Valence electron	$\Delta = +2$
Coordination number	$\Delta = +1$
Oxidation number	$\Delta = 0$

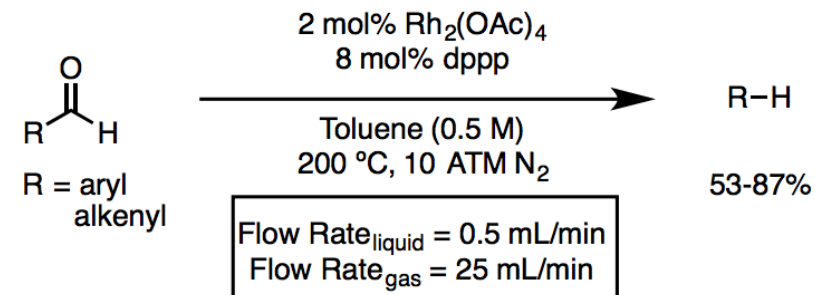
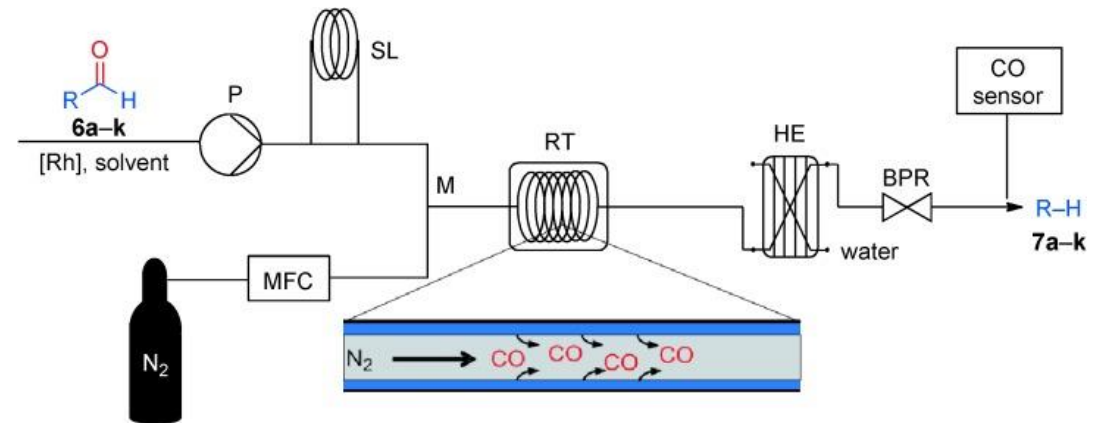
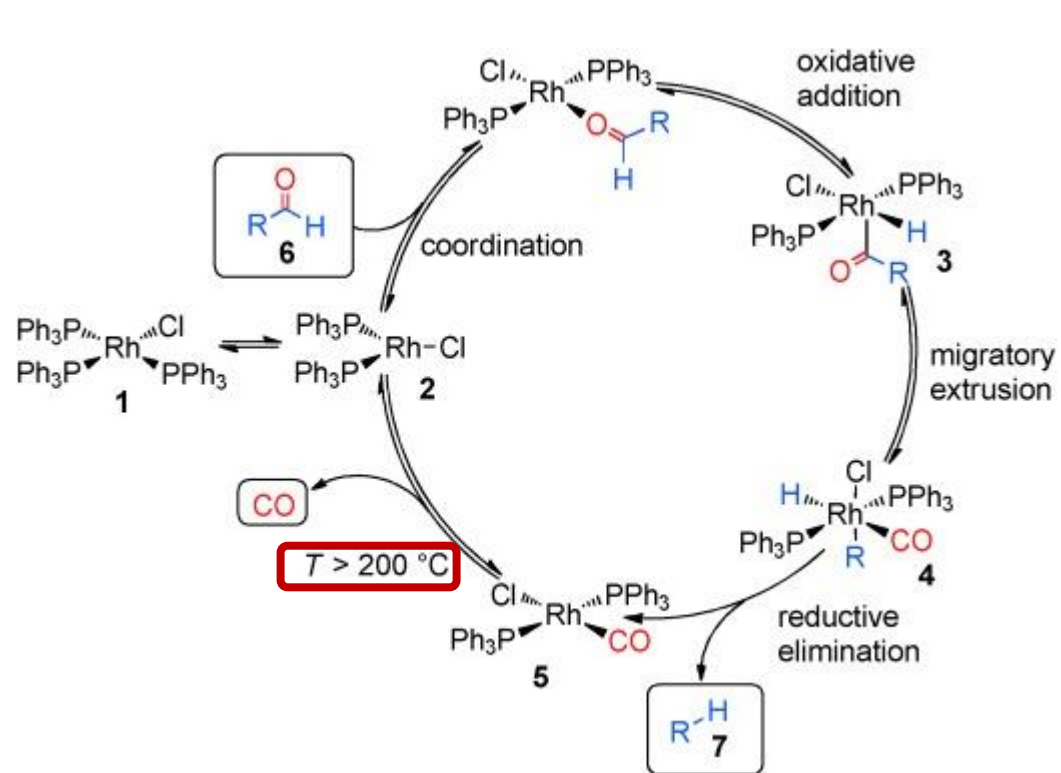


2.5.1 α -ELIMINATION – INTRODUCTION

- Reverse of migratory insertion
- Two main examples:
 - Decarbonylation
 - Carbene formation



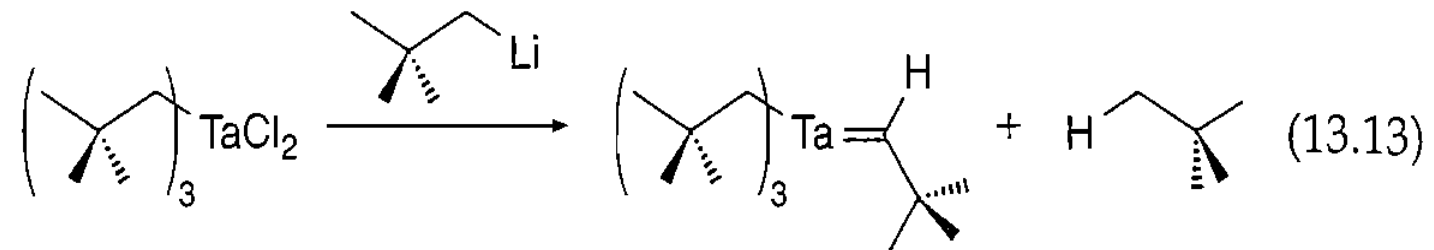
2.5.2 α - ELIMINATION – TSUIJ-WILKINSON DECARBONYLATION



Angew. Chem. Int. Ed., 2014, 53, 11557



2.5.3 α - ELIMINATION – CARBENE FORMATION

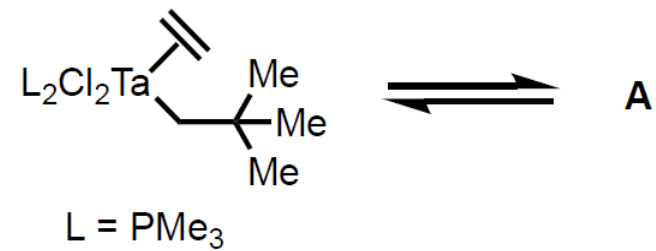


Schrock *JACS* **1974**, 96, 21. DOI: [10.1021/ja00828a061](https://doi.org/10.1021/ja00828a061)



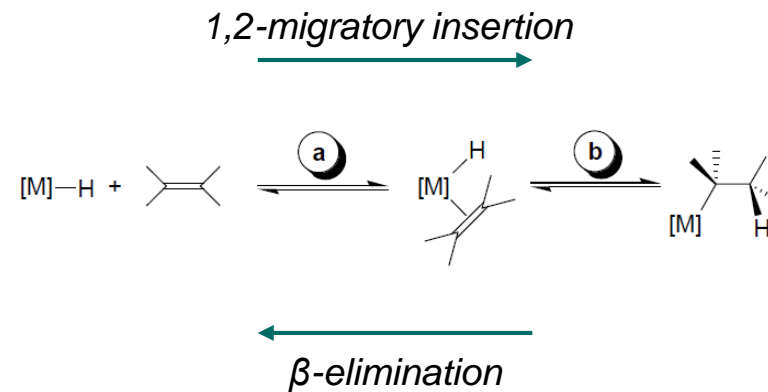
POD #4

In solution in C_6D_6 , the following tantalum complex is in equilibrium with a tautomeric form, A. **Predict the structure of A and propose a mechanism to form it.**





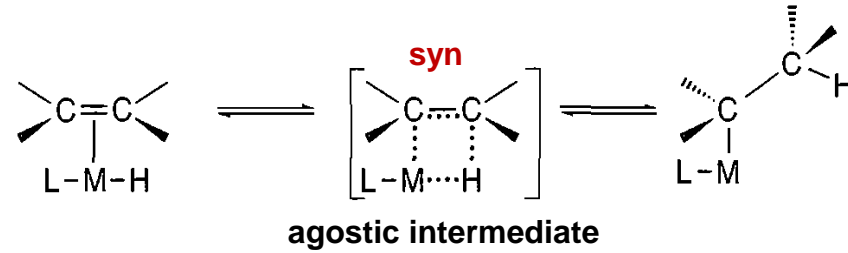
2.6 1,2-MIGRATORY INSERTION



	a	b
• Valence electron	$\Delta = +2$	$\Delta = -2$
Coordination number	$\Delta = +1$	$\Delta = -1$
Oxidation number	$\Delta = 0$	$\Delta = 0$



2.6.1 1,2-MIGRATORY INSERTION – INTRODUCTION



Aka **hydrometalation** ([M]-H insertion into unsaturated bond) or **carbometalation** ([M]-C insertion...)

Olefin insertion in [M]-H crucial step in hydrogenation, hydroformylation...

	CO (1,1)	Olefin (1,2)
[M]-H	✗	✓
[M]-aryl	✓	✓
[M]-alkyl	✓	(less common)



2.6.1 1,2-MIGRATORY INSERTION – AGOSTIC INTERACTIONS

“Evidence that carbon-hydrogen bonds may act as ligands to transition metal centres forming covalent C-H-M systems in which, formally, the C-H group donates two electrons to the metal.”

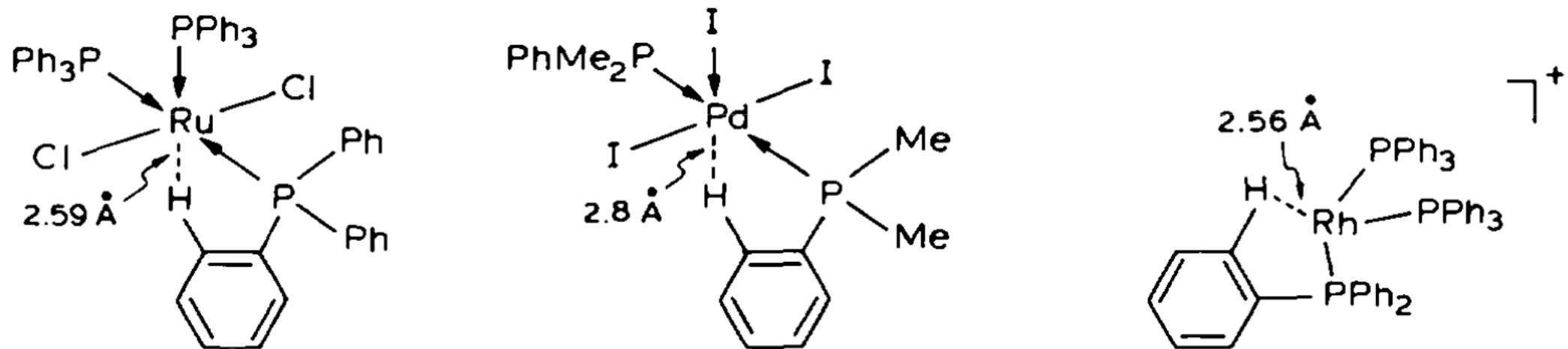
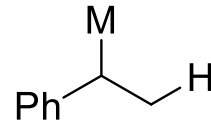
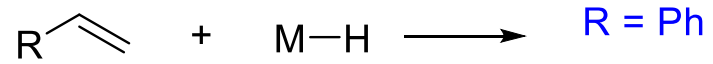


Fig. 1. The structures of compounds which gave early indications for the formation of C-H-M interactions.

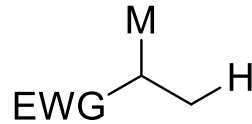
Agostic term introduced in: Brookhart *JOMC* **1983**, 250, 395. DOI: [fhwcdt](https://doi.org/10.1021/ar9501683)
Grubbs and Coates *Acc. Chem Res.* **1996**, 29, 85. DOI: [10.1021/ar9501683](https://doi.org/10.1021/ar9501683)



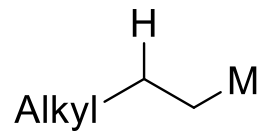
2.6.3 1,2-MIGRATORY INSERTION – REGIOSELECTIVITY



R = EWG
e.g. CO₂Me

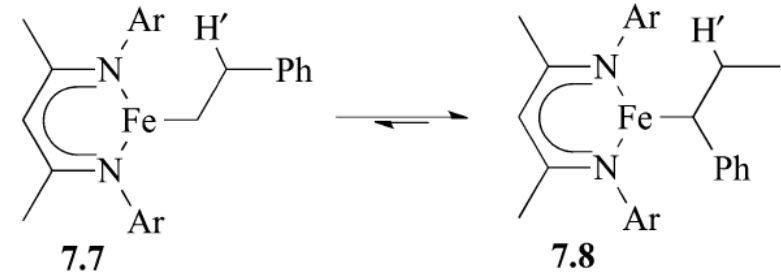


R = Alkyl



thermodynamics
(more stable C-H)

sterics

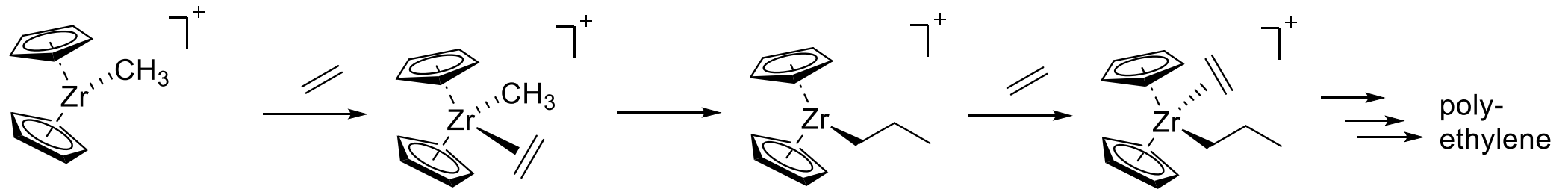




2.6.1 1,2-MIGRATORY INSERTION – EXAMPLE

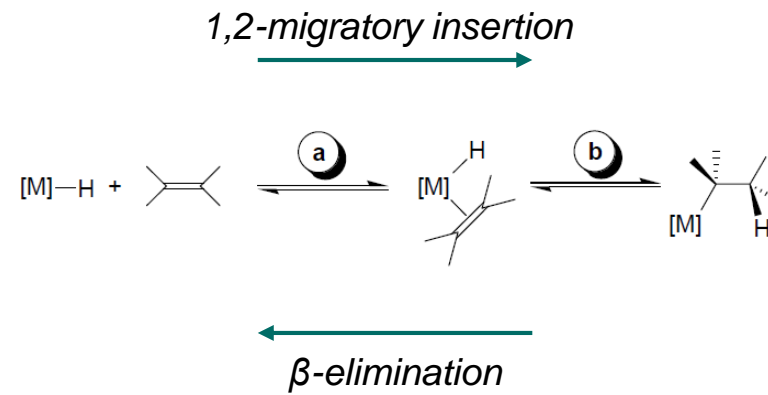
Ziegler-Natta polymerization (Ziegler PET, Natta PP)

Industrially relevant, multi Mton/y





2.7 β -ELIMINATION



	a	b
• Valence electron	$\Delta = -2$	$\Delta = +2$
Coordination number	$\Delta = -1$	$\Delta = +1$
Oxidation number	$\Delta = 0$	$\Delta = 0$

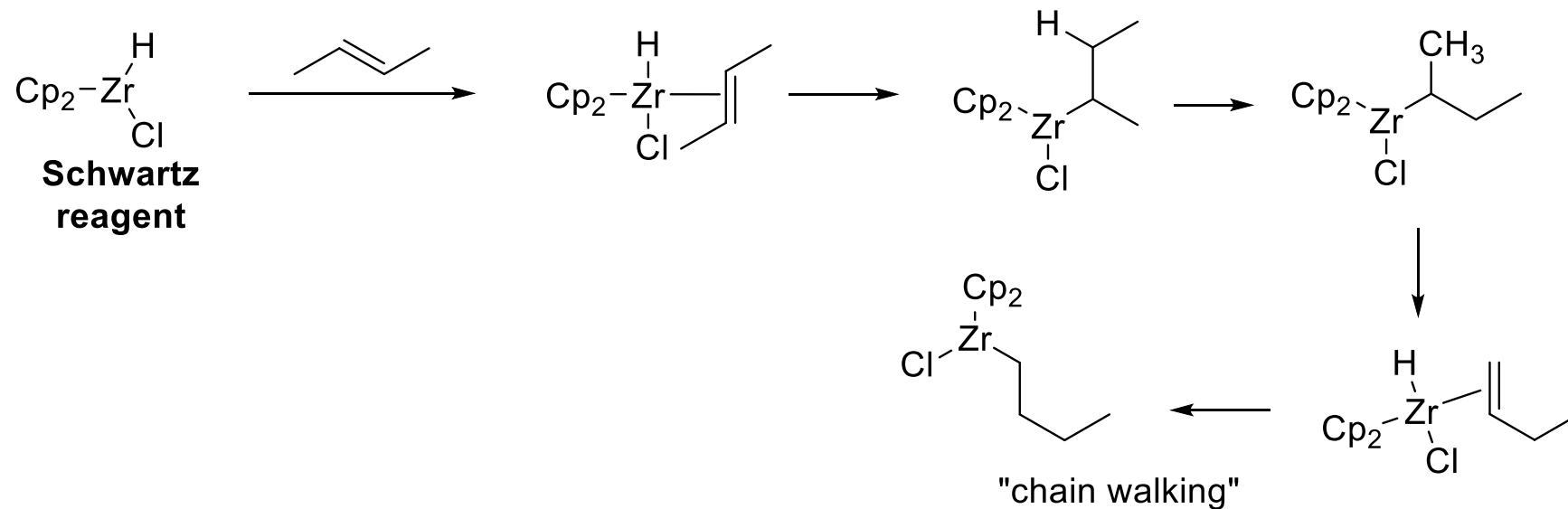


2.7.1 β -ELIMINATION – INTRODUCTION

- Reverse of 1,2-migratory insertion
- β -H elimination is the most common
- Fast, intramolecular, favored if vacant site cis to alkyl ligand to form agostic interactions
- Can be suppressed with trapping ligand



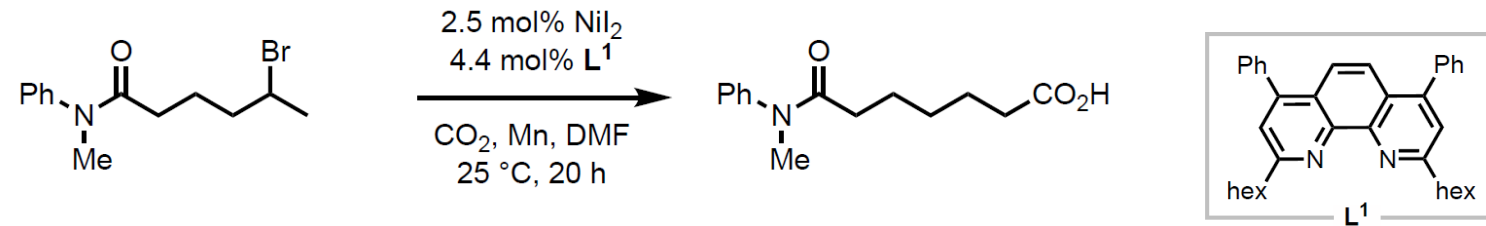
2.7.2 β -H ELIMINATION – CHAIN WALKING





2.7.2 POD #1

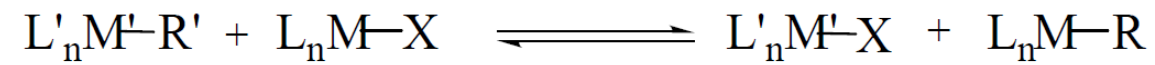
Consider the following transformation. Using the elementary steps covered so far, propose a plausible catalytic cycle.



Martin and co-workers, *Nature* **2017**, 545, 84. DOI: [10.1038/nature22316](https://doi.org/10.1038/nature22316)



2.8 TRANSMETALATION

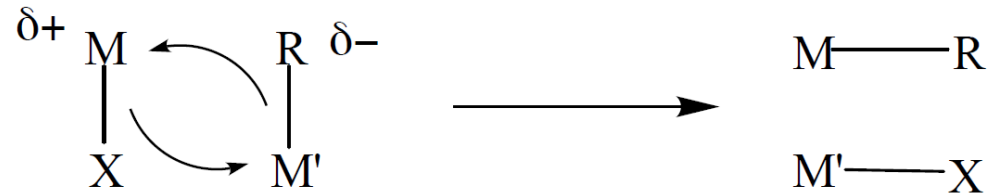


Transmetalation

Valence electron	$\Delta = 0$
Coordination number	$\Delta = 0$
Oxidation number	$\Delta = 0$



2.8.1 TRANSMETALATION – INTRODUCTION



- The transfer of an organic group from one metal center to another
- *no formal change in oxidation state* for either metal
- Often reversible, more ionic M-X favored
- Important step in cross-coupling (OA -> transmetalation -> RE)
- Mechanistically complex



2.8.1 TRANSMETALATION – TRANSMETALATION REAGENTS

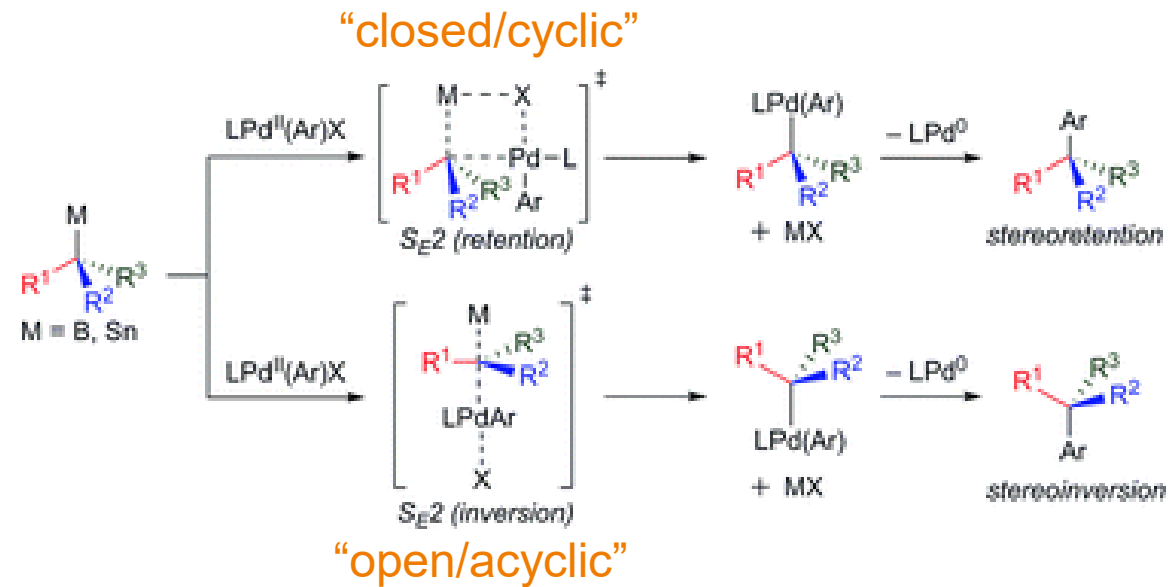
Reagent	R	Cross-coupling reaction
LiR, MgXR	vinyl, aryl, allyl, alkyl	Kumada
RZnCl	vinyl, aryl, alkyl	Negishi
RCuL _n	alkynyl, aryl	Sonogashira
RSnR' ₃	vinyl, aryl, alkynyl	Stille
RB(OR') ₂	vinyl, aryl	Suzuki
RSiR' ₃	aryl, vinyl, alkyl	Hiyama
R-9BBN	alkyl	Suzuki-Miyaura
AlR ₃ , RZrClCp ₂ , ...		



2.8.2 TRANSMETALATION – STEREOCHEMISTRY

C(sp²) coupling partner typically stereoretentive

C(sp³) coupling partner, two pathways:



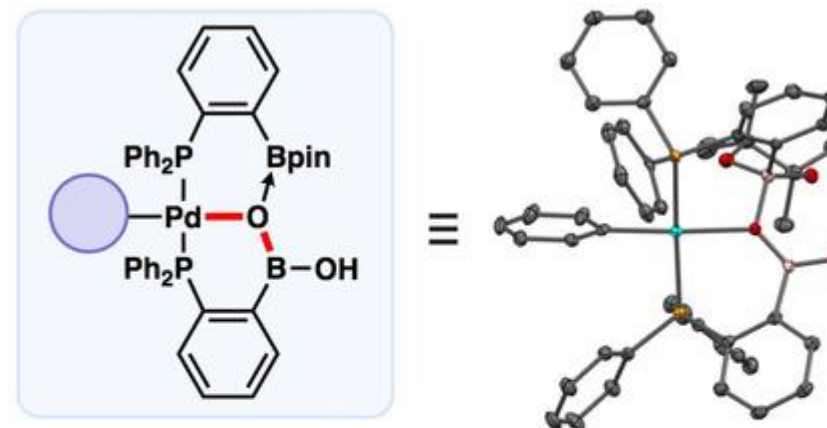
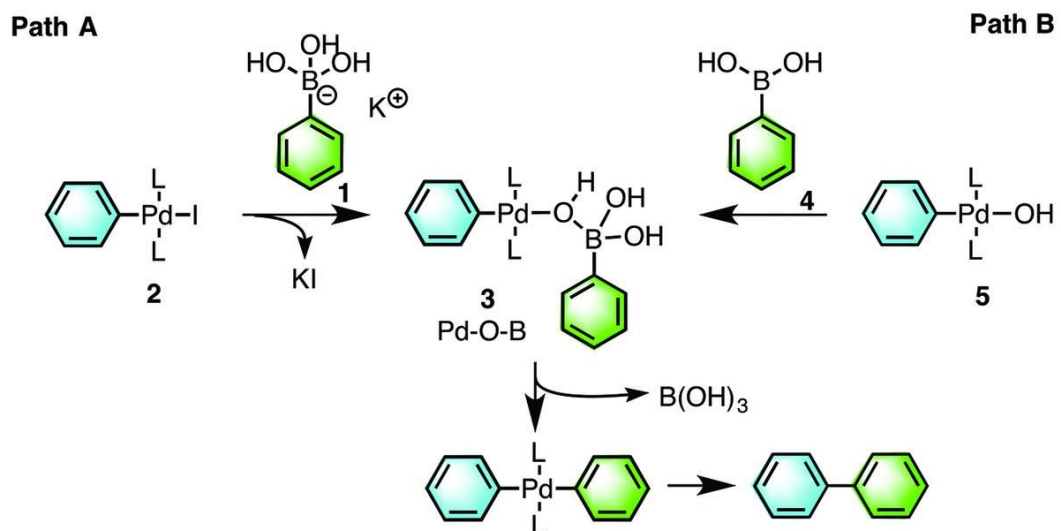
Review: Chem Sci, **2015**, 6, 5105. DOI: [10.1039/C5SC01710F](https://doi.org/10.1039/C5SC01710F)



2.8.3 TRANSMETALATION – ORGANOBORON

“Pd-O-B” intermediate

Transmetalation Pathways in the Suzuki-Miyaura Reaction



- *elusive pre-transmetalation intermediates isolated*
- *kinetically stable at ambient temperature*
- *structures secured by X-ray crystallography*
- *general synthetic method developed*

Denmark, *Science*, **2016**, 352, 329. DOI: [10.1126/science.aad6981](https://doi.org/10.1126/science.aad6981)

Bissember, *ACIE*, **2021**, 60, 14897. DOI: [10.1002/anie.202104802](https://doi.org/10.1002/anie.202104802)