Metal-catalyzed carbon-carbon bond formations

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Bibliography :

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Ei-ichi Negishi « Handbook of Organopalladium Chemistry for Organic Synthesis » (2003) Wiley-interscience

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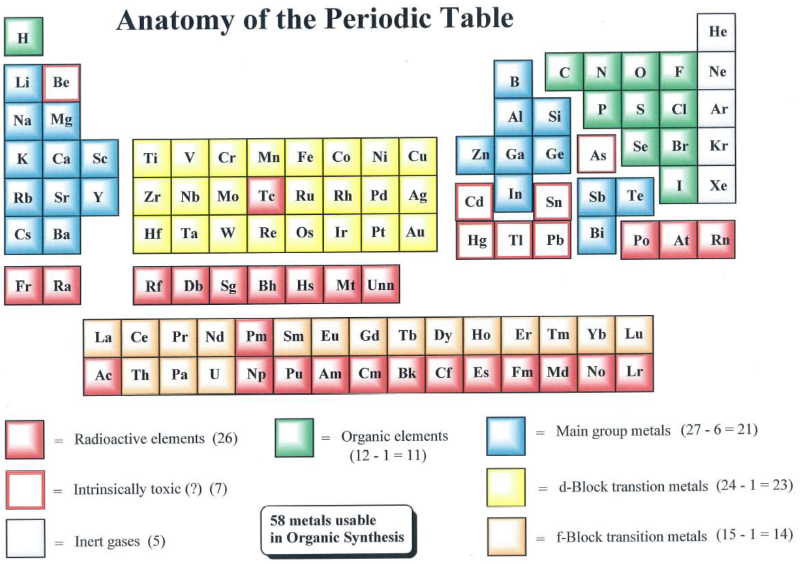
Transition metals and organic synthesis

A) C-C et C-Het bond formation

I) Background

II) Catalyzed reactions (Palladium, Nickel, Co)
   1) Negishi coupling
   2) Stille coupling
   3) Suzuki coupling
   4) Sonogashira coupling
   5) Heck coupling
   6) Buchwald-Hartwig coupling
   7) π-allyl complexes (Tsuji-Trost)
   8) CO insertion
   9) Wacker process
   10) Oxidative coupling of alkynes 2+2+2 (Volhardt)

Chemistry of Metals



Negishi's Nobel lecture (2010)

Background: the chemistry and reactivity of magnesium (Grignard: Nobel prize in 1012) and lithium reagents

$$R_1M + R_2X \xrightarrow[\mathbf{M} = \text{Li or Mg}]{} R_1\text{-}R_2 + MX$$

Quite similar types of reactions but lithium reagents > magnesium reagents

Lithium reagents are used under inert atmospher to avoid reaction with O_2

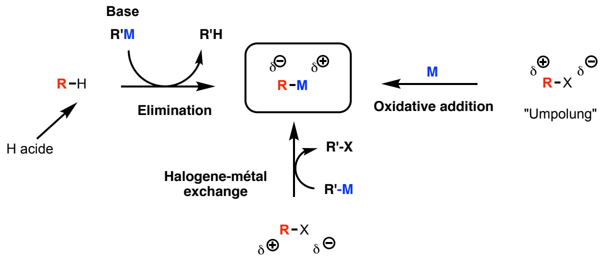
Lithium and magnesium reagents are strong nucleopiles but also strong bases.

They react violently with H_2O

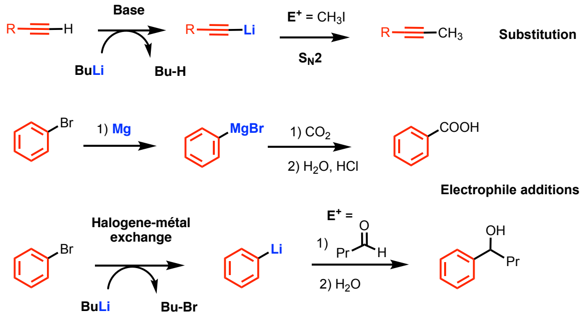
$$R\text{-}Li + H_20 \longrightarrow R\text{-}H + LiOH$$

Anhydrous apolar solvents: Et_20, THF

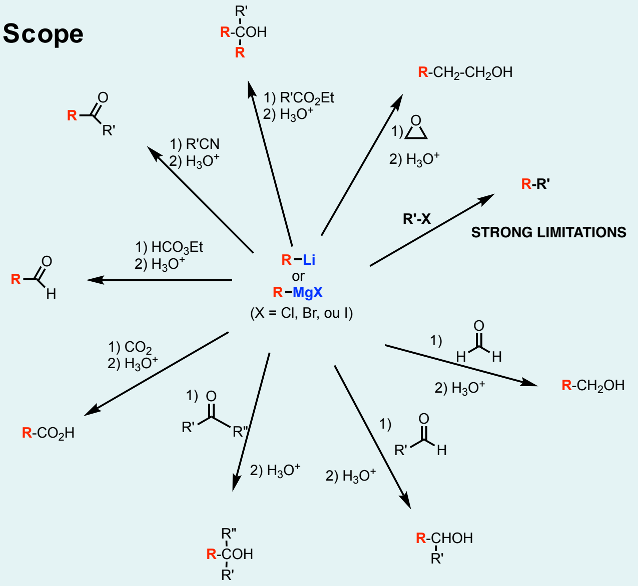
Preparation

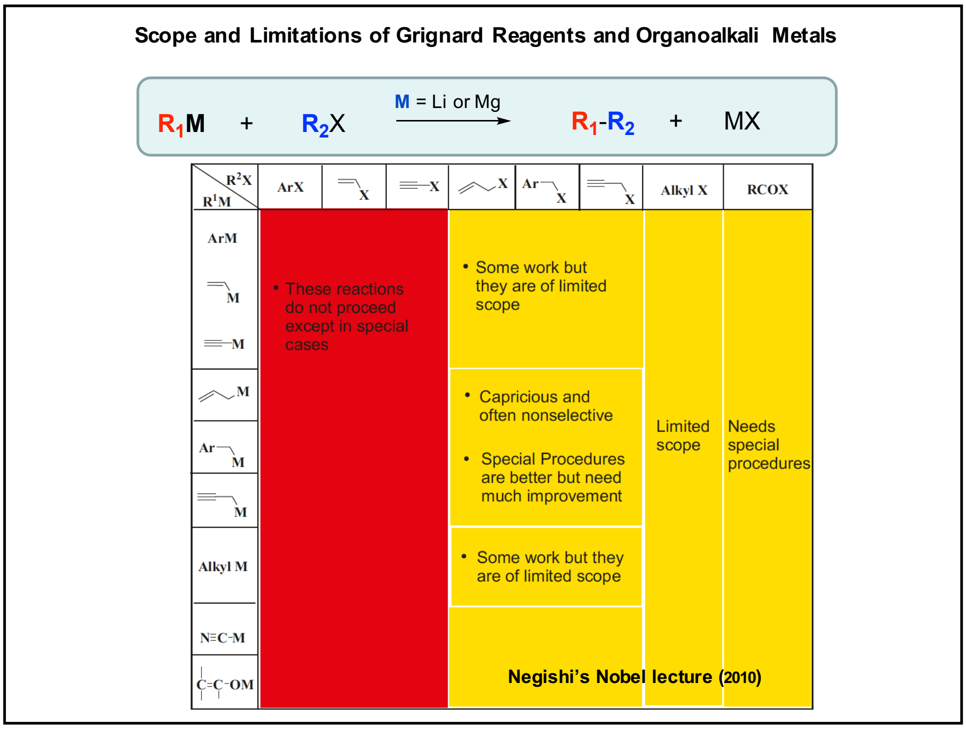


Examples



Scope





Scope and Limitations of Grignard Reagents and Organoalkali Metals

$R_1M + R_2X \xrightarrow{M = \text{Li or Mg}} R_1\text{-}R_2 + MX$

- These reactions do not proceed except in special cases

- Some work but they are of limited scope

- Capricious and often nonselective

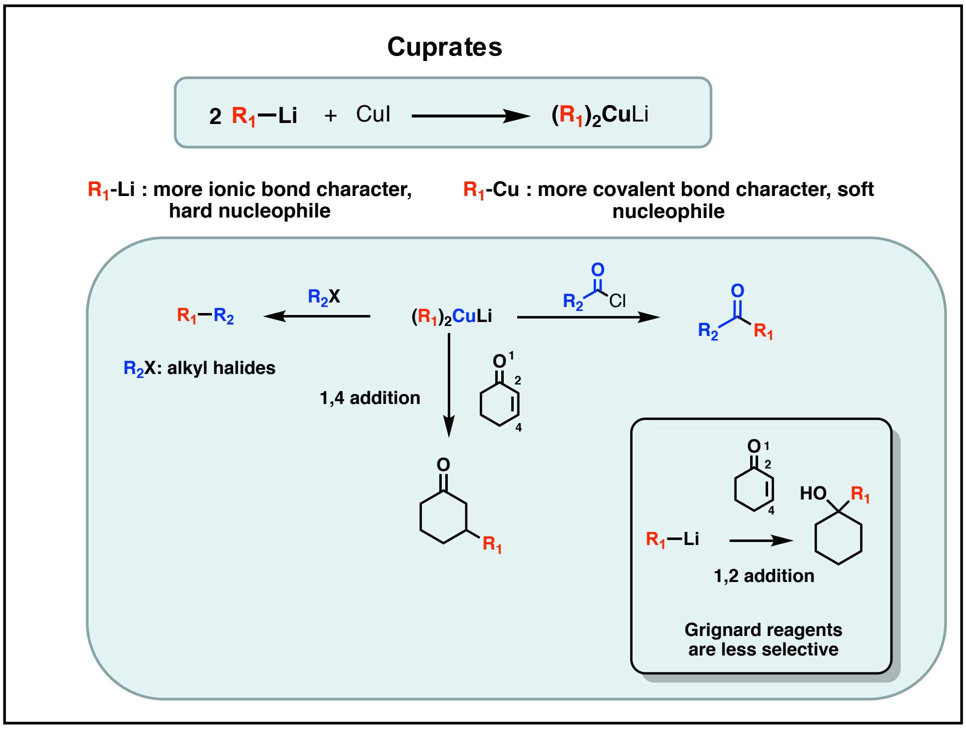
- Special Procedures are better but need much improvement

- Some work but they are of limited scope

Limited scope

Needs special procedures

Negishi's Nobel lecture (2010)



Cuprates

$2\ R_1\text{—}Li + CuI \longrightarrow (R_1)_2CuLi$

R_1-Li : more ionic bond character, hard nucleophile

R_1-Cu : more covalent bond character, soft nucleophile

R_2X: alkyl halides

1,2 addition

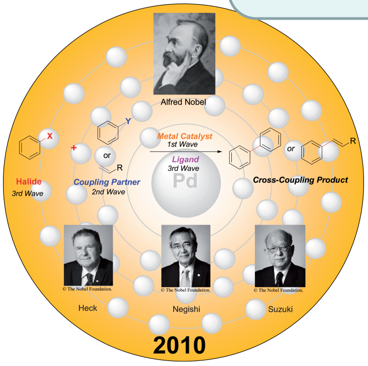
Grignard reagents are less selective

Major C-C couplings catalyzed by Pd(0)

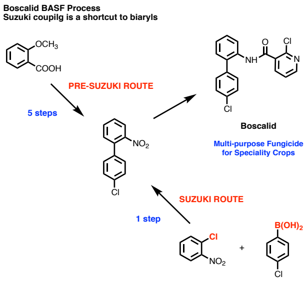
$$R_1M + R_2X \xrightarrow{PdL_n\ cat.} R_1\text{-}R_2 + MX$$

R_1= C sp, sp^2, sp^3

R_2= C sp, sp^2, sp^3



V. Snieckus *et al. Angew. Chem. Int. Ed.* 2012, **51**, 5062 – 5085



Tons
BASF, Germany

Suzuki's Nobel lecture (2010)

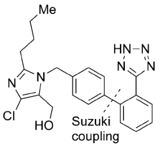
Cross-coupling reactions in total synthesis of drugs in industries

Losartan : blood pressure (hypertension)

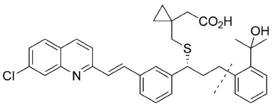
Singulair: asthma or allergy symptoms

Gleevec: blood cancer

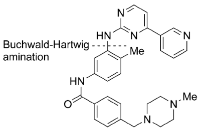
PDE472: clinical for asthma



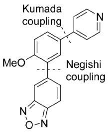
Losartan



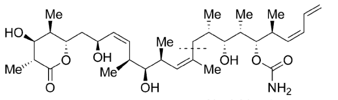
Singulair (Heck coupling)



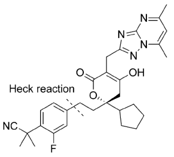
Gleevec (Imatinib)



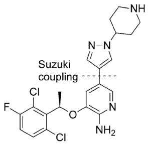
PDE472



Discodermolide



hepatitis C polymerase inhibitor



Crizotinib

Discodermolide: clinical for cancer

Crizotinib: non-small cell lung cancer

V. Snieckus *et al. Angew. Chem. Int. Ed.* 2012, **51**, 5062 – 5085

Chemistry of Transition Metals

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	
H 2,2																	He	2
Li 1	Be 1,6											B 2,0	C 2,6	N 3,0	O 3,4	F 4,0	Ne	10
Na 0,93	Mg 1,3											Al 1,6	Si 1,9	P 2,2	S 2,6	Cl 3,2	Ar	18
K 0,82	Ca 1	Sc 1,4	Ti 1,5	V 1,6	Cr 1,7	Mn 1,6	Fe 1,8	Co 1,9	Ni 1,9	Cu 1,9	Zn 1,7					Br 3,0	Kr	36
			Zr 1,3		Mo 2,2		Ru 2,2	Rh 2,3	Pd 2,2	Ag 1,9	Cd 1,7		Sn 2,0			I 2,7	Xe	54

Z = Pd, Ni, Co, Rh, Ru, Mo, etc

δ^- δ^+

C-Z : Pd-C ≠ C-Li, C-MgX

Ionic character : 2% ≠ 43%, 35%

H_20 : Stable ≠ reactive

: Catalytic ≠ stoechiometric

➡ **Different Chemistry**

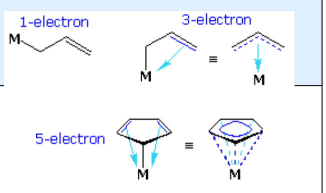
Transition metals

How to count the electron provided by the ligand for a complex?

Determine if the valence shell is filled or not?

Determine the oxidation state of the metal?

Have a first estimation of the complex reactivity?

Covalent Groups 1-electron donors (accepteur d' 1 électron)	**Coordinate Ligands** 2-electron donors (neutre)	
F, Cl, Br, I H (hydride) R- or Ar- RCO- (acyl) RO- or RCO_2- R_2N-	R_3P: (phosphine) R_3N: R_2O CO $R_2C{=}CR_2$ $RC{\equiv}CR$	

http://www.cem.msu.edu/~reusch/VirtualText/orgmetal.htm

How to determine if the valence shell is filled or not and determine the oxidation state of the metal?

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
H 2,2																	2 He
Li 1	Be 1,6											B 2,0	C 2,6	N 3,0	O 3,4	F 4,0	10 Ne
Na 0,93	Mg 1,3											Al 1,6	Si 1,9	P 2,2	S 2,6	Cl 3,2	18 Ar
K 0,82	Ca 1	Sc 1,4	Ti 1,5	V 1,6	Cr 1,7	Mn 1,6	Fe 1,8	Co 1,9	Ni 1,9	Cu 1,9	Zn 1,7					Br 3,0	36 Kr
			Zr 1,3		Mo 2,2		Ru 2,2	Rh 2,3	Pd 2,2	Ag 1,9	Cd 1,7		Sn 2,0			I 2,7	54 Xe

Ex: $PdCl_2(PPh_3)_2$?

$Pd(0)$ = 46 e^- = Kr(36) + 10 e^- (valence shell)
Ligands = 2x2 (PPh_3) + 2x1 = 6 e^-
$PdCl_2(PPh_3)_2$ = 10 + 6 = **16 e^- complex**
Remark: 2 e^- are missing to fill the valence shell and be isoelectronic of Xe, thus the complex is reactive and a Lewis acid

Oxidation: Pd^{2+} because two Cl (2x1e- electro-attractor ligand)

Complex geometries

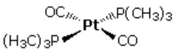
tetrahedral

square planar

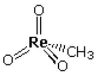
octahedral

trigonal bipyramidal

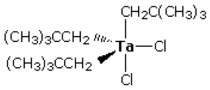
examples



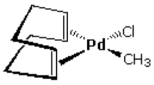
Pt(0) 18 electrons



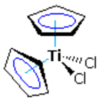
Re(VII) 14 electrons



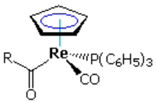
Ta(V) 10 electrons



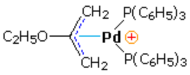
Pd(II) 16 electrons



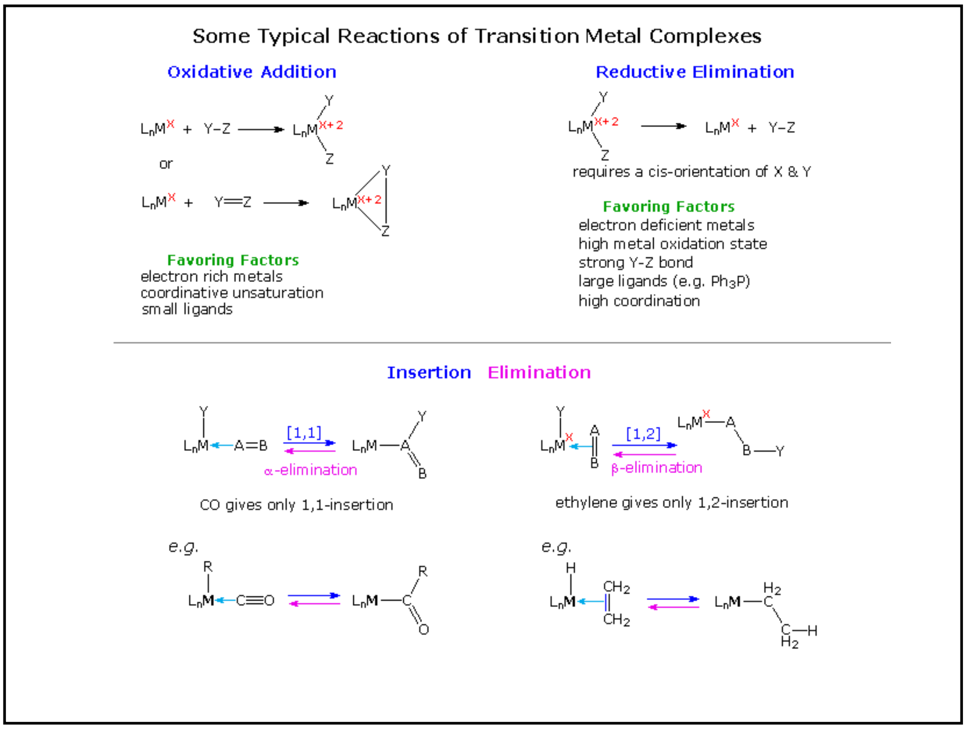
Ti(IV) 16 electrons



Re(II) 17 electrons



Pd(II) 16 electrons



Some Typical Reactions of Transition Metal Complexes

Oxidative Addition

Favoring Factors
electron rich metals
coordinative unsaturation
small ligands

Reductive Elimination

requires a cis-orientation of X & Y

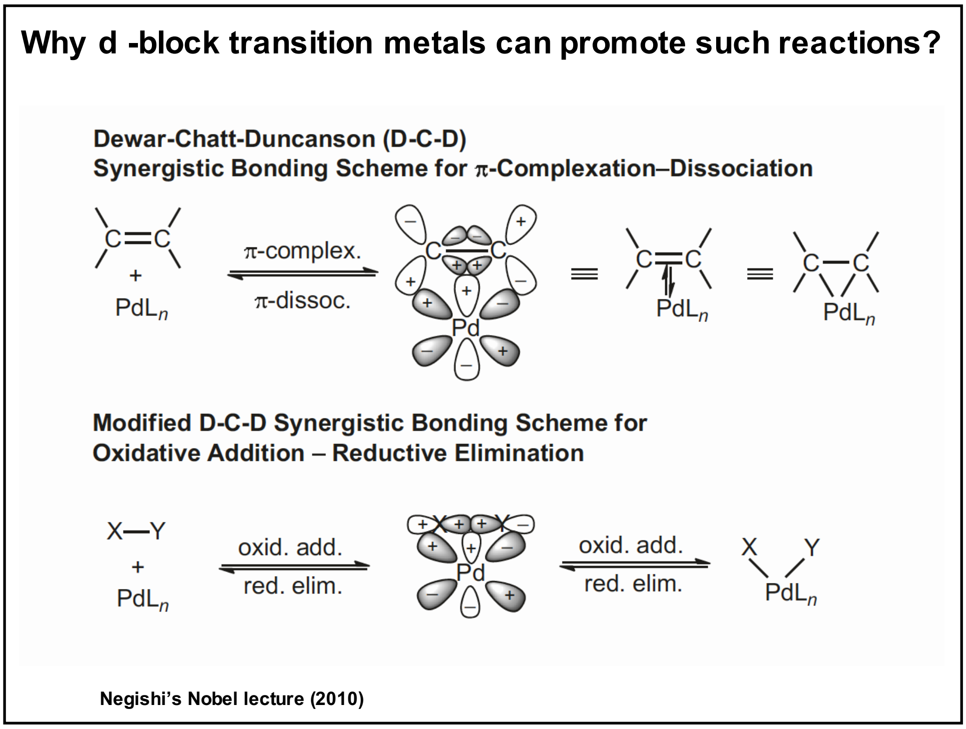
Favoring Factors
electron deficient metals
high metal oxidation state
strong Y-Z bond
large ligands (e.g. Ph_3P)
high coordination

Insertion **Elimination**

CO gives only 1,1-insertion

ethylene gives only 1,2-insertion

e.g.



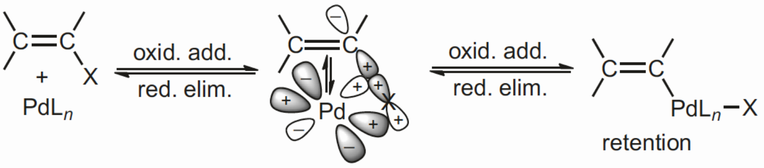
Why d -block transition metals can promote such reactions?

Dewar-Chatt-Duncanson (D-C-D)
Synergistic Bonding Scheme for π-Complexation–Dissociation

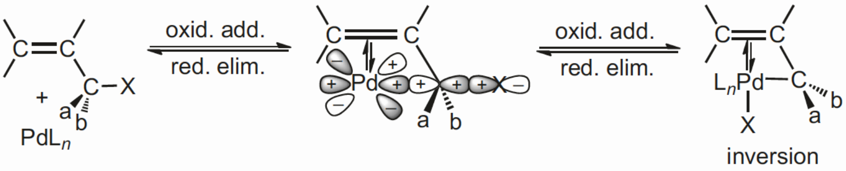
Modified D-C-D Synergistic Bonding Scheme for
Oxidative Addition – Reductive Elimination

Negishi's Nobel lecture (2010)

π-Complexation–Assisted Oxidative Addition with Alkenyl (Alkynyl or Aryl) Halides with Retention (D-C-D Synergistic π- and σ-Bonding Tandem)

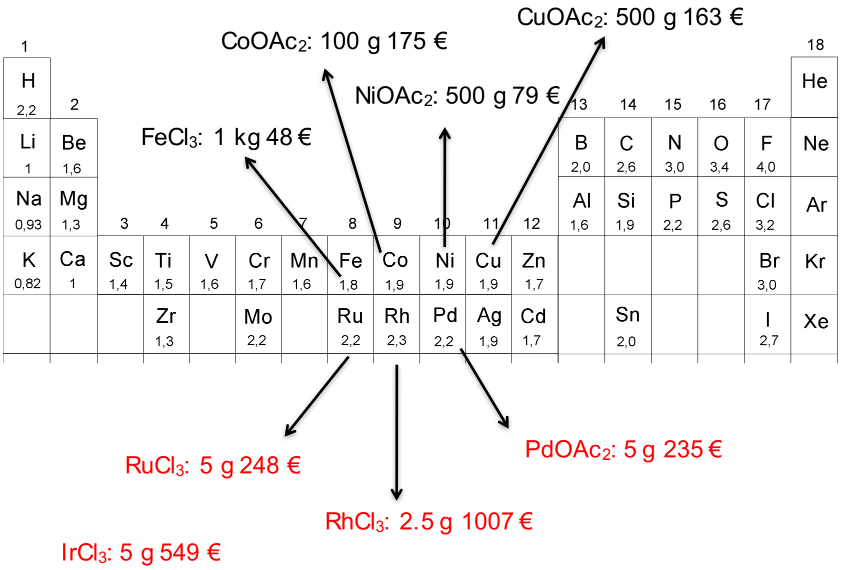


π-Complexation–Assisted Oxidative Addition with Allyl (Propargyl or Benzyl) Halides with Inversion (D-C-D Synergistic Bonding–Promoted 'S$_N$2''-like Process)



Negishi's Nobel lecture (2010)

Why transition metals of second row or more should be used in catalytic amount?



1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
H 2,2																	He
Li 1	Be 1,6											B 2,0	C 2,6	N 3,0	O 3,4	F 4,0	Ne
Na 0,93	Mg 1,3											Al 1,6	Si 1,9	P 2,2	S 2,6	Cl 3,2	Ar
K 0,82	Ca 1	Sc 1,4	Ti 1,5	V 1,6	Cr 1,7	Mn 1,6	Fe 1,8	Co 1,9	Ni 1,9	Cu 1,9	Zn 1,7					Br 3,0	Kr
			Zr 1,3		Mo 2,2		Ru 2,2	Rh 2,3	Pd 2,2	Ag 1,9	Cd 1,7		Sn 2,0			I 2,7	Xe

CuOAc$_2$: 500 g 163 €

CoOAc$_2$: 100 g 175 €

NiOAc$_2$: 500 g 79 €

FeCl$_3$: 1 kg 48 €

PdOAc$_2$: 5 g 235 €

RuCl$_3$: 5 g 248 €

RhCl$_3$: 2.5 g 1007 €

IrCl$_3$: 5 g 549 €

Major C-C, C-N, C-O couplings catalyzed by transition metal complexes

$$\text{Nu} + \underset{\text{Elec}}{R_1X} \xrightarrow{\text{Cat.}} R_1\text{-Nu}$$

Metals = Pd, Ni, Cu, Rh, Co, Ir, Fe, Ru

C-C Formation (R_1-R_2 and alkyne trimérisation(2 + 2 +2))

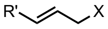
Nu = $R_2M(X)$ Zn (Negishi), Al, Zr , Mg, (Kumada-Corriu), Li, $SiOR_3$ (Hiyama-Denmark)
SnR_3 (Stille)
BL_2 (Suzuki)

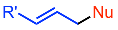
(Heck) **Nu =** R'—≡—H (Sonogashira, Vollhardt)

C-N, C-O formation

Nu
Amine/ Alcool (amide...) (Buchwald-Hartwig, Golberg, Ullmann)
↓
Nu-R_2

C-C, C-N, C-O formation (π-allyl complexes-

Nu et R_2X= 

(Tsuji-Trost)
↓


Palladium in organic synthesis

Pd° : (**Kr**) $4d^{10}$

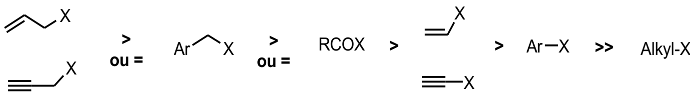
Pd^0: nucleophile
Pd^{2+}: electophile

Geometry: tetrahedral & square planar

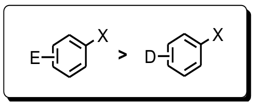
$PdOAc_2$: 5 g 235 €

⇨ catalyst

Reactivity of Pd(0) complexes, ex $Pd(PPh_3)_4$



I > OTf, Br > Cl > OZ > NZ_2...



Pd-C ≠ Mg-C ou Li-C

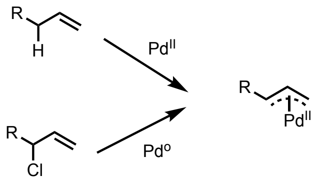
Compatibility: ketone, ester, amide, even aldehydes…

Major types of reactions involving Pd complexes

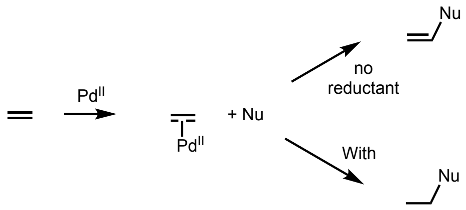
- Oxidative addition (Heck, Negishi, Stille, Suzuki, Buchwald Hartwig)

$$R-X \xrightarrow{Pd^0} R-Pd^{II}-X$$

- π-allyl-Pd complex (Tsuji-Trost)



- π-alkene-Pd^{II} complex (Wacker process)



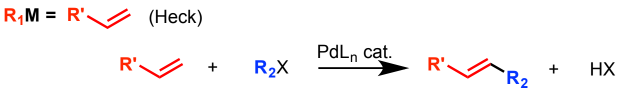
Major C-C couplings catalyzed by Pd(0)

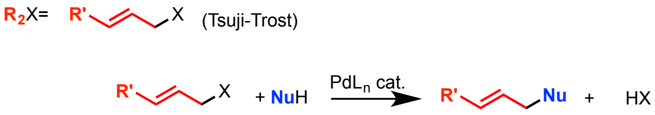
$$R_1M + R_2X \xrightarrow{PdL_n\ cat.} R_1\text{-}R_2 + MX$$

R_1= C sp, sp^2, sp^3
R_2= C sp, sp^2, sp^3

X= I > OTf > Br >> Cl

M = metal Zn, Al, Zr ...Mg, Li (Negishi) $R_1M = R'-\equiv-H(Cu)$ (Sonogashira)
SnR_3 (Stille)
BL_2 (Suzuki)

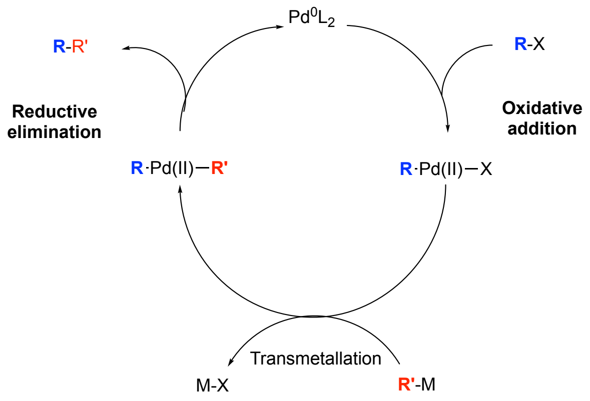




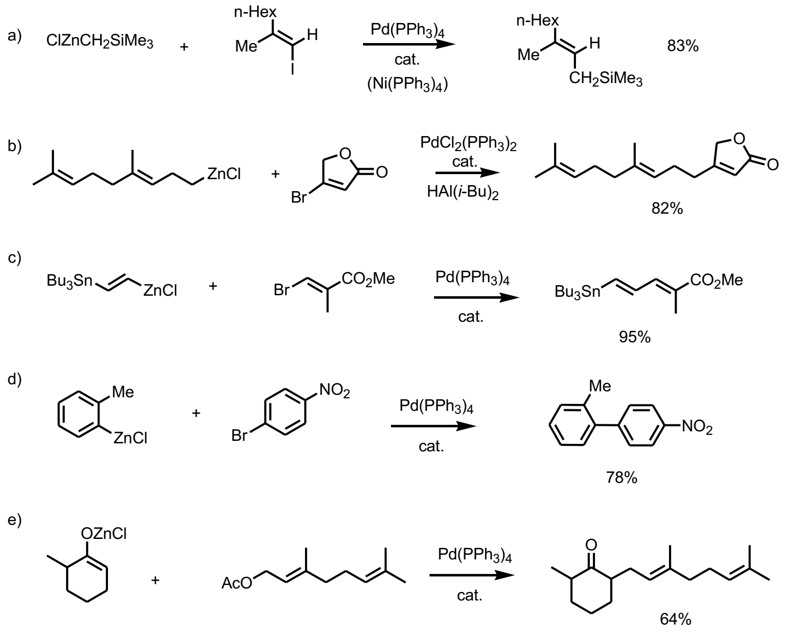
General catalytic cycle for C-C coupling catalyzed by palladium

$Pd^0L_4 \rightleftharpoons Pd^0L_2 + 2\ L$

$Pd^{2+}L_2Cl_2 \rightleftharpoons Pd^0L_2$ (generated *in situ*)

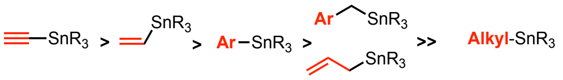


Examples of Negishi couplings

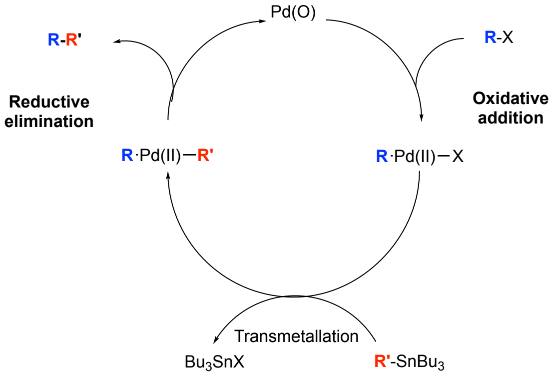


$R_1SnR_3 + R_2X \xrightarrow{PdL_n\ cat.} R_1\text{-}R_2 + R_3SnX$

I > OTf > Br > Cl

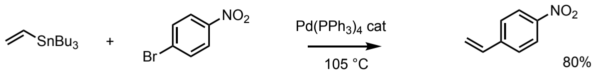


Stille coupling: catalytic cycle

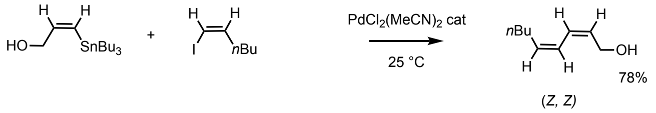


Examples of Stille couplings

a)



b)



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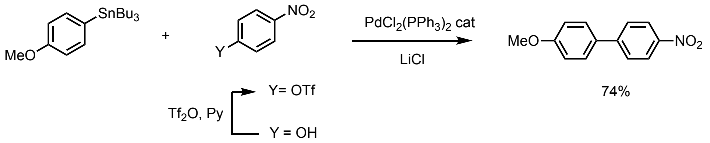
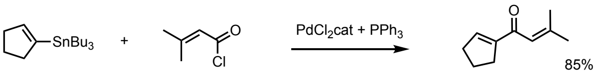


d)



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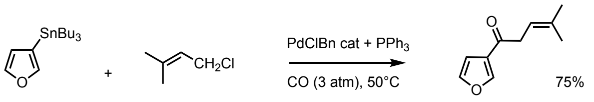
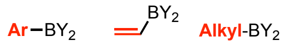
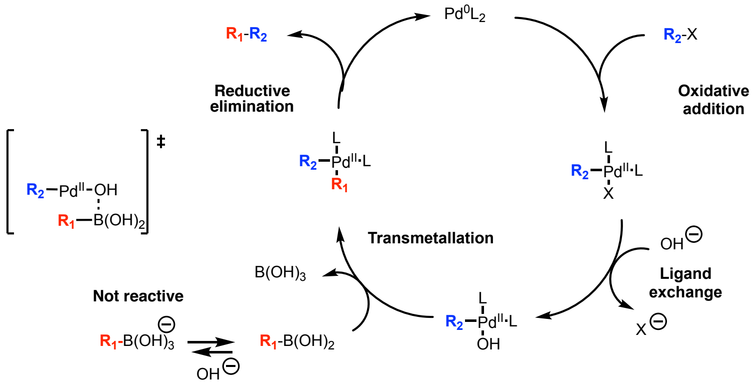


$$R_1BY_2 + R_2X \xrightarrow[\text{Base : } Na_2CO_3,\ EtONa,\ Et_3N,\ K_3PO_4...]{PdL_n\ \text{cat.}} R_1\text{-}R_2 + BY_2(OH)_2^-$$

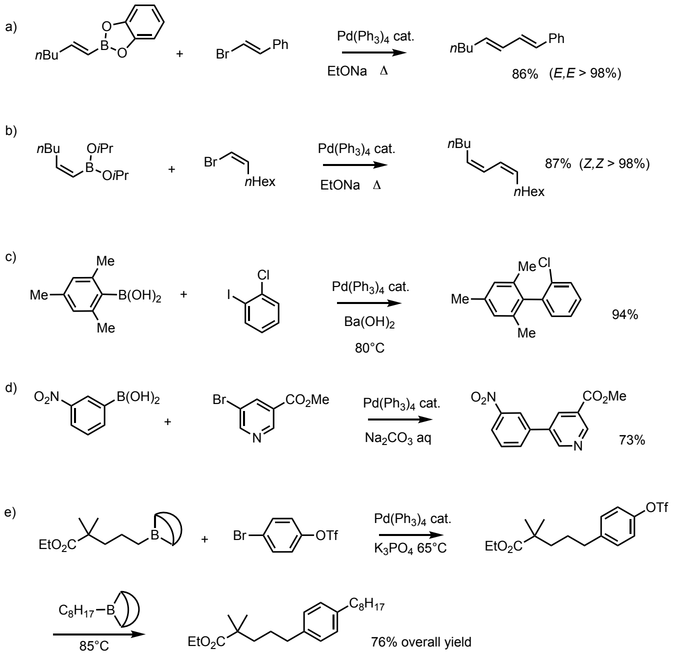
I > Br > OTf > Cl



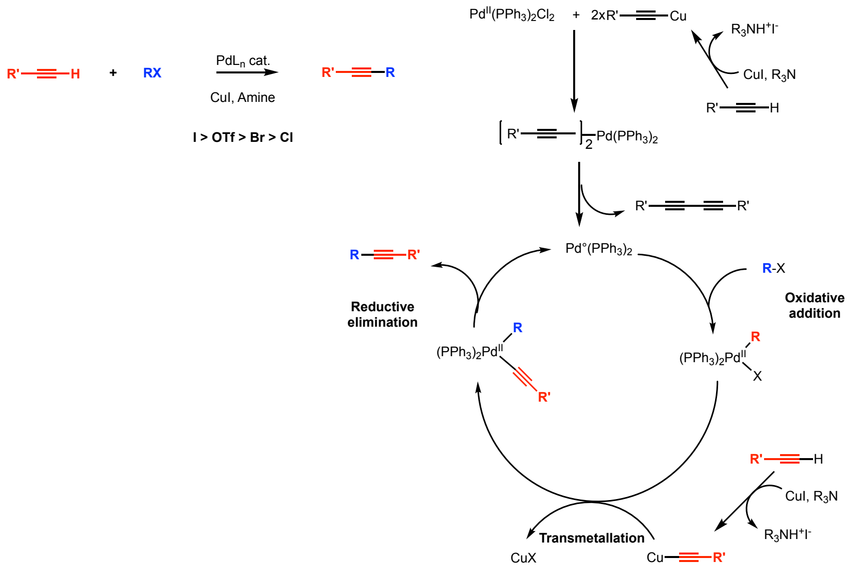
Suzuki coupling
Catalytic cycle



Examples of Suzuki couplings

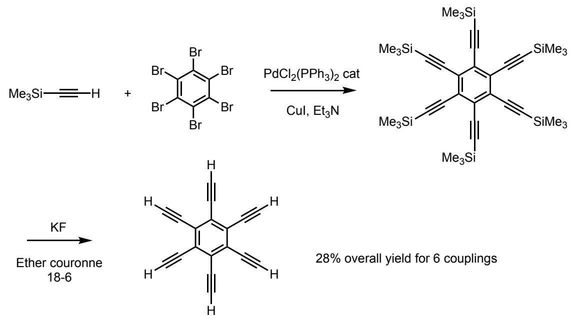


Sonogashira coupling catalytic cycle

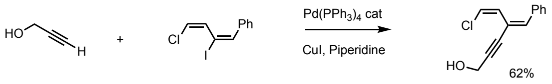


Examples of Sonogashira couplings

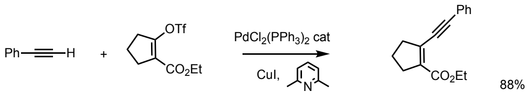
a)



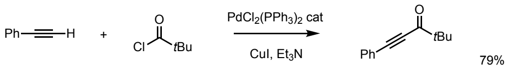
b)



c)



d)



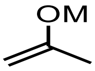
Main characteristics and choice of reagents

	Zn	B	Sn
Toxicity	No	No	Yes
Reactivity (**R**-M)	++	+ à ++	+
Chemioselectivity – sensitivity to :			
- Ketone, ester, nitro, amide, nitrile…	No	No (! Basic)	No
- Aldehyde	Yes	Yes	No
- O_2, H_20, ROH	Yes	No (RB(OR' $)_2$)	No
Regioselectivity	Yes	Yes	Yes
Stereoselectivity	Yes	Yes	Yes

$$\mathbf{R_1M} + R_2X \xrightarrow{PdL_n\ cat.} R_1\text{-}R_2 + MX$$

R_1= C sp, sp^2, sp^3

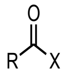
R_2= C sp, sp^2, sp^3

R-M	**Metal**
Aryl-M **Alkenyl**-M	Zn, B, Sn
$R'-\equiv-M$	Sonogashira (Zn, B, Sn)
Benzyl, propargyl, **Allyl**-M	Sn, Zn
Alkyl-M	B (Zn)
	Zn, B, Sn

$$R_1M \quad + \quad R_2X \xrightarrow{PdL_n \text{ cat.}} R_1\text{-}R_2 \quad + \quad MX$$

R_1= C sp, sp^2, sp^3

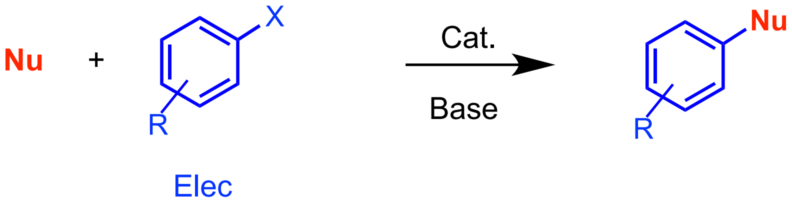
R_2= C sp, sp^2, sp^3

R-X	**Metal**
Aryl-X **Alkenyl**-X	Zn, B, Sn
Benzyl, Propargyl, **Allyl**-X	Zn, Sn
	Sn
+ **CO**	Sn (B) (R_2COR_1)

Main methods of preparing R-M

	Zn	B	Sn
Transmetallation (R-Li, R-MgX)	Yes	Yes	Yes
Oxidative addition (R-X)	possible	$(RO)_2B\text{-}B(OR)_2$ + Pd° cat.	$R_3Sn\text{-}SnR_3$ + Pd° cat.
Hydrometallation : (M-H)	($HAl(i\text{Bu})_2$ ou $HZrCp_2Cl$)	HBY_2	$HSnR_3$

Pd, Cu, Ni catalyze C-N & C-O couplings

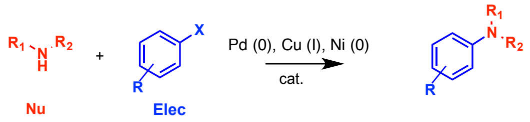


Metal = Pd (0), Cu (I), Ni (0)

Nu = Amines, alcools,
amides

C-N, C-O : Pd, Ni **(**Buchwald-Hartwig)
C-N : Cu (Goldberg)
C-O: Cu (Ullmann)

C-N formation catalyzed by Pd, Cu & Ni



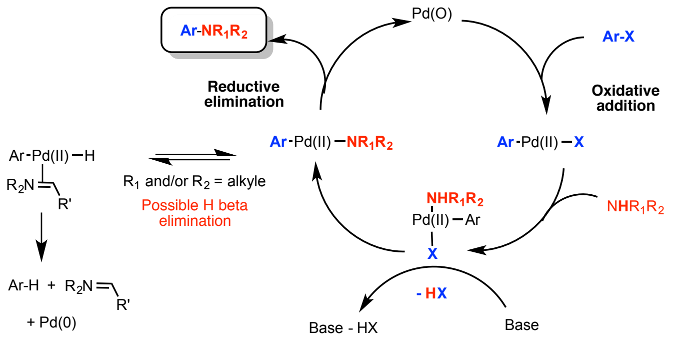
X = I, Br, Cl, OTf, etc.

Ligand = 1, 2 & 3rd
generations

R_1, R_2 = Alkyle, aryle, H

Base = *t*BuONa, Cs_2CO_3

Pallado-catalyzed cycle

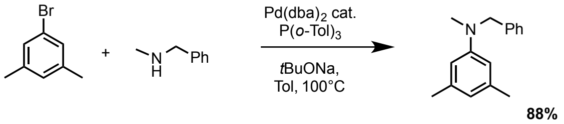


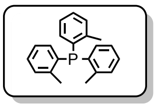
**Biphosphine ligands reduce
beta elimination**

Reaction conditions and choice of ligands depend on the the nature of the substrates

Secondary amines

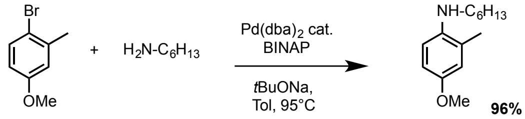
dba : dibenzylideneacetone

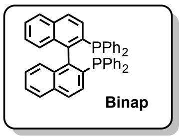




First generation of catalyst

Primary amines (beta elimination is a problem with 1st generation catalysts

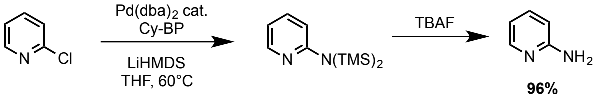


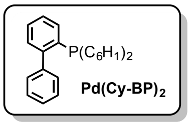


second generation

Remark: no racemisation if chiral amines are used

NH$_3$ and derivatives (NH$_2$Boc, Imine, LiHMDS, TMSCH$_2$CH$_2$SO$_2$NH$_2$, etc.)

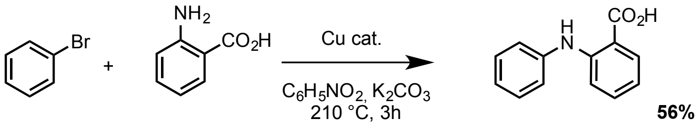




Third generation

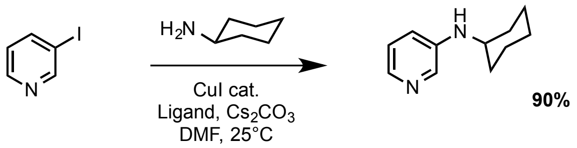
Cu catalyzes C-N coupling

1906 Goldberg

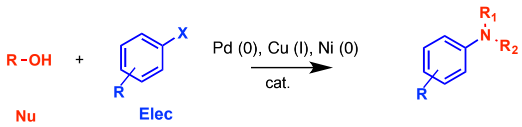


Since 2000increasing interest

New bidentate ligand (e.g. diols, diamines, dicetones) give improved yields and enalrge the scope



Pd, Ni & Cu catalyze C-O bond formation



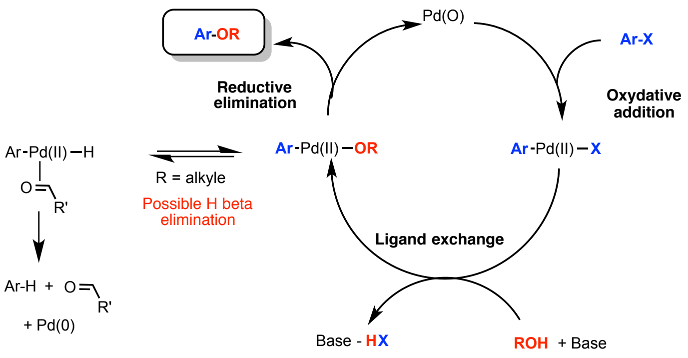
X = I, Br, Cl, OTf

Ligand

R = Alkyle, aryle

Base = NaH, K_3PO_4

Pallado-catalyzed cycle



Pd(O)

Ar-X

Oxydative addition

Ar-Pd(II)−X

Ligand exchange

ROH + Base

Base - HX

Ar-Pd(II)−OR

Reductive elimination

Ar-OR

Ar-Pd(II)−H

O=⟍R'

R = alkyle

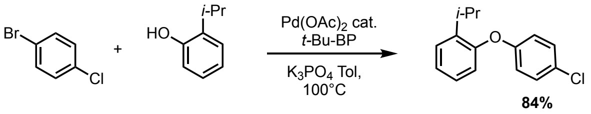
Possible H beta elimination

Ar-H + O=⟍R' + Pd(0)

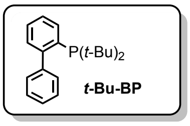
Les réactions dépendent en particulier de la nature des substrats (ex: choix du ligand)

ArOH

ligands 3G

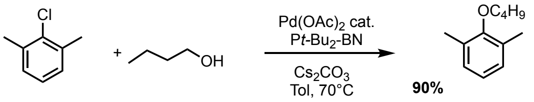


84%

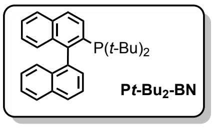


***t*-Bu-BP**

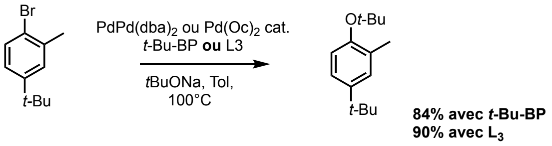
Alcool primaires, secondaires et tertiaires



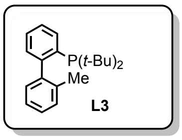
90%



P*t*-Bu$_2$-BN



84% avec *t*-Bu-BP
90% avec L$_3$



L3

dba : dibenzylidèneacétone

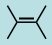
I > OTf > Br > Cl

R' = H, Alk, Ar, CN, OR, COOR …

Base: amine, K_2CO_3, $NaHCO_3$…

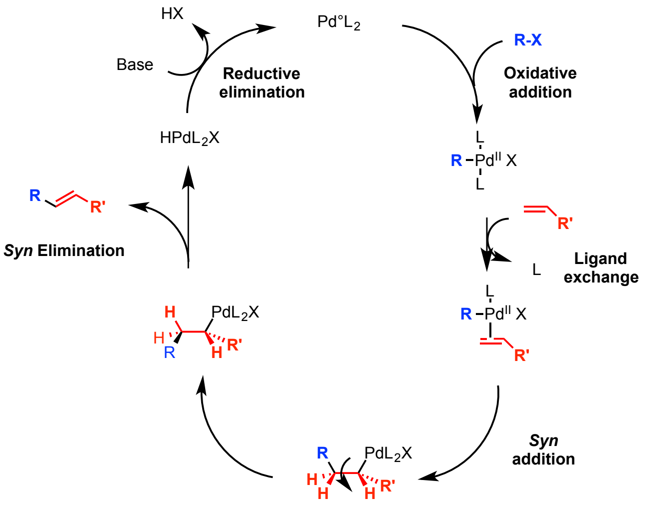
Heck coupling: catalytic cycle

Alkene reactivity



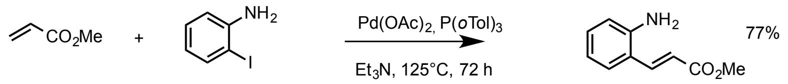
monosubstitutated> di>> tri- and tetra

With strong electron donating **R'** (D= OR, NR_2): 1,1 regio-product is obtained

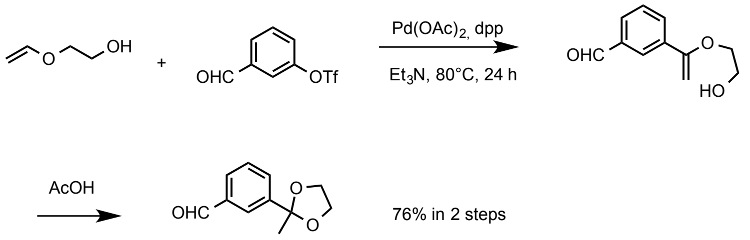


Examples of Heck couplings

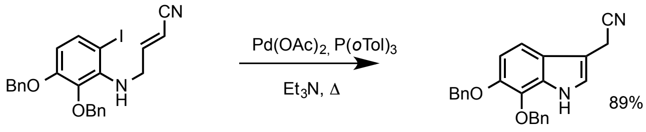
a)



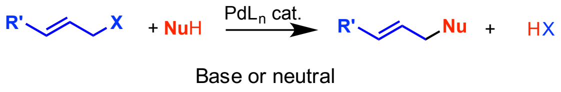
b)



c)



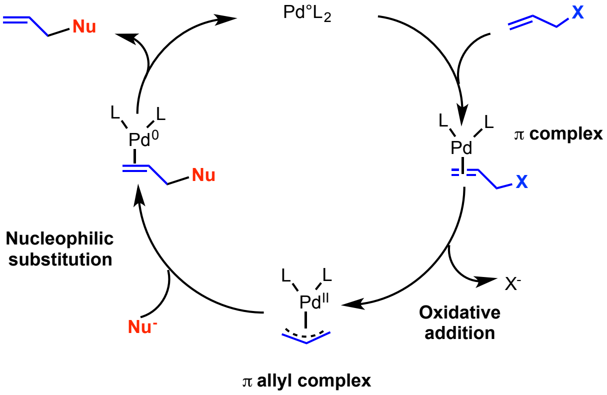
Reaction involving a π-allyl-palladium complexes



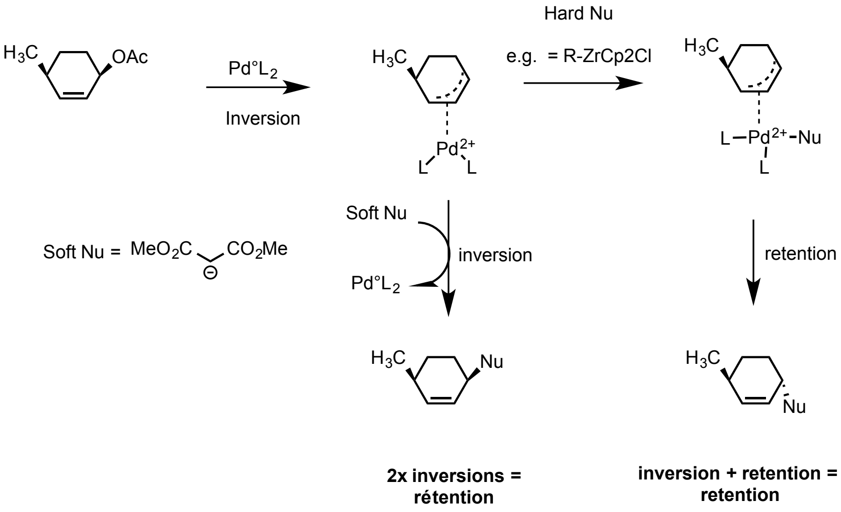
X = Cl, OAc, OCO_2R, $OP(O)(OR)_2$, SO_2R, epoxide, etc.

Nu= N_3^-, AcO^-, RS^-, $R0^-$, R_2NH, malonic ester, etc.

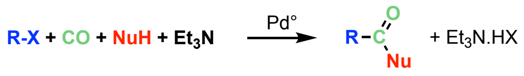
Tsuji-Trost coupling: catalytic cycle



- Oxidative addition is done with configuration inversion
- Nucleophilic addition is generally done on the least substituted carbon
- Soft nucleophiles attack on the opposite side to the metal
- Hard nucleophiles bind to the metal before being transferred

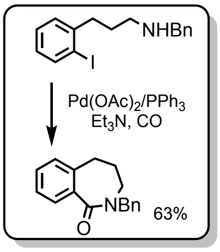


Palladium catalyzed CO insertion

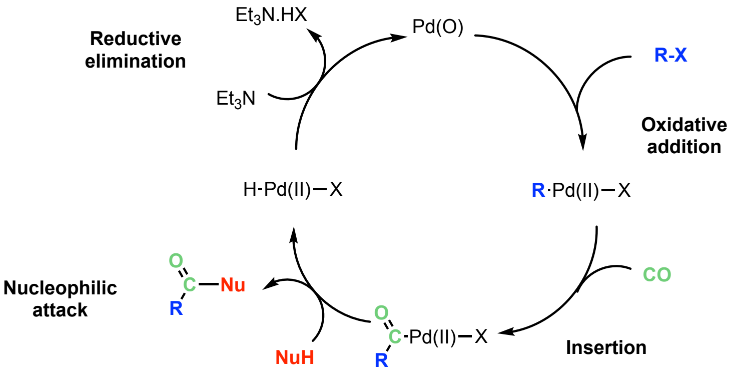


$$R\text{-}X + CO + NuH + Et_3N \xrightarrow{Pd°} R\text{-}C(=O)Nu + Et_3N.HX$$

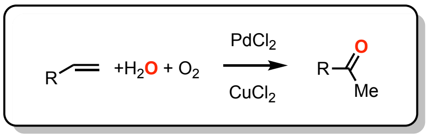
NuH: ROH, RNH_2, H_2...



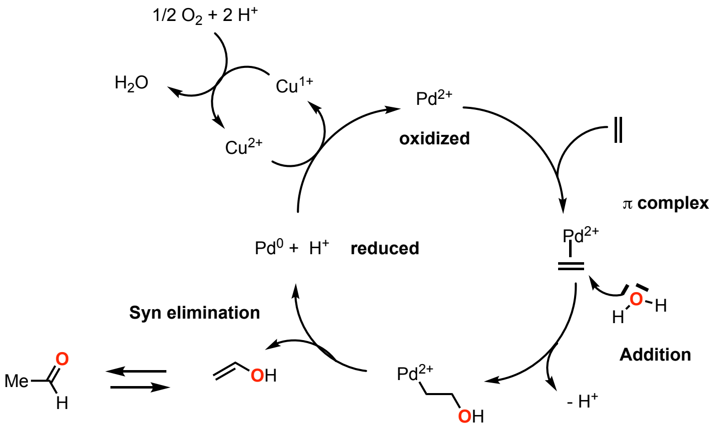
Catalytic cycle



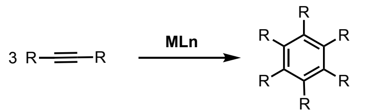
Wacker process



Catalytic cycle



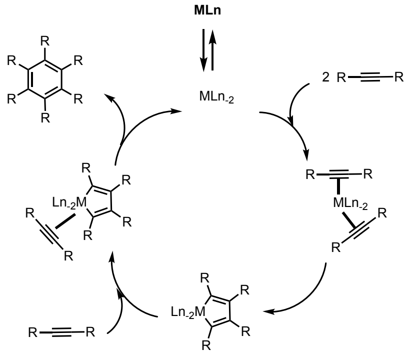
Oxidative coupling of alkynes : formation of cyclic and heterocyclic compounds



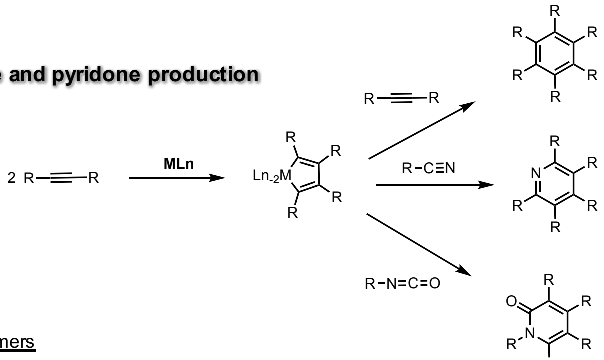
M = Co, Rh, Ir, Pd, Cu, Fe, Ru, Os, Mo, W, V, Nb, Ti, Zr, etc.

✔ Compatibility : ester, ketone, aldehyde, alcohol
✔ Activation: >60° C or irradiation

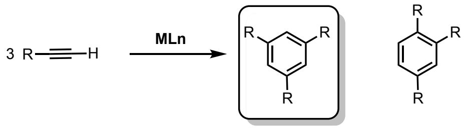
Catalytic cycle



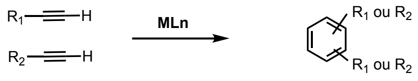
Application to pyridine and pyridone production



Problem: mixture of isomers

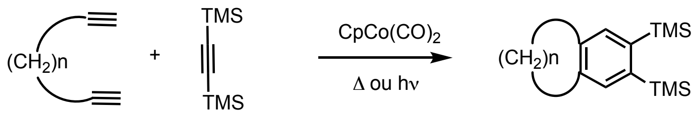


Major product: favored with large (Cat. Co)



Mixture

Volhardt strategy



Intramolecular

TMS : large protecting group

Examples