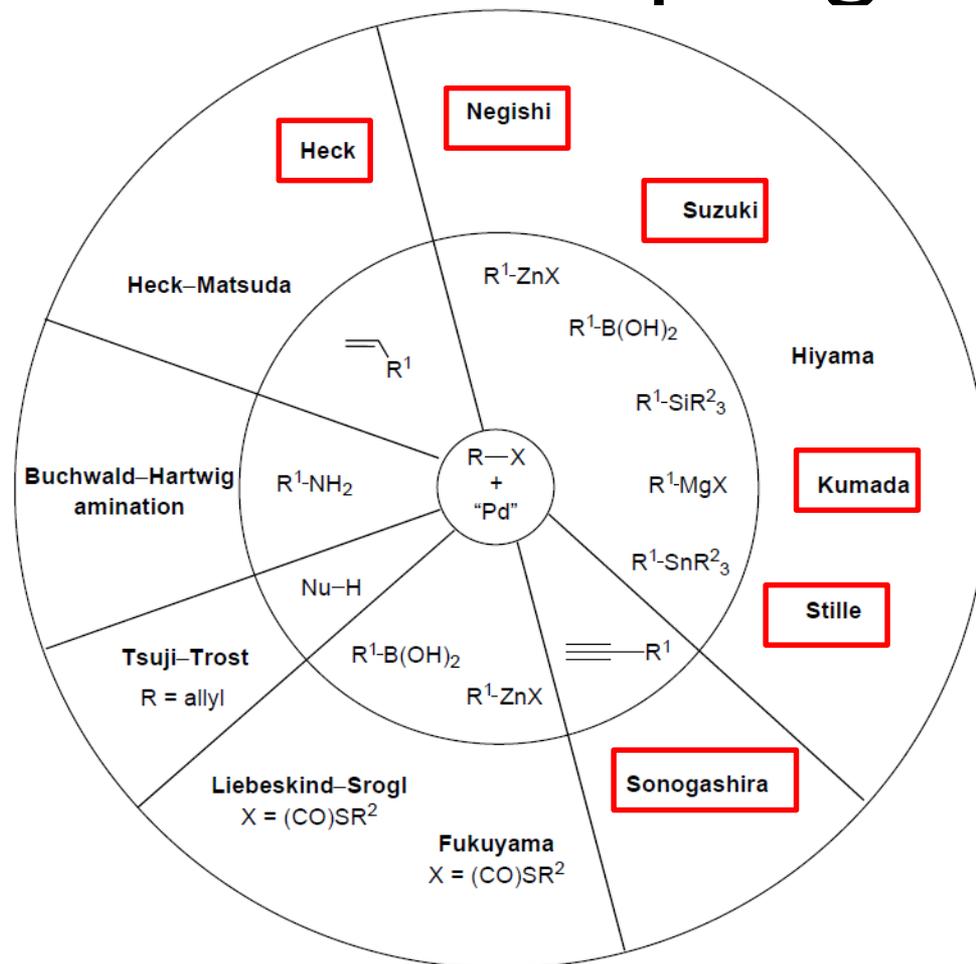
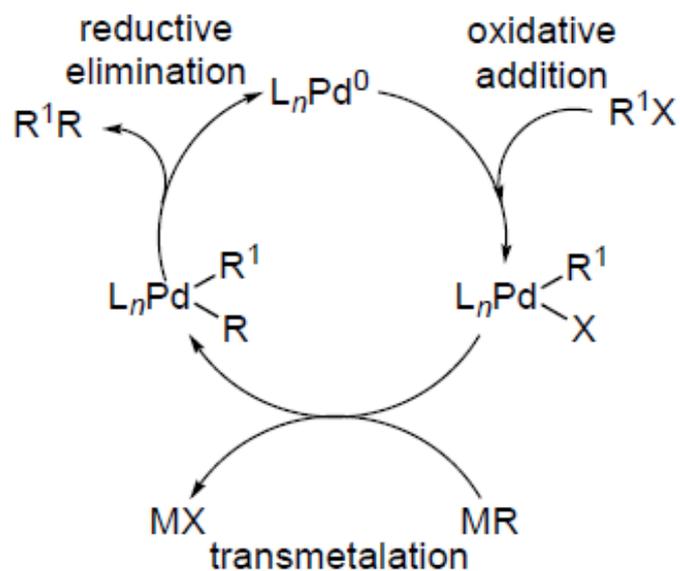


Cross-couplings



Scheme 1.1 Overview of well-established Pd-catalyzed cross-coupling reactions (R = organic group; X = halogen atom or pseudohalide such as triflate (F_3CSO_2O , Tf); "Pd" = Pd catalyst; Nu = nucleophile such as enolate or amine).

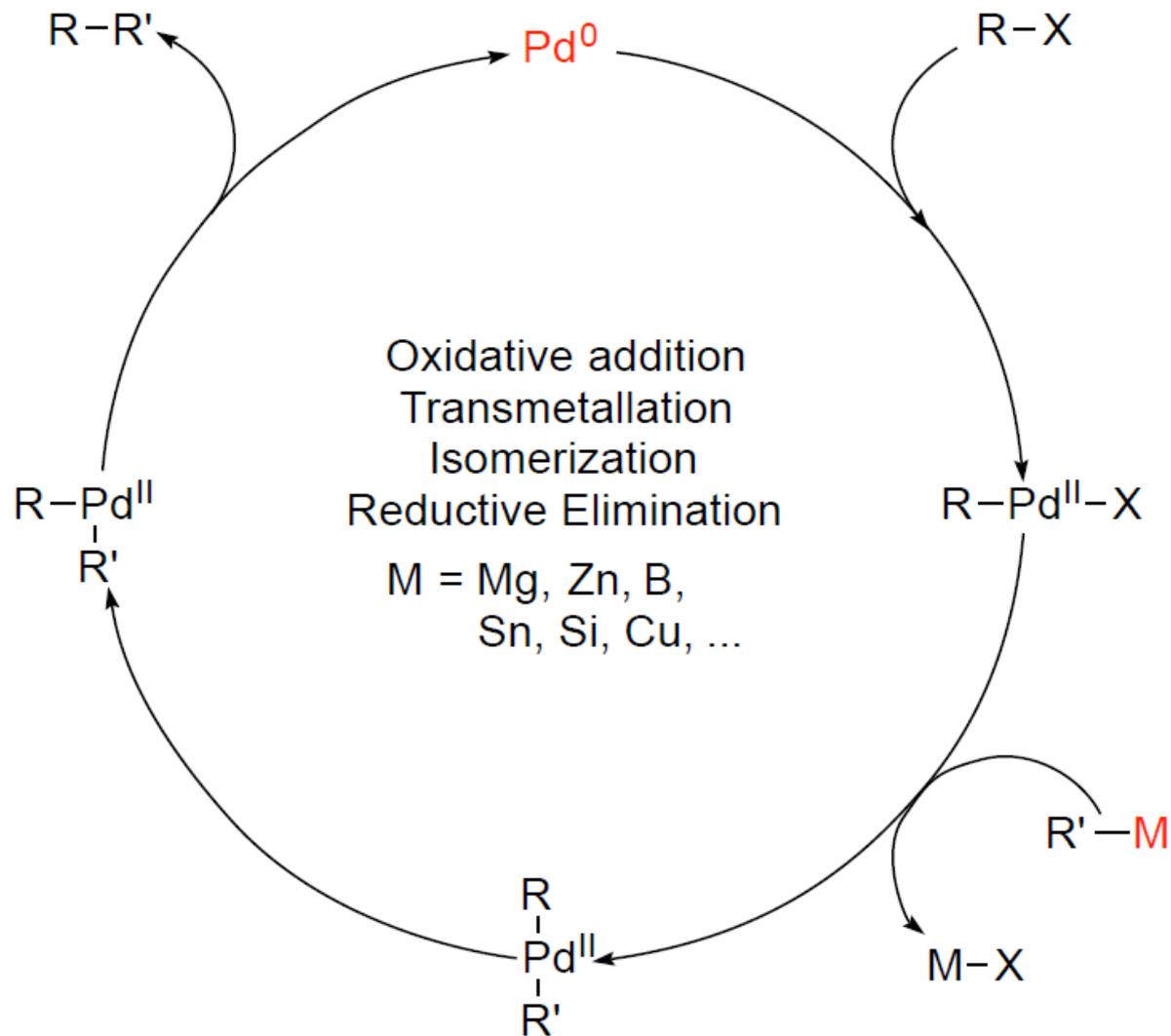
Mechanism



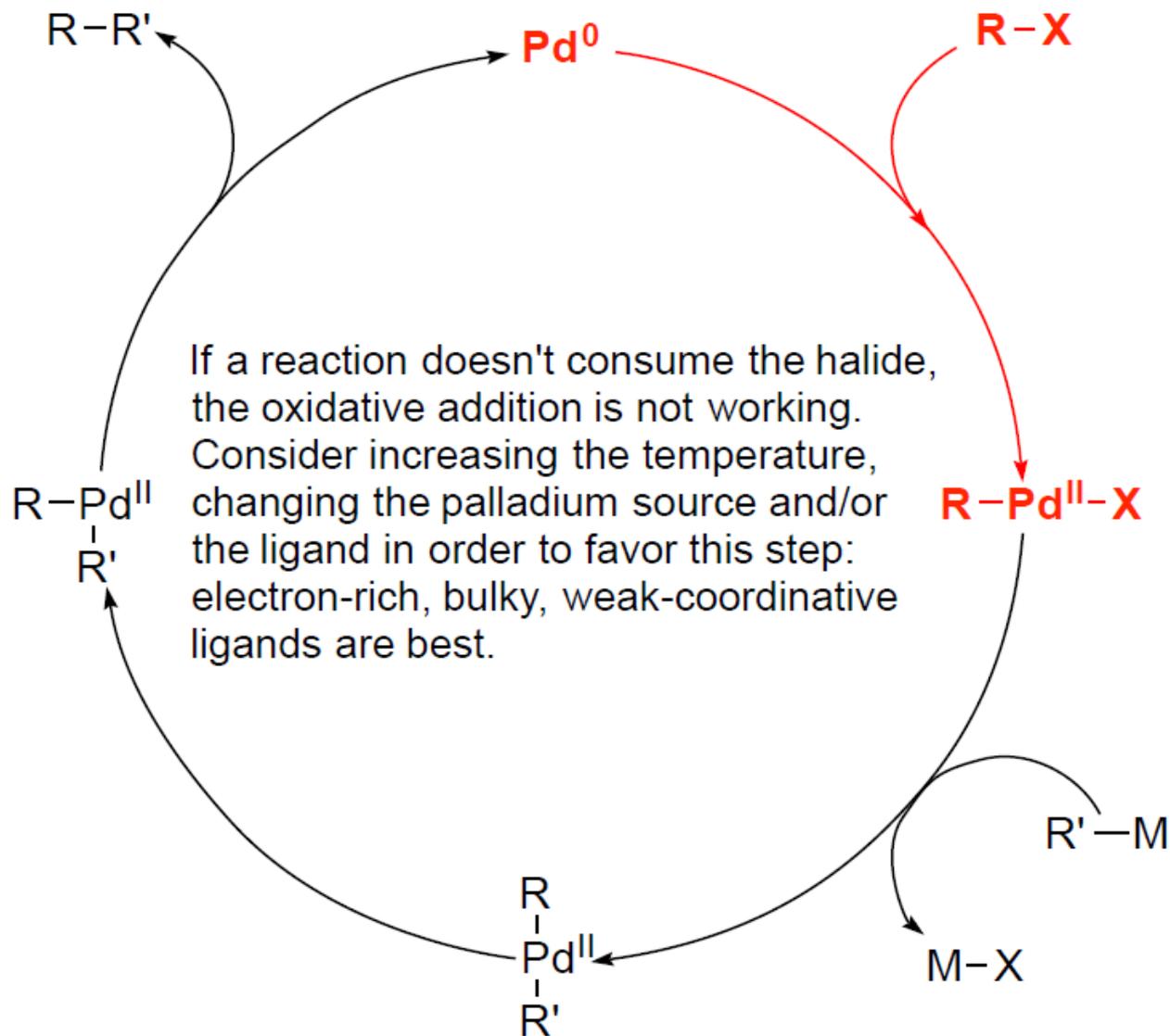
R^1-X	sp^2	sp^2	sp^2	sp	sp	sp
R^2-M	sp^3	sp^2	sp	sp^3	sp^2	sp
	Negishi (Suzuki) Stille (solo per $R^2=allyle$)	Suzuki Stille (Heck)	Sonogashira Stille	Negishi Stille (solo per $R^2=allyle$)	Stille	Sonogashira

Scheme 1.8 Standard mechanism for palladium-catalyzed C—C cross-coupling reactions.

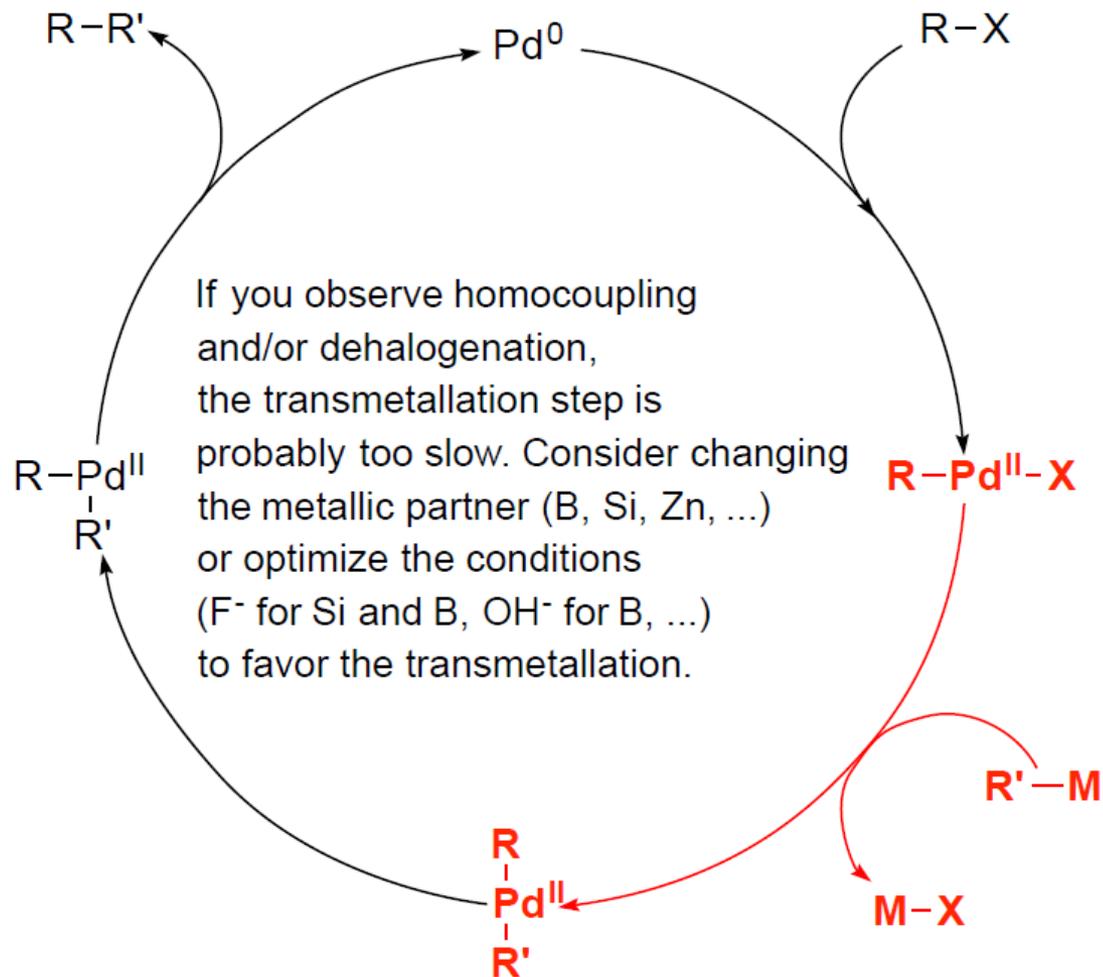
Mechanism



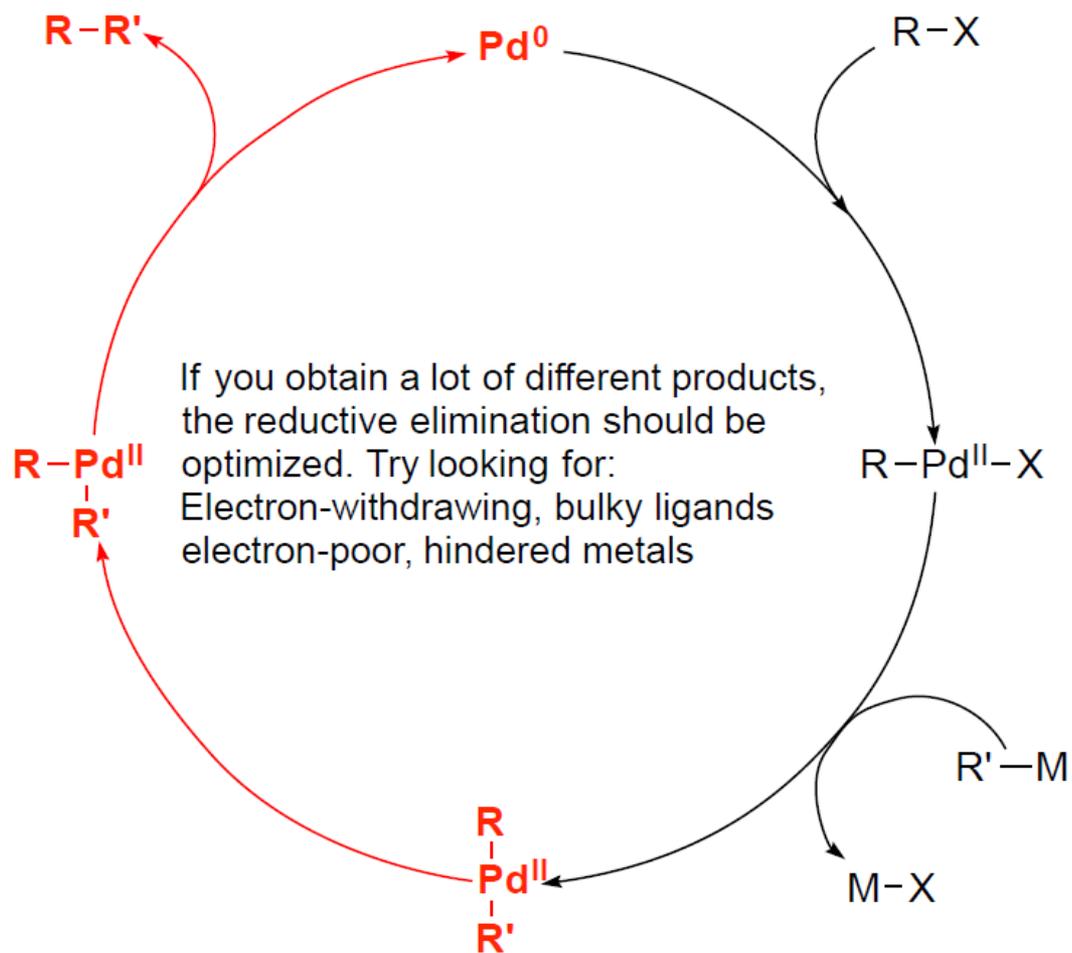
Mechanism



Mechanism



Mechanism



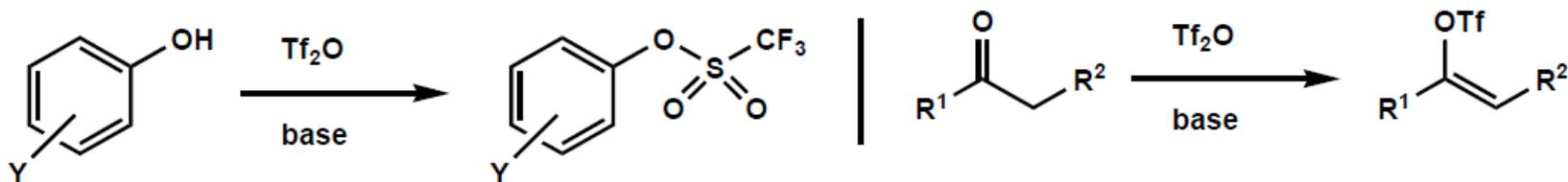
Scelta R-X e M-R'

1.2.2.1 Choice of the Carbon Electrophile

The reactivity decreases in the order $I^- > OTf^- > Br^- \gg Cl^-$. In laboratory-scale synthetic approaches, the choice will usually be aryl iodides due to the high yields under mild conditions. On the contrary, in industrial production where cost efficiency plays an important role, substrates containing chlorides as leaving group are the most favored. Iodides and bromides are less popular regarding reaction economy, but the broad availability of bromides can also be relevant.

L'ordine di reattività di R-X non dipende tanto dalla struttura di R (per esempio dai sostituenti sull'anello se R = Ar), quanto dalla natura del gruppo uscente. L'ordine è opposto a quello delle S_NAr e simile a quello delle S_N2

La possibilità di usare triflati permette l'impiego, come materiali di partenza, di fenoli o chetoni:



IMPORTANTE ASPETTO STEREOCHIMICO

Con alogenuri / triflati alchenilici la reazione di addizione ossidativa procede con completa ritenzione di configurazione. Ciò è molto utile per la sintesi di alcheni con geometria definita

Scelta R-X e M-R'

1.2.2.2 Choice of the Carbon Nucleophile – What Makes the Difference?

The higher the electronegativity of the metal, the less reactive is the carbon nucleophile. This is depicted in the higher reactivity of organoalkali compounds and Grignard compounds in comparison to organozinc or organoboron compounds.

litio	
3	453.65K
Li	513
	0.534
6.941	0.98
Lit	
+1	
[He]2s ¹	

magnesio	
12	923K
Mg	737.7
	1.738
24.31	1.31
Lit	
+2	
[Ne]3s ²	

zinco	
30	692.68K
Zn	906
	7.14
65.37	1.65
Cal	
+2	
[Ar]3d ¹⁰ 4s ²	

rame	
29	1357.77K
Cu	745
	8.96
63.55	1.9
Cal	
+1+2	
[Ar]3d ⁹ 4s ²	

stannio	
50	505.08K
Sn	709
	7.365
118.7	1.96
Cal	
+2+4	
[Kr]4d ¹⁰ 5s ² 5p ²	

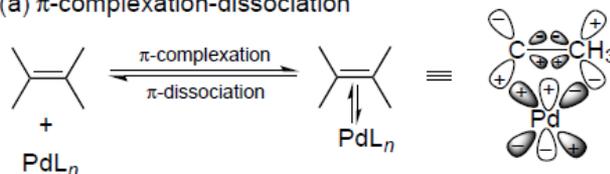
boro	
5	2349K
B	801
	2.08
10.81	2.04
Lit	
+3	
[He]2s ² 2p ¹	

Catalizzatore: Pd (0)

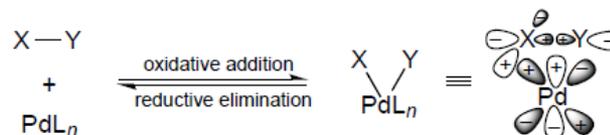
Pd shares some crucially important features with other transition metals, such as the **ability to readily interact with nonpolar p-bonds:** alkenes, alkynes, and arenes.

This interaction leads to **facile, selective, and often reversible steps:** oxidative addition, transmetalation, and reductive elimination
Other metals are cost-effective but not so efficient: Ni, Cu, Fe.

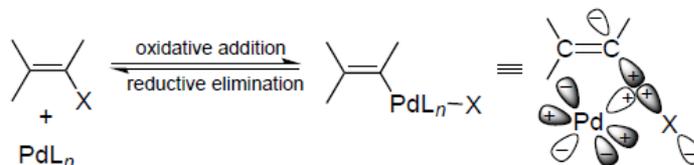
(a) π -complexation-dissociation



(b) oxidative addition–reductive elimination



(c) oxidative addition–reductive elimination of alkenyl halides under retention

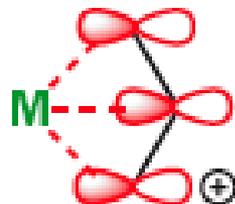


Scheme 1.10 Dewar–Chatt–Duncanson synergistic synergetic bonding schemes. (Modified from Ref. [20a].)

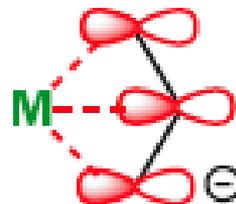
The “Hapto” Number



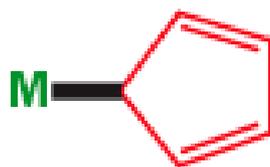
η^3
 π allyl



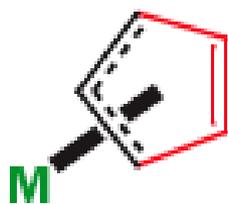
allyl cation
complex



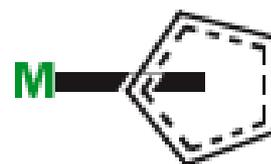
allyl anion
complex



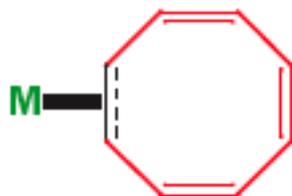
η^1
 σ complex



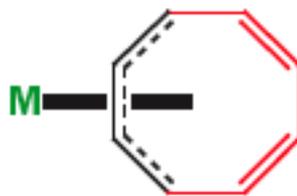
η^3
 π complex



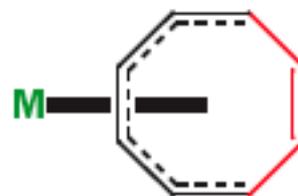
η^5
 π complex



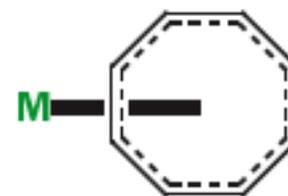
η^2



η^4

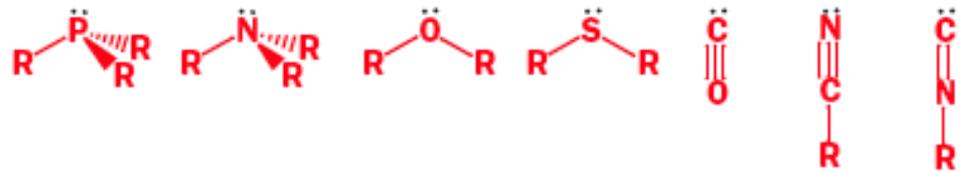


η^6

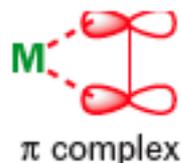


η^8

Ligand characteristics

		Formal charge	Electrons donated
anionic ligands			
Cl^- Br^- I^- CN^- OR^- H^- alkyl^-		-1	2
neutral σ-donor ligands			
		0	2
	Hapto number	Formal charge	Electrons donated
unsaturated σ- or π-donor ligands			
aryl, σ -allyl	η^1	-1	2
olefins	η^2	0	2
π -allyl cation	η^3	+1	2
π -allyl anion	η^3	-1	4
diene—conjugated	η^4	0	4
dienyls, cyclopentadienyls (anions)	η^5	-1	6
arenes, trienes	η^6	0	6
trienyls, cycloheptatrienyls (anions)	η^7	-1	8
cyclooctatetraene	η^8	0	8
carbene, nitrene, oxo	η^1	0	2

Catalizzatore: Pd



Representing bonds in transition metal complexes

It is difficult to know exactly how to draw the bonding in metal complexes and there are often several different acceptable representations. There is no problem when the metal forms a σ bond to atoms such as Cl or C as the simple line we normally use for covalent bonds means exactly what it says. The problems arise with ligands that

form σ bonds by donating both their electrons and with π complexes. Everyone writes phosphine–boron compounds with two charges but we normally draw the same sort of bond between a phosphine and, say, Pd as a simple line with no charges.



You will sometimes see π complexes drawn with simpler dotted lines going to the middle of the π bond, sometimes with dotted π bonds, and sometimes with bonds (simple or dotted) going to the ends of the old π bond. These are all acceptable as the bonding is complex as you will see. We might almost say that the ambiguity is helpful: we often don't know either the exact nature of the bonding or the number of other ligands in the complex. In the

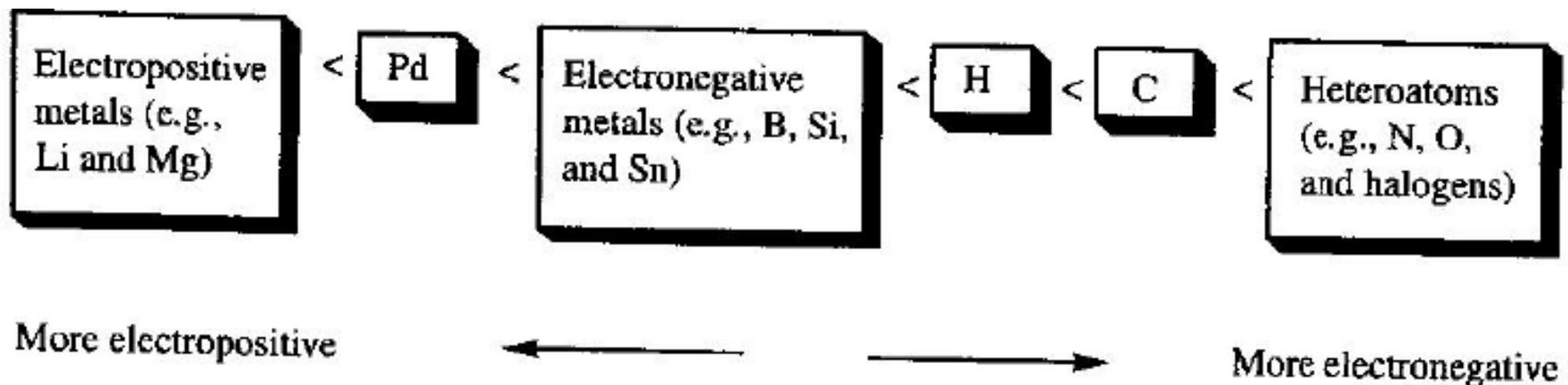
diagrams in this section we have shown the main bond from metal to ligand as a heavy line in the simplest representation but we also offer alternatives with simple and dotted bonds. Don't worry about this—things should become clearer as the chapter develops. When you have to draw the structure of a complex but you don't know the exact bonding, just draw a line from metal to ligand.

different acceptable ways to draw π complexes



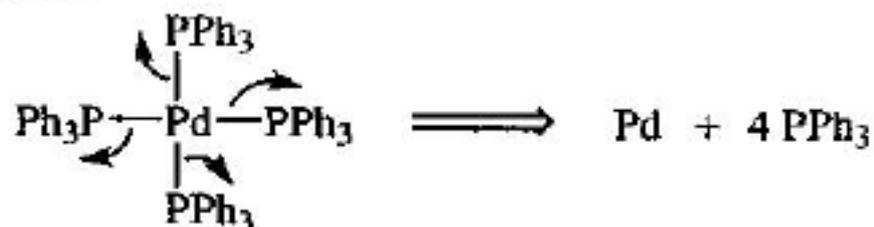
Rules for the Coordination Compounds

1. Number of valence electrons (from periodic table)
2. Correct for charge, if any (only if it belongs to that atom!)
3. Count 1 e for every covalent bond to another atom



Scheme 9

Example 1

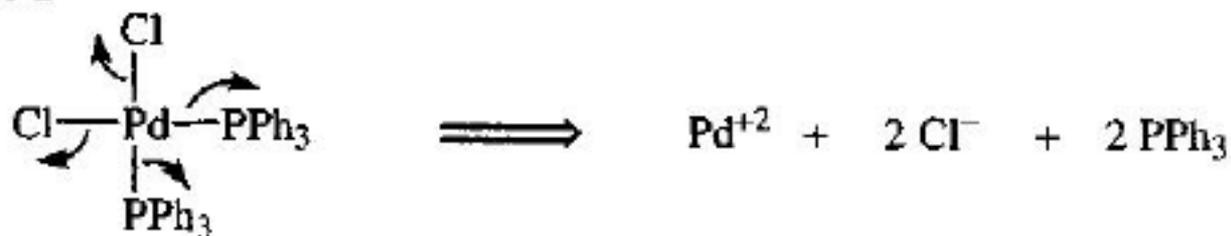


Note: Cleavage of neutral ligands does not generate charges. Recall that the Pd–PPh₃ may be represented as ⁻Ph–⁺PPh₃ and that its heterolysis as shown above will nullify the charges. For the sake of simplicity, all these details are omitted.

Atom or Group	FOS	Number of Electrons Contributed
4 × PPh ₃	0 (4 × 0)	8 (4 × 2)
Pd	0 (d ¹⁰)	→ 10
Total Number of Electrons		18

FOS = formal oxidation state

Example 2



Atom or Group	FOS	Number of Electrons Contributed
$2 \times \text{Cl}^{-}$	$-2 (-1 \times 2)$	$4 (2 \times 2)$
$2 \times \text{PPh}_3$	$0 (0 \times 2)$	$4 (2 \times 2)$
Pd	$+2 (d^8)$	8

Total Number of Electrons

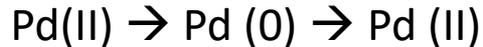
16

$$\text{Number of Lone Pairs of Electrons} = \frac{1}{2} d^n$$

$$\text{Number of Empty Orbitals} = \frac{18 - \text{Valence Shell Electrons}}{2}$$

Why is Pd so special?

1. **Pd fa facilmente scambi di 2 e-** utili nel ciclo catalitico



Ni e Cu spesso fanno scambi di 1 e- con minor selettività e maggior numero di prodotti possibili

2. **Tollera diversi gruppi funzionali**, che non devono essere protetti

3. **È sufficientemente reattivo** e con alti TON e TOF per cui la catalisi avviene anche in condizioni abbastanza blande

Reattività di altri M è un po' diversa, per es. Ni reagisce di più e tollera meno gruppi funzionali, ha meno selettività, meno TON; Pt è veloce in O.A. ma lento in R.E. (catalisi lenta)

Why is Pd so special?

Tra tutti i metalli di transizione, il palladio è senz'altro quello che può vantare la maggiore utilità nella sintesi organica.

Il palladio ha 10 elettroni nel guscio di valenza ed esiste in due stati di ossidazione: (0) e (+2).
Lo stato di ossidazione incide fortemente sulla reattività del metallo:

complessi di Pd(0)

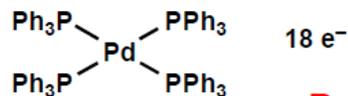
- Buoni nucleofili
- Buone basi
- Facilmente ossidabili

complessi di Pd(II)

- Buoni elettrofili
- Tendono a reagire con areni ed alcheni elettronricchi
- Tendono a reagire con basi di Lewis come ammine, fosfine, C=O
- Vengono facilmente ridotti da svariati composti organici

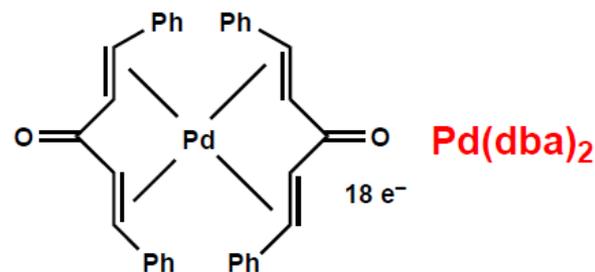
Il palladio può formare complessi stabili ed isolabili sia con 18 che con 16 elettroni. Le specie catalitiche vere e proprie hanno però spesso addirittura 14 elettroni

Catalizzatori basati su Pd(0)



Pd(PPh₃)₄

Il più usato.
Di colore giallo.
Costoso (42 €/mmole Pd)
Non tanto stabile all'aria
Può perdere attività senza darlo a vedere



Viene preparato da dba + PdCl₂ (8,6 €/mmole Pd) + MeOH
Di colore rosso ciliegia
Più stabile del precedente all'aria
Venduto come Pd₂(dba)₃•CHCl₃ (36 €/mmole Pd)

Dibenzylideneacetone = dba

Why is Pd so special?

Molto spesso però, anche per reazioni catalizzate da Pd(0), si impiegano composti di Pd(II), che sono più stabili all'aria e possono essere ottenuti con una maggiore varietà di ligandi. Infatti i composti di Pd(II) vengono ridotti *in situ* da molti composti organici. In particolare Pd(OAc)₂ è ridotto da metanolo, altri alcoli, CO, ammine terziarie, olefine, fosfine etc.



(8,6 € / mmole Pd)

Non può essere usato come tale in quanto è un oligomero insolubile



(9,0 € / mmole Pd)

solubile
molto usato



16 e⁻

(12,2 € / mmole Pd)



16 e⁻

(15,7 € / mmole Pd)



16 e⁻

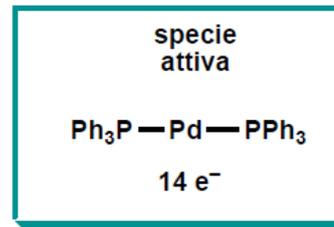
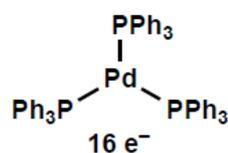
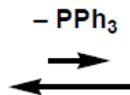
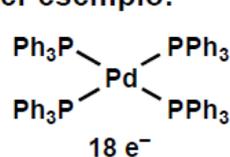
(16,5 € / mmole Pd)

ADDIZIONE OSSIDATIVA DI Pd(0) AD ALOGENURI/TRIFLATI

E' il primo stadio di una serie di trasformazioni di grande utilità sintetica. In teoria i substrati potrebbero essere tutti gli alogenuri o triflati (alchilici, arilici, alchenilici, alchinilici, etc.). In realtà questa trasformazione è usata solo per alogenuri/triflati arilici, alchenilici, alchinilici, benzilici, allilici e non per semplici alogenuri alchilici. Inoltre, nel caso dei derivati allilici, il decorso è un po' differente (lo vedremo meglio più avanti). Sicuramente i substrati più importanti sono i derivati arilici e alchenilici.

In queste trasformazioni la specie che entra nel ciclo catalitico è sempre un complesso di Pd(0) con 14 elettroni

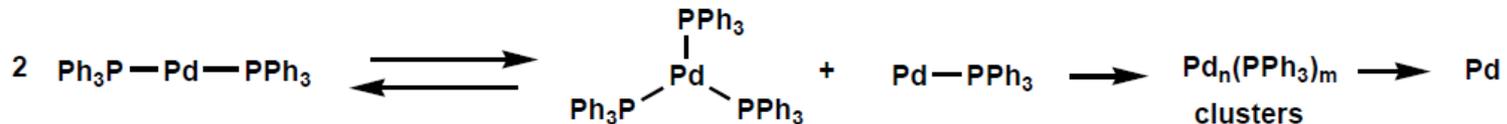
Per esempio:



Che forma di Pd?

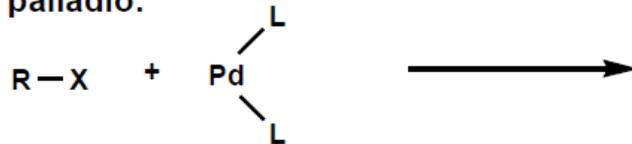
Quando si parte da Pd(OAc)₂ un problema è: quanti equivalenti di fosfina (o altro ligando) usare? Bisogna infatti tenere presente che

- a) I due ligandi sono essenziali per l'efficienza della reazione
- b) Non tutti i ligandi sono efficienti. Per esempio, partendo da Pd(dba)₂ il dba deve essere sostituito da ligandi "migliori"
- c) Usando solo 2 equivalenti di ligando si rischia la precipitazione di palladio metallico



Pertanto, a seconda della reazione, bisogna trovare la giusta situazione di compromesso tra massima concentrazione della specie attiva e minimizzazione della sottrazione di Pd come palladio metallico. Ad es. con Pd(OAc)₂ si usano spesso 3 equivalenti di fosfina.

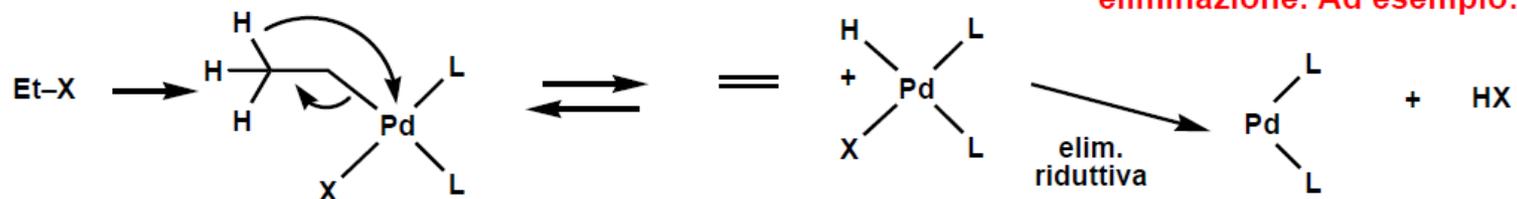
L'addizione ossidativa porta ad una specie a 16 elettroni di Pd(II) con un legame σ carbonio-palladio:



L = R₃P, RCN
 X = I, Br, Cl, OSO₂CF₃ (OTf)
 R = arile, alchenile, alchinile, benzile

in pratica è come se il palladio effettuasse una sostituzione nucleofila.

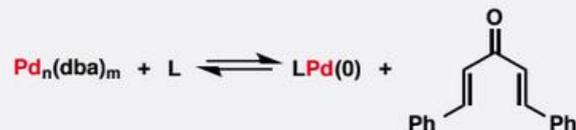
Con alogenuri alchilici la reazione è più lenta che con gli altri. Inoltre, se ci sono idrogeni in β, avviene immediatamente una β-eliminazione. Ad esempio:



Catalyst Generation



$\text{Pd}_n(\text{dba})_m$



Pros: Easily handled; convenient; commercially available.

Cons: Loses activity over time, forming Pd nanoparticles and free dba; dba can inhibit some coupling reactions; premixing is sometimes necessary.

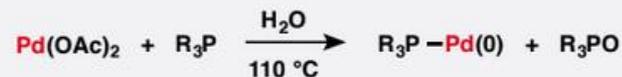
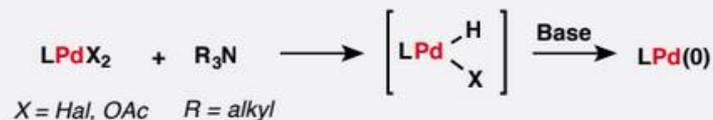
π -Allyl Pd Chloride Dimers



Pros: High reactivity; convenient; commercially available.

Cons: Temperature sensitive; less consistent commercial purity; can occasionally form inactive Pd(I) complexes.

Pd(II) Salts



Pros: Easily handled; convenient; commercially available; least expensive Pd sources.

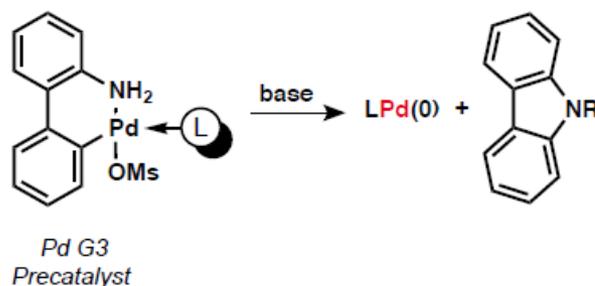
Cons: Can be inefficient; does not ensure clean, quantitative catalyst generation; excess ratio of L to Pd necessary; premixing is sometimes required.

Catalyst Generation

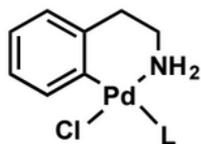
Recent advances in precatalyst development have led to the third generation Buchwald palladium precatalysts (Pd G3) that quickly and quantitatively generates active LPd(0) catalyst with phosphine ligands. PEPPSI™ precatalysts are highly effective Pd sources for *N*-heterocyclic carbene (NHC) ligands.

Pd G3 Precatalysts

Third generation palladium precatalysts are air- and moisture-stable*, phosphine-ligated palladium sources that release LPd(0) and a carbazole under basic conditions, activating at temperatures as low as -40 °C with weak base.

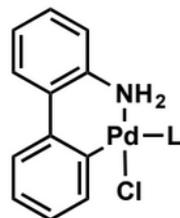


Palladacycle Precatalysts



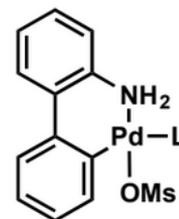
**First
Generation**

- Compatible with bulky ligands
- 3 step preparation
- Unstable intermediates
- Short life in solution



**Second
Generation**

- Simple one pot preparation
- Pd(OAc)₂ as Pd source
- Not compatible with bulkier ligands
- Poor solubility and short life in solution



**Third
Generation**

- Simple preparation with stable isolable intermediate
- Compatible with bulky ligands
- Can be prepared *in-situ*
- Long solution life (≥ 1 month)

Mode of Activation

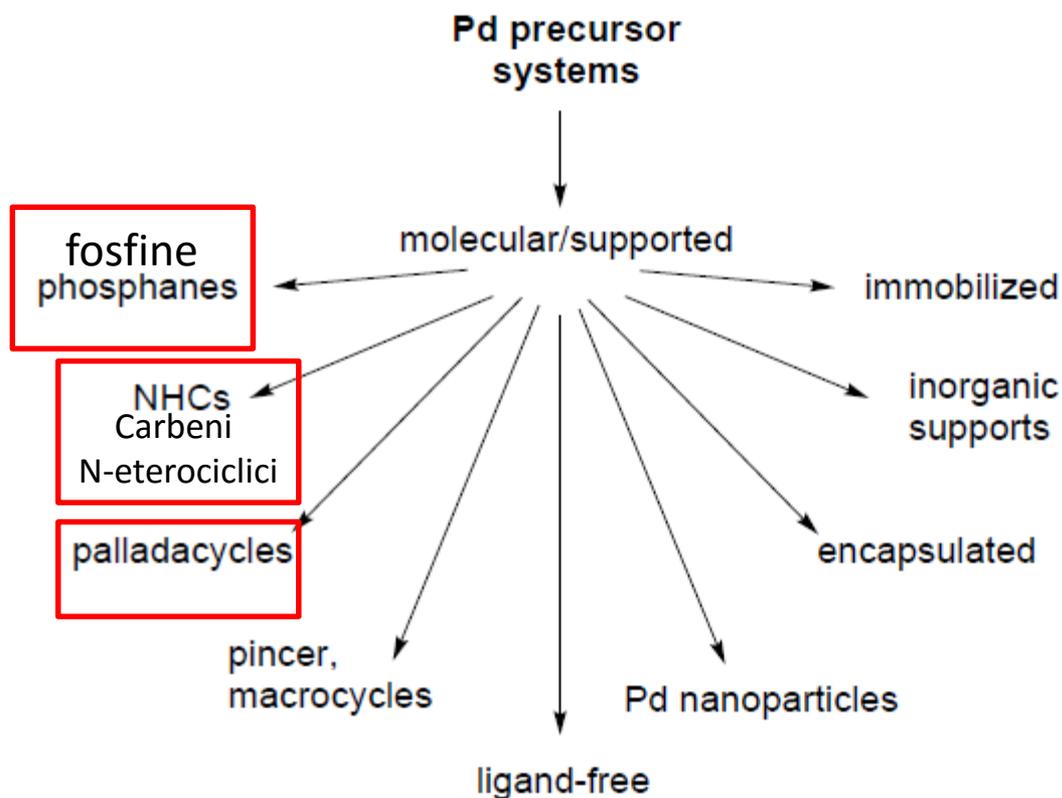


Table 6. A brief summary of precatalyst generations developed in our lab and their general mode of activation.

Conclusion

In conclusion, the use of preformed palladium precatalysts containing phosphine ligands are an efficient means to generate the desired $L_nPd(0)$ species compared to traditional means of catalyst generation with separate Pd and ligand sources. We have developed three generations of palladacyclic precatalysts to address the issues of catalyst activation (Table 6). Our third generation methanesulfonate precatalysts are readily activated, incorporate the broadest range of ligands to date and have a facile preparation that is amenable to large-scale synthesis. Additionally, by generating $LPd(0)$ more efficiently than traditional palladium sources, our palladacyclic precatalysts have made possible methodologies that would not otherwise be feasible. We anticipate that the implementation of precatalysts will greatly improve the scope of palladium catalyzed cross-coupling reactions.

Che forma di Pd?



Scheme 1.11 Most common classes of palladium precursor systems developed and applied in C—C cross-coupling reactions during the past decade.

Che forma di Pd?

Cat. omogenei sono più attivi ma meno riciclabili

LEGANTI OTTIMALI:

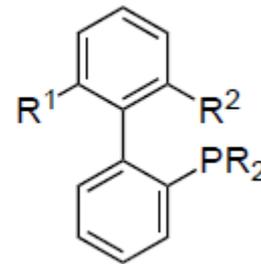
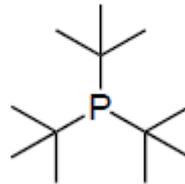
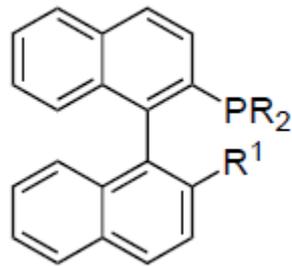
- stabilizzano Pd(0) in soluzione e riducono formazione Pd BLACK (inattivo)
- determinano solubilità dei complessi metallici
- Determinano stabilità TERMICA: spesso i precursori degradano per riscaldamento liberando le specie attive Pd (0)
- Componenti elettronici e sterici per reattività: leganti che donano e-aumentano la densità elettronica e se hanno ingombro sterico diminuiscono la forza del legame tra complesso e substrato, facilitando quindi la R.E.

FOSFINE

Sono i leganti più sensibili all'aria. Si possono deattivare ad alte temperature per decomposizione o ossidazione a P (V).

Reattività e costi sono molto variabili.

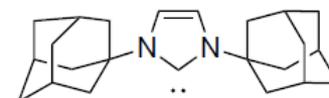
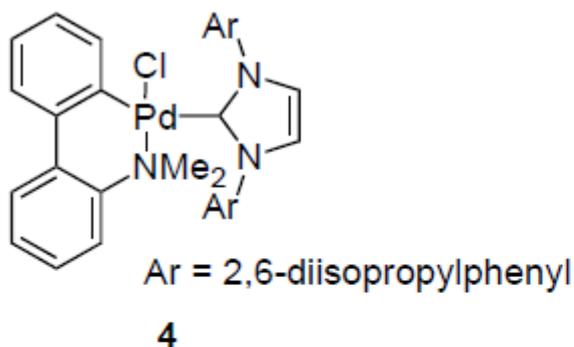
Vedi sintesi BINAP. Possono essere tossici, pericolosi (piroforici) ed avere odori molto sgradevoli.



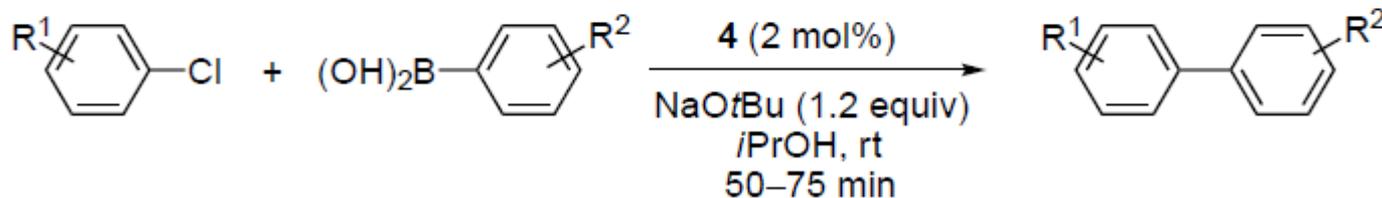
Carbeni N-eterociclici (NHC)

Sono molto meno tossici e più stabili al riscaldamento.

Se ottimizzati, permettono ottime rese in poco tempo anche per Ar-Cl poco reattivi:



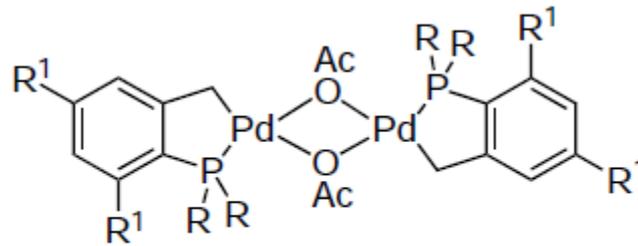
NHCs
Arduengo
J. Am. Chem. Soc.
1991, 113, 361



Scheme 1.12 Suzuki-type reaction with an NHC Pd complex as highly active catalyst [55].

Palladacicli

Molto stabili al riscaldamento, tollerano alte temperature per molte ore con pochissima deattivazione a Pd BLACK.



R = mesityl
R¹ = Me