Cross-coupling reactions

Table of contents

I. Different type of cross-coupling reactions and general mechanism

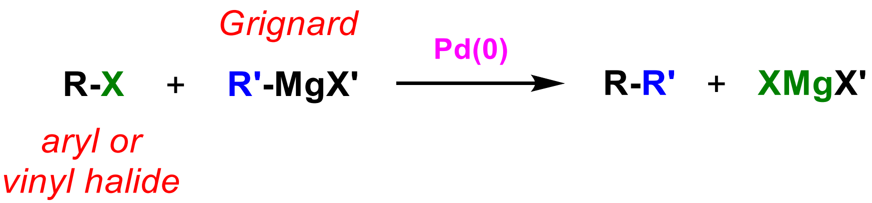
Cross-Coupling of Organometallics and Organic Halides

$$\mathrm{R\text{-}X} \quad + \quad \mathrm{R'\text{-}M} \xrightarrow{\mathrm{Pd(0)}} \mathrm{R\text{-}R'} \quad + \quad \mathrm{MX}$$

M = MgX, $ZrCp_2Cl$, ZnX, SnR_3, $B(OR)_2$, $AlMe_2$, SiR_3, Cu,…

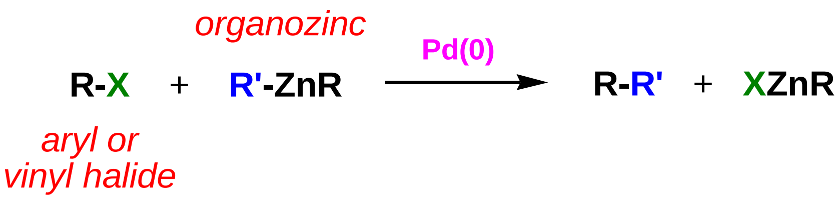
Name reactions according to nucleophiles

Kumada coupling:



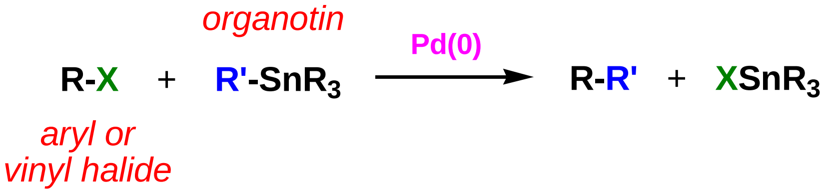
$$\text{R-X} + \text{R'-MgX'} \xrightarrow{\text{Pd(0)}} \text{R-R'} + \text{XMgX'}$$

Negishi coupling:



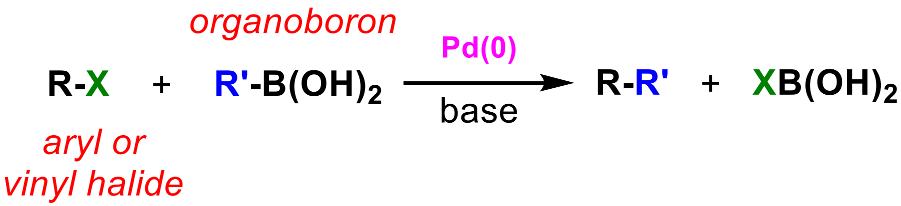
$$\text{R-X} + \text{R'-ZnR} \xrightarrow{\text{Pd(0)}} \text{R-R'} + \text{XZnR}$$

Stille coupling:



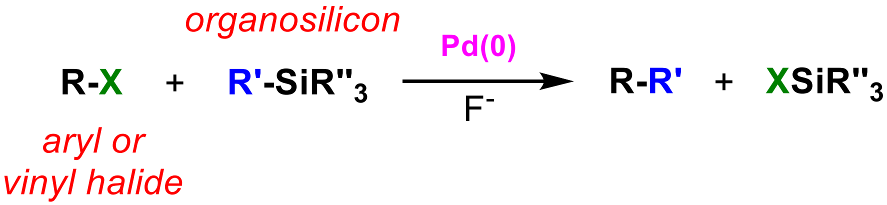
$$\text{R-X} + \text{R'-SnR}_3 \xrightarrow{\text{Pd(0)}} \text{R-R'} + \text{XSnR}_3$$

Suzuki coupling:



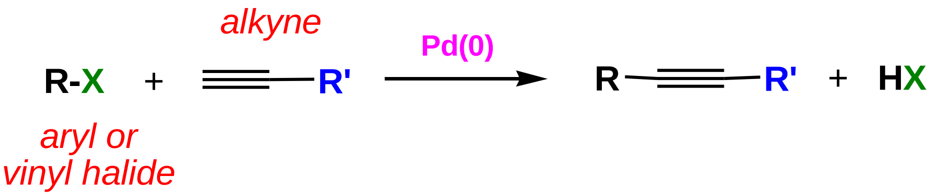
$$\text{R-X} + \text{R'-B(OH)}_2 \xrightarrow[\text{base}]{\text{Pd(0)}} \text{R-R'} + \text{XB(OH)}_2$$

Hiyama coupling:



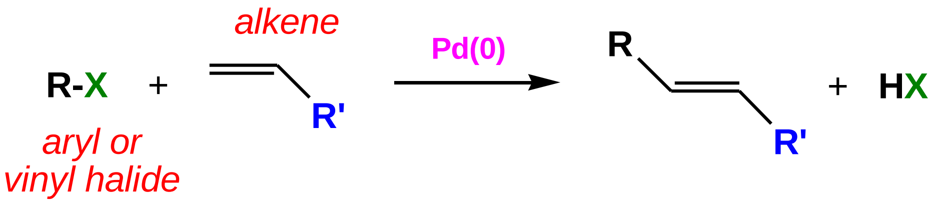
$$\text{R-X} + \text{R'-SiR''}_3 \xrightarrow[\text{F}^-]{\text{Pd(0)}} \text{R-R'} + \text{XSiR''}_3$$

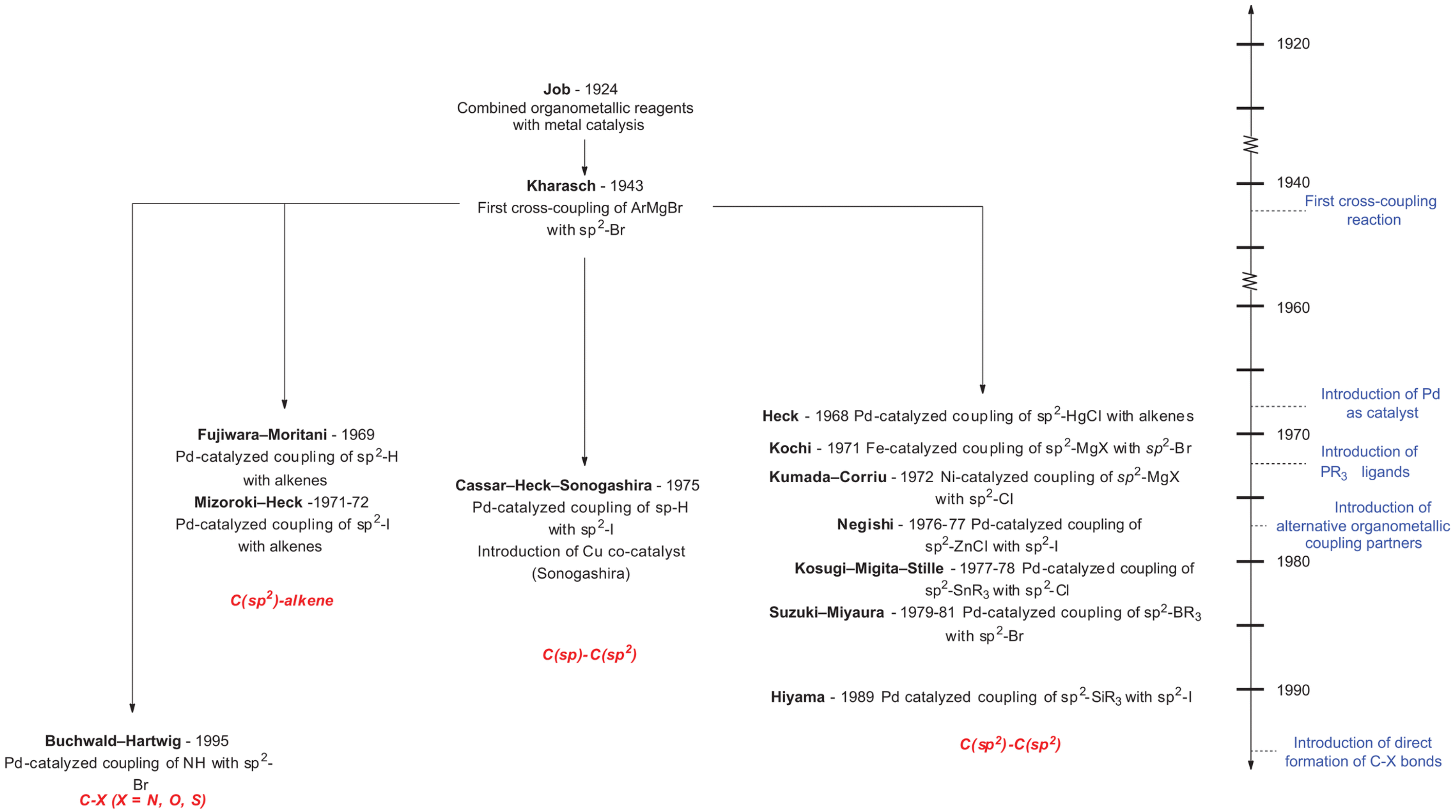
Sonogashira coupling:



$$\text{R-X} + \text{HC}\equiv\text{C-R'} \xrightarrow{\text{Pd(0)}} \text{R-C}\equiv\text{C-R'} + \text{HX}$$

Heck reaction:





Job - 1924
Combined organometallic reagents with metal catalysis

Kharasch - 1943
First cross-coupling of ArMgBr with sp^2-Br

Fujiwara–Moritani - 1969
Pd-catalyzed coupling of sp^2-H with alkenes

Mizoroki–Heck -1971-72
Pd-catalyzed coupling of sp^2-I with alkenes

C(sp^2)-alkene

Cassar–Heck–Sonogashira - 1975
Pd-catalyzed coupling of sp-H with sp^2-I
Introduction of Cu co-catalyst (Sonogashira)

C(sp)-C(sp^2)

Heck - 1968 Pd-catalyzed coupling of sp^2-HgCl with alkenes

Kochi - 1971 Fe-catalyzed coupling of sp^2-MgX with sp^2-Br

Kumada–Corriu - 1972 Ni-catalyzed coupling of sp^2-MgX with sp^2-Cl

Negishi - 1976-77 Pd-catalyzed coupling of sp^2-ZnCl with sp^2-I

Kosugi–Migita–Stille - 1977-78 Pd-catalyzed coupling of sp^2-SnR_3 with sp^2-Cl

Suzuki–Miyaura - 1979-81 Pd-catalyzed coupling of sp^2-BR_3 with sp^2-Br

Hiyama - 1989 Pd catalyzed coupling of sp^2-SiR_3 with sp^2-I

C(sp^2)-C(sp^2)

Buchwald–Hartwig - 1995
Pd-catalyzed coupling of NH with sp^2-Br

C-X (X = N, O, S)

First cross-coupling reaction

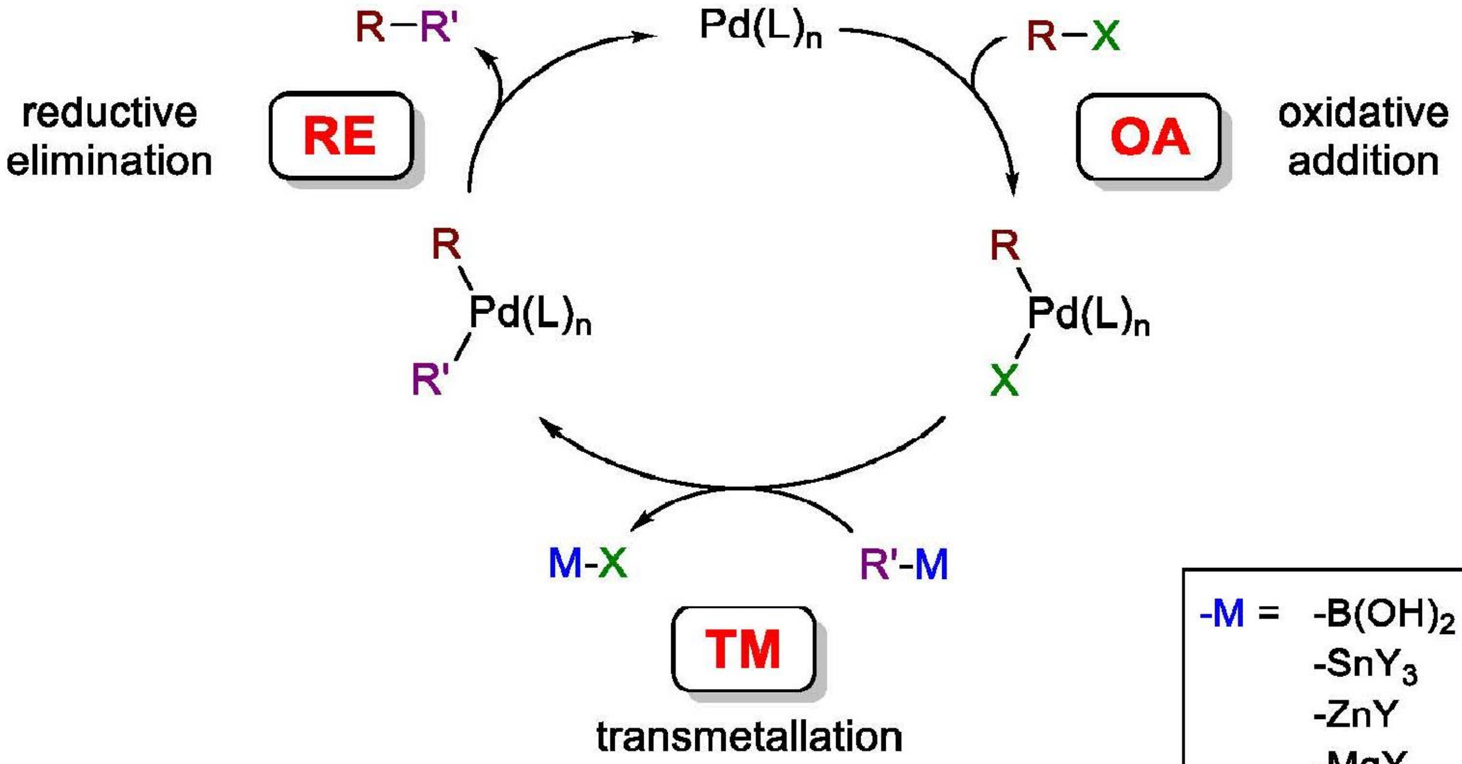
Introduction of Pd as catalyst

Introduction of PR_3 ligands

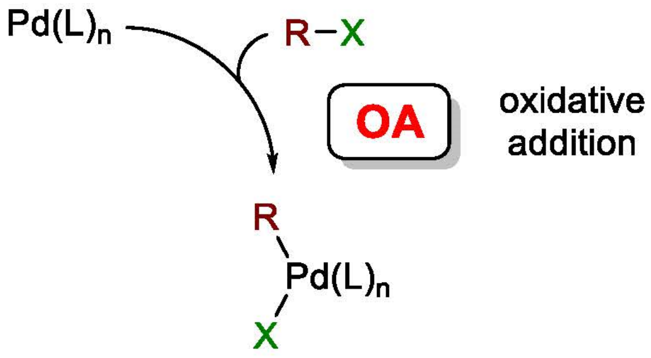
Introduction of alternative organometallic coupling partners

Introduction of direct formation of C-X bonds

General mechanism – except for Heck reaction

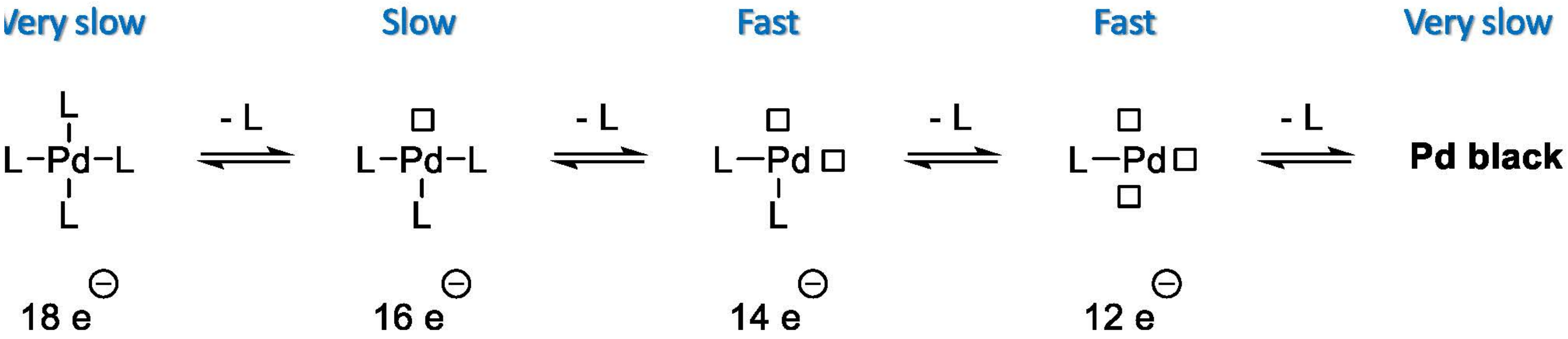


-M =	$-B(OH)_2$	*Suzuki*
	$-SnY_3$	*Stille*
	-ZnY	*Negishi*
	-MgY	*Corriu-Kumada-Tamao*



I >> Br > OTf > Cl

Why?



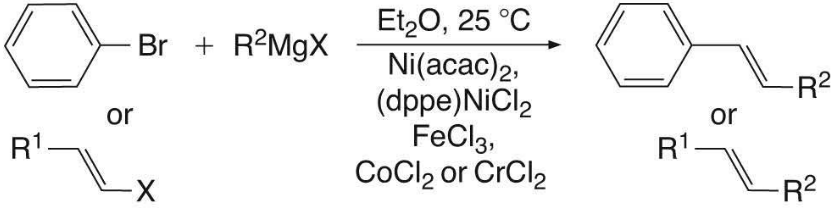
Bond energies:

C-H	411 kJ/mol
C-Cl	399
C-Br	255
C-I	213

II. Kumada coupling and its mechanism

Kumada Coupling

- In 1972 Kumada and Corriu independently reported he first Pd or Ni-catalyzed cross coupling reaction towards C-C bond formation.
- Kumada coupling involves **coupling of a Grignard reagent with alkyl, vinyl or aryl halides** in the presence of a Ni transition metal catalyst providing an economic transformation.
- Less efficient catalysts were reported earlier by Kochi (Fe) and Kharasch (Co & Cr).

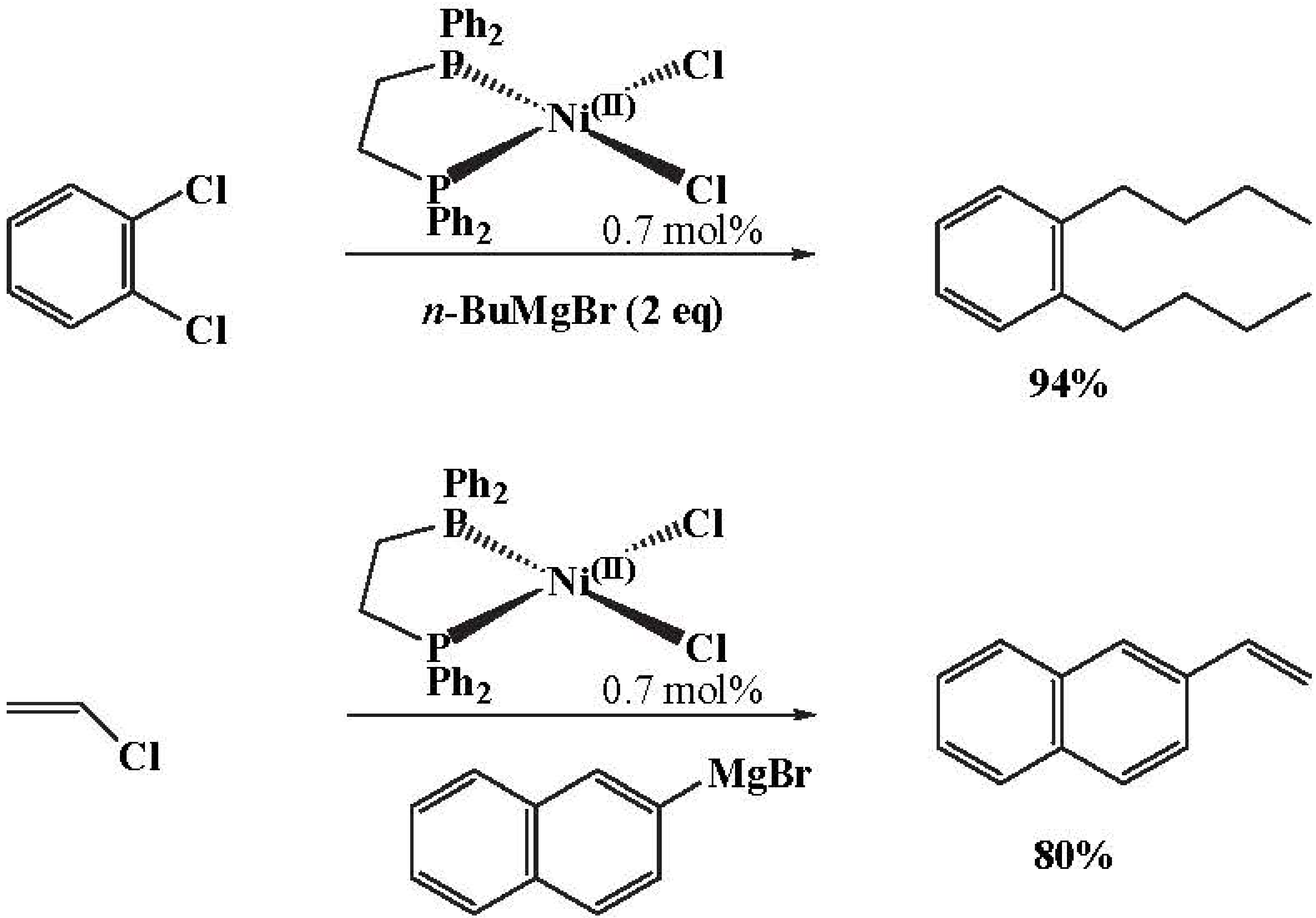


- The reaction is limited to however to halide partners that do not react with organomagnesium compounds. One example is in the industrial-scale production of styrene derivatives, and the Kumada Coupling is the method of choice for the low-cost synthesis of unsymmetrical biaryls.
- The advantage of this reaction is the direct coupling of Grignard reagents, which avoids additional reaction steps such as the conversion of Grignard reagents to zinc compounds for the starting materials in the Negishi Coupling.

Kumada’s contribution:

First use of phosphine ligands

First proposed catalytic cycle of cross-coupling – similar to today’s mechanism



Kumada *JACS* **1972** (94) 4374.

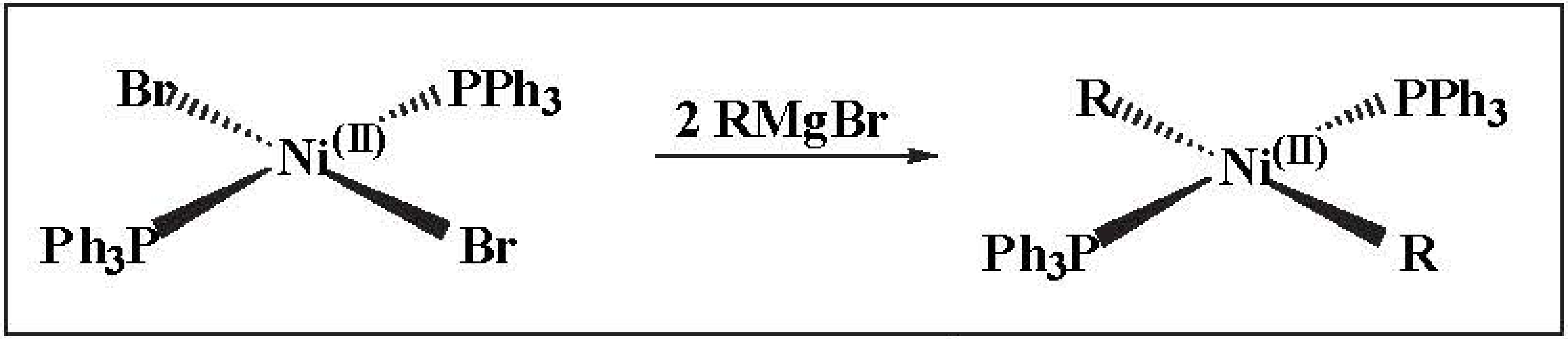
Exercise:

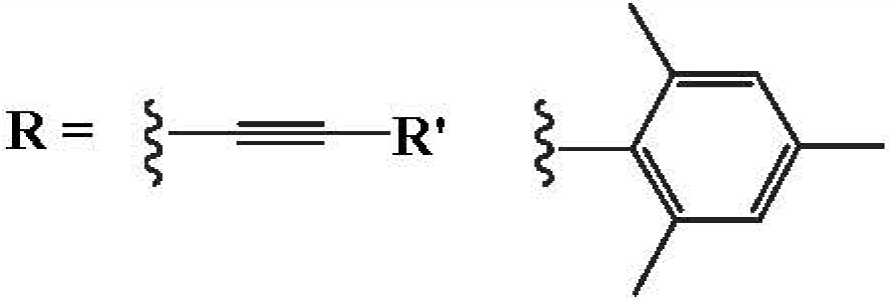
For a Ni-catalyzed Kumada coupling, a Ni(0) active species was identified. This species was generated from NiCl2.

Propose a mechanism how this species can be formed from the reaction of NiCl2 with an excess of PhMgBr. Neglect the other possible ligands on Ni.

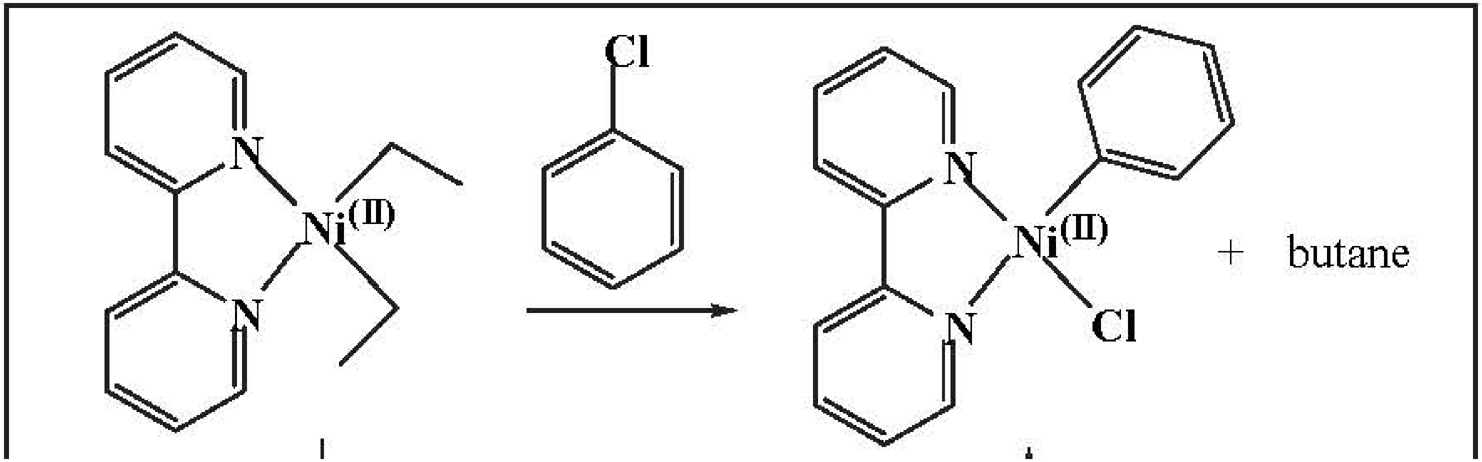
All the pieces of the catalytic cycle were in the literature...

Transmetallation: Chatt and Shaw *J. Chem. Soc.* **1960** 1718. Report the synthesis of alkyl and aryl nickel(II) complexes from the corresponding nickel(II) halides.



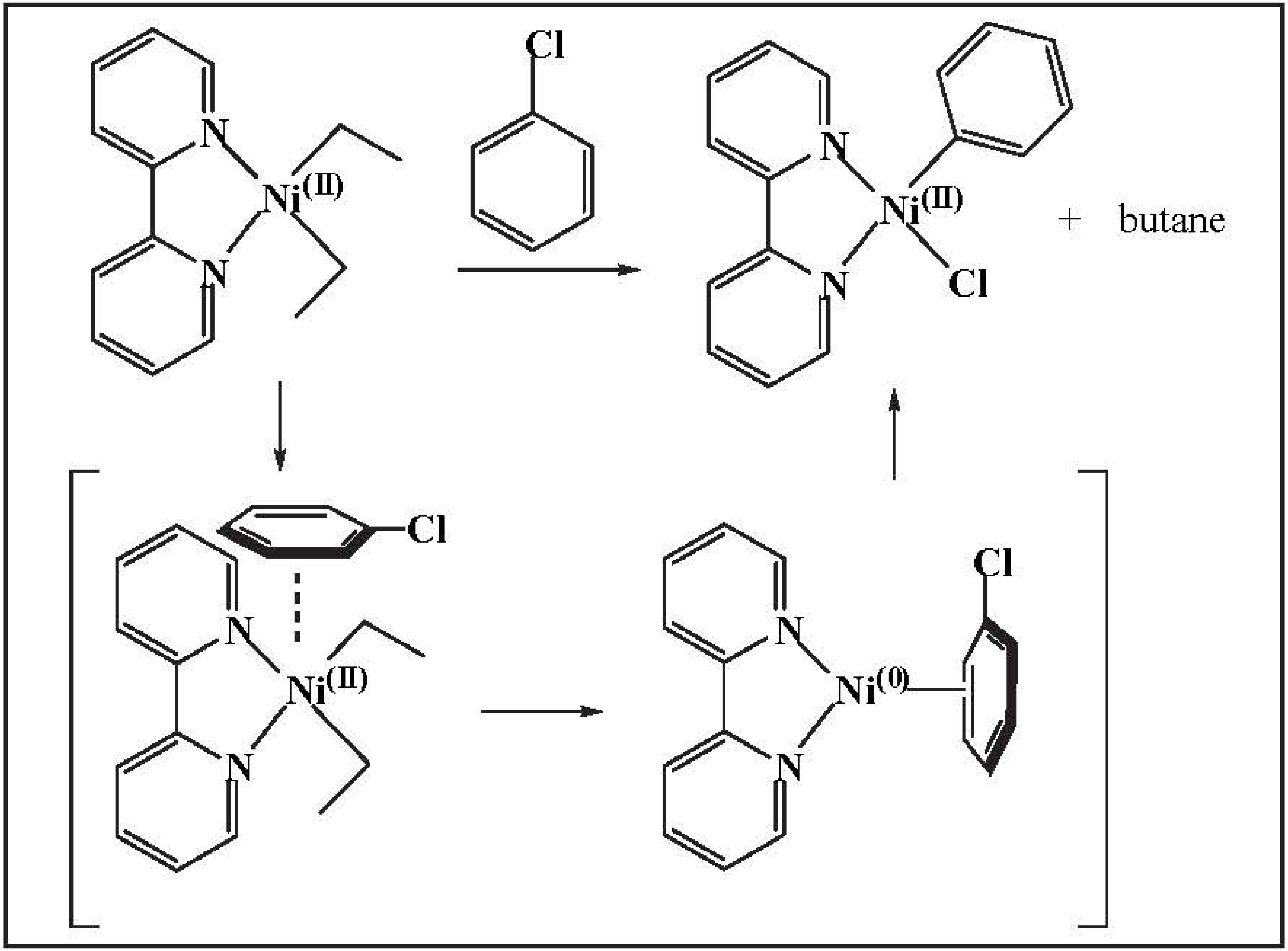


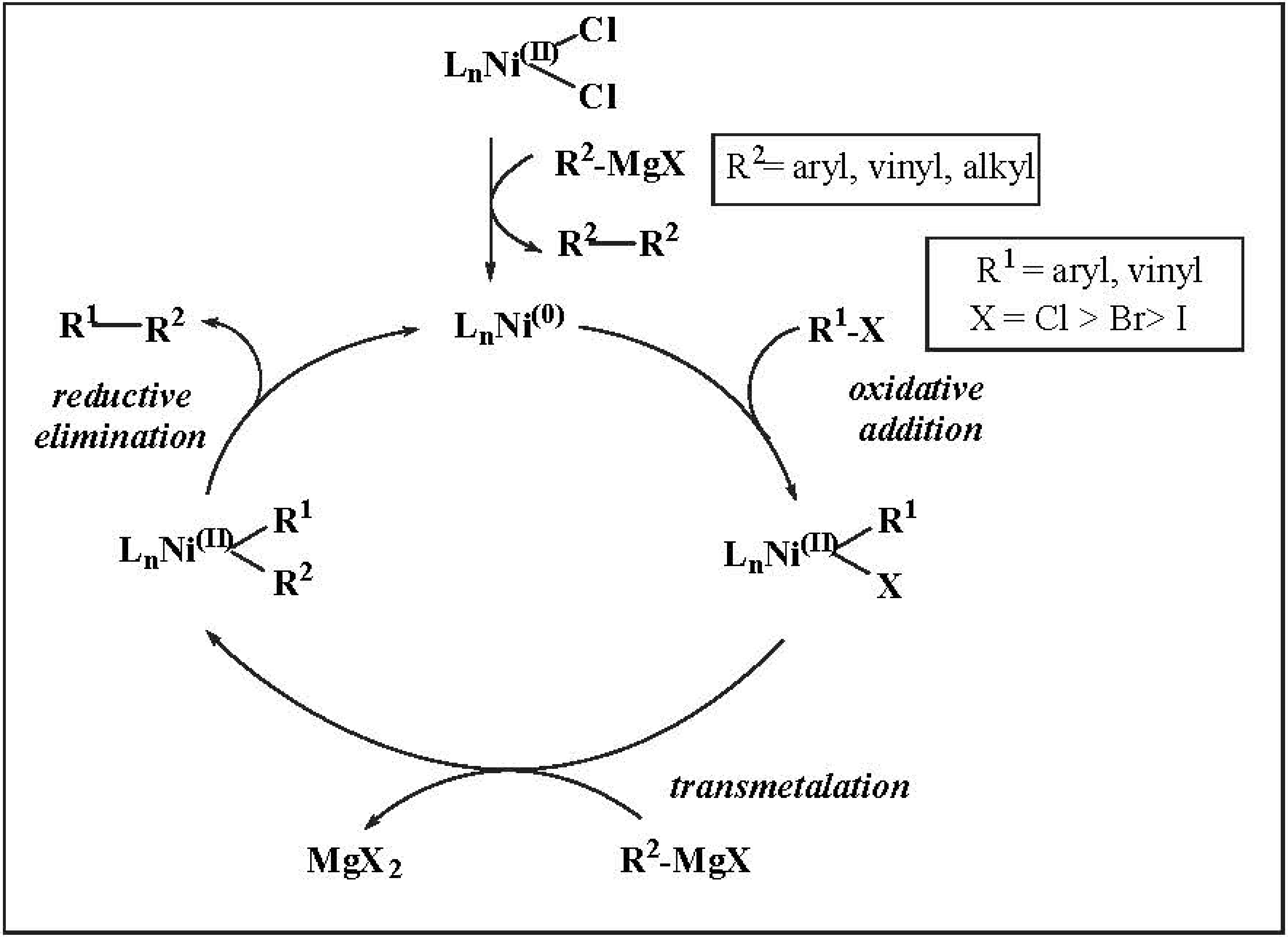
Reductive elimination/Oxidative addition: Yamamoto *JOMC* **1970** (24) C63. "Preparation of a phenyl-nickel complex, phenyl (dipyridyl)nickel chloride, an olefin dimerization catalyst.



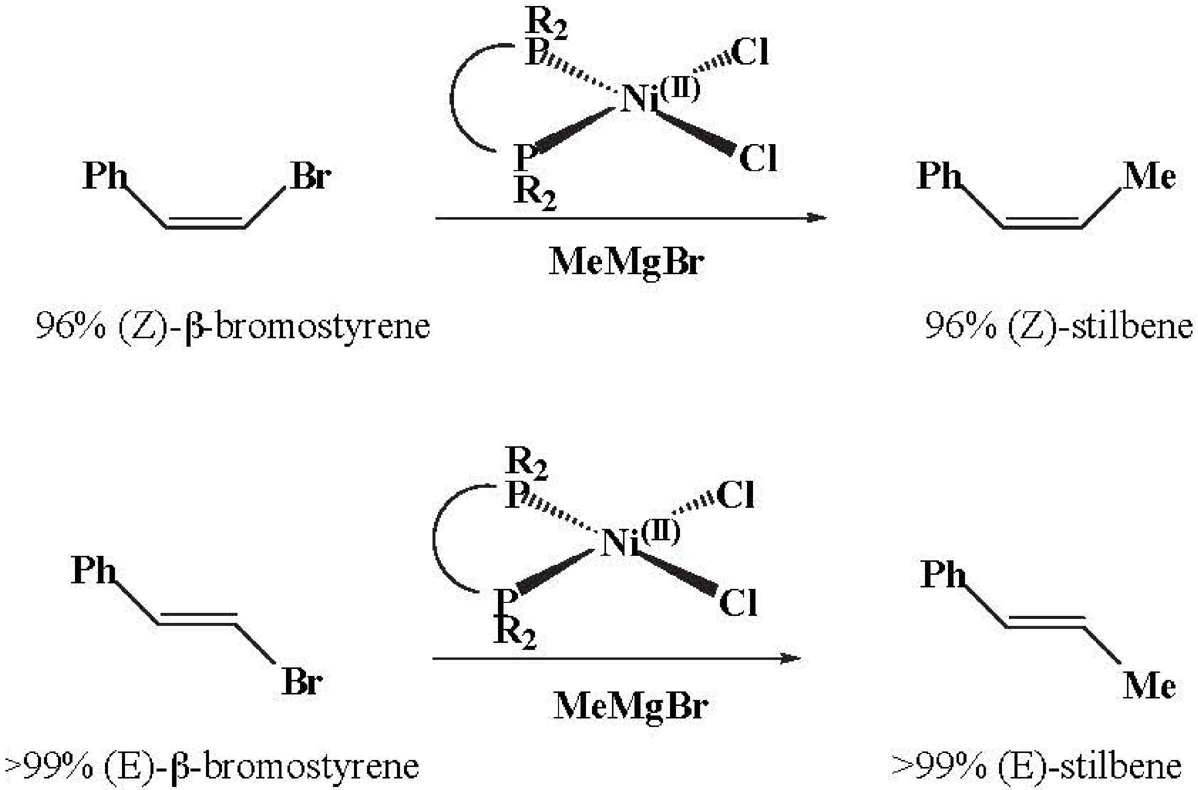
Exercise: propose a mechanism

Reductive elimination/Oxidative addition: Yamamoto *JOMC* **1970** (24) C63. "Preparation of a phenyl-nickel complex, phenyl (dipyridyl)nickel chloride, an olefin dimerization catalyst.




LnNi(II)Cl Cl
R2-MgX
R2—R2
R2= aryl, vinyl, alkyl
R1 = aryl, vinyl
X = Cl > Br> I
LnNi(0)
R1—R2
reductive elimination
R1-X
oxidative addition
LnNi(II) R1 R2
LnNi(II) R1 X
transmetalation
MgX2
R2-MgX

Stereospecific coupling:



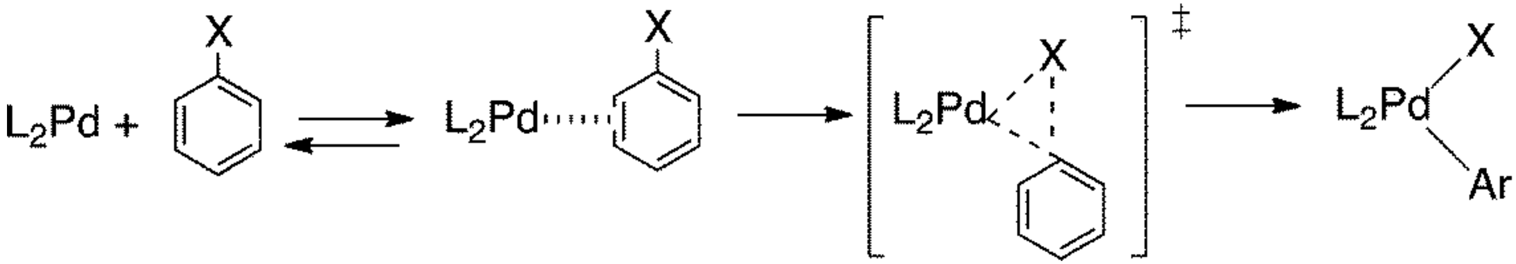
96% (Z)-β-bromostyrene

96% (Z)-stilbene

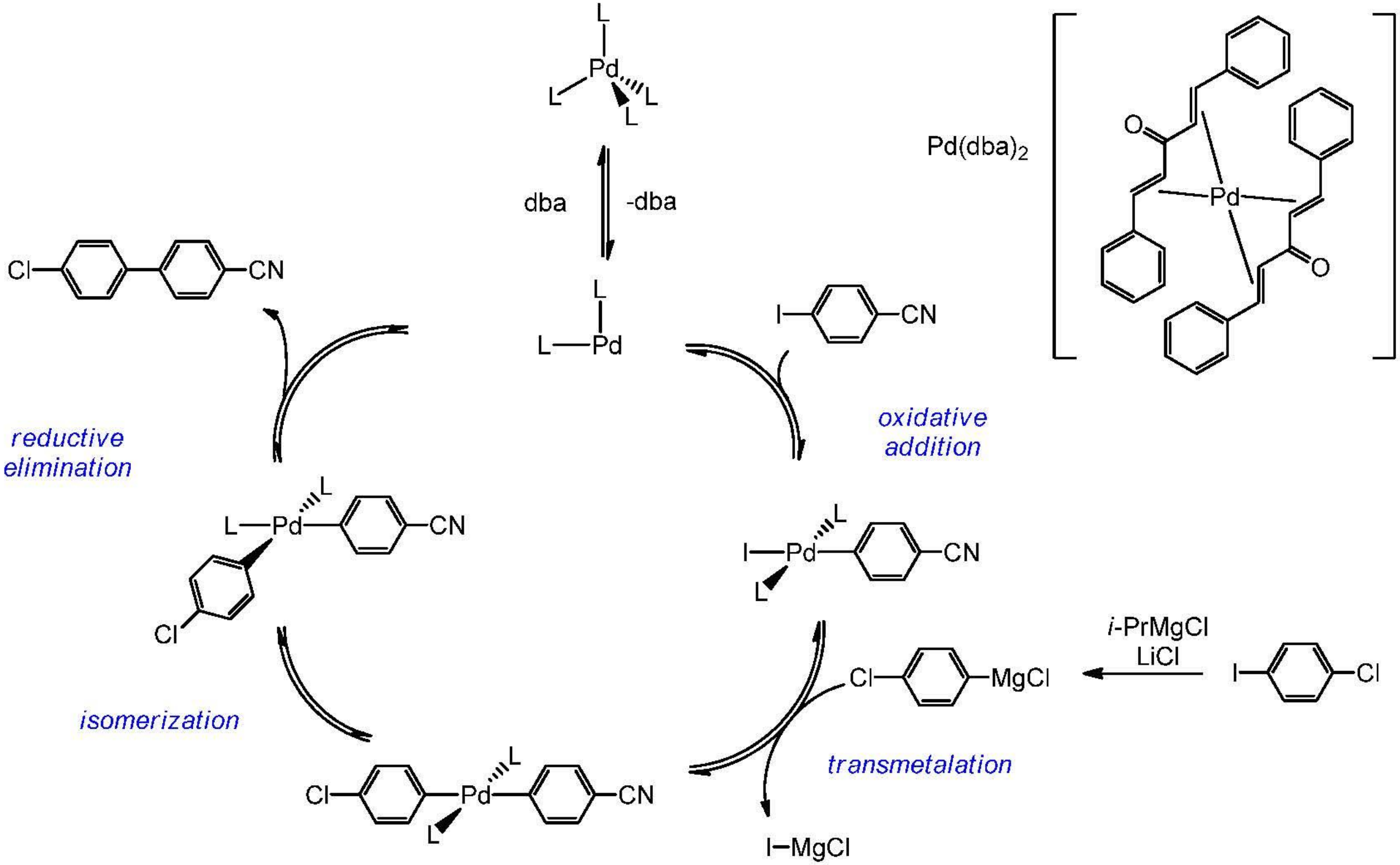
>99% (E)-β-bromostyrene

>99% (E)-stilbene

Concerted oxidative addition of aryl and vinyl halides



Mechanism.


Pd(dba)$_2$
dba
-dba
oxidative addition
transmetalation
isomerization
reductive elimination
i-PrMgCl
LiCl
I–MgCl

For this Kumada coupling reaction, the following product distributions were obtained using two different ligands, PPh_3(n = 2) and a chelating ligand dppf.

1. Propose a mechanism how these products were made.
2. Explain why the two ligands lead to different results.

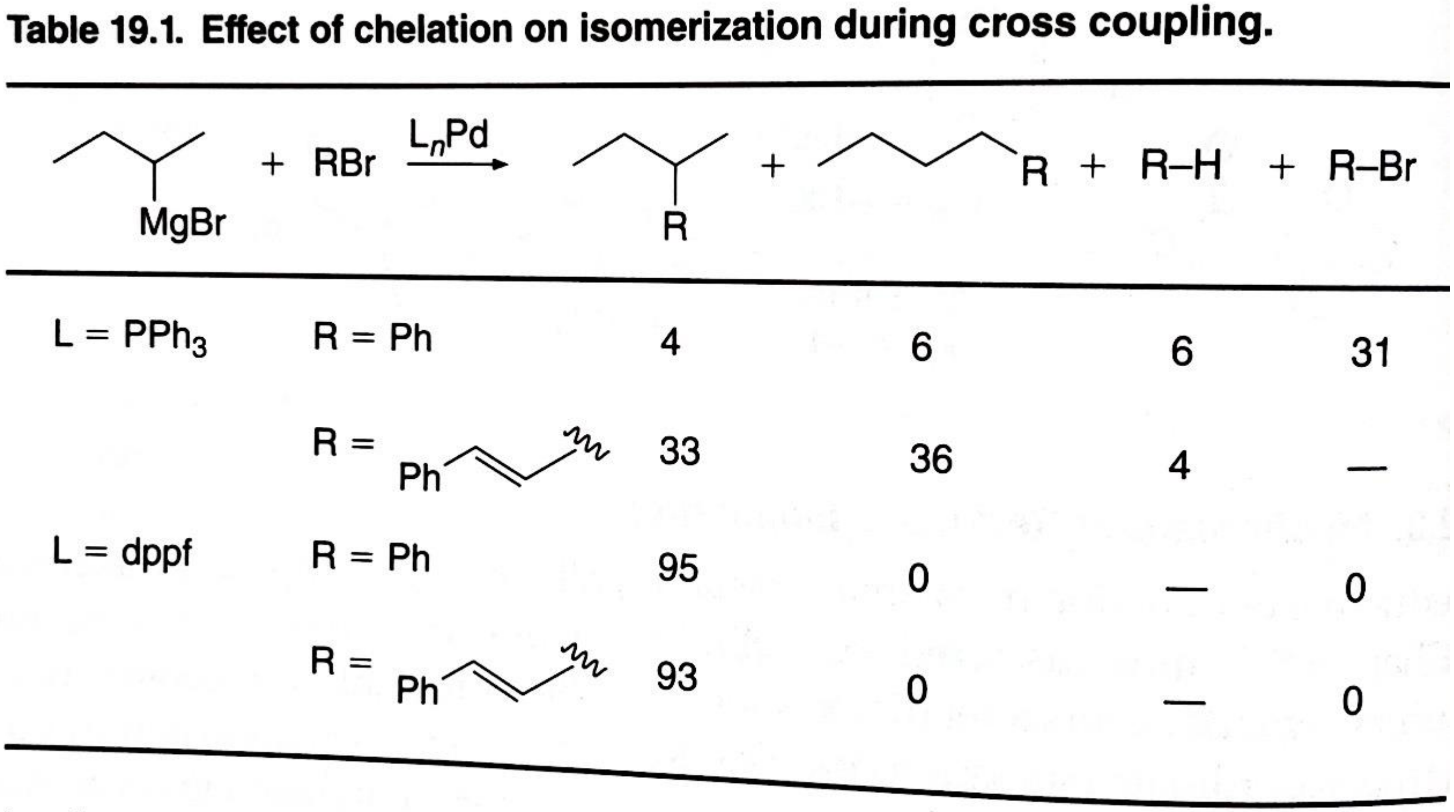
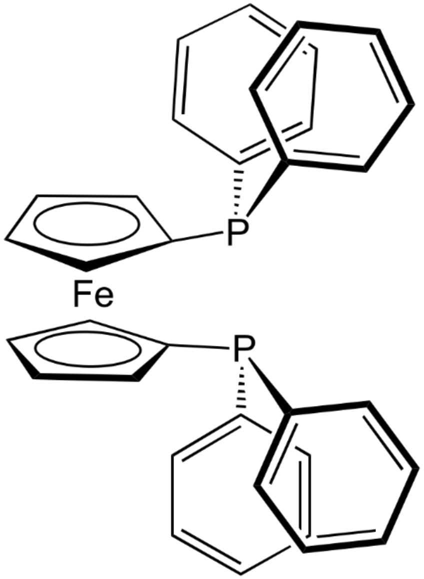


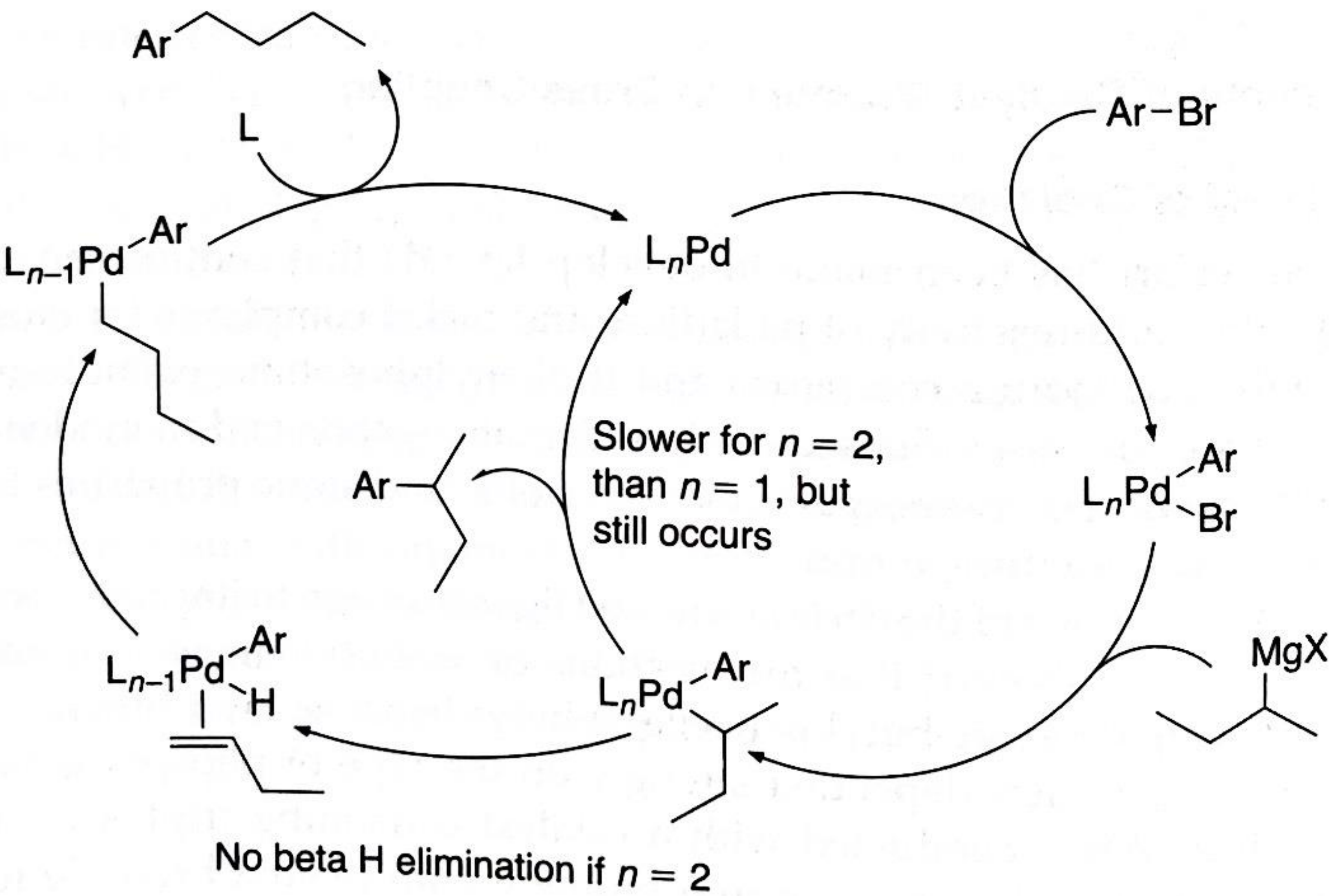
Table 19.1. Effect of chelation on isomerization during cross coupling.

MgBr	+ RBr $\xrightarrow{L_nPd}$	R	+ R	+ R–H	+ R–Br
L = PPh_3	R = Ph	4	6	6	31
	R = Ph	33	36	4	—
L = dppf	R = Ph	95	0	—	0
	R = Ph	93	0	—	0

sessing bisphosph



dppf



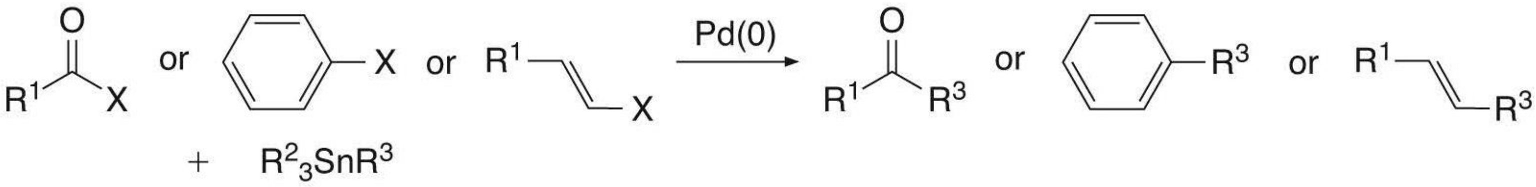
Ar
L
Ar–Br
$L_{n-1}Pd$ Ar
L_nPd
L_nPd Ar Br
Ar
Slower for *n* = 2, than *n* = 1, but still occurs
MgX
$L_{n-1}Pd$ Ar H
L_nPd Ar
No beta H elimination if *n* = 2

Scheme 19.7

III. Mechanistic insights from Stille Coupling

Stille Coupling

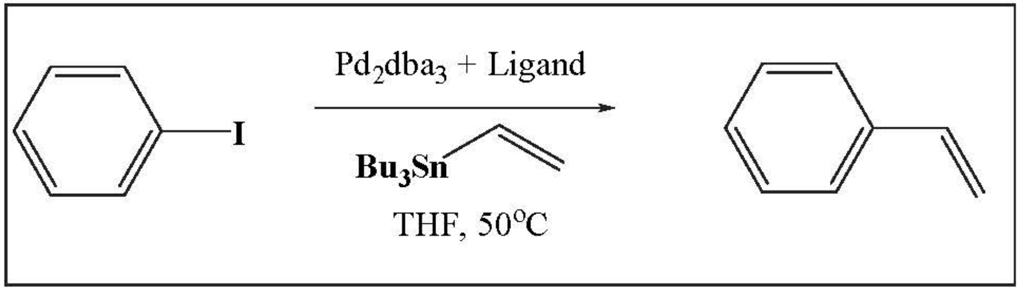
The Stille Coupling is a versatile C-C bond forming reaction between **stannanes** and **halides** or **pseudohalides**, with very few limitations on the R-groups.



Due to the toxicity of organotin compounds, this coupling is being avoided.

The same versatility is now achieved by Suzuki coupling.

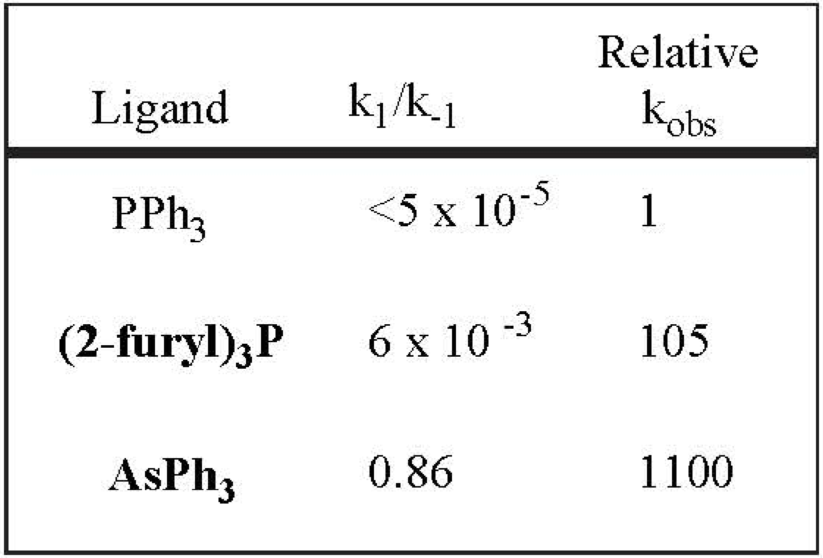
Stille: Ligand Effects



It has been observed experimentally that increasing the concentration of monodentate phosphine ligands decreases the rate of the Stille reaction. No correlation exists between cone angles (θ) and observed rates indicating that the ligand effect is not of steric origin. The ligand effect is thought to be electronic in nature where phosphines that are poor σ-donors promote the cross-coupling more effectively than those that are strong σ-donors.

Ligand	Pd:L	θ	Relative rate
PPh_3	1:2	145°	1
(2-furyl)$_3$P	1:2	ND	20
$AsPh_3$	1:2	142°	78

Farina *JACS* **1991** (113) 9585.



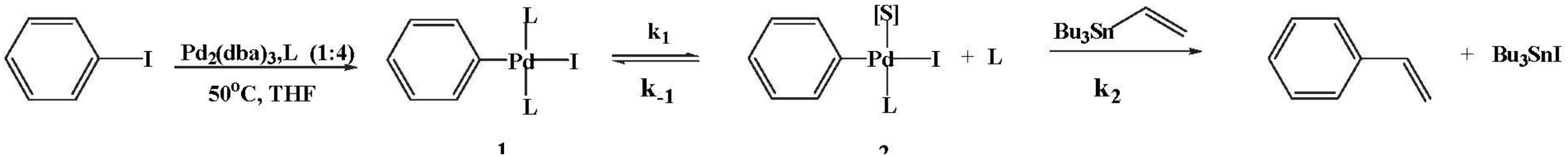
Ligand	k_1/k_{-1}	Relative k_{obs}
PPh_3	$<5 \times 10^{-5}$	1
$(2\text{-furyl})_3P$	6×10^{-3}	105
$AsPh_3$	0.86	1100

Less Electron-donating ligand leads to faster rate.

Based on this, which step cannot be the rate determining step:

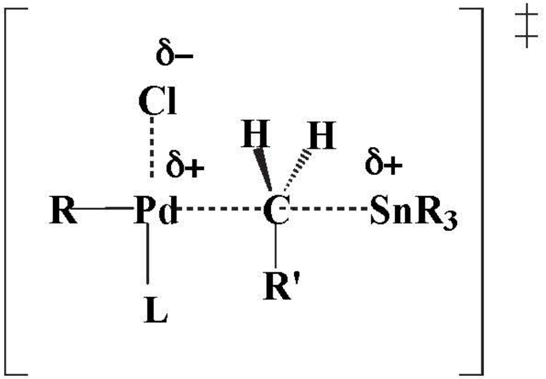
Oxidative addition; transmetallation; reductive elimination

Kinetics studies support a mechanism involving fast oxidative addition followed by a rate-determining transmetalation event which requires initial solvent/ligand exchange. This predissociation event is disfavored thermodynamically with strong donor ligands such as PPh_3, and more favored with weak donor ligands such as $AsPh_3$.



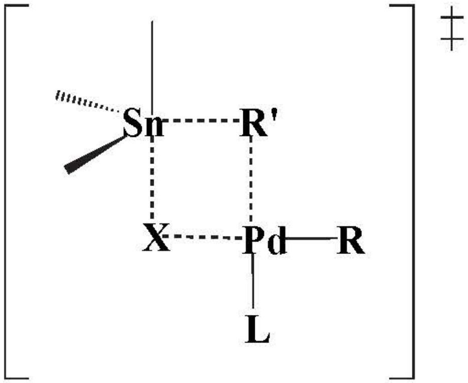
Stille: Mechanism of Pd/Sn Transmetalation

S_E2 (open)

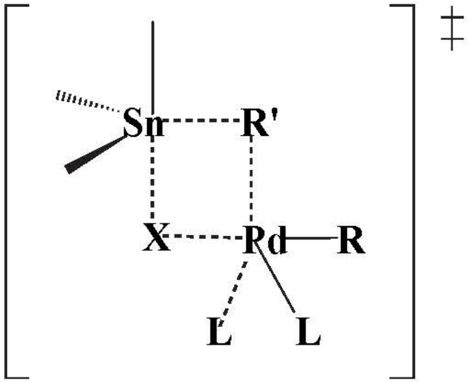


favored in highly polar
and/or nucleophilic solvents

S_E2 (cyclic)



S_E2 (cyclic, pentacoordinate)



favored in non-polar solvents

Farina *Pure & Appl. Chem.* **1996** *68:1* pp 73-78.

The mechanism for Pd/Sn transmetalation is highly dependent on reaction conditions, and the subject of ongoing debate in the literature.

IV. Suzuki Coupling and catalysts developments

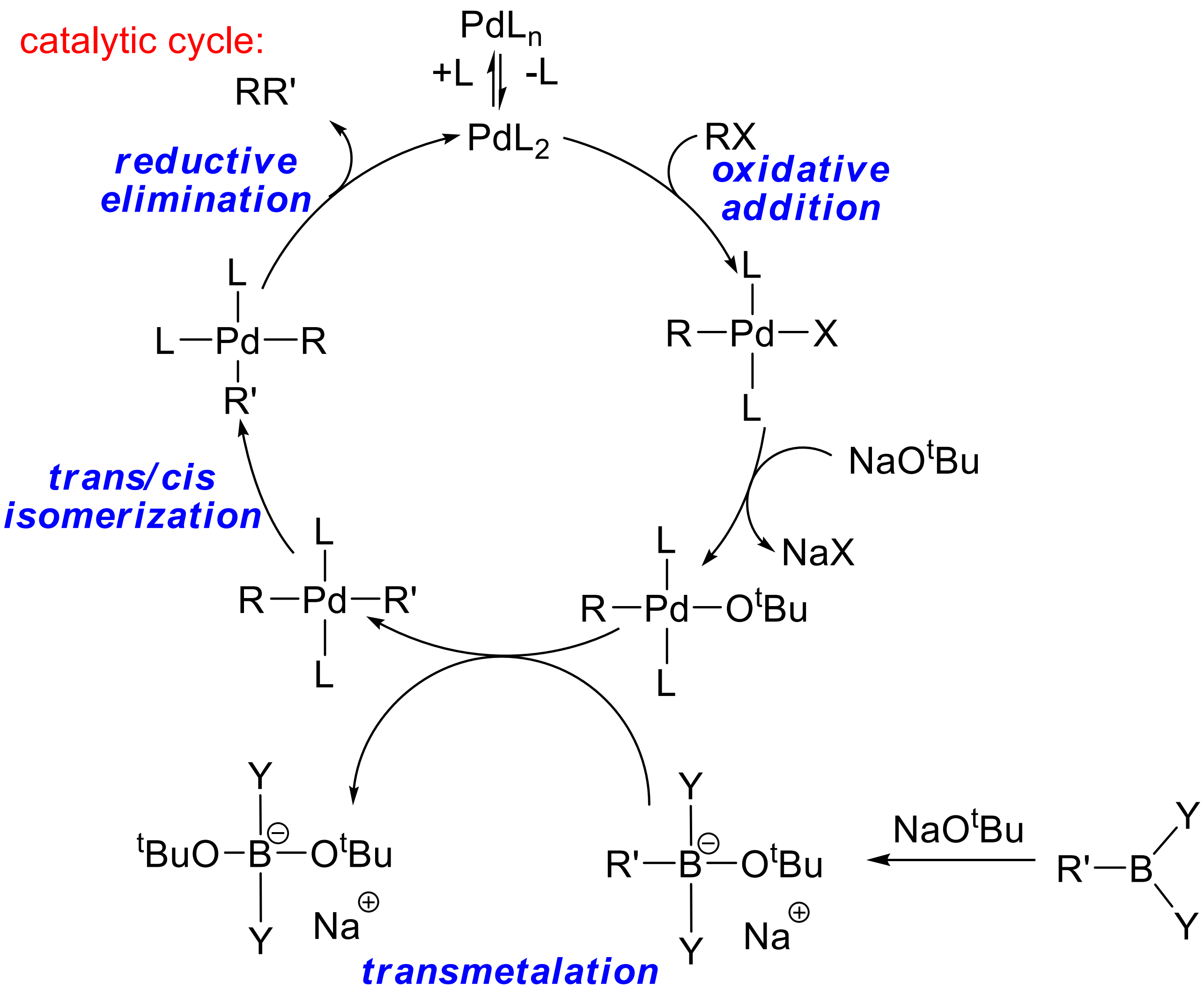
Suzuki (Suzuki-Miyaura) Coupling – one coupling to rule all

R^1= aryl, alkene (vinyl), alkyne **R^2**= H (boronic acid), alkyl (boronic ester) **R^3**= aryl, alkene (vinyl), alkyne

X = halide (I, Br, Cl*) triflate (-OTf) *Cl requires special conditions for activation

Base (alkoxide or OH^- or F^-) is required to activate the boron reagent for transmetallation

Mechanism and Role of Base in Suzuki-Miyaua Coupling

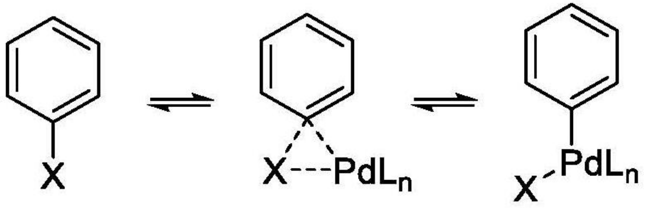


Transmetallation requires base: anionic boron reagents are more likely to transfer R’ than the neutral ones.

Better Understanding of the Mechanism

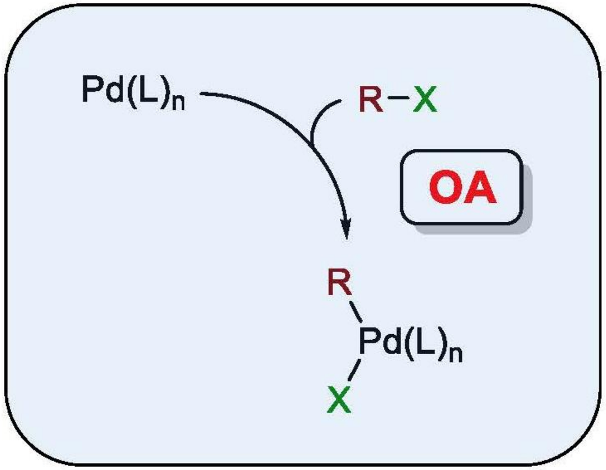
Oxidative Addition

Csp^3-X usually slow

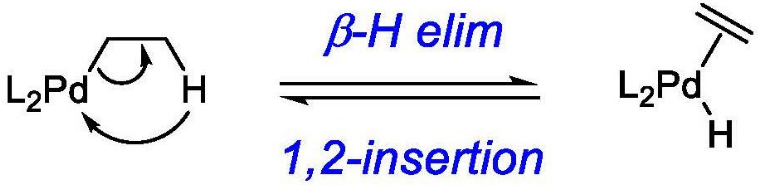


Favoured by

Electronically Rich Ligands
Bulky Ligands



Can lead to *β*-H elimination



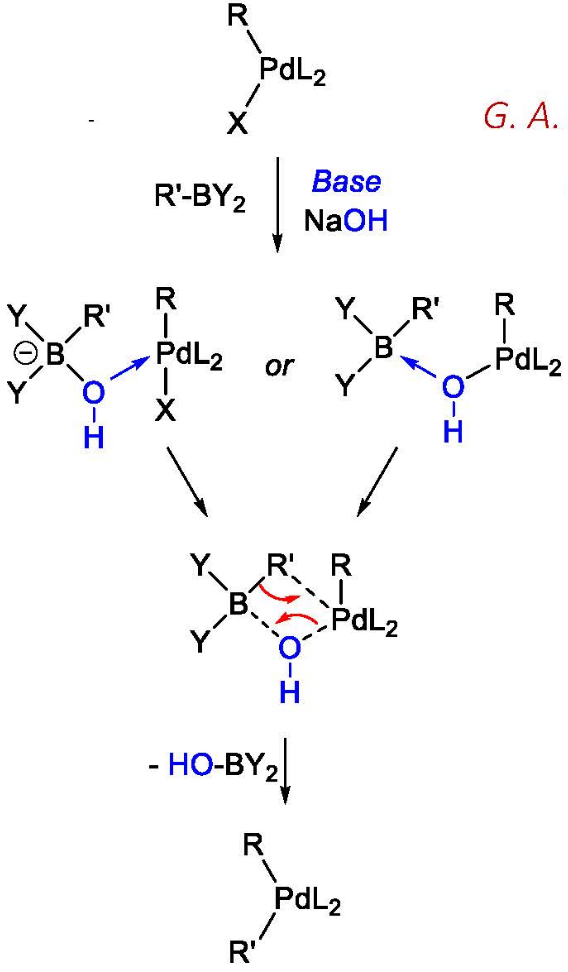
Better Understanding of the Mechanism

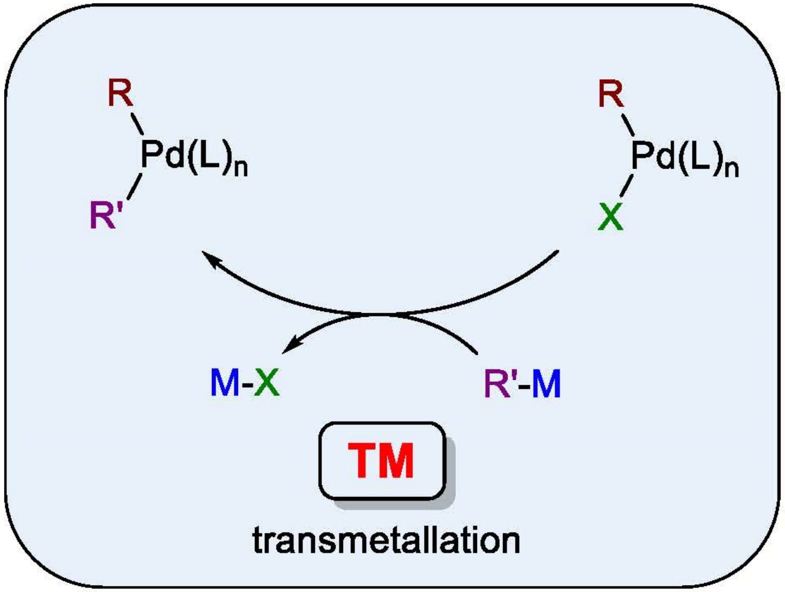
G. A. Molander Angew. Chem. Int. Ed. 2009, 48, 9240.

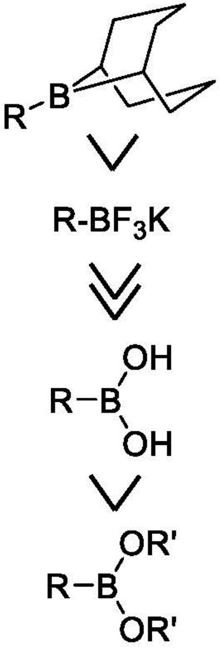
J. A. Soderquist J. Org. Chem. 1998, 63, 461.

Y. Kishi J. Am. Chem. Soc. 1987, 109, 4756.

TM is accelerated by a base

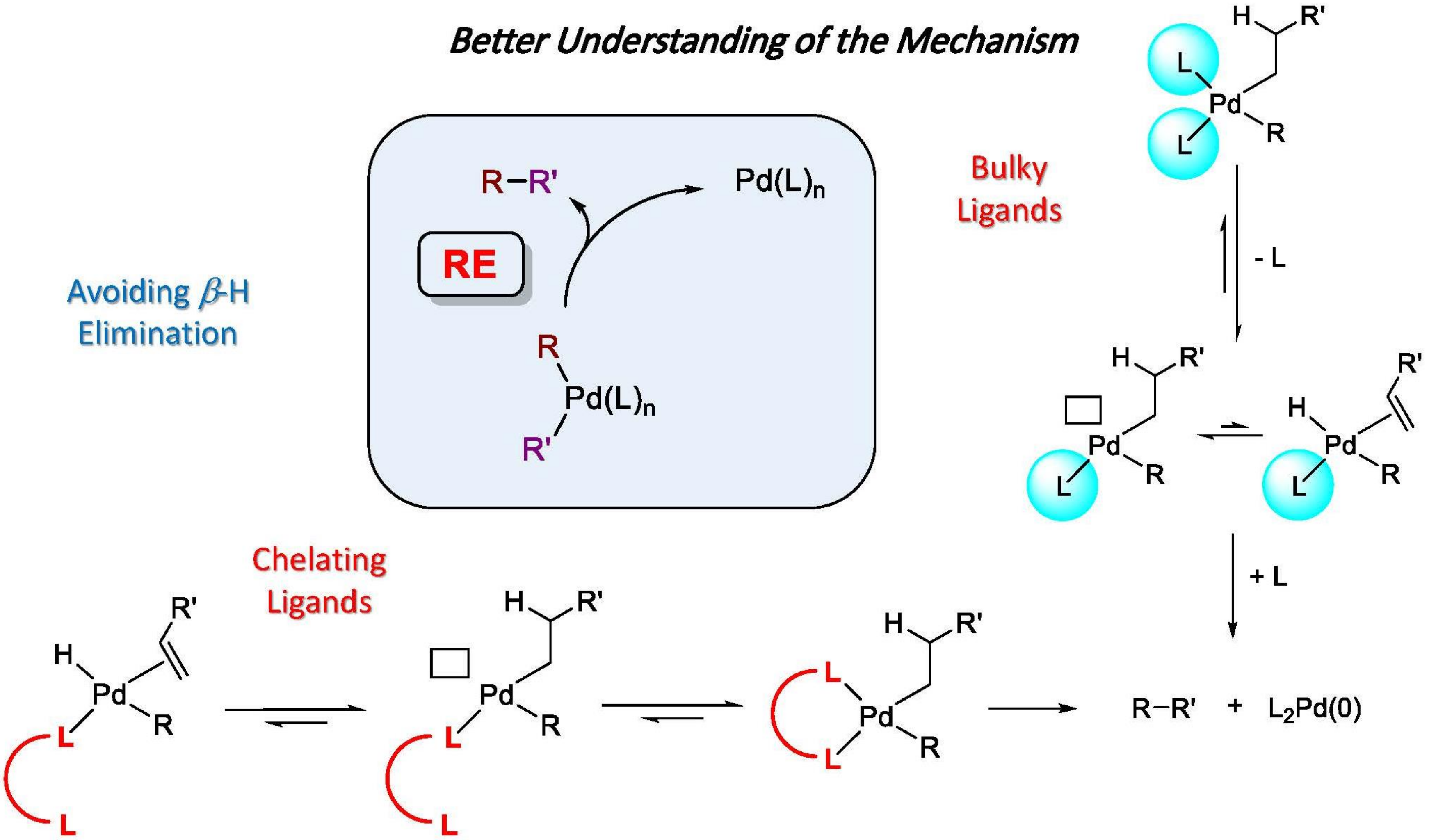






Suzuki-Miyaura Cross-Coupling Reactions

Better Understanding of the Mechanism

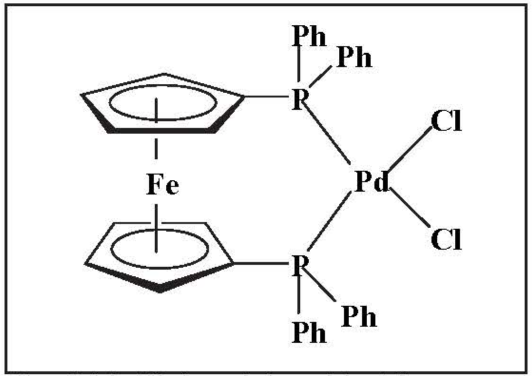


Avoiding β-H Elimination

Bulky Ligands

Chelating Ligands

Suzuki: Ligand Effects for Csp^3-Csp^2 couplings



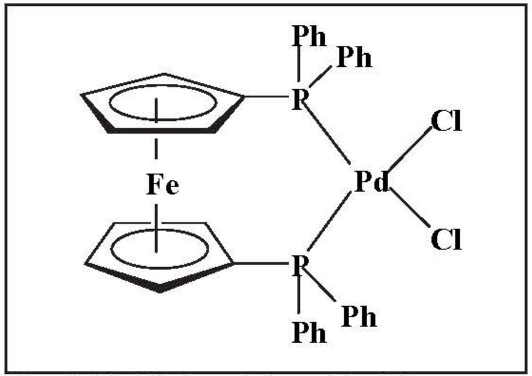
dppf, bis(diphenylphosphino)ferrocene

$PdCl_2$(dppf) is often found to be a superior catalyst for Suzuki cross coupling reactions between boron-alkyl derivatives (possessing β-hydrogens) and vinyl/aryl halides/triflates. This ligand is thought to favor reductive elimination vs. competitive β-hydride elimination for at least two reasons:

What are these two reasons?

Suzuki *JACS* **1989** (111) 314
see also **Hayashi** *JACS* **1984** (106) 158; **Brown** *Inorg. Chimica Acta*, **1994** (220) 249.
Danishevsky *ACIEE* **2001** (40) 4544.

Suzuki: Ligand Effects for Csp^3-Csp^2 couplings



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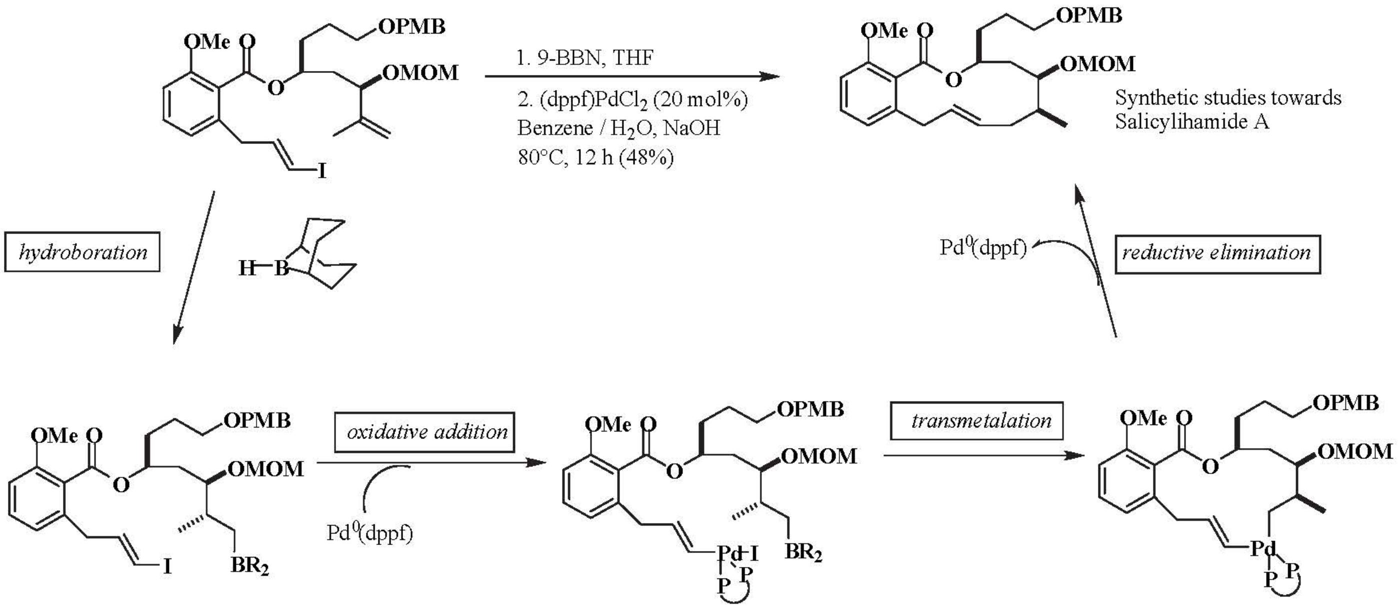
· The bidentate phosphine ligand enforces a *cis* geometry between the alkyl and vinyl/aryl substituents; this *cis* geometry is required for reductive elimination

· The large bite angle for this bidentate phosphine ligand results in a smaller angle between the alkyl and vinyl/aryl substituents. Recall that minimization of the angle between two metal-bound substituents is thought to promote reductive elimination event by increasing orbital overlap:

Suzuki *JACS* **1989** (111) 314
see also **Hayashi** *JACS* **1984** (106) 158; **Brown** *Inorg. Chimica Acta*, **1994** (220) 249.
Danishevsky *ACIEE* **2001** (40) 4544.

Hydroboration/Suzuki coupling sequence sets a new stereocenter and effects macrocyclization



1. 9-BBN, THF
2. (dppf)$PdCl_2$ (20 mol%)
Benzene / H_2O, NaOH
80°C, 12 h (48%)

Synthetic studies towards
Salicylihamide A

hydroboration

oxidative addition

transmetalation

reductive elimination

The well-documented diastereoselectivity of hydroboration reactions with 1,1-disubstituted olefins provides an opportunity to control stereochemistry as part of the coupling strategy. Alternative cyclization via macrolactonization is rendered difficult in this instance by the bulky ortho-substituted carboxylic acid.

Maier, *Org. Lett.* **2002**, *4*, 13, 2205.

"*Fu Ligands*"

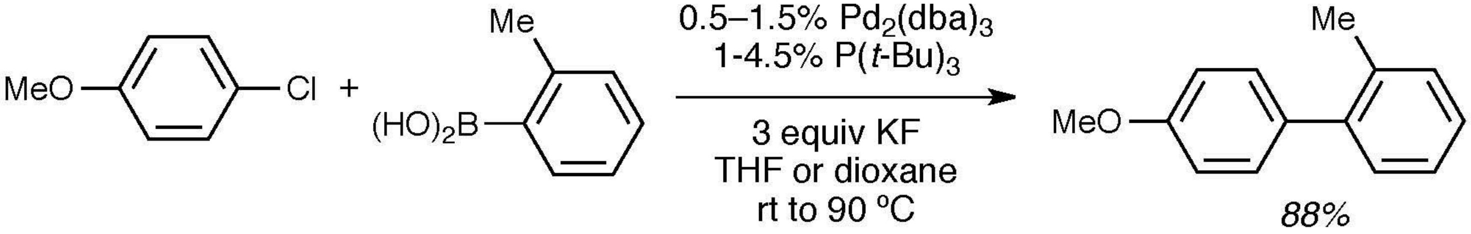
Acc. Chem. Res. **2008**, *41*, 1555.

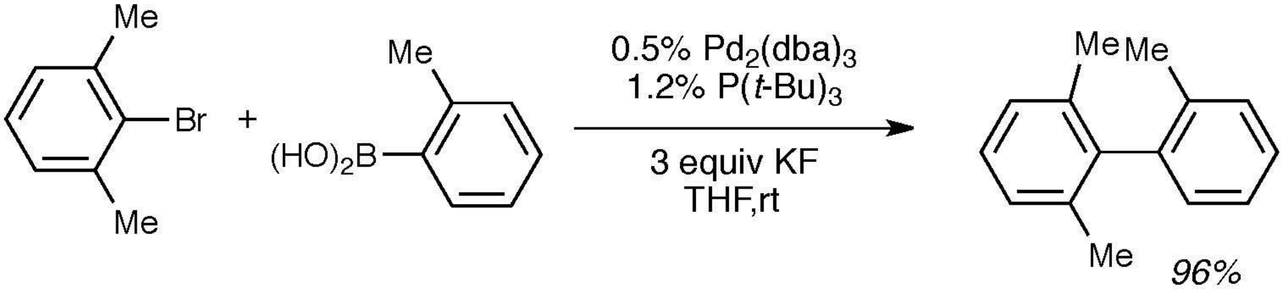
Recal that the identity of the halide has a big impact on the success of oxidative addition. Order of reactivity: I > OTf > Br >> Cl

The reactivity of the halides is related to Ph–X bond strength (kcal/mol): Cl (95), Br (80), I (65)

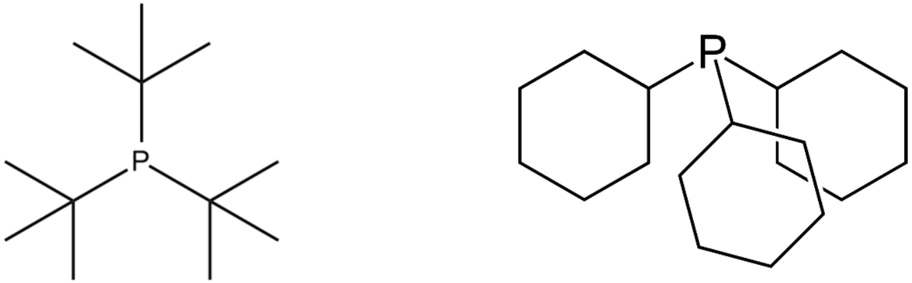
The use of bulky and strongly electron donating ligands (i.e. P(*t*-Bu)$_3$, P(*t*-Bu)2Me, PCy$_3$) has allowed cross-coupling of aryl chlorides.

It is thought that these ligands speed up the rate of oxidative addition. Aryl chlorides usualy still require heating, but bromides and iodide can undergo reaction at rt.

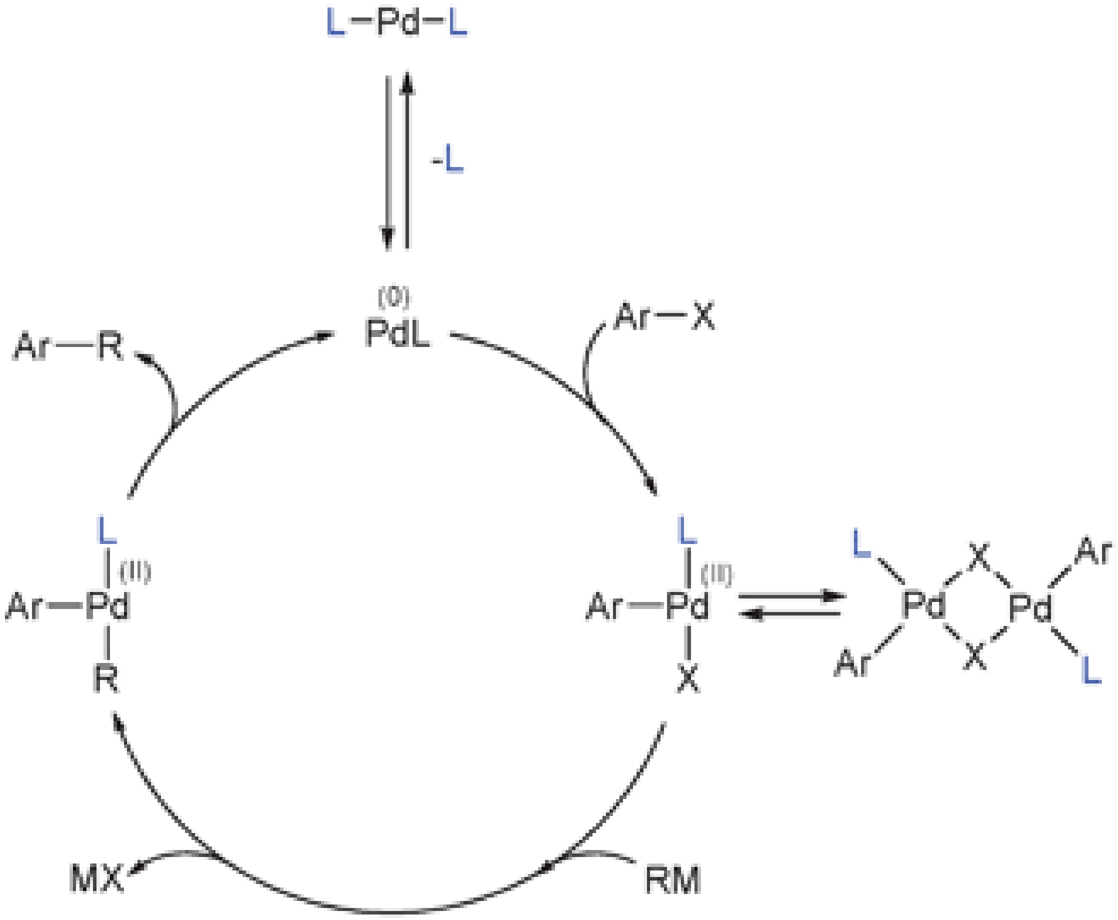




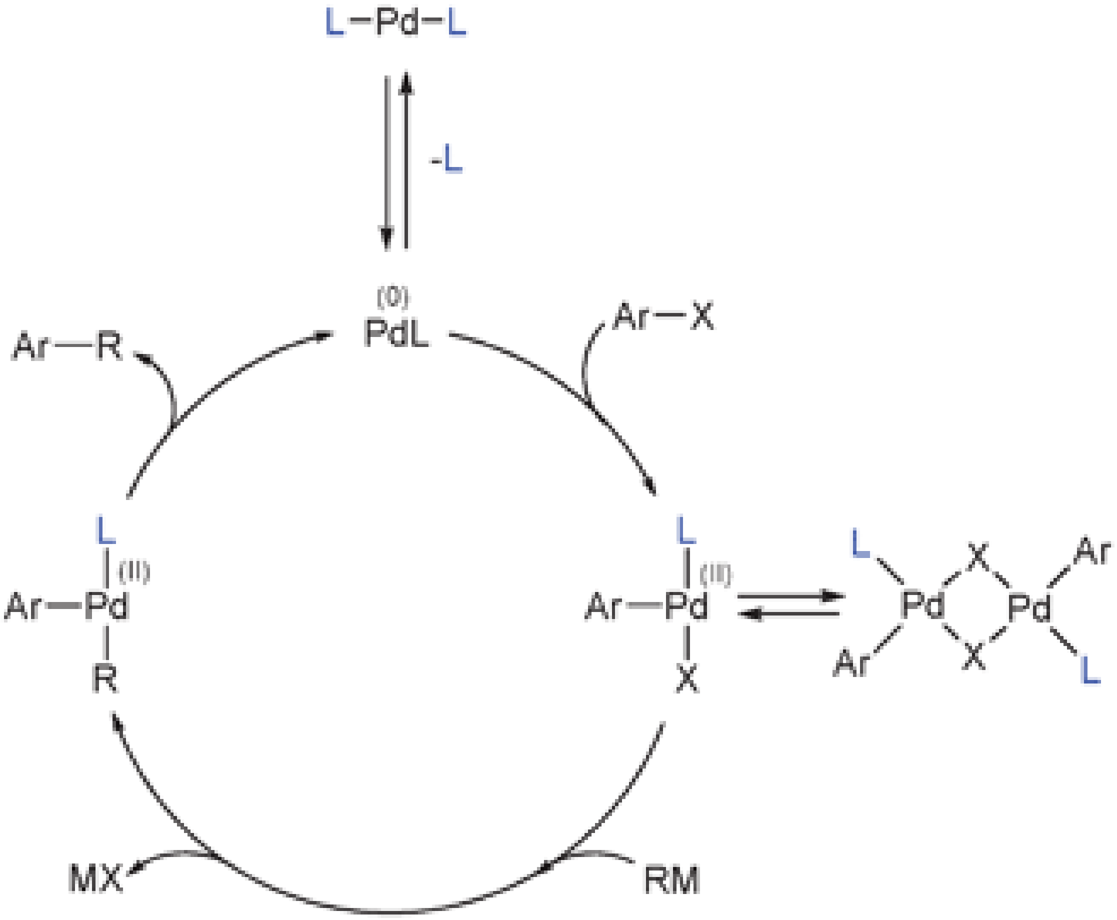
Active species: mono-ligated Pd-L due to a bulky ligand



Pd-PR_3

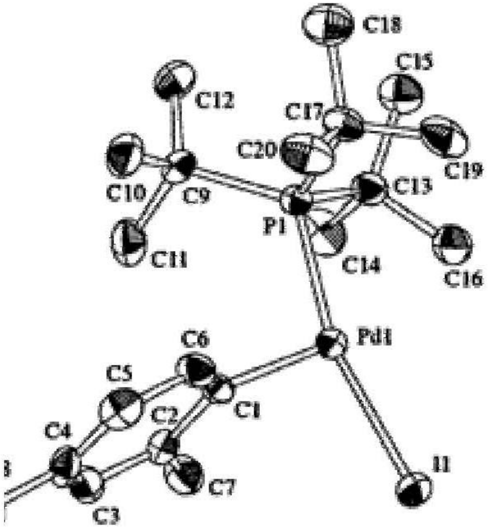


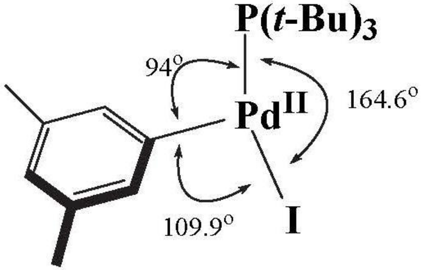
Mono-ligated Pd species more active for oxidative addition of Ar-Cl



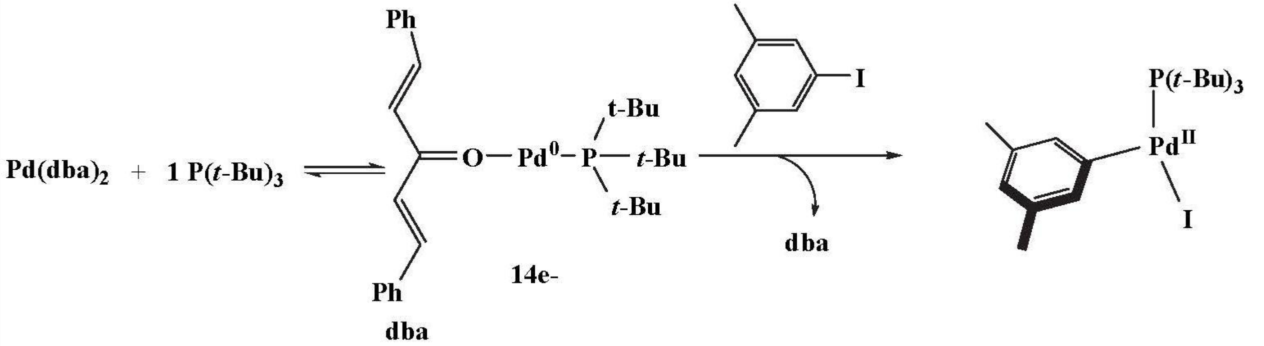
Electron-rich ligand stabilized Pd(0) versus Pd nanoparticle formation

Bulky, electron-rich phosphines





T-shaped monomer



Hartwig *JACS* **2002** (124) 9346.

factors:

Oxidative addition is faster with less bulky system.

Transmetallation is faster with less bulky system (3 vs. 4 coordinate)

Reductive elimination is faster from 3-coordinate Pd(II) than 4-coordination Pd(II) (observations)
(Sterics dominate Electronics)

(Why?)

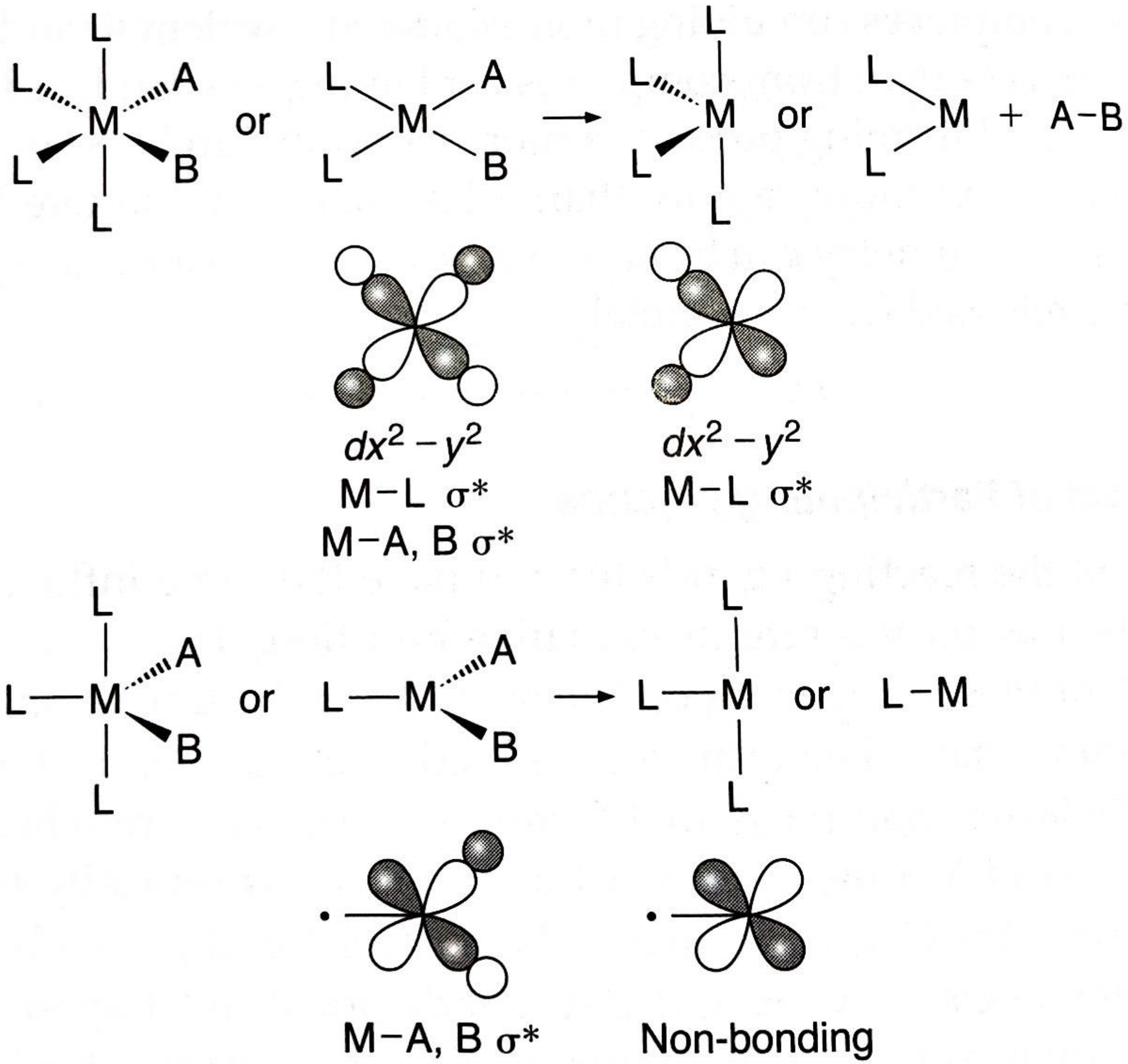
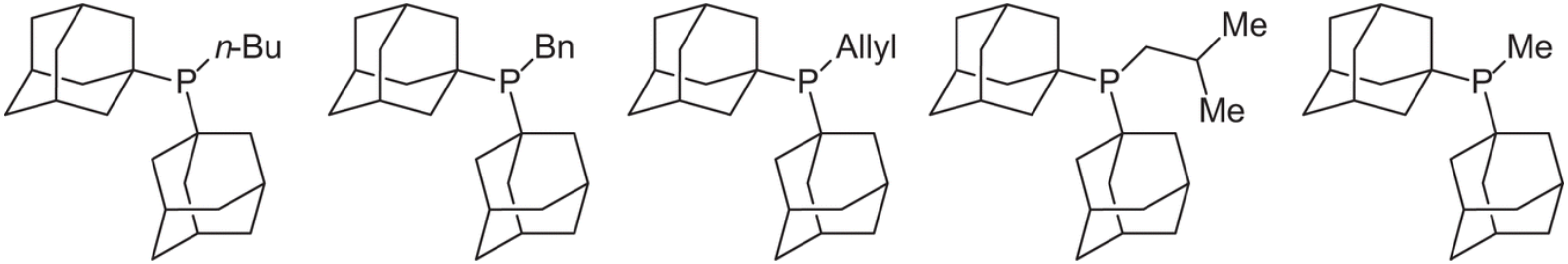


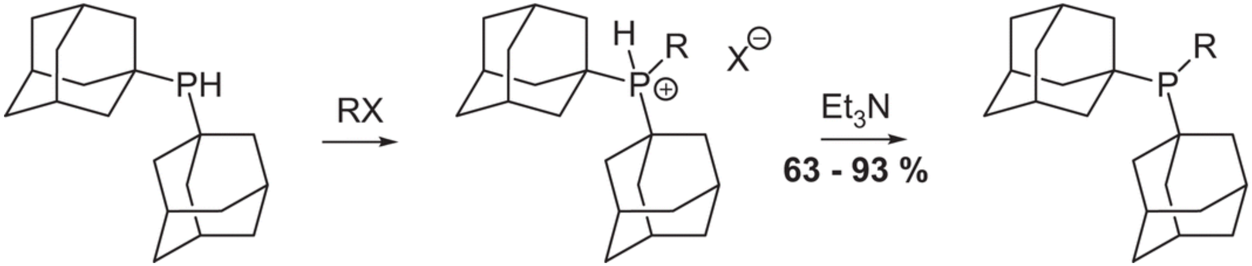
Figure 8.1.
The origin of the relative rates for reductive elimination from complexes with odd and even coordination numbers.

Ligands developed by Beller et al. Admantyl groups
Even higher bulk

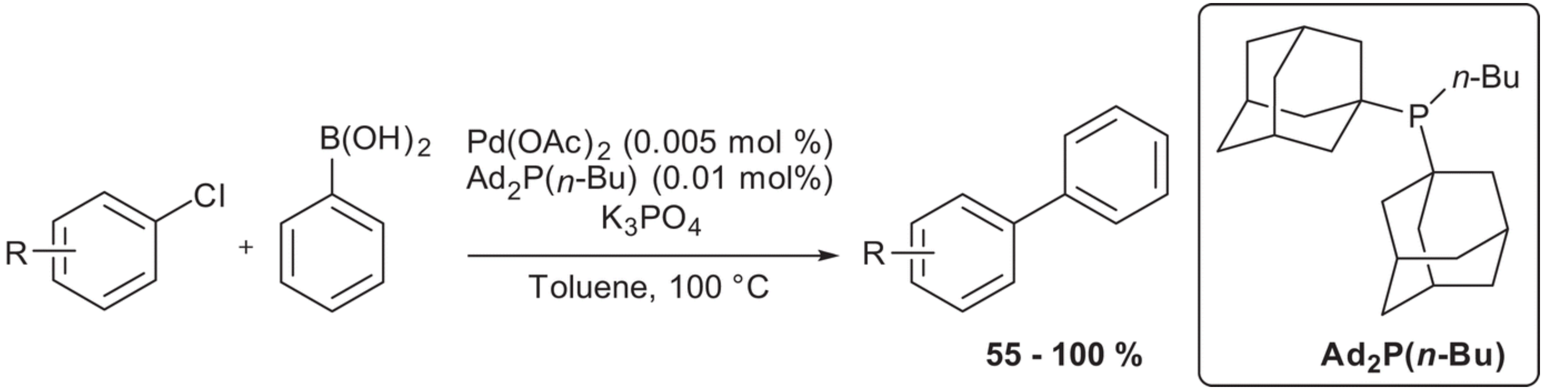
Ad_2PR Ligands Reported by Beller:



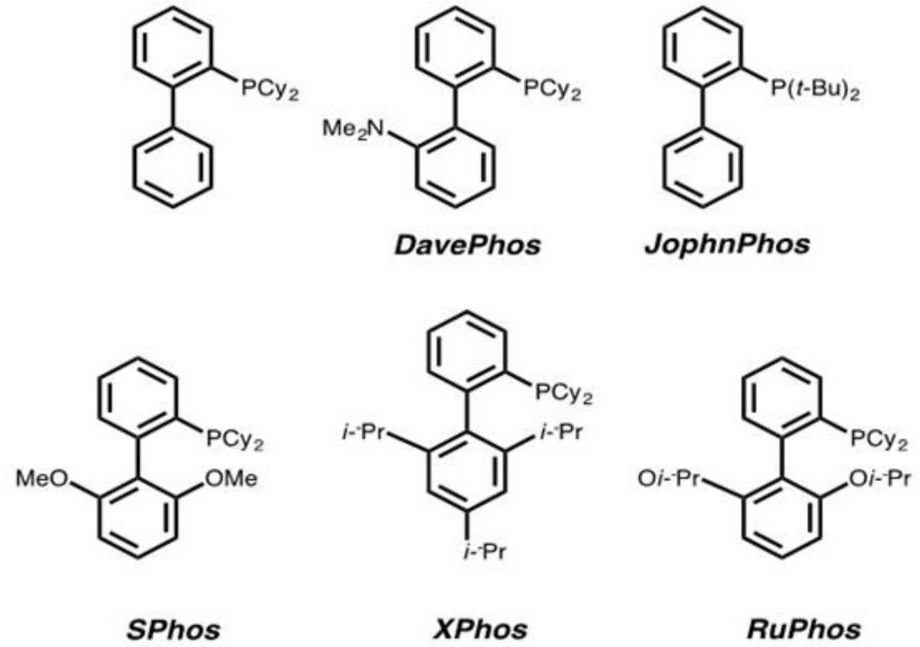
Synthesis of Ad_2PR Ligands:



Ligands developed by Beller et al. Admantyl groups
Even higher bulk

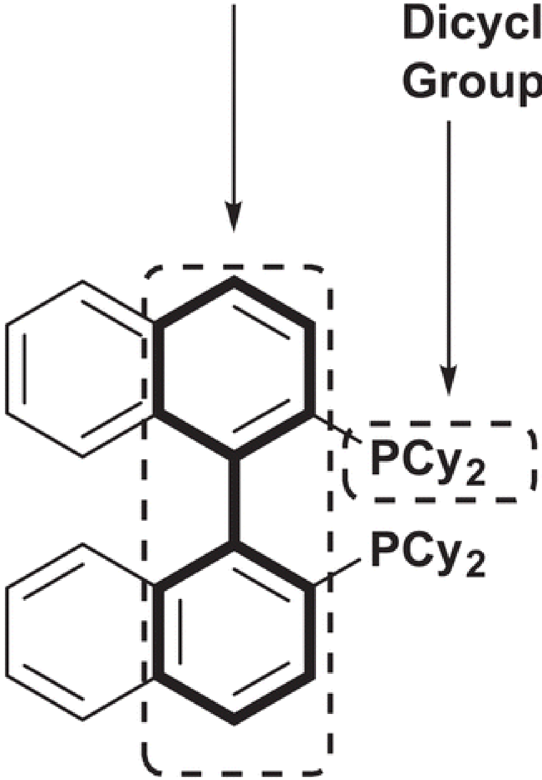


Buchwald ligands: Biaryl monophosphines



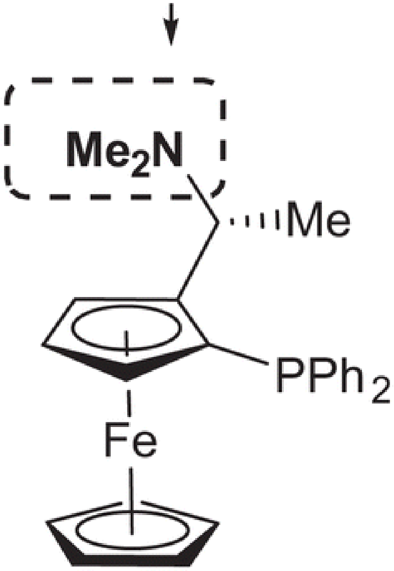
Biaryl Backbone

Electron Rich Dicyclohexylphosphino Group

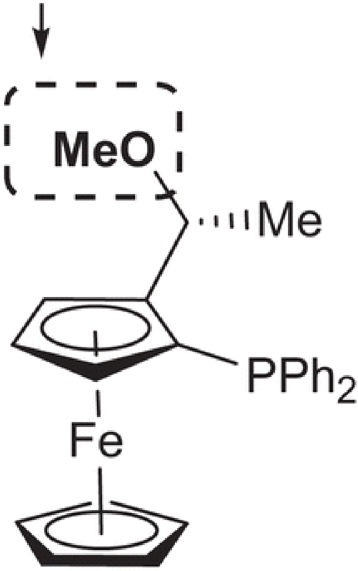


2,2'-Bis(dicyclohexylphosphino)-1,1'-binaphthyl

Weak σ-Donor Groups



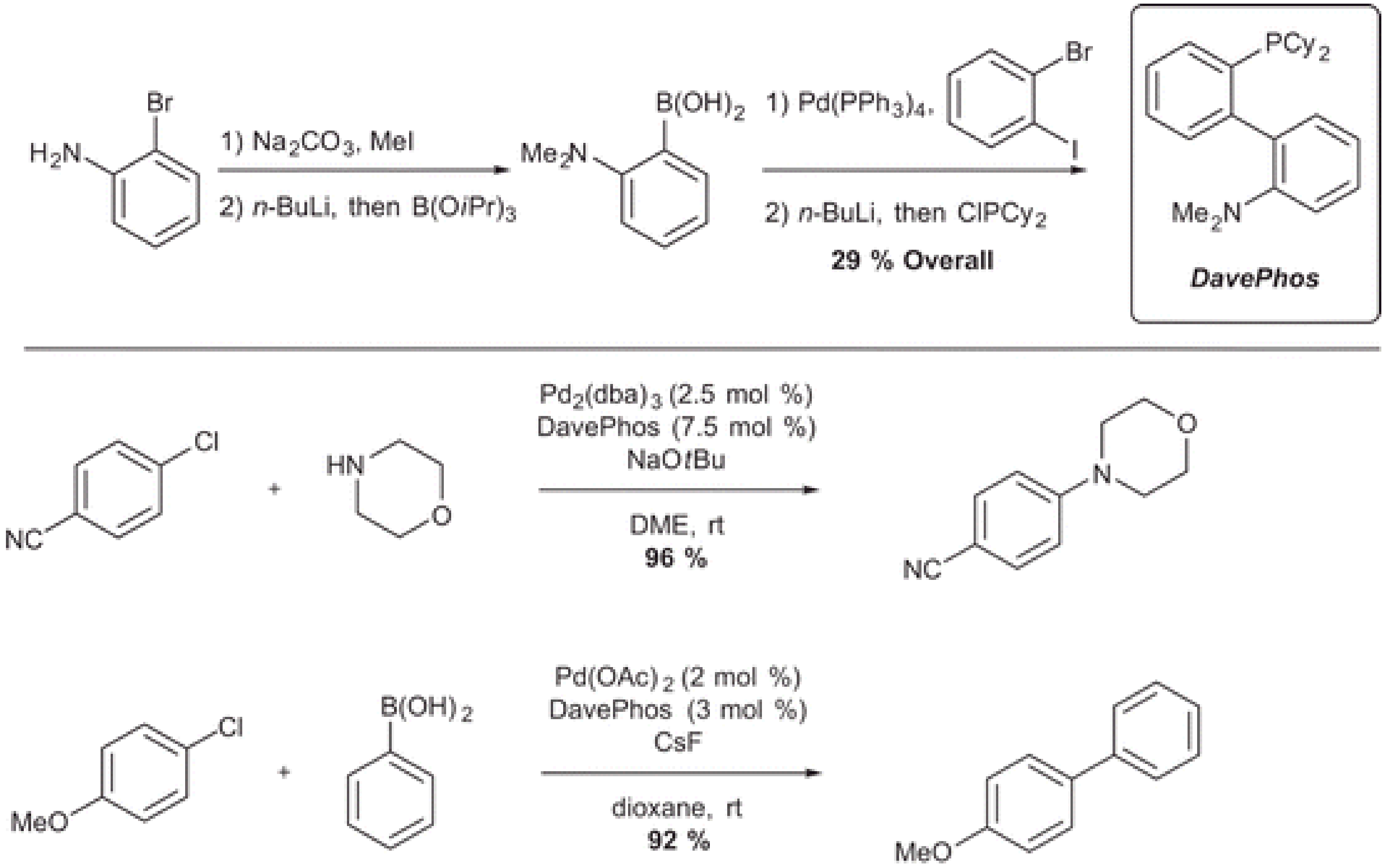
PPFA



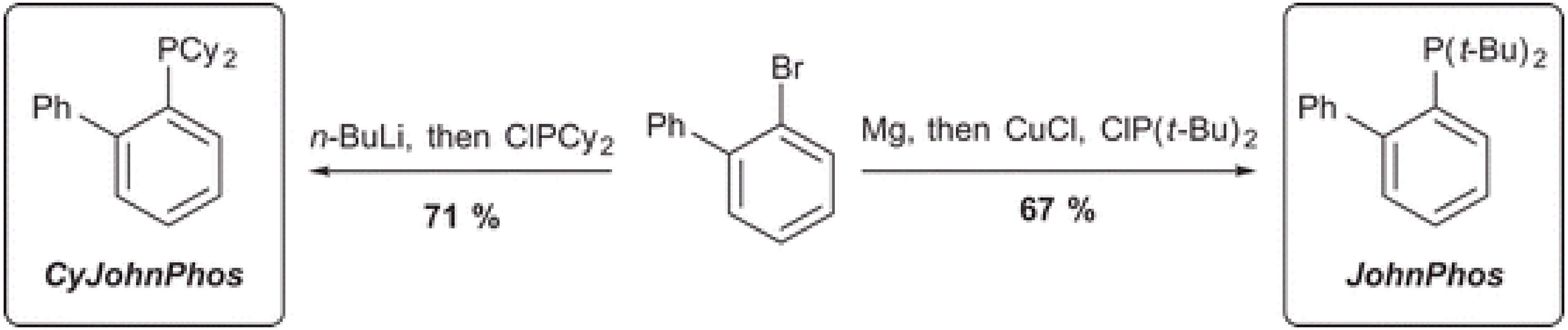
PPF-OMe

Promising results of amination of aryl chlorides using these ligands

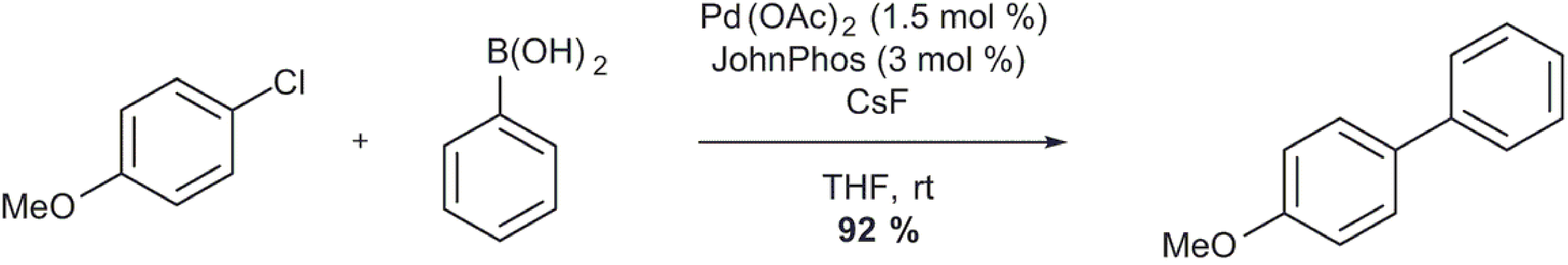
First version: DavePhos



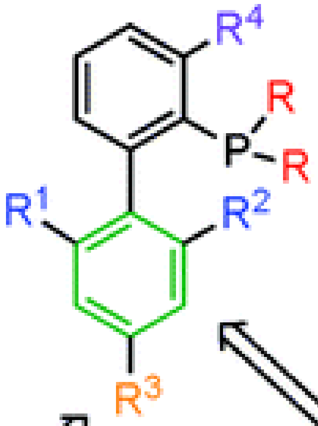
Next version: Amino group of DavePhos no longer needed



Room Temperature SMC of Aryl Chlorides



- Substituent fixes conformation of R_2P over bottom ring, enhancing rate of reductive elimination



- Alkyl groups increase electron density at phosphorus, increasing rate of oxidative addition

- Increased size of R enhances rate of reductive elimination

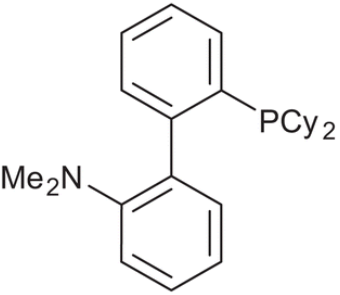
- Larger R increases $[L_1Pd(0)]$. R= Cy usually better for than R= tBu for high turnover number.

- $R^1,R^2 \neq H$ prevents cyclometallation, increasing stability

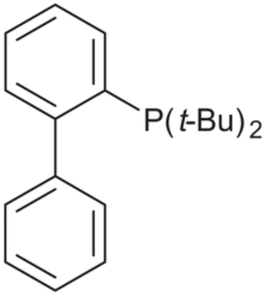
- R^1,R^2= large group (e.g., isopropyl) increases $[L_1Pd(0)]$

- $R \neq H$, usually only for ease of synthesis (e.g., XPhos)

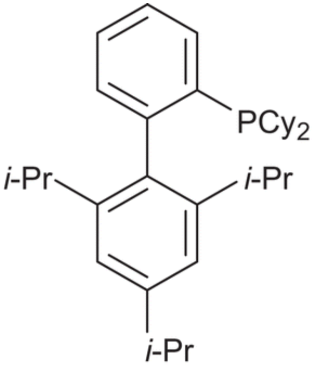
Lower aryl ring:
- Increases size of ligand, slowing rate of oxidation by O_2
- Allows stabilizing Pd-arene interactions
- Promotes reductive elimination



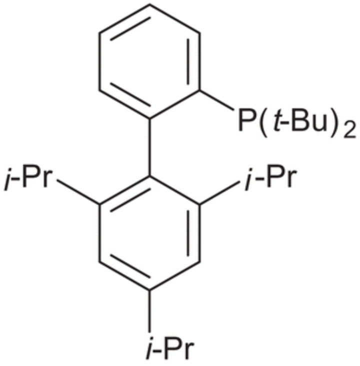
DavePhos



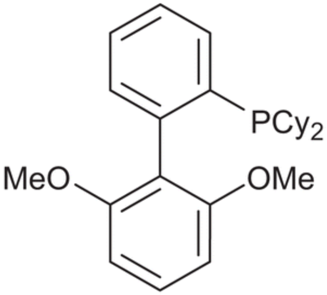
JohnPhos



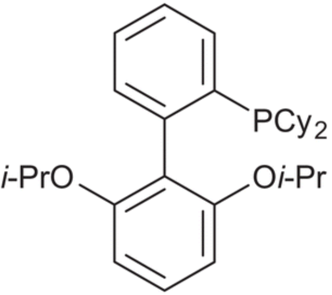
XPhos



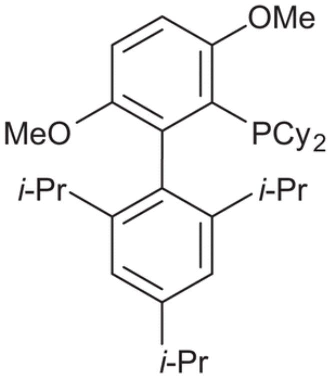
***t*BuXPhos**



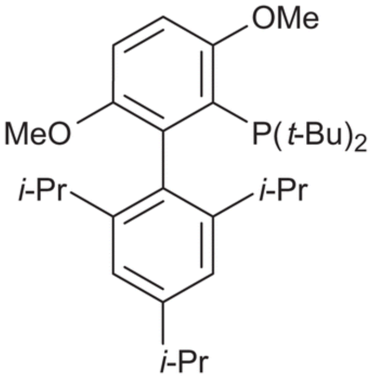
SPhos



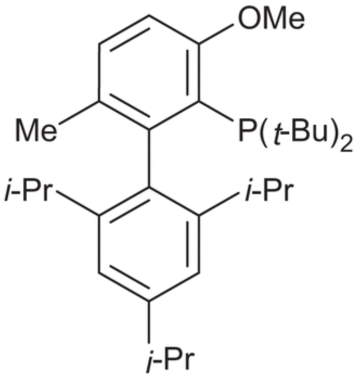
RuPhos



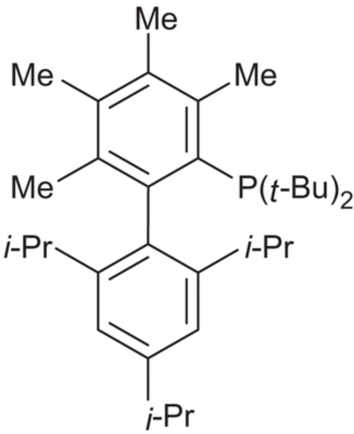
BrettPhos



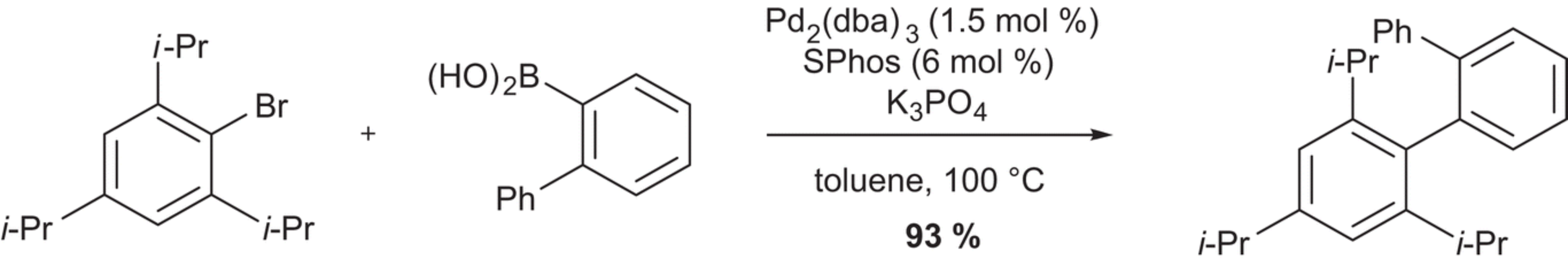
***t*BuBrettPhos**

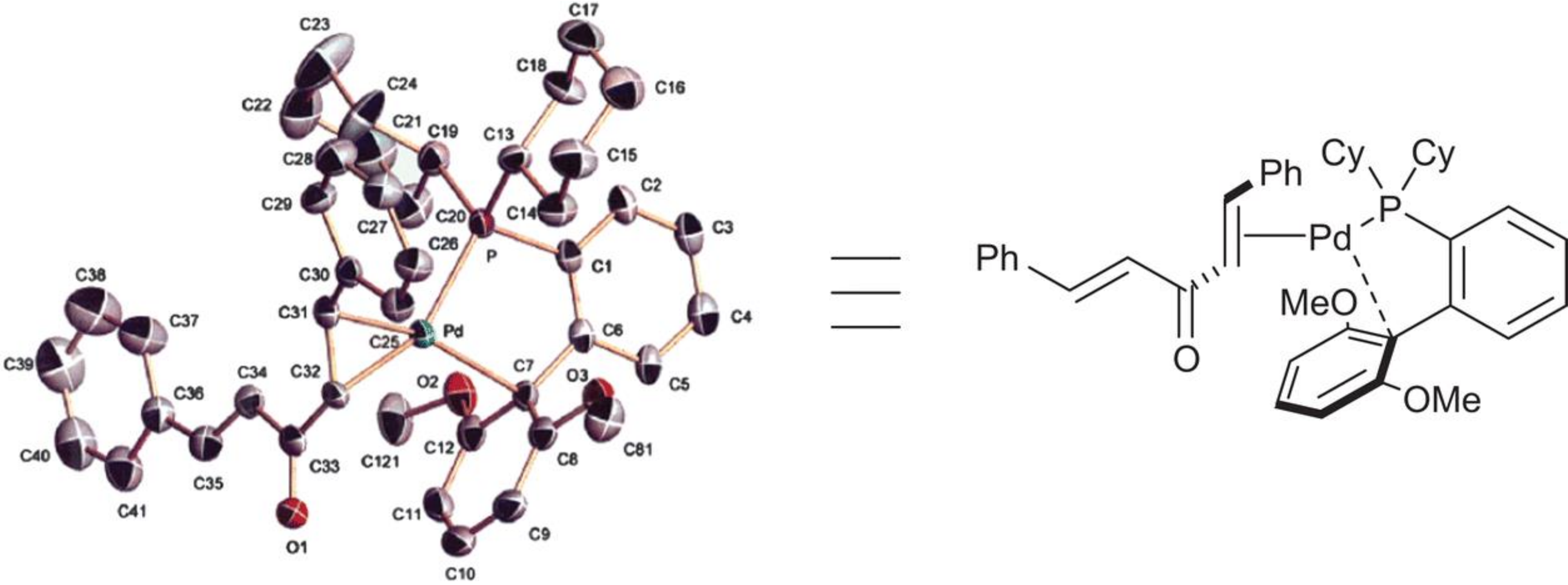


RockPhos

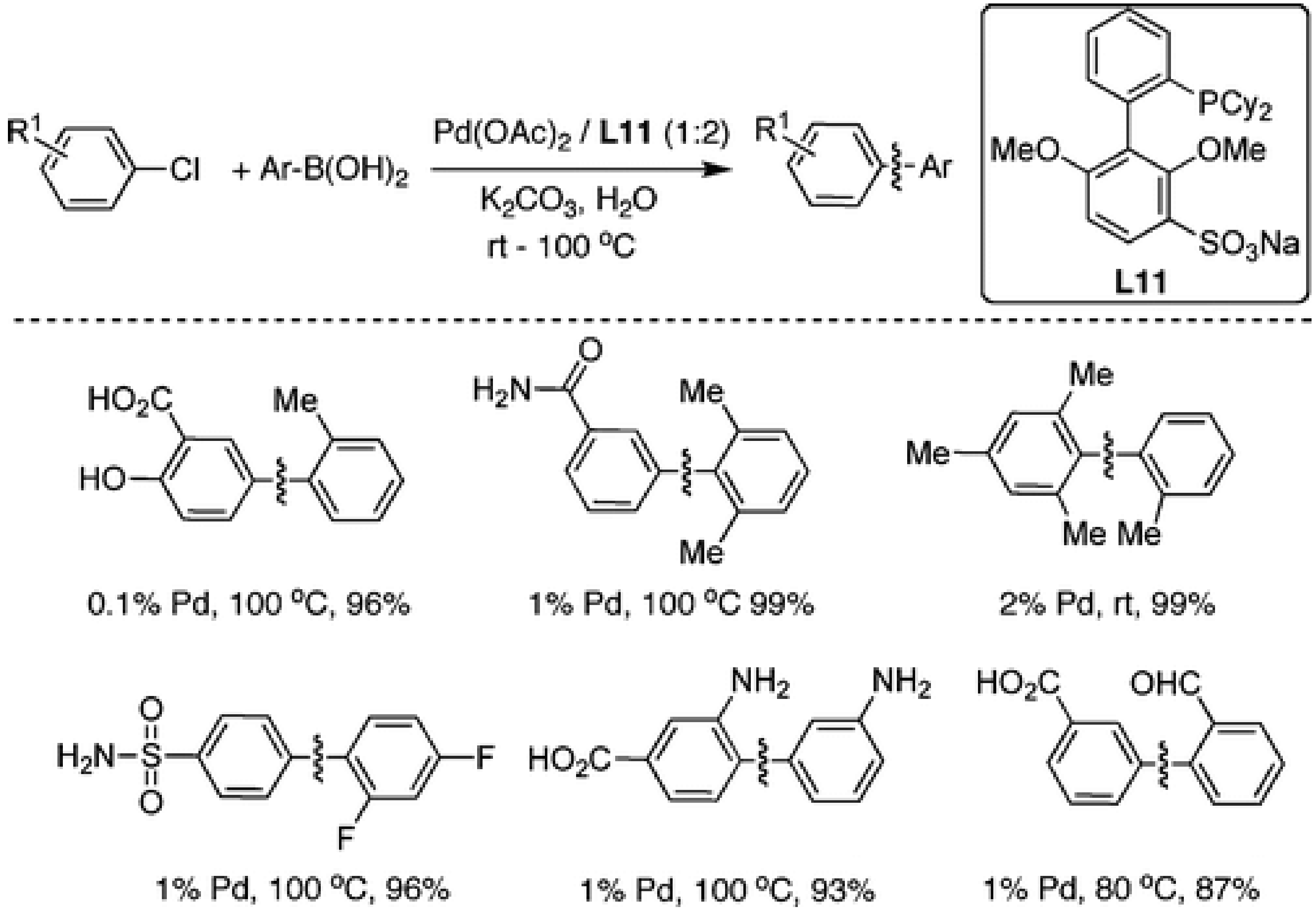


Me$_4$*t*BuXPhos


i-Pr
Br
i-Pr
i-Pr
+
(HO)2B
Ph
Pd2(dba)3 (1.5 mol %)
SPhos (6 mol %)
K3PO4
toluene, 100 °C
93 %
Ph
i-Pr
i-Pr
i-Pr


C23
C17
C18
C24
C16
C22
C21
C19
C13
C15
C28
C2
C29
C20
C14
C27
C3
C26
P
C1
C38
C30
C31
C4
C37
Pd
C6
C25
C39
C34
C32
C7
O2
O3
C5
C36
C40
C12
C8
C81
C33
C121
C35
C41
C11
C9
O1
C10
Ph
Cy
Cy
Ph
Pd
P
MeO
O
OMe

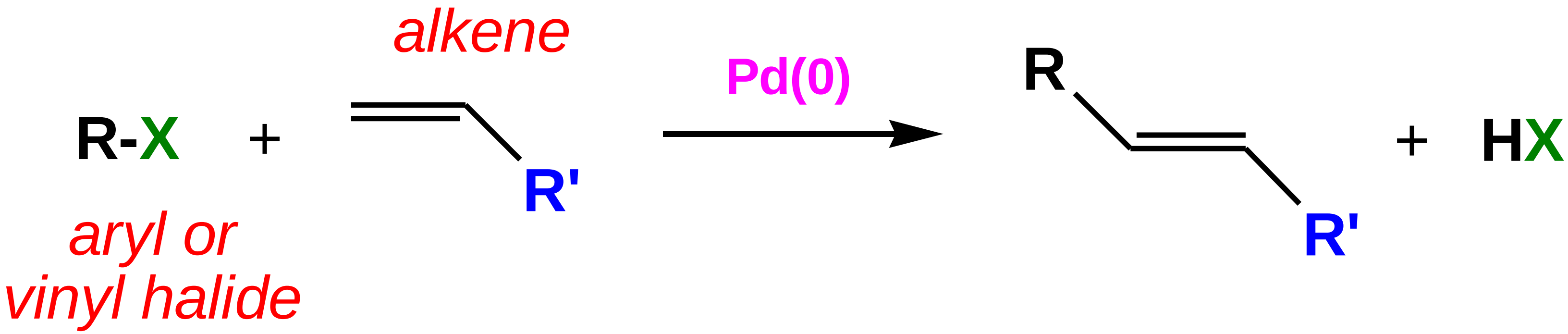
Reaction in water using a water soluble derivative

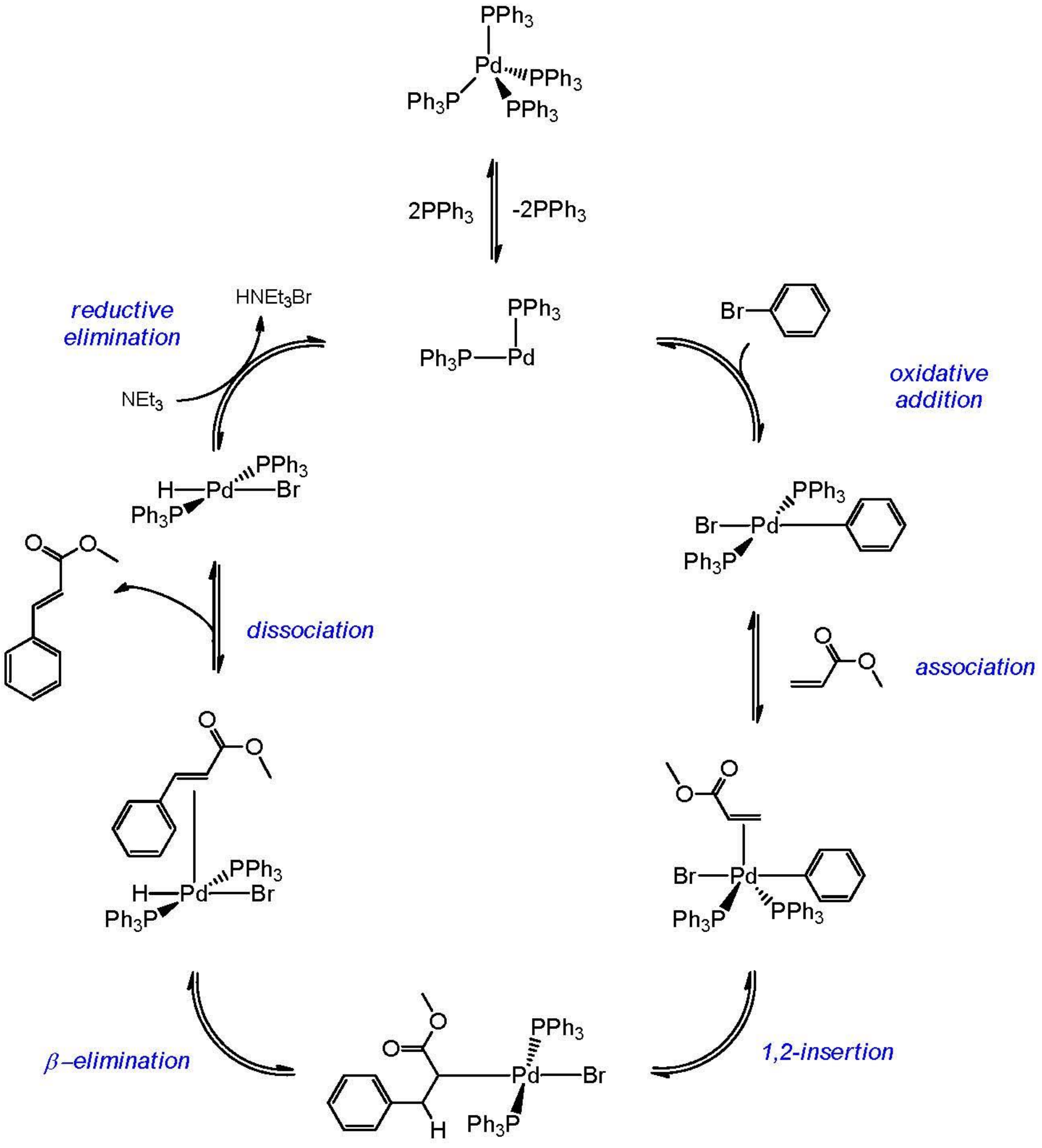


As indicated, the outstanding activity of the catalysts derived from the biarylphosphine ligands has been attributed to a combination of electronic and steric properties that enhances the rates of oxidative addition, transmetalation, and reductive elimination steps in the catalytic cycle. This can be rationalized as follows: (a) The bulky and electron-donating character of these ligands is important for stabilizing the monoligated L_1Pd intermediates, which are believed to be key species in the catalytic cycle. (b) With both these and related ligands it has been shown that oxidative addition of aryl halides is much faster with $L_1Pd(0)$ species than with more highly coordinated complexes. This is simply due to the smaller size of a $L_1Pd(0)$ complex compared with a $L_2Pd(0)$ one, allowing the substrate to approach the latter more closely and, hence, react at a faster rate. We presume that transmetalation to a $L_1Pd(Ar)X$ intermediate is faster, in general, than to a $L_2Pd(Ar)X$ complex for related reasons. (c) It is well-documented that the rate of reductive elimination from LPd(Ar)R (R = aryl, NR_2, OR) is faster than that for the same process for an analogous $L_2Pd(Ar)R$ complex. (d) Finally, studies in our laboratories have demonstrated that the addition of *ortho* substituents on the bottom ring of the biarylphosphine (eg., SPhos (**L7**) and XPhos (**L8**)) lead to a significant increase in activity and stability by preventing palladacycle formation. Additionally, this *ortho*, *ortho'* substitution increases the size of the ligand relative to those with no *ortho* substituents (thus increasing the concentration of L_1Pd species).

V. Heck coupling and its selectivity

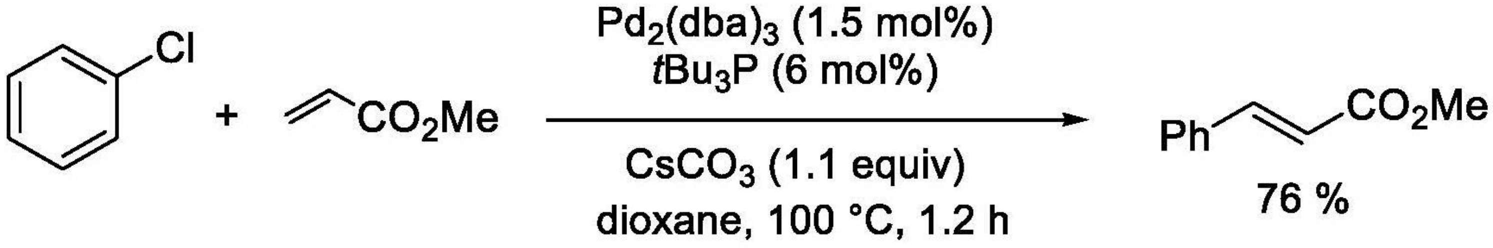
Heck reaction: efficienct alkene synthesis



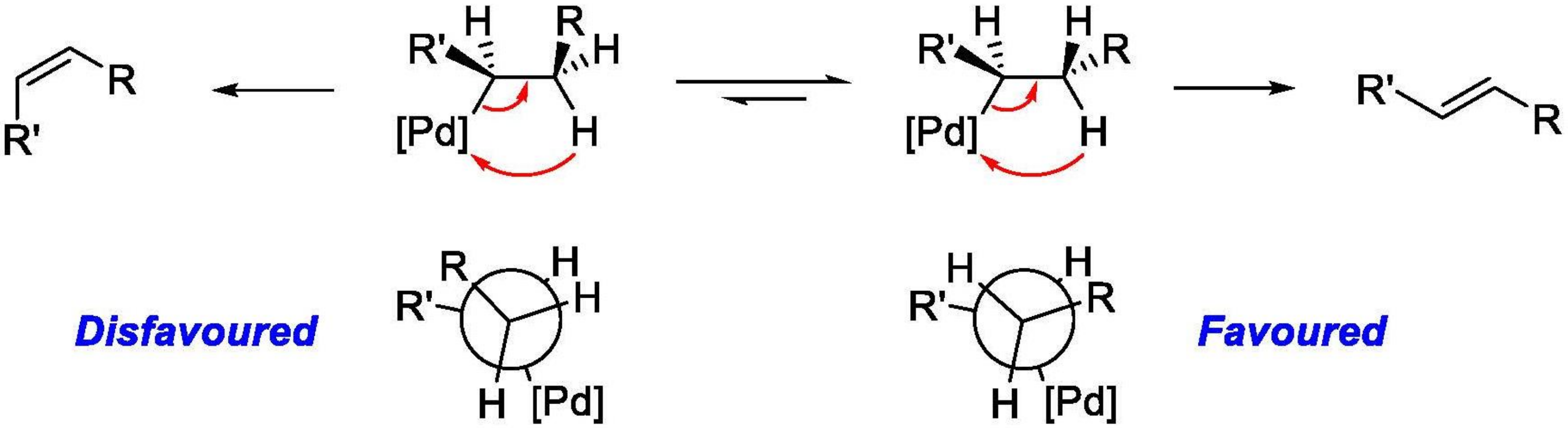


Regioselectivity controlled by 1,2-insertion

Trans-selectivity



G. C. Fu et al. J. Org. Chem. 1999, 64, 10.



I. Beletskaya et al. Chem. Rev. 2000, 100, 3009. (review)

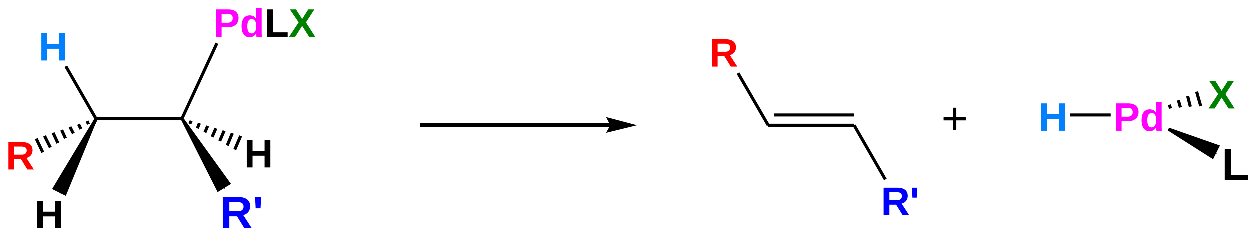
The rate of reaction and regioselectivity are sensitive to steric hindrance about the C=C bond of the vinylic partner. For simple aryl halides reacting with alkenes, the rate of reaction as a function of alkene substitution varies according to the following sequence:

	$\mathbf{CH_2{=}CH_2}$	>	$\mathbf{CH_2{=}CH\text{-}OAc}$	>	$\mathbf{CH_2{=}CH\text{-}Me}$	>	$\mathbf{CH_2{=}CH\text{-}Ph}$	>	$\mathbf{CH_2{=}C(Me)Ph}$
k_{rel}:	14,000		970		220		42		1

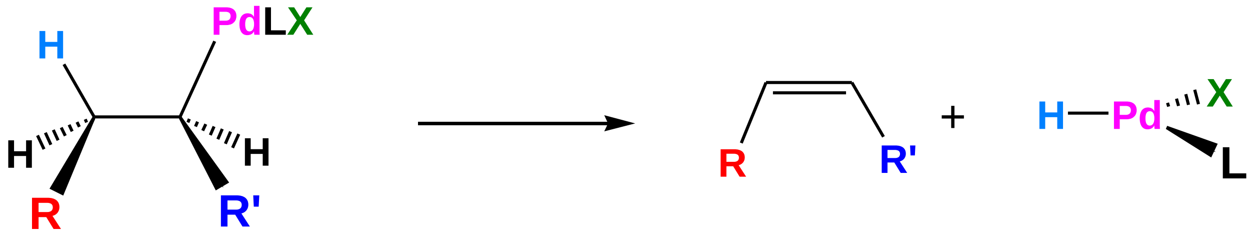
The Heck reaction differs significantly from the earlier Pd(0)-catalyzed cross-coupling reactions because:

1) **it involves an insertion after the oxidative addition step**
2) **the catalytic cycle is closed with a β-hydride elimination, whereas the other couplings end with a reductive elimination.**

In the β-hydride elimination step, the palladium and hydride must be coplanar for the reaction to take place, as this is a ***syn*** elimination process. For steric reasons, the **R** group will tend to eclipse the smallest group on the adjacent carbon as elimination occurs, leading predominantly to a *trans* double bond in the product.



major product



minor product