

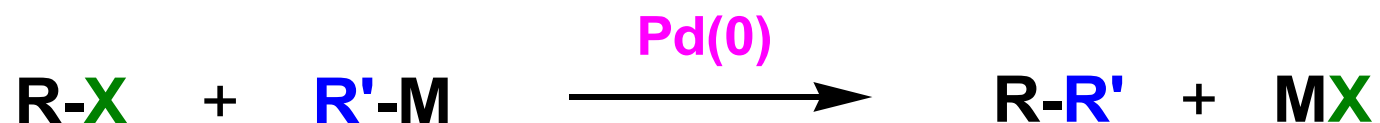
Cross-coupling reactions

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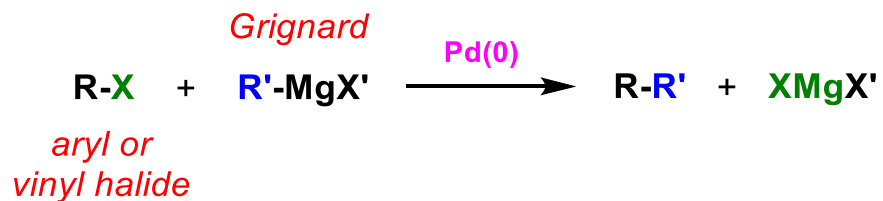
I. Different type of cross-coupling reactions and general mechanism

Cross-Coupling of Organometallics and Organic Halides

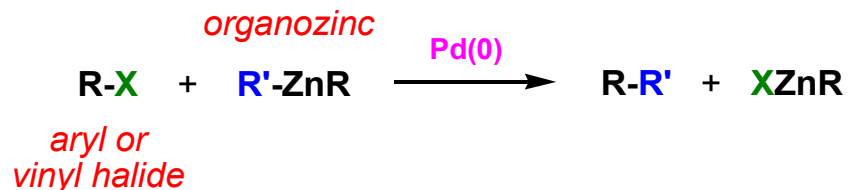


$\text{M} = \text{MgX}, \text{ZrCp}_2\text{Cl}, \text{ZnX}, \text{SnR}_3, \text{B(OR)}_2, \text{AlMe}_2, \text{SiR}_3, \text{Cu}, \dots$

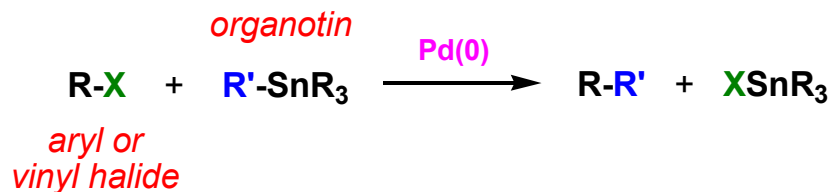
Kumada coupling:



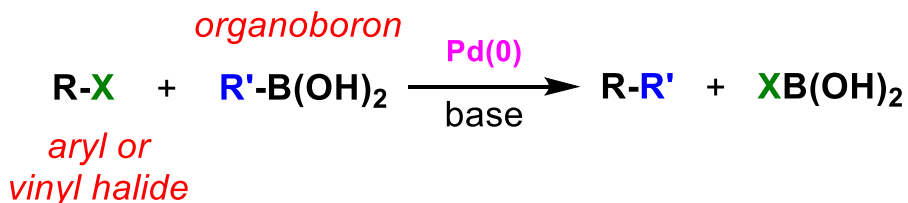
Negishi coupling:



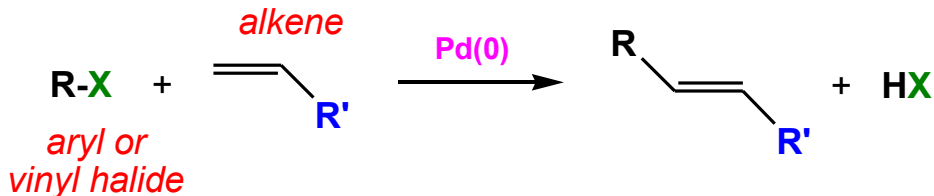
Stille coupling:



Suzuki coupling:

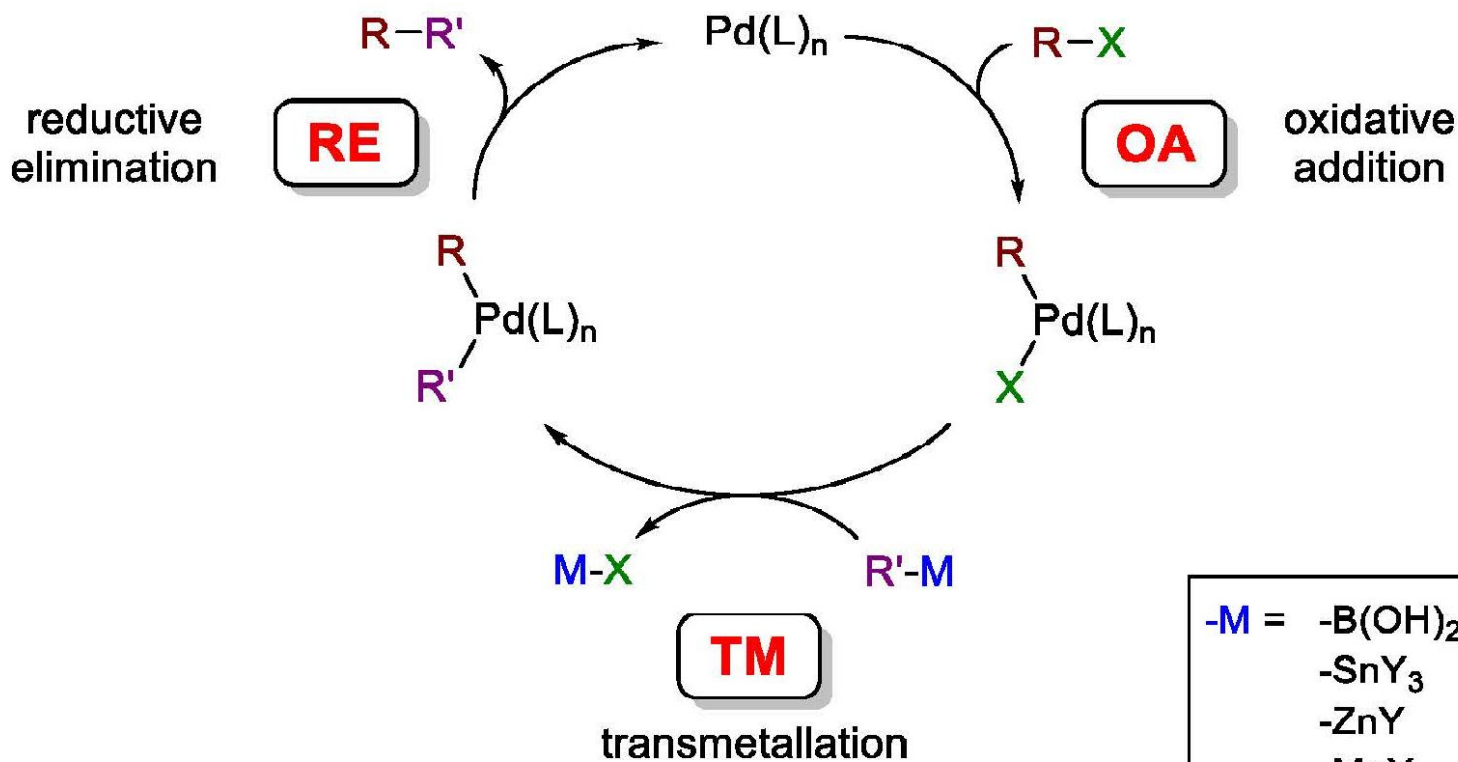


Heck reaction:



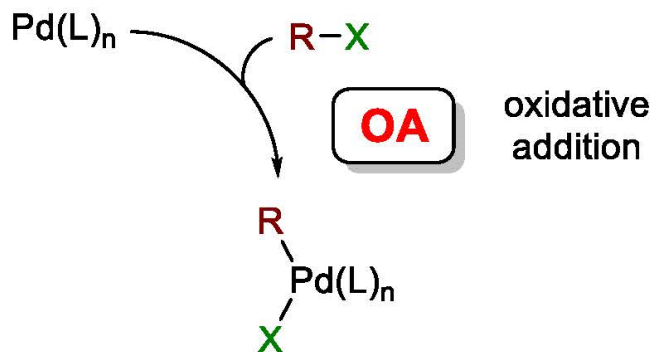
Name reactions according to nucleophiles

General mechanism – except for Heck reaction

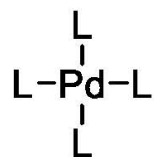


I >> Br > OTf > Cl

Why?



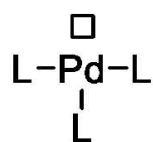
Very slow



18 e[⊖]



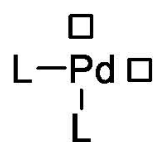
Slow



16 e[⊖]



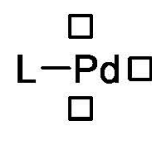
Fast



14 e[⊖]



Fast



12 e[⊖]



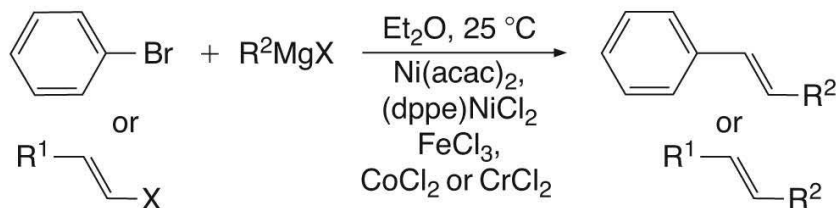
Very slow

Pd black

II. Kumada coupling and its mechanism

Kumada Coupling

- In 1972 Kumada and Corriu independently reported the 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).

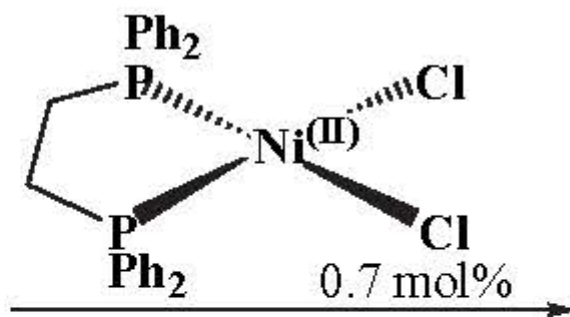
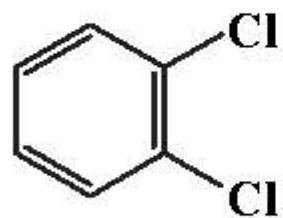


- The reaction is limited to however to halide partners that do not react with organomagnesium compounds. One example is in the industrial-scale production of styrene derivatives, and the Kumada Coupling is the method of choice for the low-cost synthesis of unsymmetrical biaryls.
- The advantage of this 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:

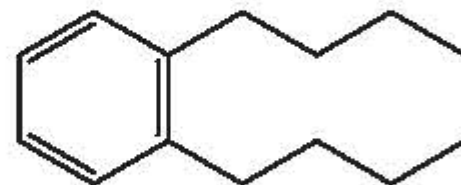
First use of phosphine ligands

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

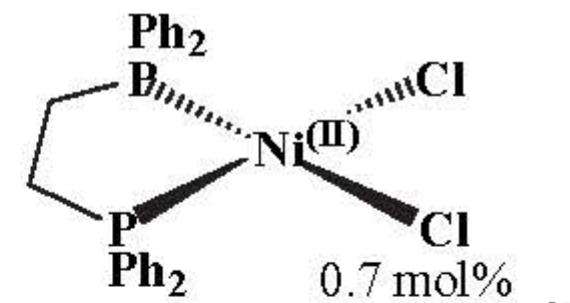
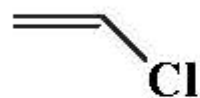


n-BuMgBr (2 eq)

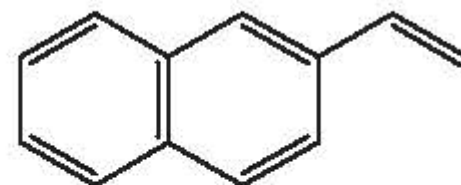
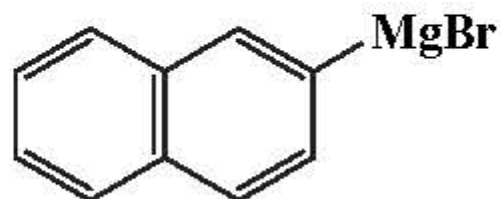
0.7 mol%



94%



0.7 mol%



80%

Kumada *JACS* 1972 (94) 4374.

Exercise:

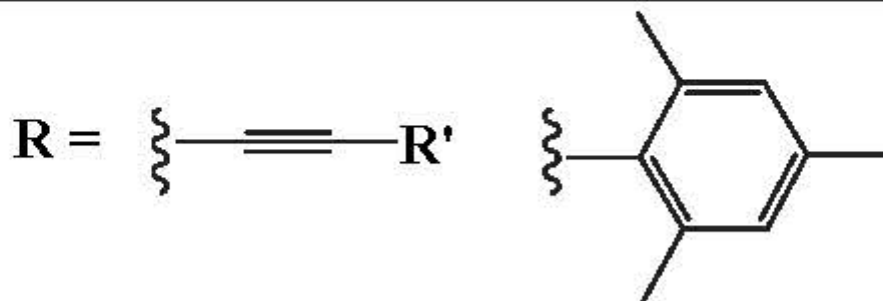
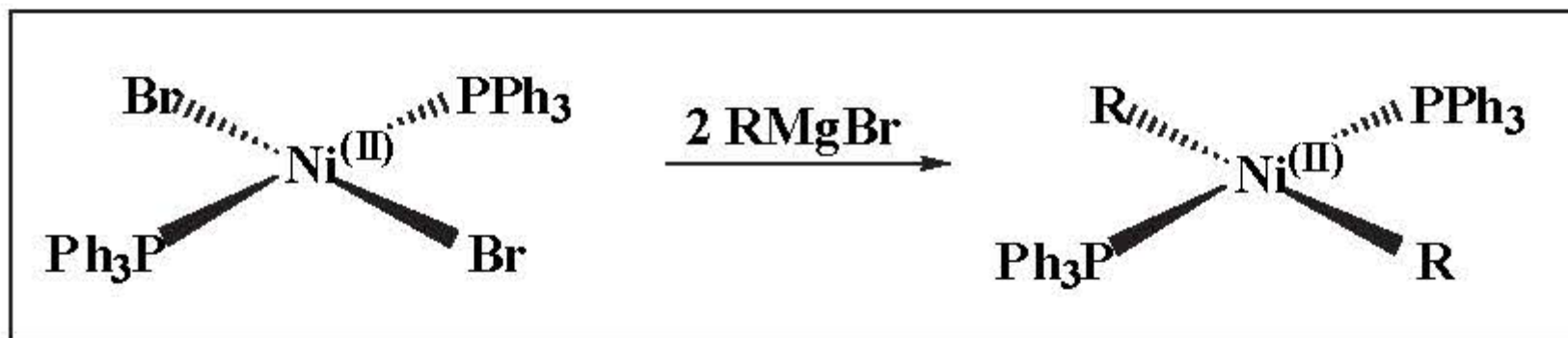
For a Ni-catalyzed Kumada coupling, a Ni(0) active species was identified. This species was generated from NiCl₂.

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.

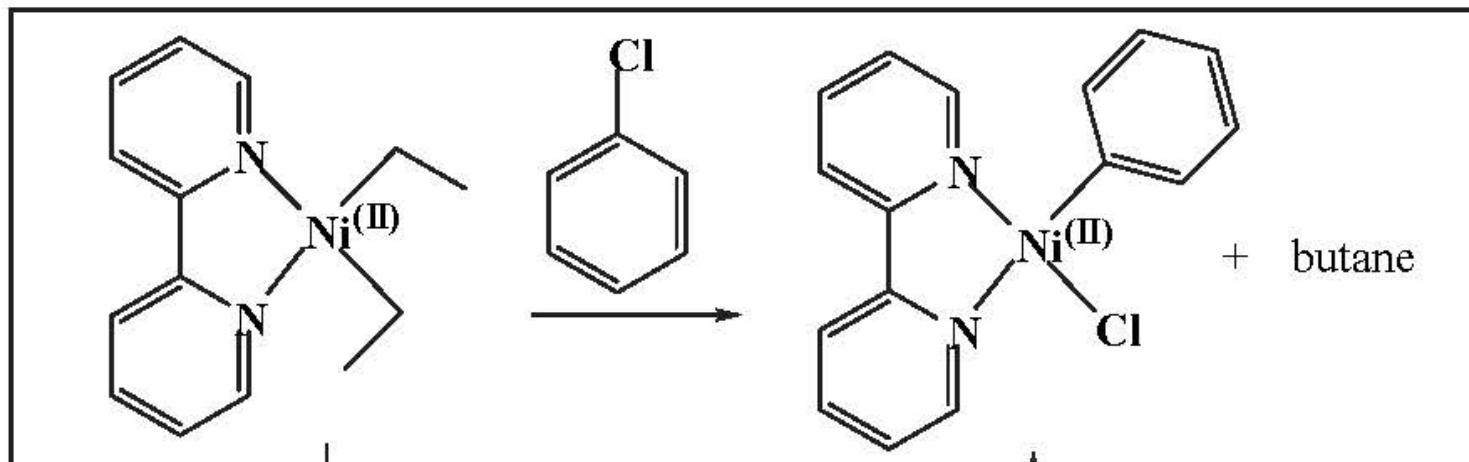
All the pieces of the catalytic cycle were in the literature...

Transmetalation: Chatt and Shaw J. Chem. Soc. 1960 1718.

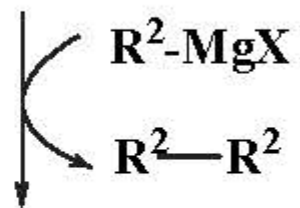
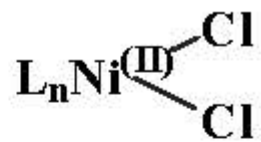
Report the synthesis of alkyl and aryl nickel(II) complexes from the corresponding nickel(II) halides.



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



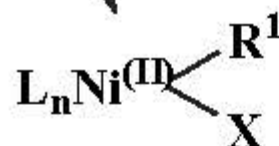
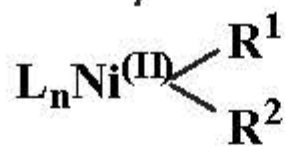
$\text{R}^2 = \text{aryl, vinyl, alkyl}$

$\text{R}^1 = \text{aryl, vinyl}$
 $\text{X} = \text{Cl} > \text{Br} > \text{I}$

$\text{R}^1\text{-R}^2$
reductive elimination

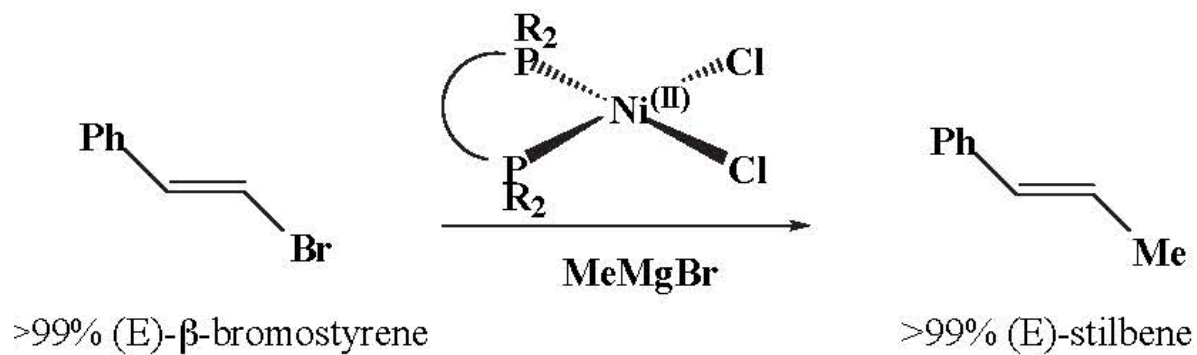
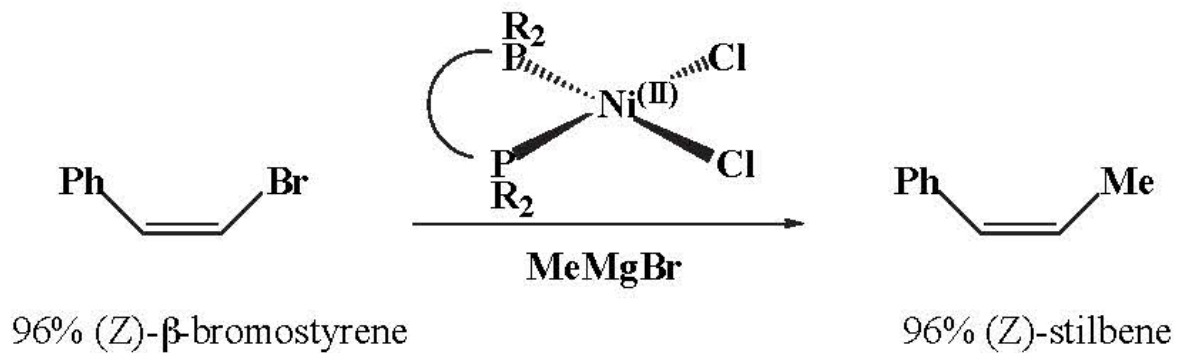


$\text{R}^1\text{-X}$
oxidative addition

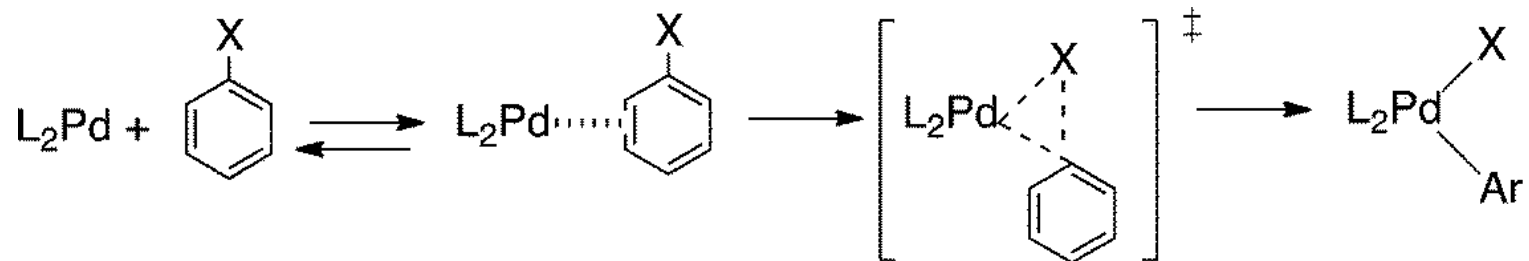


transmetalation

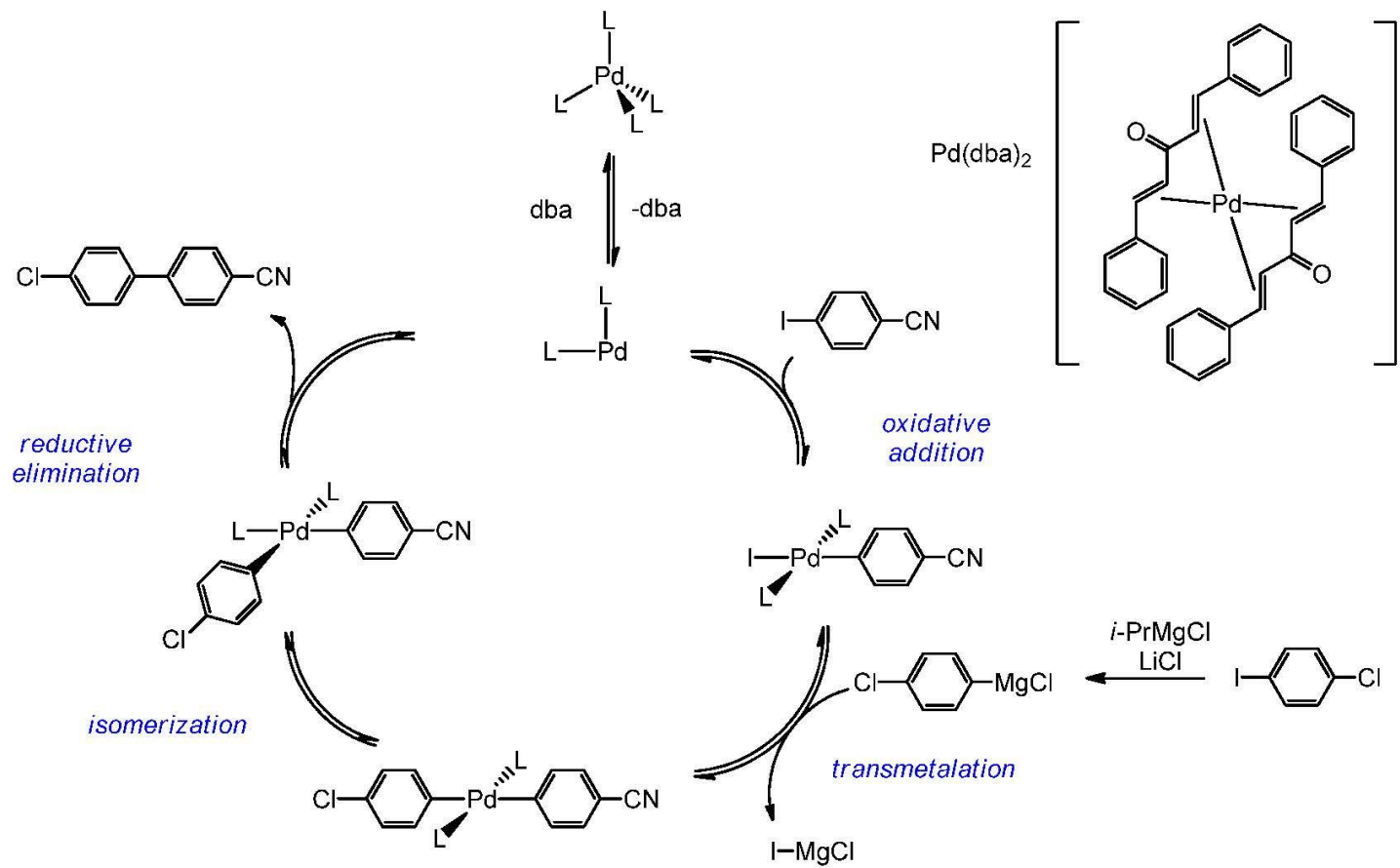
Stereospecific coupling:



Concerted oxidative addition of aryl and vinyl halides



Mechanism.



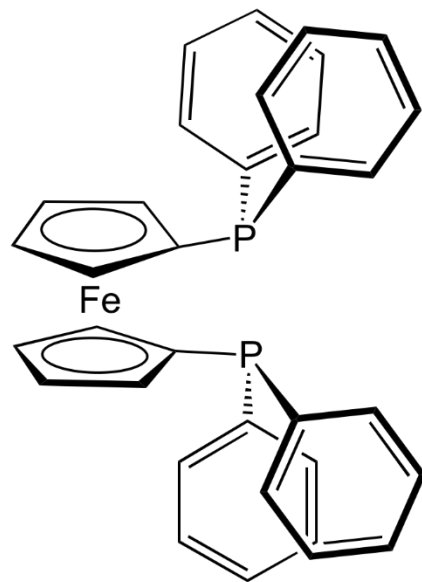
For this Kumada coupling reaction, the following product distributions were obtained using two different ligands, PPh_3 ($n = 2$) and a chelating ligand dppf.

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.

$L = \text{PPh}_3$	$R = \text{Ph}$	4	6	6	31
	$R = \text{Ph}-\text{CH}=\text{CH}-\text{wavy}$	33	36	4	—
$L = \text{dppf}$	$R = \text{Ph}$	95	0	—	0
	$R = \text{Ph}-\text{CH}=\text{CH}-\text{wavy}$	93	0	—	0

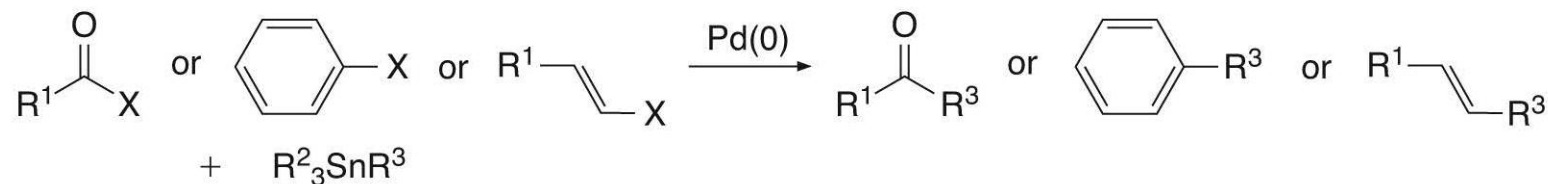
dppf



III. Mechanistic insights from Stille Coupling

Stille Coupling

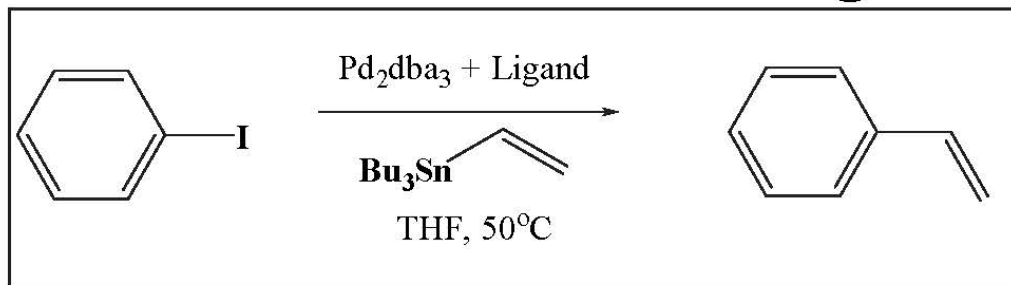
The Stille Coupling is a versatile C-C bond forming reaction between **stannanes** and **halides** or **pseudohalides**, with very few limitations on the R-groups.



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)$_3\text{P}$	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-furyl)$_3$P	6×10^{-3}	105
AsPh$_3$	0.86	1100

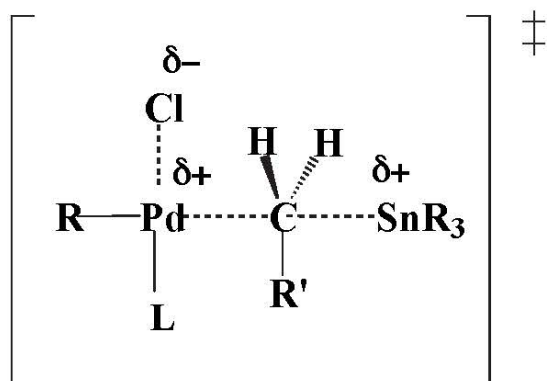
Less Electron-donating ligand leads to faster rate.

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

Oxidative addition; transmetallation; reductive elimination

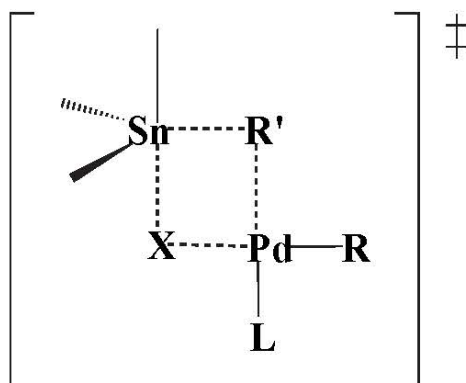
Stille: Mechanism of Pd/Sn Transmetalation

S_E2 (open)



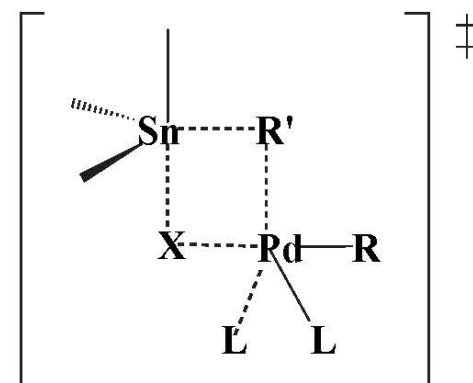
favored in highly polar
and/or nucleophilic solvents

S_E2 (cyclic)



favored in non-polar solvents

S_E2 (cyclic, pentacoordinate)



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

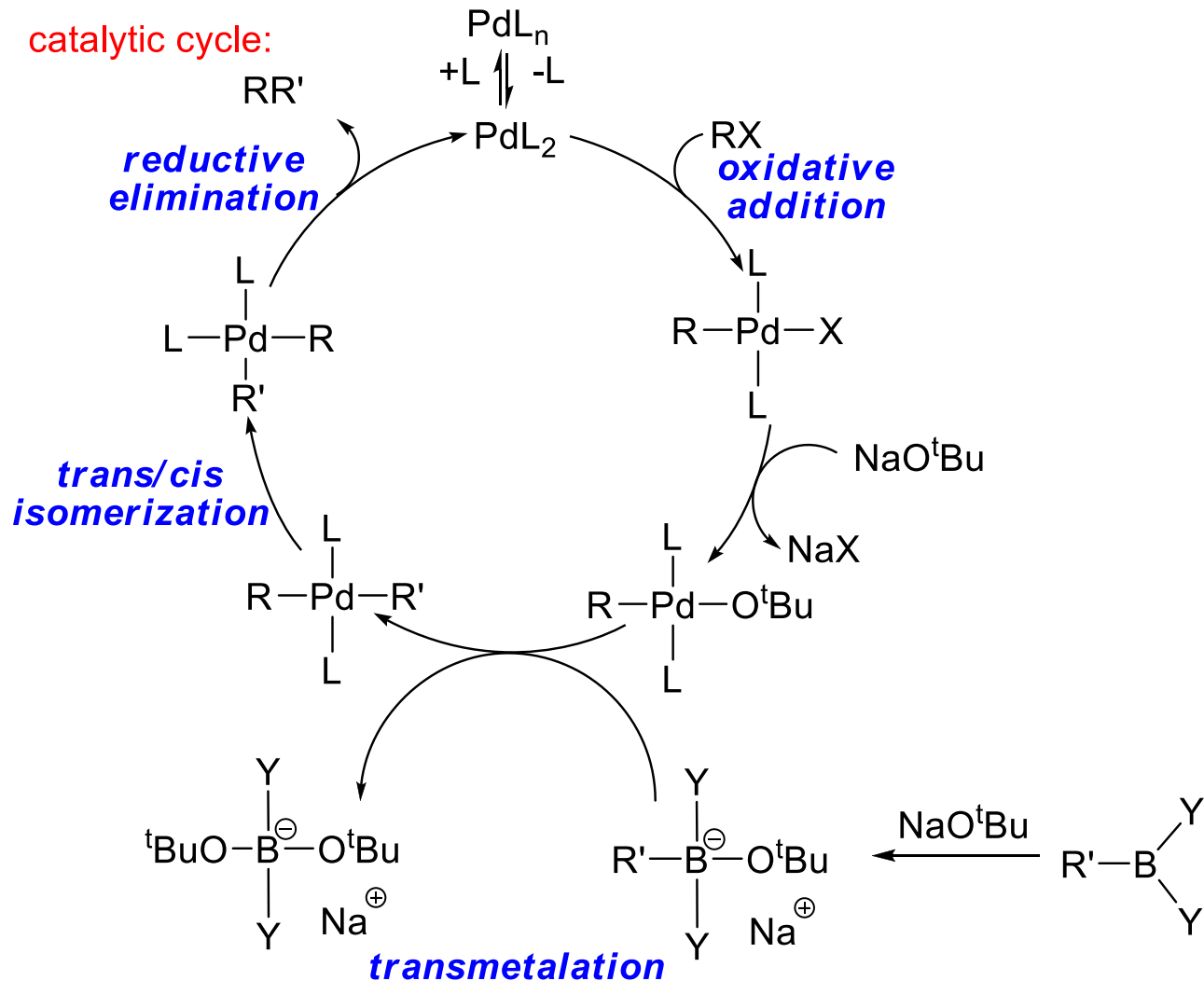
Suzuki (Suzuki-Miyaura) Coupling – one coupling to rule all



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-Miyaura Coupling

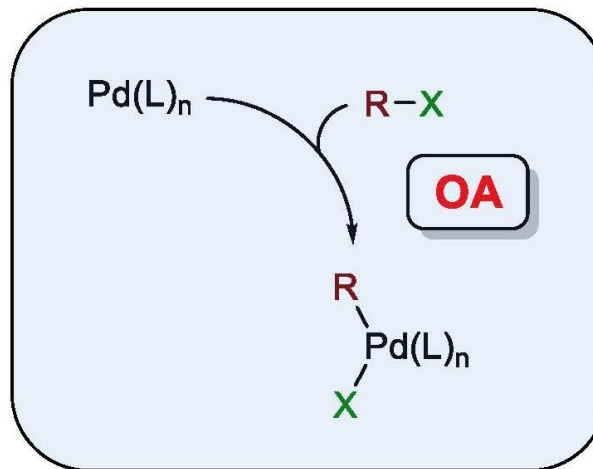
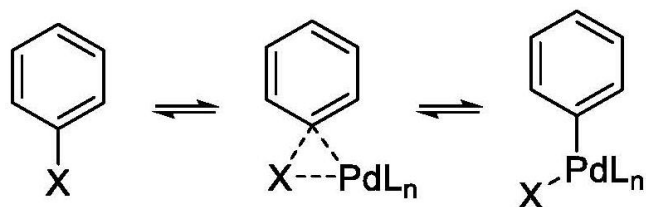


Transmetalation requires base: anionic boron reagents are more likely to transfer R' than the neutral ones.

Better Understanding of the Mechanism

Oxidative Addition

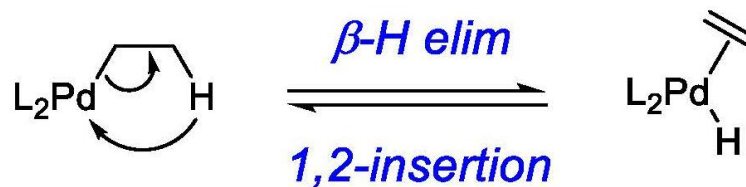
Csp³-X usually slow



Favoured by

Electronically Rich Ligands
Bulky Ligands

Can lead to β -H elimination



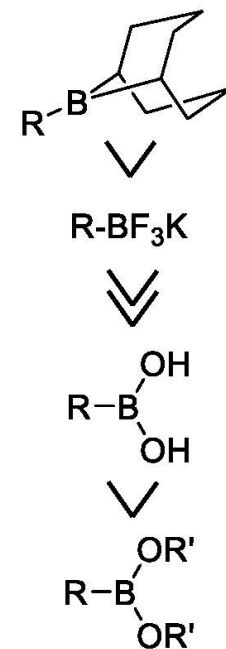
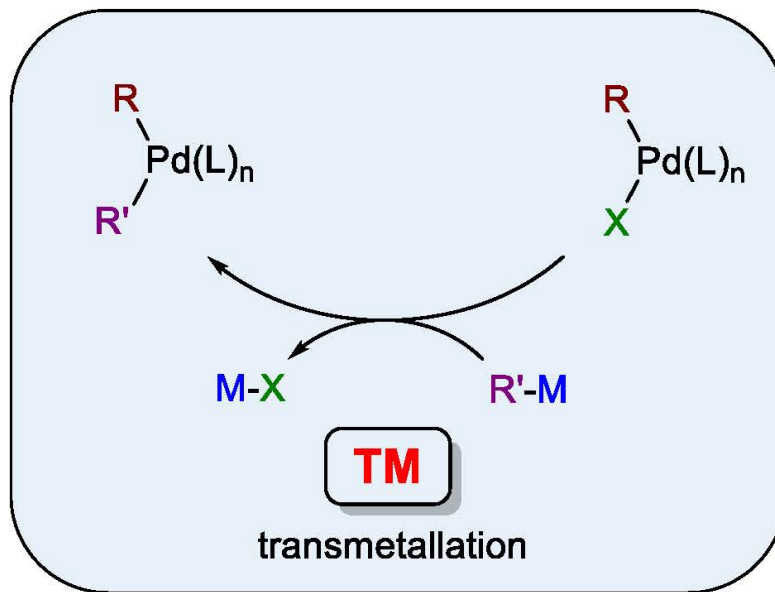
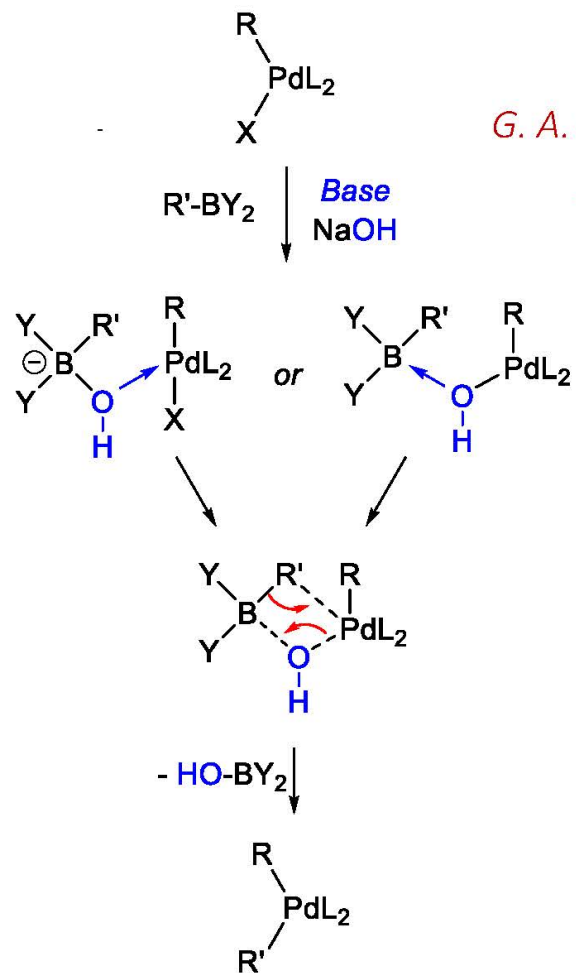
Better Understanding of the Mechanism

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

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

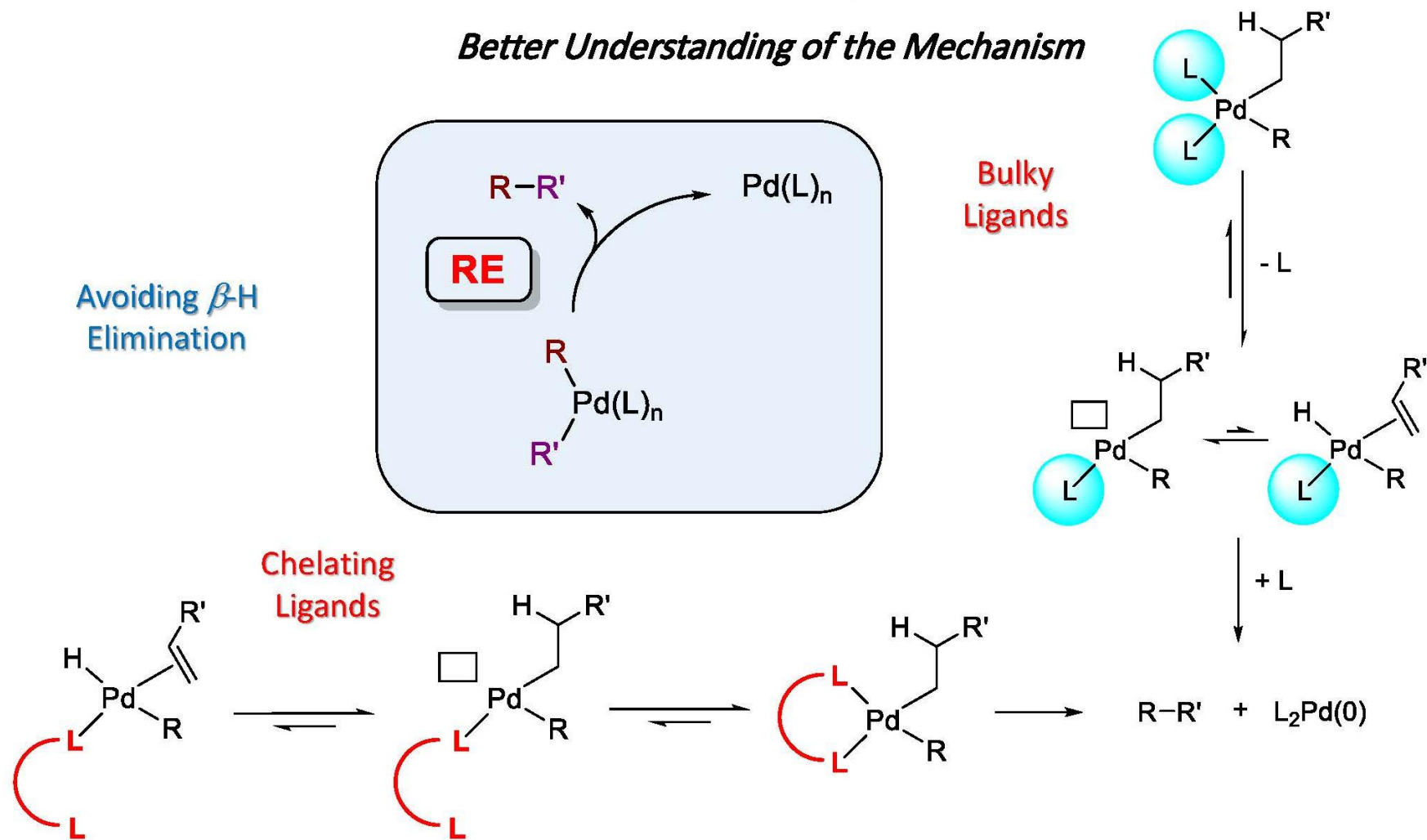
Y. Kishi *J. Am. Chem. Soc.* 1987, 109, 4756.

TM is accelerated by a base

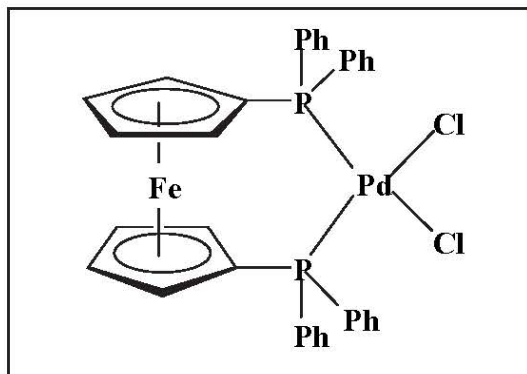


Suzuki-Miyaura Cross-Coupling Reactions

Better Understanding of the Mechanism



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



$PdCl_2(dppf)$ 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 reasons⁶⁷

What are these two reasons?

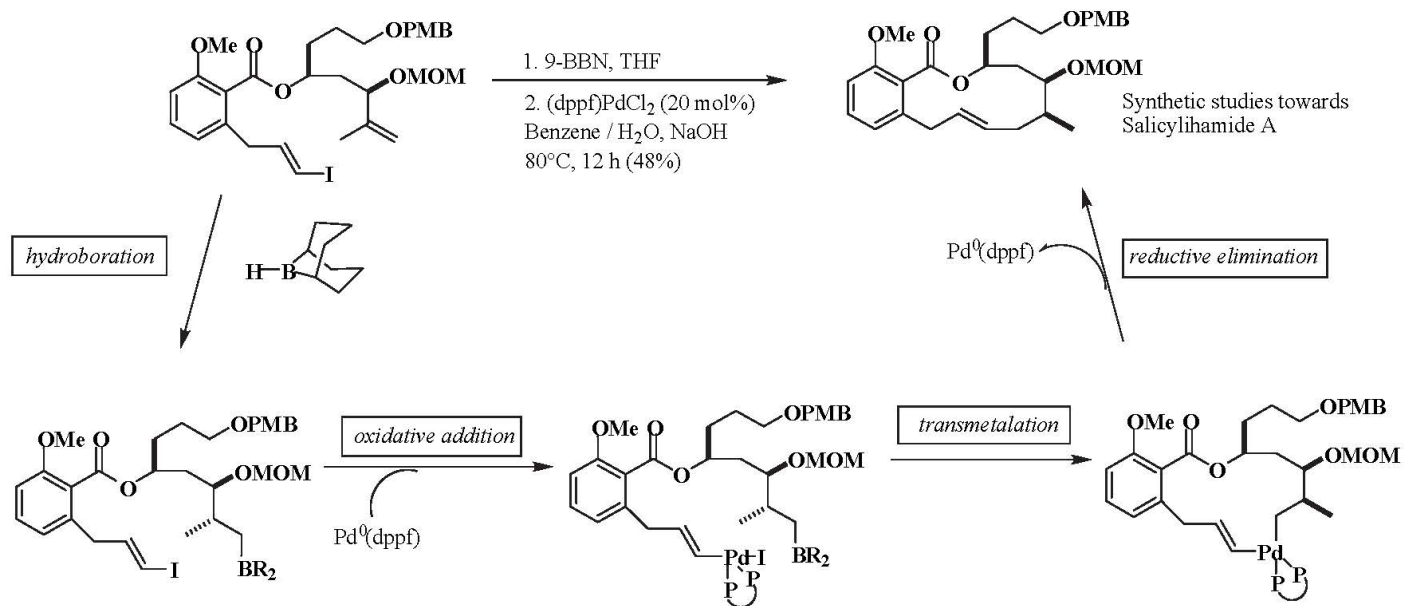
dppf, bis(diphenylphosphino)ferrocene

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



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.

"Fu Ligands"

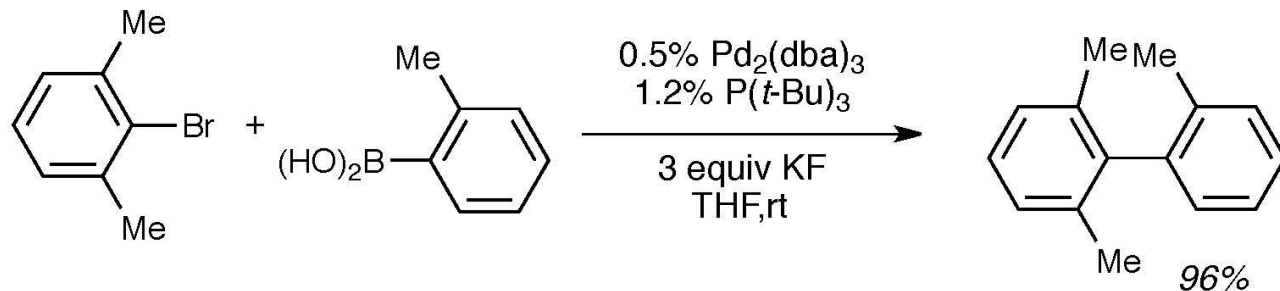
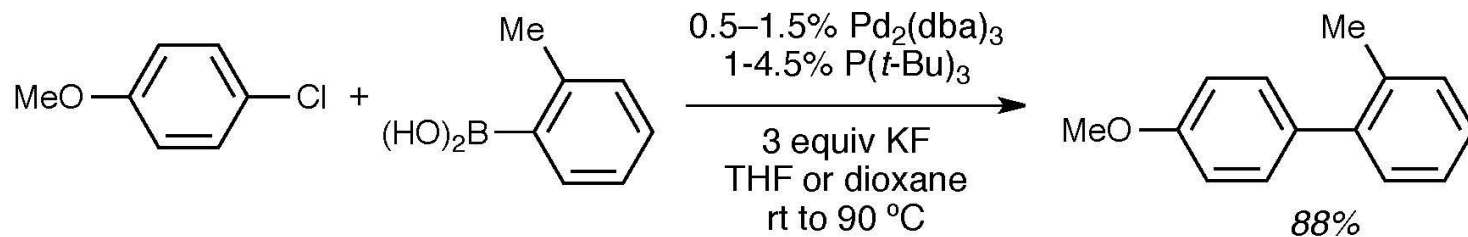
Acc. Chem. Res. 2008, 41, 1555.

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

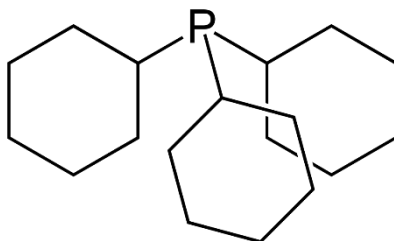
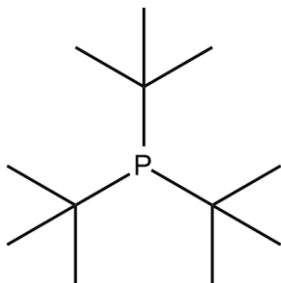
The reactivity of the halides is related to Ph-X bond strength (kcal/mol): Cl (95), Br (80), I (65)

The use of bulky and strongly electron donating ligands (i.e. P(*t*-Bu)₃, P(*t*-Bu)₂Me, PCy₃) has allowed cross-coupling of aryl chlorides.

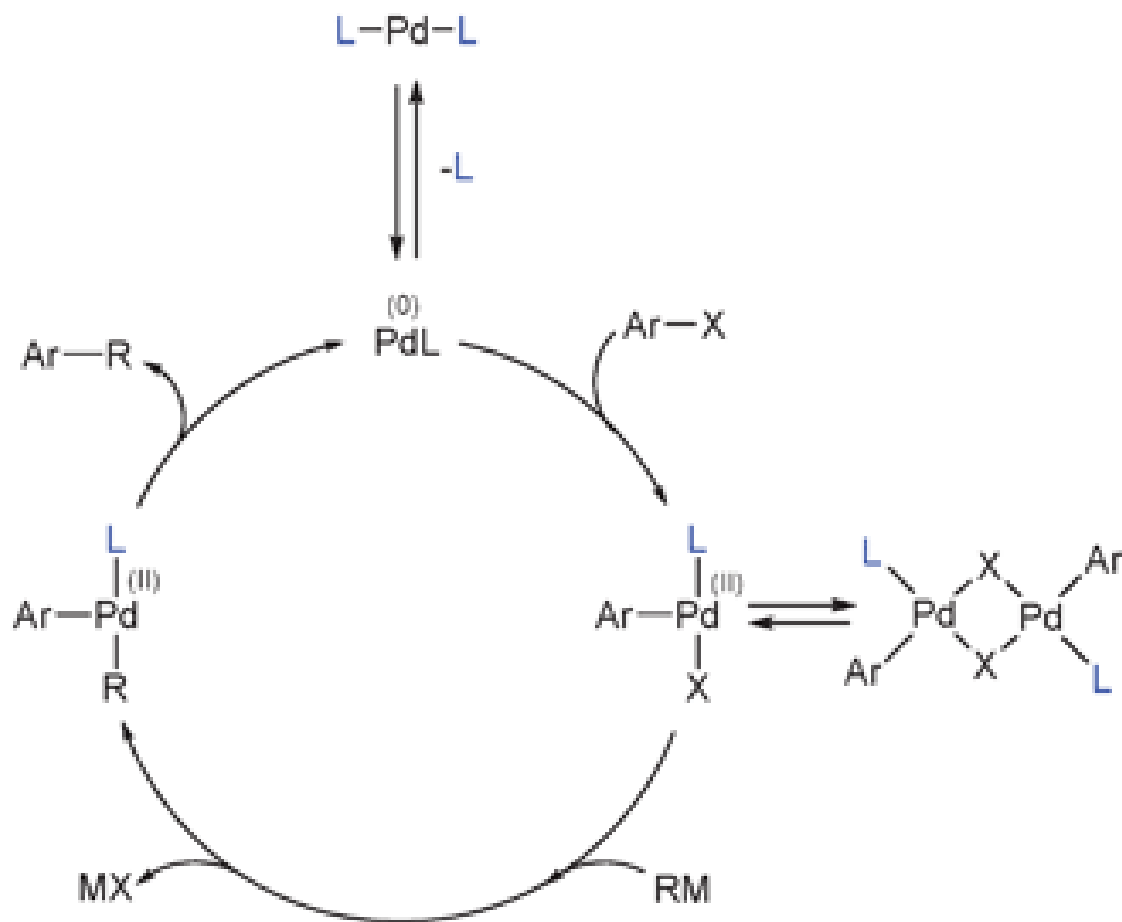
It is thought that these ligands speed up the rate of oxidative addition. Aryl chlorides usually still require heating, but bromides and iodide can undergo reaction at rt.



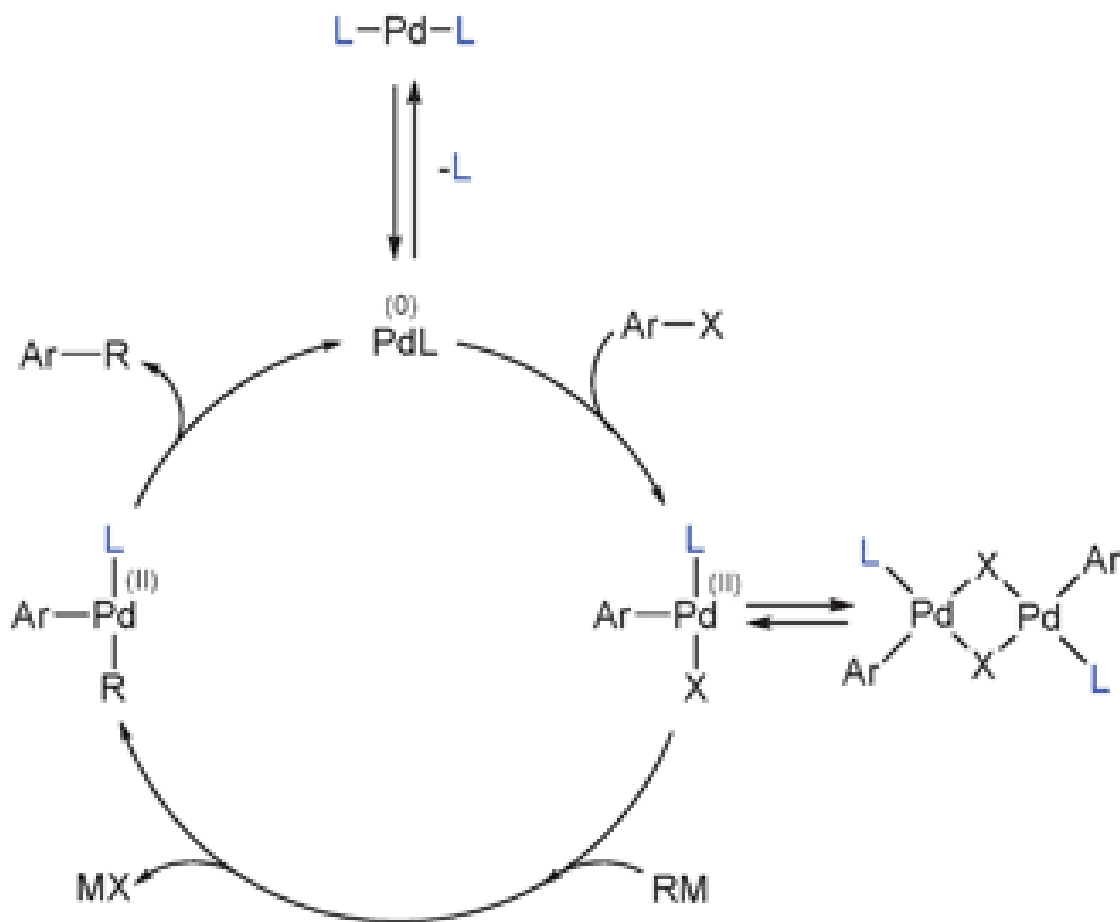
Active species: mono-ligated Pd-L due to a bulky ligand



Pd-PR₃

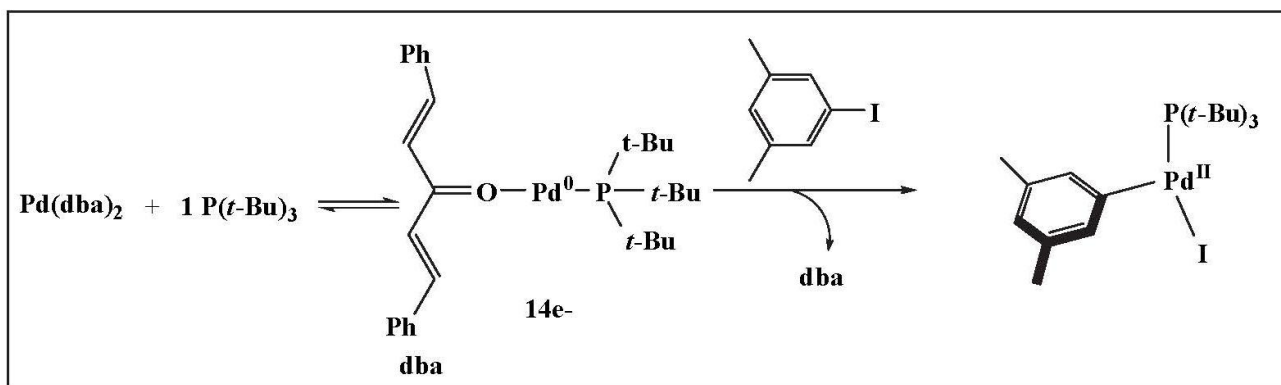
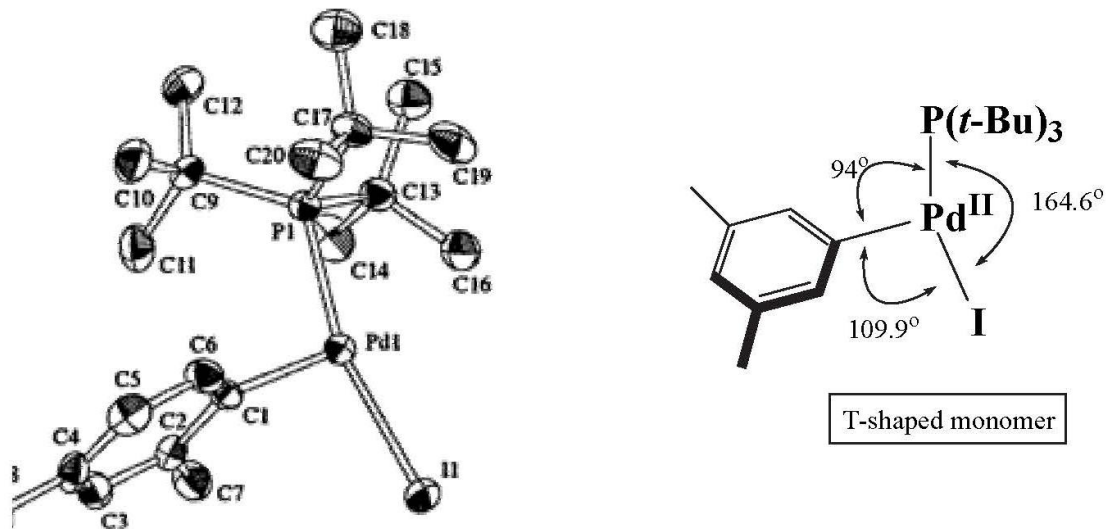


Mono-ligated Pd species more active for oxidative addition of Ar-Cl



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

Bulky, electron-rich phosphines



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?)

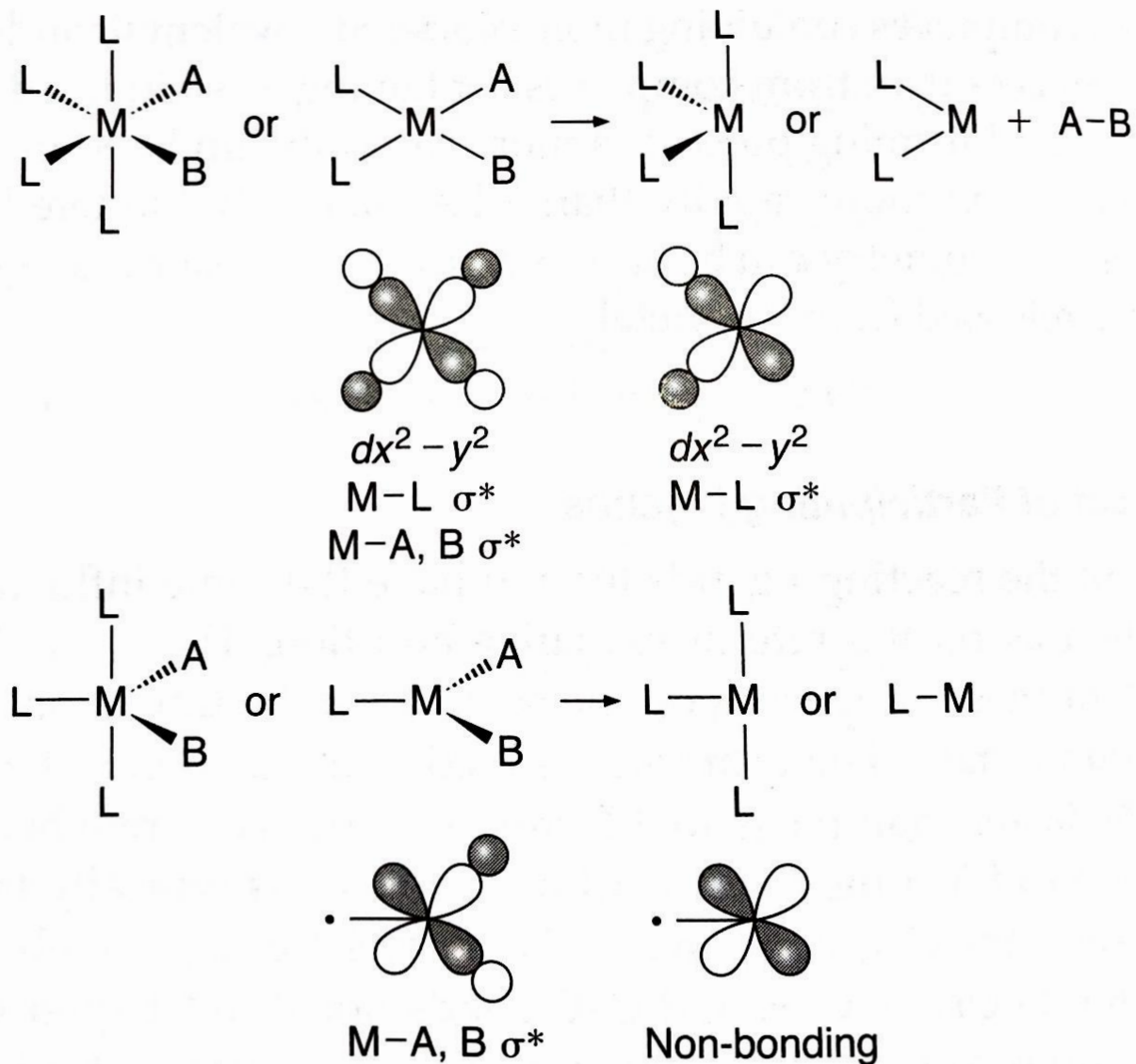


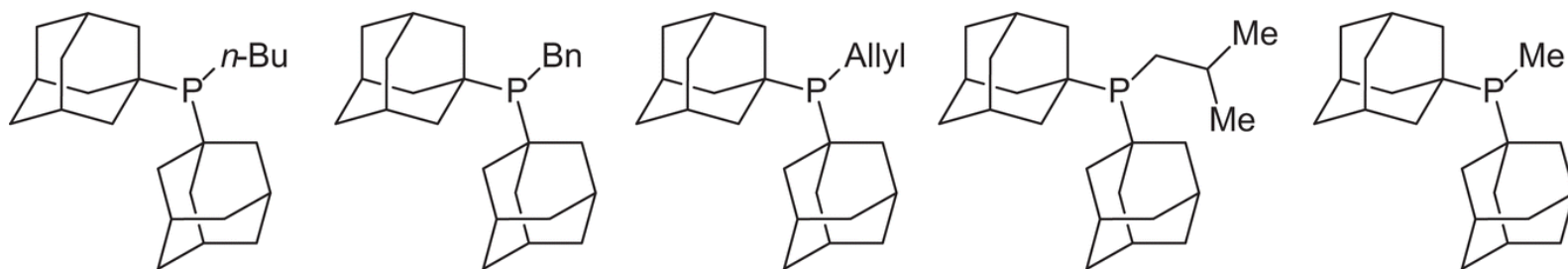
Figure 8.1.

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

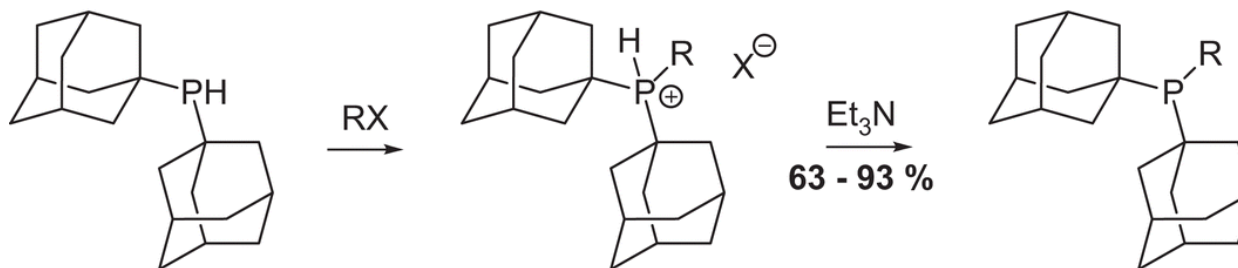
Ligands developed by Beller et al. Admantyl groups

Even higher bulk

Ad₂PR Ligands Reported by Beller:

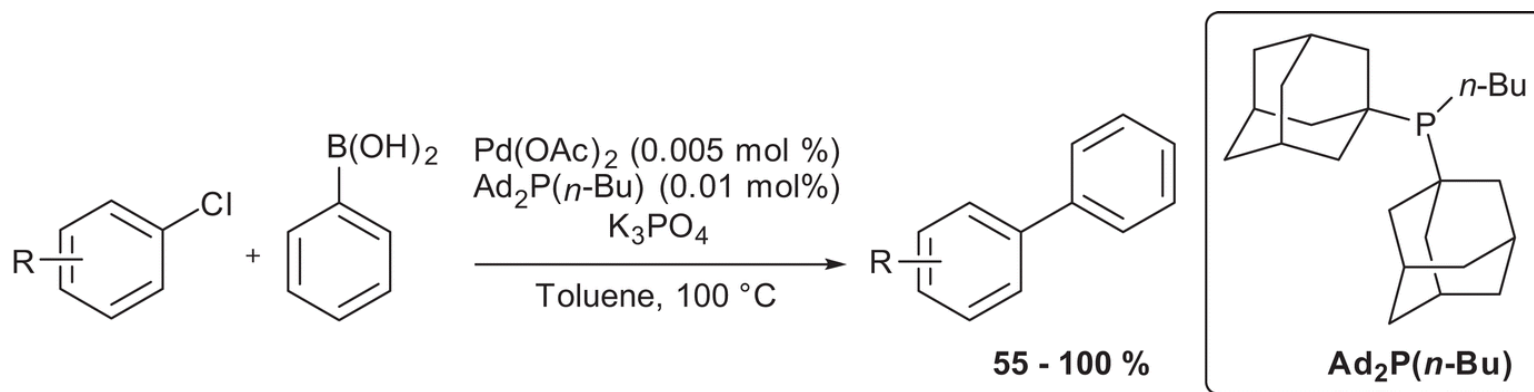


Synthesis of Ad₂PR Ligands:

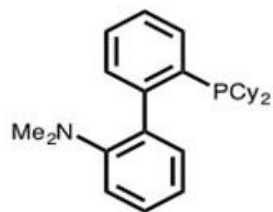
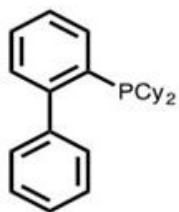


Ligands developed by Beller et al. Admantyl groups

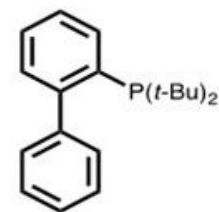
Even higher bulk



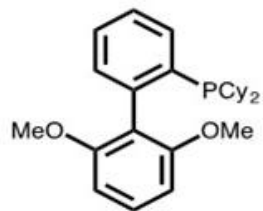
Buchwald ligands: Biaryl monophosphines



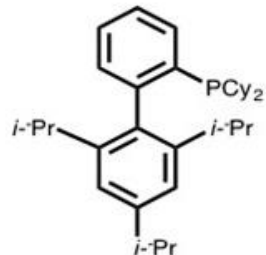
DavePhos



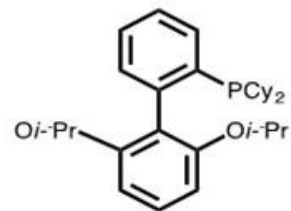
JophnPhos



SPhos



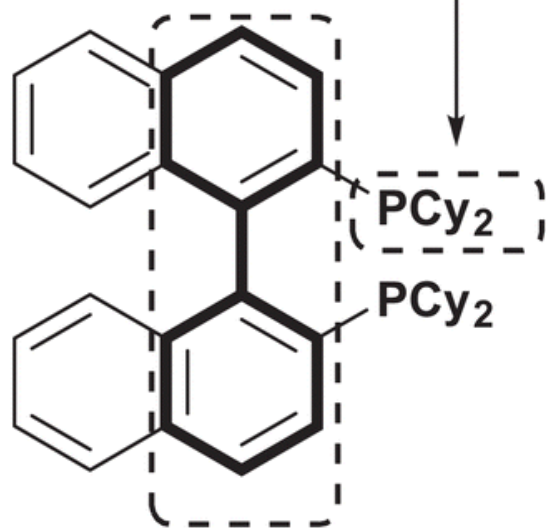
XPhos



RuPhos

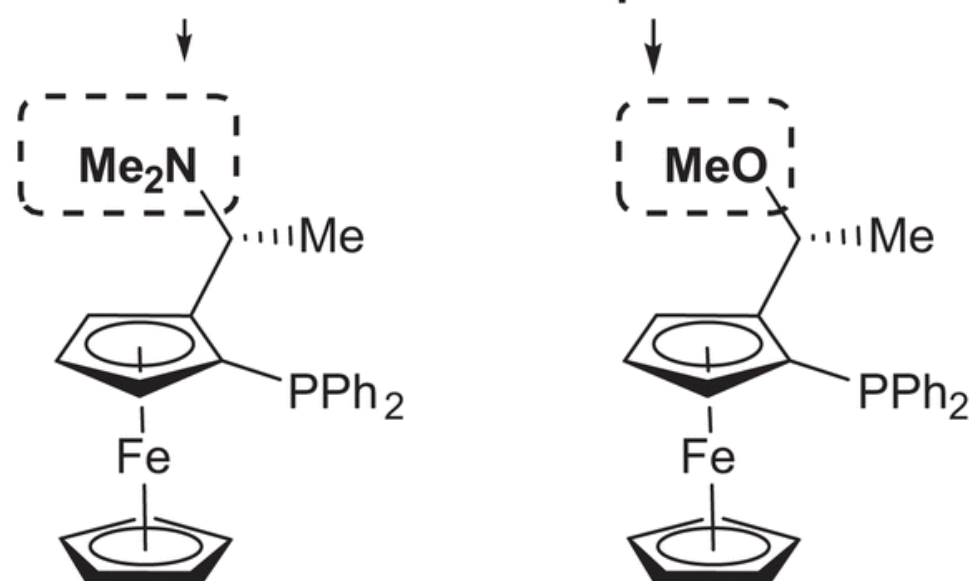
Biaryl Backbone

Electron Rich
Dicyclohexylphosphino
Group



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

Weak σ -Donor Groups

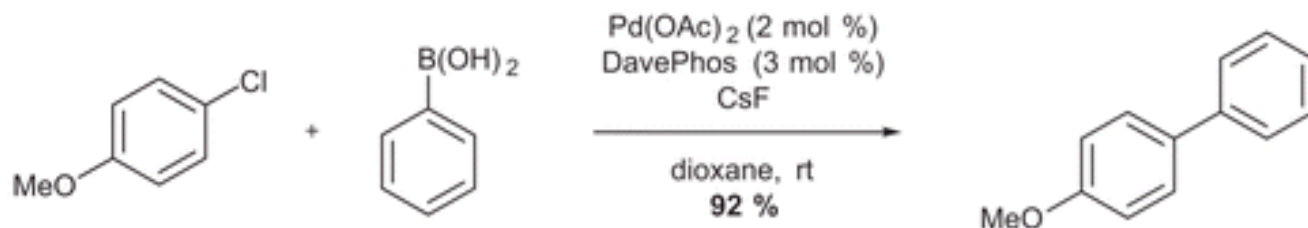
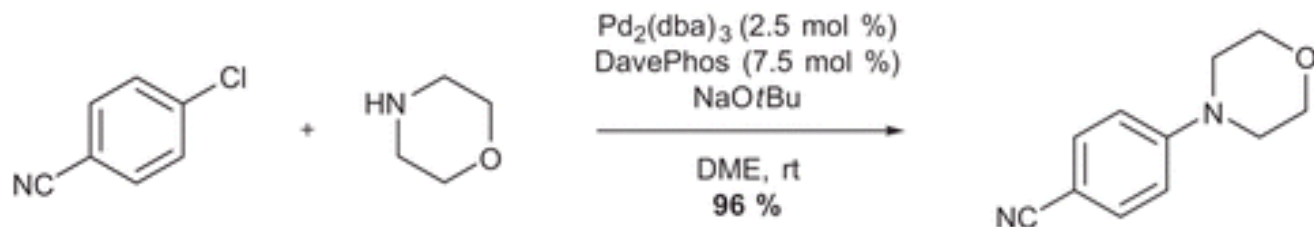
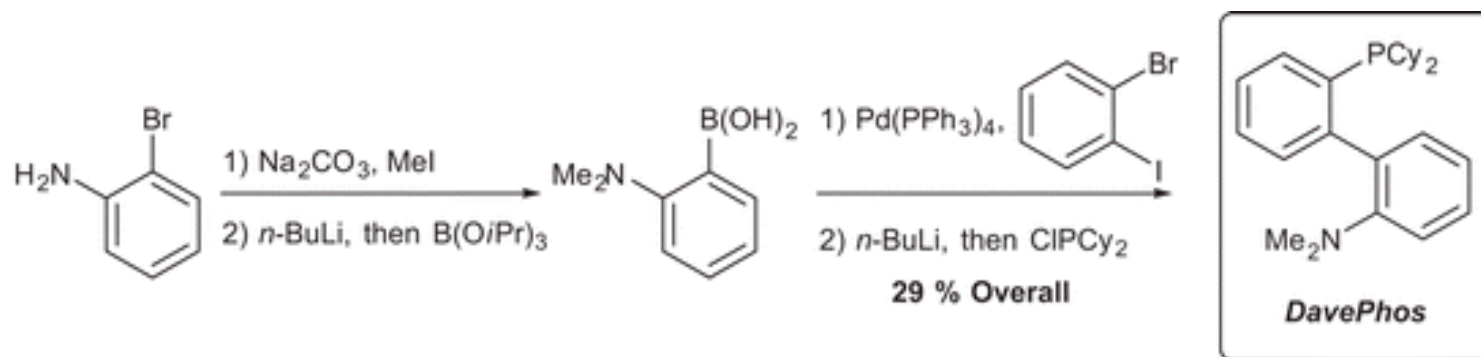


PPFA

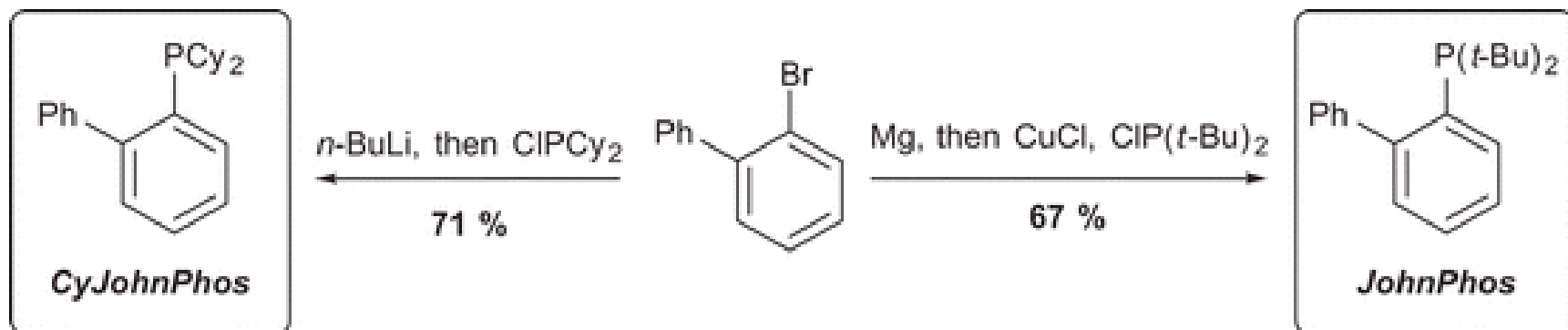
PPF-OMe

Promising results of amination of aryl chlorides using these ligands

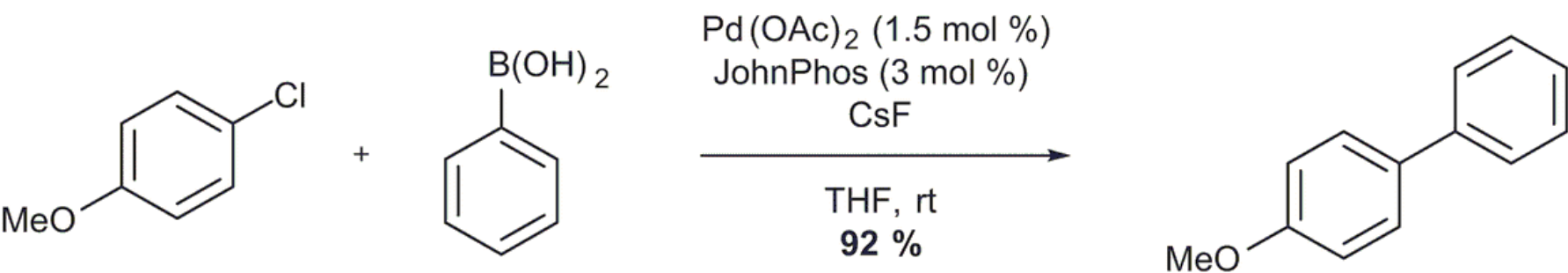
First version: DavePhos



Next version: Amino group of DavePhos no longer needed



Room Temperature SMC of Aryl Chlorides

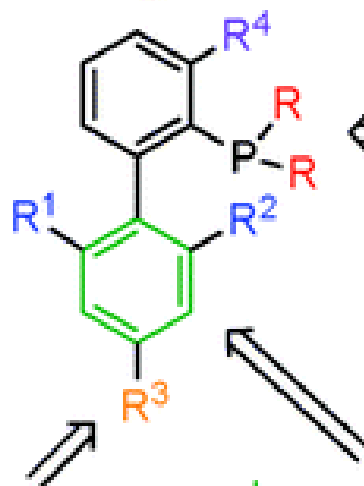


• Substituent fixes conformation of R_2P over bottom ring, enhancing rate of reductive elimination

• $R^1, R^2 \neq H$ 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)



• 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.

Lower aryl ring:

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

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.

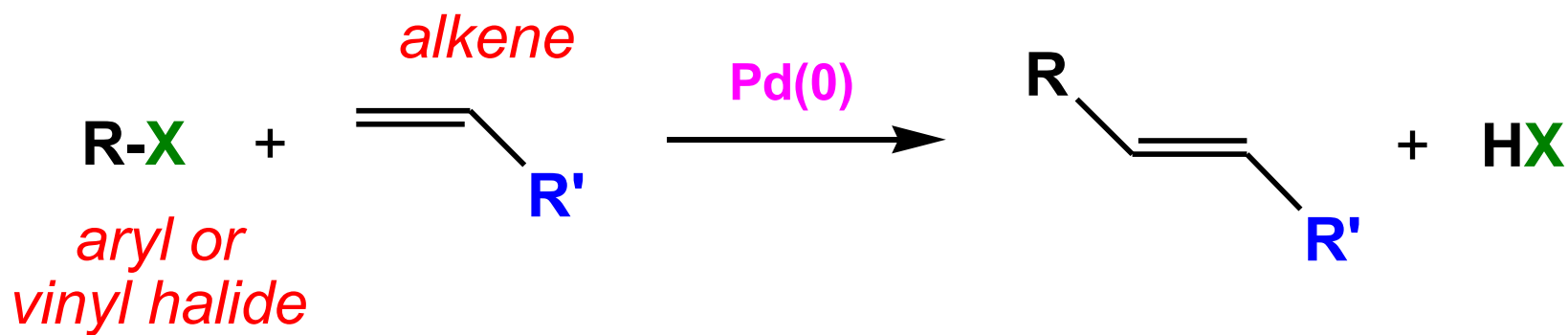
(b) Oxidative addition of aryl halides is much faster with $L_1Pd(0)$ species than with more highly coordinated complexes. This is simply due to the smaller size of a $L_1Pd(0)$ complex compared with a $L_2Pd(0)$ one, allowing the substrate to approach the latter more closely and, hence, react at a faster 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.

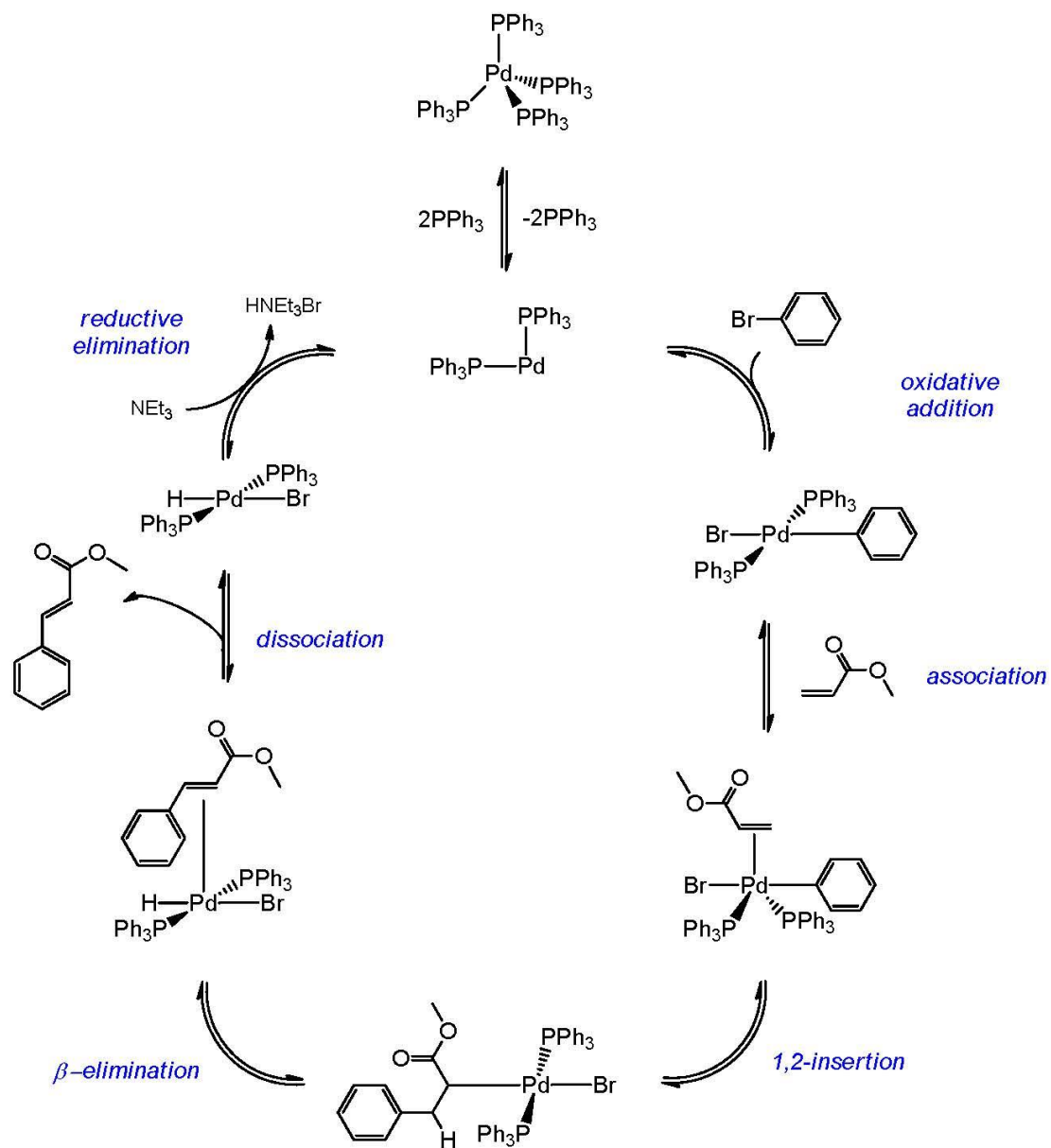
(c) It is well-documented that the rate of reductive elimination from $LPd(Ar)R$ ($R = \text{aryl}, NR_2, OR$) is faster than that for the same process for an analogous $L_2Pd(Ar)R$ complex.

(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.

V. Heck coupling and its selectivity

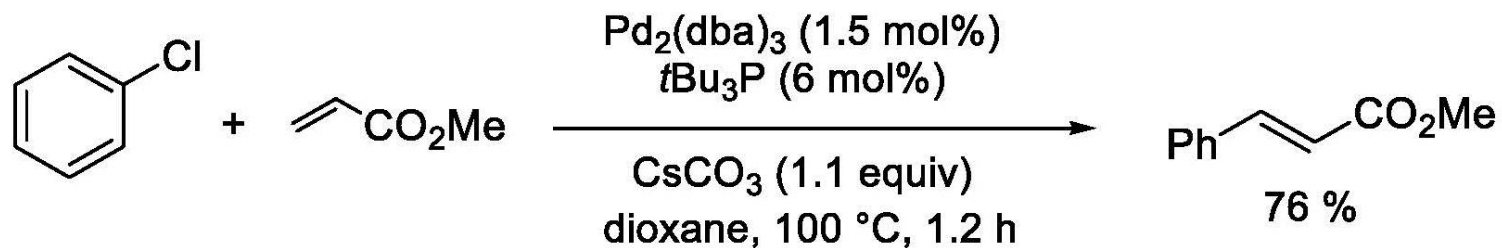
Heck reaction: efficient alkene synthesis



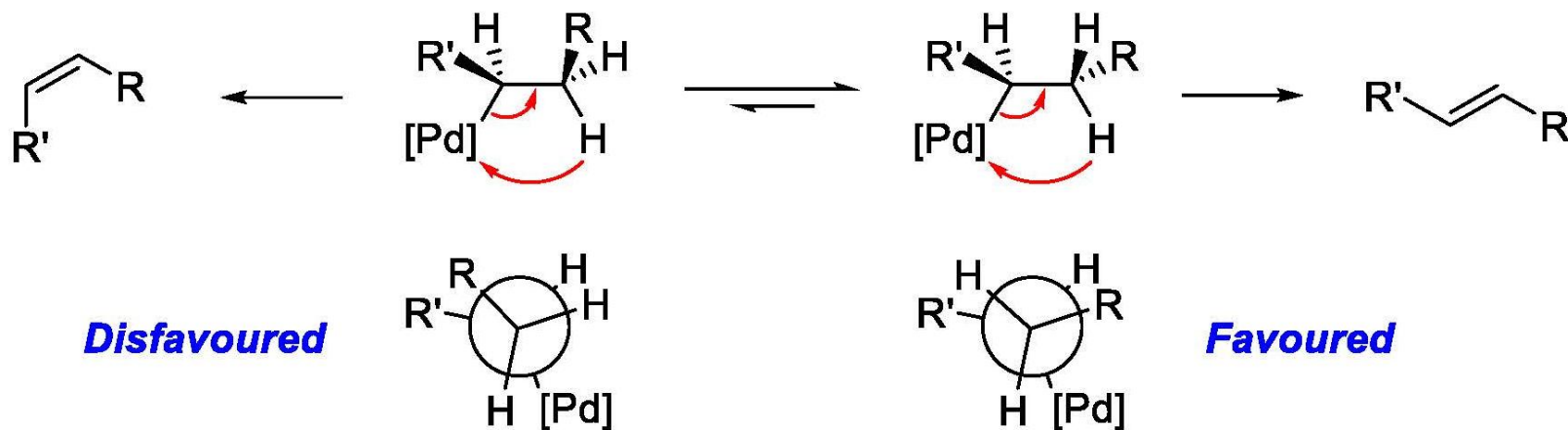


Regioselectivity controlled by 1,2-insertion

Trans-selectivity

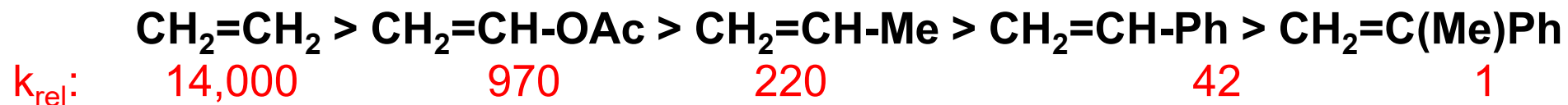


G. C. Fu et al. J. Org. Chem. 1999, 64, 10.



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:



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.

