Mechanistic Insights into Cross Coupling Reactions

Palladium?
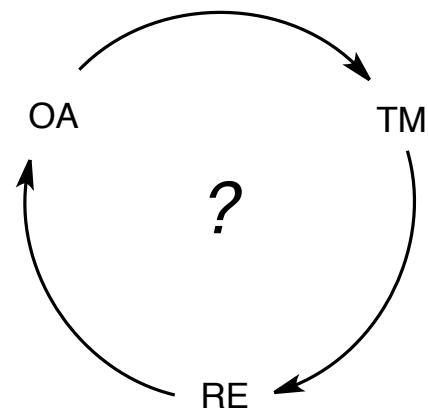
Nickel?

Ligand?

Base?

Solvent?

Temperature?

OA

TM

?

RE

what's going on?

Eric Welin

MacMillan Group Meeting

May 29, 2013

Why Should We Care?

■ as (one of) the most important reactions developed in the last 50 years, cross coupling is relevant to the world

| 2010 Nobel Prize | Richard F. Heck | Akira Suzuki | Ei-ichi Negishi |

■ 2010: 22% of all reactions in pharma are Pd-catalyzed couplings

■ 2013: Buchwald-Hartwig amination #1 reaction performed in pharma

Cooper, T. W. J.; Campbell, I. B.; Macdonald, S. J. F. *Angew. Chem. Int. Ed.* **2010**, *49*, 8082
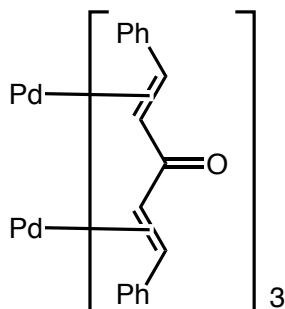
http://nextmovesoftware.com/blog/2013/04/22/pharmas-favourite-reactions/

Why Should We Care?

■ most common catalysts are Pd(PPh$_3$)$_4$ and Pd$_2$(dba)$_3$ derived systems due to "convenience"
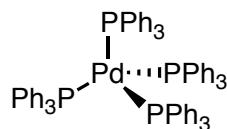
■ contains 2 extra ligands that inhibit reaction!

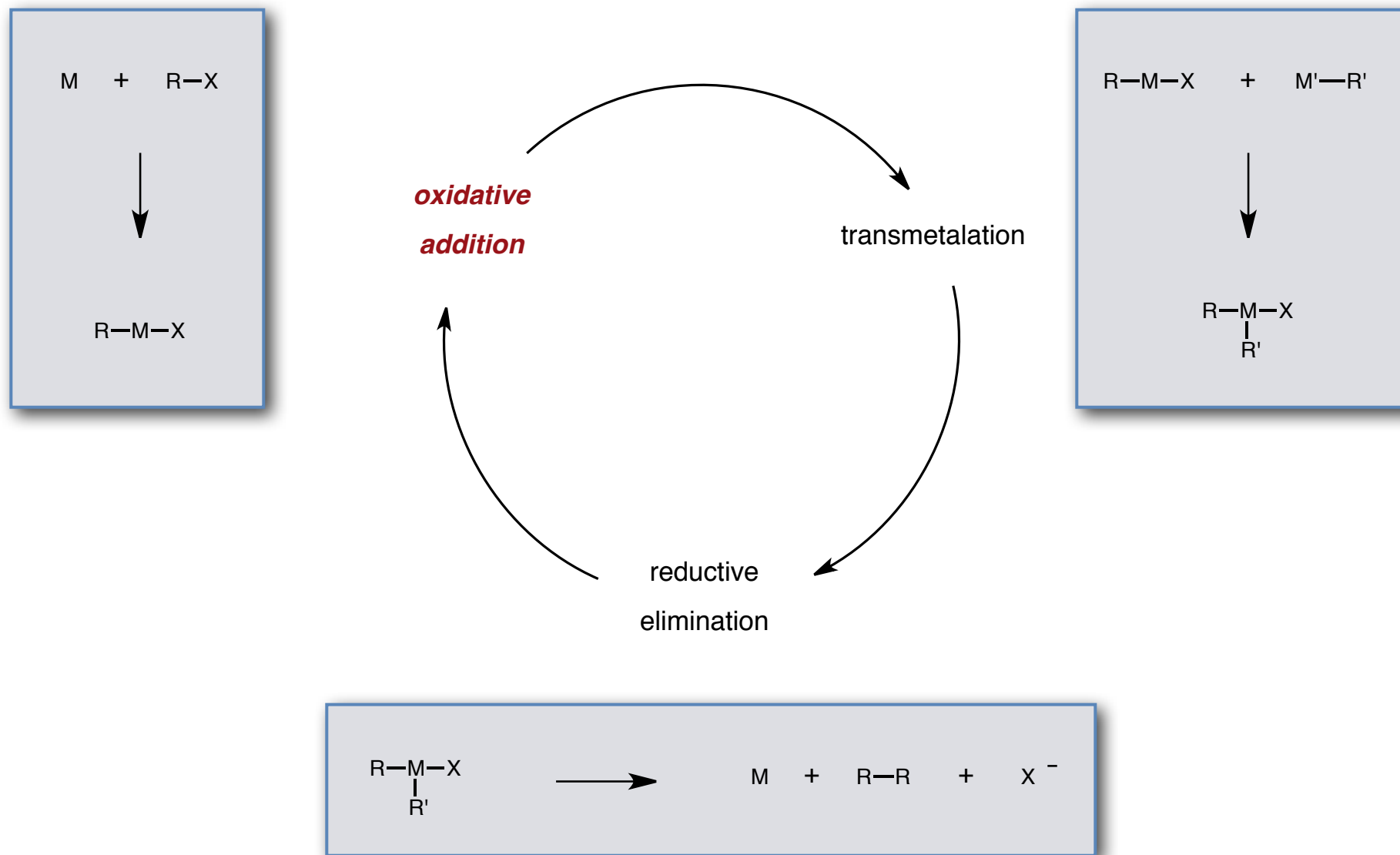■ commercially available; however, often of questionable quality

■ dba is actually a very strong ligand; often requires high temp. to dissociate

■ high temp. promotes side reactions (eg. homocoupling) and decomposition

■ mechanistic insights can lead to improved catalyst design to optimize desirable features

■ we will only chose to use new catalysts if we understand why they are superior!
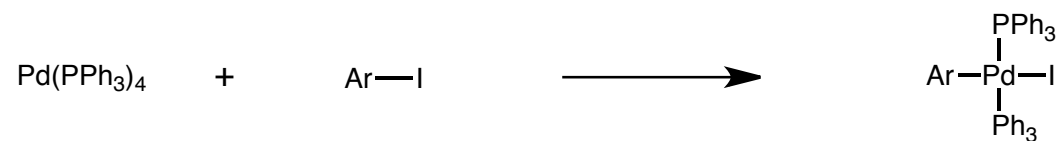
Organometallic Cross Coupling: THE Generic Cycle

M   +   R—X

↓

R—M—X

R—M—X   +   M'—R'

↓

R—M—X
|
R'

---

oxidative

addition

transmetalation

reductive

elimination

R—M—X   ⟶   M   +   R—R   +   X $^-$
|
R'

Oxidative Addition: Selected Studies

■ Tsou and Kochi

$$Ni(PEt_3)_4 \quad + \quad Ar-X \quad \longrightarrow \quad \underset{\underset{PEt_3}{|}}{\overset{\overset{PEt_3}{|}}{Ar-Ni-X}}$$

X = Cl, Br, I
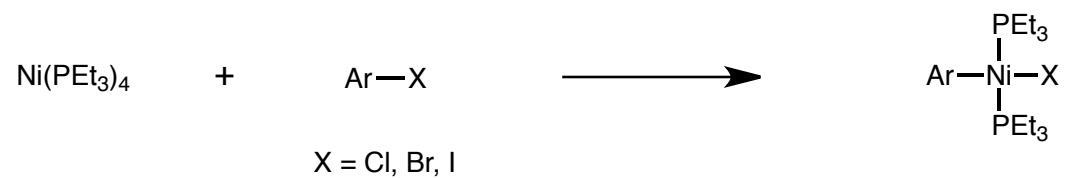
JACS, **1979**, *101*, 6319

■ Amatore and Pflüger

$$Pd(PPh_3)_4 \quad + \quad Ar-I \quad \longrightarrow \quad \underset{\underset{Ph_3}{|}}{\overset{\overset{PPh_3}{|}}{Ar-Pd-I}}$$

Organometallics, **1990**, *9*, 2276

■ Barrios-Landeros, Carrow and Hartwig

$$Pd(PR_3)_2 \quad + \quad Ar-X \quad \longrightarrow \quad \overset{\overset{PR_3}{|}}{Ar-Pd-I}$$

X = Cl, Br, I
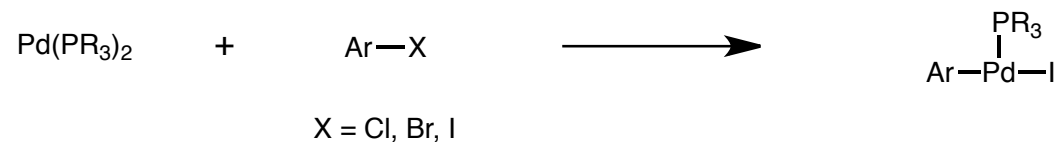
JACS, **2009**, *131*, 8141

Oxidative Addition of Aryl Halides gives Product Mixtures
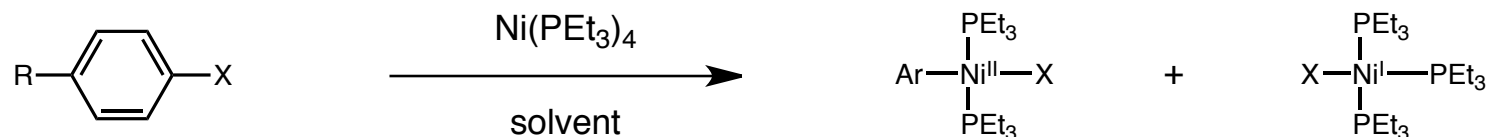
	R	X	% Ni(II)	% Ni(I)	total yield
toluene	H	I	71	18	89%
	MeO	I	58	29	87%
	C(O)Me	I	9	85	94%
THF	OMe	I	83	17	100%
	C(O)Me	I	17	55	72%
	C(O)Ph	I	4	101	105%
	H	Br	70	16	86%
	OMe	Br	89	5	94%
hexane	OMe	I	18	88	106%

distribution of products is seemingly random   ⟶   probe mechanism

Tsou, T. T.; Kochi, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 6319
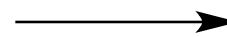
Oxidative Addition of Aryl Halides gives Product Mixtures

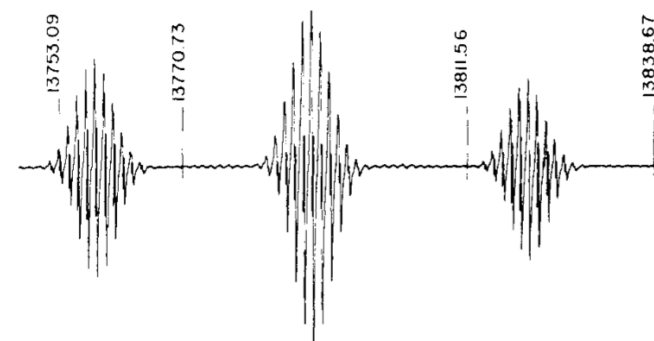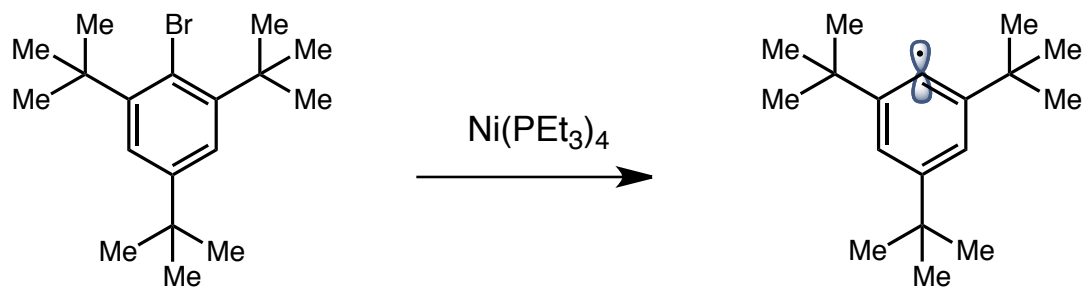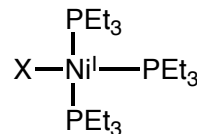- proposed pathway for Ni(I) generation:
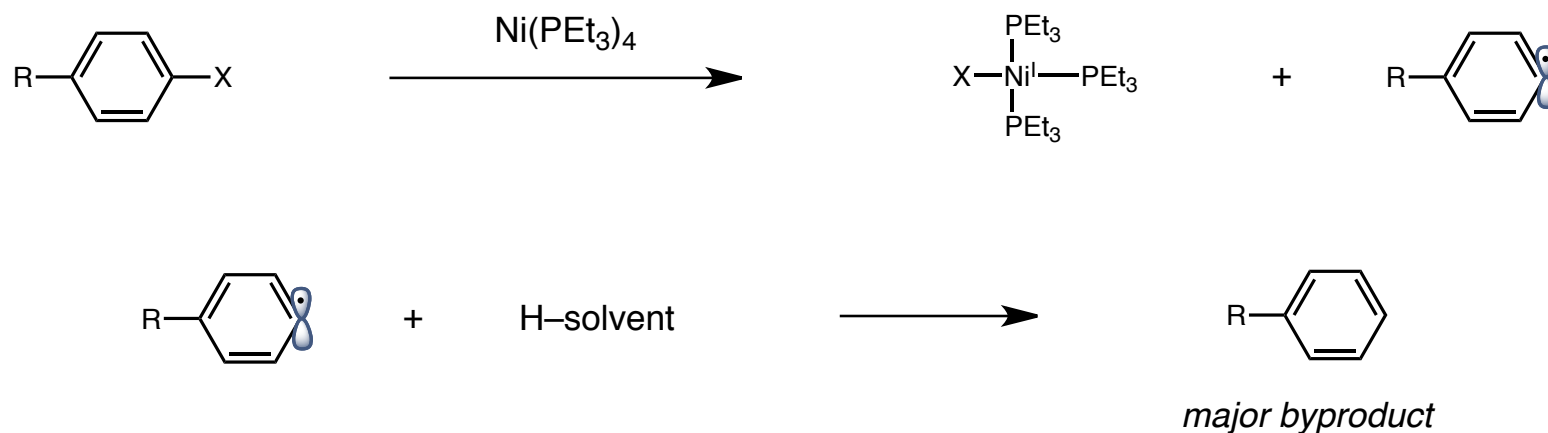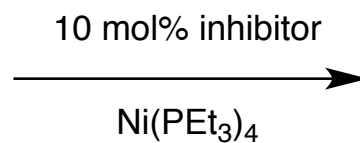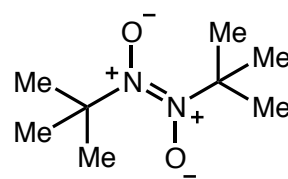

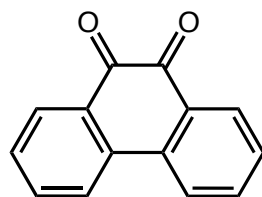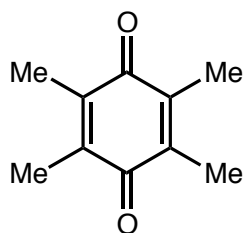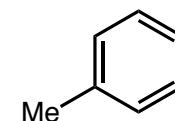- evidence for a radical mechanism

Figure 1. ESR spectrum of the 2,4,6-tri-*tert*-butylphenyl radical showing resolved *tert*-butyl protons. ^{1}H NMR field marker in kHz.

Surprising Result with Radical Inhibitors:

■ radical pathway should be shut down by inhibitors

10 mol% inhibitor

Ni(PEt₃)₄
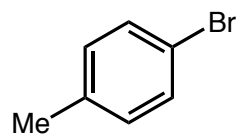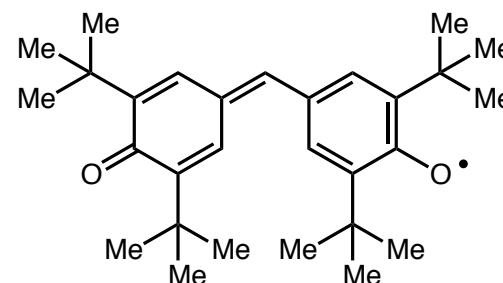
X—Niᴵ—PEt₃   +   (toluene)   70%

yields are unaffected by inhibitors!

Back to the Drawing Board – Factors Affecting Yield

■ effect of solvent, substituent, and halide

	yield of Ni(I), %		
p-substituent[a]	ArI	ArBr	ArCl
OMe	83	5	0
Me	92	70	0
H	90	16	0
Cl	79	7	0
CO_2Me	91	7	0
Me_3N^+	100	75	32
CO_2^-	22	ND	ND

[a] in THF solvent

	yield of Ni(I), %		
solvent[b]	ArI	ArBr	ArCl
hexane	46	2	0
toluene	76	6	0
THF	91	7	0

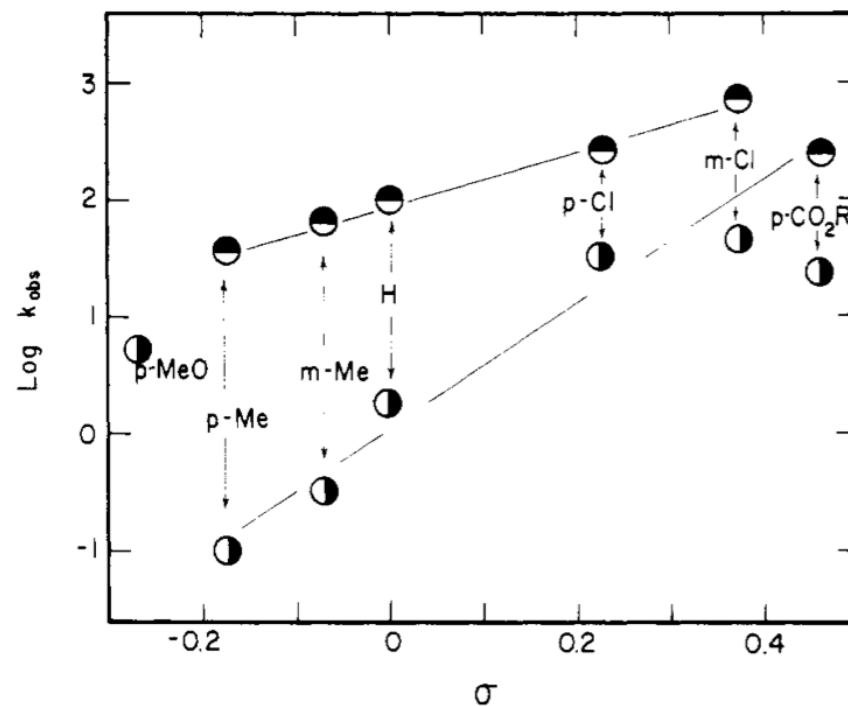[b] all arenes had *p*-CO_2Me substitution

■ yields follow the trend ArI >> ArBr > ArCl

■ yields increase with increasing solvent polarity

Back to the Drawing Board – Factors Affecting Rate

■ effect of solvent, substituent, and halide

substituent[a]	σ	log k_{obs}, M^{-1}s^{-1}	
		ArI	ArCl
p-Me	-0.17	1.54	-1.04
m-Me	-0.069	1.77	-0.51
H	0	1.98	0.27
p-Cl	0.23	2.38	1.53
m-Cl	0.37	2.81	1.64

a in THF solvent

■ large, positive ρ value for all halides (+2.0, +4.4, +5.4 for I, Br, Cl)

indicates significant negative charge buildup in transition state

Back to the Drawing Board – Factors Affecting Rate

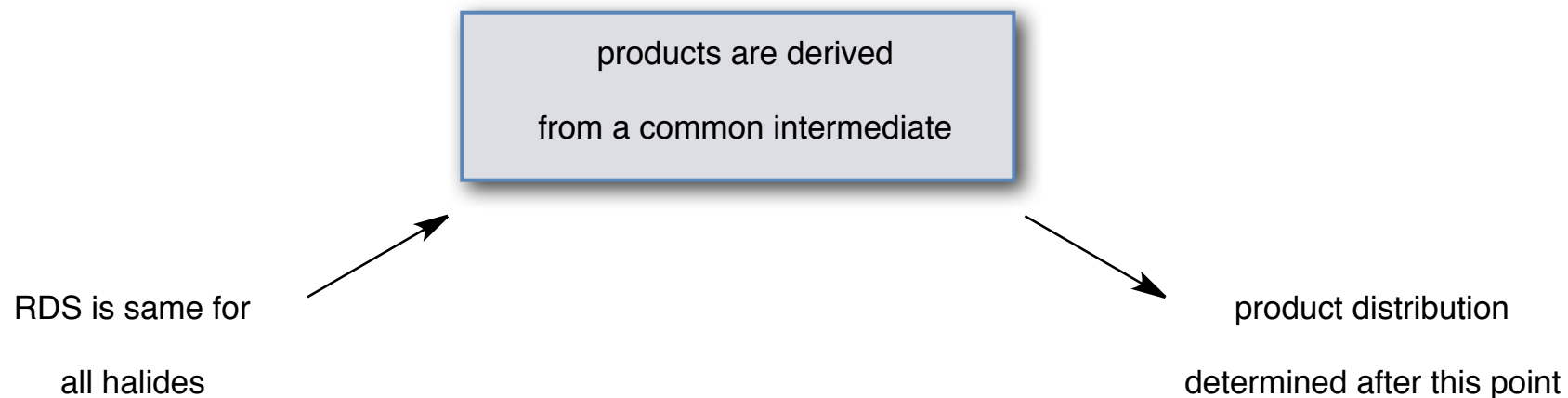■ effect of solvent, substituent, and halide

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H	0	1.98	0.27
p-Cl	0.23	2.38	1.53
m-Cl	0.37	2.81	1.64

[a] in THF solvent

Aryl Halide	k_{obs}, $M^{-1}s^{-1}$	
	hexane	THF
PhCl	0.93	1.87
PhBr	0.92	3.07
PhI	10.7	94
p-CO$_2$Me PhI	34	240

■ strong linear correlation of rates for each halide suggests that all halides

react with the same rate-determining steps

Conclusions

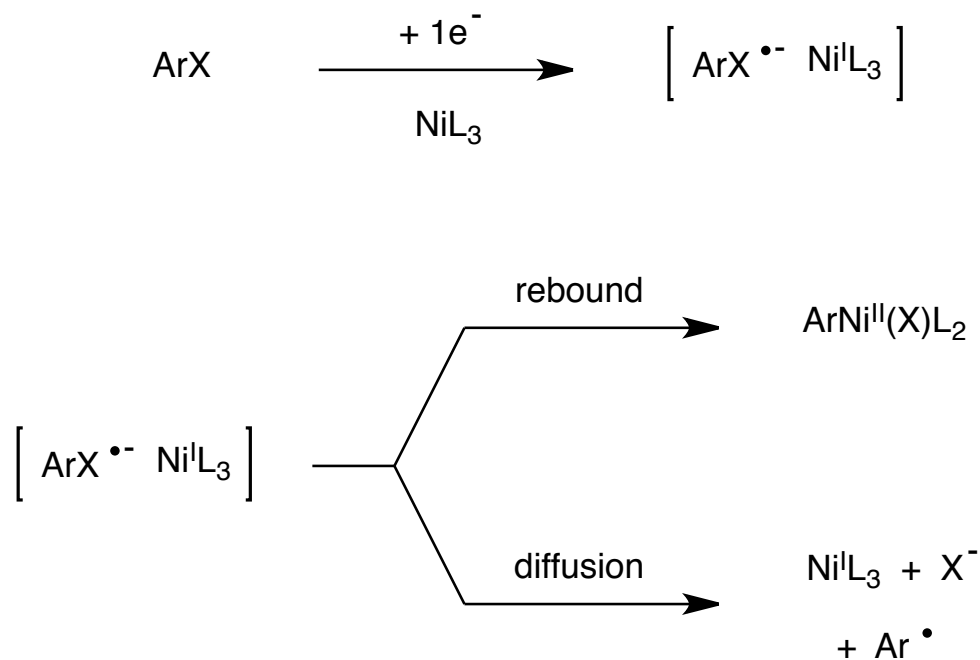■ yields follow the trend ArI >> ArBr > ArCl

■ yields increase with increasing solvent polarity

■ strong linear correlation of rates for each halide suggests that all halides

react with the same rate-determining steps

products are derived

from a common intermediate

RDS is same for

all halides

product distribution

determined after this point

Conclusions

■ CV studies strongly suggest SET as RDS

    ■ plotting rate constant vs. $E_{1/2}$ shows strong

    correlation for X = Cl, Br, and I

$$ArX \xrightarrow[\text{NiL}_3]{+\ 1e^-} \left[ArX^{\bullet-}\ Ni^IL_3 \right]$$

$$\left[ArX^{\bullet-}\ Ni^IL_3 \right] \begin{array}{c} \xrightarrow{\text{rebound}} ArNi^{II}(X)L_2 \\ \\ \xrightarrow{\text{diffusion}} Ni^IL_3\ +\ X^- \\ +\ Ar^{\bullet} \end{array}$$

Figure 9. Correlation of the polarographic half-wave potentials for the reduction of substituted (◑) iodobenzenes, (◒) bromobenzenes, and (◐) chlorobenzenes (from ref 31) with the second-order rate constants for reactions with Ni(PEt₃)₄. The dashed lines are *arbitrarily* drawn with slope = 8.5 (see text).
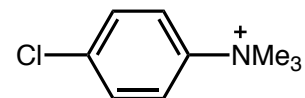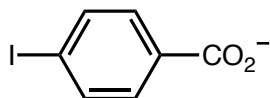
■ competing radical rebound and diffusion of the resulting aryl radical determines product distribution

Conclusions

■ How does this explanation fit the data? Nature of the formed ion pair

Ni^{II} OA

product
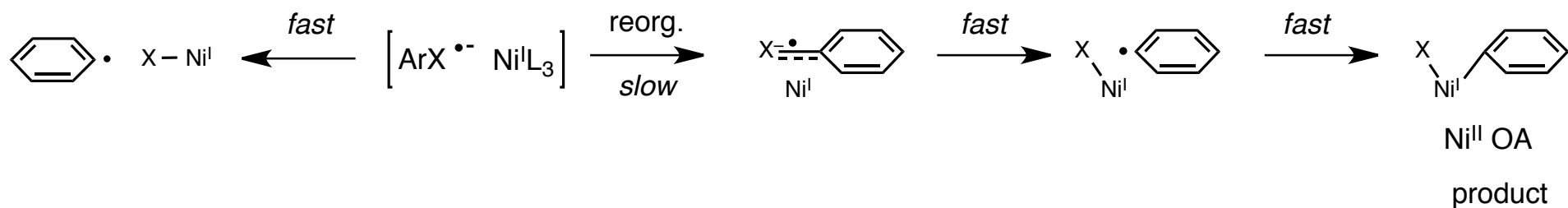
■ consistent with known half lives of aryl radical anions:

$\tau_{1/2}$: I < Br < Cl
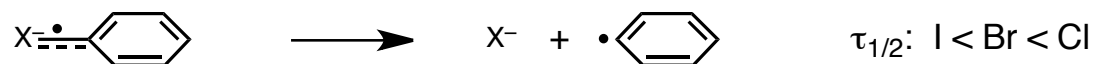
■ supported by trends observed with charged substrates:

■ only iodide that favored oxidative addition

■ only chloride that favored Ni^{I} formation

Ni(PR$_3$)$_4$ vs. Pd(PR$_3$)$_4$

■ Tetraalkylphosphine ligated Nickel complexes react via SET, but what about Palladium?

    ■ Pd(I) is less stable than Ni(I) (and very rarely observed)

    ■ oxidative addition to Pd is much slower than to Ni

Ni^0	Pd^0
electronegativity = 1.91	electronegativity = 2.20
Ni^0 ⇌ Ni^{2+} + 2 e$^-$	Pd^0 ⇌ Pd^{2+} + 2 e$^-$
E^o = 0.236 V	E^o = -0.915 V
(favorable at rt; stored in glovebox)	(not favorable at rt; stored in air)

Bratsch, S. G. *J. Phys. Chem. Ref. Data.* **1989**, *18*, 1
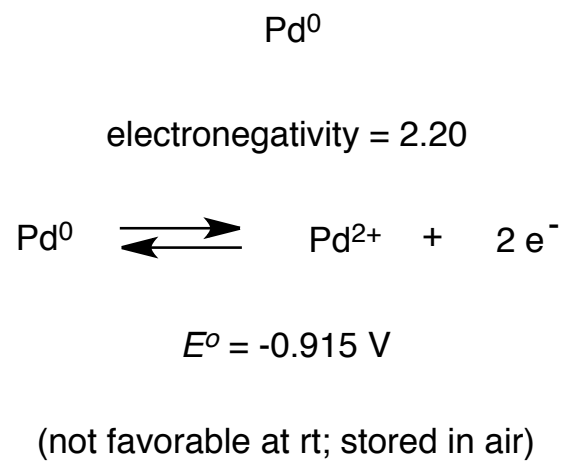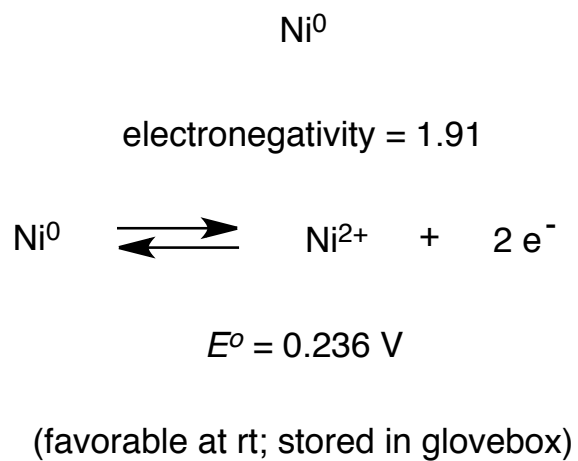
Ni(PR$_3$)$_4$ vs. Pd(PR$_3$)$_4$

■ oxidative addition with Pd(PPh$_3$)$_4$ is very slow → difficult to measure

　■ development of "ultramicroelectrodes" has enabled such studies

Pd
R- - - -X

neutral pathway

R—X　+　Pd^0　　　　　　　　　　　　　　　　　　　R—Pd^{II}—X

$\left[\text{ArX}^{\bullet-}\ \text{Pd}^{I} \right]$　⟶　$\left[\text{Ar}^{\bullet}\ \text{Pd}^{I}\text{X} \right]$

ionic pathway
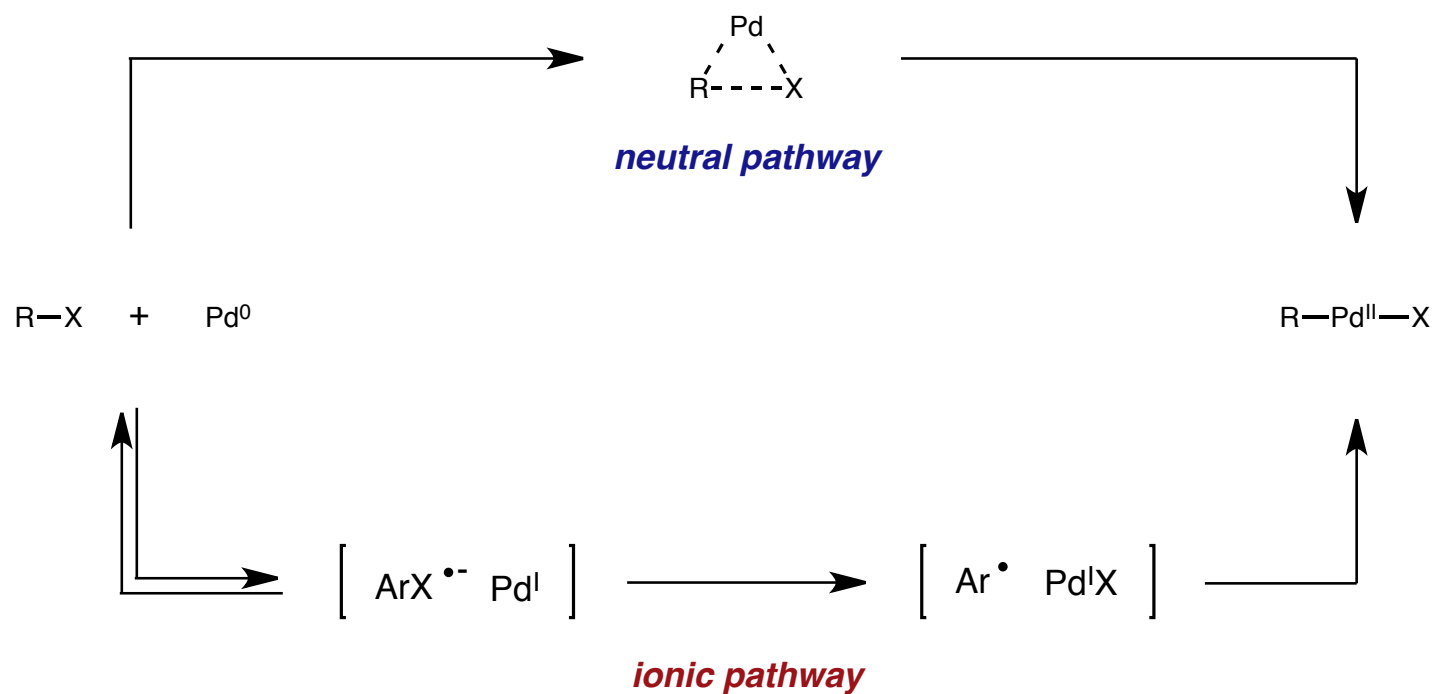
Amatore, C.; Pflüger, F. *Organometallics*, **1990**, *9*, 2276

Fauvarque, J.-F.; Pflüger, F.; Troupel, M. *J. Organomet. Chem.*, **1981**, *208*, 419

Hammett Analysis and Activation Parameters are Revealing
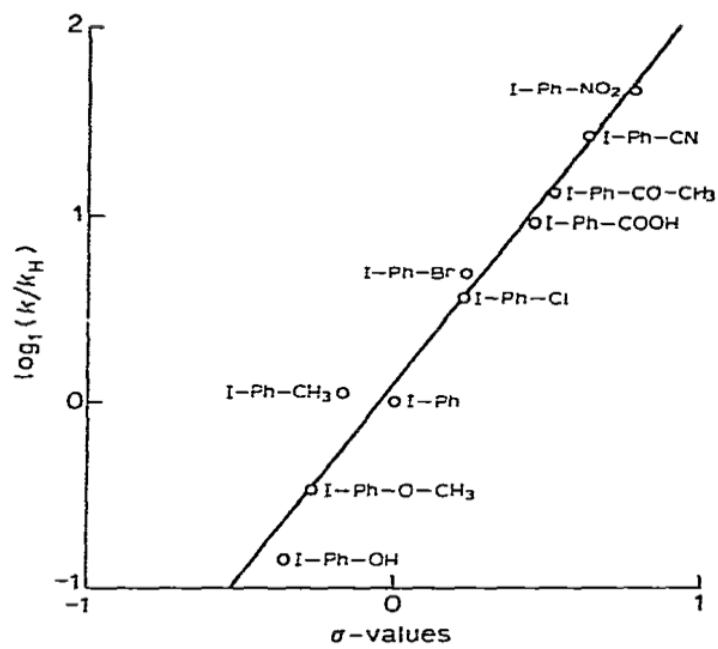
THF, $\rho = +2.0$

$\Delta H = 18$ kcal

$\Delta S = 3$ cal/K
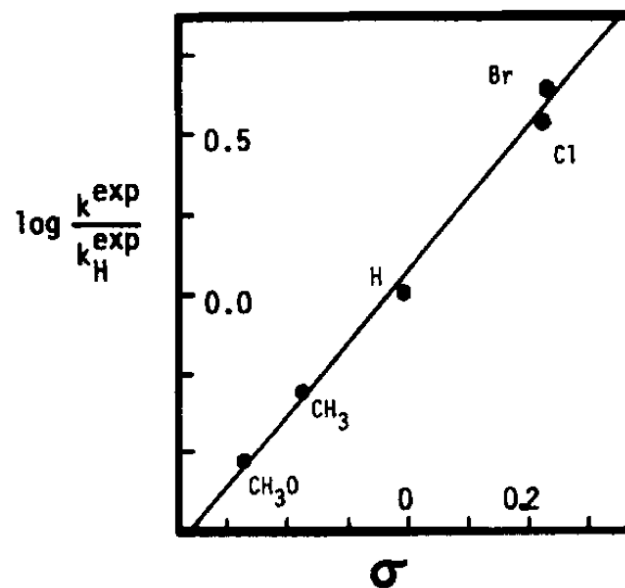
toluene, $\rho = +2.3$

$\Delta H = 18$ kcal

$\Delta S = 2$ cal/K

■ ρ value and activation parameters are nearly identical → identical mechanisms

Hammett Analysis and Activation Parameters are Revealing

$$Pd(PPh_3)_4 \xrightleftharpoons{\text{fast}} Pd(PPh_3)_3 + PPh_3 \xrightleftharpoons{\text{slow}} Pd(PPh_3)_2 + PPh_3$$
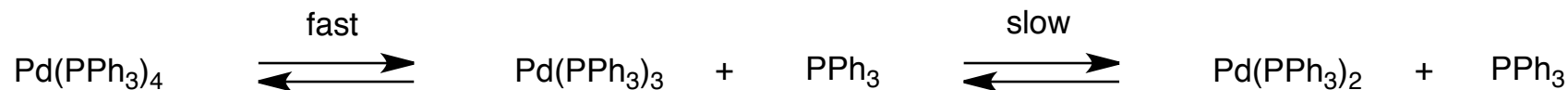
can be seen by ^{31}P NMR; rate α 1 / [PPh$_3$]
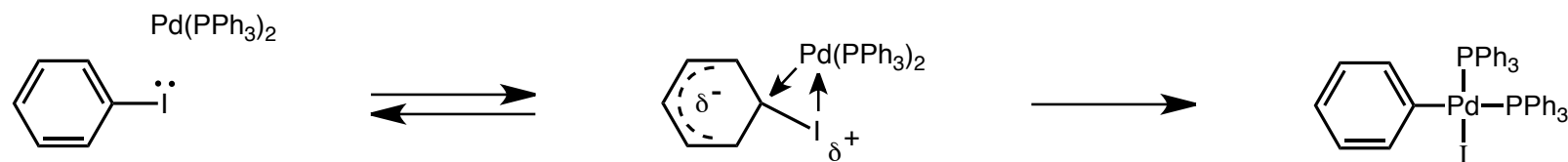
minimal charge buildup supported by identical thermodynamic and kinetic data

in THF and toluene

Extremely Large Phosphine Ligands: PdL$_2$
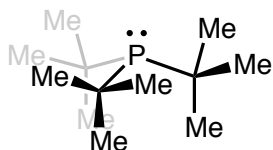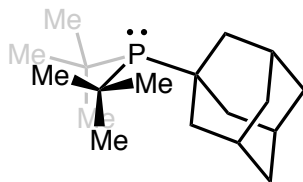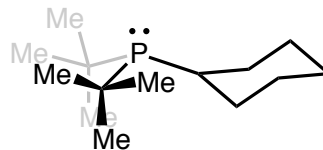
P*t*-Bu$_3$ AdP*t*-Bu$_2$ CyP*t*-Bu$_2$ PCy$_3$
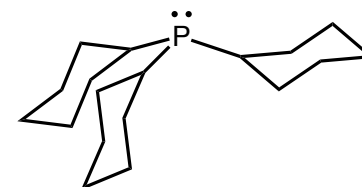
- ■ extremely large phosphine ligands provide highly active catalysts

- ■ all exist in solution as bis-ligated Pd (even with excess ligand)

- ■ all form 3-coordinate, T-shaped adducts upon oxidative addition (except PCy$_3$)
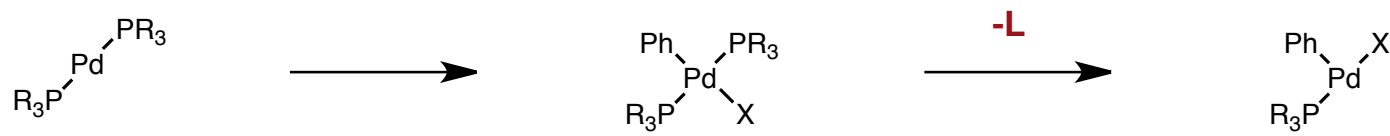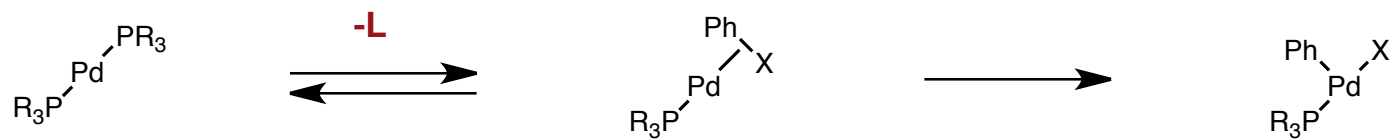
in solution   solid state

Barrios-Landeros, F.; Carrow, B.; Hartwig, J. F. *J. Am. Chem. Soc.* **2009**, *131*, 8141
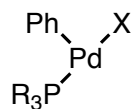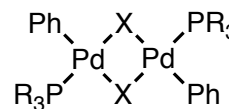
Three Possible Mechanisms to Distinguish

- **Direct**

- **Associative**

- **Dissociative**
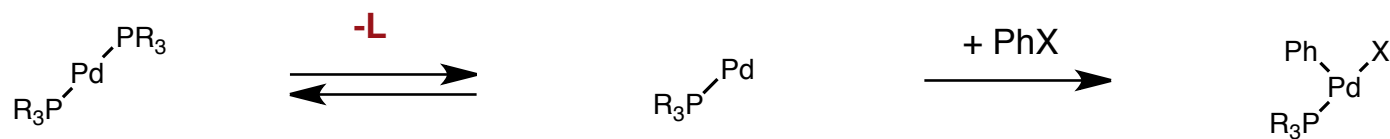
3 Mechanisms Depend on Substrates Differently

■ Direct

  ■ first order in [PhX]

  ■ zeroth order in [L]

■ Associative

  ■ if displacement is reversible,

    rate α [PhX], [L]$^{-1}$

  ■ if displacement is irreversible,

    zeroth order in [L]

■ Dissociative

  ■ if dissociation is reversible,

    rate α [PhX], [L]$^{-1}$

  ■ if dissociation is irreversible

  (by extremely rapid oxidative addition),

    zeroth order in [PhX] *and* [L]

Iodobenzene

■ iodobenzene shows first order dependence in [PhI], zeroth order in [L]

    ■ either direct or associative (irreversible)

   ■ reductive elimination study can distinguish (via microscopic reversibility)

Iodobenzene

■ iodobenzene shows first order dependence in [PhI], zeroth order in [L]

   ■ either direct or associative (irreversible)

   ■ reductive elimination study can distinguish (via microscopic reversibility)

2 ligands required

first order in [L]
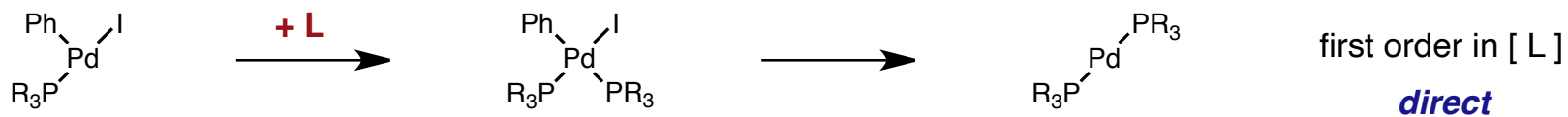
direct

1 ligand required
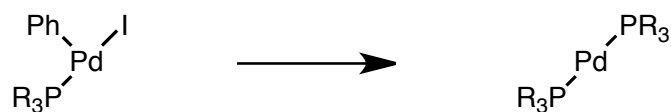
zeroth order in [L]

associative

Chlorobenzene and Bromobenzene
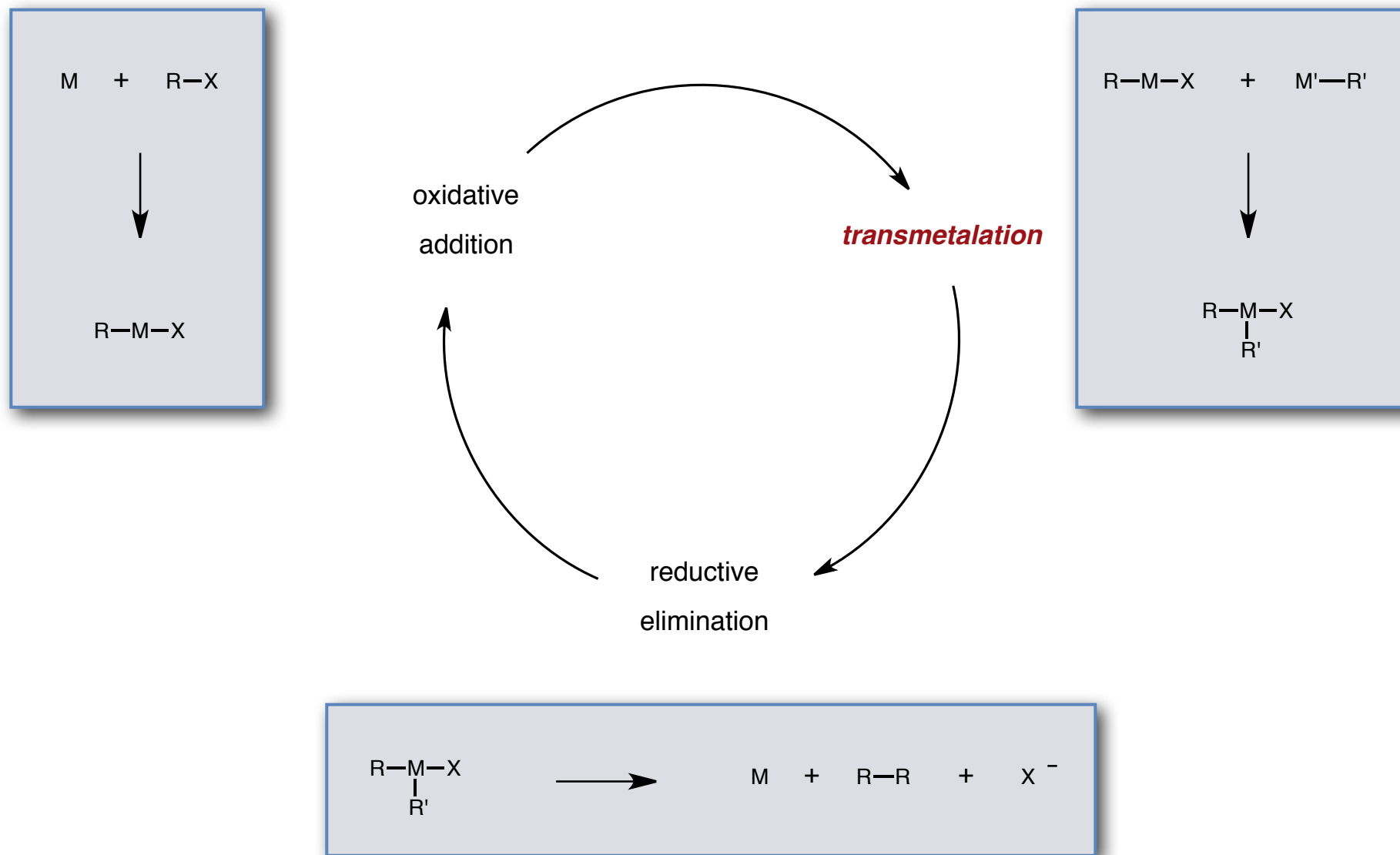
■ chlorobenzene requires ligand loss: dissociative
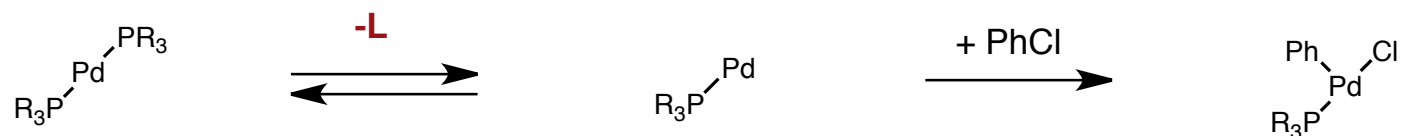
■ bromobenzene yields mixed results

   ■ combination of associative and direct for all but PCy_3

   ■ single mechanism, indistinguishable between associative and direct

ArI	ArBr	ArCl
associative	associative/direct	dissociative

loose coordination ⟶ *tight coordination*

Organometallic Cross Coupling: THE Generic Cycle

M   +   R—X

R—M—X

R—M—X   +   M'—R'

R—M—X
|
R'

oxidative
addition

transmetalation

reductive
elimination

R—M—X   M   +   R—R   +   X⁻
|
R'
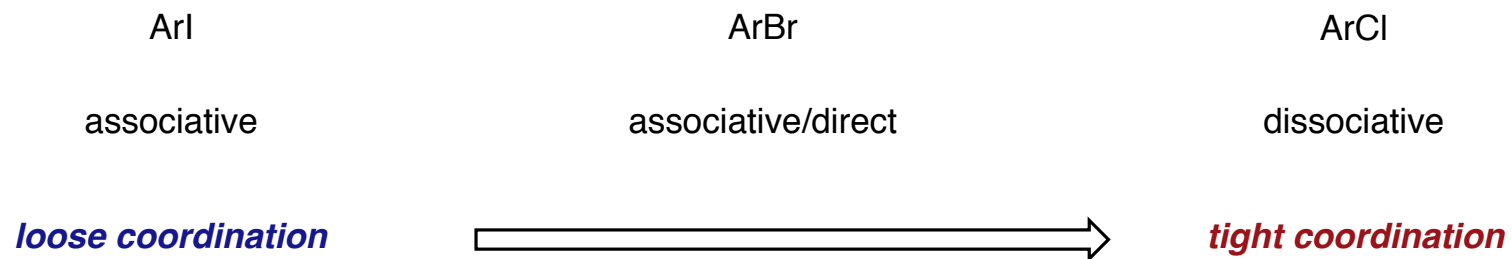
Transmetalation: the Enigma

■ defined as the transfer of an organic group from one metal center to another

    ■ ubiquitously considered the least understood step of cross coupling reactions

Metal	Named Coupling
Li	Murahashi
Mg	Kumada
Zn	Negishi
Zr	Zirconium Negishi
Sn	Stille
Cu	Sonagashira
Si	Hiyama
B	***Suzuki-Miyaura***

    ■ less fortunate metals: Al, Ge, Sb, Te, Hg, Cd, Tl

Key Feature = Equilibrium
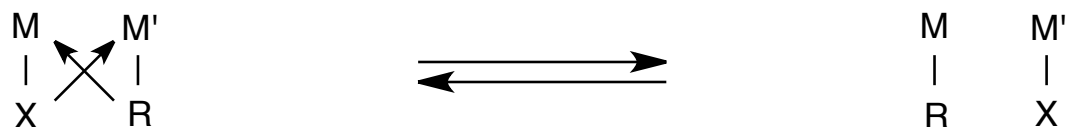
- side featuring the net most polar (most ionic) bond will be favored

- very electropositive d^0 or d^{10} metals are most common

- weaker nucleophiles in Suzuki/Hiyama couplings require activation

- Suzuki: Base
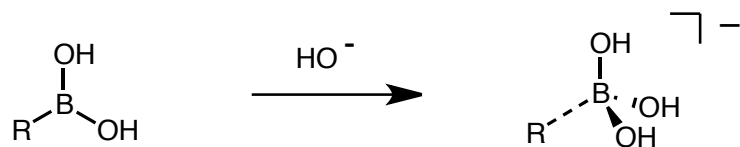
- Hiyama: Fluoride
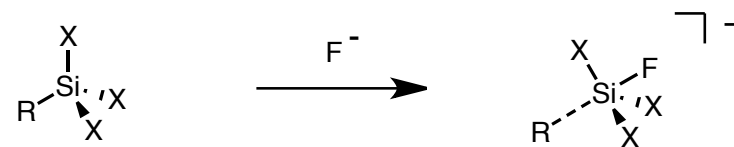
X = Cl, F, OR

Mechanistic Studies with Aryl/Vinyl Boronic Acids
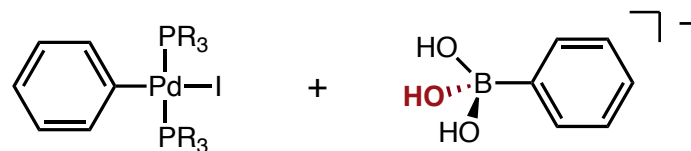
■ Maseras et al.
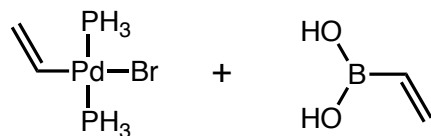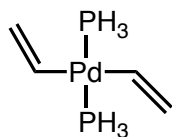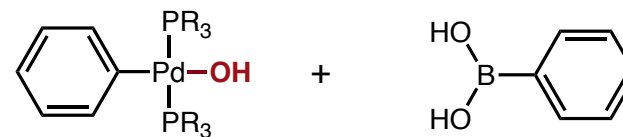
■ Carrow and Hartwig

Computational Analysis on Possible Mechanisms of Transmetalation

■ non "base-assisted"

Braga, A. A. C.; Morgon, N. H.; Ujaque, G.; Maseras, F. *J. Am. Chem. Soc.* **2005**, *127*, 9298
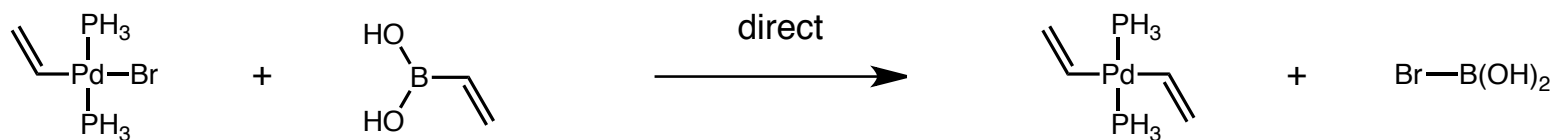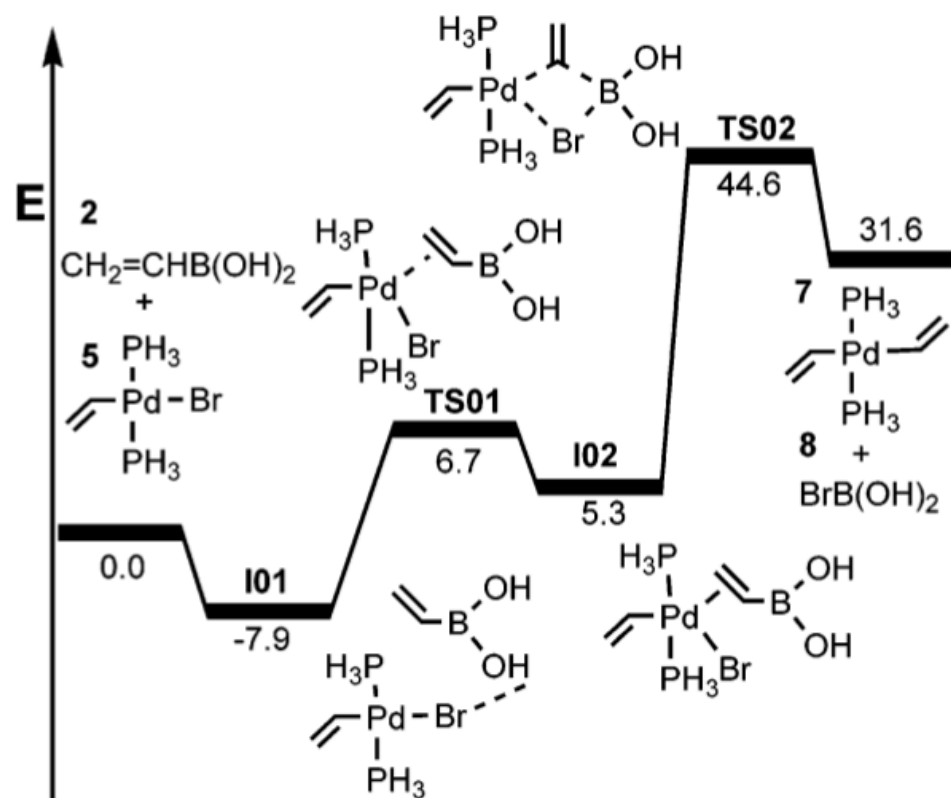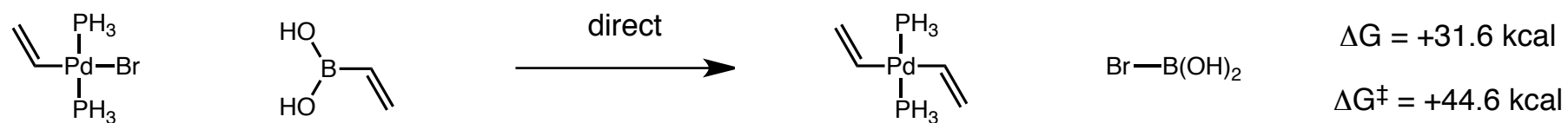
"Base Free" Transmetalation is Extremely Unfavorable

Figure 2. Energy profile for reaction path 0.

■ absence of significant driving force or attractive interactions make "base free"
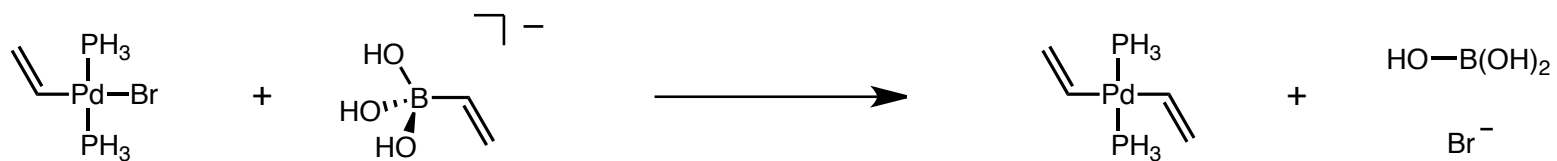
route highly unattractive

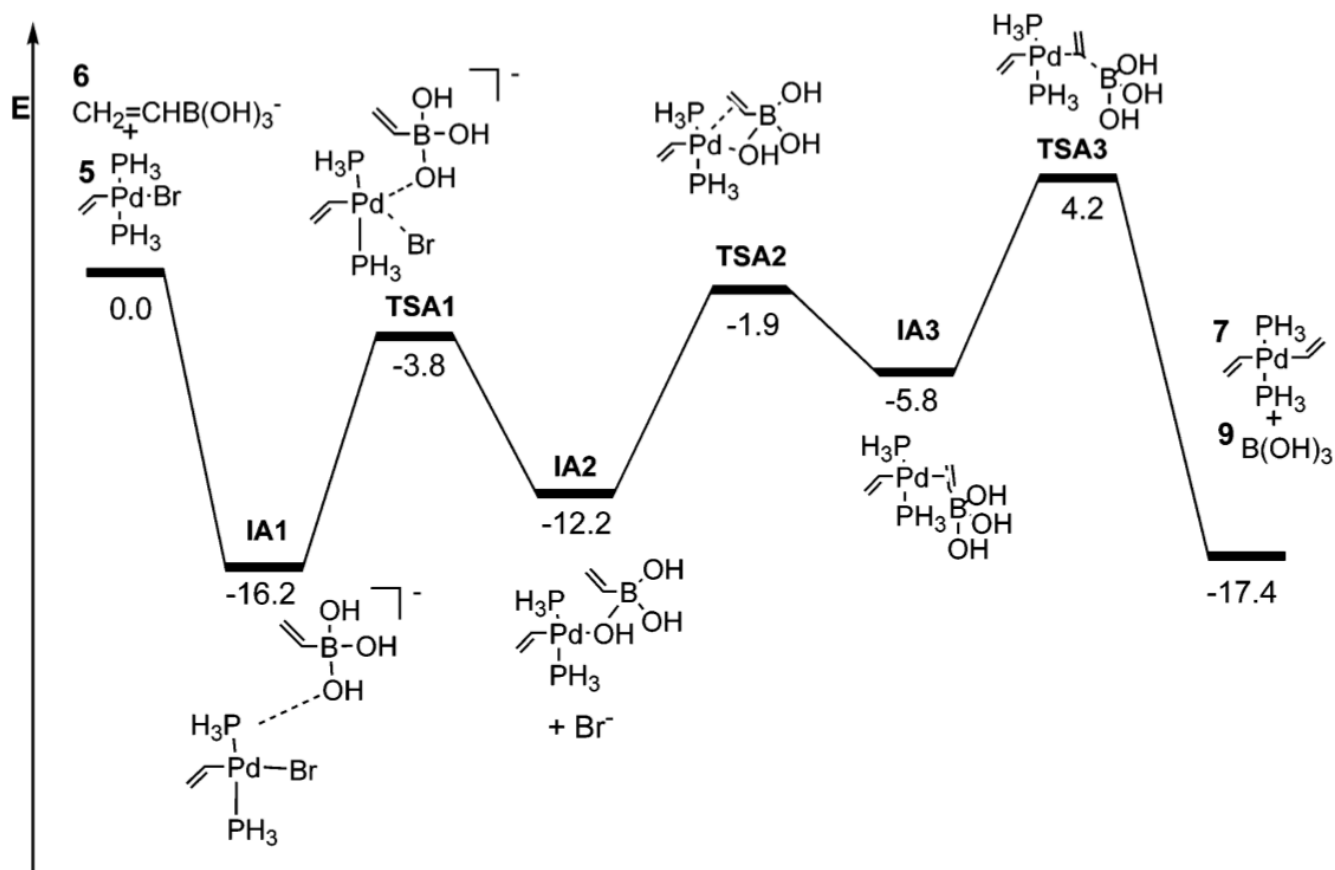# Computational Analysis on Possible Mechanisms of Transmetalation

■ non "base-assisted"

direct

$\Delta G = +31.6$ kcal

$\Delta G^{\ddagger} = +44.6$ kcal

■ Pd–Br + trihydroxyborate

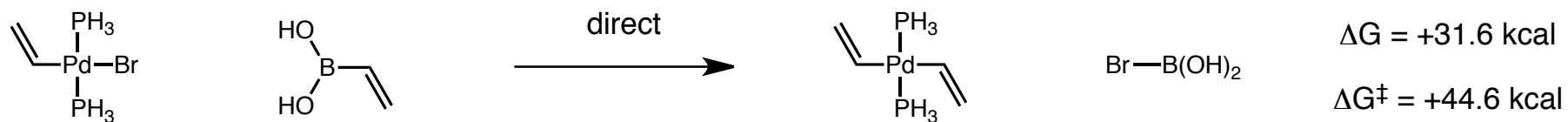# Transmetalation from Borate Species is Preferable
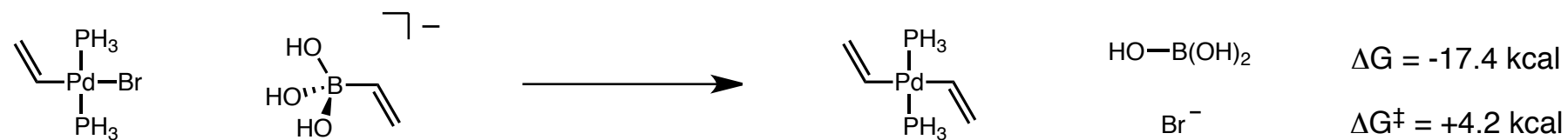

■ coordination of Pd to borate accelerates transfer

■ B-O bond strength provides driving force

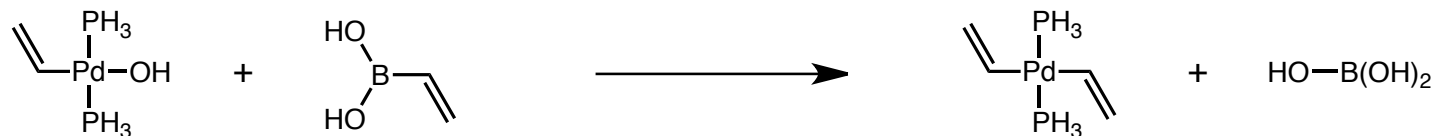Computational Analysis on Possible Mechanisms of Transmetalation

■ non "base-assisted"

direct

$\Delta G = +31.6$ kcal
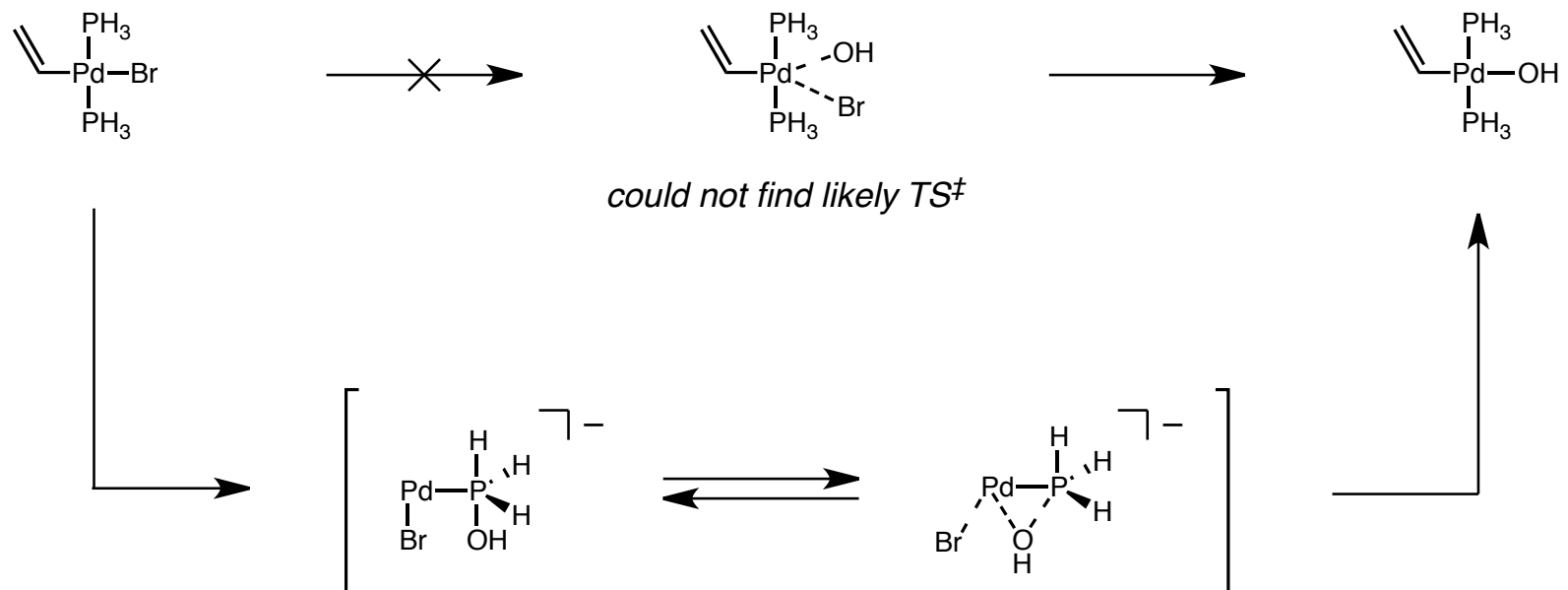
$\Delta G^{\ddagger} = +44.6$ kcal

■ Pd–Br + trihydroxyborate

$\Delta G = -17.4$ kcal

$\Delta G^{\ddagger} = +4.2$ kcal

■ Pd–OH + boronic acid

Discrepancy in Palldium Hydroxide Formation

■ direct associative addition of hydroxide to Pd is unfavorable:

could not find likely TS‡

■ consistent with observation that adding NaOH produces phosphine oxide

Matos, K.; Soderquist, J. A. *J. Org. Chem.* **1998**, *63*, 461

Boronic Acid Coordination by Pd–OH is Paramount (with caveat)
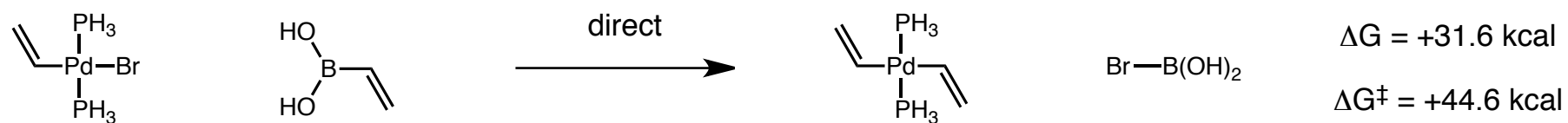

$\Delta G = -46.4$ kcal

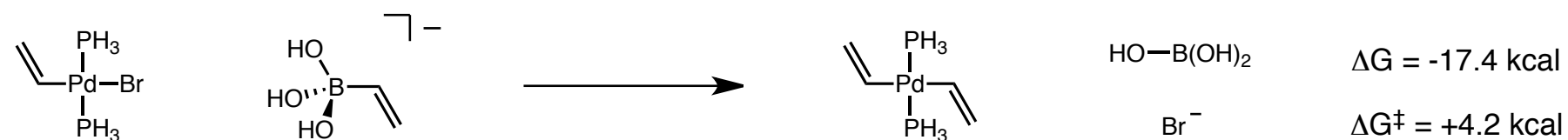$\Delta G^{\ddagger} = +6.3$ kcal

(from bromide)
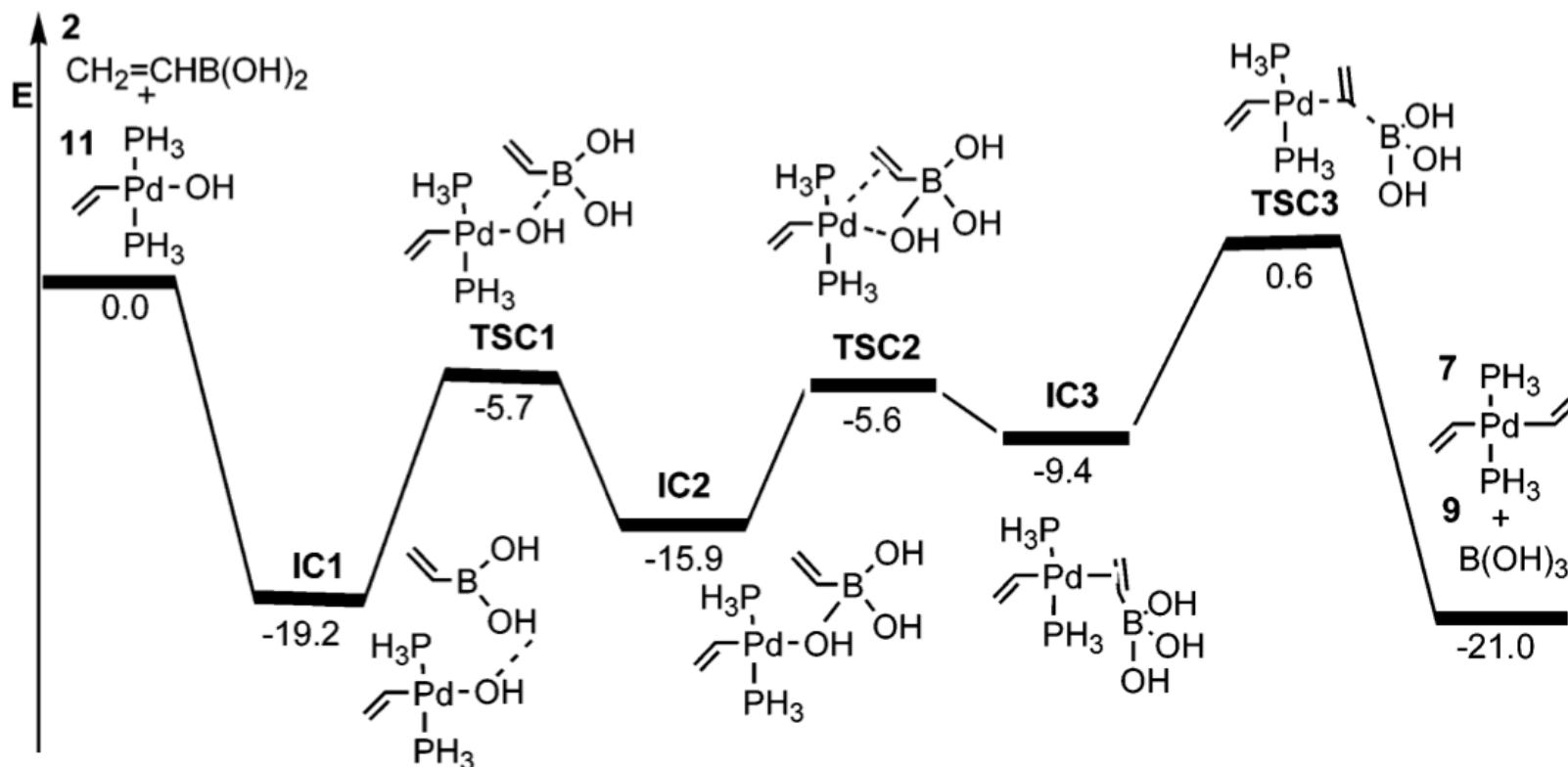
■ pathway originating at Pd–OH is nearly barrierless by comparison

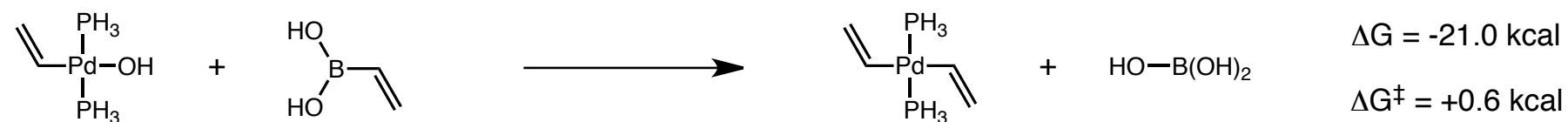# Computational Analysis on Possible Mechanisms of Transmetalation

■ non "base-assisted"

direct

ΔG = +31.6 kcal
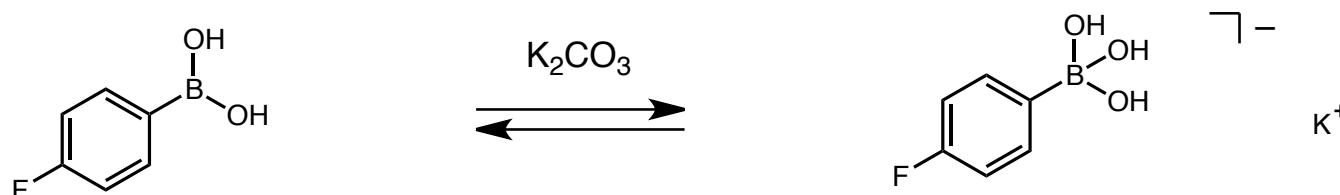
$\Delta G^{\ddagger}$ = +44.6 kcal

■ Pd–Br + trihydroxyborate

ΔG = -17.4 kcal

$\Delta G^{\ddagger}$ = +4.2 kcal

■ Pd–OH + boronic acid

ΔG = -21.0 kcal

$\Delta G^{\ddagger}$ = +0.6 kcal

■ $\Delta G^{\ddagger}$ for formation of Pd–OH species is +6.3 kcal

Experimental Techniques Required to Distinguish

■ weakly basic, organic/aqueous mixed solvent conditions chosen for study

$[ArB(OH)_2]_o = .060$ M

in acetone

| $[K_2CO_3]_o$	$[ArB(OH)_2]$	$[ArB(OH)_3^-]$
.15 M	.017 M	.043 M
.10 M	.020 M	.040 M
.03 M	.030 M	.030 M

■ dilute solution of K_2CO_3 in water added

■ concentrations differ by < 1 order of magnitude upon equilibration (consistent with data in THF)

Carrow, B. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 2116

Butters, M.; Harvey, J.; Jover, J.; Lennox, A.; Lloyd-Jones, G.; Murray, P. *Angew. Chem. Int. Ed.* **2010**, *49*, 5156

Experimental Techniques Required to Distinguish

■ weakly basic, organic/aqueous mixed solvent conditions chosen for study
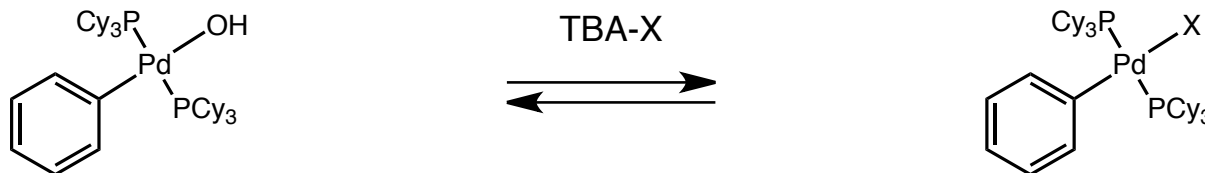
$[Pd\text{-}OH]_o$ = .0013 M

in THF

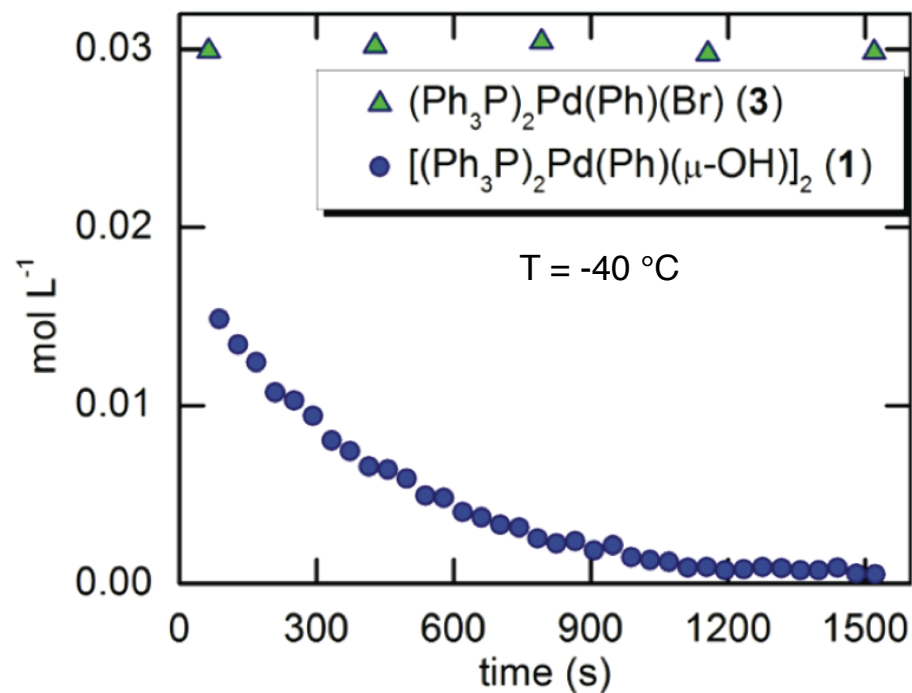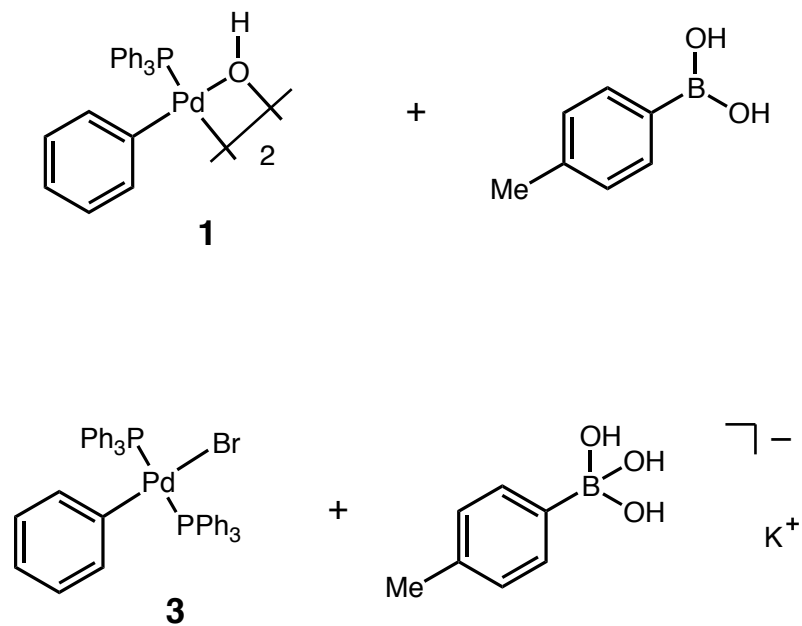■ measured K_{eq} upon adding 1 eq. TBA-X $\longrightarrow$

X	THF/H_2O 25 : 1	THF/H_2O 50 : 1
I	1.1	0.17
Br	9.3	1.3
Cl	23	3.2

■ equilibrium constants show concentrations of each species is also similar

Direct Comparison of Isolable Pd Complexes

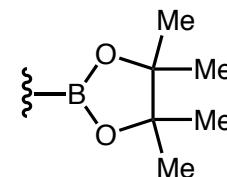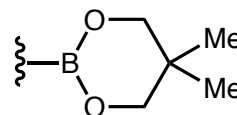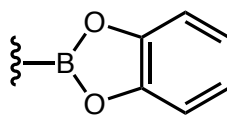■ reaction of stable Pd complexes with 10 eq. boronic acid/boronate measured kinetically
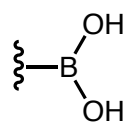

T = -40 °C
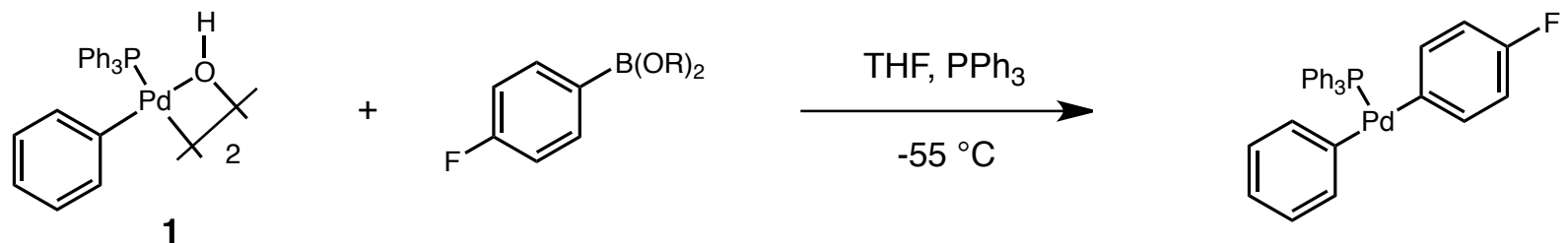
■ **1** shows $k_{obs} = 2.4 \times 10^{-3}$ ■ **3** shows $k_{obs} = 1.7 \times 10^{-7}$

Comparison with Boronic Esters

■ reactions of boronic esters with Pd-OH also outcompete Pd-X and boronate

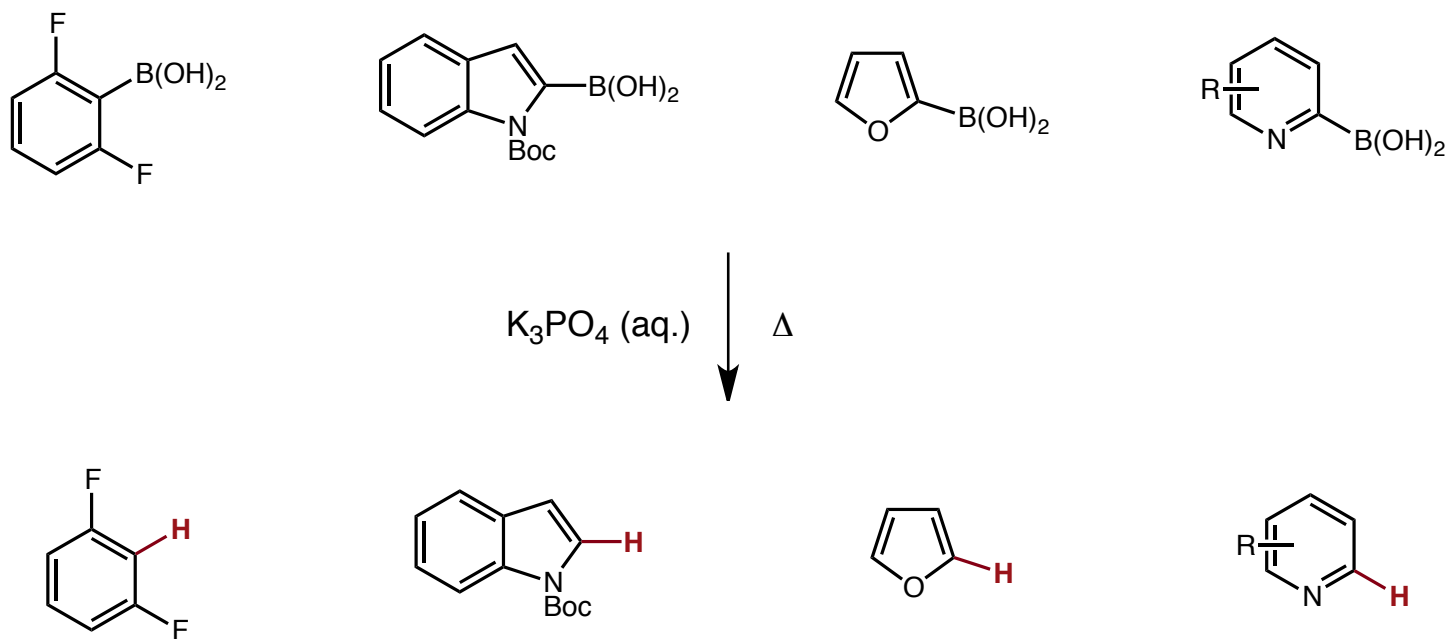
time to >95% conversion

| < 2 min | < 2 min | < 2 min | 1.5 hr |

■ all species reacted orders of magnitute faster with Pd-OH complex **1**

Protodeboration: a Common Problem

■ some boronic acids rapidly undergo protodeboration with aqueous base:
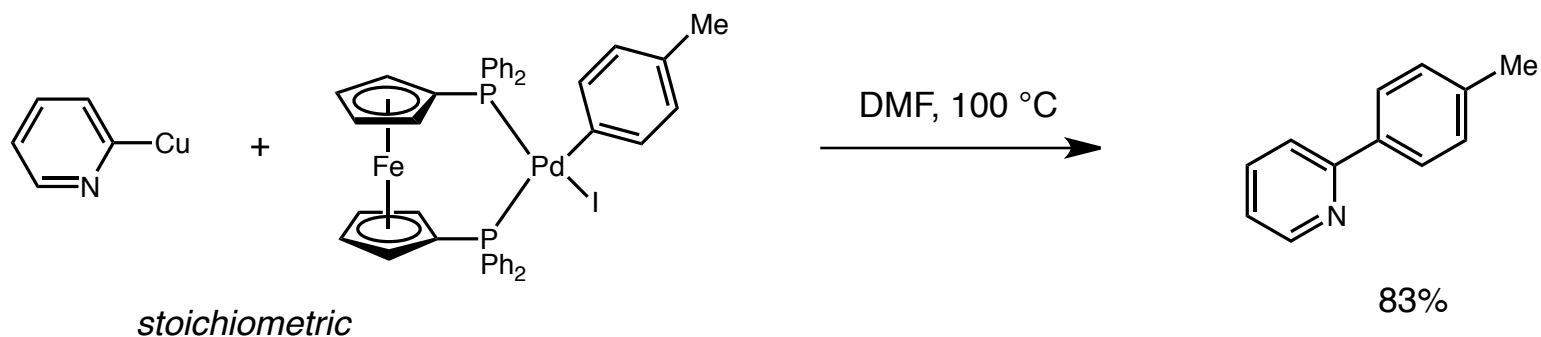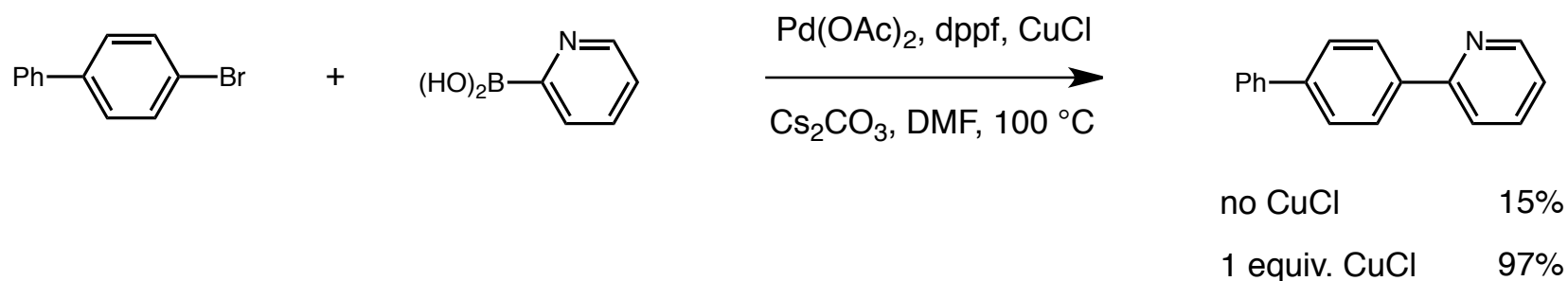

K_3PO_4 (aq.) | Δ

■ but transmetalation to Pd is ~10^4 times faster with Pd-OH generated in aqueous base!

One Approach: Addition of a Transmetalation Catalyst

■ addition of Cu(I) salts is a classic trick used to promote challenging Stille couplings
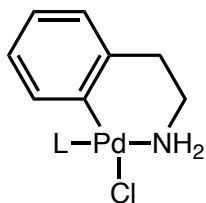
   ■ Merck process group recently disclosed a similar strategy with boronic acids:

no CuCl   15%

1 equiv. CuCl   97%

stoichiometric

83%

   ■ Addition of Cu(I) transmetalation agent allows removal of water from reaction conditions

Deng, J. Z.; Paone, D. V. *et al. Org. Lett.* **2009**, *11*, 345

# *Anther Approach: Use a Catalyst Designed to Shed its Packaging*

■ Often, highly coordinating ligands (PPh$_3$, dba) are used to stabilize Pd^0, but a different ligand is desired

   ■ High temperatures are often required to labilize Pd center; can lead to protodeboration

   ■ The solution: design a "precatalyst" that will shed its ligands rapidly under the reaction conditions:
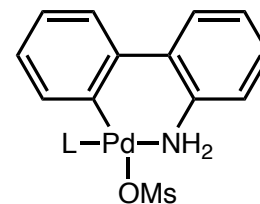
L—Pd—NH$_2$ | Cl	L—Pd—NH$_2$ | Cl	L—Pd—NH$_2$ | OMs
1st Generation	2nd Generation	3rd Generation
2008	*2010*	*2013*

■ strong base promotes reductive elimination
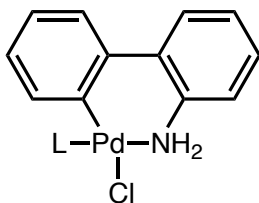
■ *weak* base promotes reductive elimination

■ like Gen. 2, but less coordinating counterion allows use of larger L (and bidentate L)

all precatalysts allow reactions to proceed at room temp.
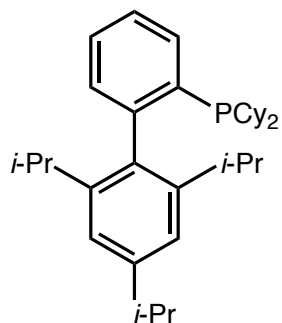
Biscoe, M. R.; Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.*, **2008**, *130*, 6686

Kinzel, T.; Zhang, Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 14073

Bruno, N. C.; Tudge, M. T.; Buchwald, S. L. *Chem. Sci.* **2013**, *4*, 916
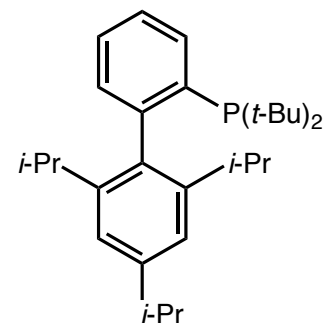
Applications of Differentially-Ligated Palladacycle Precatalysts

L = XPhos

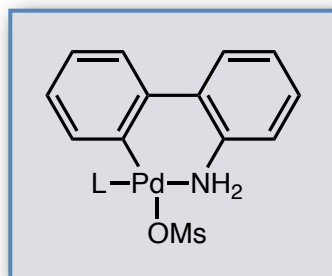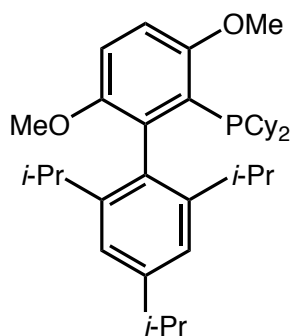

Suzuki couplings with aryl chlorides

L = *t*-BuXPhos

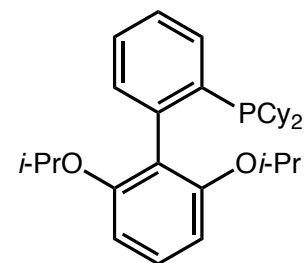direct α-arylation of *t*-butyl acetate

(with LHMDS)
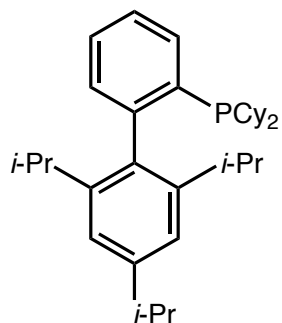

L = BrettPhos

aryl aminations with primary amines

L = RuPhos
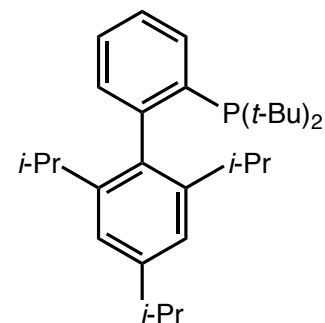

aryl aminations with secondary/tertiary amines

Bruno, N. C.; Tudge, M. T.; Buchwald, S. L. *Chem. Sci.* **2013**, *4*, 916

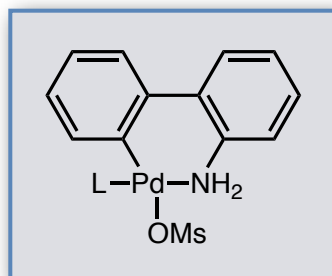*Applications of Differentially-Ligated Palladacycle Precatalysts*

L = XPhos

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Suzuki couplings with aryl chlorides

direct α-arylation of *t*-butyl acetate

(with LHMDS)
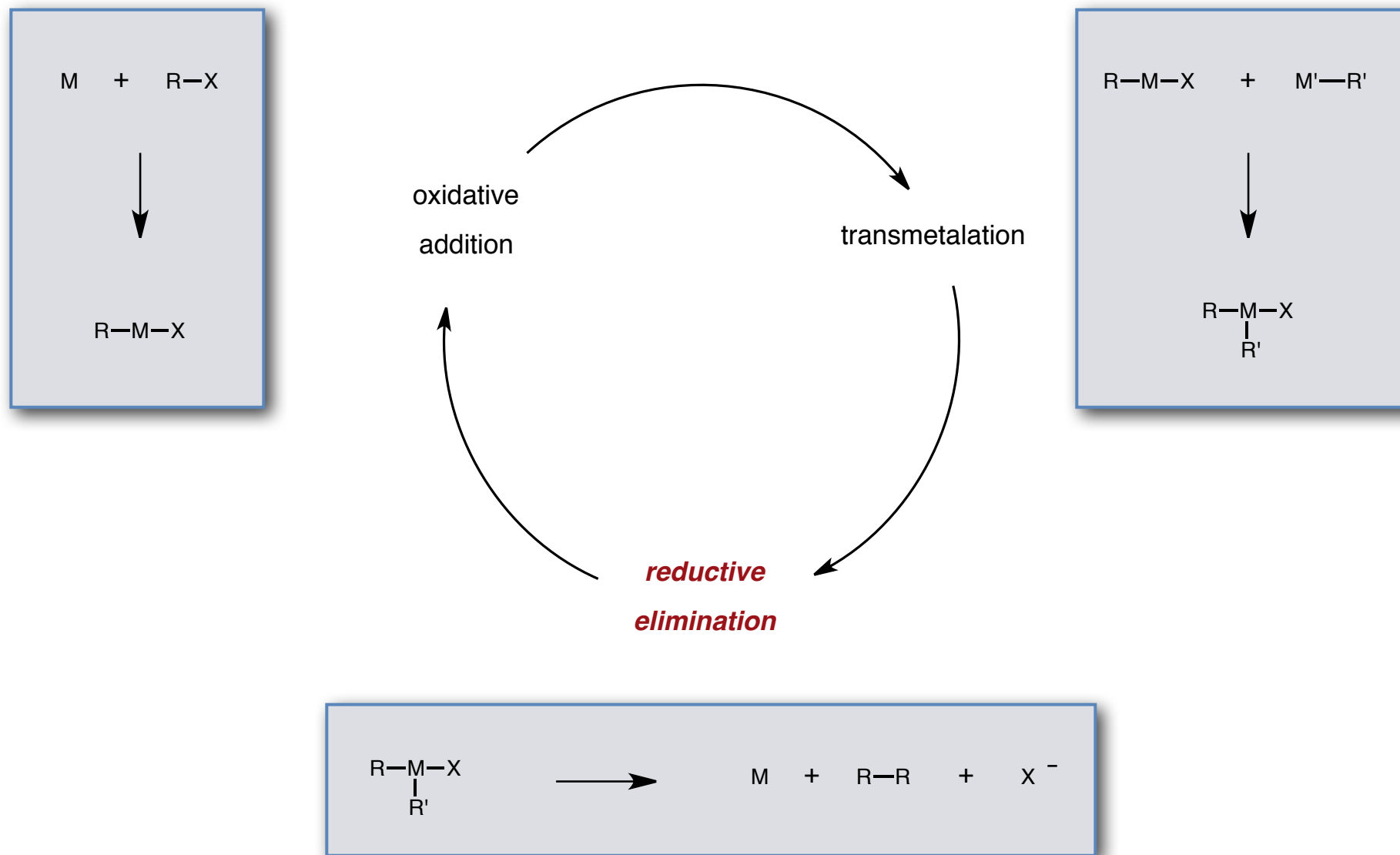
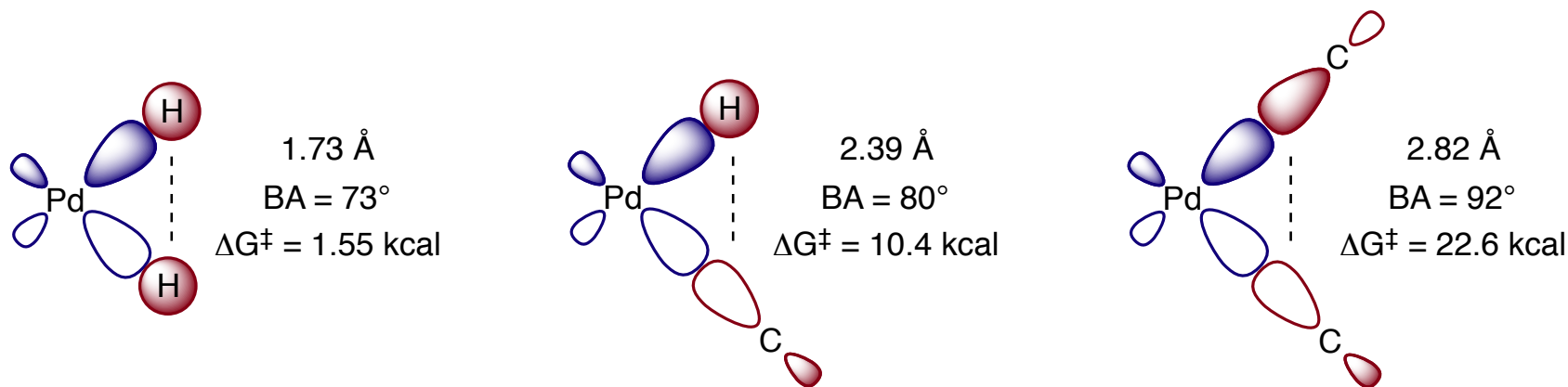BrettPhos precatalyst + RuPhos

RuPhos precatalyst + BrettPhos

successful in aryl aminations with primary,

secondary, and tertiary amines

Bruno, N. C.; Tudge, M. T.; Buchwald, S. L. *Chem. Sci.* **2013**, *4*, 916

Organometallic Cross Coupling: THE Generic Cycle

M   +   R—X

↓

R—M—X

R—M—X   +   M'—R'

↓

R—M—X
   |
   R'

---

oxidative addition

transmetalation

reductive elimination

R—M—X
 |
 R'
   ⟶   M   +   R—R   +   X$^-$

Reductive Elimination: the Bond-Forming Step

■ by comparison, much more is known about reductive elimination

■ microscopic reverse of oxidative addition

■ two ligands must have *cis* relationship to be reductively eliminated (with few exceptions)

1.73 Å
BA = 73°
$\Delta G^{\ddagger}$ = 1.55 kcal

2.39 Å
BA = 80°
$\Delta G^{\ddagger}$ = 10.4 kcal

2.82 Å
BA = 92°
$\Delta G^{\ddagger}$ = 22.6 kcal

■ Rates follow H-H > C-H > C-C (directionality of orbitals involved)

■ for carbon: sp > sp^2 > sp^3

Low, J. J.; Goddard III, W. A. *J. Am. Chem. Soc.* **1984**, *106*, 8321

Requirement of cis Geometry

■ equilibrium data shows that $(PR_3)_2PdMe_2$ isomerizes readily with coordinating solvent

3 : 1 at equilibrium

Conditions: C_6D_6 with 4 equiv THF

50 °C
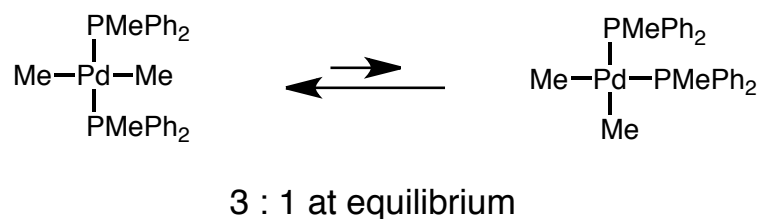
■ coordinating solvent required:
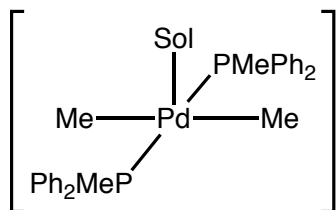
■ no isomerization in $C_2H_2Cl_4$ at 100 °C!
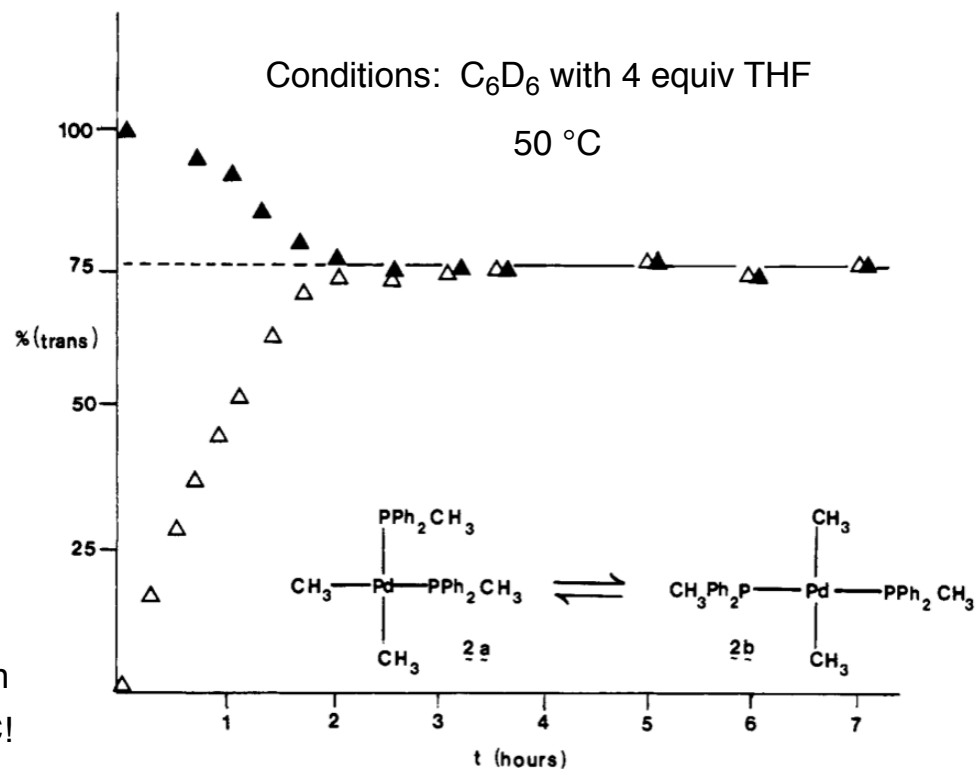
Gillie, A.; Stille, J. K. *J. Am. Chem. Soc.* **1980**, *102*, 4933

Requirement of cis Geometry

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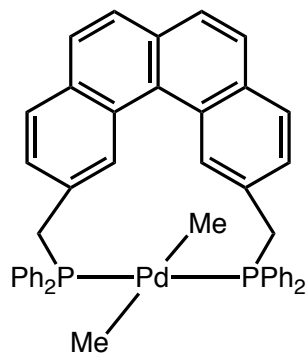

3 : 1 at equilibrium

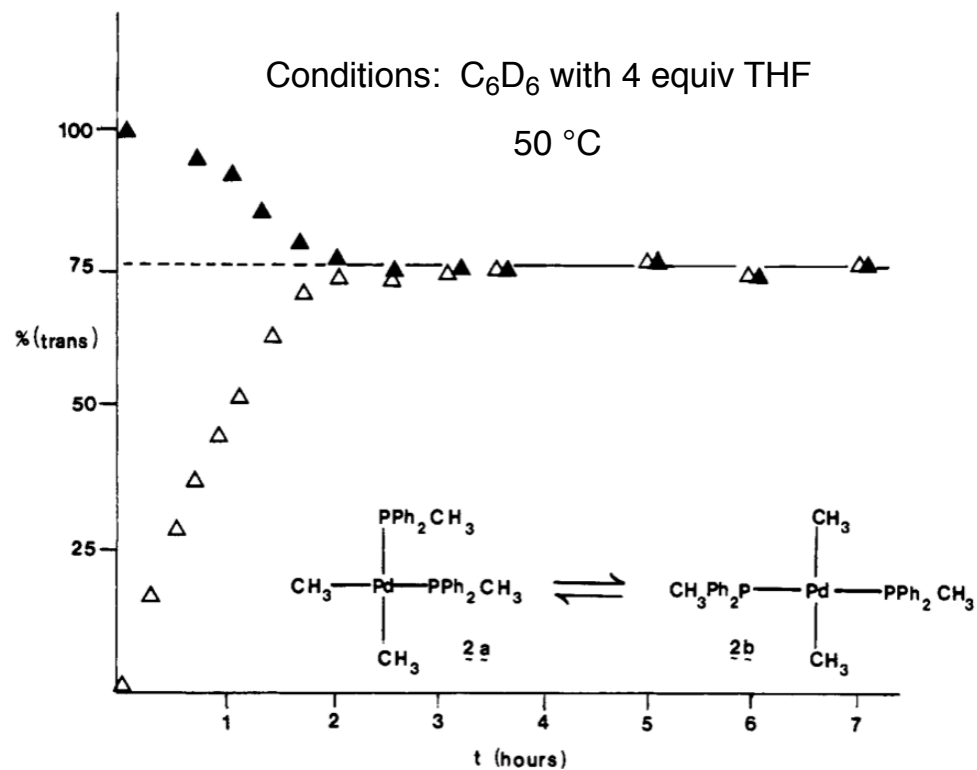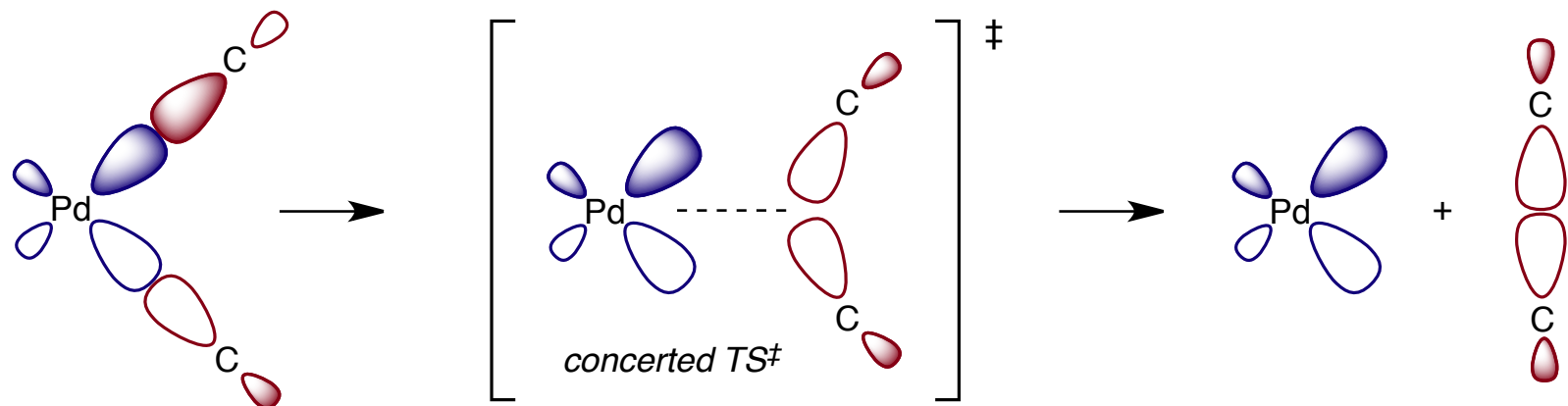Conditions: C_6D_6 with 4 equiv THF

50 °C
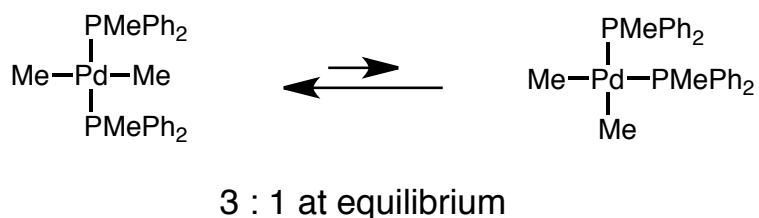
■ *cis* geometry required:

■ no reductive elimination in DMSO at 100 °C!

TRANSPhos

Gillie, A.; Stille, J. K. *J. Am. Chem. Soc.* **1980**, *102*, 4933

Elimination vs. Migration Mechanisms

■ Elimination:

concerted TS‡

■ Migration:

3-centered TS‡
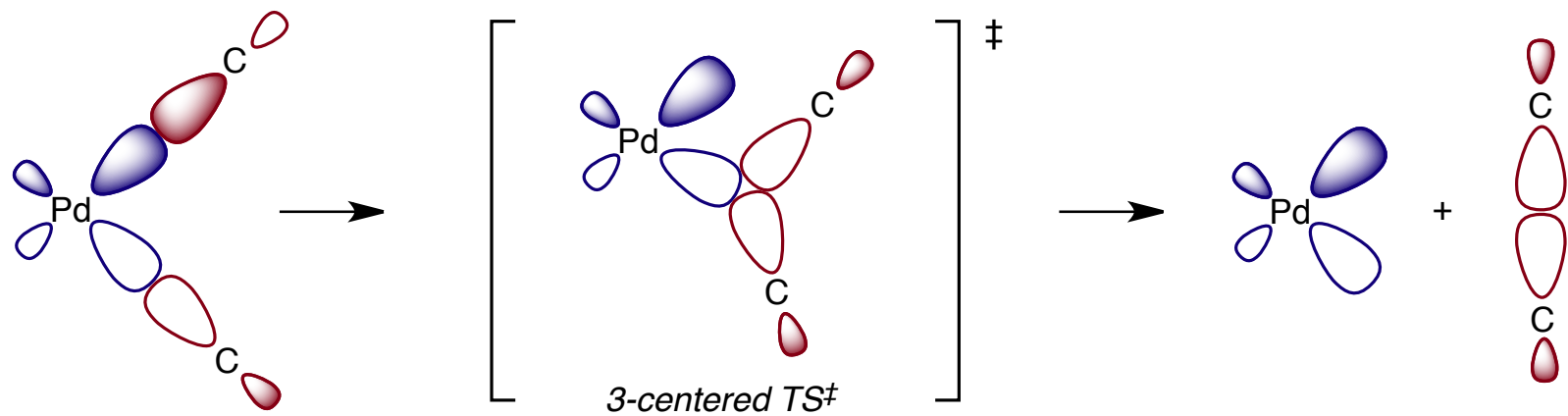
■ Migration mechanism predicted to have ~ 30% lower $\Delta G^{\ddagger}$

Calhorda, M. J.; Brown, J. M.; Cooley, N. A. *Organometallics*, **1991**, *10*, 1431
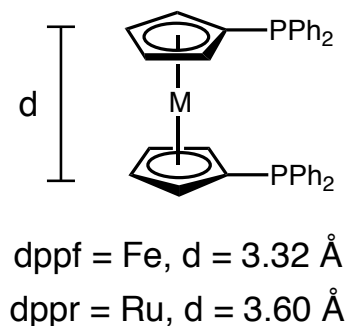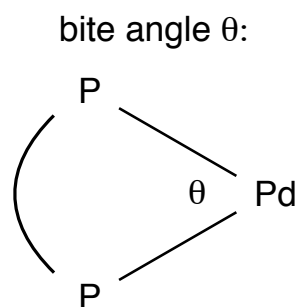
Effect of Bite Angle in Chelating Phosphine Ligands

■ bis(diphenylphosphino)ferrocene has received much attention as a highly active catalyst system:
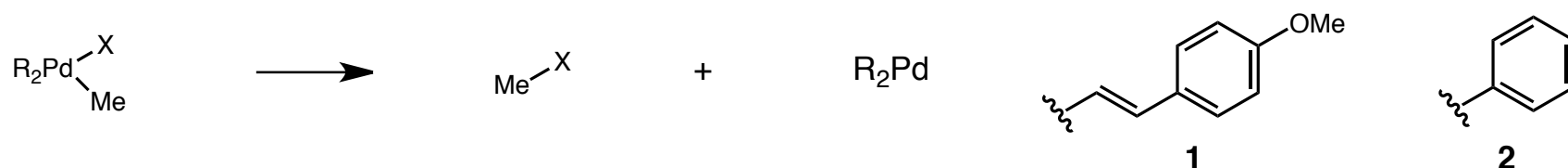
■ theory: large bite angle forces carbon groups into close proximity, favoring reductive elimination

■ changing metal from Fe to Ru should increase d → increase θ

bite angle θ:

dppf = Fe, d = 3.32 Å
dppr = Ru, d = 3.60 Å

ligand	θ	1*	2*
dppp	89°	10 °C	30 °C
dppf	97°	-30 °C	0 °C
dppr	105-110°	-35 °C	-5 °C

* lowest temperature required to observe reductive elimination

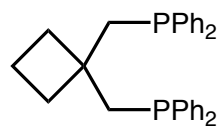■ small differences attributed to low barrier to Cp scissoring vibration (ie θ is fluxional)

Brown, J. M.; Guiry, P. J. *Inorg. Chim. Acta.* **1994**, *220*, 249

Effect of Bite Angle in Chelating Phosphine Ligands

■ similar study using only alkyl linked bisphosphines
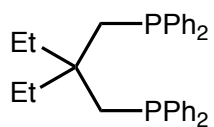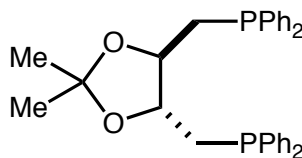
ligand	θ	k_{obs}
dppe	85°	2.1 x 10^{-6}
1	*	2.1 x 10^{-5}
dppp	89°	5.0 x 10^{-5}
2	*	7.4 x 10^{-5}
DIOP	100°	1.0 x 10^{-2}

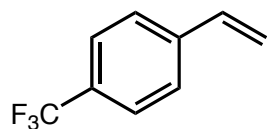* unknown; synthesized for this study

■ overall trend holds: large bite angle accelerates reductive elimination

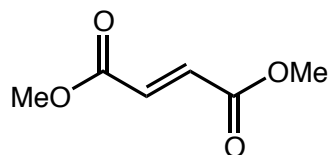# Ligand Electronic Properties also Have a Strong Effect

■ metal is reduced in the product; π-acidic ligands can help accelerate

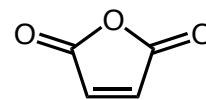$$R_2Pd^{II}{\overset{R^1}{\underset{R^2}{\big\langle}}} \xrightarrow{\text{RE}} R_2Pd^0 \quad + \quad {\overset{R^1}{\underset{R^2}{|}}}$$

■ with nickel:

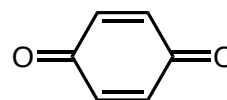Knochel et al.

ACIE, **1998**, *37*, 2387

Doyle et al.

JACS, **2012**, *134*, 9541

■ with palladium:

Schwartz et al.
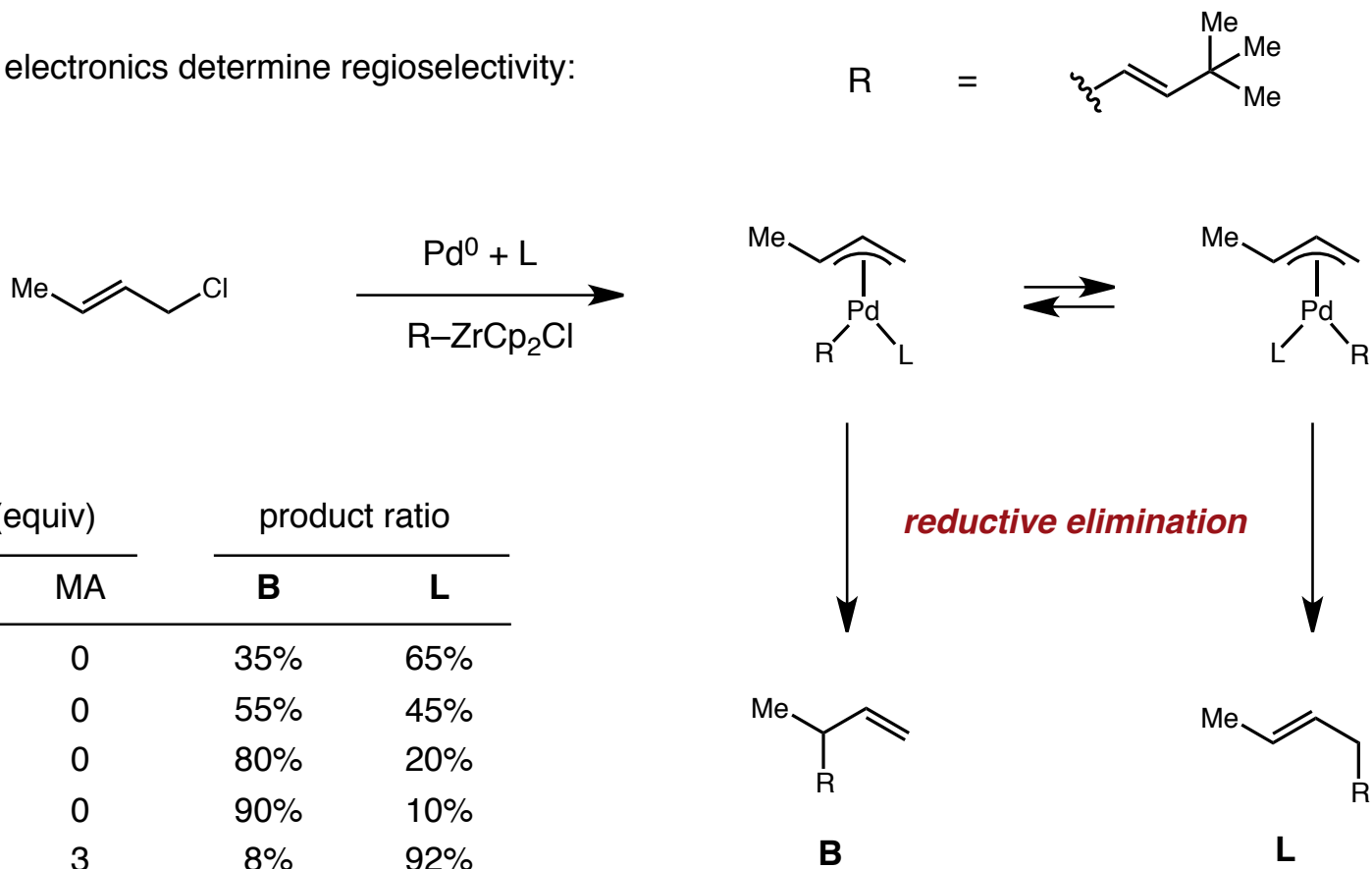
JACS, **1982**, *104*, 1310
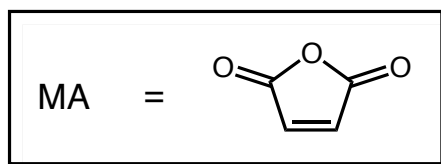
White et al.

JACS, **2005**, *127*, 6970

Johnson, J. B.; Rovis, T. *Angew. Chem. Int. Ed.* **2008**, *47*, 840

Maseras, F.; Espinet, P. *et al. J. Am. Chem. Soc.* **2009**, *131*, 3650

Ligand Electronic Properties also Have a Strong Effect

■ ligand electronics determine regioselectivity:

R   =

Me—CH=CH—CH$_2$—Cl

$\xrightarrow{\text{Pd}^0 + \text{L}}{\text{R–ZrCp}_2\text{Cl}}$

reductive elimination

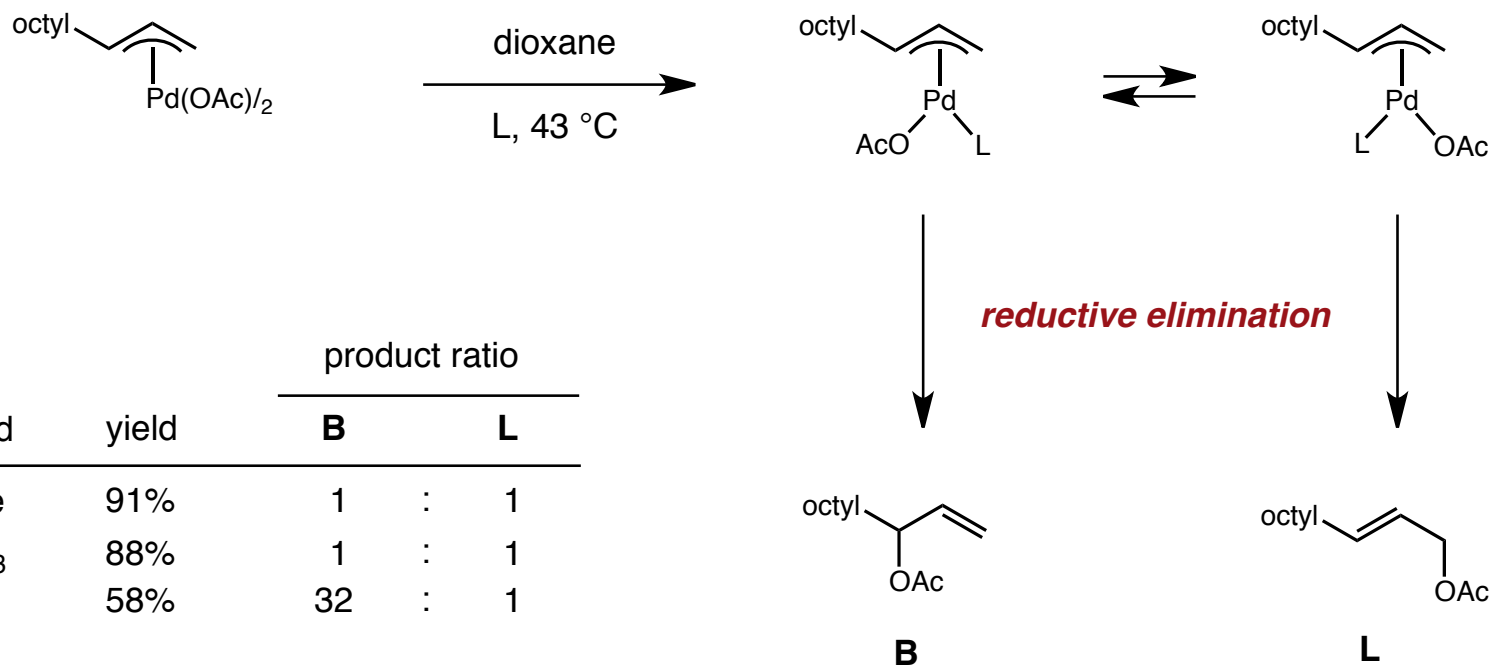| ligand (equiv)		product ratio	
PPh$_3$	MA	**B**	**L**
0	0	35%	65%
2	0	55%	45%
4	0	80%	20%
9	0	90%	10%
0	3	8%	92%

B

L

■ switching to π-acid ligand promotes linear selectivity

MA   =

Temple, J. S.; Riediker, M.; Schwartz, J. *J. Am. Chem. Soc.* **1982**, *104*, 1310

Hayasi, Y.; Riediker, M.; Temple, J. S.; Schwartz, J. *Tetrahedron Lett.* **1981**, *22*, 2629

Ligand Electronic Properties also Have a Strong Effect

■ opposite regioselectivity observed when acetate replaces R:

reductive elimination

ligand	yield	product ratio B	L
dppe	91%	1	:	1
PPh$_3$	88%	1	:	1
BQ	58%	32	:	1

BQ = O=⟨⟩=O
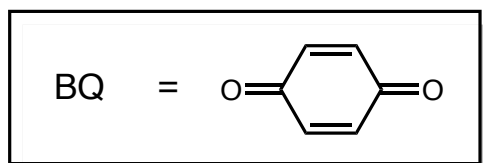
■ now π-acid ligand gives branched product selectively!

Chen, M. S.; Prabagaran, N.; Labenz, N. A.; White, M. C. *J. Am. Chem. Soc.* **2005**, *127*, 6970

Differences in Reactivity Produce Differences in Selectivity

■ comparison of the conditions reveals a clear difference in reactivity:
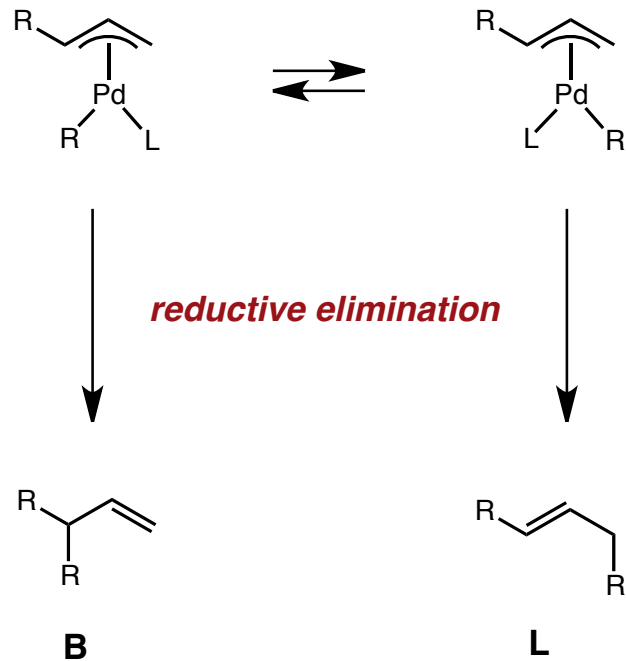
■ Schwartz (for stoichiometric variant):
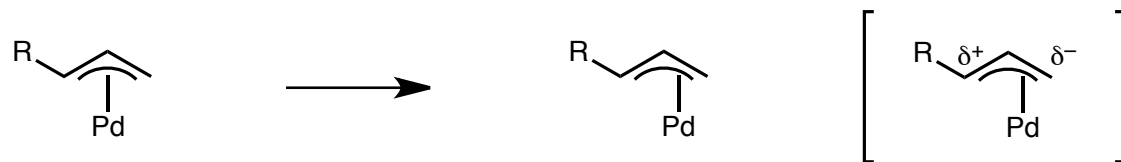
■ R = vinyl (sp^2), -78 °C, 5 min, 96%

■ *RE is fast*

■ White:

■ R = OAc (sp^3), 43 °C, 6 hr, 58%

■ *RE is slow*

The "Trans Effect" and how it Affects Complex Stability

■ in reality, the π-allyl ligand is not symmetric → Pd sits closer to primary terminus (sterics)

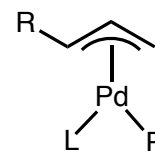■ this terminus is now a stronger σ-donor

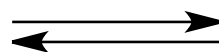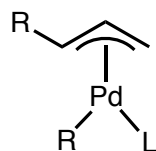
■ in ground state, σ-donor ligands (phosphine) sit cis to primary terminus, while

π-acceptor ligands (MA, BQ) sit trans

preferred for

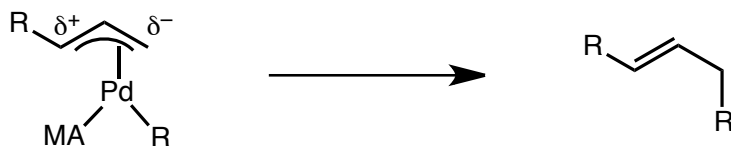*L = PR$_3$*

preferred for

L = MA, BQ

Appleton, T. G.; Clark, H. C.; Manzer, L. E. *Coord. Chem. Rev.* **1973**, *10*, 335
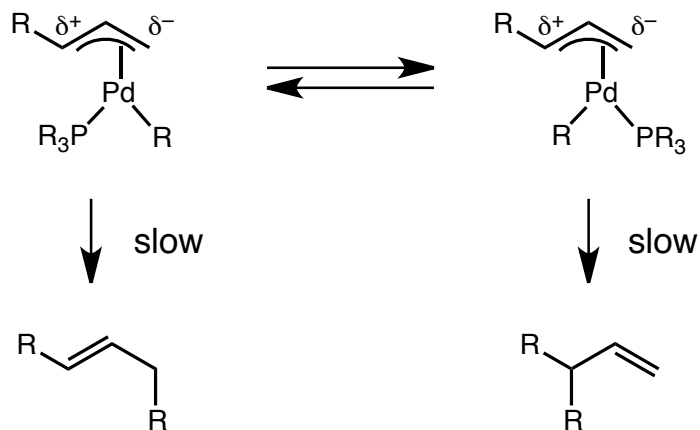
How this Relates to Anything Meaningful

■ Case 1: fast reductive elimination (Schwartz):

■ elimination occurs from more stable
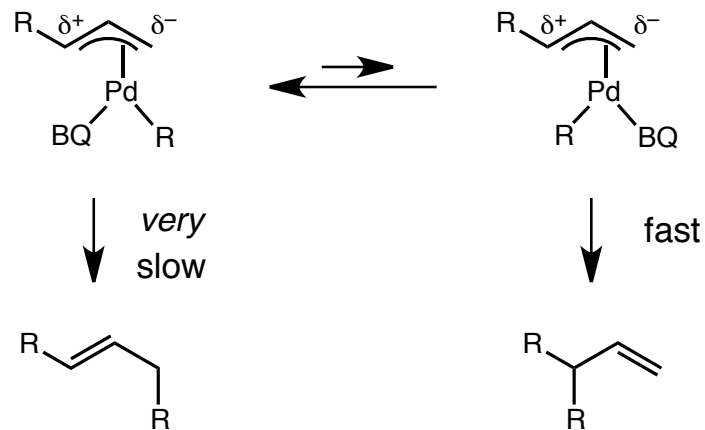complex, high linear selectivity observed

■ Case 2: slow reductive elimination (White):

■ donor ligand (phosphine)

slow

slow

■ low B : L selectivity because phosphines
are also weak π-acceptors

■ acceptor ligand (MA, BQ)

very slow

fast

■ major isomer is too stable to eliminate;
high branched selectivity from Curtin-Hammett principle