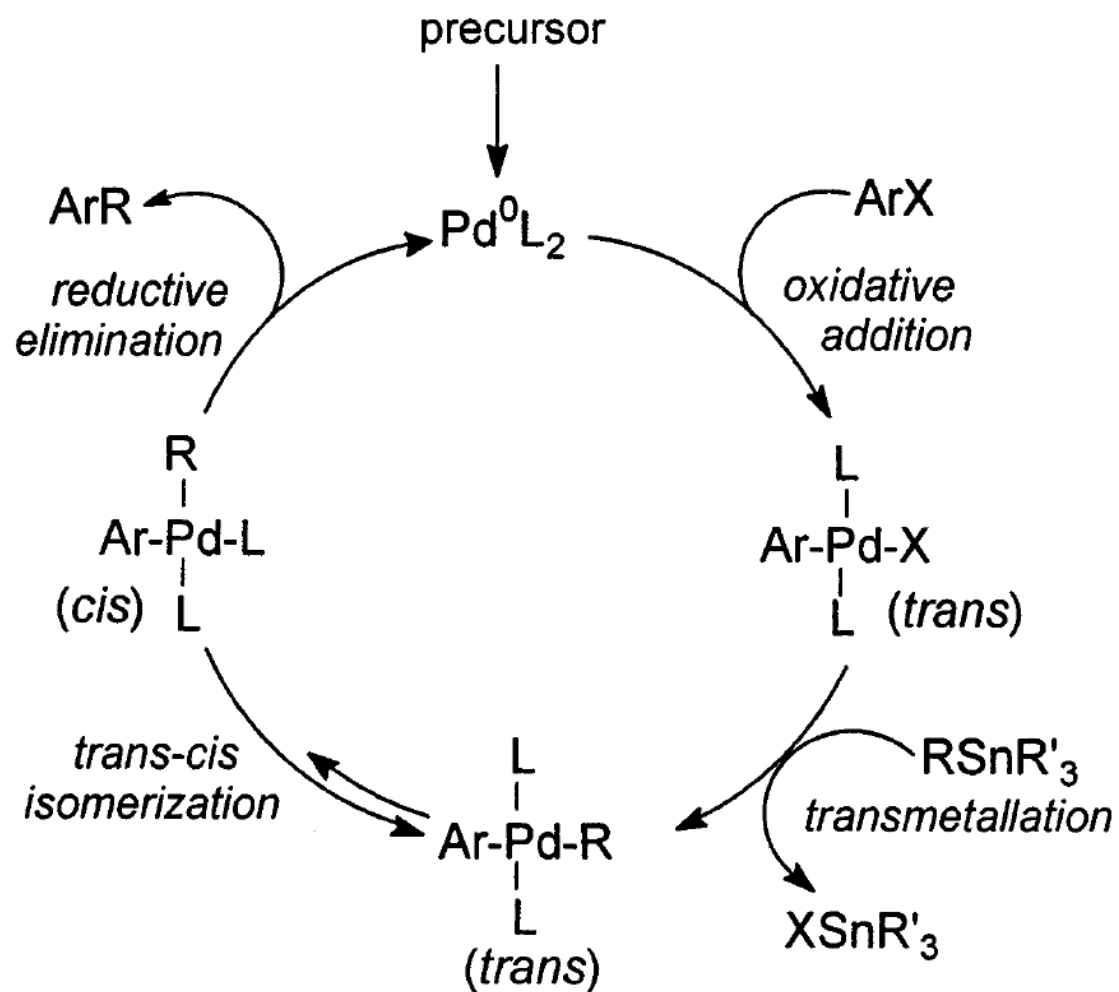


Transmetalation from Tin to Palladium in the Stille Reaction

Peter J. Yao
Group Meeting
24 Jan 06

Classical Mechanism

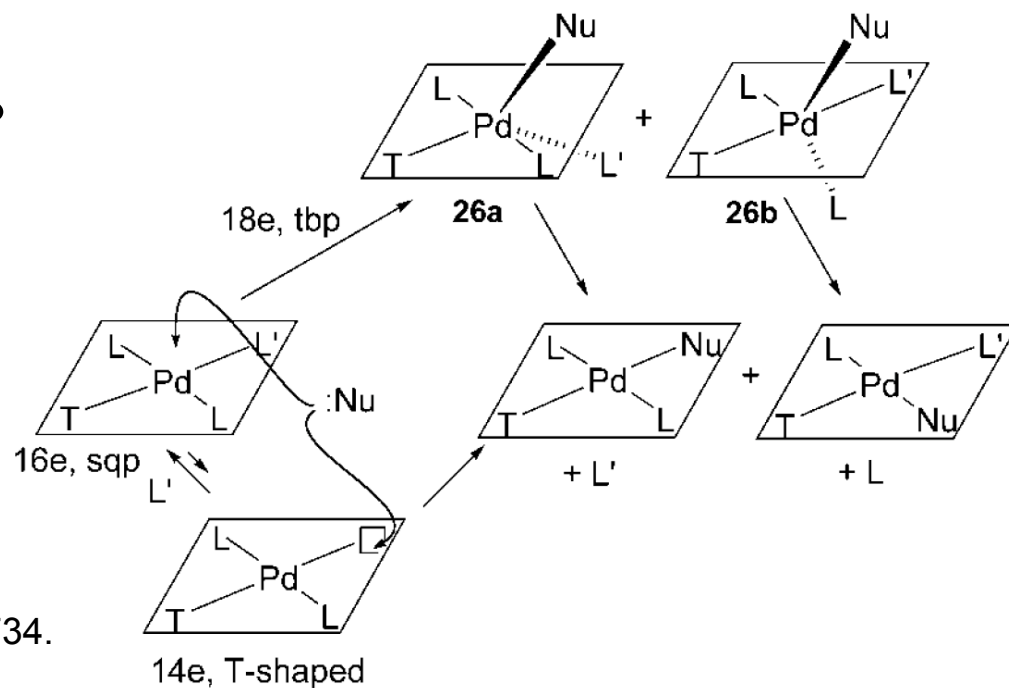


Transmetalation

Mechanism of transmetalation is not as well known as oxidative addition and reductive elimination

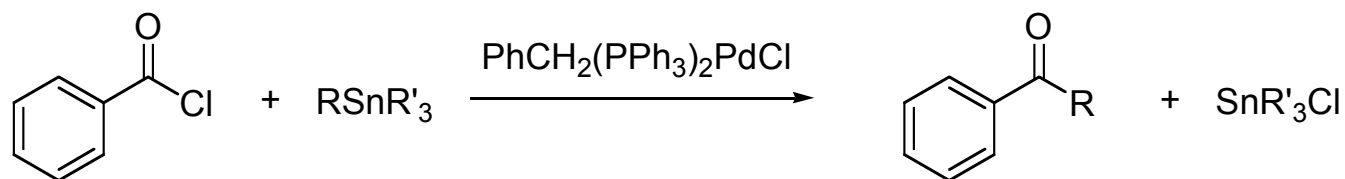
Several important questions:

- When is transmetalation rate-limiting?
- Inversion or retention at α -carbon?
- Which is displaced, X or L?
- **Associative or dissociative?**



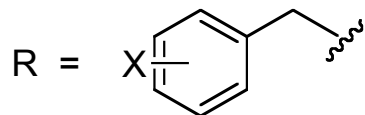
Early Mechanistic Studies

Coupling of organostannanes with acid chlorides



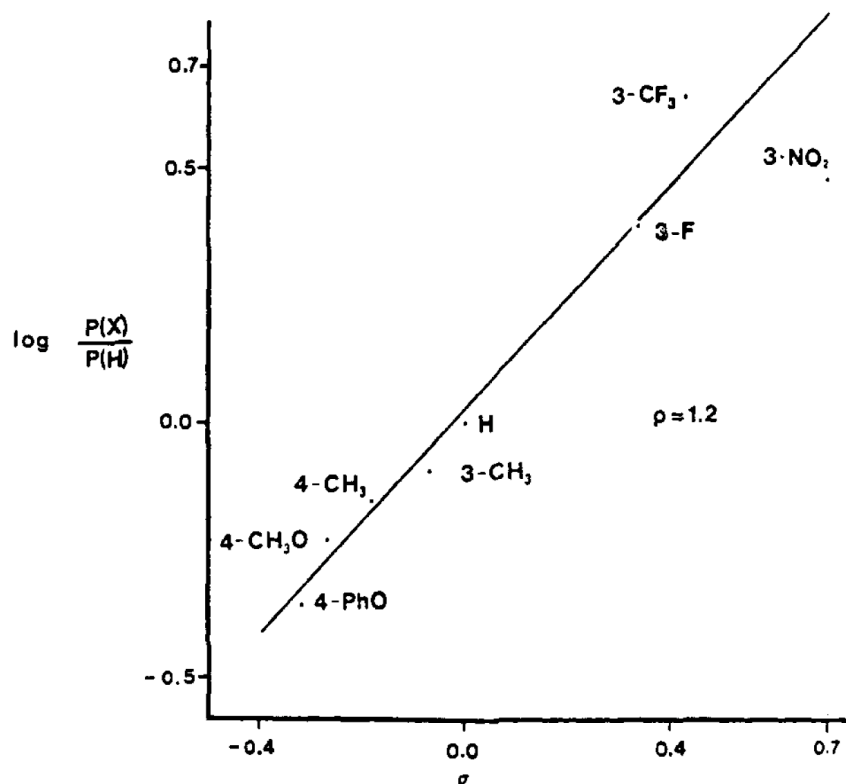
Stille, J. K. *JACS* **1983**, *105*, 6129-6137.

Hammett study, 5 mol% [Pd] in HMPA



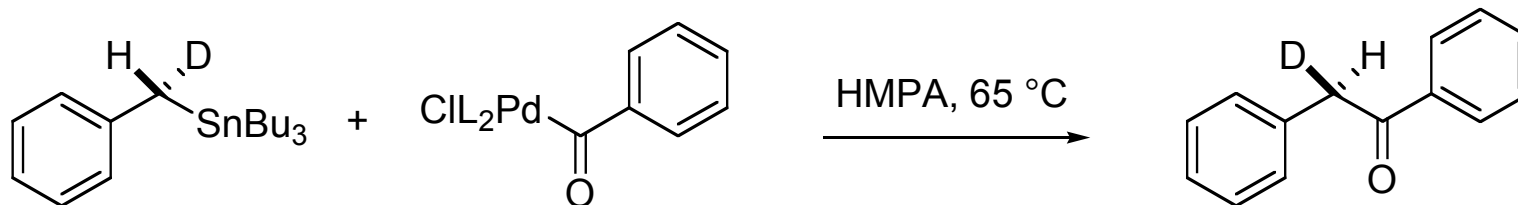
ρ correlates with σ better than σ'

Positive ρ suggests C-Sn breaking precedes C-Pd making in TS



Early Mechanistic Studies

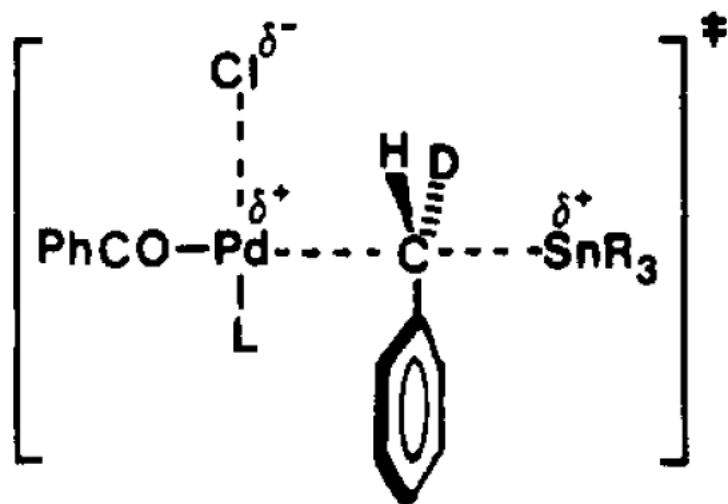
Inversion at α -carbon



Starting from (*S*)-(+)-Benzyl- α -*d* alcohol, er 92/8

er 64/36

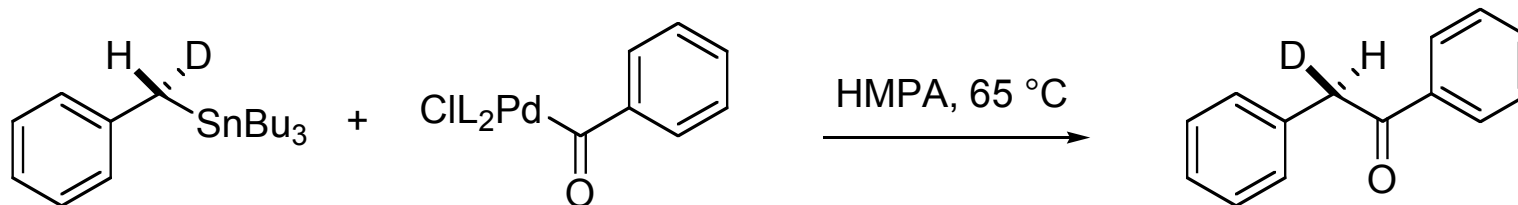
Taking racemization and deuterium isotope effect into account, estimated 65% stereospecificity – **inversion**



Postulated an open transition state
 $S_{\text{E}}2$ electrophilic cleavage
Prior dissociation of L?

Early Mechanistic Studies

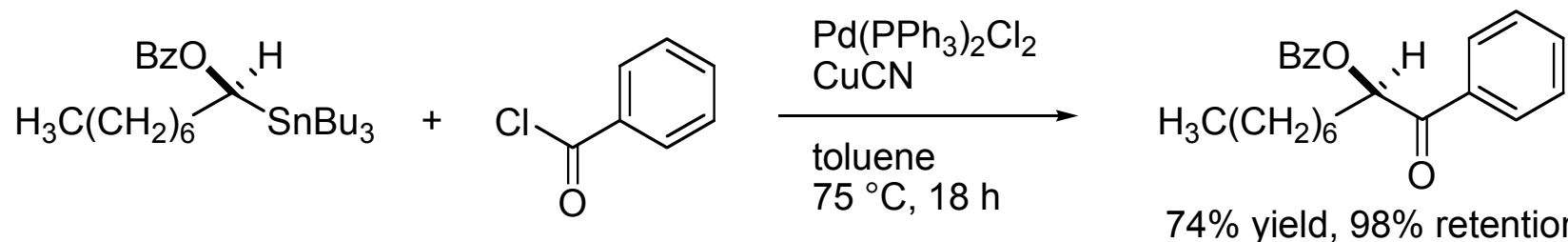
Inversion at α -carbon



Starting from (*S*)-(+)-Benzyl- α -*d* alcohol, er 92/8

er 64/36

Retention at α -carbon

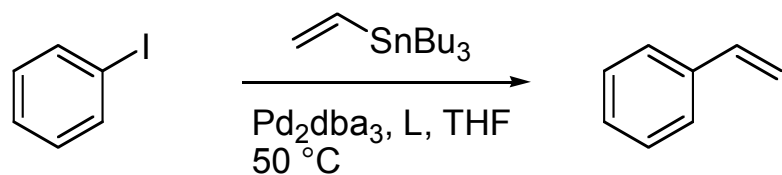


Falck, J. R. *JACS* **1994**, *116*, 1-5.

74% yield, 98% retention

Ligand Effects

Farina studied the effect of ligands on coupling of vinyltributylstannane with various electrophiles



Pd:L ratio = 1:4

L	rel. rate	yield (72 h)
PPh_3	1.0	15.2
$(2\text{-MeC}_6\text{H}_4)_3\text{P}$	35.2	19
AsPh_3	1100	>95
$(2\text{-furyl})_3\text{P}$	105	>95

Pd:L ratio = 1:2

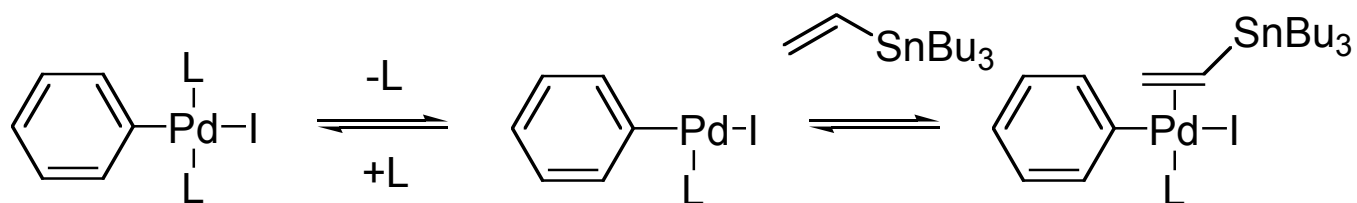
PPh_3	19	15.2
$(2\text{-MeC}_6\text{H}_4)_3\text{P}$	119	25
AsPh_3	391	>95
$(2\text{-furyl})_3\text{P}$	1480	>95

Good σ -donors are poor at promoting coupling

Excess ligand inhibits the reaction

Ligand Effects – Dissociative Mechanism

Farina suggested that ligand dissociation is key for transmetalation



(The 14-electron T-shaped complex is not explicitly shown in the text)

Solvent coordination is often shown rather than an empty coordination site.

More Evidence for Dissociative Mechanism

Hartwig studied transmetalation to a dimeric complex



Hartwig, J. F. *JACS* **1995**, *117*, 11598-11599.



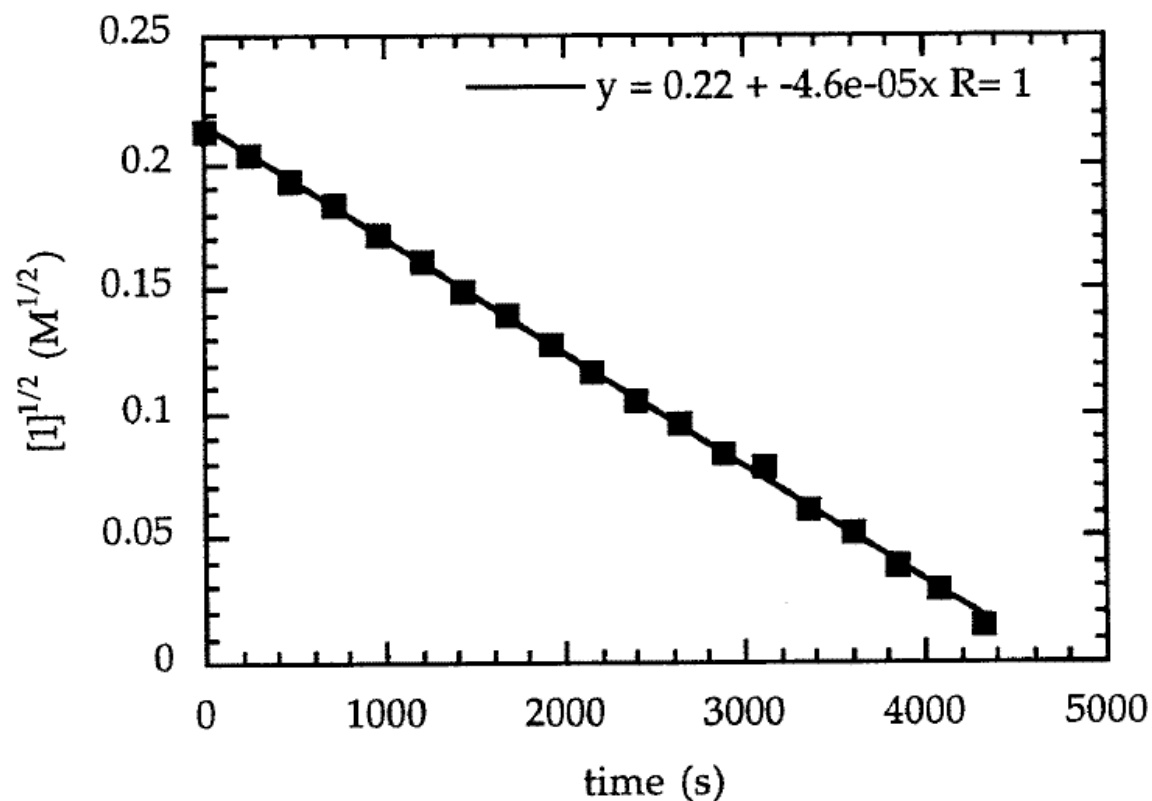
Assuming pre-equilibrium, then:

$$\text{rate} = Kk_2[\text{dimer}]^{1/2}[\text{PhSnMe}_3]$$

Integrated form:

$$[\text{dimer}]^{1/2} = -k_{\text{obs}} t$$

Transmetalation Kinetics

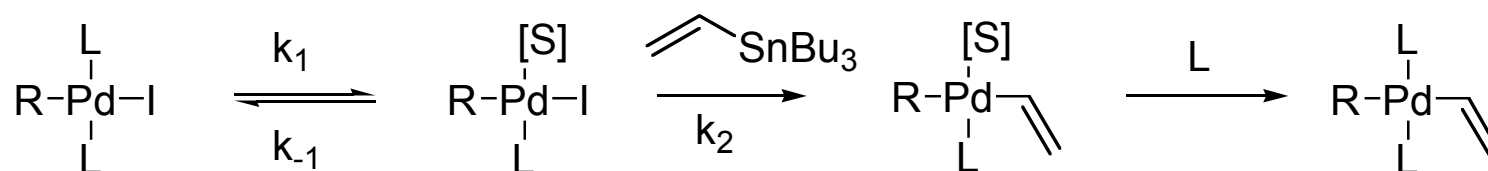


The data fits nicely... does that mean a 14-e T-shaped complex exists in solution? Espinet suggests an agostic interaction with a C-H bond in the *o*-methyl on $P(o\text{-tolyl})_3$.

Is the pre-equilibrium model accurate?

Another Proposal

Espinet questioned the feasibility of a dissociative mechanism



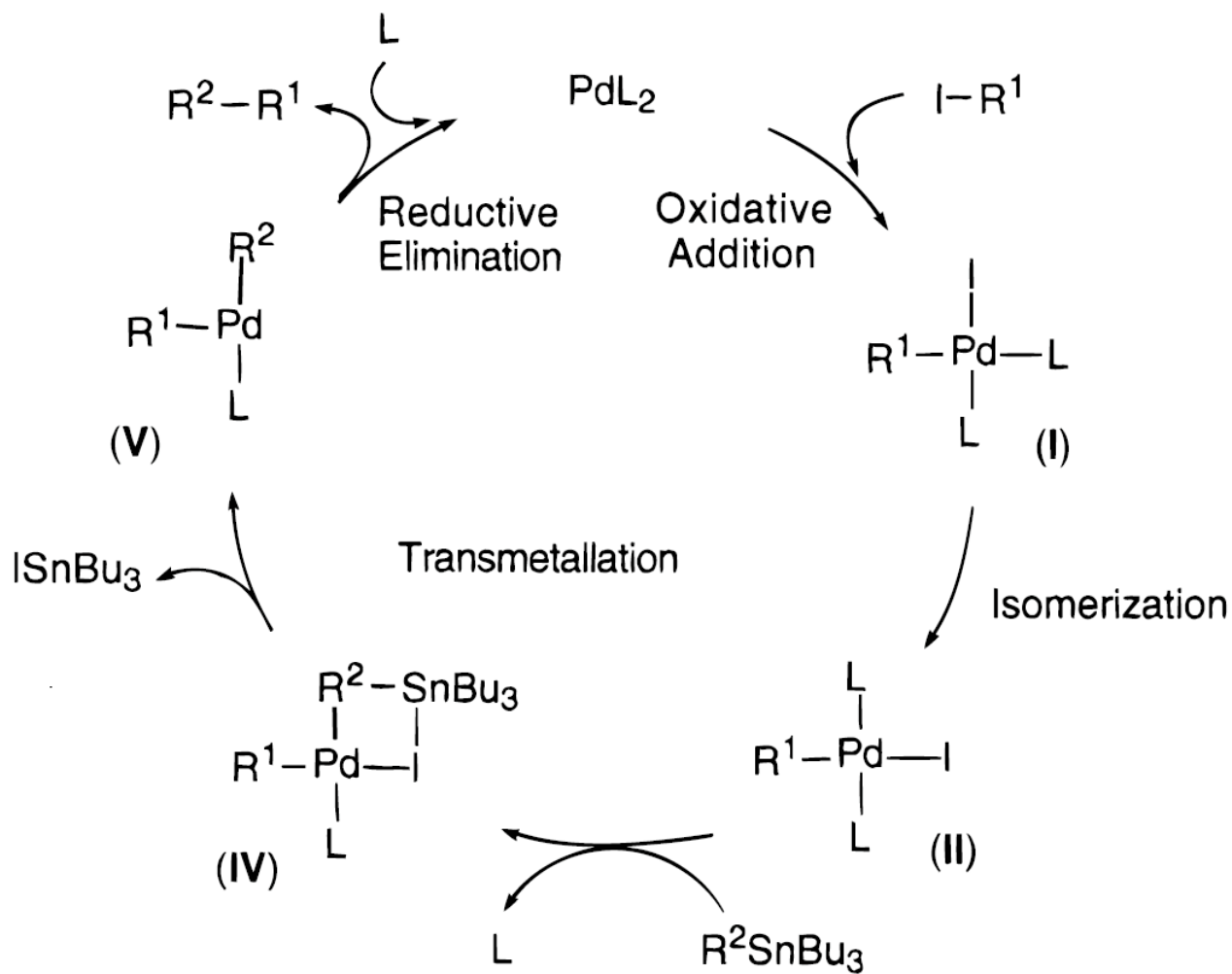
Using $K = k_1/k_{-1} = 8.6 \times 10^{-4} \text{ M}$ ($\text{R} = \text{Ph}$, $\text{L} = \text{AsPh}_3$) and $[\text{Pd}]_{\text{total}} = 3.2 \times 10^{-3} \text{ M}$, he calculated that $[\text{PdPhI}(\text{AsPh}_3)] = 1.3 \times 10^{-3} \text{ M}$ *i.e.* 40% dissociation.

He also argued against X-for-R' substitution in the classical mechanism because it necessitates a fast *trans-cis* isomerization.

Another Proposal

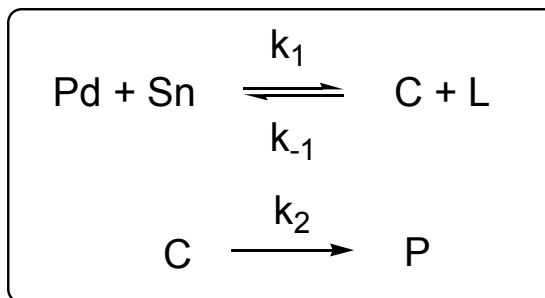
Espinet's initial proposal

Espinet, P. *JACS* **1998**, *120*, 8978-8985.



Rate Expressions

Associative



Pd = RPdL_2X
Sn = vinylSnBu₃
C = cyclic intermediate
P = RPdL(vinyl)

Steady-state assumption: $\frac{d[\text{C}]}{dt} = 0$

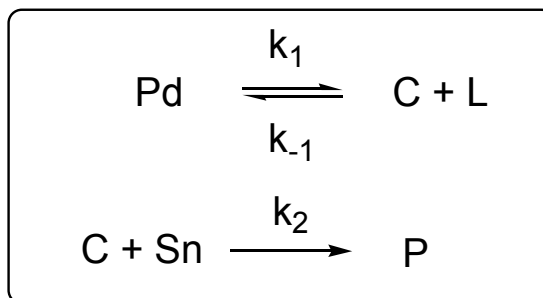
$$\text{rate} = \frac{k_1 k_2}{k_{-1}[\text{L}] + k_2} [\text{Pd}][\text{Sn}]$$

Pre-equilibrium assumption: $K = \frac{k_1}{k_{-1}} = \frac{[\text{C}][\text{L}]}{[\text{Pd}][\text{Sn}]}$

$$\text{rate} = \frac{K k_2 [\text{Pd}][\text{Sn}]}{[\text{L}] + K[\text{Sn}]}$$

Rate Expressions

Dissociative



Pd = RPdL_2X
Sn = vinylSnBu_3
C = RPdLX
P = RPdL(vinyl)

Steady-state assumption: $\frac{d[\text{C}]}{dt} = 0$

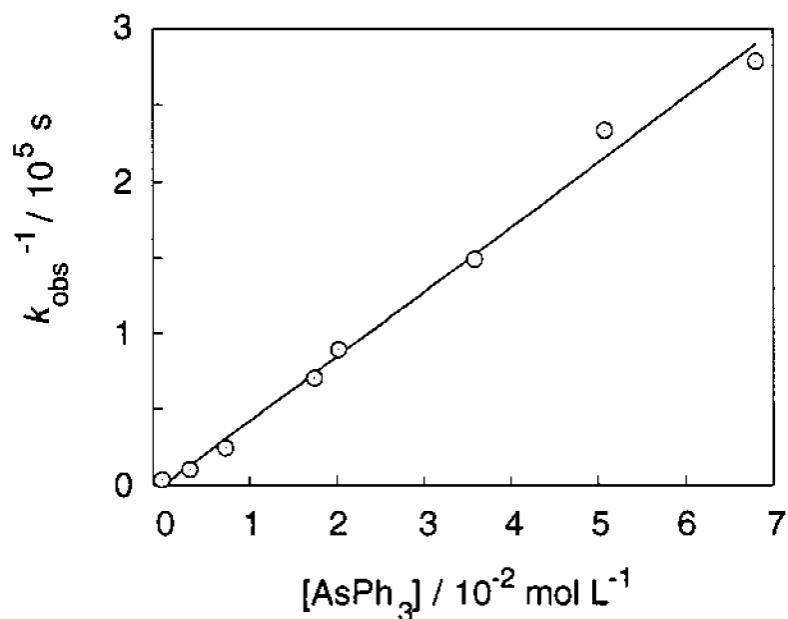
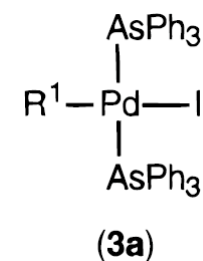
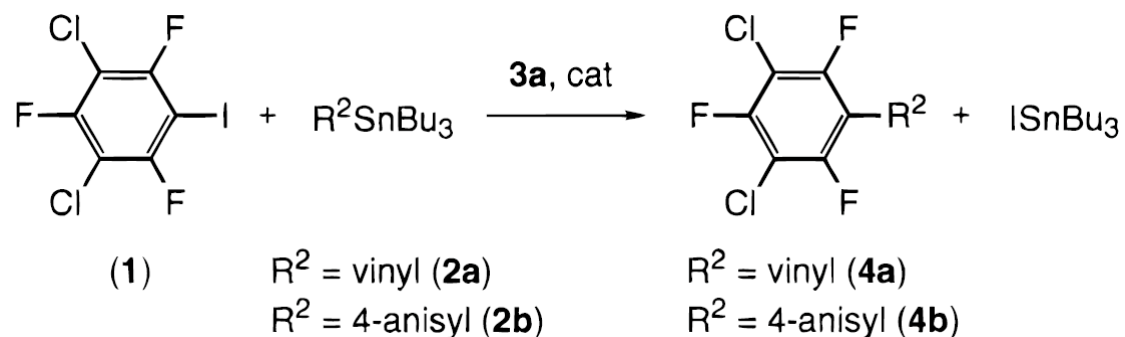
$$\text{rate} = \frac{k_1 k_2}{k_{-1}[\text{L}] + k_2[\text{Sn}]} [\text{Pd}] [\text{Sn}]$$

Pre-equilibrium assumption: $K = \frac{k_1}{k_{-1}} = \frac{[\text{C}][\text{L}]}{[\text{Pd}]}$

$$\text{rate} = \frac{K k_2 [\text{Pd}] [\text{Sn}]}{[\text{L}] + K}$$

Kinetic Studies

Coupling monitored by ^{19}F -NMR

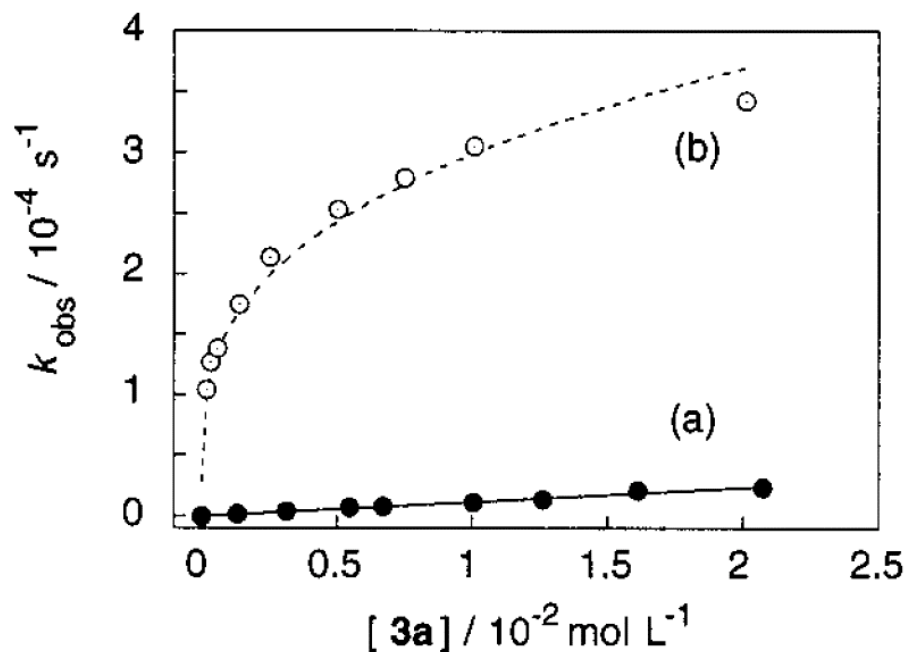


Retardation by adding free ligand
(for coupling with (vinyl)SnBu₃)

Kinetic Studies

(a) Catalyst activity, showing a first order dependence on [catalyst]

(b) Without addition of AsPh_3



Eyring plots of $\ln(k_{\text{obs}}/T)$ vs. $1/T$ give ΔH^\ddagger and ΔS^\ddagger

R^2	solvent	$\Delta H^\ddagger_{\text{obs}}/\text{kJ mol}^{-1}$	$\Delta S^\ddagger_{\text{obs}}/\text{J K}^{-1} \text{mol}^{-1}$
vinyl	THF	50 ± 2	-155 ± 7
vinyl ^a	THF	91 ± 4	-56 ± 15
vinyl	PhCl	70.0 ± 1.7	-104 ± 6
4-anisyl	THF	72.8 ± 1.1	-100 ± 3

negative ΔS^\ddagger consistent with associative rate-controlling step

^a With $[\text{AsPh}_3] = 0.02 \text{ mol L}^{-1}$.

Dissociative vs. Associative

Experimentally, the form of the rate equation is

$$rate = \frac{a}{[L]^+ b} [Pd] [Sn]$$

Dissociative

Consider both steady-state and pre-equilibrium models

- Steady-state

$$rate = \frac{k_1 k_2}{k_{-1} [L]^+ + k_2 [Sn]} [Pd] [Sn]$$

For small values of [L], rate $\sim k' [Pd]$ i.e. zero-order in [Sn]

- Pre-equilibrium

$$rate = \frac{K k_2 [Pd] [Sn]}{[L]^+ + K}$$

This equation fits the empirical rate equation. However it gives a value of $K_{\text{dissociation}} = 0.013 \text{ mM}$, 12% of $[Pd]_{\text{total}}$ which should be observable by NMR.

Dissociative vs. Associative

Experimentally, the form of the rate equation is

$$rate = \frac{a}{[L]^+ b} [Pd][Sn]$$

Associative

The steady-state model has the correct form of the rate equation.

$$rate = \frac{k_1 k_2}{k_{-1}[L]^+ + k_2} [Pd][Sn]$$

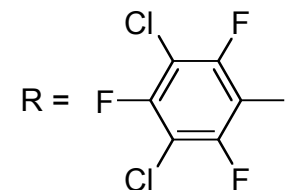
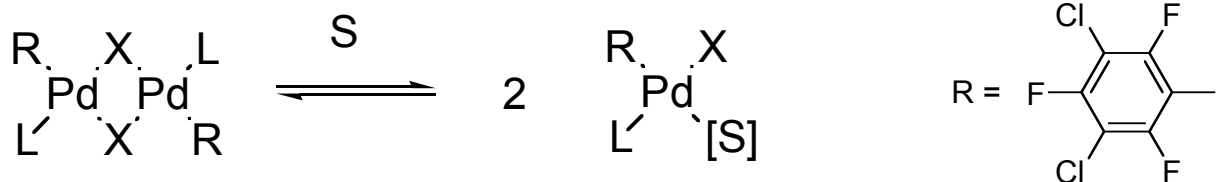
$$k_1 = 0.034 \text{ M}^{-1} \text{ s}^{-1} \quad k_2/k_{-1} = 0.069 \text{ mM}$$

However, this does not tell us about the structure of intermediate C. For example C can be a π -complex of the vinyl portion with Pd.

Geometry and Coordination at Palladium

Amatore claimed in a study on oxidative addition to have evidence of a 14-e T-shaped Pd complex, observable by $^1\text{H-NMR}$ and CV.

Espinet investigated this claim further by looking at the equilibrium:



In chloroform and THF, only the dimer is observed.

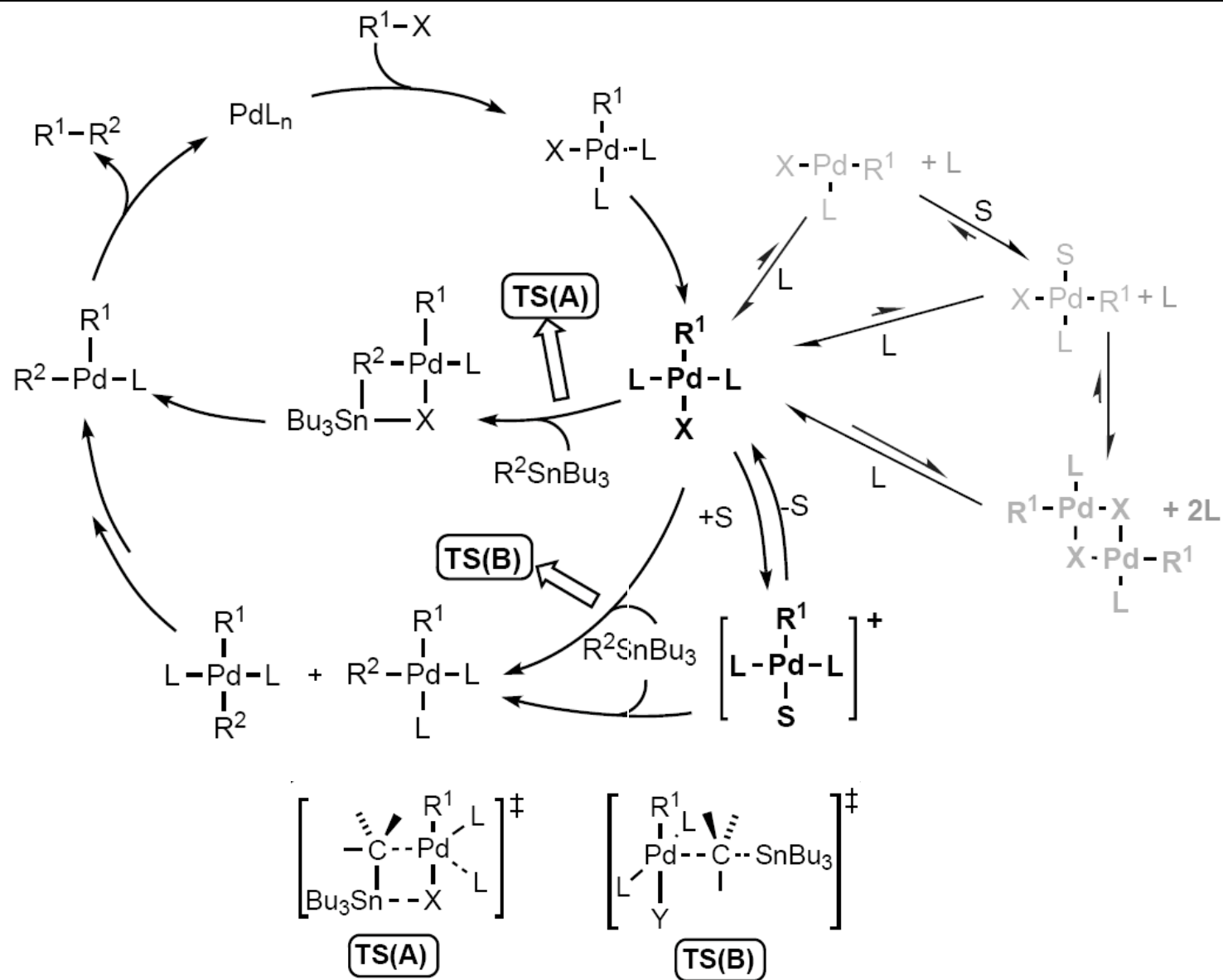
However in DMF the monomer is observed.

Which is the active species for transmetalation? Espinet suggested it is always $[\text{PdPh}(\text{AsPh}_3)_2]$.

Amatore, C. *Chem. Eur. J.* **2001**, 7, 2134-2142.

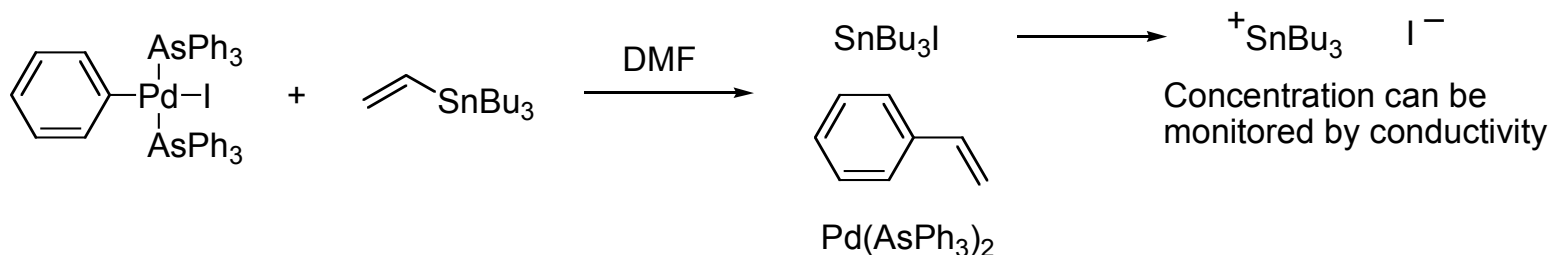
Espinet, P. *Chem. Eur. J.* **2002**, 8, 4843-4853.

Modified Proposal (Espinete)

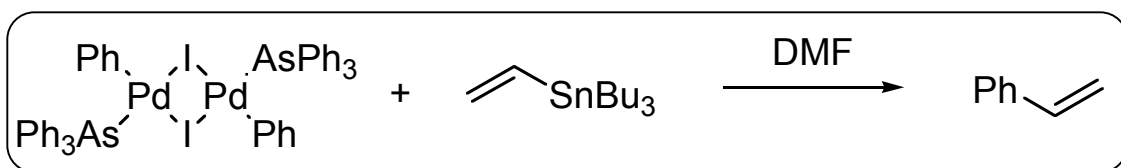


Reinvestigating the Mechanism in DMF

Amatore reinvestigated the reaction in DMF using a clever technique to monitor the reaction rate.



First, the reaction of dimer with 2 eq. (vinyl)SnBu₃ was monitored:

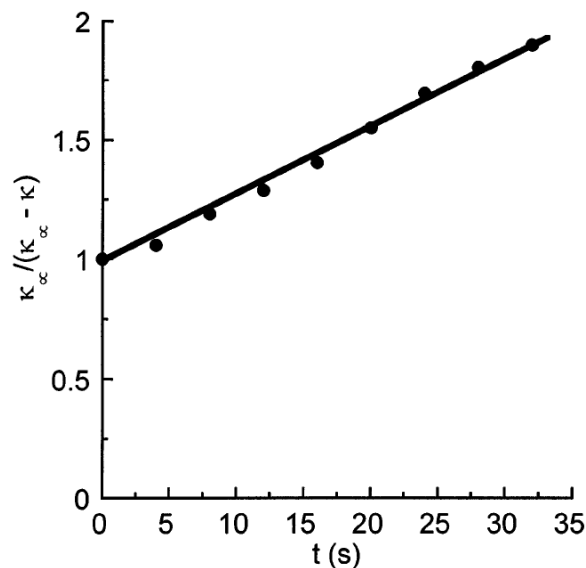


Data fits the equation:

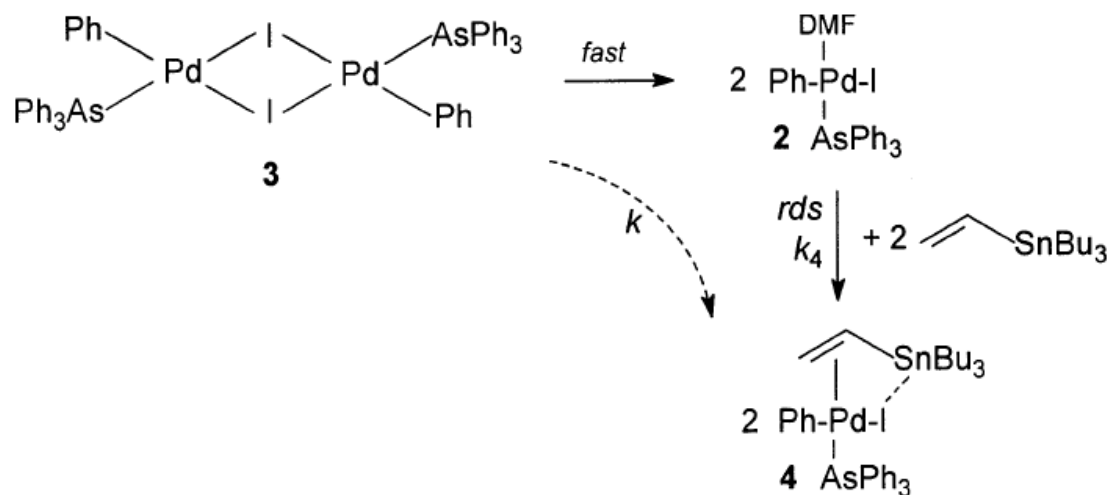
$$1/x = k_{\text{app}} t + 1$$

Consistent with 1:1 reaction between reagents in stoichiometric amounts

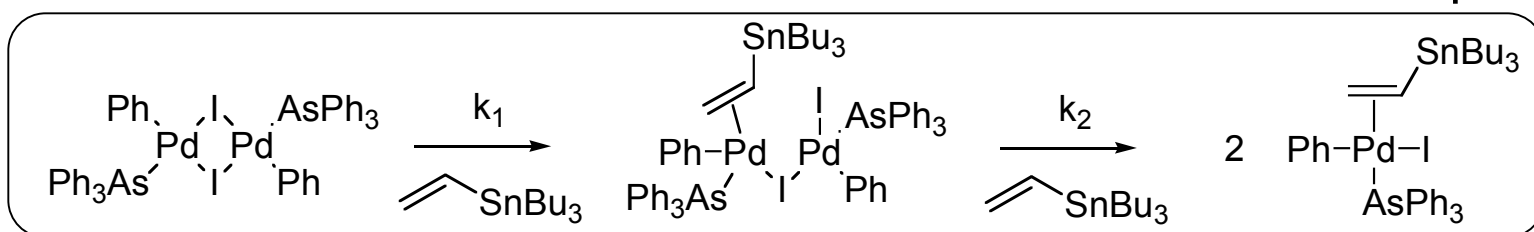
Amatore, C. *JACS* **2003**, *125*, 4212-4222.



Mechanism in DMF



The dimer or the DMF-coordinated monomer can be the active species.

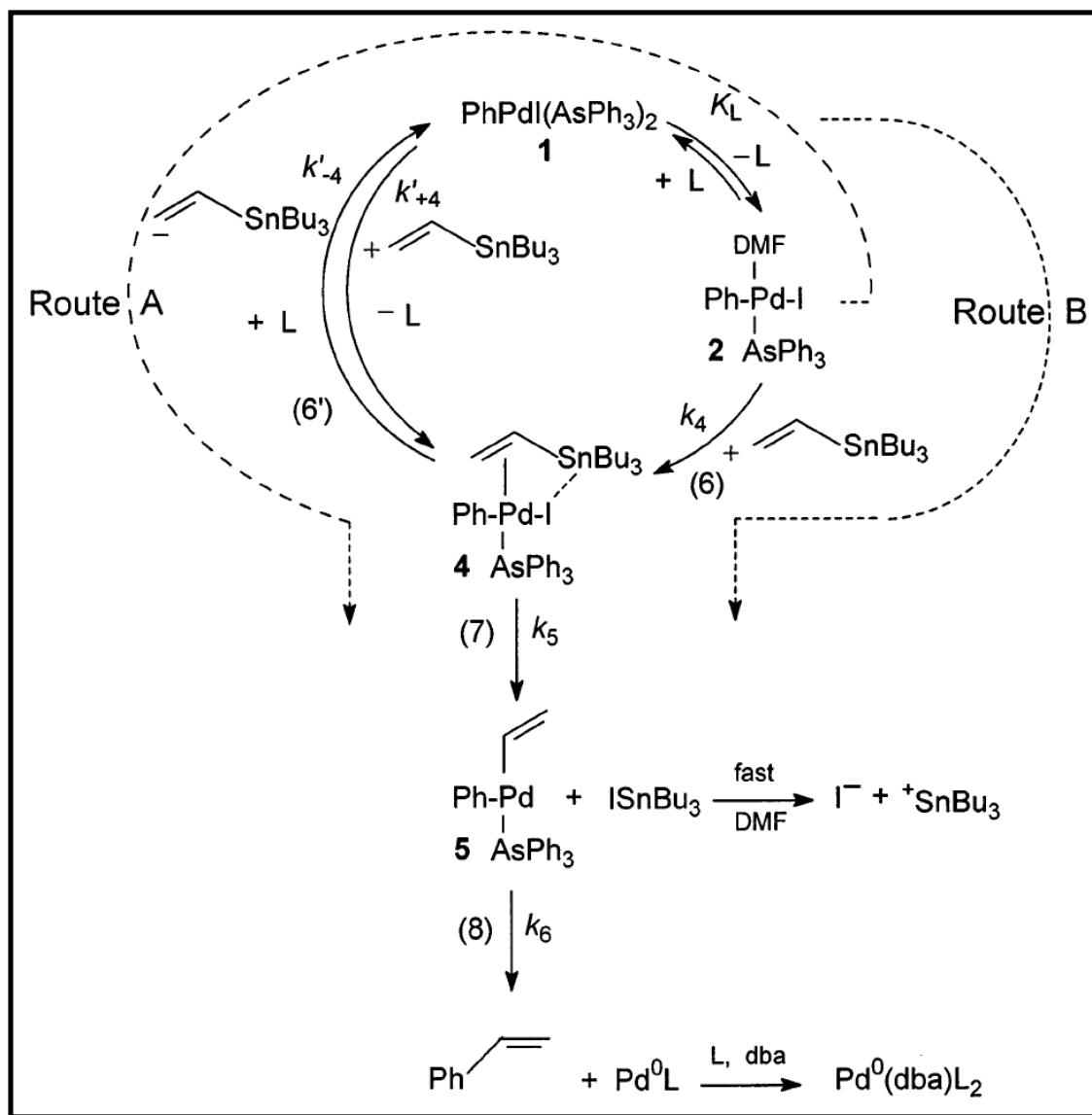


If $k_2 > k_1$ (steady-state) then rate law has the same form as the 1:1 reaction.

They cannot be distinguished by kinetics.

Fortunately as shown by UV-vis, the dimer in DMF is quantitatively converted to monomer.

Rate Expressions



Dimer does not participate, but DMF and AsPh_3 can exchange to give two possible reactive species.

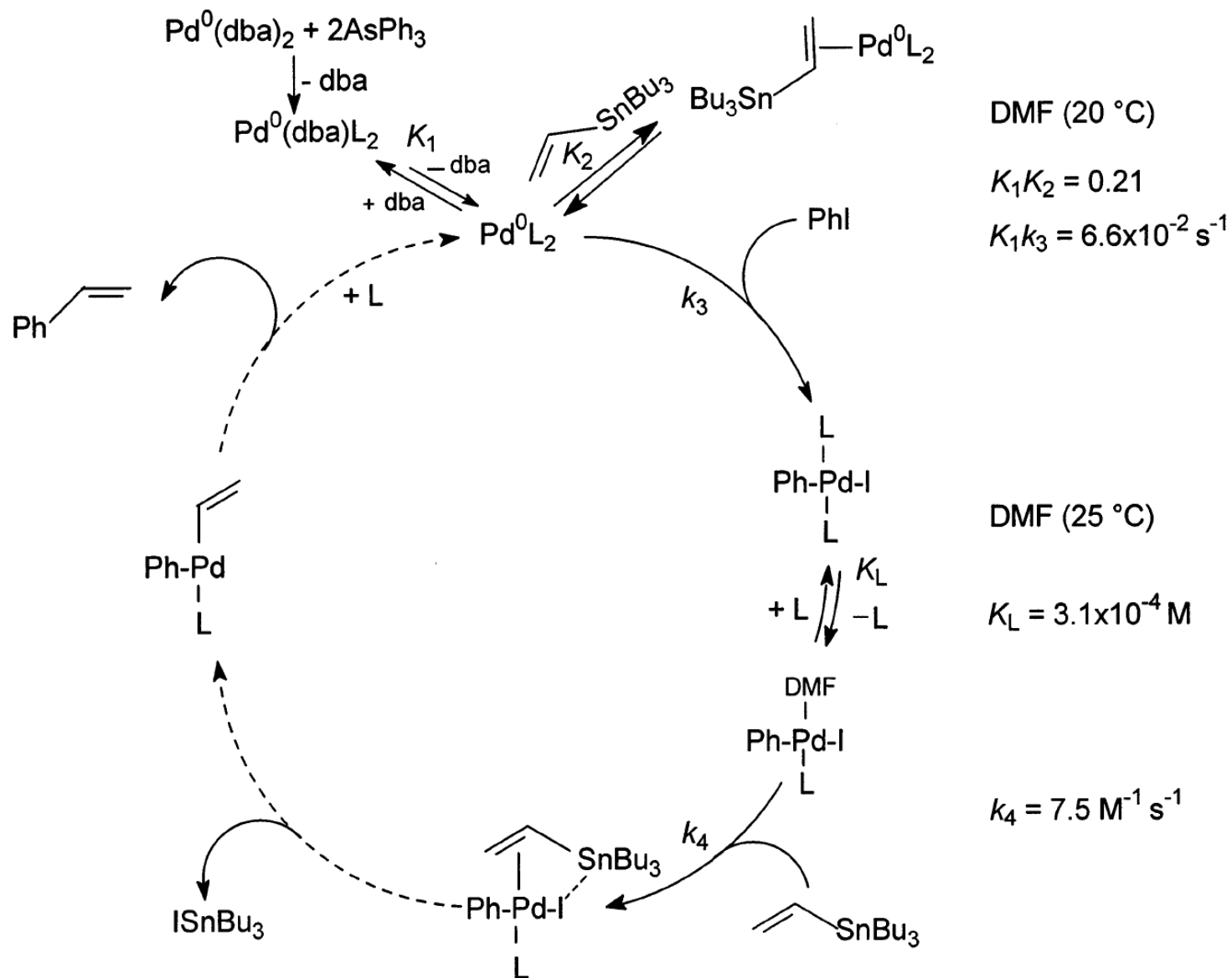
A (steady-state in 4)

$$\text{rate} = \frac{k'_{+4} k_5 [1] [\text{Sn}]}{k'_{-4} [\text{L}] + k_5} \cdot \frac{[\text{L}] + K_L}{[\text{L}]}$$

B (pre-equilibrium)

$$\text{rate} = \frac{k_4 K_L [\text{Pd}] [\text{Sn}]}{[\text{L}] + K_L}$$

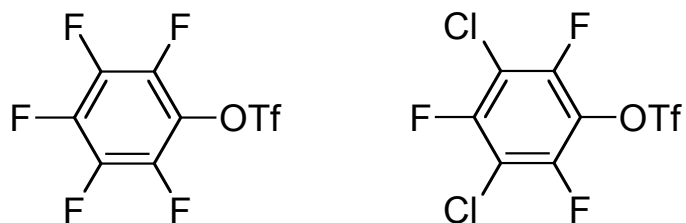
Modified Proposal (Amatore)



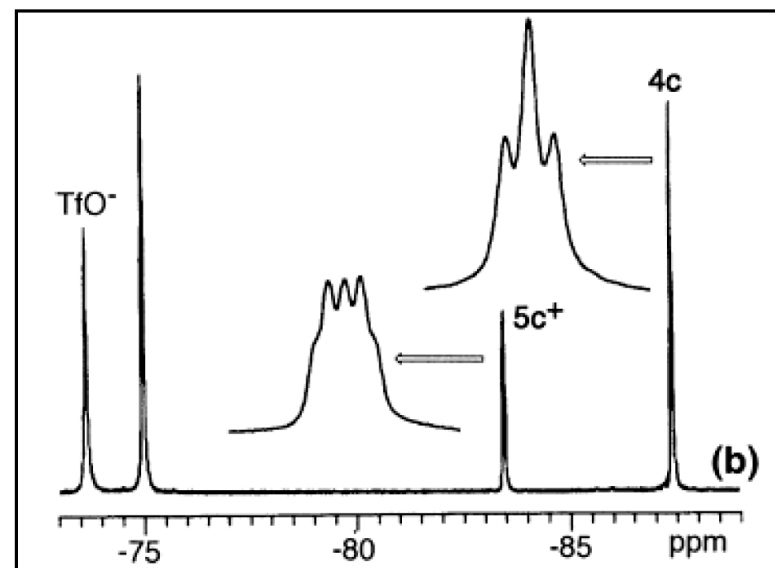
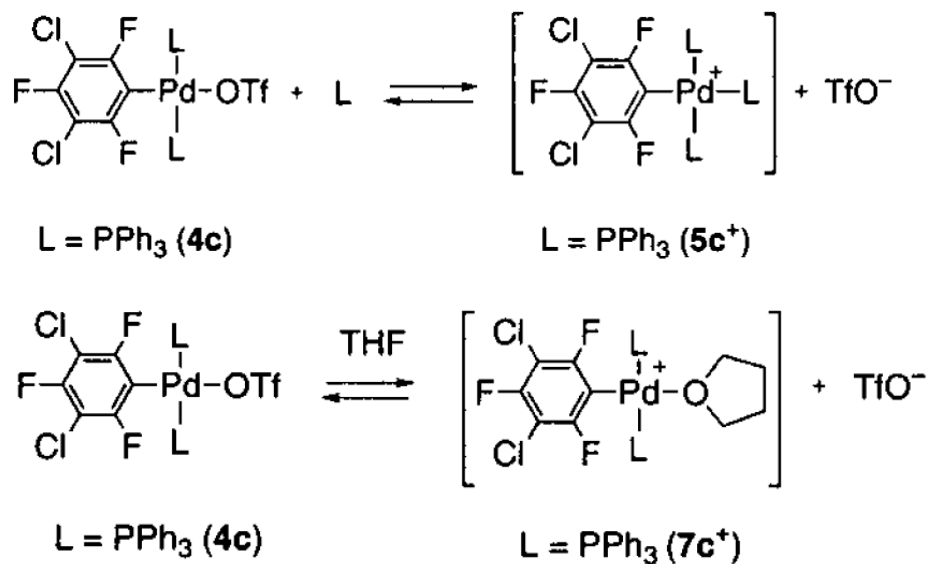
Coupling with Triflates - Even More Complex

Espinet used ^{19}F -NMR to study coupling of fluoroaryl triflates with vinyltributylstannane, with and without addition of LiCl.

Espinet, P. *JACS* **2000**, *122*, 11771-11782.

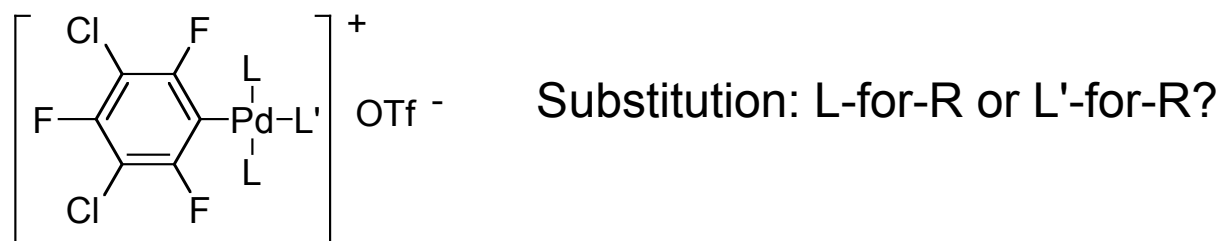


Excess ligand or coordinating solvents can ionize triflate.

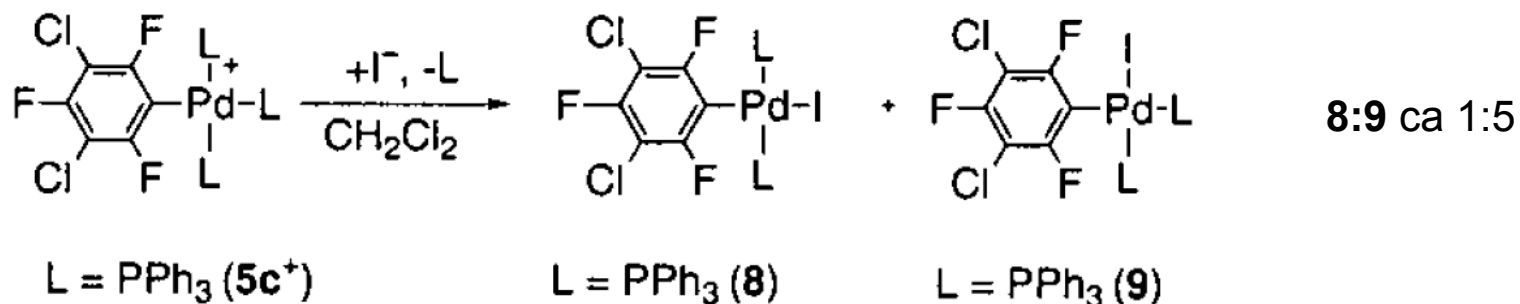


It Gets Worse

The cationic species can undergo transmetalation as well.

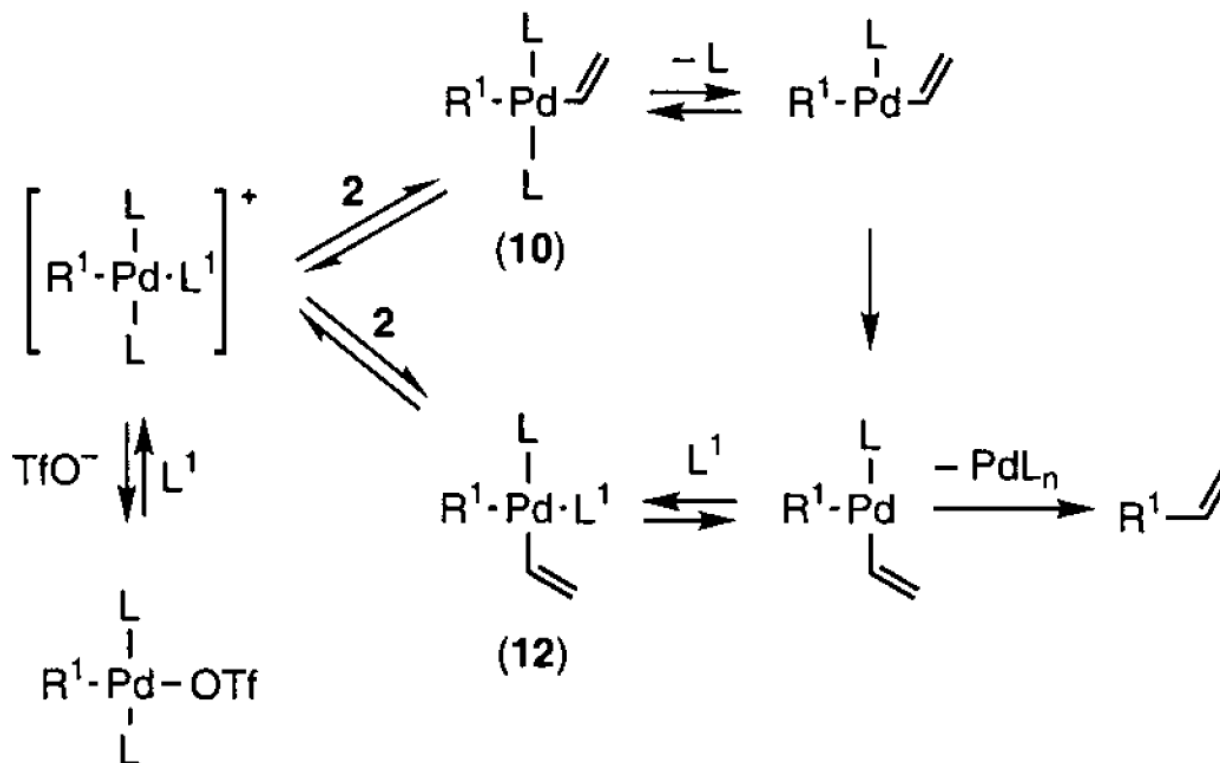


Iodide nucleophile:



What happens when the nucleophile is (vinyl)SnBu₃?

Coupling with Cationic Species



$S_{\text{E}}2(\text{open-}cis)$ gives **12** which can undergo rapid reductive elimination.

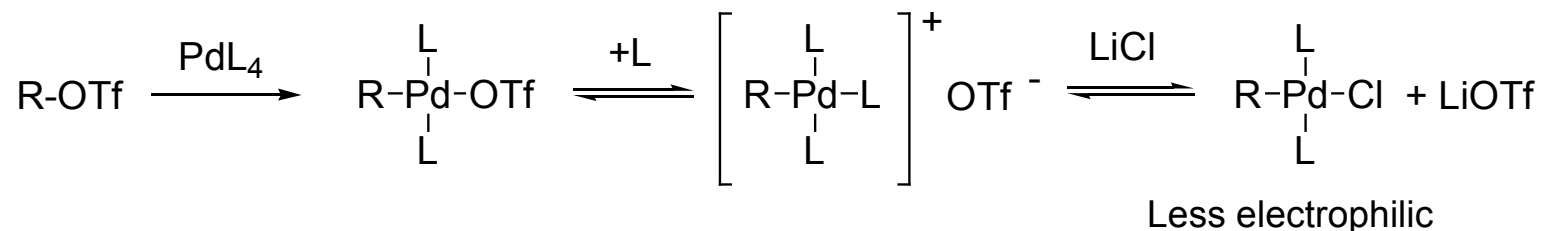
$S_{\text{E}}2(\text{open-}trans)$ gives **10** which can undergo slow isomerization and then reductive elimination.

Effect of LiCl

entry	L	solvent	additive ^b	conversion (%)	
				10 h	24 h
1	PPh ₃	PhCl	none	86	96
2	PPh ₃	PhCl	LiCl	92	100
3	PPh ₃	THF	none	65	100
4	PPh ₃	THF	LiCl	0	6
5	AsPh ₃	PhCl	none	6	7
6	AsPh ₃	PhCl	LiCl	5	7
7	AsPh ₃	THF	none	13	14
8	AsPh ₃	THF	LiCl	79	87

In some cases LiCl accelerates the reaction (1 vs. 2, 7 vs. 8), while in others it has a retarding effect.

Rate deceleration

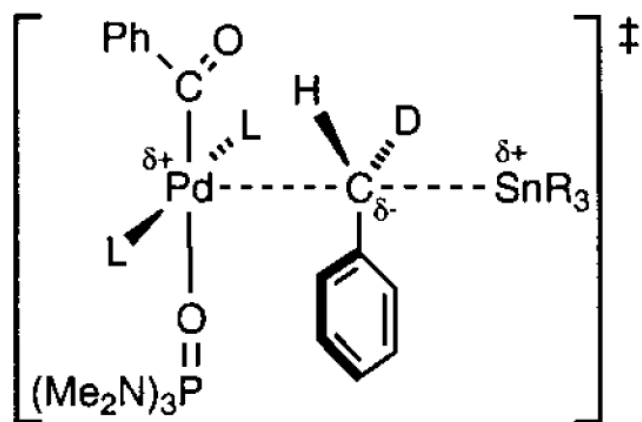


Rate acceleration occurs when *oxidative addition is rate-limiting*, by generation of $[\text{PdCl}_n(\text{AsPh}_3)_{4-n}]^{n-}$, a more nucleophilic species

Transmetalation - Cyclic vs. Open

S_E2 (cyclic) favored in nonpolar solvents with bridging groups present.

Stereochemistry: S_E2 (open) is invertive while S_E2 (cyclic) is retentive.



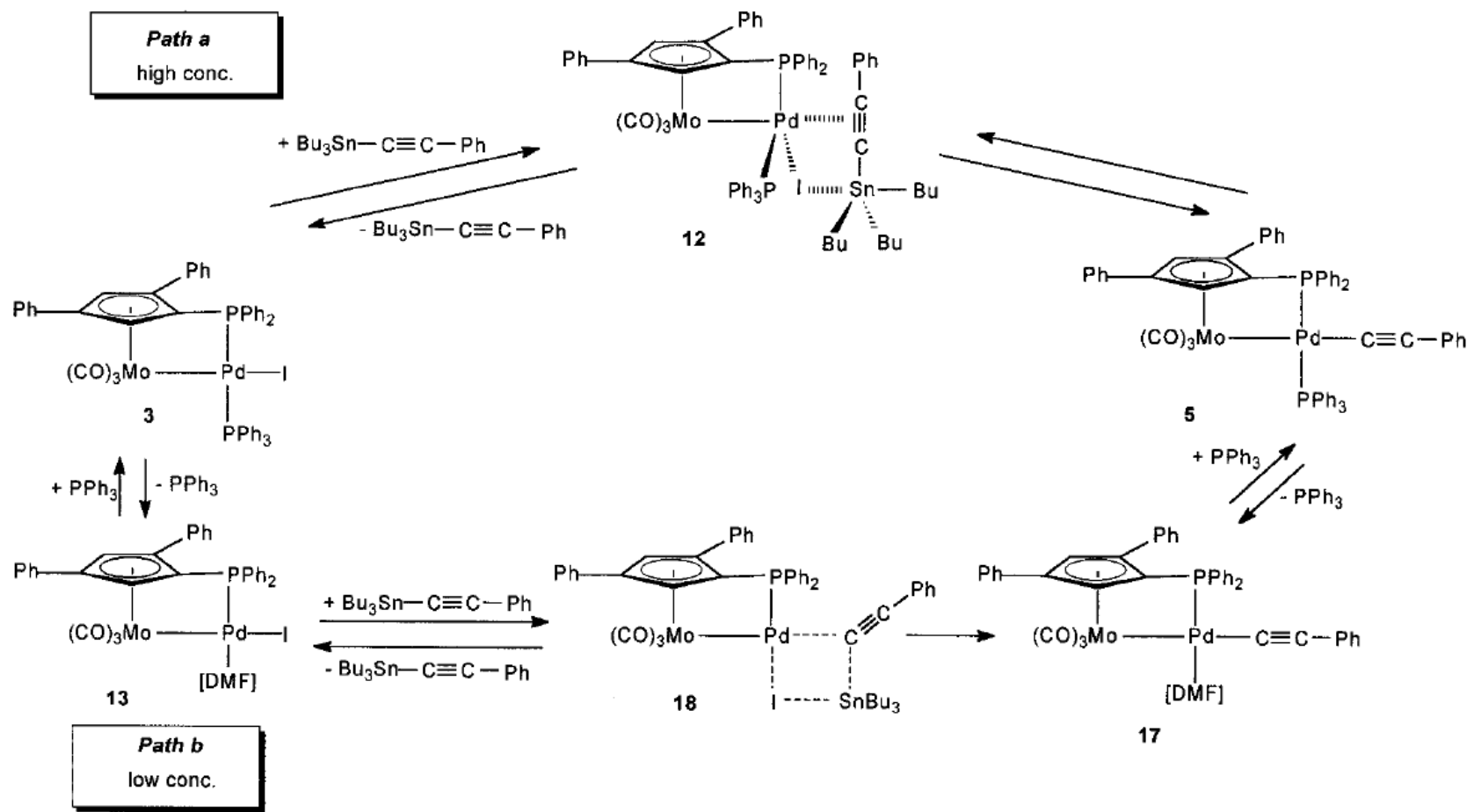
Inversion from the S_E2 (open) TS in Stille's early report

In polar coordinating solvents S_E2 (open) is favored.

This essentially completes Espinet's proposed mechanism.

Another Intepretation

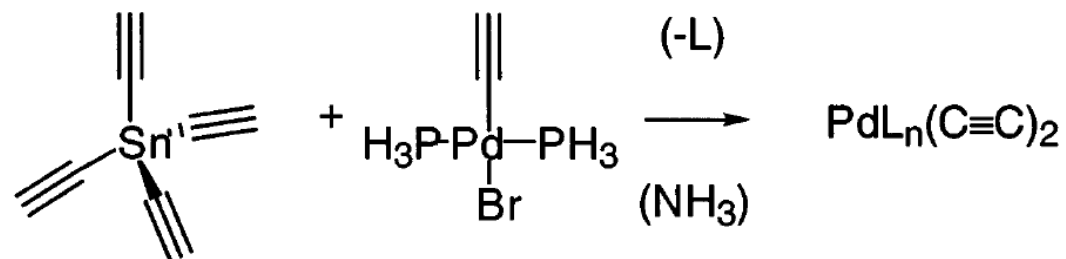
Lo Sterzo has used palladium to catalyze metal-carbon bond formation, forming metal acetylides (Fe, Ru, W, Mo) from trialkyltinacetylides.



Lo Sterzo, C. *JACS* **2002**, *124*, 1060-1071.

DFT Analysis

Farina isn't finished with the Stille reaction yet...



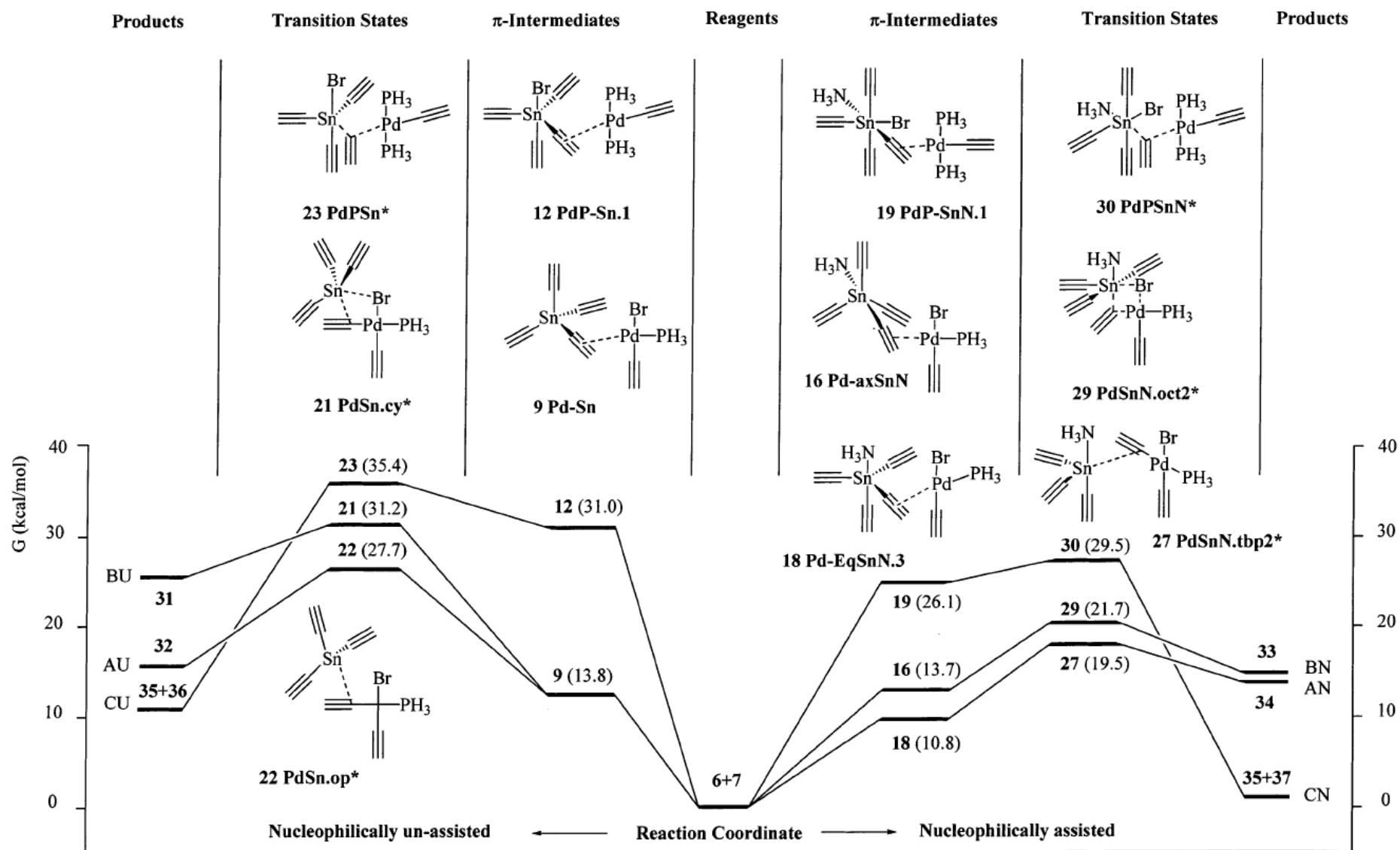
Tetraethynyltin and bromoethynyl Pd complex chosen to reduce number of rotamers in search for transition states.

NH₃ used as a nucleophile to coordinate to Sn and assist transmetalation.

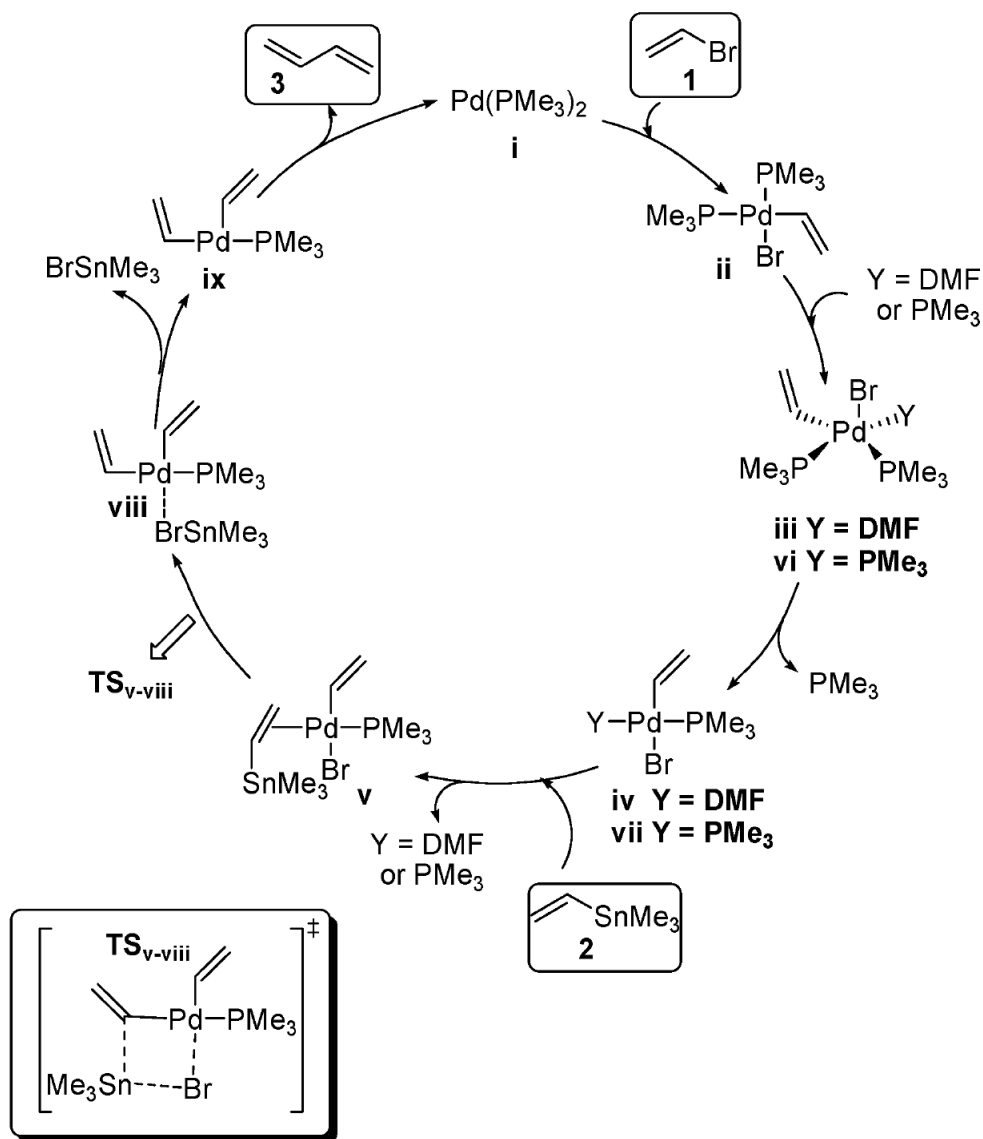
No energy minima or transition states with five-coordinate Pd were found. Global minimum energy TS is open with no Sn-Br interaction.

Napolitano, E.; Farina, V.; Persico, M. *Organometallics* **2003**, 22, 4030-4037.

DFT Analysis



Another DFT Analysis



The cyclic associative transition state **TS_{v-viii}** has the largest ΔG^\ddagger of the cycle.

However the transmetalation is not concerted. First η^2 -coordination helps displace a ligand. Then transmetalation and BrSnMe_3 elimination.

Conclusions

Espinet's proposed cycle with the key associative transmetalation is an important advance from the classical mechanism.

There are still many important issues that need to be resolved.

Pitifully, neglect of the coordination sphere of the metal is quite common in the literature of metal-catalyzed organic transformations. We hope that this paper will serve to draw attention on its mechanistic relevance in some cases.

Espinet in a footnote in his *JACS* **1998** paper.

