Stille-coupling

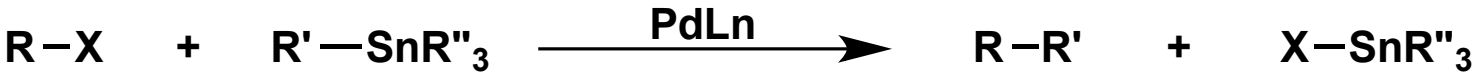
Comprehensive catalytic cycle and mechanistic factors

2014. 10. 11. M2 Hanada

Index

Outline

Stille coupling (Migita-Kosugi-Stille coupling)



(X = halide, OTf)

Kosugi, M.; Sasazawa, K.; Shimizu, Y.; Migita, T. *Chem. Lett*. **1977**, 301.

Milstein, D.; Stille, J. K. *J. Am. Chem. Soc*. **1978**, *100*, 3636.

Feature

- Organostannane
- Mild condition → Broad substrate scope, synthetic applycation

John Kenneth Stille (1930-1989)
He received B.A and M.A. degrees from the University of Arizona and received his Ph.D. from the University of Illinois, where he studied under Carl Marvel.
Stille began his independent career at the University of Iowa in 1957 before moving to Colorado State University in 1977.

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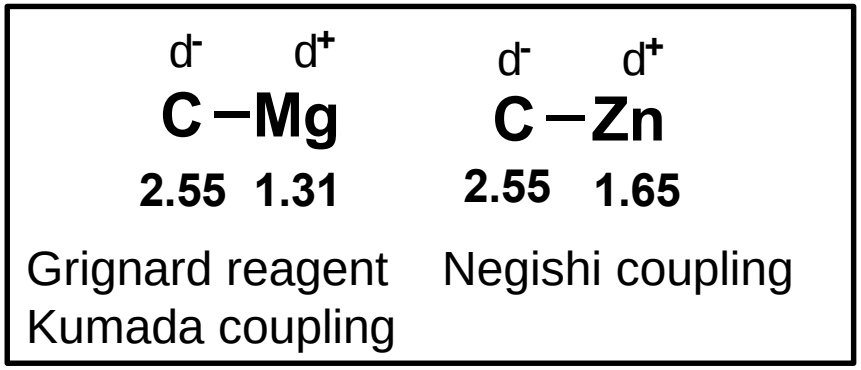
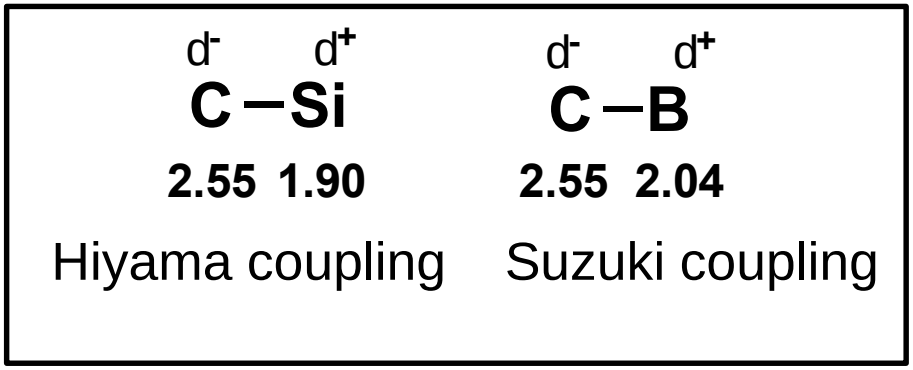
Organostannane Feature

◯ Air and moisture stable, tolerant of many functional groups.
→Due to low polarity of the C-Sn bond
◯ Synthesized under mild condition
× Highly toxic (and stannane byproduct is often inseparable .)

High polarity bond



Similar polarity bond



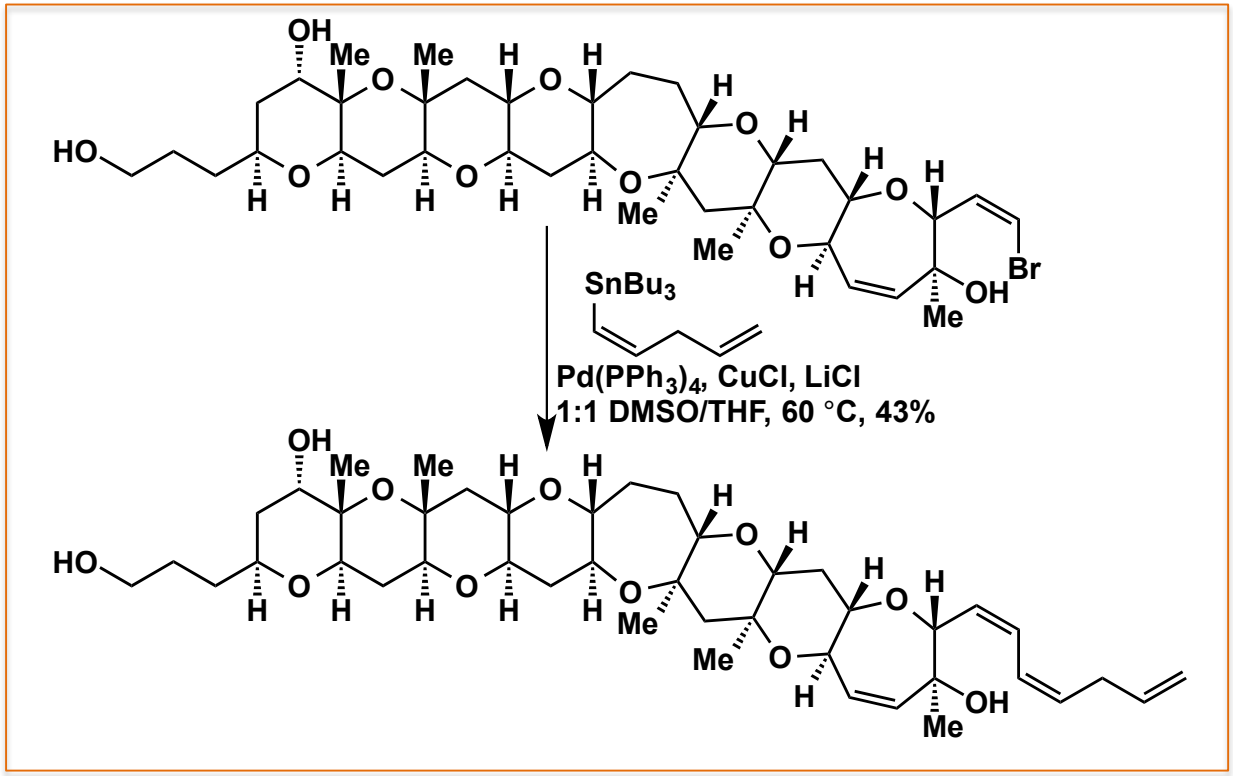
Espinet, P. ; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 4704.

Synthetic applications

Mild reaction condition and functional group tolerance

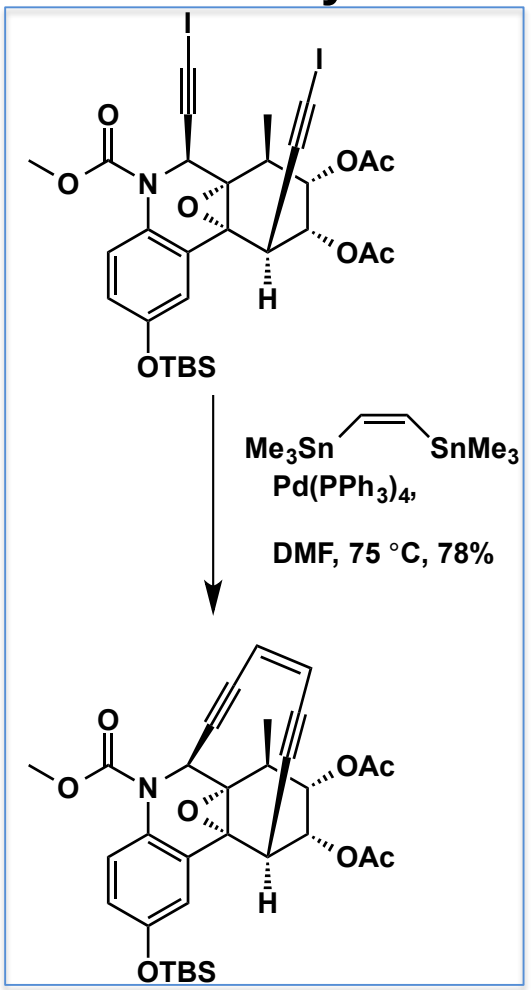
→ Applicable to the late stage of total synthesis

The last step of Ganbierol



Sasaki, M. *et al*., *J. Am. Chem. Soc*. **2002**, *124*, 14983.

Intermediate of Dynemicin A



Danishefsky, S. J. *et al*., *J. Am. Chem. Soc*. **1996**, *118*, 9509.

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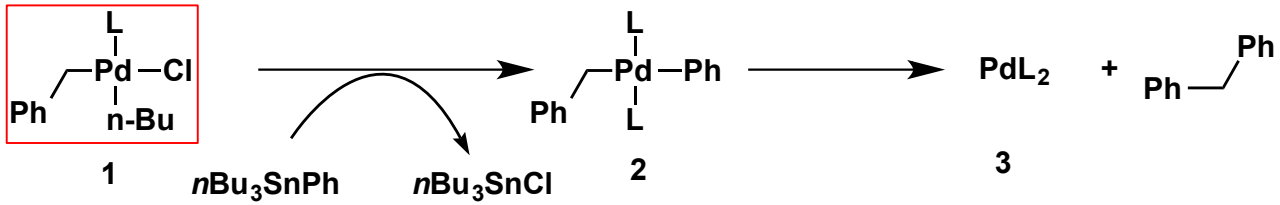
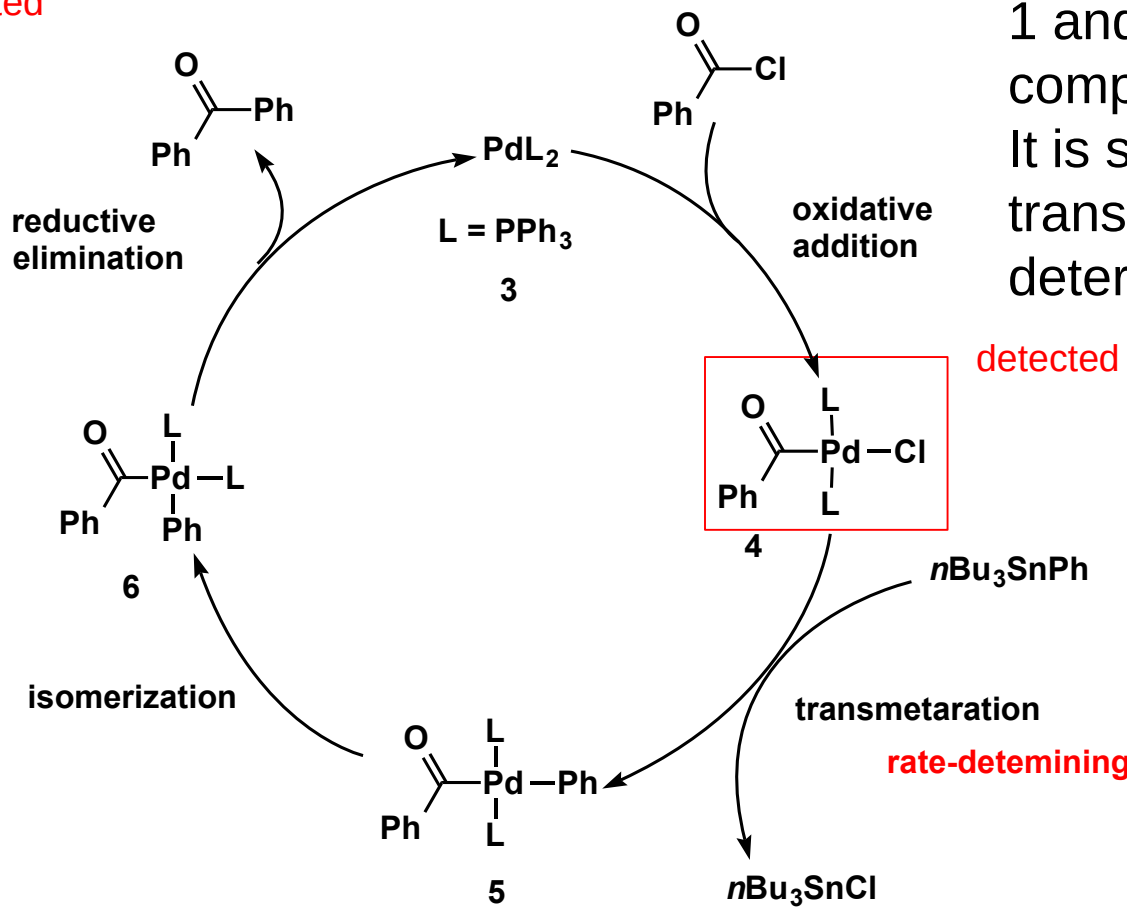
Original mechanistic proposal

1986 Stille



detected

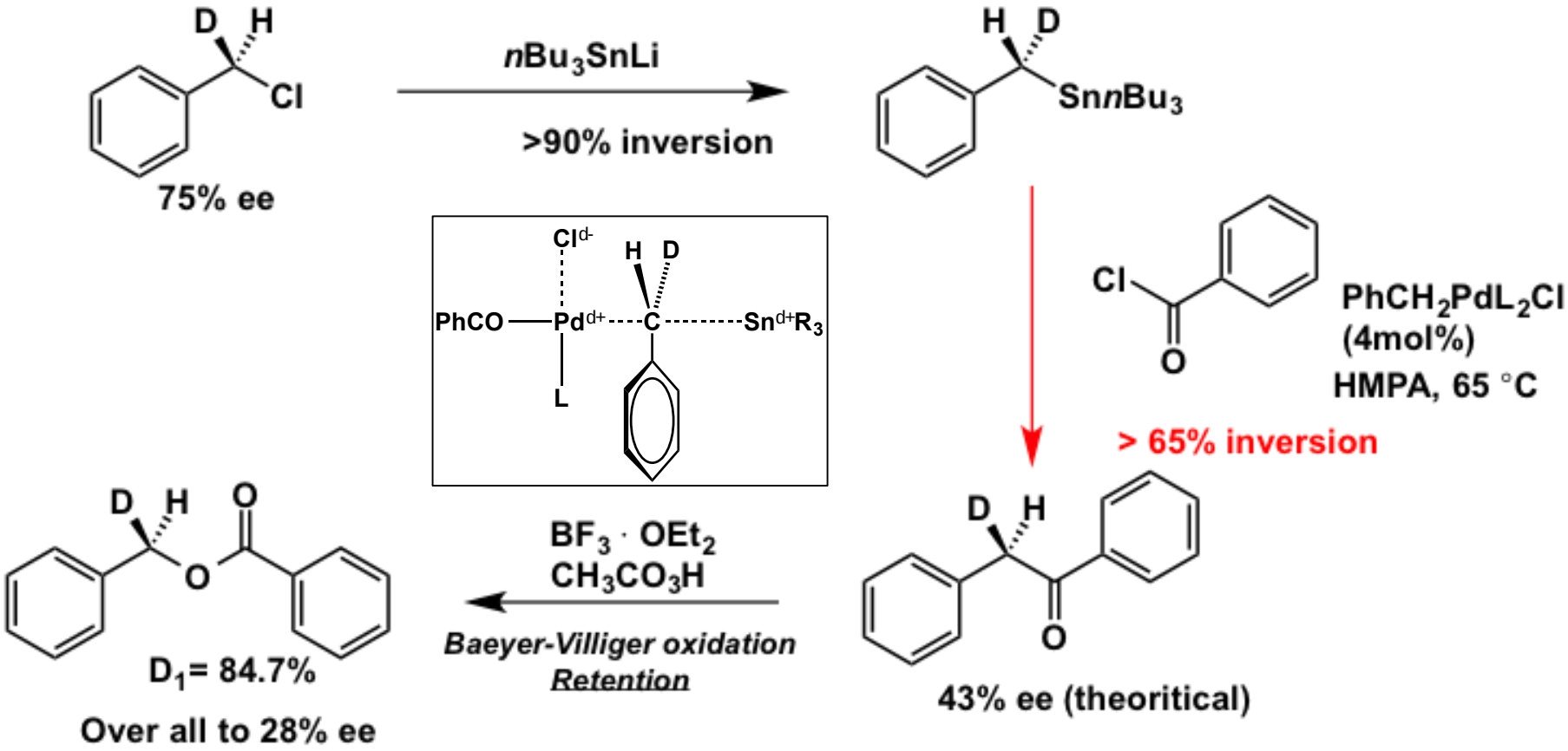


detected

1 and 4 are only detectable Pd compound.(^{31}P NMR)
It is suggested that transmetalation is the rate-determining.

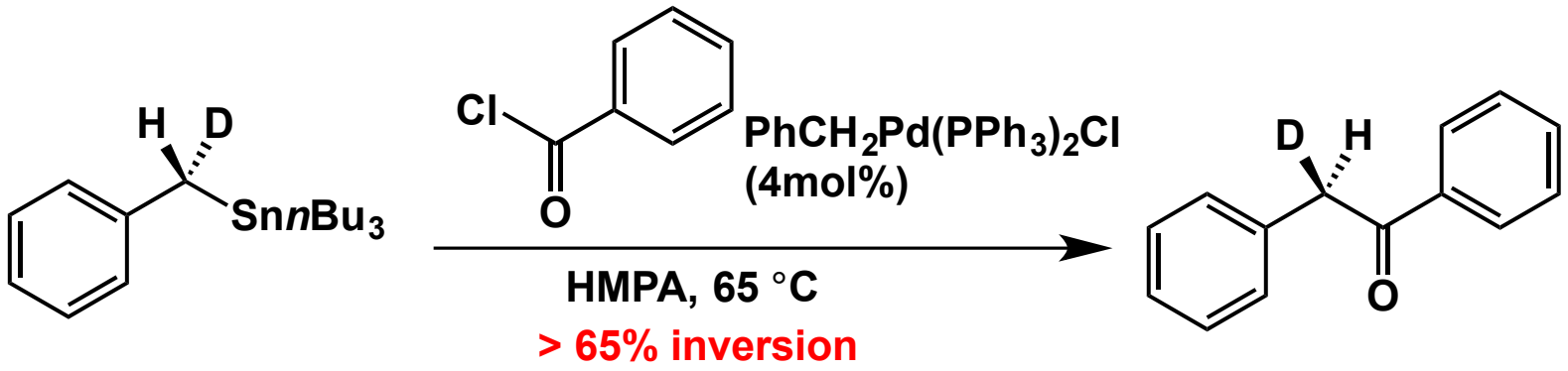
Stille, J.K. *Angew. Chem. Int. Ed.* **1986**, *25*, *508.*

Stereochemistry of transmetalation

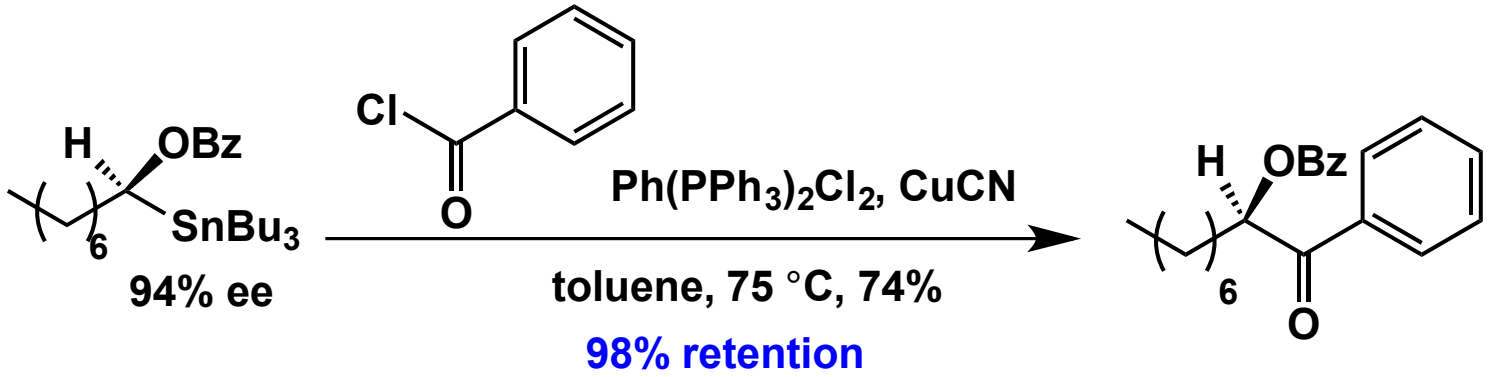


Labadie, J. W. Stille, J. K. *J. Am. Chem. Soc*. **1983**, *105*, 6129.

Retention? Inversion?



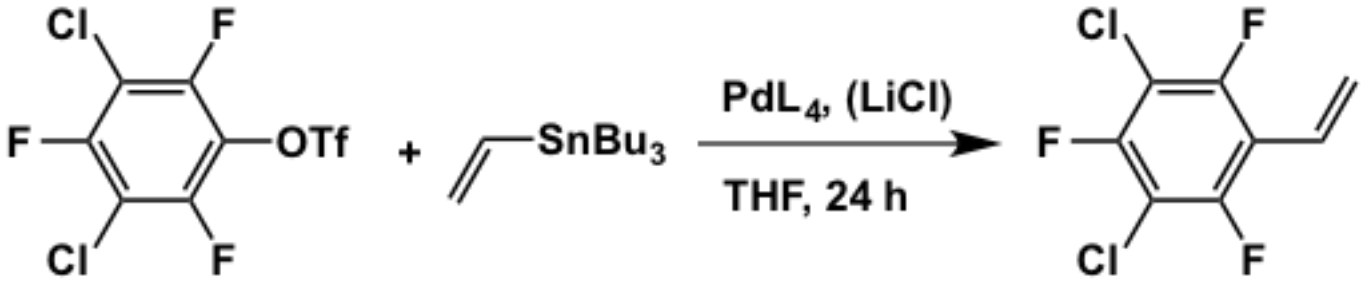
Labadie, J. W. Stille, J. K. *J. Am. Chem. Soc*. **1983**, *105*, 6129.



Falck, J. R. *et al*., *J. Am. Chem. Soc.* **1994**, *116*, 1.

Additive effect?

LiCl effect is different depending on ligand.



L	additive	yield (%)
PPh_3	none	100
PPh_3	LiCl	6
$AsPh_3$	none	14
$AsPh_3$	LiCl	87

Espinet, P. *et al. J. Am. Chem. Soc.* **2000**, *122*, 11771.

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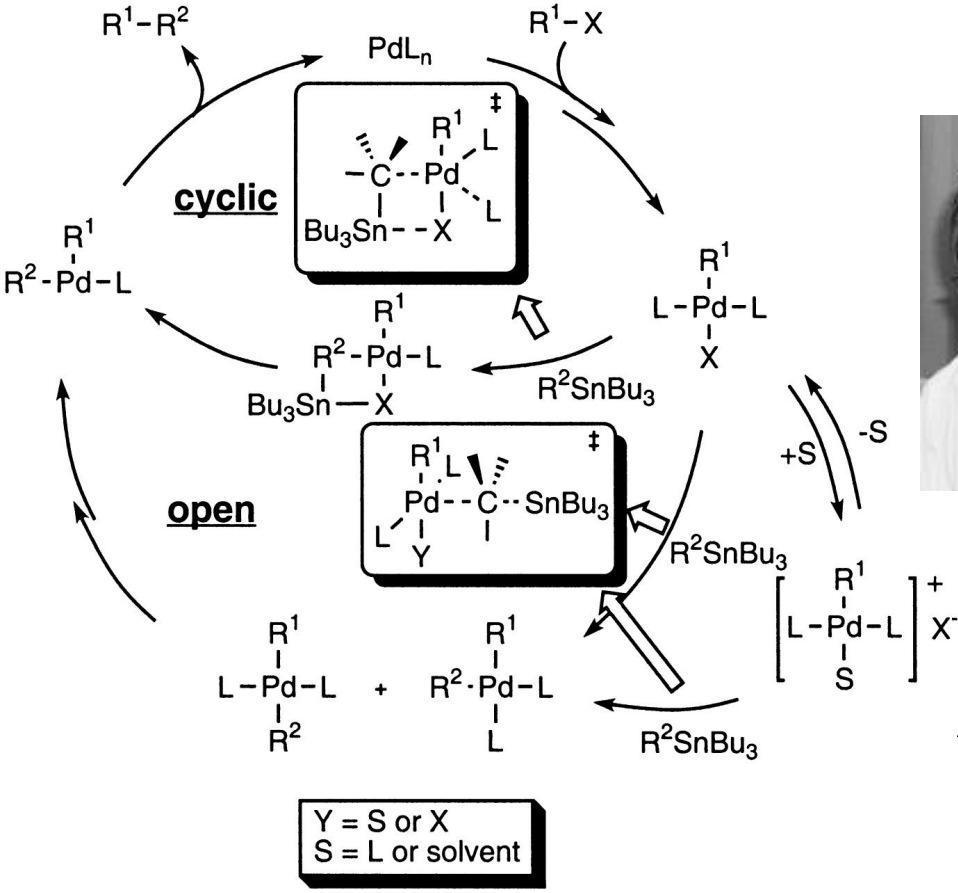
Dual pathway



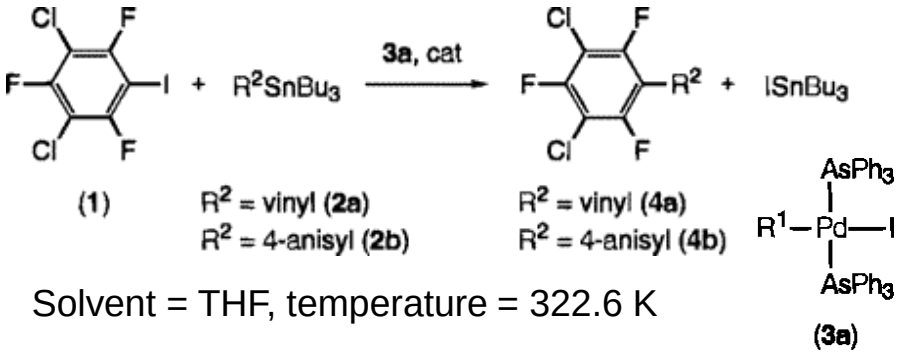
Prof. Pablo Espinet (Spain)

Prof. Espinet is founder (in 2007) and director of the Institute CINQUIMA (Center of Innovation in Chemistry and Advanced Materials).

Research topics : molecular dynamics in solution, mechanism of the Stille reaction, other metal-catalyzed reactions (Negishi, Sonogashira), molecular materials.

Espinet, P. ; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 4704.

Kinetics study of transmetalation by ^{19}F NMR monitoring



Solvent = THF, temperature = 322.6 K

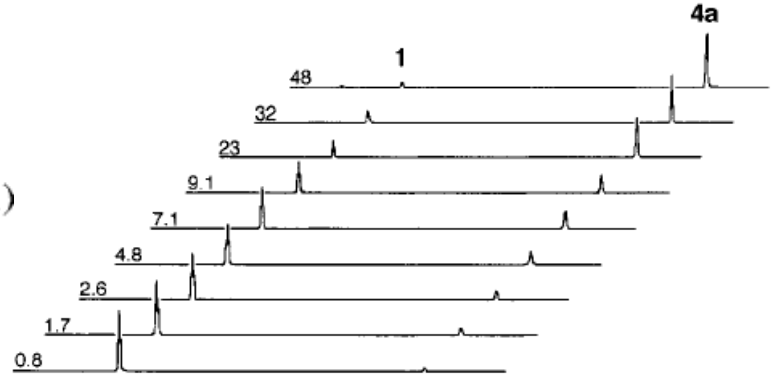


Figure 1. ^{19}F NMR (282 MHz, F^4 region) spectra sequence (intervals in hours) of the coupling of $C_6Cl_2F_3I$ (**1**, 0.2 mol L^{-1}) with (CH_2=CH)$SnBu_3$ (**2a**, 0.2 mol L^{-1}) catalyzed by *trans*-[$Pd(C_6Cl_2F_3)I(AsPh_3)_2$] (**3a**, 0.01 mol L^{-1}) and $AsPh_3$ (0.02 mol L^{-1}), in THF at 322.6 K. The product is $C_6Cl_2F_3(CH{=}CH_2)$ (**4a**).

$$\ln([1]_0 - [1]_1) = k_{obs}\, t$$

The concentration of 1 is stoichiometrically linked to that of 2.

k_{obs}^{-1} vs [AsPh3] and k_{obs} vs [3a] : good linear dependence each

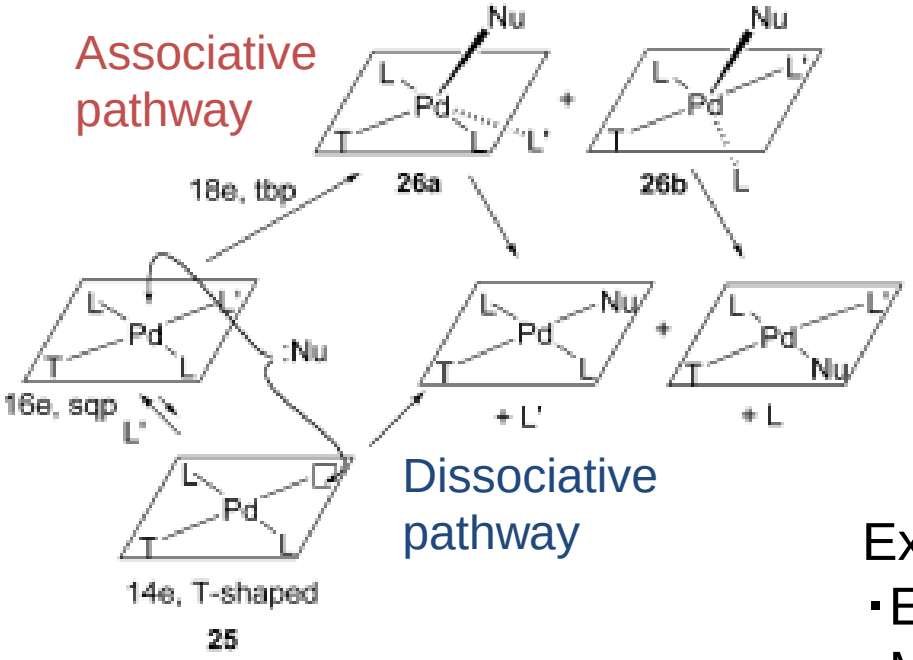
$$r_{obs} = k_{obs}[2a] = \frac{a\,[3a]}{[AsPh_3] + b}[2a]$$

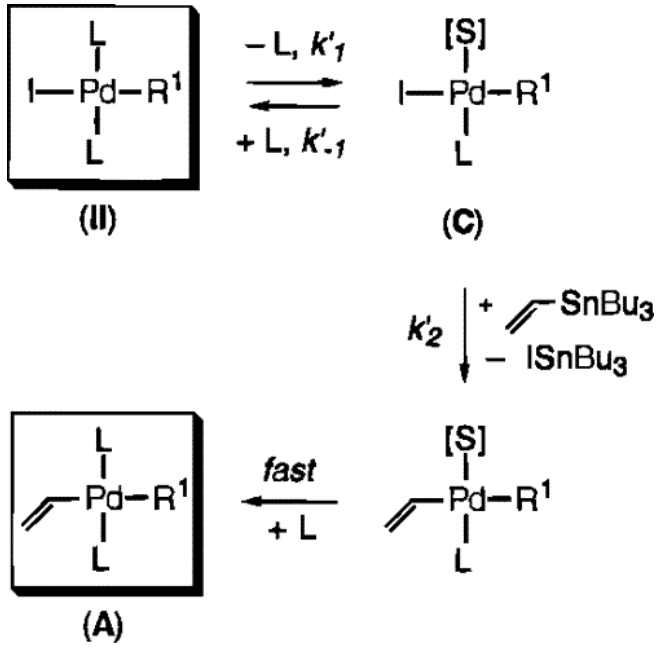
a = (2.32±0.09) ×10^{-5} s^{-1} b = (6.9±0.3) ×10^{-4} mol L^{-1}

Casado, A. L. Espinet, P. *J. Am. Chem. Soc.* **1998**, *120*, 8978.

Dissociative pathway theory

Dissociative pathway :
Ligand dissociation occurs previous to transmetalation.



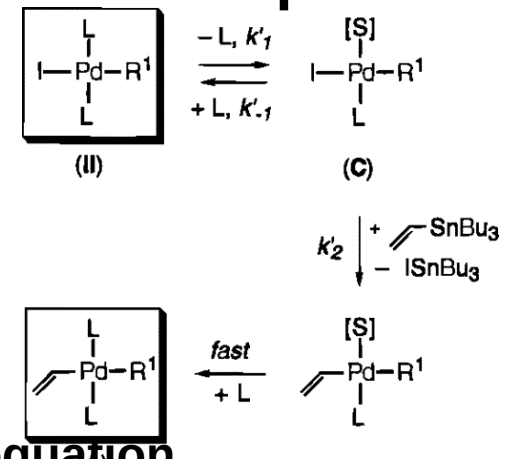


Experimental consistence

- Excess ligand retards the reaction.
- Modest donicity ($AsPh_3$) ligand is effective. (than PPh_3)
- The first-order dependence on stannane (Slow transmetalation from **C**)

Casado, A. L. Espinet, P. *J. Am. Chem. Soc.* **1998**, *120*, 8978.

Experimental inconsistency of the dissociative pathway



Theoritical equation

If : Late dissociation (rate-determining)

$$r_{obs} = k_{obs}[2a] = \frac{k'_2 K_{dis}[3a]_{total}}{K_{dis} + [AsPh_3][2a]}[2a]$$

$$\approx k'_1[3a] \quad ([AsPh_3] \approx 0)$$

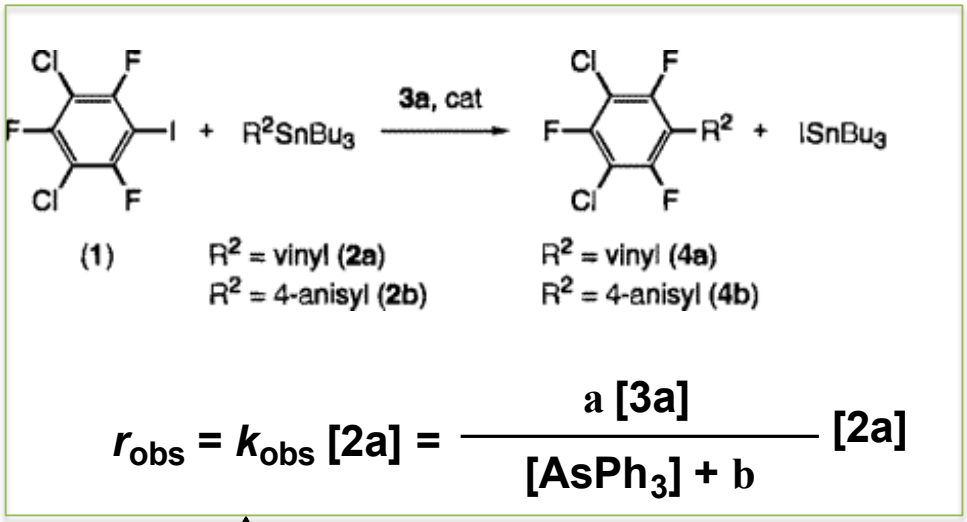
If: Fast dissociation

$$r_{obs} = k_{obs}[2a] = \frac{k'_2 K_{dis}[3a]_{total}}{K_{dis} + [AsPh_3]}[2a]$$

$k'_2 = 1.8 \times 10^{-1}\ s^{-1}$ $K_{dis} = 1.3 \times 10^{-4}\ mol\ L^{-1}$

$K_{dis} = k'_1/k'_{-1}$

Experimental result



$$r_{obs} = k_{obs}[2a] = \frac{a[3a]}{[AsPh_3] + b}[2a]$$

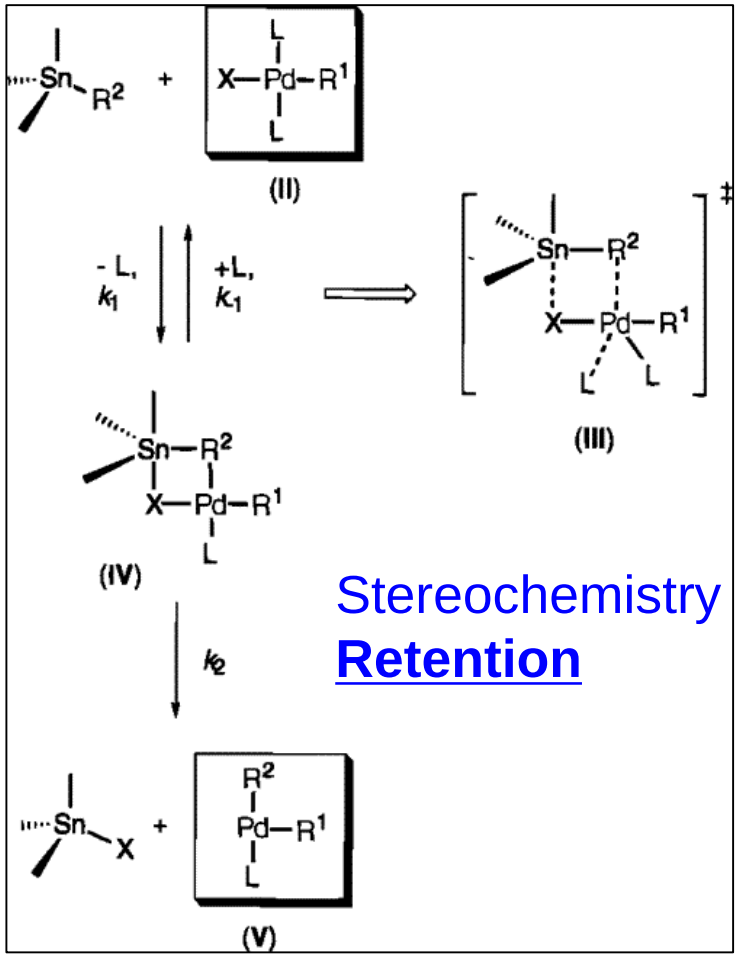
inconsistent

→ zeroth order with respect to [2a]

→ 12% of 3a should be dissociated as C, but it was not detected.

Casado, A. L. Espinet, P. *J. Am. Chem. Soc.* **1998**, *120*, 8978.

Associative (cyclic) transmetalation



Stereochemistry
Retention

(*trans*-[PdR_1R_2L] was not observed, so *cis* addition was proposed.)

Cyclic pathway equation

$$d[IV]/dt = k_1[2a][3a] - k_{-1}[IV][AsPh_3] - k_2[IV] = 0$$

$$[IV] = \frac{k_1[2a][3a]}{k_{-1}[AsPh_3] + k_2} \qquad r_{obs} = k_2[IV]$$

$$r_{obs} = k_{obs}[2a] = \frac{k_1 k_2 [3a]}{k_{-1}[AsPh_3] + k_2}[2a]$$

$$k_1 = 0.034\ mol^{-1}\ L\ s^{-1}$$

$$k_2/k_{-1} = 6.9 \times 10^{-4}\ mol\ L^{-1}$$

Reasonable

Experimental result

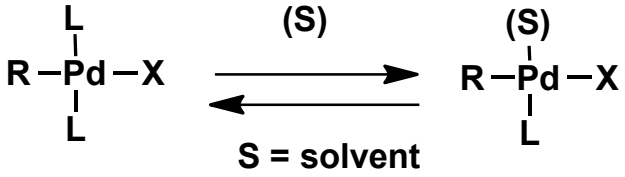
$$r_{obs} = k_{obs}[2a] = \frac{a[3a]}{[AsPh_3] + b}[2a]$$

$a = (2.32 \pm 0.09) \times 10^{-5}\ s^{-1}$ $b = (6.9 \pm 0.3) \times 10^{-4}\ mol\ L^{-1}$

Casado, A. L. Espinet, P. *J. Am. Chem. Soc.* **1998**, *120*, 8978.

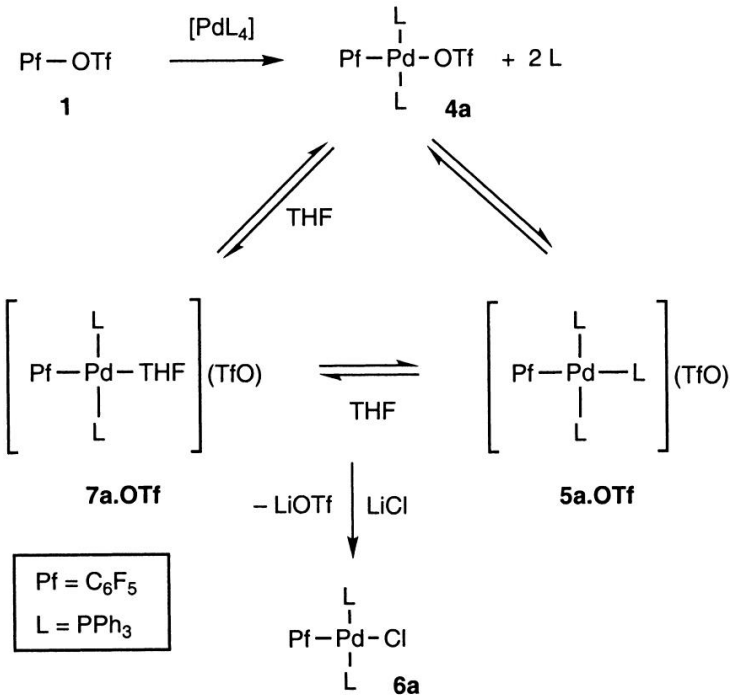
Triflate : (1) Solvent coordinating

Neutral intermediate : Previously proposed solvent coordinatng intermediate

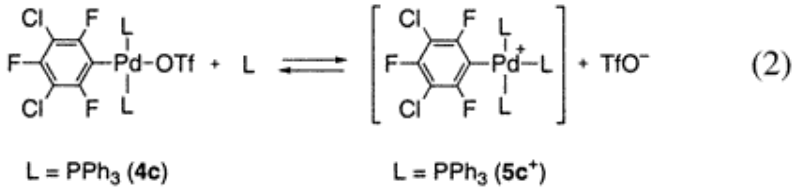


Farina, V. *Pure & Appl. Chem*. **1996**, *68*, 73.

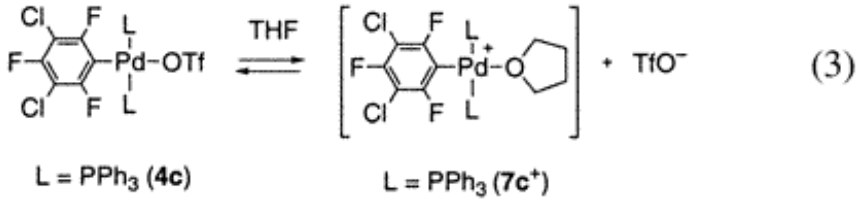
Cationic intermediates were characterized by Espinet *et al*.



$CDCl_3$, CH_2Cl_2, PhCl : non-coordinating

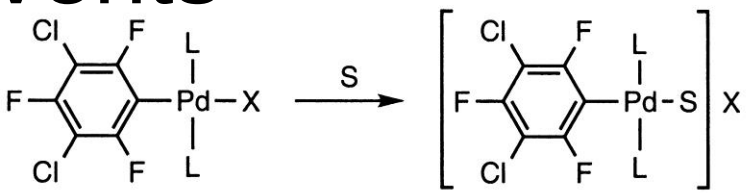


THF: coordinating



Espinet, P. *et al. J. Am. Chem. Soc.* **2000**, *122*, 11771.

Polar solvents



F_{ortho}: δ = -86.9, t

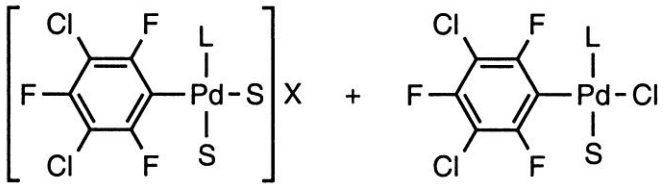
Stable

w/o PPh_3	w/ PPh_3
62.5%	53%

L = PPh_3
S = HMPA

L ⇅ S, X = Cl

w/o PPh_3	w/ PPh_3
17.5%	0%



F_{ortho}: δ = -85.8, d

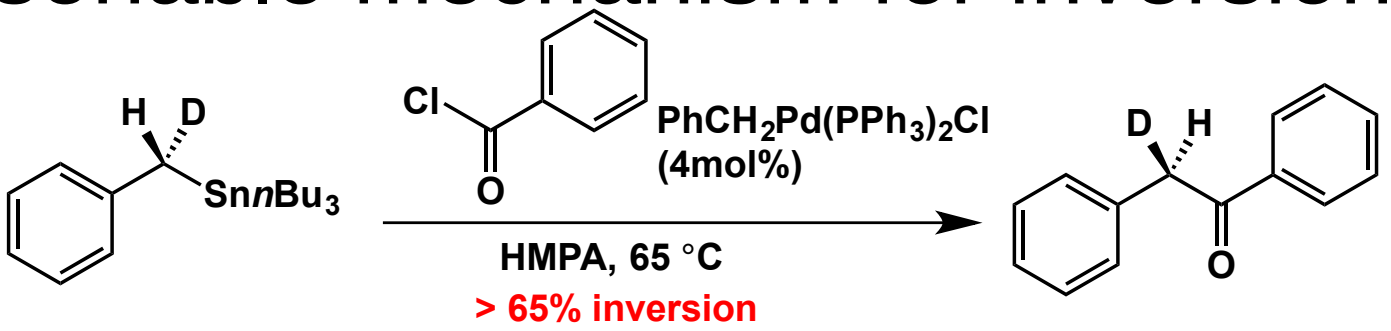
F_{ortho}: δ = -88.1, d

w/o PPh_3	w/ PPh_3
20%	47%

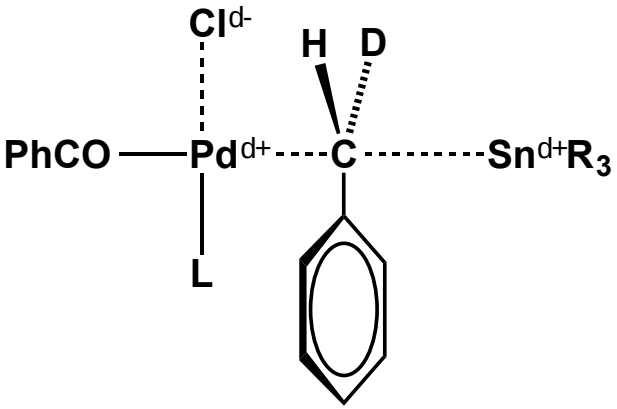
In polar coordinating solvents, solvent coordinating complex is stable even though X is halide.
(NMP(less coordinative than HMPA) is able to displace triflate and PPh_3 trans to R, but cannot displace halides trans to R or PPh_3 cis to R)

Espinet, P. *et al. J. Am. Chem. Soc.* **2000**, *122*, 11771.

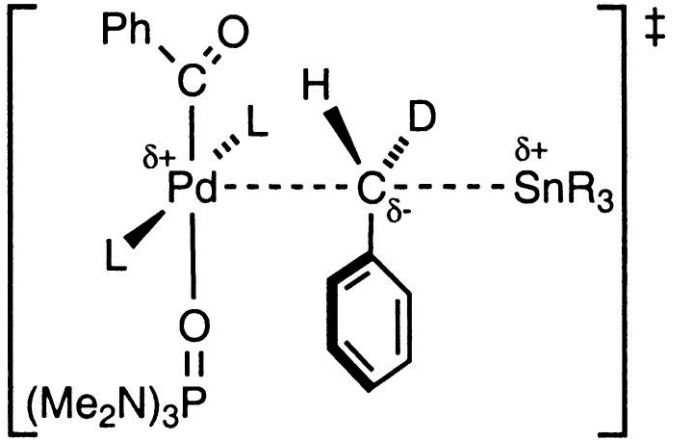
S_E2 open pathway: reasonable mechanism for inversion



First stille proposed intermediate



Espinet *et al.* proposed intermediate

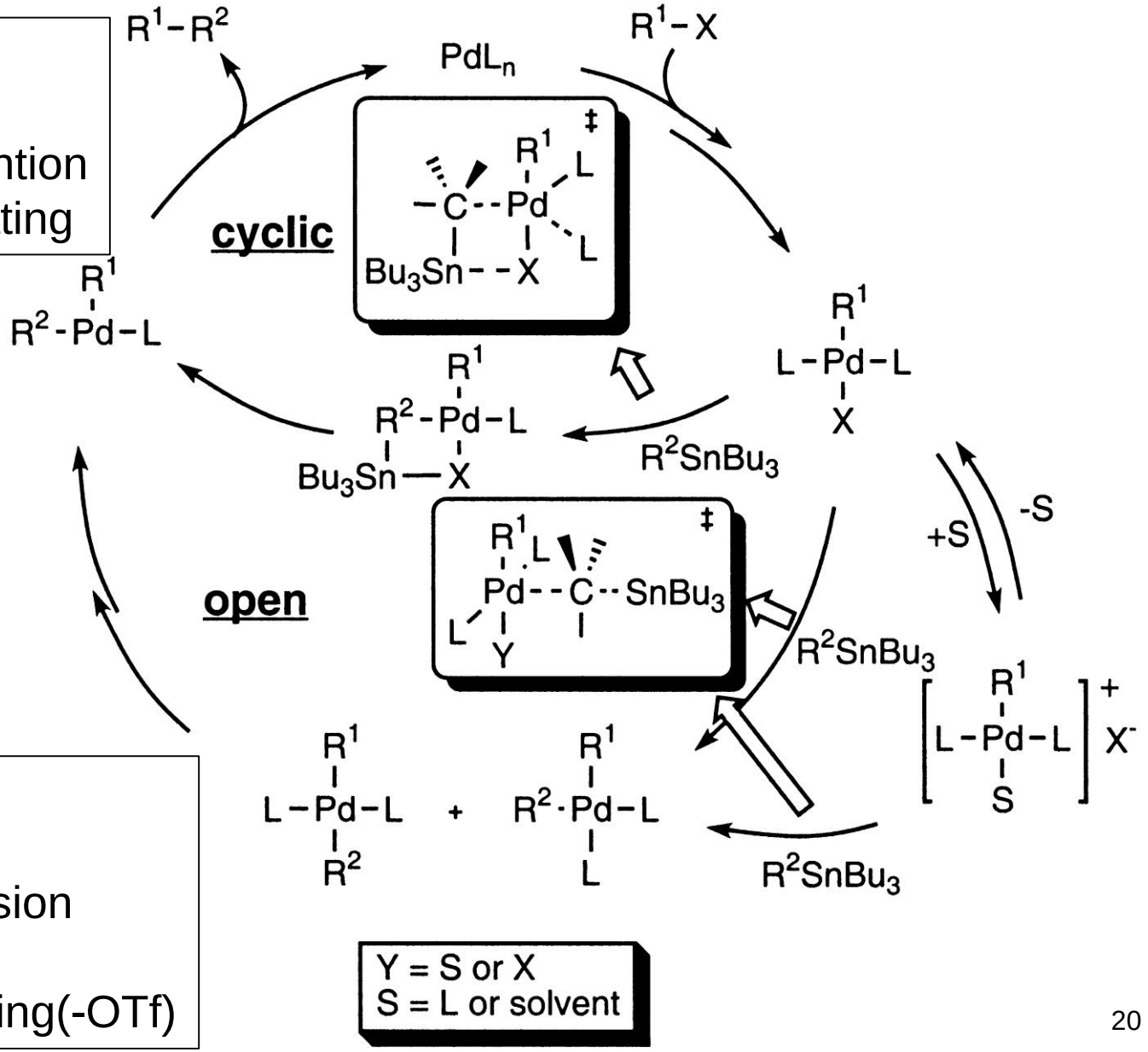


- Associative pathway
- HMPA coordinated intermediate
- The bridging ability of HMPA is poor.

Espinet, P. *et al. J. Am. Chem. Soc.* **2000**, *122*, 11771.

Short summary

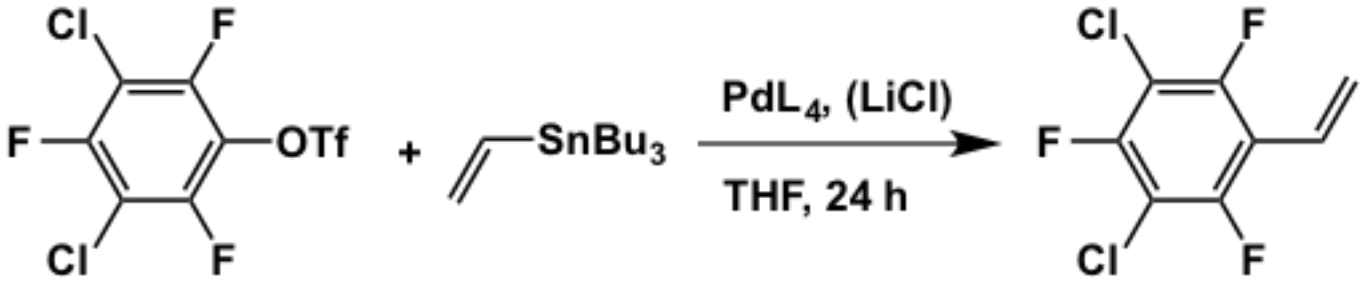
Cyclic:
X = Halide
Stereochemistry: retention
Solvent: non-coordinating



Open:
X = Halide, or –Otf
Stereochemistry: inversion
Solvent: coordinating
(non-coordinating(-OTf)

Triflate : (2) Role of LiCl

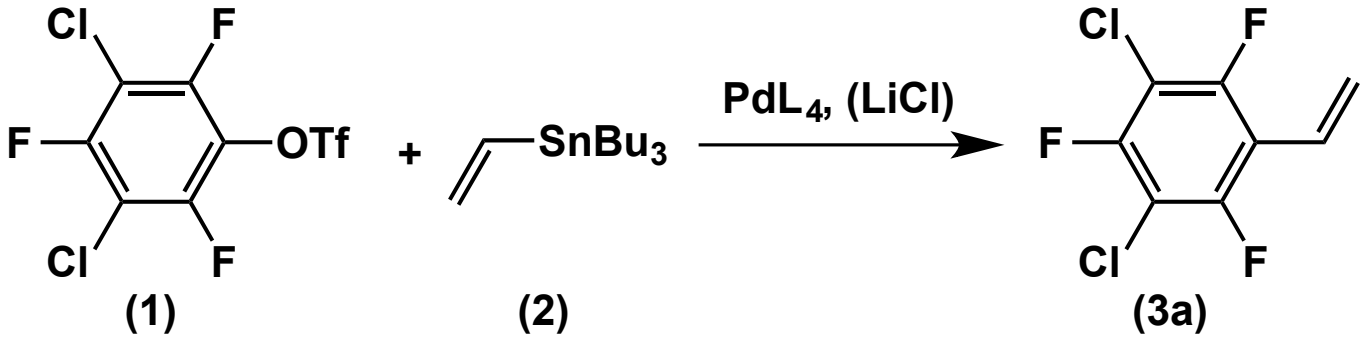
LiCl effect is different depending on ligand.



L	additive	yield (%)
PPh_3	none	100
PPh_3	LiCl	6
$AsPh_3$	none	14
$AsPh_3$	LiCl	87

Espinet, P. *et al. J. Am. Chem. Soc.* **2000**, *122*, 11771.

Oxidative addition speed



AsPh3 is less coordinating ligand than PPh3. Thus, it is supposed effective.

Table 2. Organopalladium(II) Species Formed upon the Oxidative Addition of C_6F_5–OTf (**1**) to $[PdL_4]$[a]

entry	L	solvent	additive[b]	complex(es)[c]
1	PPh_3	PhCl	none	*trans*-$[PdR(OTf)L_2]$ $[PdRL_3]^+$
2	PPh_3	PhCl	LiCl	*trans*-$[PdR(OTf)L_2]$ $[PdRL_3]^+$ *trans*-$[PdRClL_2]$
3	PPh_3	THF	none	*trans*-$[PdR(THF)L_2]^+$ $[PdRL_3]^+$
4	PPh_3	THF	LiCl	*trans*-$[PdRClL_2]$
5	$AsPh_3$	PhCl	none	none
6	$AsPh_3$	PhCl	LiCl	none
7	$AsPh_3$	THF	none	none
8	$AsPh_3$	THF	LiCl	*trans*-$[PdRClL_2]$

[a] After 30 min at 20 °C; $[\mathbf{1}] = 0.2$ mol L^{-1}, $[PdL_4] = 0.01$ mol L^{-1}. [b] $[LiCl] = 0.2$ mol L^{-1}. [c] R = C_6F_5.

PPh_3:
Oxidative addition is **fast**.

$AsPh_3$:
Oxidative addition is **slow**.

Espinet, P. *et al. J. Am. Chem. Soc.* **2000**, *122*, 11771.

Difference between ligands

Table 2. Organopalladium(II) Species Formed upon the Oxidative Addition of C_6F_5–OTf (**1**) to $[PdL_4]$[a]

entry	L	solvent	additive[b]	complex(es)[c]
1	PPh_3	PhCl	none	*trans*-$[PdR(OTf)L_2]$ $[PdRL_3]^+$
2	PPh_3	PhCl	LiCl	*trans*-$[PdR(OTf)L_2]$ $[PdRL_3]^+$ *trans*-$[PdRClL_2]$
3	PPh_3	THF	none	*trans*-$[PdR(THF)L_2]^+$ $[PdRL_3]^+$
4	PPh_3	THF	LiCl	*trans*-$[PdRClL_2]$
5	$AsPh_3$	PhCl	none	none
6	$AsPh_3$	PhCl	LiCl	none
7	$AsPh_3$	THF	none	none
8	$AsPh_3$	THF	LiCl	*trans*-$[PdRClL_2]$

[a] After 30 min at 20 °C; [**1**] = 0.2 mol L^{-1}, $[PdL_4]$ = 0.01 mol L^{-1}. [b] [LiCl] = 0.2 mol L^{-1}. [c] R = C_6F_5.

PPh_3:
Oxidative addition is **fast**.

$AsPh_3$:
Oxidative addition is **slow**.

Table 1. Coupling Reactions between C_6F_5–OTf (**1**) and $Sn(CH{=}CH_2)Bu_3$ (**2**) Catalyzed by $[PdL_4]$: Conversion to C_6F_5–$CH{=}CH_2$ (**3a**)[a]

				conversion (%)	
entry	L	solvent	additive[b]	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

[a] At 50 °C; [**1**] = [**2**] = 0.2 mol L^{-1}, $[PdL_4]$ = 0.01 mol L^{-1}. [b] [LiCl] = 0.2 mol L^{-1}.

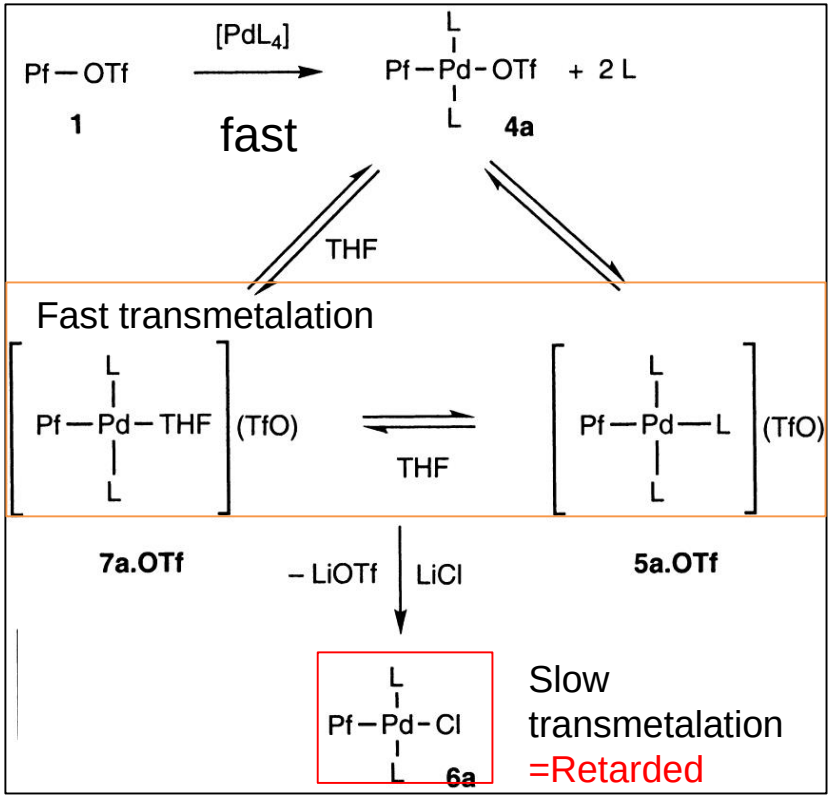
PPh_3 in THF:
LiCl **retards** the reaction.

$AsPh_3$ in THF:
LiCl **accelerates** the reaction.

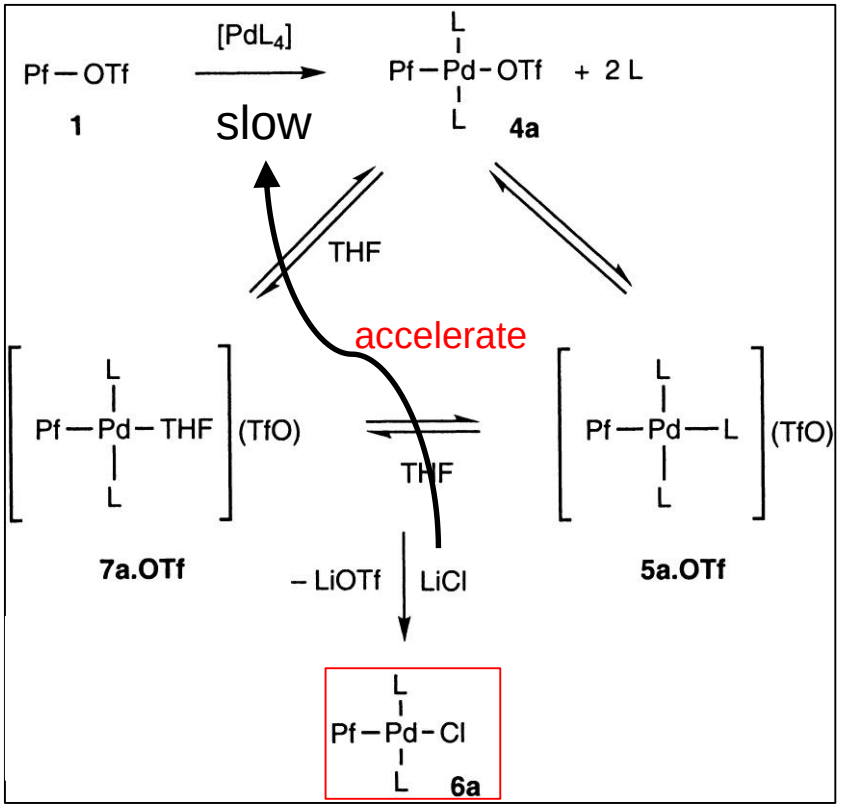
Espinet, P. *et al. J. Am. Chem. Soc.* **2000**, *122*, 11771.

Mechanistic explanation

L = PPh_3 (rds is transmetalation.)



L = $AsPh_3$ (*rds is oxidative addition*.)

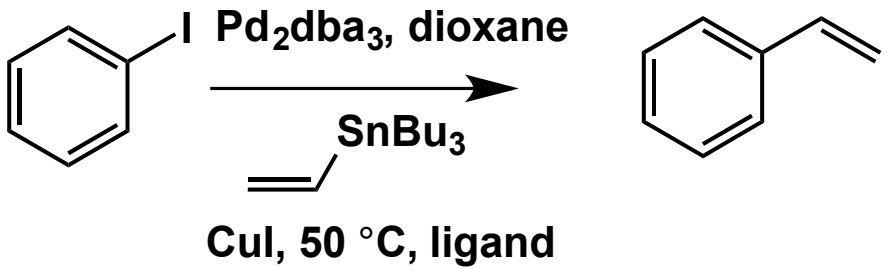


LiCl is effective in only slow oxidative addition reaction.
(In some reactions, other effect is also suggested.)

Espinet, P. *et al. J. Am. Chem. Soc.* **2000**, *122*, 11771.

Additive study : copper effect

Copper effect: Cu(I) salt accelerate the reaction



In the absence of CuI

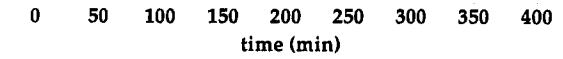
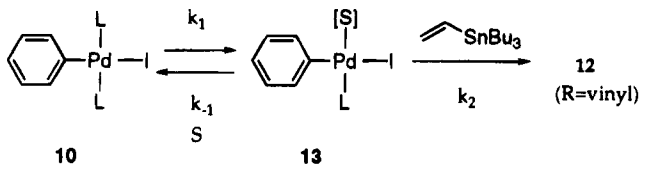


Figure 1. Kinetics of the coupling between iodobenzene (C_0 = 0.139 M) and vinyltributyltin (C_0 = 0.139 M), catalyzed by Pd_2dba_3 (5% mol Pd) and triphenylphosphine (20% ligand) in dioxane at 50 °C. k_{obs}: 2.66×10^{-5} min^{-1} (r^2 = 0.994).

Scheme 1



$$k_{obs} = \frac{k_2 K\,[Pd][\text{stannane}]}{[L] + K}$$

S=Solvent

$K = k_1/k_{-1}$

basicity, *i.e.*, (pentafluorophenyl)diphenylphosphine (comparable in donicity to the more popular trifurylphosphine, TFP),[3] and finally a "soft" highly dissociating ligand such as $AsPh_3$. Different ratios of Pd to ligand and Cu to Pd were explored. Concentrations of **1** and **2** were estimated

In the presence of CuI

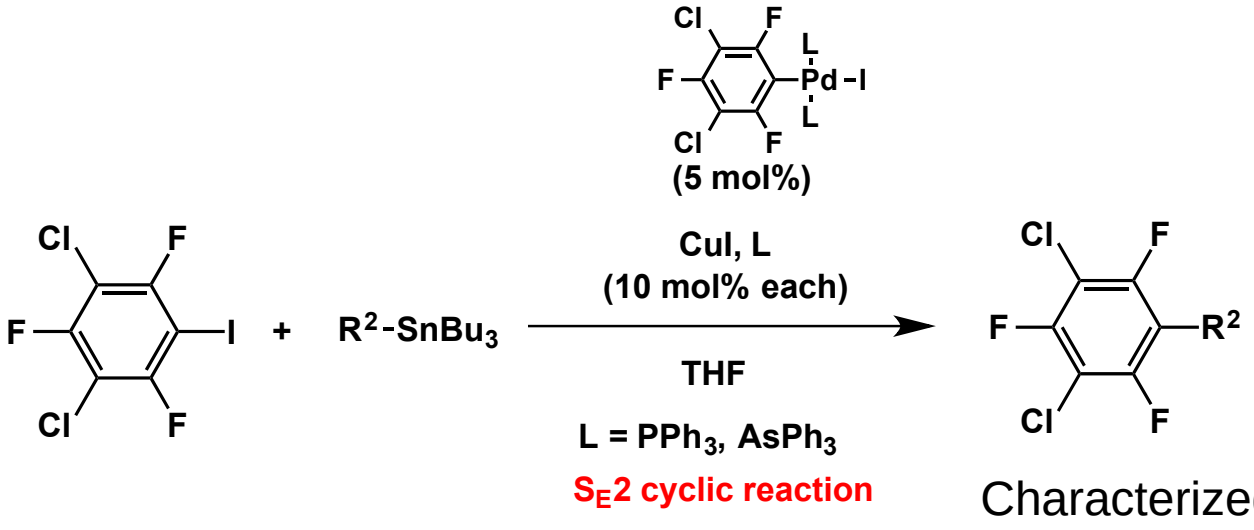
Figure 2. Kinetics of the coupling between iodobenzene (C_0 = 0.139 M) and vinyltributyltin (C_0 = 0.139 M), catalyzed by Pd_2dba_3 (5% mol Pd) and triphenylphosphine (20% ligand) *in the presence of 15% CuI* in dioxane at 50 °C. k_{obs}: 5.90×10^{-3} min^{-1} (r^2 = 1.00).

Table 1. Effect of Added CuI on the Rate of the Palladium-Catalyzed Coupling between Iodobenzene and Vinyltributyltin in Dioxane at 50 °C (Eq 1)[a]

entry	ligand	Pd:L:CuI molar ratio	$10^5 k_{obs}$ (min^{-1}) [st dev][b]	HPLC yield[c] (%)
1	PPh_3	1:4:0	2.66 [0.35]	85
2	PPh_3	1:4:1	13.5 [1.1]	91
3	PPh_3	1:4:2	303 [31]	>95
4	PPh_3	1:4:3	590 [37]	78
5	PPh_3	1:4:4	523 [49]	45
6	PPh_3	1:4:2 (CuBr)[d]	260 [12]	90
7	PPh_3	1:2:0	170 [61]	91
8	PPh_3	1:2:2	547 [44]	56
9	PPh_3	1:4:2 + LiI (200%)	64.5 [9.8]	71
10	PPh_3	1:4:0 + LiI (200%)	1.70 [0.16]	nd
11	PPh_3	1:6:0	1.19 [0.08]	nd
12	PPh_3	1:6:2	5.82 [1.1]	nd
13	PPh_3	1:6:4	271 [77]	74
14	F_5C_6-PPh_2	1:4:0	185 [11]	>95
15	F_5C_6-PPh_2	1:4:1	367 [38]	>95
16	F_5C_6-PPh_2	1:4:2	401 [39]	>95

Liebeskind, J. S. *et al. J. Org. Chem.* **1994**, *59*, 5905.

Kinetic study of copper effect



Characterized by ^{19}F NMR.

Table 2. Determination of the Copper Effect in Couplings of $C_6Cl_2F_3I$ (1) with R^2SnBu_3 (2a,b) Catalyzed by *trans*-$[Pd(C_6Cl_2F_3)IL_2]$ (3, 4)[a]

R^2	L	$k^0_{obs}/10^{-5}$ s^{-1}	$k'_{obs}/10^{-5}$ s^{-1}	$k''_{obs}/10^{-5}$ s^{-1}	$(k''_{obs} - k'_{obs})/(k^0_{obs} - k'_{obs})$
vinyl	$AsPh_3$	33.7 ± 0.4	1.12 ± 0.03	1.60 ± 0.03	0.015 ± 0.001
vinyl	PPh_3	0.99 ± 0.04	≈0	0.311 ± 0.005	0.314 ± 0.014
aryl	$AsPh_3$	1.94 ± 0.02	0.118 ± 0.02	0.122 ± 0.02	0.002 ± 0.016
aryl	PPh_3	0.054 ± 0.002	≈0	0.016 ± 0.002	0.30 ± 0.04

[a] $[1]_0 = [2]_0 = (2.000 \pm 0.017) \times 10^{-1}$ mol L^{-1}, [3] or [4] $= (1.00 \pm 0.03) \times 10^{-2}$ mol L^{-1}, THF, 322.6 K. See definition of k^0_{obs}, k'_{obs}, and k''_{obs} in the text.

k^0_{obs} → Pd only k'_{obs} → Pd : L : Cu =1 : 2 : 0

k''_{obs} → Pd: L : Cu = 1 : 2 : 2

$(k''_{obs} - k'_{obs})/(k^0_{obs} - k'_{obs})$ → the fraction of autoretardation compensated by CuI

Casado, A. L.; Espinet, P. *Organometallics*, **2003**, *22*, 1305.

Evaluation of the copper effect

Table 2. Determination of the Copper Effect in Couplings of $C_6Cl_2F_3I$ (1) with R^2SnBu_3 (2a,b) Catalyzed by *trans*-[$Pd(C_6Cl_2F_3)IL_2$] (3, 4)[a]

R^2	L	$k^0_{obs}/10^{-5}$ s^{-1}	$k'_{obs}/10^{-5}$ s^{-1}	$k''_{obs}/10^{-5}$ s^{-1}	$(k''_{obs} - k'_{obs})/(k^0_{obs} - k'_{obs})$
vinyl	$AsPh_3$	33.7 ± 0.4	1.12 ± 0.03	1.60 ± 0.03	0.015 ± 0.001
vinyl	PPh_3	0.99 ± 0.04	≈0	0.311 ± 0.005	0.314 ± 0.014
aryl	$AsPh_3$	1.94 ± 0.02	0.118 ± 0.02	0.122 ± 0.02	0.002 ± 0.016
aryl	PPh_3	0.054 ± 0.002	≈0	0.016 ± 0.002	0.30 ± 0.04

[a] $[1]_0 = [2]_0 = (2.000 \pm 0.017) \times 10^{-1}$ mol L^{-1}, [3] or [4] = $(1.00 \pm 0.03) \times 10^{-2}$ mol L^{-1}, THF, 322.6 K. See definition of k^0_{obs}, k'_{obs}, and k''_{obs} in the text.

No new Pd species were observed by ^{19}F NMR.
→CuI did not react with Pd complex directly nor promote the dissociation of the ligand.

$(k''_{obs} - k'_{obs})/(k^0_{obs} - k'_{obs})$ → the fraction of autoretardation compensated by CuI

CuI compensates 30% autoretardation for PPh_3, and 1% for $AsPh_3$. (R^2 = aryl)

In the presence of CuI
$[AsPh3]_{free} = 1.5 \times 10^{-2}$ mol L^{-1} → CuI captured 25% released $AsPh_3$.
$[PPh_3]_{free} = 2.1 \times 10^{-4}$ mol L^{-1} → CuI captured 99% released PPh_3.

Copper salt is more effective scavenger when the ligand is PPh_3.

Casado, A. L.; Espinet, P. *Organometallics*, **2003**, *22*, 1305.

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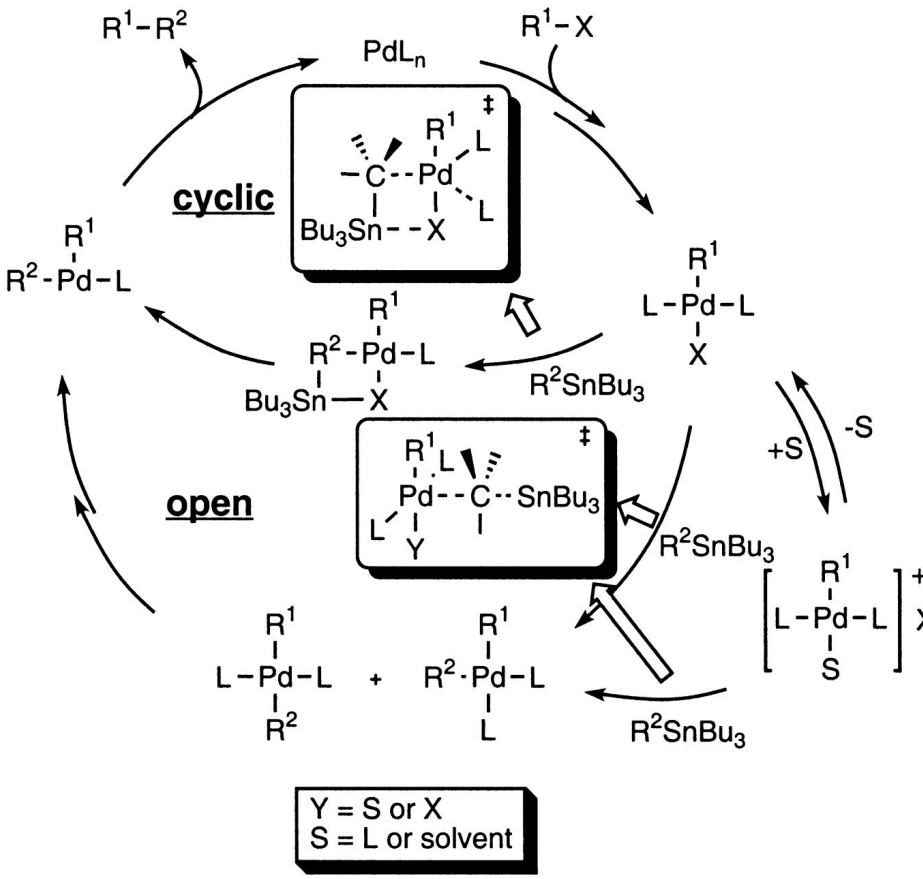
Summary



Dual pathway catalytic cycle

- Open pathway → inversion products
- Cyclic pathway→ retention ones.

- Coordinative solvent gives open pathway products.

- Rate-determining step: usually transmetalation, but in some cases it is oxidative addition. (ex. X = OTf, L=$AsPh_3$)

- LiCl: effective only slow oxidative addition (ex. X = OTf,L = $AsPh_3$)
- CuI: scavenger of free ligand (for especially PPh_3 rather than $AsPh_3$)

Index

Perspective

0. The author suggests that this dual reaction pathways might be found in reactions like Suzuki-Miyaura coupling. (Due to similarity of the polarity of boron compound)

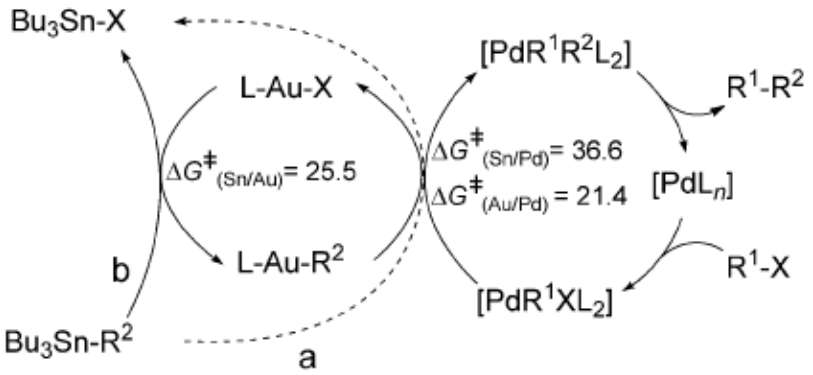
1. Furture direction of this field

- New cocatalyst - Development of the current reaction paradigm
- Giving to an explain to some phenomenon (selectivity etc.)

- Changing from Palladium to another metal

2. What Stille coupling (or other reaction) should overcome next?

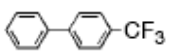
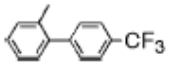
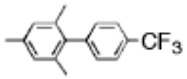
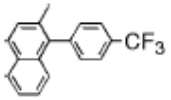
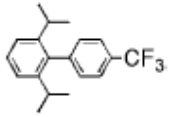
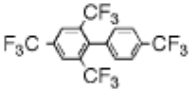
New cocatalyst: Gold



Scheme 3. Pathways for a) the classical Stille and b) the gold cocatalyzed processes, including the transition-state energies for the rate-determing step when X = Cl and R^2 = 2-methyl-1-(4-(trifluoromethyl)-phenyl)naphthalene.

Gold cocatalyst improves the yield even in some reaction which doesn't proceed at all without gold.

Table 2: Palladium-catalyzed cross-coupling of *p*-$CF_3C_6H_4I$ (**1**) with various $ArSn(nBu)_3$ compounds using L = $AsPh_3$, and added LiCl in both the absence and presence of a gold cocatalyst.[a]

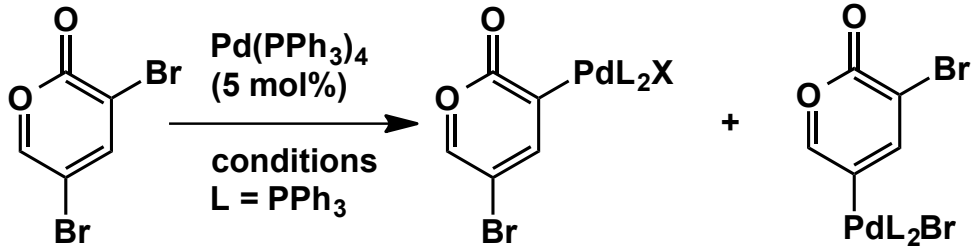
Entry	Au cat.	Product	*t* [h]	Yield [%]	Other products (Yield [%])
1	yes		5	83	**2**(7), **3**(10)
2	–		5	68	**1**(22), **2**(5), **3**(5)
3	yes		6	89	**2**(8), **3**(3)
4	–		6	4	**1**(80), **2**(3), **3**(12)
5	yes		24	84	**1**(<1), **2**(8), **3**(6)
6	–		24	<1	**1**(85), **2**(3), **3**(10)
7	yes		24	90	**2**(4), **3**(6)
8	–		24	0	**1**(81), **2**(5), **3**(11)
9	yes		48	64	**1**(1), **2**(19), **3**(1)
10	–		48	0	**1**(19), **2**(38), **3**(29)
11	yes		48	0	**1**(22), **2**(36), **4**(42)
12	–		48		**1**(90), **2**(2), **4**(2)

[a] Reaction conditions: MeCN, 80 °C, [*p*-$CF_3C_6H_4I$] = 0.10 M, [$ArSn(nBu)_3$] = 0.11 M, [$AsPh_3$] = 4.07×10^{-3} M, [LiCl] = saturated solution. Pd catalyst: [$PdCl_2(AsPh_3)_2$] = 2×10^{-3} M, Au catalyst: [$AuCl(AsPh_3)$] = 2×10^{-3} M. The reactions were monitored until total conversion of the starting *p*-$CF_3C_6H_4I$ was observed, or for the time indicated. Yields were determined by peak integration of the ^{19}F NMR spectra, and are average of two runs.

Espinet, P. et al. *Angew. Chem. Int. Ed.* **2013**, *52*, 2189.

Giving explanation to some phenomena

- Regiocontrolled oxidative addition with CuI

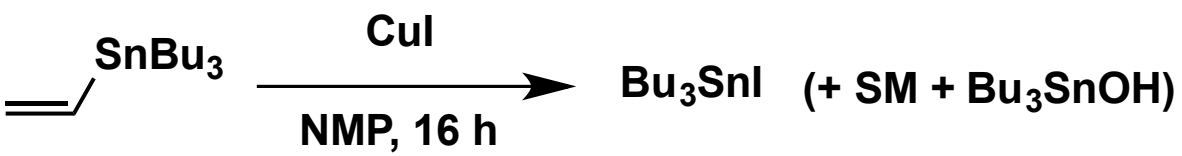


1 5a: X = Br, 5b: X=I 6

entry	conditions	ratio (5:6)[12]
1	toluene/100 °C	100:0
2	toluene/CuI(1.0 equiv)/100 °C	100:0
3	DMF/50 °C	100:0
4	DMF/CuI(1.0 equiv)/50 °C	30:70

Cho, C. –G. *et al. J. Am. Chem. Soc.* **2003**, *125*, 14288.

- Cu transmetalation possibility



※Only in polar solvents

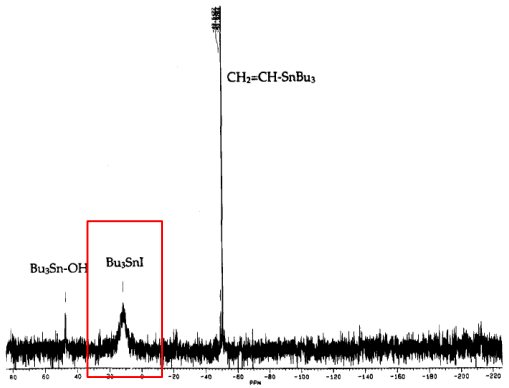
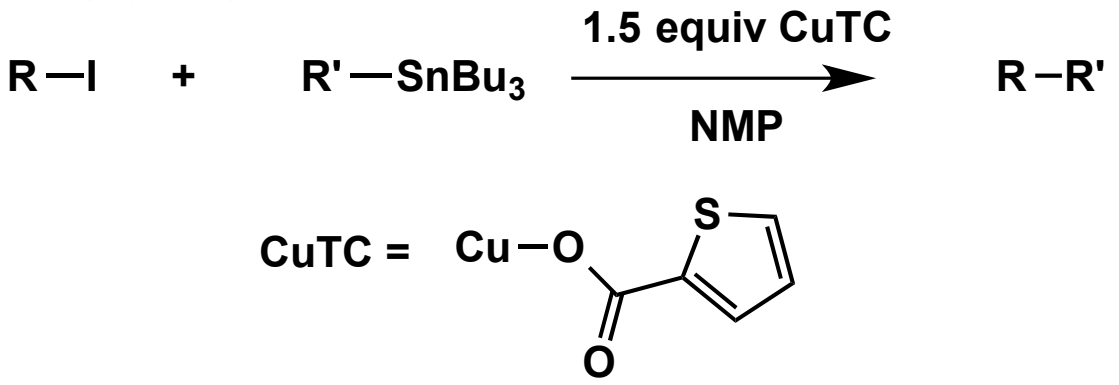


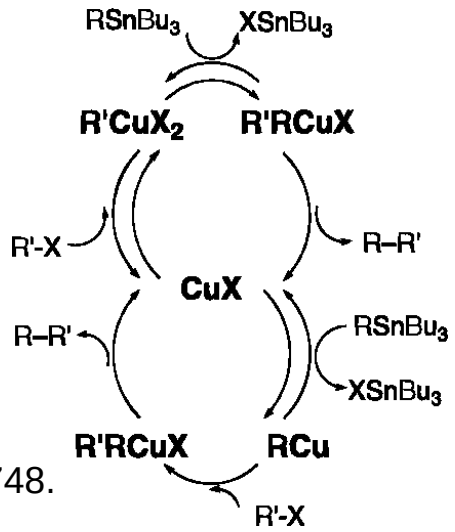
Figure 5. ^{119}Sn-NMR. Experiment 1: 0.18 M CuI in dry NMP + 1 equiv of vinyltributyltin, rt, 16 h.

Liebestkind, *et al. J. Org. Chem.* **1994**, *59*, 5905.

Changing from Pd to another metal

- CuTC

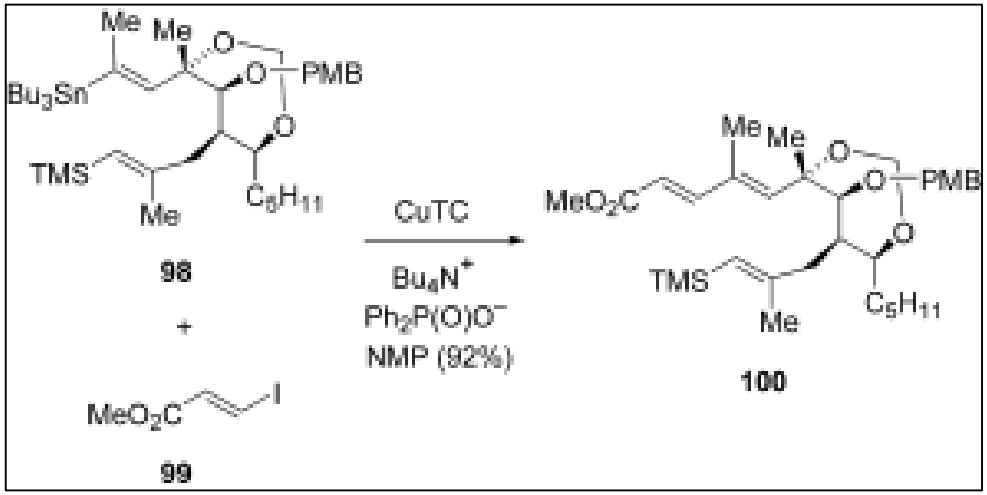




Alled, G. D.; Liebeskind, L. S *J. Am. Chem. Soc.* **1996**, *118*, 2748.

Wang,M; Lin, Z.; *Organometallics* **2010**, *29*, 3077.

Total Synthesis of Formamicinone



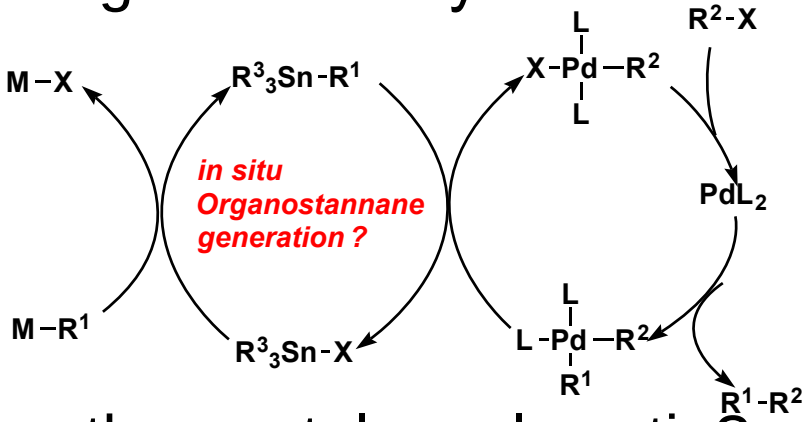
Roush, W. R. *et al. Org. Lett.* **2003**, *5*, 377.

What Stille coupling (or other reaction) should overcome? (just my view)

×Sn toxicity – high toxicity, stoichiometric amount

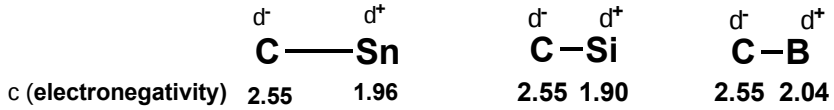
Possible answer

1. Reducing Sn →catalytic amount of tin?



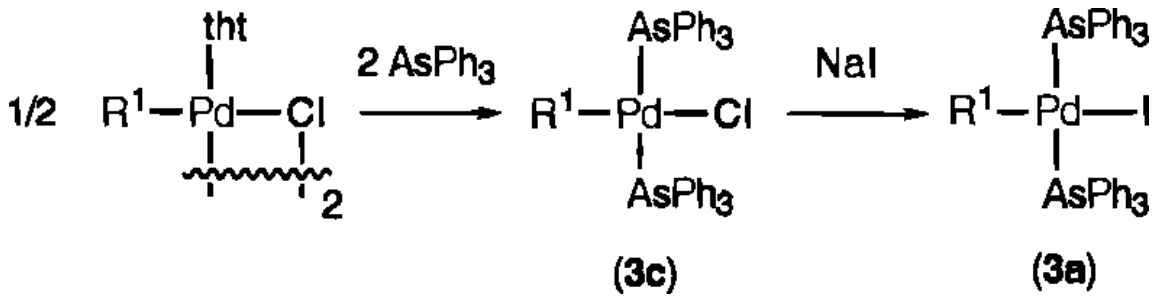
2. Some other metals replace tin?

(cf: C-H sililation, C-H borylation)

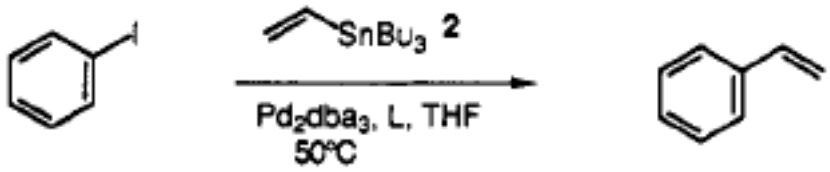


Or others?

Thank you for your kind attention.


1/2
tht
R1—Pd—Cl
2
2 AsPh3
AsPh3
R1—Pd—Cl
AsPh3
NaI
AsPh3
R1—Pd—I
AsPh3

(3c) (3a)



1 3

Table I
Vinyltr
(Pd:L

entry	ligand	rel rate[b]	θ[c]	ν[d]	yield,[e] %
1	PPh_3	1.0 (0.38)	145	2068.9	15.2
2	$MePPh_2$	<0.07	136	2067.0	<2
3	$P(CH_2CH_2CN)_3$	<0.07	132	2078.0	<2
4	$(4\text{-}MeOC_6H_4)_3P$	<0.07	145	2066.1	<2
5	$[2,4,6\text{-}(MeO)_3C_6H_2]_3P$	<0.07	184		<2
6	$(4\text{-}FC_6H_4)_3P$	0.60 (0.08)	145	2071.3	10.7
7	$(4\text{-}ClC_6H_4)_3P$	0.71 (0.10)	145	2072.8	nd
8	$(2\text{-}MeC_6H_4)_3P$	35.2 (2.4)	194	2066.6	19
9	$(2\text{-furyl})_3P$	105 (2.4)			>95
10	$(2\text{-tienyl})_3P$	4.8 (0.5)			68.6
11	$Ph_2PC_6F_5$	24.3 (0.7)	158	2074.8	>95
12	$PhP(C_6H_5)_2$	950 (4.1)		2078.5	58.3[f]
13	$P(C_6F_5)_3$	*g*	184	2090.9	13.2
14	$P(OPh)_3$	95.2 (9.1)	130	2083.5	88[f]
15	$P(OiPr)_3$	42.8 (5.3)	131	2075.9	25[f]
16	$AsPh_3$	1100 (95)	142		>95
17	$SbPh_3$	13.2 (1.5)	142		56.4

[a] 0.16 M PhI and stannane, 3.2 mM Pd, 12.8 mM ligand. [b] For PPh_3 first-order rate constant was 4.6×10^{-5} min^{-1}; each rate is the average of two or three determinations. The figure in parentheses is the standard deviation. [c] Cone angle; see ref 17. [d] IR frequency of $Ni(CO)_3L$ complex; see ref 17. [e] HPLC yield after 72 h. [f] Catalyst decomposed. Catalyst apparently still active in all other cases. [g] Indicated conversion and catalyst decomposition were instantaneous (<2 min).

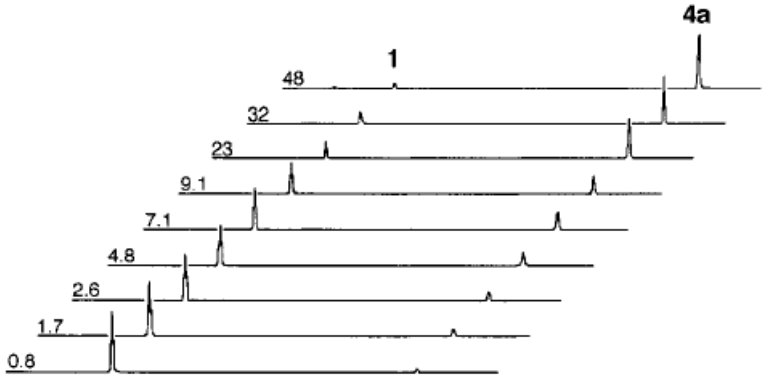


Figure 1. ^{19}F NMR (282 MHz, F^4 region) spectra sequence (intervals in hours) of the coupling of $C_6Cl_2F_3I$ (**1**, 0.2 mol L^{-1}) with $(CH_2{=}CH)SnBu_3$ (**2a**, 0.2 mol L^{-1}) catalyzed by *trans*-$[Pd(C_6Cl_2F_3)I(AsPh_3)_2]$ (**3a**, 0.01 mol L^{-1}) and $AsPh_3$ (0.02 mol L^{-1}), in THF at 322.6 K. The product is $C_6Cl_2F_3(CH{=}CH_2)$ (**4a**).

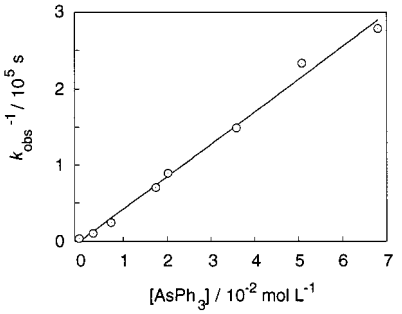


Figure 2. Retarding effect of the addition of $AsPh_3$ on the coupling of $C_6Cl_2F_3I$ (**1**, 0.2 mol L^{-1}) and $(CH_2{=}CH)SnBu_3$ (**2a**, 0.2 mol L^{-1}) catalyzed by *trans*-$[Pd(C_6Cl_2F_3)I(AsPh_3)_2]$ (**3a**, 0.01 mol L^{-1}) in THF at 322.6 K.

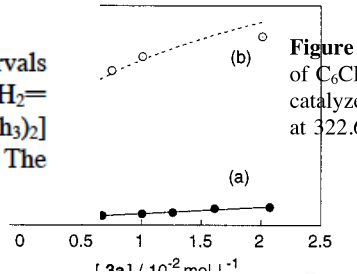
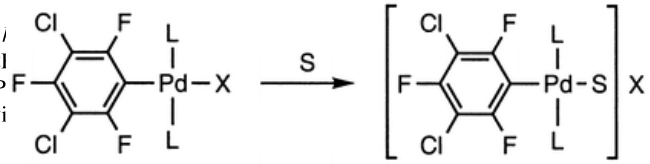
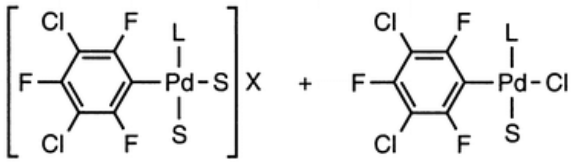


Figure 3. (
L^{-1}) and (Cl
Cl$_2$F$_3$)I(AsP
L^{-1}); (b) wi



F_{ortho}: δ = -86.9, t

L = PPh_3
S = HMPA



F_{ortho}: δ = -85.8, d

F_{ortho}: δ = -88.1, d