

Recent Advances in Cross-Coupling Reactions

06 03 18

O. Introduction

>2% change between 1985-1996 & 1997-2002

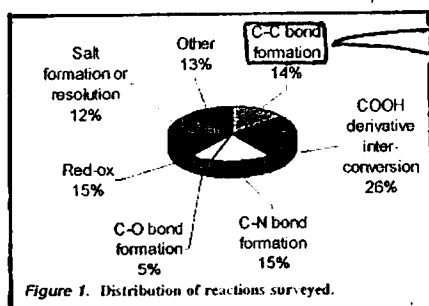


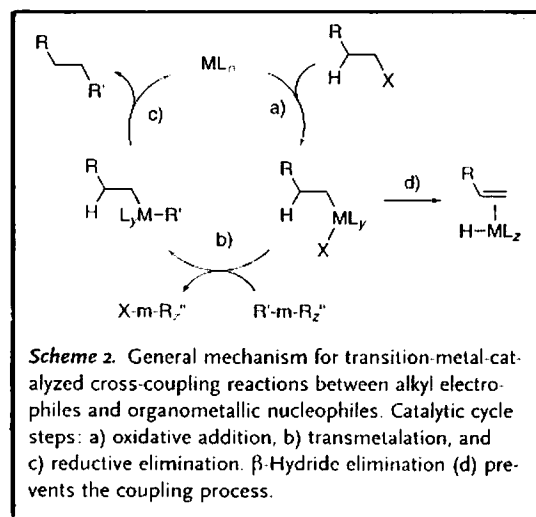
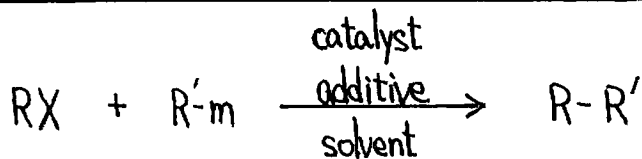
Table 1. Subclassification of carbon-carbon bond-forming reactions

entry	reaction category	C-C bond formations		
		1985-2002 no. of reactions (% of total)	1985-1996 no. of reactions (% of total)	1997-2002 no. of reactions (% of total)
1	aldol	59 (17.8)	42 (20.2)	17 (13.7)
2	enolate addition to imine/nitrile	3 (0.9)	2 (1.0)	1 (0.8)
3	Claisen	46 (13.9)	31 (14.9)	15 (12.1)
4	enolate alkylation	37 (11.1)	22 (10.6)	15 (12.1)
5	Grignard addition	31 (9.3)	21 (10.1)	10 (8.1)
6	cyanide addition	8 (2.4)	7 (3.4)	1 (0.8)
7	Wittig olefination	4 (1.2)	4 (1.9)	0 (0)
8	Michael addition	24 (7.2)	14 (6.7)	10 (8.1)
9	Lithium carbanion addition	15 (4.5)	3 (1.4)	12 (9.7)
10	total anionic C-C bond formation (entries 1-9)	227 (68.4)	146 (70.2)	81 (65.3)
11	Friedel-Crafts acylation	34 (10.2)	24 (11.5)	10 (13.7)
12	Friedel-Crafts aldehyde	3 (0.9)	3 (1.4)	0 (0)
13	Friedel-Crafts alkylation	4 (1.2)	3 (1.4)	1 (0.8)
14	iminium ion addition	8 (2.4)	6 (2.9)	2 (1.6)
15	Duff reaction	14 (4.2)	10 (4.8)	4 (3.2)
16	total cationic C-C bond formation (entries 11-15)	63 (19.0)	46 (22.1)	17 (13.7)
17	cross-coupling	27 (8.1)	9 (4.3)	18 (14.3)
18	miscellaneous	15 (4.5)	7 (3.4)	8 (6.4)
19	total	332 (100)	208 (100)	124 (100)

△ Reactions scaled in the GMP facilities at the Pfizer-Groton site

Org. Process Res. Dev. 2005, 9, 253.

"The use of Pd-catalyzed cross-coupling reactions has significantly increased."



Angew. Chem. Int. Ed. 2003, 42, 384.

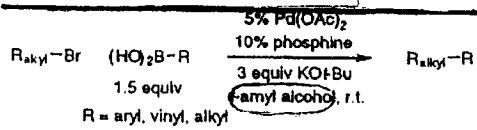
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| IV. R'-m | modified organosilicon reagents |
| V. Additive | Lewis / Brønsted bases |

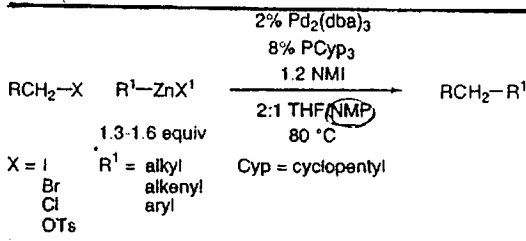
I. Solvent - SN2-type oxidative addition in

Pd-catalyzed reactions of 1°-RX

Polar solvents are often used in Fu's reactions.

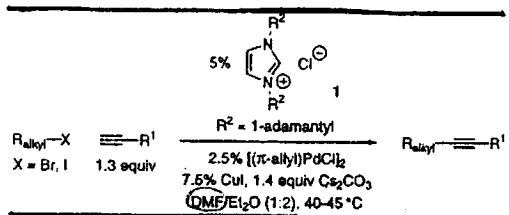


JACS, 2002, 124, 13662.

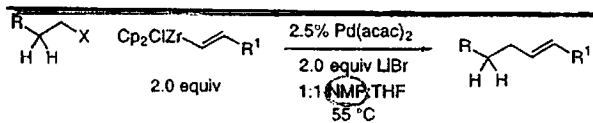


$\Delta S^\ddagger = -63 \text{ eu} > 0$
 - associative
 SN2-type

JACS, 2003, 125, 12528.



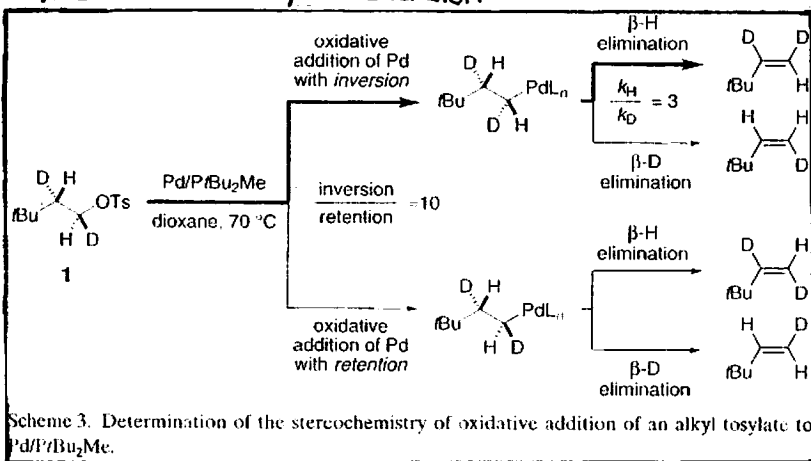
JACS, 2003, 125, 13662.



JACS, 2004, 126, 82.

Table 1-3; Angew. Chem. Int. Ed. 2003, 42, 5749. →

4. Stereochemistry: Inversion



↓
Oxidative addition proceeds via SN2.

Oxidative addition (inversion)
+ transmetalation (retention)

Angew. Chem. Int. Ed. 2002, 41, 3910.

1. Solvent effect: The more polar, the faster.

Table 1: Correlation between solvent polarity and the activation barrier for oxidative addition.^[a]

Entry	Solvent	Polarity	ΔG^\ddagger [kcal.mol ⁻¹]
1	hexane	0.68	> 23.0 ^[b]
2	toluene	1.66	20.0
3	THF	2.08	19.5
4	tert-aryl alcohol	2.46 ^[d]	18.1
5	NMP ^[d]	2.62	18.0
6	DMF ^[d]	2.80	17.8

[a] All data are the average of two runs. [b] No reaction at 0-60°C. ΔG^\ddagger was calculated for 60°C. [c] Value for tert-butanol. [d] NMP = N-methylpyrrolidinone. [d] DMF = dimethylformamide.

2. Leaving group effect: I > Br > OTs > Cl >> F

Table 2: Effect of the leaving group on the rate of oxidative addition.^[a]

Entry	X	t _{1/2}
1	I	2.2 h at -60°C
2	Br	2.3 h at 0°C
3	Cl	2.0 d at 60°C
4	F	< 2% reaction after 43 h at 60°C
5	OTs ^[b]	10.4 h at 40°C

[a] All data are the average of two runs. [b] Ts = toluenesulfonyl.

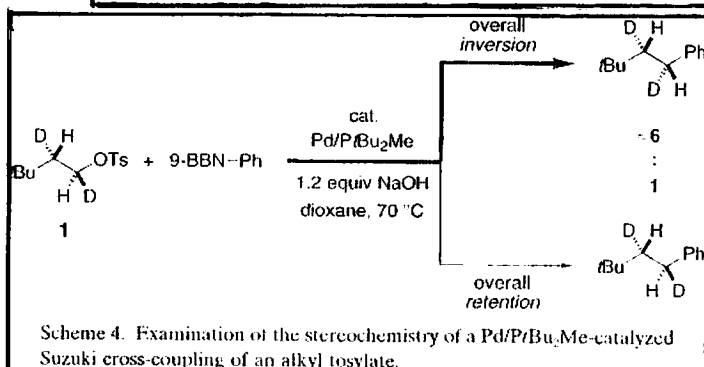
3. Steric effect: The less hindered, the faster.

Table 3: Correlation between the steric demand of the electrophile and the activation barrier for oxidative addition.^[a]

Entry	R-Br	k _{rel}	ΔG^\ddagger [kcal.mol ⁻¹]
1	n-pentyl-Br	1.0	19.5
2	Me-CH ₂ -CH ₂ -Br	0.19	20.3
3	Me-CH ₂ -Br	0.054	21.0
4	Me-Br	< 0.0001	> 24.0 ^[b]

↳ 10⁴ times faster

[a] All data are the average of two runs. [b] Extrapolated from a reaction run at 60°C.



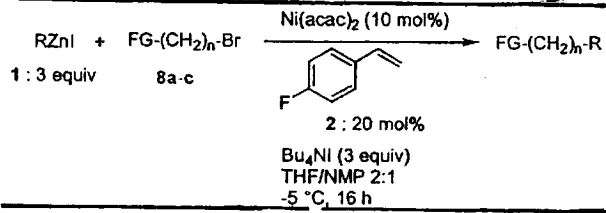
Scheme 4. Examination of the stereochemistry of a Pd/PtBu₂Me-catalyzed Suzuki cross-coupling of an alkyl tosylate.

II. Catalyst System — Radicalic oxidative addition for 2°-RX

i) for 1°-RX

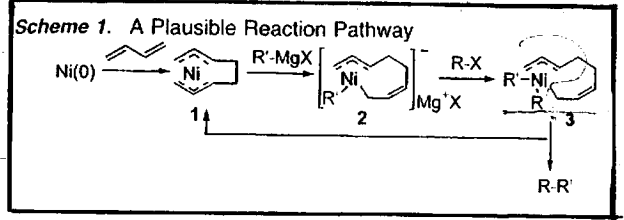
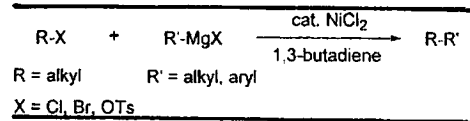
a. Fu's Pd-system (Pd + bulky trialkyl P or NHC)
See P2.

b. Knochel's Ni-system



JOC 2002, 67, 79.

c. Kambe's Ni-system



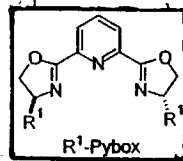
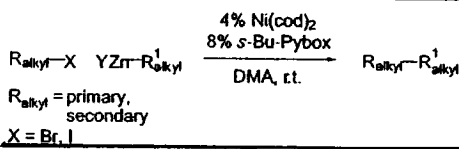
JACS, 2002, 124, 4223.

ii) for 2°-RX

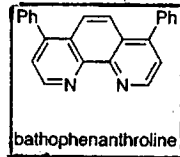
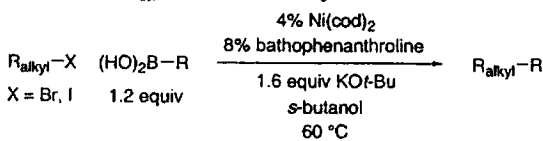
asym. ver. JACS 2005, 127, 4594.

JACS 2005, 127, 10482.

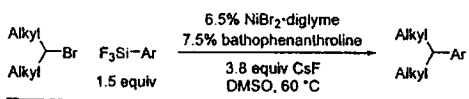
a. Fu's Ni-system



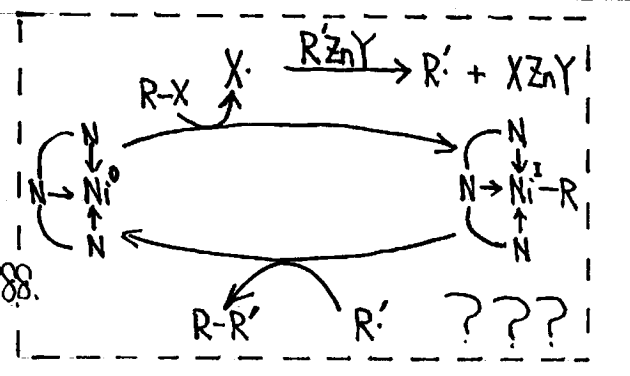
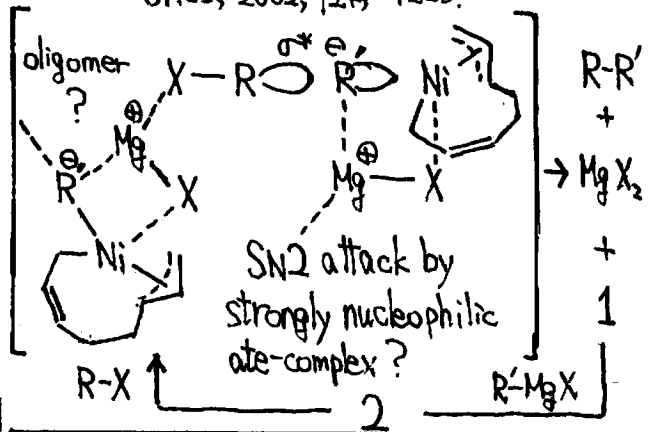
JACS 2003, 125, 14726



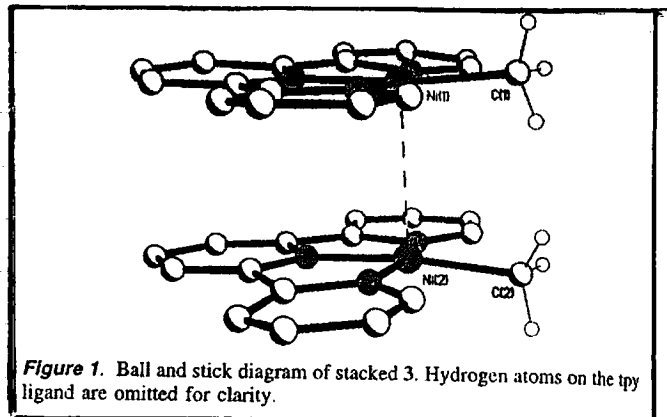
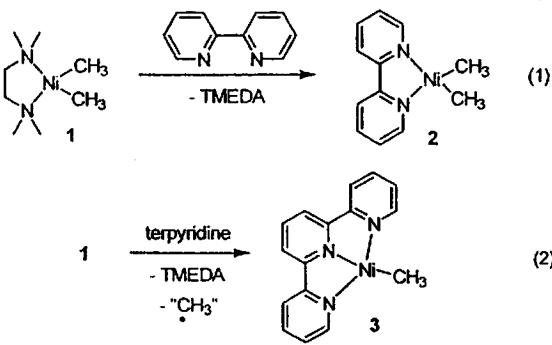
JACS 2004, 126, 1340.



JACS, 2004, 126, 7788.



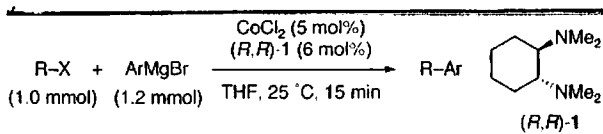
▽ "Evidence for a Ni^{II} active species"



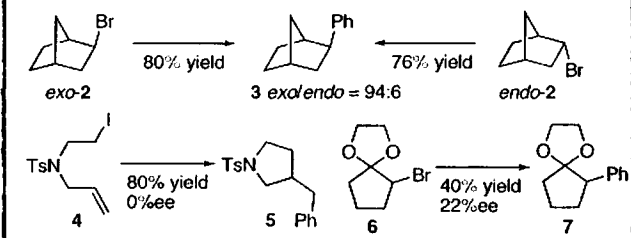
Vivic et al. JACS, 2004, 126, 8100.

- magnetic susceptibility $\mu_{\text{eff}} = 1.64 \mu_B$ in THF
- two quasi-reversible waves in the cyclic voltammogram at -1.47 & -0.92 V vs Ag/Ag⁺ in THF

b. Oshimas Co system

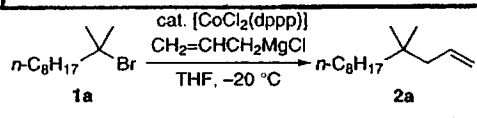


Scheme 1. Justification of the Existence of Carbon-centered Radicals: Conditions Are the Same as Those in Table 1



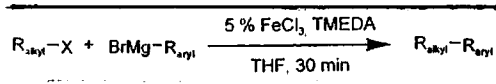
JACS, 2006, 128, 1886.

c. Allylation of 3°-RX!



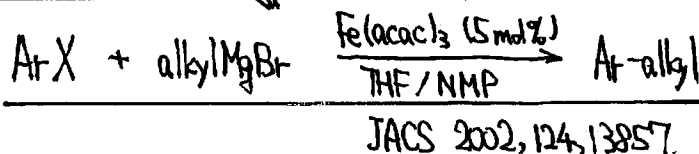
Angew. Chem. Int. Ed. 2002, 41, 4137.

c. Nakamura's Fe system



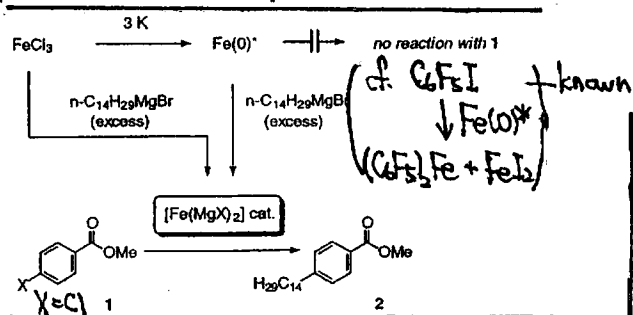
JACS 2004, 126, 3687.

Fürstner proposes Ni^0 as active species.

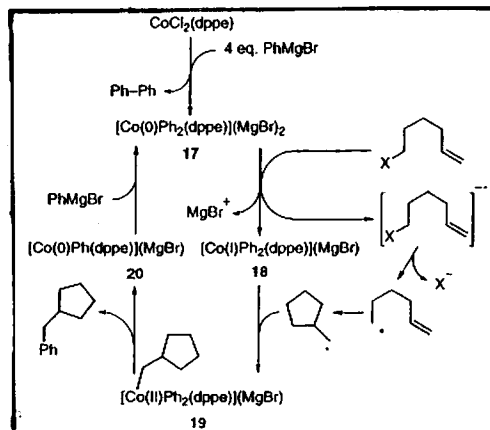
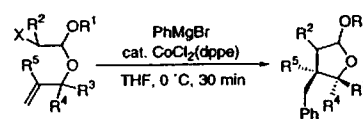


It seems reasonable, but ...

- C_6FeI should be much more reactive than 1.
- Fe(0) solubility is low.

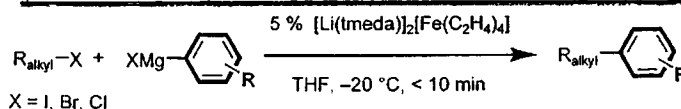


Cobalt-Catalyzed Phenylative Radical Cyclization⁹

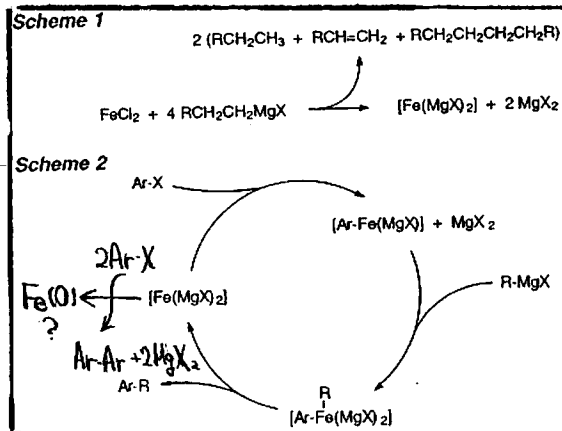


JACS 2001, 123, 5374.

d. Fürstner's Fe system



Angew. Chem. Int. Ed. 2004, 43, 3955.



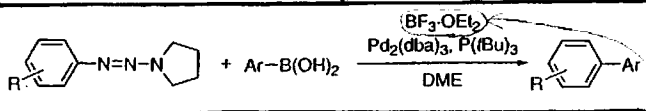
iii) for Ar-Cl

• bulky trialkyl P, NHC as ligand

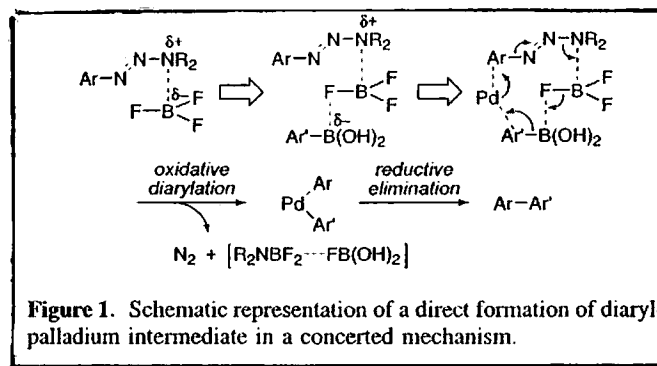
Oxidative addition generally proceeds via three-centered concerted pathway.

III. RX Nucleophile activation by electrophile

i) Ar-N=N-NR₂ Tamao et al. OL, 2004, 6, 617.

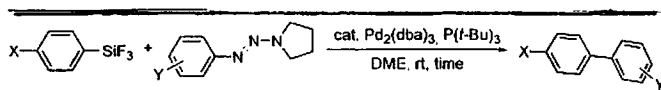


• Ar-N≡N⁺X⁻ unstable
 • Ar-N=N-NR₂ stable
 but TFA or HBF₄ is necessary for generation of Ar-N≡N⁺X⁻ in situ.



entry	R	Ar	yield [%] ^b 10 min, 1 h
1	<i>o</i> -Me	<i>p</i> -MeO-C ₆ H ₄ (2)	81, 91(72) ^d
2	<i>m</i> -Me	<i>p</i> -MeO-C ₆ H ₄ (2)	88, 92(80) ^d
3	<i>p</i> -Me (1)	<i>p</i> -MeO-C ₆ H ₄ (2)	98, 98(91) ^d
4	<i>p</i> -MeO	<i>p</i> -Me-C ₆ H ₄	94, 94
5	2,4,6-Me ₃	<i>p</i> -MeO-C ₆ H ₄ (2)	85, 90
6	<i>p</i> -F	<i>p</i> -MeO-C ₆ H ₄ (2)	73, 81
7	<i>p</i> -Cl	<i>p</i> -MeO-C ₆ H ₄ (2)	64, 74(68) ^d
8 ^c	<i>p</i> -Br	<i>p</i> -MeO-C ₆ H ₄ (2)	30, 40
9 ^c	<i>p</i> -I	<i>p</i> -MeO-C ₆ H ₄ (2)	tr, tr
10	<i>p</i> -TfO	<i>p</i> -MeO-C ₆ H ₄ (2)	43, 52(41) ^d
11	<i>p</i> -MeCO	<i>p</i> -MeO-C ₆ H ₄ (2)	31, 58
12	<i>p</i> -Et ₂ N	<i>p</i> -MeO-C ₆ H ₄ (2)	97, 97
13	<i>p</i> -Me (1)	1-naphthyl	88, 90(78) ^d
14	<i>p</i> -Me (1)	2-thienyl	94, 94(84) ^d
15	<i>p</i> -Me (1)	2-furyl	0, 0

^a Reaction conditions: 1-aryltriazene (0.50 mmol), areneboronic acid (1.0 mmol), Pd₂(dba)₃ (2 mol %), P(tBu)₃ (8 mol %), BF₃·OEt₂ (0.50 mmol), room temperature, DME (5.0 mL). ^b Yields are determined by GC analysis with eicosane as an internal standard. ^c Using 5 mol % of Pd₂(dba)₃ without phosphine ligand. See ref 11. ^d Isolated yields.



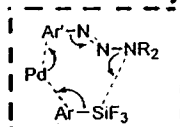
Adv. Synth. Catal. 2004, 346, 1689.

Entry	X	Y	Yield ^(b)
3	H	<i>p</i> -Me	74%
4	OMe	<i>p</i> -Me	60%
5	F	<i>p</i> -Me	82%
9	Me	<i>p</i> -F	38%
10	Me	<i>p</i> -Cl	42%
11	Me	<i>p</i> -Br	trace
12	Me	<i>p</i> -I	0%

Entry 3-5 Different tendency from Suzuki-coupling.

Entry 9-10 C-F activation?

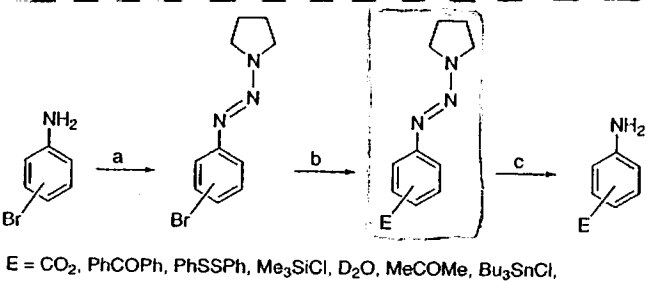
• No need of BF₃·OEt₂
 • -SiMe₃, -Si(OMe)₃, -SiCl₃, -SiMe₂F, -SiMeF₂ -X
 → "direct acid-base interaction between -SiF₃ & -NR₂"



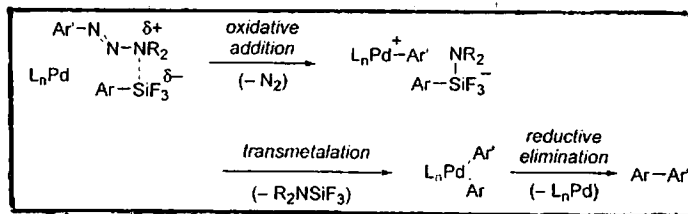
Without BF₃·OEt₂ — N.R.

"The 1-aryltriazenes did not react with BF₃·OEt₂ in the absence of either the Pd catalyst or boronic acids."

Preparation of 1-aryltriazenes



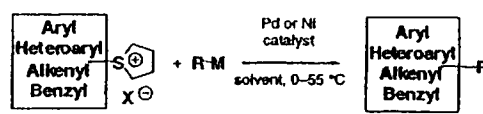
E = CO₂, PhCOPh, PhSSPh, Me₃SiCl, D₂O, MeCOMe, Bu₃SnCl.



"This mechanism is also possible."

seems O.K.

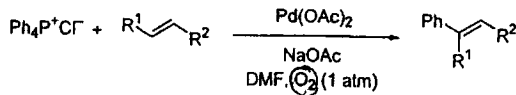
unlikely? cf.



Liebeskind et al. JACS 1997, 119, 12376

ii) $\text{Ph}_4\text{P}^+\text{Cl}^-$ as an Arylating Reagent

Table 1: Heck olefinations with 1.^[a]

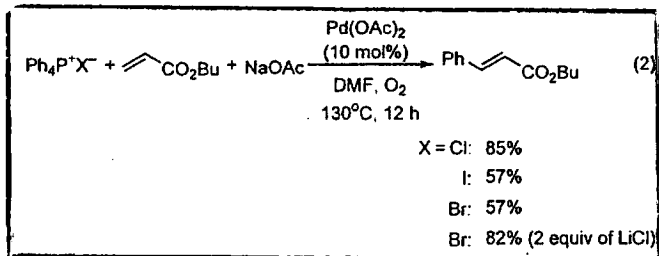


[a] Reaction conditions: alkenes (3.0 equiv), catalyst (10 mol%), NaOAc (3.0 equiv), 130 °C, 12 h under O₂ (1 atm).

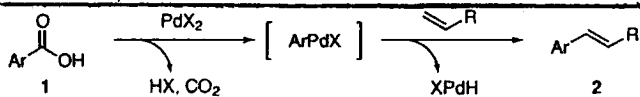
Chang et al. *Angew. Chem. Int. Ed.* 2005, 44, 6166.

$\text{Ph}_4\text{P}^+\text{Cl}^-$ plays "a dual role."

1. "a source of the arylating group"
 2. "a stabilizing ligand on palladium complex"
- ↳ but O₂ is necessary to obtain good yield....



ArCO₂H



Myers et al. *JACS*, 2002, 124, 11250.

Entry	Acid	Alkene	Product	Reaction Time (h)	Isolated Yield (%)
1 ^b				1	91
2				3	71
3				1	92
14				3	85

^a Conditions: acid (1 equiv), alkene (1.5 equiv), Pd(O₂CCF₃)₂ (0.2 equiv), Ag₂CO₃ (3 equiv), 5% DMSO-DMF, 120 °C, except as noted. ^b Reaction conducted at 80 °C.

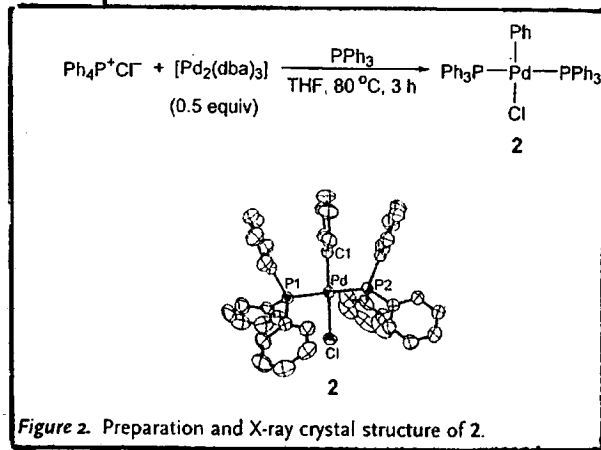
- Electron-rich acid gives higher yield.
- Acids lacking ortho substituents — C-H insertion

"Pd-mediated cleavage of the PC bond"

• ESI-MS

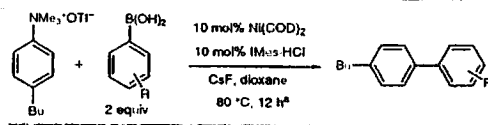
peaks of $[(\text{Ph}_3\text{P})_2\text{PdPh}(\text{MeCN})_m] (m=1-3)$

• X-ray



Counter anion effect

ArMe₃N⁺OTf⁻

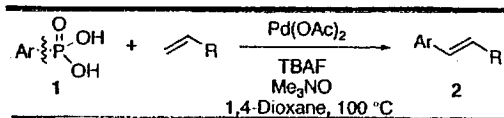


ArMe₃N⁺I⁻ — "reduced yield"

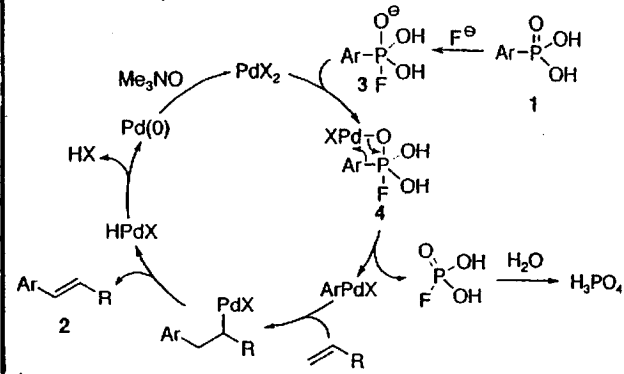
Macmillan et al. *JACS* 2003, 125, 6046.

Harder counter anion gives higher yield?

ArP(O)(OH)₂



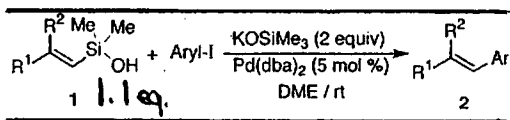
Scheme 2. Proposed Mechanism



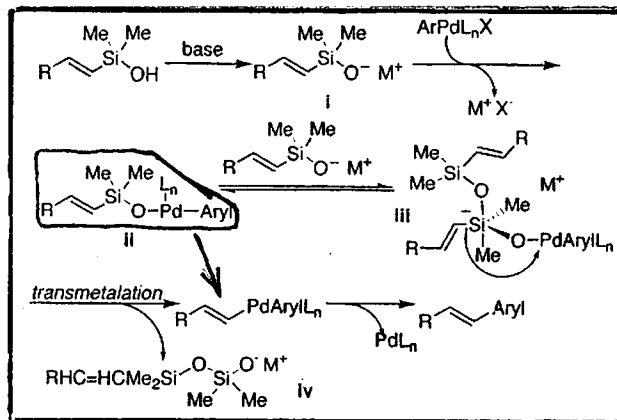
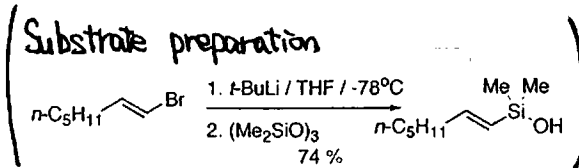
Oshima et al. *JACS*, 2003, 125, 1484.

V. R-m

1) R-SiMe₂OH — intramolecular transmetalation



Denmark et al. JACS 2001, 123, 6439.



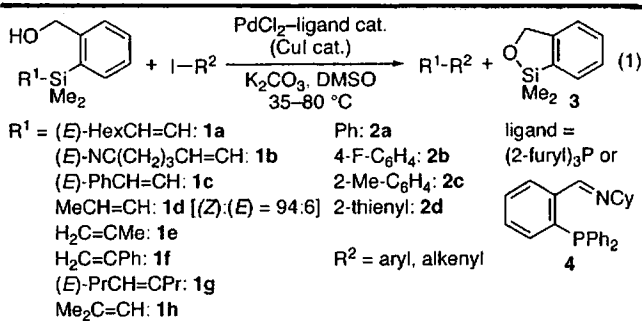
Kinetic study supports this mechanism. (JACS, 2004, 126, 4876.)

• "Pd-O-Si" linkage formation → intramolecular transmetalation

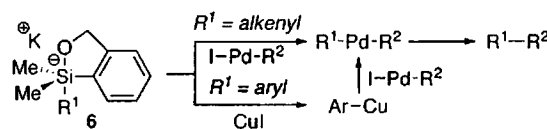
• Transmetalation from ii, not ate-complex iii, is possible.

F⁻ source (instead of base) — different mechanism
JACS. 2004, 126, 4865.

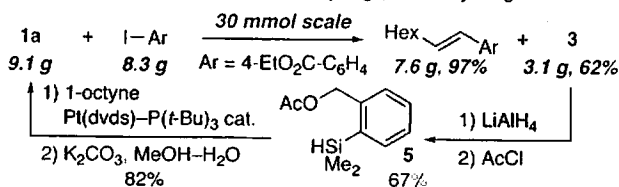
ii) R-SiMe₂OH — intramolecular activation



Scheme 2. Plausible Reaction Pathway



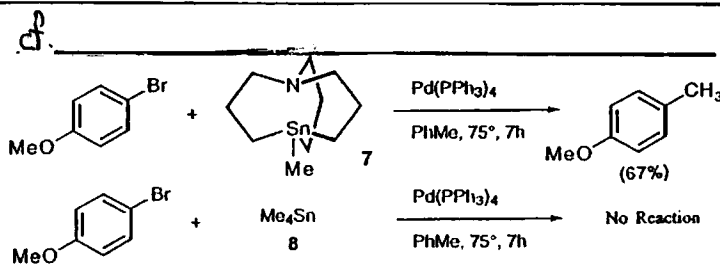
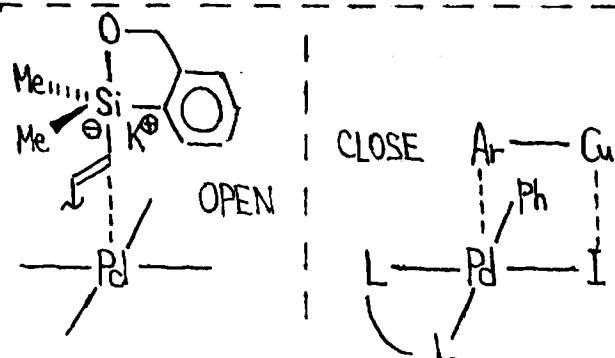
Scheme 1. Gram-Scale Cross-Coupling and Recycling of 3



R = alkenyl — PdCl₂ (1 mol%), (2-furyl)₃P (2 mol%)
 K₂CO₃ (2 eq) in DMSO at 35°C
 R = aryl — PdCl₂ (3 mol%), 4 (4 mol%), CuI (1 mol%)
 K₂CO₃ (1.7 eq) in DMSO at 50°C

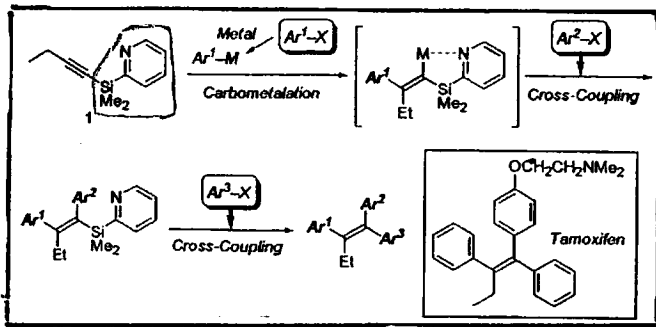
Δ "the metal residue of the cross-coupling is demonstrated for the first time to be reused for the next coupling."

Hiyama et al. JACS. 2005, 127, 6952.

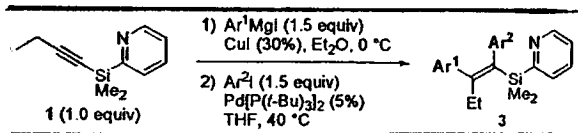


Vedejs et al. JACS 1992, 114, 6556.

iii) -SiMe₂

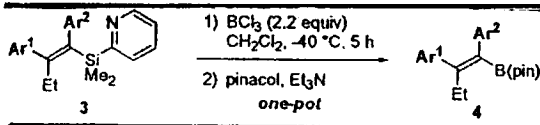


Yoshida et al. JACS 2003, 125, 4670.
Adv. Synth. Catal. 2004, 346, 1824

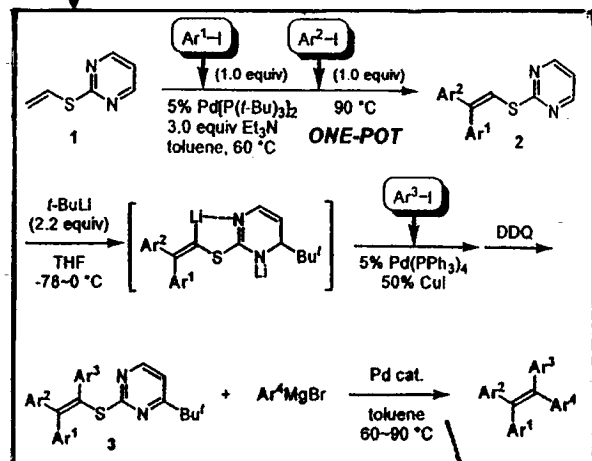
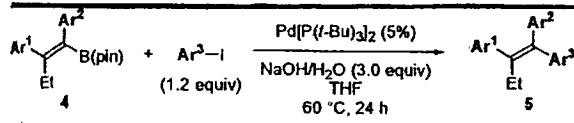


"The directing effect of the 2-pyridyl group is important."

"Ph₂CuMgI as active species?"

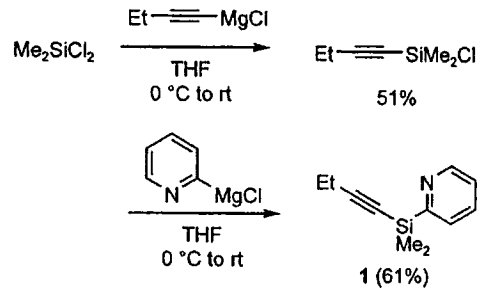


Hiyama coupling X (when Ar²=H, O.K.)
Si/B exchange (Naso et al. J. Chem. Soc., Chem. Commun., PPS 2523.)



JACS, 2004, 126, 11778.

(14-72%)



Scheme 3. Synthesis of (1-butynyl)dimethyl(2-pyridyl)silane (1).

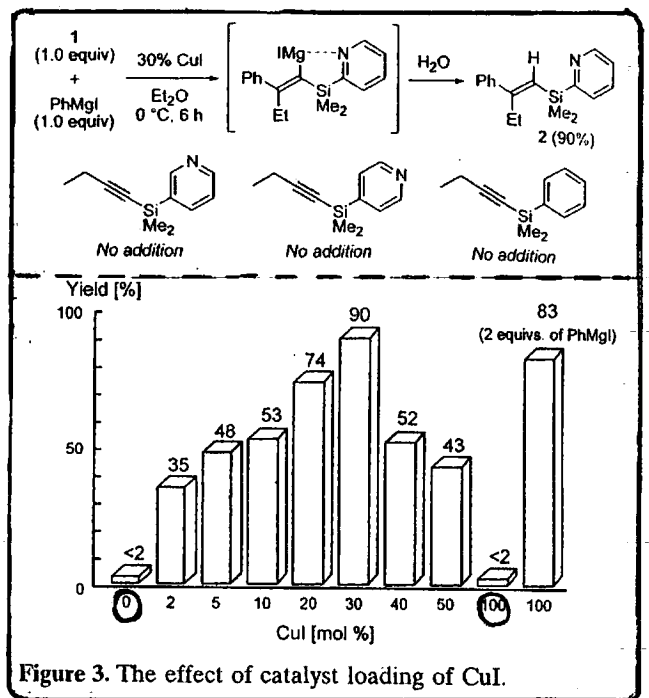
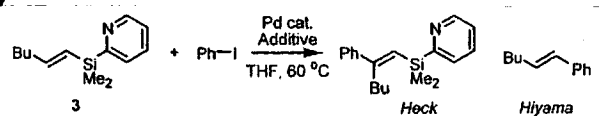
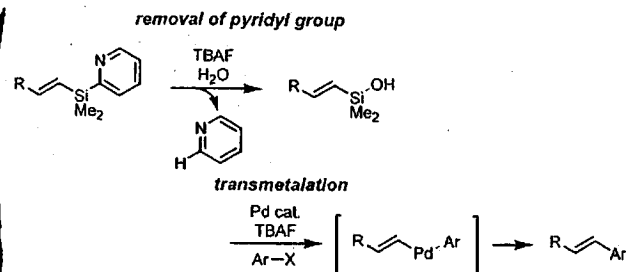


Figure 3. The effect of catalyst loading of CuI.

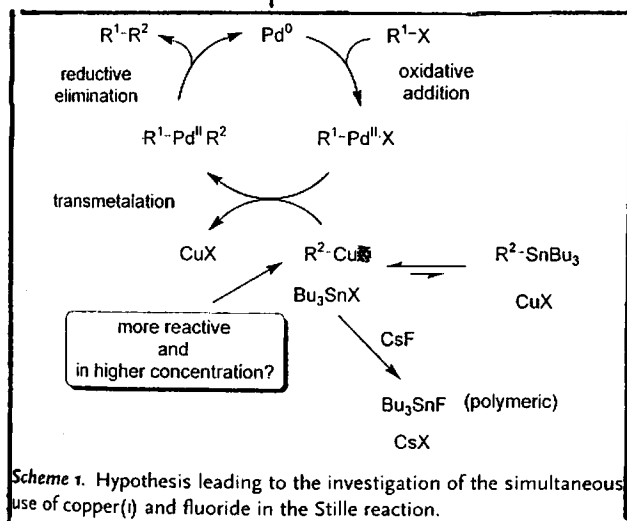


catalyst (5 mol%)	additive (1.2 equiv)	ratio (Heck/Hiyama) (yield)
Pd ₂ (dba) ₃ /TFP	Et ₃ N	100/0 (94%)
Pd ₂ (dba) ₃ /TFP	TBAF	0/100 (59%)
PdCl ₂ (PhCN) ₂	TBAF	0/100 (99%)



JACS, 2001, 123, 11577.

V. Additive Synergic effect of Cu^I & F^-



- Cu^I salt — organo copper in polar solvents
 - ligand scavenger in etheral solvents
 - F^- source — Bu_3SnF formation (insoluble)
- Baldwin et al. *Angew. Chem. Int. Ed.* 2004, 43, 1132.

Table 1: The individual and combined effects of CuI and CsF on the coupling of 1 and 2.

Entry	Reagents ^[a]	Yield [%] ^[b]
1	$[\text{Pd}(\text{PPh}_3)_4]$	2
2	$[\text{Pd}(\text{PPh}_3)_4]$, CsF	8
3	$[\text{Pd}(\text{PPh}_3)_4]$, CuI	46
4	$[\text{Pd}(\text{PPh}_3)_4]$, CsF and CuI	98
5	CsF and CuI	0

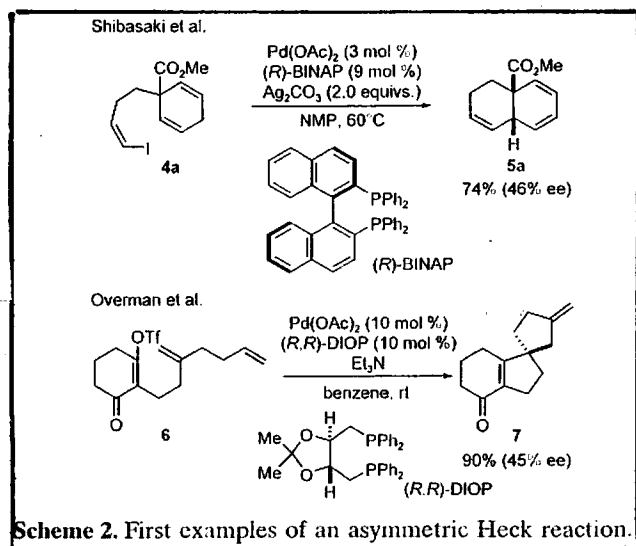
[a] $[\text{Pd}(\text{PPh}_3)_4]$ (10%), CuI (20%), CsF (2.0 equiv). [b] Yields are isolated yields of 3 and are the average of two repeat experiments. Remaining mass balance is recovered starting materials.

Table 2: Evaluating alternative conditions on the coupling of 4 and 2.

Entry	Reagents ^[a]	Yield [%] ^[d]
1	PdCl_2 , PtBu_3 , CuI , CsF , $\text{DMF}^{[b]}$	92
2	PdCl_2 , PtBu_3 , CsF , DMF	29
3	$[\text{Pd}_2(\text{dba})_3]$, PtBu_3 , CsF , dioxane ^[c]	16
4	$[\text{Pd}_2(\text{dba})_3]$, PtBu_3 , CuI , CsF , dioxane	10

[a] PdCl_2 (2%) or $[\text{Pd}_2(\text{dba})_3]$ (1%), PtBu_3 (4%), CuI (4%), CsF (2.0 equiv). [b] Conditions B. [c] Reagent combination reported by Fu et al.^[10]. [d] Yields are isolated yields and are the average of two repeat experiments. Remaining mass balance is recovered starting materials.

• Ag salts in Heck reaction

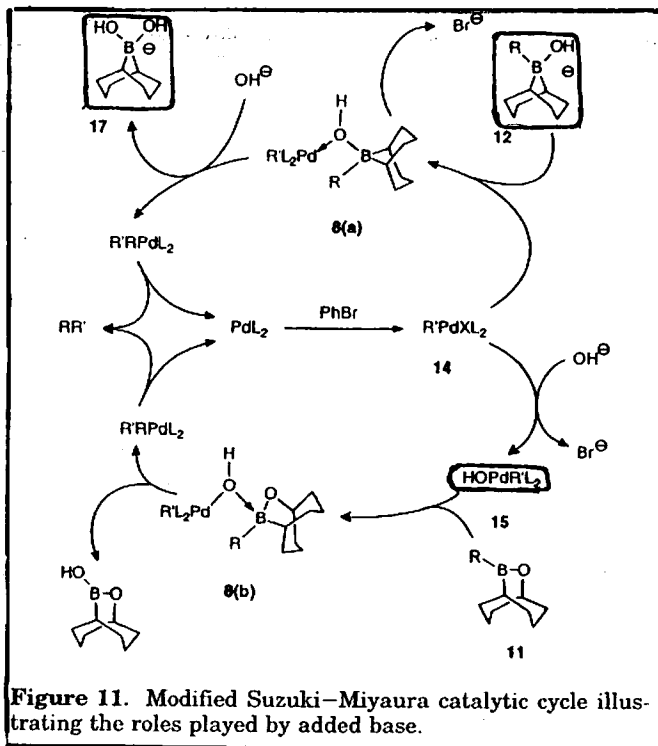


Shibasaki et al. *JOC*, 1989, 54, 4738.
Overman et al. *JOC*, 1989, 54, 5846.

- Prevention of product re-insertion into B-H bond.
- Generation of cationic Pd species.

Fc — Acceleration of reductive elimination

• Base effects



Soderquist et al. *JOC* 1998, 63, 461.

Knochel et al. *Angew. Chem. Int. Ed.* 1998, 37, 2387.