# Hiyama, Liebeskind and Nigishi Coupling

# **Buchwald-Hartwig Coupling**

Wanbin Group Literature Seminar

Report Time:2010.03.06

Reporter: Yang, Guoqiang

# 有机化学反应

羟醛缩合类反应

偶联反应

**(或过渡金属催化下的C-X键形成反应)**

氧化反应

还原反应

环化反应

重排反应

# Outline

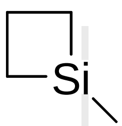
- Concise Introduction of Hiyama Coupling
- Concise Introduction of Nigishi Coupling
- Concise Introduction of Liebeskind Coupling
- **The Development of Buchwald-Hartwig Coupling**

# Ⅰ Concise Introduction of Hiyama Coupling

$$R^1\text{-}SiY_3 \; + \; R^2\text{-}X \xrightarrow[\text{activator}]{\text{Pd cat.}} R^1\text{-}R^2$$

$R^1$ = alkyl, alkynyl, alkenyl, aryl

$SiY_3$ = $SiMe_3$; $SiMe_2F$; $SiMeF_2$; $SiF_3$;
$Si(OR)_3$ (Tamao-Ito)



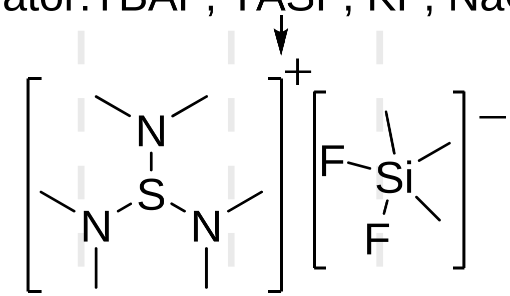
(Denmark)

$R^2$ = alkenyl, aryl, allylic

X =Cl, Br, I, $OSO_2F_3$, $OCO_2Et$

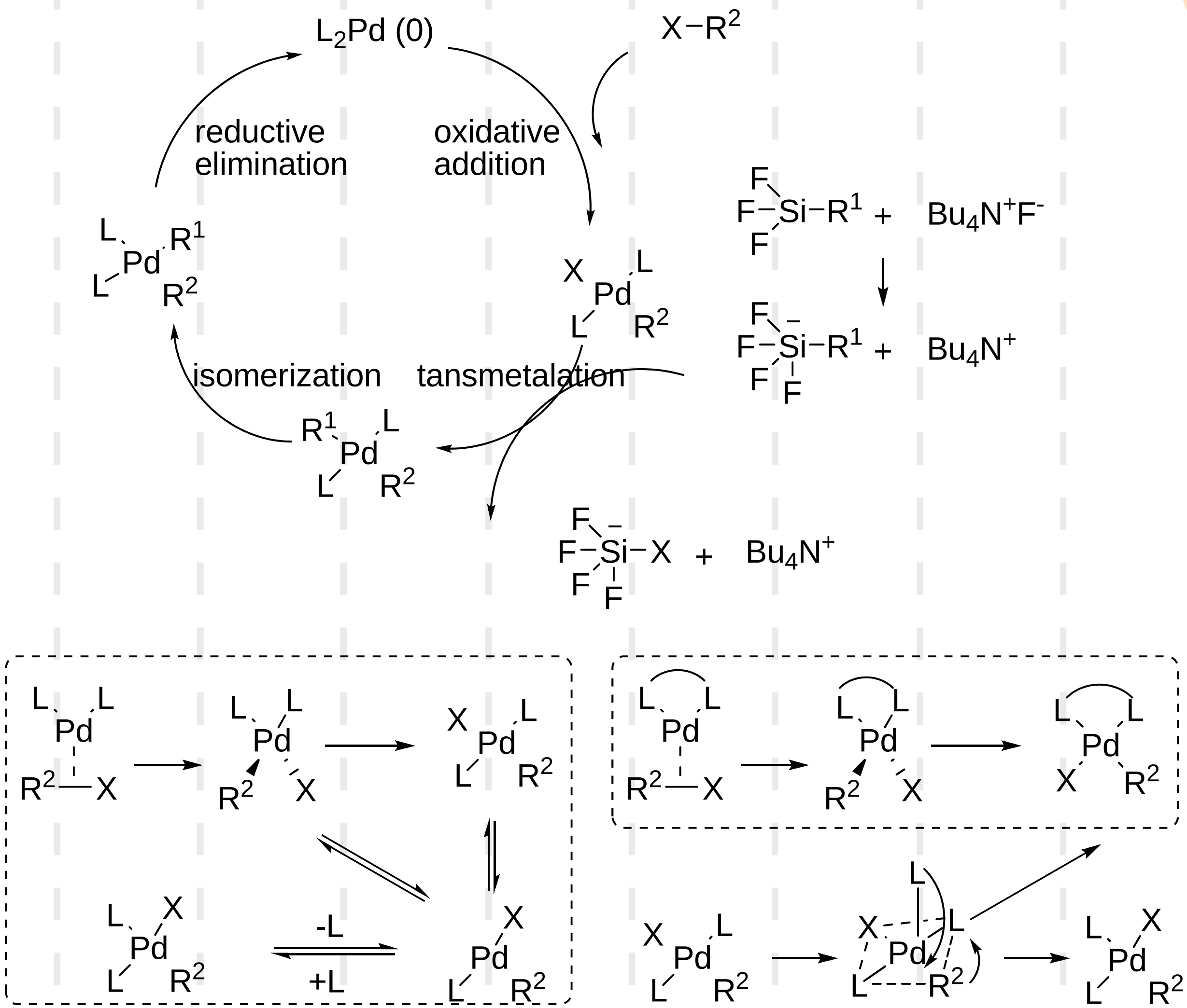
Pd cat.: $(\eta\text{-}C_3H_5PdCl)_2$, $Pd(PPh_3)_4$....

activator:TBAF, TASF, KF, NaOH, $RO^-$

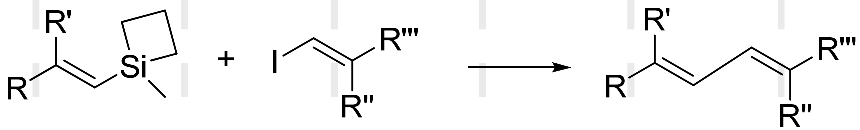


# Mechanism

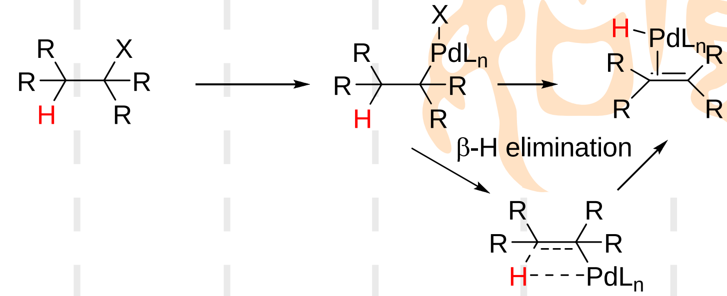
Coupling Reactions: Oxidative Addition—Transmetallization—Reductive Elimination

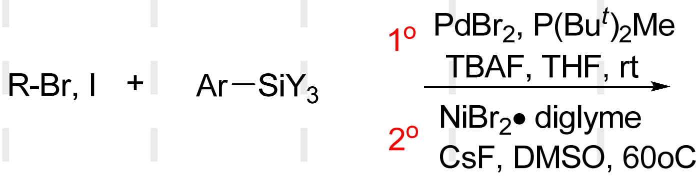


# 易操作，低毒，官能团耐受性强----反应时间长，温度高

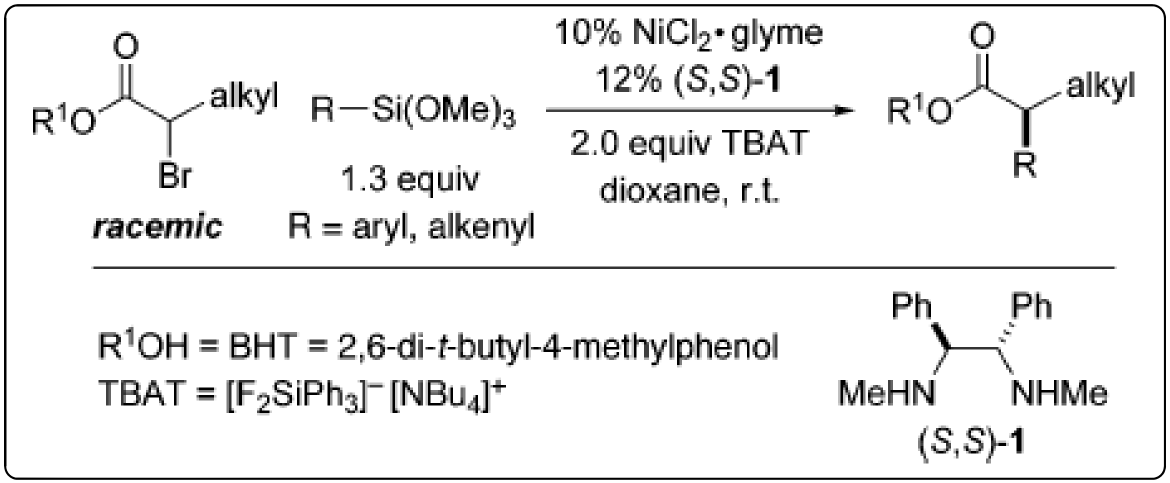



[3]




[4,5]




[6]


1） Hatanaka, Y.; Hiyama, T. *JOC*. **1988**, *53*, 918;

2) Tamao, K.; Kobayashi, K.; Ito, Y. *TL*. **1989**, *30*, 6051;

3) Denmark, S. E.; Choi, J. Y. *JACS*. **1999**,*121*, 5821;

4) Lee, J.-Y.; Fu, G. C. *JACS*. **2003**, *125*, 5616;

5) Powell, D. A.; Fu, G. C. *JACS*. **2004**, *126*, 7788.

6) Dai, X.; Strotman, N. A.; Fu, G. C. *JACS*. **2008**, *130*, 3302-3303

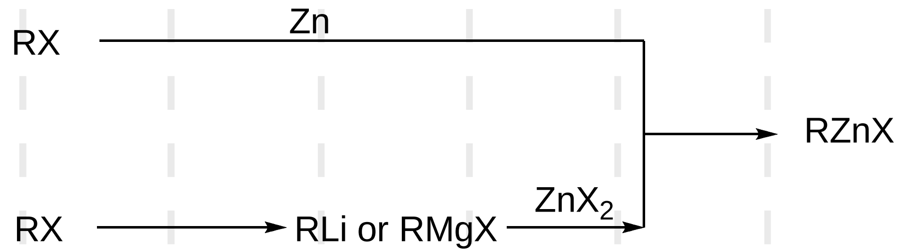
# Ⅱ Concise Introduction of Nigishi Coupling

$$R^1\text{-}ZnX' + R^2\text{-}X \xrightarrow{\text{Pd, Ni cat.}} R^1\text{-}R^2$$

$(R^1\text{-}Al, Zr + ZnX'_2)$

Na(0.9) < Li(1.0) < Mg(1.2) < Al(1.5) < Zn (1.6) < In (1.7) < Sn(1.8) < Si(1.8~2.0) < B(2.0)

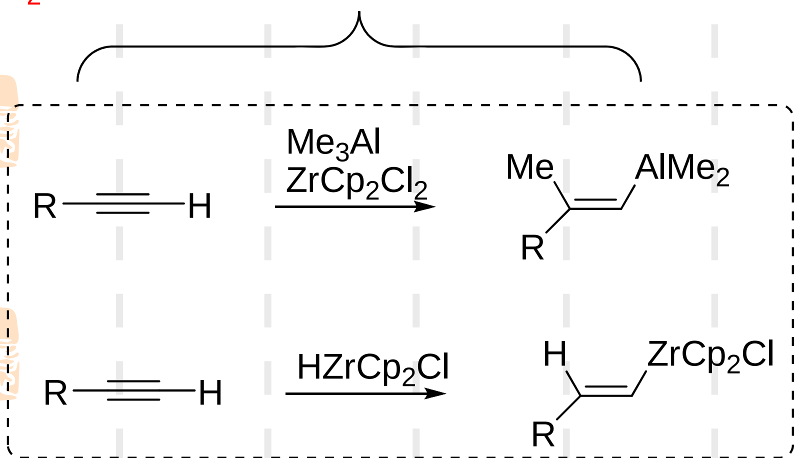
The first type

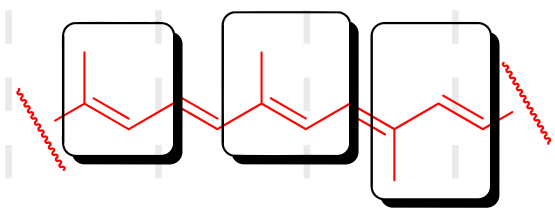


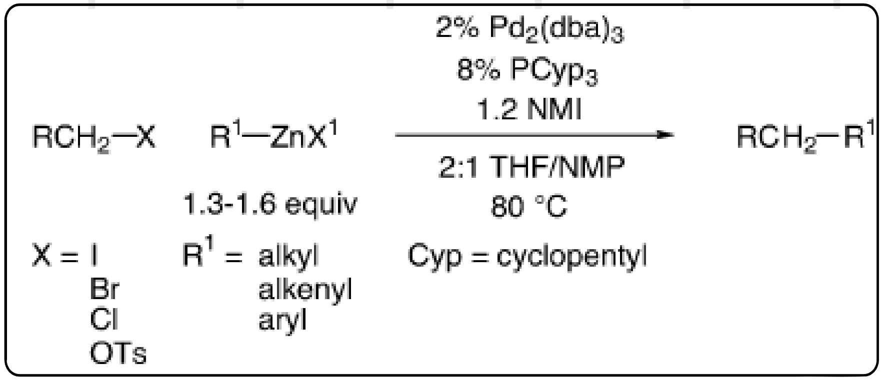

The second type

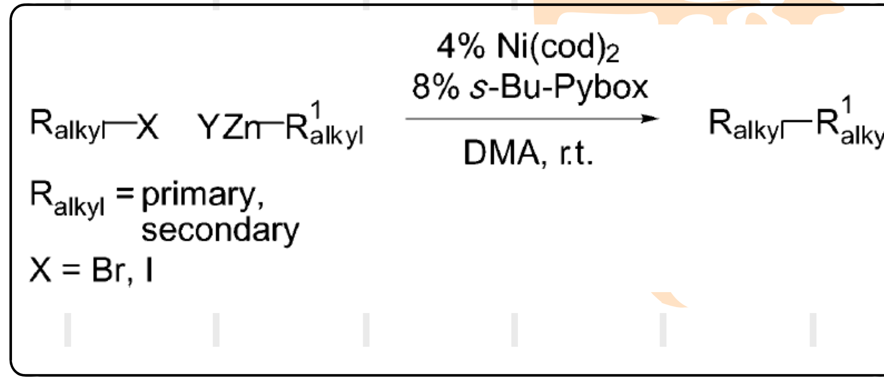
$R^1$–Al, Zr  $R_2$–X $\xrightarrow[ZnX'_2]{cat.}$ $R^1$–$R^2$

$ZnX'_2$ as additive

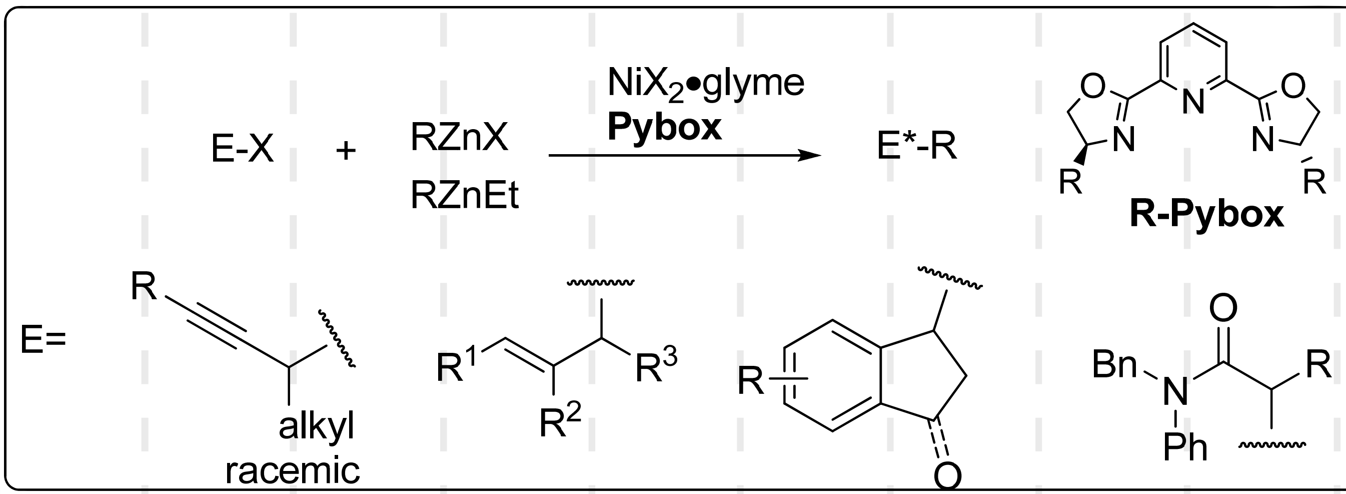




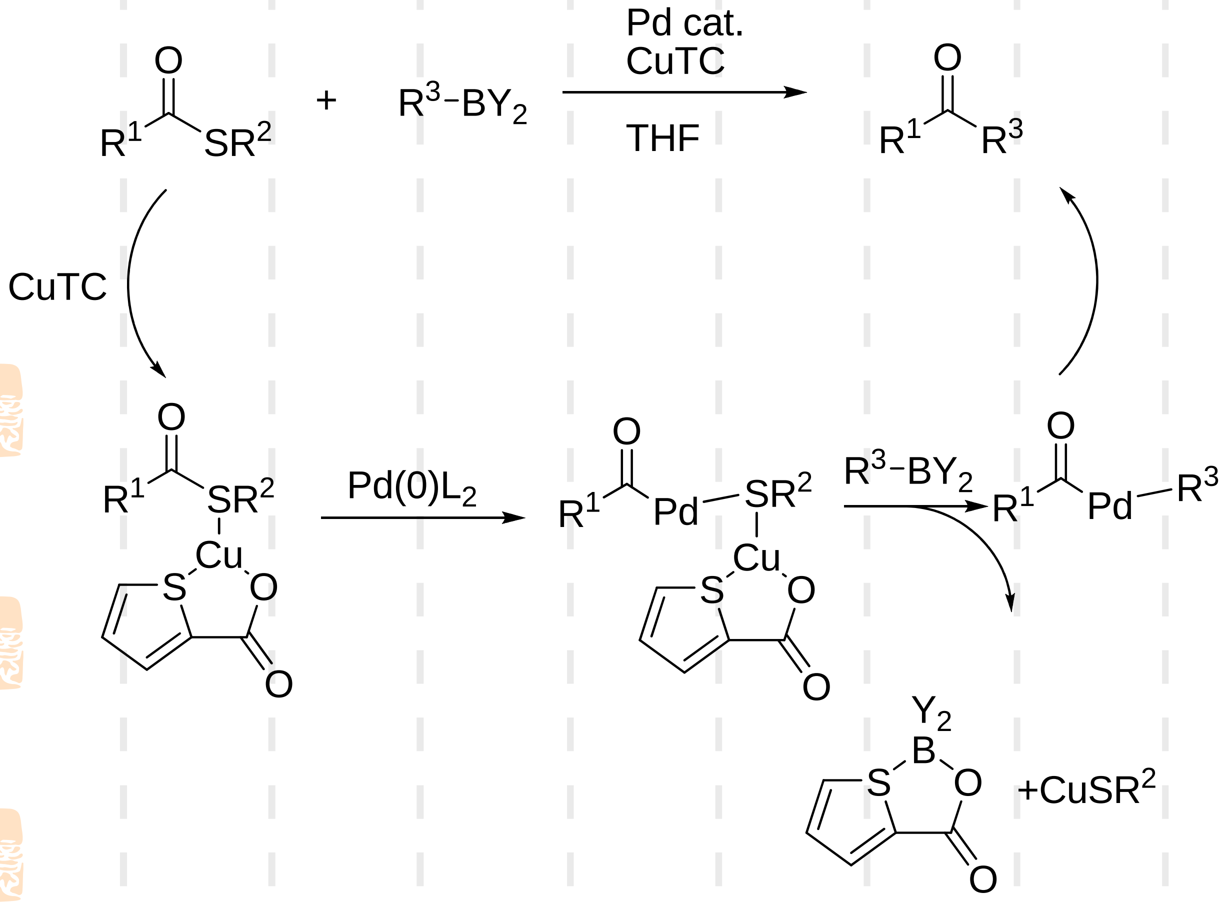

Enantioselective

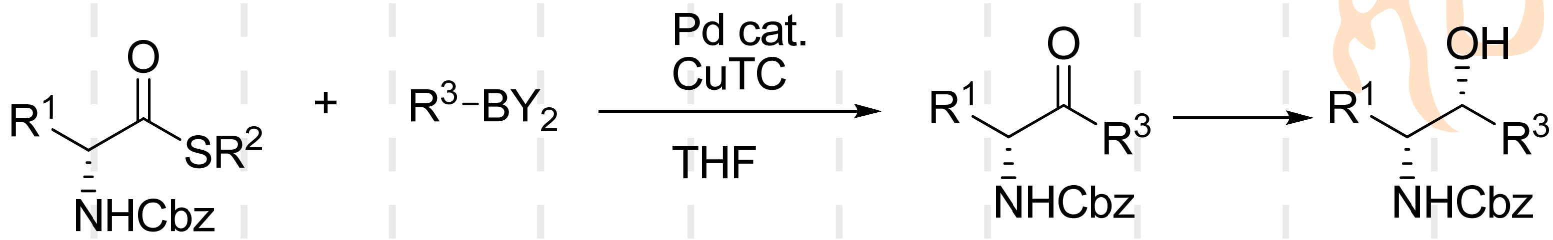




7) Devasagayaraj, A.; Studemann, T.; Knochel, P. *Angew. Chem., Int. Ed.* **1995**, *34*, 2723-2725;
8) Zhou, R.; Fu, G.C. *JACS*. **2003**, *125*, 12527-12530;
9) Zhou, R.; Fu, G.C. *JACS*. **2003**, *125*, 14726-14727;
10) Fischer, C.; Fu, G. C. *JACS*. **2005**, *127*, 4594-4595;
11) Arp, F. O.; Fu, G. C. *JACS*. **2005**, *127*, 10482-10483;
12) Son, S.; Fu, G. C. *JACS*, **2008**, *130*, 2756-2757

# Ⅲ Concise Introduction of Liebeskind Coupling







M = Sn, In

In: no need of CuTC

13） Liebeskind, L. S.; Strogl, J. *JACS*. **2000**, *122*, 11260;

14) Fasett, B. W.; Liebeskind, L.S. *JOC*. **2005**, *70*, 4851.

# Ⅳ The Development of Buchwald-Hartwig Coupling

- Definition
- Development of First Generation Ligand
- Mechanism Study Spring Out the Second Generation Ligands and Third Generation Ligands
- Fourth Generation Ligands

# Definition

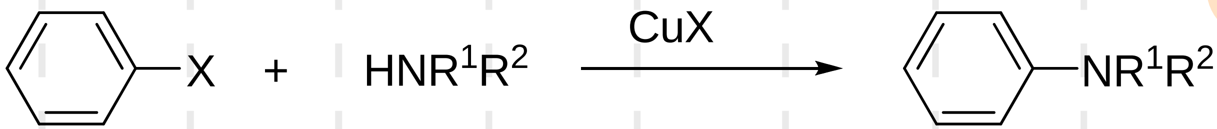
$$Ar{-}X \quad + \quad HNu \xrightarrow[\text{Base}]{ML_n} Ar{-}Nu$$

X = I, OTf, Br, Cl    Nu = $NR^1R^2$, OR, $CR^1R^2$EWG

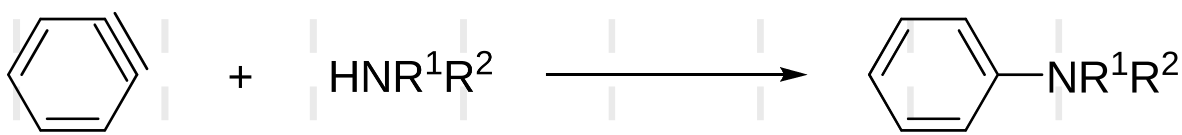
M = Pd, Cu, Ni

# Previous Aryl Aminations

Ullman
1901



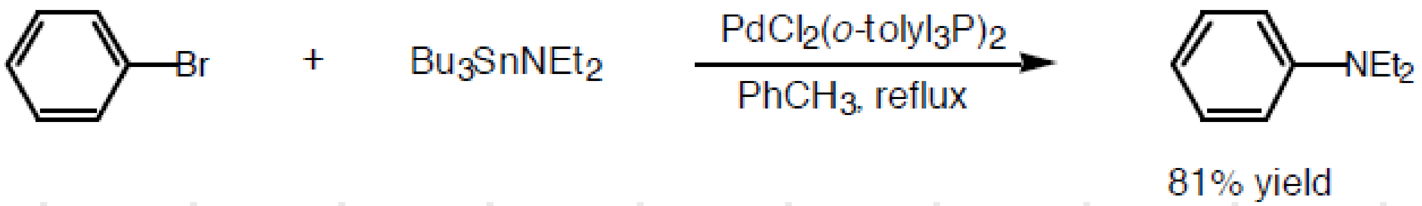

- Scope has been expanded to include a tremendous variety of nucleophiles.
- Limited by harsh reaction conditions, stoichiometric metal.
- Multiple mechanisms thought to be operating, catalytic species poorly defined.




- Functional group compatibility low.
- Regiocontrol is a problem.

Biehl, E. *JOC.*, **1987**, *52*, 2619

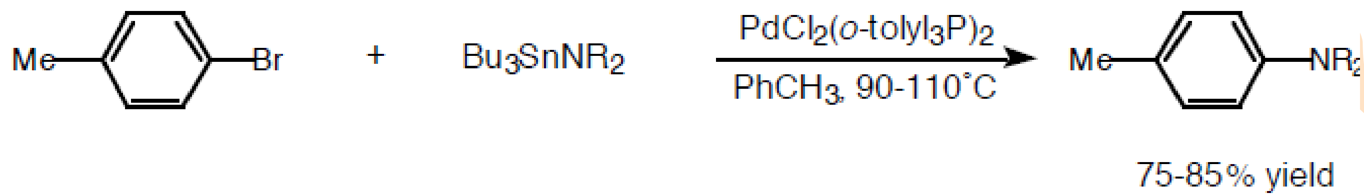
# Migita makes the major breakthrough

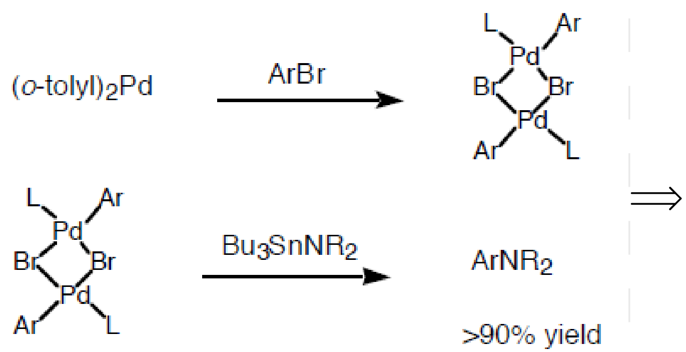


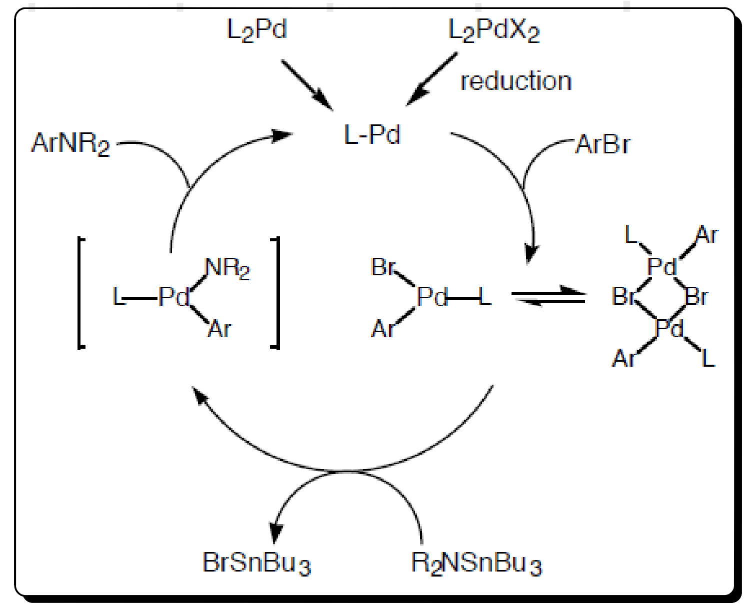

- First example of a palladium-catalyzed aryl-amine coupling.
- Aryl bromides are only viable aromatic substrates.
- Reaction scope is very limited, but reactions are clean and mild.
- Tin amides are toxic, sensitive compounds.


Kosugi, M.; Kameyama, M.; Migita, T. *Chem. Lett*., **1983**, 927
Kosugi, M.; Kameyama, M.; Sano, H.; Migita, T. *Nippon Kagaku Kaishi* , **1985**, *3*, 547

# Hartwig: Closer Looking Researcher



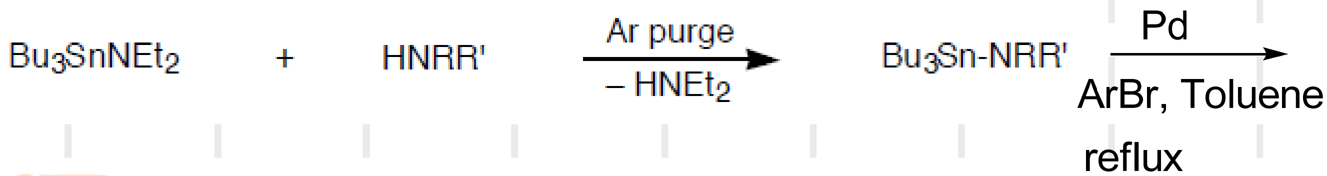

- Palladium dimer implicated in catalytic cycle
- Dimer does not exchange Ar in crossover experiments
- In presence of tin amines, dimer is suspected to irreversibly dissociate to monomeric form

- Phosphine inhibition implies monophosphine Pd is active species
- As in Stille couplings, tin transmetalation appears to be the rate-limiting step

Paul, F.; Patt, J.; Hartwig, J. *JACS* , **1994**, *116*, 5969

# Buchwald: beginning an indepent, overlapping research

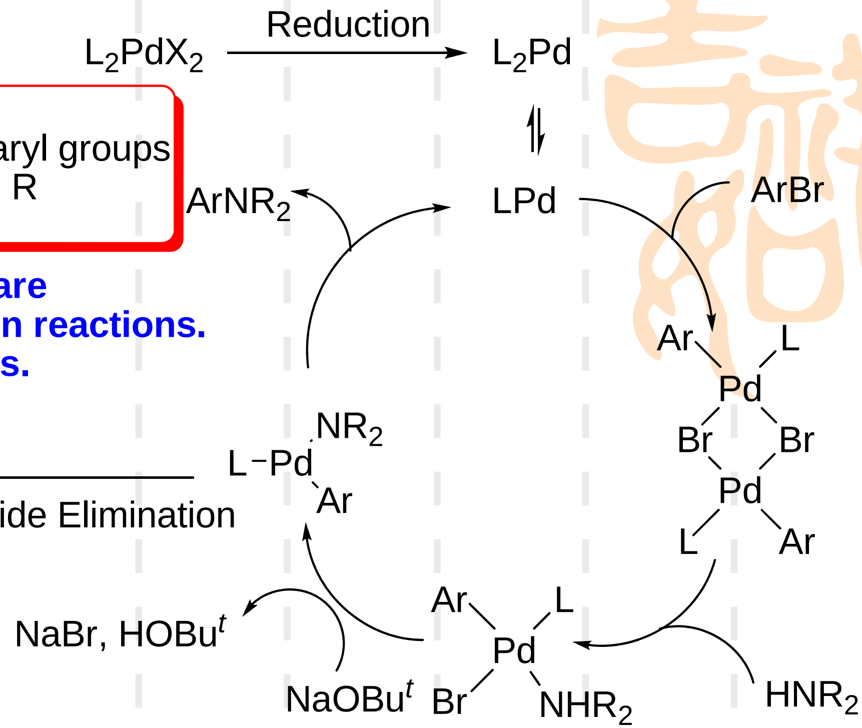
Buchwald expands the scope of the reaction by generating tin amines *in situ*



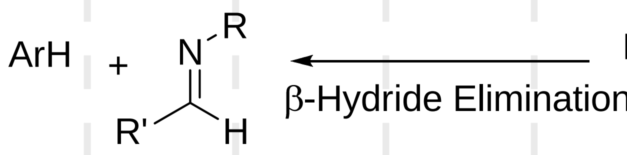

- Reaction still restricted to aryl bromides.
- Only secondary amines and primary anilines can be used.
- o-Substituted aryls not reported.
- Catalyst loadings of less than 2% are typical, most reactions run 24 h.

Guram, A.; Buchwald, S. J. Am. Chem. Soc. , 1994, 116, 7901

# Tin-free aryl-amine couplings




Accelerated by:
1. Electron withdrawing aryl groups
2. Larger, more donating R
3. **Larger L**




- **Most qualitative steric and electronic effects are consistent with analogous C-C bond formation reactions.**
- **More nucleophlic amines are better substrates.**

**Mechanism:**

- A new catalytic cycle is proposed in which the base deprotonates Pd-amine complexes
- Pd(0) shown to be resting state of catalyst, so oxidative addition is now the rate-limiting step
- Inverse first-order dependence on phosphines from the monomer suggests dissociative, three-coordinate complex is dominant in the catalytic cycle
- First-order dependence on synthetic monomer or dimer
- Rate of reaction for dimer is phosphine-independent.
- Mixture of dimers do not cross over, implying irreversible cleavage to three-coordinate palladium monomer

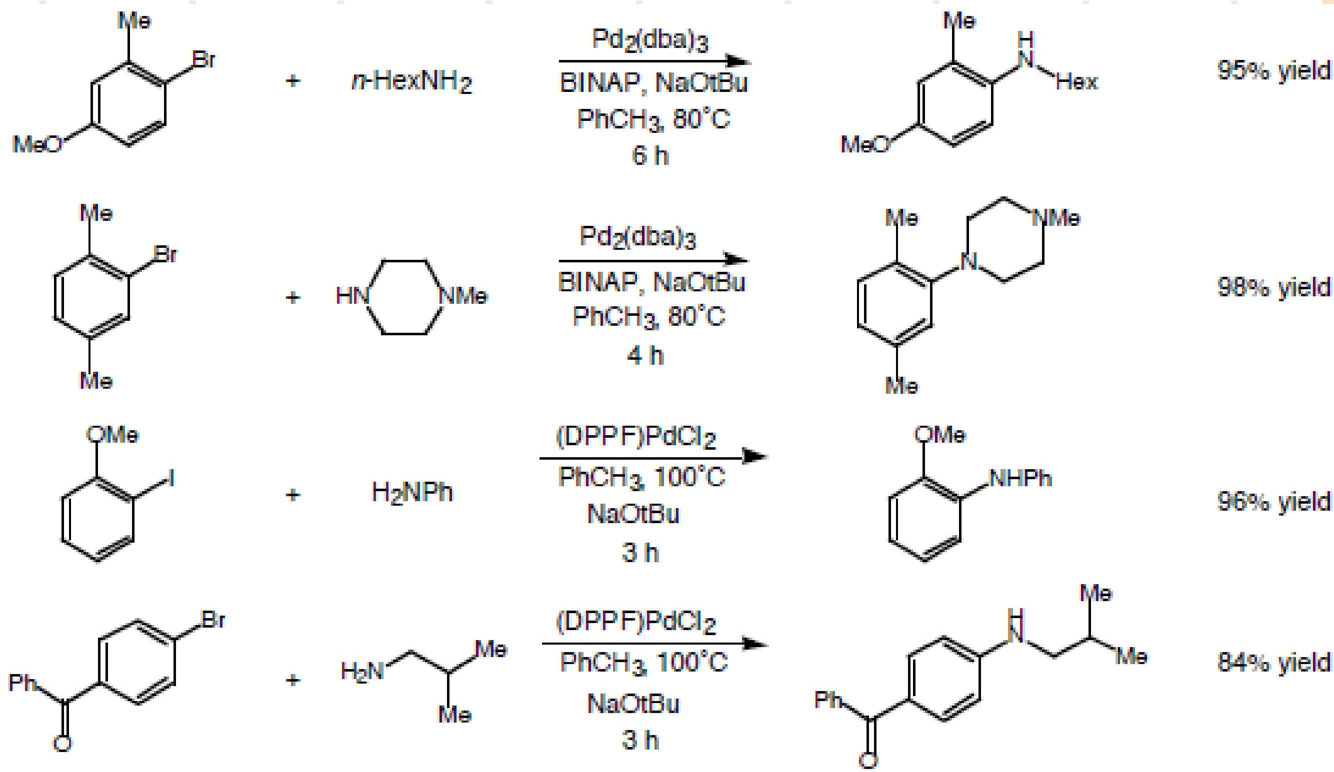
**Substrate Scope:**

- Primary amines can be coupled with electron-withdrawing aryl halides
- Cyclic secondary amines and alkyl anilines are good substrates
- Most acyclic secondary alkyl amines are problematic with electron-rich or neutral aryl halides


Guram, A.; Rennels, R.; Buchwald, S. *ACIEE*, **1995**, *34*, 1348
Louie, J.; Hartwig, J. *Tet. Lett.*, **1995**, 3609
Driver, M.; Hartwig, J. *JACS.* , **1995**, *117*, 4708
Paul, F.; Baranano, D.; Richards, S.; Hartwig, J. *JACS* , **1996**, *118*, 3626

# Bidentate Ligands: A Dramatic Advance

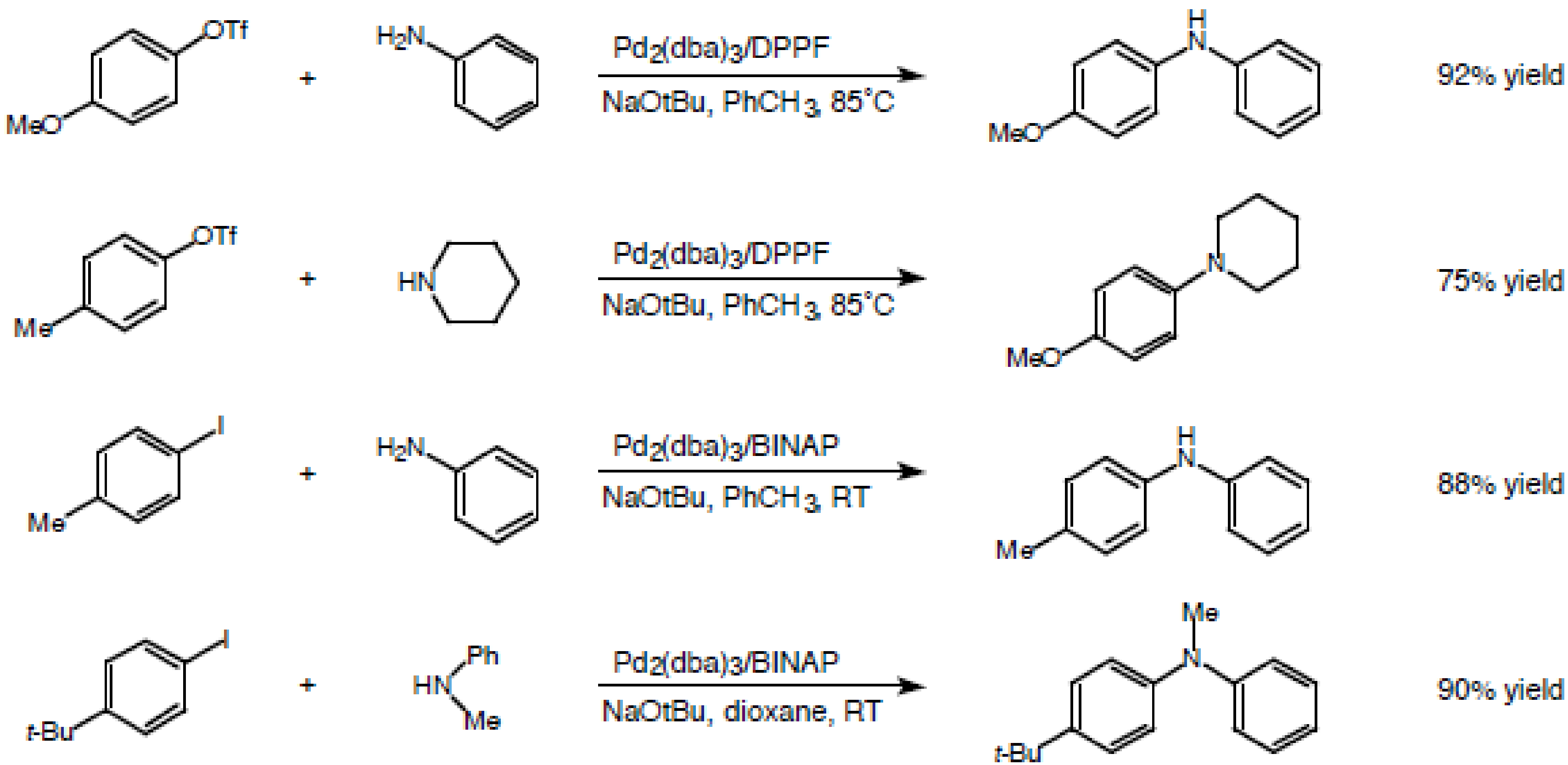
Catalyst loadings are typically 0.5-1.0 mol%, and reactions are typically faster




## Mechanistic Revision

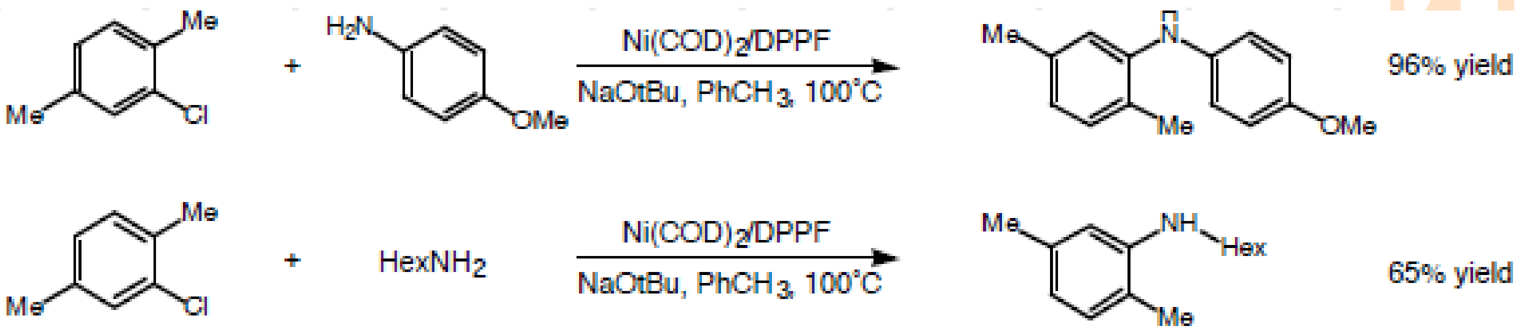
- Reductive elimination from four-coordinate complex now proposed
- Intermediate demonstrated by 31P NMR, and synthesis of isolable 4-coordinate arylamino palladium species
- **Enforced cis geometry of coupling partners thought to suppress "β-hydrogen elimination:** Hartwig argues "β-hydrogen elimination possible only with empty coordination site on 14-electron complex cis to alkyl amine
- **Followup mechanistic studies show rates of monodentate phosphine reactions are a competition between three- and four-coordinate complexes**

Wolfe, J.; Wagaw, S.; Buchwald, S. *J. Am. Chem. Soc.*, **1996**, *118*, 7215
Driver, M. ; Hartwig, J. *J. Am. Chem. Soc.*, **1996**, *118*, 7217
Driver, M. ; Hartwig, J. *J. Am. Chem. Soc.*, **1997**, *119*, 8232

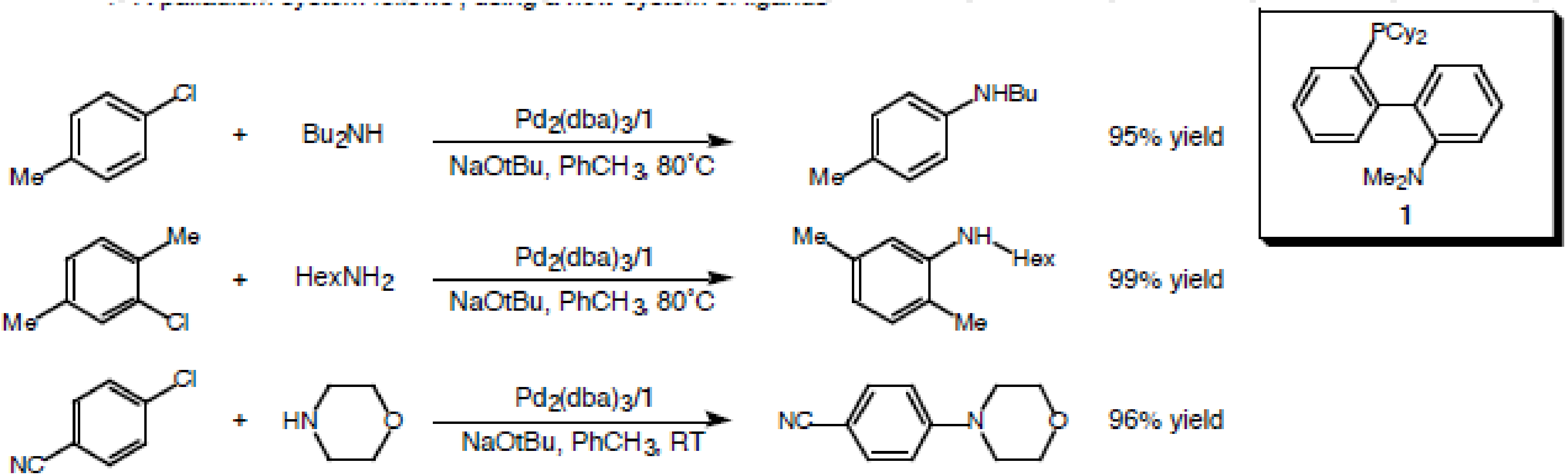



Louie, J.; Driver, M.; Hamann, B.; Hartwig, J. *JOC*., **1997**, *62*, 1268
Wolfe, J.; Buchwald, S. *JOC* **1996**, *61*, 1133

# Aryl Chlorides: The Search For a Practical System

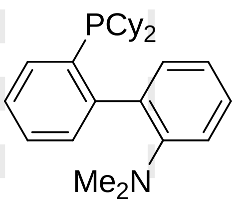


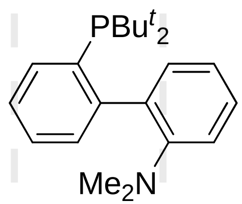

Wolfe, J.; Buchwald, S. *J. Am. Chem. Soc.*, **1997**, *119*, 6054

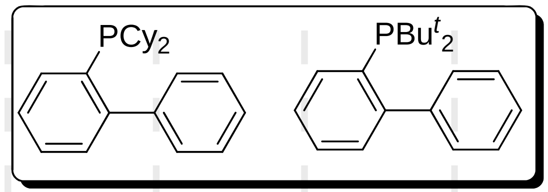



Old, D. W.; Wolfe, J.; Buchwald, S. *J. Am. Chem. Soc.*, **1998**, *120*, 9722

# Back to the Monodentate Ligands: Third-Generation

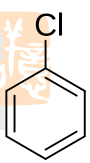


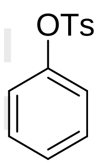



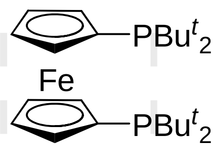




Buchwald

Wolfe, J.; Buchwald, S. *ACIEE*, **1999**, *38*, 2413

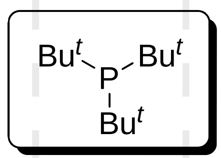


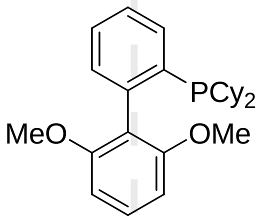




Hartwig

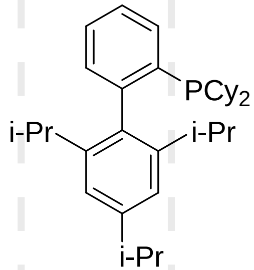
Hamann, B.; Hartwig, J. *J. Am. Chem. Soc.*, **1998**, *120*, 7369
Kawatsura, M.; Hartwig, J. *J. Am. Chem. Soc.*, **1999**, *121*, 1473



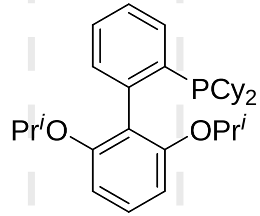

Hartwig



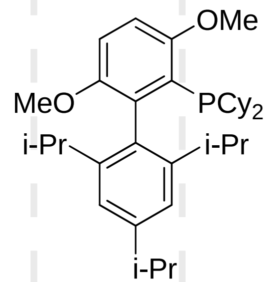
SPhos

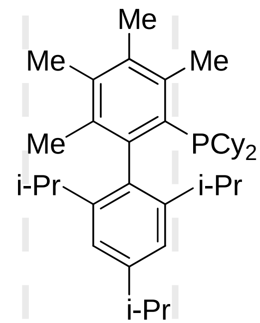


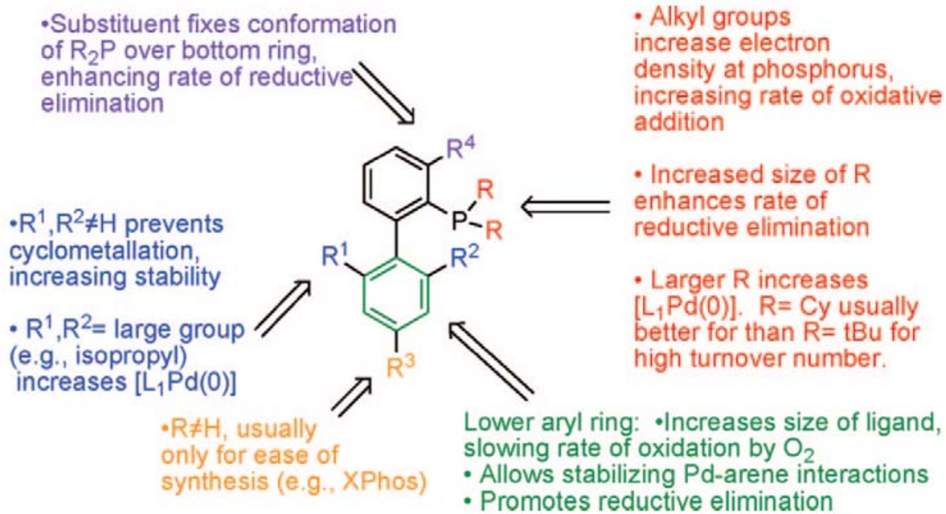
XPhos



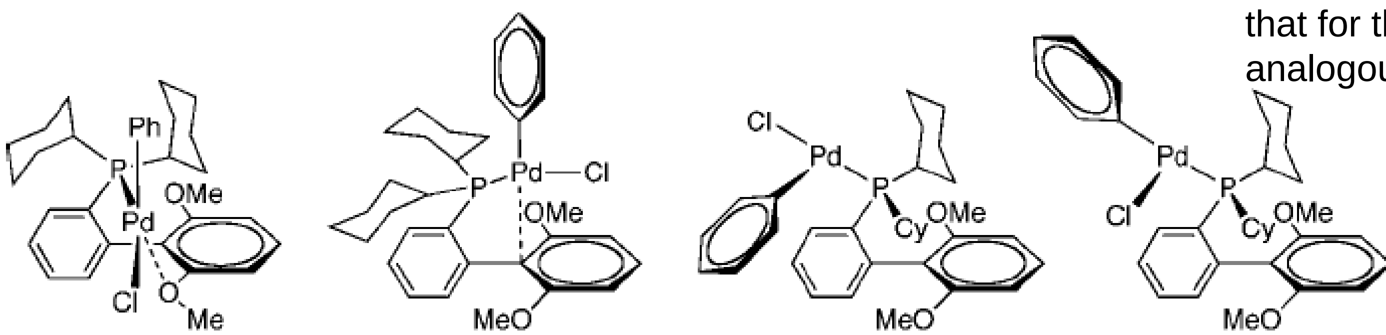
RuPhos





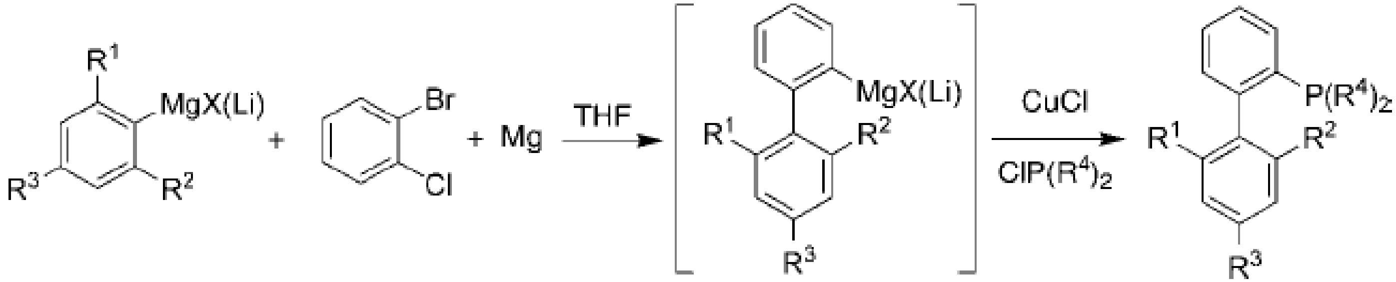


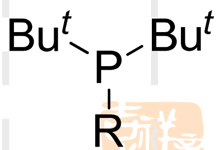

Smaller size of a $L_1Pd(0)$ complex compared with a $L_2Pd(0)$ one, allowing the substrate to approach the latter more closely and, hence, react at a faster rate. We presume that transmetalation to a $L_1Pd(Ar)X$ intermediate is faster, in general, than to a $L_2Pd(Ar)X$ complex for related reasons. (c) It is well-documented that the rate of reductive elimination from LPd(Ar)R (R ) aryl, $NR_2$, OR) is faster than that for the same process for an analogous $L_2Pd(Ar)R$ complex



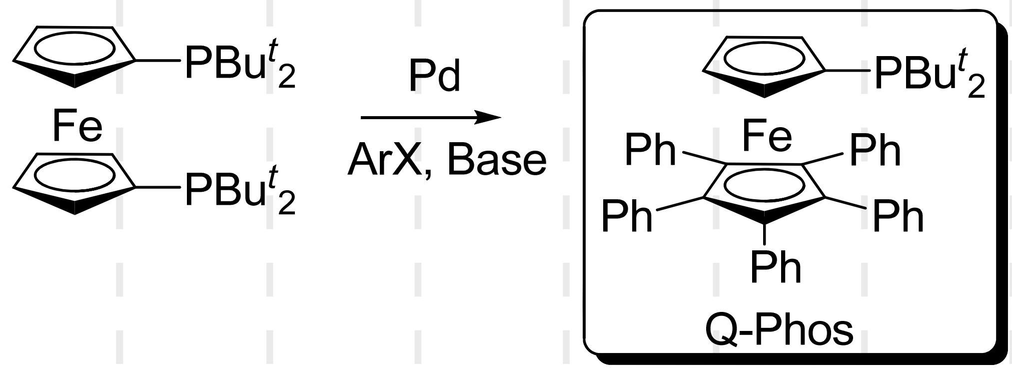
I | II | III | IV

$E_{rel}$ = 0.8 Kcal/mol | $E_{rel}$ = 7.1 Kcal/mol | $E_{rel}$ = 18.0 Kcal/mol

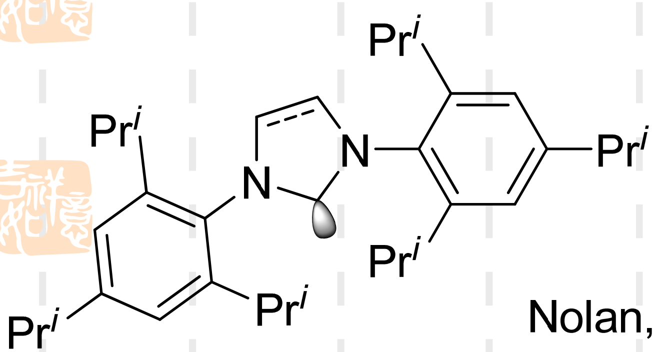


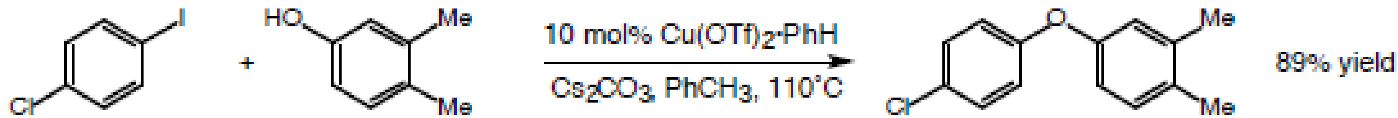

$R = Bu^t$, 1-Ad




Hartwig

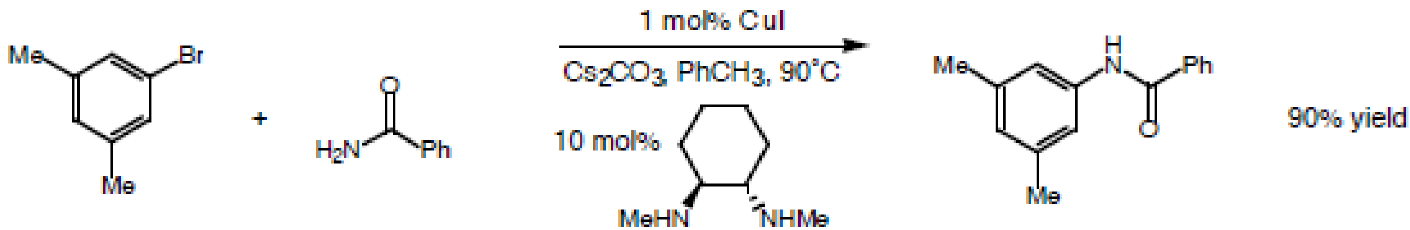



Nolan, S.P.

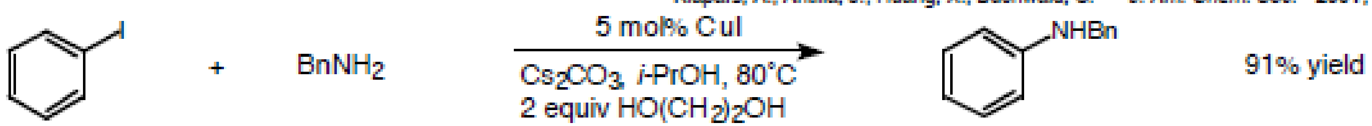



Marcoux, J.-F.; Doye, S.; Buchwald, S. *J. Am. Chem. Soc.* **1997**, *119*, 10539

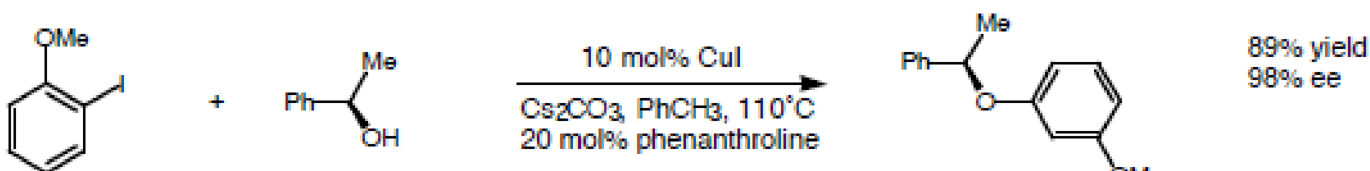
- Addition of ligands expands the scope of the reaction dramatically




Klapars, A.; Antilla, J.; Huang, X.; Buchwald, S. *J. Am. Chem. Soc.* **2001**, *123*, 7727




Kwong, F.; Klapars, A.; Buchwald, S. *Org. Lett.* **2002**, *4*, 581




- Mechanistic work is in progress

Wolter, M.; Nordmann, G.; Job, G.; Buchwald, S. *Org. Lett.* **2002**, *4*, 973

# First Generation

monodentate Ph

- Less selectivity.
- Typically require high loadings of palladium.

# Second Generation

co-hindered
**bi**dentate Ph

- They are reactive toward couplings of primary amines, often generate monoarylation in good selectivity.
- Typically require high loadings of palladium.

# Third Generation

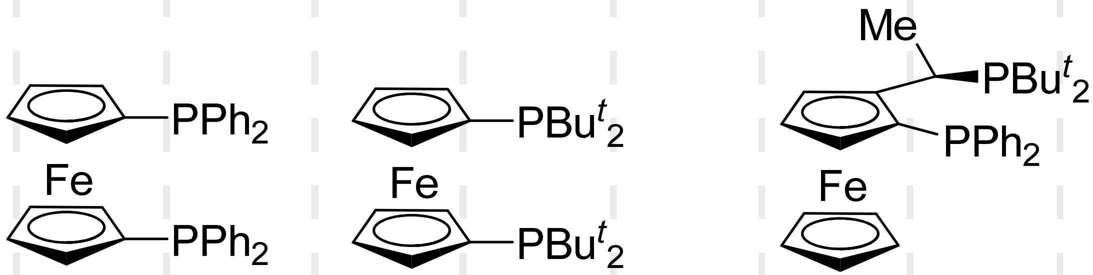
electron donation and bulky
monodentate Cy, $Bu^t$

- They are less reactive toward couplings of primary amines, often generate mixtures of monoarylation and diarylation products
- Typically require high loadings of palladium for the coupling of heteroaromatic halides.
- Typically low loadings of palladium for most of the substrates.

# Fourth Generation

**bi**dentate and co-hindered
electron donation and bulky

- They are reactive toward couplings of primary amines, often generate monoarylation in good selectivity.
- More typically low loadings of palladium: for the coupling of heteroaromatic halides and for thioetherification



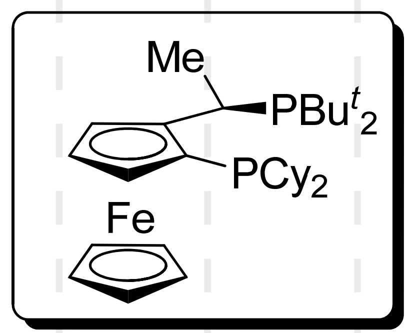

DPPF

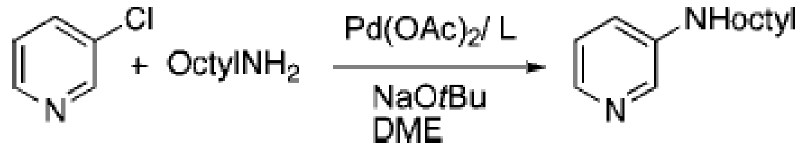
second generation

**Hartwig**

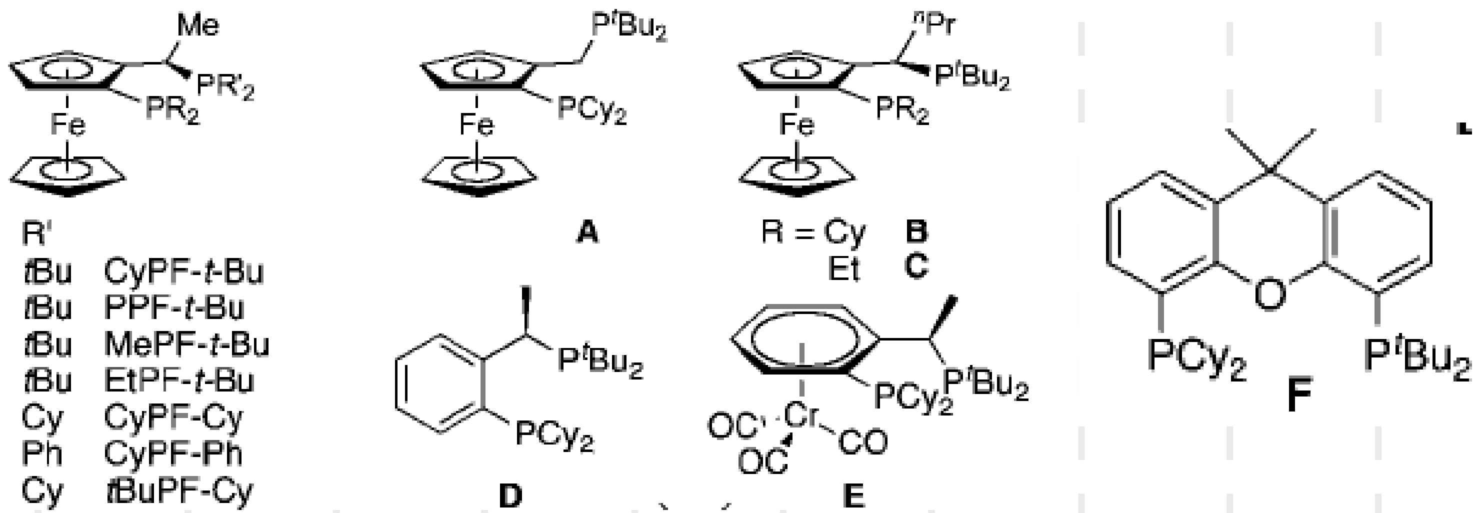
third generation

More electron donating and bulky






| entry | ligand | loading | $T$ (°C) | $t$ (h) | yield (%) |
| --- | --- | --- | --- | --- | --- |
| 1 | CyPF-*t*-Bu | 0.005 | 90 | 24 | 93 |
| 2 | PPF-*t*-Bu | 1.0 | 90 | 24 | 67 |
| 3 | MePF-*t*-Bu | 0.005 | 90 | 24 | <5 |
| 4 | EtPF-*t*-Bu | 0.005 | 90 | 24 | <5 |
| 5 | CyPF-Cy | 1.0 | 90 | 24 | 46 |
| 6 | CyPF-Ph | 1.0 | 90 | 24 | 48 |
| 7 | *t*BuPF-Cy | 0.005 | 90 | 24 | 62 |
| 8 | **A** | 0.005 | 90 | 24 | 50 |
| 9 | **B** | 0.001 | 100 | 48 | 16 |
| 10 | **B** | 0.005 | 90 | 24 | 93 |
| 11 | **C** | 0.005 | 90 | 24 | <5 |
| 12 | **D** | 0.005 | 90 | 24 | <5 |
| 13 | **E** | 0.005 | 90 | 24 | <5 |
| 14 | **F** | 0.005 | 90 | 24 | <5 |




| R | R' | |
| --- | --- | --- |
| Cy | *t*Bu | CyPF-*t*-Bu |
| Ph | *t*Bu | PPF-*t*-Bu |
| Me | *t*Bu | MePF-*t*-Bu |
| Et | *t*Bu | EtPF-*t*-Bu |
| Cy | Cy | CyPF-Cy |
| Cy | Ph | CyPF-Ph |
| *t*Bu | Cy | *t*BuPF-Cy |

# Scope and loading

$$\text{Ar-X} + \text{NH}_2\text{R} \xrightarrow[\text{NaOBu}^t]{\text{10ppm-1 mol\% Pd/ Josiphos}} \text{Ar—NHR}$$

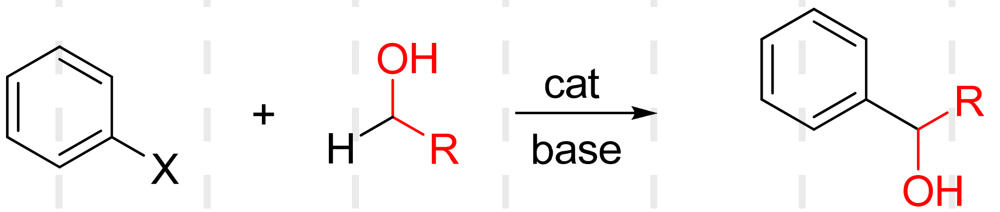
X = Cl, Br, I

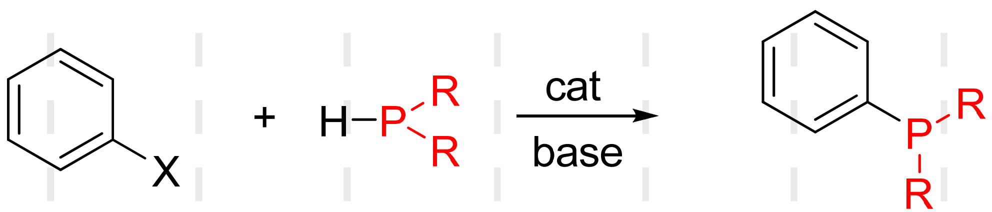
$$\text{Ar-X} + \text{NH}_3\text{(200psi)} \xrightarrow[\text{NaOBu}^t]{\text{1 mol\% Pd/ Josiphos}} \text{Ar—NH}_2$$

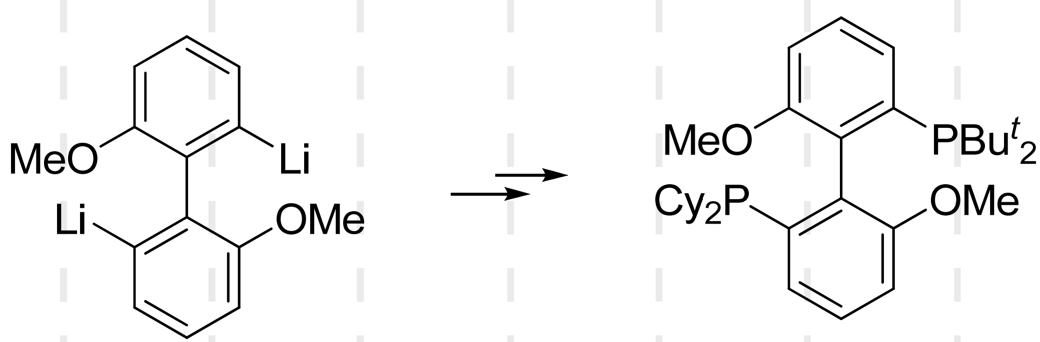
X = Cl, Br, I

$$\text{Ar-Cl} + \text{HSR} \xrightarrow[\text{NaOBu}^t]{\text{0.01-3 mol\% Pd/ Josiphos}} \text{Ar—SR}$$

# My Idea


X
+
OH
H
R
cat
base
R
OH


X
+
H–P
R
R
cat
base
R
P
R


MeO
Li
Li
OMe
MeO
PBu$^{t}_{2}$
$Cy_2P$
OMe

Steric Bulky

Electron Donating

Bidentate: Prevent Displacement

Pd Cat. C-N Formation Like C-C Formation

- Thank you!