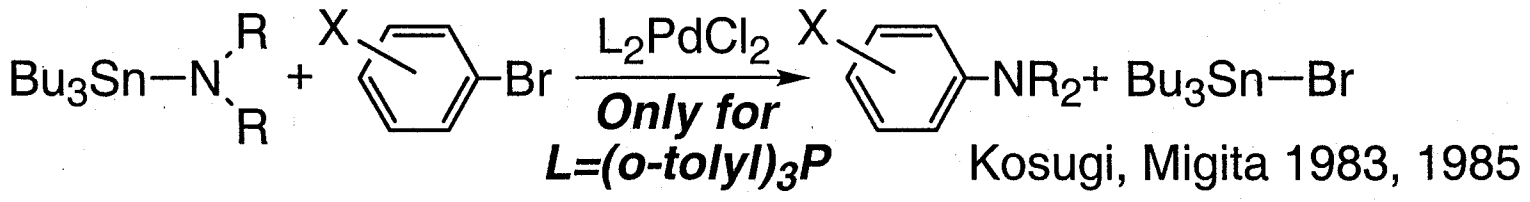
Palladium-Catalyzed Aromatic Amination



Kosugi, Migita 1983, 1985

Synthesis:

Problems:

- Tin reagents: air sensitive and toxic
- Scope was narrow
- Too much catalyst

Potential:

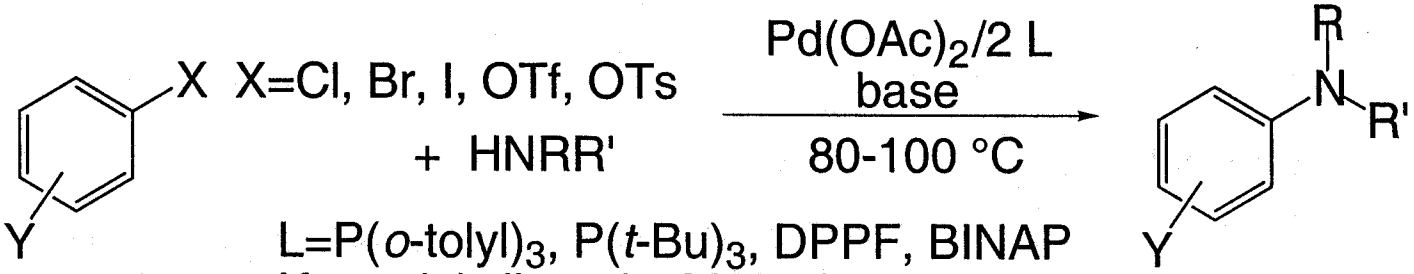
- Pharmaceuticals
- Redox Active Macromolecules
- New Ligands for Metals

Mechanism:

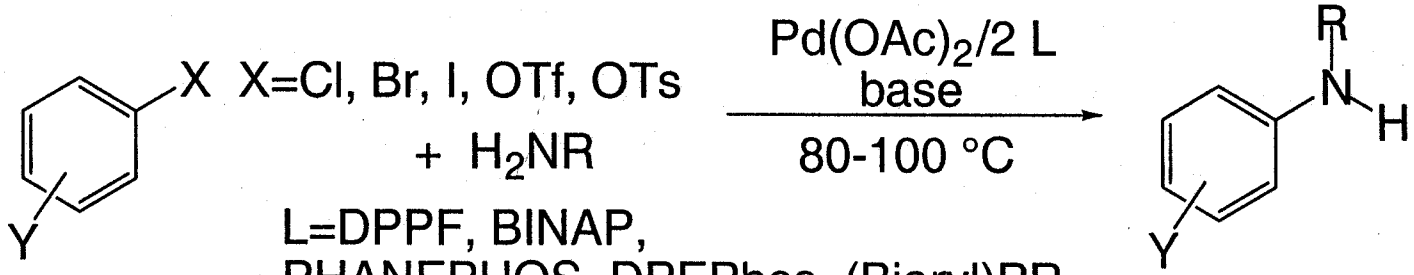
- New chemistry of palladium amides?
- C-X bond formation by organometallic compounds?

Current Arylation Processes

Review: Hartwig, J.F. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2046-2067



L=P(*o*-tolyl)$_3$, P(*t*-Bu)$_3$, DPPF, BINAP
Kumada's ligands, MAP, (Biaryl)PR$_2$,
heterocyclic carbene



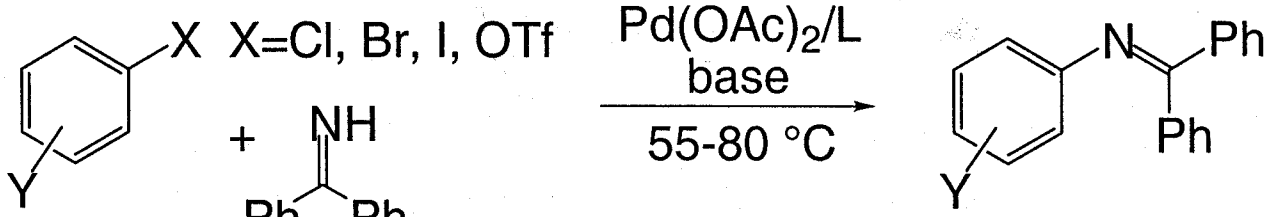
L=DPPF, BINAP,
PHANEPHOS, DPEPhos, (Biaryl)PR$_2$
heterocyclic carbene

base = NaO-*t*-Bu, Cs_2CO_3

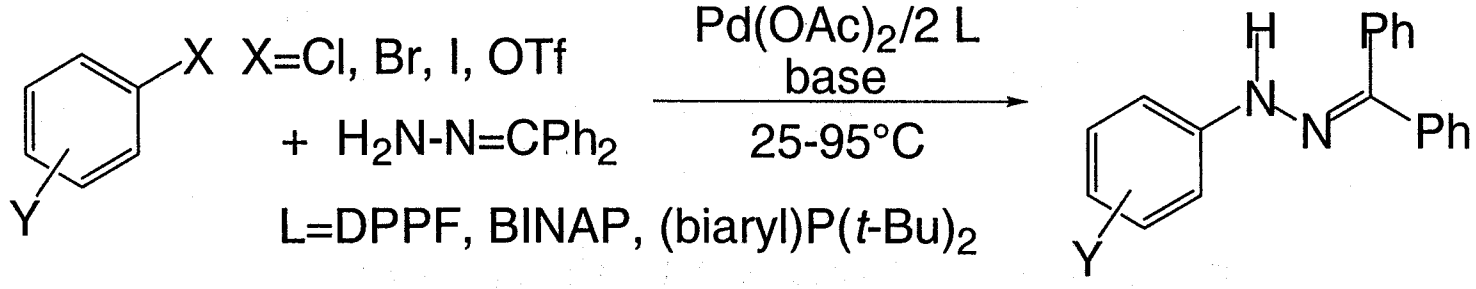
DPPF=1,1'-*bis*-(diphenylphosphino)ferrocene

BINAP=2,2'-*bis*-(diphenylphosphino)-1,1'-binaphthyl

Current Arylation Processes

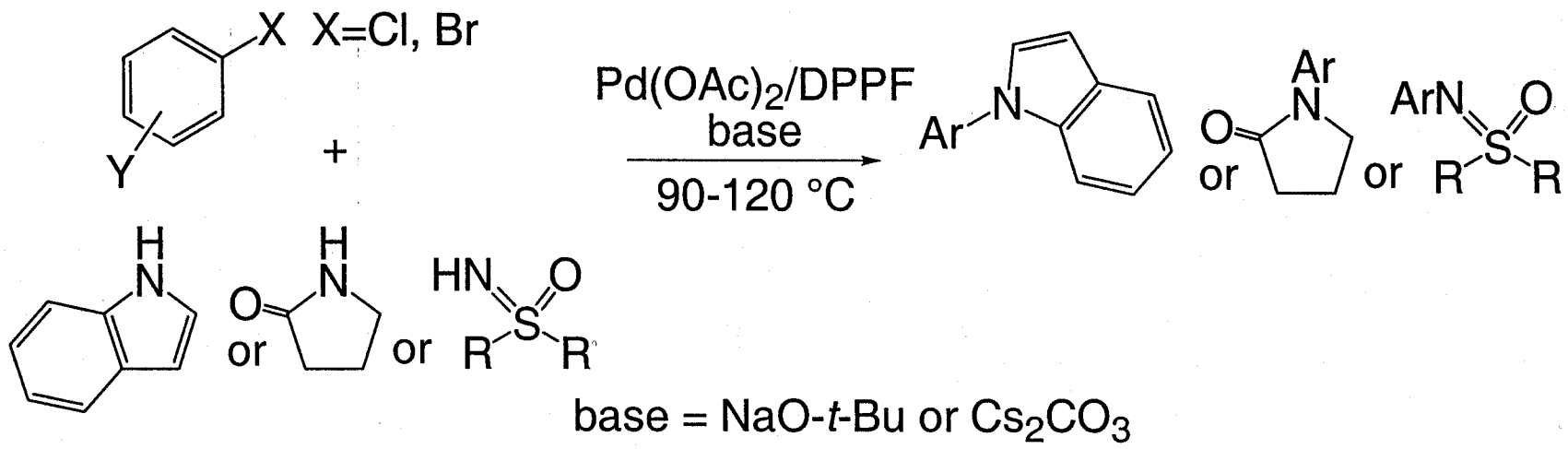


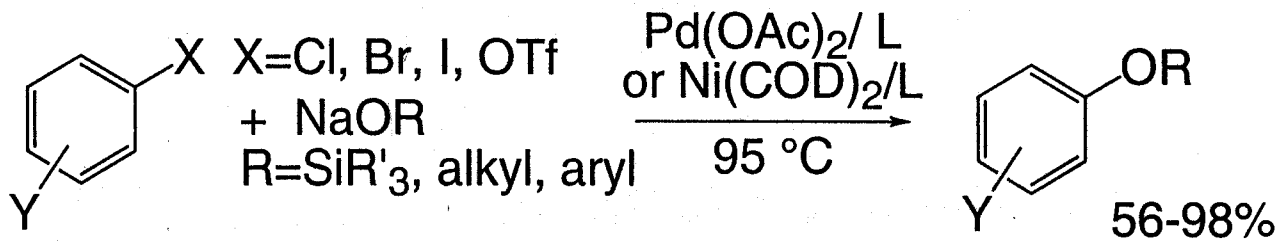
base = NaO-*t*-Bu or Cs_2CO_3
L=DPPF or BINAP, heterocyclic carbene



L=DPPF, BINAP, (biaryl)P(*t*-Bu)$_2$

Current Arylation Processes

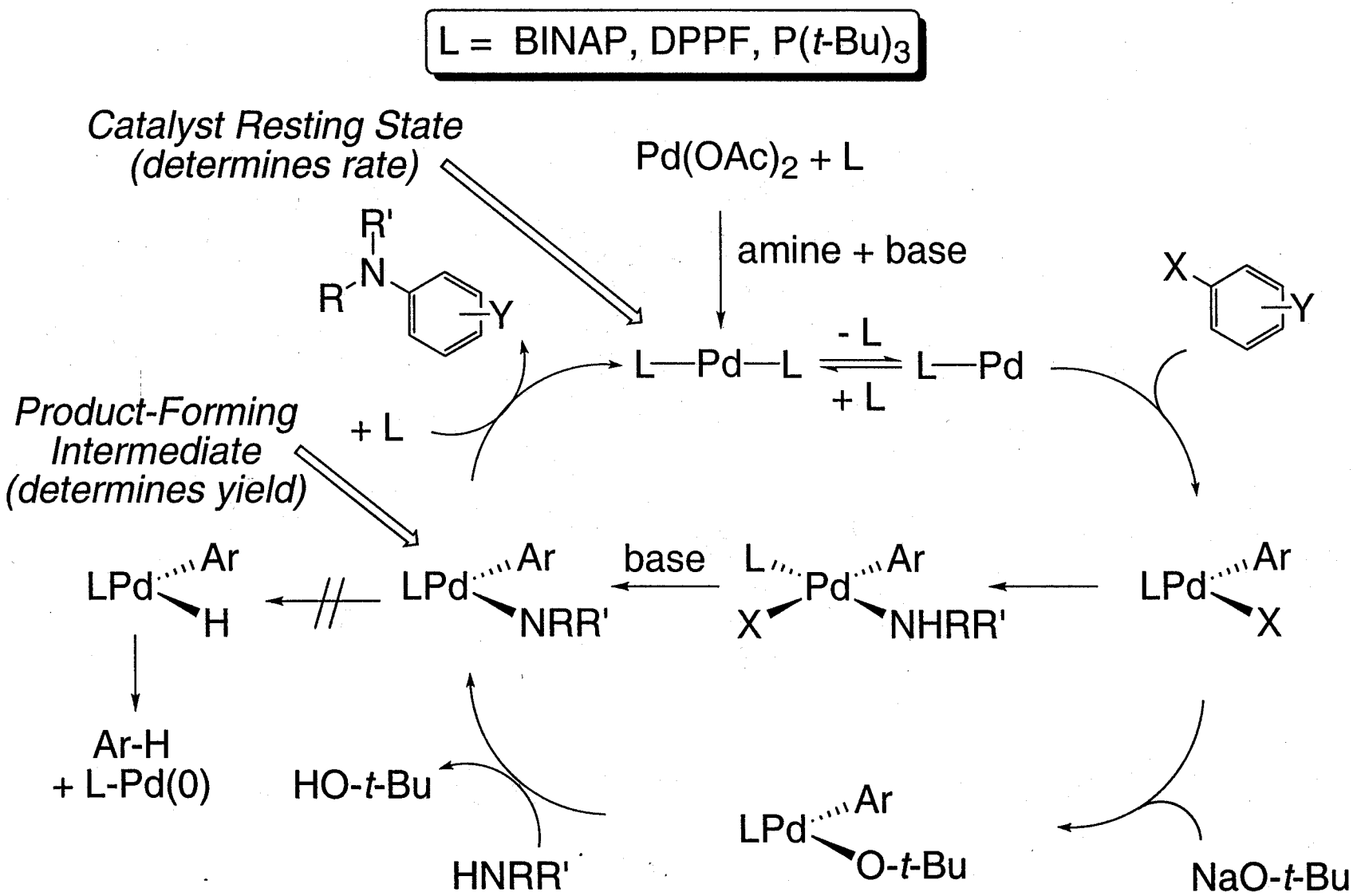




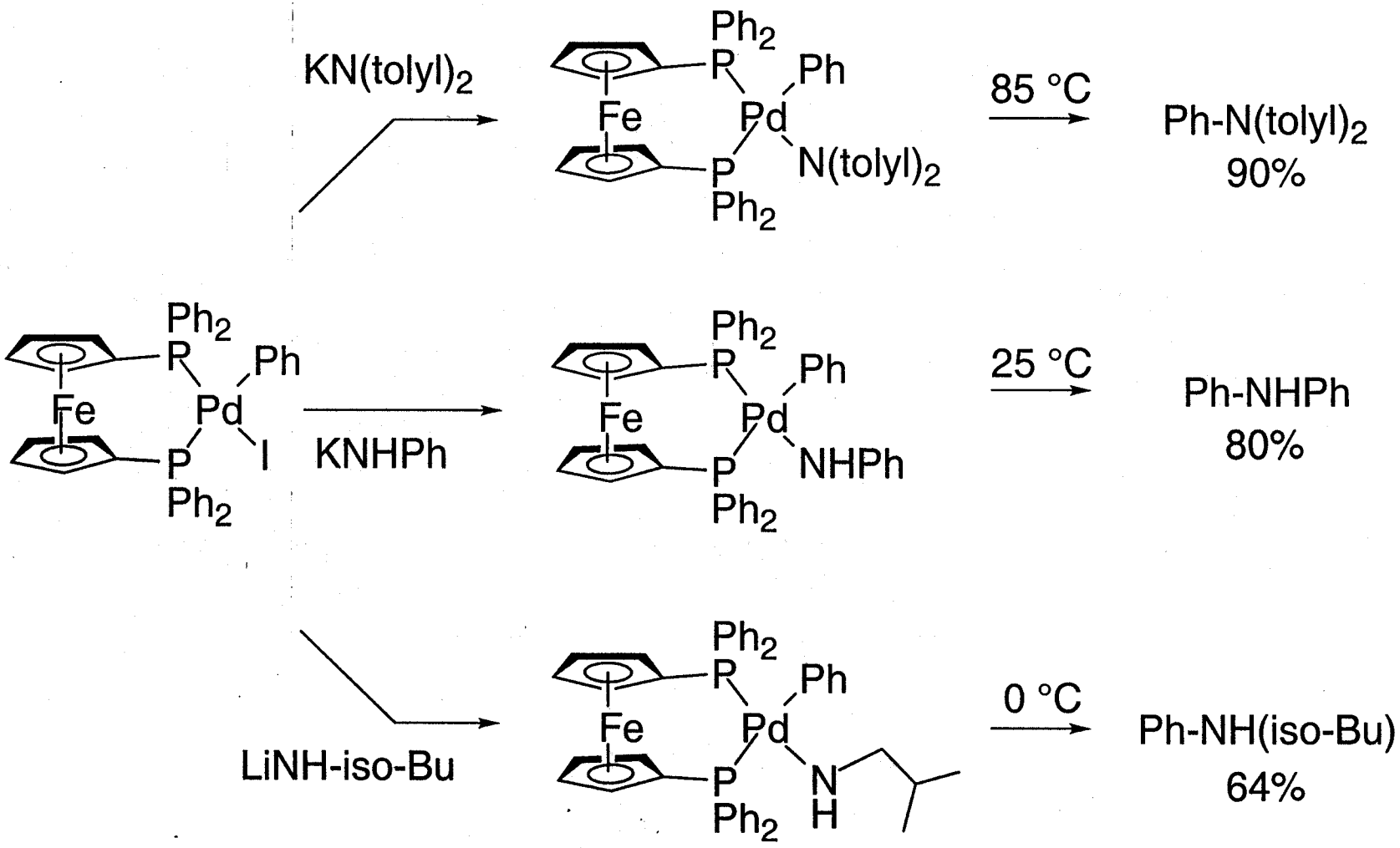
For Y= *p*-EWG L = DPPF or BINAP
For Y≠ *p*-EWG L=FcP(*t*-Bu)$_2$ or (Biaryl)P(*t*-Bu)$_2$

Review: Hartwig, J.F. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2046-2067

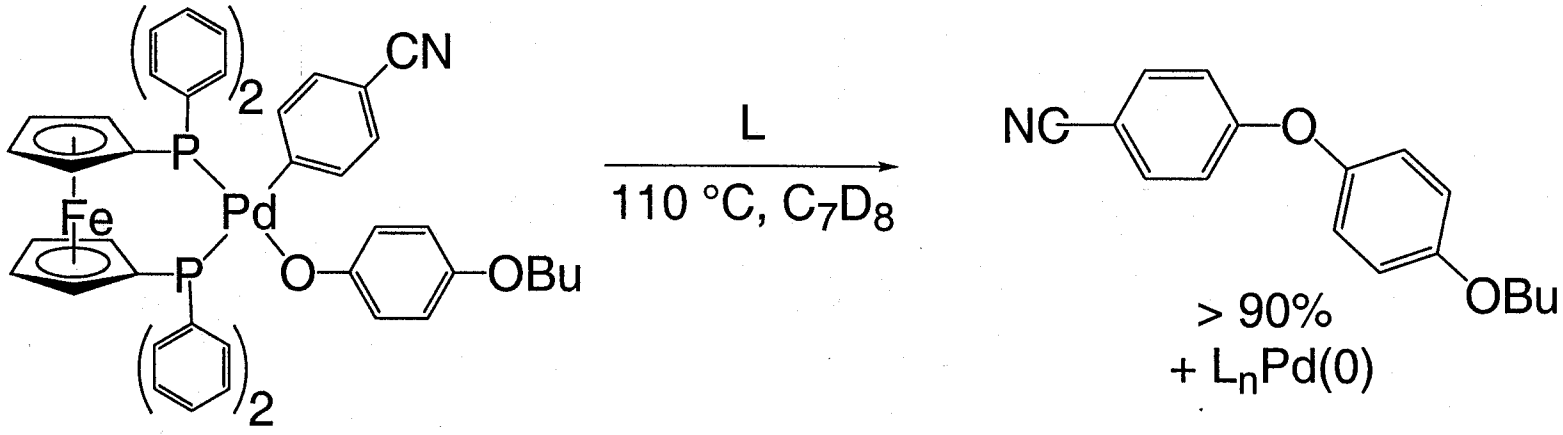
Summary of Amination Mechanism



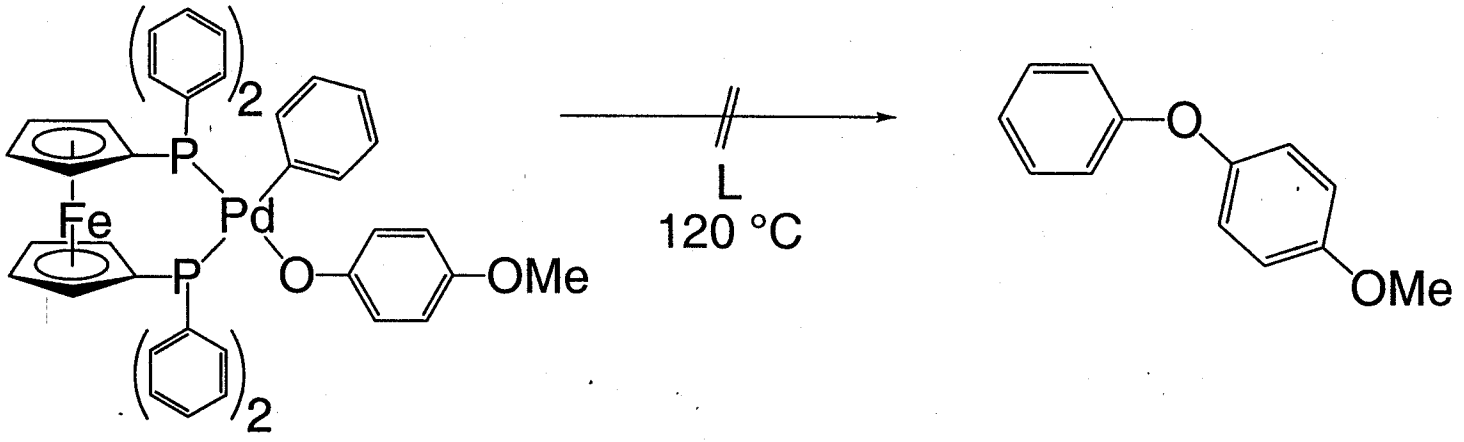
Pd-Amido Complexes with Bis-Phosphines



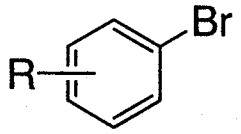
Reductive Elimination of Diaryl Ether...



But No Elimination Without a Withdrawing Group



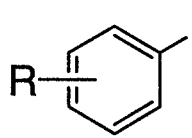
Mild Amination with P(t-Bu)$_3$



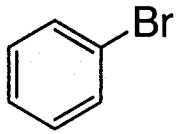
R=donating or withdrawing; o, m or p

\+ $HN(alkyl)_2$ + NaO-*t*-Bu

1% $Pd(dba)_2$ / 1% $P(t\text{-}Bu)_3$ → room temperature, 6h

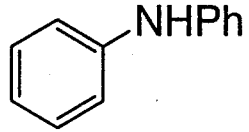


83-95%

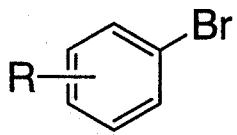


\+ H_2NPh + NaO-*t*-Bu

1% $Pd(dba)_2$ / 1% $P(t\text{-}Bu)_3$ → room temperature, 1 h



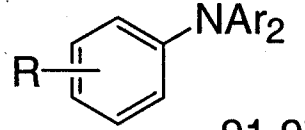
97 %



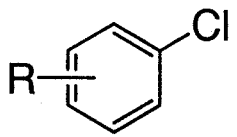
R=donating or withdrawing; o, m or p

\+ $HNAr_2$ + NaO-*t*-Bu

1% $Pd(dba)_2$ / 1% $P(t\text{-}Bu)_3$ → room temperature, 15-60 min



91-97 %

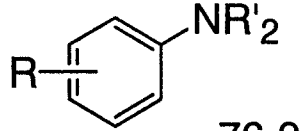


R=donating or withdrawing; o, m or p

\+ HNR'_2 + NaO-*t*-Bu

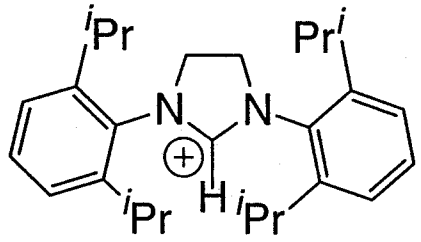
R'=alkyl, aryl

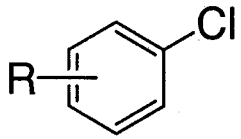
1-5% $Pd(dba)_2$ / 1-5% $P(t\text{-}Bu)_3$ → 25-70 °C, 4-24 h



76-97 %

Mild Amination with Saturated Carbene Ligands

L= 



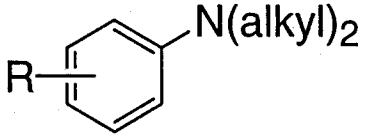
R=2, 4-Me, 4-OMe, 4-CN

\+ $HN(alkyl)_2$ + NaO-*t*-Bu

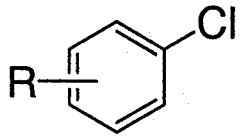
1% $Pd(dba)_2$ / 1% L

room temperature, 3-20h

5000 turnovers at 100 °C



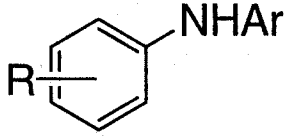
86-100%



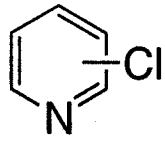
\+ H_2NAr + NaO-*t*-Bu

1% $Pd(dba)_2$ / 1% L

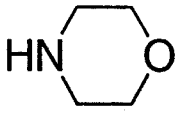
room temperature, 18 h



82 %



R=donating or withdrawing; o, m or p

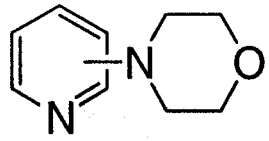
\+ 

\+ NaO-*t*-Bu

R'=alkyl, aryl, H

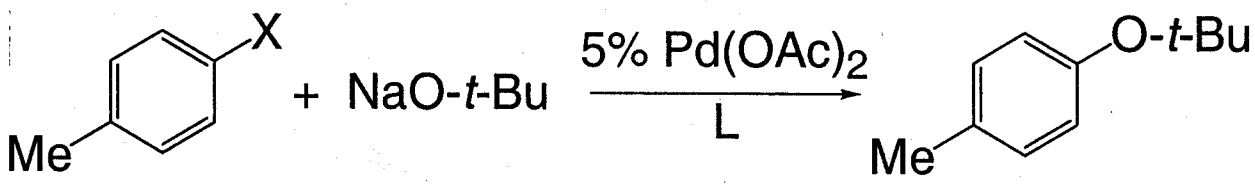
1-2% $Pd(dba)_2$ / 1-2% L

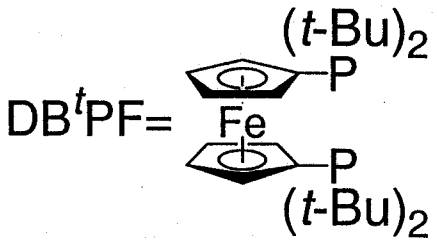
room temperature, 4-24 h



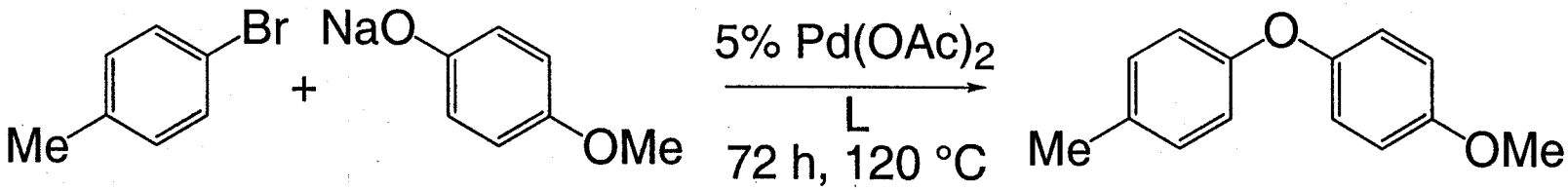
91-97 %

Hindered Alkylphosphines Improve Ether Synthesis



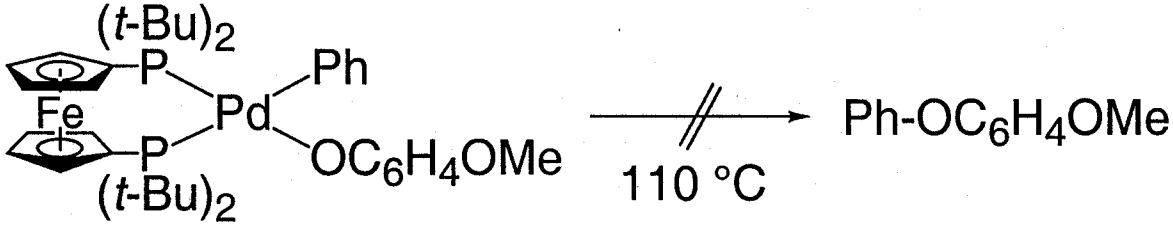


L=BINAP	X=Br	53 %
L=DPPF	X=Br	38 %
L=P(*o*-tolyl)$_3$	X=Br	0 %
L=P(*t*-Bu)$_3$	X=Cl	100 %
L=DB^{t}PF	X=Cl	89 %



L=BINAP	0 %
L=DPPF	0 %
L=P(*o*-tolyl)$_3$	0 %
L=P(*t*-Bu)$_3$	20 %
L=DB^{t}PF	48%

Can DB^{t}PF induce Ether Formation without EWG?



A Closer Look: