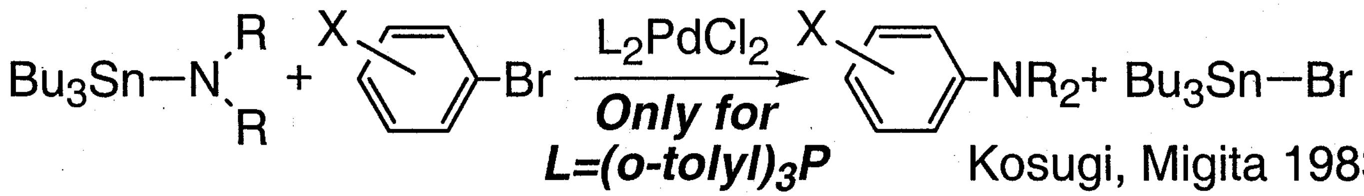
Palladium-Catalyzed Aromatic Amination



Kosugi, Migita 1983, 1985

Synthesis:

Problems:

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

Potential:

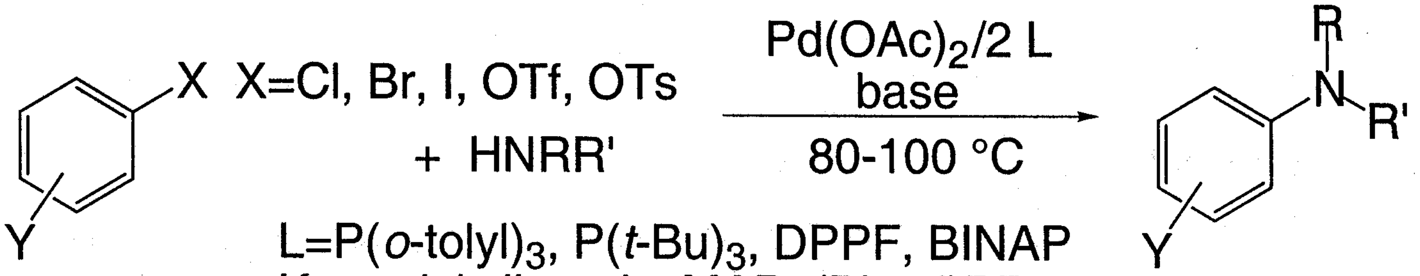
- Pharmaceuticals
- Redox Active Macromolecules
- New Ligands for Metals

Mechanism:

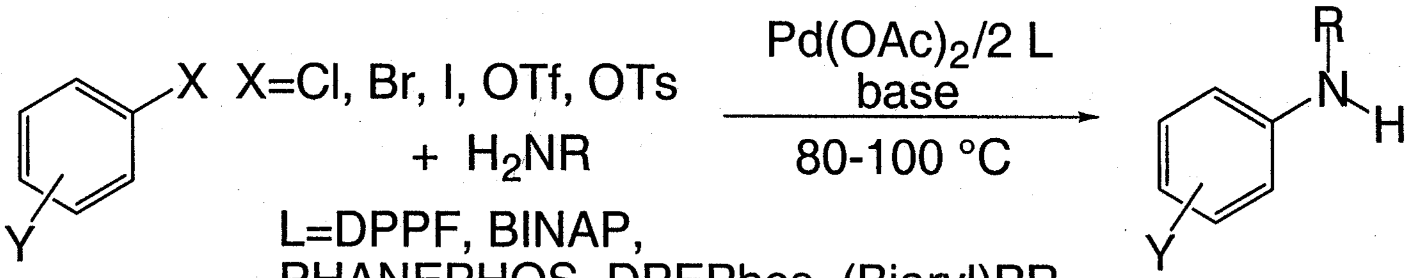
- New chemistry of palladium amides?
- C-X bond formation by organometallic compounds?

Current Arylation Processes

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



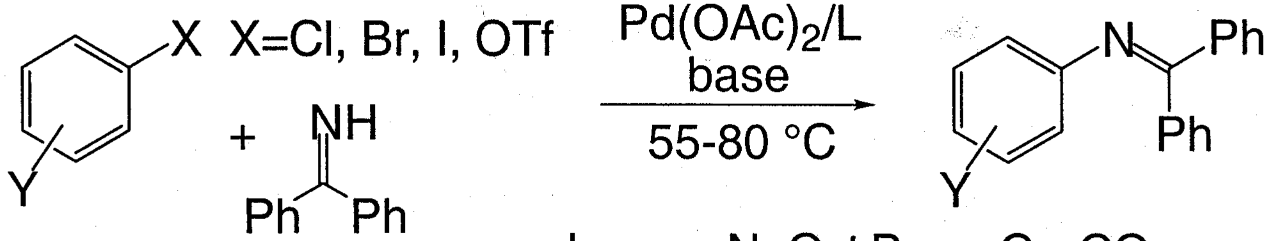
L=P(*o*-tolyl)$_3$, P(*t*-Bu)$_3$, DPPF, BINAP
Kumada's ligands, MAP, (Biaryl)PR$_2$,
heterocyclic carbene



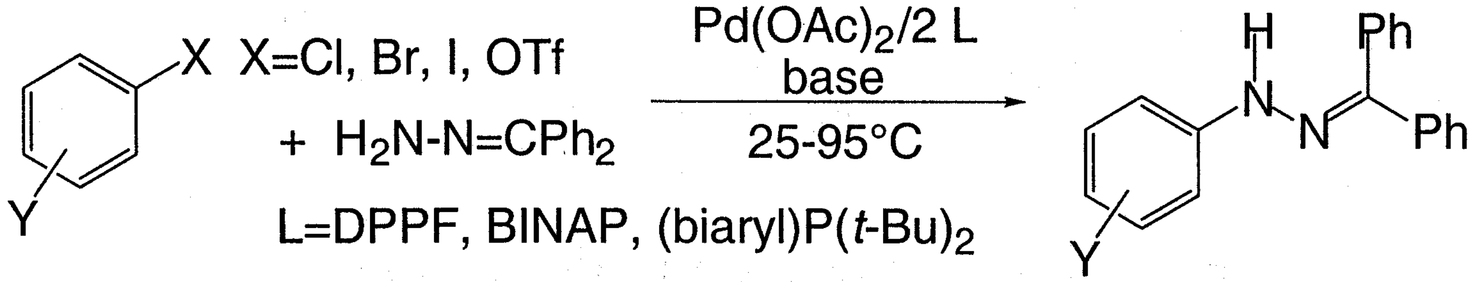
L=DPPF, BINAP,
PHANEPHOS, DPEPhos, (Biaryl)PR$_2$
heterocyclic carbene

base = NaO-*t*-Bu, Cs_2CO_3
DPPF=1,1'-*bis*-(diphenylphosphino)ferrocene
BINAP=2,2'-*bis*-(diphenylphosphino)-1,1'-binaphthyl

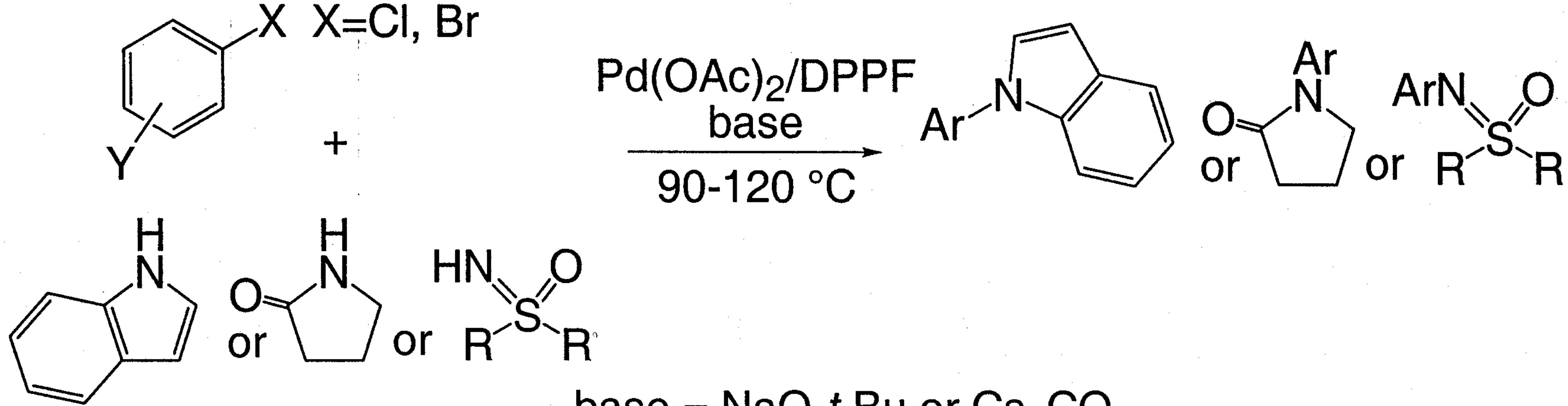
Current Arylation Processes



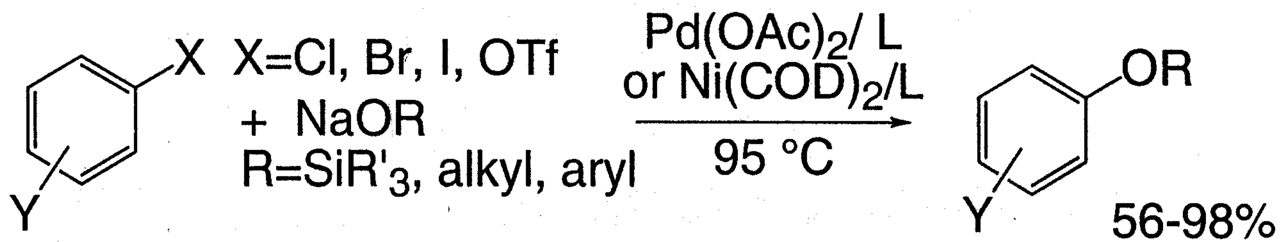
base = NaO-*t*-Bu or Cs_2CO_3
L=DPPF or BINAP, heterocyclic carbene



Current Arylation Processes



base = NaO-*t*-Bu or Cs_2CO_3

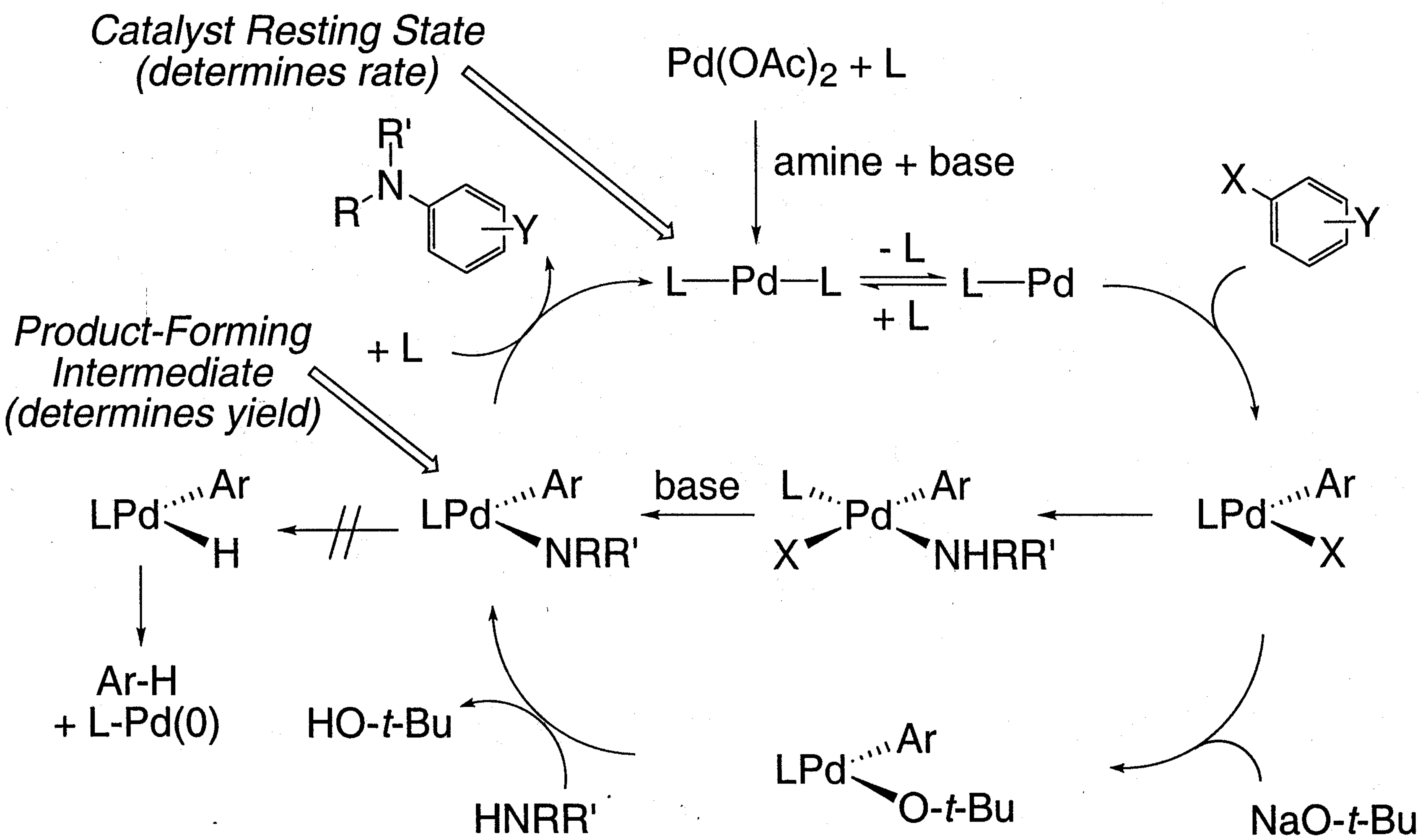


For Y= *p*-EWG L = DPPF or BINAP
For Y≠ *p*-EWG L=FcP(*t*-Bu)$_2$ or (Biaryl)P(*t*-Bu)$_2$

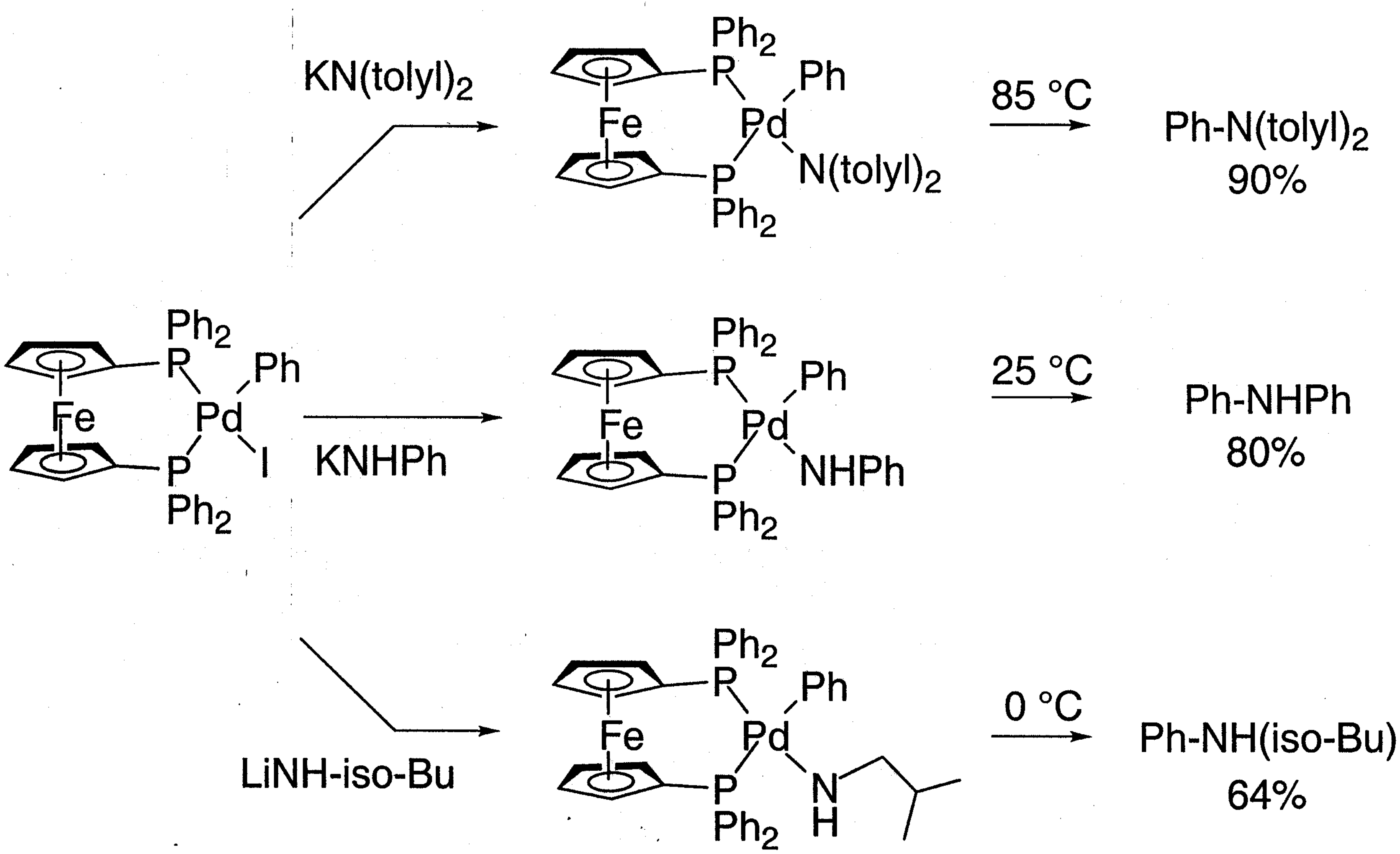
Review: Hartwig, J.F. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2046-2067

Summary of Amination Mechanism

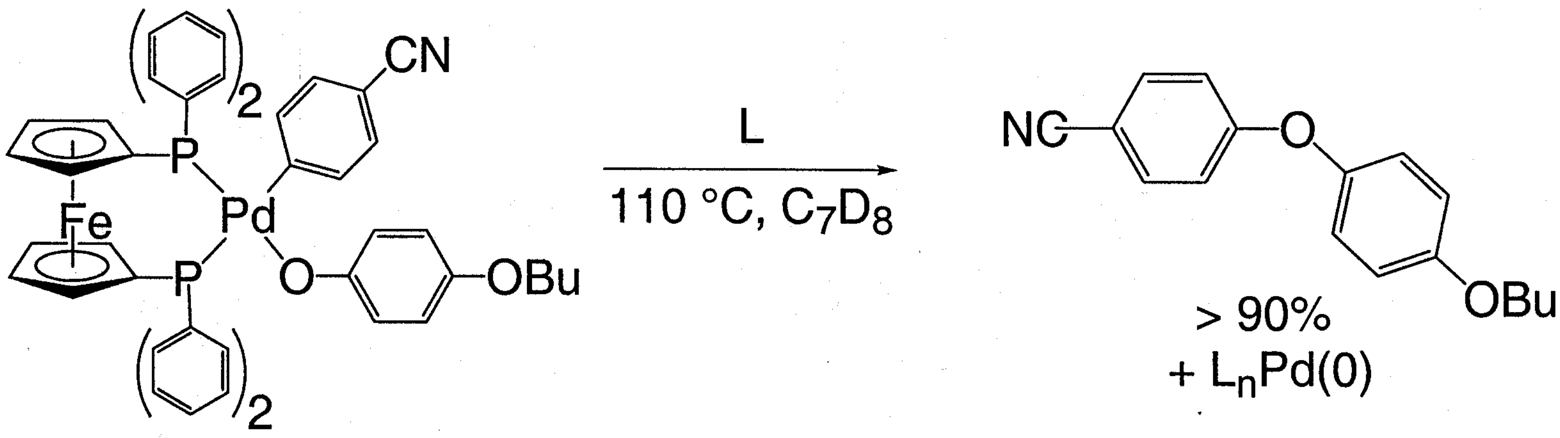
L = BINAP, DPPF, P(*t*-Bu)$_3$



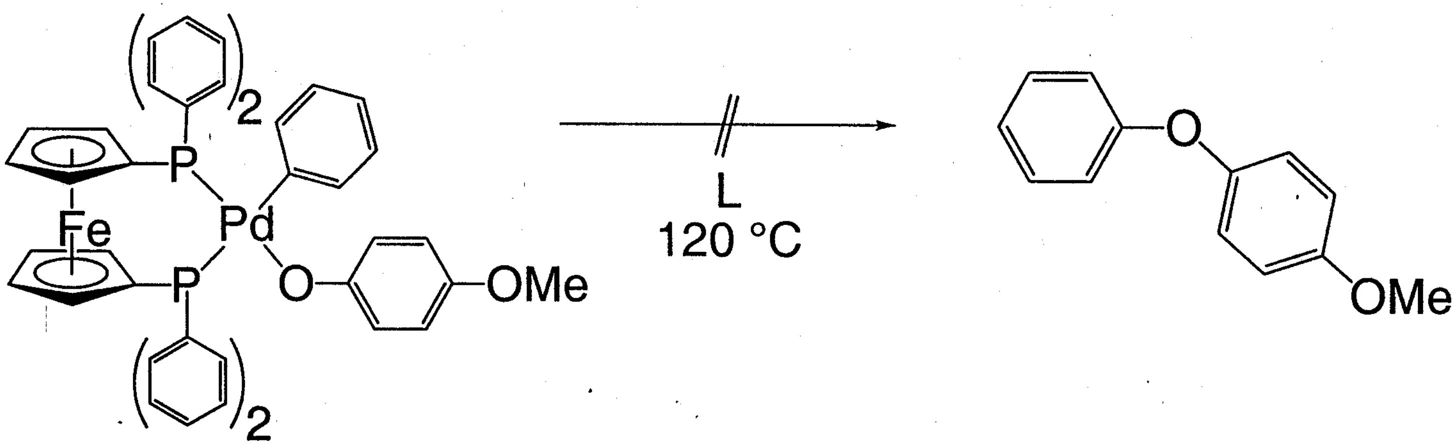
Pd-Amido Complexes with Bis-Phosphines



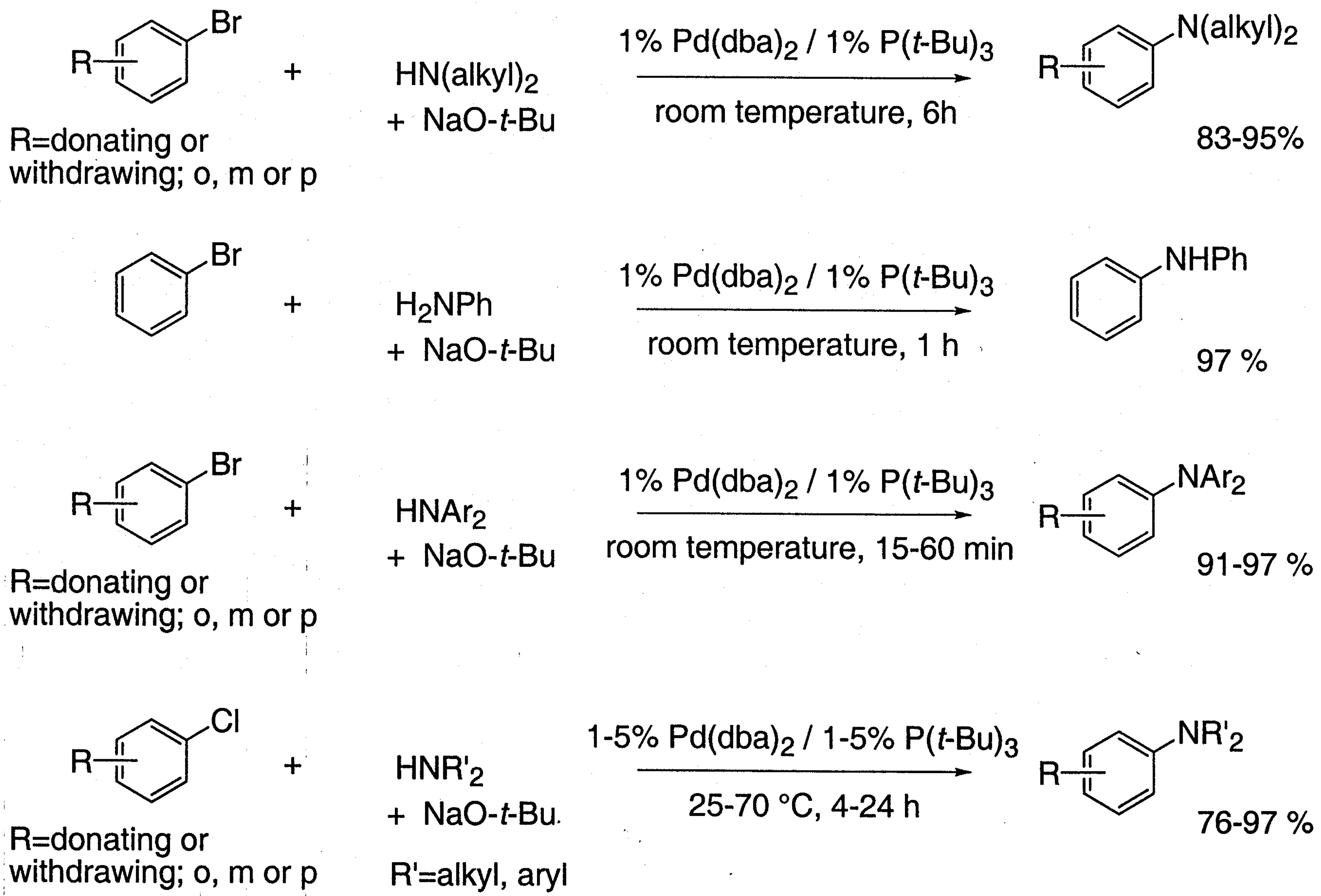
Reductive Elimination of Diaryl Ether...



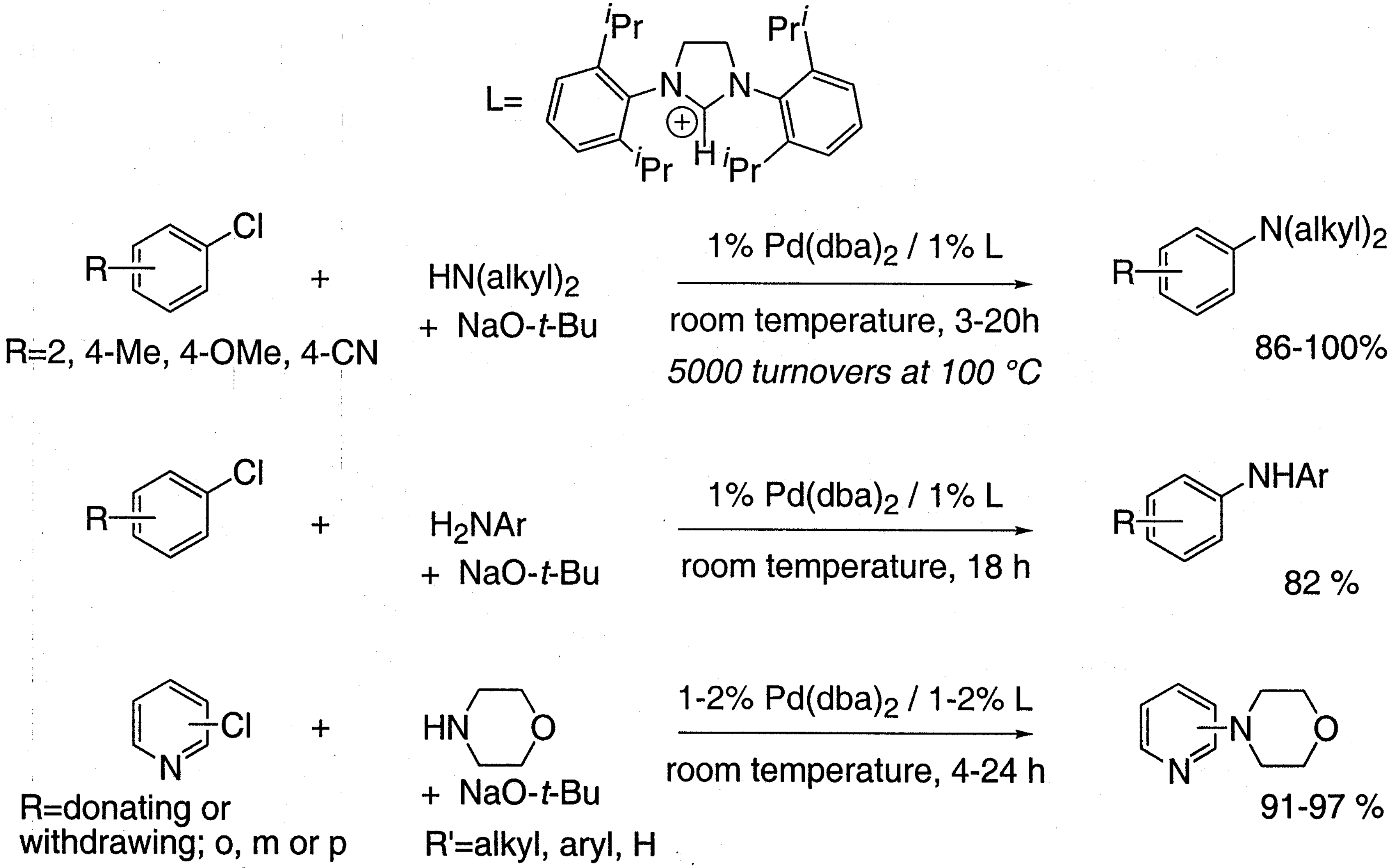
But No Elimination Without a Withdrawing Group



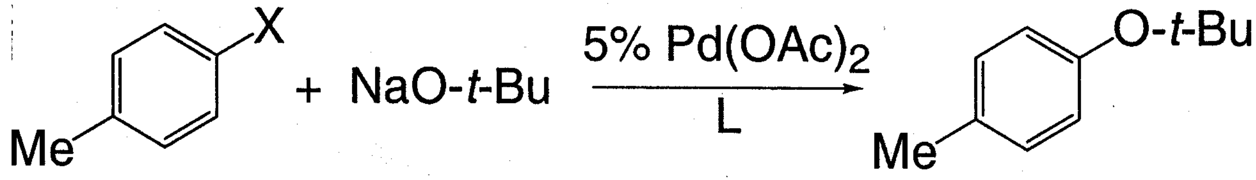
Mild Amination with $P(t\text{-}Bu)_3$



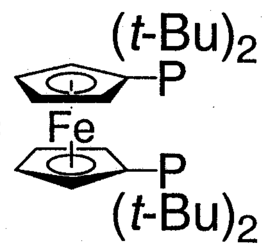
Mild Amination with Saturated Carbene Ligands



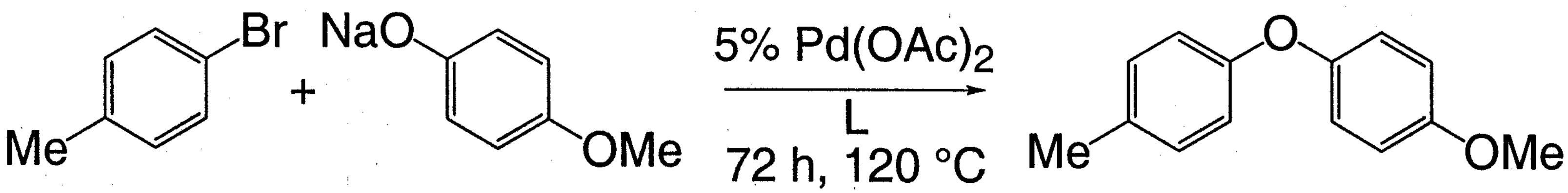
Hindered Alkylphosphines Improve Ether Synthesis



DB^{t}PF=

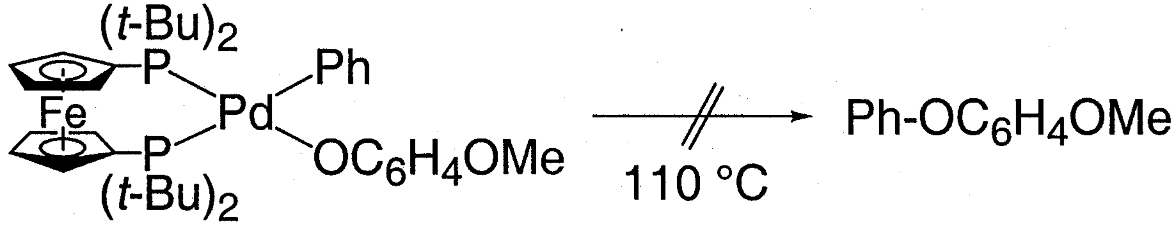


L=BINAP	X=Br	53 %
L=DPPF	X=Br	38 %
L=P(*o*-tolyl)$_3$	X=Br	0 %
L=P(*t*-Bu)$_3$	X=Cl	100 %
L=DB^{t}PF	X=Cl	89 %

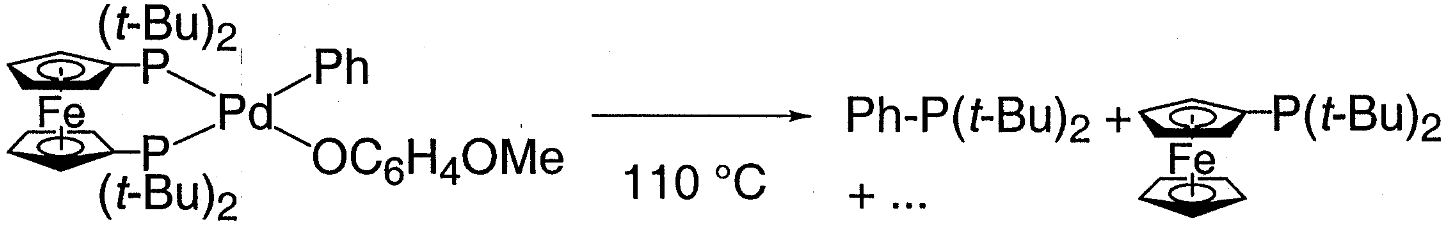


L=BINAP	0 %
L=DPPF	0 %
L=P(*o*-tolyl)$_3$	0 %
L=P(*t*-Bu)$_3$	20 %
L=DB^{t}PF	48%

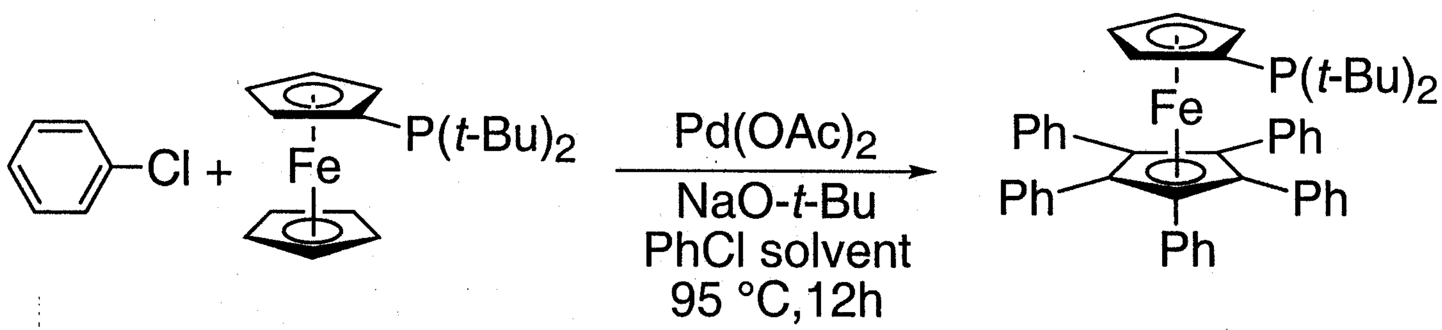
Can DB^{t}PF induce Ether Formation without EWG?



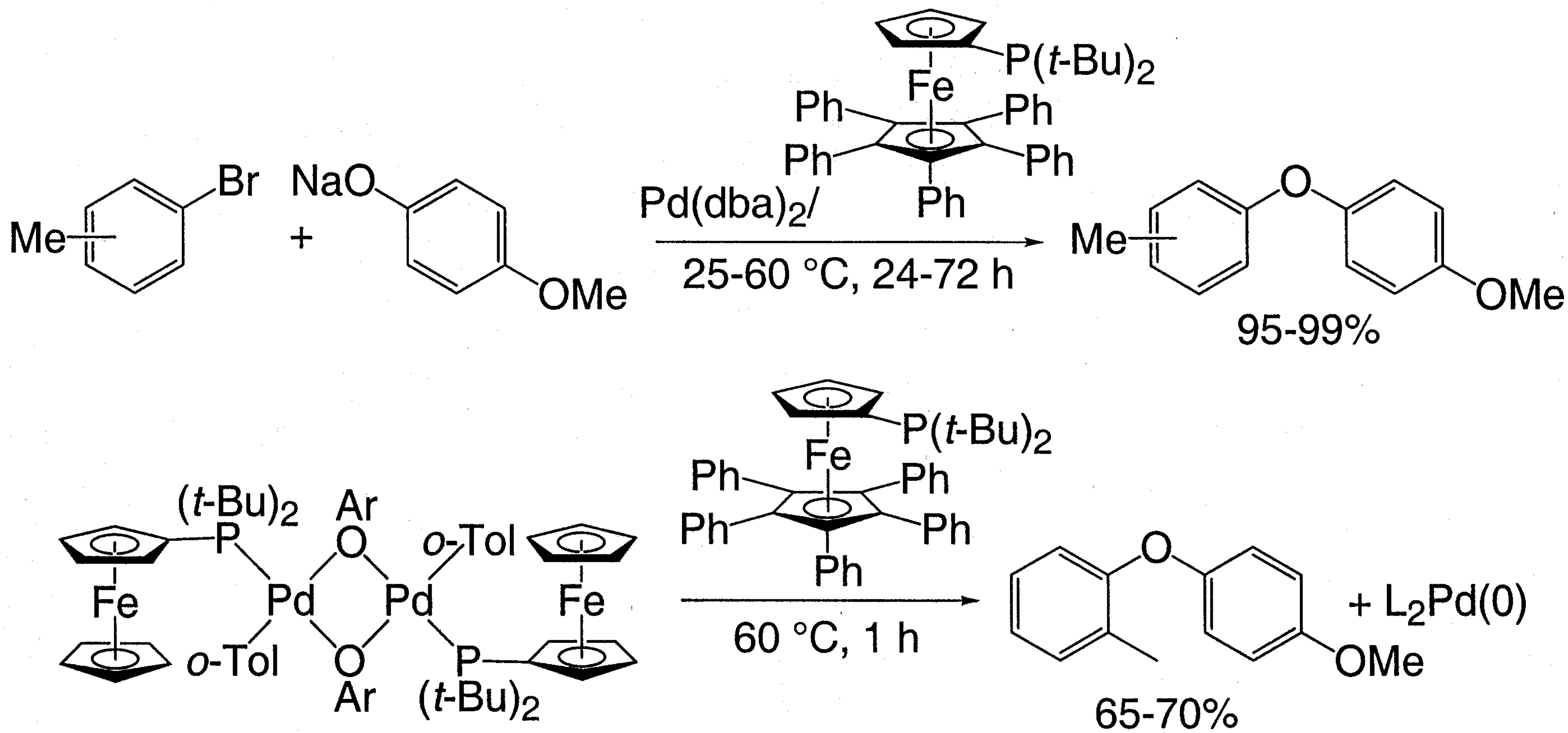
A Closer Look:



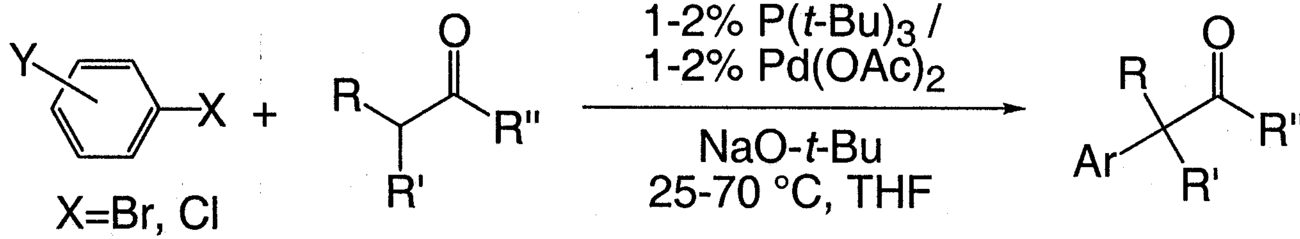
The Catalyst Changes

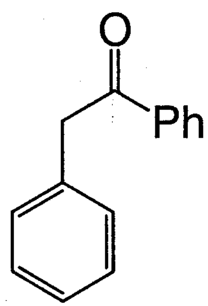


Very Mild Synthesis of Diaryl Ethers

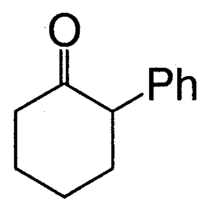


Mild Ketone Arylations

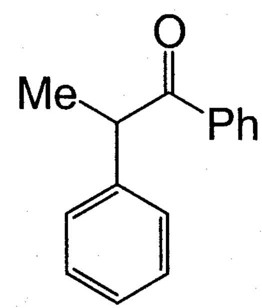




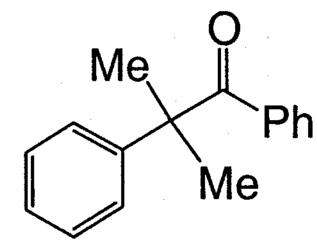
X=Br: 96%



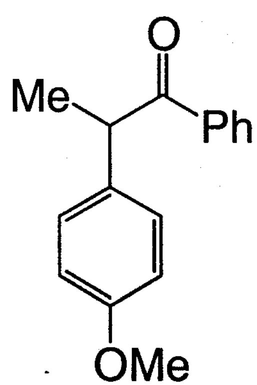
X=Br: 73 %



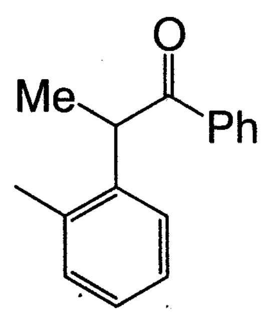
0.5 mol% 97%
0.005 mol% <24h, 97%
X=Cl 2mol% 90%



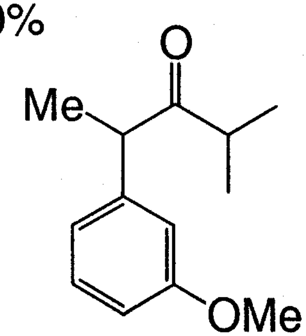
X=Br 92 %
X=Cl 82% (3-OMe)



X=Cl: 90%

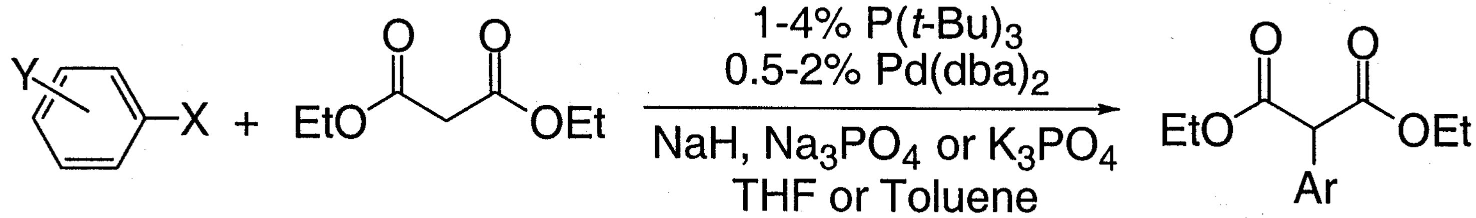


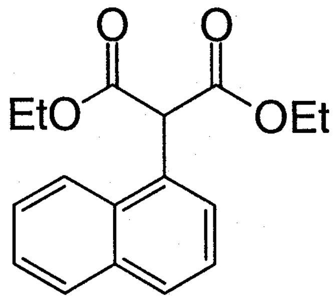
X=Cl 80%



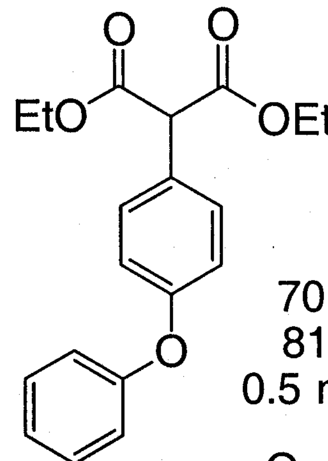
X=Br 83 %
(74:26 ratio)
X=Cl 69 %
(76:24 ratio)

Arylation of Malonates

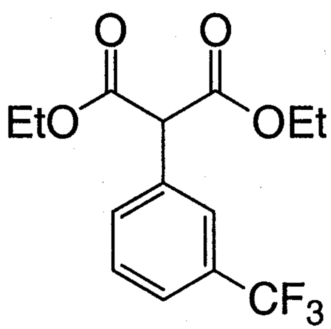




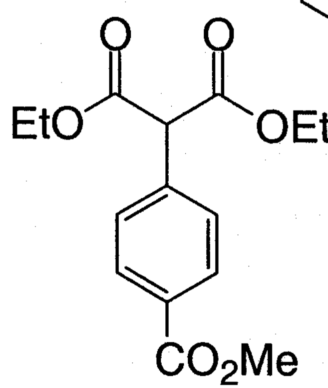
70 °C
84 %



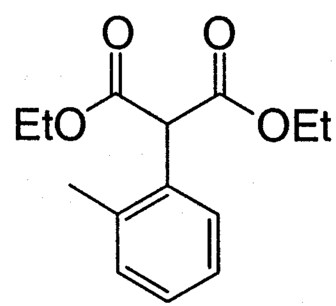
70 °C
81 %
0.5 mol%



70 °C
92 %

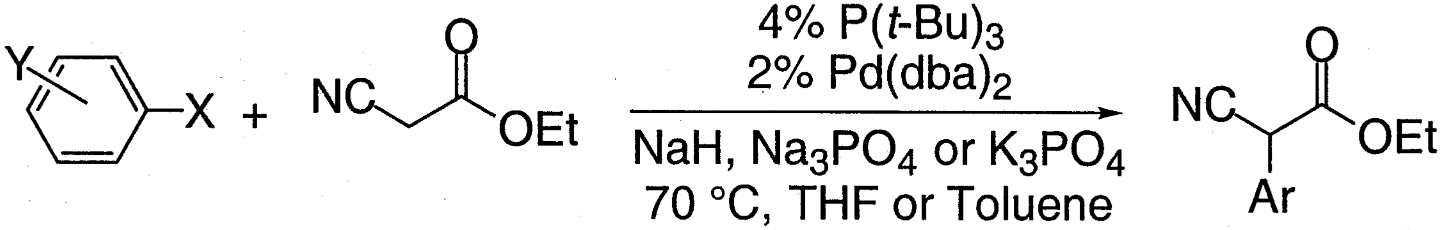


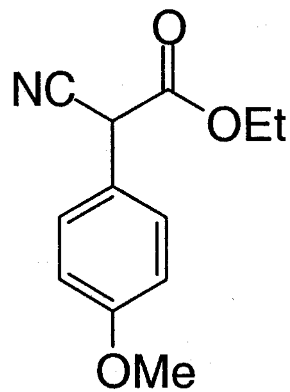
50 °C
86 %



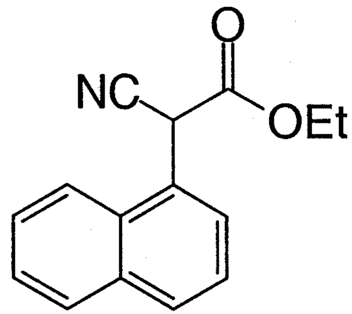
70 °C
82 %

Arylation of Cyanoesters

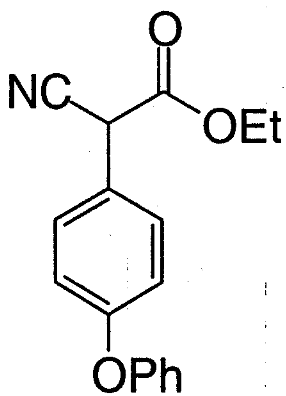




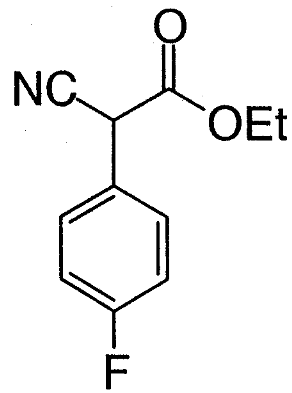
80 %



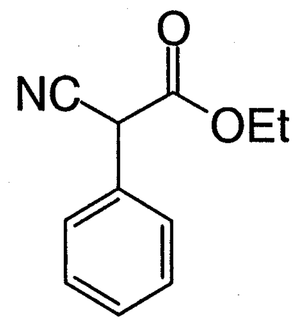
83 %



90%



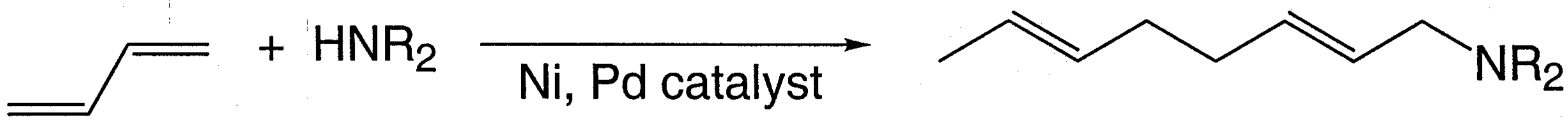
93%



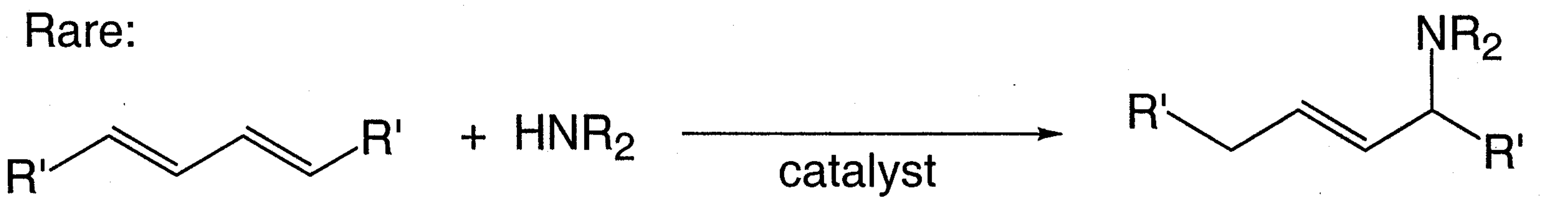
X=Cl
100 °C
91 %

Catalytic Hydroamination of Dienes

Well known:



Rare:

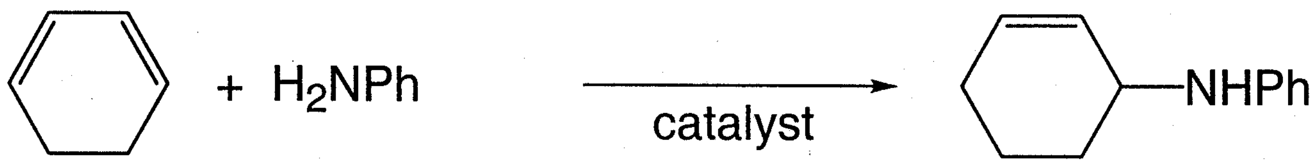


only for Ni, morpholine

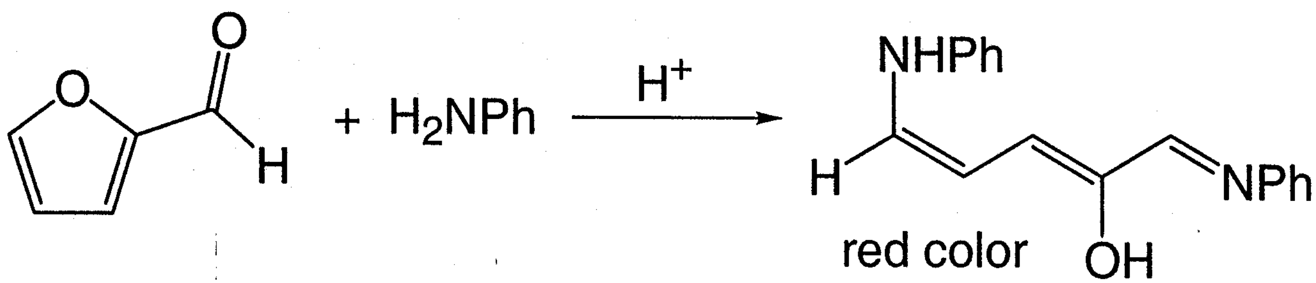
Objectives:
- Substituted dienes
- Arylamines amines

Questions:
- Is nickel necessary?
- What ligand properties are optimal?

Spot Test: Catalytic Diene Hydroamination



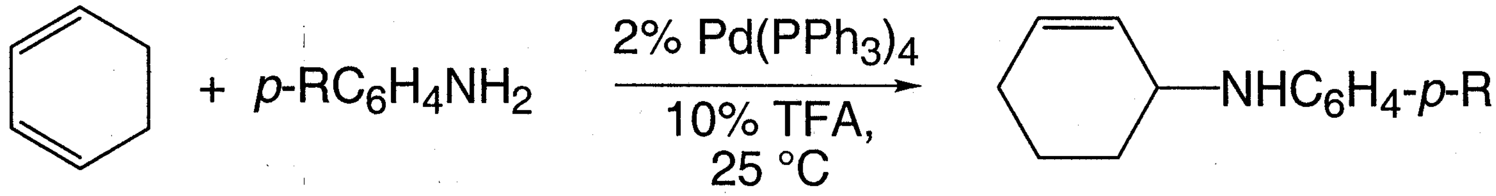
Analysis for Aniline: Furfural, HOAc



Unreacted amine: Red

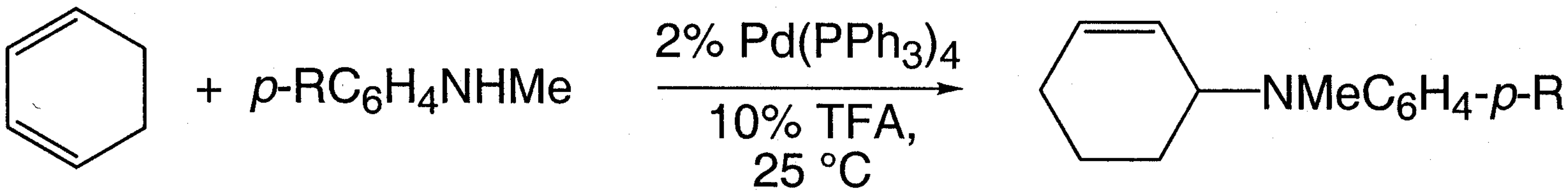
Complete reaction: clear or the color of the catalyst

Preliminary Scope of Diene Hydroamination



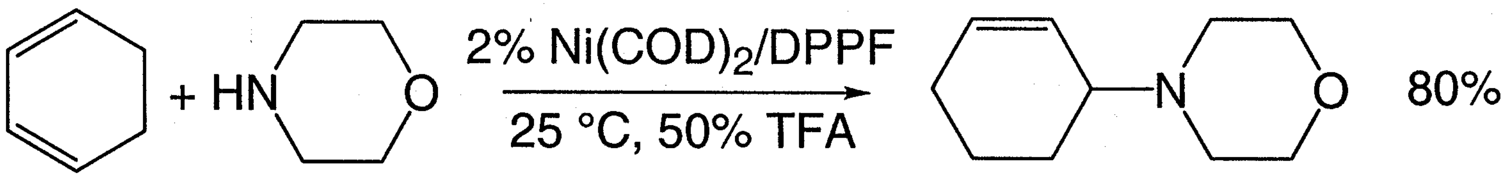
R = H, Me, CF_3, COOEt, OMe

78-99%

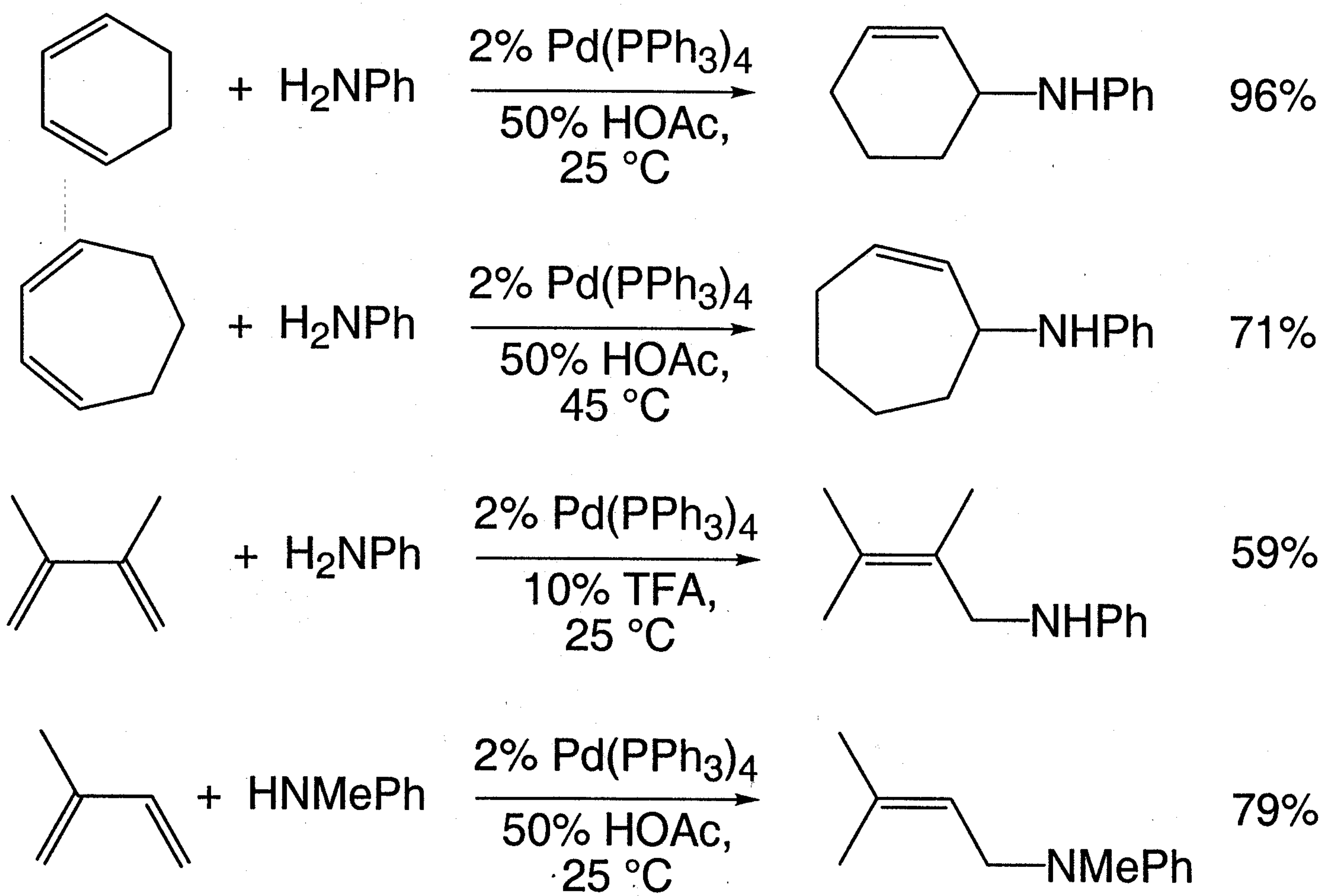


R = H, OMe

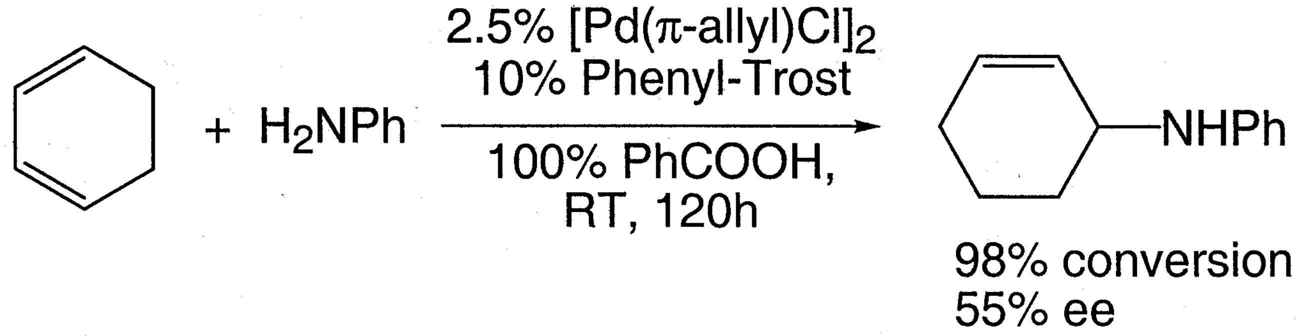
97%, 98%

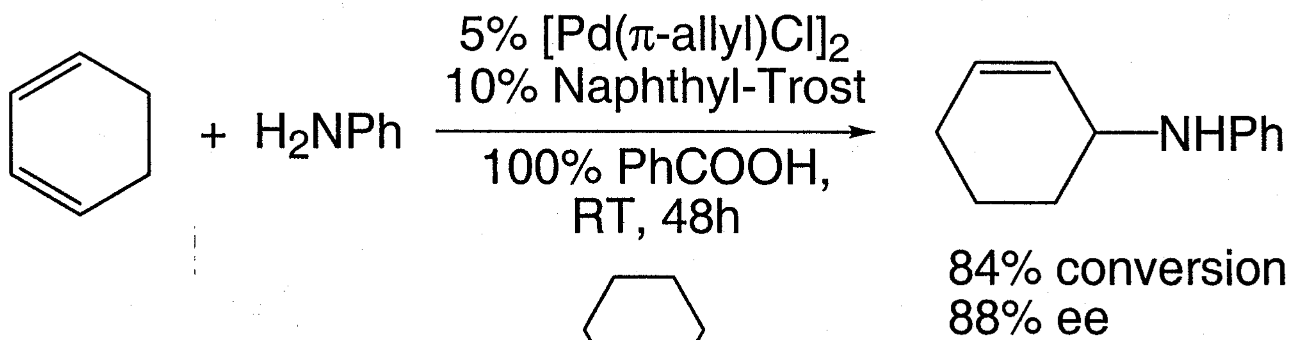


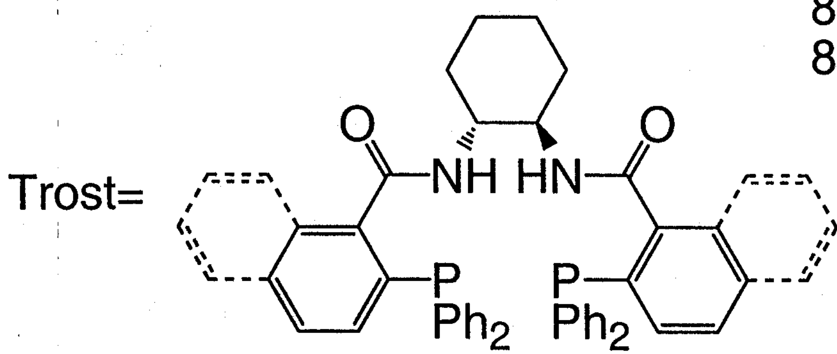
Preliminary Scope of Diene Hydroamination



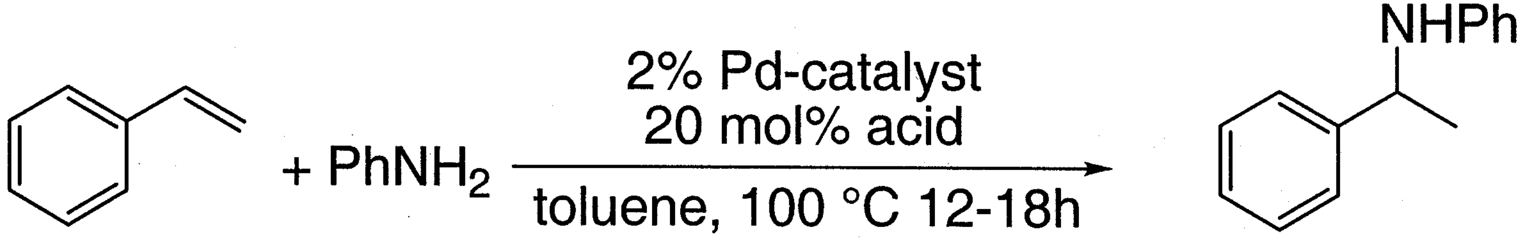
Toward An Enantioselective Version







Vinylarene Hydroamination

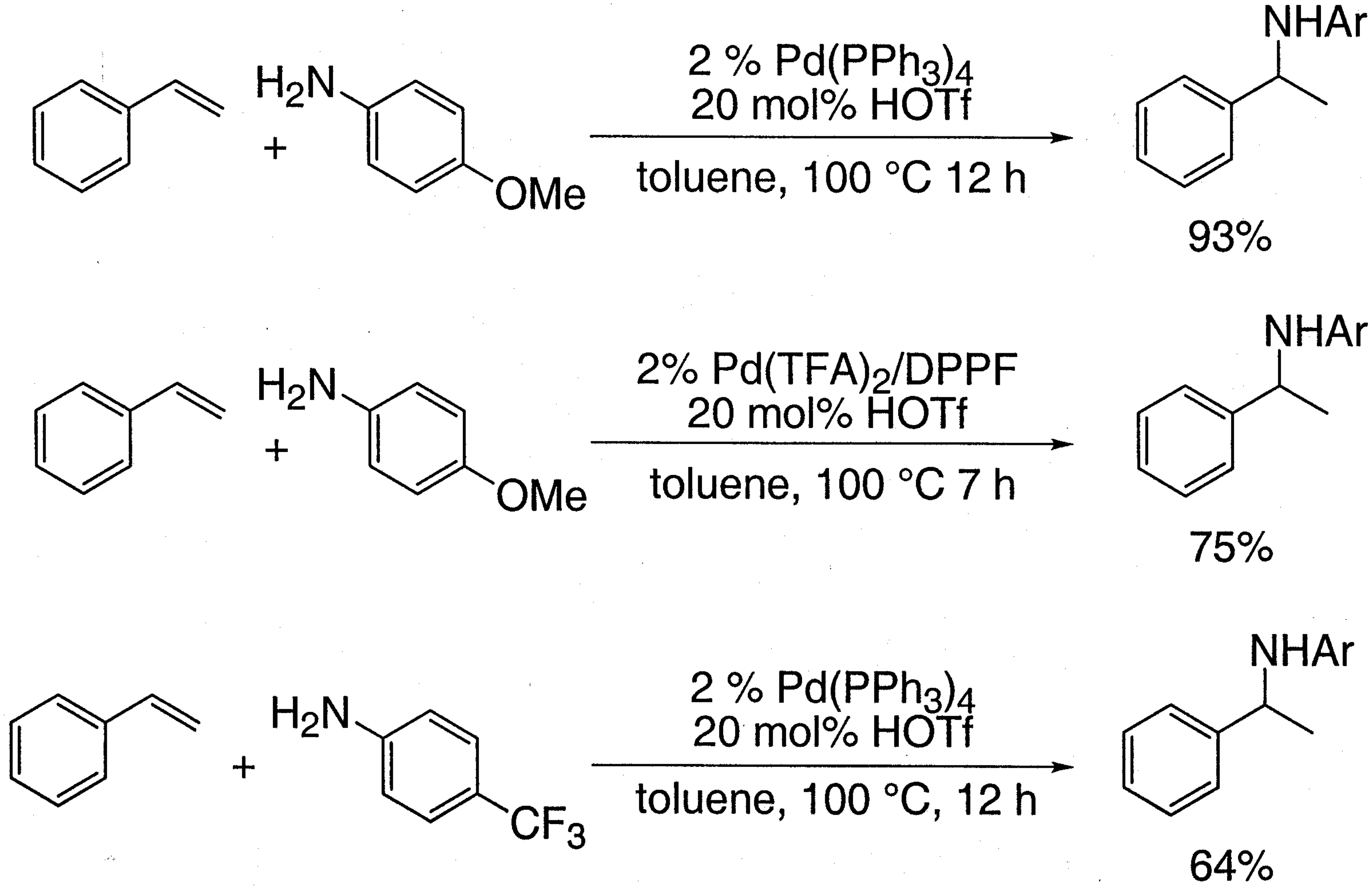


91-100% isolated

Role of the Acid:

Palladium / Ligand	Acid	Yield
2% [Pd(PPh_3)$_4$]		0%
2% [Pd(PPh_3)$_4$]	20% TFA	63%
2% [Pd(PPh_3)$_4$]	20% TfOH	91%
2% Pd(TFA)$_2$ / 8% PPh_3		30%
2% Pd(TFA)$_2$ / 8% PPh_3	20% TFA	68%
2% [Pd(TFA)$_2$] / 3% DPPF		71%
2% [Pd(TFA)$_2$] / 3% DPPF	20% TfOH	100%
2% [(DPPF)Pd(OTf)$_2$]		100%

Vinylarene Hydroamination



Asymmetric Vinylarene Hydroamination