# (Hetero)aromatic Functionalisation 1 – *C-N and C-O Bond Formation*

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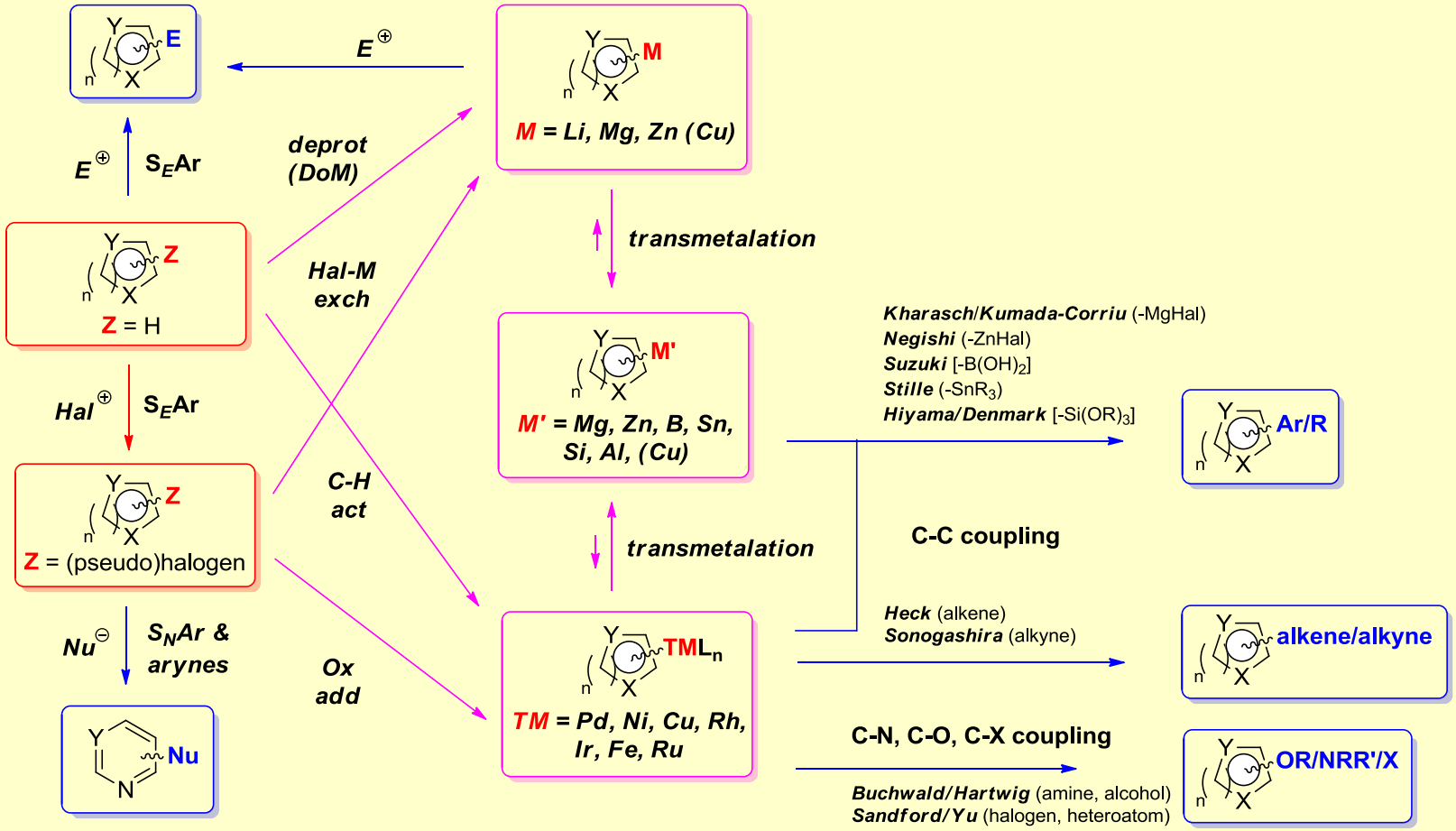
***Villars Summer School***
***29th Aug – 2nd Sept 2010***

# Format and scope of lecture

- ***Pd, Ni & Cu catalysed C-N cross-coupling***
  - intramolecular heterocycle formation
  - intermolecular…latest developments

- ***Pd, Ni & Cu catalysed C-O cross-coupling***
  - intramolecular heterocycle formation
  - intermolecular…latest developments

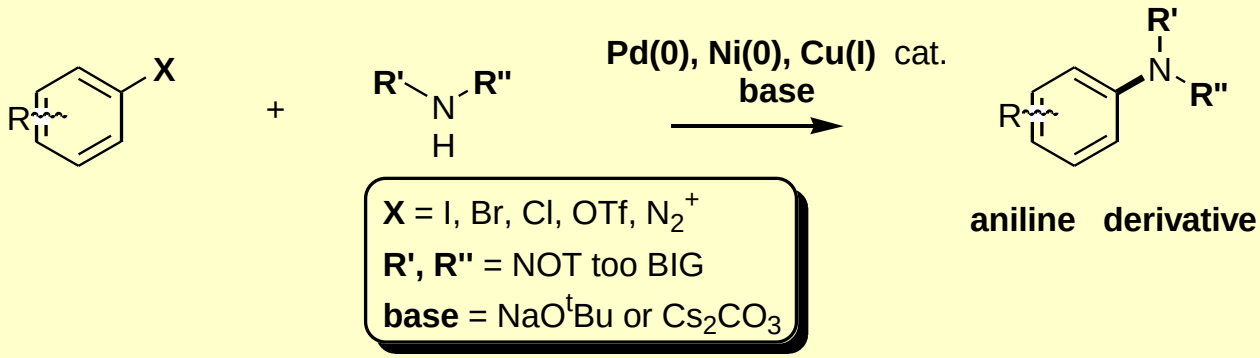
# (Hetero)aromatic functionalisation strategies



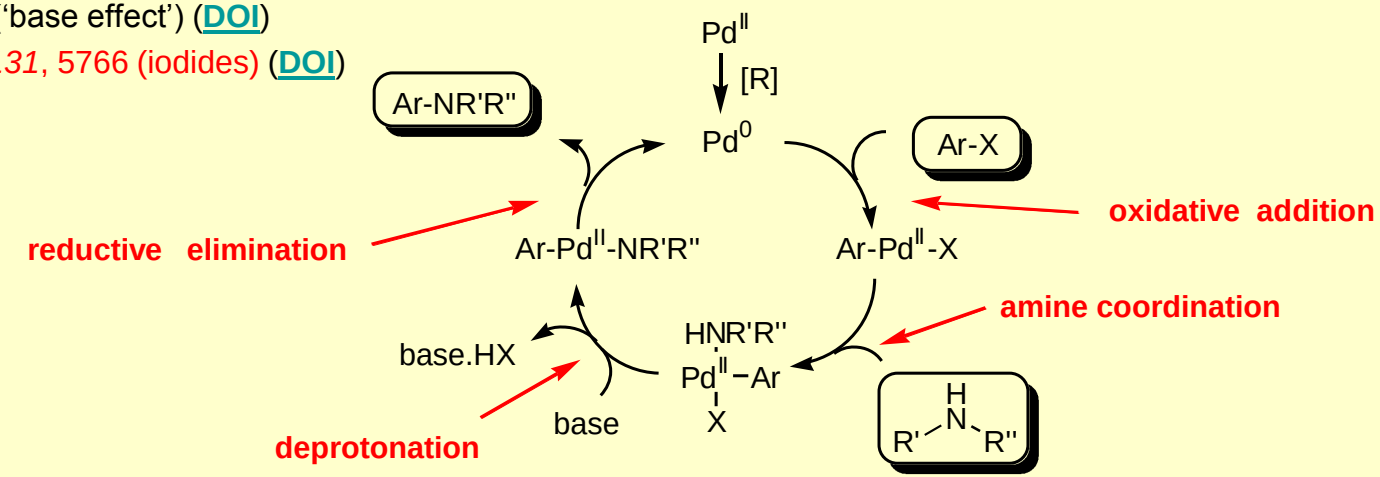
# Pd, Ni & Cu catalysed C-N cross-coupling

# C-N bond ‘cross-coupling’ – *nucleophilic amination*

- ***prior art:*** *$S_EAr$ nitration, then reduction, then alkylation or reductive amination; Goldberg reaction.*
- ***reviews:*** Buchwald *Angew. Chem. Int. Ed.* **2008**, *47*, 6338 (DOI); Evano *Chem. Rev.* **2008**, *108*, 3054 (DOI); Mauger *Aldrichimica Acta* **2006**, *39*, 17 (DOI); Kunz *Synlett* **2003**, 2428 (Cu) (DOI); Prim *Tetrahedron* **2002**, *58*, 2041 (Pd) (DOI); Hartwig *Angew. Chem. Int. Ed.* **1998**, *37*, 2046; Frost, *J. Chem. Soc., Perkin Trans. 1* **1998**, 2615 (DOI); Hartwig *Synlett* **1997**, 329 (DOI)
- ***overall scheme:***

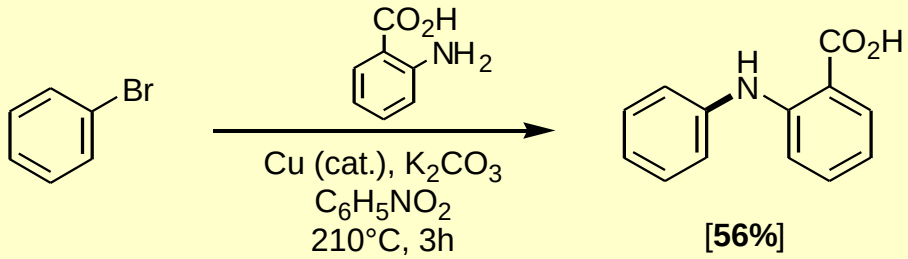



- ***mechanism (Pd):***
  - Buchwald, Hartwig & Blackmond *J. Am. Chem. Soc.* **2006**, *128*, 3584 (DOI)
  - Maes *J. Org. Chem.* **2004**, *69*, 6010 (‘base effect’) (DOI)
  - Buchwald *J. Am. Chem. Soc.* **2009**, *131*, 5766 (iodides) (DOI)



# Historical development

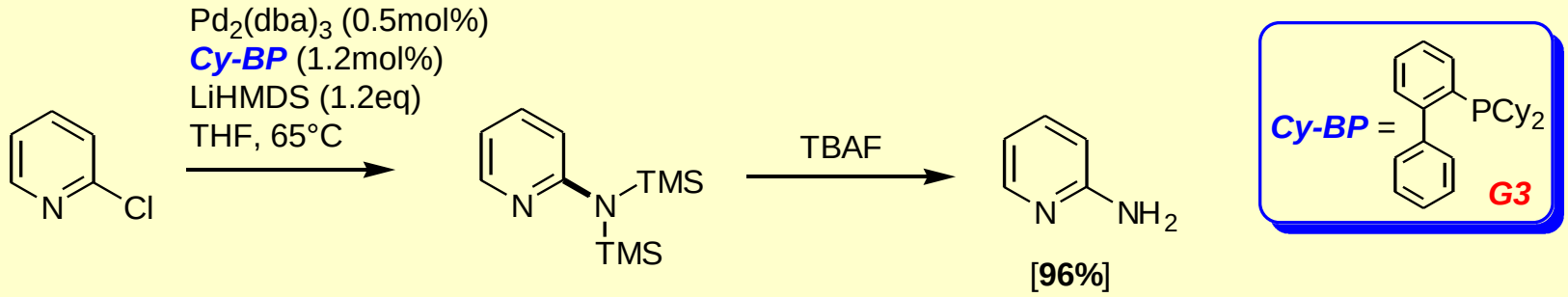
- ***1906: Goldberg reaction (Cu)***
  - Goldberg *Chem. Ber.* **1906**, *39*, 1691




- ***1995-2000: Buchwald-Hartwig amination [Pd (& Ni)]***
  - ***FIRST GENERATION (G1):***
    - ***ligand:*** P(*o*-Tol)$_3$
    - ***aryl halide substrate:*** X = Br or I; Ar = non-hindered, electron poor or neutral
    - ***amine nucleophile:*** cyclic secondary
    - ***typical conditions:*** Pd(0), P(*o*-Tol)$_3$, NaO$^t$Bu or LiHMDS, toluene, 80-100 °C
  - ***SECOND GENERATION (G2):***
    - ***ligand:*** chelating diphosphines
    - ***aryl halide substrate:*** X = Br, I or OTf; Ar = electron rich, poor or neutral, heteroaromatic
    - ***amine nucleophile:*** cyclic secondary, primary and anilines
    - ***typical conditions:*** Pd(0),DPPF or BINAP, $Cs_2CO_3$ or $K_3PO_4$, toluene, 80-100 °C
  - ***THIRD GENERATION (G3):***
    - ***ligand:*** electron rich monodentate phosphines OR *N*-heterocyclic stable carbenes (NHCs)
    - ***aryl halide substrate:*** X = Cl, Br, I, OTf or OTs; Ar = electron rich, poor or neutral, heteroaromatic
    - ***amine nucleophile:*** secondary (cyclic & acyclic), primary and anilines
    - ***typical conditions:*** Pd(0),electron rich monophosphine/carbene, NaO$^t$Bu, $Cs_2CO_3$ or $K_3PO_4$, toluene, rt-100 °C
- ***2000-: Renaissance of Goldberg-type amination (Cu):***
  - chelating ***diamine*** and ***diol*** ligands

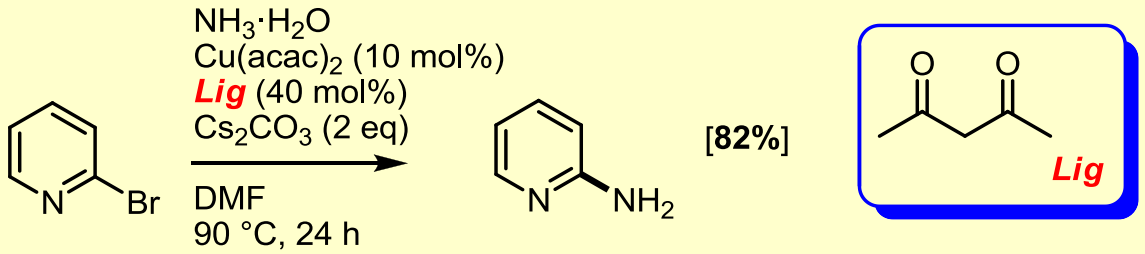
# Coupling of ammonia equivalents (Pd)

- ***highlight:*** Willis *Angew. Chem. Int. Ed.* **2007**, *46*, 3402 (also → phenols) (DOI)
- ***Ar-Br/Cl ↔ ammonia equivalents (Pd):***
  - ***$NH_3$:***
    - Hartwig *J. Am. Chem. Soc.* **2009**, *131*, 11049 (DOI); Hartwig *J. Am. Chem. Soc.* **2006**, *128*, 10028 (DOI); Buchwald *J. Am. Chem. Soc.* **2007**, *129*, 10354 (DOI)
  - ***allyl and diallylamines:***
    - Buchwald *J. Org. Chem.* **2000**, *65*, 1144 (DOI), Putman *Tet. Lett.* **1998**, *39*, 1313 (DOI)
  - ***$NH_2Boc$:***
    - ***deprotection:*** TFA
    - Hartwig *J. Org. Chem.* **1999**, *64*, 5575 (DOI)
  - ***benzophenone imine:***
    - ***deprotection:*** hydroxylamne hydrochloride
    - Buchwald *Tet. Lett.* **1997**, *38*, 6367 (DOI), Hartwig *J. Am. Chem. Soc.* **1998**, *120*, 827 (DOI), Buchwald *J. Organomet. Chem.* **1999**, *576*, 125 (DOI)
  - ***LiHMDS, $Ph_3SiNH_2$, $LiNH_2$, $TMSCH_2CH_2SO_2NH_2$ & nicotiamide:***
    - ***deprotection*** (LiHMDS & $TMSCH_2CH_2SO_2NH_2$): TBAF
    - Hartwig *Org. Lett.* **2001**, *3*, 2729 (DOI), Buchwald *Org. Lett.* **2001**, *3*, 3417 (DOI); Sivakumar *Tet. Lett.* **2008**, *49*, 4585 (DOI)
    - Pujol *Tetrahedron* **2009**, *65*, 1951 (DOI) – nicotinamide → free $NH_2$ directly

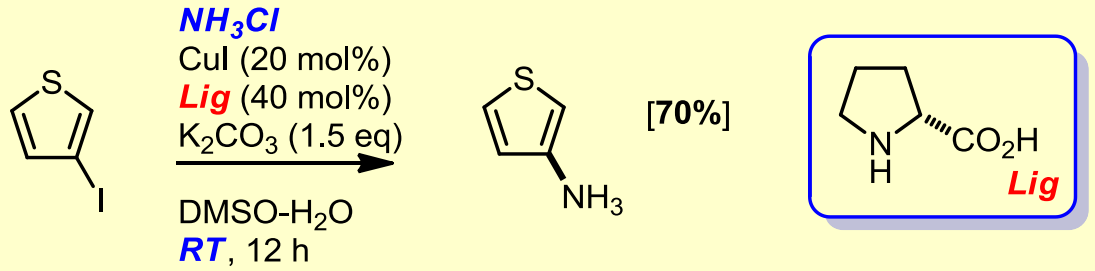


# Coupling of ammonia equivalents (Cu)

- ***Ar-Br/Cl/I ↔ ammonia (Cu):***
  - ***$NH_3$:***
    - Taillefer *Angew. Chem. Int. Ed.* **2008**, *47*, 1 (DOI)

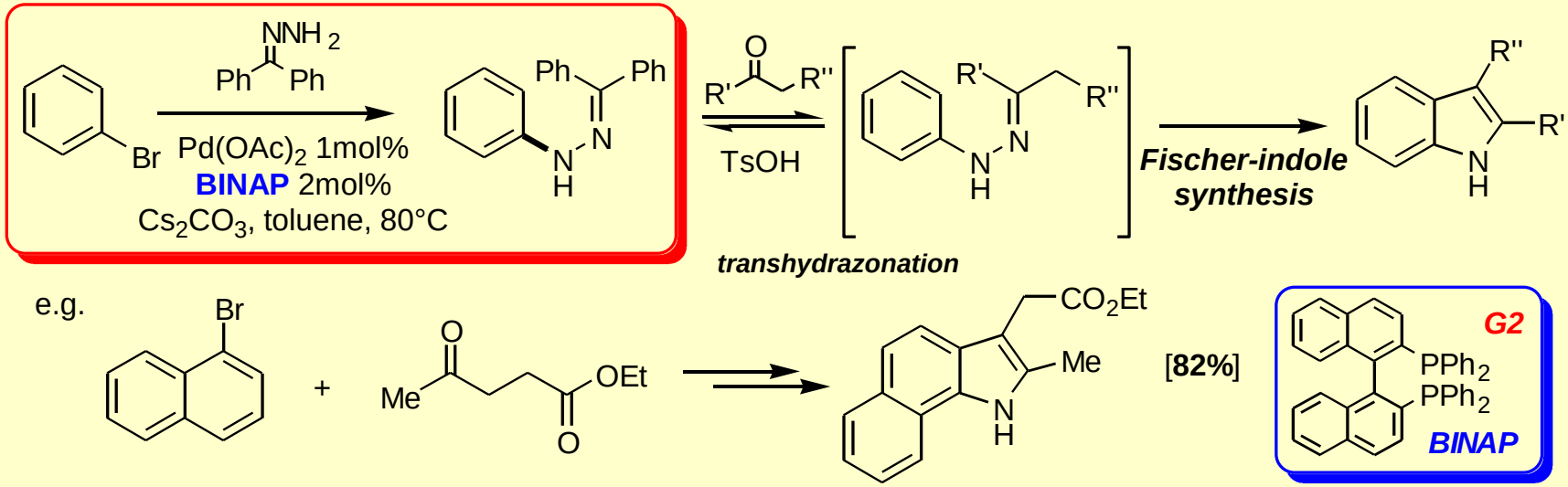



    - Thadani *Chem. Commun*. **2008**, 6200 (DOI) – using NHC-ligated CuCl (5 mol%) in MeOH/NMP at 90 ° C
    - Wolf *Chem. Commun*. **2009**, 3035 (DOI) – using $Cu_2O$ (5 mol%) in 1,4-dioxane at 110 °C
    - Zhao *Synlett* **2010**, 1355 (DOI) – using CuI (10 mol%) in DMF with $K_3PO_4$ at ***RT***
  - ***$NH_4Cl$:***
    - Chang *Chem. Commun.* **2008**, 3052 (DOI)

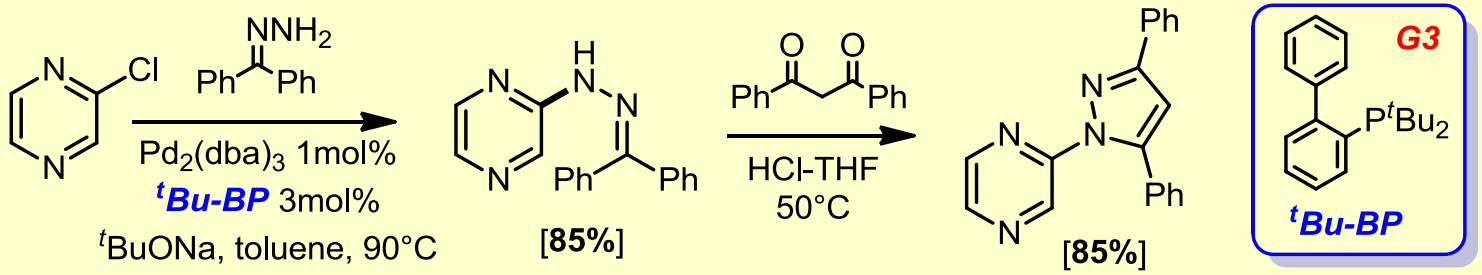


# *Inter*molecular coupling of hydrazones (Pd)

- ***Ar-Br ↔ benzophenone hydrazone (Pd) - Fischer indole synthesis:***
  - Buchwald *J. Am. Chem. Soc.* **1998**, *120*, 6621 (DOI); Hartwig *Angew. Chem., Int. Ed.* **1998**, *37*, 2090 (DOI); Buchwald *J. Am. Chem. Soc.* **1999**, *121*, 10251 (DOI)

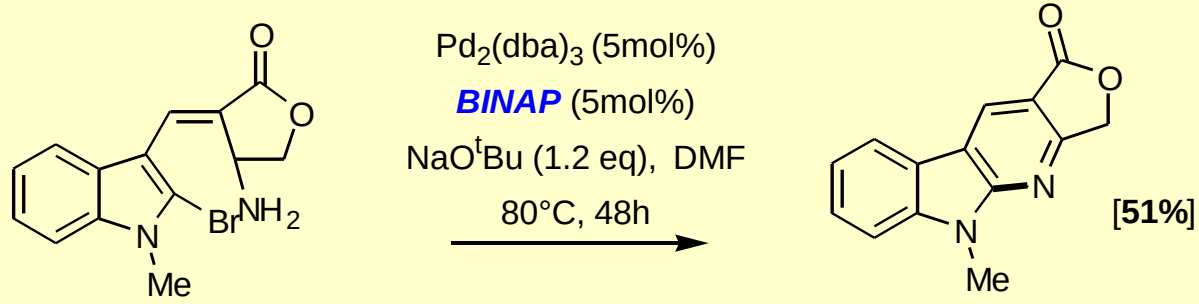


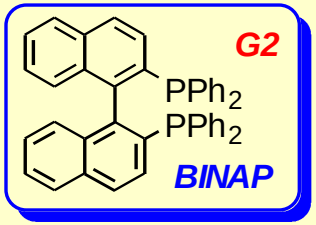

- ***Ar-Cl ↔ benzophenone hydrazone (Pd) - pyrazole synthesis:***
  - Haddad *Tet. Lett.* **2004**, *45*, 5935 (DOI)



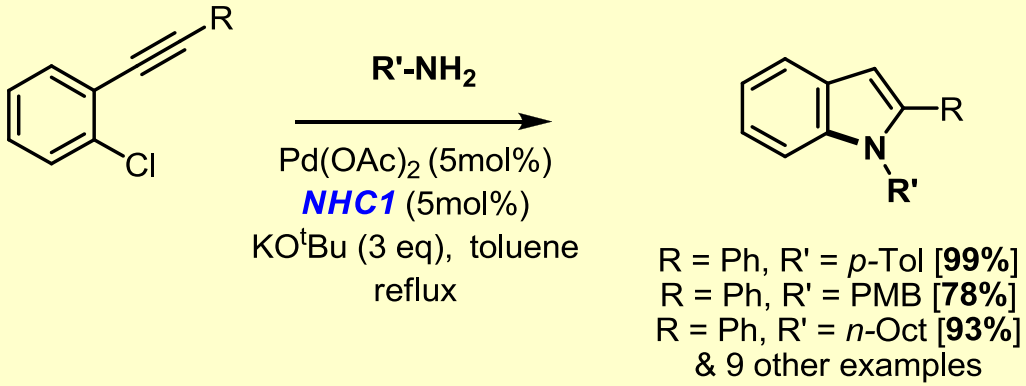
# *Intra-* & *inter*molecular coupling of 1° amines (Pd)

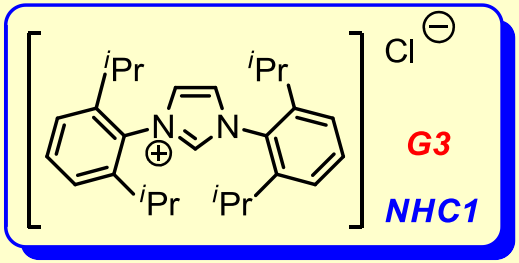
- ***Ar-Br ↔ intramolecular 1° amine (Pd) - pyrido[2,3-b]indole synthesis:***
  - Dodd *Tet. Lett.* **1998**, *39*, 2119 (DOI) & Bedford *Chem. Commun.* **2002**, 2310 (DOI)



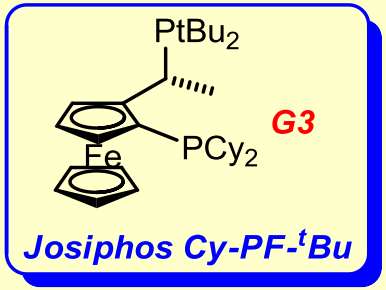




- ***Ar-Cl ↔ 1° amine (Pd) – N-substituted indole synthesis:***
  - Ackermann *Org. Lett.* **2005**, *7*, 439 (DOI)



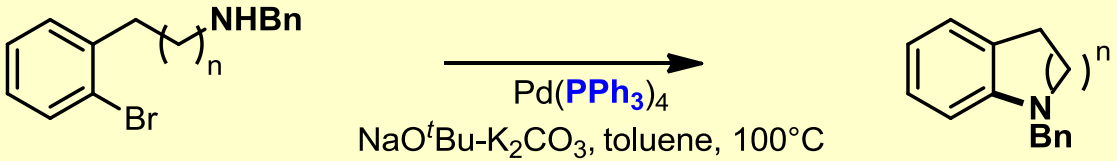



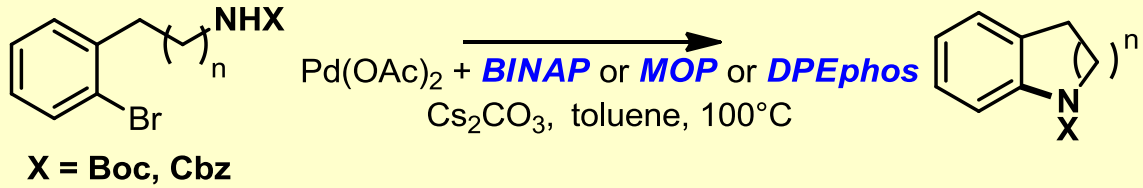

- ***Ar-Cl/Br/I ↔ 1° amine & anilines (Pd)*** – ***Pd(OAc)$_2$/Josiphos***
  - broad scope; high TONs (even to 0.0005 mol%):
  - Hartwig *J. Am. Chem. Soc.* **2008**, *130*, 6586 (DOI)
  - See also: Buchwald *J. Am. Chem. Soc*. **2008**, *130*, 13552 (DOI)

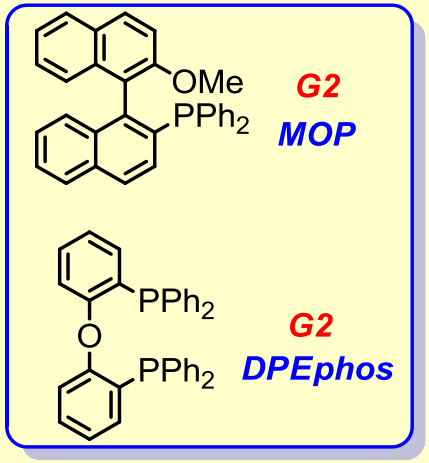


# *Intra*molecular coupling of 2° amines (Pd)

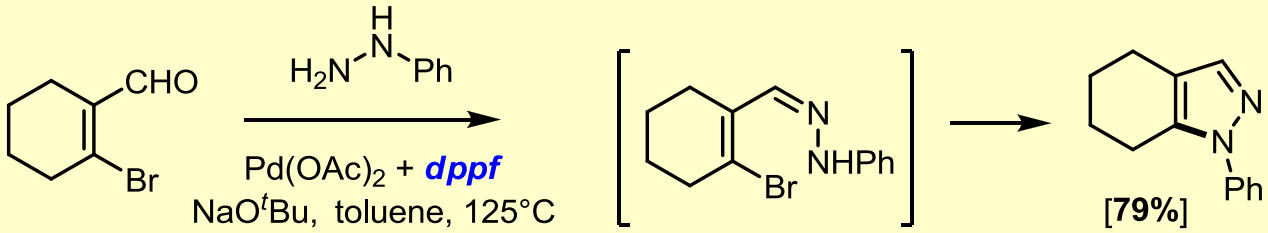
- ***Ar-Br ↔ intramolecular 2° amines, acylsulfonamides & carbamates (Pd):***
  - formation of 5-, 6-, and 7-membered rings
  - Buchwald *Angew. Chem., Int. Ed.* **1995**, *34*, 1348 (DOI); Buchwald *Tetrahedron* **1996**, *52*, 7525 (DOI); Buchwald *J. Am. Chem. Soc.* **1997**, *119*, 8451 (DOI); Buchwald *Org. Lett.* **1999**, *1*, 35 (DOI)

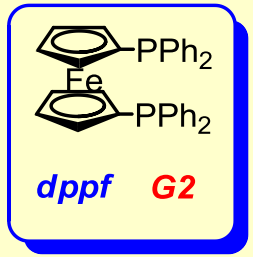


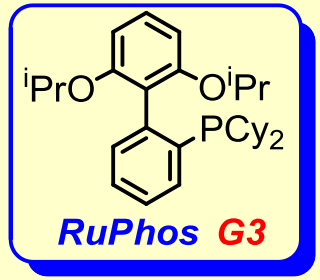




- ***vinyl-Br ↔ intramolecular aniline → pyrazoles (Pd):***
  - Cho *Tetrahedron* **2006**, *62*, 6388 (DOI)



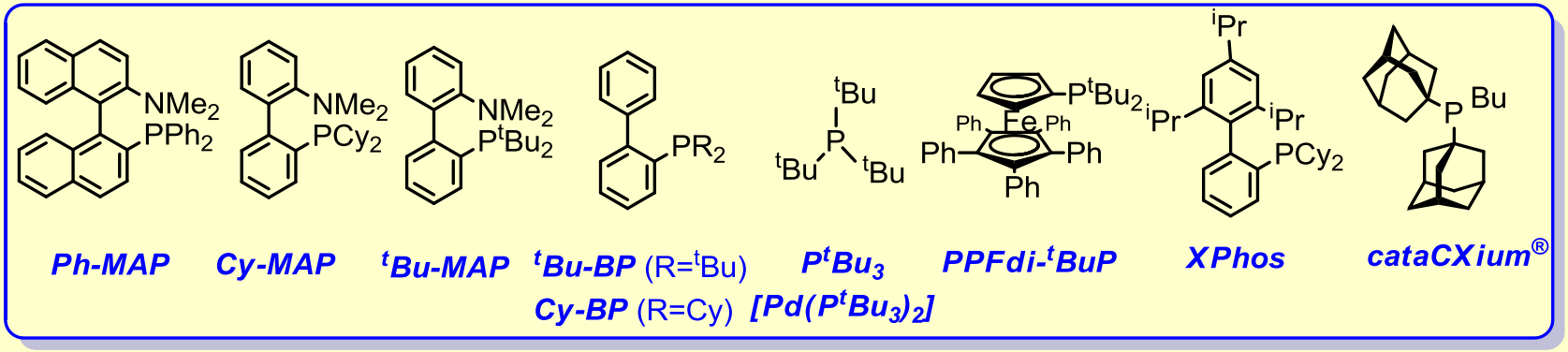




- ***Aryl bromide ↔ intramolecular aniline → benzimidazoles (Pd):***
  - Buchwald *Angew. Chem., Int. Ed.* **2007**, *46*, 7509 (DOI);

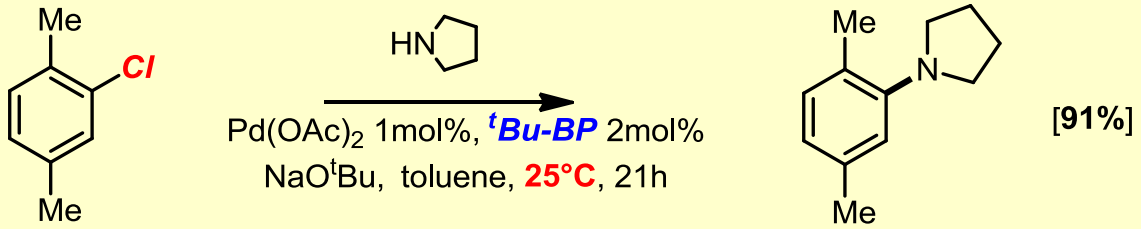


# *Inter*molecular coupling of 2° amines (Pd)

- ***Ar-Br & Ar-Cl ↔ 2° amines (Pd):*** review of (industrial) development: Buchwald *Adv. Synth. Catal*. **2006**, *348*, 23 (DOI)
  - ***G3 phosphine ligand systems***. ***Highlight:*** Stürmer *Angew. Chem. Int. Ed.* **1999**, *38*, 3307 (DOI)
  - ***Ph-MAP:*** Kocovsky *Tet. Lett*. **1998**, *39*, 9289 (DOI)
  - ***Cy-MAP:*** Buchwald *J. Am. Chem. Soc.* **1998**, *120*, 9722 (DOI)
  - ***$^t$Bu-MAP***, ***Cy-BP***, ***$^t$Bu-BP:*** Buchwald *Angew. Chem., Int. Ed.* **1999**, *38*, 2413 (DOI) & *J. Org. Chem.* **2000**, *65*, 1158 (DOI) & **2001**, 66, 3820 (solid-supported) (DOI) & *Org. Lett.* **2002**, *4*, 2885 (DOI)
  - ***P(tBu)$_3$:*** Nishiyama *Tet. Lett.* **1998**, *39*, 617 (DOI), & Hartwig *J. Org. Chem.* **1999**, *64*, 5575 (DOI) & **2002**, *67*, 6479 (DOI)
  - ***PPFditBuP:*** Hartwig *J. Org. Chem.* **2002**, *67*, 5553 (DOI)
  - ***azaphosphatranes:*** Verkade *Org. Lett.* **2003**, *5*, 815 (DOI) & *Org. Lett.* **2005**, *7*, 4427 (vinyl halides) (DOI)
  - ***XPhos:*** Buchwald *J. Am. Chem. Soc.* **2003**, *125*, 6653 (DOI) & *Org. Lett.* **2005**, *7*, 3965 (heteroaryl halides) (DOI)
  - ***cataCXium®:*** Beller *Tetrahedron* **2005**, *61*, 9705 (DOI)



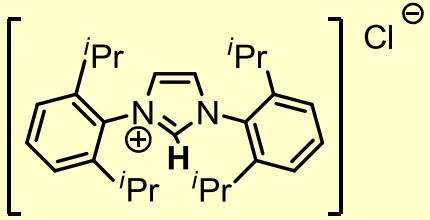

*e.g.*



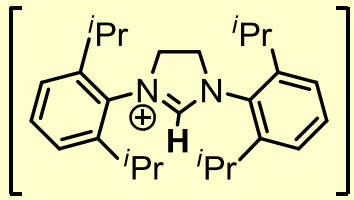

[**91%**]

# *Inter*molecular coupling of 2° amines (Pd) cont.

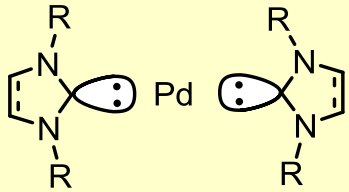
- ***Ar-Cl ↔ 2° amines (Pd):***
  - ***G3 N-heterocyclic carbene (NHC) ligand systems:***
  - ***in situ generation:*** Nolan *Org. Lett.* **1999**, *1*, 1307 (DOI); Nolan *J. Org. Chem.* **2001**, *66*, 7729 (DOI); Nolan *Org. Lett.* **2002**, *4*, 2229 (DOI); Hartwig *Org. Lett.* **2000**, *2*, 1423 (DOI)
  - ***pre-formed*:** Caddick *Org Biomol. Chem.* **2008**, *6*, 2820 (DOI) &*Chem. Commun.* **2001**, 1388 (DOI) & *Tetrahedron* **2005**, *61*, 9710 (DOI)
  - ***no catalyst!:*** using $CsOH{\cdot}H_2O$ in DMSO *via* arynes? Adapa *Synlett* **2004** 1747 (DOI)



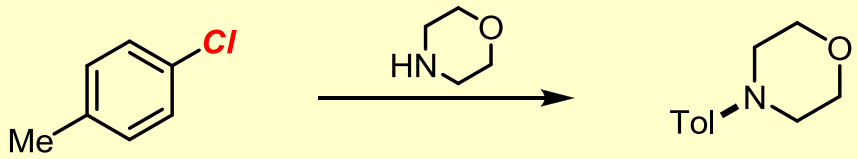

imidazolium salt ***NHC1***
(Nolan)



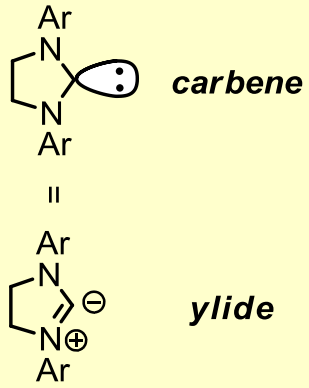

dihydroimidazolium salt ***NHC2***
(Hartwig)




R = 2,6-di($^i$Pr)$C_6H_3$ ***NHC3*** & R = *t*-Bu ***NHC4***
Pd(0) complexes (Caddick & Cloke)

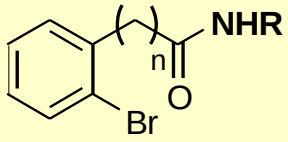



$Pd_2(DBA)_3$, ***NHC1*** 1mol%, KO$^t$Bu, 1,4-dioxane, **100°C**: [**100%**]
$Pd(DBA)_2$ 1mol%, ***NHC2*** 1mol%, NaO$^t$Bu, DME, **25°C**: [**82%**]
***NHC3*** 1mol%, KO$^t$Bu, 1,4-dioxane, **100°C**: [**99%**]



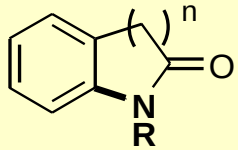
# *Intra*- & *inter*molecular coupling of amides (Pd)

- ***Ar-Br ↔ intramolecular amides (Pd):***
  - formation of 5-, 6-, and 7-membered rings
  - Buchwald *Tetrahedron* **1996**, *52*, 7525 (DOI) & *Org. Lett.* **1999**, *1*, 35 (DOI)

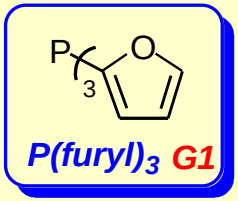



R = Me, Bn, $^t$Bu

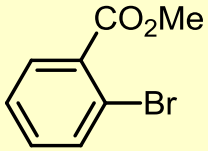
$Pd_2(DBA)_3$ + **P(*o*-Tol)$_3$** or **P(furyl)$_3$**
$K_2CO_3$ or $Cs_2CO_3$, toluene, 110°C

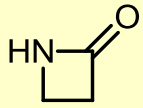



n = 1 [**59-99%**]
n = 2 [**44-82%**]
n = 3 [**5-44%**]

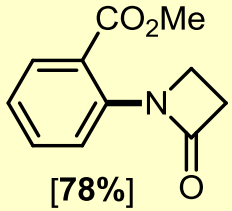



- ***Ar-Br ↔ intermolecular lactams (Pd):***
  - Buchwald *Org. Lett.* **2000**, *2*, 1101 (DOI); Buchwald *J. Am. Chem. Soc.* **2002**, *124*, 6043 (DOI)
  - with ***ureas***: Beletskaya *Tet. Lett.* **2001**, *42*, 4381 (DOI); Kotecki *Org. Lett.* **2009**, *11*, 947 (DOI)

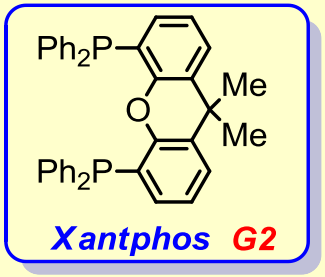


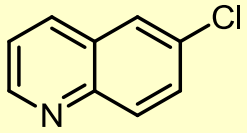

$Pd_2(OAc)_2$ + **Xantphos**
$Cs_2CO_3$, 1,4-dioxane, 100 °C

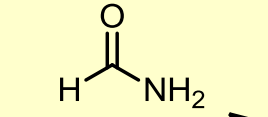



[**78%**]

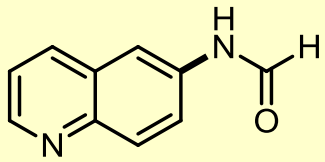



- ***Ar-Cl ↔ intermolecular 1° amides and sulfonamides (Pd):***
  - *NB.* Me group α to phosphine prevents κ$^2$-amidate
  - Buchwald *J. Am. Chem. Soc.* **2007**, *129*, 13001 (DOI) & *Tetrahedron* **2009**, *65*, 6576 (DOI)

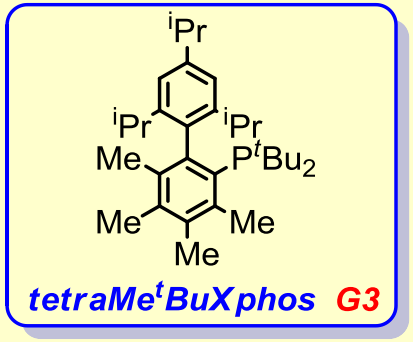



$Pd_2dba_3$ + **tetraMe$^t$BuXphos**
$K_3PO_4$, $^t$BuOH, RT

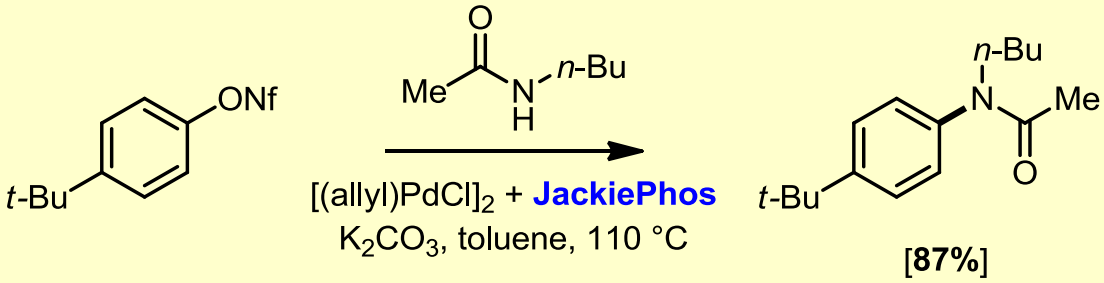


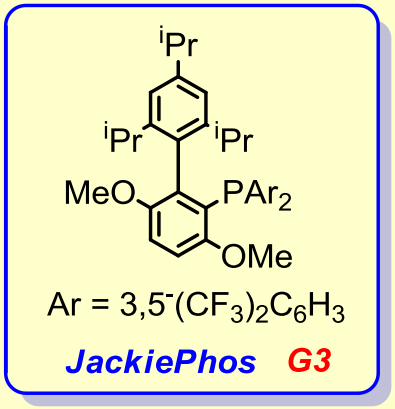

[**85%**]

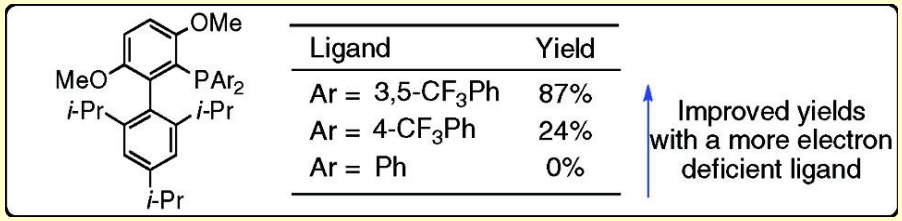


# *Inter*molecular coupling of amides (Pd) – *state-of-the-art*

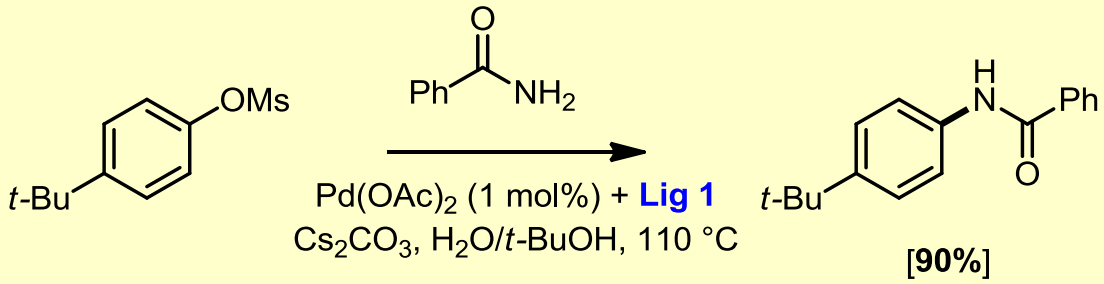
- ***Ar-ONf, Ar-OTf, Ar-Cl ↔ intermolecular 2° amides (Pd):***
  - New, electron deficient ligand important for amide bonding to $Pd^{II}$ intermediate (by DFT)
  - Buchwald *J. Am. Chem. Soc.* **2009**, *131*, 16720 (DOI)

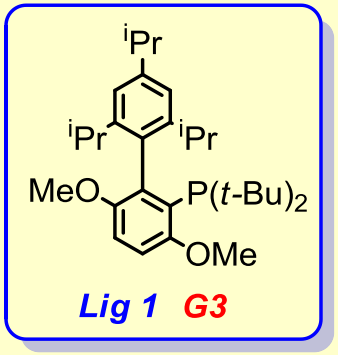


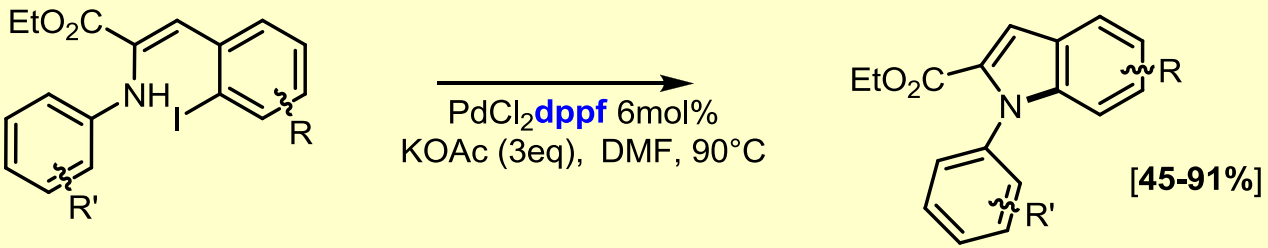

- ***Ar-OMs ↔ intermolecular 1° amides (Pd):***
  - Buchwald *Org. Lett.* **2010**, *12*, 2350 (DOI)

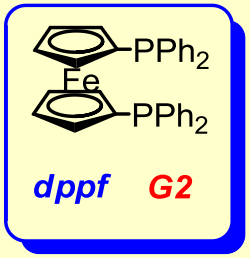


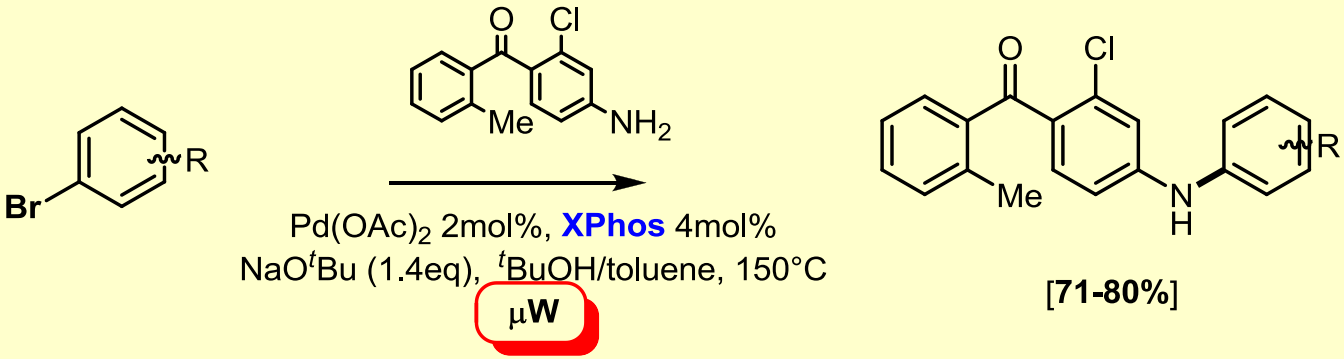
# *Intra-* & *inter*molecular coupling of anilines (Pd)

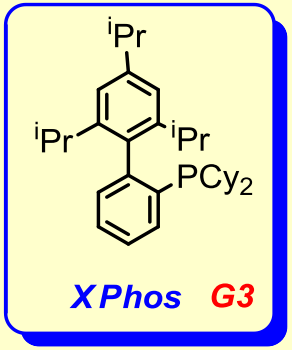
- ***Ar-I ↔ intramolecular aniline (Pd) – indole synthesis:***
  - Brown *Tet. Lett.* **2000**, *41*, 1623 (DOI)



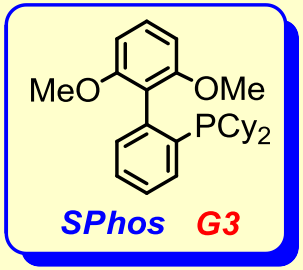




- ***Ar-Br/Cl ↔ intermolecular aniline (Pd) – synthesis of EO-1221 analogues (p38a MAP kinase inhibitors):***
  - Skjaerbaek *J. Org. Chem.* **2004**, *69*, 4936 (DOI)



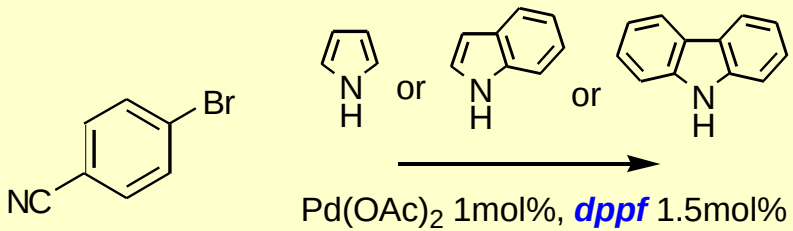



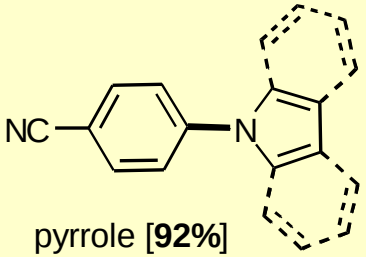

- ***Ar-Cl ↔ intermolecular aniline (in presence of aliphatic amines)***
  - Buchwald *Angew. Chem., Int. Ed.* **2007**, *46*, 7232 (DOI) – using ***SPhos***
- ***Ar-Br ↔ intramolecular aniline (Pd) – synthesis of peptidic marcocycles:***
  - Iqbal *J. Org. Chem.* **2006**, *71*, 8954 (DOI)



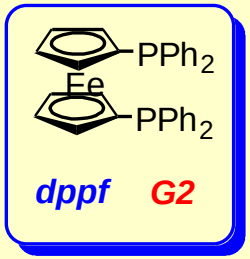
# *Inter*molecular coupling of azoles (Pd)

- ***Ar-Br ↔ azoles (Pd):***
  - ***dppf:*** Hartwig *J. Am. Chem. Soc.* **1998**, *120*, 827 (DOI)
  - ***P$^t$Bu$_3$:*** Hartwig *J. Org. Chem.* **1999**, *64*, 5575 (DOI) & Watanabe *Tet. Lett.* **2000**, *41*, 481 (DOI)
  - ***Cy-MAP:*** Buchwald *Org. Lett.* **2000**, *2*, 1403 (DOI)



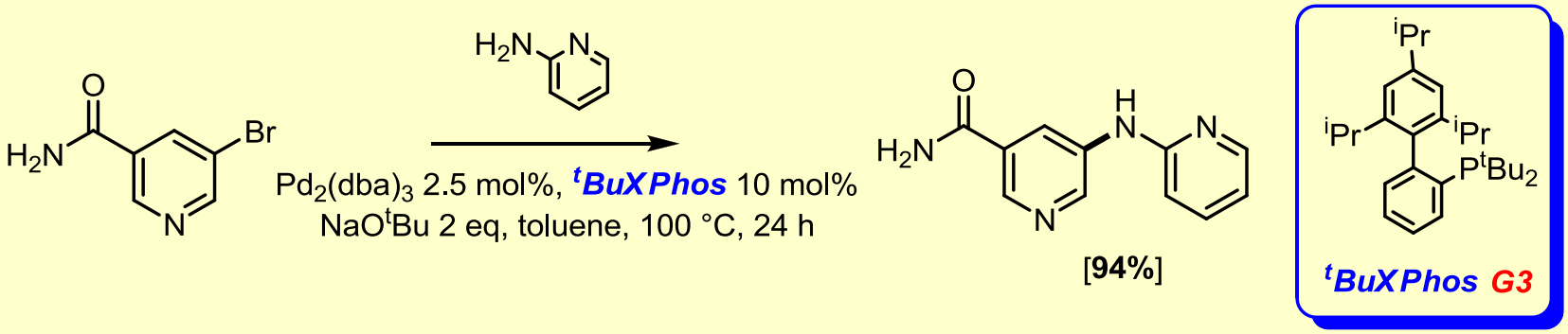




pyrrole [**92%**]
indole [**98%**]
carbazole [**90%**]

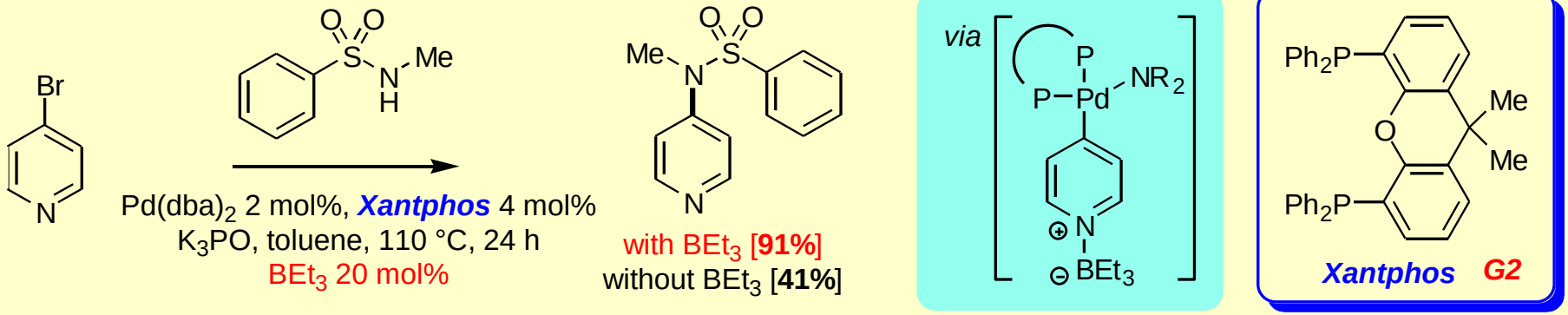


# *Inter*molecular coupling of amino- & haloazines (Pd)

- ***2-Br-pyridines ↔ volatile amines (Pd):***
  - ***dppp:*** Li *J. Org. Chem.* **2007**, *72*, 3606 (DOI)
- ***azine-Br/azine-Cl ↔ azine-$NH_2$ (Pd):***
  - ***$^t$Bu-BA:*** Buchwald *Angew. Chem. Int. Ed.* **2006**, *45*, 6523 (DOI)
  - See also: Hartwig *Org. Lett*. **2008**, *10*, 4109 (DOI) – using ***Josiphos [(CyPF-tBu)$PdCl_2$]*** which is air stable

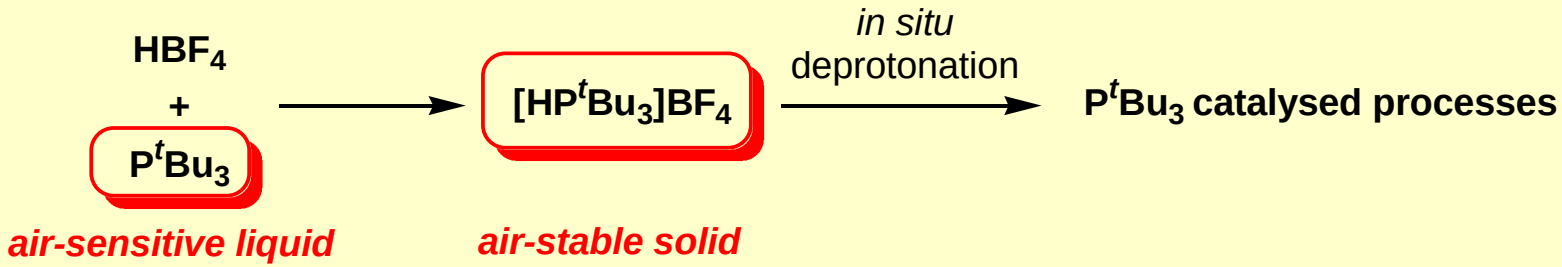



- ***Lewis acid acceleration of Red. Elim. for azine halide substrates (Pd):***
  - Hartwig *J. Am. Chem. Soc.* **2007**, *129*, 7734 (DOI)

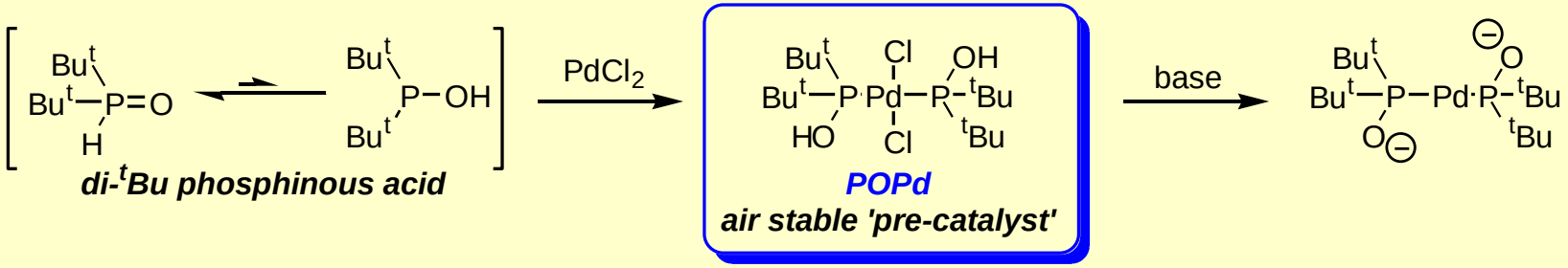


# Air-stable trialkylphosphonium salts & pre-catalysts

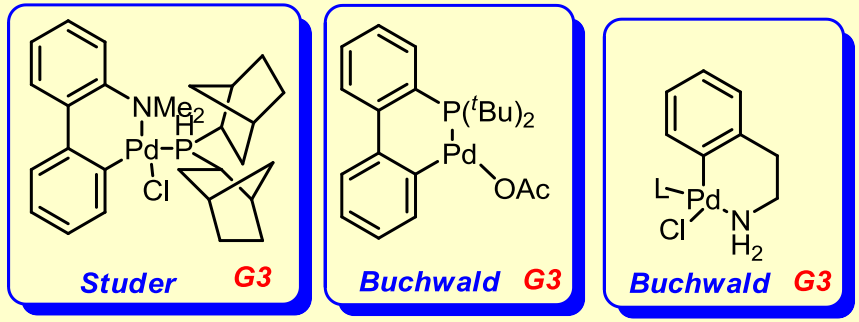
- ***phosphonium salts as practical replacements for air-sensitive alkyl phosphines:***
  - Fu *Org. Lett.* **2001**, *3*, 4295 (DOI)




- ***air stable Pd(II)-phosphinous acid complexes:***
  - Li *Angew. Chem. Int. Ed.* **2001**, *40*, 1513 (DOI); Li *J. Org. Chem.* **2001**, *66*, 8677 (DOI)

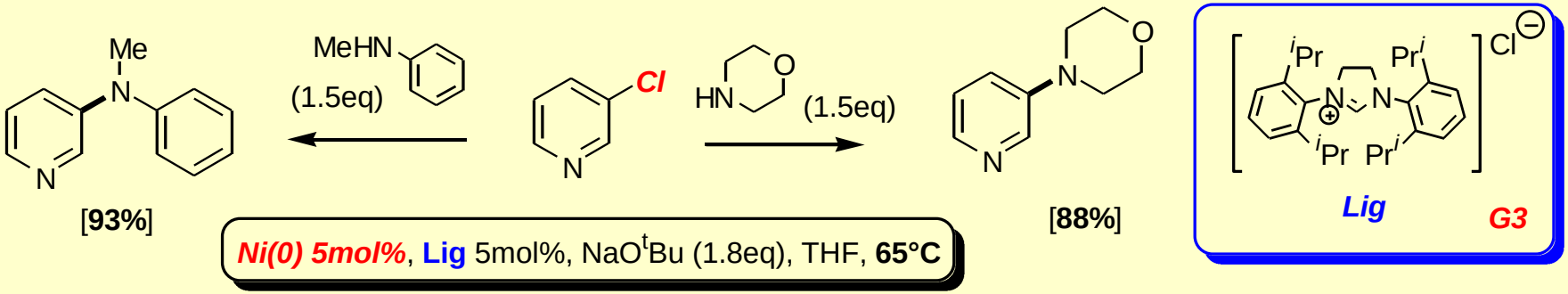



- ***air stable palladacycles:***
  - Studer *Angew. Chem. Int. Ed.* **2002**, *41*, 3668 (DOI)
  - Buchwald *Org. Lett.* **2003**, *5*, 2413 (DOI)
  - Buchwald *J. Am. Chem. Soc.* **2008**, *130*, 6686 (DOI)



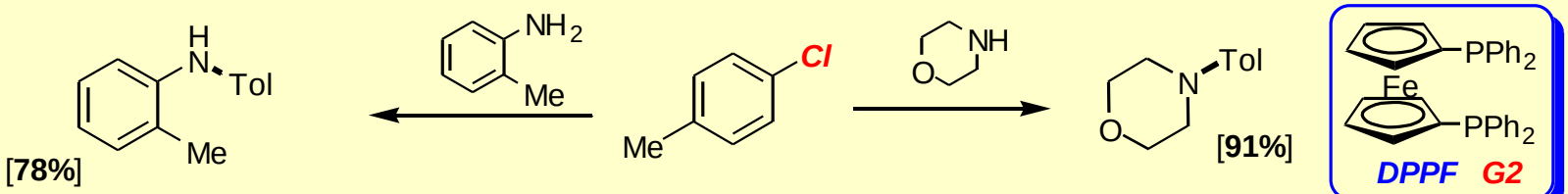
# Ni catalysis

- ***Ar-Cl ↔ intra- & intermolecular 2° amines & anilines (Ni):***
  - Fort *J. Org. Chem.* **2002**, *67*, 3029 (DOI); Fort *Org. Lett.* **2003**, *5*, 2311 (DOI)




***Ni(0) 5mol%***, **Lig** 5mol%, NaO$^t$Bu (1.8eq), THF, **65°C**

- ***Ar-Cl ↔ 2° amines & anilines (Ni/C):***
  - ***heterogeneous catalysis:***
  - Lipschutz *Angew. Chem. Int. Ed.* **2000**, *39*, 4492 (DOI); Lipschutz *J. Org. Chem.* **2003**, *68*, 1190 (DOI)



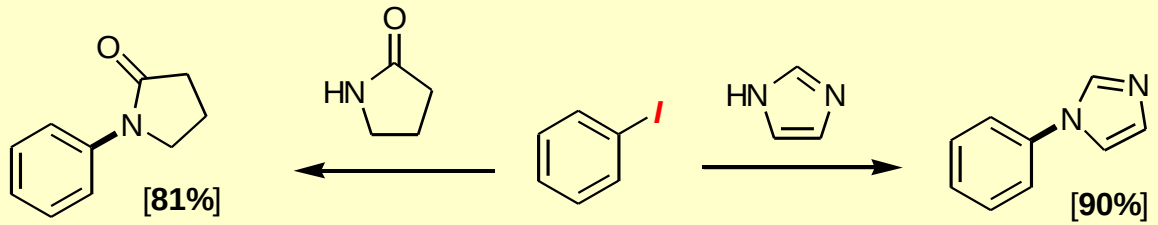

***conditions:*** ***Ni/C 2-10 mol%***, **DPPF** 4-20 mol%, LiO$^t$Bu, 1,4-dioxane, 130°C

  - See also: Knochel *J. Org. Chem.* **2008**, *73*, 1429 (DOI) – Ni(acac)$_2$/PMHS

# Fe catalysis

- ***Ar-Br/Ar-I ↔ azoles & 2° amides (Fe/Cu):***
  - ***cheap and commercially available catalyst/ligands***
  - Taillefer *Angew. Chem. Int. Ed.* **2007**, *46*, 934 (DOI)

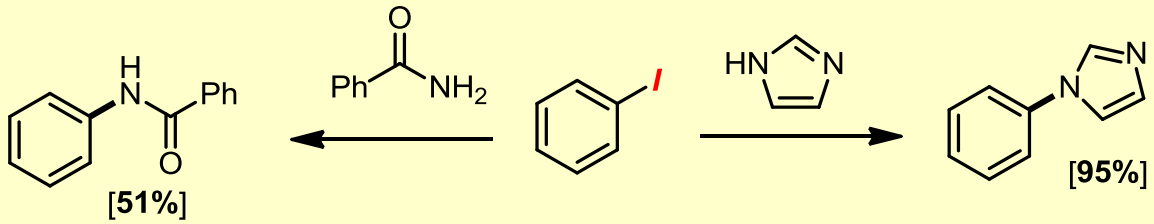
***e.g.***




***conditions:*** ***$Fe(acac)_3$ 30 mol%, CuO 10 mol%***, $Cs_2CO_3$ 2 eq, DMF, 90 °C, 30 h

- ***Ar-Br/Ar-I ↔ azoles, anilines, 1° amines, 2° amines & 1° amides (Fe):***
  - ***Ligand free, graphite-supported Fe (filter off and use for up to 5 cycles)***
  - Rao *J. Org. Chem.* **2009**, *74*, 7514 (DOI)

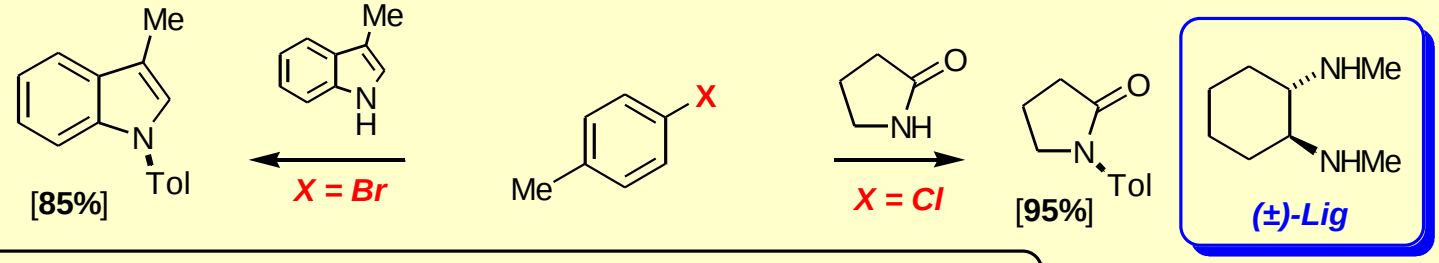
***e.g.***




***conditions:*** ***Fe/Cg 5 wt%***, KOH 2 eq, DMSO, 120 °C, 24 h

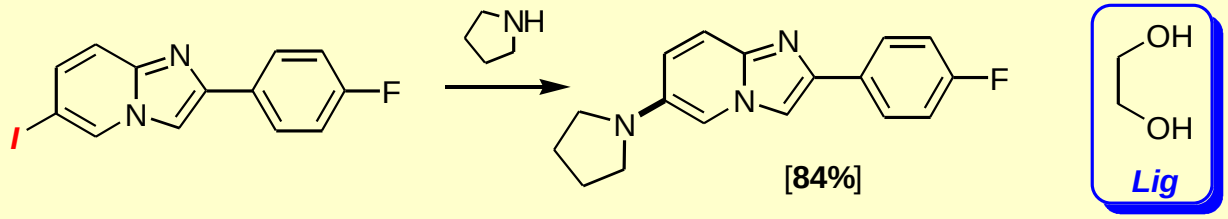
# Cu catalysis

- ***Ar-Cl ↔ 2° amines, anilines, amides & azoles (Cu):***
  - ***catalytic Goldberg coupling - review:*** Kunz *Synlett* **2003**, 2428 (DOI); ***mechanism:*** Buchwald *J. Am. Chem. Soc.* **2009**, *131*, 78 (DOI) & *J. Am. Chem. Soc.* **2005**, *127*, 4120 (DOI); ***comparison of ligands:*** Wiederman *Tet. Lett*. **2006**, *47*, 6011 (DOI)
  - ***diamine ligands:*** Buchwald *J. Am. Chem. Soc.* **2001**, *123*, 7727 (DOI), Buchwald *J. Am. Chem. Soc.* **2002**, *124*, 7421 (DOI); Buchwald *J. Am. Chem. Soc.* **2002**, *124*, 11684 (DOI), Kang *Synlett* **2002**, 427 (DOI), Buchwald *J. Org. Chem*. **2004**, *69*, 5578 (DOI), You *J. Org. Chem.* **2007**, *72*, 2737 (DOI), Mino *Synlett* **2008**, 614 (DOI)




***conditions:*** ***CuI 1 mol%***, **Lig** 10 mol%, $K_3PO_4$ 2eq, 1,4-dioxane, **110 °C**

  - ***diol & triol ligands:*** Buchwald *Org. Lett.* **2002**, *4*, 581 (DOI), Buchwald *J. Org. Chem.* **2003**, *68*, 4367 (DOI), Chen *Org. Lett*. **2007**, *8*, 5609 (DOI); ***MW acceleration*** see: Lange *Tet. Lett.* **2002**, *43*, 1101 (DOI); ***solvent free*** see: Li *J. Org. Chem*. **2006**, *71*, 8324 (DOI)

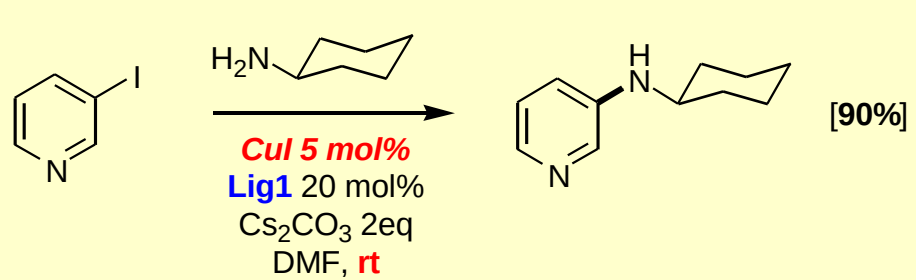



***conditions:*** ***CuI 10 mol%***, **Lig** 200 mol%, $K_3PO_4$ 2eq, IPA, **110 °C**

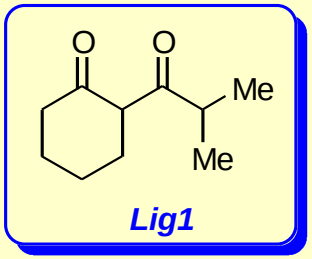
  - ***benzotriazole ligand:*** Verma *Tet. Lett*. **2007**, *48*, 4207 (DOI); ***amino acid ligands:*** Ma *J. Org. Chem.* **2005**, *70*, 5164 (DOI); ***diazaphospholane ligand:*** Liu *J. Org. Chem.* **2007**, *72*, 8969 (DOI); ***N-hydroxyimide ligand:*** Jiang *J. Org. Chem.* **2007**, *72*, 8943 (DOI); ***pyrrole-2-carboxylic acid ligand:*** Buchwald *J. Org. Chem.* **2008**, *73*, 5167 (DOI); ***ligand free:*** You *J. Org. Chem*. **2009**, *74*, 2200 (DOI); with MW acceleration: Wu *Tet. Lett.* **2003**, *44*, 3385 (***sulfonamides***) (DOI)

# Cu catalysis *state-of-the-art*

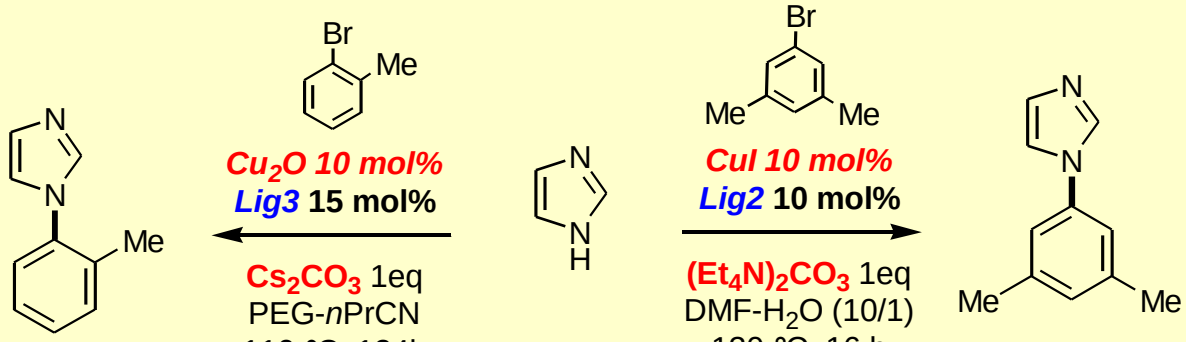
- ***Ar-I ↔ 1°/2° amines, anilines at RT (Cu):***
  - Buchwald *J. Am. Chem. Soc.* **2006**, *128*, 8742 (DOI) [& Liu *Angew. Chem. Int. Ed*. **2009**, *48*, 1 (DOI) using organic ionic base]




[**90%**]

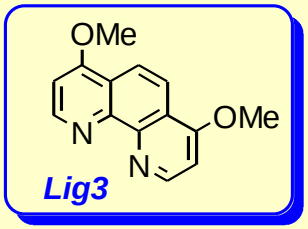



- ***Ar-Br/Ar-I ↔ imidazoles (Cu):***
  - Buchwald *Org. Lett.* **2006**, *8*, 2779 (***Lig2***) (DOI), Liu *J. Org. Chem.* **2005**, *70*, 10135 (***Lig3***) (DOI), Buchwald *J. Org. Chem.* **2007**, *72*, 6190 (DOI)




[**85%**]

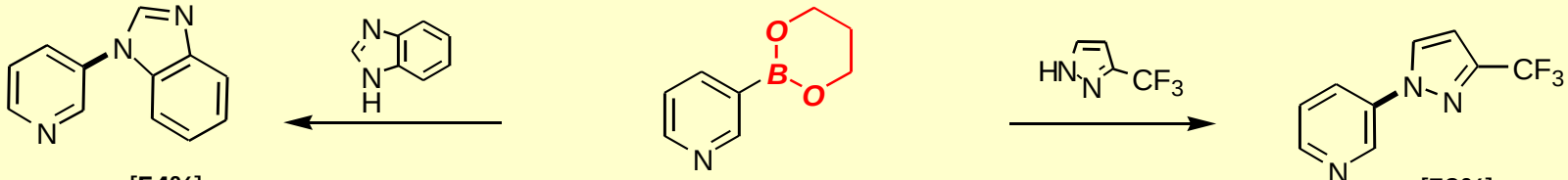
[**80%**]

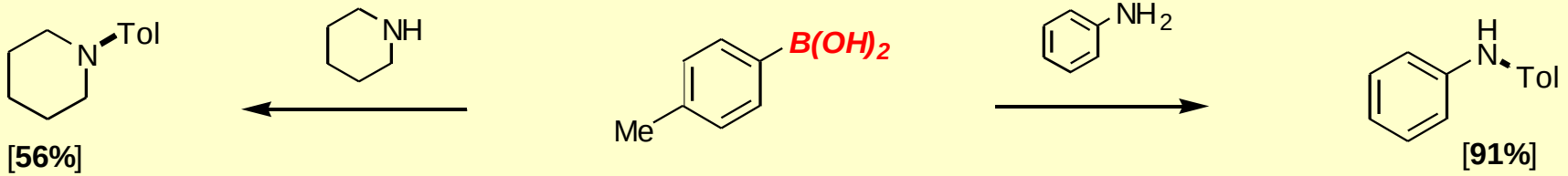

- ***Ar-Br/Ar-I ↔ R-NH$_2$ in water (Cu):*** Wan *Synthesis* **2006**, 3955 (DOI)
- ***Ar-Br/Cl ↔ imidazoles no ligand (Cu):*** You *J. Org. Chem.* **2007**, *72*, 8535 (DOI)

# Cu catalysed amination of boronic acids

- ***stoichiometric*: $Cu(OAc)_2$ promoted amination of boronic acids with amines, sulfonamides, carbamates amides, imides, and ureas:**
  - Chan *Tet. Lett*. **1998**, *39*, 2933 [Cu(II)] (DOI); Lam *Tet. Lett.* **1998**, *39*, 2941 [Cu(II)] (DOI); Lam *Synlett* **2000**, 674 [Cu(II), also ***stannanes***] (DOI); Chan *Tet. Lett.* **2003**, *44*, 3863 (DOI); Gundersen *Tet. Lett.* **2003**, *44*, 3359 (DOI); Lam *J. Combi. Chem.* **2000**, *2*, 29 [Cu(II), on solid phase] (DOI); Sreedhar *Synthesis* **2008**, 795 (DOI)



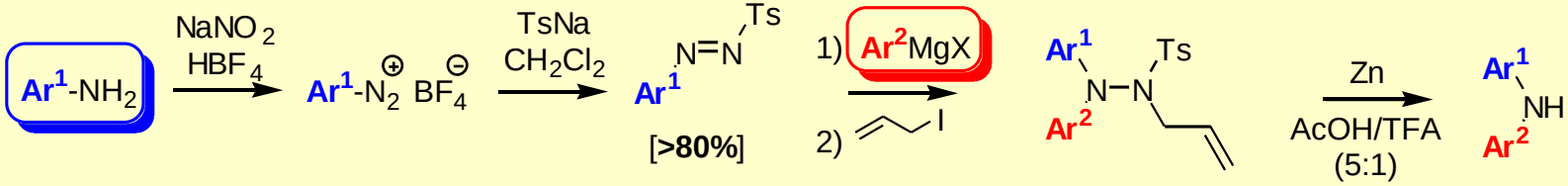

  - ***siloxanes:*** Lam *J. Am. Chem. Soc.* **2000**, *122*, 7600 (DOI); ***iodonium salts:*** Kang *Synlett* **2000** 1022 (DOI)
- ***catalytic*: $Cu(OAc)_2$ catalysed amination of boronic acids with amines and anilines:**
  - Collman *Org. Lett.* **2000**, *2*, 1233 [Cu(I)] (DOI); Collman *J. Org. Chem.* **2001** *66*, 1528 [Cu(I)] (DOI); Buchwald *Org. Lett.* **2001**, *3*, 2077 [Cu(II)] (DOI); Lam *Tet. Lett.* **2001**, *42*, 3415 [Cu(II)] (DOI); van Strijdonck *Tet. Lett.* **2004**, *45*, 7659 [Cu(II)] (DOI); Chiang *Org. Lett.* **2004**, *6*, 3079 [Cu(II), on solid phase] (DOI)



# C-N bond formation – *electrophilic amination*

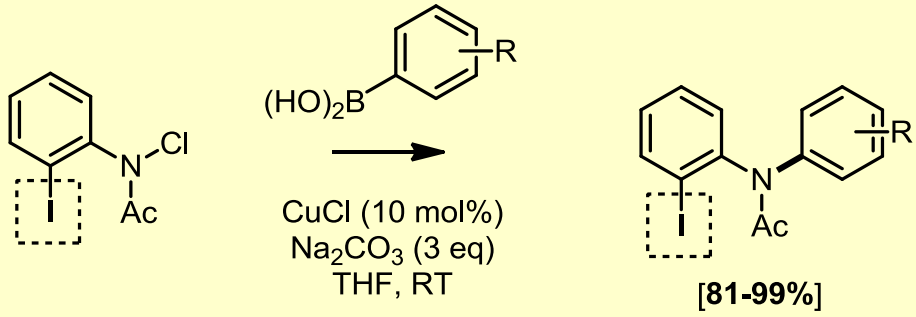
- ***aryl Grignard reagents + nitroarenes:***
  - Knochel *J. Am. Chem. Soc.* **2002**, *124*, 9390 (DOI) (*NB.* requires 2 eq of Grignard reagent)

- ***aryl & alkyl Grignard reagents + arylazo tosylates:***
  - Knochel *Angew. Chem. Int. Ed.* **2004**, *43*, 897 (DOI)



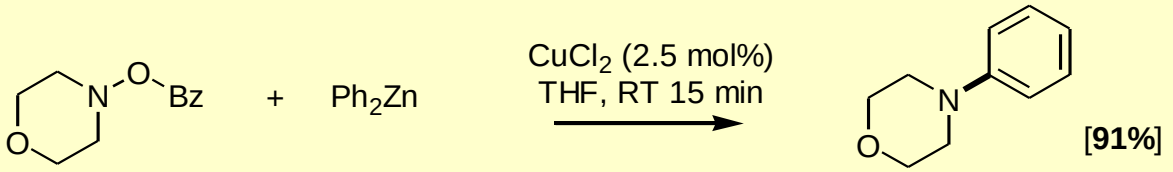

- ***oxidative coupling of aryl Cuprate reagents + lithium amides:***
  - Knochel *Angew. Chem. Int. Ed.* **2006**, *45*, 7838 (DOI) & Knochel *Synthesis* **2007**, 1272 (DOI)

- ***aryl boronic acids + N-chloroamides with CuCl catalysis:***
  - Lei *Angew. Chem. Int. Ed.* **2008**, *47*, 6414 (DOI)

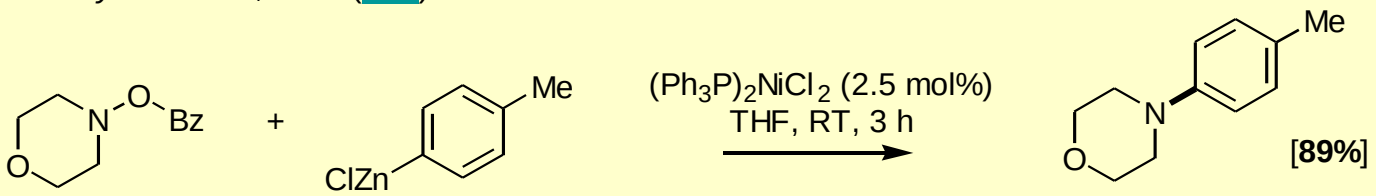


# C-N bond formation – *electrophilic amination*

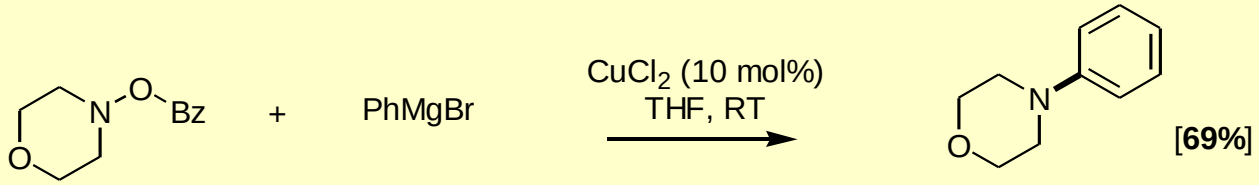
- ***$R_2Zn$ + O-benzoylhydroxylamines with $CuCl_2$ (cat.):***
  - Johnson *J. Am. Chem. Soc.* **2004**, *126*, 5680 (DOI) & *J. Org. Chem.* **2005**, *70*, 364 (DOI) & *J. Org. Chem.* **2006**, *71*, 219 (DOI)




- ***RZnX + O-benzoylhydroxylamines with $Ni(PPh_3)_2Cl_2$ (cat.):***
  - Johnson *Synlett* **2005**, 1799 (DOI)



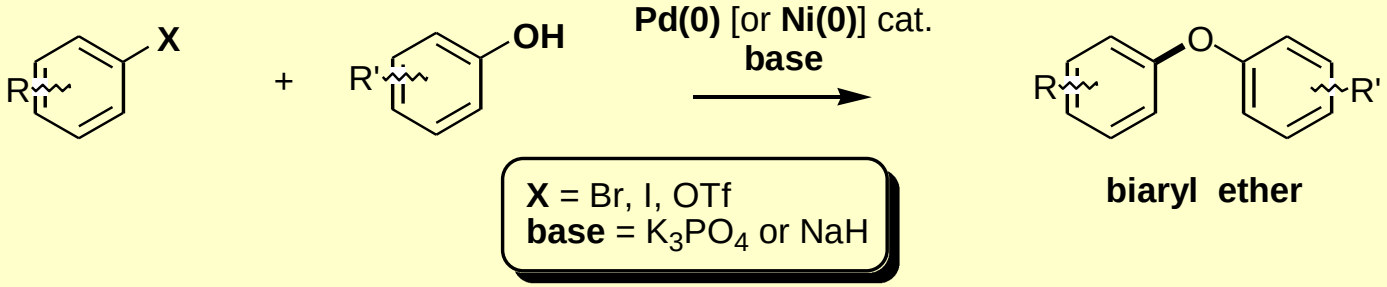

- ***RMgX + O-benzoylhydroxylamines with $CuCl_2$ (cat.):***
  - Johnson *Org. Lett.* **2007**, *9*, 1521 (also mechanistic studies confirm $S_N2$) (DOI)



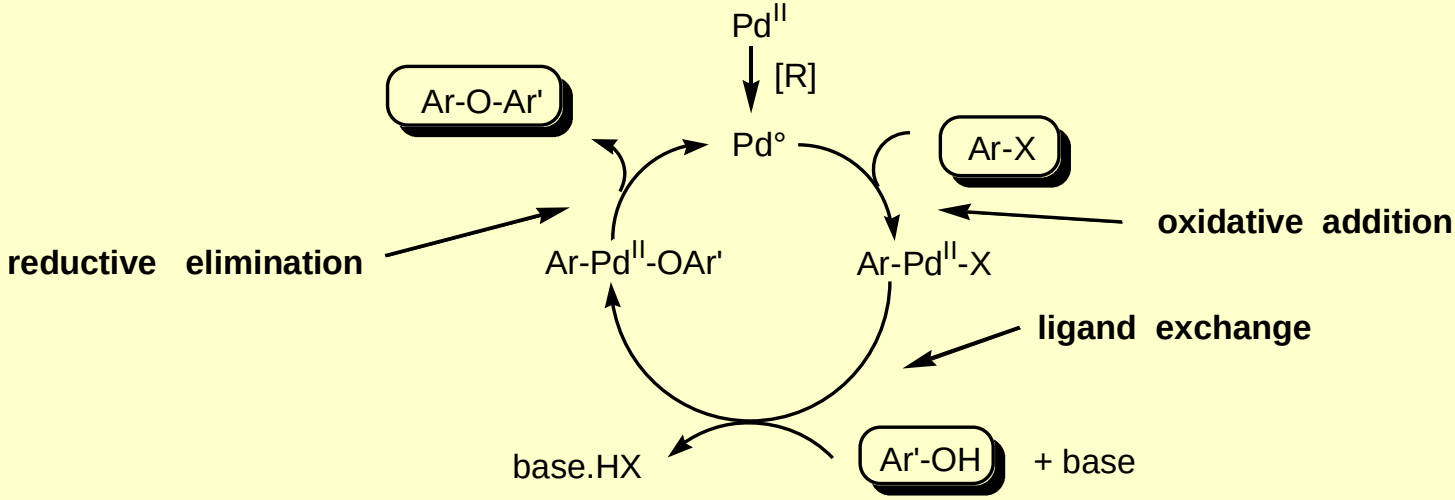
# Pd, Ni & Cu catalysed C-O cross-coupling

# C-O bond cross-coupling - overview

- ***prior art:*** *the copper mediated Ullmann biaryl ether synthesis*
- ***reviews:*** Kikelj *Synthesis* **2006**, 2271 (DOI); Thomas *Angew. Chem. Int. Ed.* **2003**, *42*, 5400 (DOI); Sawyer *Tetrahedron* **2000**, *56*, 5045 (DOI); Theil *Angew. Chem. Int. Ed.* **1999**, 38, 2345 (DOI); Hartwig *Angew. Chem. Int. Ed.* **1998**, 37, 2046 (DOI); Frost *J. Chem. Soc., Perkin Trans. 1* **1998**, 2615 (DOI); Hartwig *Synlett* **1997**, 329 (DOI)
- ***overall scheme:***

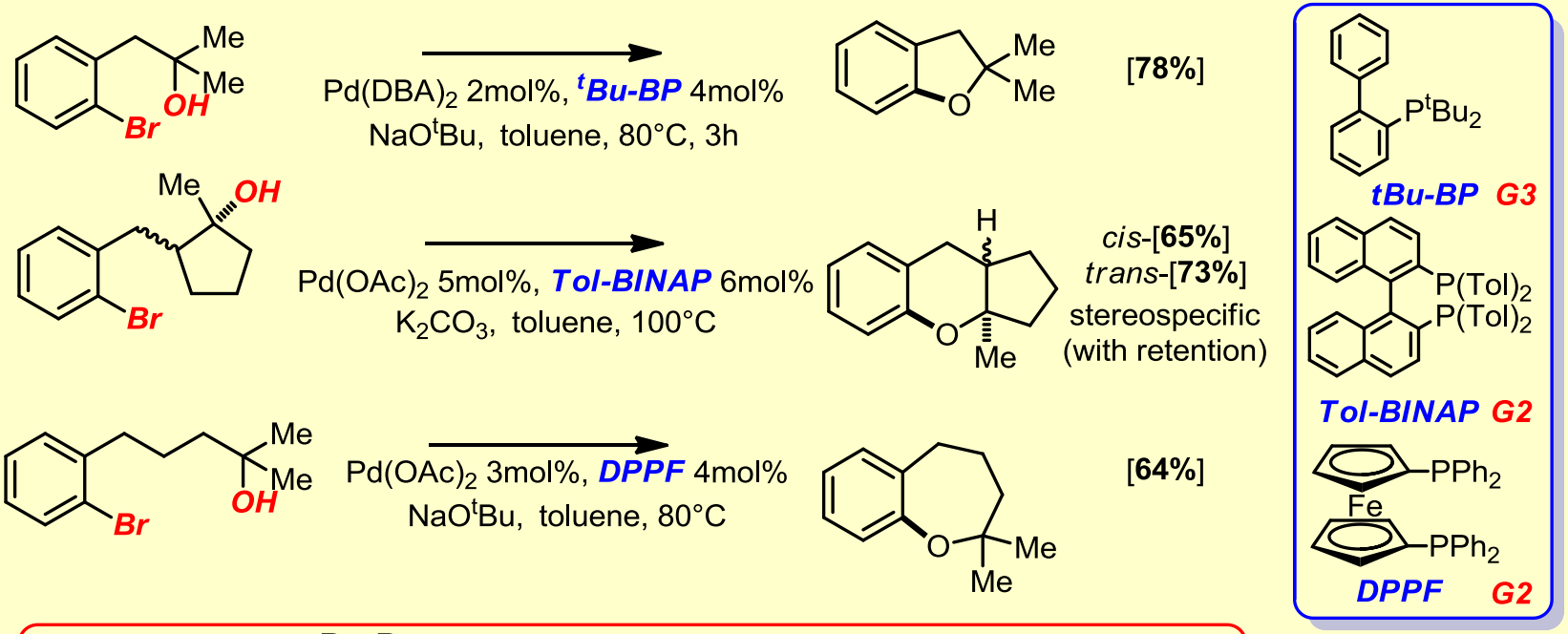



- ***mechanism:***



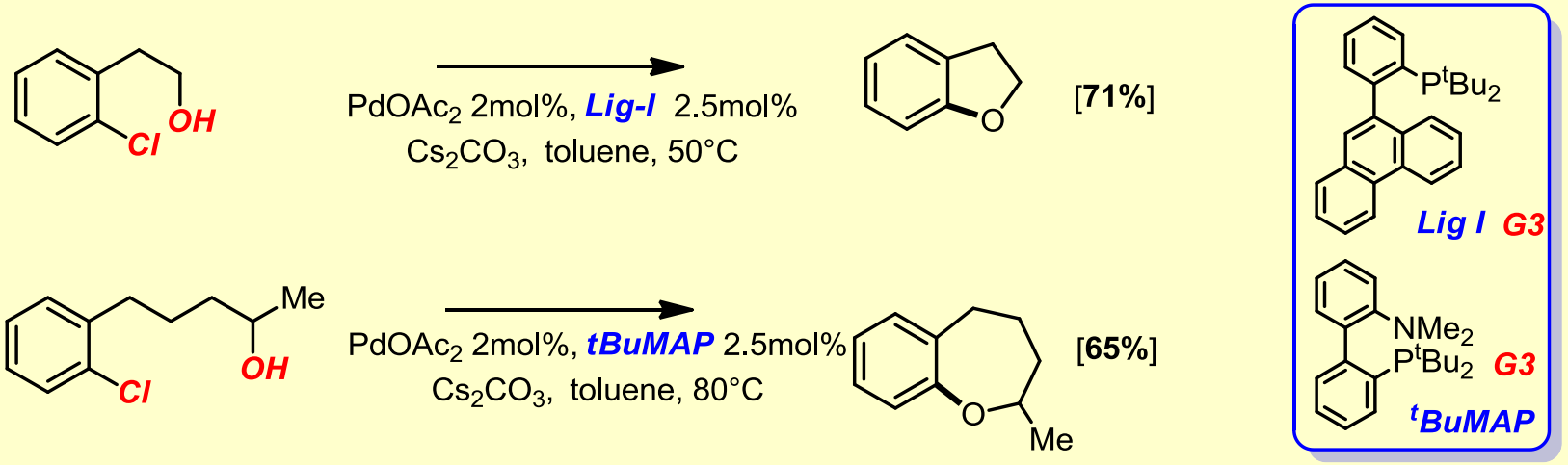
# *Intra*molecular coupling of 3° alcohols (Pd)

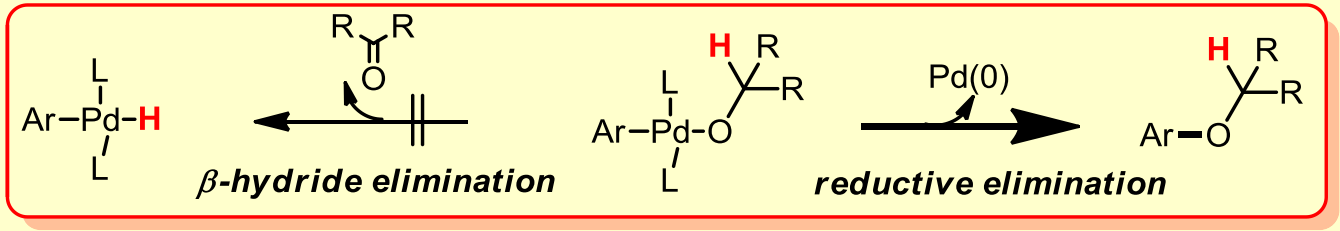
- ***Ar-Br ↔ intramolecular 3° alcohols (Pd):***
  - formation of 5-, 6-, and 7-membered rings
  - ***BINAP*** or ***DPPF***: Buchwald *J. Am. Chem. Soc.* **1996**, *118*, 10333 (DOI)
  - ***$^{t}$Bu-BP***: Hartwig *J. Am. Chem. Soc.* **1999**, *121*, 3224 (DOI)



# *Intra*molecular coupling of 1°/2° alcohols (Pd)

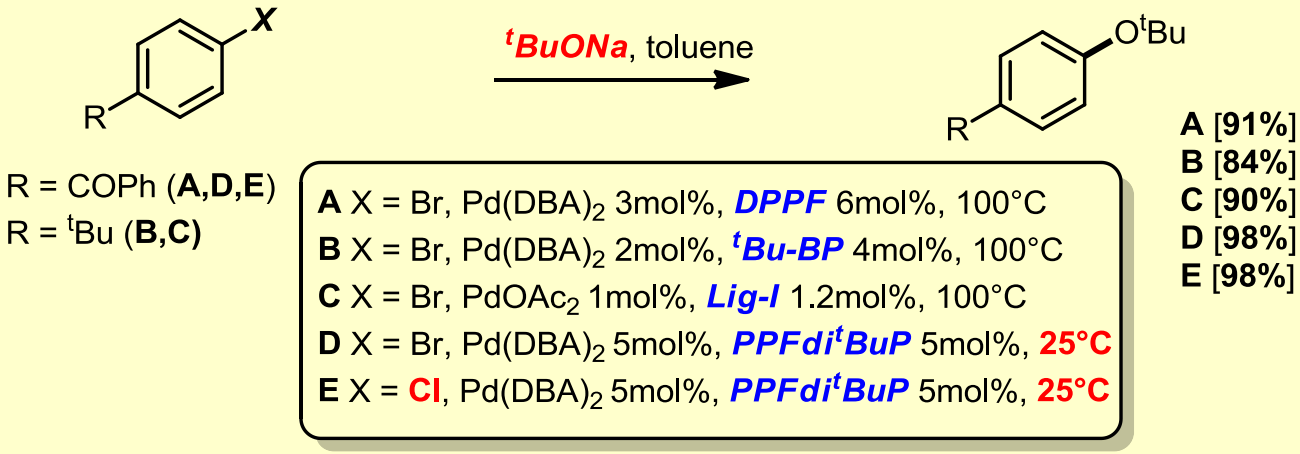
- ***Ar-Cl ↔ intramolecular 1° and 2° alcohols (Pd):***
  - formation of 5-, 6-, and 7-membered rings
  - Buchwald *J. Am. Chem. Soc.* **2000**, *122*, 12907 (DOI); Buchwald *J. Am. Chem. Soc.* **2001**, *123*, 12202 (DOI)

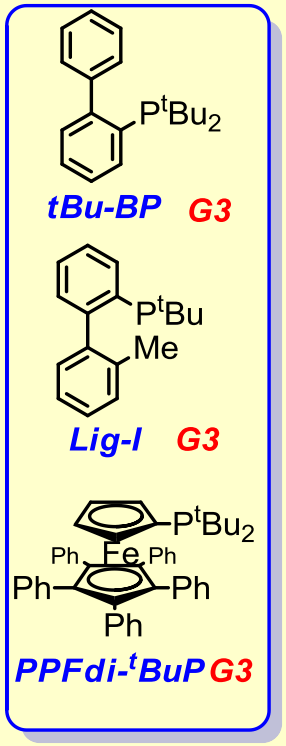


# *Inter*molecular coupling of 3° alcohols/silanols (Pd)

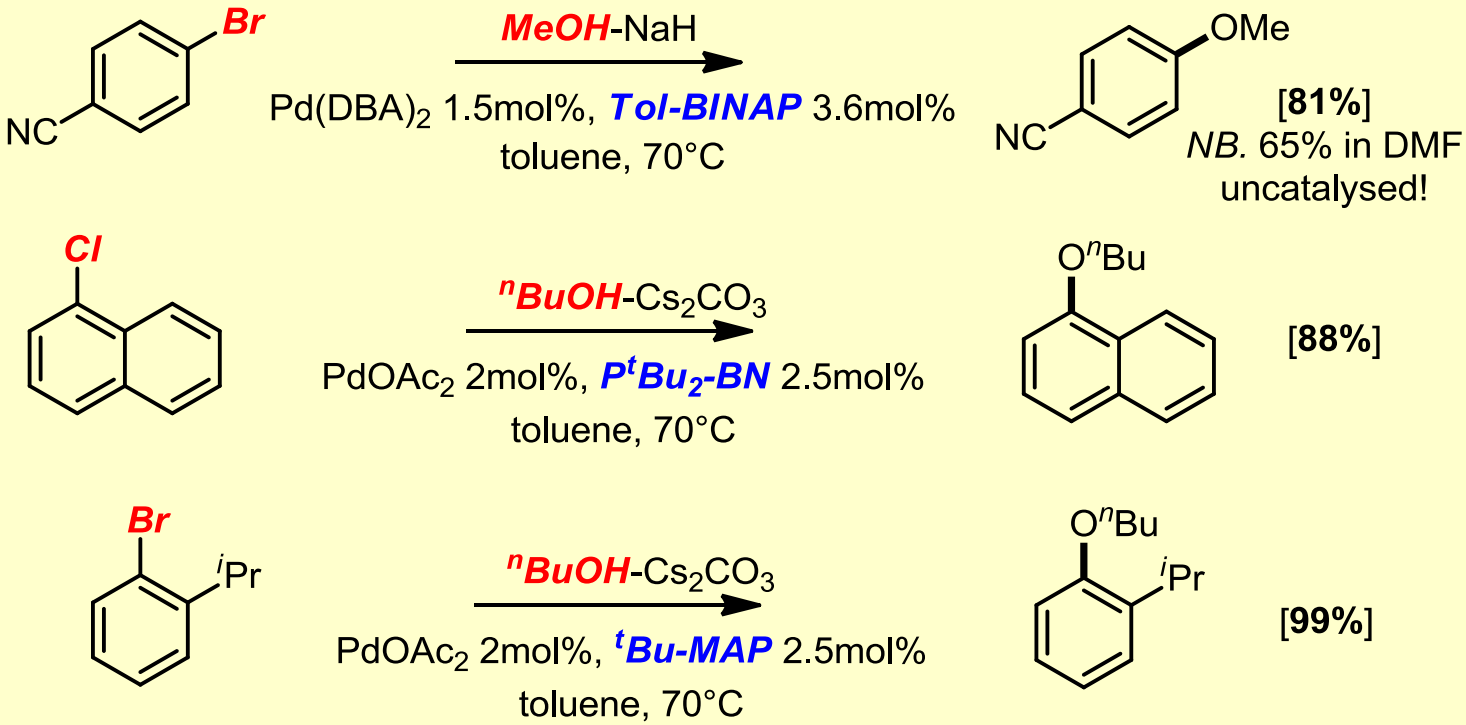
- ***Ar-Br ↔ intermolecular 3° alkyl- and silanols (Pd & Ni):***
  - ***$^t$Bu/Ar ethers***, Pd(0), ***DPPF***: Hartwig *J. Am. Chem. Soc.* **1996**, *118*, 13109 (DOI)
  - ***$^t$Bu/Ar ethers***, Pd(0), ***$^t$Bu-BP***: Hartwig *J. Am. Chem. Soc.* **1999**, *121*, 3224 (DOI)
  - ***$^t$Bu/Ar ethers***, Pd(0), ***Lig-I***: Buchwald *J. Org. Chem.* **2001**, *66*, 2498 (DOI)
  - ***alkyl or silyl/Ar ethers***, Ni(0), ***DPPF***: Hartwig *J. Org. Chem.* **1997**, *62*, 5413 (DOI)
  - ***$^t$Bu and silyl/Ar ethers***, Pd(0), ***PPFdi-tBuP***: Hartwig *J. Am. Chem. Soc.* **2000**, *122*, 10718 (DOI)

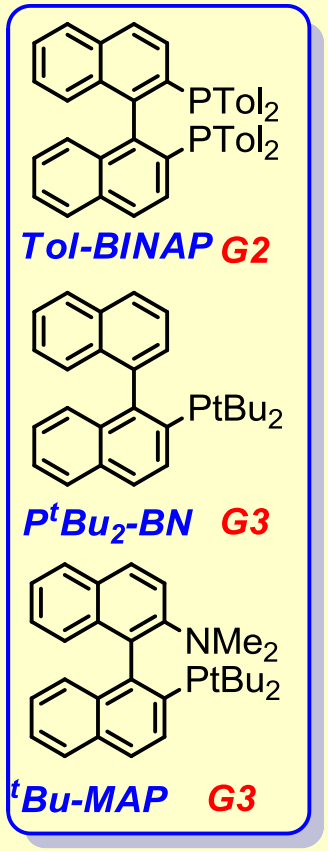


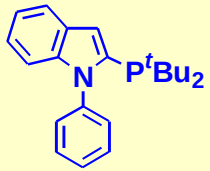
# *Inter*molecular coupling of 1° alcohols (Pd)

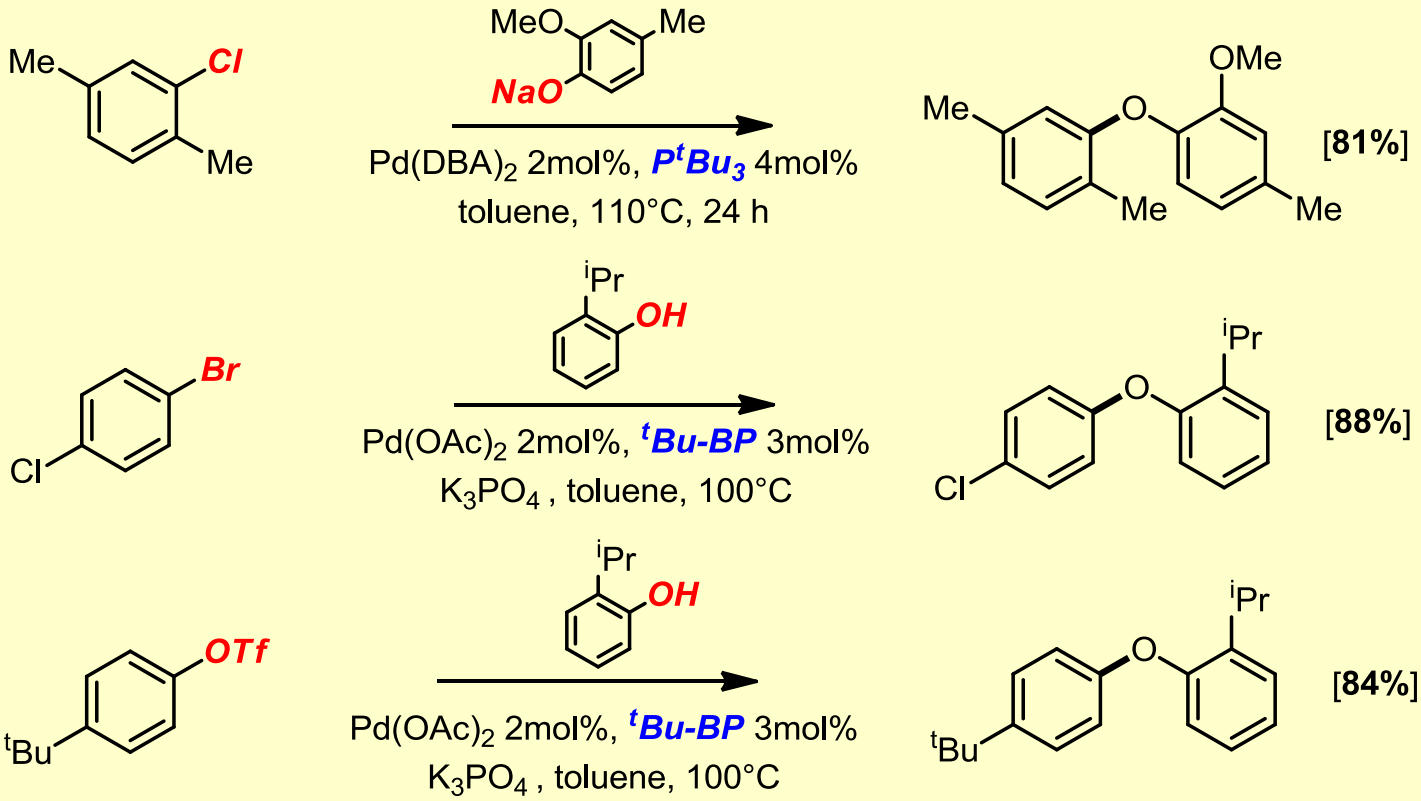
- ***Ar-Hal ↔ intermolecular 1° alkyl alcohols (Pd):***
  - 2° alcohols & substrates with *o*- or *p*-electron donating groups still problematic
  - ***alkyl/Ar ethers***, Pd(0), ***Tol-BINAP***: Buchwald *J. Am. Chem. Soc.* **1997**, *119*, 3395 (DOI)
  - ***alkyl/Ar ethers***, Pd(0), ***$^{t}$Bu-MAP***, ***P$^{t}$Bu$_2$-BN***: Buchwald *J. Am. Chem. Soc.* **2001**, *123*, 10770 (DOI)



# *Inter*molecular coupling of phenols (Pd) – *biaryl ether formation*

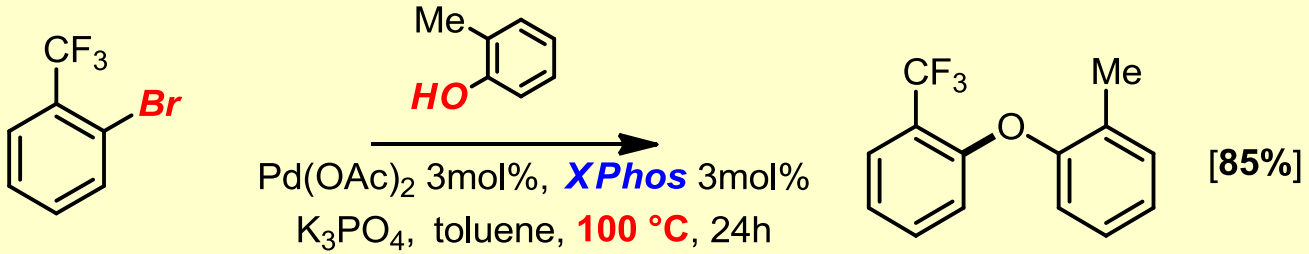
- ***Ar-Hal ↔ intermolecular phenols (Pd):***
  - ***reviews:*** Theil *Angew. Chem. Int. Ed.* **1999**, *38*, 2345 (DOI); Sawyer *Tetrahedron* **2000**, *56*, 5045 (DOI)
  - ***DPPF***: Hartwig *Tet Lett*. **1997**, *38*, 8005 (DOI)
  - ***P$^t$Bu$_3$***: Hartwig *J. Am. Chem. Soc.* **1999**, *121*, 3224 (DOI) & *J. Am. Chem. Soc.* **2000**, *122*, 10718 (DOI)
  - ***$^t$Bu-BP***: Buchwald *J. Am. Chem. Soc.* **1999**, *121*, 4369 (DOI)
  -  : Beller *Tet. Lett.* **2005**, *46*, 3237 (DOI)



# *Inter*molecular coupling of phenols (Pd) – *state-of-the-art*

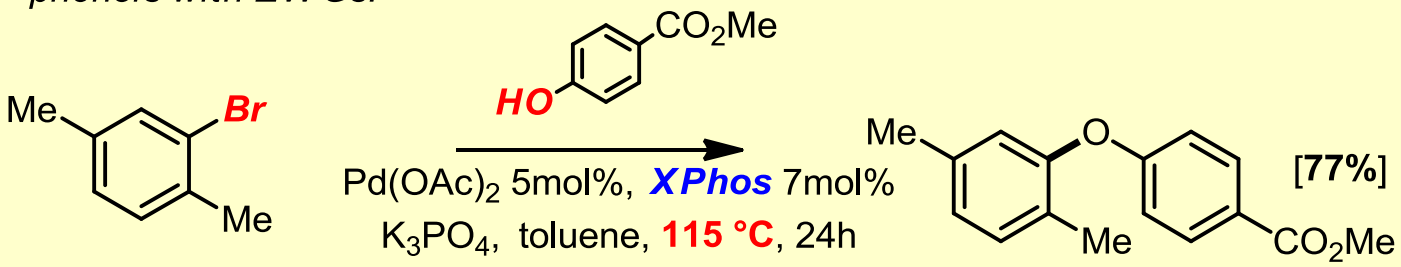
- ***Ar-Hal ↔ intermolecular phenols (Pd):***
  - Buchwald *Angew. Chem. Int. Ed.* **2006**, *45*, 4321 (DOI)

*aryl halides with EWG at ortho position:*

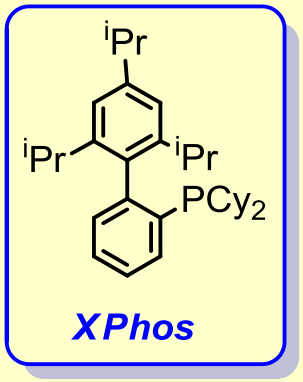



**[85%]**

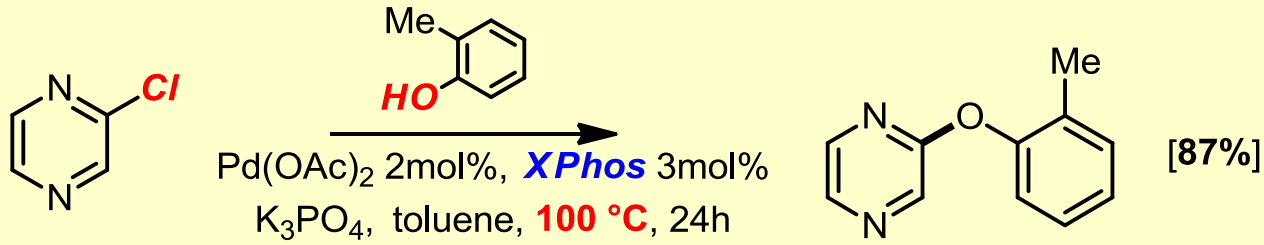
*phenols with EWGs:*




**[77%]**



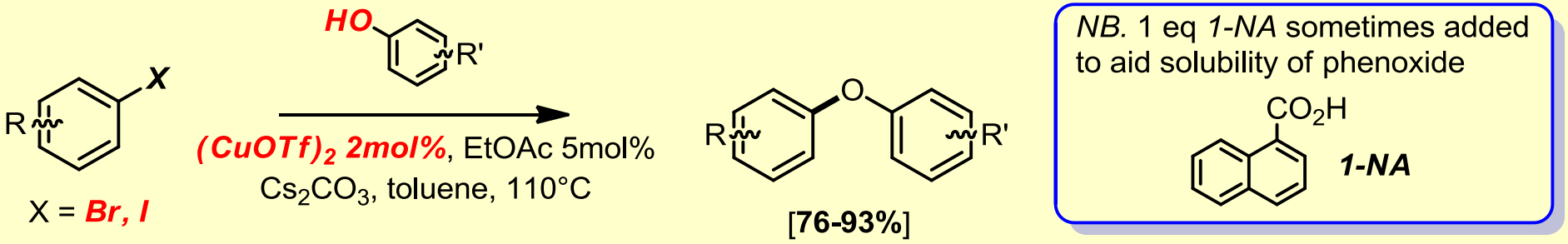

*heteroaryl halides:*




**[87%]**

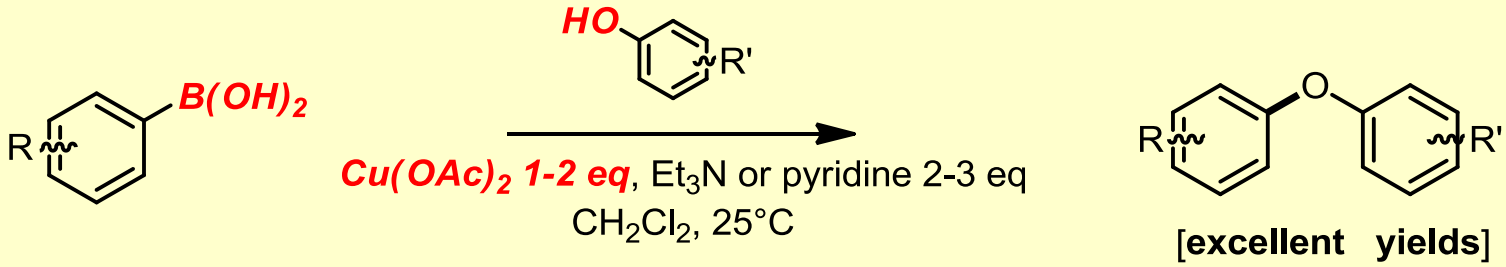
# *Inter*molecular coupling of phenols (Cu) - *biaryl ether formation*

- ***Cu(I) cat. etherification of Ar-Br with phenols:***
  - ***catalytic Ullmann coupling:*** electron rich and deficient partners react; di-*ortho*-substituted phenols give low yields (20-30%)
  - Buchwald *J. Am. Chem. Soc*. **1997**, *119*, 10539 (DOI); see also: Liu *Synlett* **2008**, 221 using proline carboxamide ligand (DOI)




  - See also Zhang *Chem.Commun.* **2007**, 3186 (DOI) – CuI (20 mol%), $Cs_2CO_3$, 145 °C, $Si(OEt)_4$ as solvent

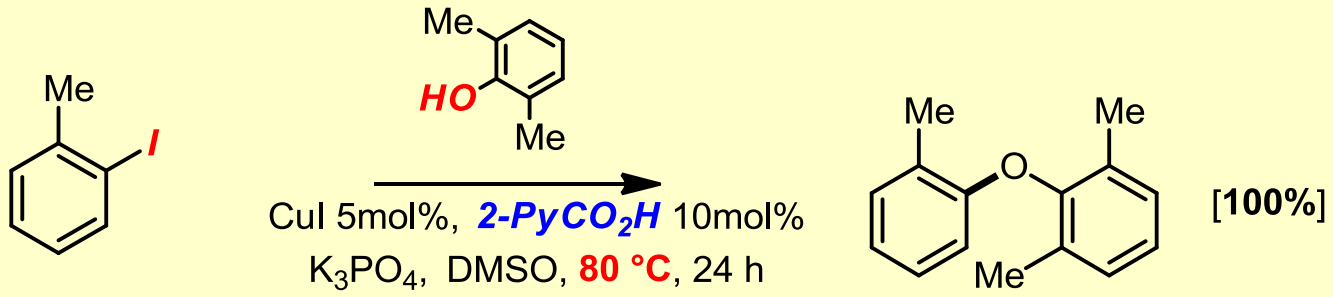
- ***Cu(I) cat. etherification of Ar-B(OH)$_2$ with phenols:***
  - Chan *Tet. Lett*. **1998**, *39*, 2933 (DOI); Evans *Tet. Lett*. **1998**, *39*, 2937 (DOI)

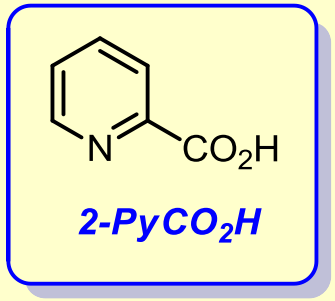


# *Inter*molecular coupling of phenols (Cu) – *state-of-the-art*

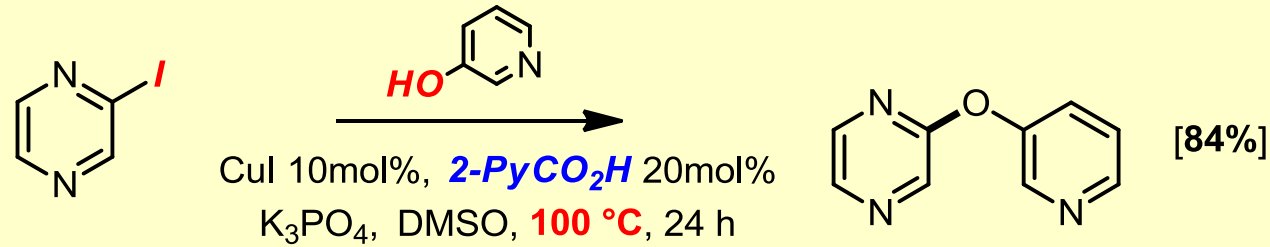
- ***Ar-Hal & Het-Hal ↔ intermolecular hindered phenols (Cu):***
  - Buchwald *J. Org. Chem.* **2010**, *75*, 1791 (DOI)

*hindered biaryl ethers:*

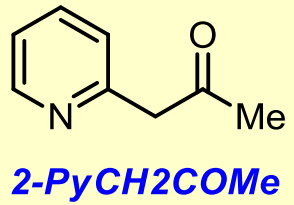



*heteroaryl halides & phenols:*

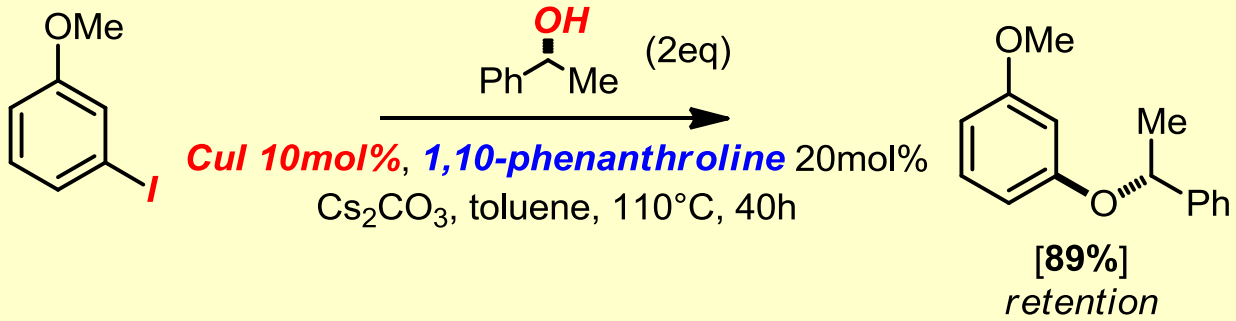



- ***Ar-Hal & Het-Hal ↔ intermolecular phenols (Cu):***
  - Ding *J. Org. Chem.* **2009**, *74*, 7187 (DOI)
  - CuBr 5-10 mol%, $Cs_2CO_3$, DMSO, 80-120 °C; **2-PyCH$_2$COMe**
  - Wide range of steric and electronic demand tolerated

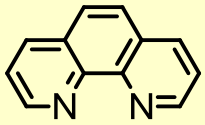


# *Inter*molecular coupling with 1°/2° alcohols (Cu & Fe)

- ***Ar-I ↔ intermolecular 1° and 2 ° alcohols (Cu):***
  - ***catalytic Ullmann coupling:*** *NOT air sensitive*
  - Buchwald *Org. Lett.* **2002**, *4*, 973 (DOI); Buchwald *J. Org. Chem.* **2008**, *73*, 284 (DOI); see also: Sekar *J. Org. Chem.* **2009**, *74*, 3675 (DOI)

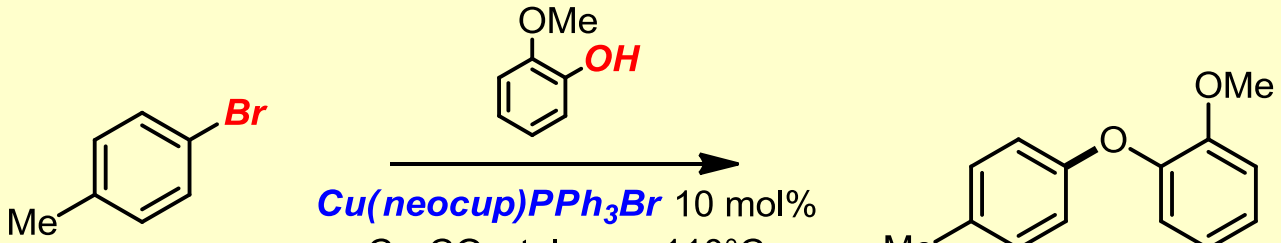



[**89%**]
*retention*

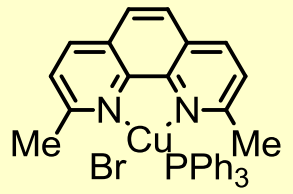



***1,10-phenanthroline***

- ***Ar-Br ↔ intermolecular phenols (Cu):***
  - air and moisture stable, organic soluble catalysts formed from CuBr + $PPh_3$ + phenanthroline
  - Venkatarman *Org. Lett.* **2001**, *3*, 4315 (DOI)




[**83%**]

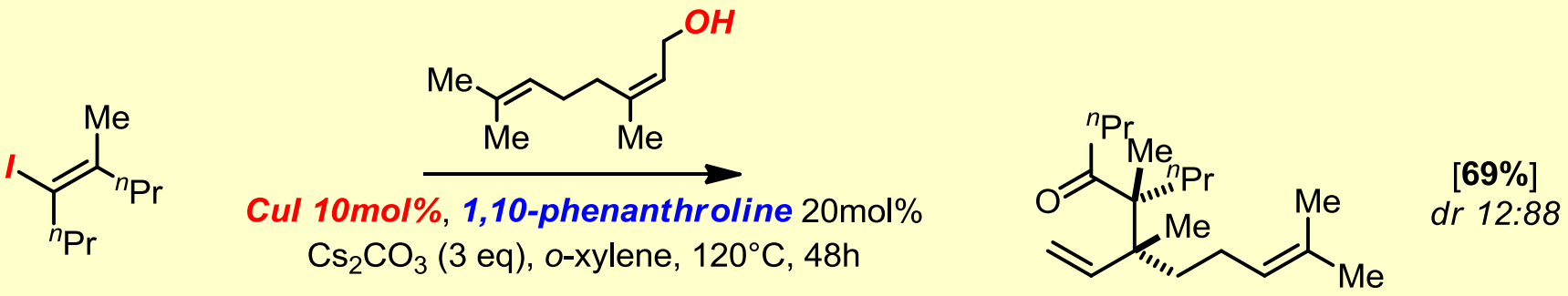


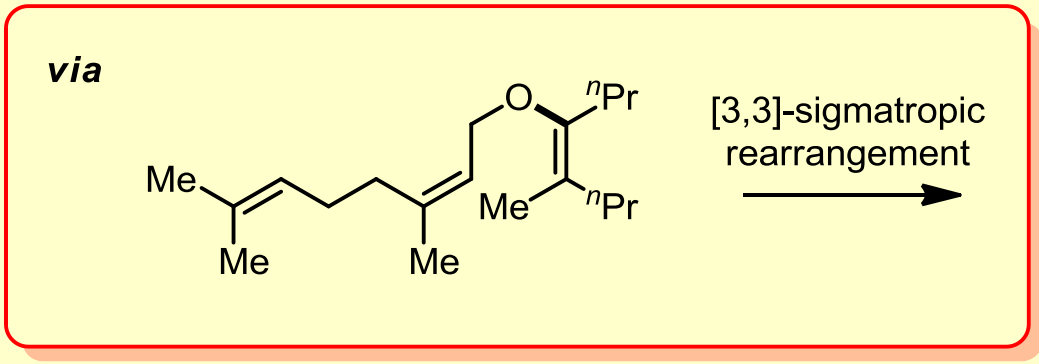

***Cu(neocup)PPh$_3$Br***

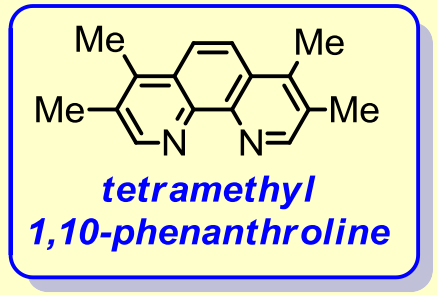
- ***Ar-I ↔ intermolecular phenols (Fe):***
  - Bolm *Angew. Chem. Int. Ed.* **2008**, *47*, 586 (DOI)…Fe(III) or is it the Cu(I) impurities? See: Buchwald *Angew. Chem. Int. Ed.* **2009**, *48*, 5586 (DOI)

# Tandem etherification/Claisen rearrangement

- ***Cu(I) cat. etherification of vinyl-I with allyl alcohols then Claisen rearrangement:***
  - Buchwald *J. Am. Chem. Soc.* **2003**, *125*, 4978 (DOI)



# Summary

- ***Pd, Ni & Cu catalysed C-N cross-coupling***
  - intramolecular heterocycle formation
  - intermolecular…latest developments

- ***Pd, Ni & Cu catalysed C-O cross-coupling***
  - intramolecular heterocycle formation
  - intermolecular…latest developments