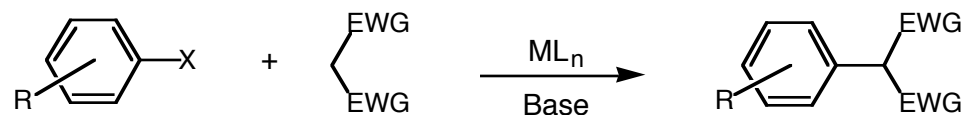
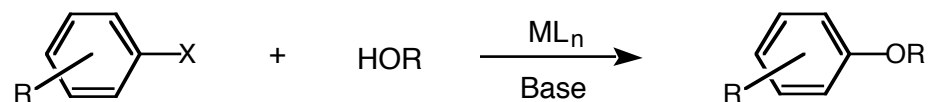
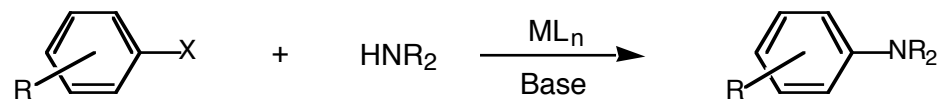


Buchwald-Hartwig Chemistry

Ian Mangion
MacMillan Group Meeting
July 30, 2002

- ◆ Historical context
- ◆ Development of initial catalytic systems
- ◆ Mechanistic studies and rational design
- ◆ Reaction Scope

Definition of Buchwald-Hartwig Chemistry



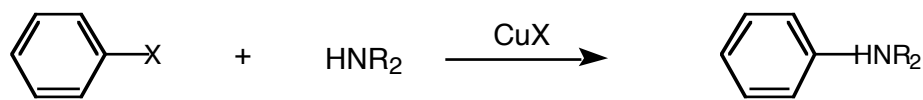
X = I, OTf, Br, Cl
M = Pd, Ni, Cu

- ◆ Over 70 publications from Buchwald
- ◆ Over 50 publications from Hartwig
- ◆ Several comprehensive reviews

Buchwald, S.; Muci, A. *Top. Curr. Chem.* **2002**; *219*, 133-209
Hartwig, J. *Pure Appl. Chem.* **1999**, *71*, 1417
Buchwald, S.; Yang, B. *J. Orgmet. Chem.* **1999**, *576*, 125
Hartwig, J.; *ACIEE.* **1998**, *37*, 2046
Hartwig, J. *Acc. Chem. Res.* **1998**, *31*, 852
Buchwald *et al.* *Acc. Chem. Res.* **1998**, *31*, 805

Aryl Aminations Before Buchwald-Hartwig

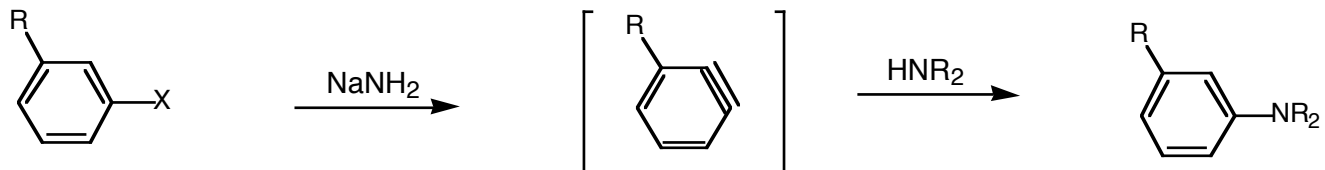
- ◆ Ullman discovers *ipso*-substitution of aryl halides mediated by copper in 1901



Lindley, J. *Tetrahedron*, **1984**, *40*, 1433

- ◆ 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

- ◆ Aryne chemistry allows for amination of an expanded scope of aryl halides

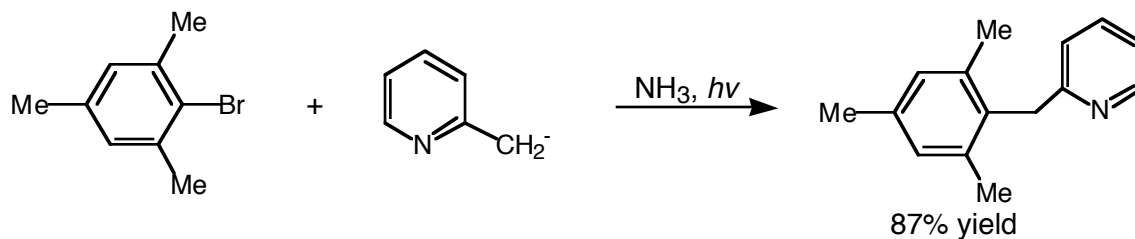


Biehl, E. *J. Org. Chem.*, **1987**, *52*, 2619

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

The Move Towards a General Reaction

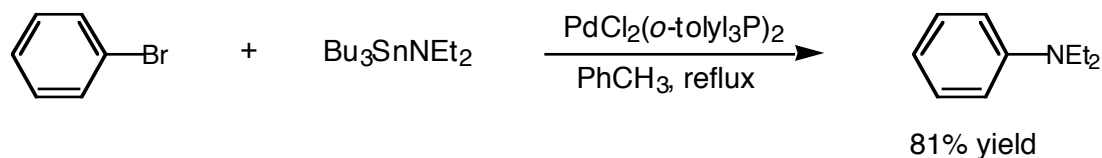
- ◆ Bunnett introduces the S_{RN1} mechanism to the picture



Bunnett, J. *Acc. Chem. Res.*, **1978**, *11*, 413

- ◆ Demanding couplings can be accomplished
- ◆ Reaction conditions are mildest yet
- ◆ All drawbacks associated with radical mechanisms are present

- ◆ Migita makes the major breakthrough

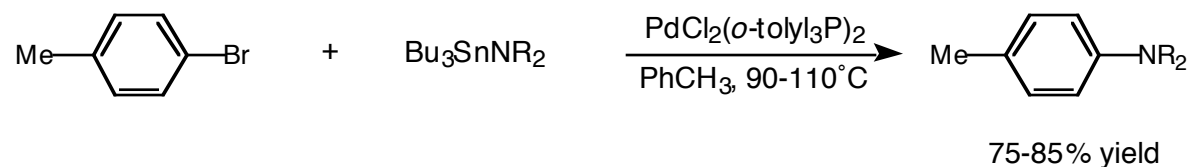


Kosugi, M.; Kameyama, M.; Migita, T. *Chem. Lett.*, **1983**, 927
Kosugi, M.; Kameyama, M.; Sano, H.; Migita, T. *Nippon Kagaku Kaishi*, **1985**, *3*, 547

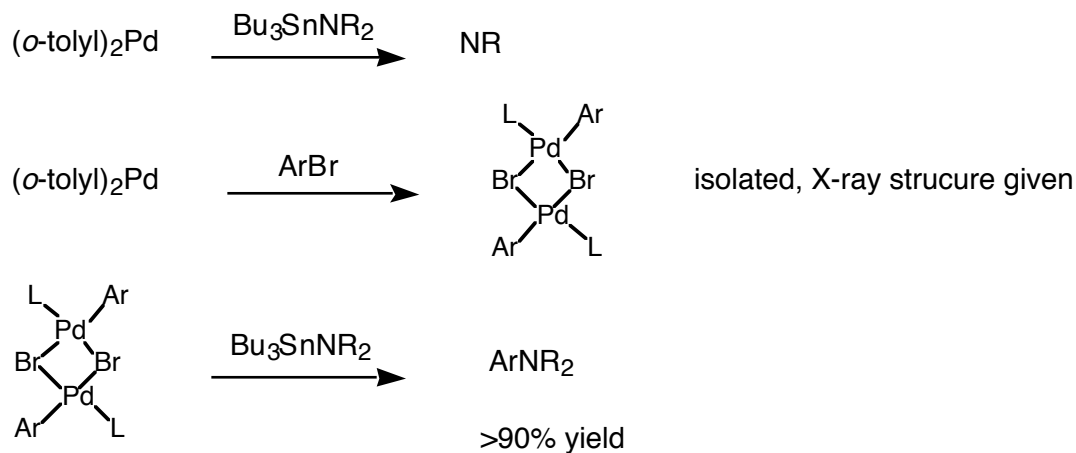
- ◆ First example of a palladium-catalyzed aryl-amine coupling
- ◆ Aryl bromides are only viable aromatic substrates
- ◆ Reaction scope is very limited, but reactions are clean and mild
- ◆ Tin amides are toxic, sensitive compounds
- ◆ This work goes unreferenced for a decade

Hartwig Takes a Closer Look

- ◆ The mechanism of Migita's reaction is studied for the first time

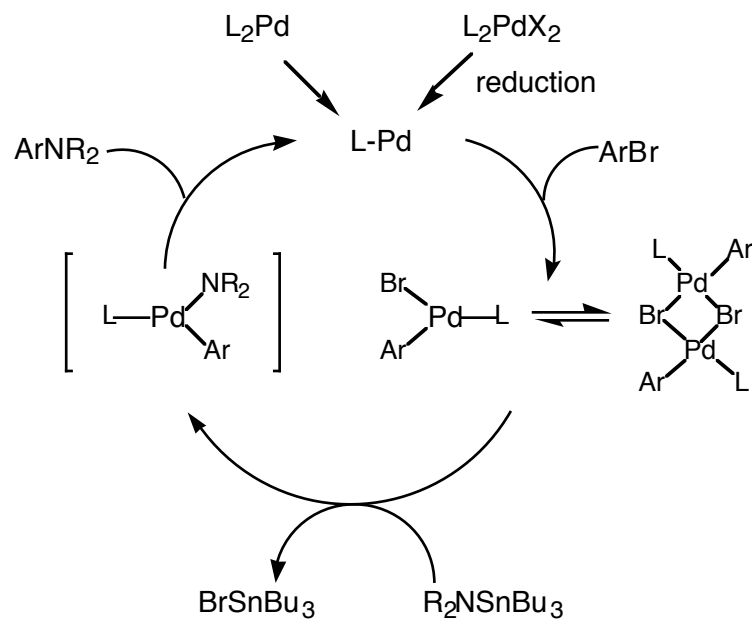


- ◆ Oxidative addition, reductive elimination suspected
- ◆ Hartwig probes for Pd(0) complexes and isolable intermediates



- ◆ 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

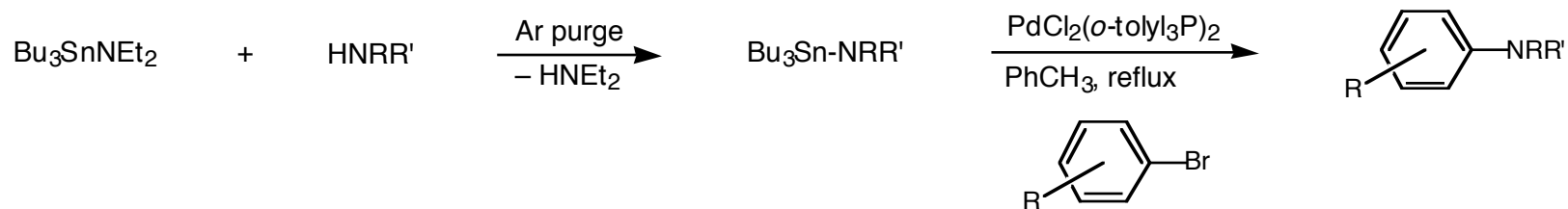
Proposed Catalytic Cycle



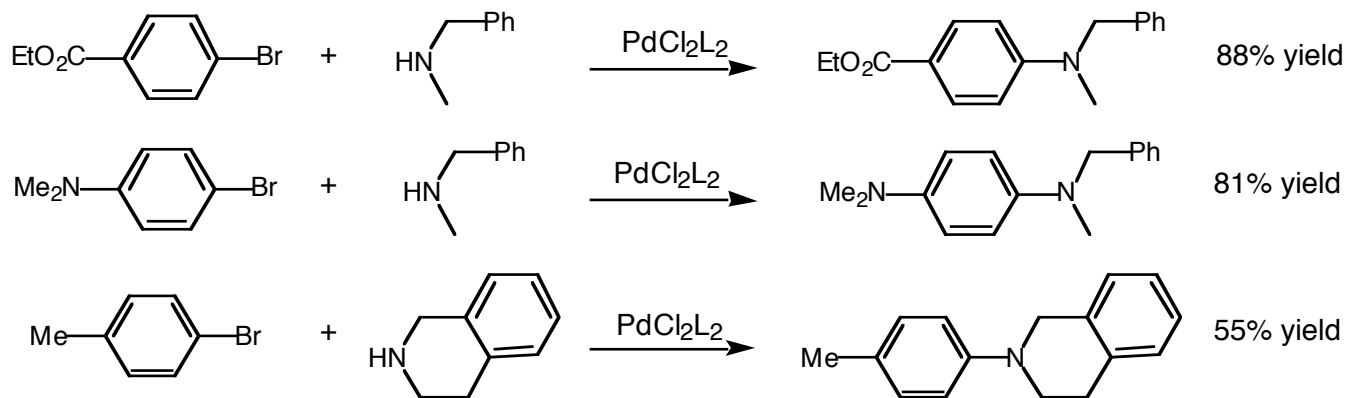
- ◆ Phosphine inhibition implies monophosphine Pd is active species
- ◆ Pd(0) sources can catalyze the reaction
- ◆ As in Stille couplings, tin transmetalation appears to be the rate-limiting step

Buchwald Enters the Field

- ◆ Three months after Hartwig's paper is submitted, Buchwald submits the following work, beginning an ongoing trend of independent, overlapping research
- ◆ Buchwald expands the scope of the reaction by generating tin amines *in situ*

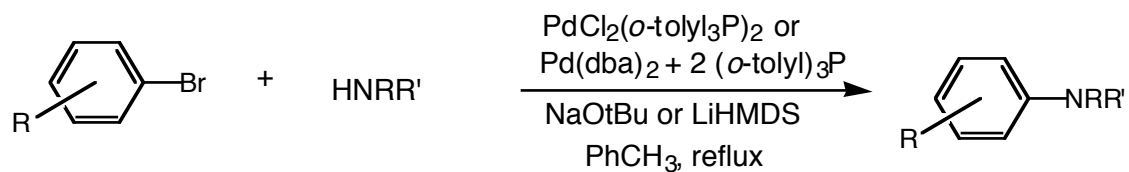


- ◆ Use of tin reagents is still required, but a large variety of amines are made available through transmetalation
- ◆ Reaction still restricted to aryl bromides
- ◆ Only secondary amines and primary anilines can be used
- ◆ *o*-substituted aryls not reported
- ◆ Catalyst loadings of less than 2% are typical, most reactions run 24 h

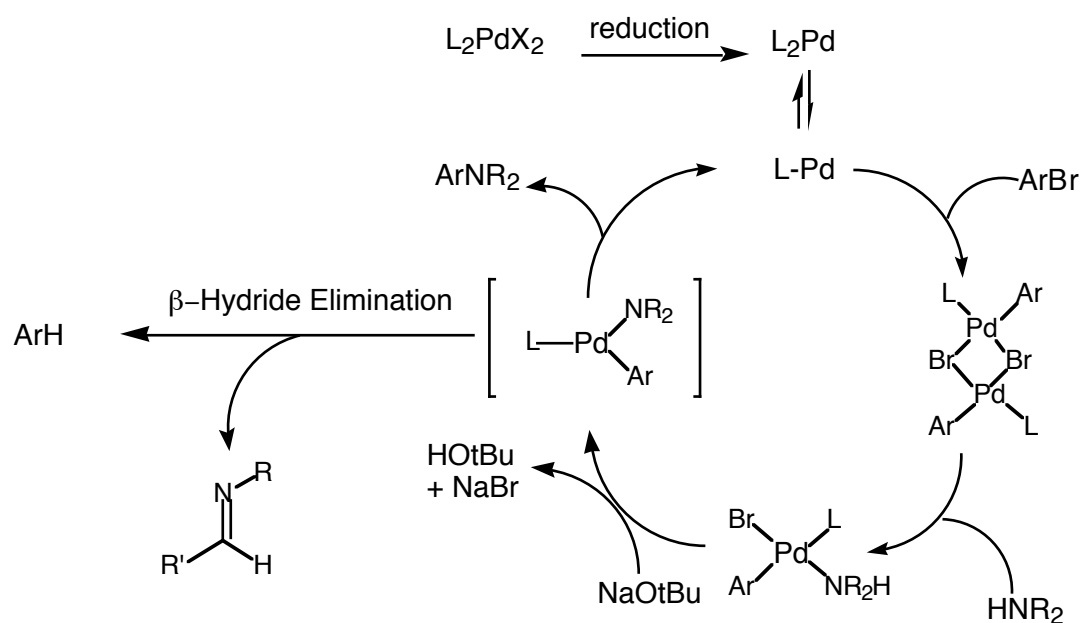


Tin-Free Catalysis

- ◆ Once again in quick succession, Buchwald and Hartwig publish methods for tin-free aryl-amine couplings

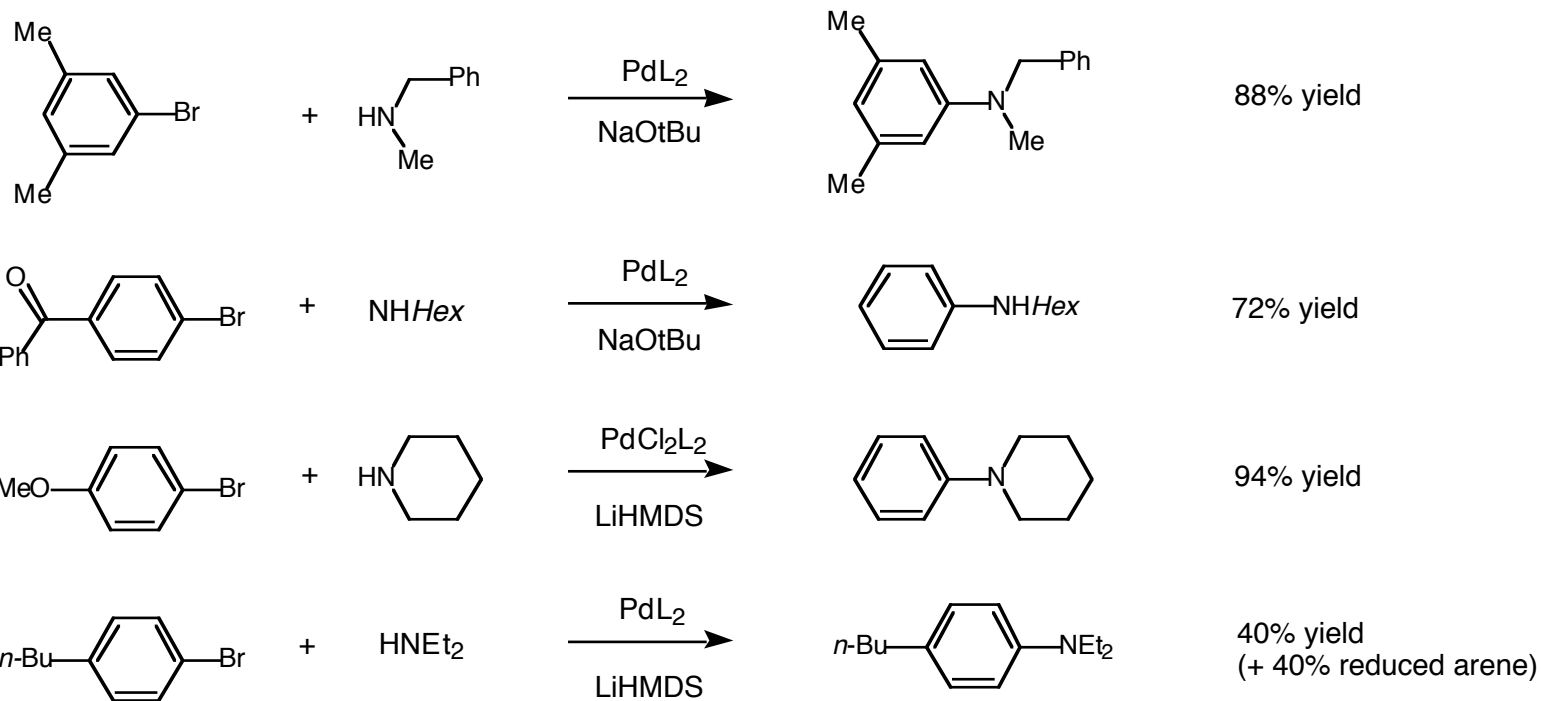


- ◆ A new catalytic cycle is proposed in which the base deprotonates Pd-amine complexes
- ◆ Pd(0) shown to be resting state of catalyst, so oxidative addition is now the rate-limiting step



Expansion of Scope

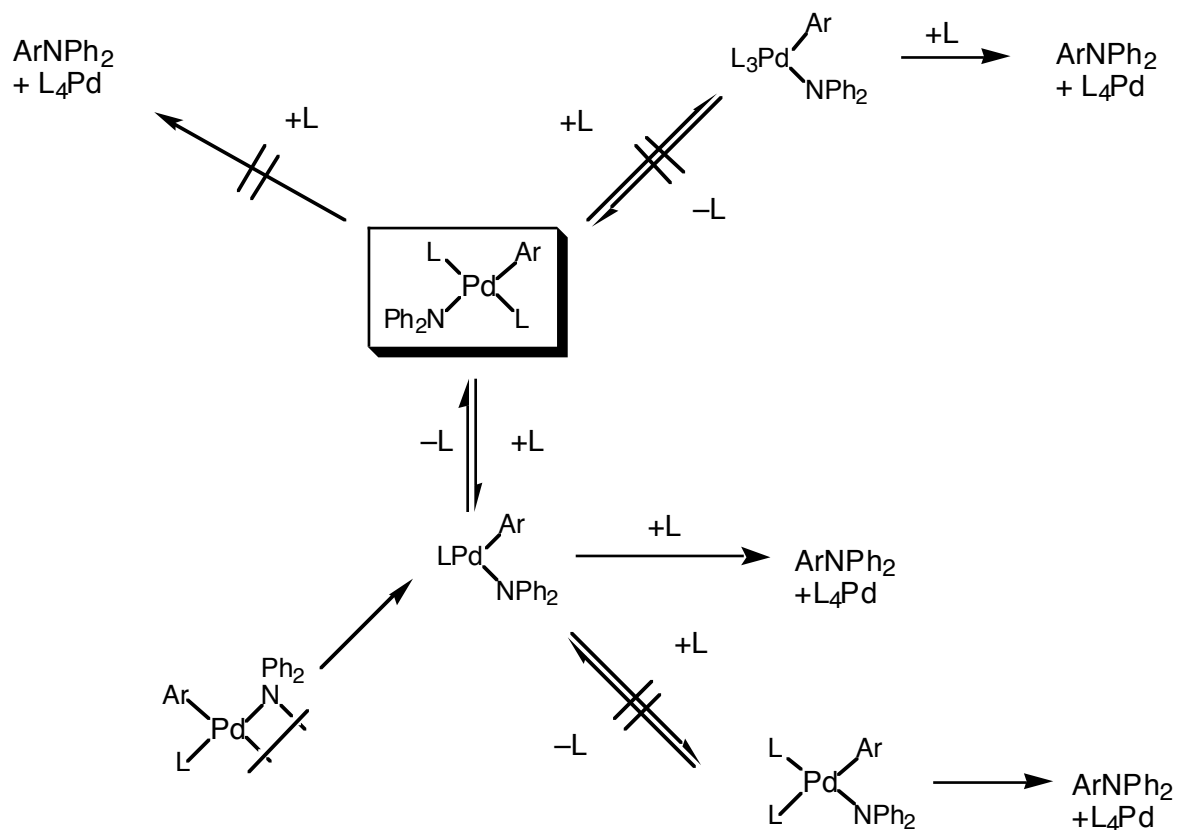
- ◆ The new conditions allow for greater substrate scope



L = (o-tolyl)₃P

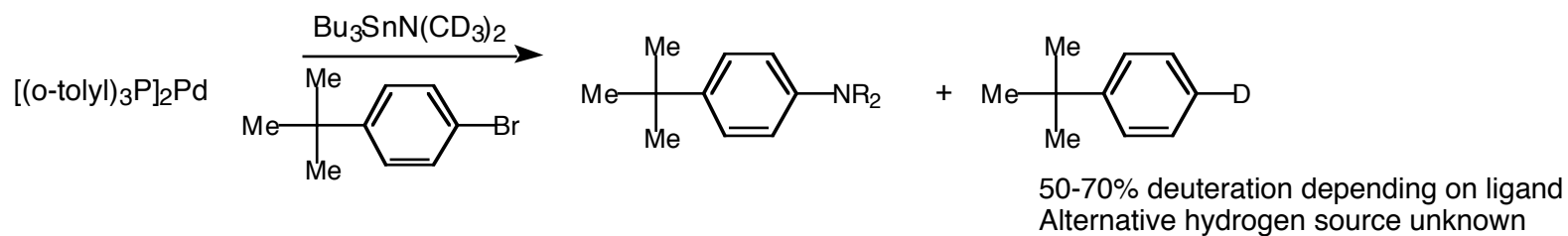
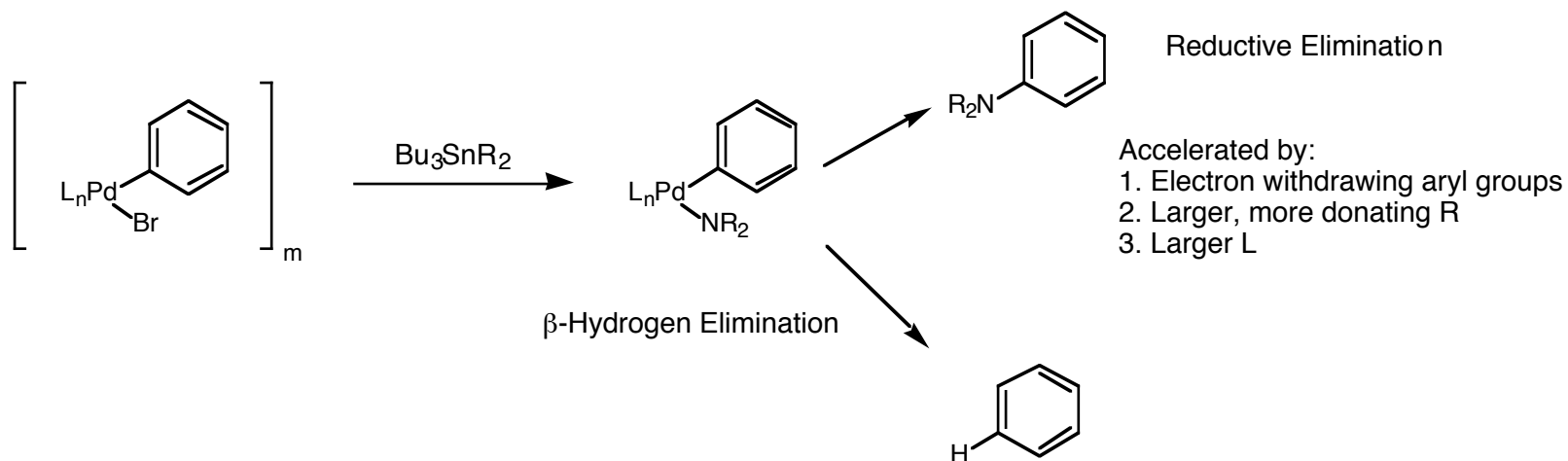
- ◆ Primary amines can be coupled with electron-withdrawing aryl halides
- ◆ Cyclic secondary amines and alkyl anilines are good substrates
- ◆ Most acyclic secondary alkyl amines are problematic with electron-rich or neutral aryl halides

Role of the Phosphines: Early Studies



- ◆ 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.

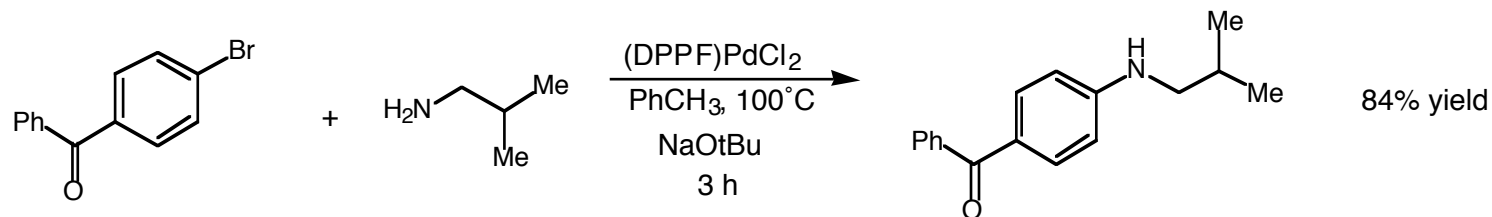
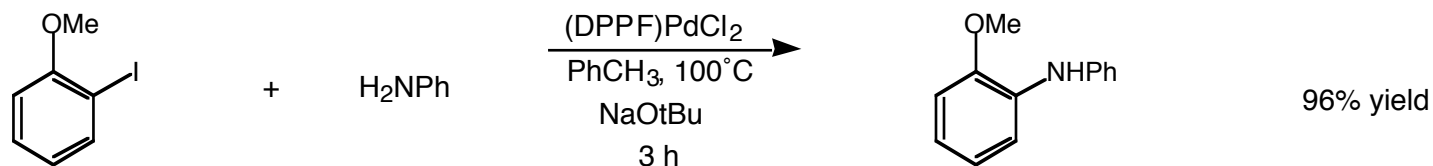
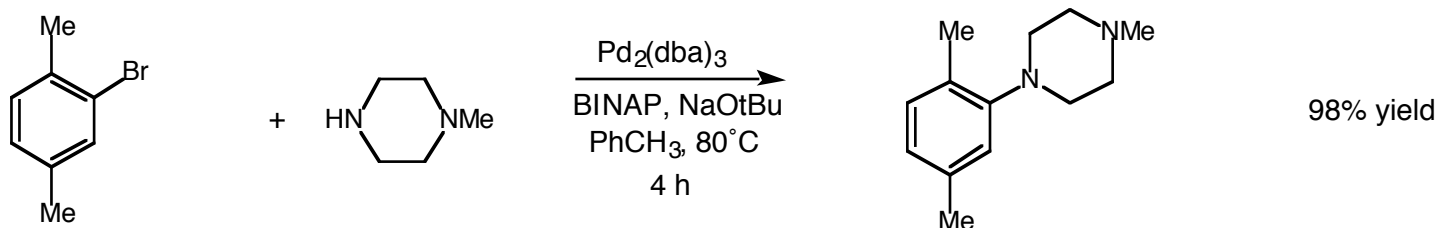
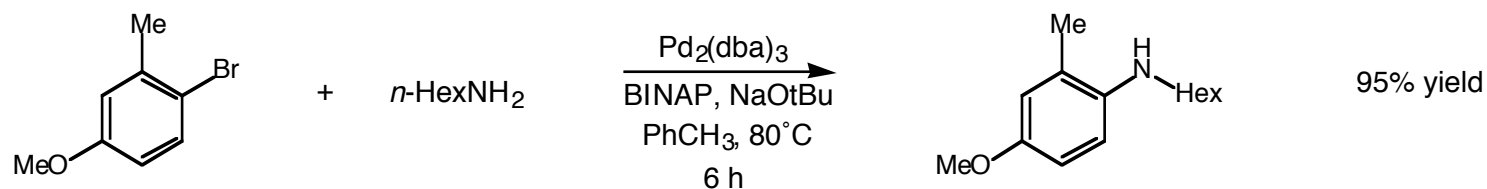
Further Considerations in Reaction design



- ◆ Most qualitative steric and electronic effects are consistent with analogous C-C bond formation reactions
- ◆ Perturbations that drive reductive elimination enhance the rate of amination over aryl hydrodehalogenation
- ◆ More nucleophilic amines are better substrates
- ◆ More than one mechanism competes to produce reduced arenes
- ◆ Pd(II) and Pd(0) sources are both competent, but small amounts of arene reduction attributed to Pd(II) reduction

Bidentate Ligands: A Dramatic Advance

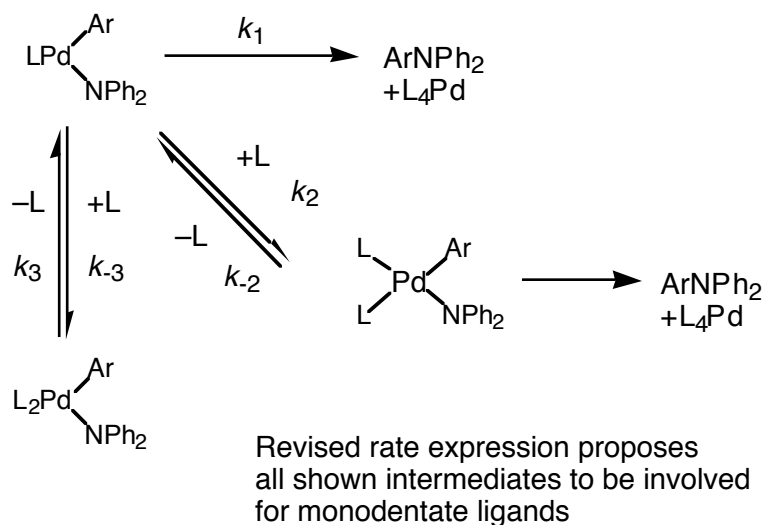
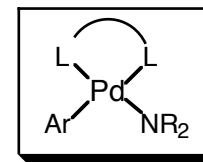
- ◆ In back-to-back communications, Buchwald and Hartwig report vast improvements in scope and yield by use of bidentate phosphine ligands
- ◆ Catalyst loadings are typically 0.5-1.0 mol%, and reactions are typically faster



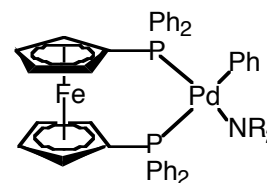
Wolfe, J.; Wagaw, S.; Buchwald, S. *J. Am. Chem. Soc.*, **1996**, *118*, 7215
Driver, M.; Hartwig, J. *J. Am. Chem. Soc.*, **1996**, *118*, 7217

Bidentate Ligands: Mechanistic Revision

- ◆ Reductive elimination from four-coordinate complex now proposed
- ◆ Intermediate demonstrated by ^{31}P 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



DPPF intermediates synthesized

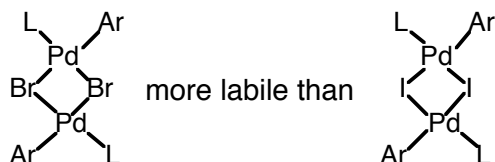


R = tolyl, *iso*Bu

These compounds give coupling products when heated, in up to 90% yield

Aryl Iodides and Triflates: Challenging Substrates

- ◆ Buchwald proposes that monodentate phosphine ligands were ineffective with aryl iodides because they allowed more stable palladium iodide dimers to form.
- ◆ Experiments perturbing steric bulk of amine suggest steric difference between I and Br might be important as well



van der Waals radii:

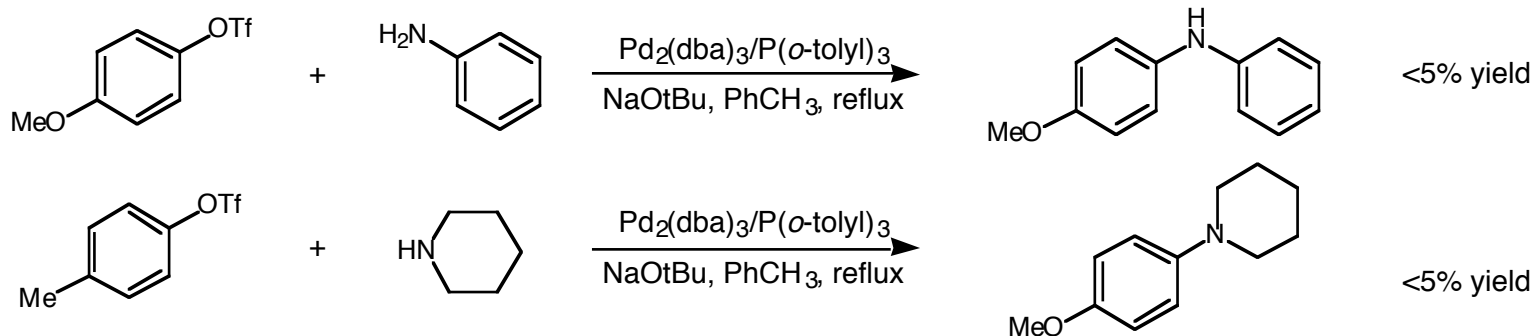
Cl (1.75 Å) < Br (1.85 Å) < I (1.96 Å)

$\Delta\Delta G_{298K}$ for DIPA with Pd dimers = 4.6 kcal mol⁻¹

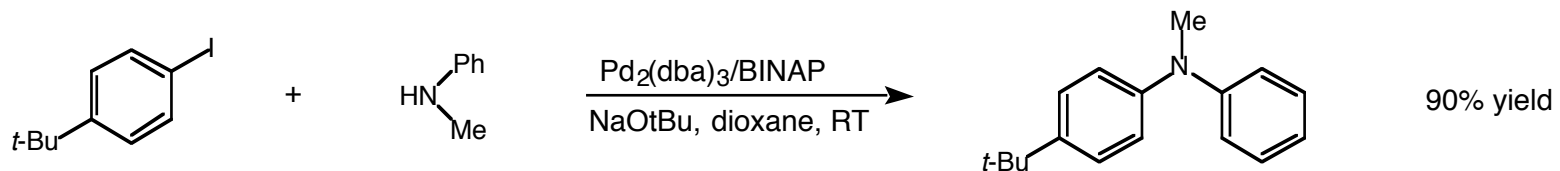
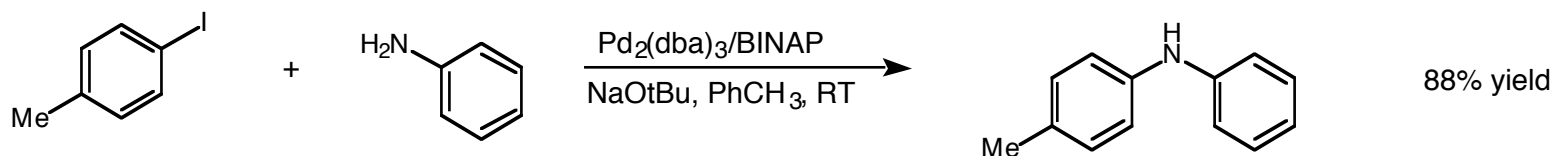
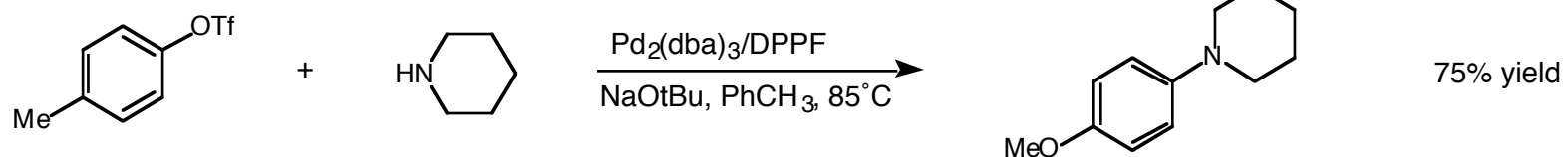
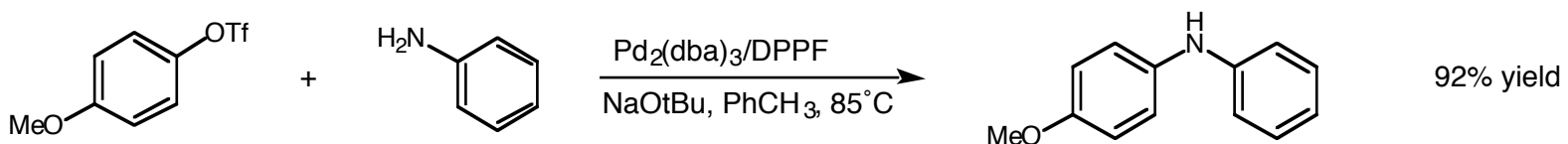
$\Delta\Delta G_{298K}$ for BnNH₂ with Pd dimers = 2.7 kcal mol⁻¹

(bulkier amines more sensitive to size of I)

- ◆ Pd-C and Pd-P rotation barriers found to be greater for larger halides
- ◆ Triflates are prone to cleavage to phenols by nucleophilic bases at a rate competitive to reductive elimination



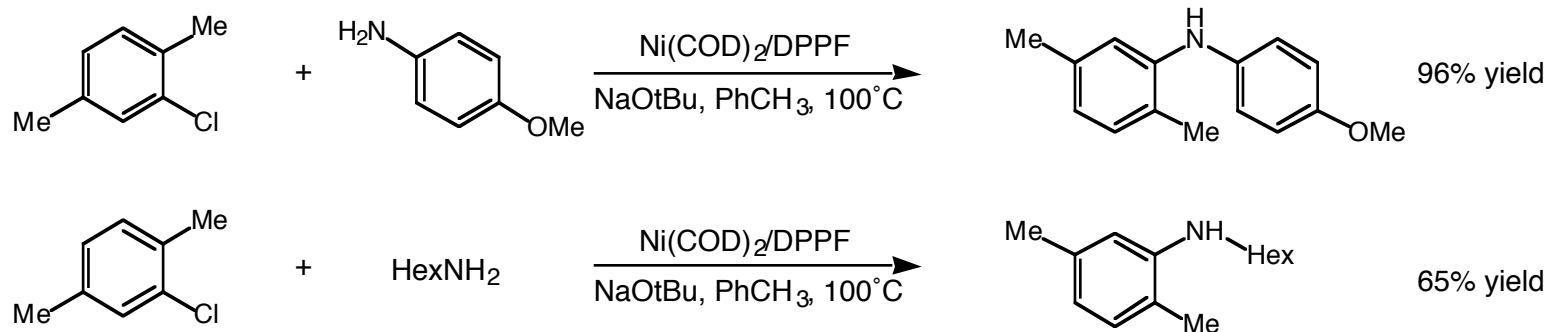
A General Solution



- ◆ Previously unusable iodides and triflates are now excellent substrates
- ◆ Increased catalytic activity allows for milder conditions

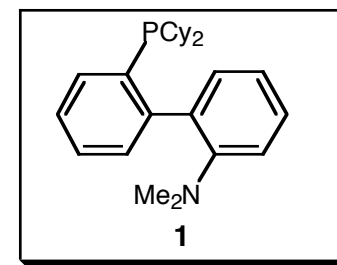
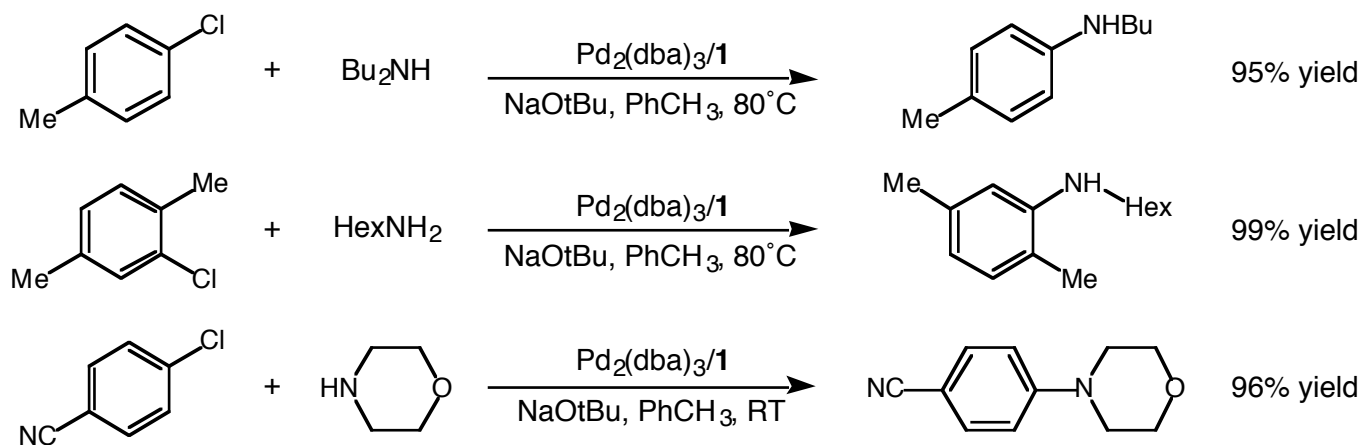
Aryl Chlorides: The Search For a Practical System

- ◆ Finding little success with existing palladium systems, Buchwald develops a nickel-based catalyst for the amination of aryl chlorides.



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

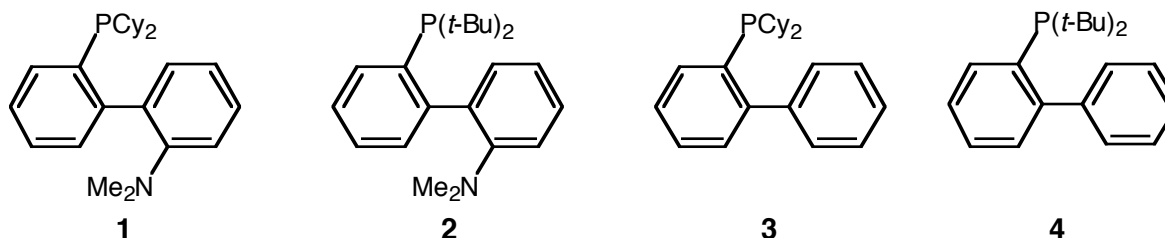
- ◆ A palladium system follows, using a new system of ligands



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

An Unexpected Development

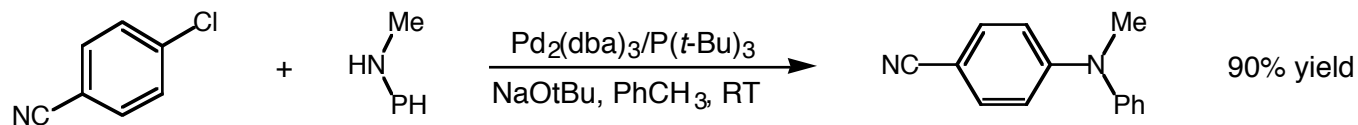
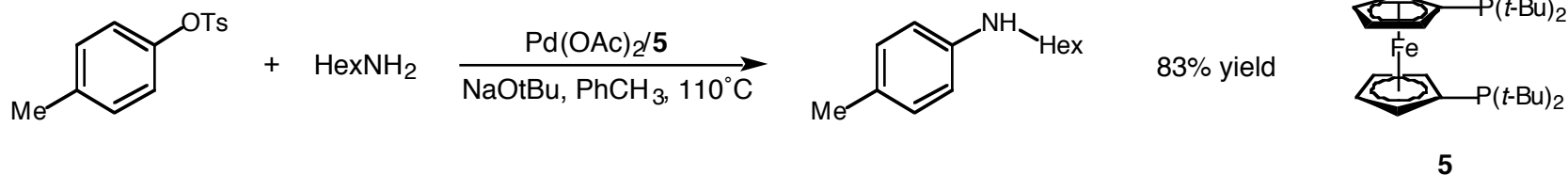
- Further studies on this new class of ligand demonstrates that bidentate binding is unnecessary!



- Ligands **3** and **4** are sometimes better ligands than **1**

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

- Hartwig discovers the same effect through experimentation with bulky bidentate ligands
- Ligand **5** is found to be more general and effective than DPPF, and even allows coupling of tosylates
- $P(t-Bu)_3$ is then found to be a remarkably active ligand

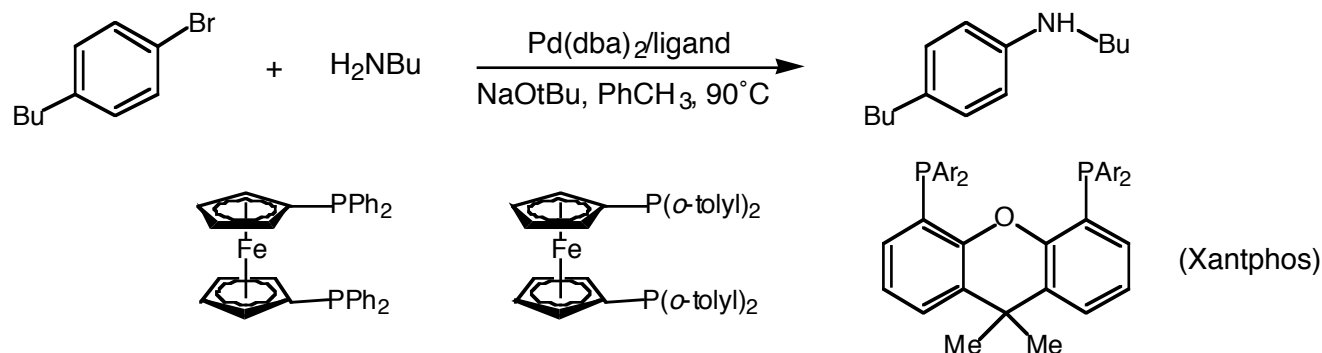


- Functional group compatibility is increased with the above ligands by use of K_3PO_4 or Cs_2CO_3 as bases

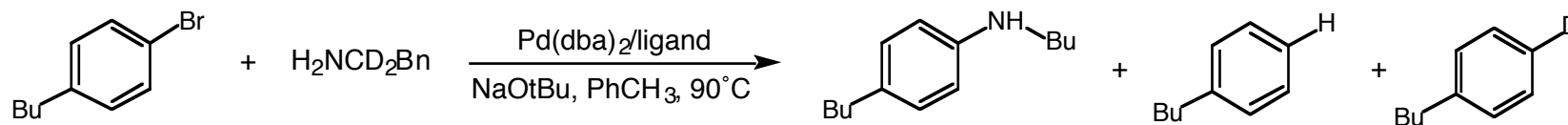
Hamann, B.; Hartwig, J. *J. Am. Chem. Soc.*, **1998**, *120*, 7369
 Kawatsura, M.; Hartwig, J. *J. Am. Chem. Soc.*, **1999**, *121*, 1473

More Studies On Ligand Effect

- ◆ Hartwig performed a systematic study of steric, electronic, and geometric ligand perturbations



- ◆ Using a small set of model reactions and ligand sets like the ones shown, Hartwig finds the following:
 - Enlarging ligand size increases the rate of dehydrohalogenation of arenes as well as β -hydrogen elimination. This effect is postulated to be due to partial dissociation to a three-coordinate complex.
 - Adding electron withdrawing groups to ligand aryl groups does not help partition the reactions towards reductive elimination.
 - Increasing bite angle speeds dehydrohalogenation through increased β -hydrogen elimination, again by three-coordinate complexes.
 - Three-coordinate partially dissociated ligands seen in ^{31}P NMR for largest bidentate systems.

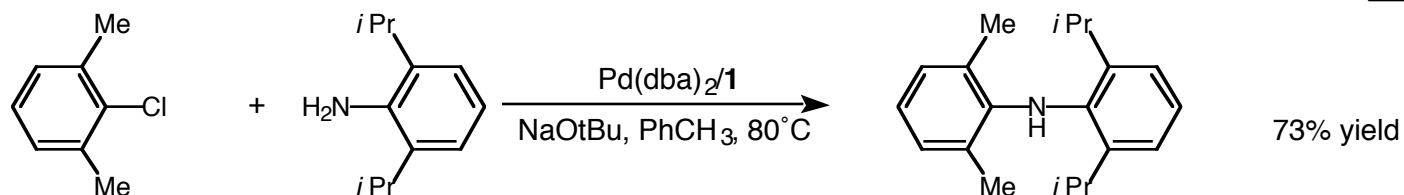
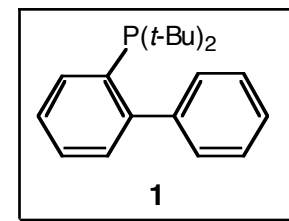


Ligand	% Arene	% Arene from β -Elim
DPPF	4.4	1.6
DTPF	34	4.8
DPPDPE	40	11
DPPX	24	15

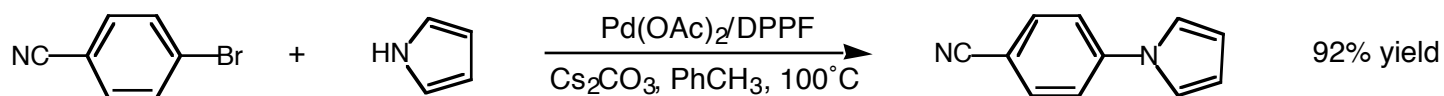
Hamann, B.; Hartwig, J. *J. Am. Chem. Soc.*, **1998**, *120*, 7369
 Kawatsura, M.; Hartwig, J. *J. Am. Chem. Soc.*, **1999**, *121*, 1473

Continuing Expansion of Scope

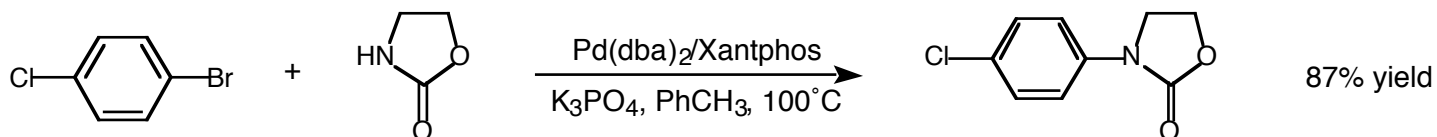
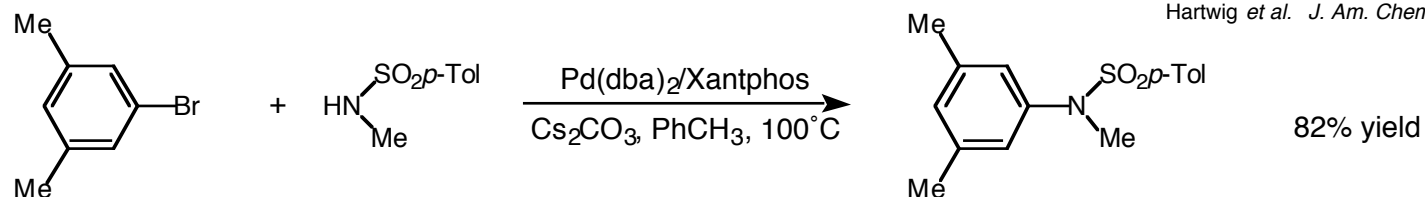
- ◆ The aforementioned studies prove that a number of monodentate and bidentate ligands can be used for aryl-amine couplings, and that generality may not be a simple goal
- ◆ Larger varieties of ligand families allow for wider screening of new reactions



Buchwald *et al.* *J. Org. Chem.*, **2000**, *65*, 1158

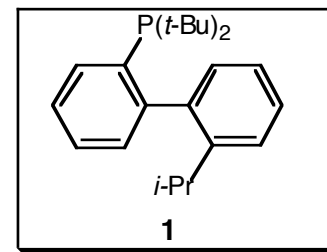
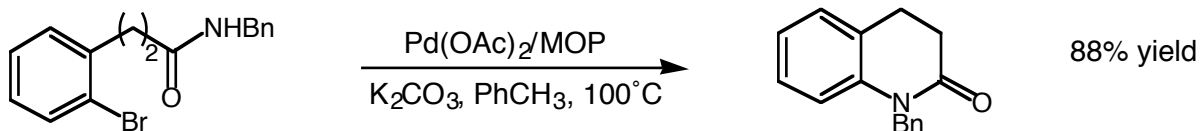
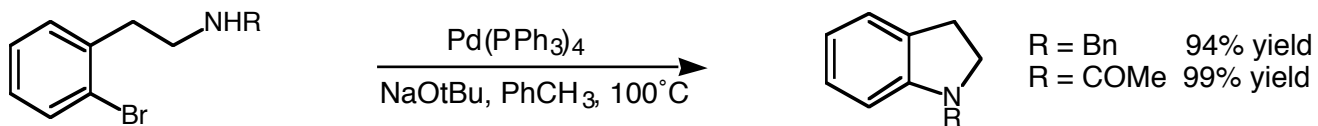


Hartwig *et al.* *J. Am. Chem. Soc.*, **1998**, *120*, 827

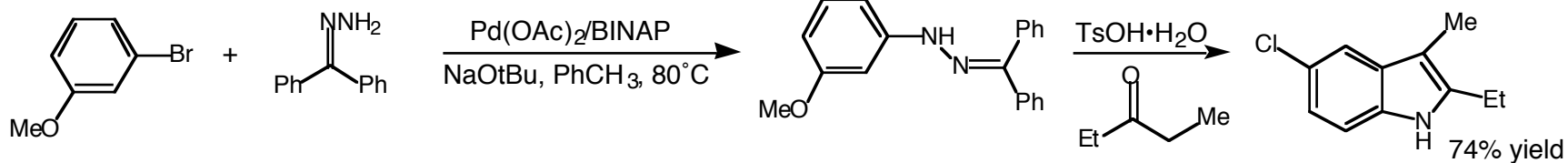
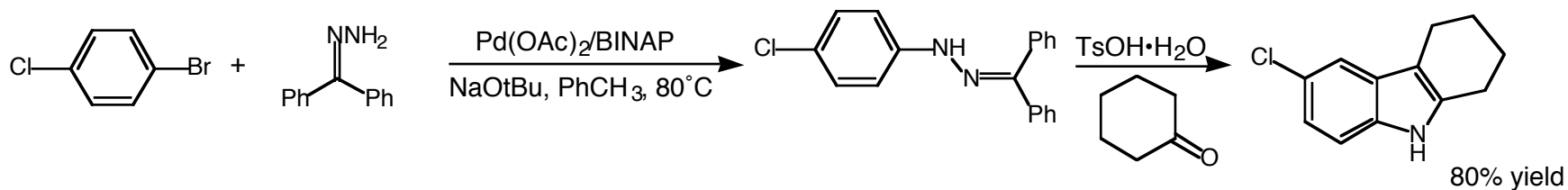
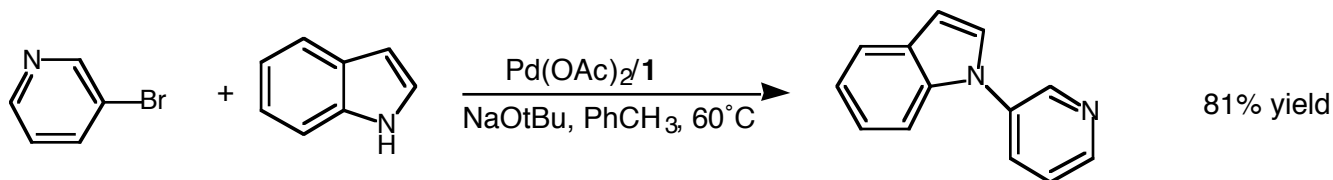


Yin, J. Buchwald, S. *J. Am. Chem. Soc.*, **2002**, *124*, 6043

More Aryl-Amine Coupling Strategies



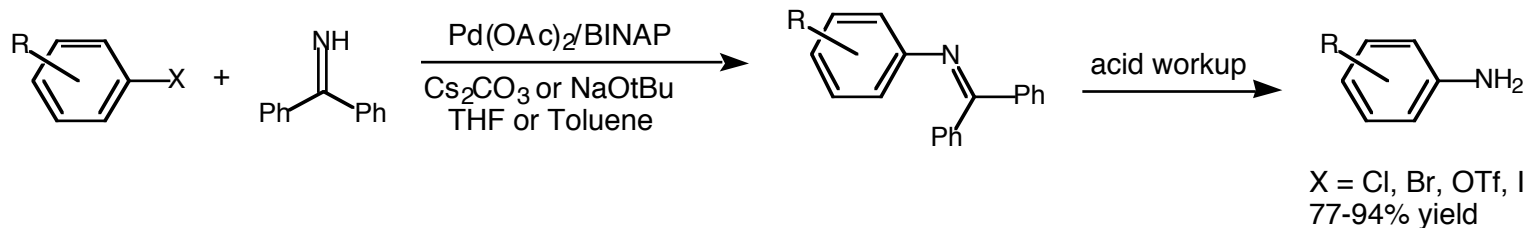
Wolfe, J.; Rennels, R.; Buchwald, S. *Tetrahedron*, **1996**, *52*, 7525
 Yang, B.; Buchwald, S. *Org. Lett.*, **1999**, *1*, 35



Wagaw, S.; Yang, B.; Buchwald, S. *J. Am. Chem. Soc.*, **1999**, *121*, 10251

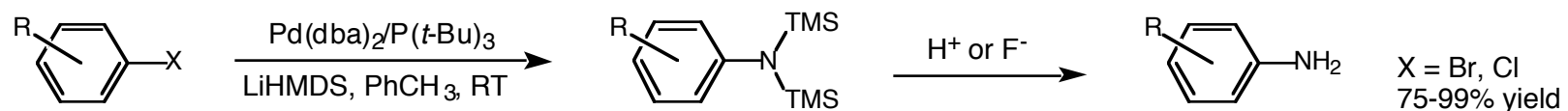
Ammonia Equivalents for Pd Couplings

- ◆ Ammonia fails in aryl-amine couplings, so alternatives have been developed to introduce free amines



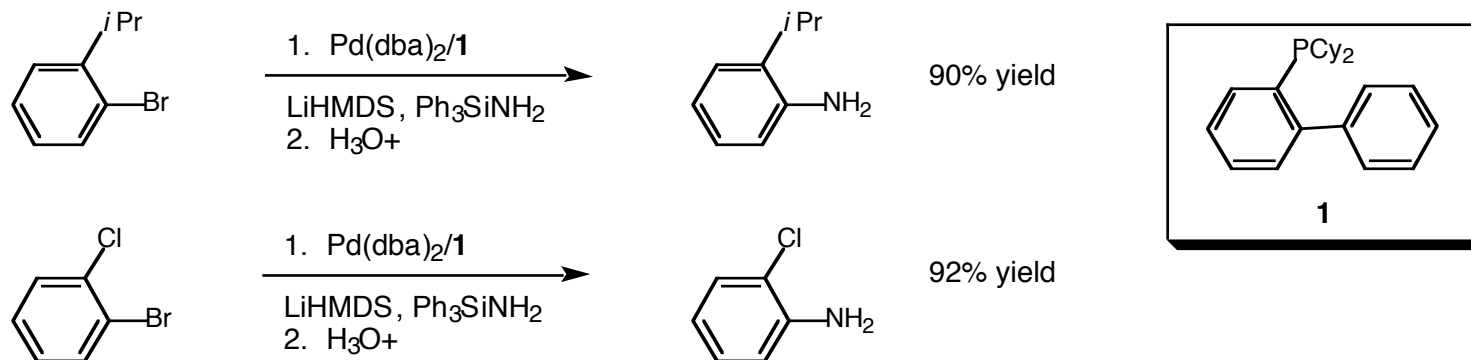
Wolfe, J.; Åhman, J.; Sadighi, J.; Singer, R.; Buchwald, S. *Tet. Lett.*, **1997**, *38*, 6367

- ◆ Hartwig's $\text{P}(t\text{-Bu})_3$ system couples LiHMDS, but does not tolerate ortho substituents



Lee, S.; Jorgensen, M.; Hartwig, J. *Org. Lett.*, **2001**, *3*, 2729

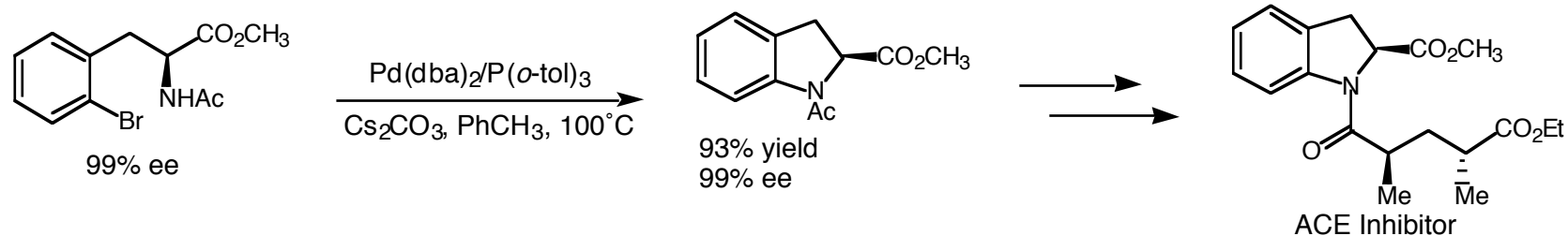
- ◆ Buchwald's system gets around this limitation



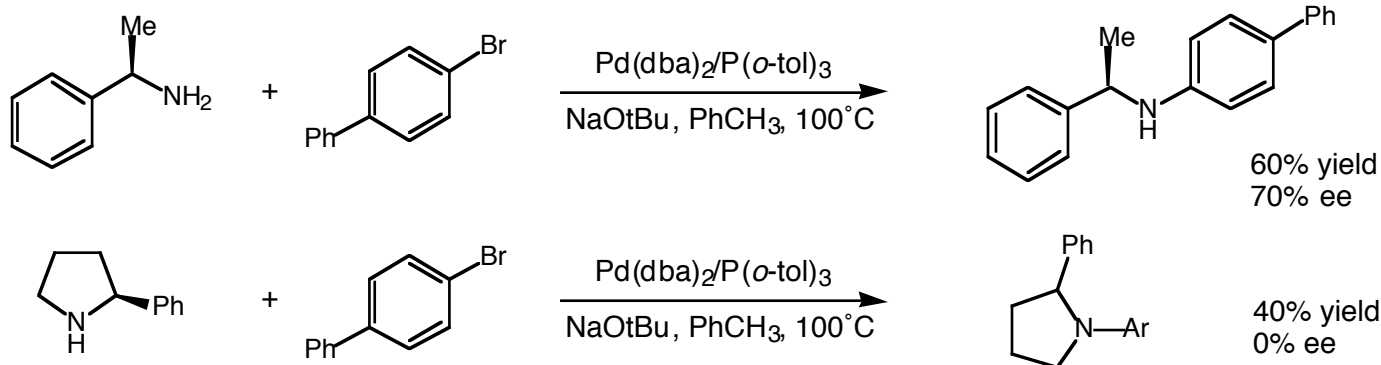
Huang, X.; Buchwald, S. *Org. Lett.*, **2001**, *3*, 3417

Synthetic Challenge: Chiral Substrates

- ◆ Intramolecular chiral amine couplings are possible with the original Pd system
- ◆ β -hydrogen elimination shown to be difficult from 6- or 7-membered metallacycles



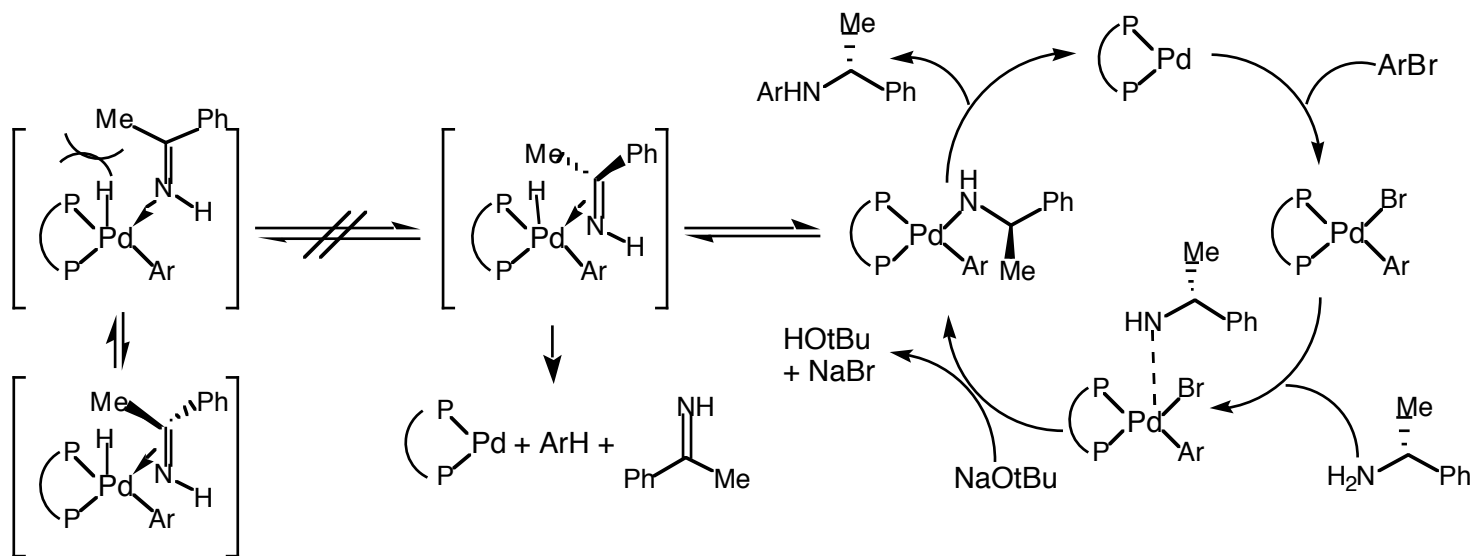
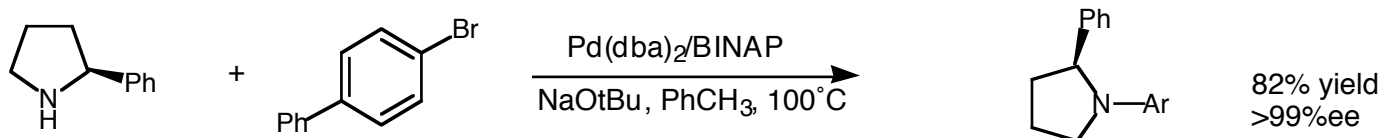
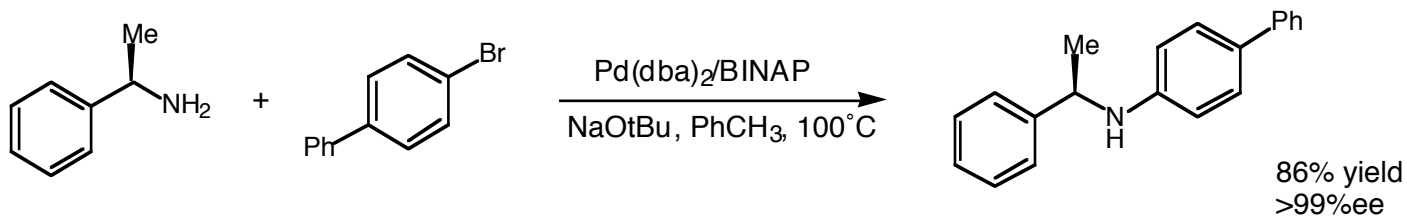
- ◆ Intermolecular cases prove to be difficult



- ◆ The following observations are made:
 - Control experiments show that amine racemization requires a palladium complex and an aryl bromide
 - Racemization does not occur after product formation
 - Recovered starting material amines show racemization
 - Deuterated imines added to the reaction are not incorporated into the product

BINAP Saves the Day

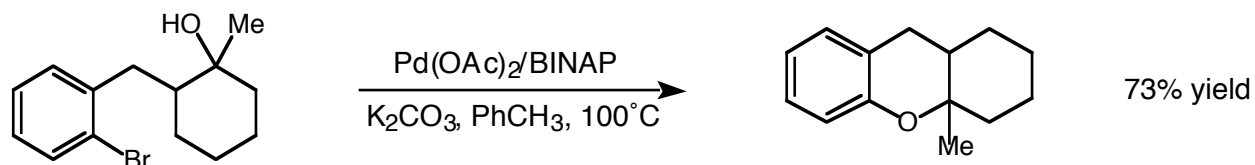
- ◆ Use of a bidentate ligand suppresses racemization



- ◆ Purported racemization pathway shut down with bidentate ligand
- ◆ No experiments reported with chiral BINAP

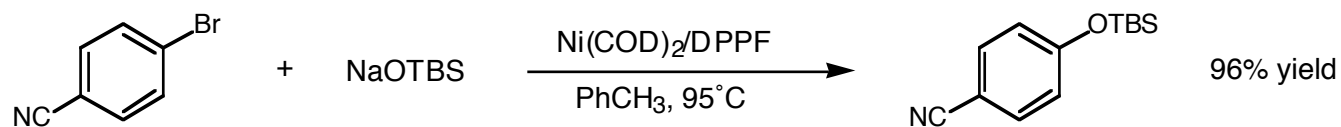
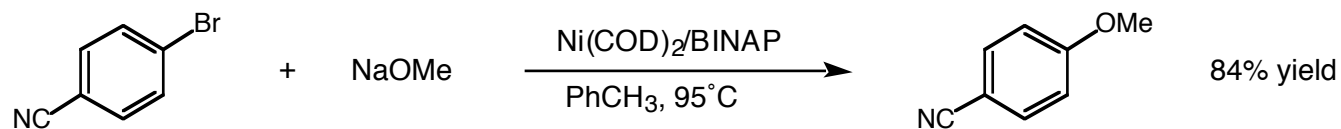
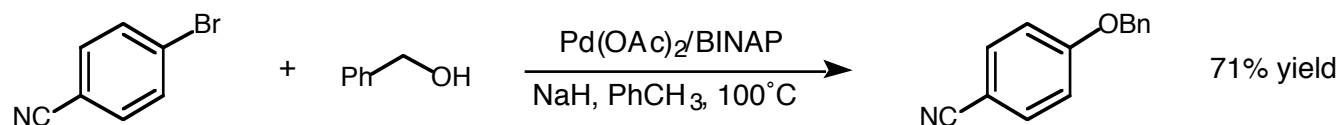
Aryl Ether Technology

- ◆ Development of Ar-O bond forming reactions develops along similar lines as did aryl-amine couplings
Substrate scope is initially limited, but gradually expands with ligand improvement
- ◆ The first examples are intramolecular, applicable only to tertiary or certain secondary alcohols



Palucki, M.; Wolfe, J.; Buchwald, S. *J. Am. Chem. Soc.*, **1996**, *118*, 10333

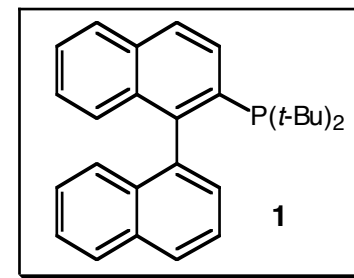
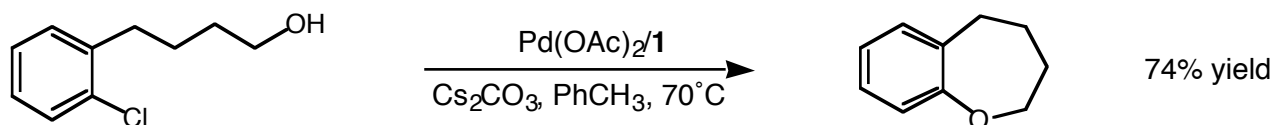
- ◆ First intermolecular examples involve electron poor aryl halides



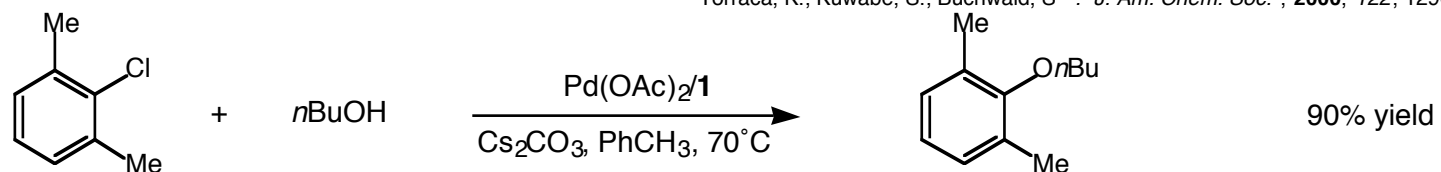
Mann, G.; Hartwig, J. *J. Am. Chem. Soc.*, **1996**, *118*, 13109
Mann G.; Hartwig, J. *J. Am. Chem. Soc.*, **1997**, *62*, 5413
Palucki, M.; Wolfe, J.; Buchwald, S. *J. Am. Chem. Soc.*, **1997**, *119*, 3395

New Ligand Development

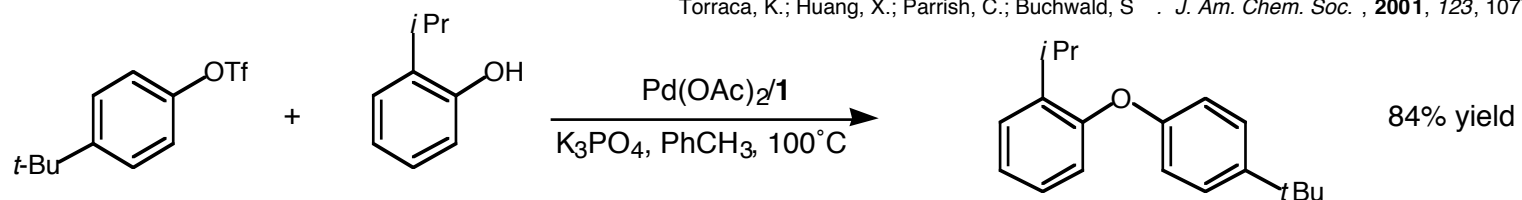
- Using a class of ligands similar to his best for aryl-amine couplings, Buchwald finds that difficult cases of aryl ether formations have been rendered facile



Torraca, K.; Kuwabe, S.; Buchwald, S. *J. Am. Chem. Soc.*, **2000**, *122*, 12907

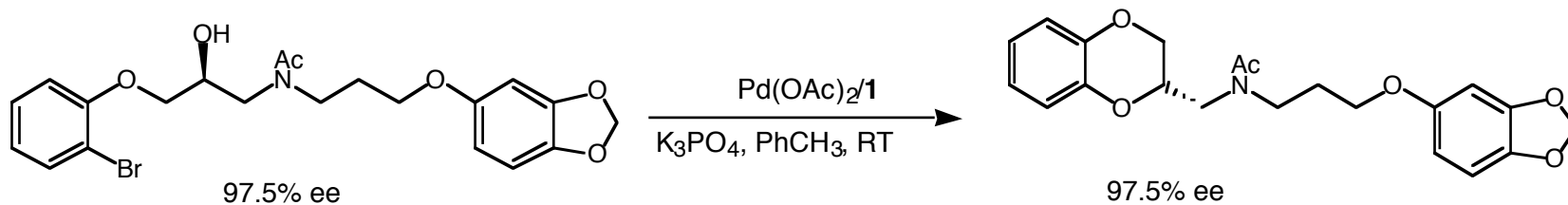


Torraca, K.; Huang, X.; Parrish, C.; Buchwald, S. *J. Am. Chem. Soc.*, **2001**, *123*, 10770



Buchwald *et al.* *J. Am. Chem. Soc.*, **1999**, *121*, 4369

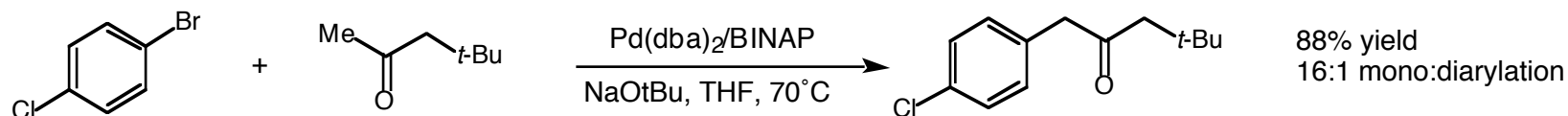
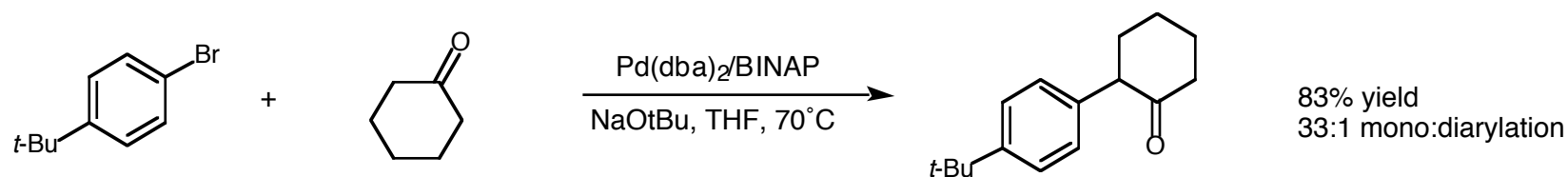
- Synthesis of MKC-242



Kuwabe, S.; Torraca, K.; Buchwald, S. *J. Am. Chem. Soc.*, **2001**, *123*, 12202

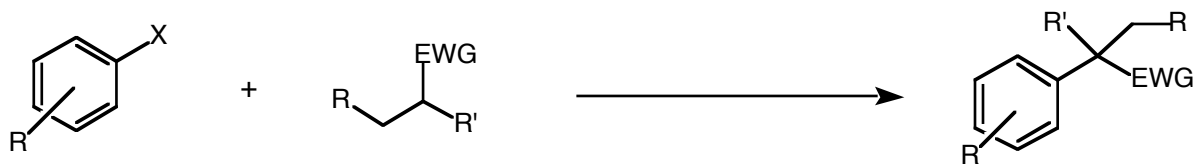
Carbon-Aryl Bond Forming Reactions

- ◆ Buchwald and Hartwig concurrently disclose methods for α -arylation of ketones, leading to a number of publications on arylation of acidic carbons



Palucki, M.; Buchwald, S. *J. Am. Chem. Soc.*, **1997**, *119*, 11108
Hamann, B.; Hartwig, J. *J. Am. Chem. Soc.*, **1997**, *119*, 12382

- ◆ Principally through Buchwald's biphenyl monophosphine ligands, reaction scope is expanded



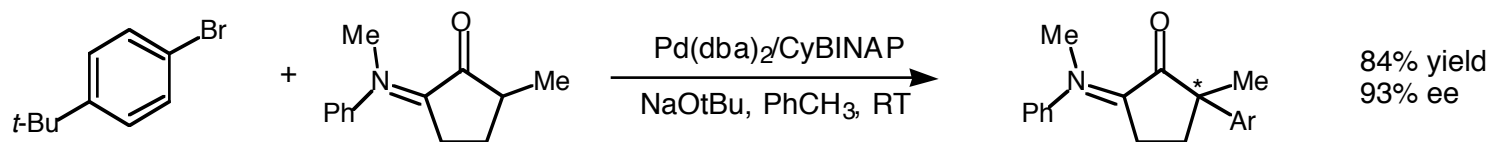
R = EWG, EDG
X = Cl, Br, OTf, I

EWG = Ketone, Ester, Nitroalkane, Nitrile, Amide

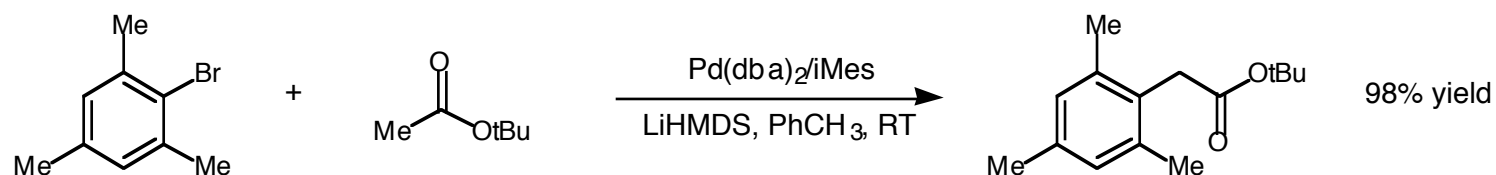
Shaugnessy, K.; Hamann, B.; Hartwig, J. *J. Org. Chem.* **1998**, *63*, 6546
Moradi, W.; Buchwald, S. *J. Am. Chem. Soc.* **2001**, *123*, 7996
Hamada, T.; Chieffi, A.; Åhman, J.; Buchwald, S. *J. Am. Chem. Soc.* **2002**, *124*, 1261
Vogl, E.; Buchwald, S. *J. Org. Chem.* **2002**, *67*, 106
Lloyd-Jones, G. *ACIEE.*, **2002**, *41*, 953

Example Reactions

- ◆ Asymmetric arylation discovered by Buchwald (very substrate specific)

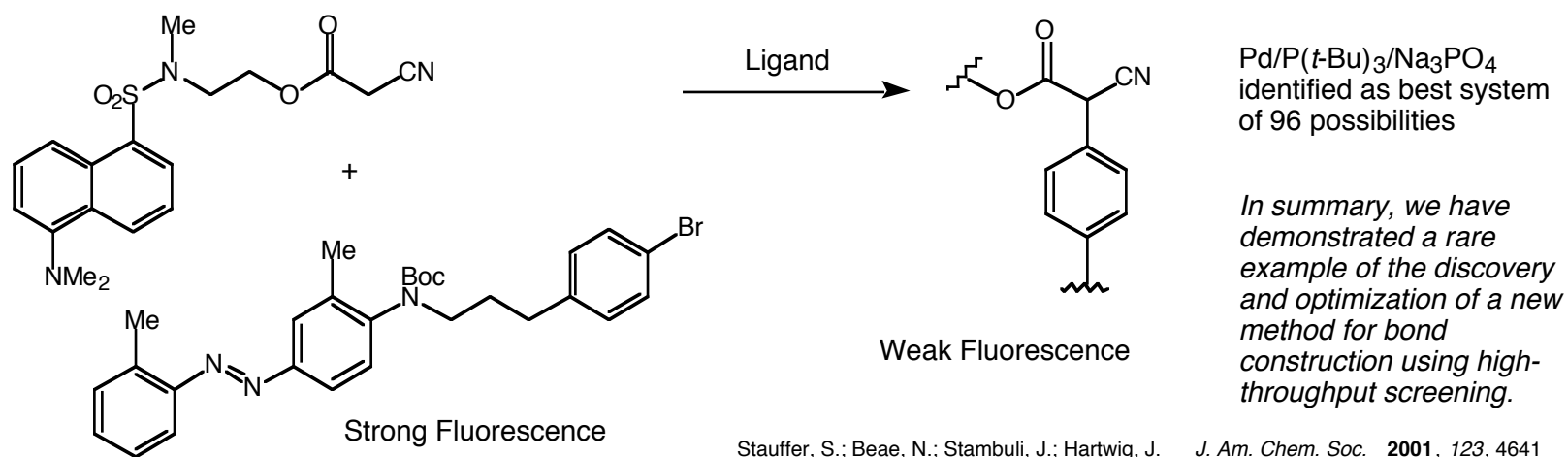


Hamada, T.; Chieffi, A.; Åhman, J.; Buchwald, S. *J. Am. Chem. Soc.* **2002**, *124*, 1261



Lee, S.; Beare, N.; Hartwig, J. *J. Am. Chem. Soc.* **2001**, *123*, 8410

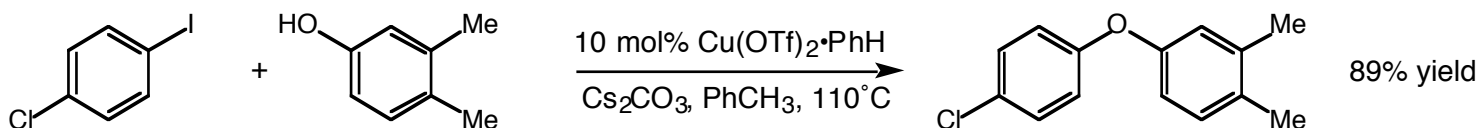
- ◆ Hartwig uses fluorescence technology to develop an optimized ligand system for arylation of cyanoacetates



Stauffer, S.; Beae, N.; Stambuli, J.; Hartwig, J. *J. Am. Chem. Soc.* **2001**, *123*, 4641

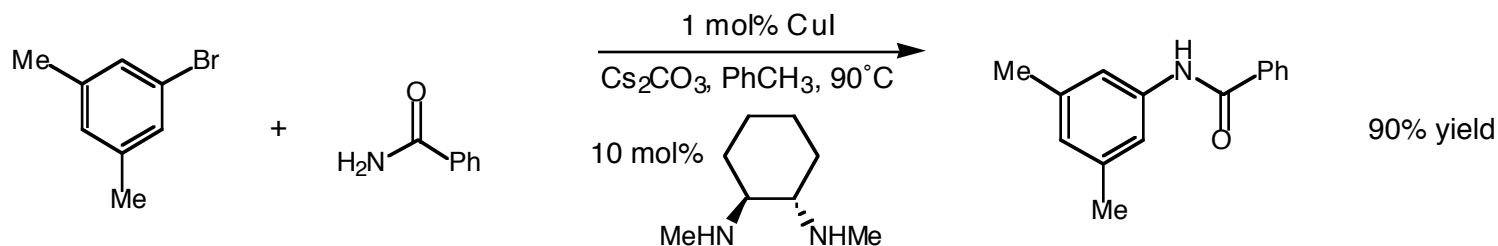
Where Are They Now?

- ◆ Buchwald has diverged from Hartwig by developing copper catalysts for a variety of Buchwald-Hartwig-type reactions
- ◆ These catalysts have the considerable advantage of stability, ease of use, and low cost

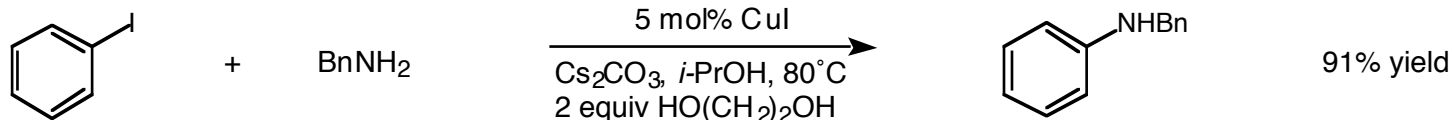


Marcoux, J.-F.; Doye, S.; Buchwald, S. *J. Am. Chem. Soc.* **1997**, *119*, 10539

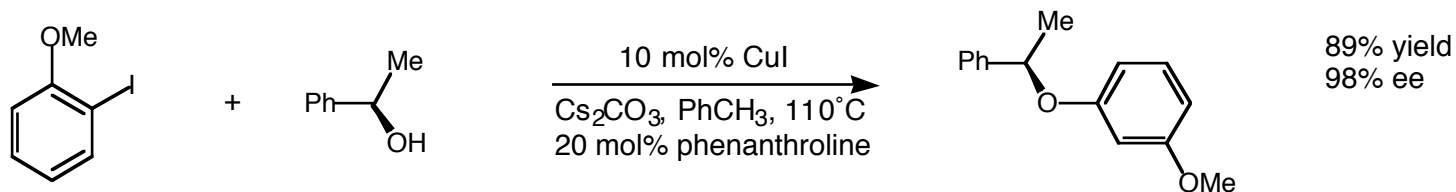
- ◆ Addition of ligands expands the scope of the reaction dramatically



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

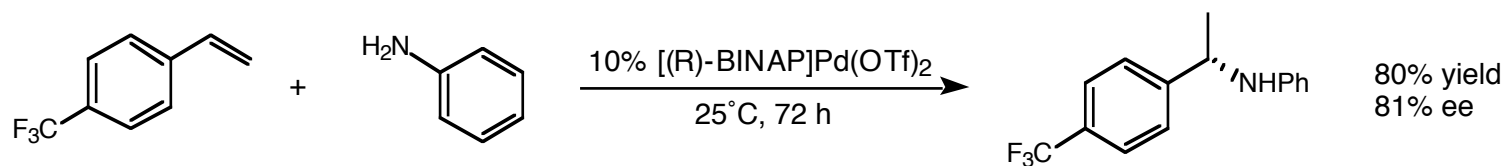


- ◆ Mechanistic work is in progress

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

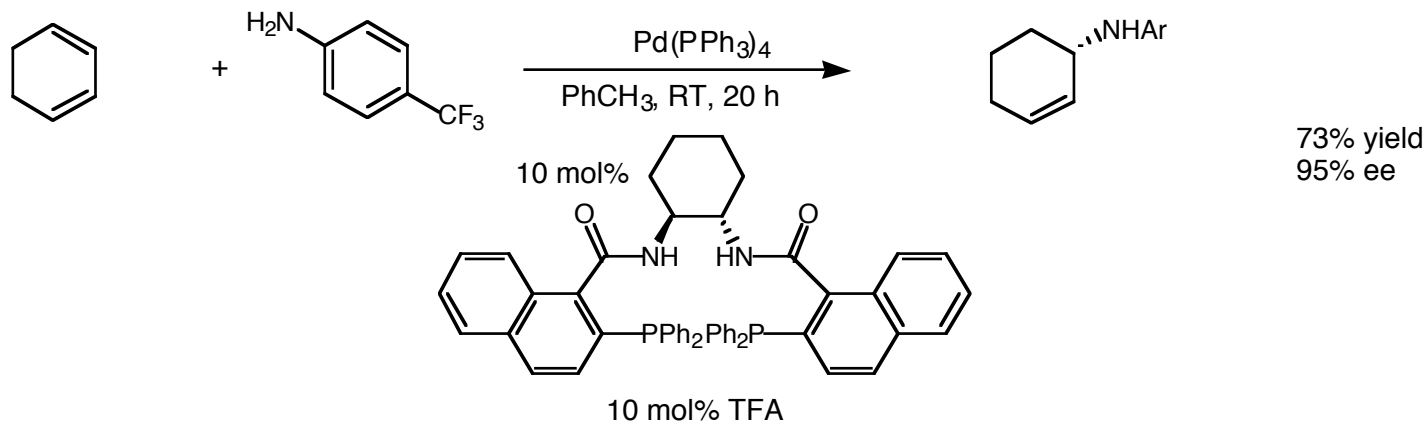
Dr. Hartwig, I Presume

- ◆ Hartwig has pioneered a new variety of amine-sp² coupling by catalytic hydroaminations



Kawatsura, M.; Hartwig, J. *J. Am. Chem. Soc.* **2000**, *122*, 9546

- ◆ Colorimetric high-throughput screens identify a highly active catalyst system

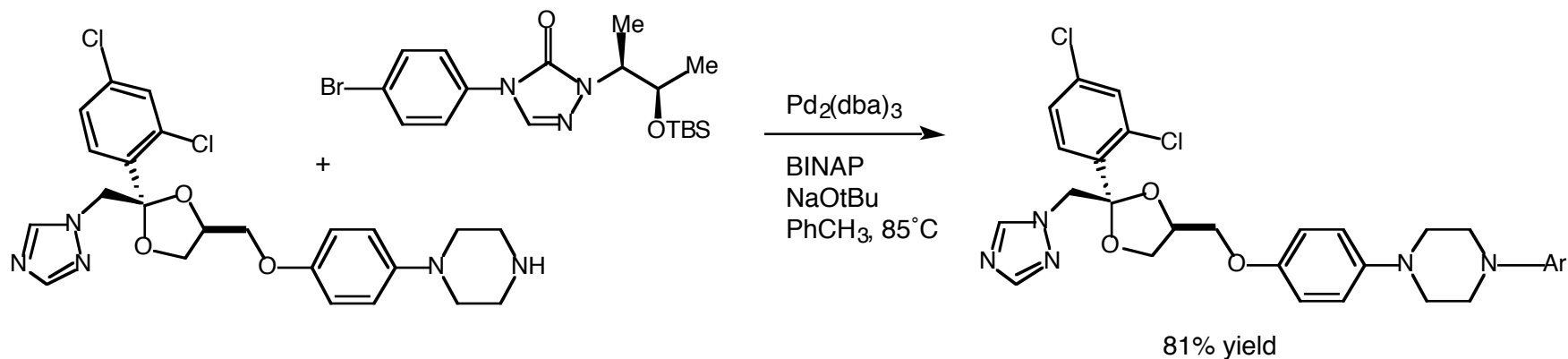


- ◆ Mechanism is presumed to go through Pd-alkene activation followed by nucleophilic attack of the aniline
- ◆ Further studies of this system have currently focused on racemization problems and elucidating the mechanism and kinetics

Lober, O.; Kawatsura, M.; Hartwig, J. *J. Am. Chem. Soc.* **2001**, *123*, 4366
Pawlas, J.; Nakao, Y.; Kawatsura, M.; Hartwig, J. *J. Am. Chem. Soc.* **2002**, *124*, 3669

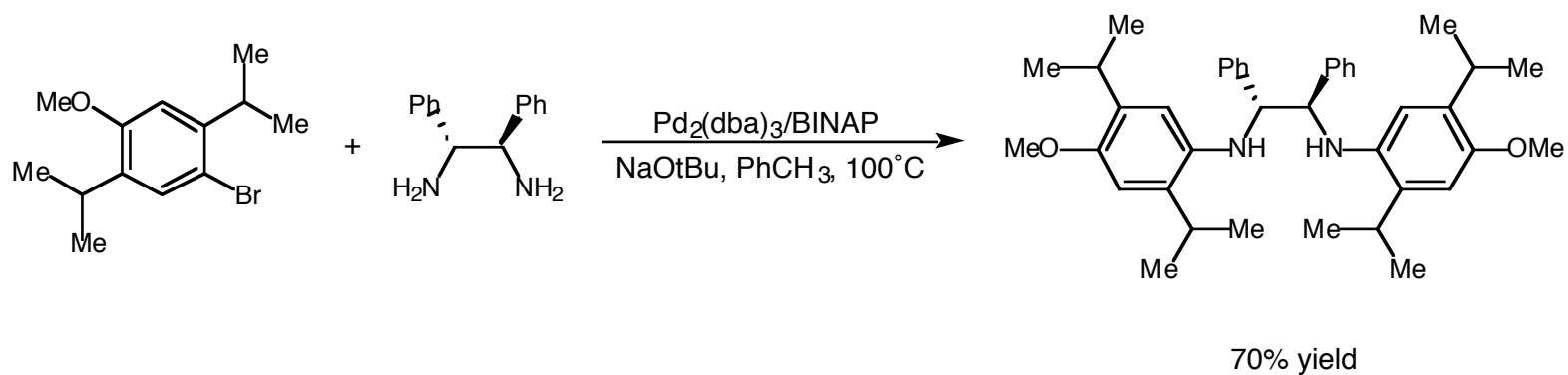
Buchwald and Hartwig Around You

- ◆ Aryl aminations are used in synthesis, though most often to make pharmaceuticals



Kung *et al.* *J. Med. Chem.* **1999**, *42*, 4705

- ◆ The Grubbs group has used a particularly difficult pair of substrates to make precursors to chiral IMes ligands for asymmetric cross-metathesis



Grubbs, R. H. *unpublished results*

Summary

- ◆ Buchwald-Hartwig chemistry provides a reliable, general means for the coupling of aryl halides and sulfonates to a variety of N, O, and C nucleophilic sources.
- ◆ Ligand development has led to greater mechanistic understanding and use of milder conditions
- ◆ This methodology awaits use in a complex total synthesis
- ◆ The continuingly qualitative understanding of many aspects of these reactions means that any serious attempt to use it should involve optimization of the wide range of conditions now available