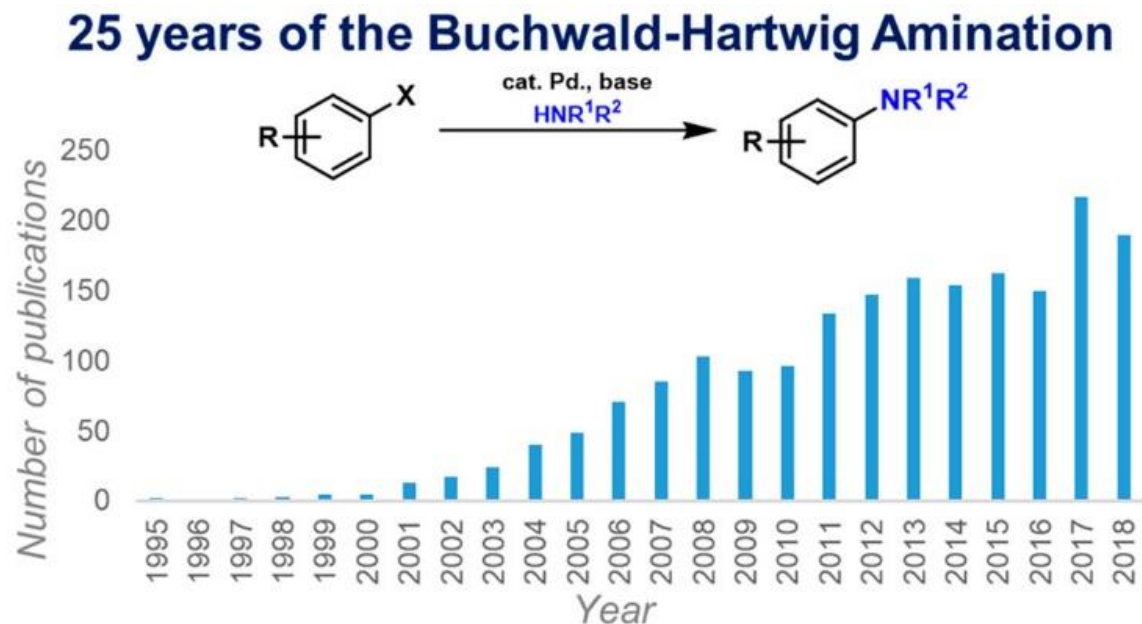
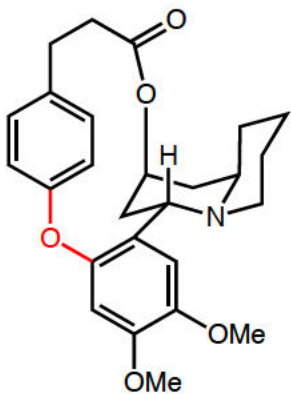


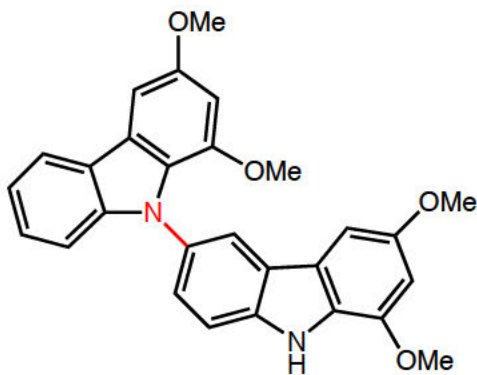
Pd-Catalyzed C-N Cross-Coupling Reactions: the Buchwald-Hartwig coupling



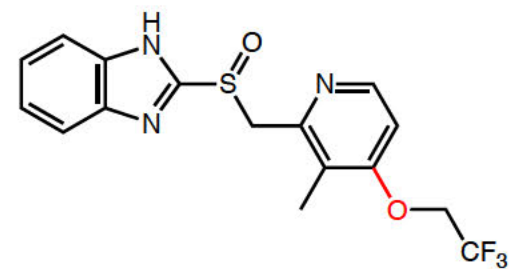
Why C–N and C–O Couplings?



vertaline

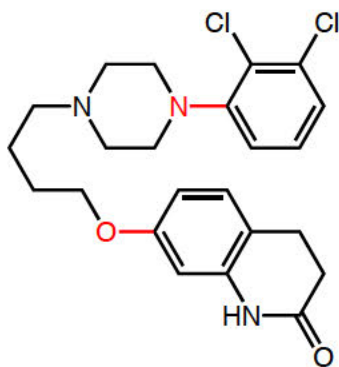


murrastifoline A



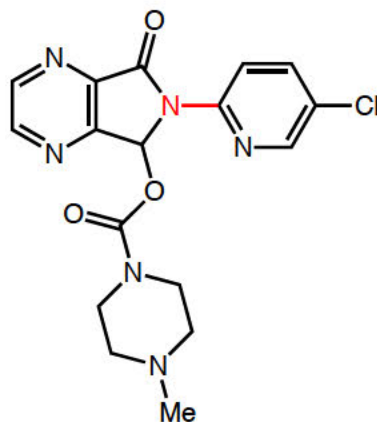
Prevacid

Used to treat gastric reflux disease



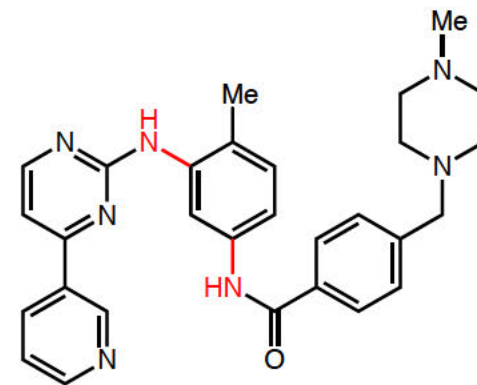
Abilify

Used to treat schizophrenia and bipolar mania



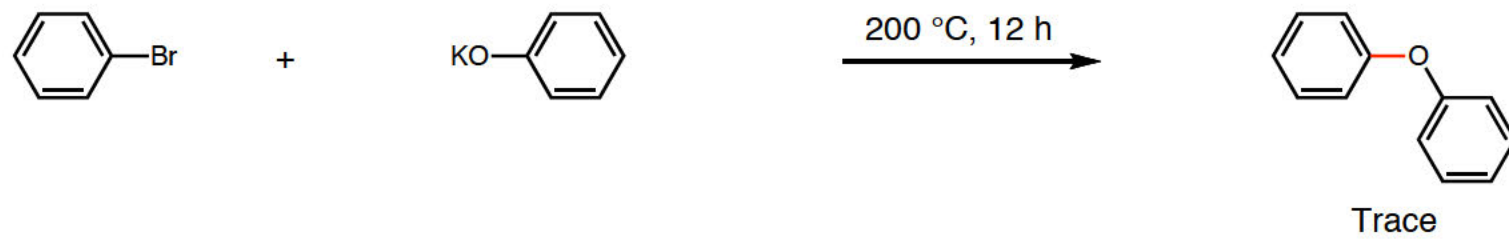
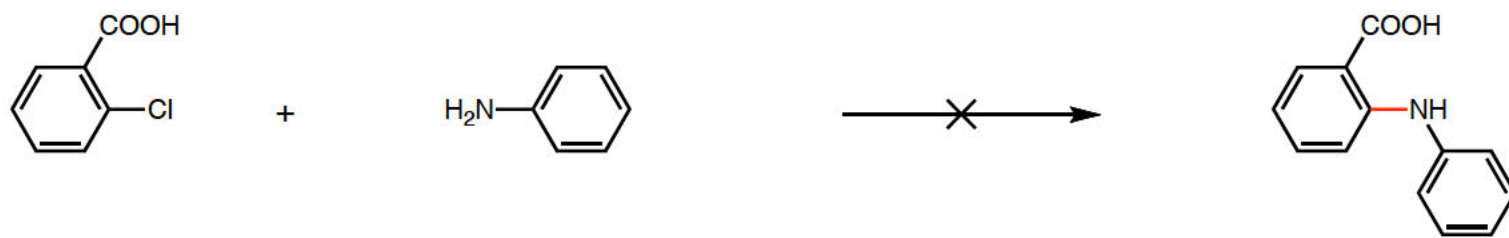
Lunesta

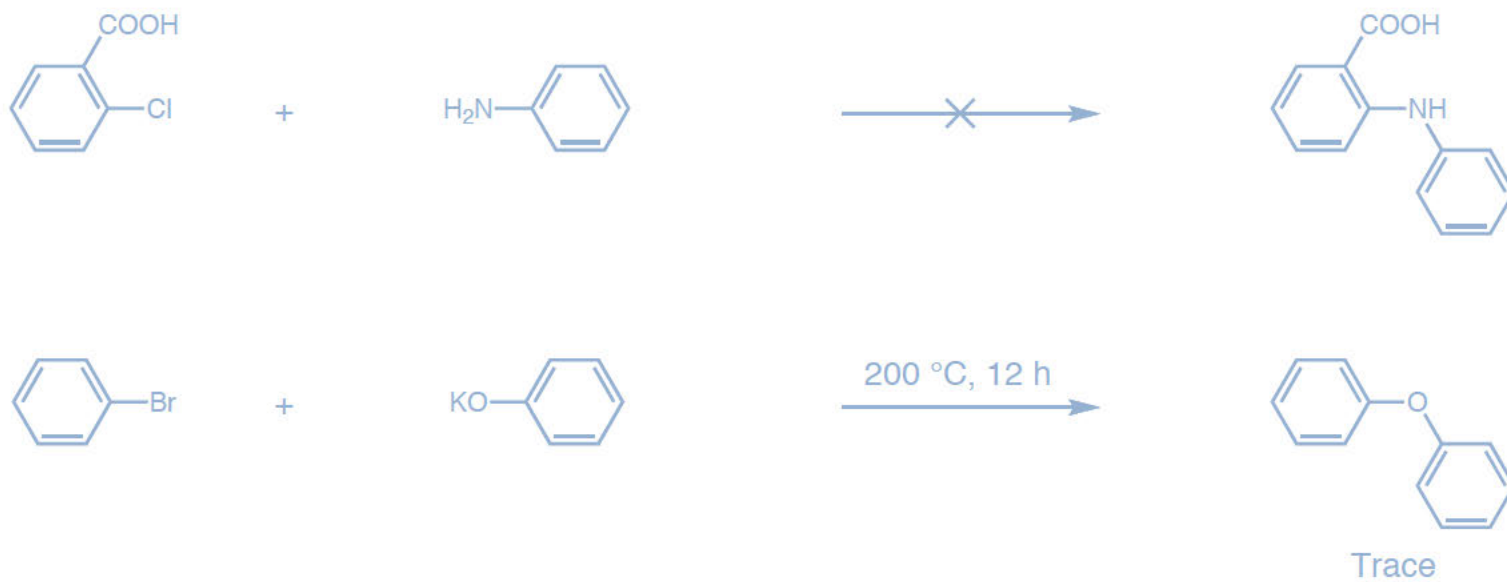
Used to treat insomnia



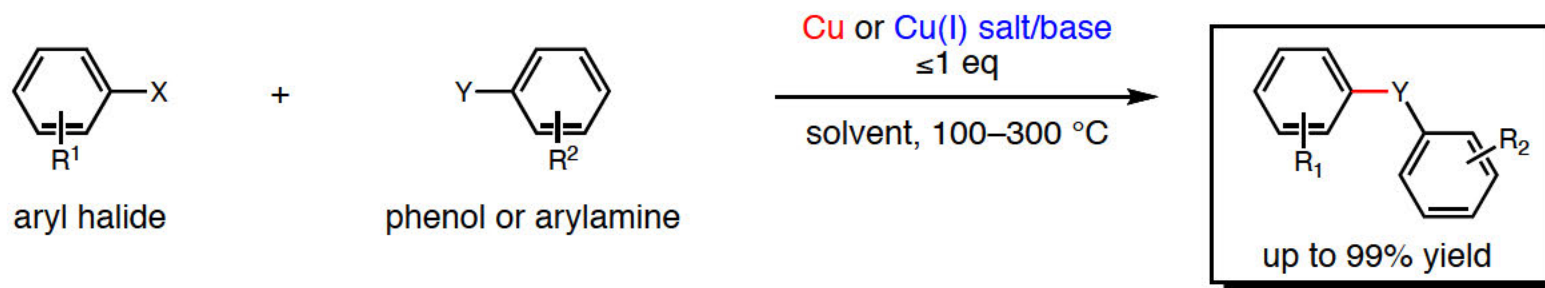
Gleevec

Used to treat chronic myeloid leukemia





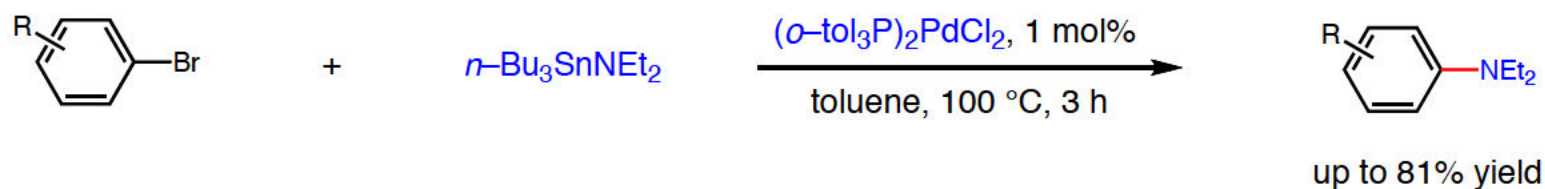
■ Biaryl ether and amine synthesis (Ulmann 1903 and Goldberg 1906)



Ulmann, F. *Chem. Ber.* **1903**, *36*, 2382.

Goldberg, I *Chem. Ber.* **1906**, *39*, 1691.

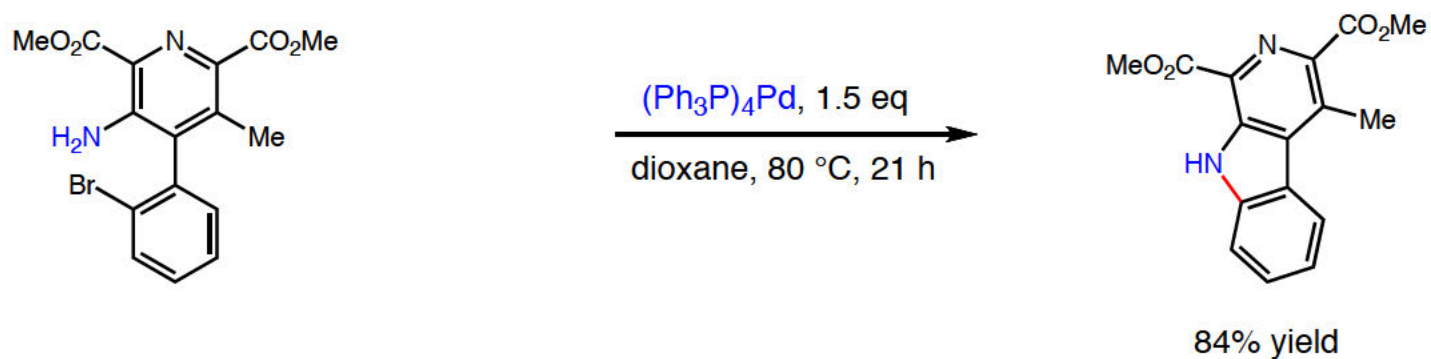
■ Migita introduced the first catalytic version in 1983.



The reaction was proposed to follow the oxidative-addition, transmetalation and reductive-elimination sequence.

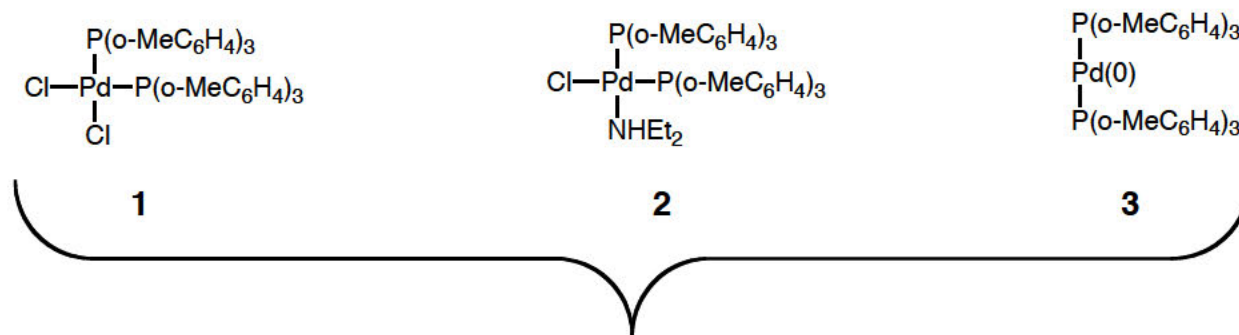
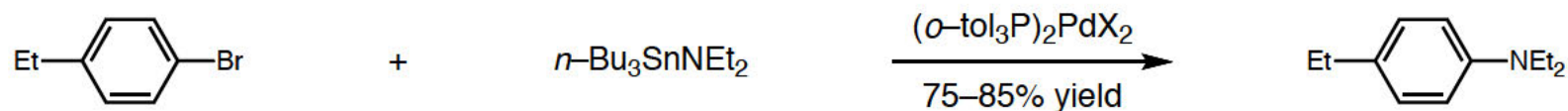
Migita, T. *et al Chem. Lett.* **1983**, 927.

■ Boger introduced Pd(0) mediated intramolecular amination with free amine in 1984.



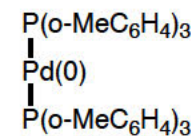
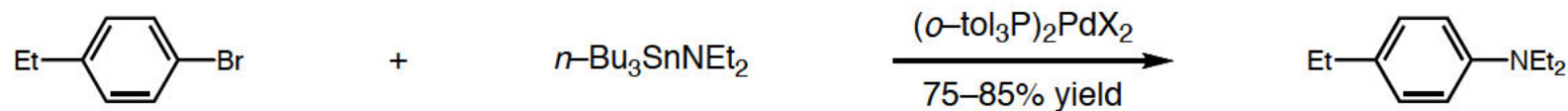
Boger, D. L., Panek, J. S. *Tet. Lett.* **1984**, 25, 3175.

■ Feb. 22, 1994 the Hartwig group submitted a mechanistic study of Migita's reaction.



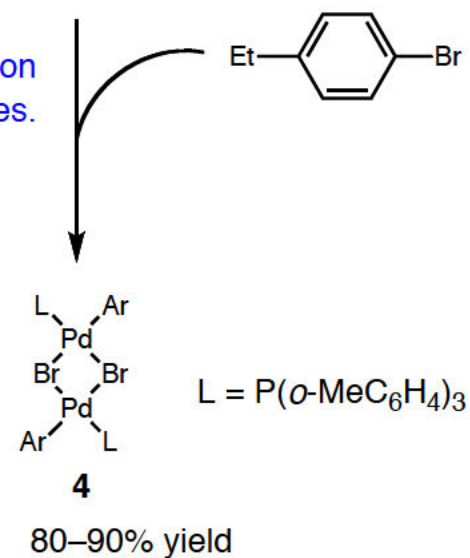
◆ 1, 2, and 3 showed catalytic reactivity and the reaction was faster with 3
=> Pd(0) is a preferred catalyst and intermediate.

■ Feb. 22, 1994 the Hartwig group submitted a mechanistic study of Migita's reaction.

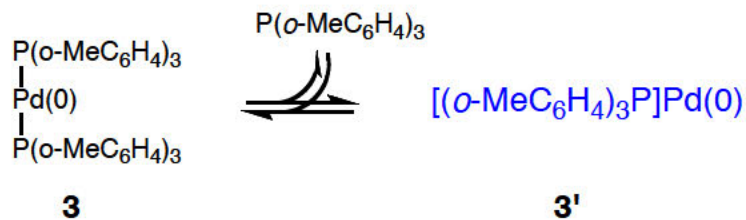
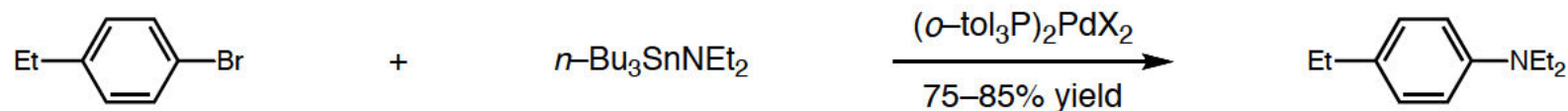


3

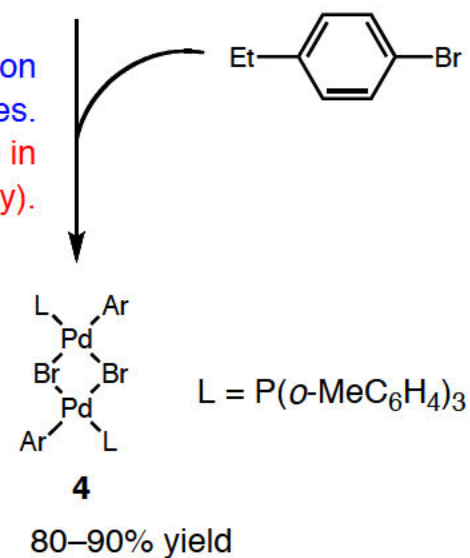
◆ The rate formation of **4** decreases as the concentration of ligand increases.



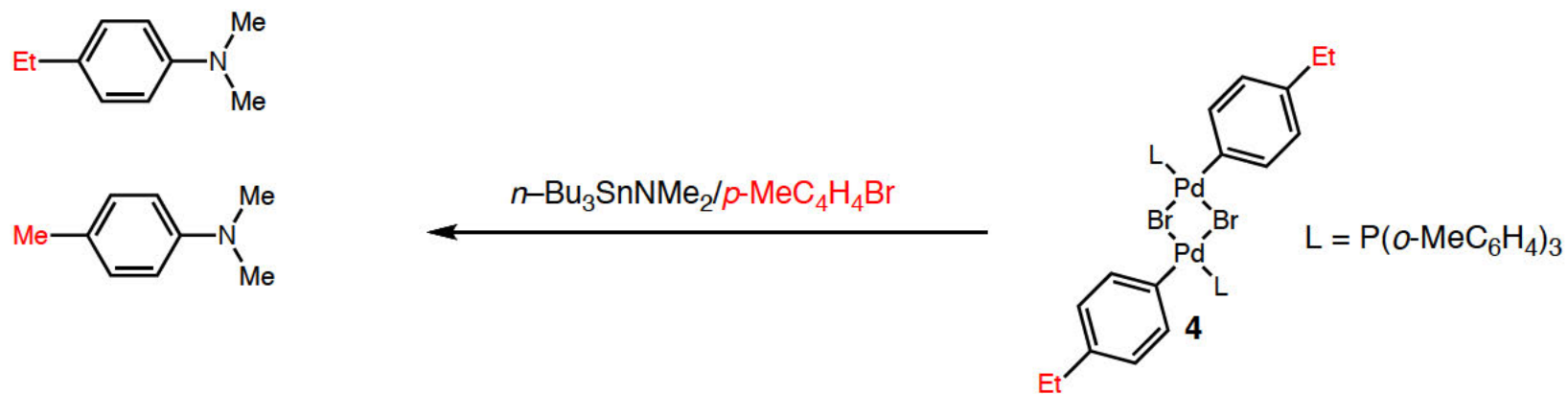
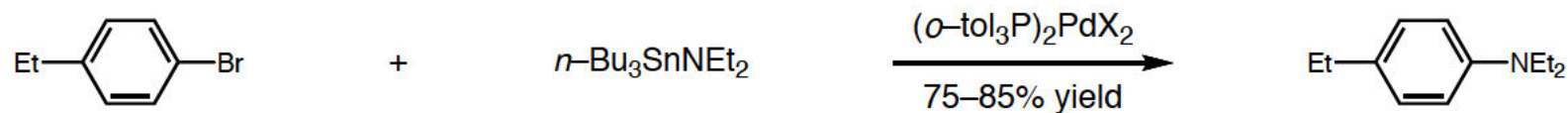
■ Feb. 22, 1994 the Hartwig group submitted a mechanistic study of Migita's reaction.



◆ The rate formation of **4** decreases as the concentration of ligand increases.
 => $(o\text{-MeC}_6\text{H}_4)_3\text{PPd}(0)$ **may be** a direct intermediate in the catalytic cycle (favorable possibility).

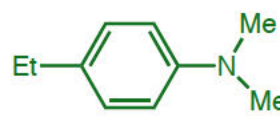
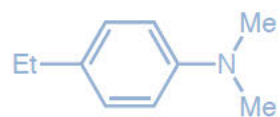
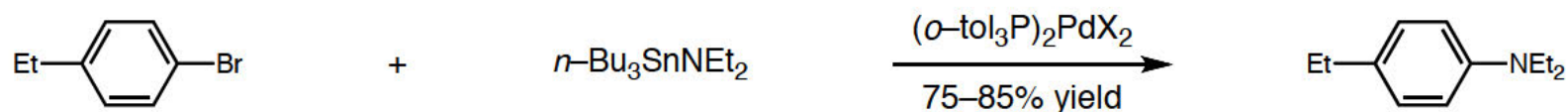


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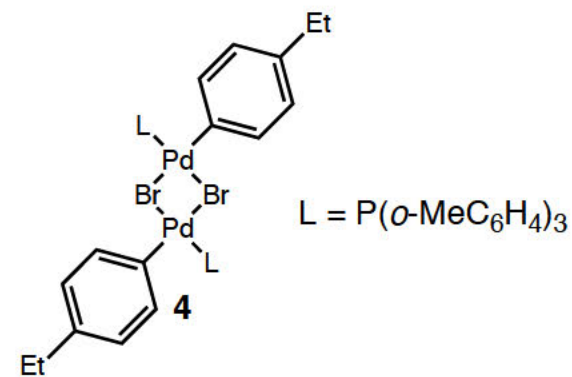


Hartwig, J. F. *et al* *JACS* **1994**, *116*, 5969.

■ Feb. 22, 1994 the Hartwig group submitted a mechanistic study of Migita's reaction.



60–70% yield

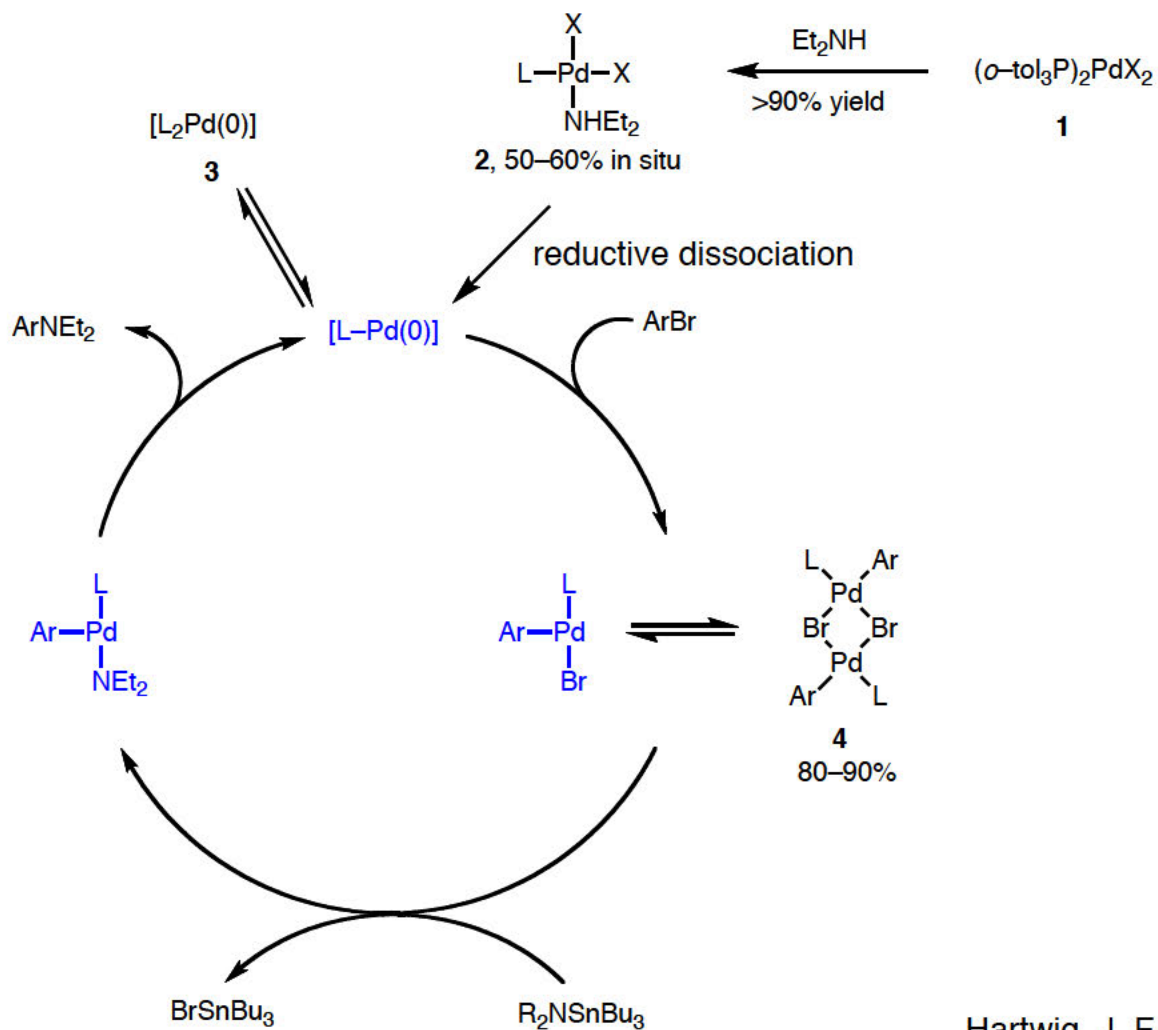
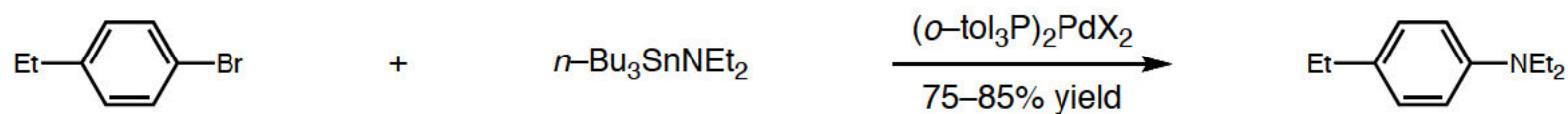


=> **4** or the corresponding monomer is directly involve in the catalytic cycle.

=> Transmetalation and reductive elimination are most likely to occur.

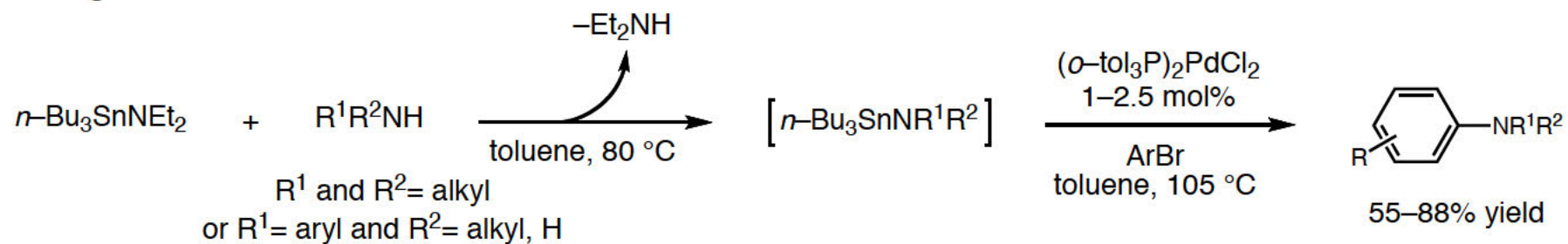
Hartwig, J. F. *et al* *JACS* **1994**, *116*, 5969.

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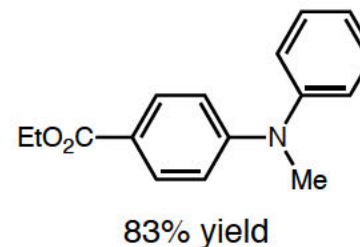
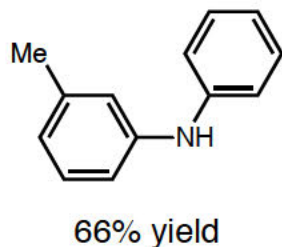
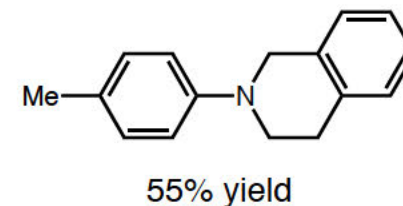
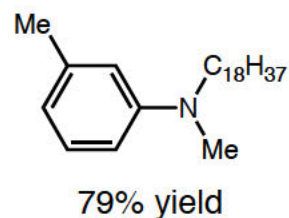
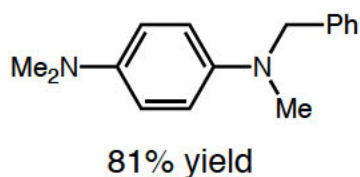
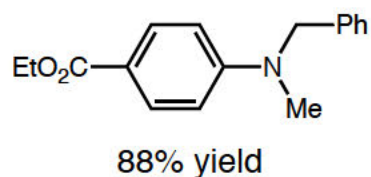


Hartwig, J. F. *et al* *JACS* **1994**, *116*, 5969.

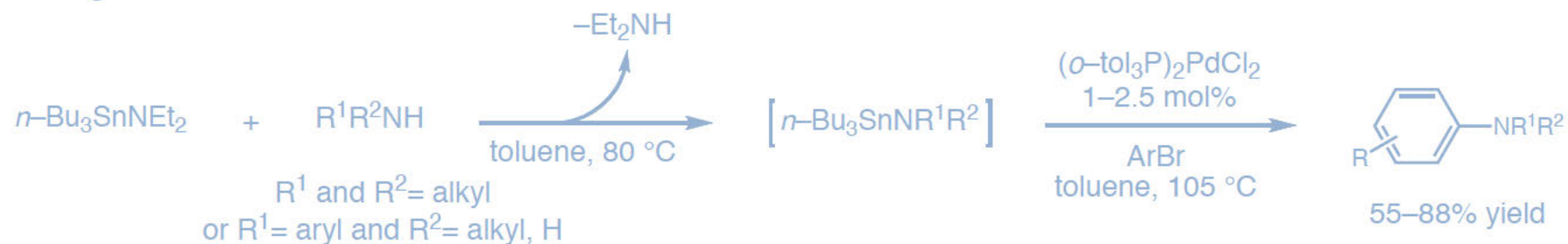
■ May 23, 1994 the Buchwald group submitted a amine scope expansion report of Migita's reaction via in situ generated aminostannanes.



Guram, A. S. and Buchwald, S. L. *JACS* **1994**, *116*, 7901.

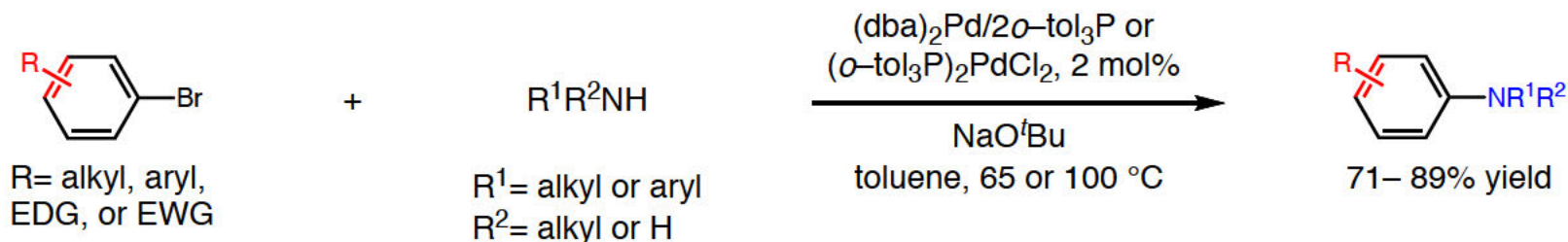


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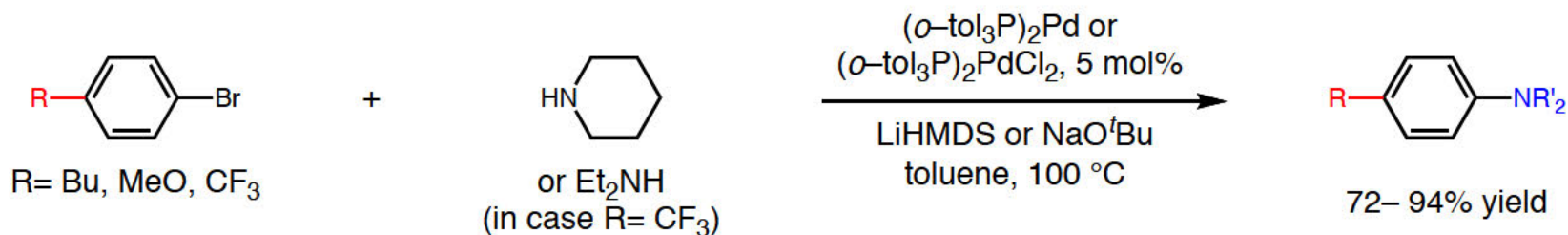


Guram, A. S. and Buchwald, S. L. *JACS* **1994**, *116*, 7901.

- Tin-free aminations were reported by both the Buchwald and Hartwig groups in 1995:
The **Buchwald–Hartwig amination**.

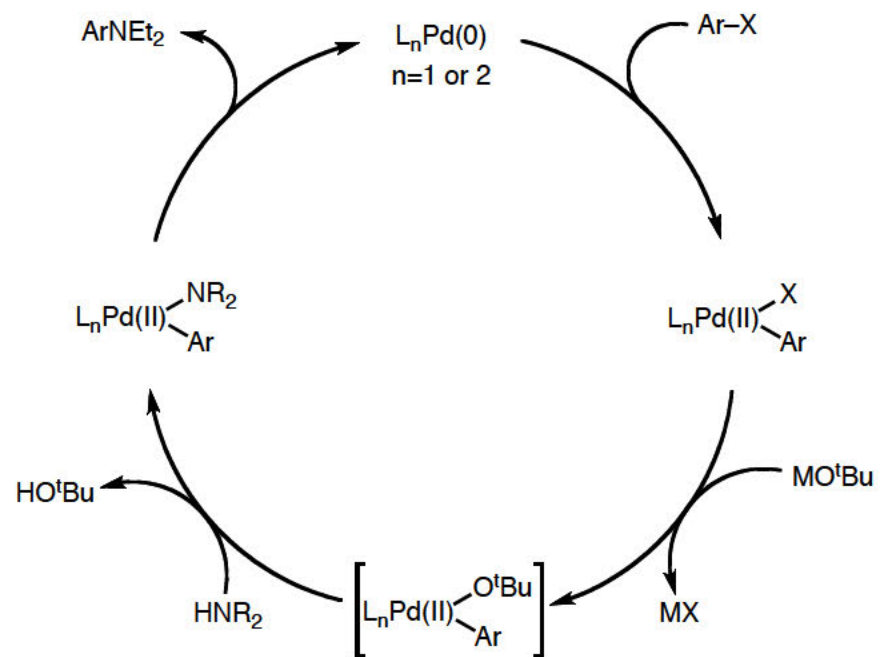


(Submitted on Jan 17, 1995; revised March 13 1995) Buchwald, S. L. *et al* *ACIE* **1995**, *34*, 1348.

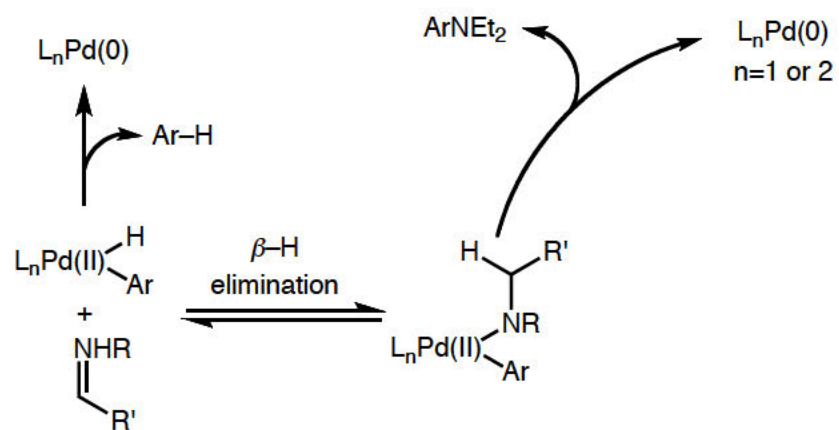


(Submitted on March 6, 1995) Louie, J., Hartwig, J. F. *Tet. Lett.* **1995**, *36*, 3069.
(from mechanistic study)

The Mechanistic Scheme that You Normally See



The Mechanistic Scheme that You Normally See

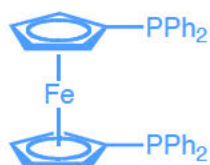
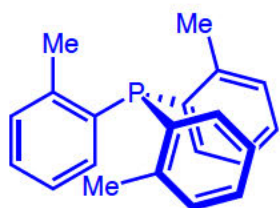
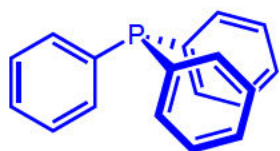


"An important part of the art of organometallic chemistry is to pick suitable spectator ligand sets to facilitate certain types of reactions."

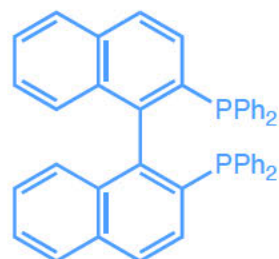
Robert. H. Crabtree

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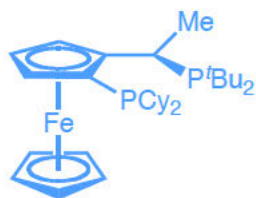
Robert. H. Crabtree



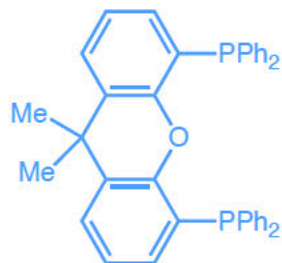
DPPF



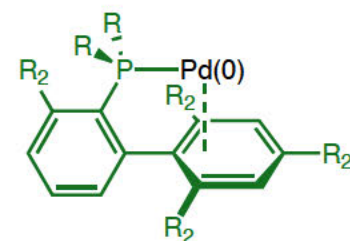
BINAP



Josiphos

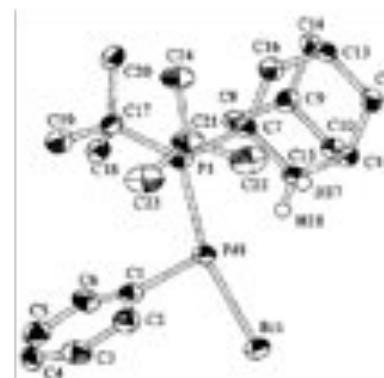
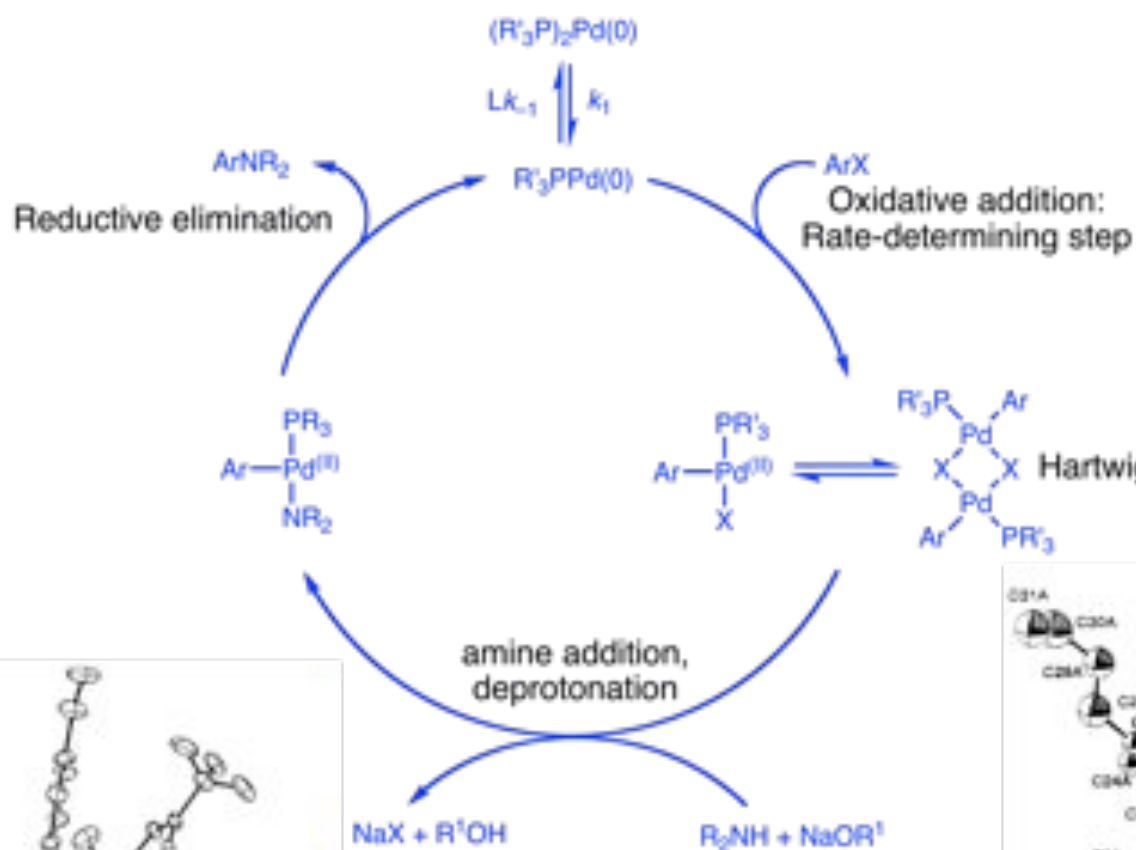


Xantphos

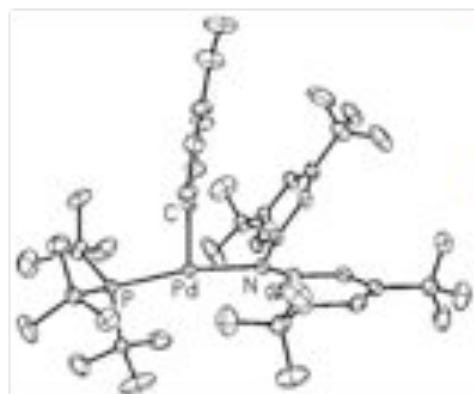


Biarylphosphine

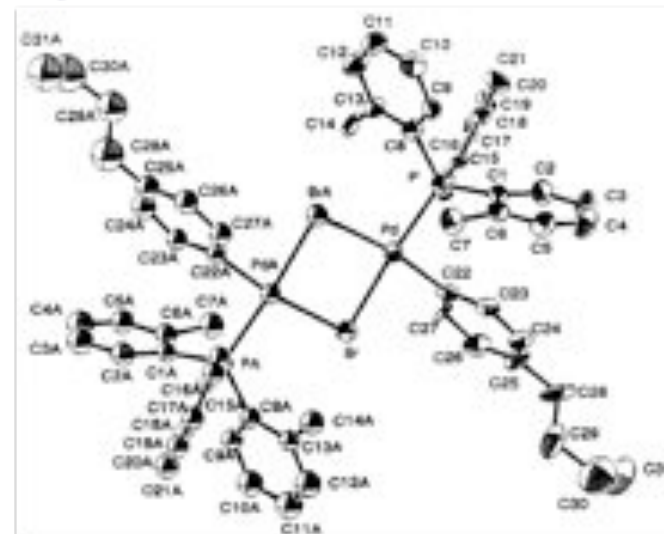
Mechanistic Study with Monodentate Hinderd Phosphine Ligands



X-ray structure of
 $[(1-AdP^tBu_2)Pd(C_6H_5)(Br)]$
 Hartwig, J. F. *et al JACS* 2002, 124, 9346.



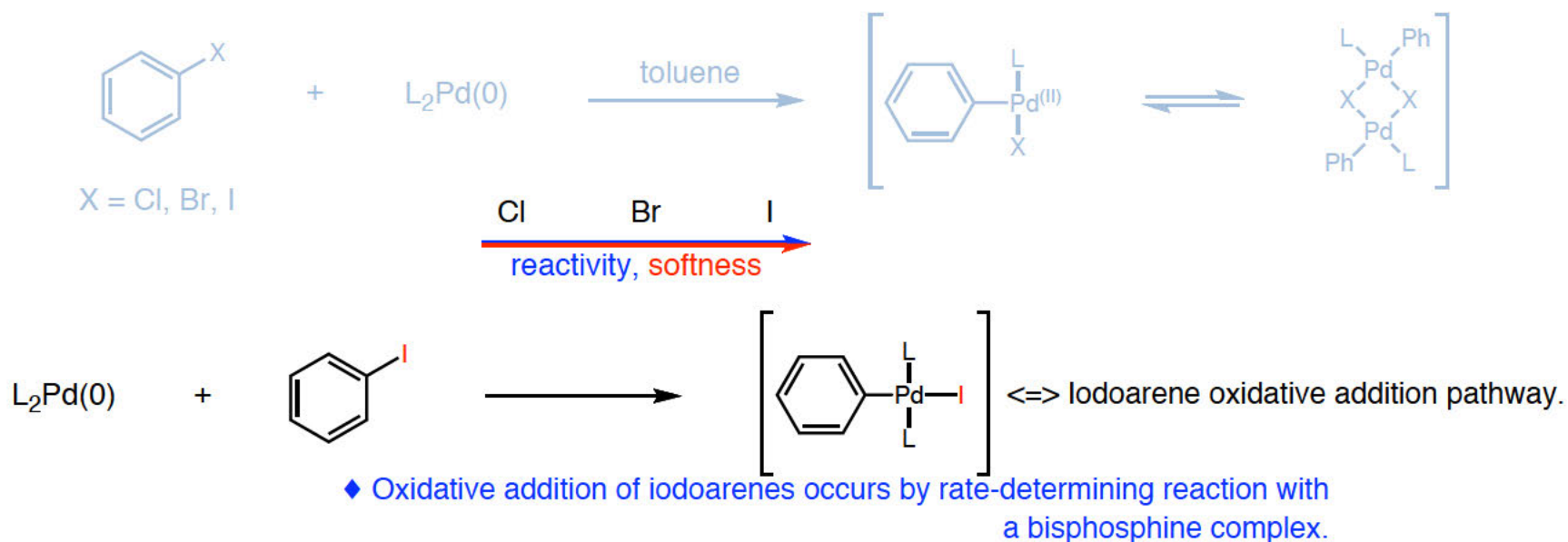
ORTEP diagram of
 $(^tBu_3P)Pd(MeOC_6H_4)N(3,5-(CF_3)_2C_6H_3)_2$
 Hartwig, J. F. *et al JACS* 2004, 126, 5344.
 Buchwald, S. L. *et al Organometallics* 1996, 15, 2745(solution struct.)



ORTEP diagram of
 $[(o-tol_3P)Pd(4-nBuC_6H_4)(Br)]_2$
 Hartwig, J. F. *et al Organometallics* 1995, 14, 3030.

Oxidative Addition with Monodentate Hindered Phosphine Ligands

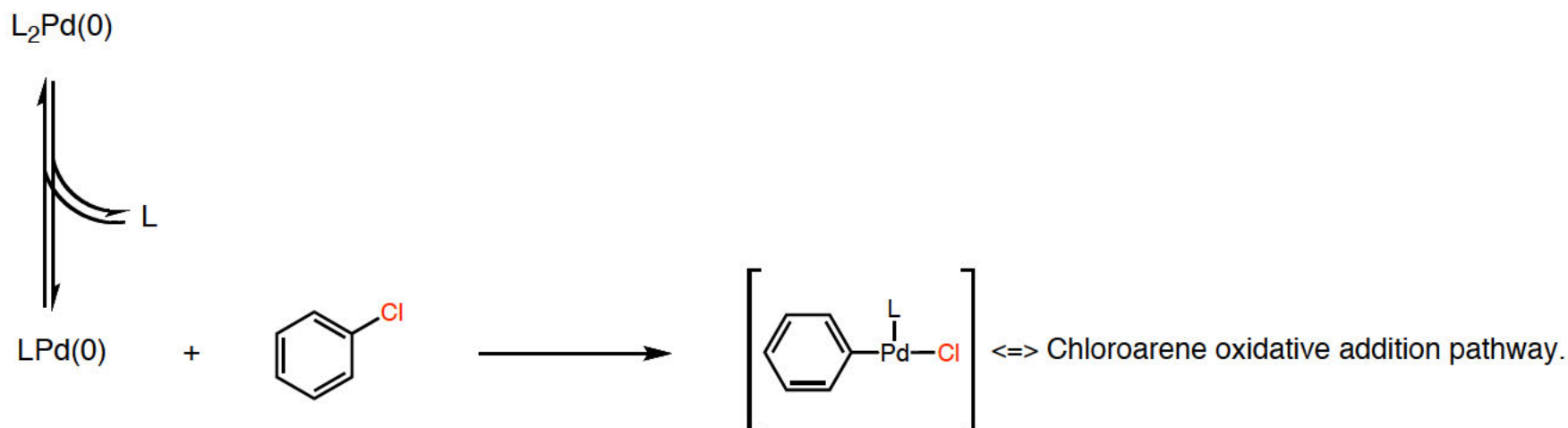
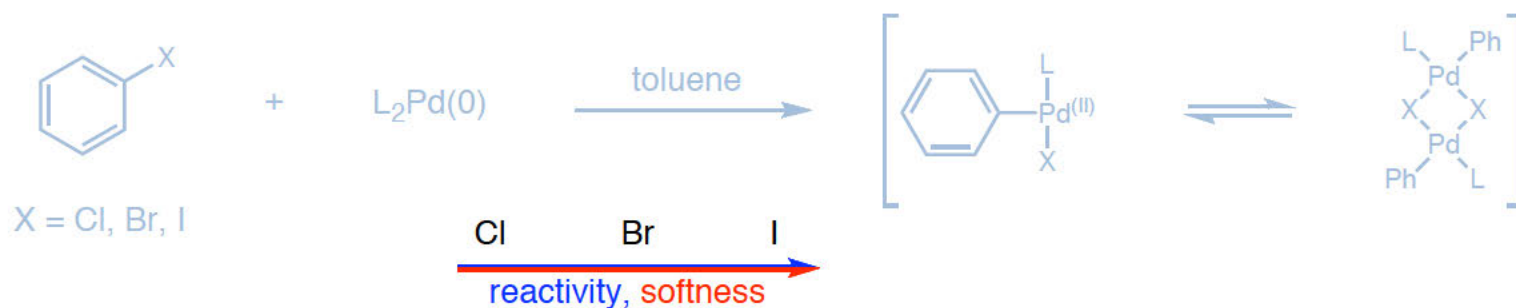
- Kinetic study of the oxidative addition reaction between phenyl halides and $[(R_3P)_2Pd(0)]$ complexes



(with *Q-phos*) Barrios-Landeros, F. and Hartwig, J. F. *JACS* **2005**, *127*, 6944.
Hartwig, J. F. *et al JACS* **2009**, *131*, 8141.

Oxidative Addition with Monodentate Hindered Phosphine Ligands

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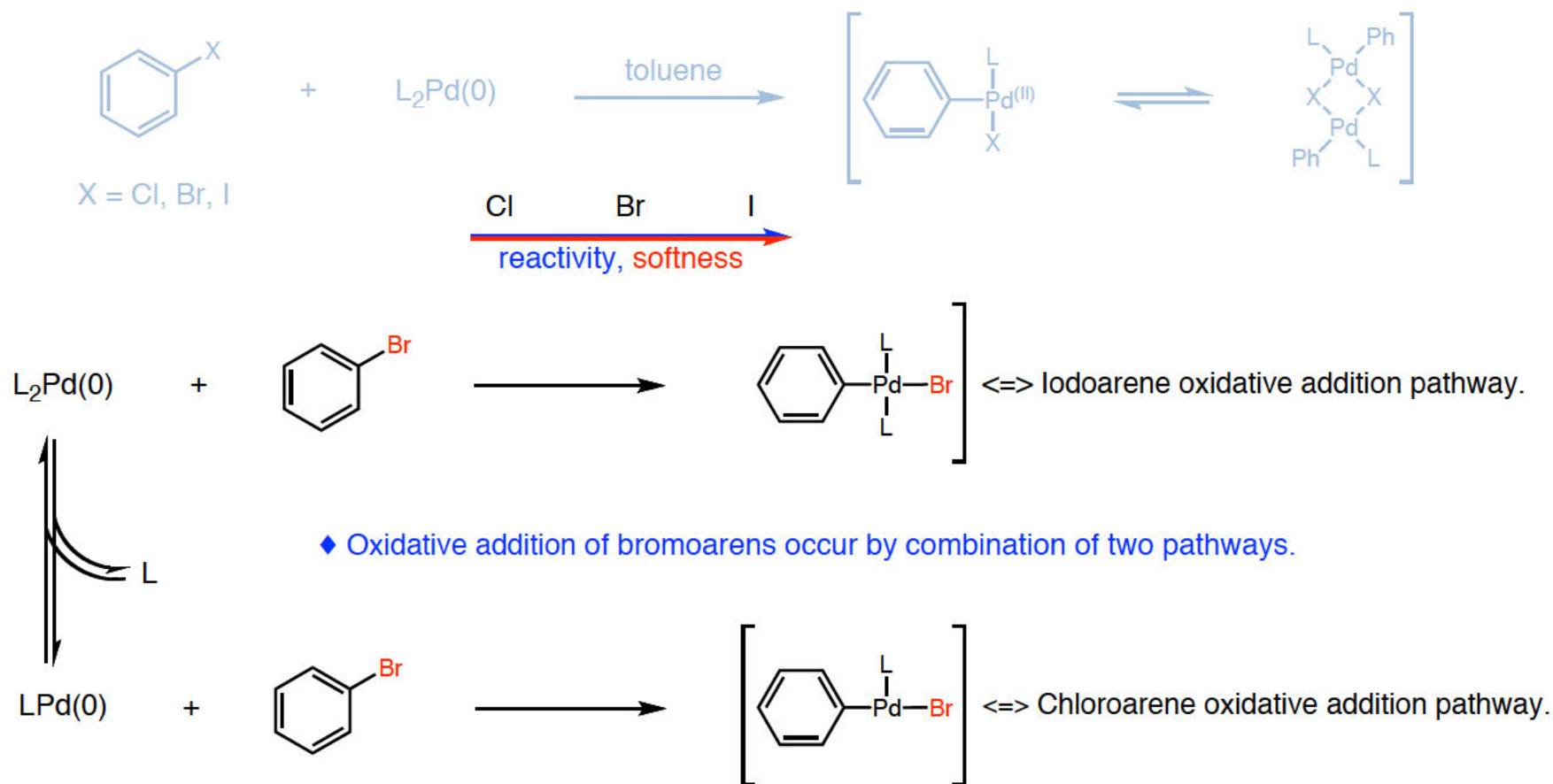


- ◆ Oxidative addition of chloroarenes occur by rate-determining reaction with a monophosphine complex.

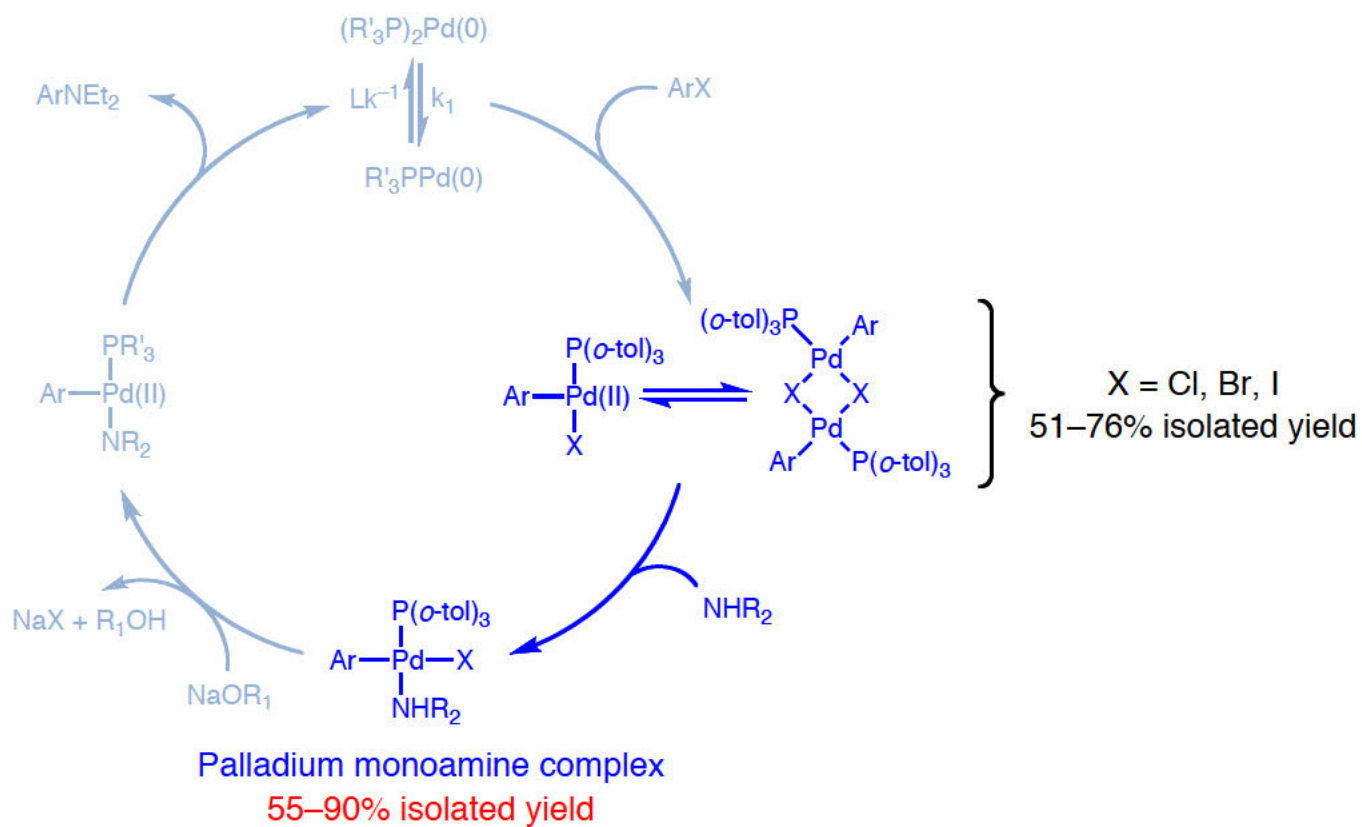
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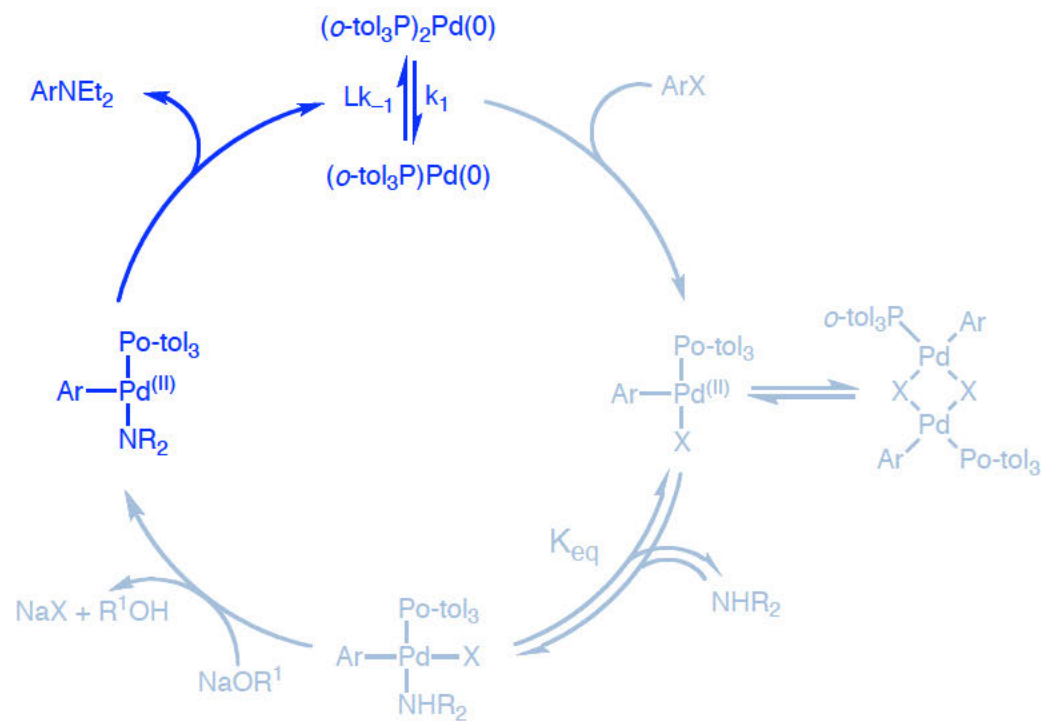


Formation of Palladium Monoamine Complexes

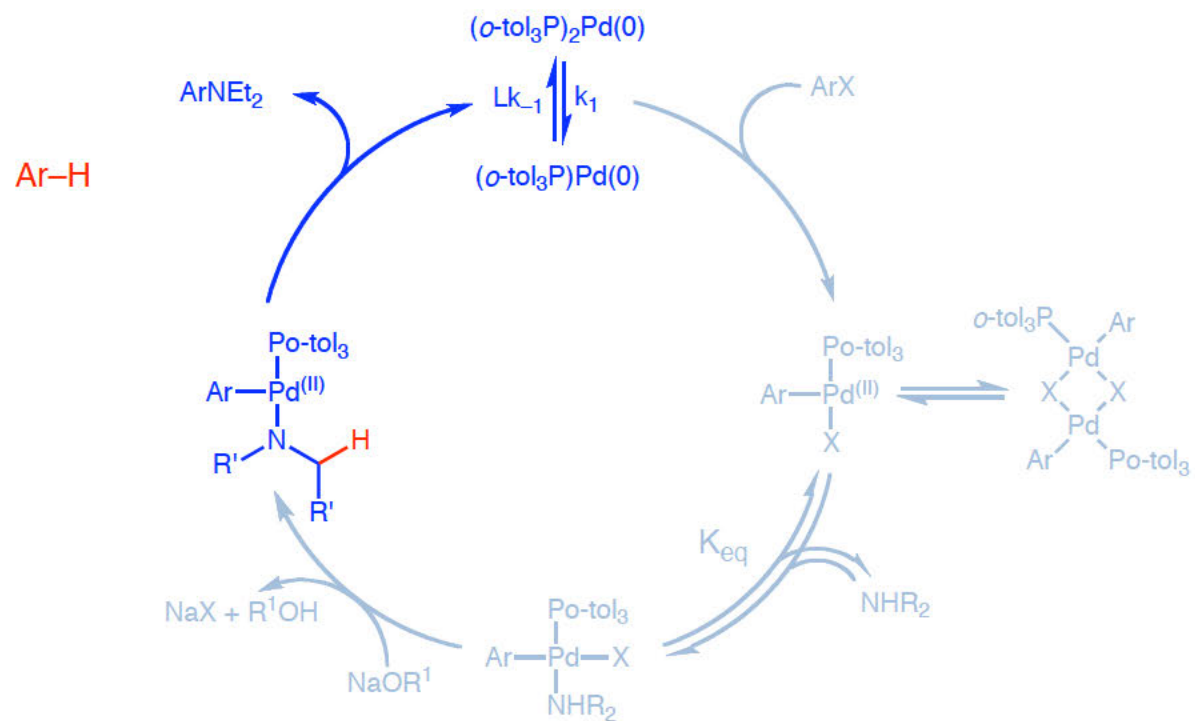


Buchwald, S. L. *et al Organometallics* **1996**, *15*, 2745.
 Widenhoefer, R. A. and Buchwald, S. L. *Organometallics* **1996**, *15*, 2755.

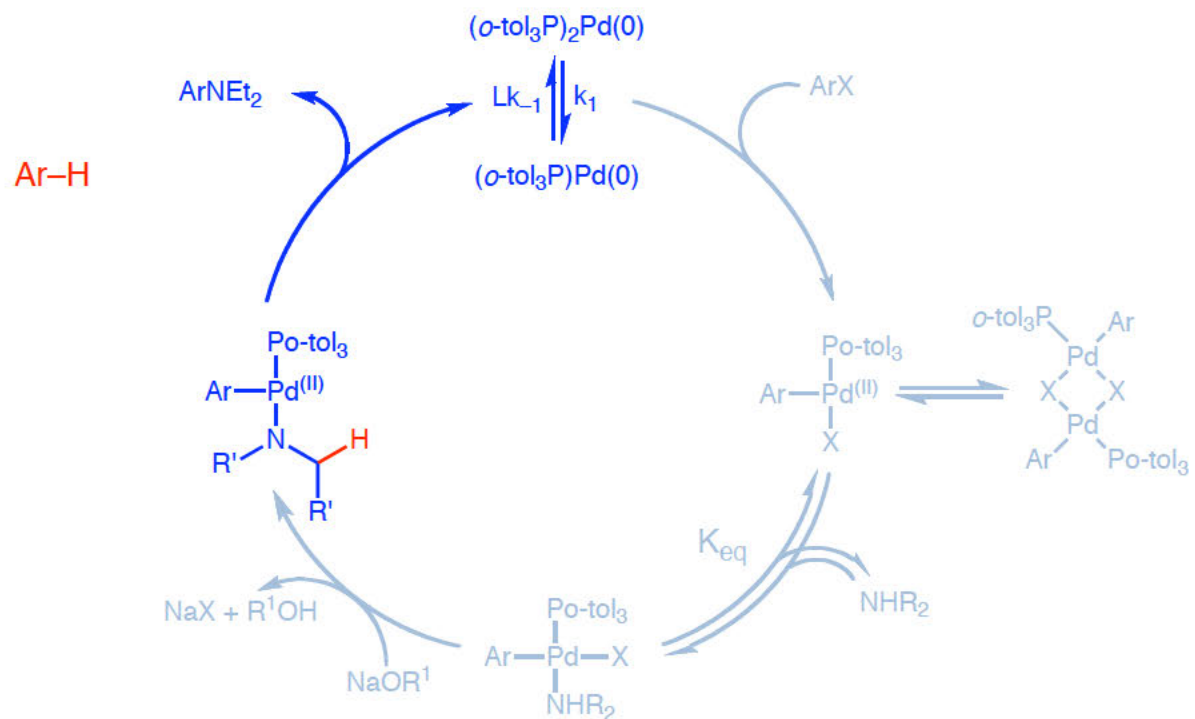
Reductive Elimination with Monodentate Hindered Phosphine Ligands



Reductive Elimination with Monodentate Hindered Phosphine Ligands

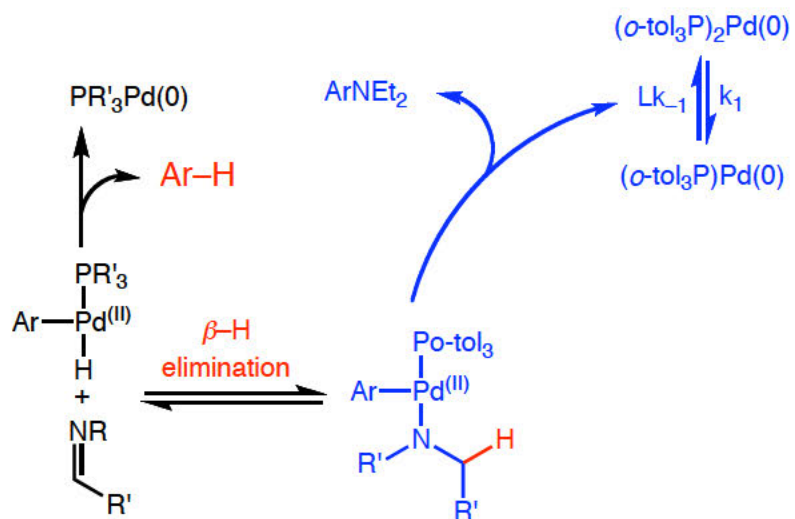


Reductive Elimination with Monodentate Hindered Phosphine Ligands



◆ Where does the reductive arene (Ar-H) product come from?

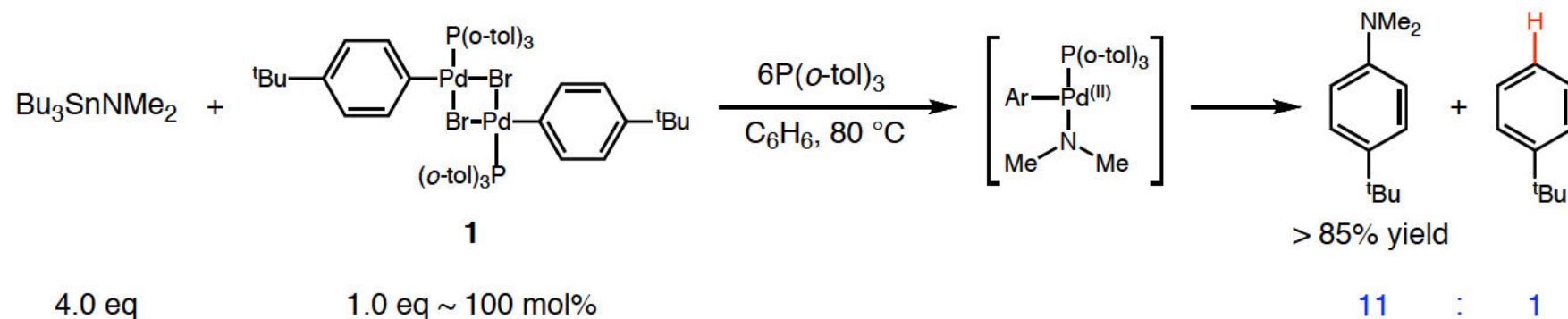
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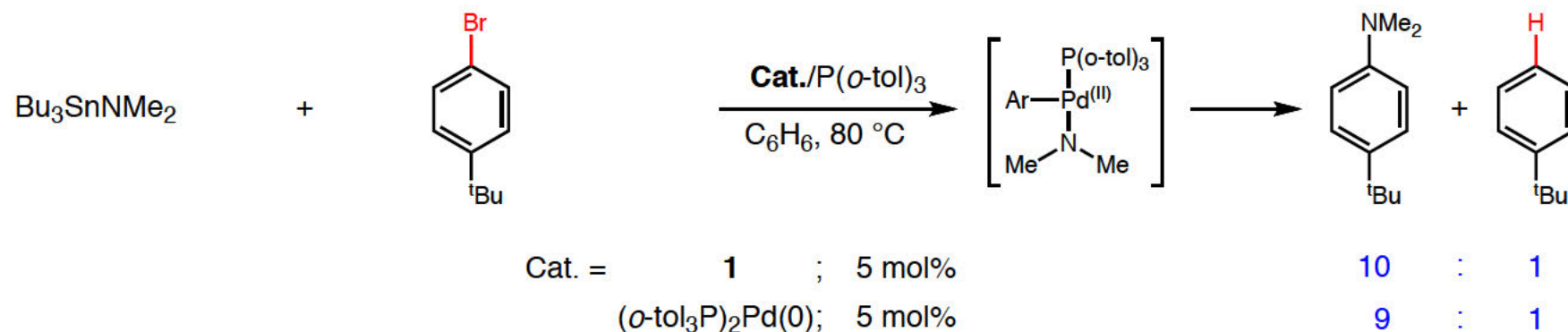
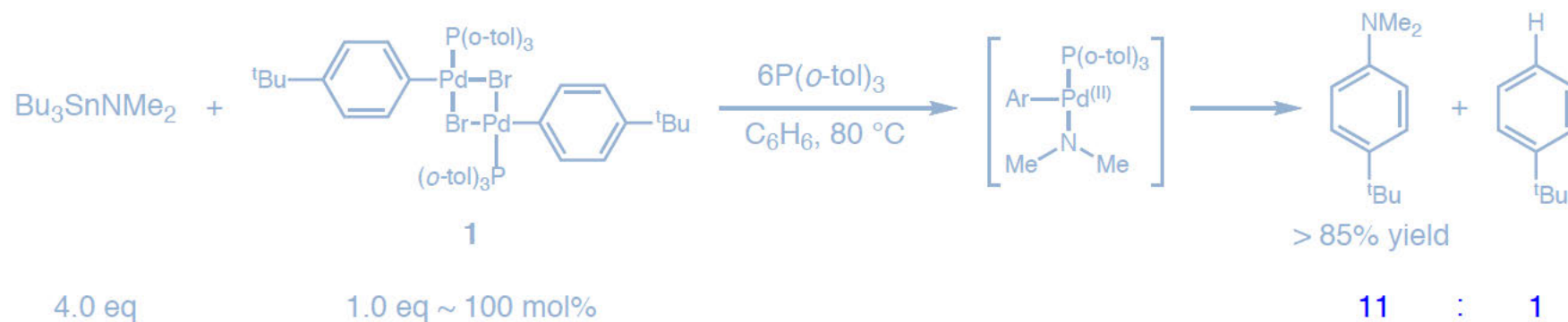
Reductive Elimination with Monodentate Hindered Phosphine Ligands

■ Formation of arene from catalytic cycle



Reductive Elimination with Monodentate Hindered Phosphine Ligands

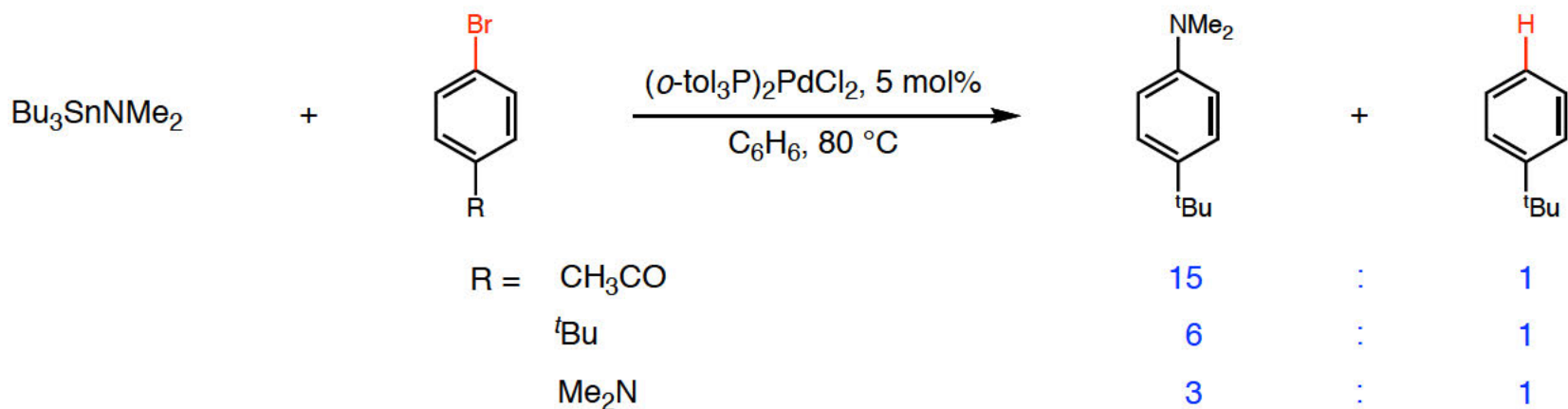
■ Formation of arene from catalytic cycle



=> The catalytic cycle produces ~ 10 : 1 coupling amine : arene, regardless the amount of intermediate **1** or catalyst $[\text{L}_2\text{Pd}(0)]$.

Reductive Elimination with Monodentate Hindered Phosphine Ligands

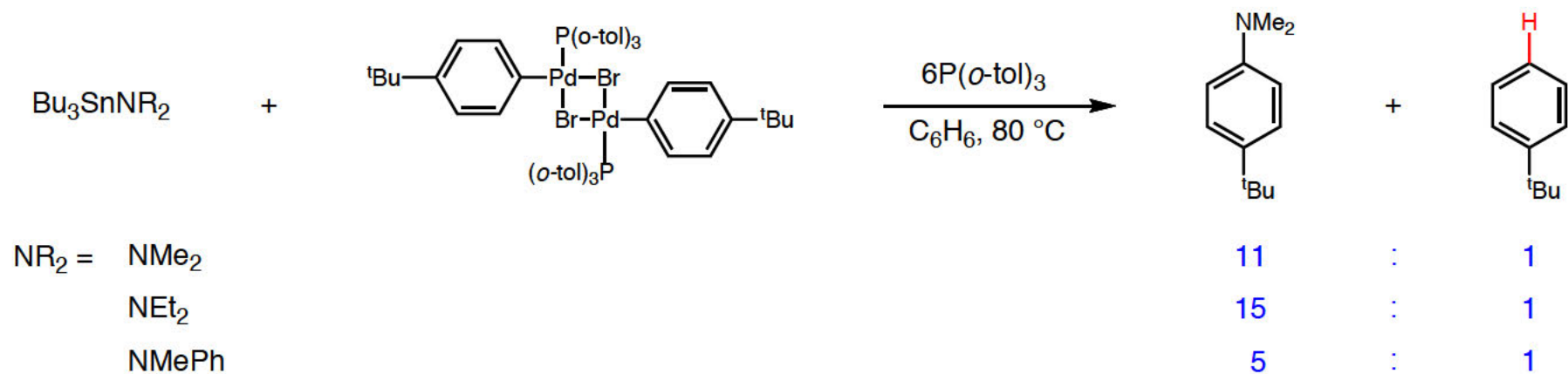
■ Effect of substituent of aryl halide on coupling amine : arene ratio



=> EWG on the arene ring accelerates the reductive elimination toward the coupling amine formation.

Reductive Elimination with Monodentate Hindered Phosphine Ligands

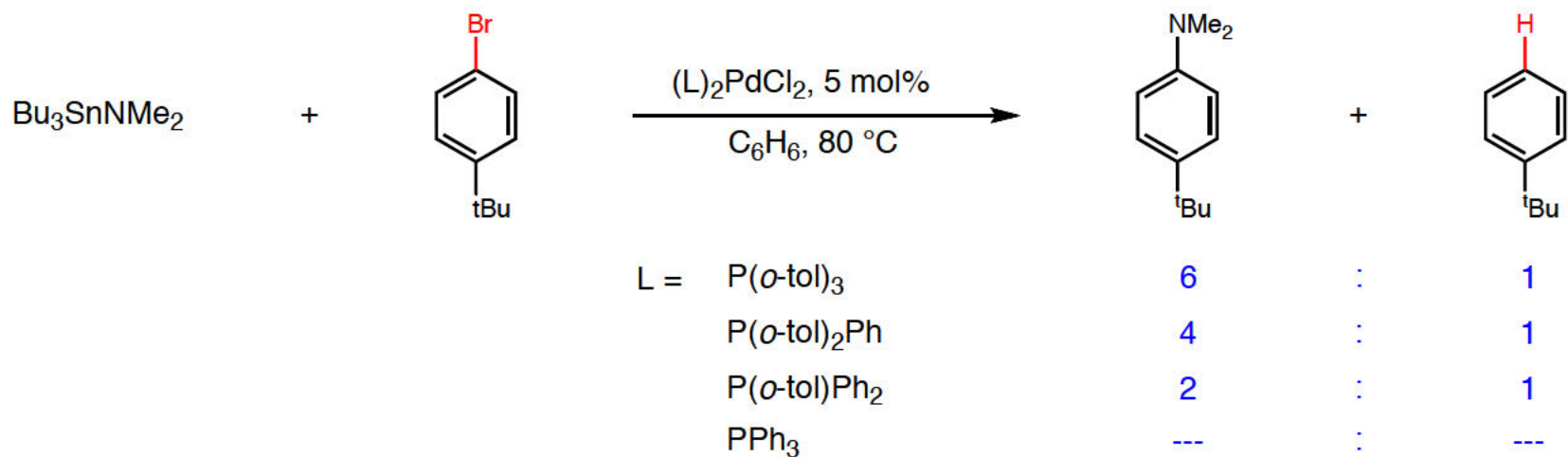
■ Effect of amine on coupling amine : arene ratio



=> Large and EDG on the amine accelerates the reductive elimination toward the coupling amine formation.

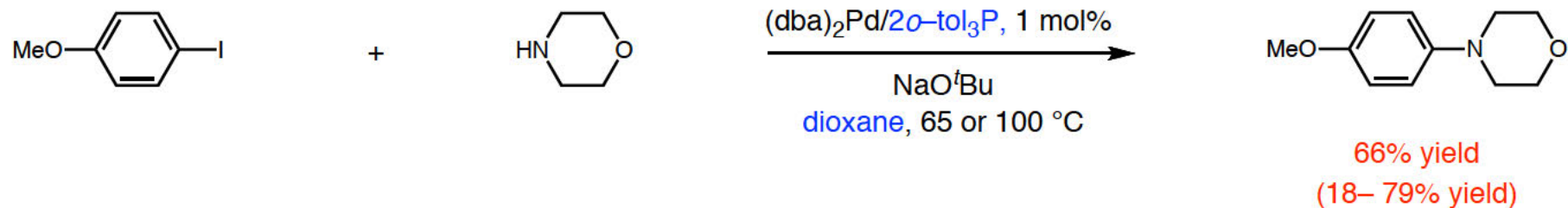
Reductive Elimination with Monodentate Hindered Phosphine Ligands

■ Effect of ligand on coupling amine : arene ratio

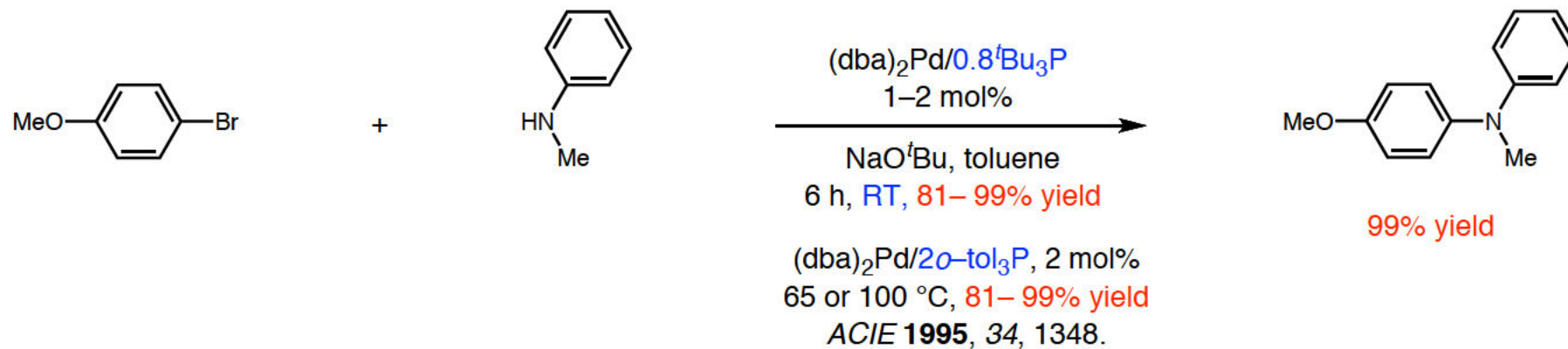


=> Large ligands accelerates the reductive elimination toward the coupling amine formation.

Aminations with Monodentate Hindered Phosphine Ligands

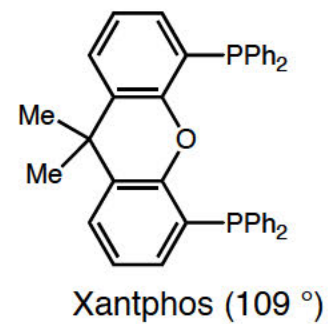
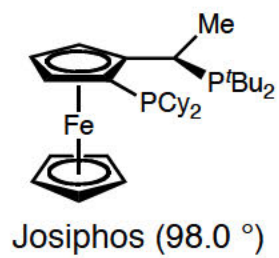
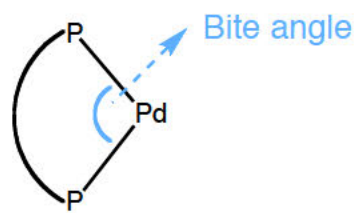
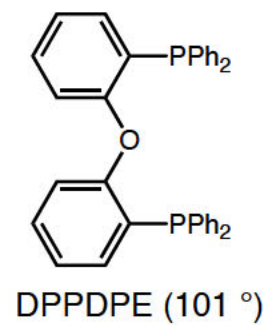
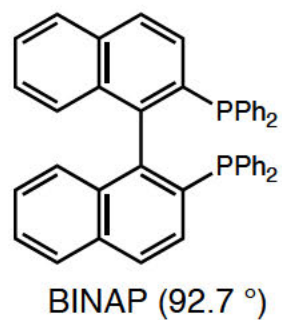
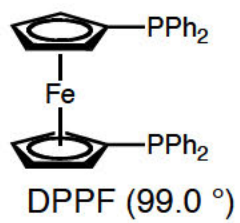


Wolfe, J. and Buchwald, S. L. *JOC* **1996**, *61*, 1133.



Hartwig, J. F. *et al JOC* **1999**, *64*, 5575.

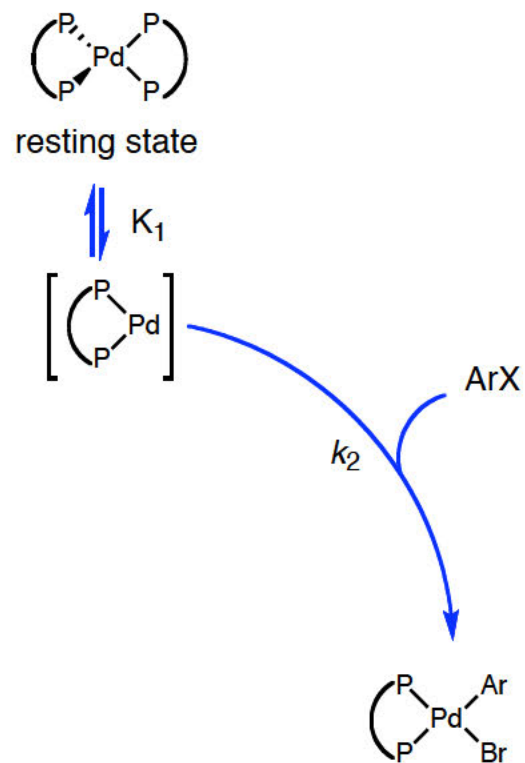
Bidentate Phosphine Ligands



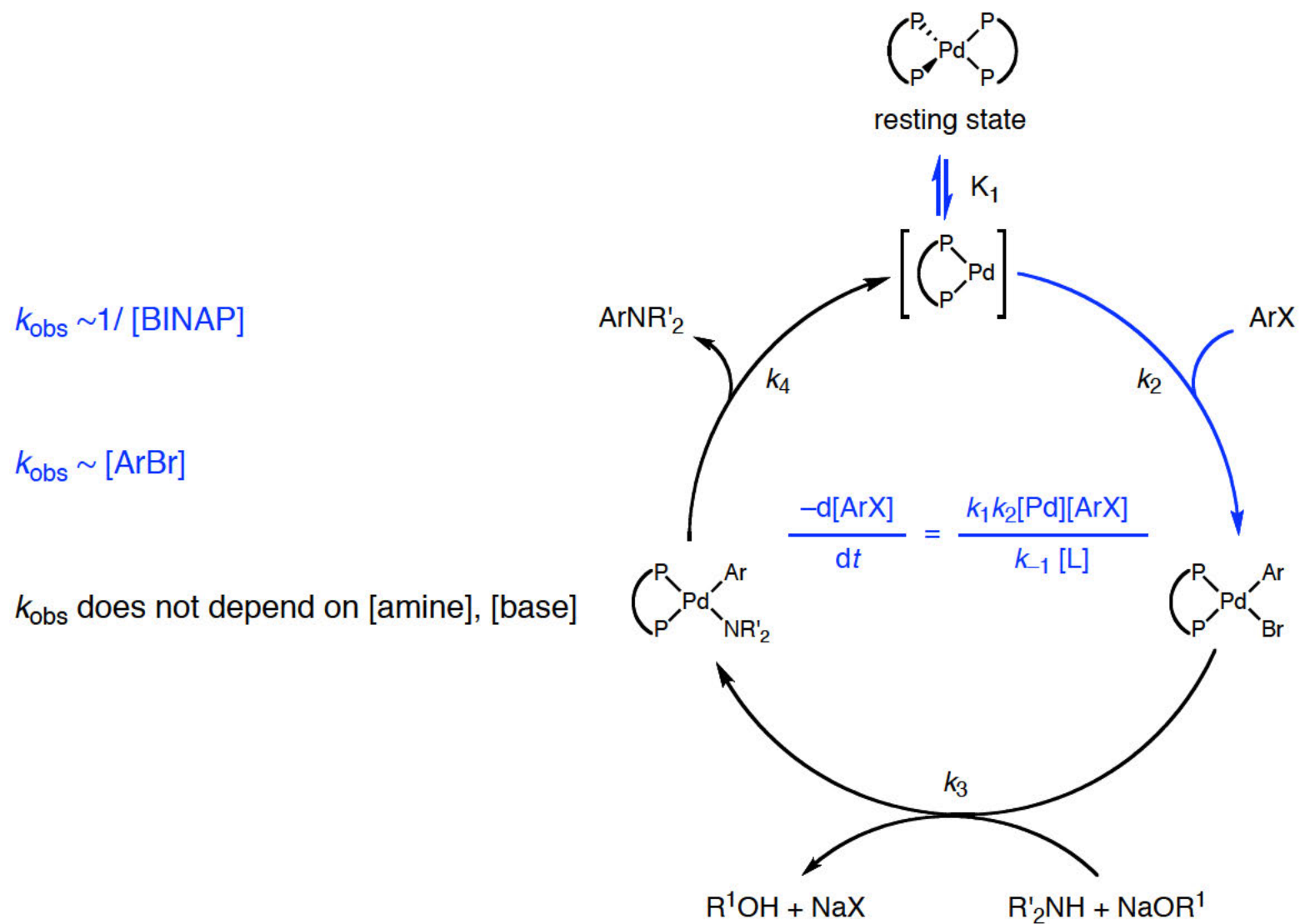
Amination with BINAP Ligand - Mechanistic Conclusion

$$k_{\text{obs}} \sim 1/[\text{BINAP}]$$

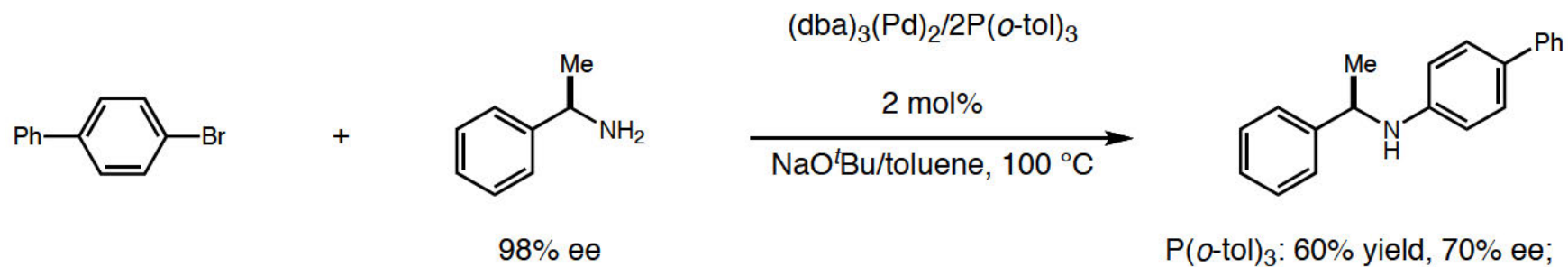
$$k_{\text{obs}} \sim [\text{ArBr}]$$



Amination with BINAP Ligand - Mechanistic Conclusion

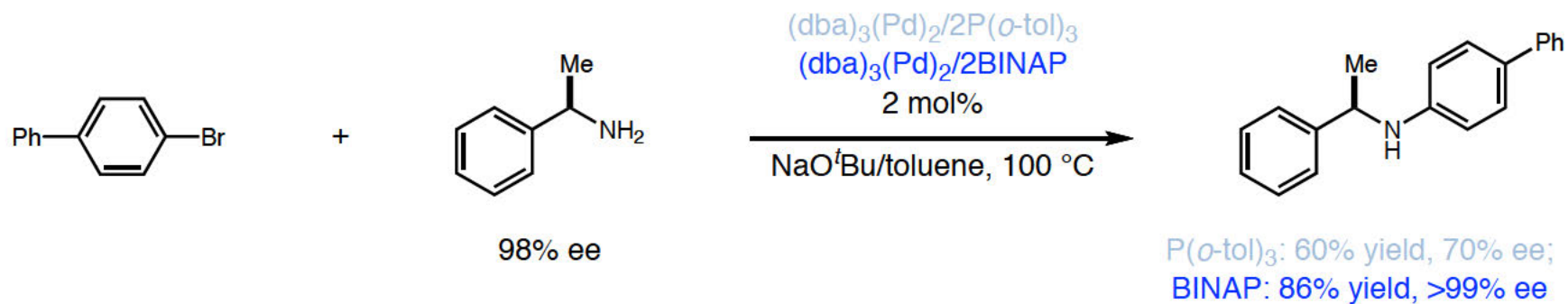


Amination with Bidentate Ligands - Coupling of Chiral Amines with Aryl Bromides



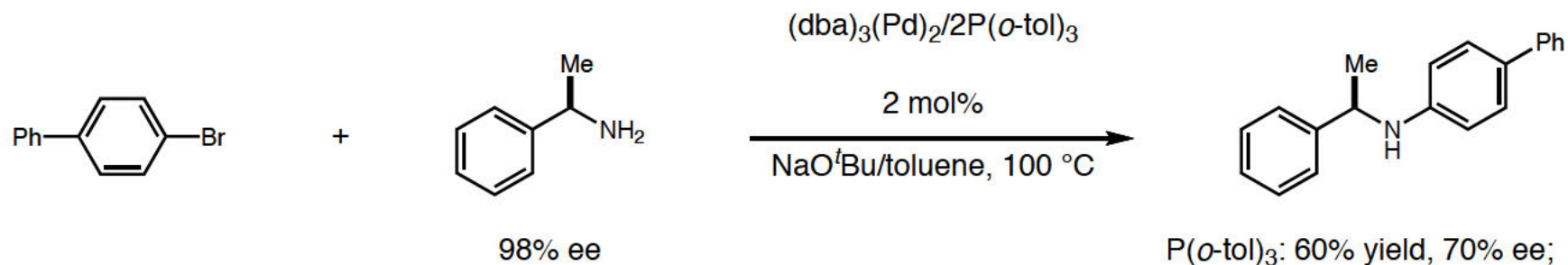
Buchwald, S. L. *et al* *JACS* **1997**, *119*, 8451.

Amination with Bidentate Ligands - Coupling of Chiral Amines with Aryl Bromides

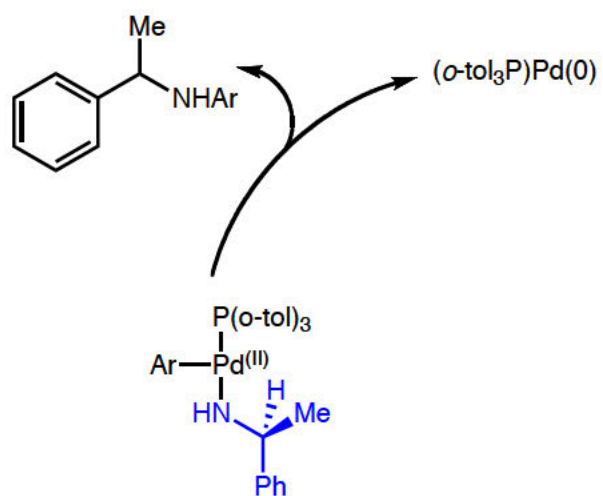


Buchwald, S. L. *et al* *JACS* **1997**, *119*, 8451.

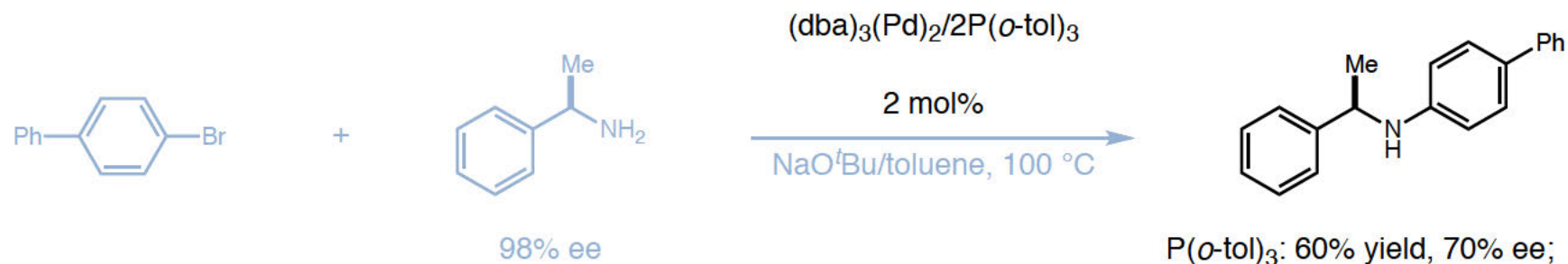
Amination with Bidentate Ligands - Coupling of Chiral Amines with Aryl Bromides



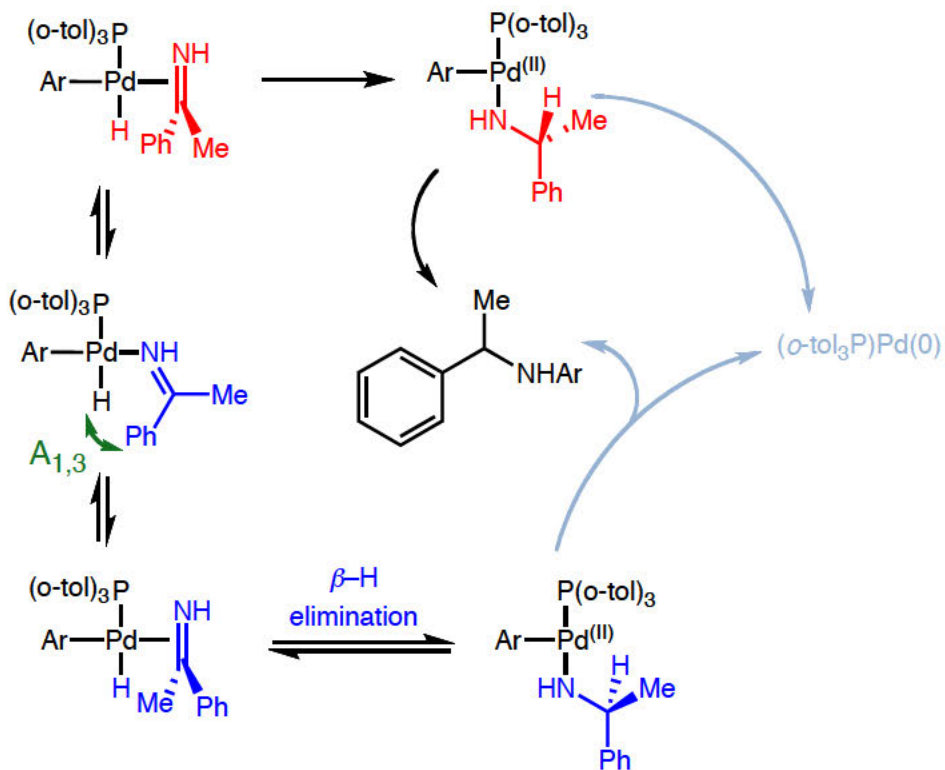
Buchwald, S. L. *et al* *JACS* **1997**, *119*, 8451.



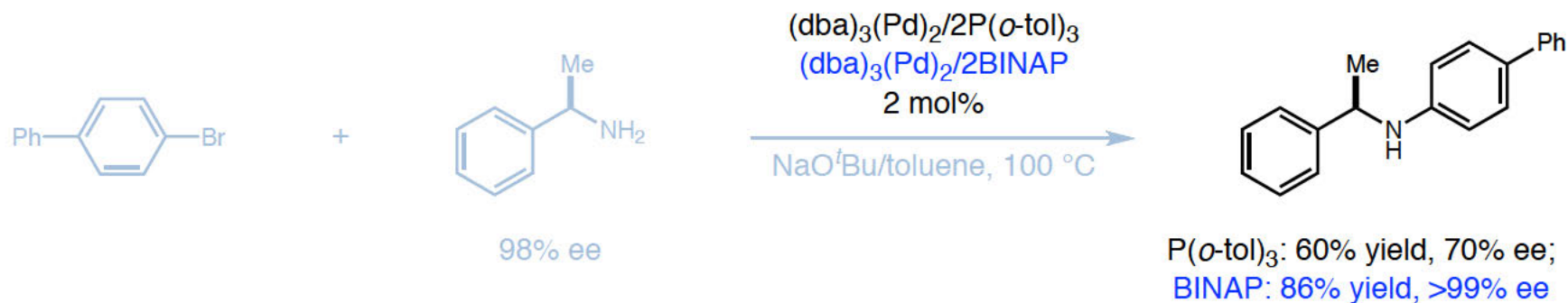
Amination with Bidentate Ligands - Coupling of Chiral Amines with Aryl Bromides



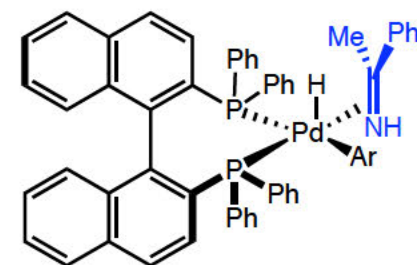
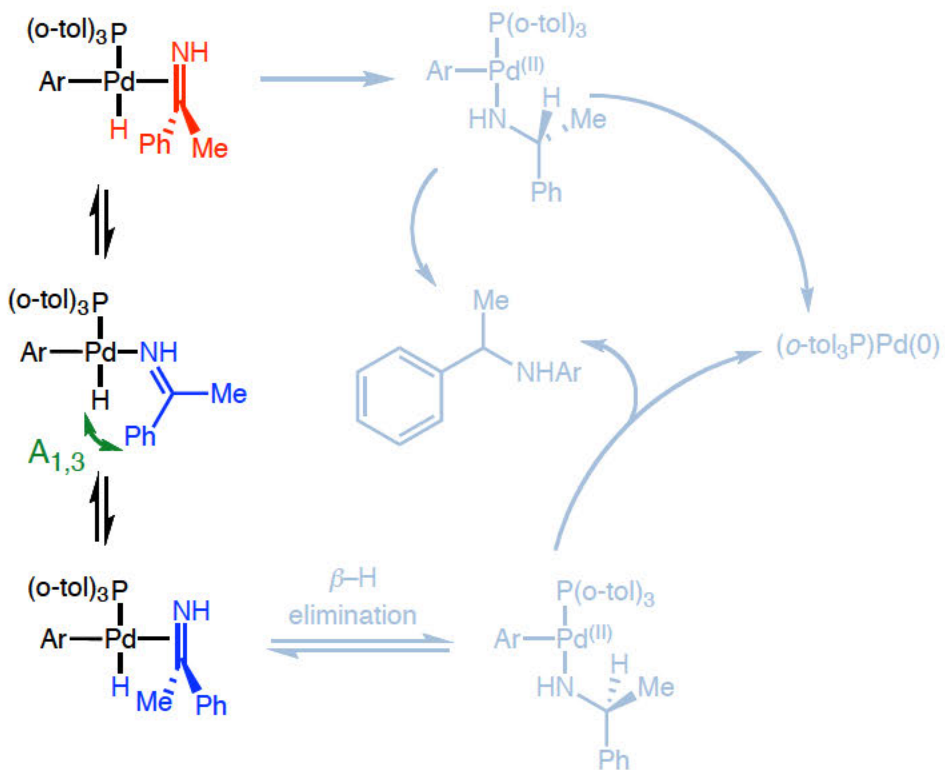
Buchwald, S. L. *et al* *JACS* **1997**, *119*, 8451.



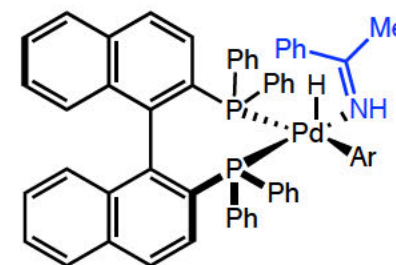
Amination with Bidentate Ligands - Coupling of Chiral Amines with Aryl Bromides



Buchwald, S. L. *et al* *JACS* **1997**, *119*, 8451.

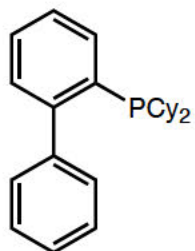


Bidentate ligand,
hinder beta-H elimination

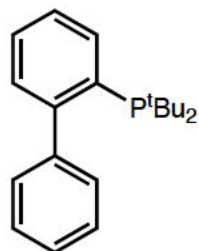


Biarylphosphine Ligand

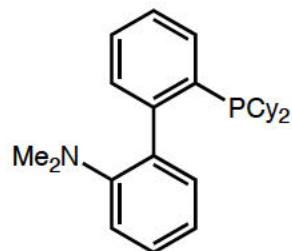
(ligands for gold, silver, rhodium, ruthenium and copper)



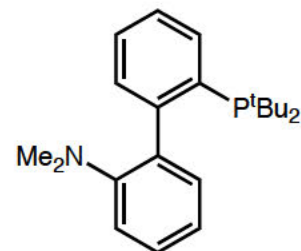
JohnPhos (Cy)



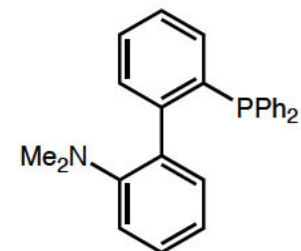
JohnPhos



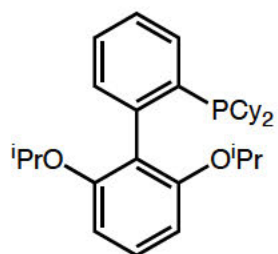
DavePhos
(Buchwald, 1998)



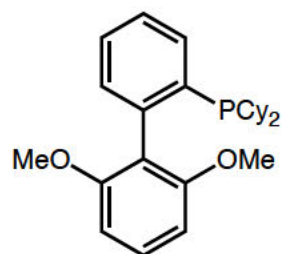
DavePhos (^tBu)



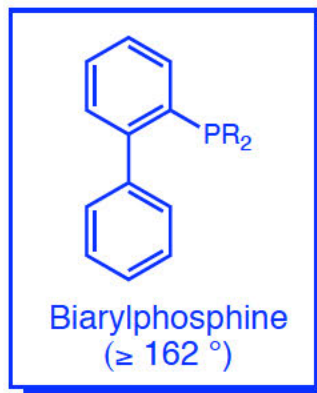
DavePhos (Ph)



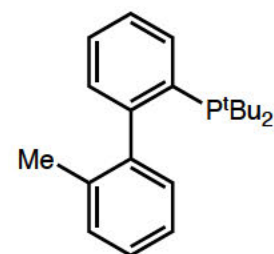
RuPhos



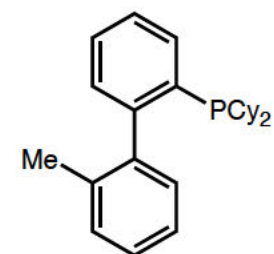
SPhos



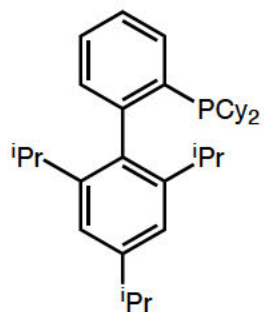
Biarylphosphine
($\ge 162^\circ$)



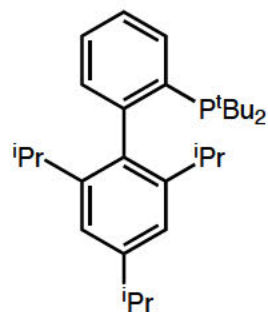
MePhos (^tBu)



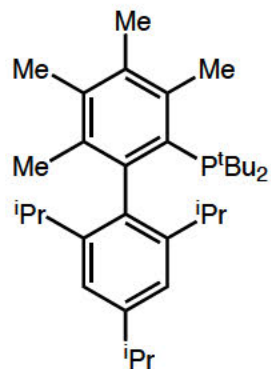
MePhos



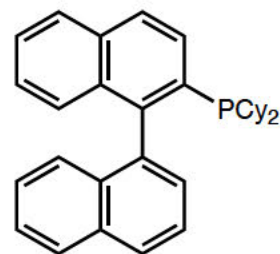
XPhos



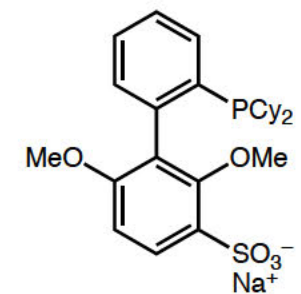
XPhos (^tBu)



XPhos (4Me^tBu)

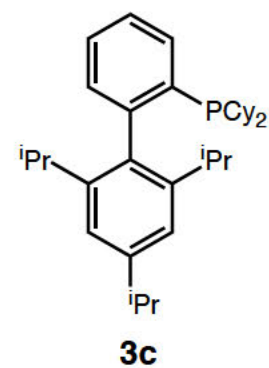
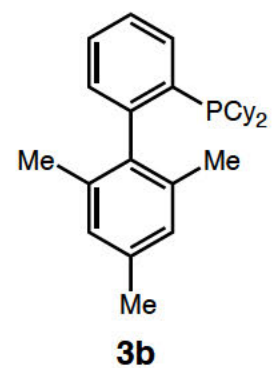
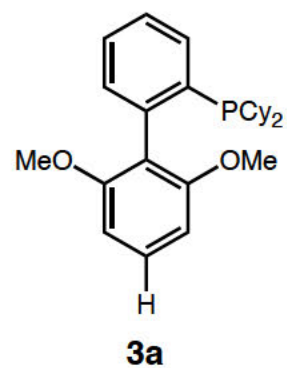
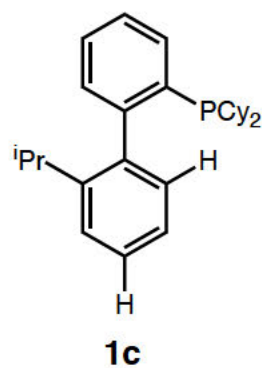
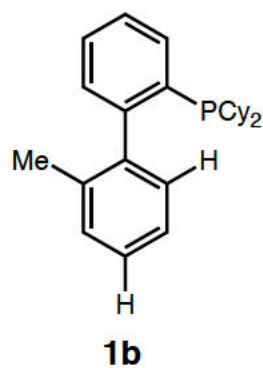
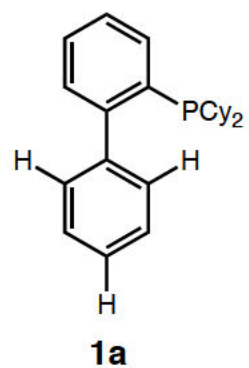
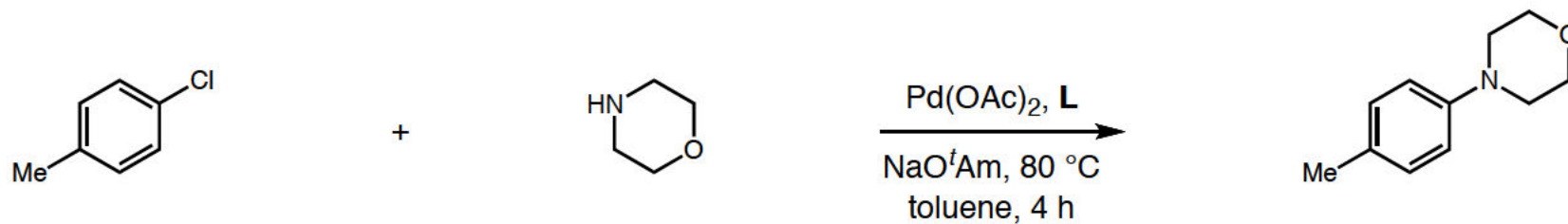


Johnphos (NaphCy)



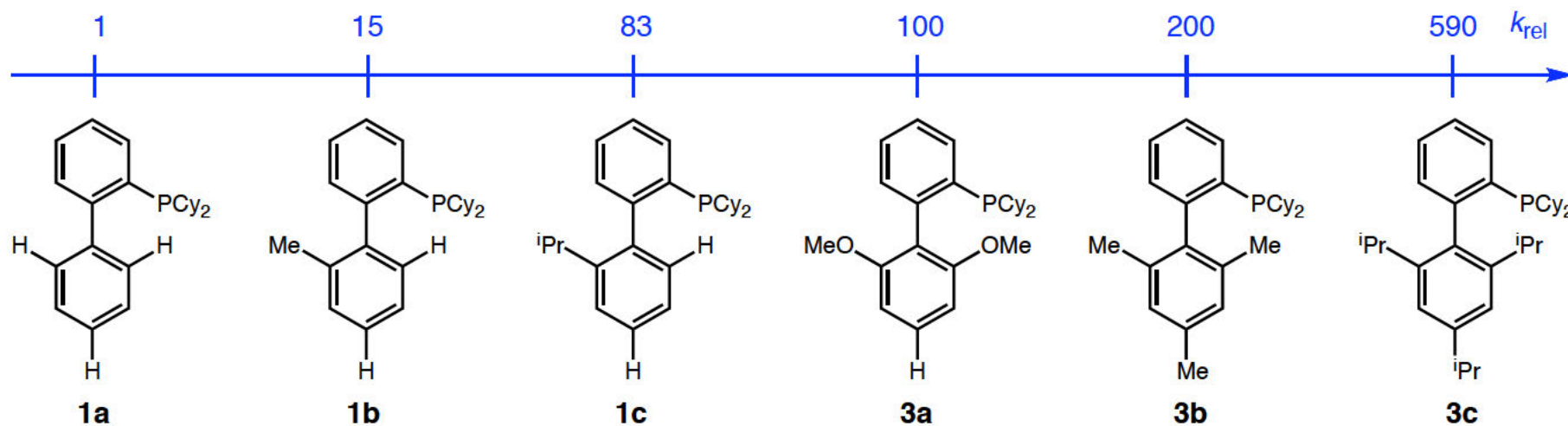
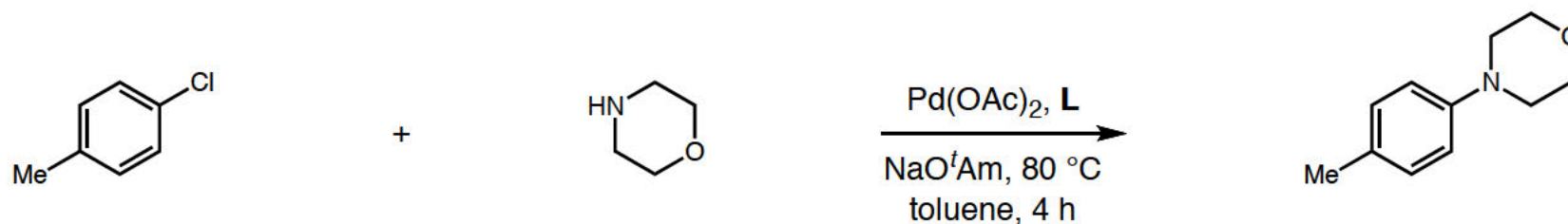
Surry, D. S. and Buchwald, S. L. *ACIE* **2008**, 47, 6388.

Biarylphosphine Ligands - Effects of Substituents on Lower Aryl Ring



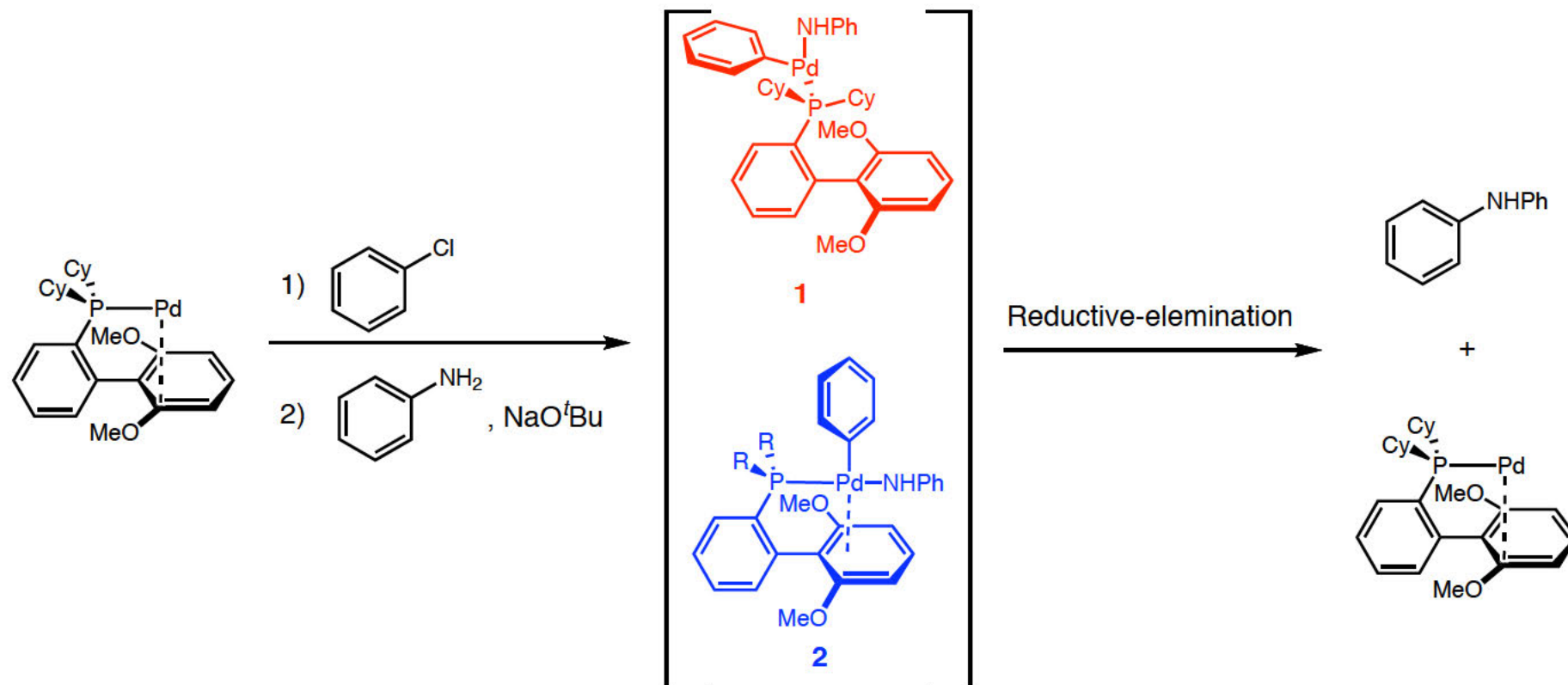
Buchwald, S. L. *et al* *JACS* **2003**, 125, 13978.
Strieter, E. R. and Buchwald, S. L. *ACIE* **2006**, 45, 925.

Biarylphosphine Ligands - Effects of Substituents on Lower Aryl Ring

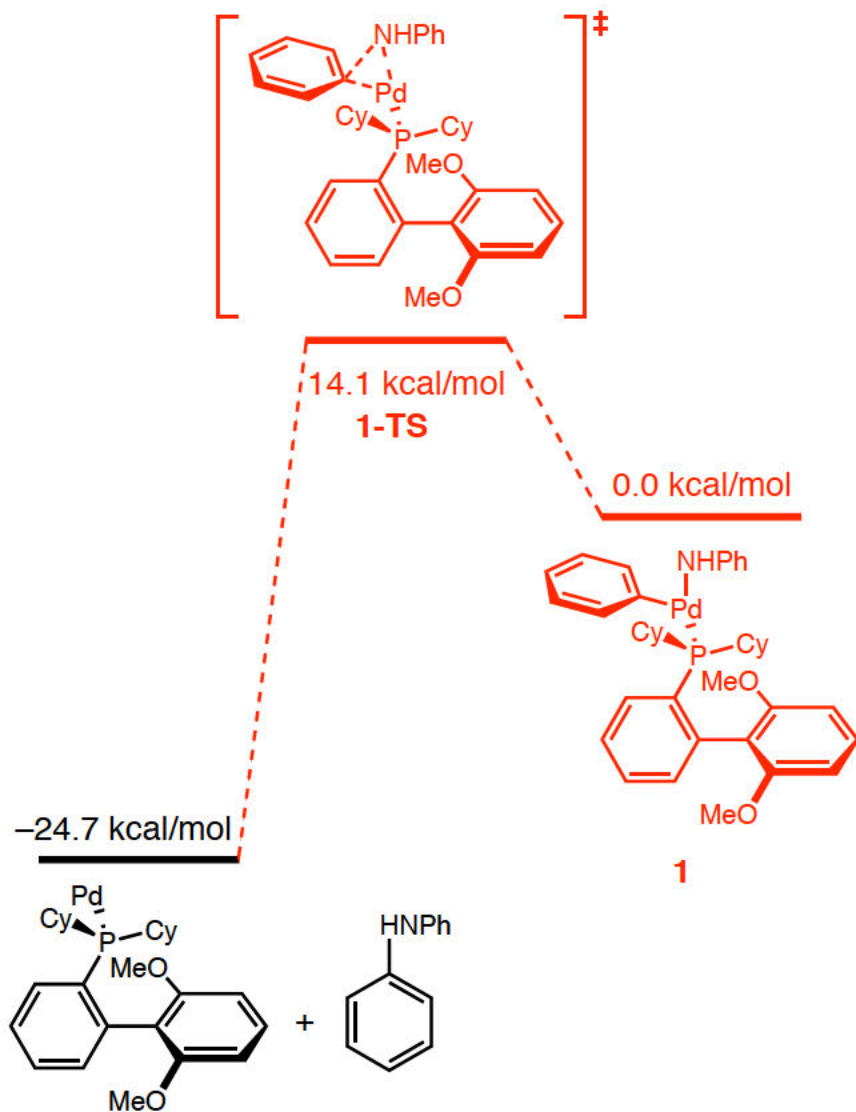


Buchwald, S. L. *et al* *JACS* **2003**, 125, 13978.
Strieter, E. R. and Buchwald, S. L. *ACIE* **2006**, 45, 925.

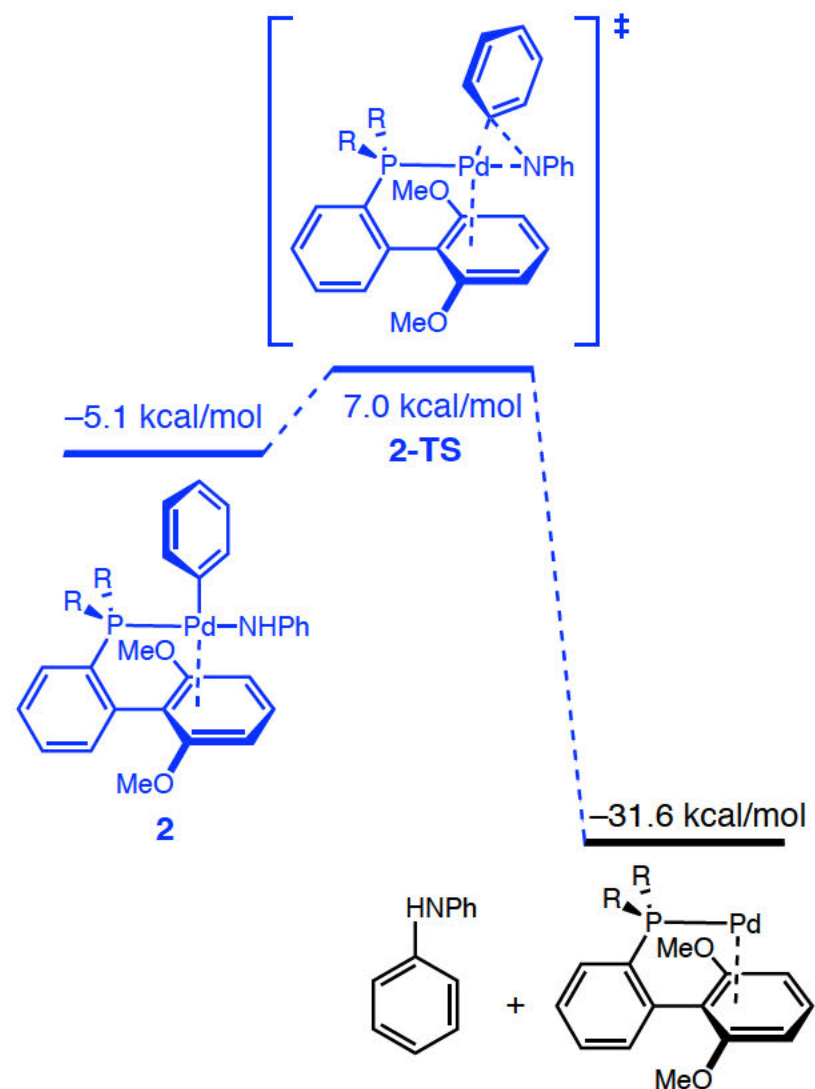
Biarylphosphine Ligands - Reductive Elimination via DFT Study



Biarylphosphine Ligands - Reductive Elimination via DFT Study

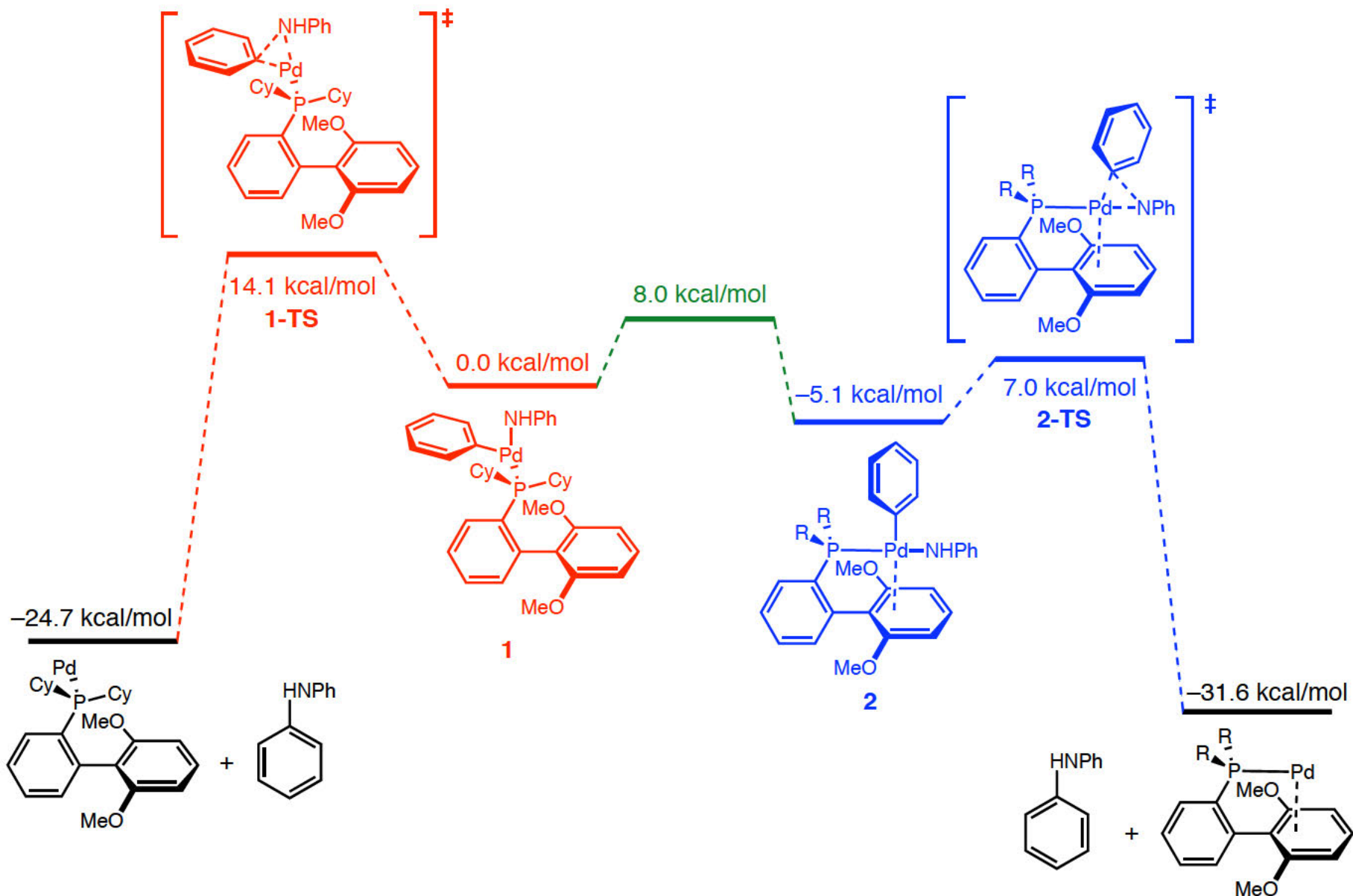


Biarylphosphine Ligands - Reductive Elimination via DFT Study

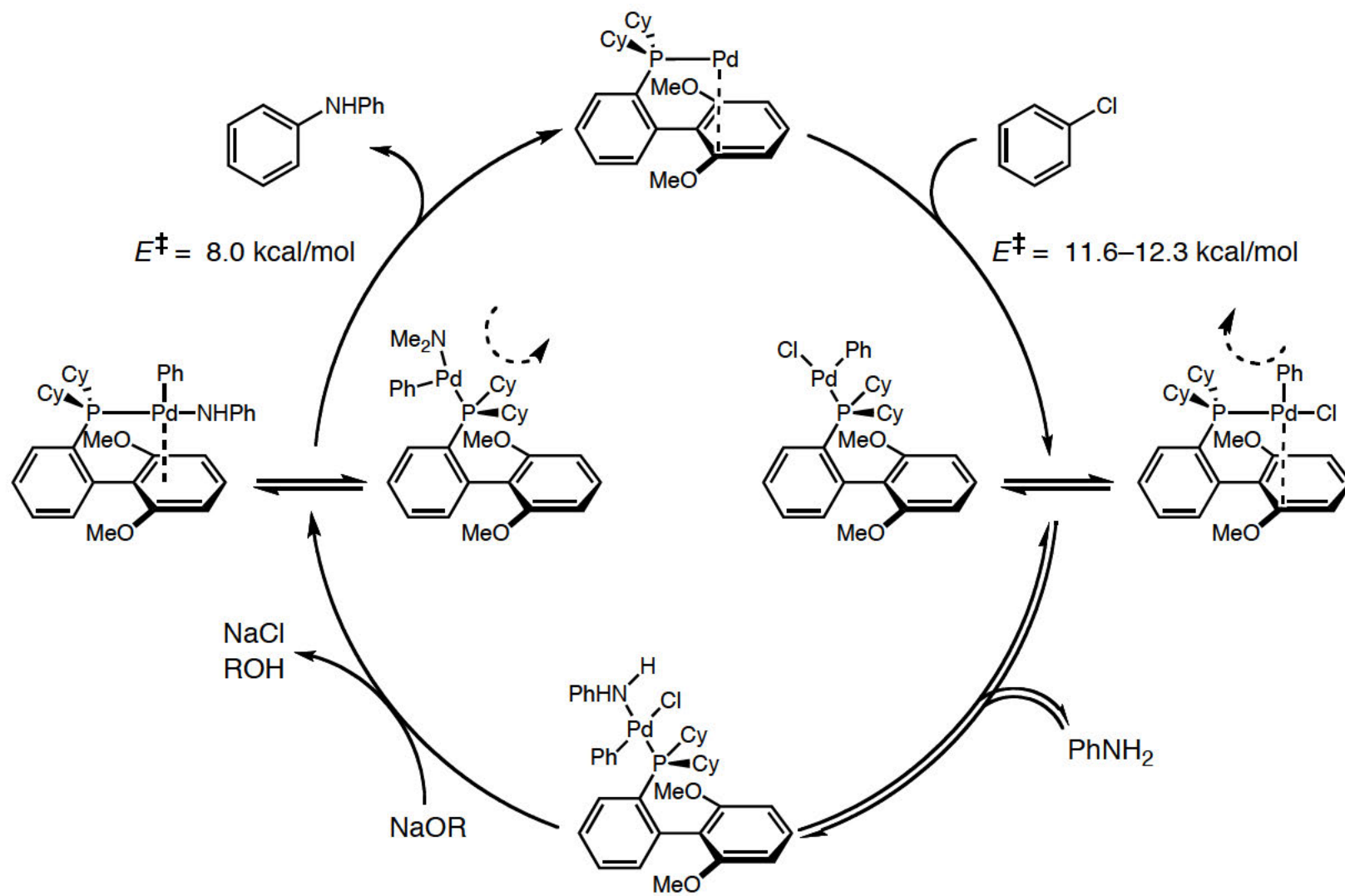


Barder, E. T. and Buchwald, S. L. *JACS* **2007**, *129*, 12003.

Biarylphosphine Ligands - Reductive Elimination via DFT Study

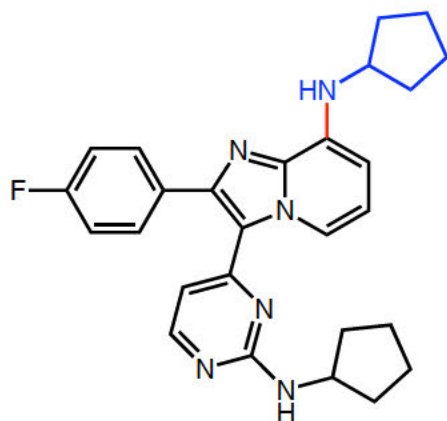


Biarylphosphine Ligands - Proposed Mechanism via DFT Study



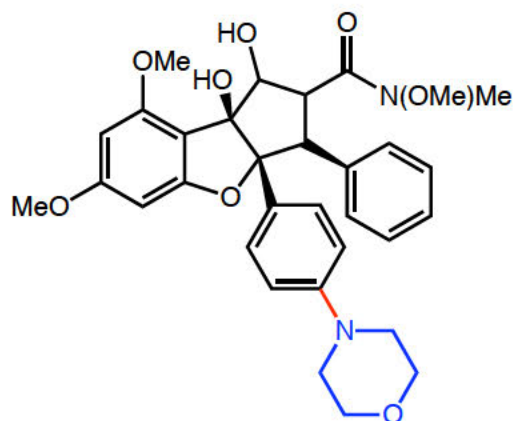
Amination with Biarylphosphine Ligands

some examples in pharmaceutical synthesis



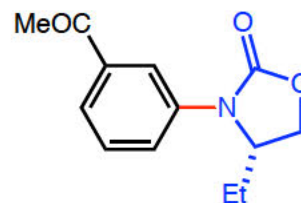
92% (Cl)

GalaxoSmithKline
synthesis of
antitherpes agents



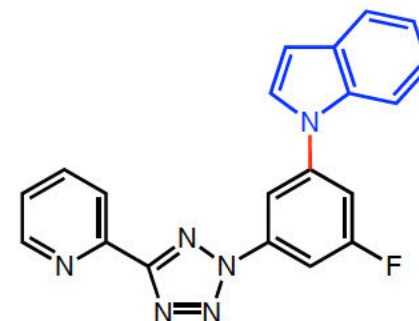
41% (Br)

Novartis synthesis of
rocaglamine analogs



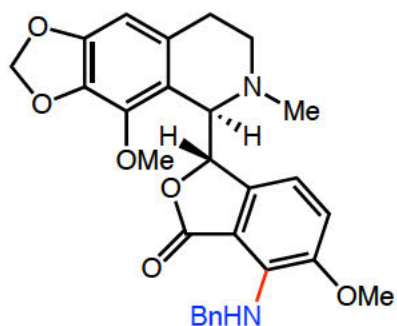
94% (Cl)

Pfizer synthesis of
N-Aryl oxazolidinones



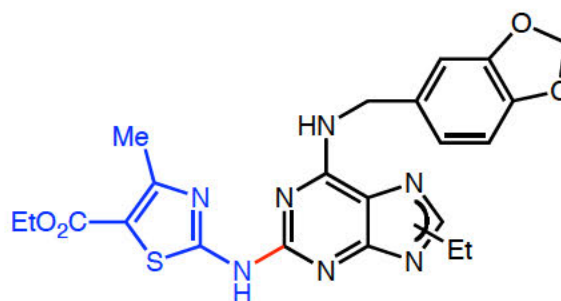
(I)

Merck synthesis of
mGlu5 receptor
antagonist



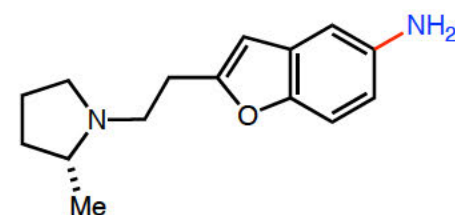
80% (OTf)

Athersys synthesis of
noscapine analogs



(Cl)

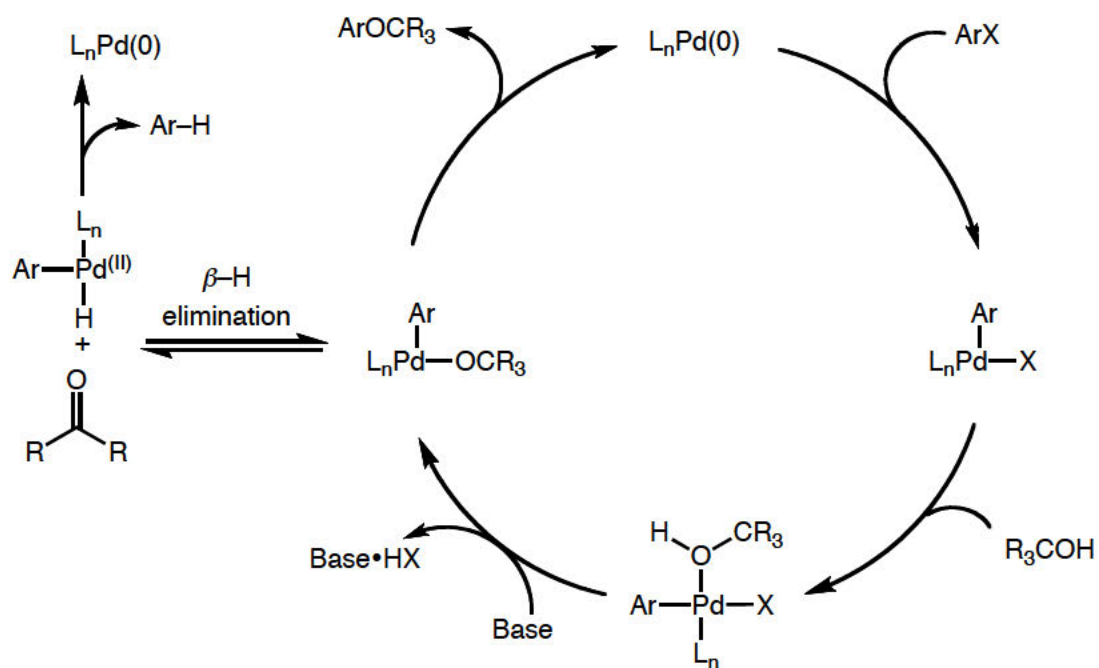
BMS synthesis of
phosphodiesterase 7
inhibitors



80% (Br)

Abbot synthesis of
histamine receptor
H₃ antagonists

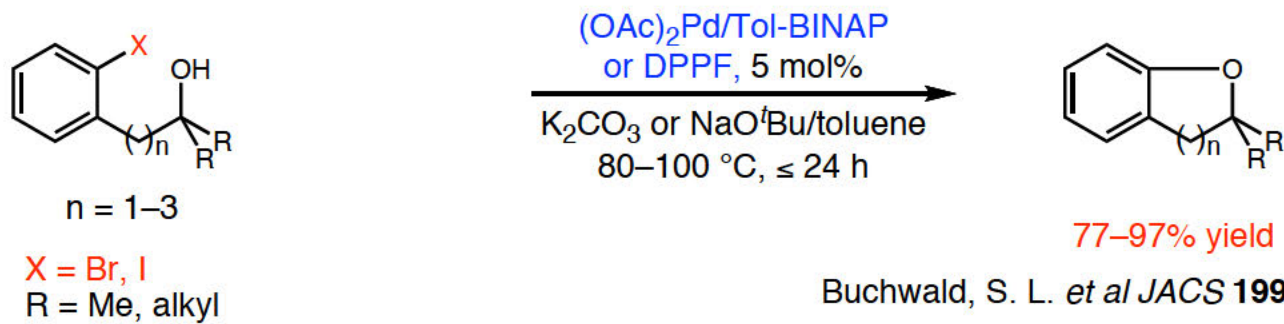
C–O Coupling with Pd Complexes-Mechanistic Overview



- The nucleophilicity of alcohols is much weaker than that of amines
- β -H elimination products are stable.

C–O Coupling with Pd Complexes

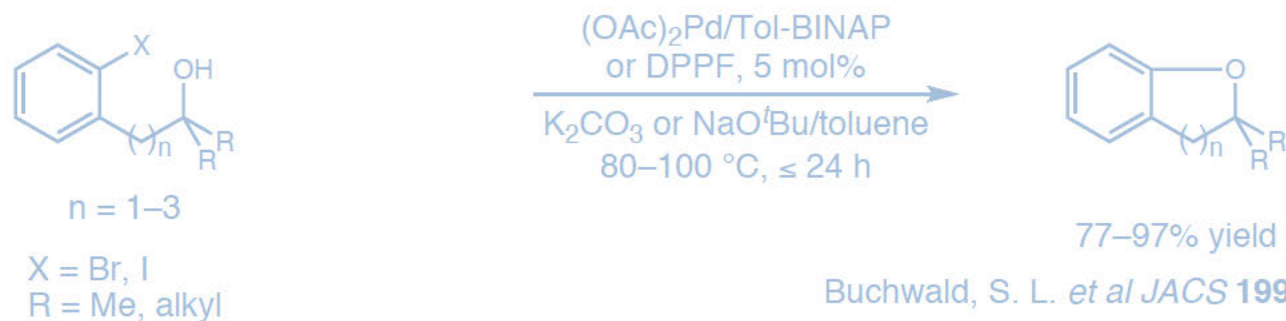
scope limitation with bidentate phosphine ligands



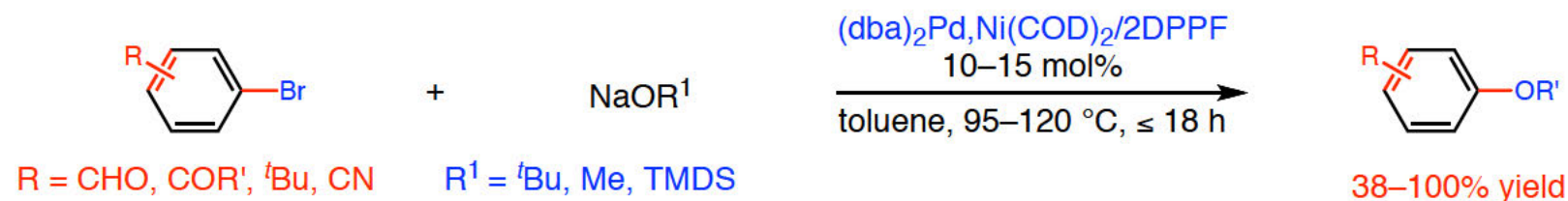
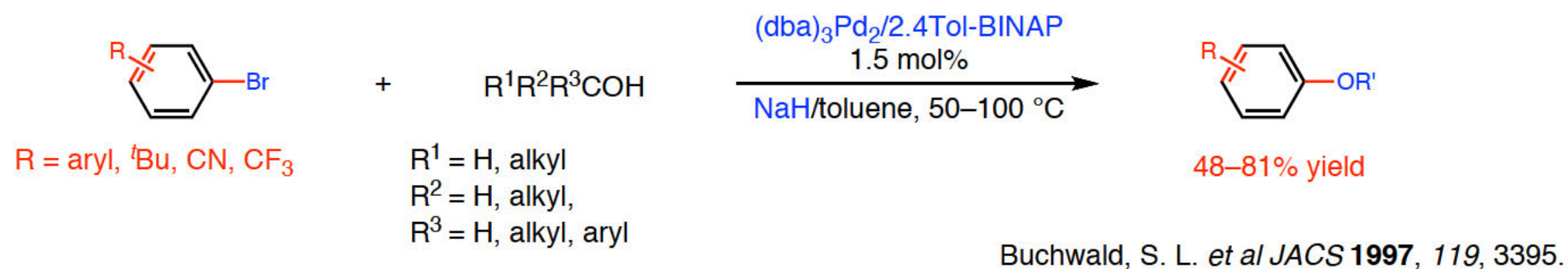
Buchwald, S. L. *et al JACS* **1996**, *118*, 10333.

C–O Coupling with Pd Complexes

scope limitation with bidentate phosphine ligands



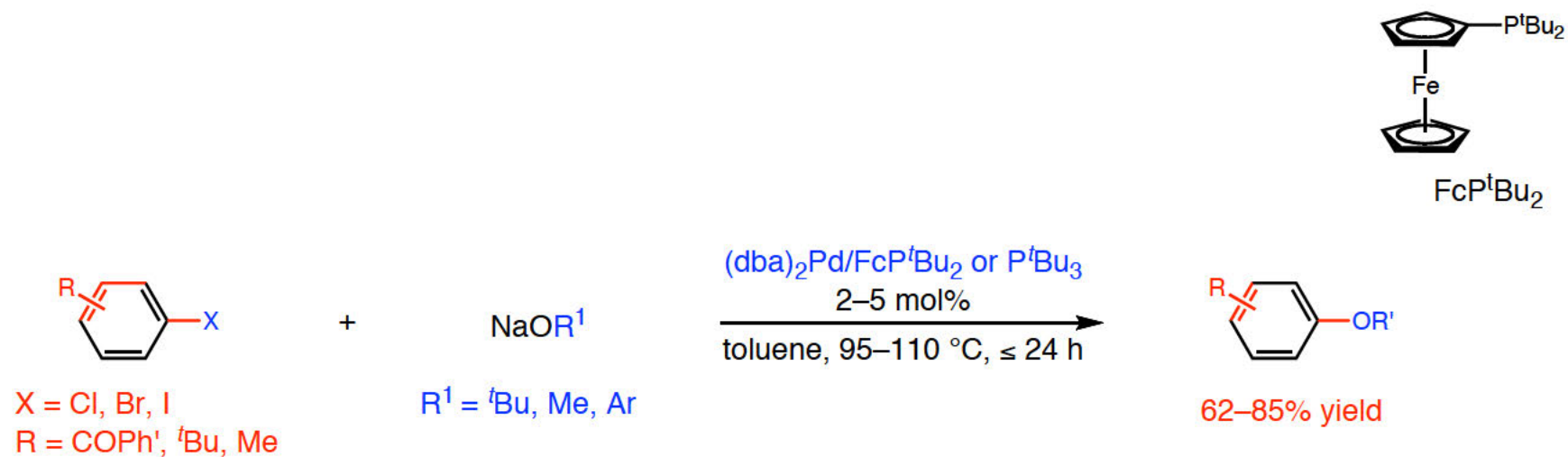
■ Intermolecular C–O coupling were successful with alkoxides



Mann, G. and Hartwig, J. F. *JACS* **1996**, *118*, 13109.
 Mann, G. and Hartwig, J. F. *JACS* **1997**, *119*, 5413.

C–O Coupling with Pd Complexes

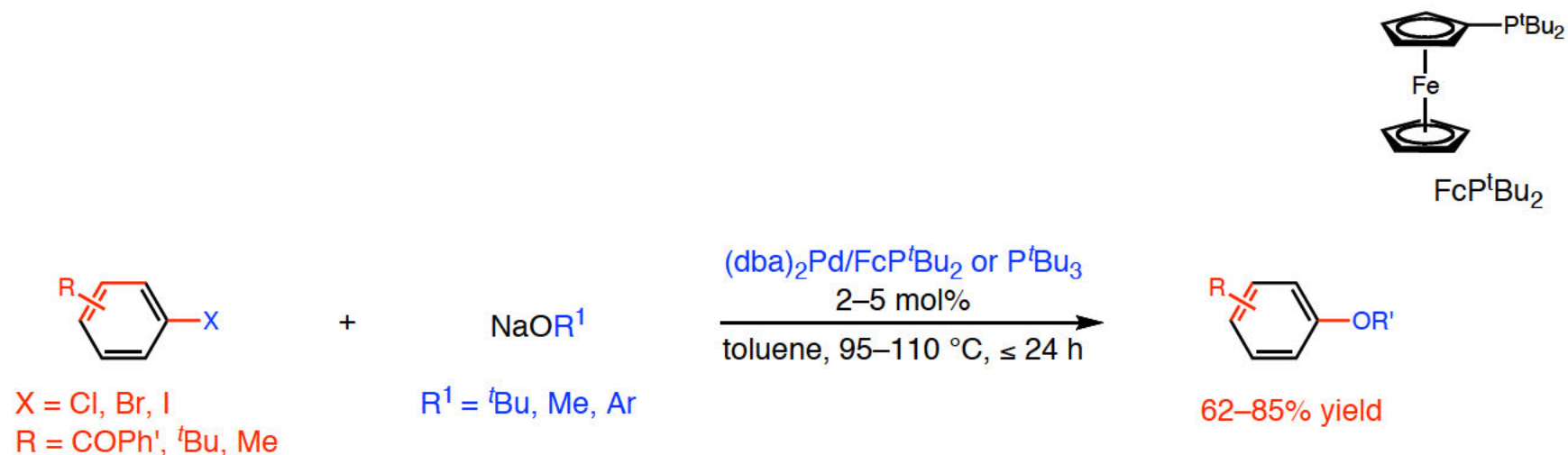
scope improvement with electron-rich bulky monodentate phosphine ligands



Hartwig, J. F. *et al* *JACS* **1999**, *121*, 3224.

C–O Coupling with Pd Complexes

scope improvement with electron-rich bulky monodentate phosphine ligands



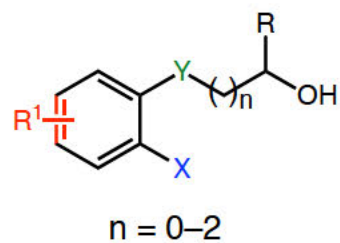
Hartwig, J. F. *et al* *JACS* **1999**, *121*, 3224.

- ◆ Sterically hindered electron-rich alkylphosphine ligands accelerate reductive elimination step.

⇒ Why don't they try XXXXXXXXXX or biarylphosphine ligands???

C–O Coupling with Pd Complexes

problem solving with biarylphosphine ligands

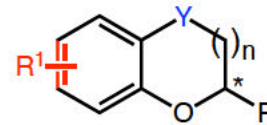
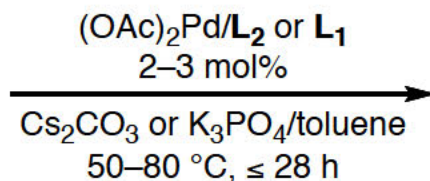


X = Br, I

Y = CH₂, O, NMe(H)

R = Me, alkyl, ester, carbamate

R¹ = Me, CN, CO₂Me

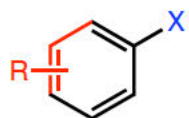


65–95% yield

≥ 97% ee

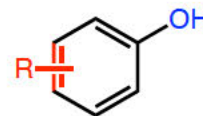
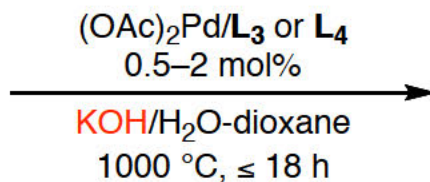
Buchwald, S. L. *et al JACS* **2000**, *122*, 12907.

Buchwald, S. L. *et al JACS* **2001**, *123*, 12202.



X = Cl, Br

R = alkyl, EWG, EDG



80–98% yield

Buchwald, S. L. *et al JACS* **2008**, *128*, 10694.

