Stephen L. Buchwald
(MIT since 1984)
Camille Dreyfus Professor of Chemistry

John F. Hartwig
(Yale 1992-2006, UIUC 2006–now)
Kenneth L. Reinhart Jr. Professor of Chemistry

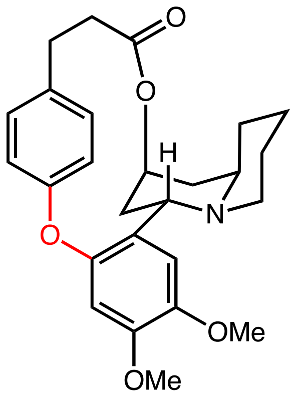
Pd in Buchwald–Hartwig C–N and C–O Couplings

Phong V. Pham

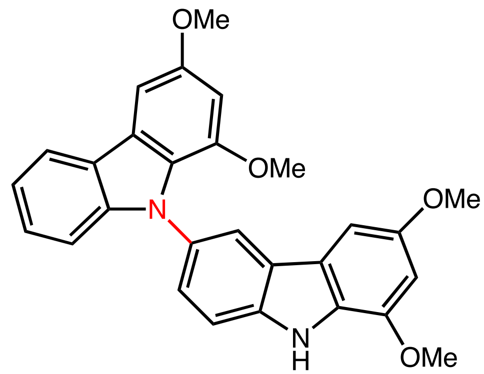
MacMillan Group Meeting

Princeton, Dec. 16, 2009

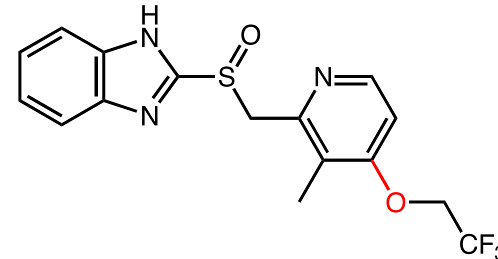
Why C–N and C–O Couplings?



vertaline

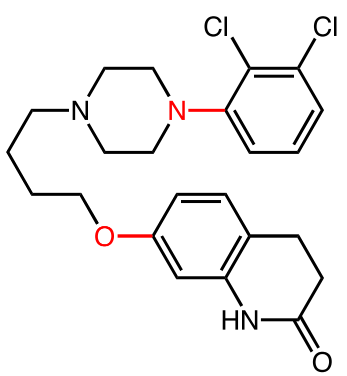


murrastifoline A



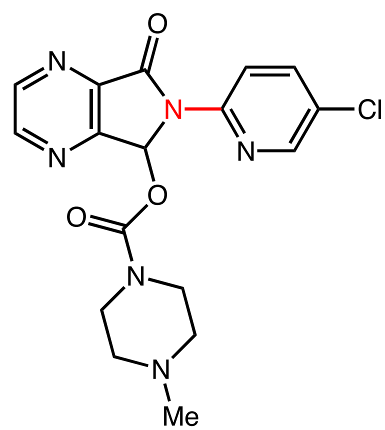
Prevacid

Used to treat gastric reflux disease



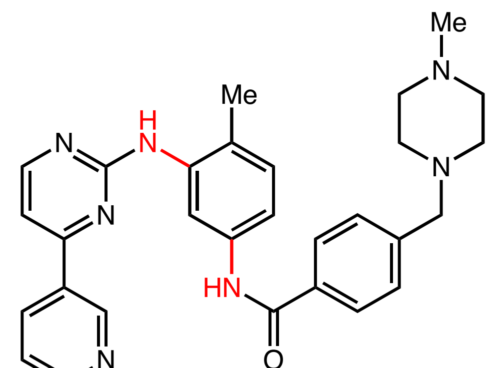
Abilify

Used to treat schizophrenia and bipolar mania



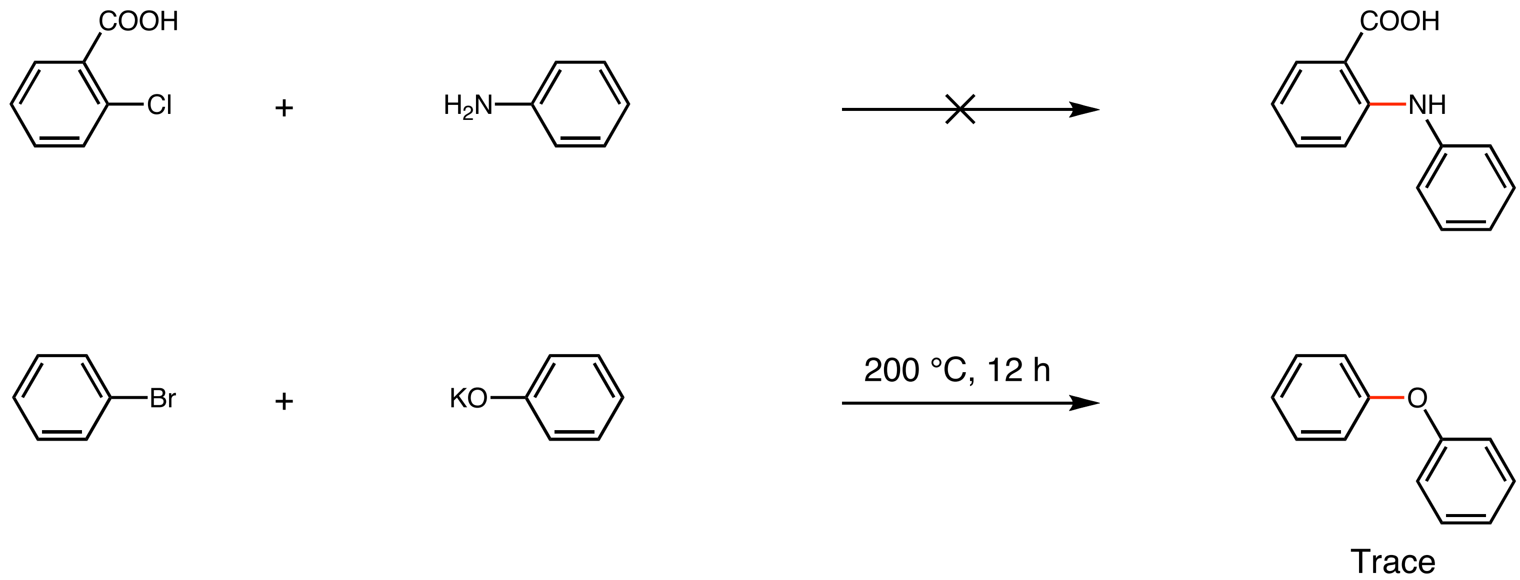
Lunesta

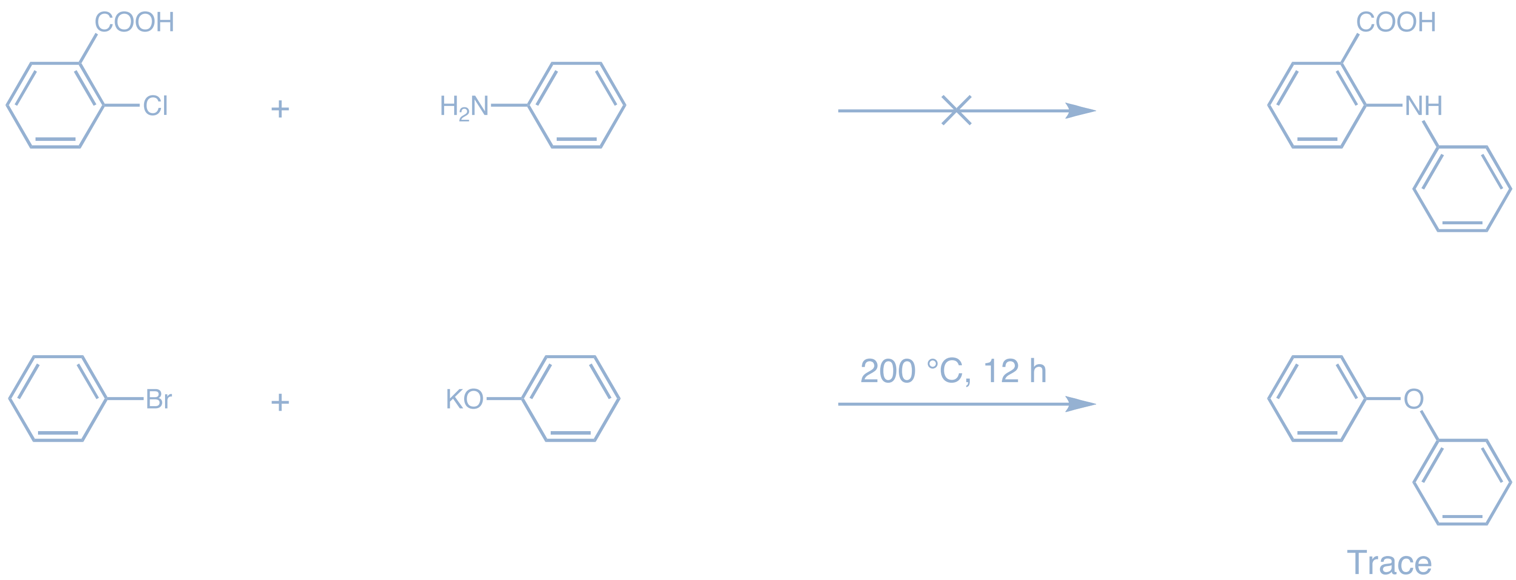
Used to treat insominia



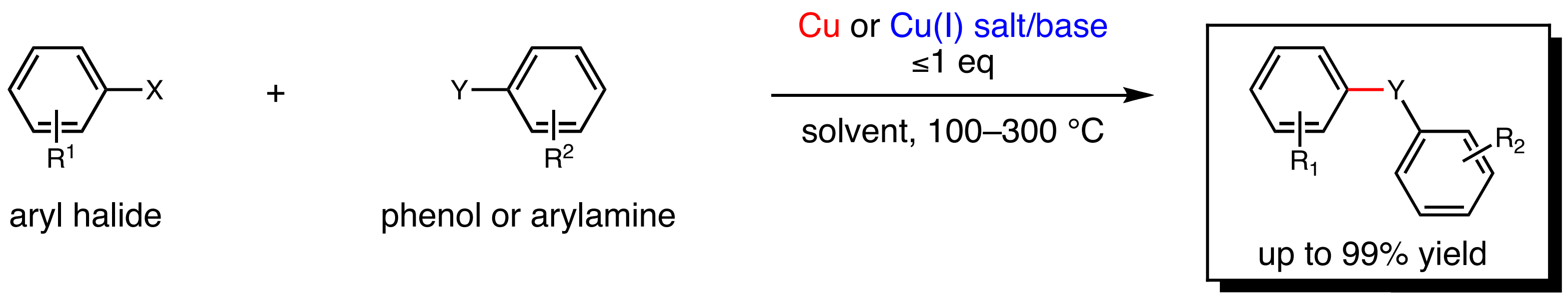
Gleevec

Used to treat chronic myeloid leukemia


COOH
Cl
+
H_2N
COOH
NH
Br
+
KO
200 °C, 12 h
O
Trace



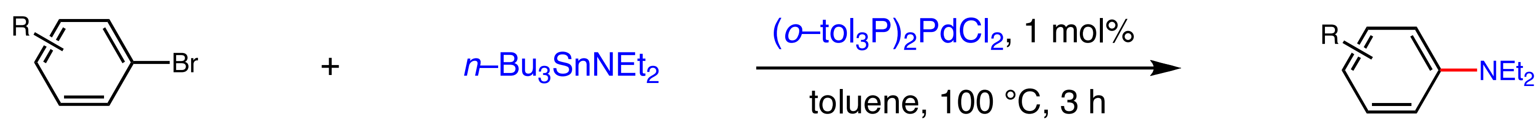
■ Biaryl ether and amine synthesis (Ulmann 1903 and Goldberg 1906)



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

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

■ Migita introduced the first catalytic version in 1983.

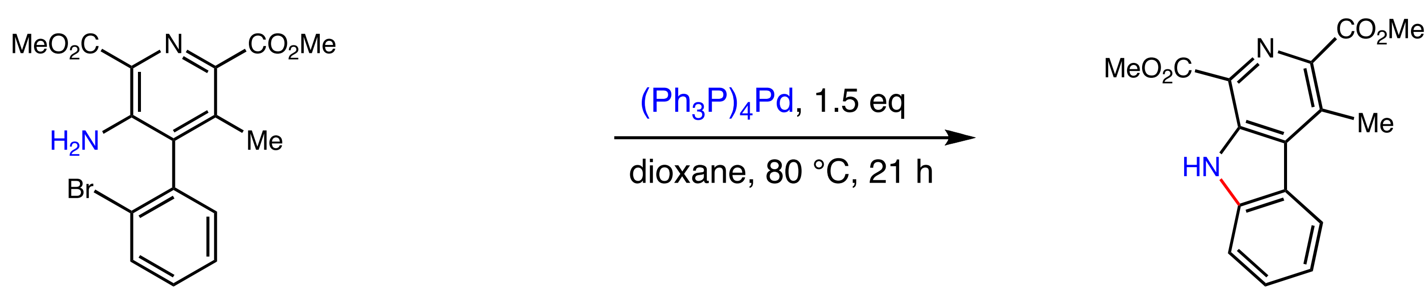


up to 81% yield

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

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

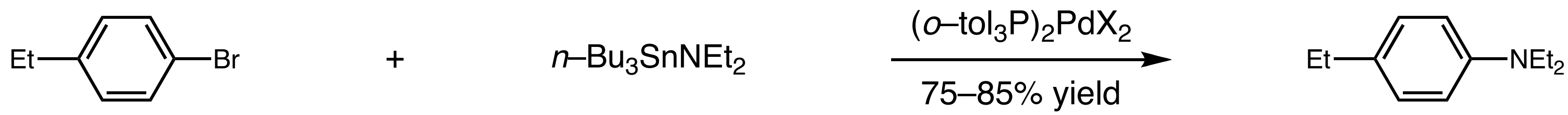
■ Boger introduced Pd(0) mediated intramolecular amination with free amine in 1984.

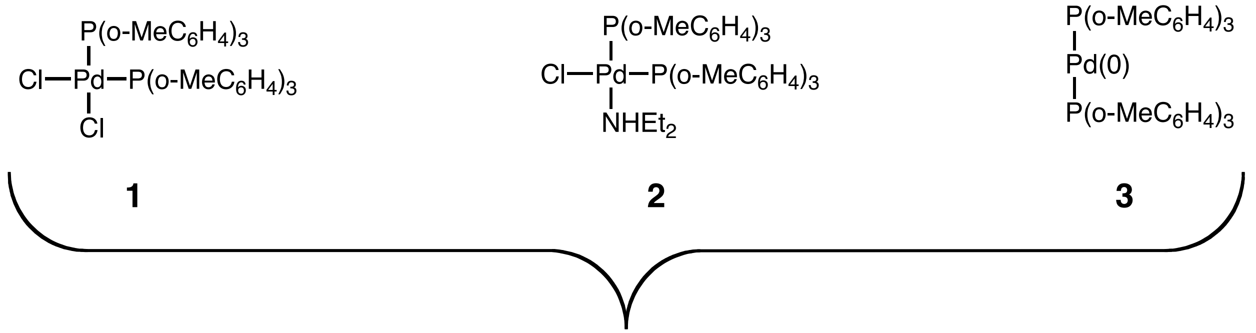


84% yield

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.





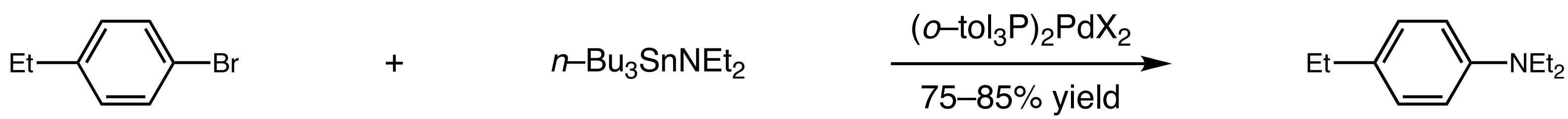
1 **2** **3**

♦ **1**, **2**, and **3** showed catalytic reactivity and the reaction was faster with **3**

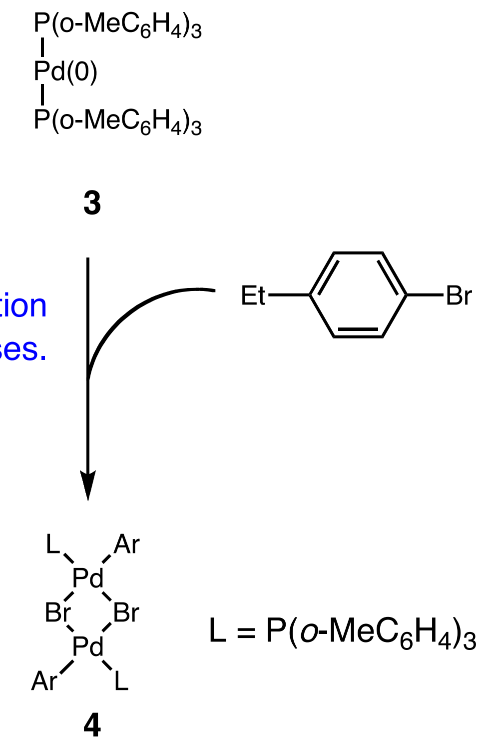
=> Pd(0) is a preferred catalyst and intermediate.

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

■ 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.



80–90% yield

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

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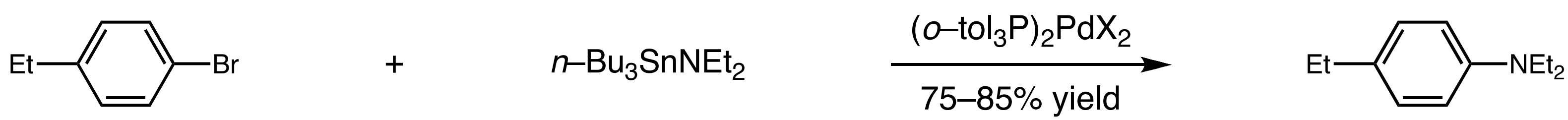
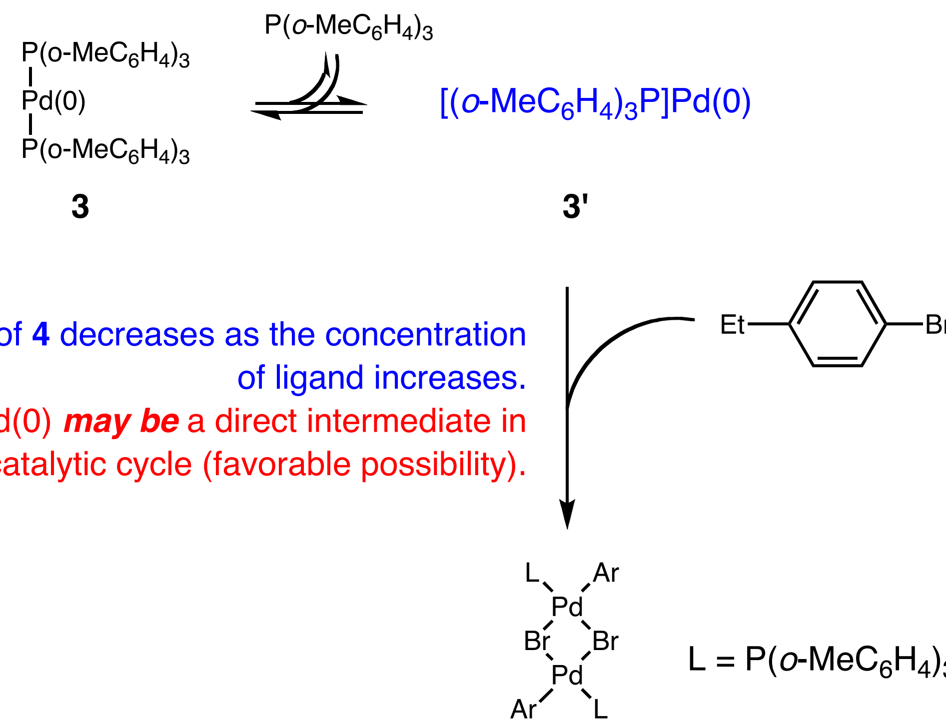




3 **3'**

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

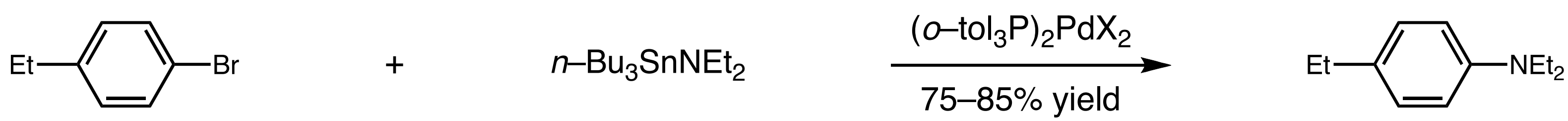
=> (o-$MeC_6H_4)_3PPd(0)$ ***may be*** a direct intermediate in the catalytic cycle (favorable possibility).

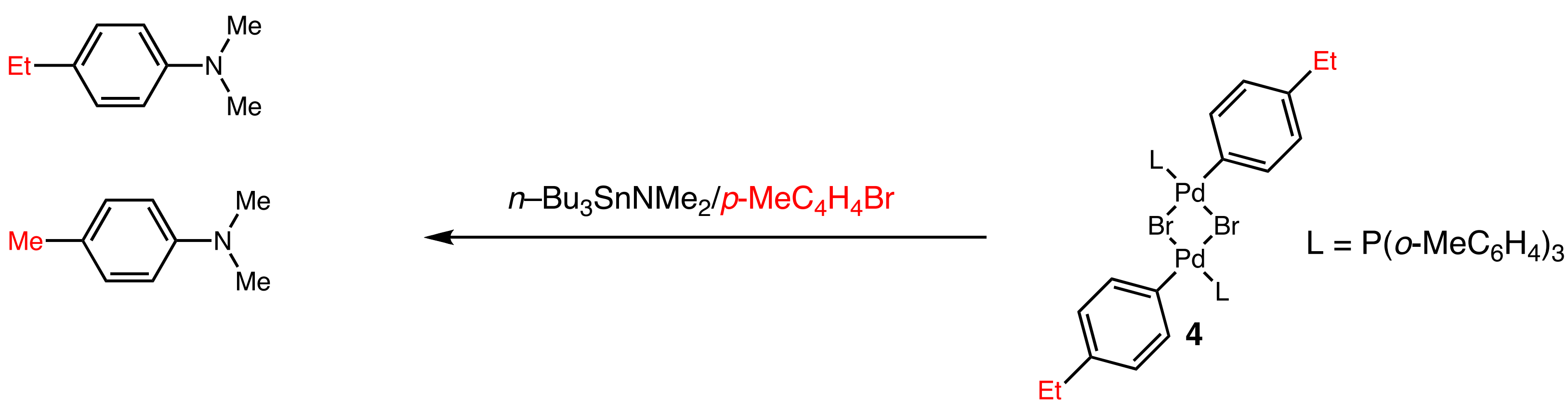
4

80–90% yield

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

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





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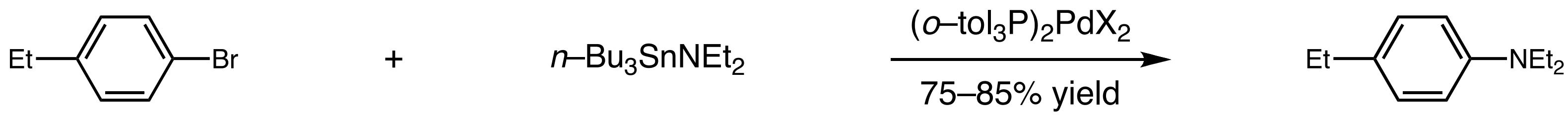

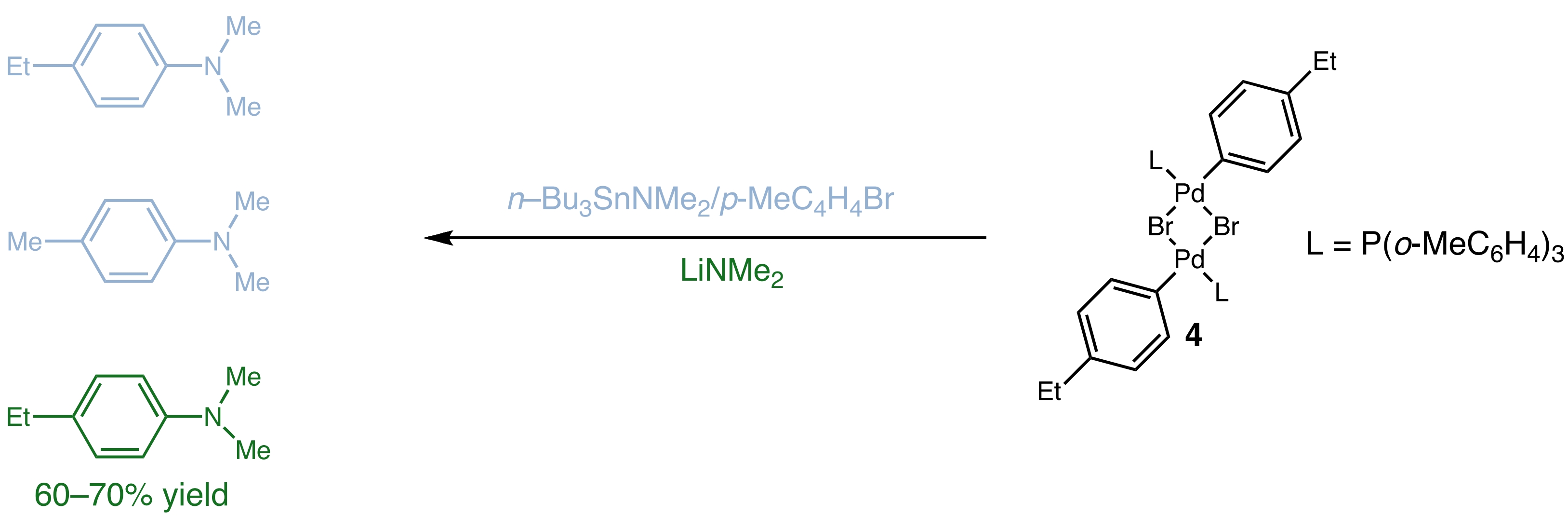

=> **4** or the corresponding monomer is directly involve in the catalytic cycle.

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

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

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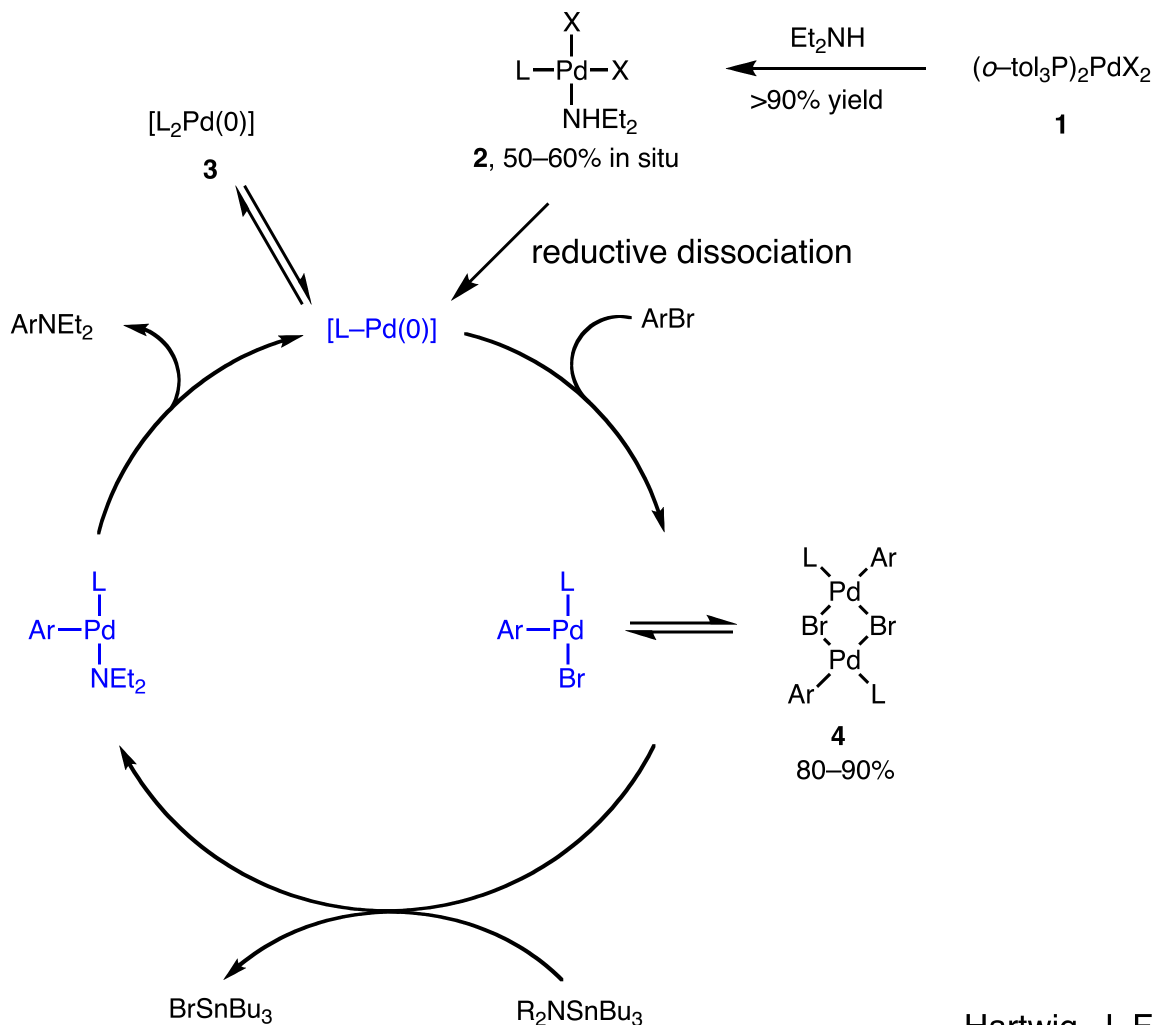
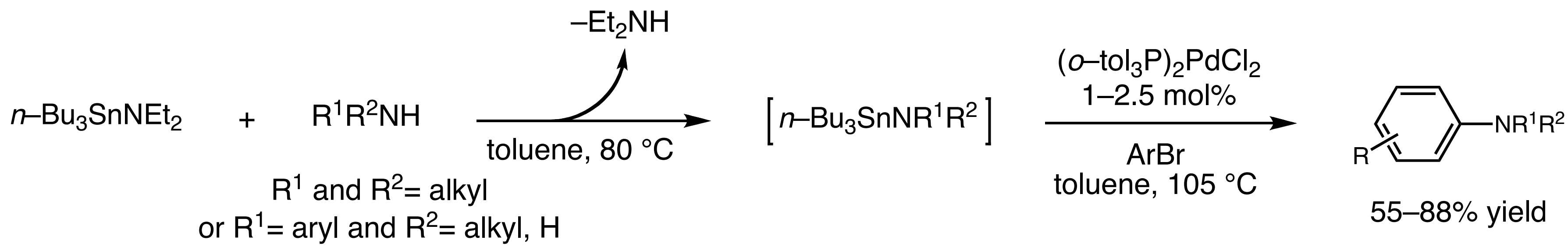
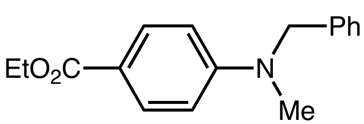


Hartwig, J. F. *et al JACS* **1994**, *116*, 5969.

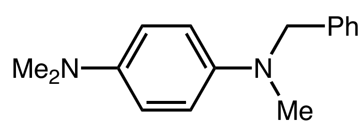
■ May 23, 1994 the Buchwald group submitted a amine scope expansion report of Migita's reaction via in situ generated aminostannanes.



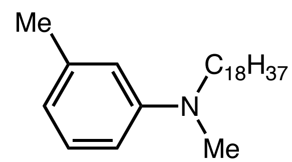
Guram, A. S. and Buchwald, S. L. *JACS* **1994**, *116*, 7901.



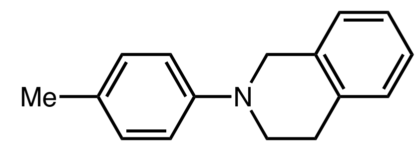
88% yield



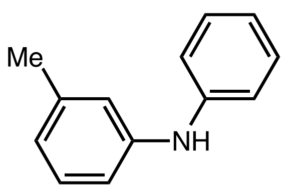
81% yield



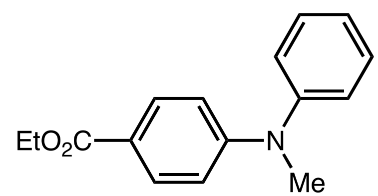
79% yield



55% yield

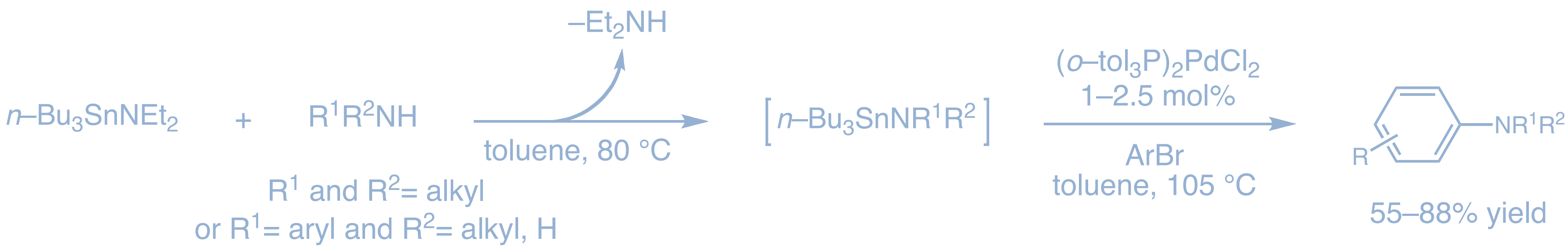


66% yield



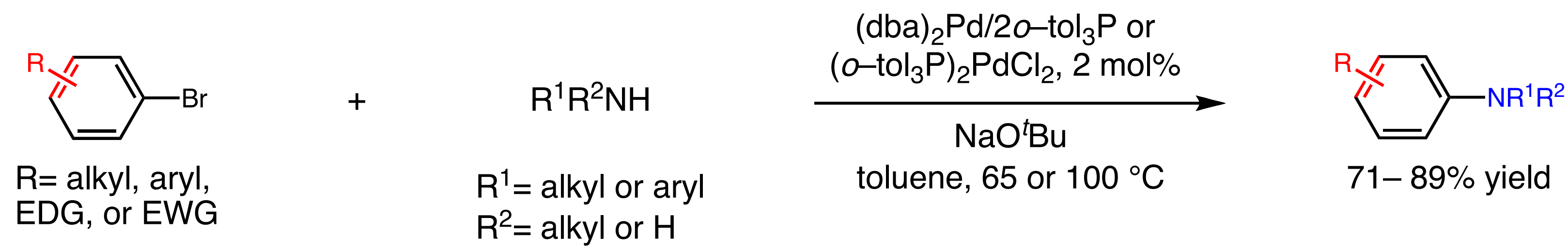
83% yield

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

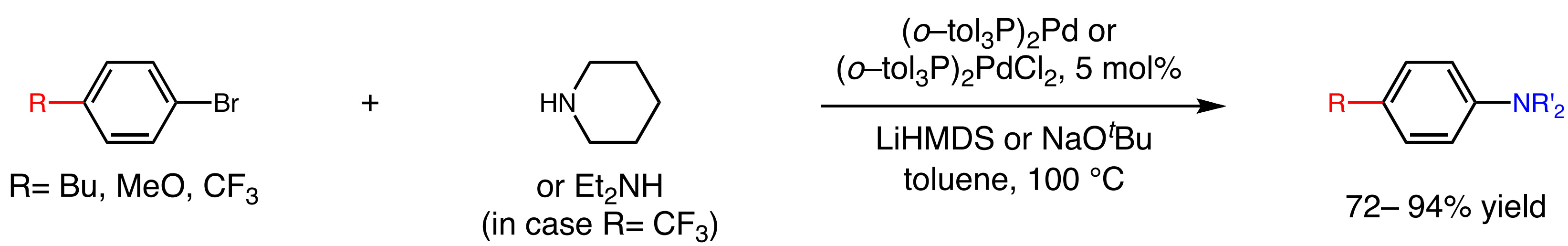


Guram, A. S. and Buchwald, S. L. *JACS* **1994**, *116*, 7901.

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

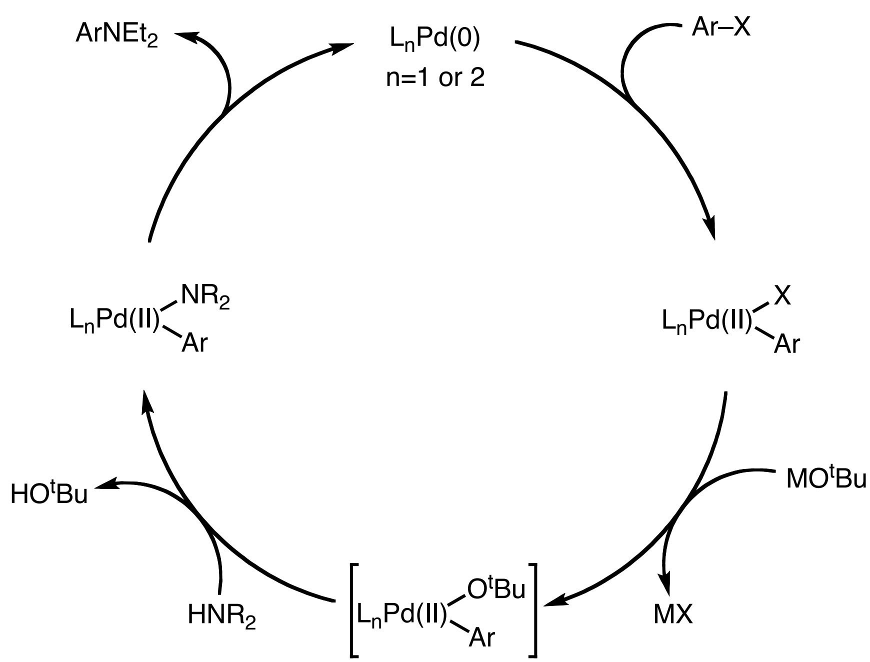


(Submitted on Jan 17, 1995; revised March 13 1995) Buchwald, S. L. *et al ACIE* **1995**, *34*, 1348.

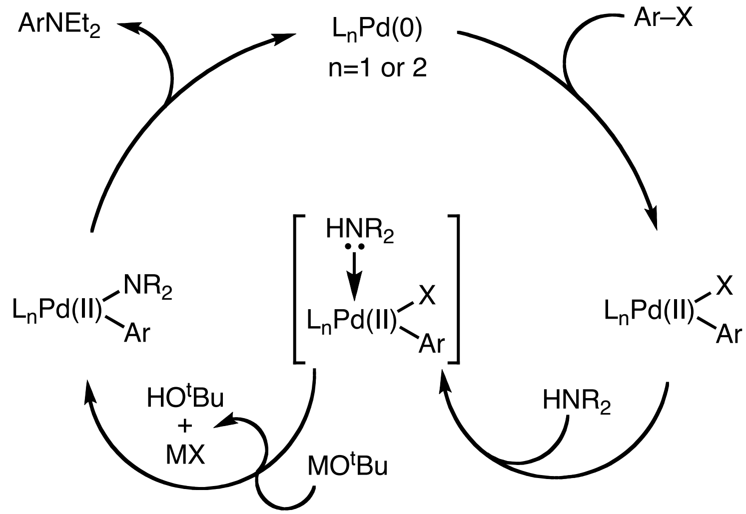


(*Submitted on March 6, 1995)* Louie, J., Hartwig, J. F. *Tet. Lett.* **1995**, *36*, 3069.
(from mechanistic study)

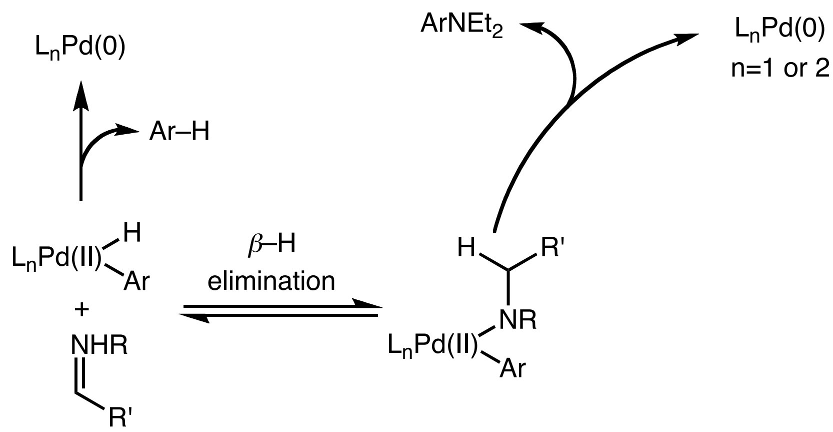
The Mechanistic Scheme that You Normally See



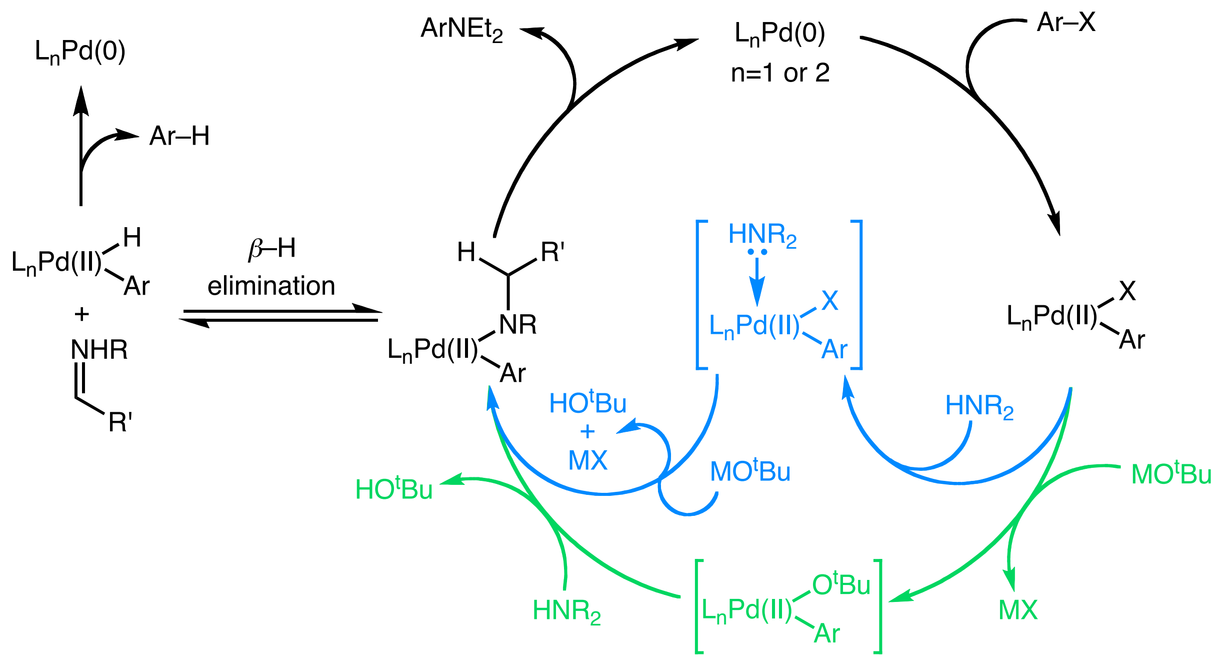
The Mechanistic Scheme that You Normally See



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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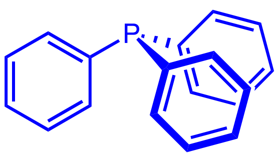
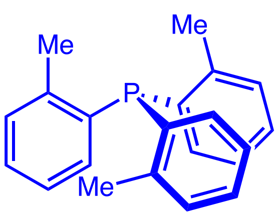
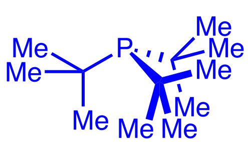
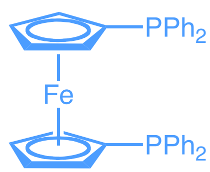
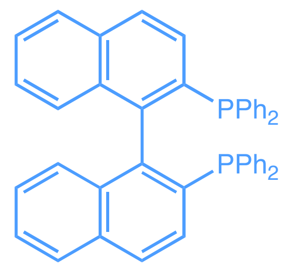




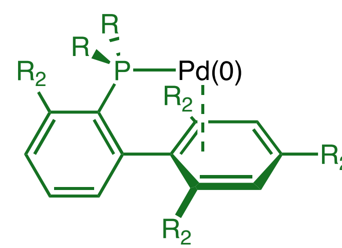




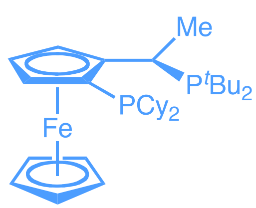
DPPF



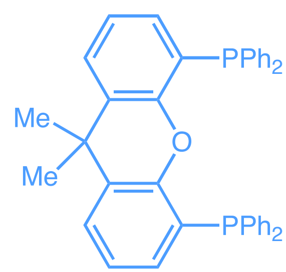
BINAP



Biarylphosphine

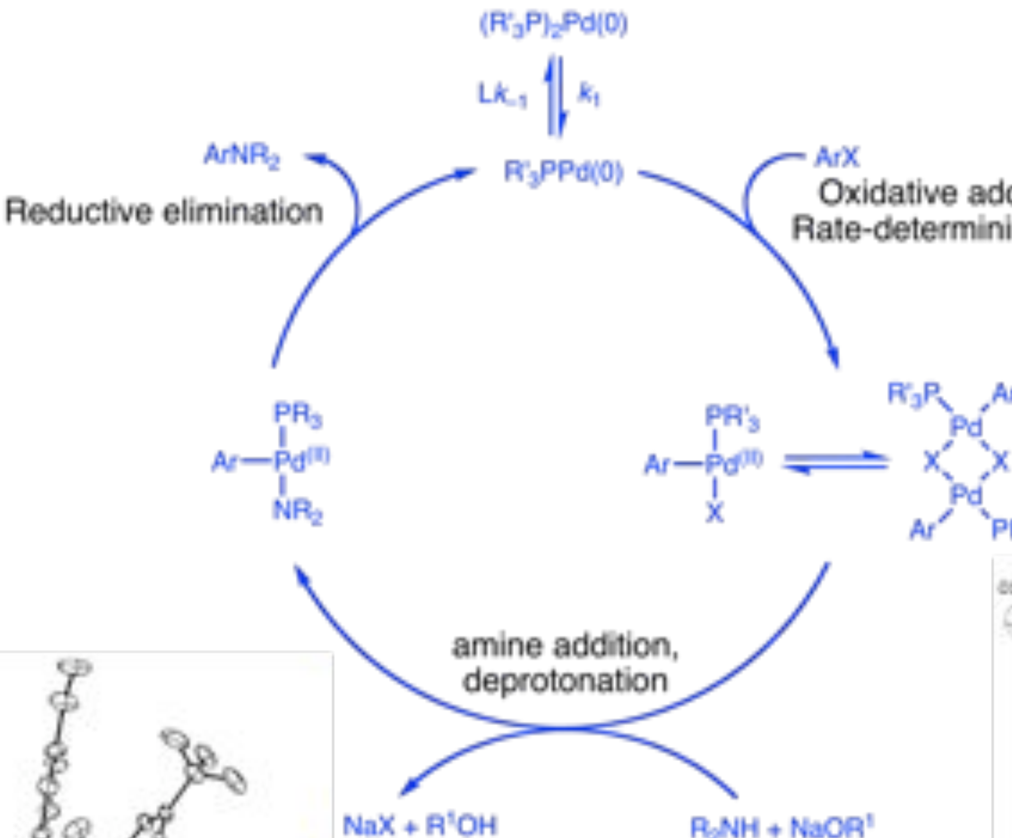


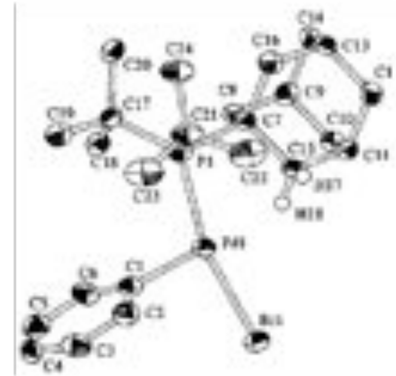
Josiphos



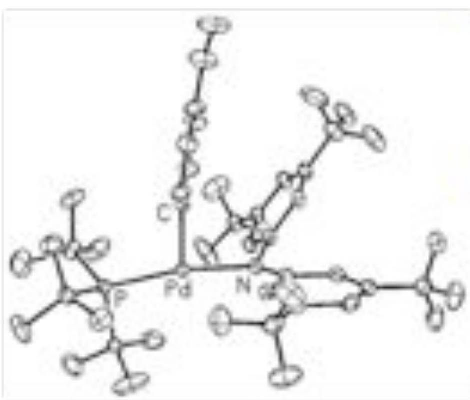
Xantphos

Mechanistic Study with Monodentate Hindred Phosphine Ligands

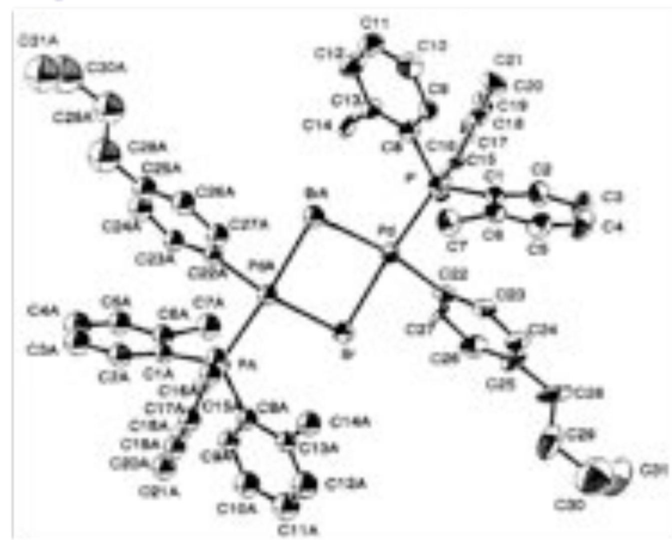




X-ray structre of
$[(1\text{–}AdP^tBu_2)Pd(C_6H_5)(Br)$
Hartwig, J. F. *et al JACS* **2002**, *124*, 9346.



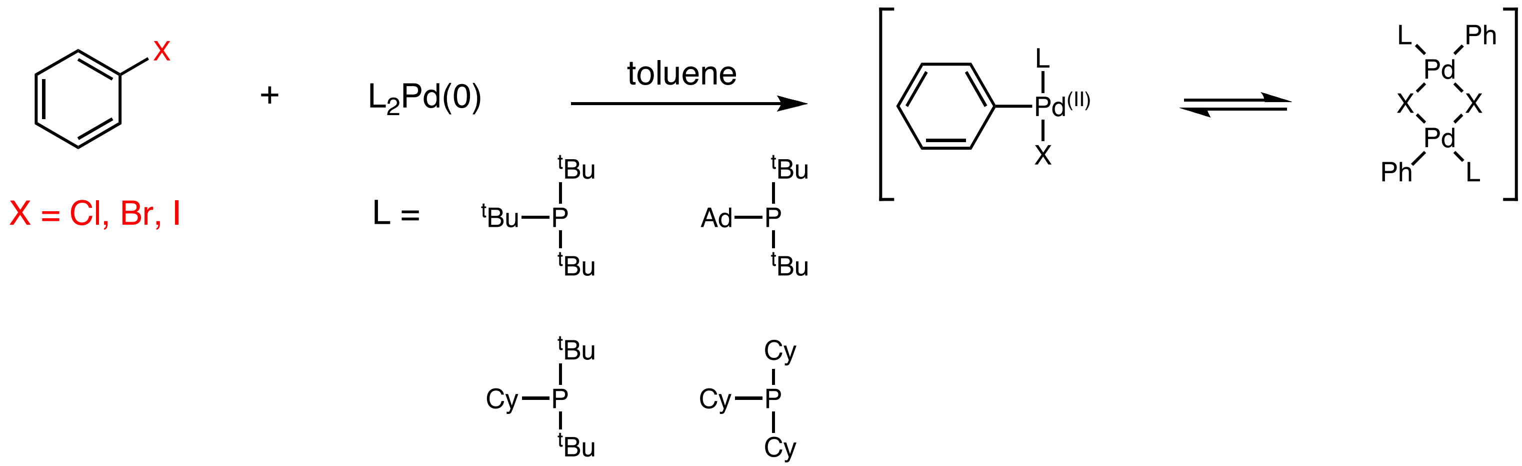
ORTEP diagram of
$(^tBu_3P)Pd(MeOC_6H_4)N(3,5\text{-}(CF_3)_2C_6H_3)_2$
Hartwig, J. F. *et al JACS* **2004**, *126*, 5344.
Buchwald, S. L. *et al Organometallics* **1996**, *15*, 2745(solution struct.)



ORTEP diagram of
$[(o\text{-}tol_3P)Pd(4\text{-}nBuC_6H_4)(Br)]_2$
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



♦ The rate constant of the oxidative addition depends on concentration of phenyl halide.

♦ Kinetic data show that the mechanism of the oxidative addition depends on the identity of the halide more than on the steric bulk of the ligand.

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

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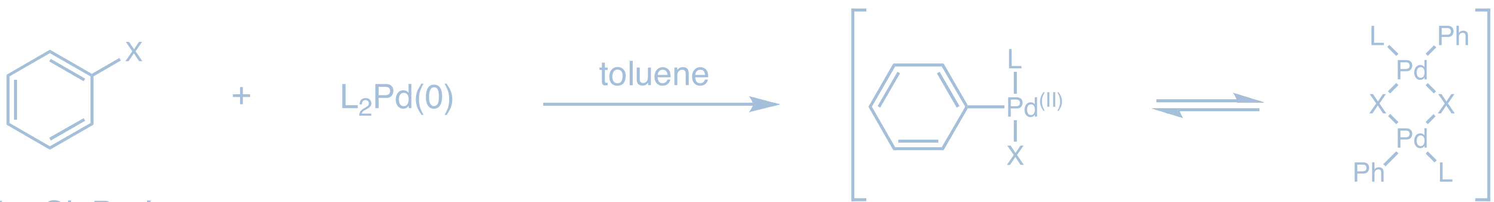
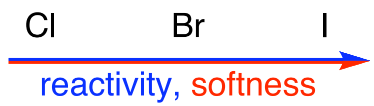
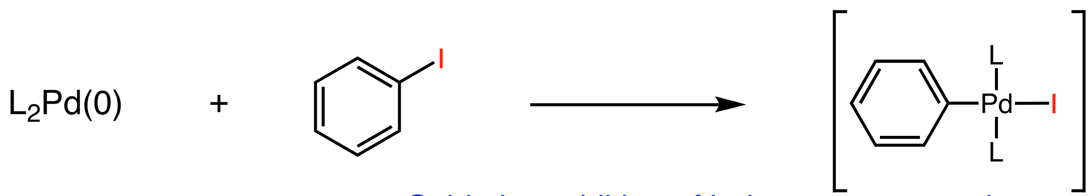


X = Cl, Br, I





<=> Iodoarene oxidative addition pathway.

♦ Oxidative addition of iodoarenes occurs by rate-determining reaction with a bisphosphine complex.

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

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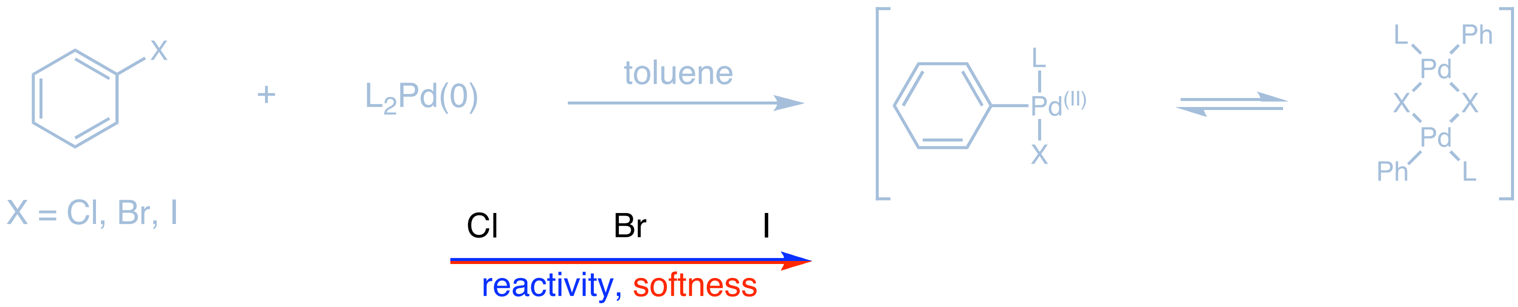

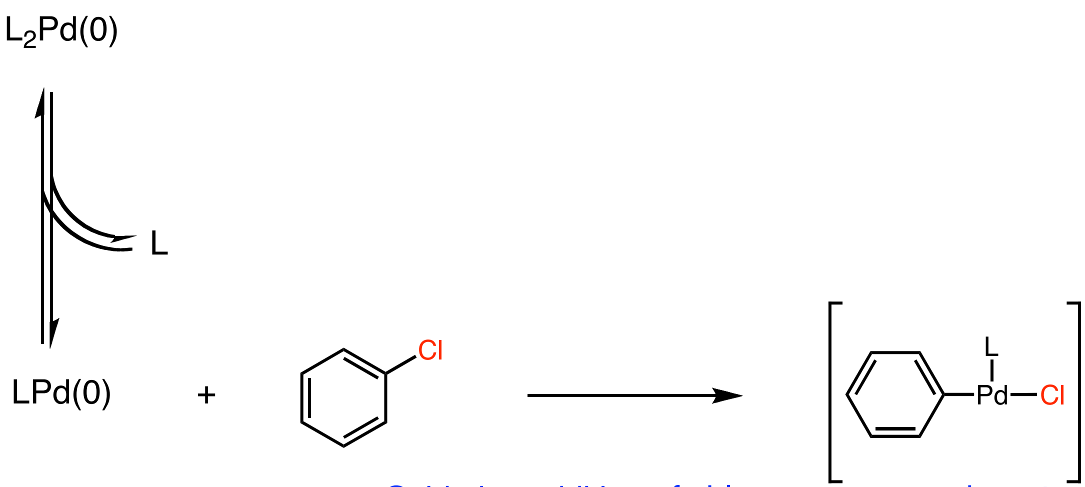

<=> Chloroarene oxidative addition pathway.

♦ Oxidative addition of chloroarens occur by rate-determining reaction with a monophosphine complex.

(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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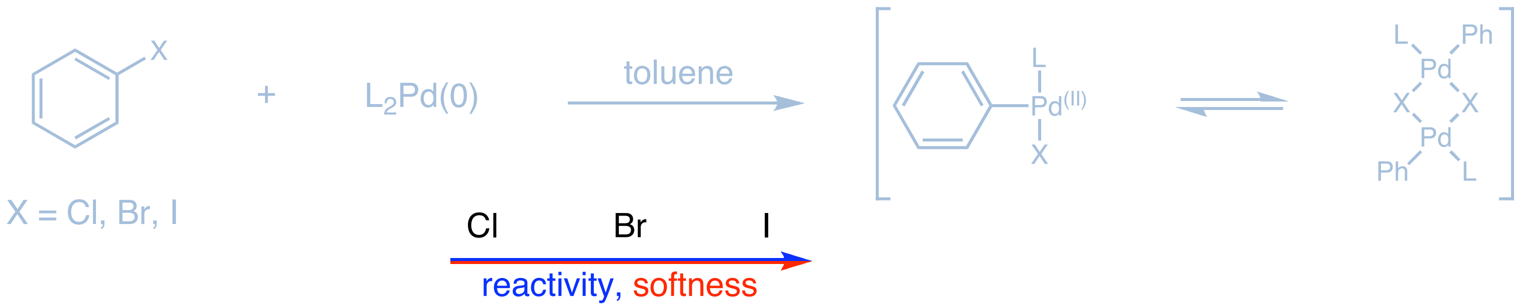
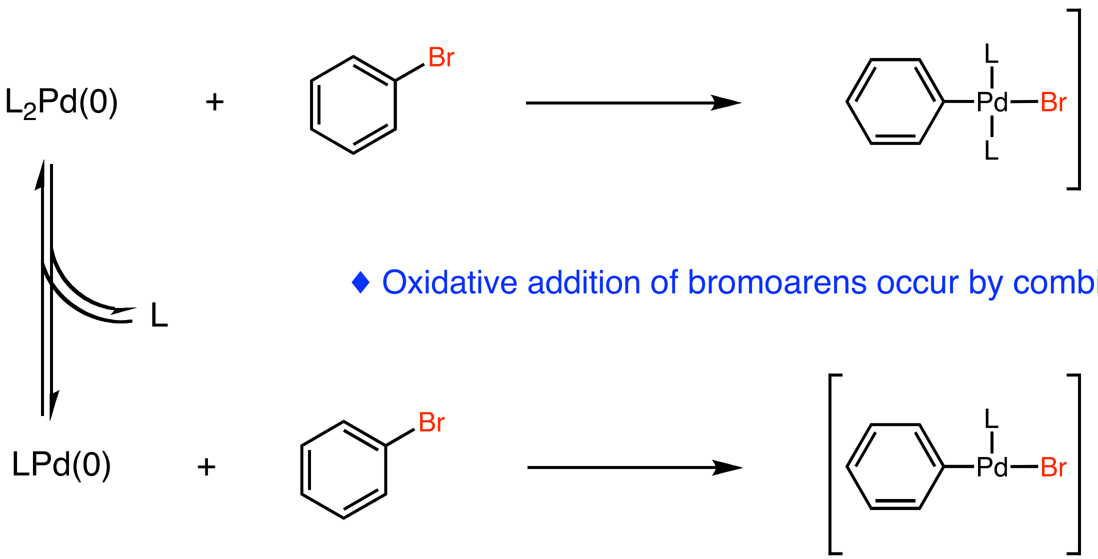




<=> Iodoarene oxidative addition pathway.

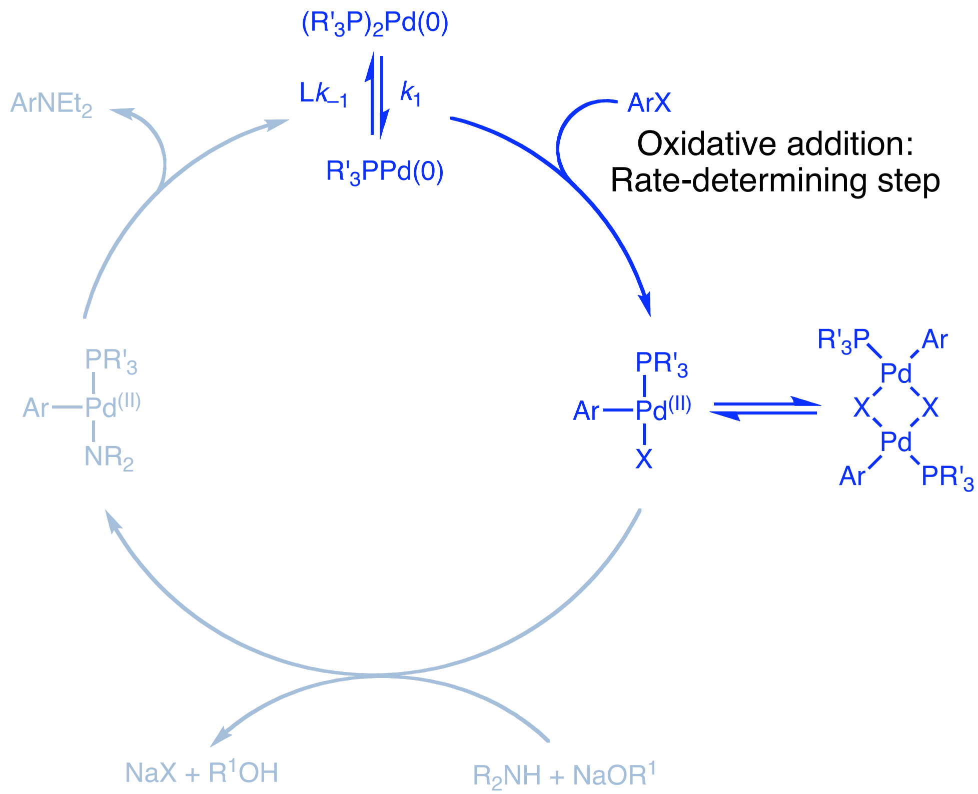
♦ Oxidative addition of bromoarens occur by combination of two pathways.

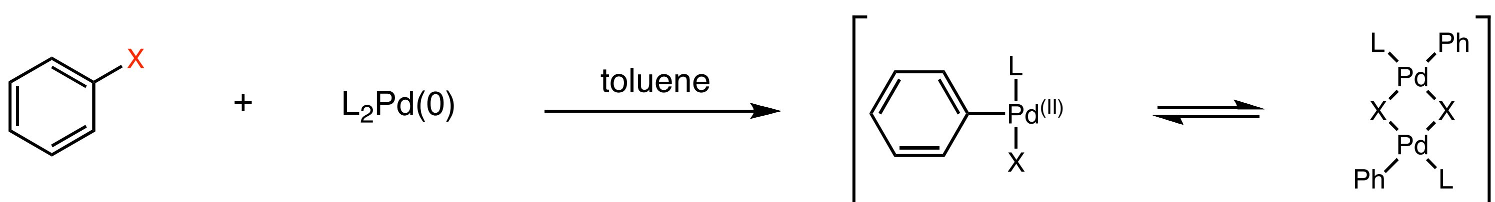
<=> Chloroarene oxidative addition pathway.

(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 of Aryl Halides in Amination Reactions

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



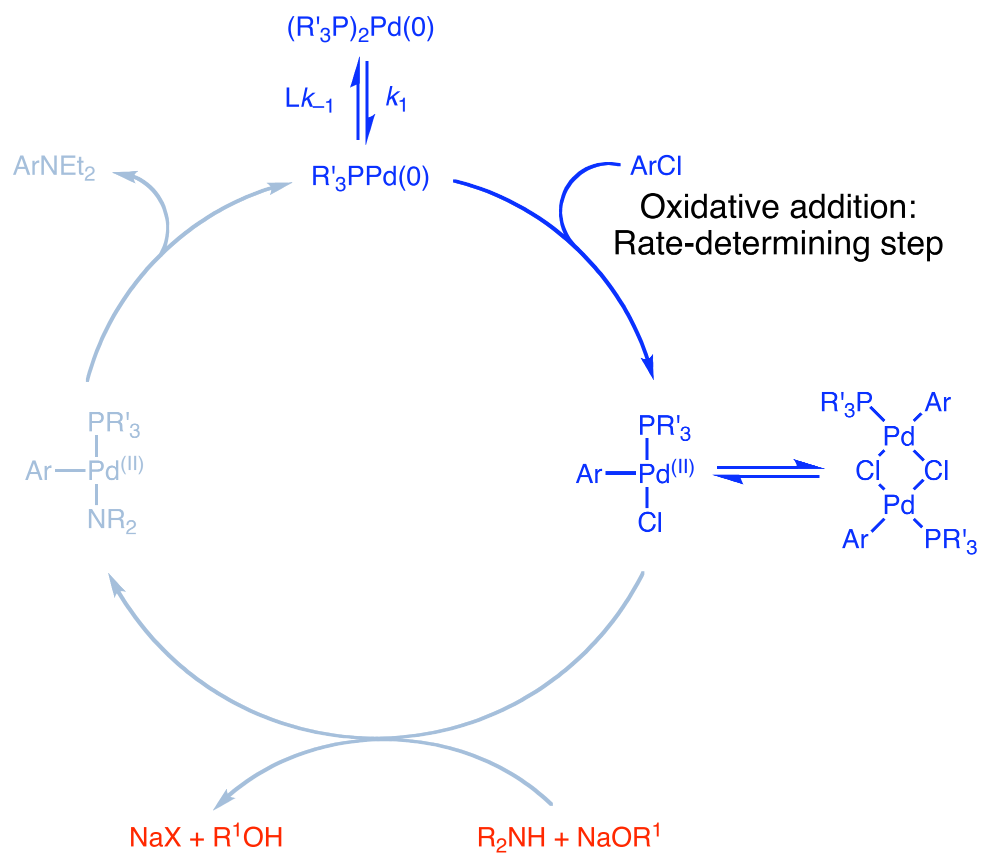


X = Cl, Br, I

Barrios-Landeros, F. and Hartwig, J. F. *JACS* **2005**, *127*, 6944.
Hartwig, J. F. *et al JACS* **2009**, *131*, 8141.

Oxidative Addition of Aryl Chorides in Amination Reactions

■ Base-induced oxidative addition of aryl chlorides in amination reactions

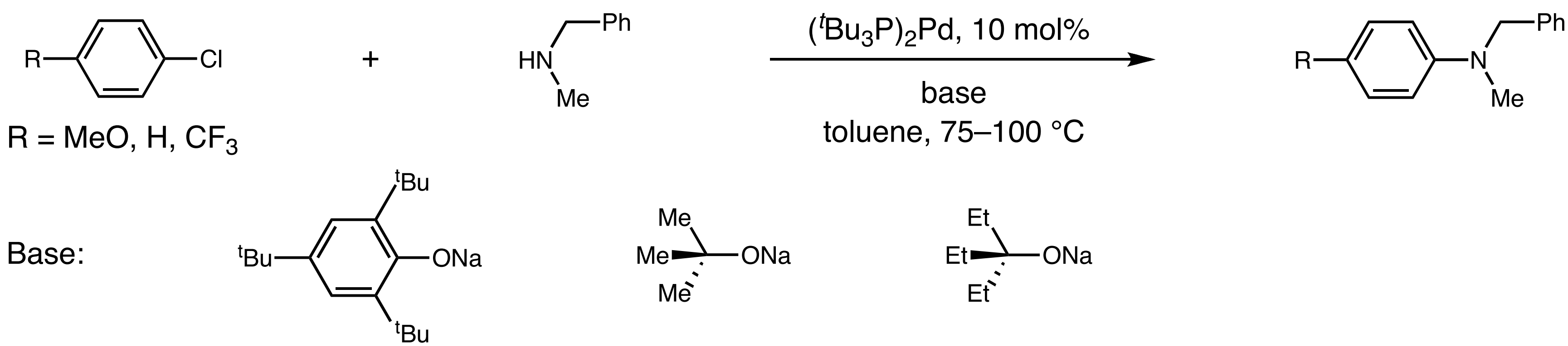


♦ How does the base effect on the amination of aryl chlorides catalyzed by $L_2P(0)$?

Alcazar-Roman, L. M. and Hartwig, J. F. *JACS* **2001**, *123*, 12905.
Shekhar, S. and Hartwig, J. F. *Organometallics* **2007**, *26*, 340.

Oxidative Addition of Aryl Chorides in Amination Reactions

■ Kinetic study on base-induced oxidative addition of aryl chlorides in amination reactions



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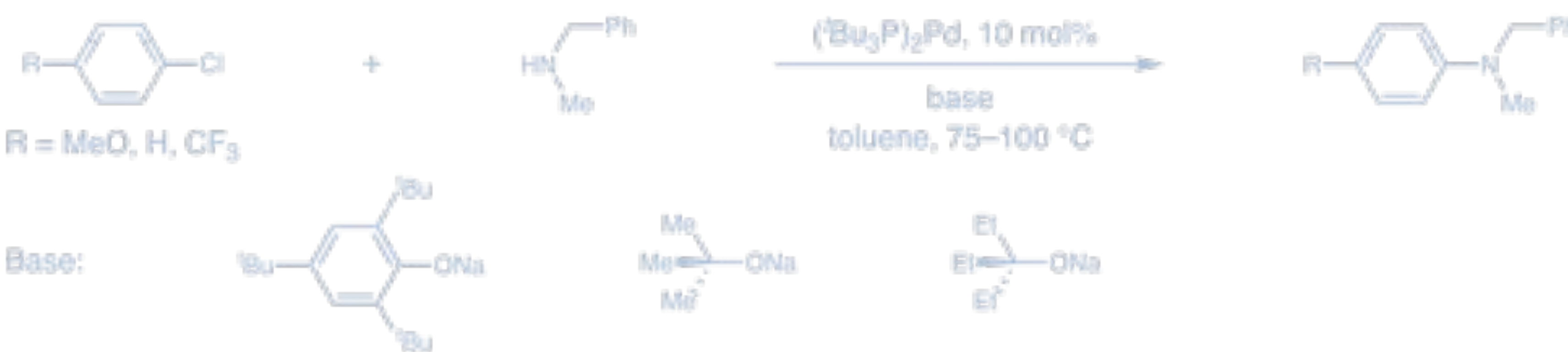
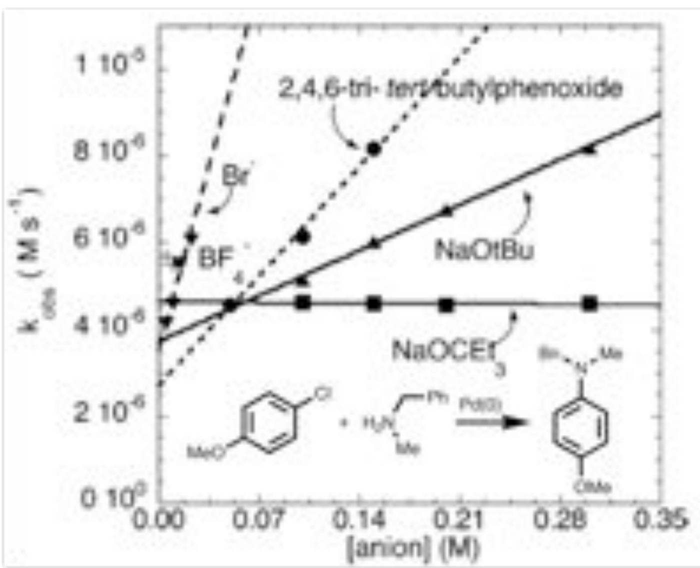
Shekhar, S. and Hartwig, J. F. *Organometallics* **2007**, *26*, 340.

Oxidative Addition of Aryl Chorides in Amination Reactions

■ Kinetic study on base-induced oxidative addition of aryl chlorides in amination reactions





♦ The reaction rate depends on the concentration of ArCl and Pd(0).

k_{obs} ~ [ArCl], [(^{t}Bu$_3$P)$_2$Pd)]

♦ The reaction rate of electron-rich ($MeOC_6H_4Cl$) and electron-neutral (PhCl) aryl chlorides depends on both identities and concentration of bases (except the bulky base).

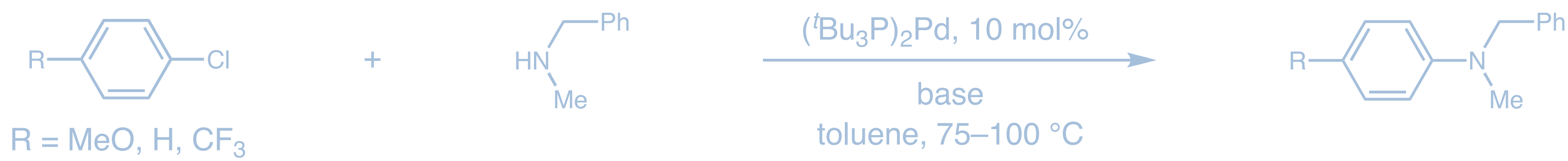
k_{obs} ~ [^{t}BuONa], [^{t}Bu$_3$C$_6$H$_2$ONa]

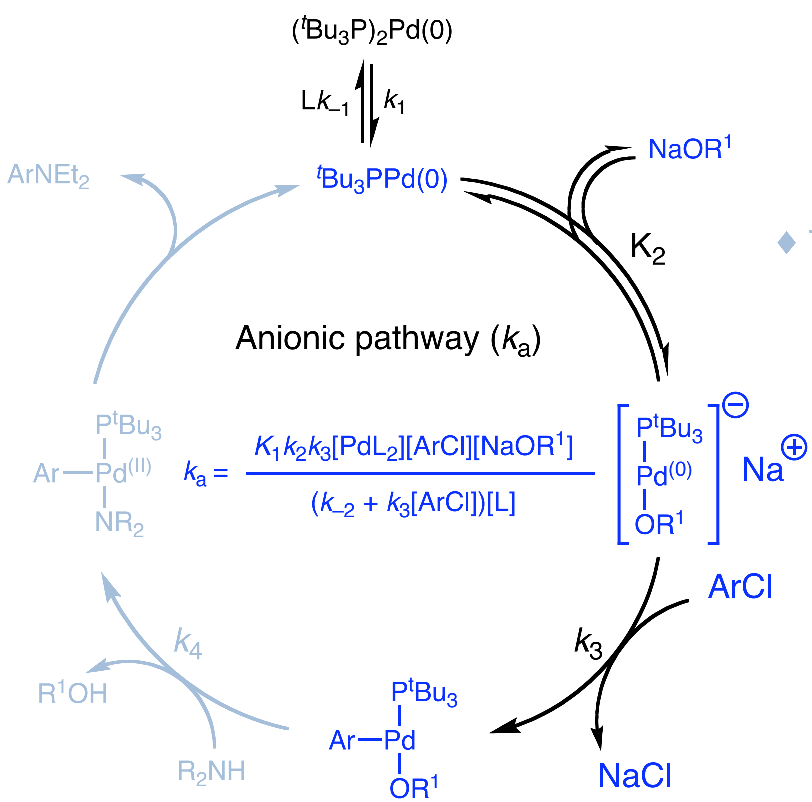
k_{obs} does not depend on [Et_3CONa]

Alcazar-Roman, L. M. and Hartwig, J. F. *JACS* **2001**, *123*, 12905.
Shekhar, S. and Hartwig, J. F. *Organometallics* **2007**, *26*, 340.

Oxidative Addition of Aryl Chorides in Amination Reactions

■ Kinetic study on base-induced oxidative addition of aryl chlorides in amination reactions-anionic pathway





♦ The reaction rate depends on the concentration of ArCl and Pd(0).

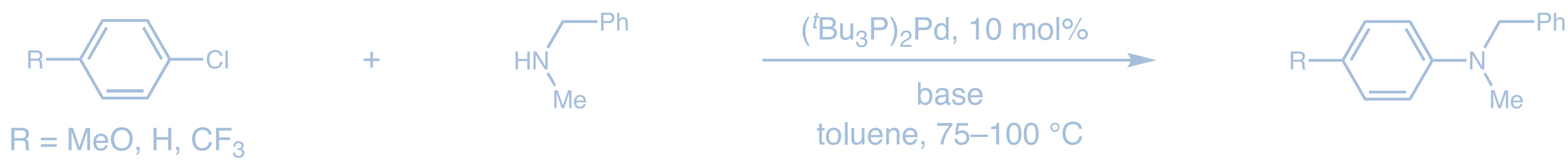
k_{obs} ~ [ArCl], [(^{t}Bu$_3$P)$_2$Pd)]

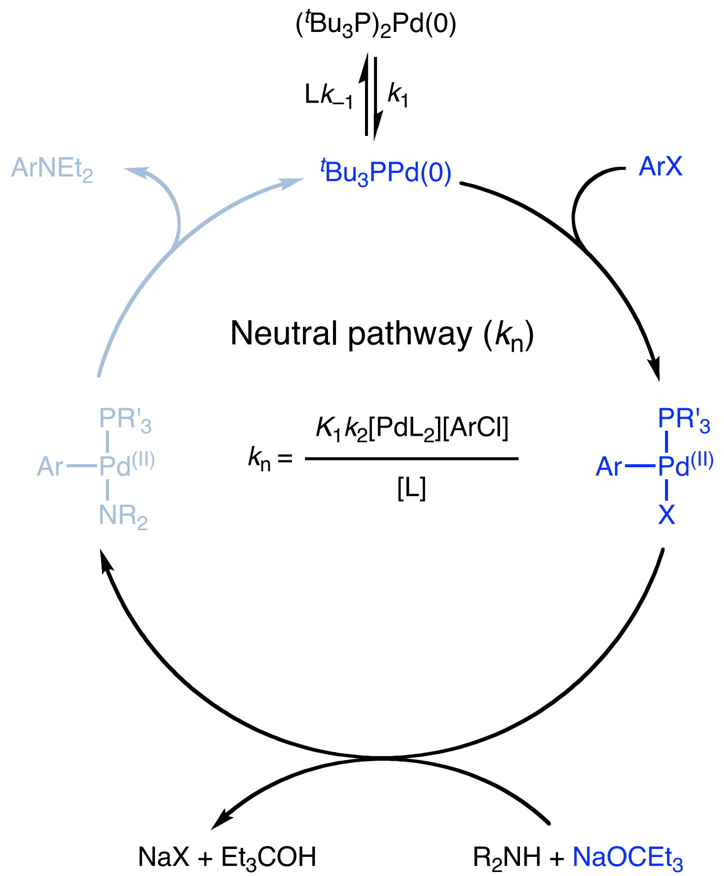
♦ k_{obs} ~ [^{t}BuONa] or [^{t}Bu$_3$C$_6$H$_2$ONa] <=> anionic pathway.

Alcazar-Roman, L. M. and Hartwig, J. F. *JACS* **2001**, *123*, 12905.
Shekhar, S. and Hartwig, J. F. *Organometallics* **2007**, *26*, 340.

Oxidative Addition of Aryl Chorides in Amination Reactions

■ Kinetic study on base-induced oxidative addition of aryl chlorides in amination reactions-neutral pathway





♦ The reaction rate depends on the concentration of ArCl and Pd(0).

$k_{obs} \sim [ArCl], [({}^tBu_3P)_2Pd)]$

♦ k_{obs} does not depends on $[Et_3CONa]$ <=> neutral pathway

Alcazar-Roman, L. M. and Hartwig, J. F. *JACS* **2001**, *123*, 12905.
Shekhar, S. and Hartwig, J. F. *Organometallics* **2007**, *26*, 340.

Oxidative Addition of Aryl Halides in Amination Reactions

■ The combination of anionic and neutral pathways-a reasonable model for oxidative addtion of aryl halides

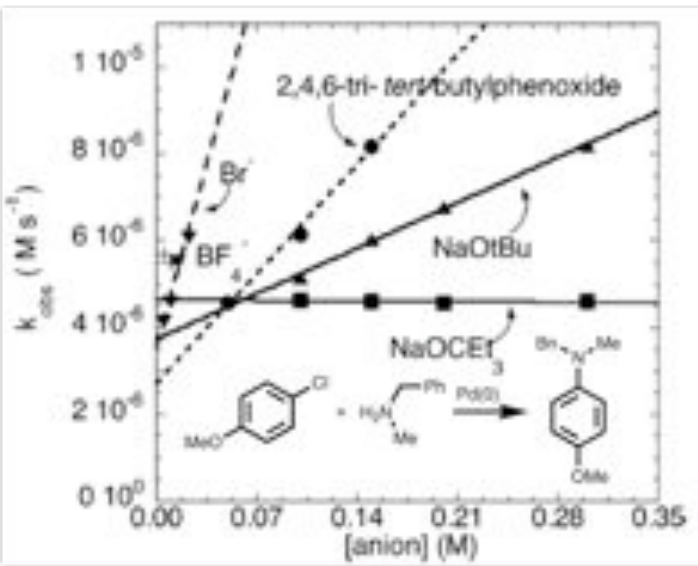
$$k_{obs} = k_{anionic} + k_{neutral}$$

Alcazar-Roman, L. M. and Hartwig, J. F. *JACS* **2001**, *123*, 12905.
Shekhar, S. and Hartwig, J. F. *Organometallics* **2007**, *26*, 340.

Oxidative Addition of Aryl Halides in Amination Reactions

■ The combination of anionic and neutral pathways-a reasonable model for oxidative addtion of aryl halides

$$k_{obs} = k_{anionic} + k_{neutral}$$



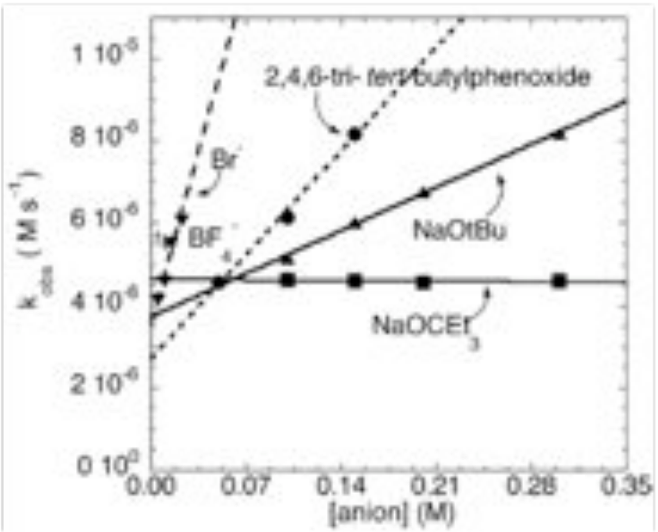
♦ Relatively smaller (^{t}BuONa) or softer ($^{t}Bu_3C_6H_2ONa$) bases promote anionic mechanism ($k_{obs} \approx k_{anionic}$).

♦ More bulky triethylmethoxide (Et_3CO^-) promotes neutral mechanism ($k_{obs} \approx k_{neutral}$).

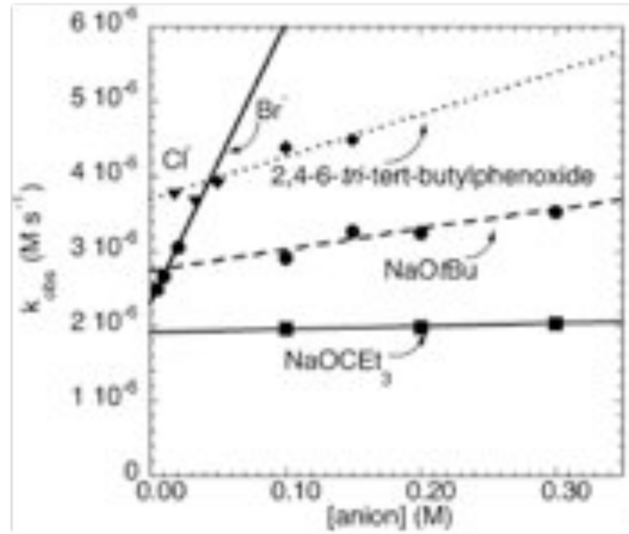
Alcazar-Roman, L. M. and Hartwig, J. F. *JACS* **2001**, *123*, 12905.
Shekhar, S. and Hartwig, J. F. *Organometallics* **2007**, *26*, 340.

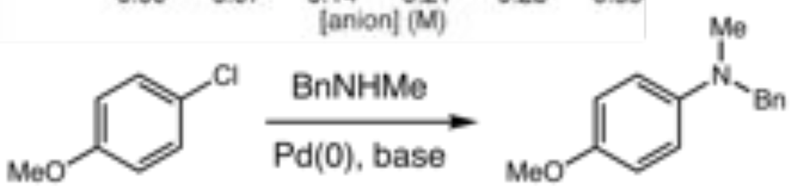
Oxidative Addition of Aryl Halides in Amination Reactions

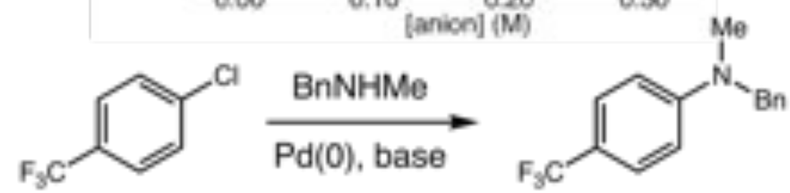
■ The combination of anionic and neutral pathways-a reasonable model for oxidative addtion of aryl halides



$k_{obs} = k_{anionic} + k_{neutral}$



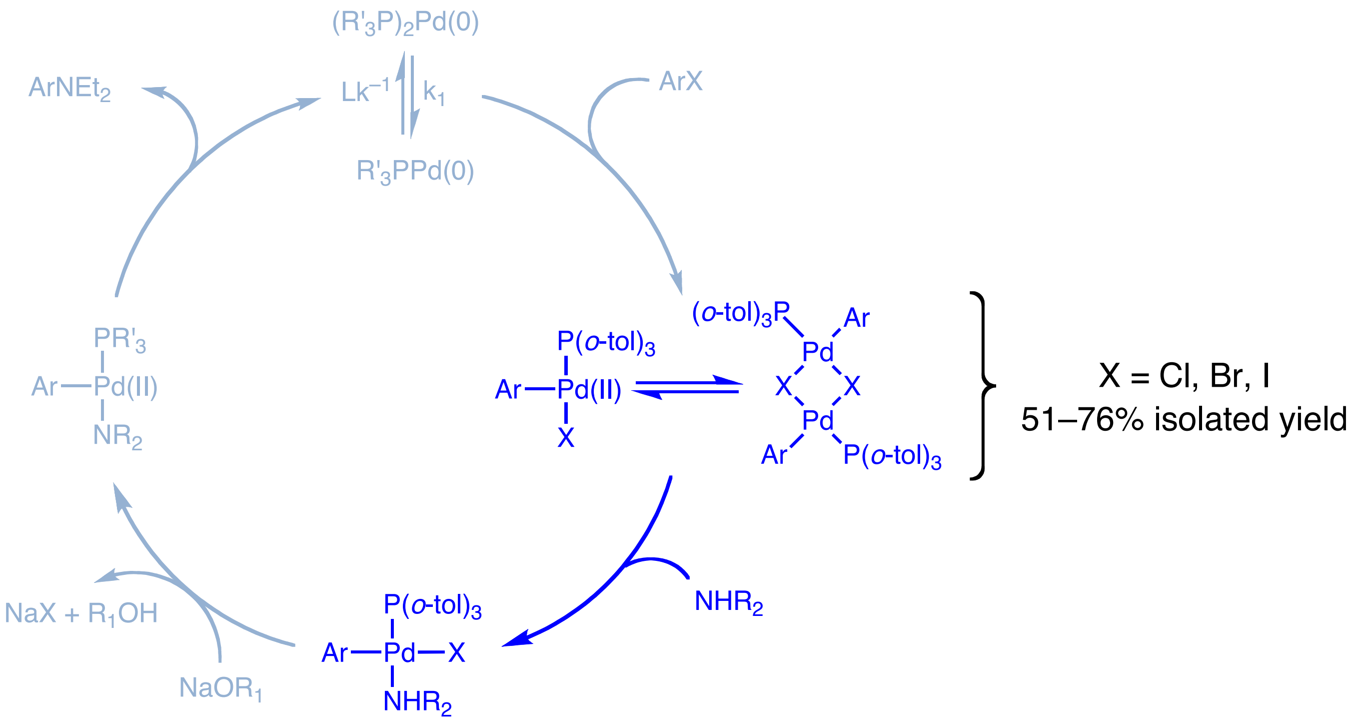




◆ More reactive aryl halides such as eleclectron-poor aryl chloride, aryl bromide, etc. promote neutral mechanism ($k_{obs} \approx k_{neutral}$).

Alcazar-Roman, L. M. and Hartwig, J. F. *JACS* **2001**, *123*, 12905.
Shekhar, S. and Hartwig, J. F. *Organometallics* **2007**, *26*, 340.

Formation of Palladium Monoamine Complexes

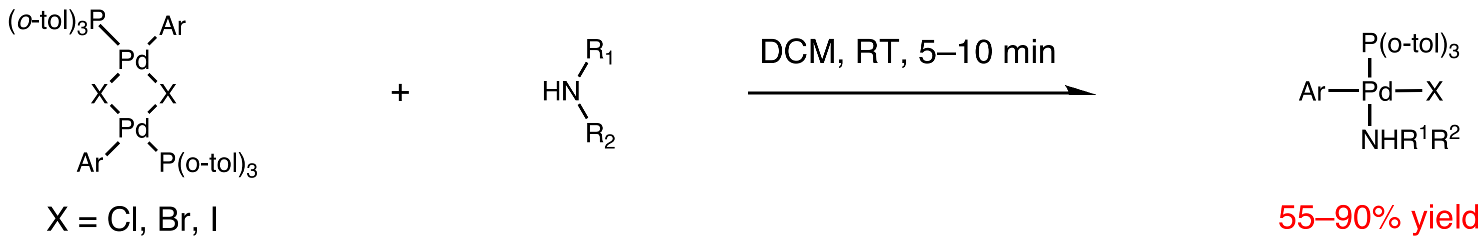


Palladium monoamine complex
55–90% isolated yield

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

Thermodynamic Study on the Formation of Palladium Monoamine Complexes

■ The formation of palladium monoamine complexes from palladium aryl halide dimers



♦ The reaction is reversible or irreversible depending on the identities of halides and amine.

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

Thermodynamic Study on the Formation of Palladium Monoamine Complexes

■ The formation of palladium monoamine complexes from palladium aryl halide dimers

X = Cl, Br, I

55–90% yield

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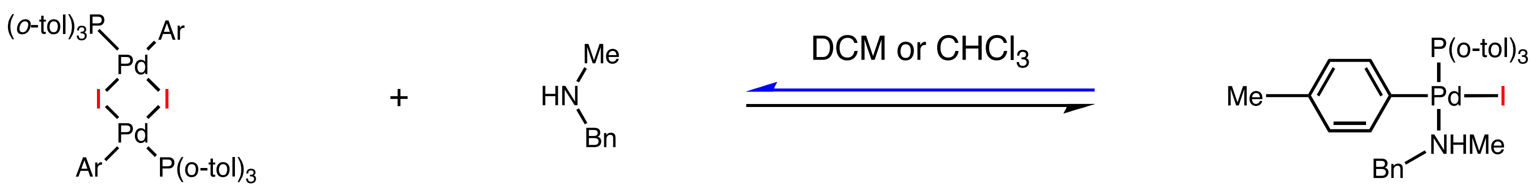

1 eq 1 eq : 4 eq

No reverse reaction observed with corresponding amine adducts of aryl chloride or bromide.

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

Thermodynamic Study on the Formation of Palladium Monoamine Complexes

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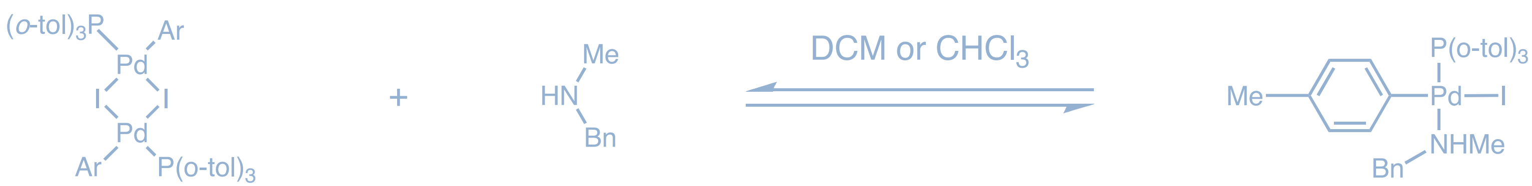
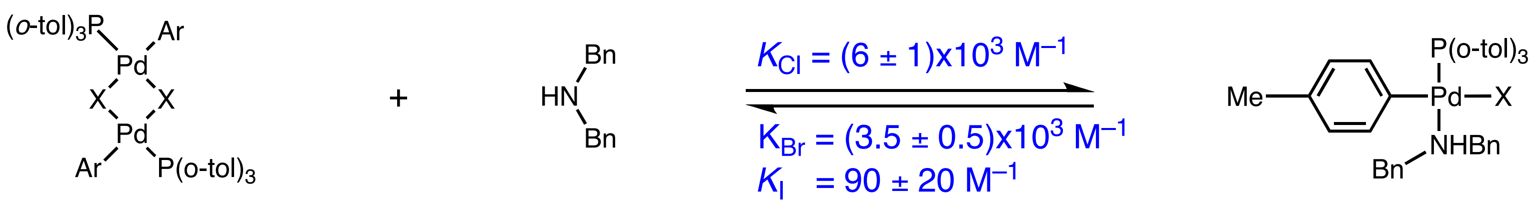


1 eq   1 eq   :   4 eq

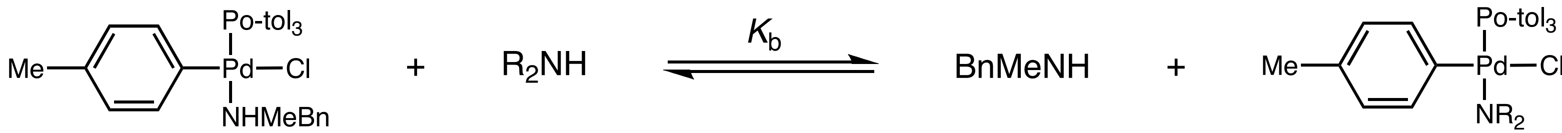


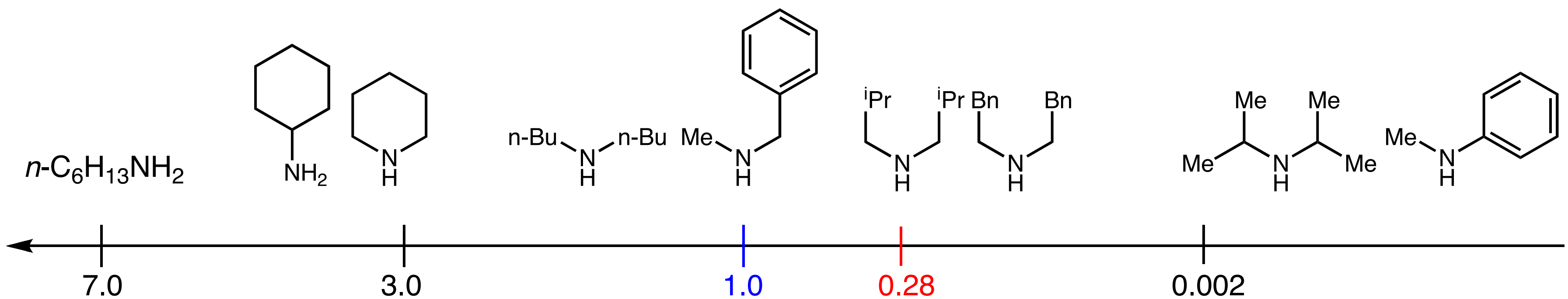
X = Cl, Br, I

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

Thermodynamic Study on the Formation of Palladium Monoamine Complexes

■ The formation of palladium monoamine complexes - binding affinity of amines to the palladium aryl halide



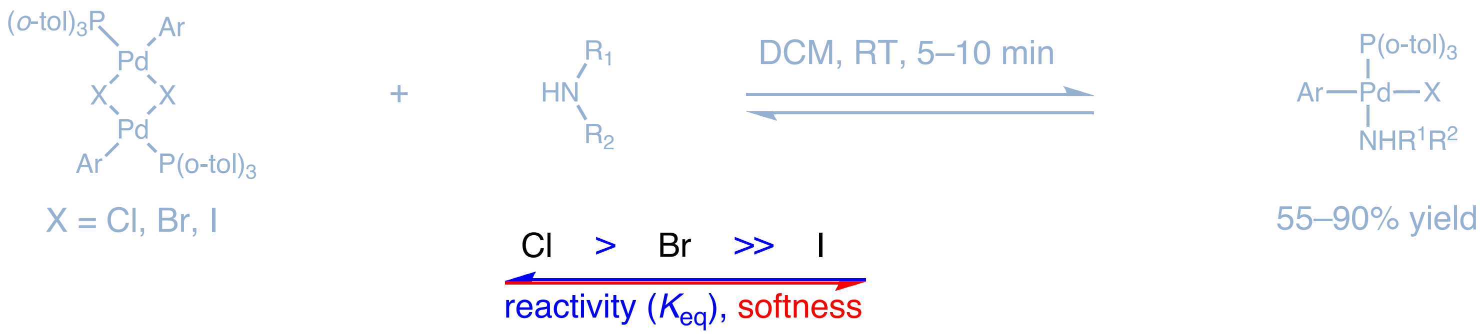


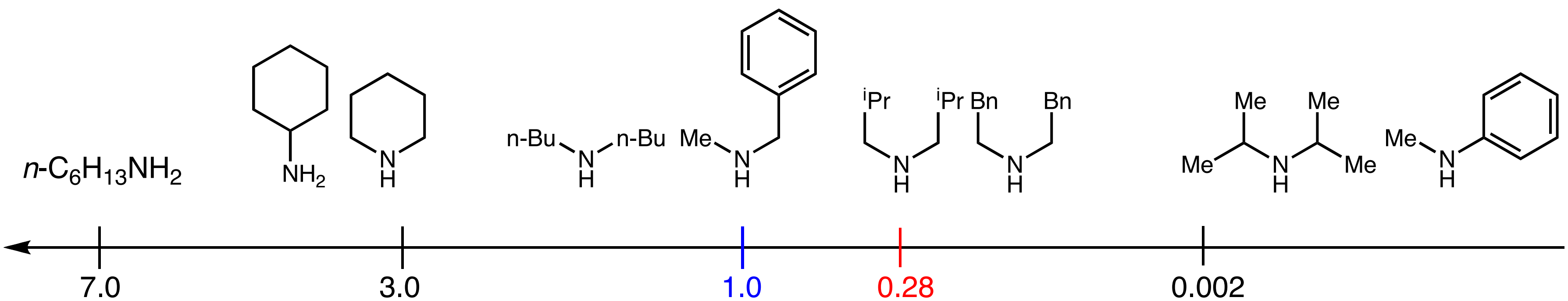
K_b : binding affinity of amine to the palladium aryl halide complex.

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

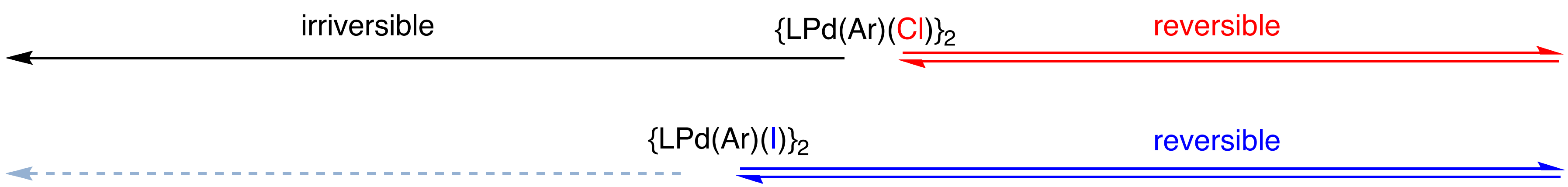
Thermodynamic Study on the Formation of Palladium Monoamine Complexes

■ The formation of palladium monoamine complexes from palladium aryl halide dimers





K_b : binding affinity of amine to the palladium aryl halide complex.



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

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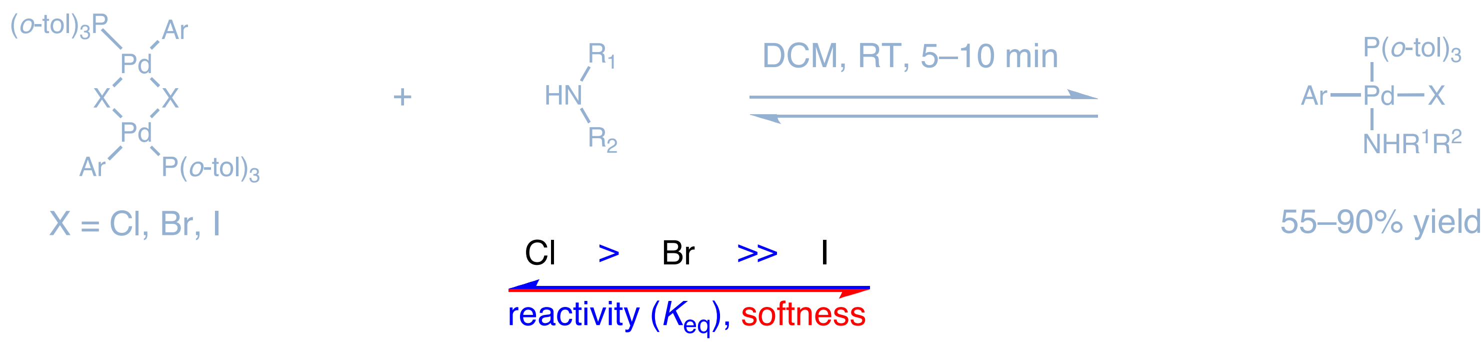
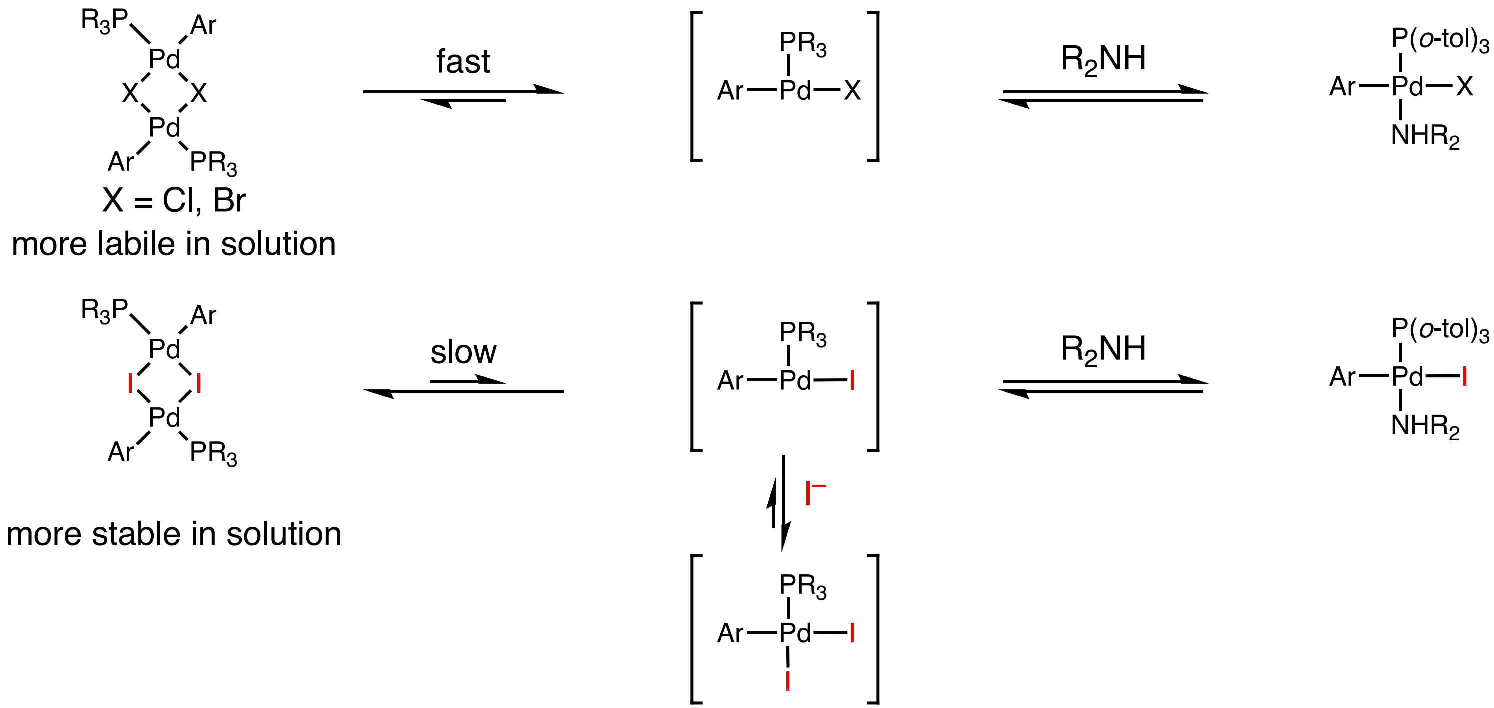
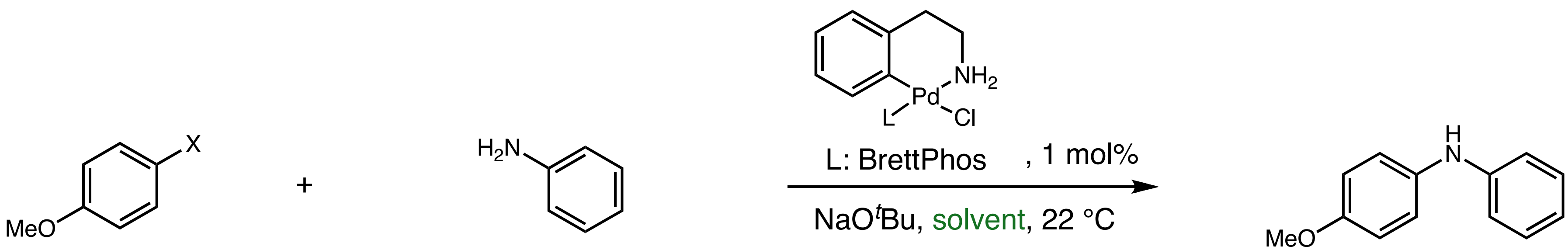




Buchwald, S. L. *et al Organometallics* **1996**, *15*, 2745.
Widenhoefer, R. A. and Buchwald, S. L. *Organometallics* **1996**, *15*, 2755.

Do Not Be Misled - Oxidative Addition Still Takes Control



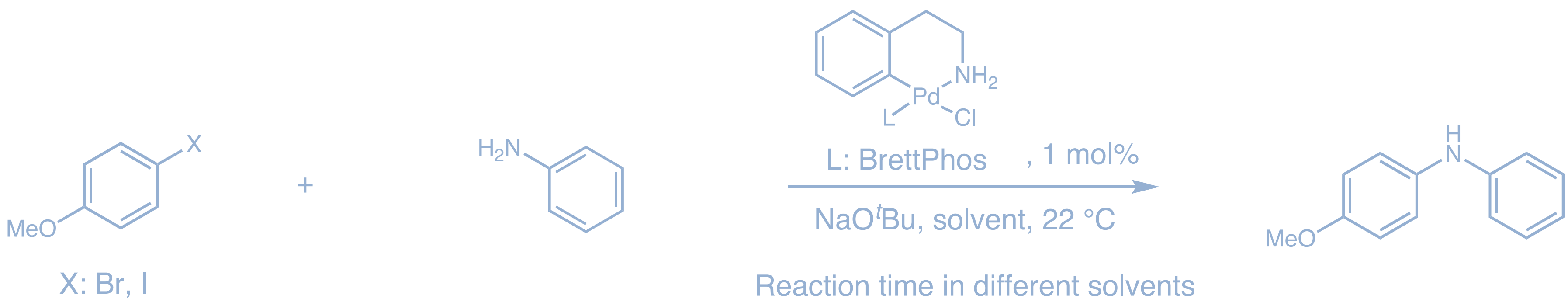
X: Br, I

Reaction time in different solvents

	toluene	dioxane	DME
Br	6 min	10 min	10 min
I	6 min	23 min	70 min

Buchwald, S. L. *et al JACS* **2009**, *131*, 5766.

Do Not Be Misled - Oxidative Addition Still Takes Control



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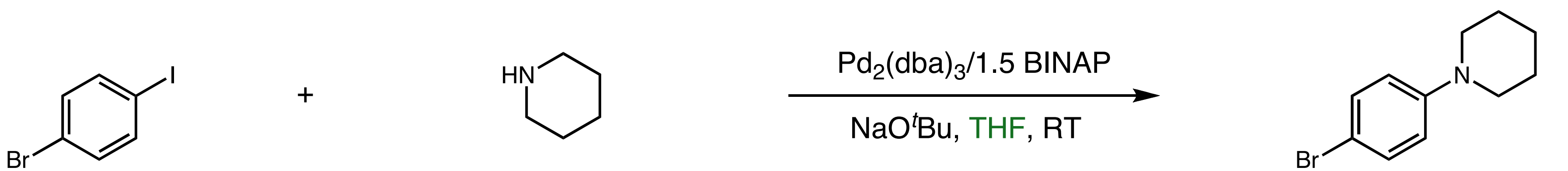
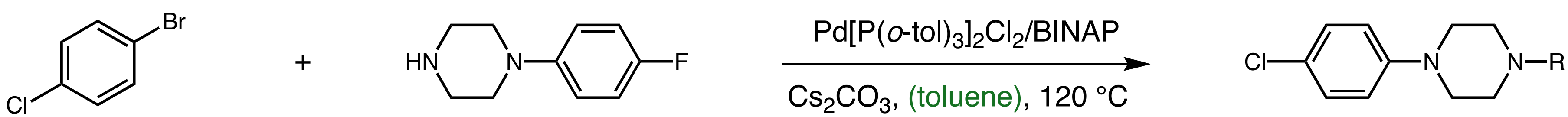


84 % yield

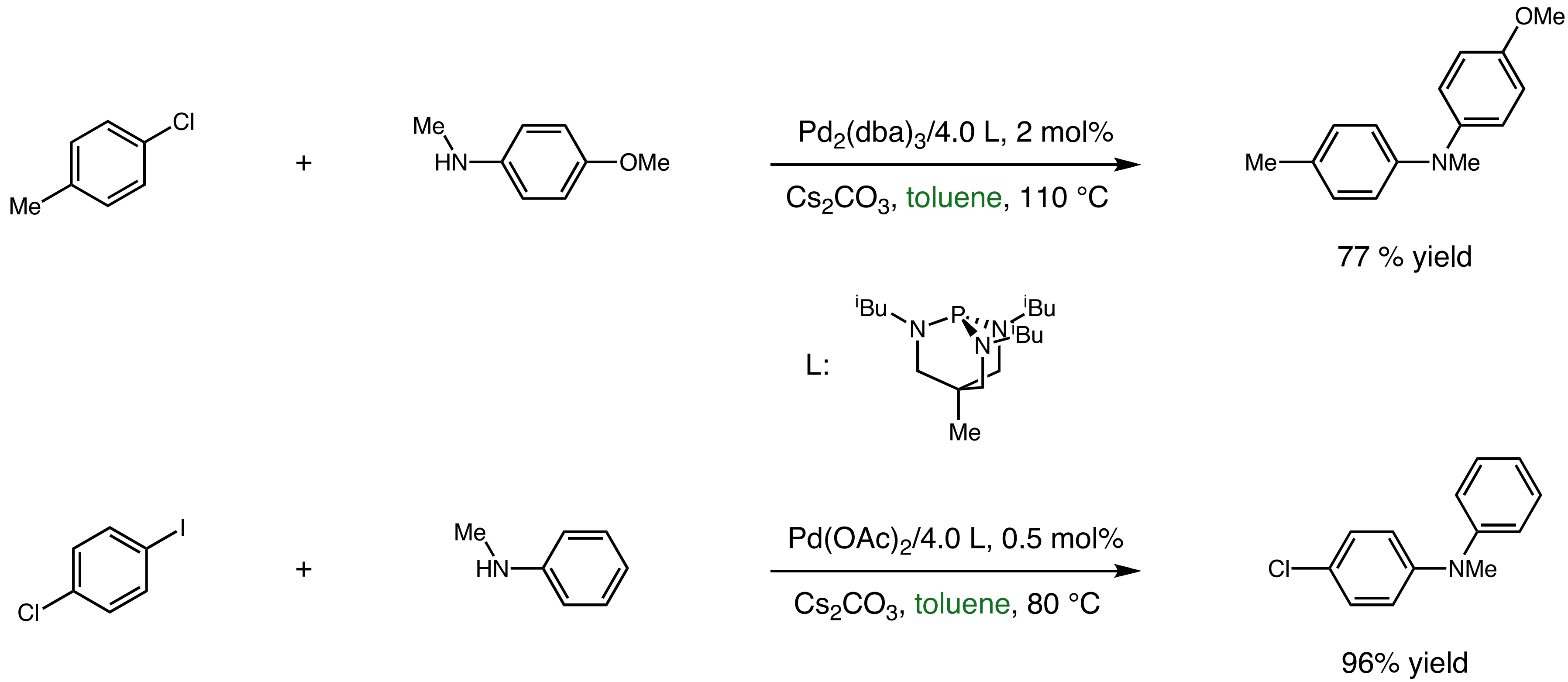
Wolfe, J. P. and Buchwald, S. L. *JOC* **1997**, *62*, 6066.



79 % yield

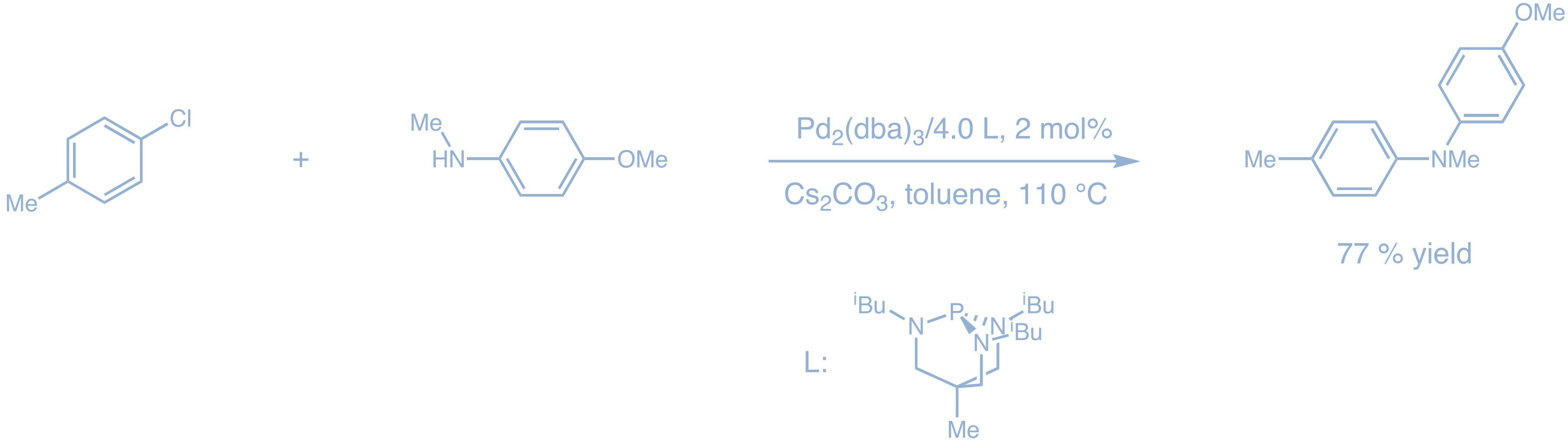
Pujol, M. D. *et al Tet.* **2006**, *62*, 9010.

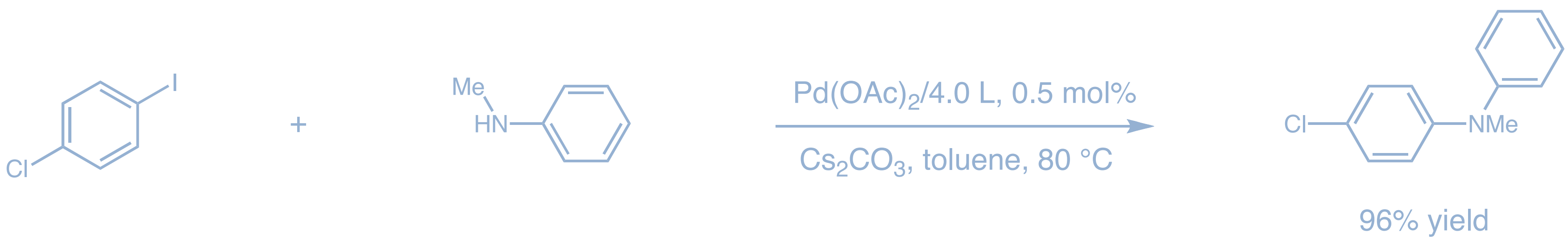
Do Not Be Misled - Oxidative Addition Still Takes Control



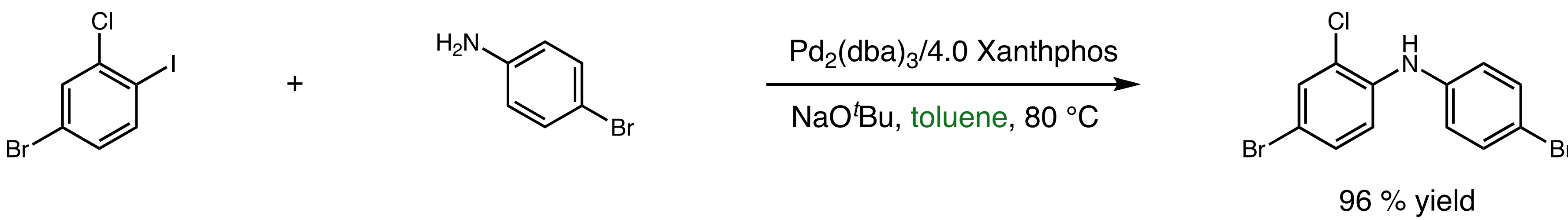
Verkade, J. G. *et al JOC* **2003**, *68*, 8416.

Do Not Be Misled - Oxidative Addition Still Takes Control



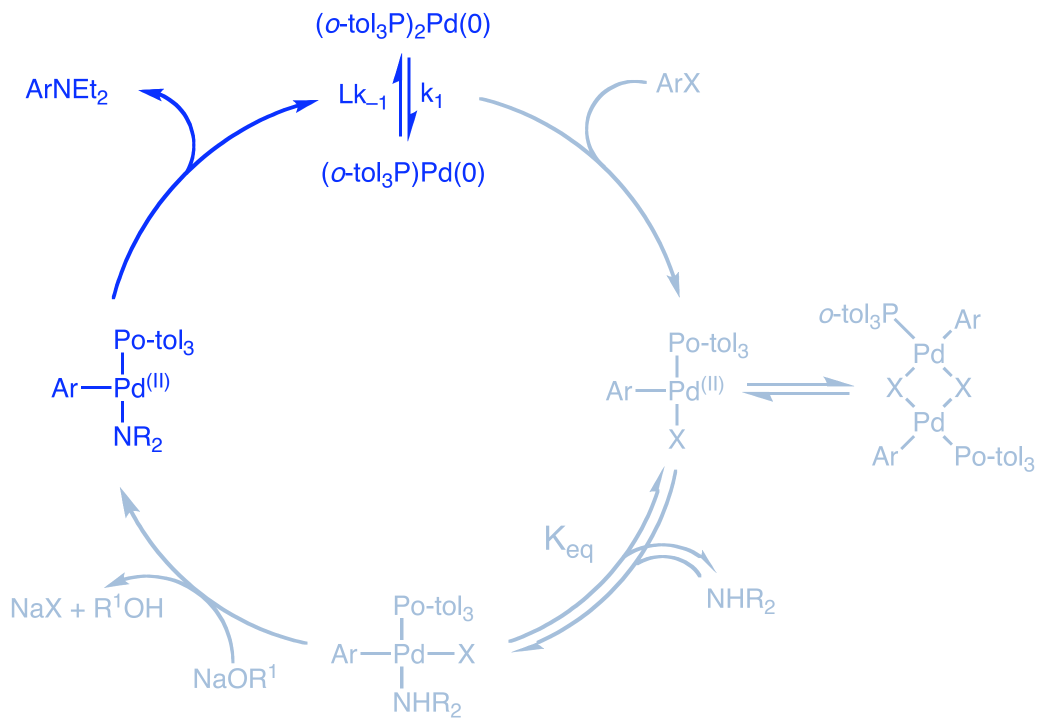


Verkade, J. G. *et al JOC* **2003**, *68*, 8416.



Jørgensen, M. *et al Tet.* **2008**, *64*, 2938.

Reductive Elimination with Monodentate Hindered Phosphine Ligands



Hartwig, J. F. *et al JACS* **1996**, *118*, 3626.

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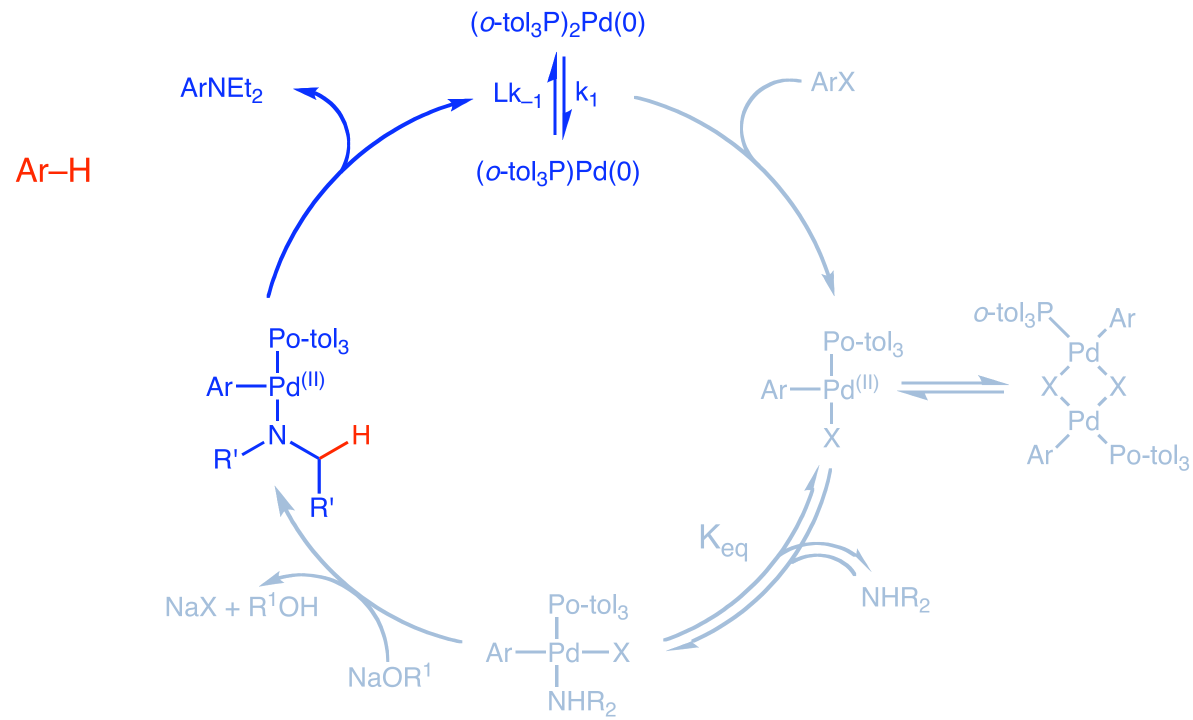

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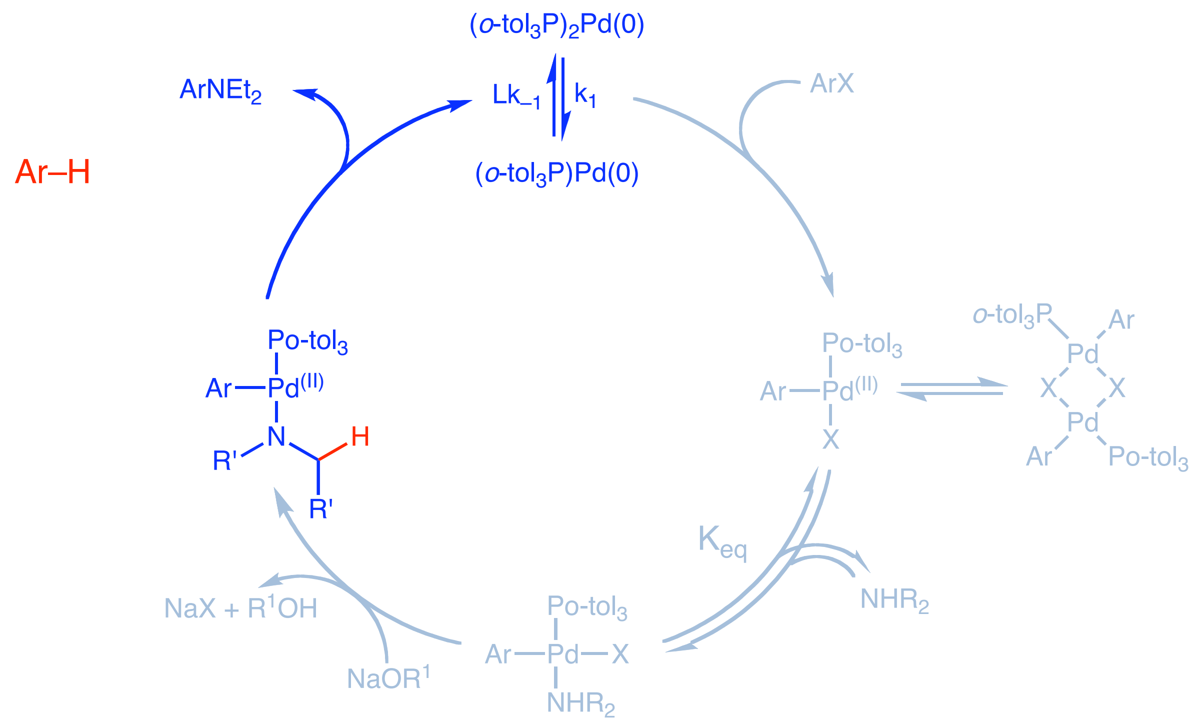
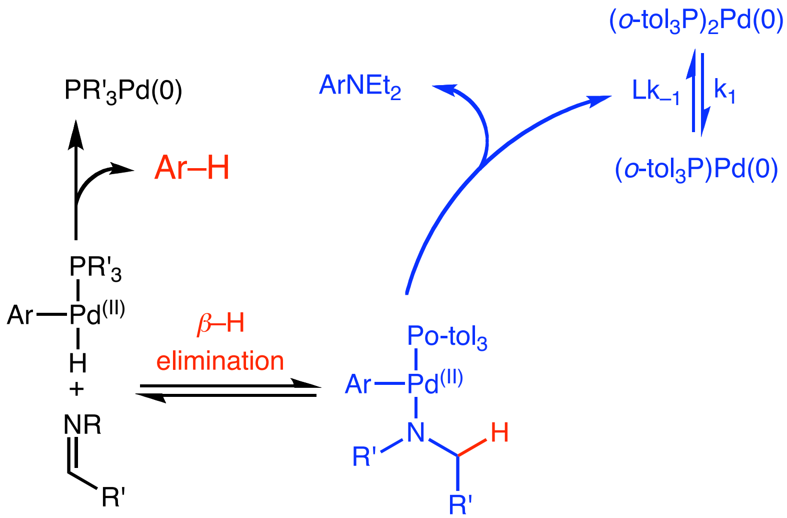


♦ Where does the reductive arene (Ar–H) product come from?

Hartwig, J. F. *et al JACS* **1996**, *118*, 3626.

Reductive Elimination with Monodentate Hindered Phosphine Ligands



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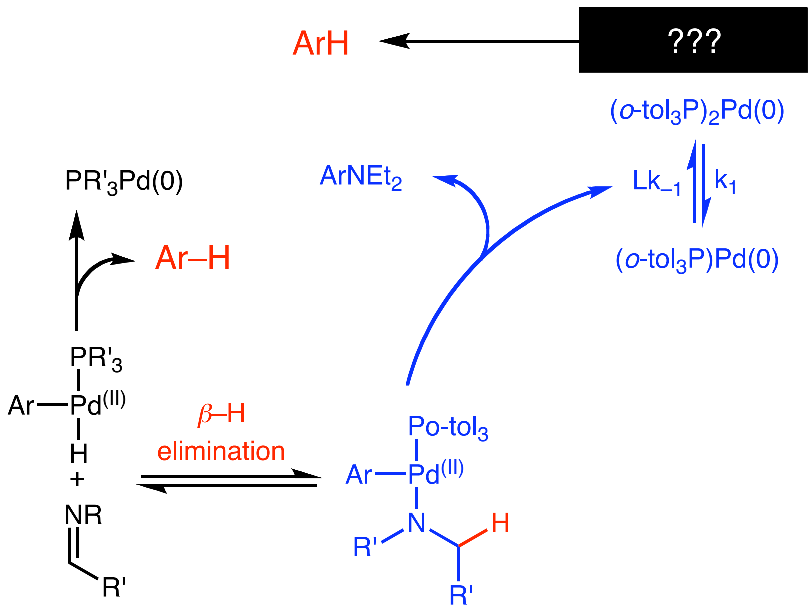

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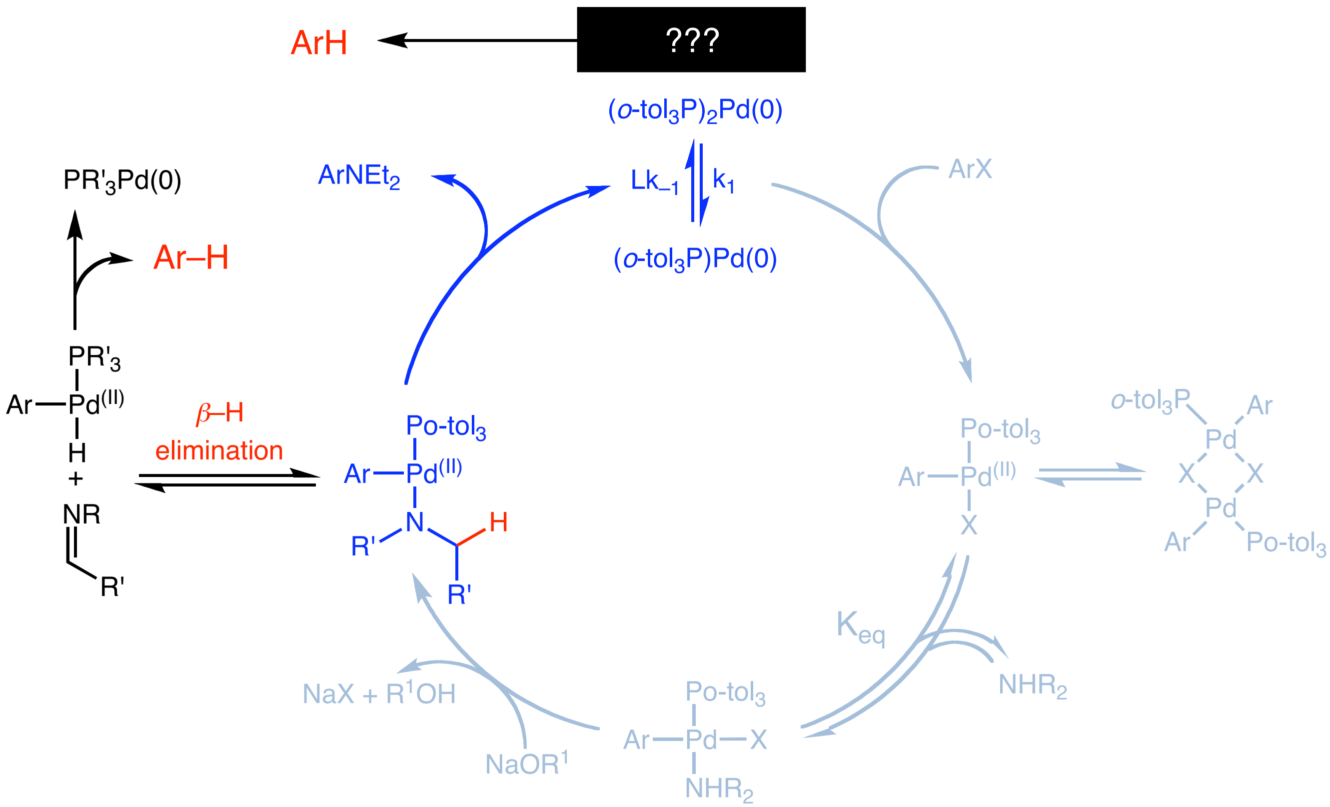


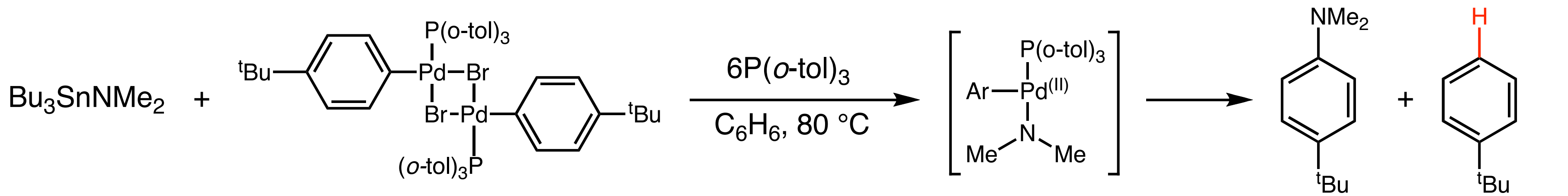
♦ Where does the reductive arene (Ar–H) product come from?

♦ What factors effect the ratio of coupling amine : Ar–H?

Hartwig, J. F. *et al JACS* **1996**, *118*, 3626.

Reductive Elimination with Monodentate Hindered Phosphine Ligands

■ Formation of arene from catalytic cycle



1

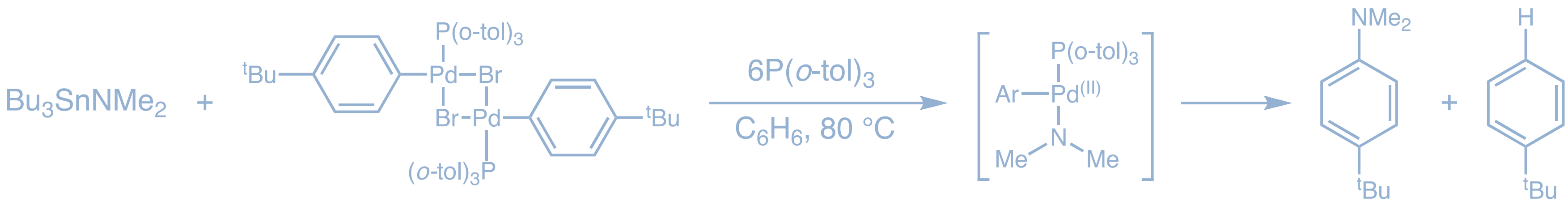
> 85% yield

4.0 eq	1.0 eq ~ 100 mol%	11	:	1
4.0 eq, Bu_3SnNMe_2-d_6		25	:	1 (0.7D)

Hartwig, J. F. *et al JACS* **1996**, *118*, 3626.

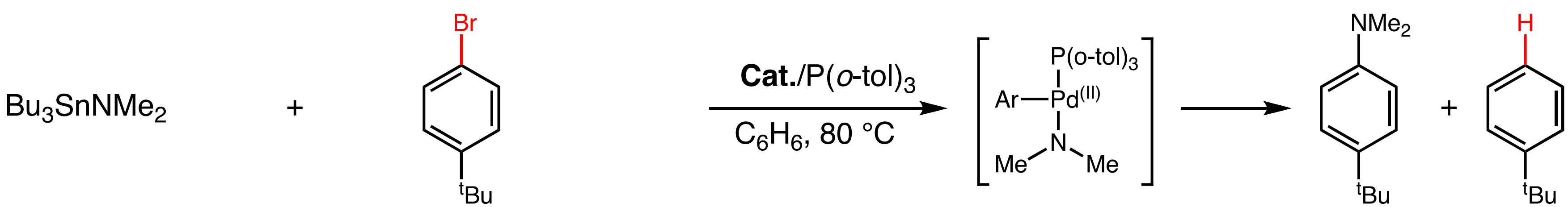
Reductive Elimination with Monodentate Hindered Phosphine Ligands

■ Formation of arene from catalytic cycle



1 > 85% yield

4.0 eq 1.0 eq ~ 100 mol% 11 : 1



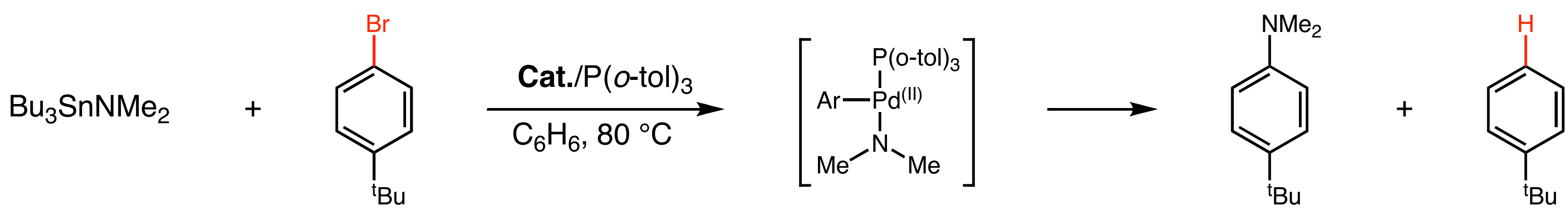
Cat. =	**1** ;	5 mol%	10 : 1
	(*o*-tol$_3$P)$_2$Pd(0);	5 mol%	9 : 1

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

Hartwig, J. F. *et al JACS* **1996**, *118*, 3626.

Reductive Elimination with Monodentate Hindered Phosphine Ligands

■ Formation of arene from outside of catalytic cycle

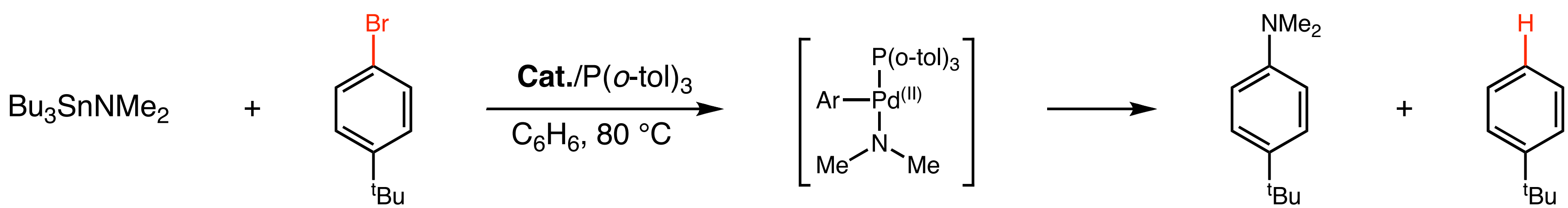


Cat. = **1**;	5 mol%	10	:	1
(*o*-tol$_3$P)$_2$Pd(0);	5 mol%	9	:	1
(*o*-tol$_3$P)$_2$PdCl$_2$;	5 mol%	6	:	1

Hartwig, J. F. *et al JACS* **1996**, *118*, 3626.

Reductive Elimination with Monodentate Hindered Phosphine Ligands

■ Formation of arene from outside of catalytic cycle



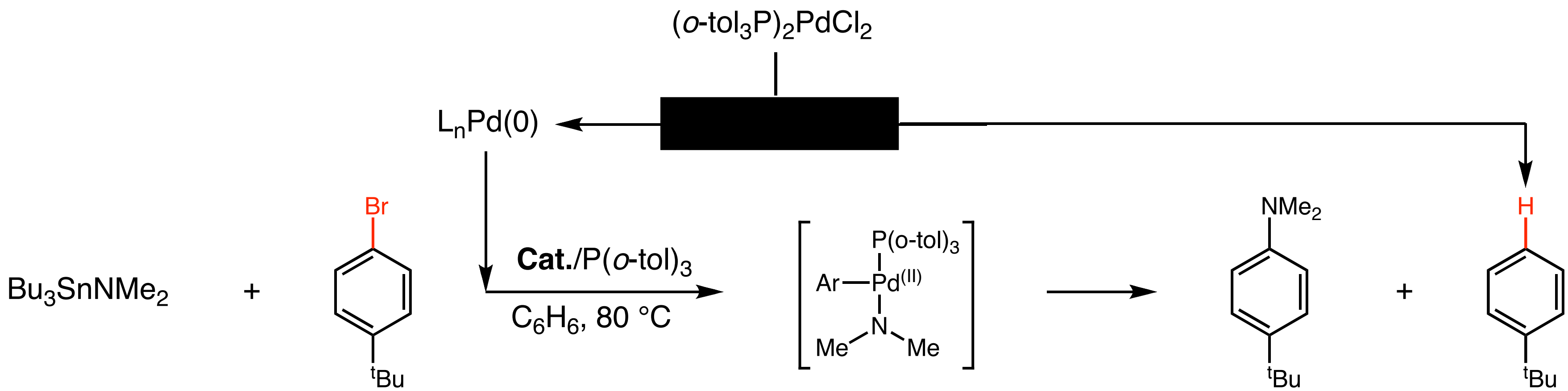
Cat.	Loading	ArNMe₂	:	ArH
Cat. = **1**	5 mol%	10	:	1
(o-tol$_3$P)$_2$Pd(0)	5 mol%	9	:	1
(o-tol$_3$P)$_2$PdCl$_2$	0.5 mol%	9	:	1
(o-tol$_3$P)$_2$PdCl$_2$	5 mol%	6	:	1
(o-tol$_3$P)$_2$PdCl$_2$	25 mol%	4	:	1

=> The formation of arene should also be from the reduction of Pd(II) precusor to Pd(0) (mechanism has been unclear).

Hartwig, J. F. *et al JACS* **1996**, *118*, 3626.

Reductive Elimination with Monodentate Hindered Phosphine Ligands

■ Formation of arene from outside of catalytic cycle



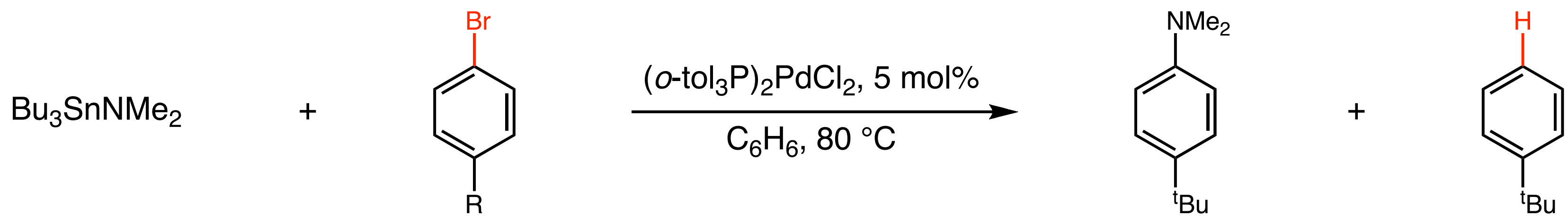
Cat. = **1** ;	5 mol%	10	:	1
(o-tol$_3$P)$_2$Pd(0);	5 mol%	9	:	1
(o-tol$_3$P)$_2$PdCl$_2$;	0.5 mol%	9	:	1
(o-tol$_3$P)$_2$PdCl$_2$;	5 mol%	6	:	1
(o-tol$_3$P)$_2$PdCl$_2$;	25 mol%	4	:	1

=> The formation of arene should also be from the reduction of Pd(II) precusor to Pd(0)
(mechanism has been unclear).

Hartwig, J. F. *et al JACS* **1996**, *118*, 3626.

Reductive Elimination with Monodentate Hindered Phosphine Ligands

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



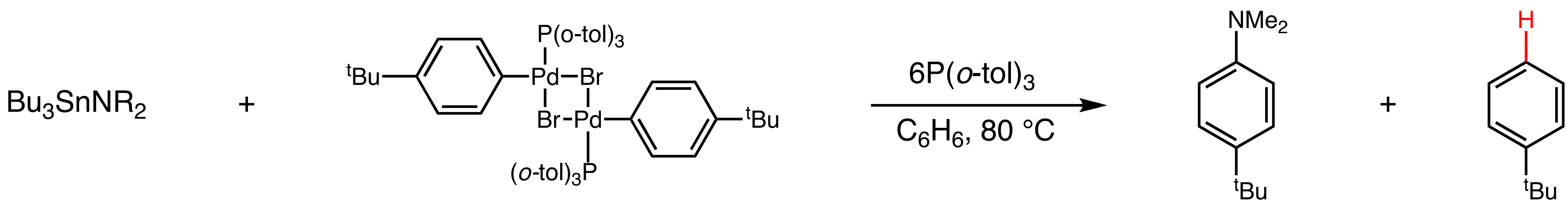
R =	amine		arene
CH_3CO	15	:	1
${}^tBu$	6	:	1
Me_2N	3	:	1

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

Hartwig, J. F. *et al JACS* **1996**, *118*, 3626.

Reductive Elimination with Monodentate Hindered Phosphine Ligands

■ Effect of amine on coupling amine : arene ratio



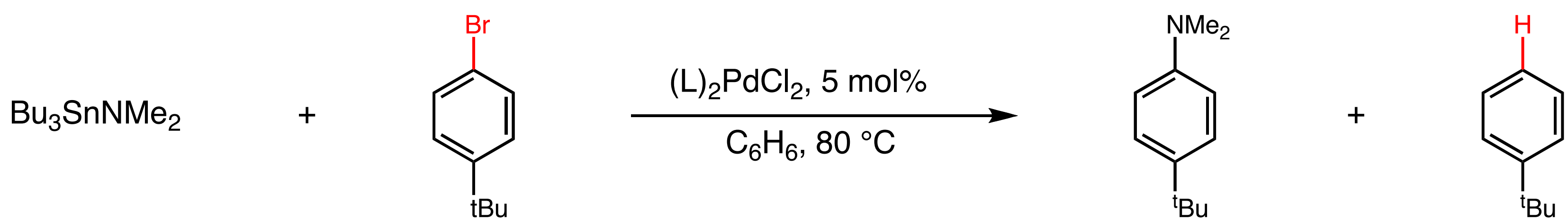
NR_2 =	NMe_2	11	:	1
	NEt_2	15	:	1
	NMePh	5	:	1

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

Hartwig, J. F. *et al JACS* **1996**, *118*, 3626.

Reductive Elimination with Monodentate Hindered Phosphine Ligands

■ Effect of ligand on coupling amine : arene ratio

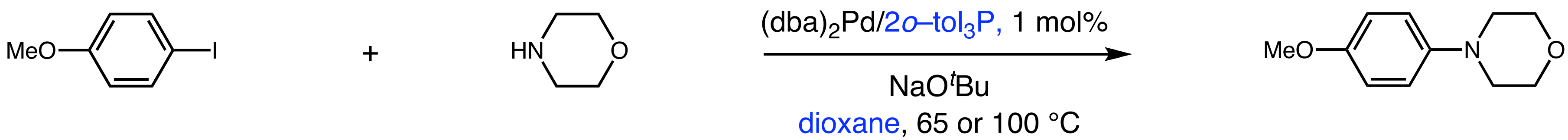


L =	P(*o*-tol)$_3$	6	:	1
	P(*o*-tol)$_2$Ph	4	:	1
	P(*o*-tol)Ph$_2$	2	:	1
	PPh$_3$	---	:	---

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

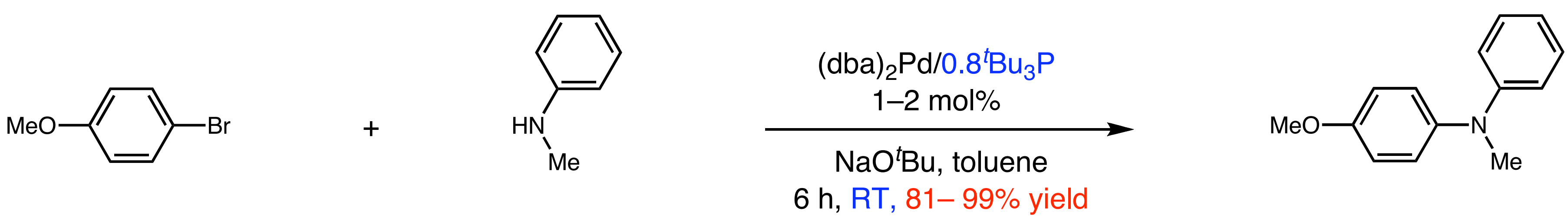
Hartwig, J. F. *et al JACS* **1996**, *118*, 3626.

Aminations with Monodentate Hindered Phosphine Ligands



66% yield
(18– 79% yield)

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

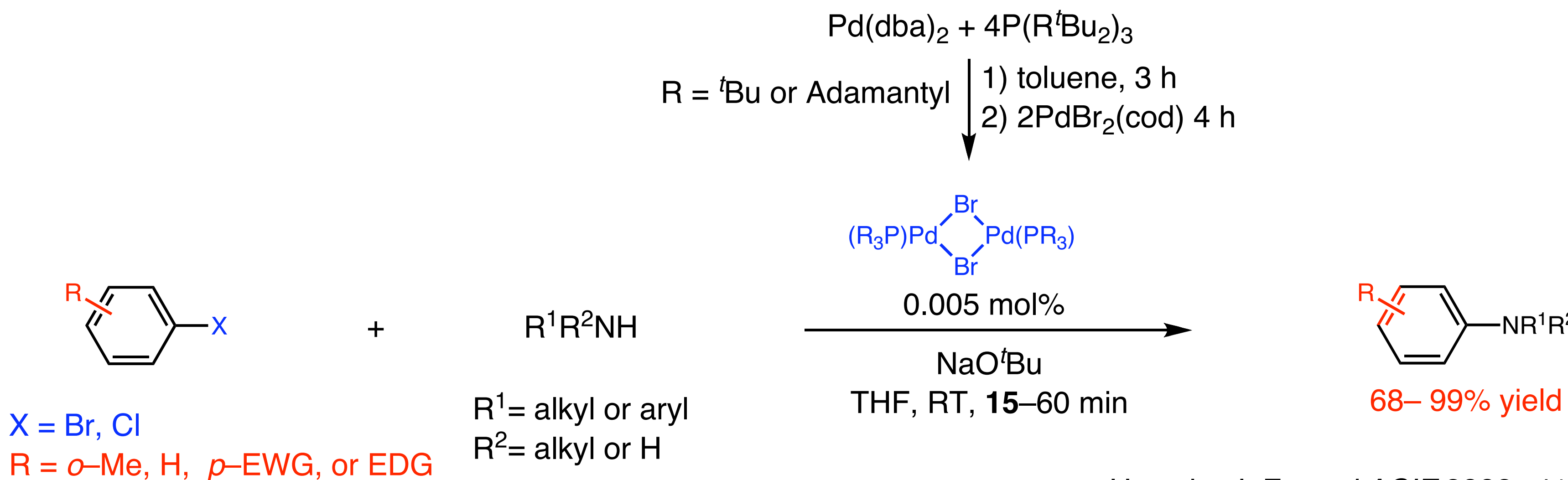


99% yield

$(dba)_2Pd/2o$–tol_3P, 2 mol%
65 or 100 °C, 81– 99% yield
ACIE **1995**, *34*, 1348.

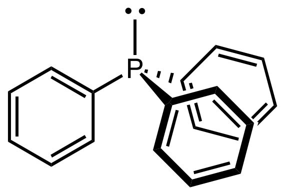
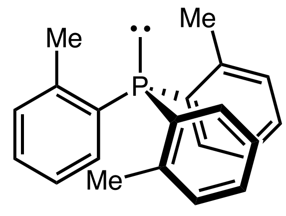
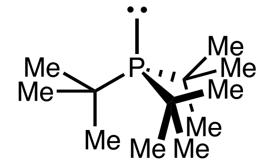
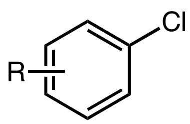
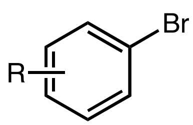
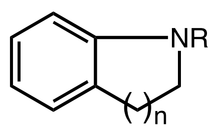
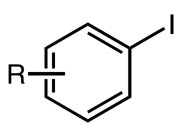
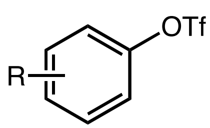
Hartwig, J. F. *et al JOC* **1999**, *64*, 5575.

Aminations with Monodentate Hindered Phosphine Ligands

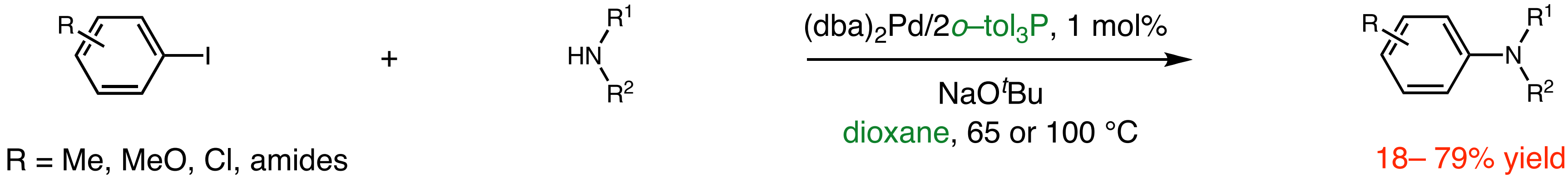


Hartwig, J. F. *et al ACIE* **2002**, *41*, 4746.

C–N Coupling with Monophosphine Ligands

	 $(Ph)_3P$ (145 °)	 (o-tol)$_3$P (194 °)	 (^{t}Bu)$_3$P (182 °)
			*Amination*: *ACIE* **2002**, *41*, 4746 *Het.amination*: *JOC* **1999**, *64*, 5575 *Amidation*: *JOC* **1999**, *64*, 5575 *ArNH$_2$*: *OL* **2001**, *3*, 2729
	 *Intra amination*:*Tet* **1996**, *36*, 7525	*Amination*: *ACIE* **1995**, *34*, 1348 *TL* **1995**, *36*, 3069 *Intra amidation*:*Tet* **1996**, *36*, 7525	*Amination*: *ACIE* **2002**, *41*, 4746 *Het.amination*: *JOC* **1999**, *64*, 5575 *Amidation*: *JOC* **1999**, *64*, 5575 *ArNH$_2$*: *OL* **2001**, *3*, 2729
	*Intra amination*:*Tet* **1996**, *36*, 7525	*Amination*: *JOC* **1996**, *61*, 1133	
			*ArNH$_2$*: *OL* **2001**, *3*, 2729

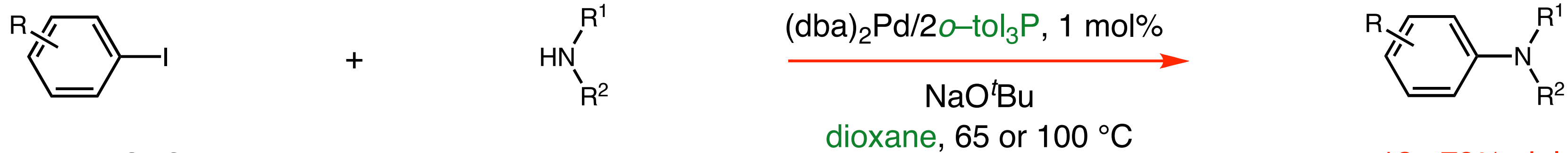
Aminations of Aryl Iodides



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

*"Our original attemps to utilize aryl iodides as substrates were also largely unsuccesful...**Running reaction in dioxane was the key for this technique**."*

Aminations of Aryl Iodides

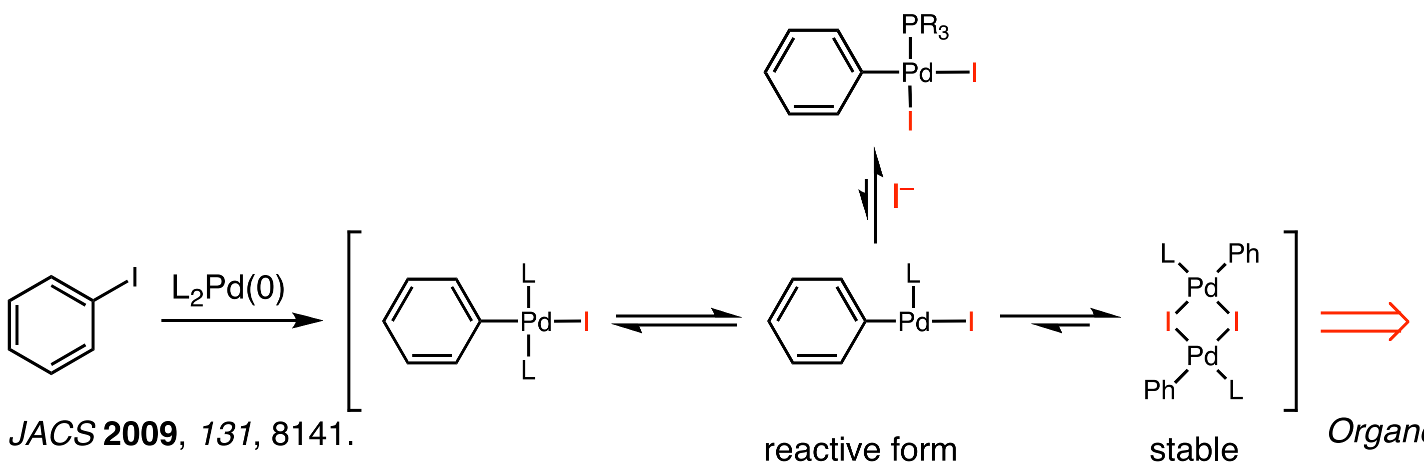


R = Me, MeO, Cl, amides

18– 79% yield

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

"Our original attemps to utilize aryl iodides as substrates were also largely unsuccesful... ***Running reaction in dioxane was the key for this technique****."*

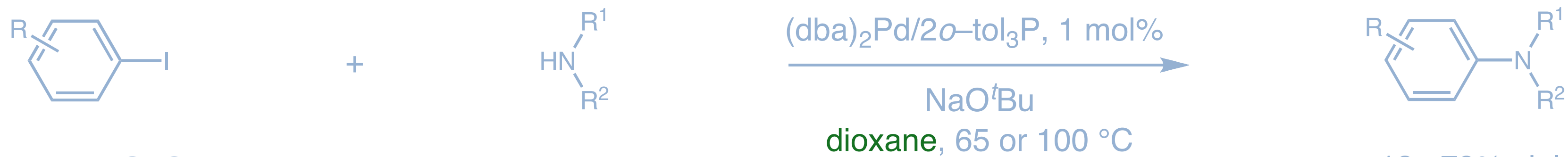


JACS **2009**, *131*, 8141.

React more slowly with amines compared to aryl chloride or aryl bromides

Organometallics **1996**, *15*, 2755.

Aminations of Aryl Iodides



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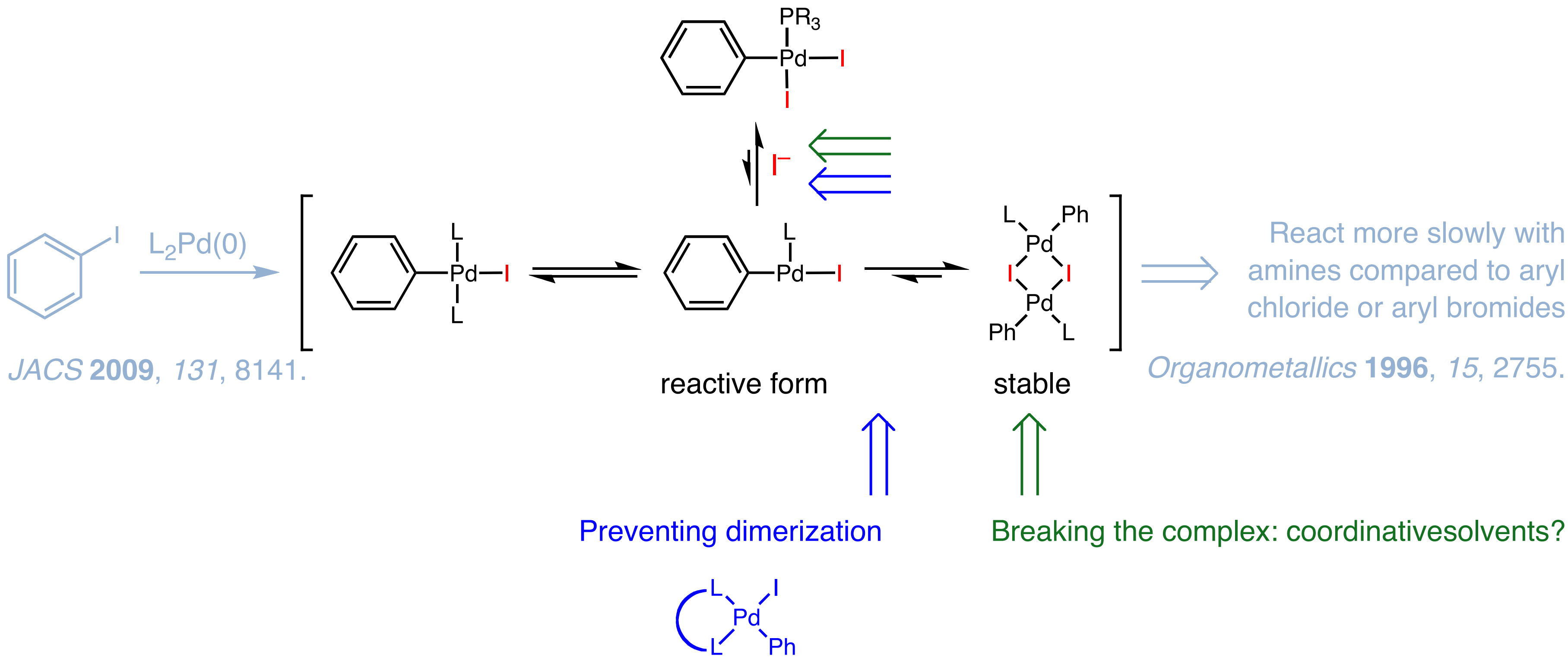
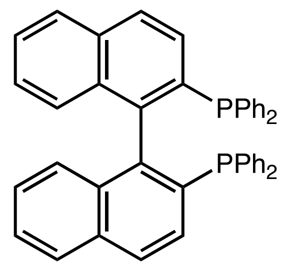


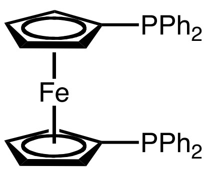
JACS **2009**, *131*, 8141.

Organometallics **1996**, *15*, 2755.

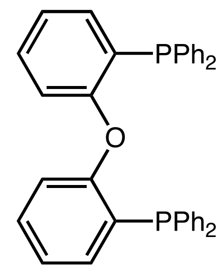
Bidentate Phosphine Ligands



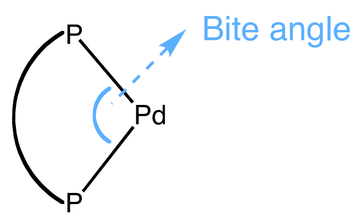
BINAP (92.7 °)

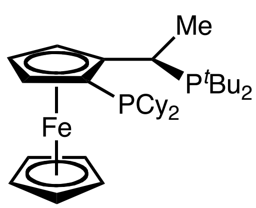


DPPF (99.0 °)

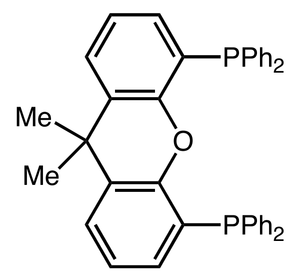


DPPDPE (101 °)



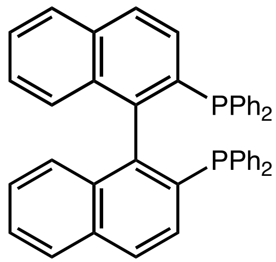
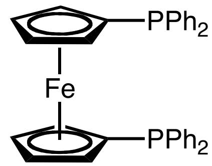
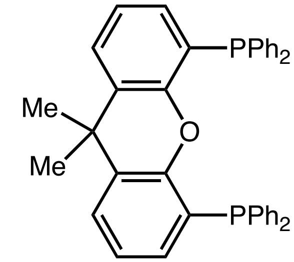
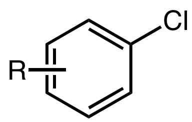
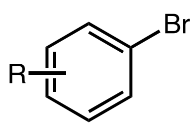
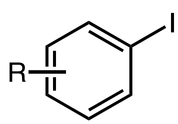
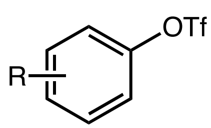
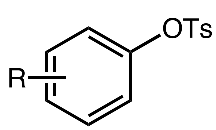


Josiphos (98.0 °)



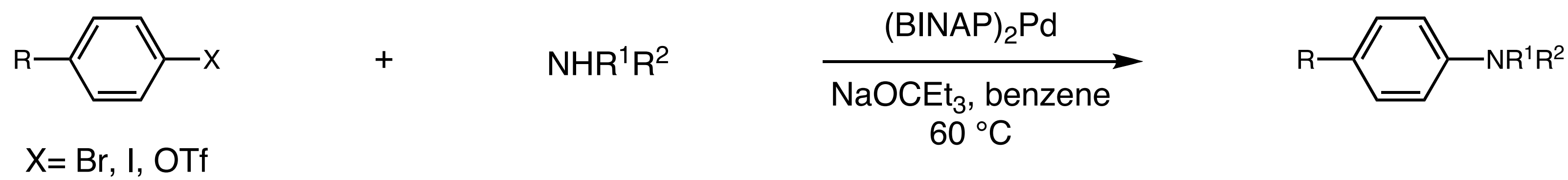
Xantphos (109 °)

C–N Coupling with Biphosphine Ligands

	 BINAP (92.7 °)	 DPPF (99.0 °)		 Xantphos (109 °)
				
	*Amination*: *JACS* **1996**, *118*, 7215; *JACS* **1997**, *119*, 8451; *Imination*: *TL* **1997**, *38*, 6367	*Amination*: *JACS* **1996**, *118*, 7217; *Imination* and *het.amination*: *JACS* **1998**, *120*, 827		*Imination*: *JACS* **1999**, *121*, 10251; *Amidation*: *OL* **1999**, *1*, 35; *JACS* **2002**, *124*, 6043 & **2007**, *129*, 7734
	*Imination*: *TL* **1997**, *38*, 6367	*Amination*: *JACS* **1996**, *118*, 7217		*Amidation*: *OL* **1999**, *1*, 35; *JACS* **2002**, *124*, 6043 and **2007**, *129*, 7734
	*Imination*: *TL* **1997**, *38*, 6367	*Amination*: *JOC* **1997**, *62*, 1268		*Amidation*: *OL* **1999**, *1*, 35; *JACS* **2002**, *124*, 6043 and **2007**, *129*, 7734
				

Amination with BINAP Ligand

■ Hartwig's study on amination with $Pd(BINAP)_2$ as a catalyst.



Amine = n-$C_6H_{13}NH_2$ i-$C_4H_9NH_2$ $BnNH_2$ $MeOC_6H_4NH_2$ $PhNH_2$

Hartwig, J. F. *et al JACS* **2000**, *122*, 4618.
Alcazer-Roman, L. M. and Hartwig, J. F. *Organometallics* **2002**, *21*, 491.

Amination with BINAP Ligand

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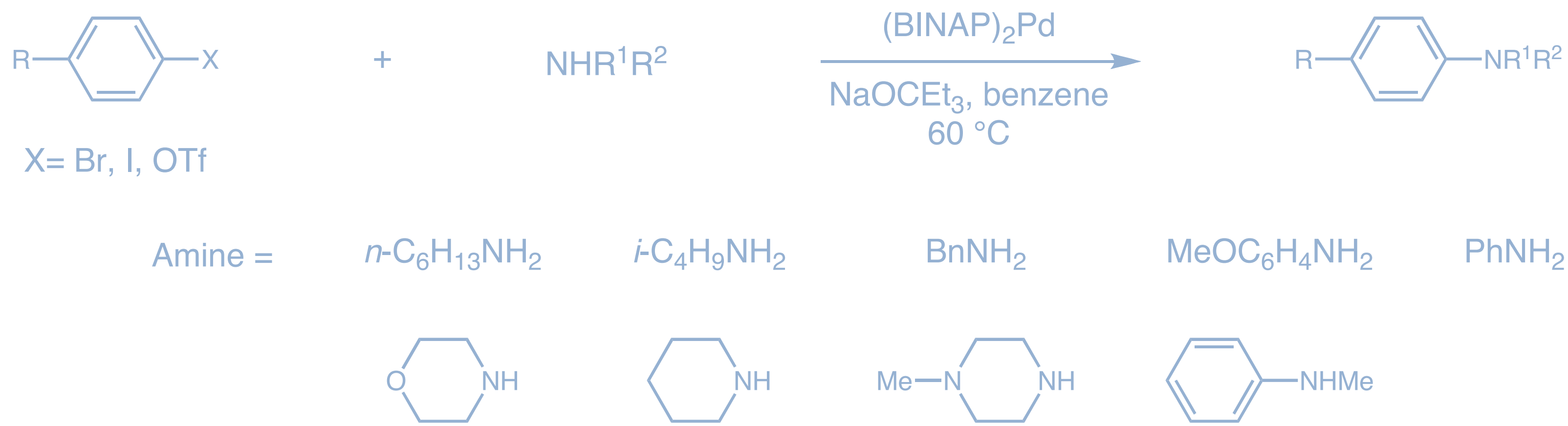

♦ Zero-order in amine (primary or second) and base.

♦ Zero-order in ArX (when [ArX]>>[L]) and ~ first-order when [ArX] was small.

♦ First-order in catalyst, inverse first-order in added ligand. Reaction rate is dictated by ligand dissocitation step <=> k_{obs} ~ $[(BINAP)_2Pd]$, 1/[BINAP].

Hartwig, J. F. *et al JACS* **2000**, *122*, 4618.
Alcazer-Roman, L. M. and Hartwig, J. F. *Organometallics* **2002**, *21*, 491.

Amination with BINAP Ligand

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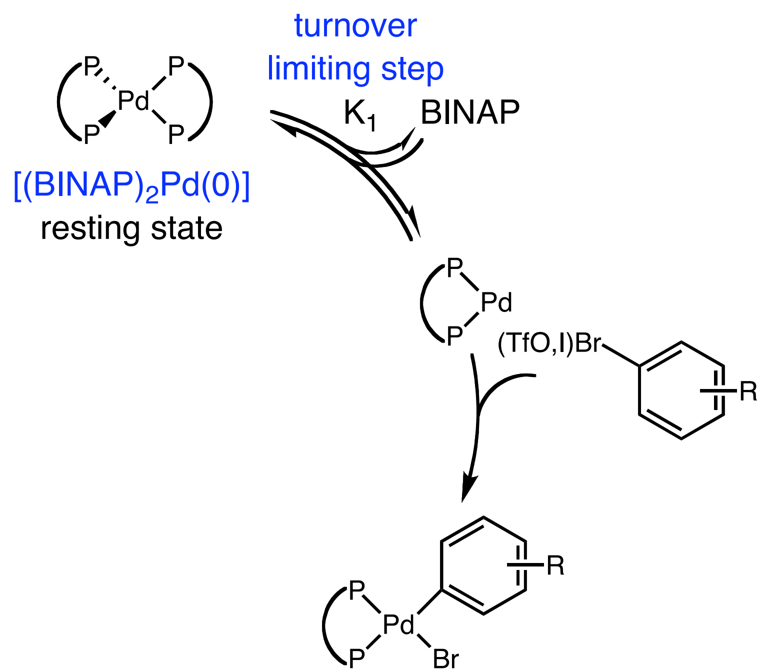
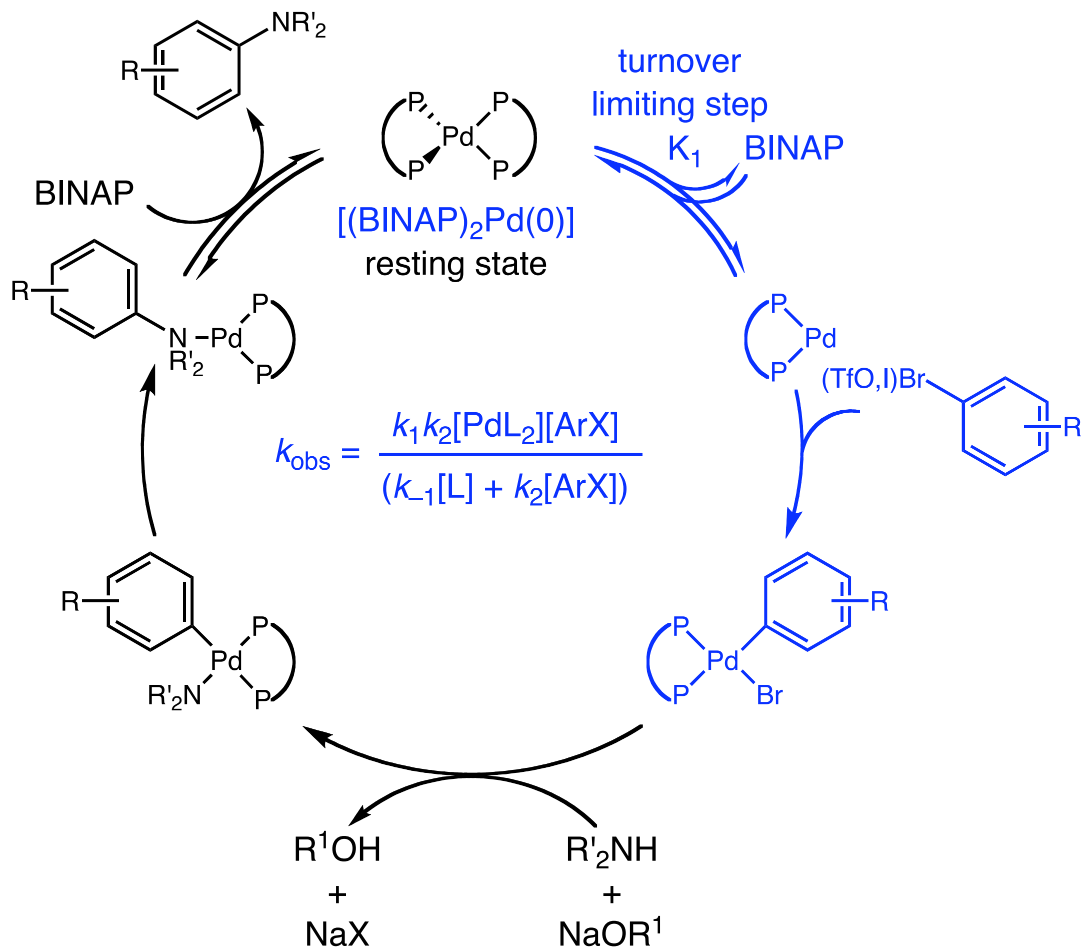


Hartwig, J. F. *et al JACS* **2000**, *122*, 4618.
Alcazer-Roman, L. M. and Hartwig, J. F. *Organometallics* **2002**, *21*, 491.

Amination with BINAP Ligand

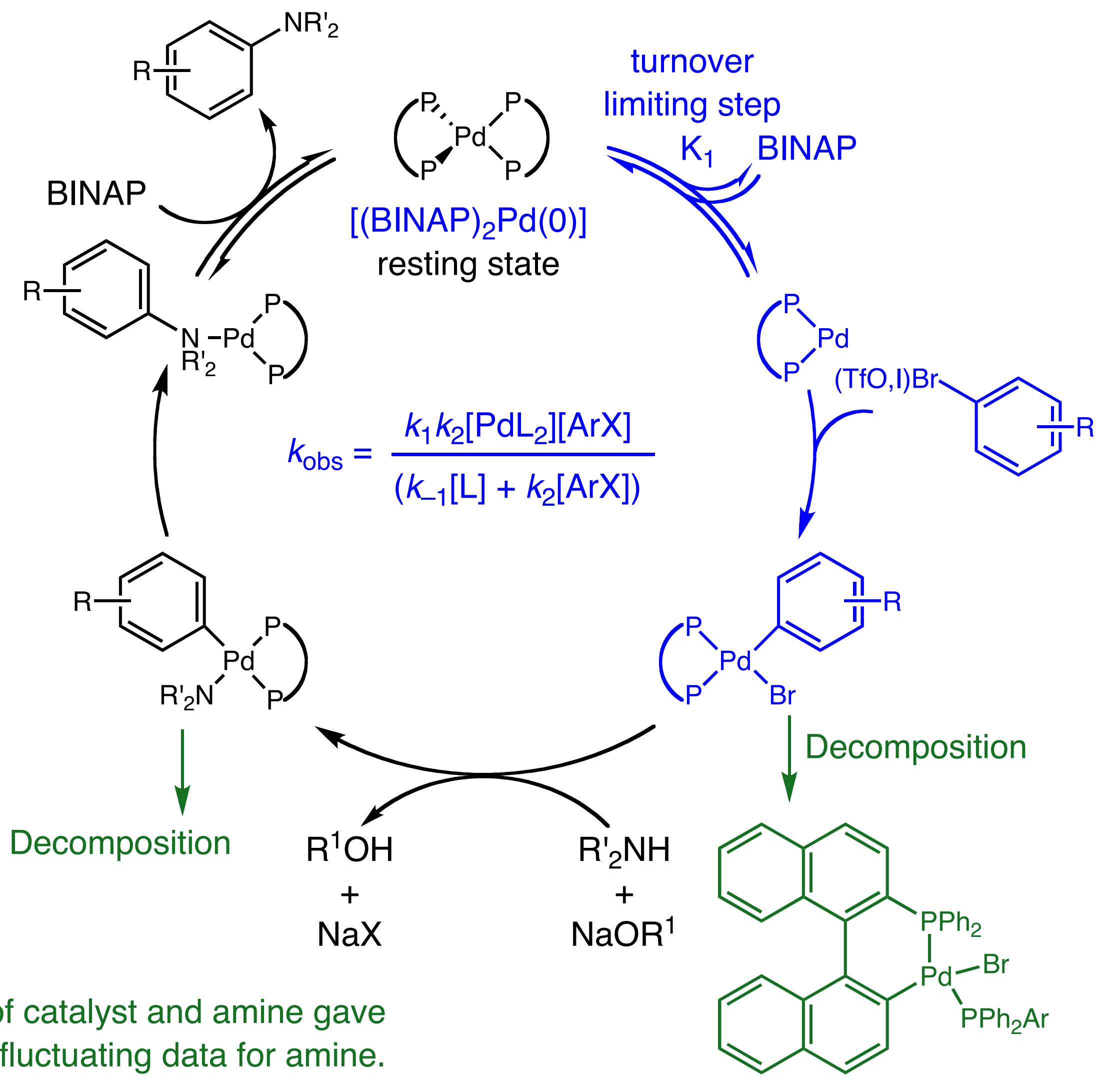
■ Hartwig's study on amination with Pd(BINAP)$_2$ as a catalyst.



Hartwig, J. F. *et al JACS* **2000**, *122*, 4618.
Alcazer-Roman, L. M. and Hartwig, J. F. *Organometallics* **2002**, *21*, 491.

Amination with BINAP Ligand

■ Hartwig's study on amination with $Pd(BINAP)_2$ as a catalyst.

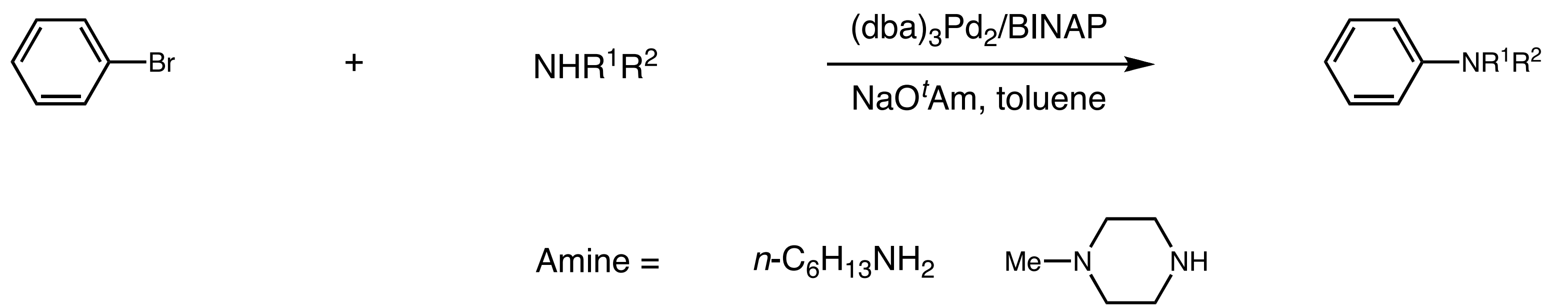


♦ The decomposition of catalyst and amine gave slightly fluctuating data for amine.

Hartwig, J. F. *et al JACS* **2000**, *122*, 4618.
Alcazer-Roman, L. M. and Hartwig, J. F. *Organometallics* **2002**, *21*, 491.

Amination with BINAP Ligand

■ Blackmond and Buchwald's study on amination with $Pd(BINAP)_2$ under synthetically relevant conditions.



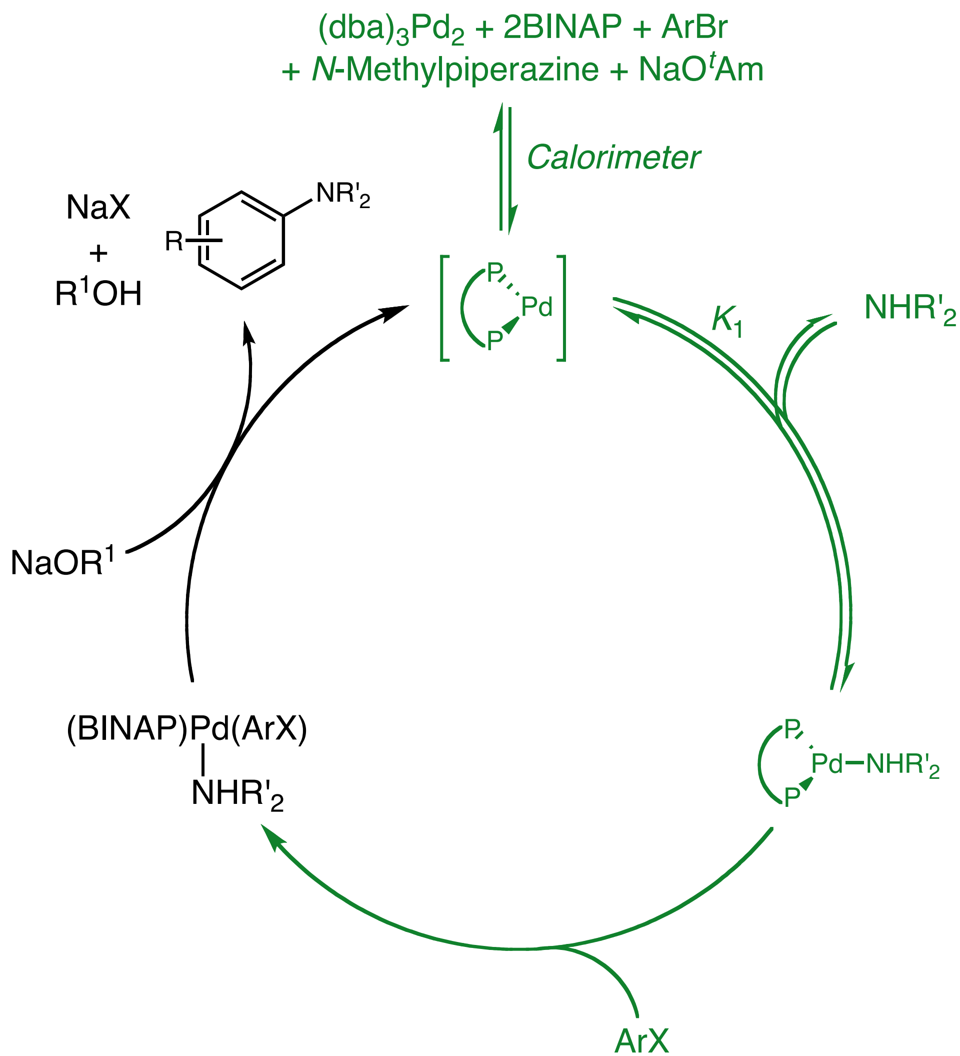
♦~ First-order in ArX; zero-order in base.

♦ The rate of amination with primary amine (~ first-order) and secondary amine (first-order) are different.

Blackmond, D. G. and Buchwald, S. L. *et al JACS* **2002**, *124*, 14104.

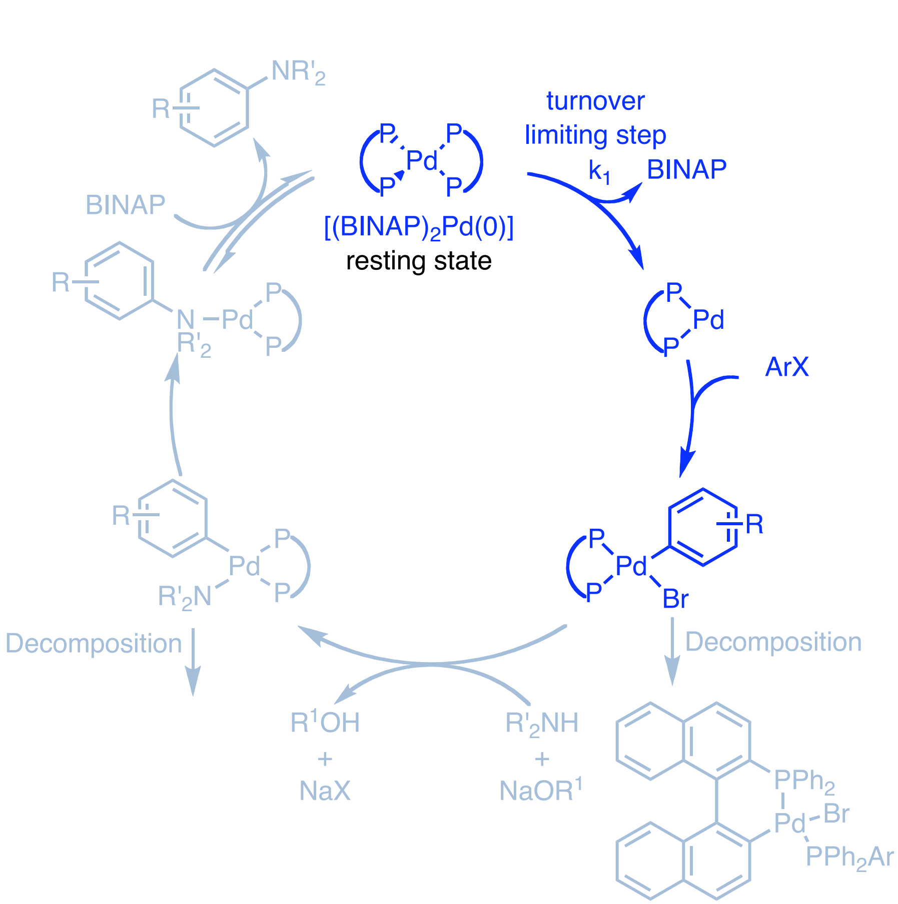
Amination with BINAP Ligand

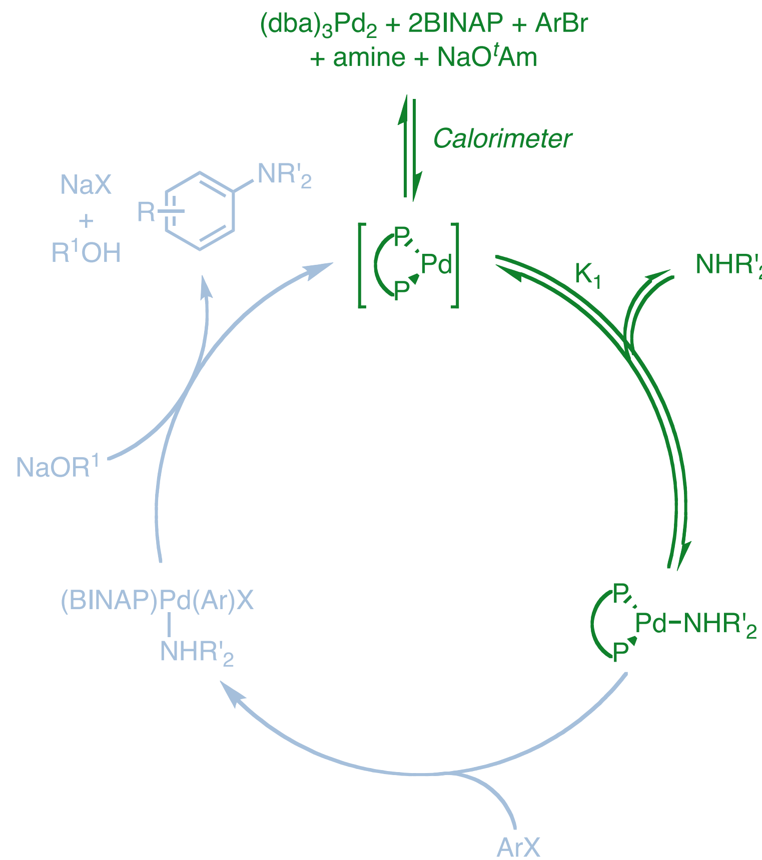
■ Blackmond and Buchwald's study on amination with $Pd(BINAP)_2$ under synthetically relevant conditions.



Blackmond, D. G. and Buchwald, S. L. *et al JACS* **2002**, *124*, 14104.

Amination with BINAP Ligand-Mechanistic Contradiction

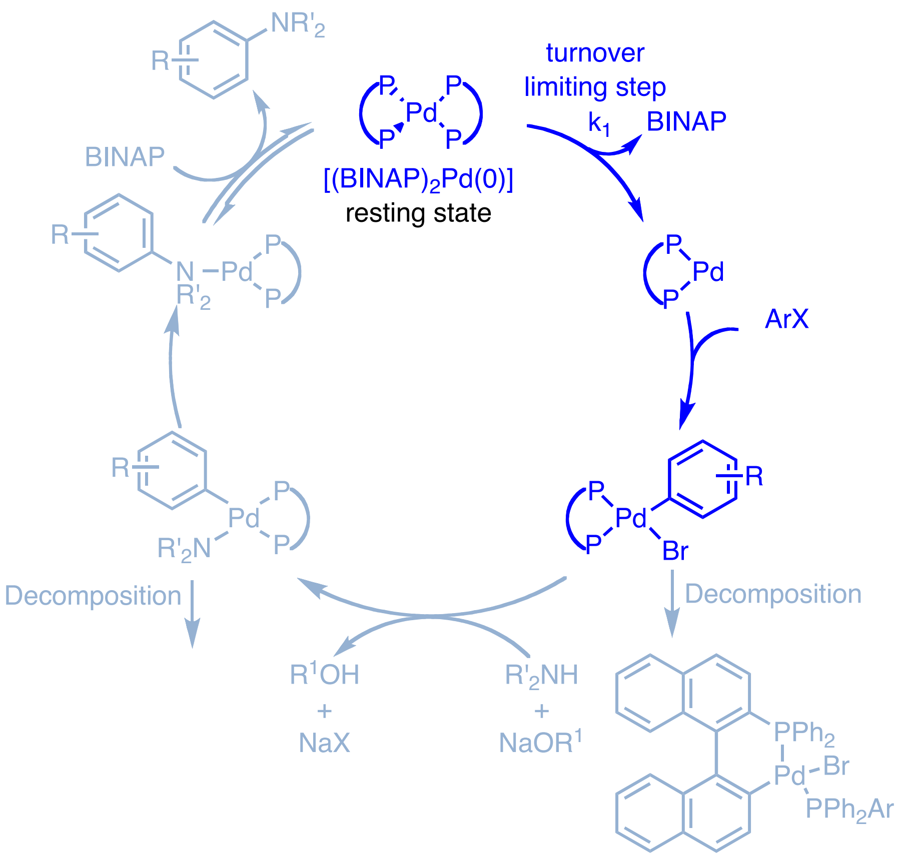


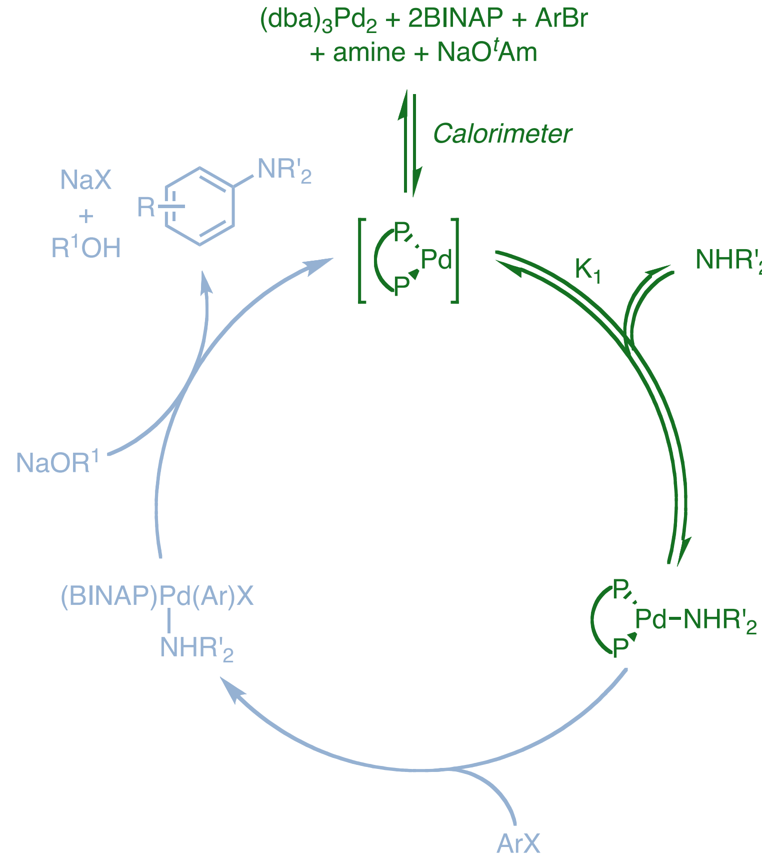


"This work suggests that conclusions from kinetic studies may be meaningful only for the conditions under which they are carried out, calling into question the use of conventional kinetic methods in this system."

Blackmond, D. G. and Buchwald, S. L. *et al JACS* **2002**, *124*, 14104.

Amination with BINAP Ligand-Mechanistic Contradiction



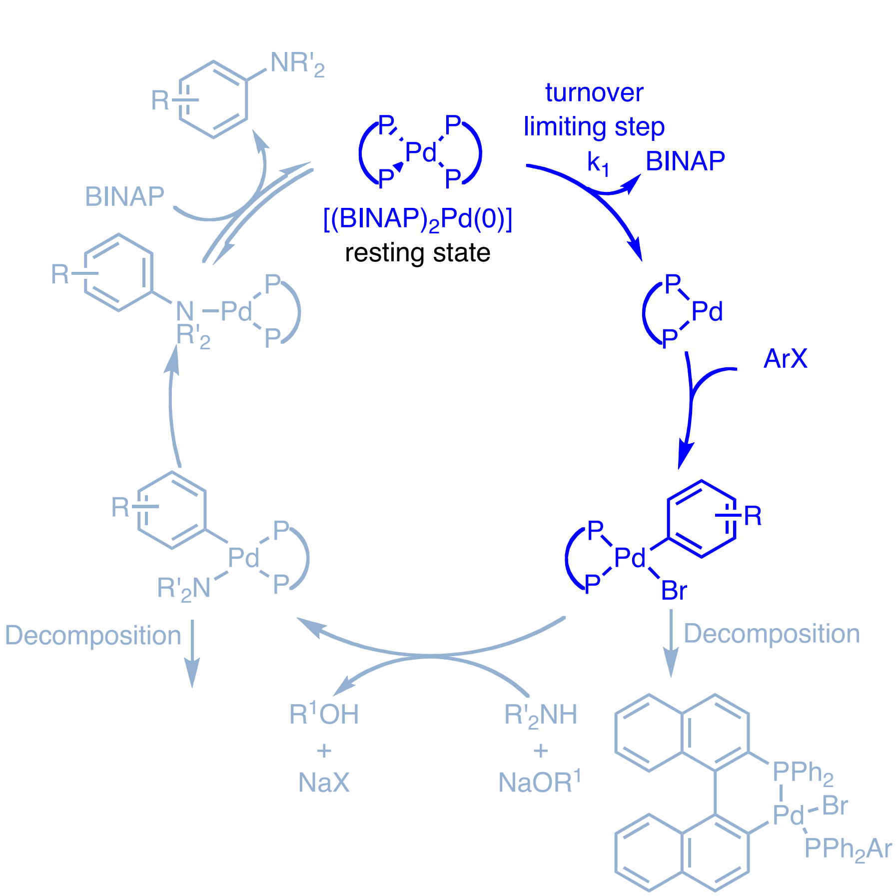


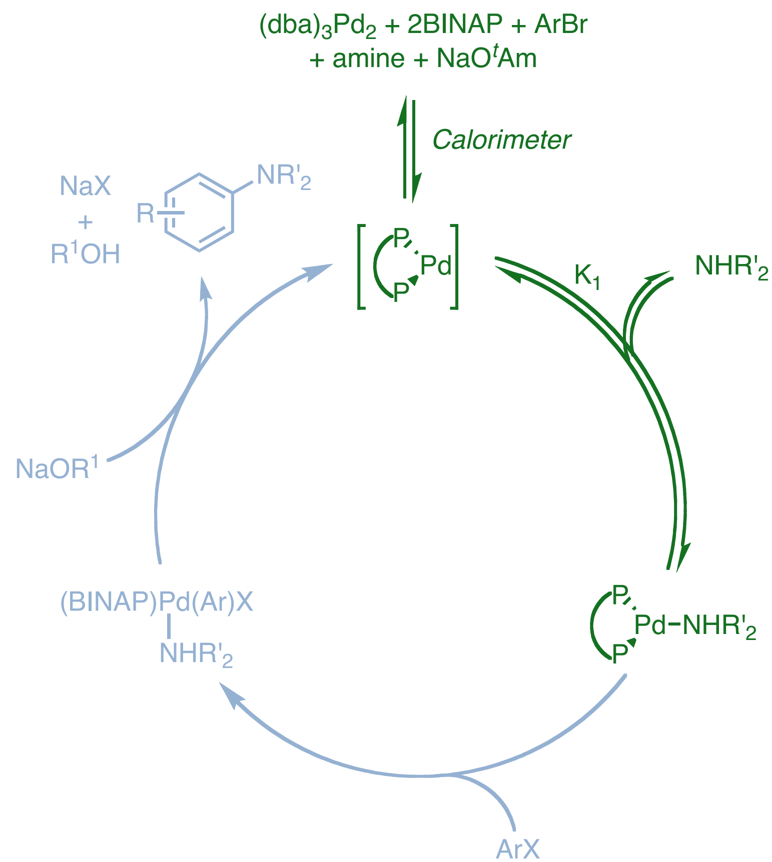
♦ The addtion of phenyl bromide to (BINAP)Pd is faster than to [(BINAP)Pd(amine)] and depends very little on the presence or absence amine or on the amount of amine.

Hartwig, J. F. *et al OL* **2006**, *8*, 851.

Blackmond, D. G. and Buchwald, S. L. *et al JACS* **2002**, *124*, 14104.

Amination with BINAP Ligand-Mechanistic Contradiction





♦ The addtion of phenyl bromide to (BINAP)Pd is faster than to [(BINAP)Pd(amine)] and depends very little on the presence or absence amine or on the amount of amine.

"These data underscore the value of studying the stoichiometric reactions of isolated complexes when assessing the mechanism of a catalytic process."

"This work suggests that conclusions from kinetic studies may be meaningful only for the conditions under which they are carried out, calling into question the use of conventional kinetic methods in this system."

Hartwig, J. F. *et al OL* **2006**, *8*, 851.

Blackmond, D. G. and Buchwald, S. L. *et al JACS* **2002**, *124*, 14104.

Amination with BINAP Ligand - Mechanistic Re-evaluation

■ [Pd] species generated in situ by Blackmond and Buchwald

$Pd_2(dba)_3$ + BINAP $\xrightarrow[\text{60 °C, 1 h}]{\text{NaO}^t\text{Am/benzene}}$ (BINAP)Pd(dba) (**1**) + other components **1-IS**

Hartwig, J. F.; Blackmond, D. G. and Buchwald, S. L. *et al JACS* **2006**, *128*, 3584.

Amination with BINAP Ligand - Mechanistic Re-evaluation

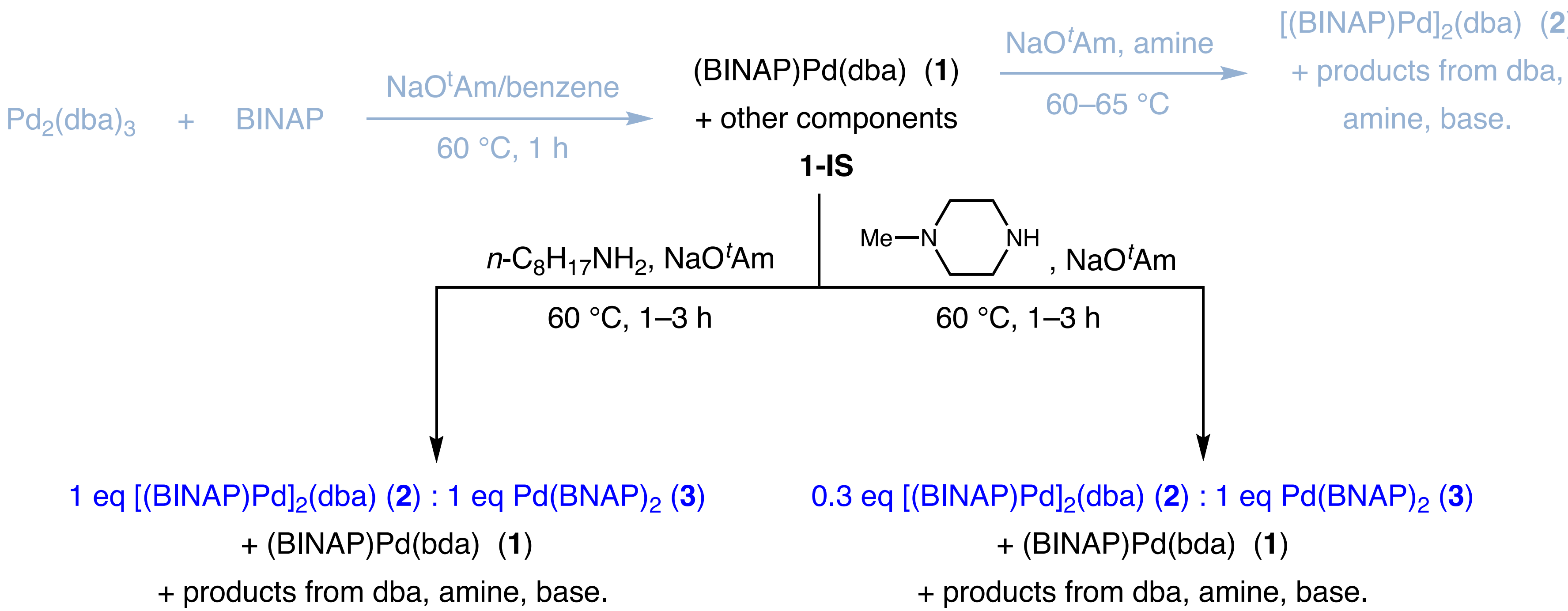
■ [Pd] species generated in situ by Blackmond and Buchwald

$Pd_2(dba)_3$ + BINAP —(NaO^{t}Am/benzene, 60 °C, 1 h)→ (BINAP)Pd(dba) (**1**) + other components **1-IS** —(NaO^{t}Am, amine, 60–65 °C)→ $[(BINAP)Pd]_2(dba)$ (**2**) + products from dba, amine, base.

Hartwig, J. F.; Blackmond, D. G. and Buchwald, S. L. *et al JACS* **2006**, *128*, 3584.

Amination with BINAP Ligand - Mechanistic Re-evaluation

■ [Pd] species generated in situ by Blackmond and Buchwald



♦ **2** and **3** decompose over the time of catalytic reactions of secondary amine and aryl bromides.

Hartwig, J. F.; Blackmond, D. G. and Buchwald, S. L. *et al JACS* **2006**, *128*, 3584.

Amination with BINAP Ligand - Mechanistic Re-evaluation

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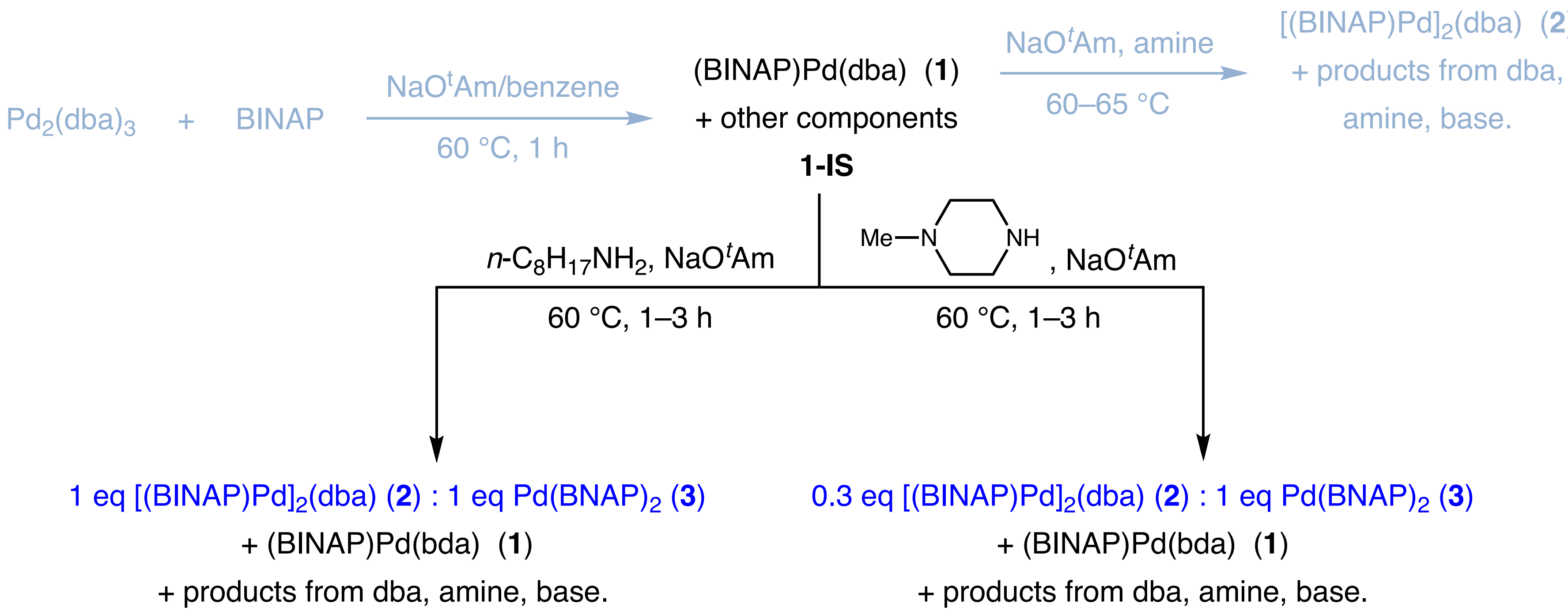


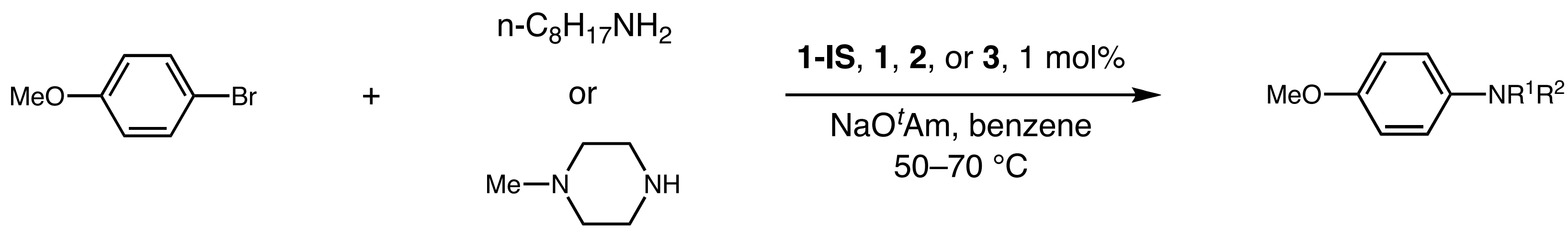
♦ **2** and **3** decompose over the time of catalytic reactions of secondary amine and aryl bromides.

=> The ratios of [Pd] intermediates (**1, 2** and **3**) depend on the conditions by which catalysts are generated.

Hartwig, J. F.; Blackmond, D. G. and Buchwald, S. L. *et al JACS* **2006**, *128*, 3584.

Amination with BINAP Ligand - Mechanistic Re-evaluation

■ Re-evaluate the amination reactions with primary and secondary amine



Hartwig, J. F.; Blackmond, D. G. and Buchwald, S. L. *et al JACS* **2006**, *128*, 3584.

Amination with BINAP Ligand - Mechanistic Re-evaluation

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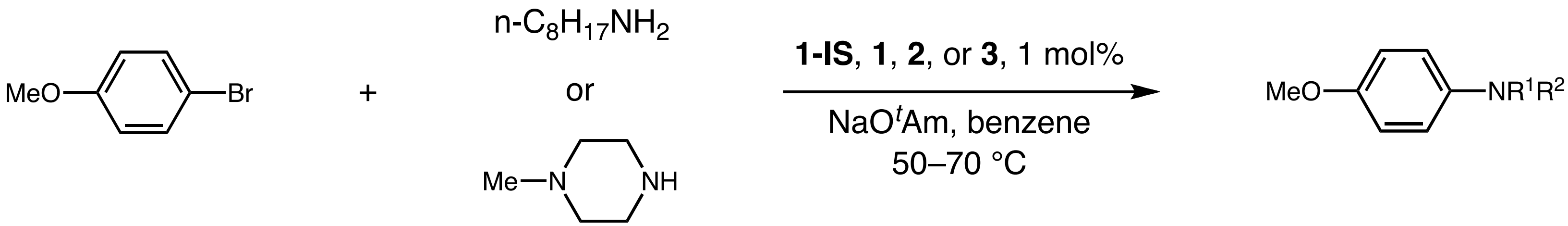

(BINAP)Pd(dba) (**1**) << Pd(BNAP)$_2$ (**3**) < [(BINAP)Pd]$_2$(dba) (**2**)

increasing reactivity

Hartwig, J. F.; Blackmond, D. G. and Buchwald, S. L. *et al JACS* **2006**, *128*, 3584.

Amination with BINAP Ligand - Mechanistic Re-evaluation

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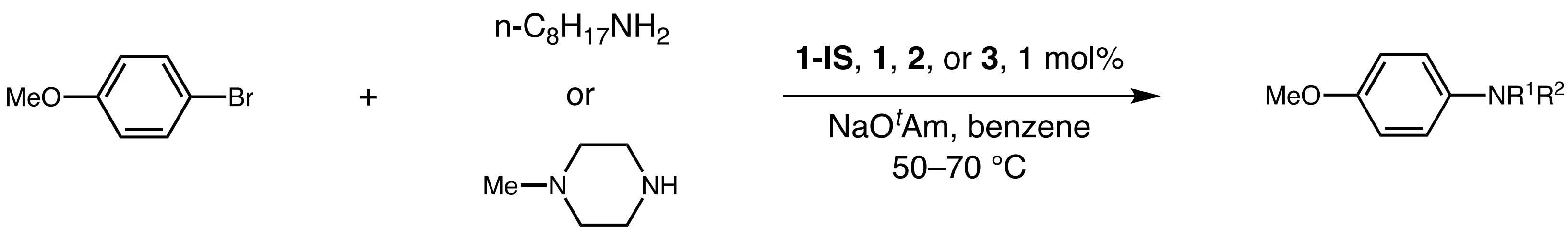


(BINAP)Pd(dba) (**1**) << Pd(BNAP)$_2$ (**3**) < [(BINAP)Pd]$_2$(dba) (**2**)

→ increasing reactivity

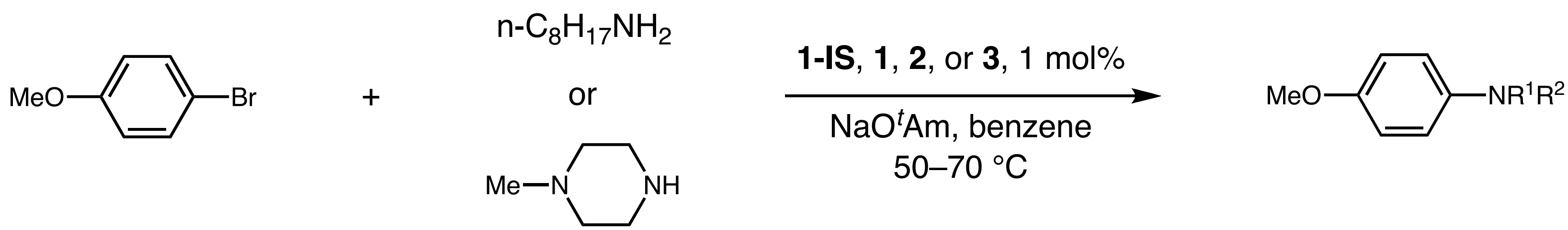
♦ The reaction rate with **1-IS** depends on the identities of amine, but does not depend on the concentration of amine.

♦ The reaction rate with **2** and **3** are independent of the identities of and concentration of amine.

Hartwig, J. F.; Blackmond, D. G. and Buchwald, S. L. *et al. JACS* **2006**, *128*, 3584.

Amination with BINAP Ligand - Mechanistic Re-evaluation

■ Re-evaluate the amination reactions with primary and secondary amine



(BINAP)Pd(dba) (**1**) << $Pd(BNAP)_2$ (**3**) < $[(BINAP)Pd]_2(dba)$ (**2**)

→ increasing reactivity

♦ The reaction rate with **1-IS** depends on the identities of amine, but does not depend on the concentration of amine.

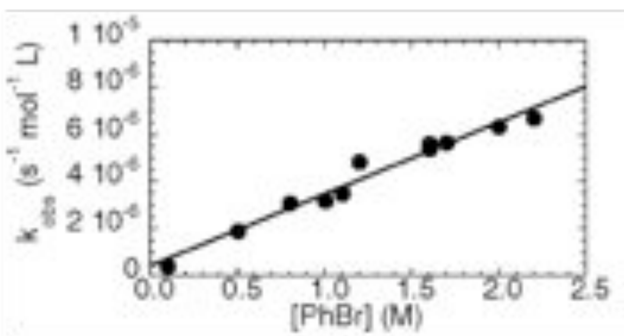
♦ The reaction rate with **2** and **3** are independent of the identities of and concentration of amine.

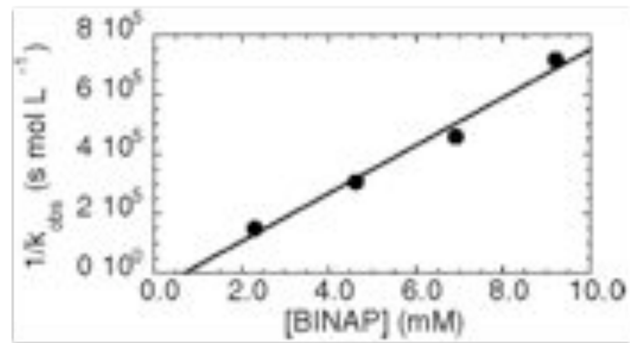
=> The dependence of reaction rate with **1-IS** on identities of amines can be attributed to catalyst deactivation occuring during the reaction of secondary amines <=> occuring off of the catalytic cycle.
(Blackmond and Buchwald's data corrected)

Hartwig, J. F.; Blackmond, D. G. and Buchwald, S. L. *et al. JACS* **2006**, *128*, 3584.

Amination with BINAP Ligand - Mechanistic Re-evaluation

■ Re-evaluate the amination reactions with aryl bromides and and BINAP





◆ The reaction is first-order in aryl bromides (Hartwig's data corrected).

k_{obs} ~ [ArBr]

◆ The reaction is invert first-order in ligand (BINAP).

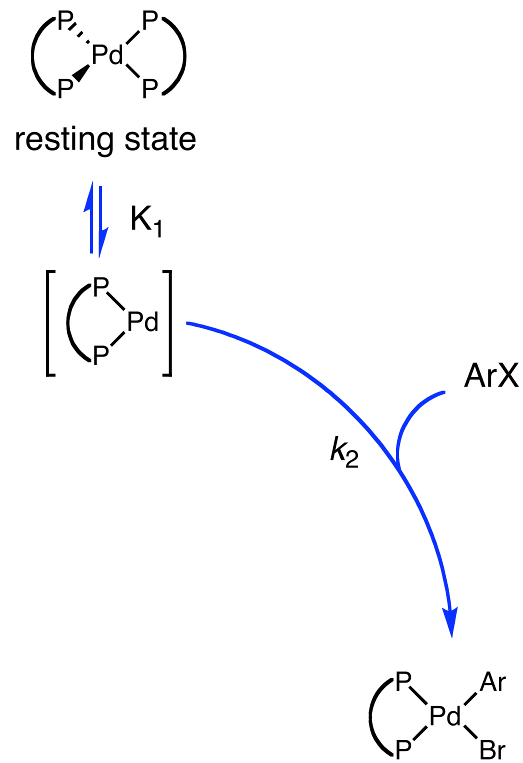
k_{obs} ~1/ [BINAP]

Hartwig, J. F.; Blackmond, D. G. and Buchwald, S. L. *et al JACS* **2006**, *128*, 3584.

Amination with BINAP Ligand - Mechanistic Conclusion

k_{obs} ~1/ [BINAP]

k_{obs} ~ [ArBr]



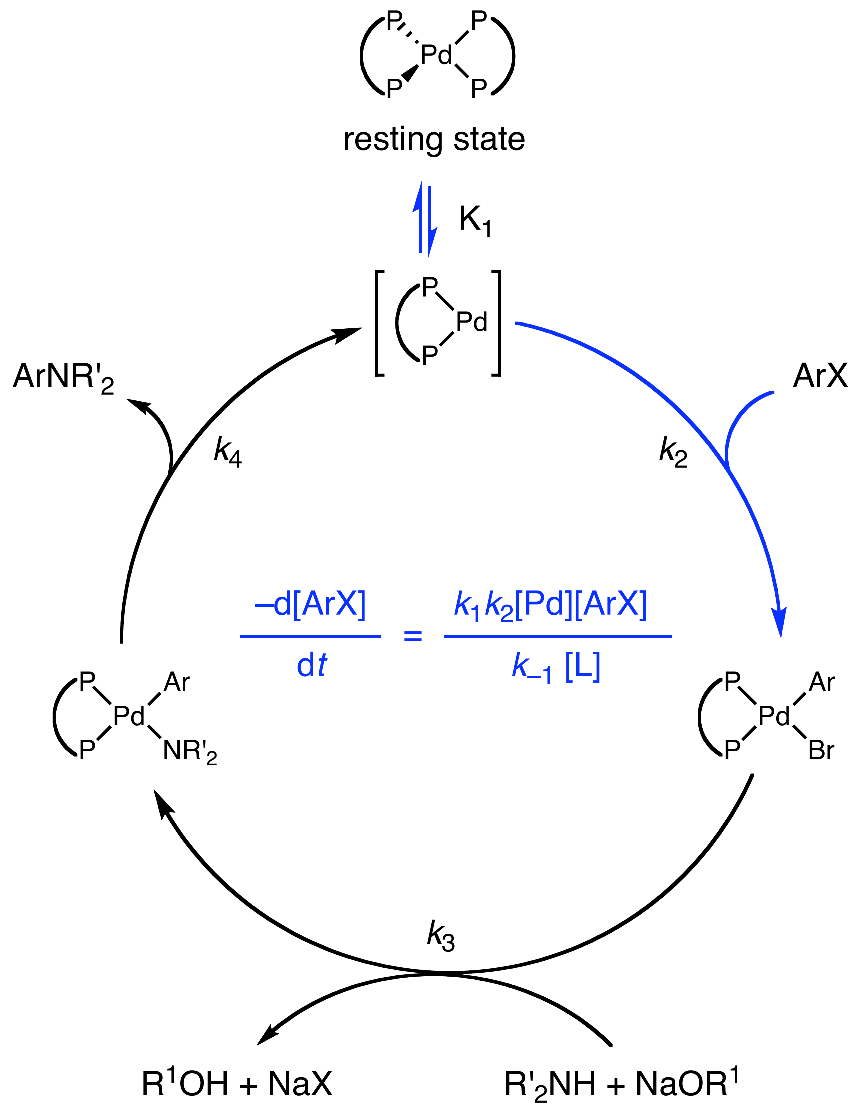
Hartwig, J. F.; Blackmond, D. G. and Buchwald, S. L. *et al JACS* **2006**, *128*, 3584.

Amination with BINAP Ligand - Mechanistic Conclusion

k_{obs} ~1/ [BINAP]

k_{obs} ~ [ArBr]

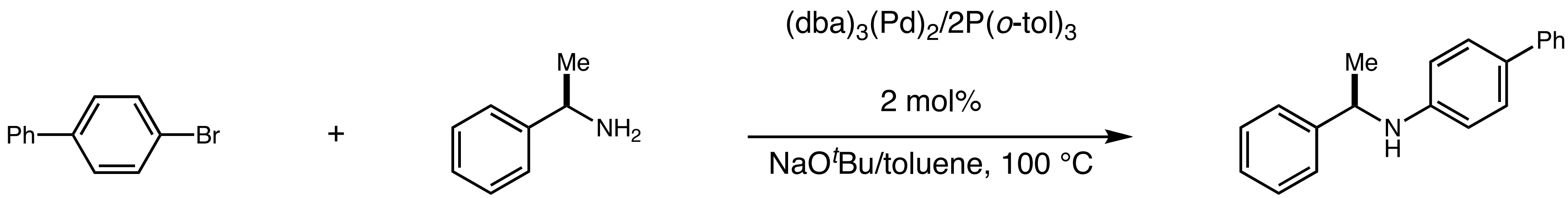
k_{obs} does not depend on [amine], [base]



$$\frac{-d[ArX]}{dt} = \frac{k_1 k_2 [Pd][ArX]}{k_{-1}\,[L]}$$

Hartwig, J. F.; Blackmond, D. G. and Buchwald, S. L. *et al JACS* **2006**, *128*, 3584.

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

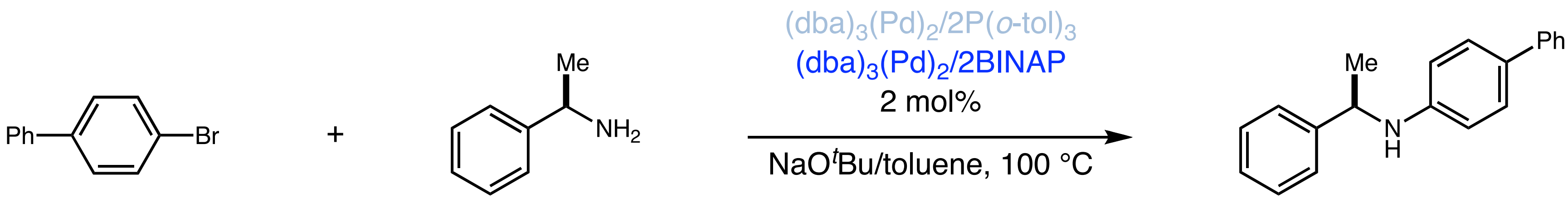


98% ee

$P(o\text{-tol})_3$: 60% yield, 70% ee;

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

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

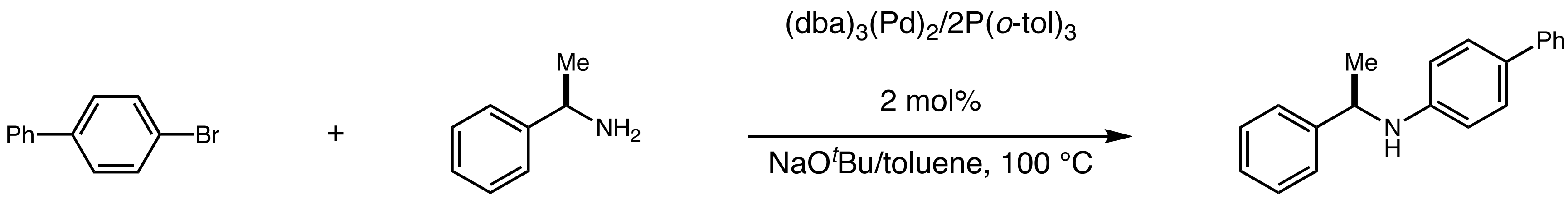


98% ee

$P(o\text{-tol})_3$: 60% yield, 70% ee;
BINAP: 86% yield, >99% ee

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

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



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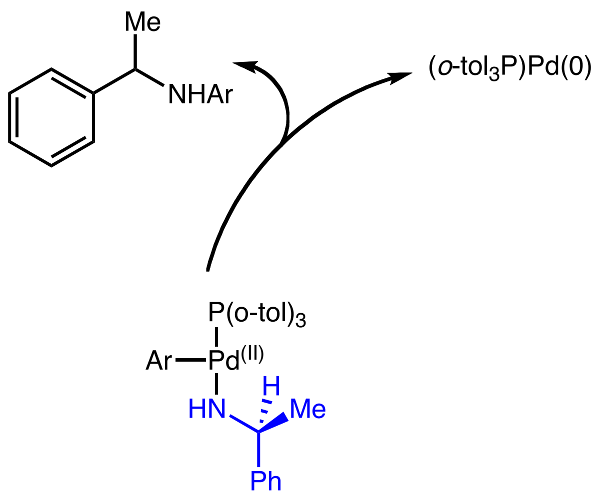
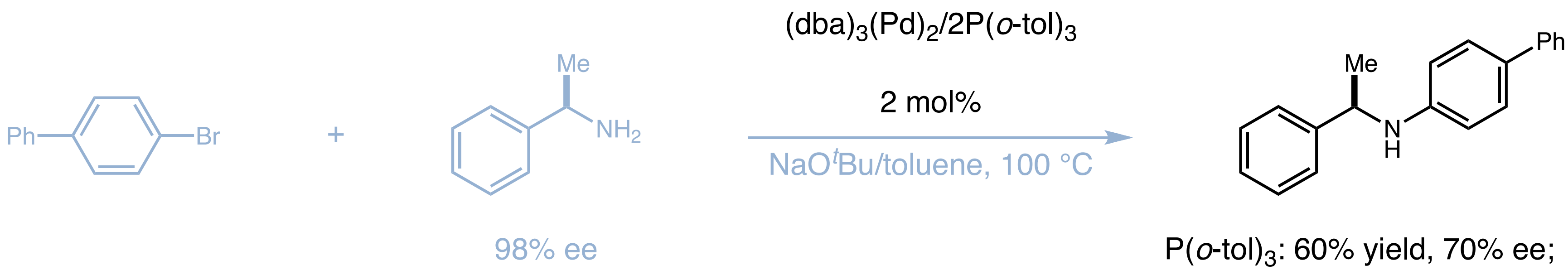
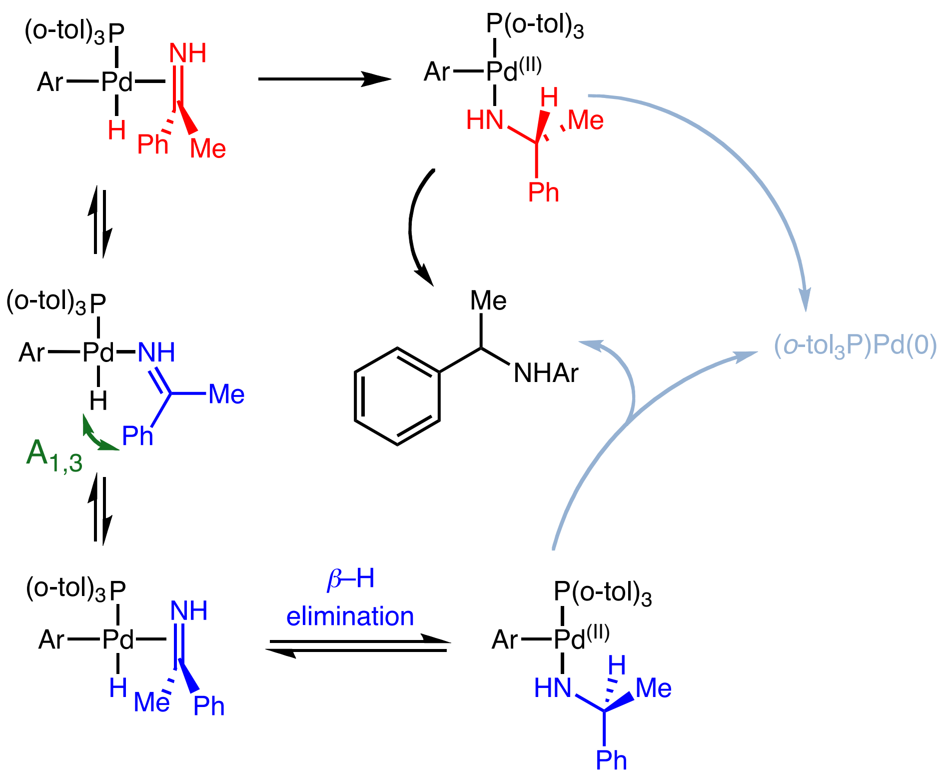


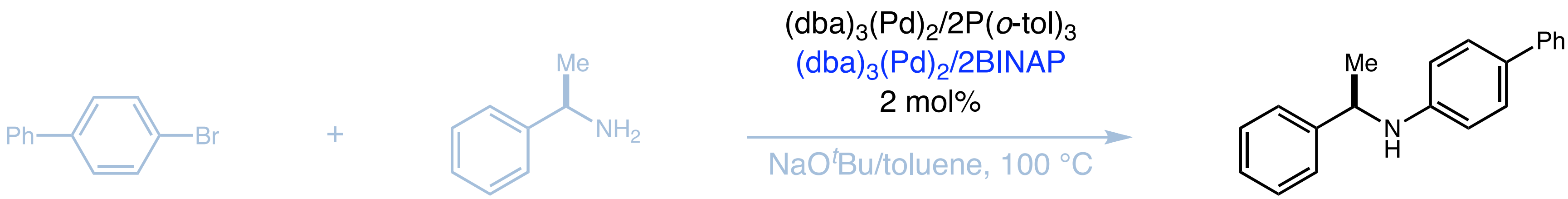
Amination with Bidentate Ligands - Coupling of Chiral Amines with Aryl Bromides



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



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



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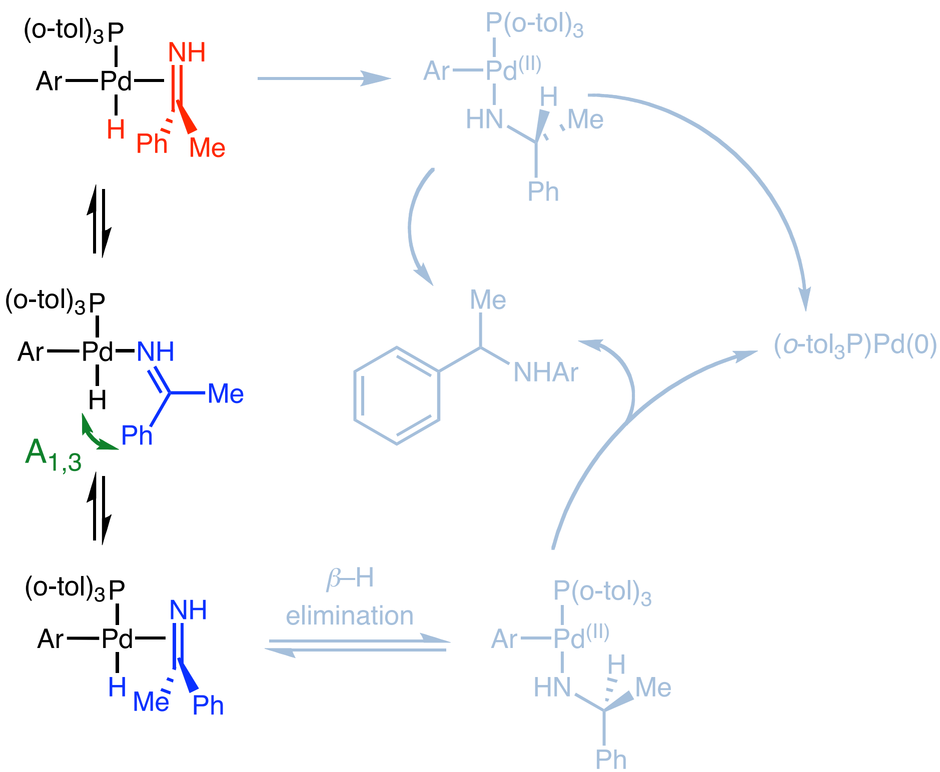
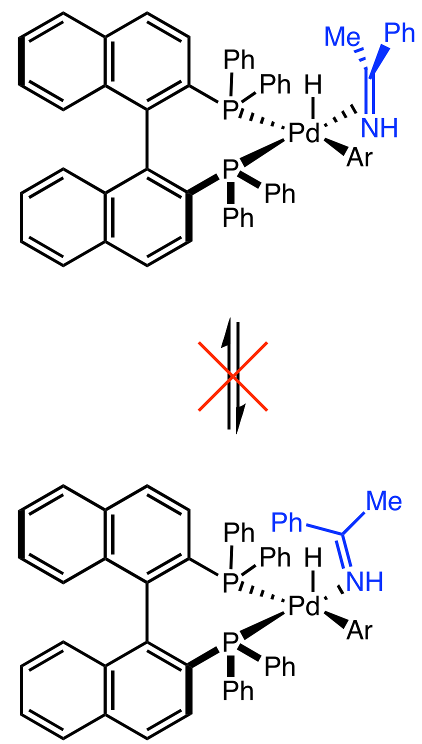
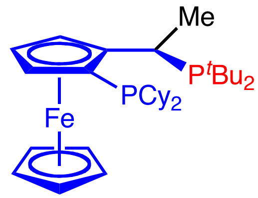




Amination with Josiphos Ligand - Scope Enlargement

♦ Inherent chelating properties of the aromatic bisphosphine ligands.



Josiphos (98.0 °)

♦ Inherent steric properties and strong electron donation of hindered trialkylphosphine ligands.

♦ Lowering the catalyst loading and broadening the scope of reaction.

Hartwig, J. F. *ACS* **2008**, *41*, 1534.

Amination with Josiphos Ligand - Scope Enlargement

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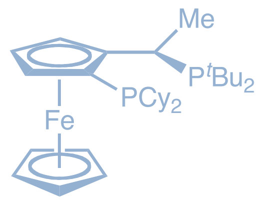

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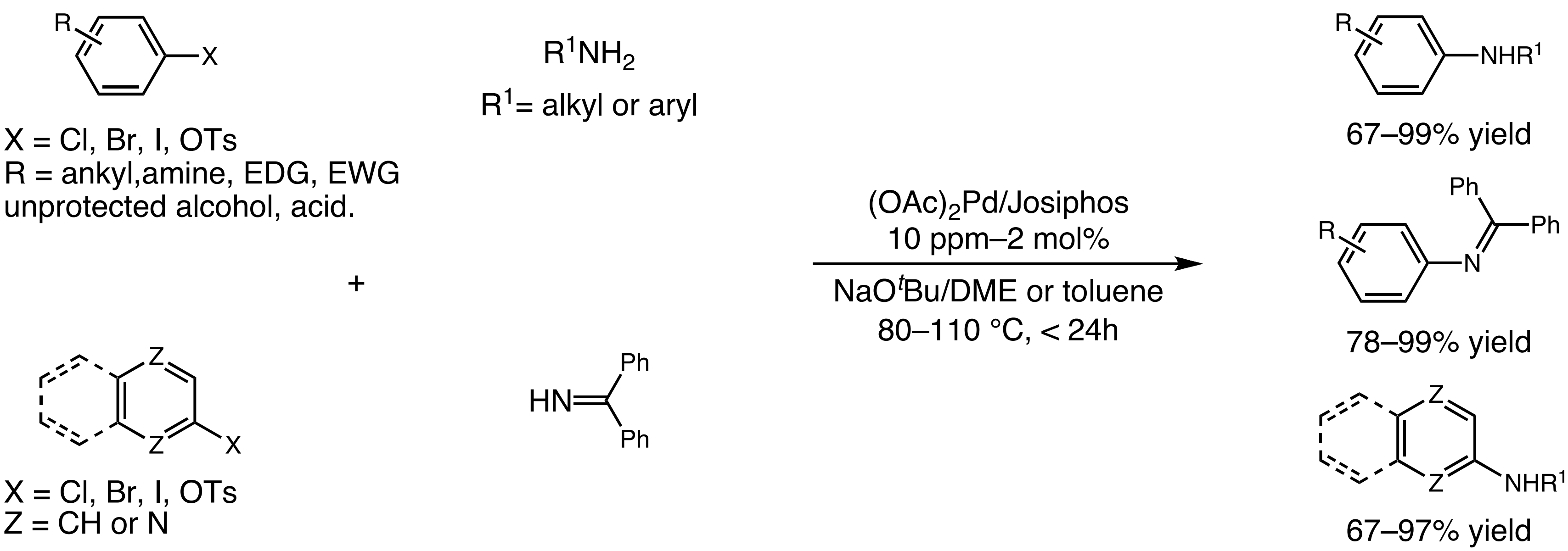
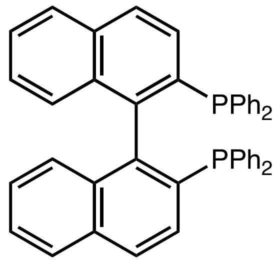
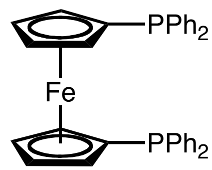
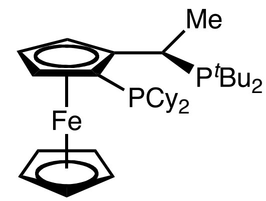
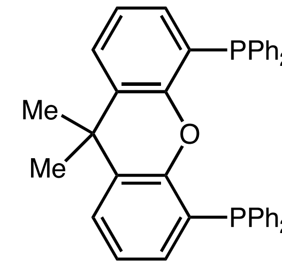
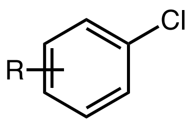
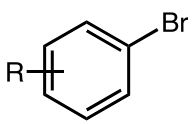
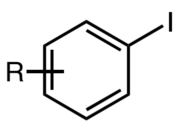
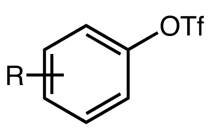
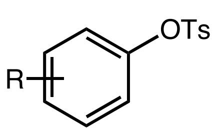
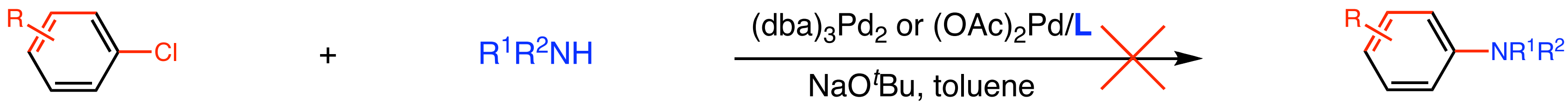


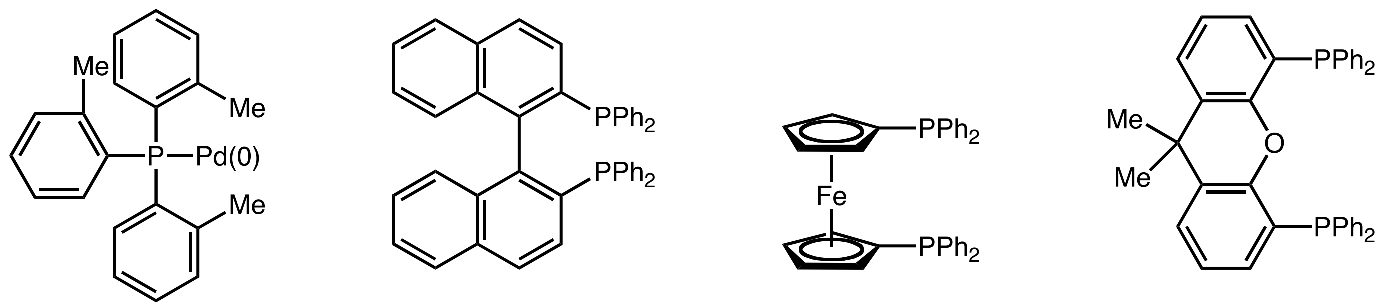
Hartwig, J. F. *et al ACIE* **2005**, *44*, 1371.
Shen, Q. and Hartwig, J. F. *OL* **2008**, *10*, 4109.
Hartwig, J. F. *et al JACS* **2008**, *130*, 6586.
Ogata, T. and Hartwig, J. F. *JACS* **2008**, *130*, 13848.

C–N Coupling with Biphosphine Ligands

	 BINAP (92.7 °)	 DPPF (99.0 °)	 Josiphos (98.0 °)	 Xantphos (109 °)
			*Amination*: *ACIE* **2005**, *44*, 1371; *Imination*: *JACS* **2008**, *130*, 6586 & 13848. *Ar*NH_2: *JACS* **2006**, *128, 10028;* **2009**, *131*, *11049*	
	*Amination*: *JACS* **1996**, *118*, 7215; *JACS* **1997**, *119*, 8451; *Imination*: *TL* **1997**, *38*, 6367	*Amination*: *JACS* **1996**, *118*, 7217; *Imination* and *het.amination*: *JACS* **1998**, *120*, 827	*Amination*: *ACIE* **2005**, *44*, 1371; *Imination* and *het.amination*: *JACS* **2008**, *130*, 6586 & 13848; *AAr*NH_2: *JACS* **2006**, *128, 10028;* **2009**, *131*, *11049*	*Amination*: *Tet.* **2008**, *64*, 2938. *Imination*: *JACS* **1999**, *121*, 10251; *Amidation*: *OL* **1999**, *1*, 35; *JACS* **2002**, *124*, 6043 & **2007**, *129*, 7734
	*Imination*: *TL* **1997**, *38*, 6367	*Amination*: *JACS* **1996**, *118*, 7217	*Amination*: *ACIE* **2005**, *44*, 1371; *Imination*: *JACS* **2008**, *130*, 6586 & 13848; *Ar*NH_2: *JACS* **2006**, *128, 10028;* **2009**, *131*, *11049*	*Amination*: *Tet.* **2008**, *64*, 2938. *Amidation*: *OL* **1999**, *1*, 35; *JACS* **2002**, *124*, 6043 and **2007**, *129*, 7734
	*Imination*: *TL* **1997**, *38*, 6367	*Amination*: *JOC* **1997**, *62*, 1268	*Ar*NH_2: *JACS* **2006**, *128, 10028;* **2009**, *131*, *11049*	*Amidation*: *OL* **1999**, *1*, 35; *JACS* **2002**, *124*, 6043 and **2007**, *129*, 7734
			*Amination*: *ACIE* **2005**, *44*, 1371; *Imination*: *JACS* **2008**, *130*, 6586 & 13848; *Ar*NH_2: *JACS* **2006**, *128, 10028;* **2009**, *131*, *11049*	

Amination with Biarylphosphine Ligands - Amination of Aryl Chlorides

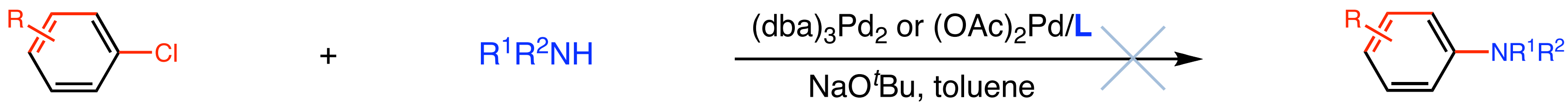


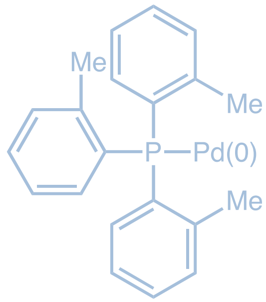


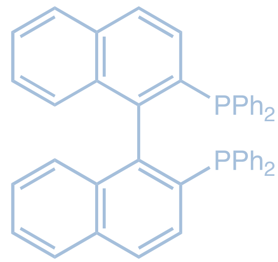
		BINAP	DPPF	Xantphos
Used in amination	1983	1996	1996	1999

- Not electron-rich enough for the oxidative addition or aryl chloride

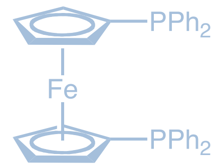
Amination with Biarylphosphine Ligands - Amination of Aryl Chlorides



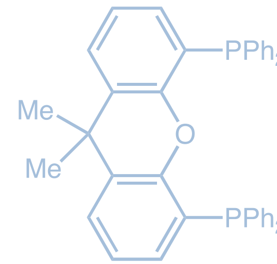




BINAP



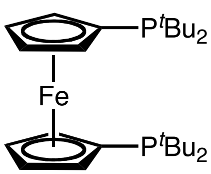
DPPF

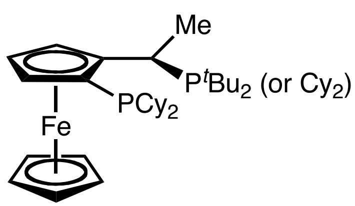


Xantphos

Used in amination	1995	1996	1996	1999

- Not electron-rich enough for the oxidative addition or aryl chloride

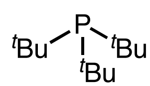




Josiphos (98.0 °)

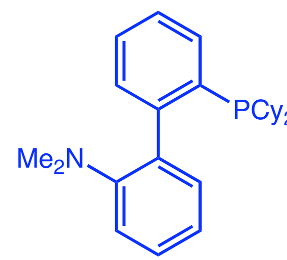
Hartwig *JACS* **1998**, *120*, 7369.

92–99% yield



Hartwig *JOC* **1999**, *64*, 5575.

64–97% yield



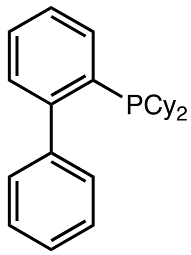
DavePhos

Buchwald *JACS* **1998**, *120*, 9722.

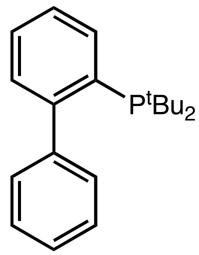
81–98% yield

Biarylphosphine Ligand

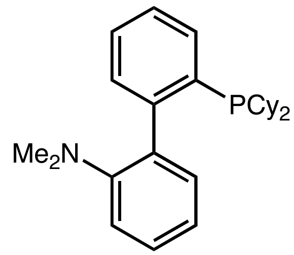
(ligands for gold, silver, rhodium, ruthenium and copper)



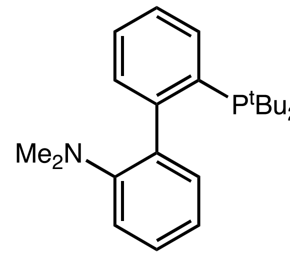
JohnPhos (Cy)



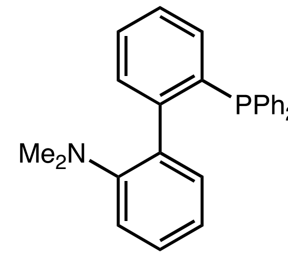
JohnPhos



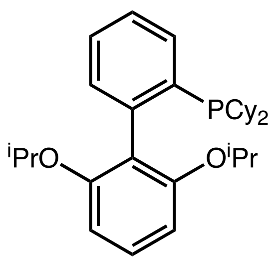
DavePhos
(Buchwald,1998)



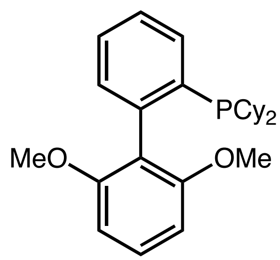
DavePhos (^{t}Bu)



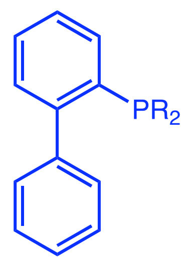
DavePhos (Ph)



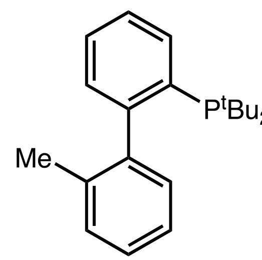
RuPhos



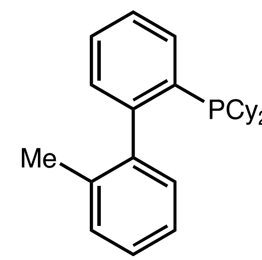
SPhos



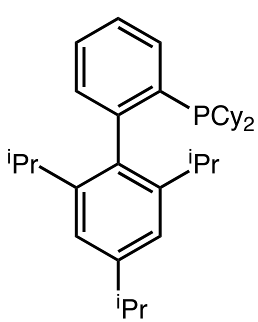
Biarylphosphine
(≥ 162 °)



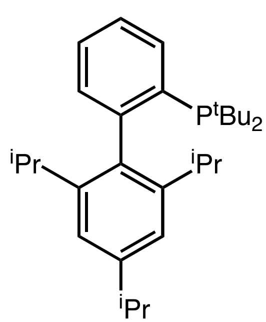
MePhos (^{t}Bu)



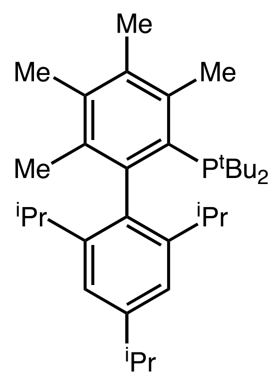
MePhos



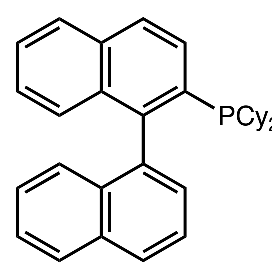
XPhos



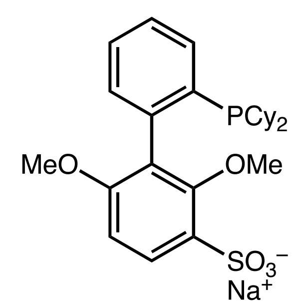
XPhos (^{t}Bu)



XPhos (4Me^{t}Bu)

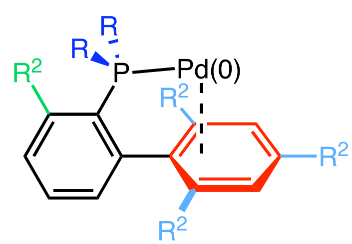


Johnphos (NaphCy)



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

Biarylphosphine Ligands - Important Structural Features



active complex

- ♦ Alkyl groups increase electron-density at phosphorus, promote oxidative addition.
- ♦ Increased steric bulk at P promotes reductive elimination.
- ♦ Large substituents on P promote the formation of $[L_1Pd(0)]$.

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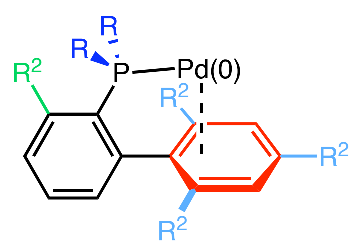
Biarylphosphine Ligands - Important Structural Features

♦ Substituent fixes conformation enhances rate of reductive elimination.



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

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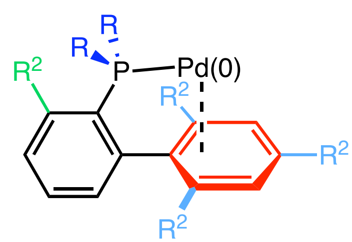


active complex

♦ Large substituents prevent cyclometalation, increase stability.

♦ Large substituents on ring promote the formation of [L_1Pd(0)].

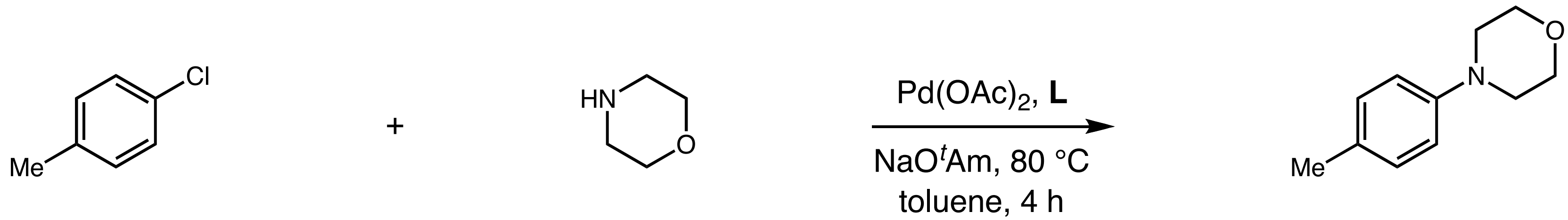
♦ Lower aryl ring retards oxidation by O_2.

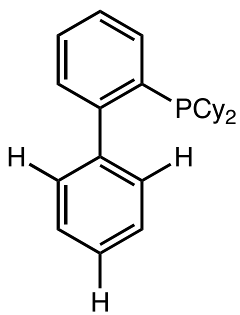
♦ Lower aryl ring allows stabilizing Pd–arene interactions.

♦ Lower aryl ring promotes reductive elimination.

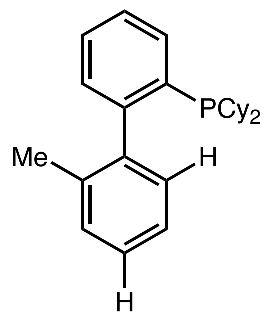
Surry, D. S. and Buchwald, S. L. *ACIE* **2008**, *47*, 6388.

Biarylphosphine Ligands - Effects of Substutuents on Lower Aryl Ring

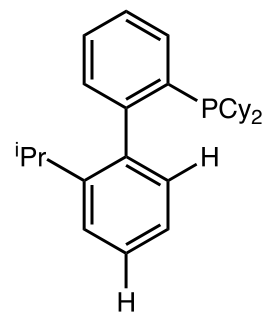




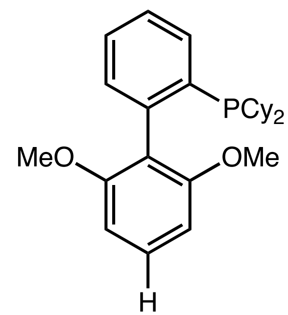
1a



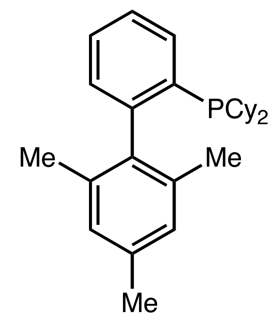
1b



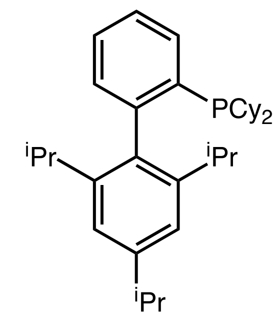
1c



3a



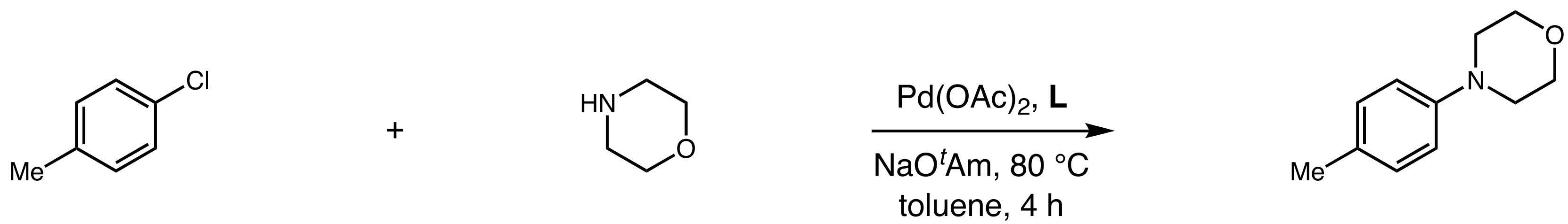
3b

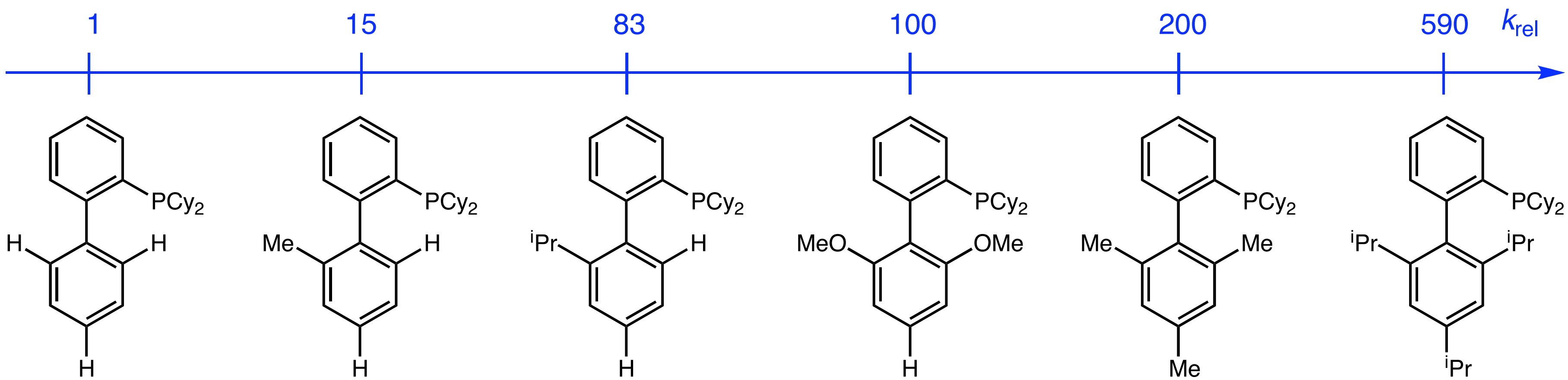


3c

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

Biarylphosphine Ligands - Effects of Substutuents on Lower Aryl Ring





1a **1b** **1c** **3a** **3b** **3c**

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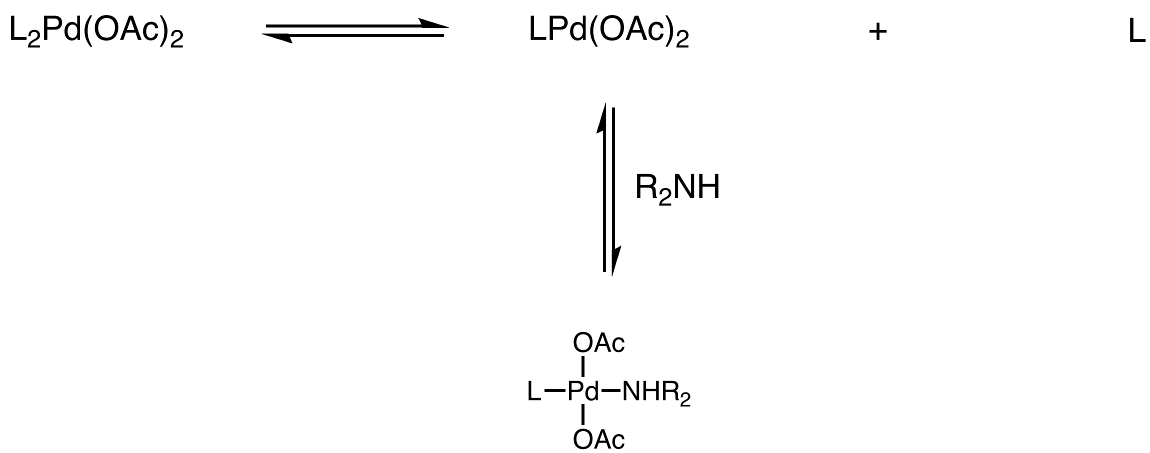

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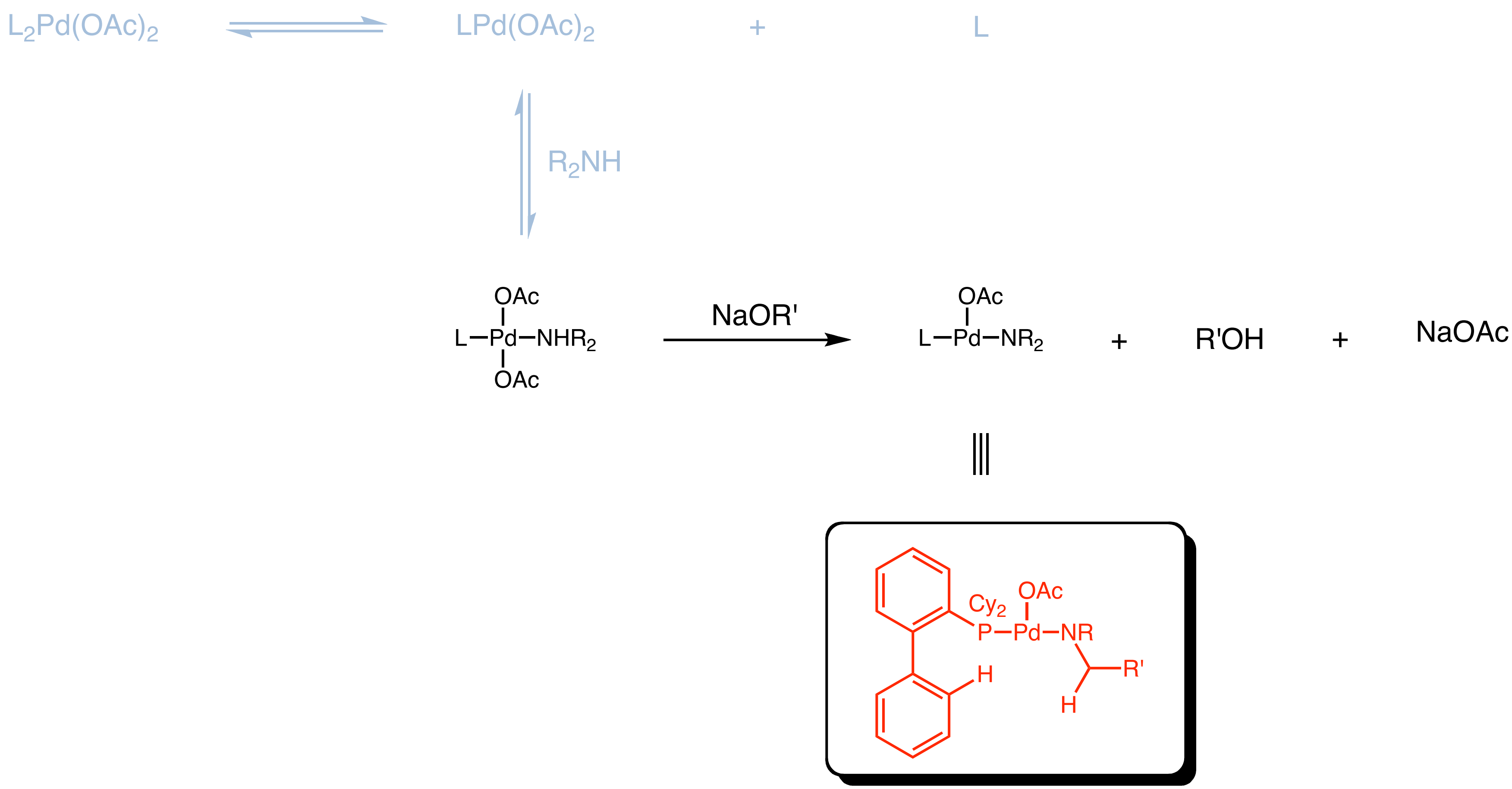

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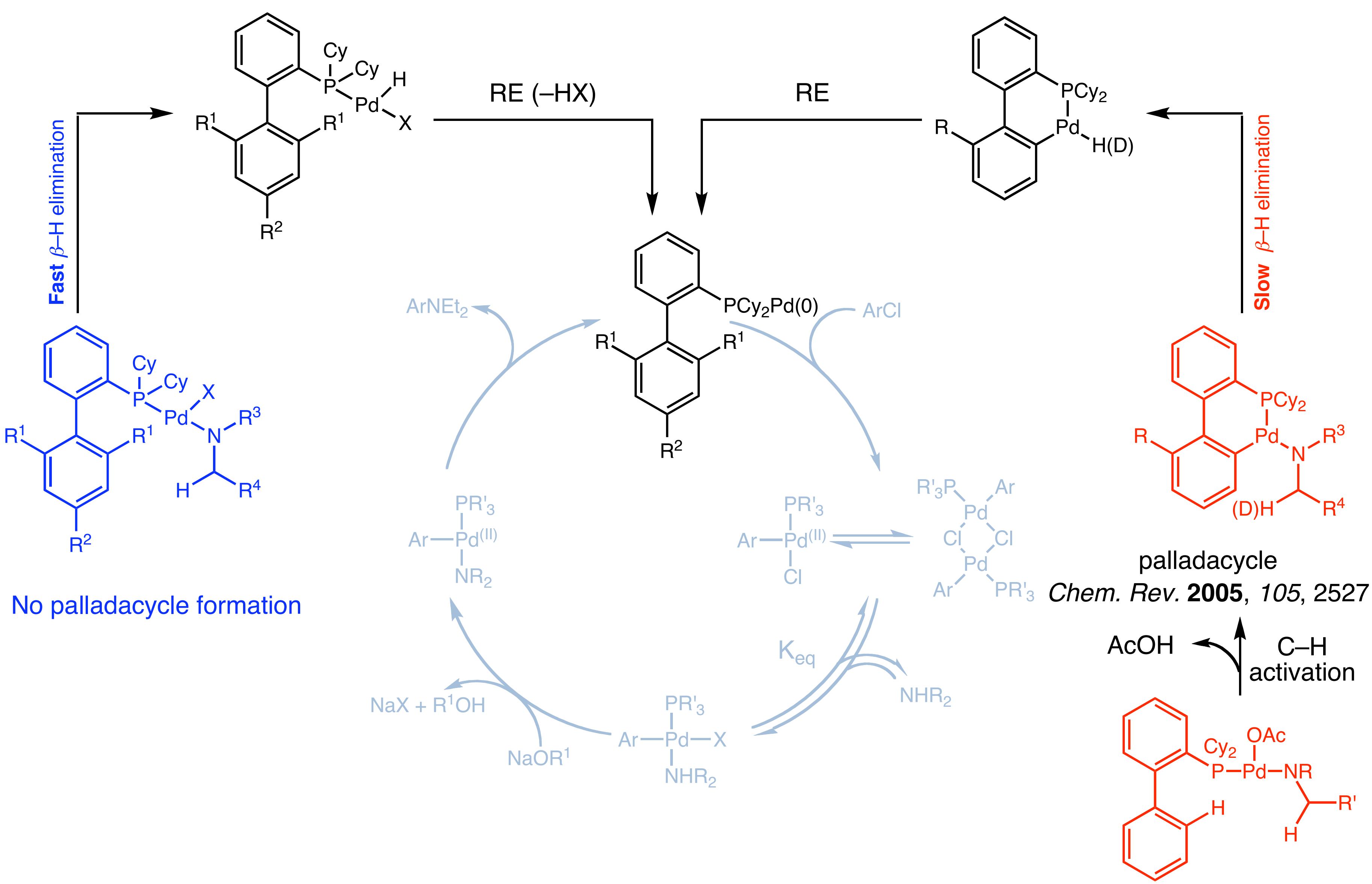
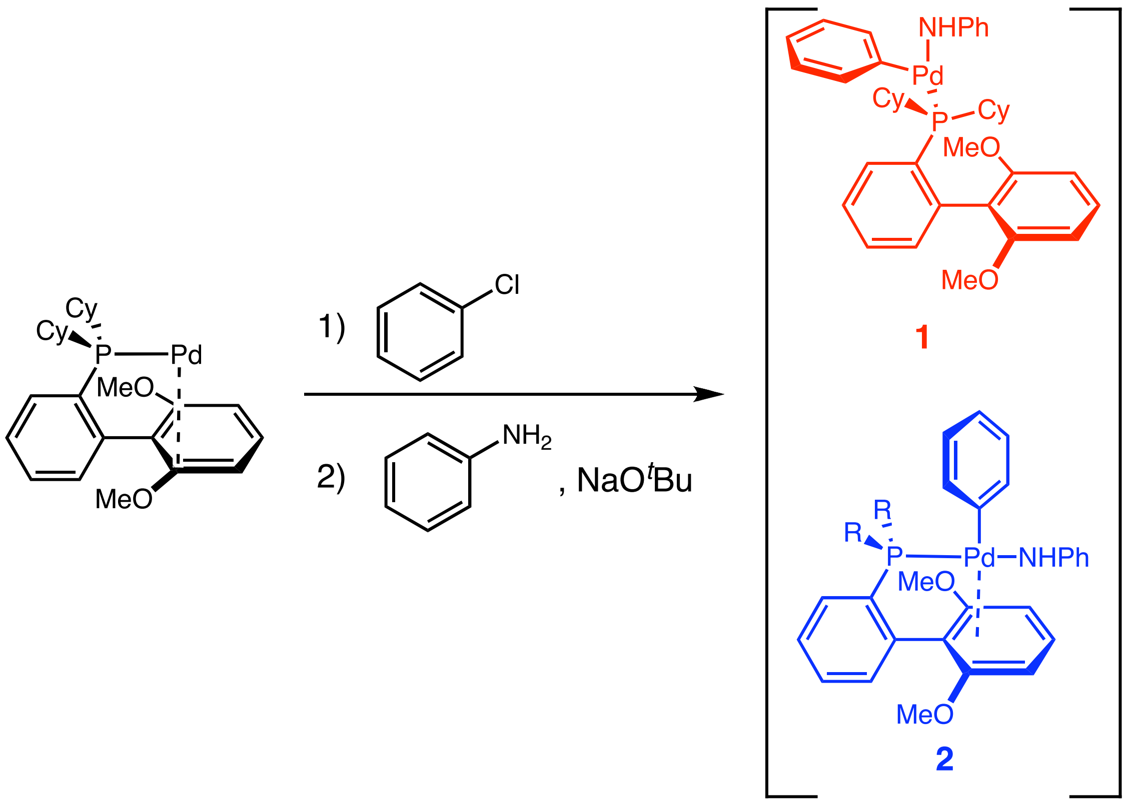


Buchwald, S. L. *et al JACS* **2003**, 125, 13978.
Strieter, E. R. and Buchwald, S. L. *ACIE* **2006**, *45*, 925.

Biarylphosphine Ligands - Reductive Elimination via DFT Study



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

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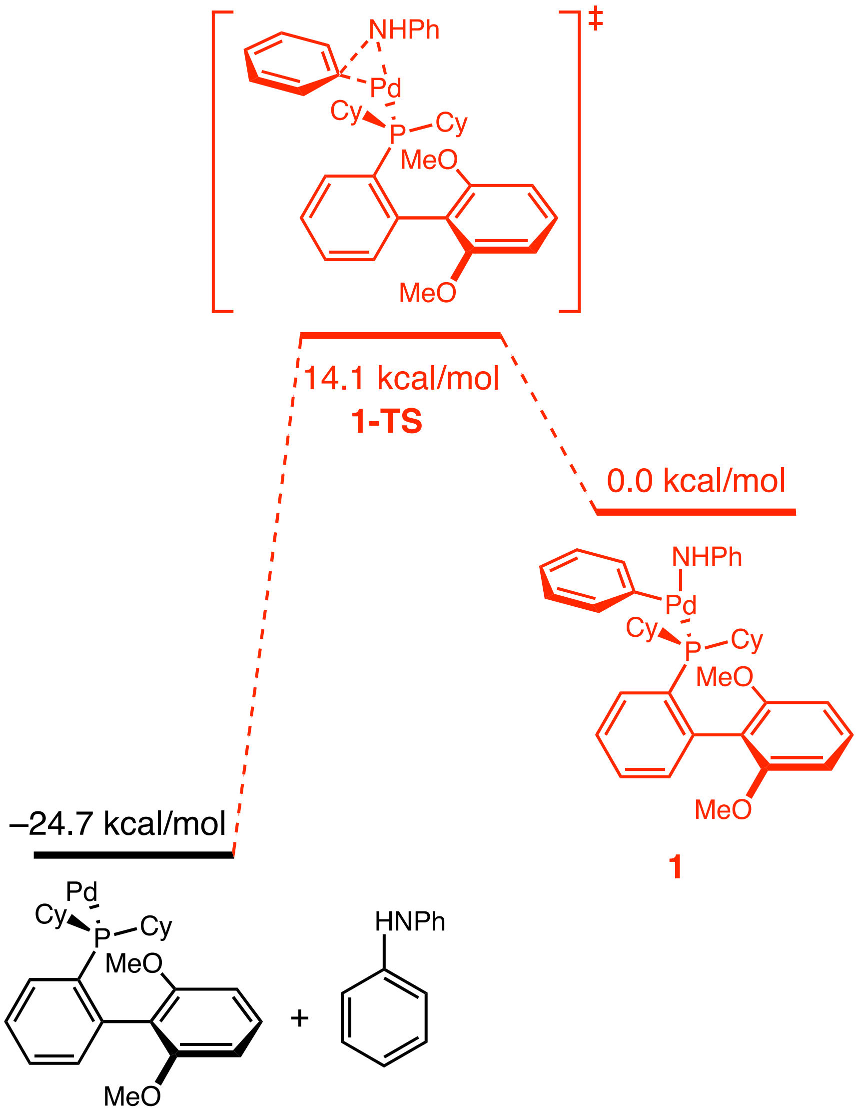

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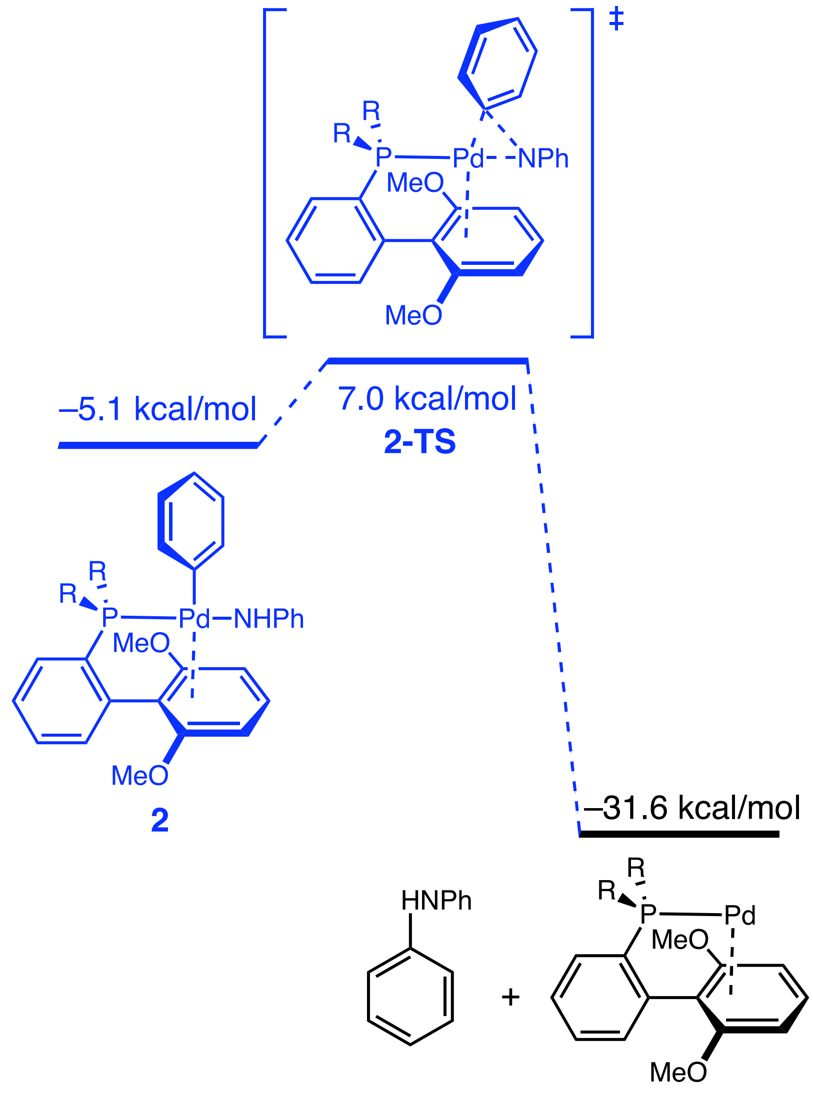

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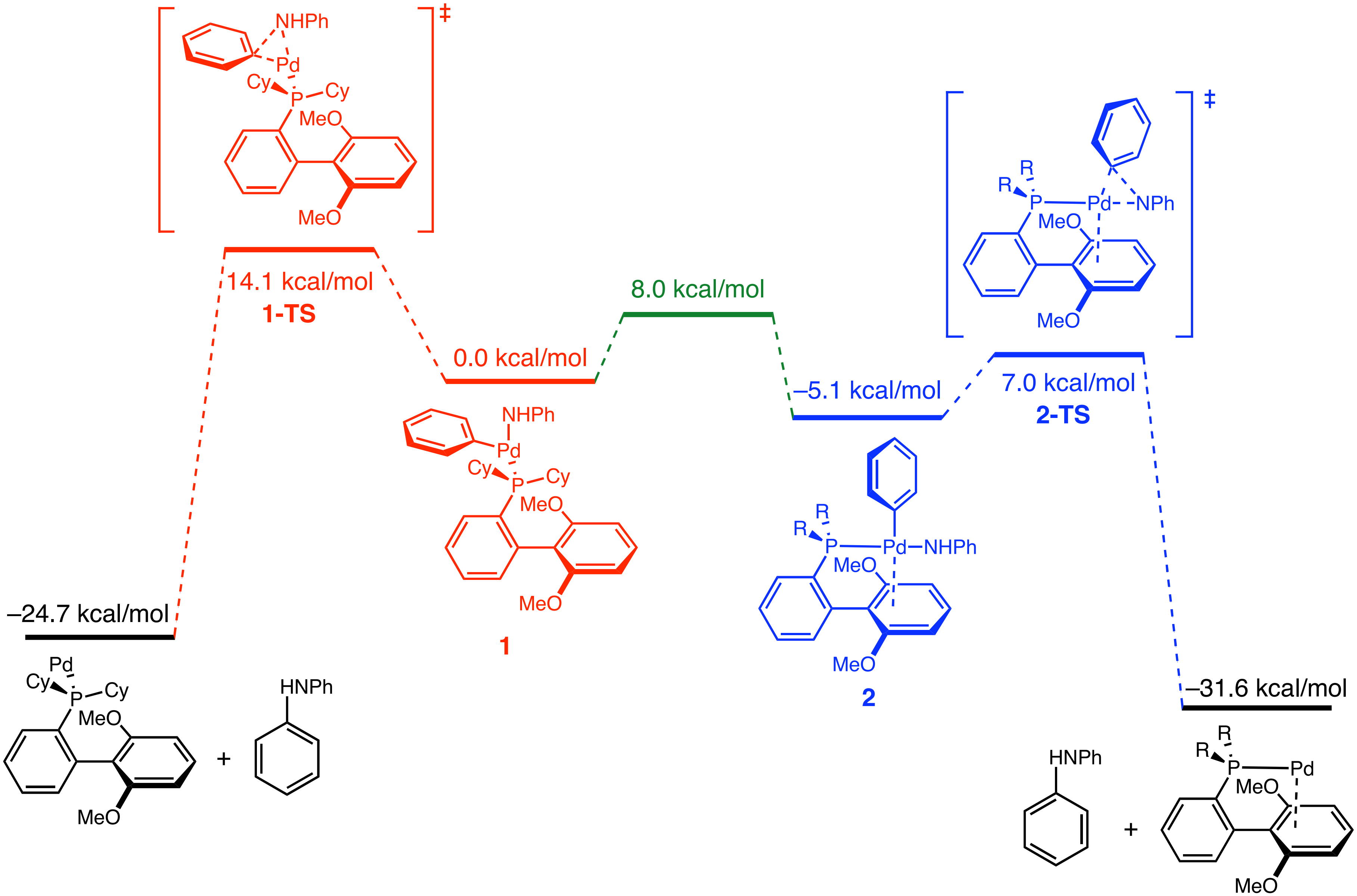
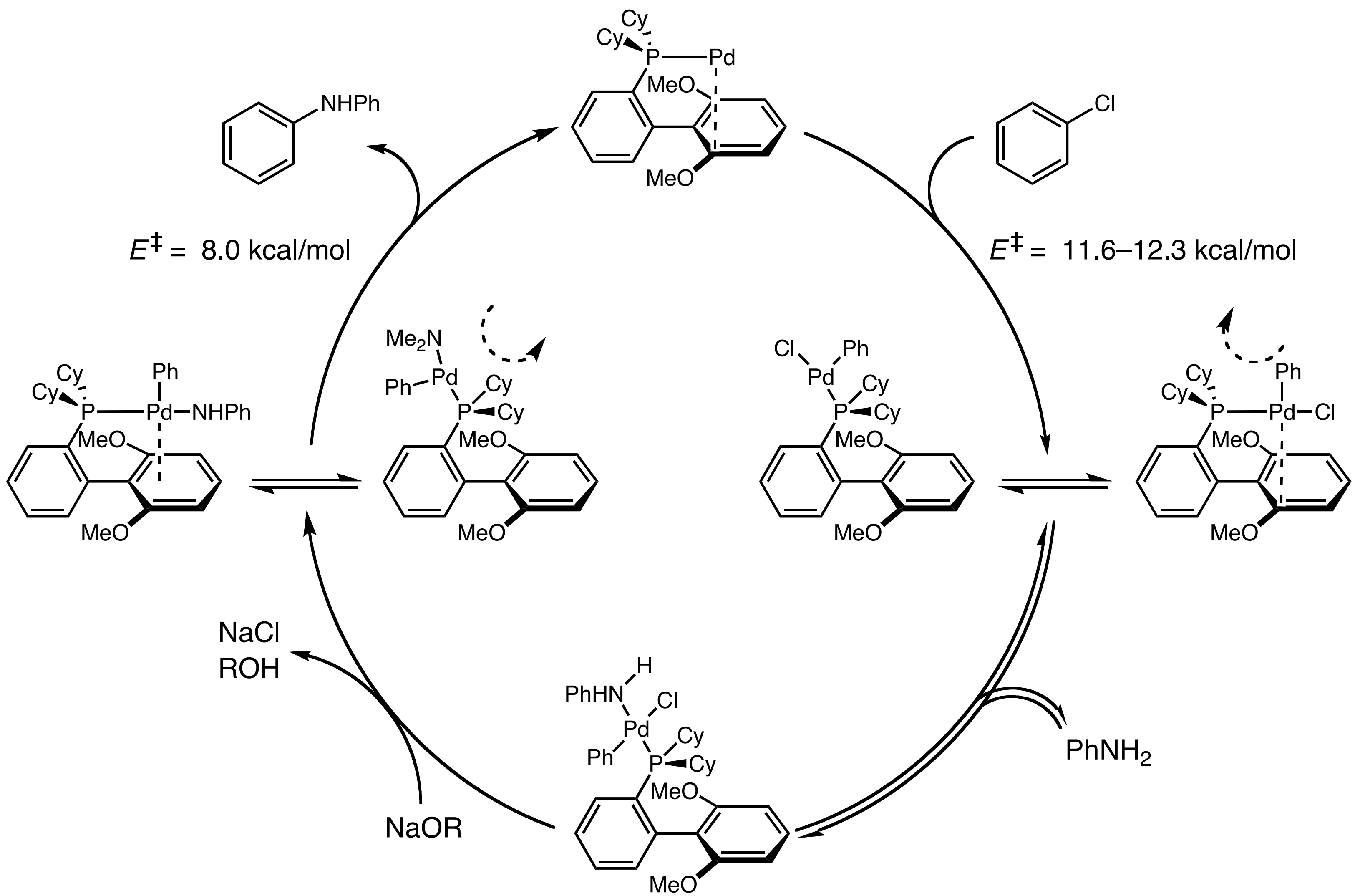


Barder, E. T. and Buchwald, S. L. *JACS* **2007**, *129*, 12003.

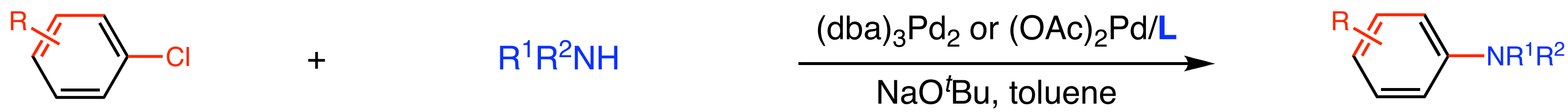
Biarylphosphine Ligands - Proposed Mechanism via DFT Study

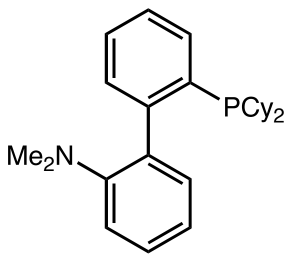


Barder, E. T. and Buchwald, S. L. *JACS* **2007**, *129*, 12003.

Amination with Biarylphosphine Ligands

amination of aryl chlorides





DavePhos

Buchwald *JACS* **1998**, *120*, 9722.

$(dba)_3Pd_2$/3**L**, 0.5 mol%

RT–100 °C; 81–98% yield

R = MeO, Me, CN, COMe, CO_2Me

R^1= H, alkyl or aryl; R^2= alkyl

Amination with Biarylphosphine Ligands

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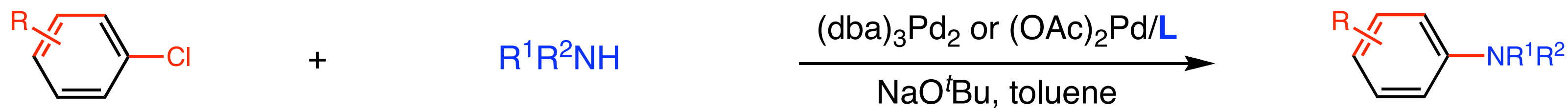

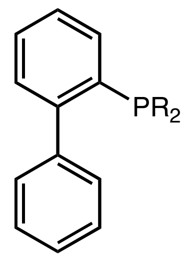

JohnPhos (R = ^{t}Bu)

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$(OAc)_2Pd$/1-2**L** (^{t}Bu), 1–2 mol%

RT, ≤ 20 h; 81–99% yield

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$(OAc)_2Pd$/1-2**L** (Cy), 0.05–5 mol%, K_3PO_4 (FgT)

DME, 100–110 °C, ≤ 1 d; 69–95% yield

Amination with Biarylphosphine Ligands

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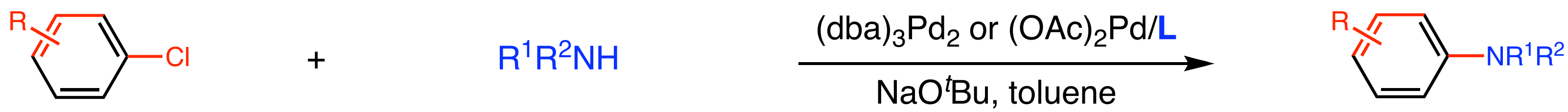

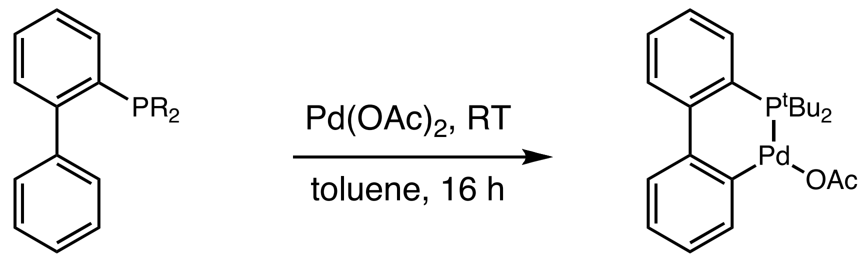

Air and thermally stable catalyst (Strem)

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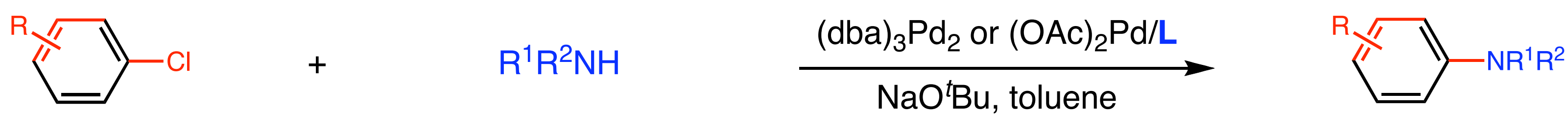
Amination with Biarylphosphine Ligands

amination of aryl chlorides



L = Xphos(3^{i}Pr)
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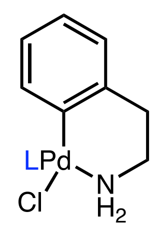


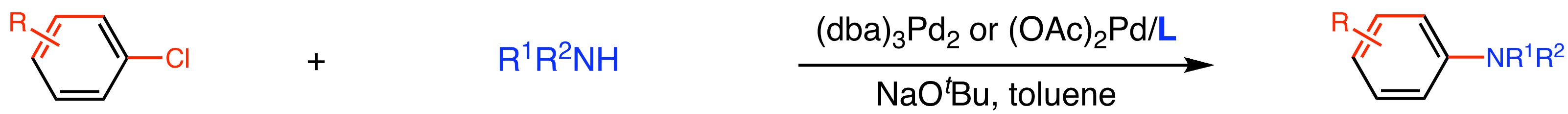
Higly active catalysts.

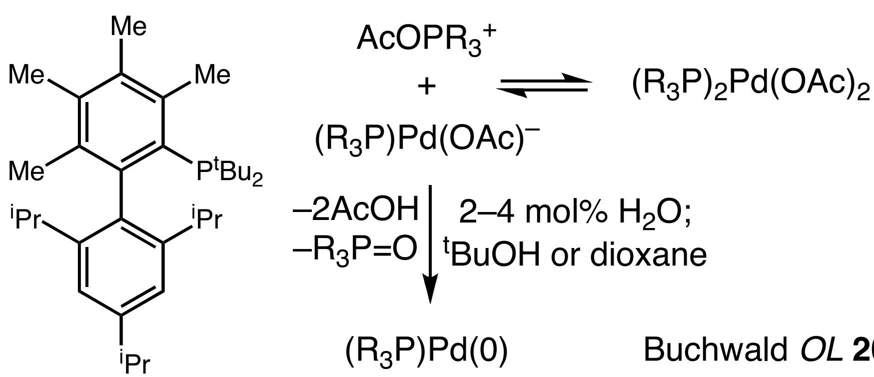
Buchwald *JACS* **2008**, *130*, 6686.

Electron-deficient amines: 83–99% yield
10 min C–N bond forming with 0.1 mol% cat: 93–98% yield
Reaction at –10–25 °C, ≤ 24 h: 82–99% yield

Amination with Biarylphosphine Ligands

amination of aryl chlorides



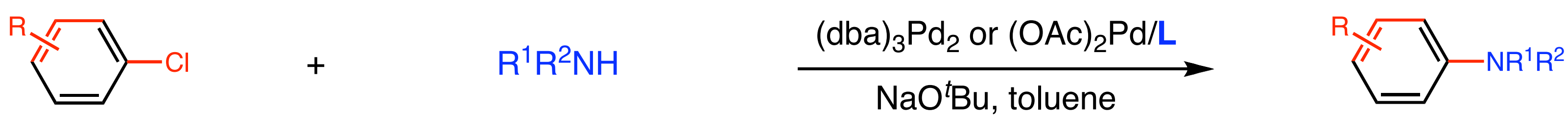


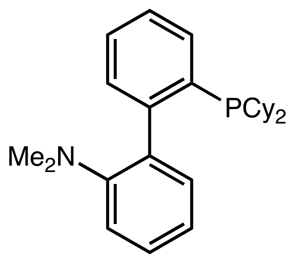
Buchwald *OL* **2008**, *10*, 3505.

For electron deficient amines; lower the catalyst loading; shorter reaction time; exclusion of additive.

Amination with Biarylphosphine Ligands

amination of aryl chlorides





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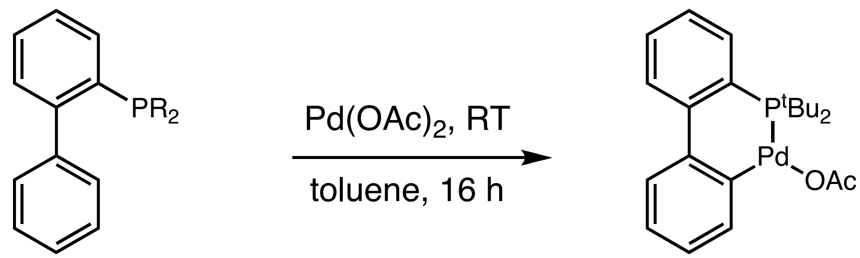

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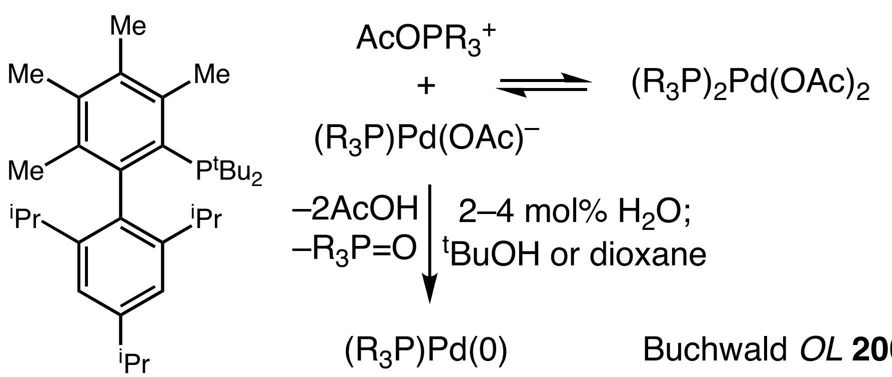

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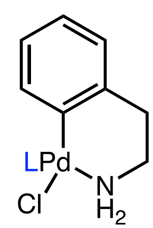
RuPhos(2O^{i}Pr)



Higly active catalysts.

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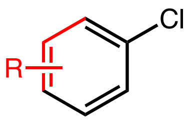
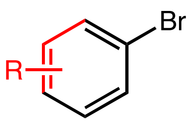
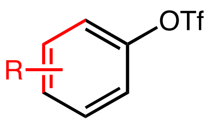
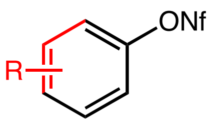
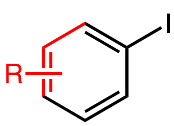
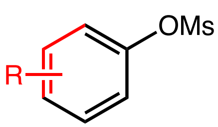
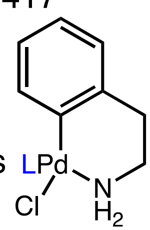
Buchwald *TL* **2009**, *50*, 3672.

Electron-deficient amines: 83–99% yield

10 min C–N bond forming with 0.1 mol% cat: 93–98% yield

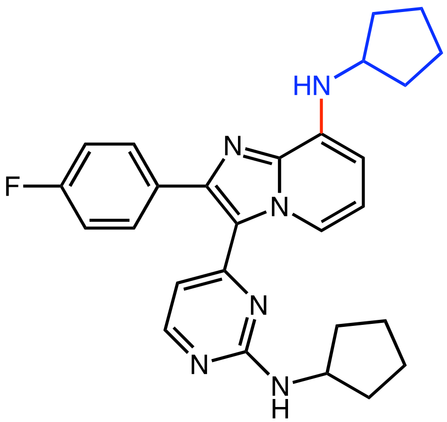
Reaction at –10–25 °C, ≤ 24 h: 82–99% yield

C–N Coupling with Biarylphosphine Ligands

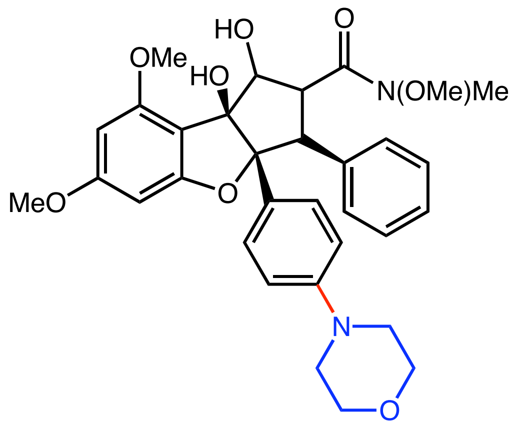
	$ArNR_2$	ArNHHet	$ArNH_2$	ArNHCOR	$ArNO_2$
		Ruphos, Xphos (^{t}Bu), Xphos (4Me^{t}Bu), *OL* **2005**, *7*, 3965; *ACIE* **2006**, *45*, 6523	Johnphos (Cy, ^{t}Bu) , Davephos (^{t}Bu), *OL* **2001**, *3*, 3417; *JACS* **2007**, *129*, 10354	Xphos (4Me^{t}Bu), *JACS* **2007**, *129*, 13001	Brettphos, *JACS* **2009**, *131*, 12898
	Johnphos, *JOC* **2000**, *65*, 1158				
	Johnphos, *JOC* **2000**, *65*, 1158			Xphos, Xphos (4Me^{t}Bu), *JACS* **2003**, *125*, 6653; *JACS* **2007**, *129*, 13001	Brettphos, *JACS* **2009**, *131*, 12898
	Johnphos, Davephos, *JOC* **2003**, *68*, 9563 & **2006**, *71*, 430				Brettphos, *JACS* **2009**, *131*, 12898
	Davephos, *JOC* **2001**, *3*, 3417				
	Brettphos  *JACS* **2008**, *130*, 13552 and **2009**, *131*, 5766.				

Amination with Biarylphosphine Ligands

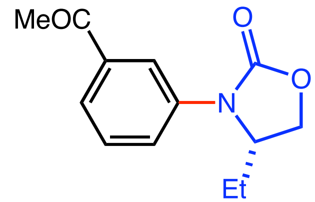
some examples in pharmaceutical synthesis



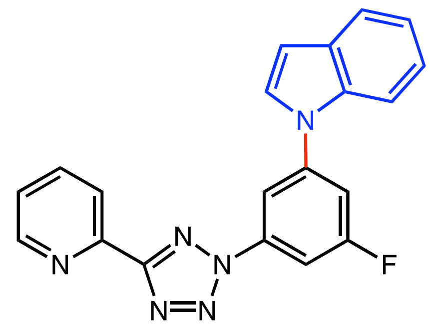
92% (Cl)
GalaxoSmithKline synthesis of antiherpes agents



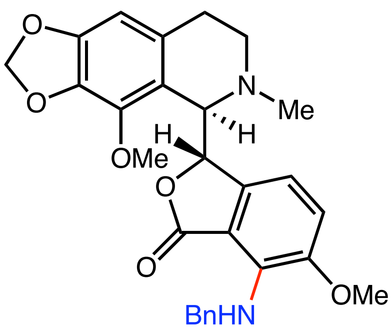
41% (Br)
Novartis synthesis of rocaglamine analogs



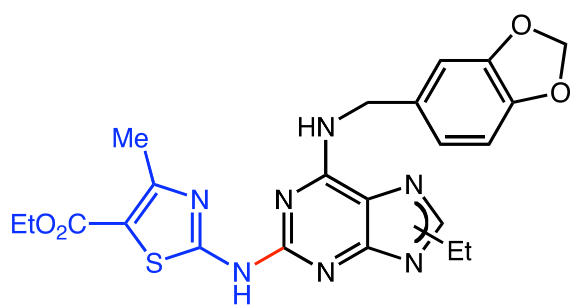
94% (Cl)
Pfizer synthesis of *N*-Aryl oxazolidinones



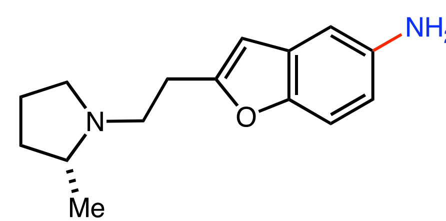
(I)
Merk synthesis of mGlu5 receptor antagonist



80% (OTf)
Athersys synthesis of noscapine analogs



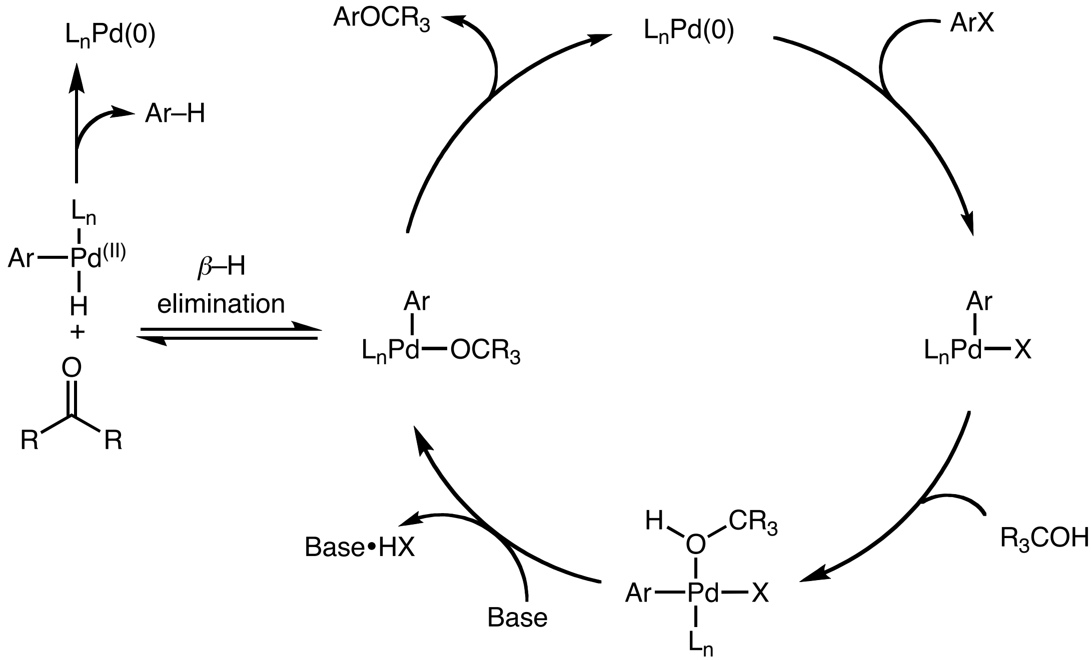
(Cl)
BMS synthesis of phosphodiesterase 7 inhibitors



80% (Br)
Abbot synthesis of histamine receptor H_3 antagonists

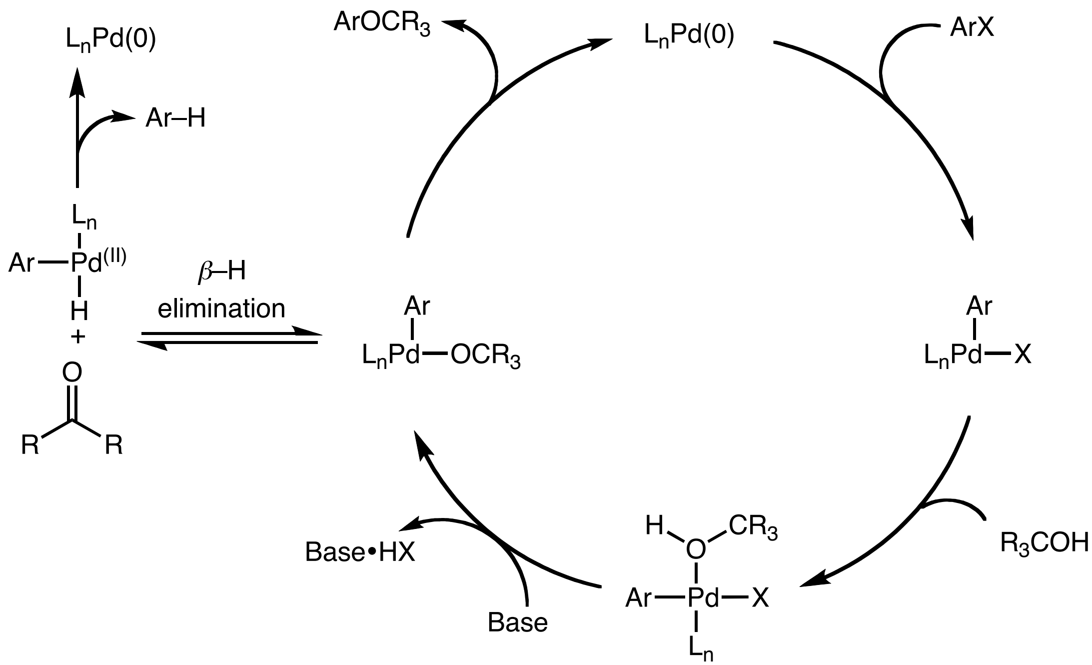
Surry, D. S. and Buchwald, S. L. *ACIE* **2008**, *47*, 6388.

C–O Coupling with Pd Complexes-Mechanistic Overview



Buchwald, S. L. *et al JACS* **1997**, *119*, 3395.
Hartwig, J. F. *et al ACIE* **2007**, *46*, 7674.

C–O Coupling with Pd Complexes-Mechanistic Overview



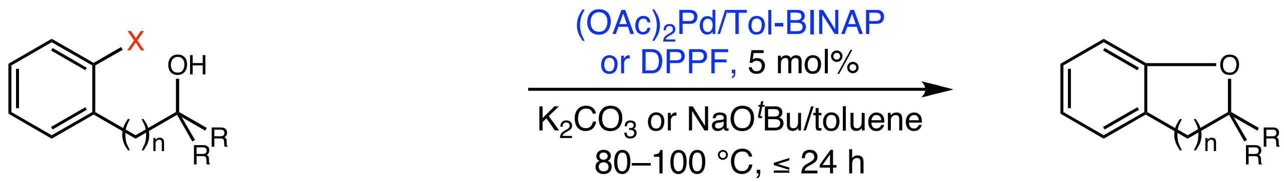
■ The nucleophilicity of alcohols is much weaker than that of amines

■ *β*–H elemination products are stable.

Buchwald, S. L. *et al JACS* **1997**, *119*, 3395.
Hartwig, J. F. *et al ACIE* **2007**, *46*, 7674.

C–O Coupling with Pd Complexes

scope limitation with bidentate phosphine ligands



n = 1–3

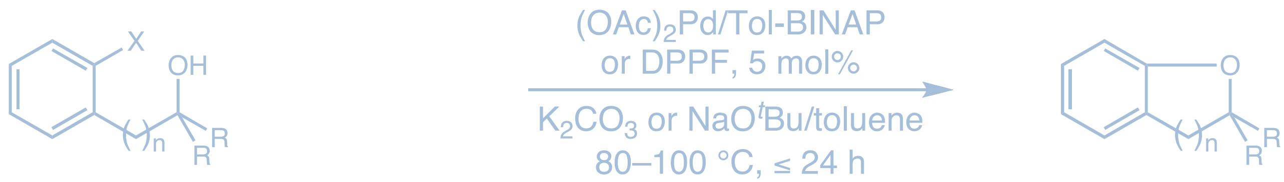
X = Br, I
R = Me, alkyl

77–97% yield

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

C–O Coupling with Pd Complexes

scope limitation with bidentate phosphine ligands



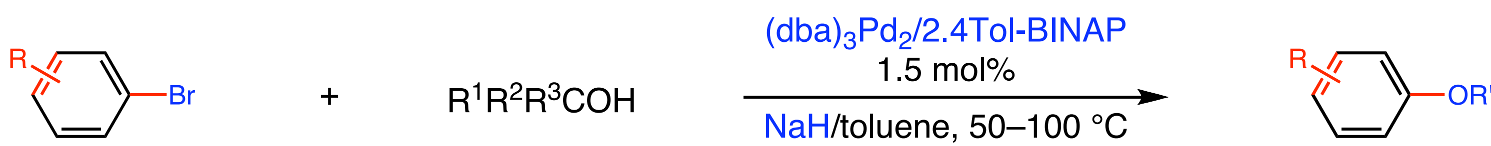
n = 1–3

X = Br, I
R = Me, alkyl

77–97% yield

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

■ Intermolecular C–O coupling were successful with alkoxides

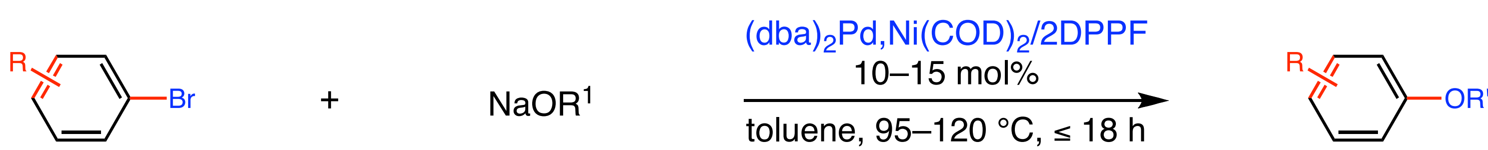


R = aryl, ^{t}Bu, CN, CF_3

R^1 = H, alkyl
R^2 = H, alkyl,
R^3 = H, alkyl, aryl

48–81% yield

Buchwald, S. L. *et al JACS* **1997**, *119*, 3395.



R = CHO, COR', ^{t}Bu, CN

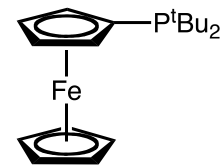
R^1 = ^{t}Bu, Me, TMDS

38–100% yield

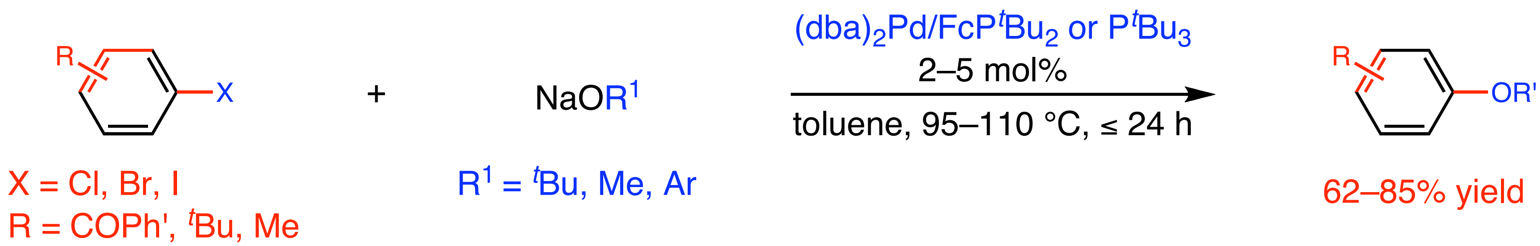
Mann, G. and Hartwig, J. F. *JACS* **1996**, *118*, 13109.
Mann, G. and Hartwig, J. F. *JACS* **1997**, *119*, 5413.

C–O Coupling with Pd Complexes

scope improvement with electron-rich bulky monodentate phosphine ligands



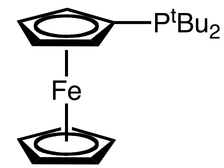
FcP^{t}Bu$_2$



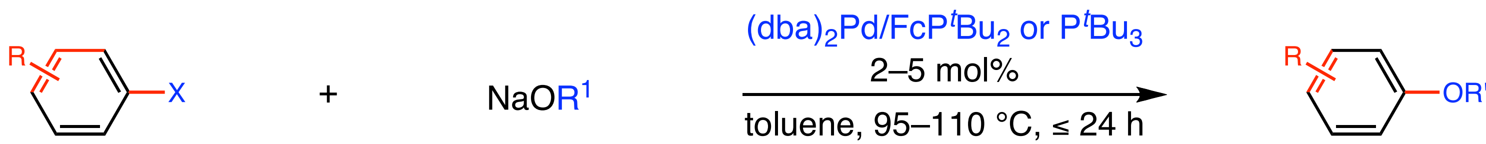
Hartwig, J. F. *et al JACS* **1999**, *121*, 3224.

C–O Coupling with Pd Complexes

scope improvement with electron-rich bulky monodentate phosphine ligands



FcP^{t}Bu$_2$



X = Cl, Br, I
R = COPh', ^{t}Bu, Me

R^1 = ^{t}Bu, Me, Ar

62–85% yield

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

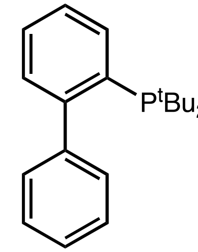
♦ Sterically hindered electron-rich alkylphosphine ligands accelerate reductive elimination step.

⟹ **Why don't they try Josiphos or biarylphosphine ligands???**

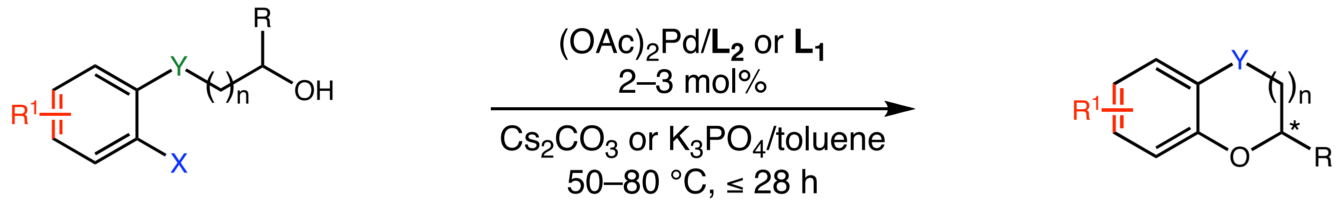
C–O Coupling with Pd Complexes

problem solving with biarylphosphine ligands

L₁



JohnPhos

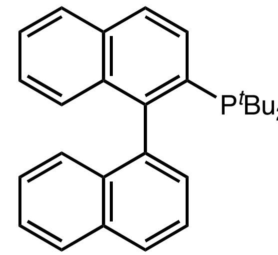


n = 0–2

65–95% yield
≥ 97% ee

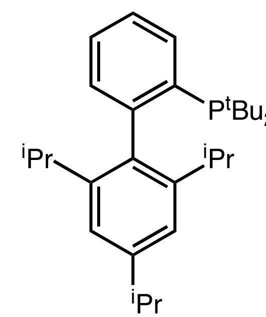
X = Br, I
Y = CH_2, O, NMe(H)
R = Me, alkyl, ester, carbamate
R^1 = Me, CN, CO_2Me

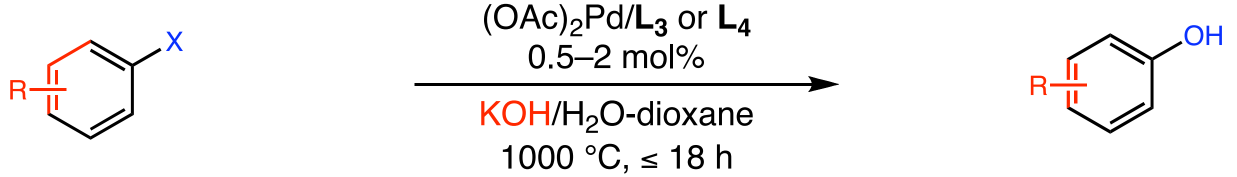
L₂



Buchwald, S. L. *et al JACS* **2000**, *122*, 12907.
Buchwald, S. L. *et al JACS* **2001**, *123*, 12202.

L₃

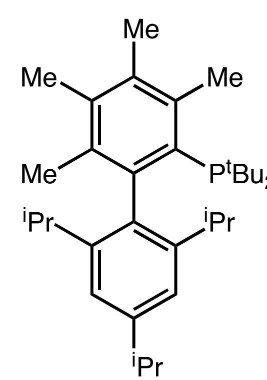




X = Cl, Br
R = alkyl, EWG, EDG

80–98% yield

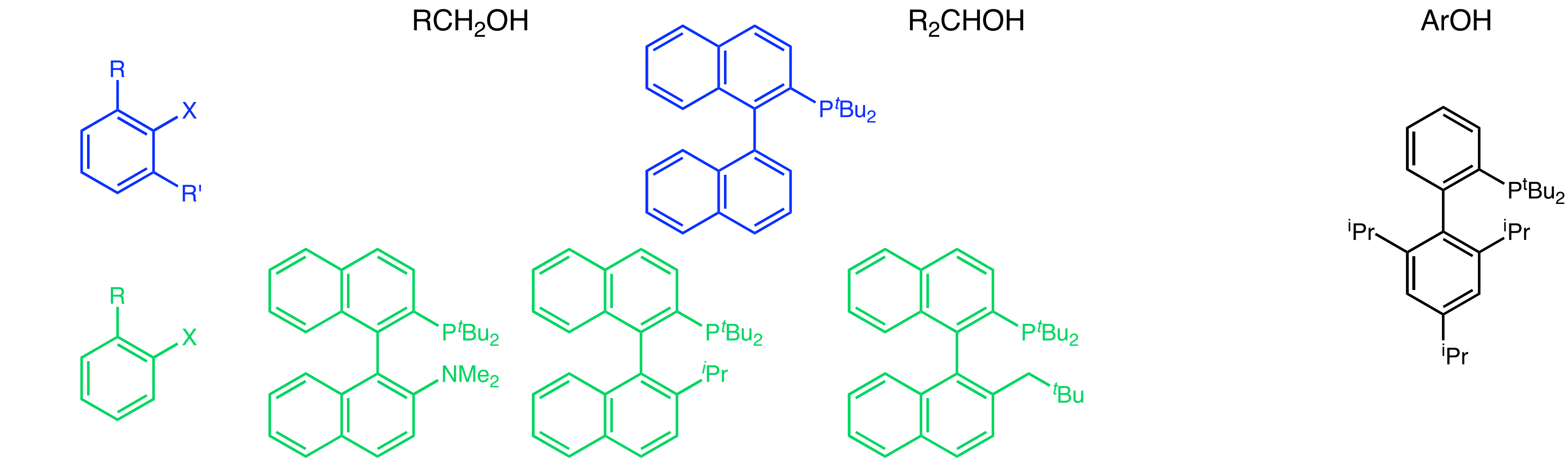
L₄

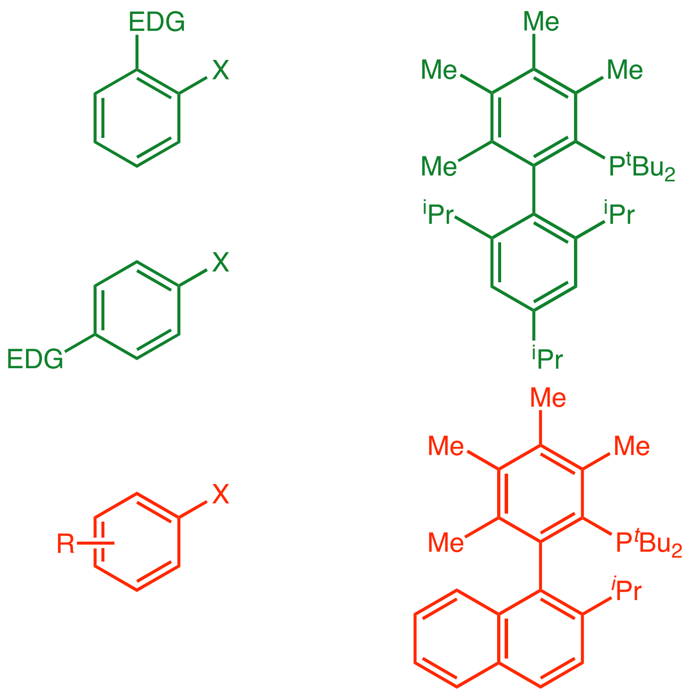


Buchwald, S. L. *et al JACS* **2008**, *128*, 10694.

C–O Coupling with Pd Complexes

biarylphosphine ligand summary





Buchwald, S. L. *et al JACS* **1999,** *121,* 4369.
Buchwald, S. L. *et al JACS* **2001,** *123,* 10770.
Buchwald, S. L. *et al JACS* **2005,** *127,* 8146.
Buchwald, S. L. *et al ACIE* **2006,** *45,* 4321.