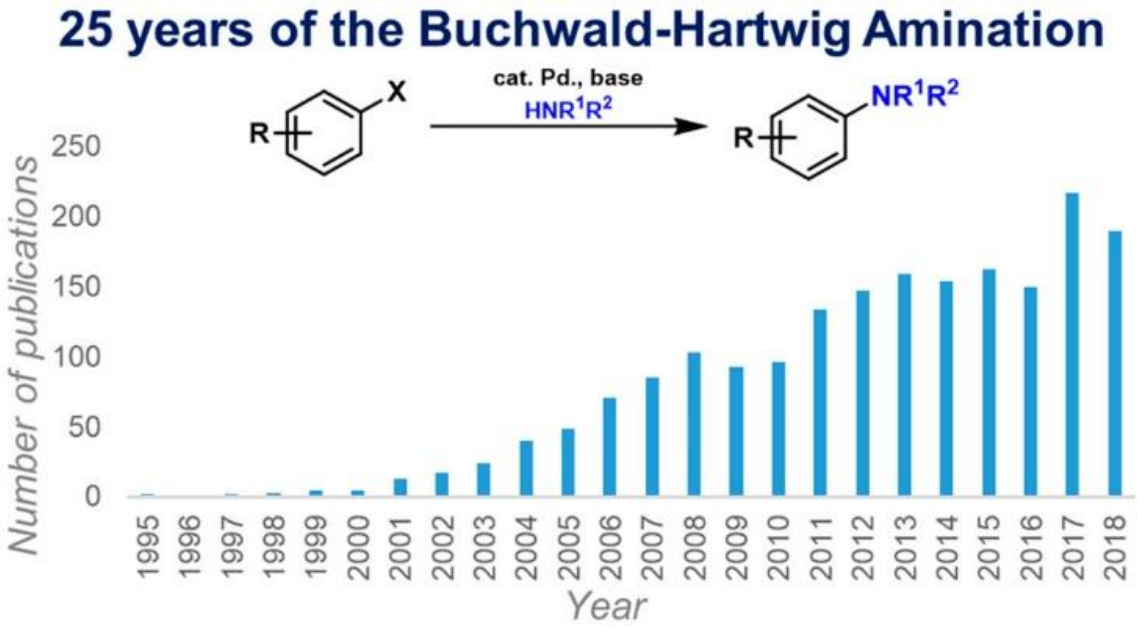
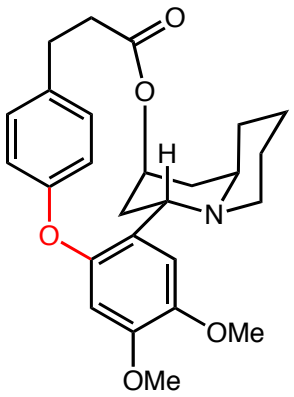
Pd-Catalyzed C-N Cross-Coupling Reactions:

the Buchwald-Hartwig coupling

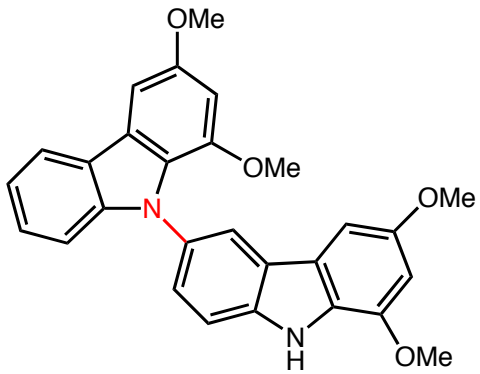


Slides from Prof. Phong V. Pham

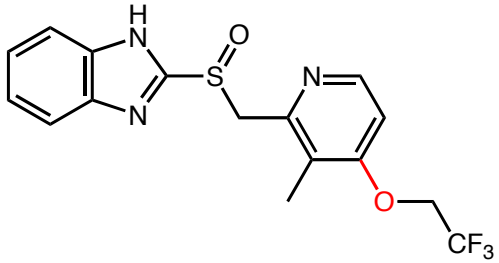
Why C–N and C–O Couplings?



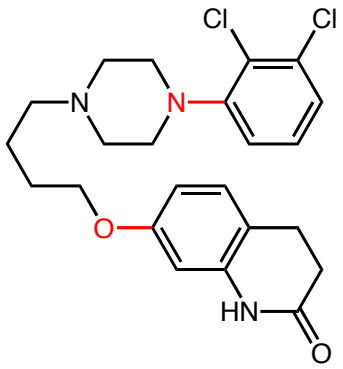
vertaline



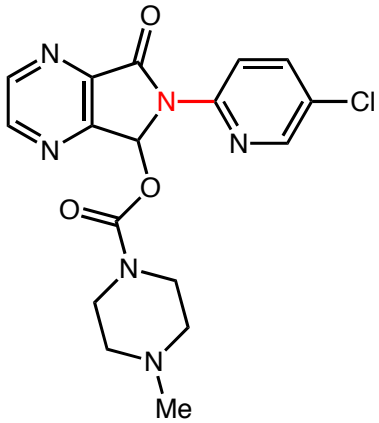
murrastifoline A



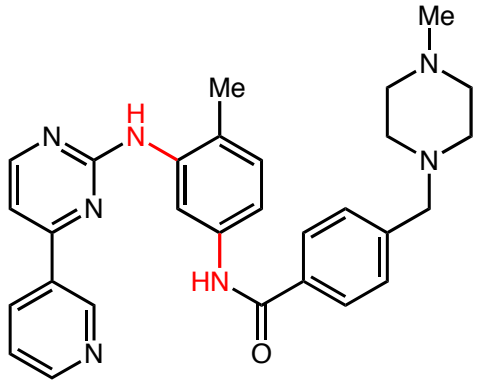
Prevacid
Used to treat gastric reflux disease



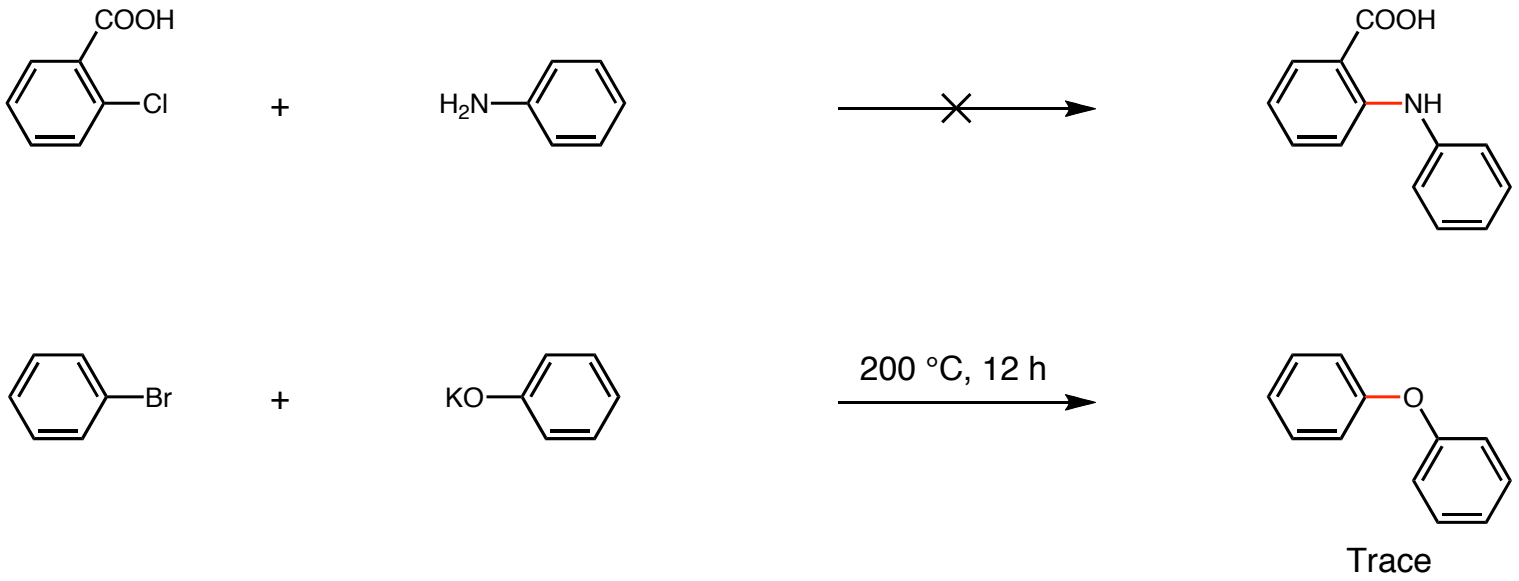
Abilify
Used to treat schizophrenia and bipolar mania

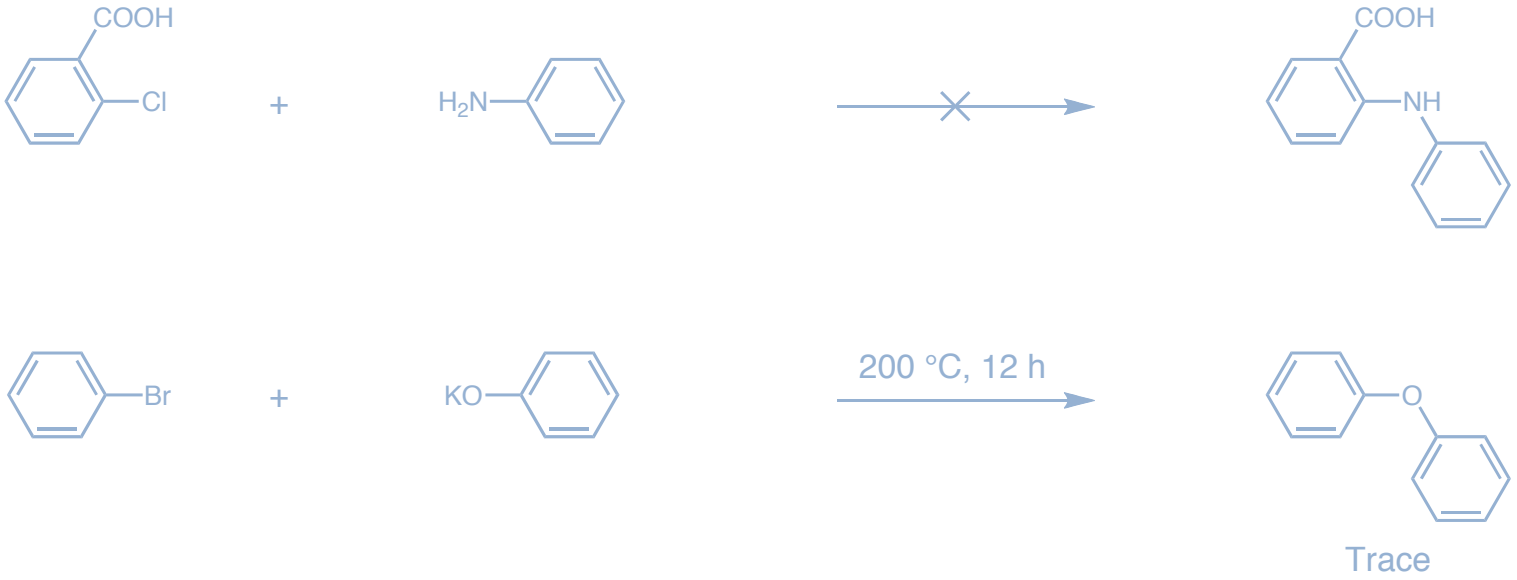


Lunesta
Used to treat insominia

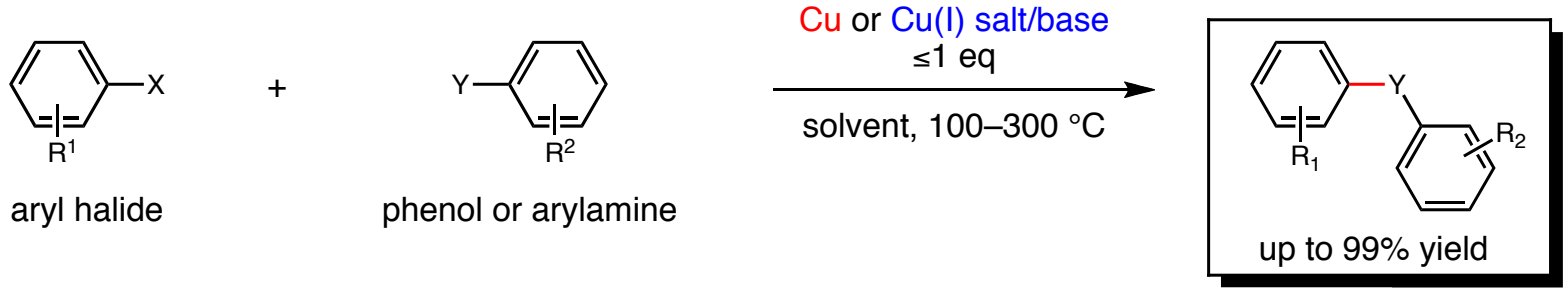


Gleevec
Used to treat chronic myeloid leukemia


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



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



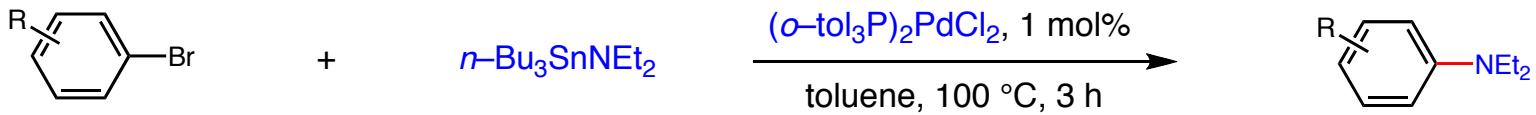
aryl halide

phenol or arylamine

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

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

■ Migita introduced the first catalytic version in 1983.

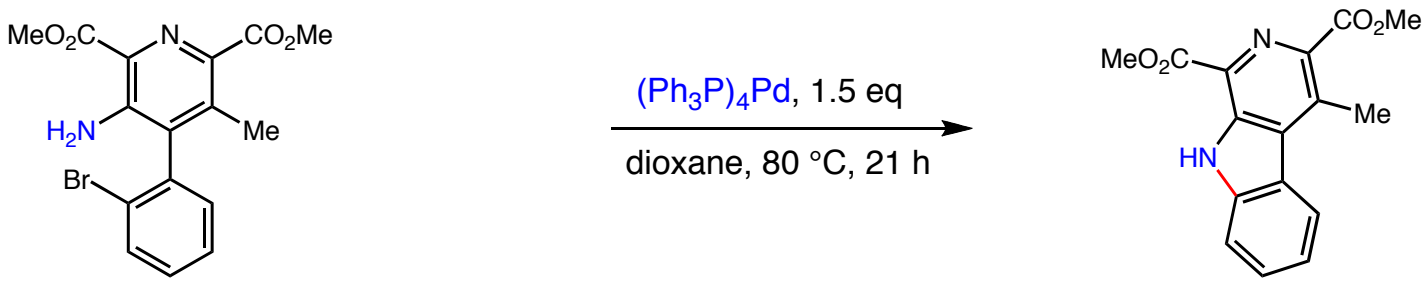


up to 81% yield

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

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

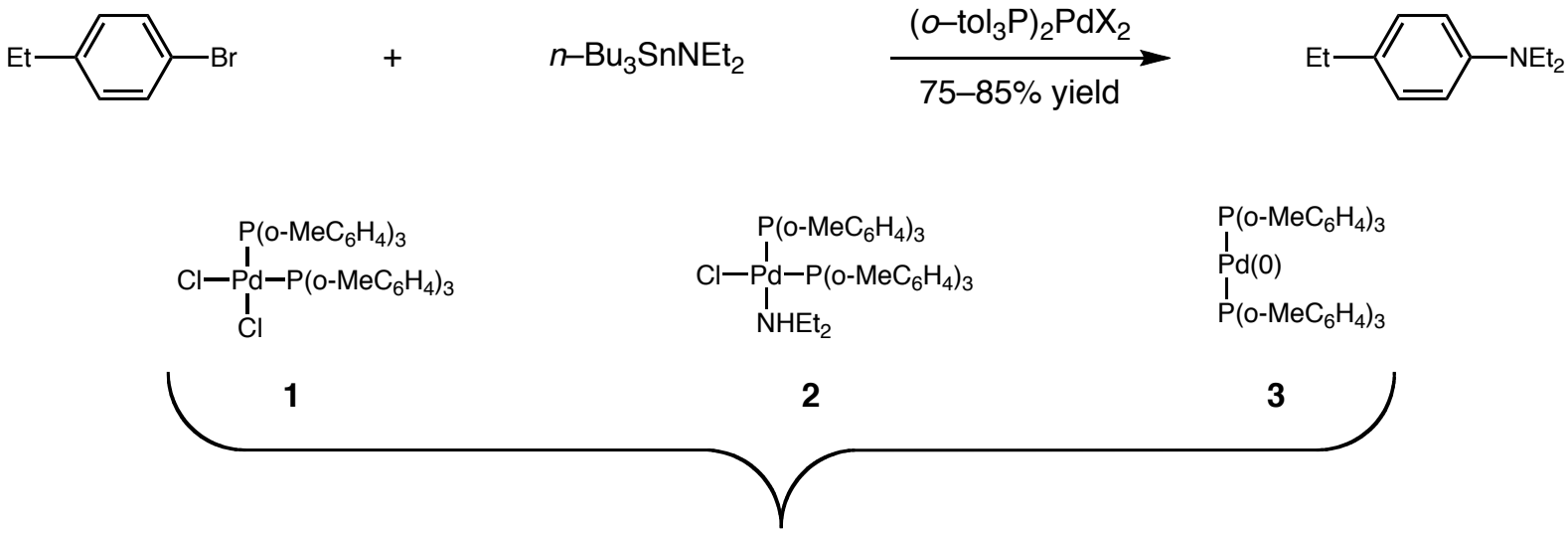
■ Boger introduced Pd(0) mediated intramolecular amination with free amine in 1984.



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.

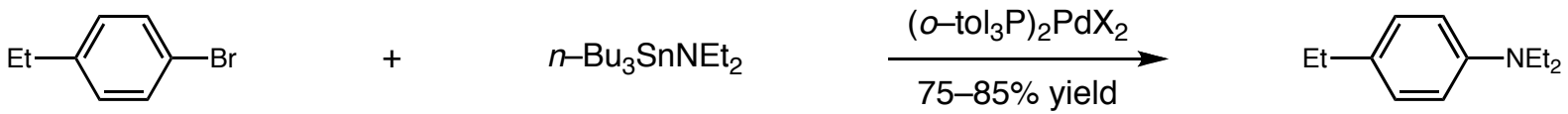


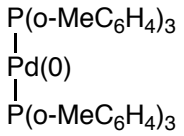
♦ **1**, **2**, and **3** showed catalytic reactivity and the reaction was faster with **3**

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

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

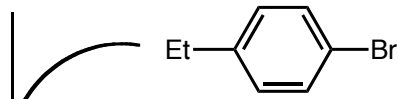
■ Feb. 22, 1994 the Hartwig group submitted a mechanistic study of Migita's reaction.

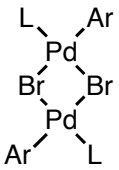




3

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





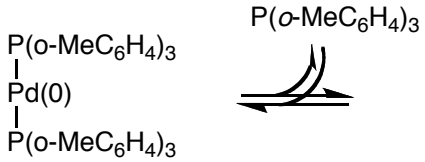
L = P(*o*-MeC$_6$H$_4$)$_3$

4

80–90% yield

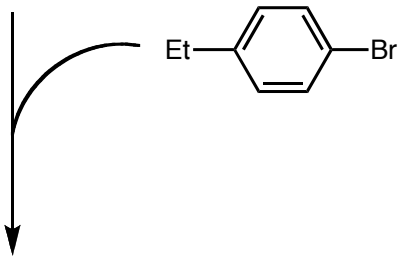
Hartwig, J. F. *et al JACS* **1994**, *116*, 5969.

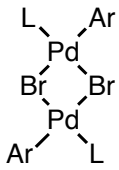
■ Feb. 22, 1994 the Hartwig group submitted a mechanistic study of Migita's reaction.



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).





L = P(o-$MeC_6H_4)_3$

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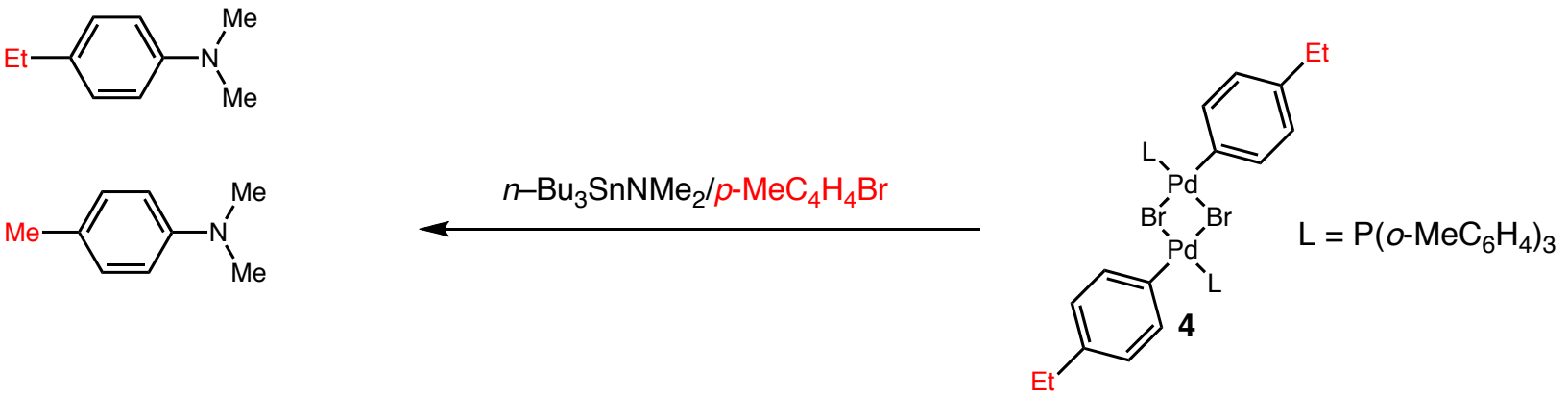

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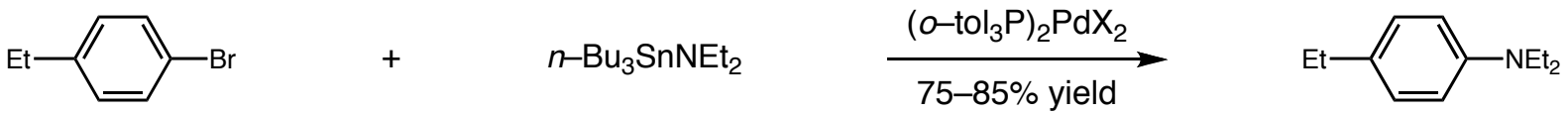
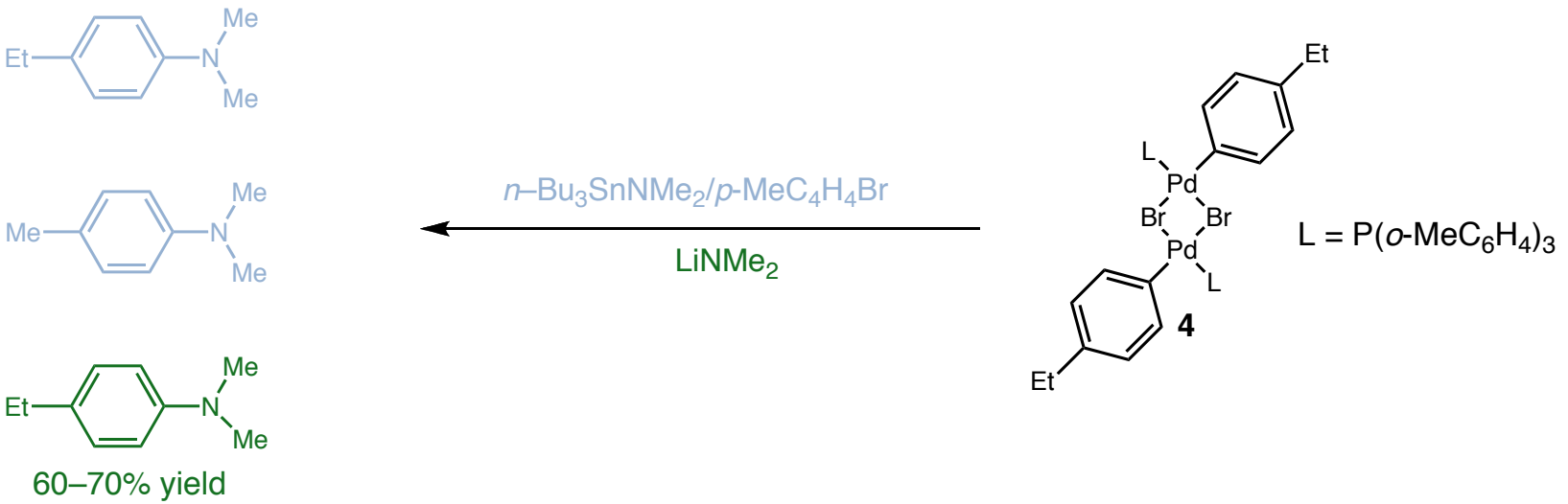


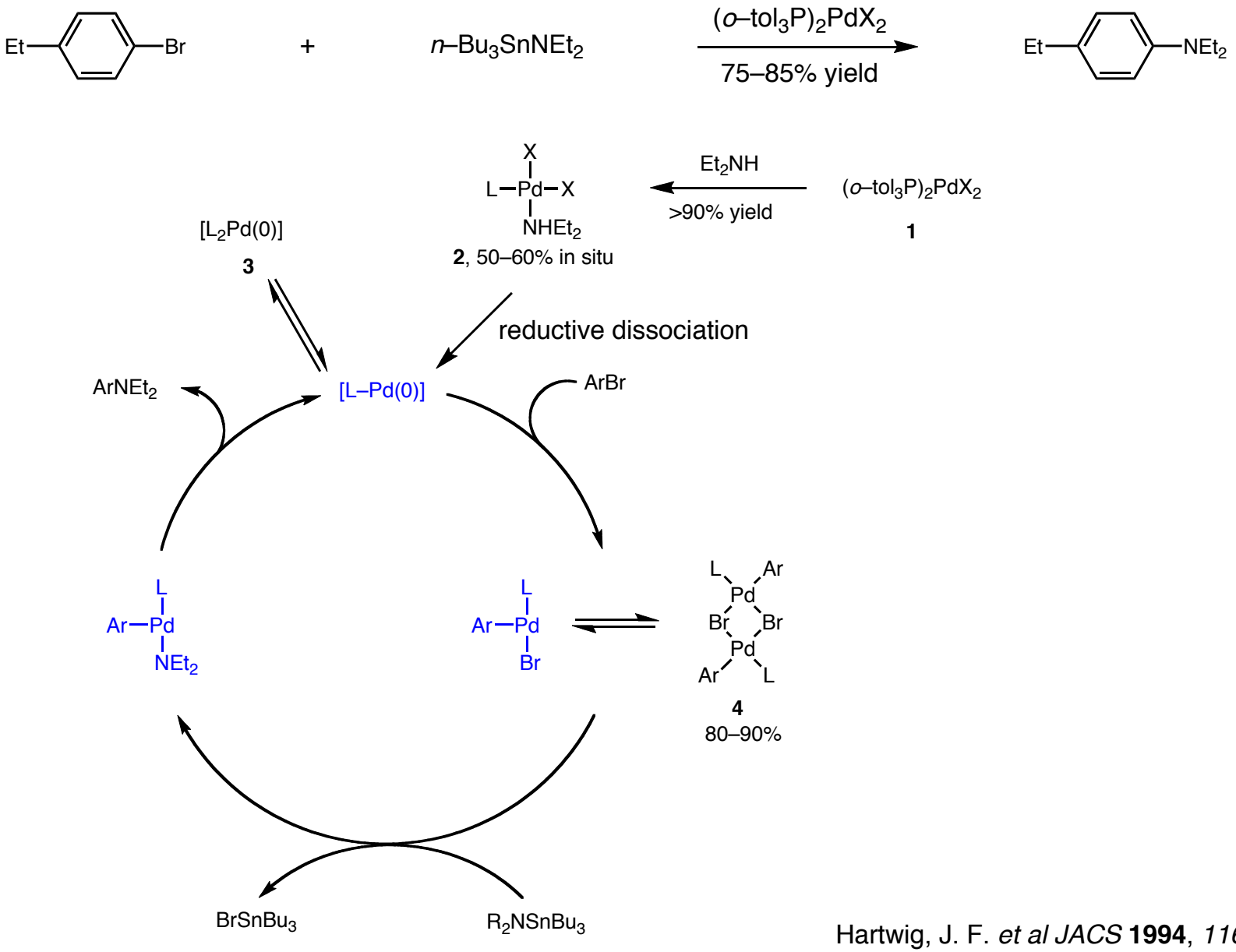


=> **4** or the corresponding monomer is directly involve in the catalytic cycle.

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

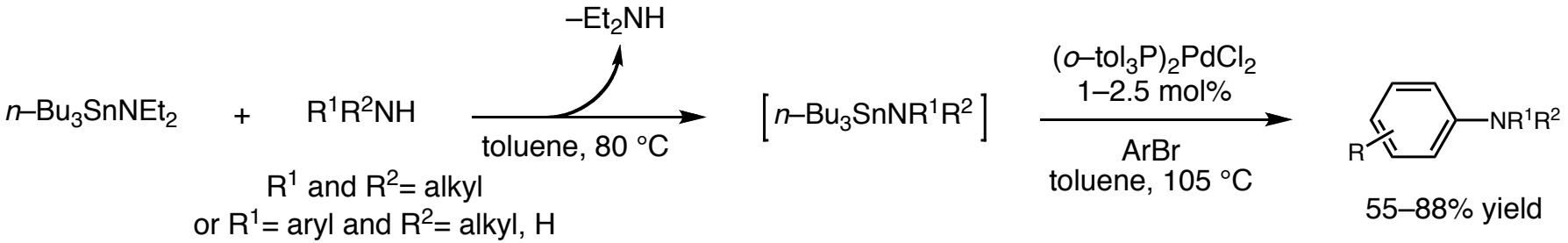
Hartwig, J. F. *et al JACS* **1994**, *116*, 5969.

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

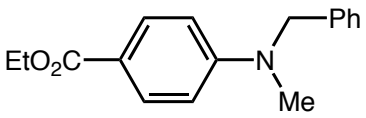


Hartwig, J. F. *et al JACS* **1994**, *116*, 5969.

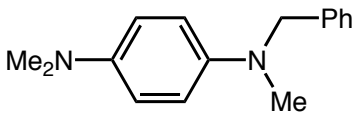
■ May 23, 1994 the Buchwald group submitted a amine scope expansion report of Migita's reaction via in situ generated aminostannanes.



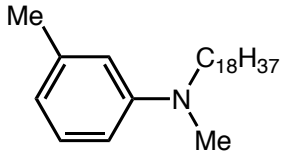
Guram, A. S. and Buchwald, S. L. *JACS* **1994**, *116*, 7901.



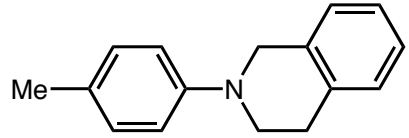
88% yield



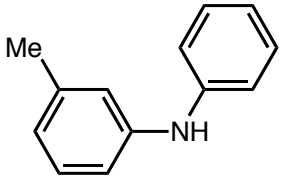
81% yield



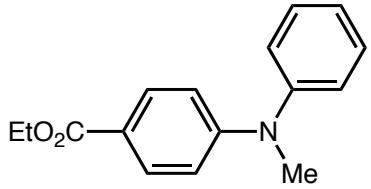
79% yield



55% yield

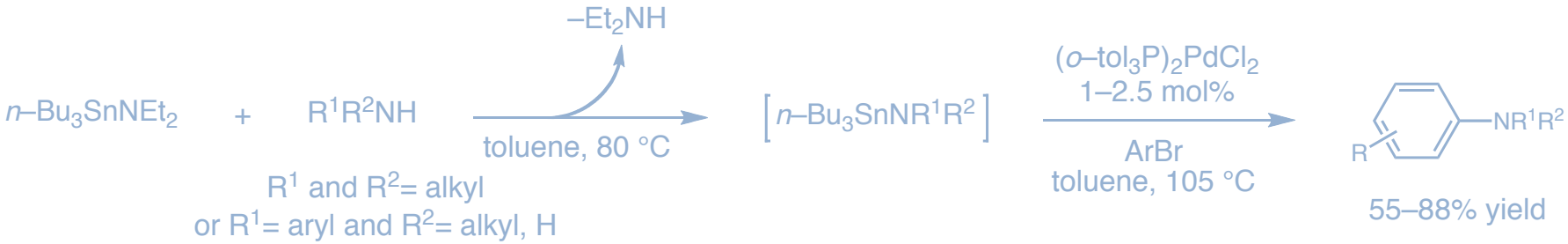


66% yield



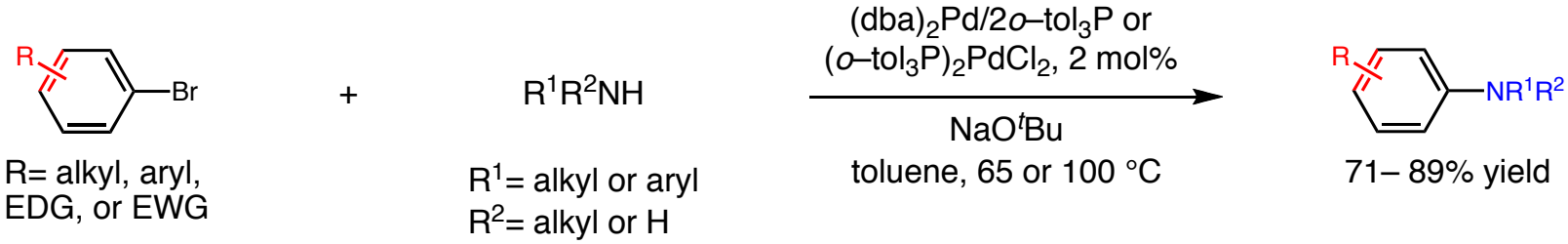
83% yield

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

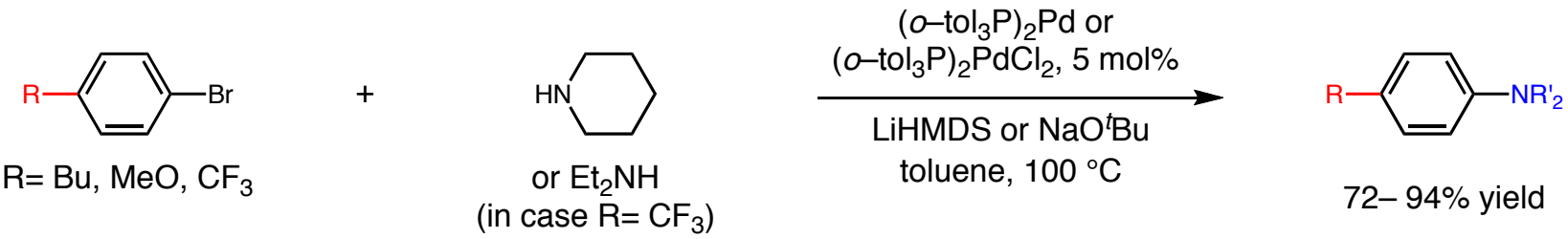


Guram, A. S. and Buchwald, S. L. *JACS* **1994**, *116*, 7901.

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

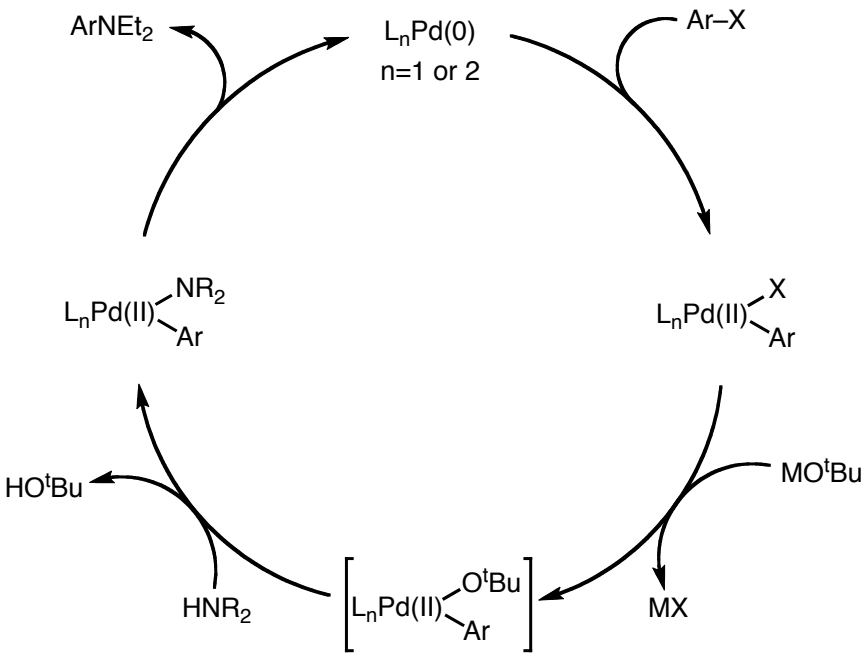


(Submitted on Jan 17, 1995; revised March 13 1995) Buchwald, S. L. *et al ACIE* **1995**, *34*, 1348.

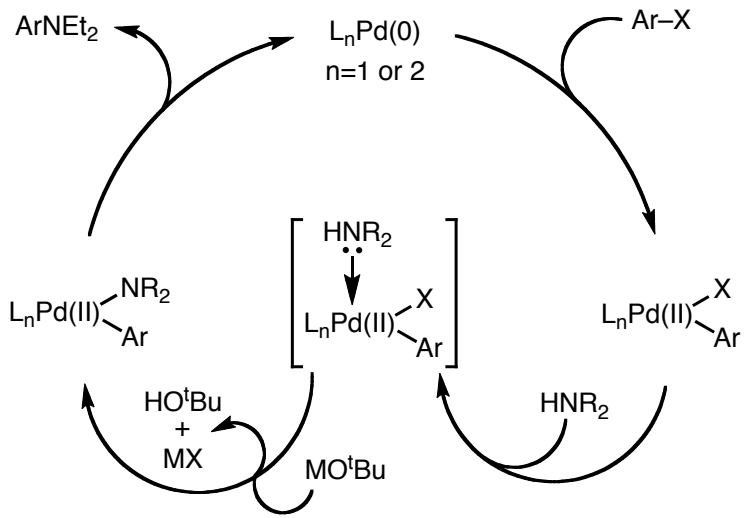


(*Submitted on March 6, 1995)* Louie, J., Hartwig, J. F. *Tet. Lett.* **1995**, *36*, 3069.
(from mechanistic study)

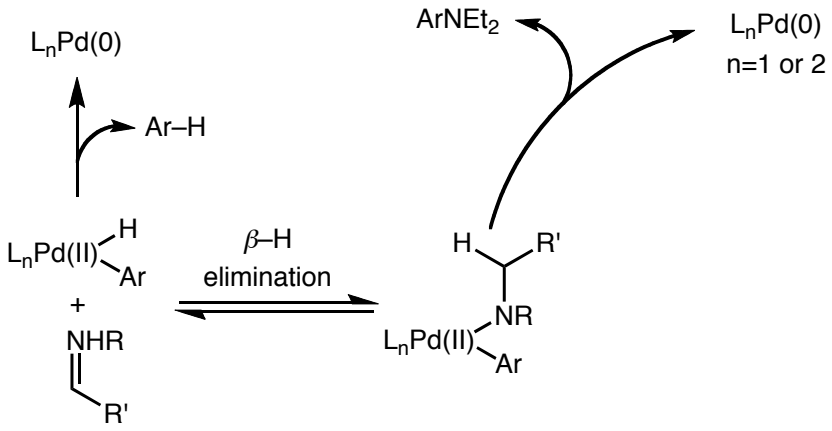
The Mechanistic Scheme that You Normally See



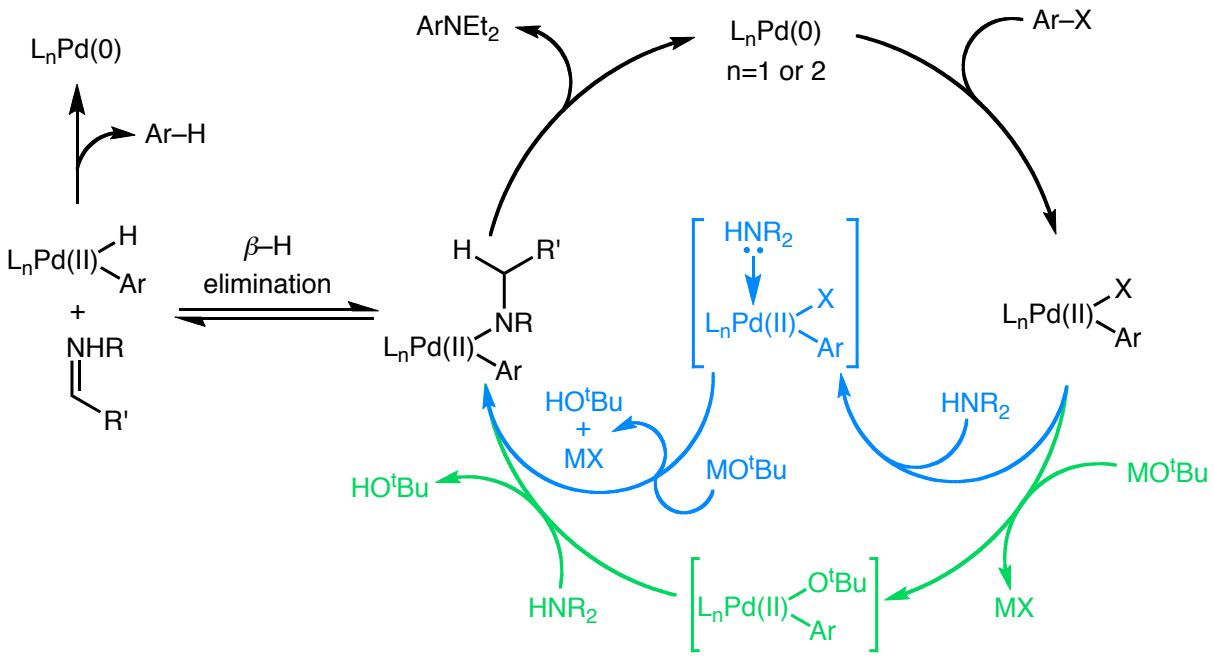
The Mechanistic Scheme that You Normally See



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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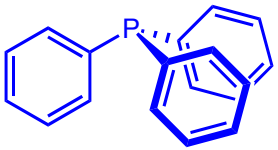

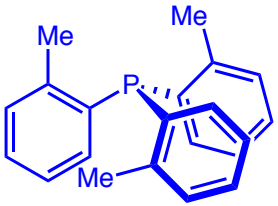

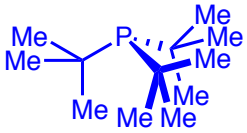

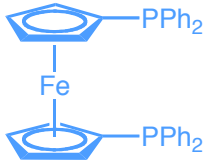

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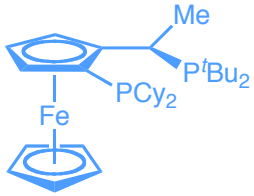
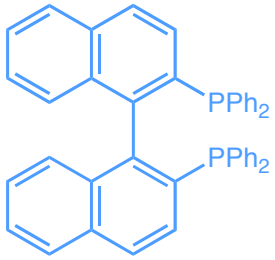
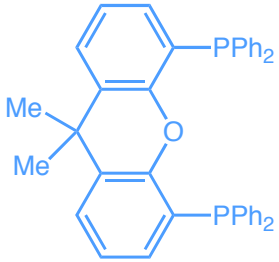


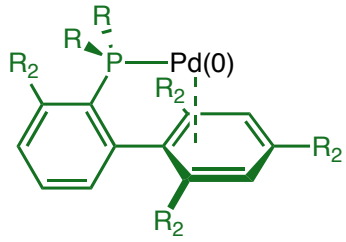
Josiphos



BINAP

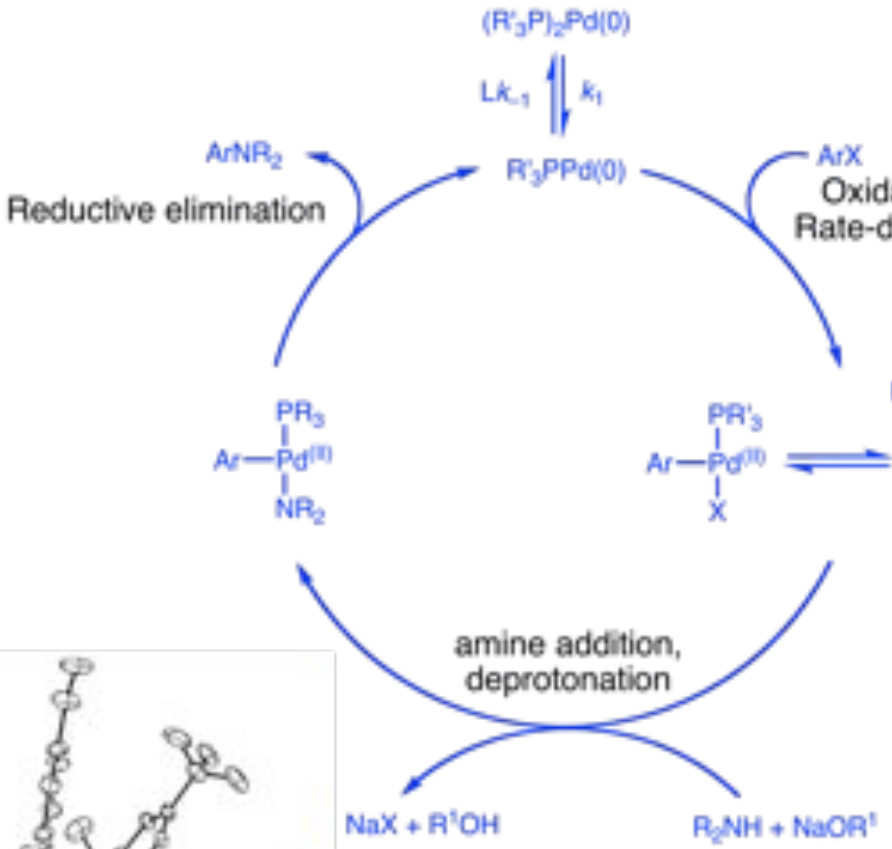


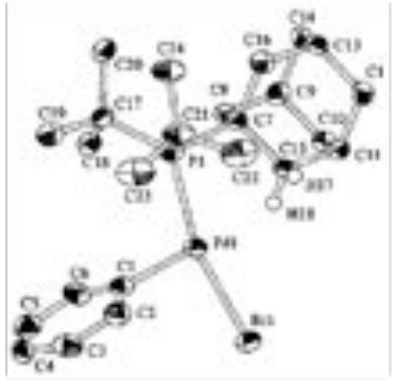
Xantphos



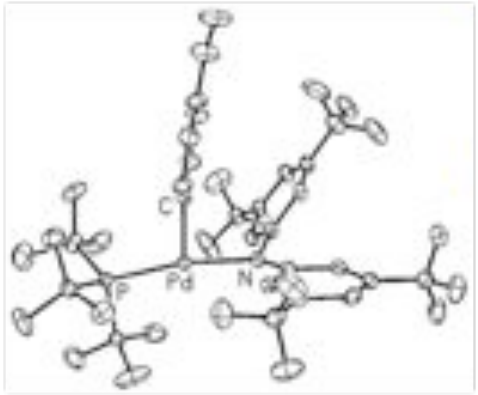
Biarylphosphine

Mechanistic Study with Monodentate Hindred Phosphine Ligands

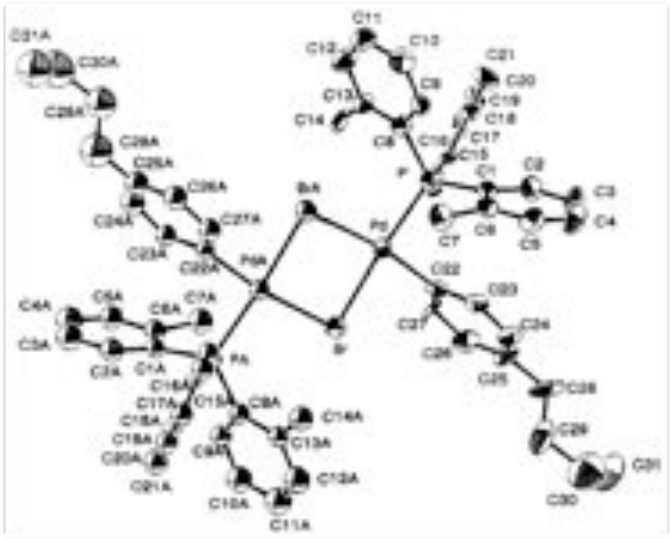




X-ray structre of
$[(1\text{–AdP}^t\text{Bu}_2)\text{Pd}(C_6H_5)(\text{Br})$
Hartwig, J. F. *et al JACS* **2002**, *124*, 9346.



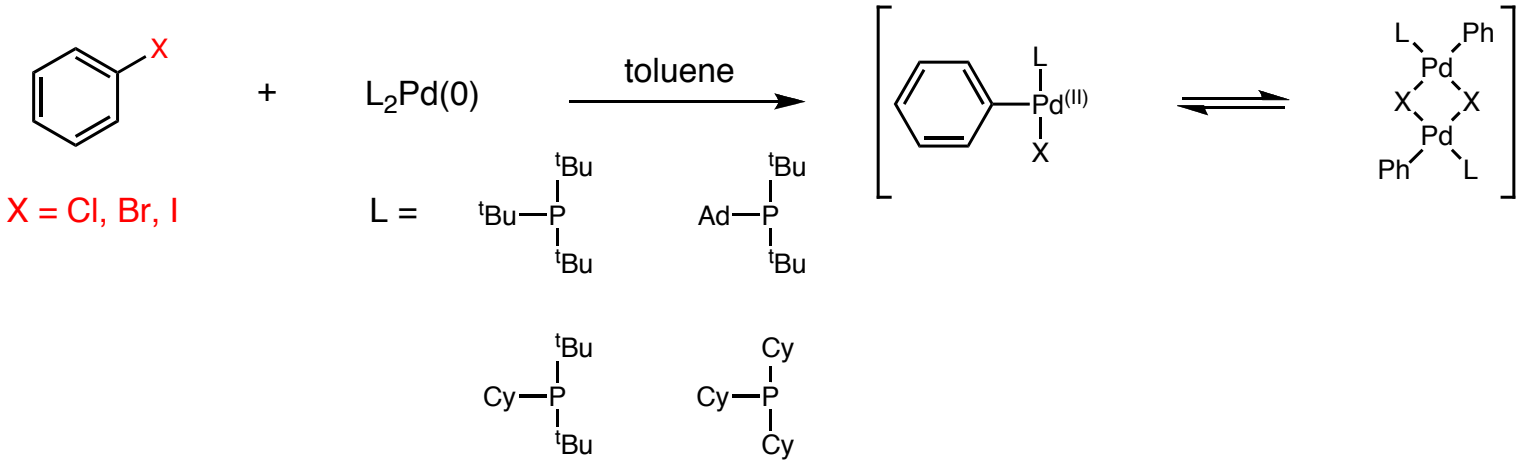
ORTEP diagram of
$(^t\text{Bu}_3\text{P})\text{Pd}(\text{MeOC}_6\text{H}_4)\text{N}(3,5\text{-}(\text{CF}_3)_2C_6H_3)_2$
Hartwig, J. F. *et al JACS* **2004**, *126*, 5344.
Buchwald, S. L. *et al Organometallics* **1996**, *15*, 2745(solution struct.)



ORTEP diagram of
$[(o\text{-tol}_3\text{P})\text{Pd}(4\text{-}n\text{BuC}_6\text{H}_4)(\text{Br})]_2$
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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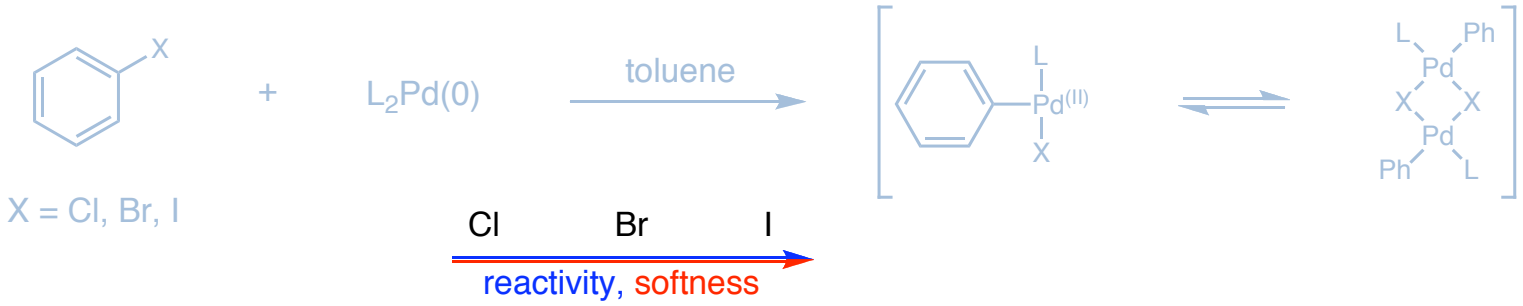

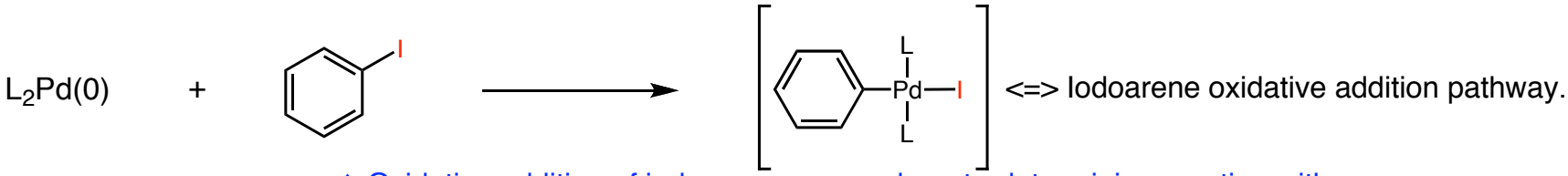

♦ Oxidative addition of iodoarenes occurs by rate-determining reaction with a bisphosphine complex.

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

Oxidative Addition with Monodentate Hindered Phosphine Ligands

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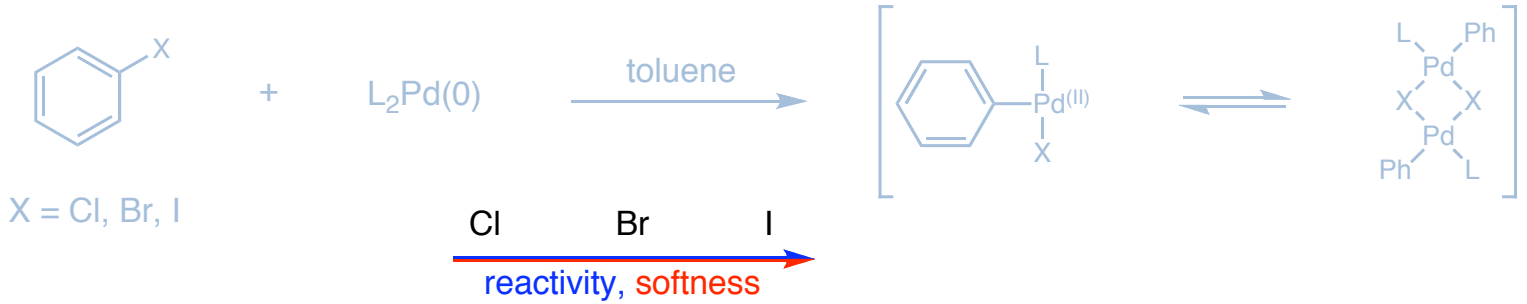
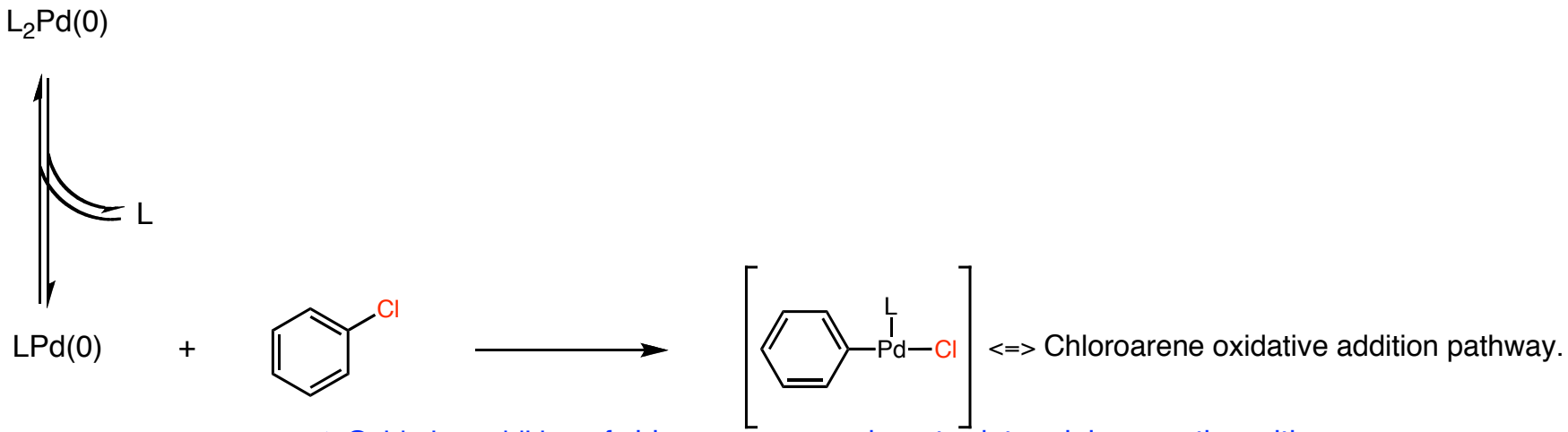


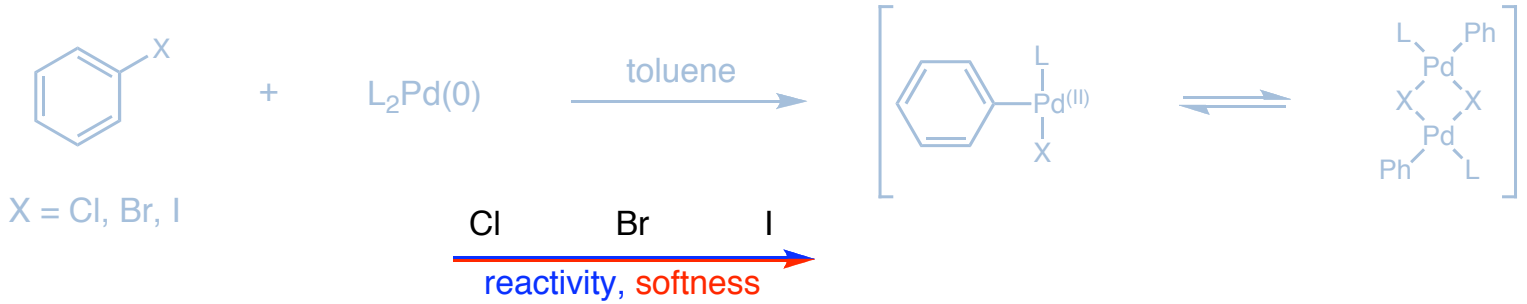


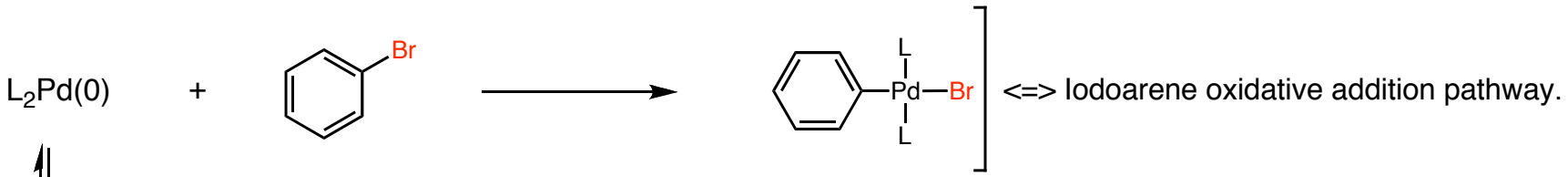
♦ Oxidative addition of chloroarens occur by rate-determining reaction with a monophosphine complex.

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

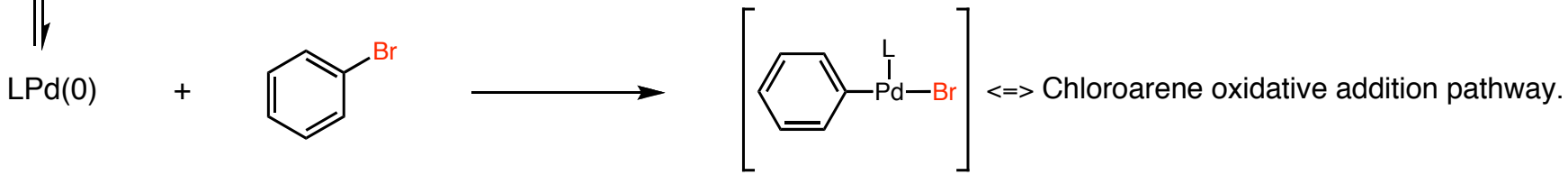
Oxidative Addition with Monodentate Hindered Phosphine Ligands

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



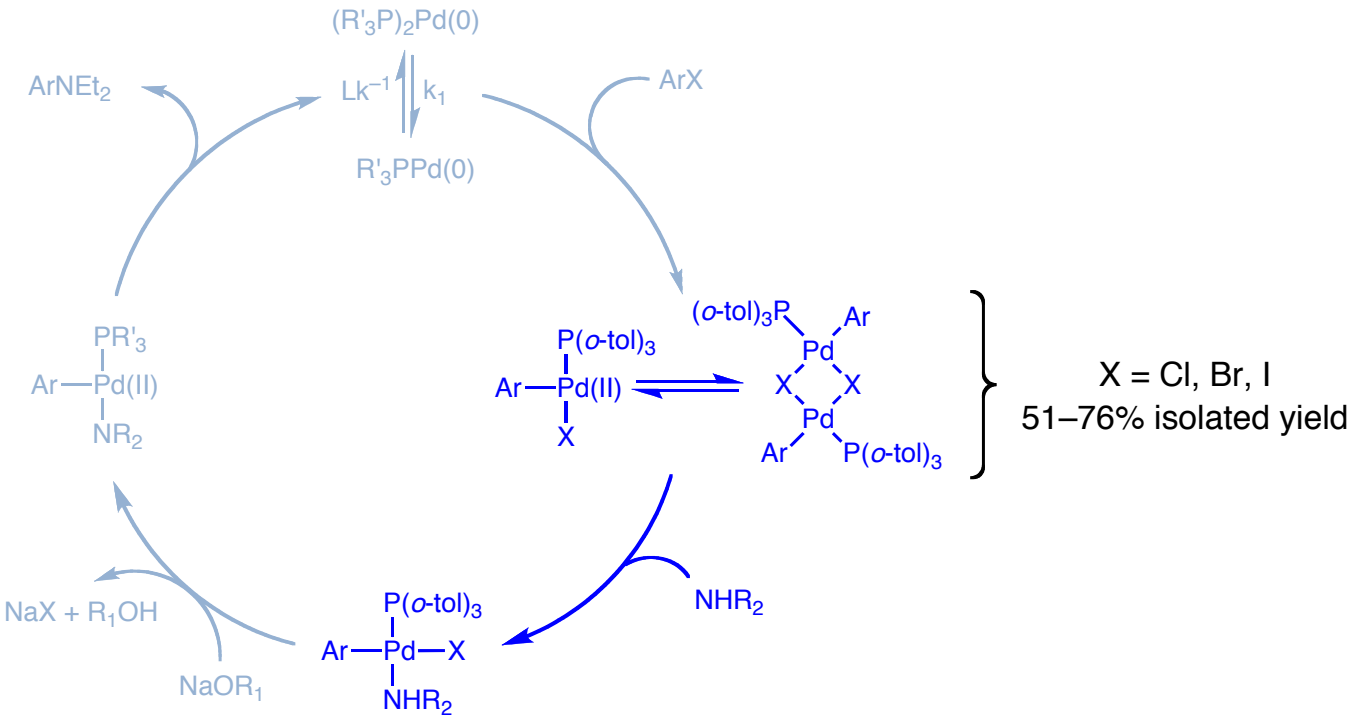


♦ Oxidative addition of bromoarens occur by combination of two pathways.



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

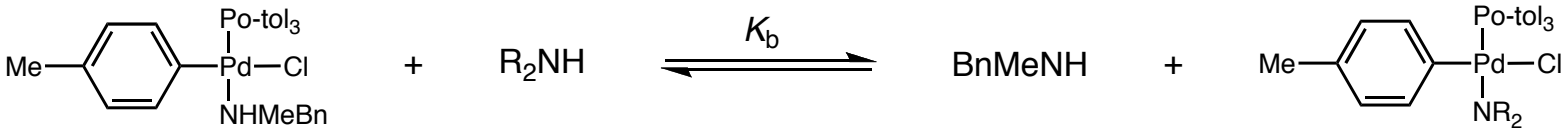
Formation of Palladium Monoamine Complexes

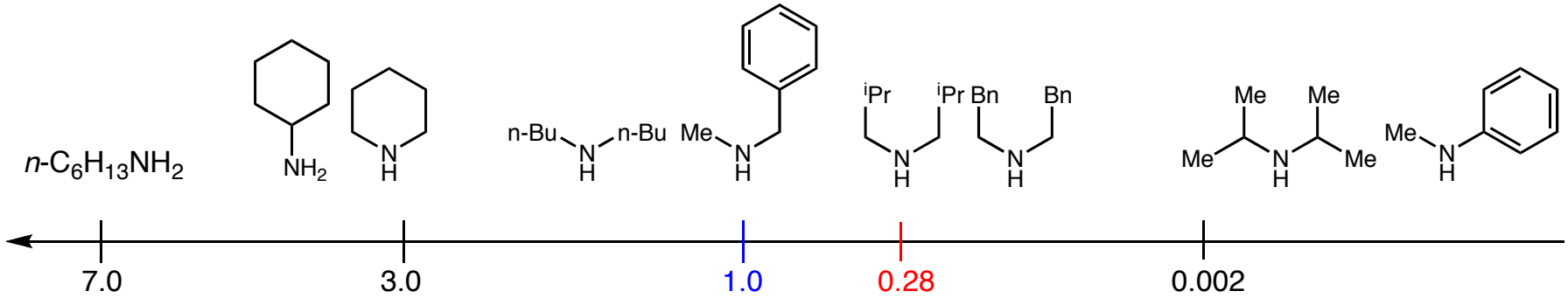


Buchwald, S. L. *et al Organometallics* **1996**, *15*, 2745.
Widenhoefer, R. A. and Buchwald, S. L. *Organometallics* **1996**, *15*, 2755.

Thermodynamic Study on the Formation of Palladium Monoamine Complexes

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

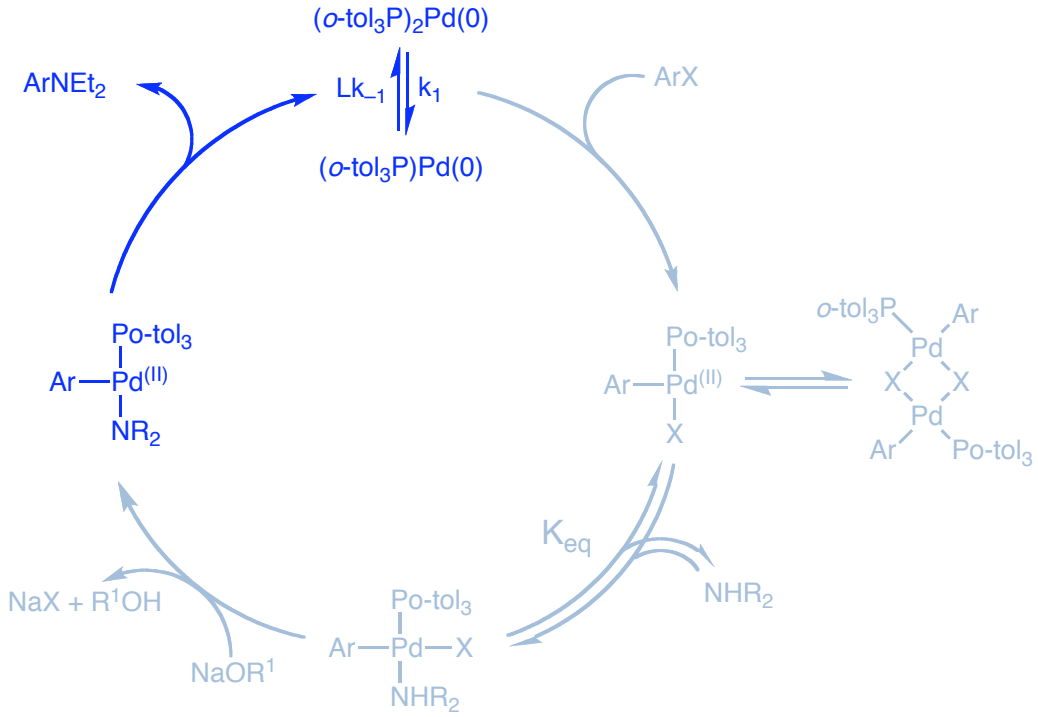




K_b : binding affinity of amine to the palladium aryl halide complex.

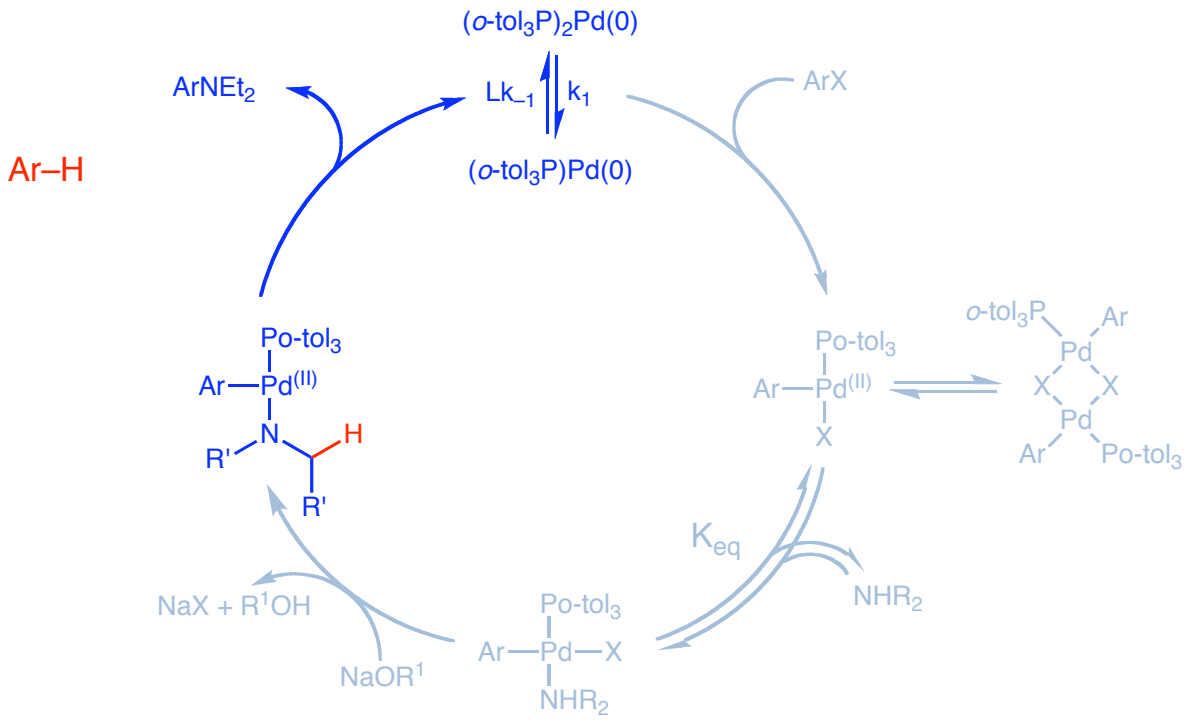
Buchwald, S. L. *et al Organometallics* **1996**, *15*, 2745.
Widenhoefer, R. A. and Buchwald, S. L. *Organometallics* **1996**, *15*, 2755.

Reductive Elimination with Monodentate Hindered Phosphine Ligands



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

Reductive Elimination with Monodentate Hindered Phosphine Ligands



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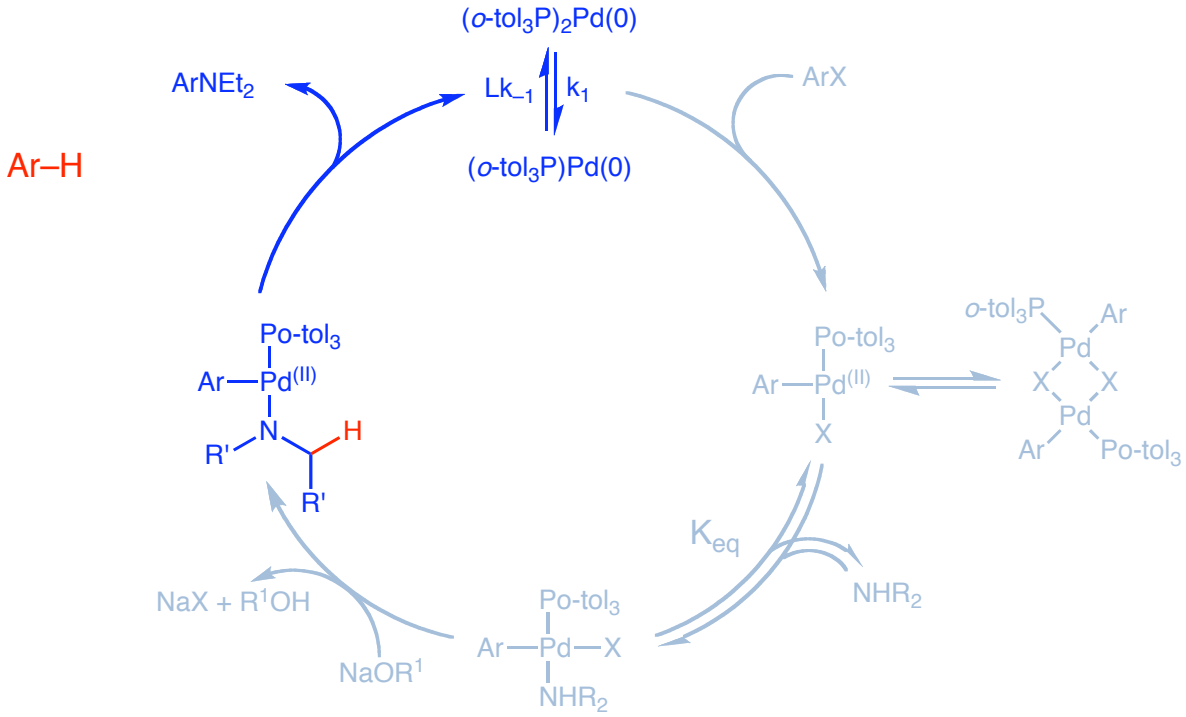
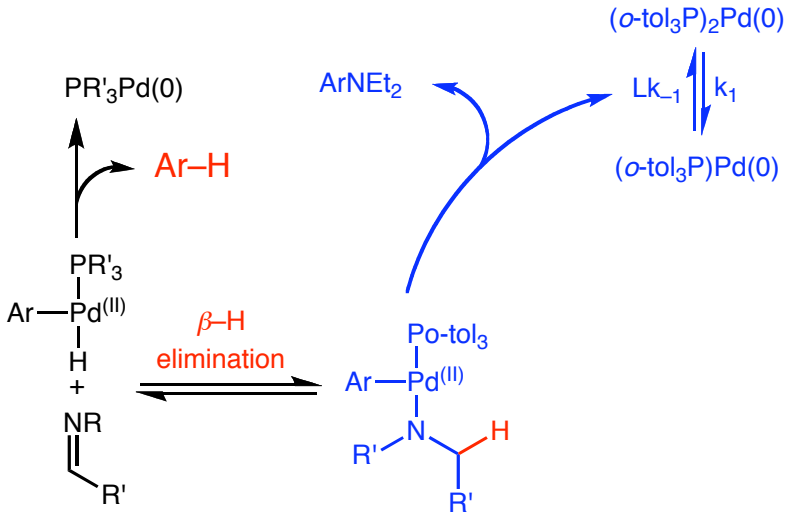


♦ Where does the reductive arene (Ar–H) product come from?

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

Reductive Elimination with Monodentate Hindered Phosphine Ligands



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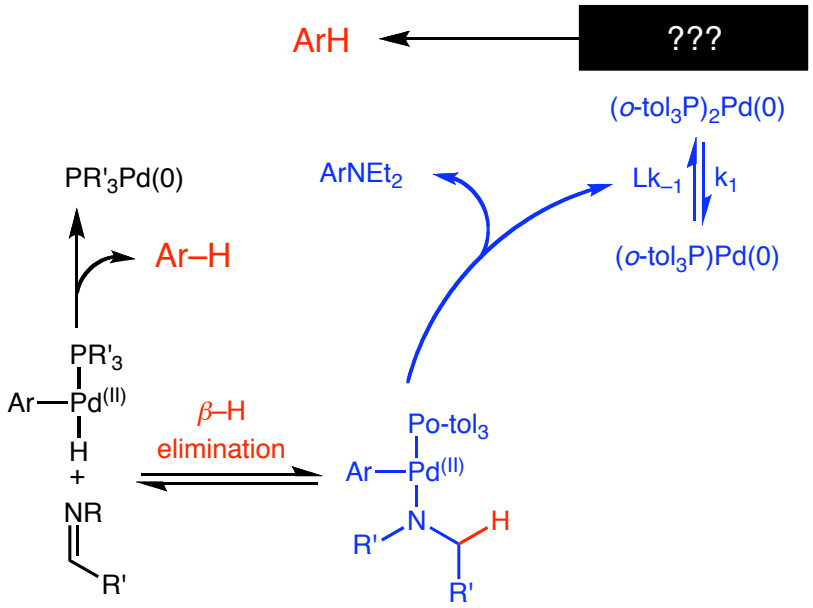

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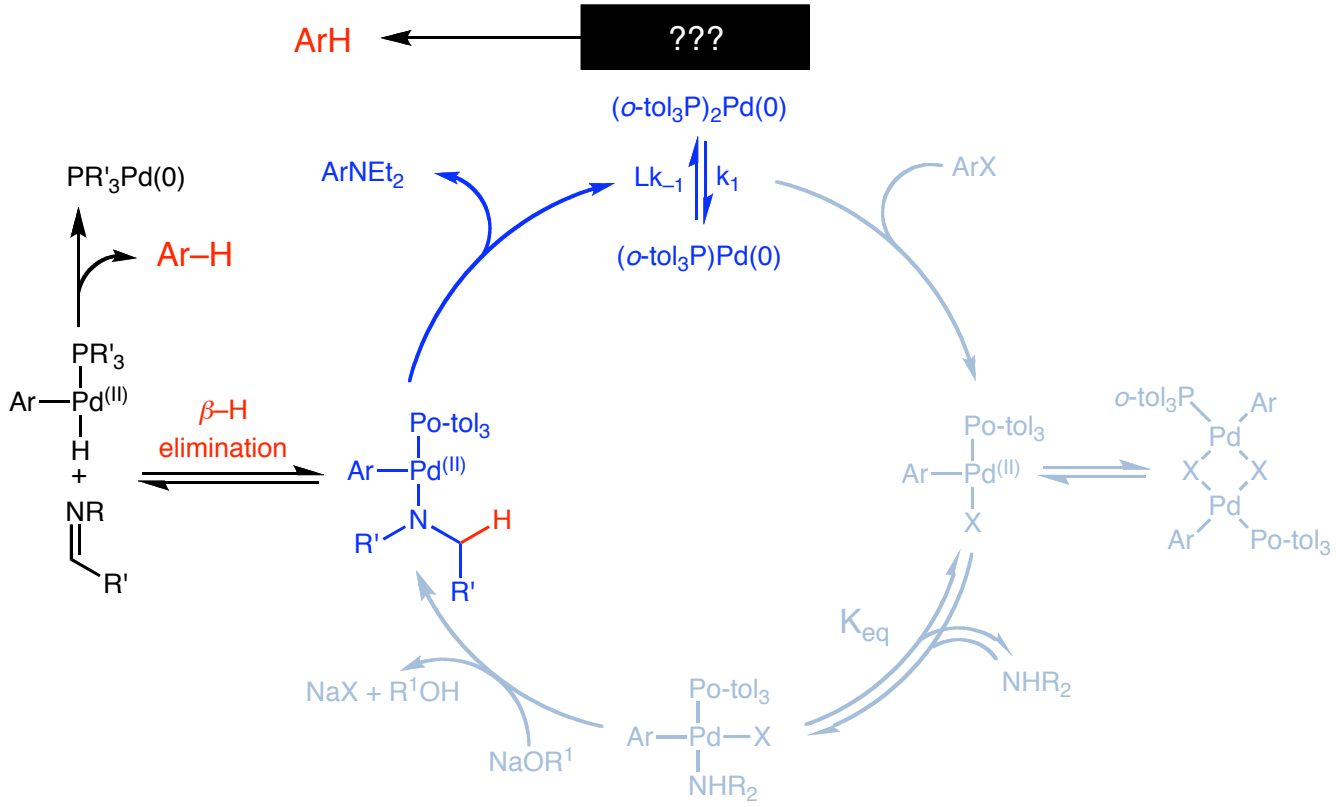


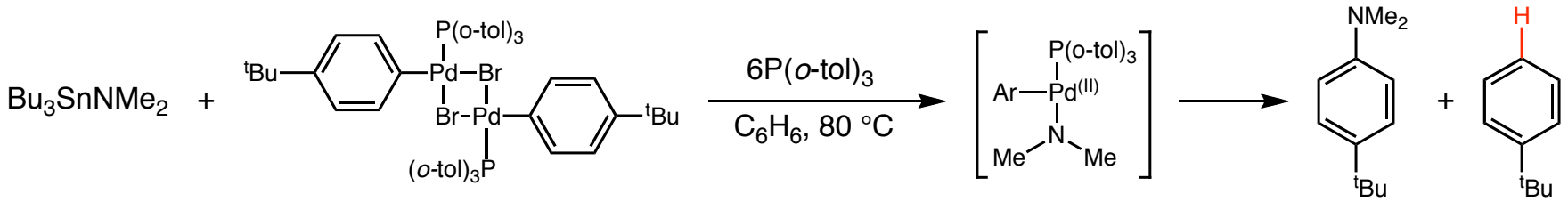
♦ Where does the reductive arene (Ar–H) product come from?

♦ 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

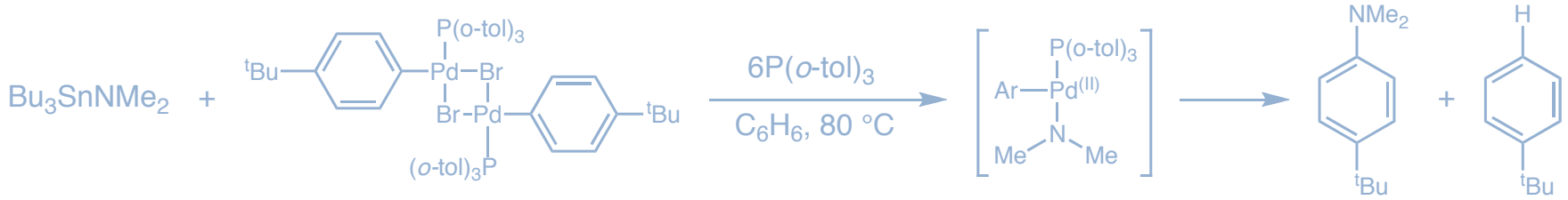
> 85% yield

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



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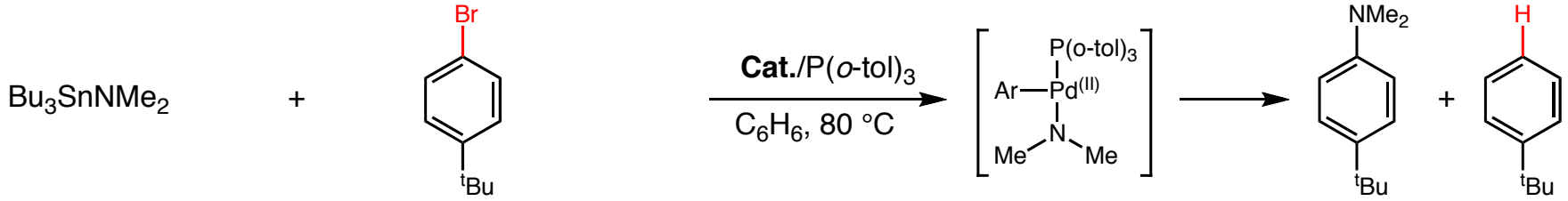
> 85% yield

4.0 eq 1.0 eq ~ 100 mol% 11 : 1



Cat. = **1** ; 5 mol% 10 : 1

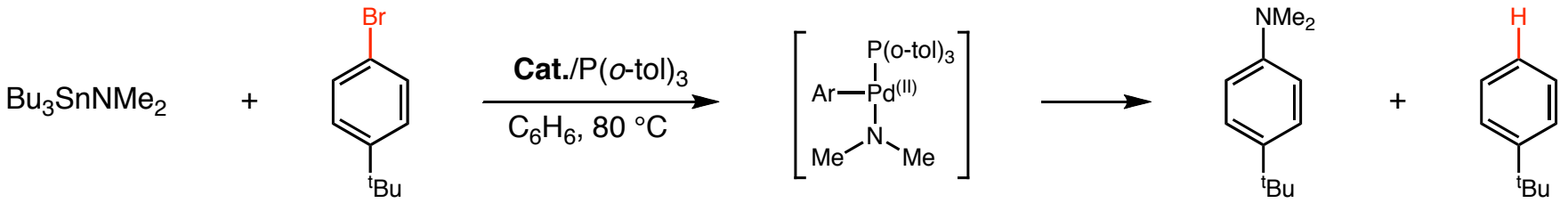
$(o\text{-tol}_3P)_2Pd(0)$; 5 mol% 9 : 1

=> The catalytic cycle produces ~ 10 : 1 coupling amine : arene, regardless the amount of intermediate **1** or catalyst $[L_2Pd(0)]$.

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

Reductive Elimination with Monodentate Hindered Phosphine Ligands

■ Formation of arene from outside of catalytic cycle

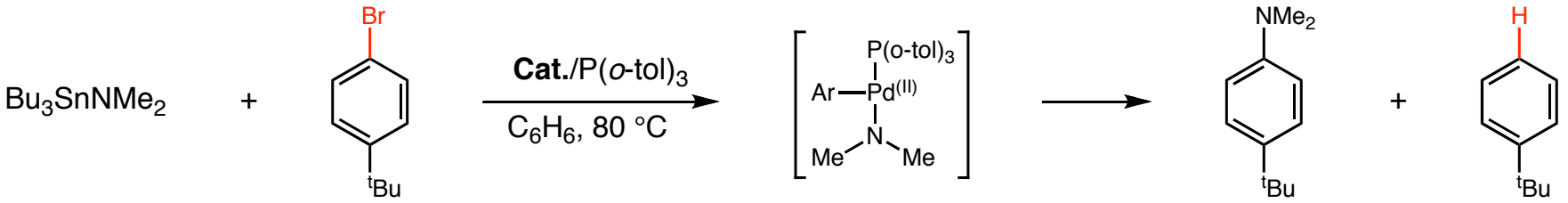


Cat. =	**1**	;	5 mol%	10	:	1
	(o-tol$_3$P)$_2$Pd(0);		5 mol%	9	:	1
	(o-tol$_3$P)$_2$PdCl$_2$;		5 mol%	6	:	1

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

Reductive Elimination with Monodentate Hindered Phosphine Ligands

■ Formation of arene from outside of catalytic cycle



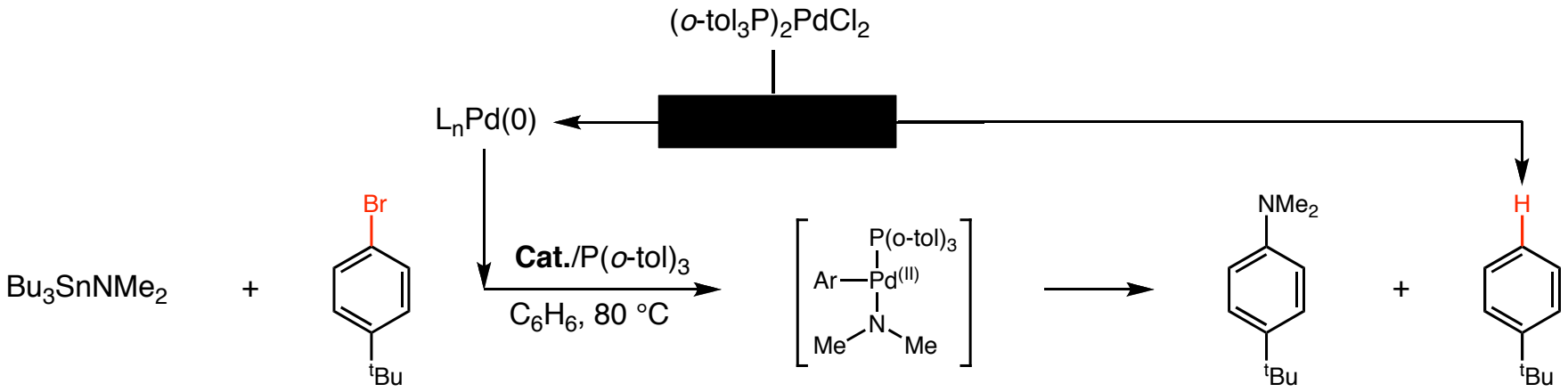
Cat. =	**1**	; 5 mol%	10	:	1
	(o-tol$_3$P)$_2$Pd(0)	; 5 mol%	9	:	1
	(o-tol$_3$P)$_2$PdCl$_2$	; 0.5 mol%	9	:	1
	(o-tol$_3$P)$_2$PdCl$_2$	; 5 mol%	6	:	1
	(o-tol$_3$P)$_2$PdCl$_2$	; 25 mol%	4	:	1

=> 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



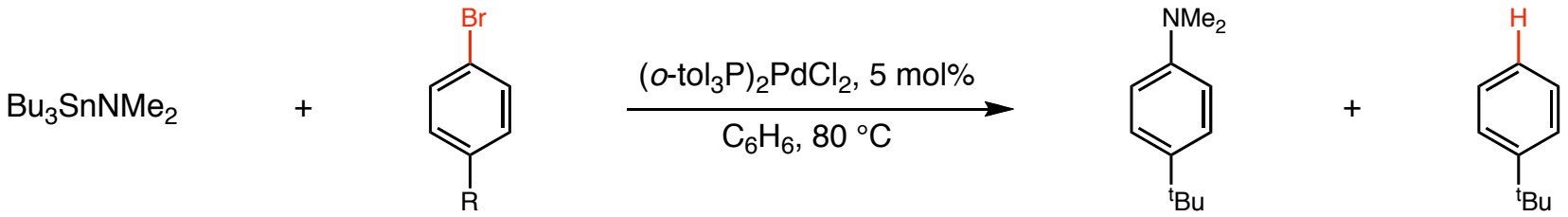
Cat. =	**1**	; 5 mol%	10	:	1
	(*o*-tol$_3$P)$_2$Pd(0);	5 mol%	9	:	1
	(*o*-tol$_3$P)$_2$PdCl$_2$;	0.5 mol%	9	:	1
	(*o*-tol$_3$P)$_2$PdCl$_2$;	5 mol%	6	:	1
	(*o*-tol$_3$P)$_2$PdCl$_2$;	25 mol%	4	:	1

=> 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



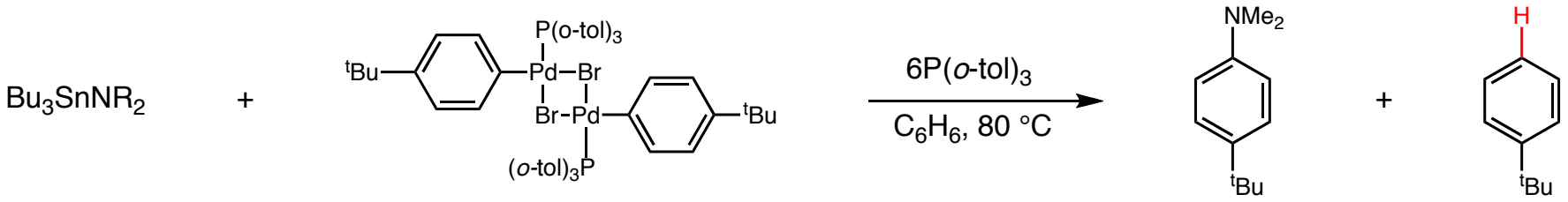
R =				
	CH_3CO	15	:	1
	^{t}Bu	6	:	1
	Me_2N	3	:	1

=> 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



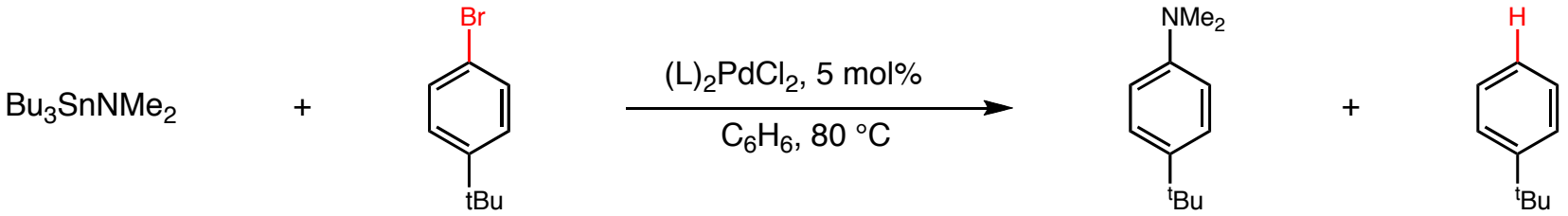
NR_2 =				
	NMe_2	11	:	1
	NEt_2	15	:	1
	NMePh	5	:	1

=> 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.

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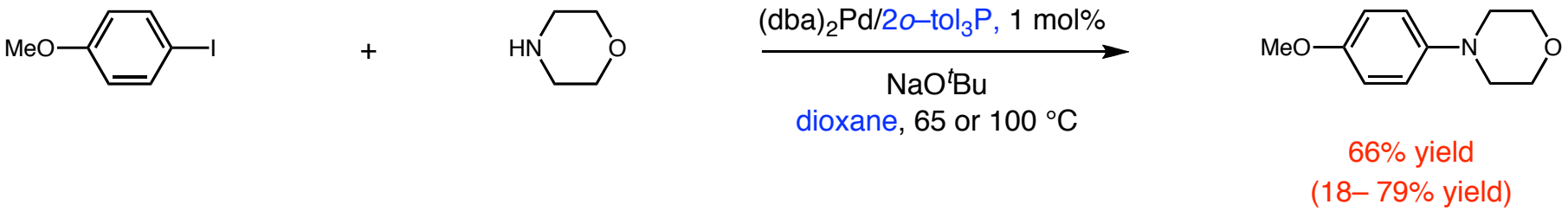
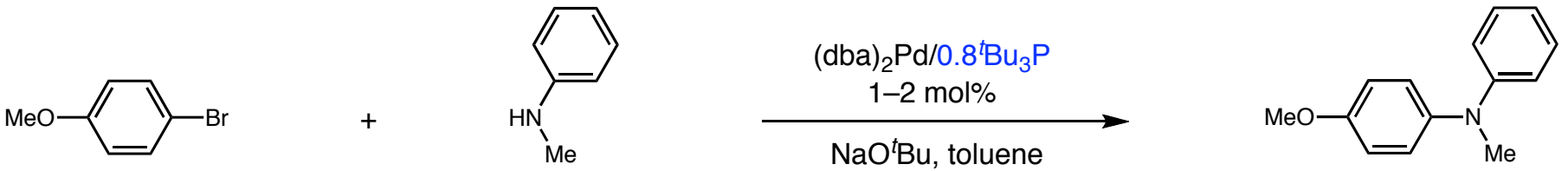
Aminations with Monodentate Hindered Phosphine Ligands



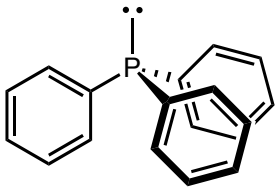
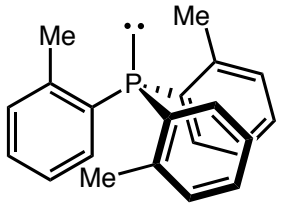
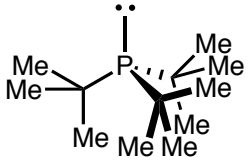
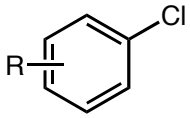
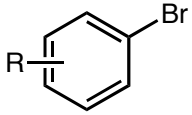
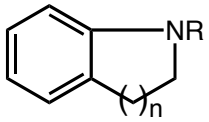
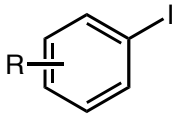
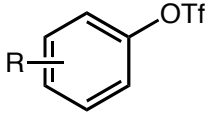
Wolfe, J. and Buchwald, S. L. *JOC* **1996**, *61*, 1133.



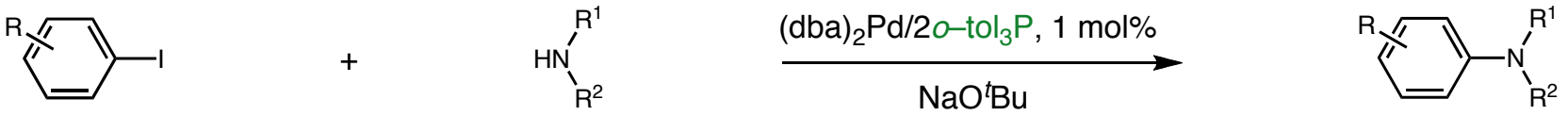
(dba)$_2$Pd/2*o*–tol$_3$P, 2 mol%
65 or 100 °C, 81– 99% yield
ACIE **1995**, *34*, 1348.

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

C–N Coupling with Monophosphine Ligands

	 $(Ph)_3P$ (145 °)	 $(o\text{-tol})_3P$ (194 °)	 $(^tBu)_3P$ (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



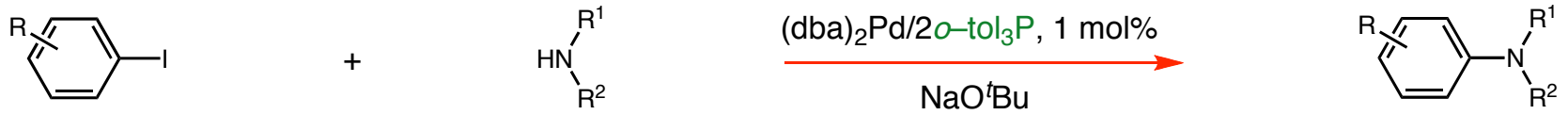
R = Me, MeO, Cl, amides

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**."*

Aminations of Aryl Iodides



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

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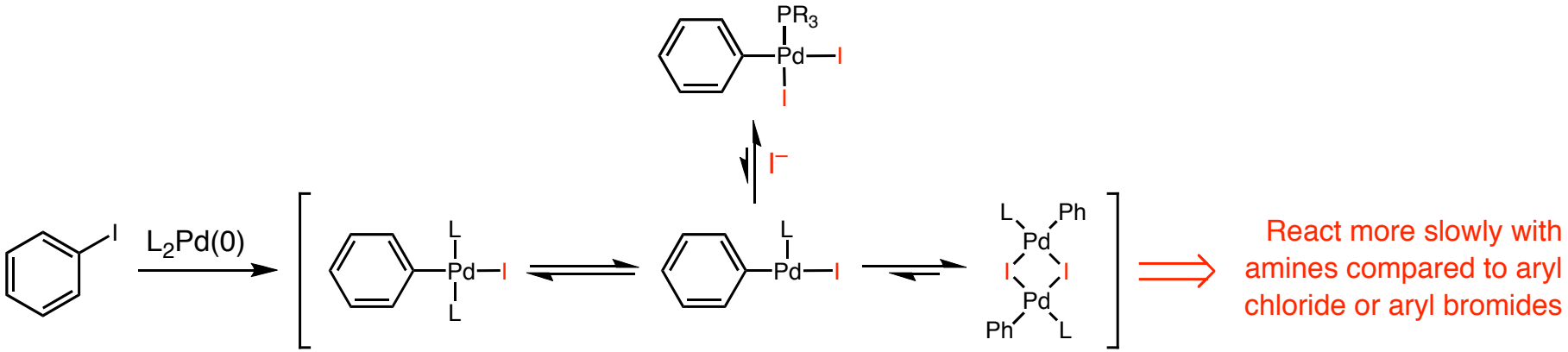


JACS **2009**, *131*, 8141.

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

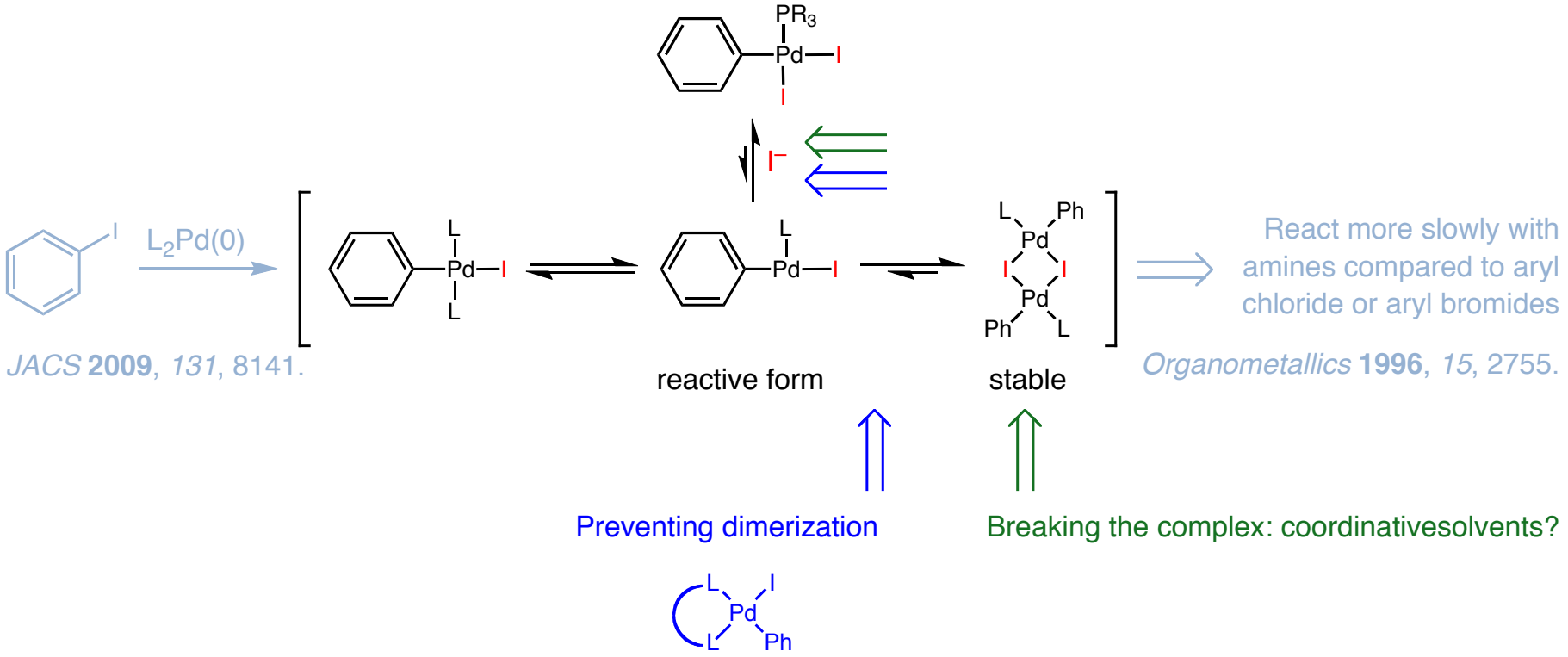
Aminations of Aryl Iodides

R = Me, MeO, Cl, amides

18– 79% yield

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

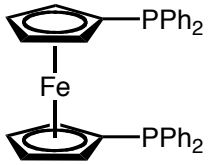
*"Our original attemps to utilize aryl iodides as substrates were also largely unsuccesful...**Running reaction in dioxane was the key for this technique**."*



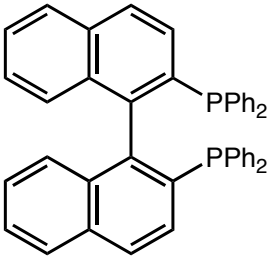
JACS **2009**, *131*, 8141.

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

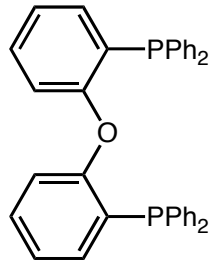
Bidentate Phosphine Ligands



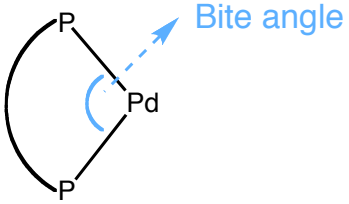
DPPF (99.0 °)

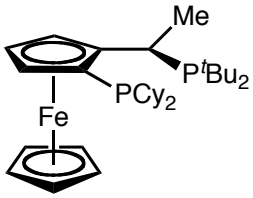


BINAP (92.7 °)

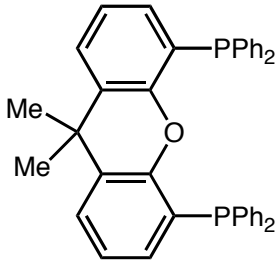


DPPDPE (101 °)



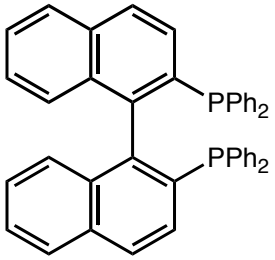
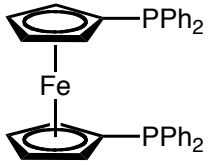
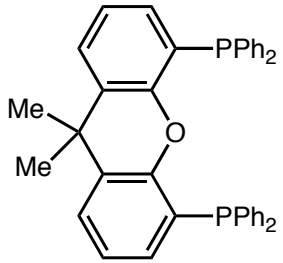
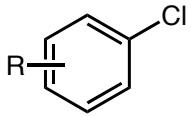
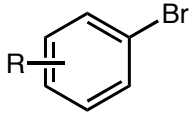
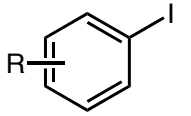
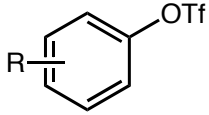
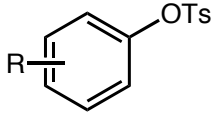


Josiphos (98.0 °)



Xantphos (109 °)

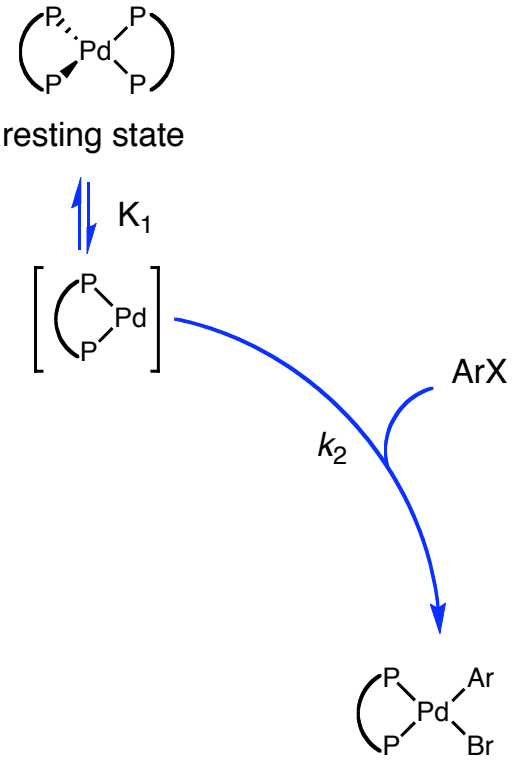
C–N Coupling with Biphosphine Ligands

	 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 - Mechanistic Conclusion

k_{obs} ~1/ [BINAP]

k_{obs} ~ [ArBr]



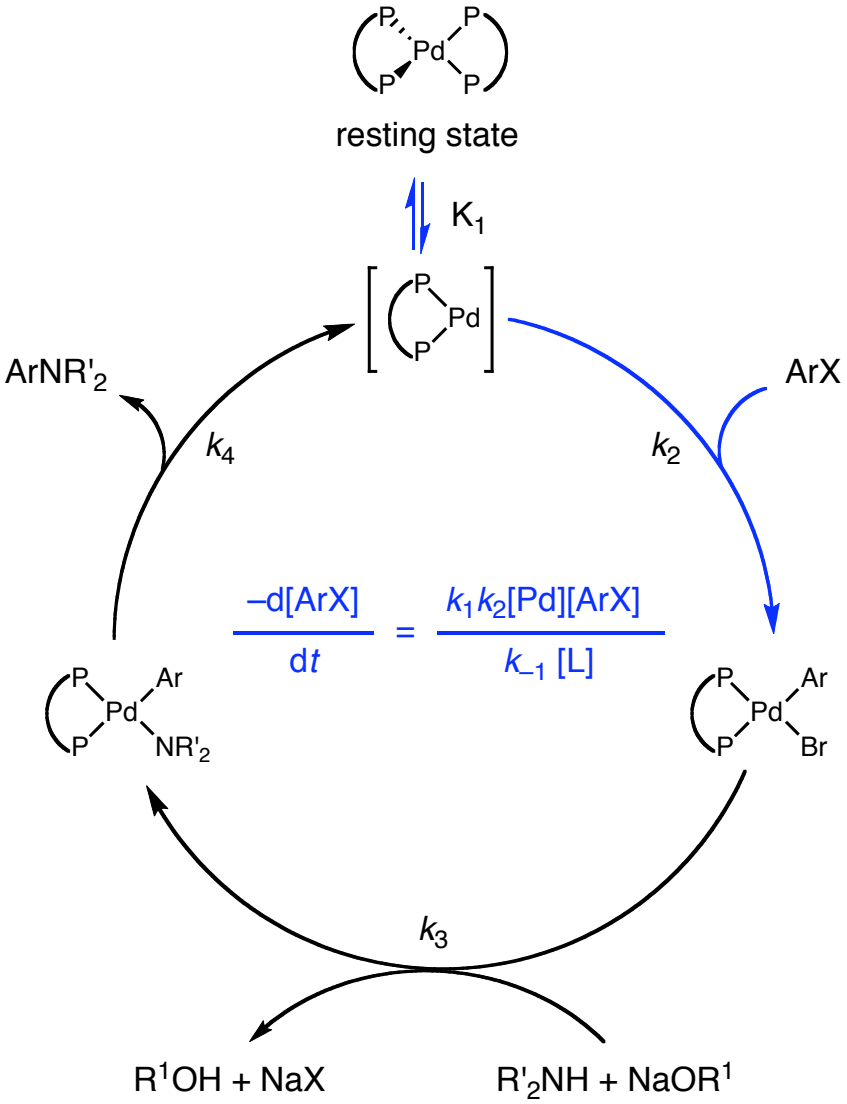
Hartwig, J. F.; Blackmond, D. G. and Buchwald, S. L. *et al JACS* **2006**, *128*, 3584.

Amination with BINAP Ligand - Mechanistic Conclusion

k_{obs} ~1/ [BINAP]

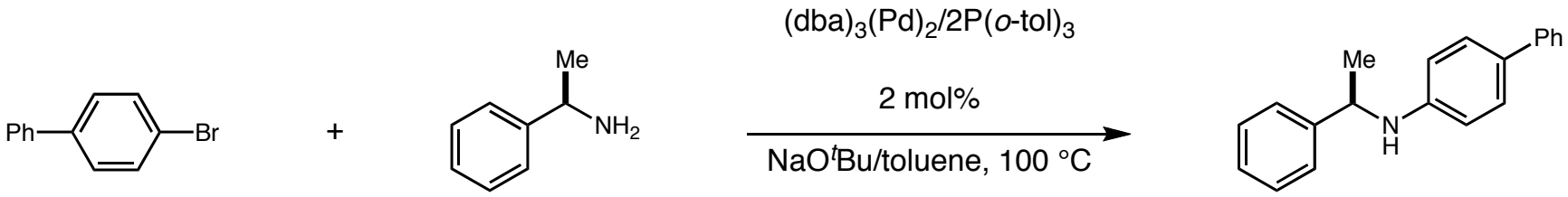
k_{obs} ~ [ArBr]

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



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

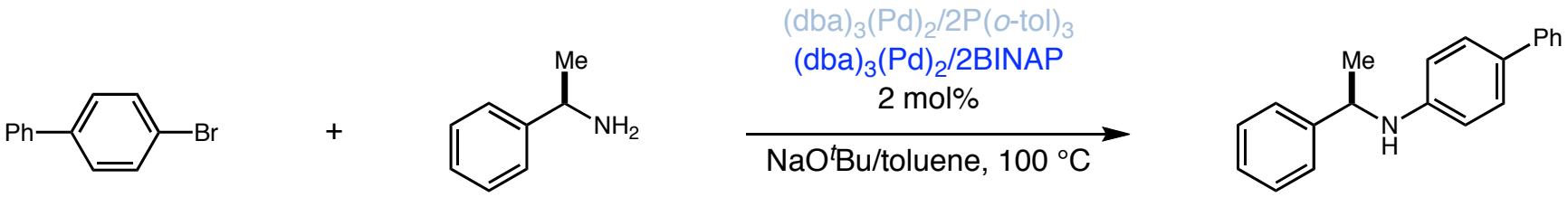


98% ee

P(*o*-tol)$_3$: 60% yield, 70% ee;

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

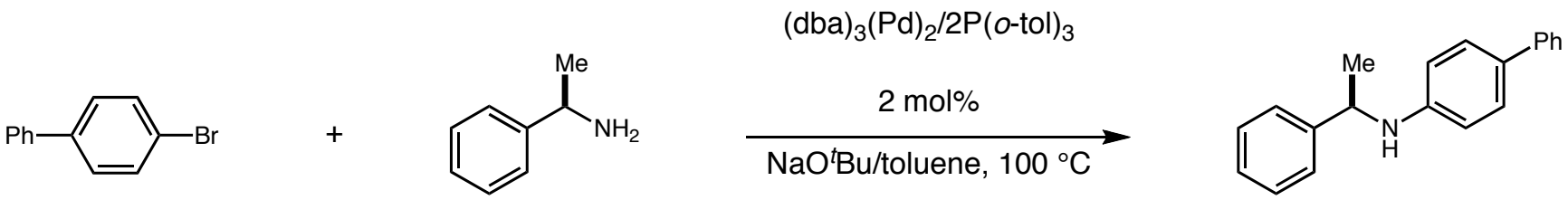
Amination with Bidentate Ligands - Coupling of Chiral Amines with Aryl Bromides



P(*o*-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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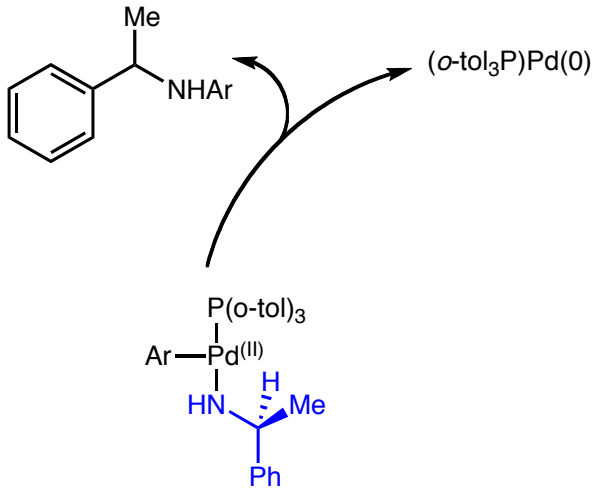

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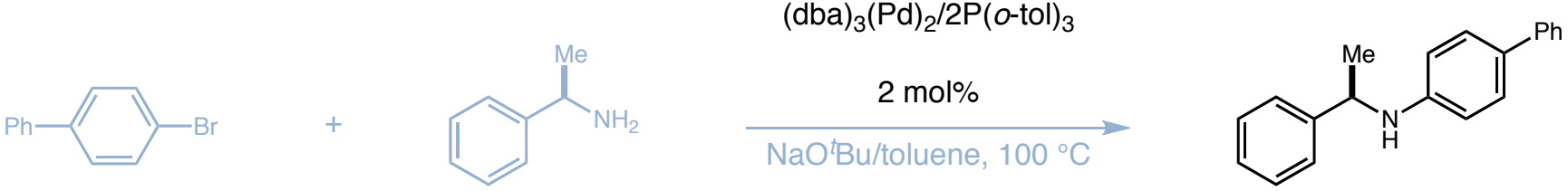

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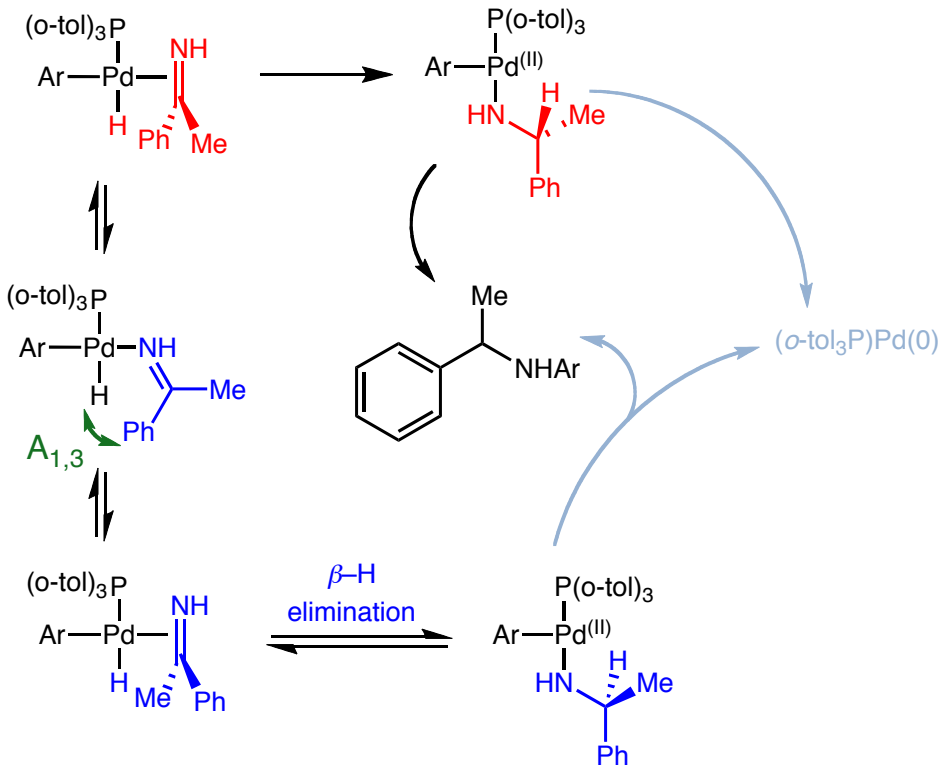
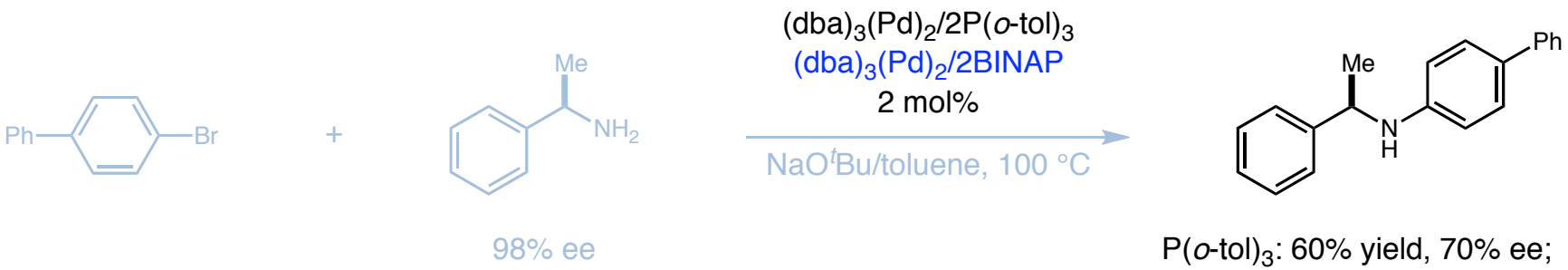


Amination with Bidentate Ligands - Coupling of Chiral Amines with Aryl Bromides



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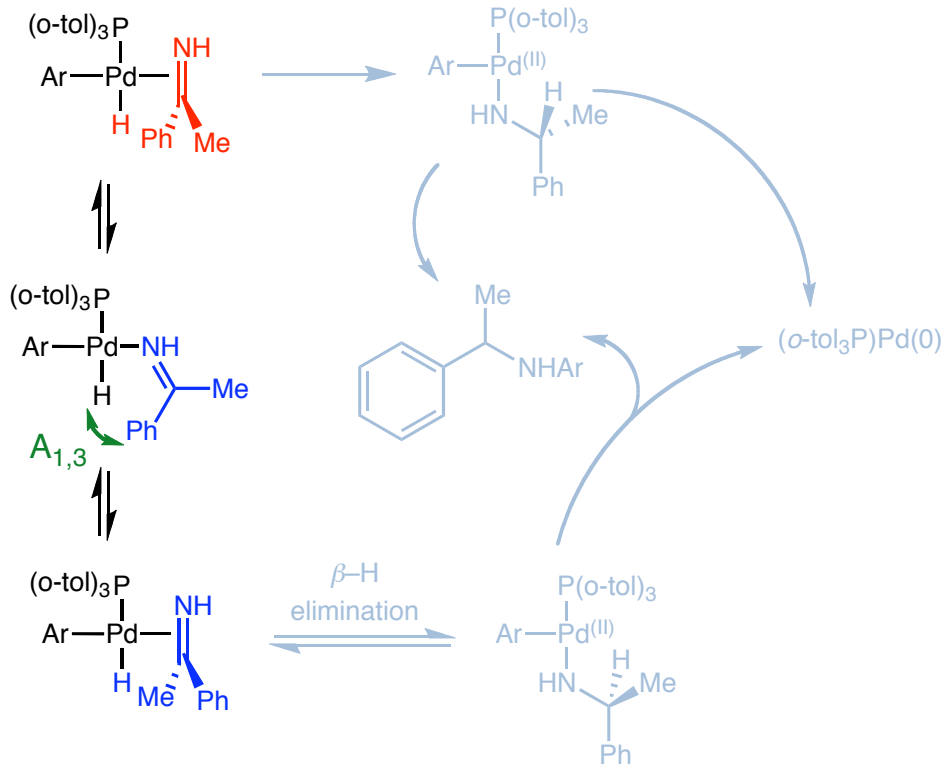
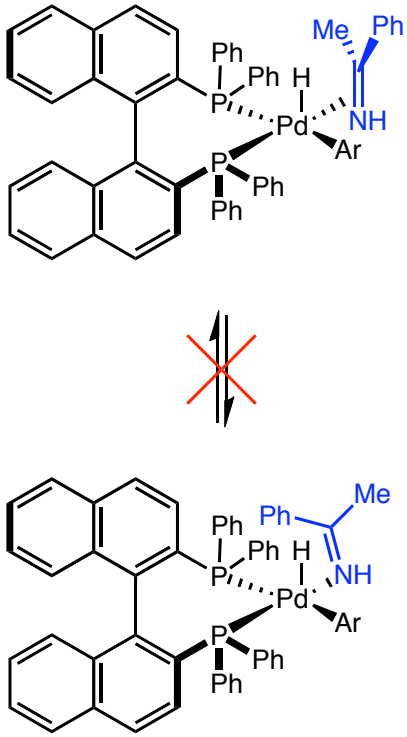
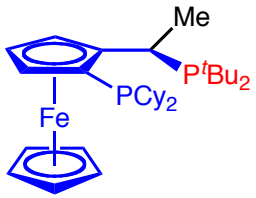




Amination with Josiphos Ligand - Scope Enlargement

♦ 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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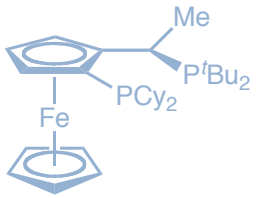

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Josiphos (98.0 °)

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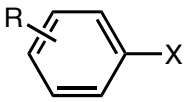
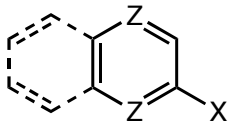
Hartwig, J. F. *ACS* **2008**, *41*, 1534.



X = Cl, Br, I, OTs
R = ankyl,amine, EDG, EWG
unprotected alcohol, acid.

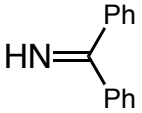
+



X = Cl, Br, I, OTs
Z = CH or N

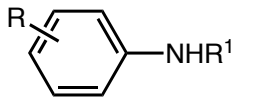
R^1NH_2

R^1= alkyl or aryl

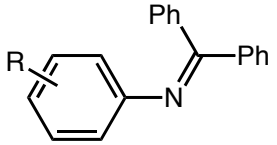


$(OAc)_2Pd$/Josiphos
10 ppm–2 mol%

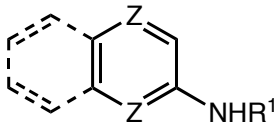
NaO^{t}Bu/DME or toluene
80–110 °C, < 24h



67–99% yield



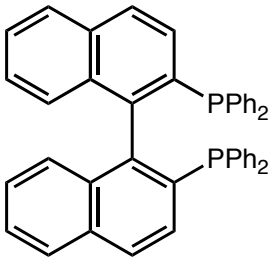
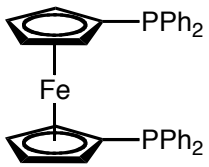
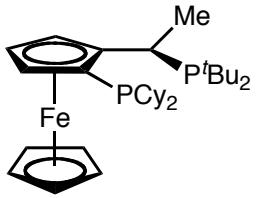
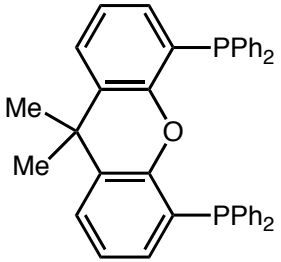
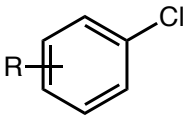
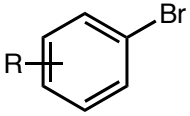
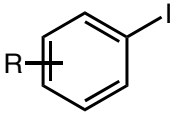
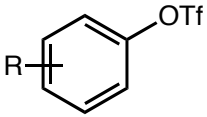
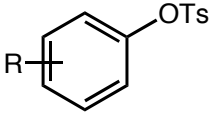
78–99% yield



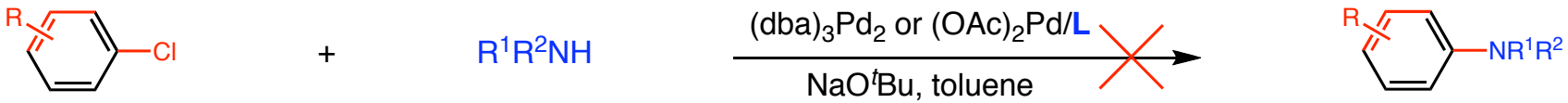
67–97% yield

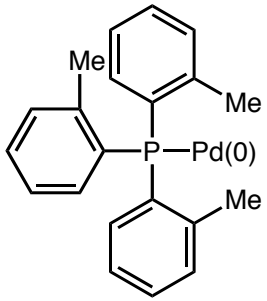
Hartwig, J. F. *et al ACIE* **2005**, *44*, 1371.
Shen, Q. and Hartwig, J. F. *OL* **2008**, *10*, 4109.
Hartwig, J. F. *et al JACS* **2008**, *130*, 6586.
Ogata, T. and Hartwig, J. F. *JACS* **2008**, *130*, 13848.

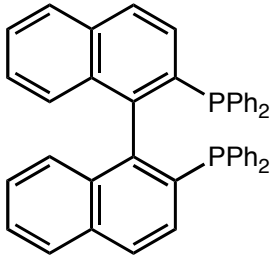
C–N Coupling with Biphosphine Ligands

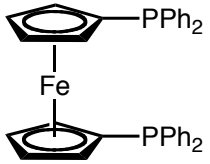
	 BINAP (92.7 °)	 DPPF (99.0 °)	 Josiphos (98.0 °)	 Xantphos (109 °)
			*Amination*: *ACIE* **2005**, *44*, 1371; *Imination*: *JACS* **2008**, *130*, 6586 & 13848. *ArNH$_2$*: *JACS* **2006**, *128, 10028;* **2009**, *131*, *11049*	
	*Amination*: *JACS* **1996**, *118*, 7215; *JACS* **1997**, *119*, 8451; *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; *AArNH$_2$*: *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; *ArNH$_2$*: *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	*ArNH$_2$*: *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; *ArNH$_2$*: *JACS* **2006**, *128, 10028;* **2009**, *131*, *11049*	

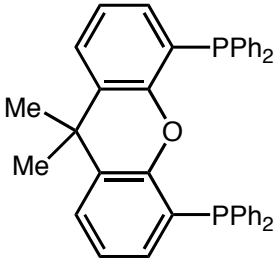
Amination with Biarylphosphine Ligands - Amination of Aryl Chlorides







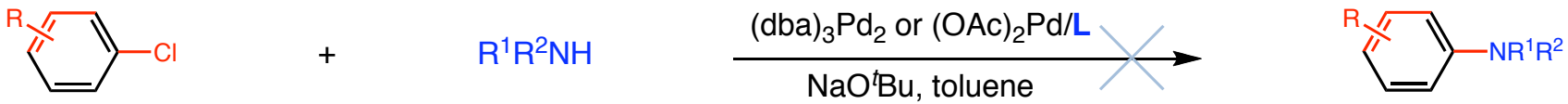


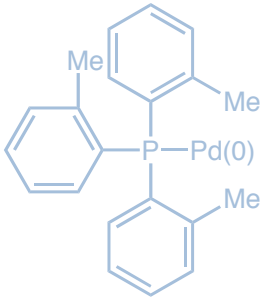


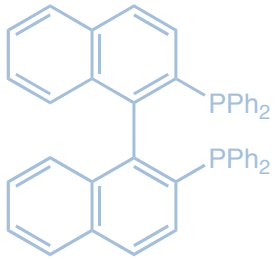
		BINAP	DPPF	Xantphos
Used in amination	1983	1996	1996	1999

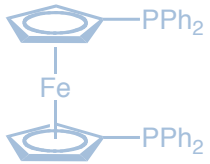
■ Not electron-rich enough for the oxidative addition or aryl chloride

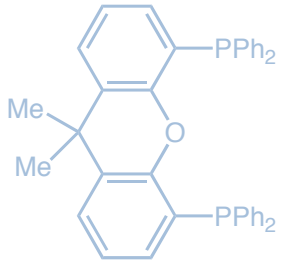
Amination with Biarylphosphine Ligands - Amination of Aryl Chlorides







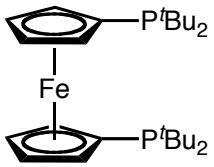


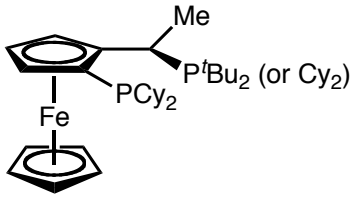


BINAP DPPF Xantphos

Used in amination 1995 1996 1996 1999

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

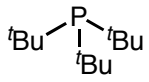




Josiphos (98.0 °)

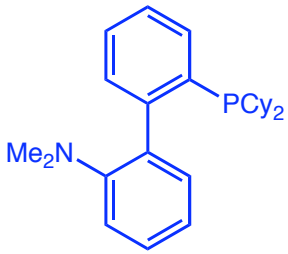
Hartwig *JACS* **1998**, *120*, 7369.

92–99% yield



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

64–97% yield



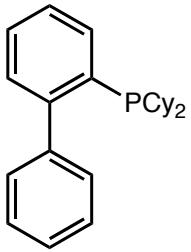
DavePhos

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

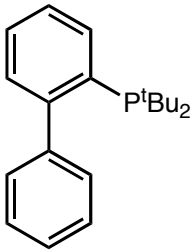
81–98% yield

Biarylphosphine Ligand

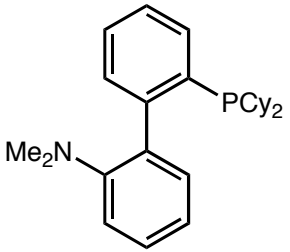
(ligands for gold, silver, rhodium, ruthenium and copper)



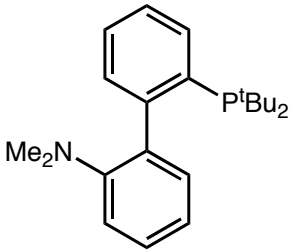
JohnPhos (Cy)



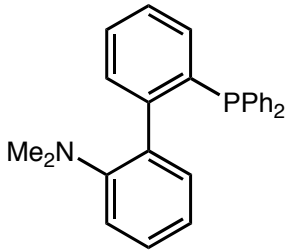
JohnPhos



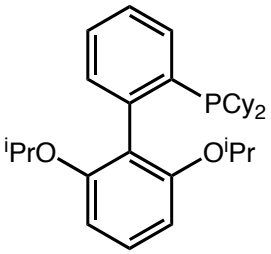
DavePhos
(Buchwald,1998)



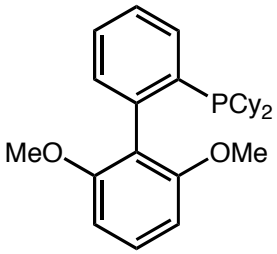
DavePhos (*t*Bu)



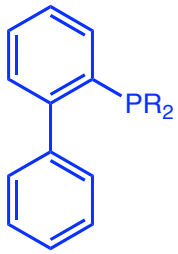
DavePhos (Ph)



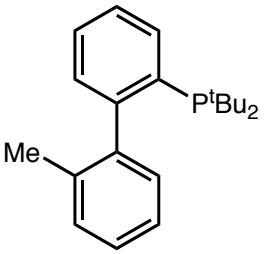
RuPhos



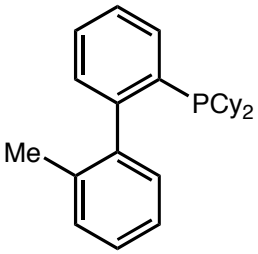
SPhos



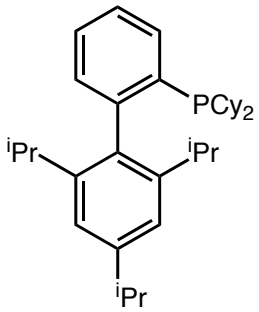
Biarylphosphine
(≥ 162 °)



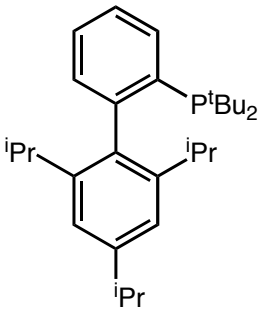
MePhos (*t*Bu)



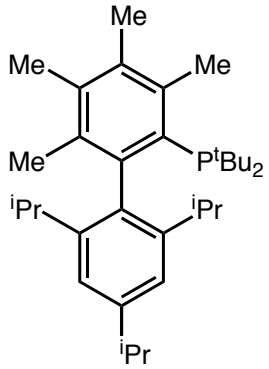
MePhos



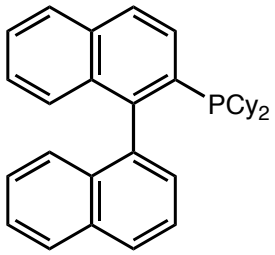
XPhos



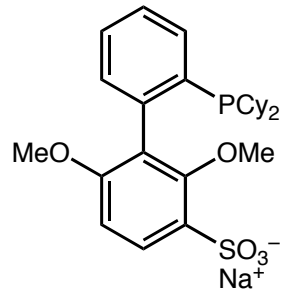
XPhos (*t*Bu)



XPhos (4Me*t*Bu)

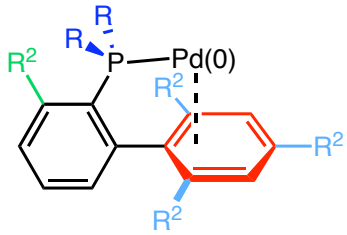


Johnphos (NaphCy)



Surry, D. S. and Buchwald, S. L. *ACIE* **2008**, 4*7*, 6388.

Biarylphosphine Ligands - Important Structural Features



active complex

♦ Alkyl groups increase electron-density at phosphorus, promote oxidative addition.

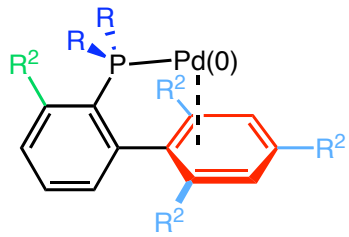
♦ Increased steric bulk at P promotes reductive elimination.

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

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

Biarylphosphine Ligands - Important Structural Features

♦ Substituent fixes conformation enhances rate of reductive elimination.



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Biarylphosphine Ligands - Important Structural Features

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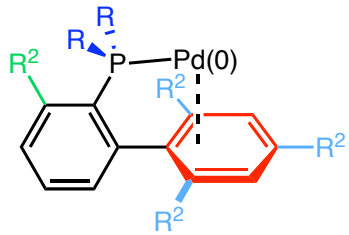


active complex

♦ Large substituents prevent cyclometalation, increase stability.

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

♦ 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)].

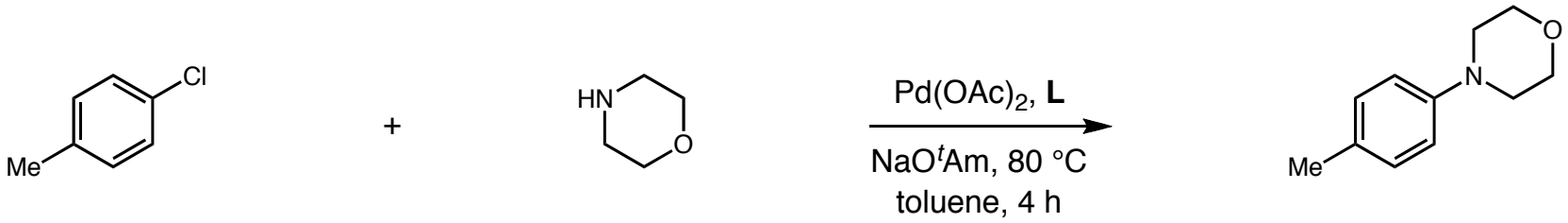
♦ Lower aryl ring retards oxidation by O_2.

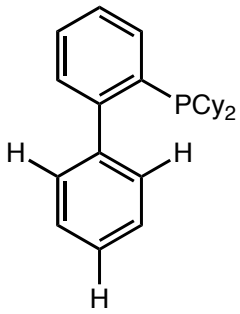
♦ Lower aryl ring allows stabilizing Pd–arene interactions.

♦ Lower aryl ring promotes reductive elimination.

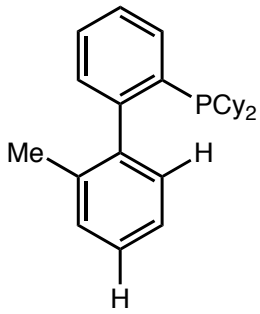
Surry, D. S. and Buchwald, S. L. *ACIE* **2008**, *47*, 6388.

Biarylphosphine Ligands - Effects of Substutuents on Lower Aryl Ring

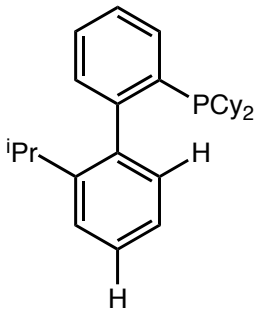




1a



1b



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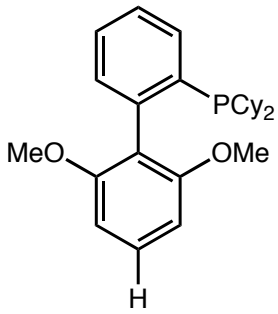

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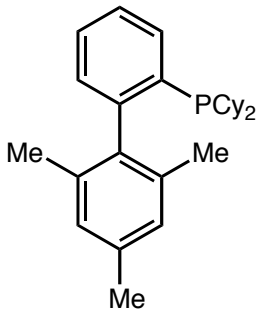

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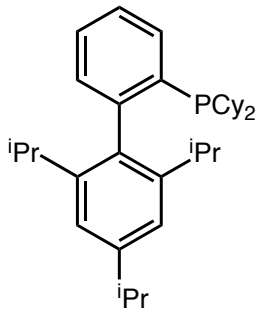
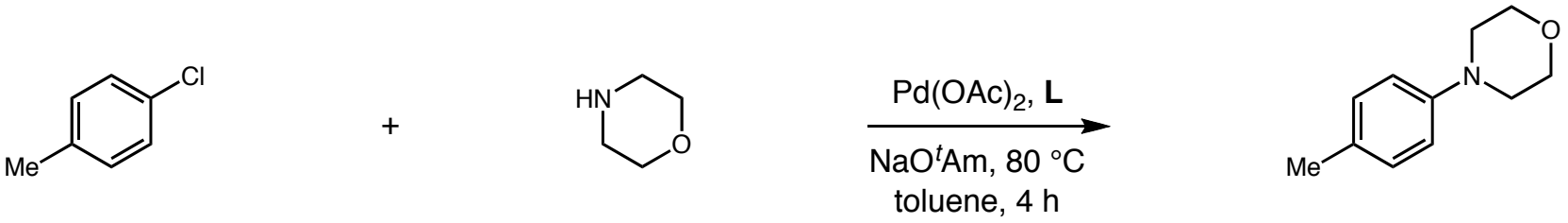
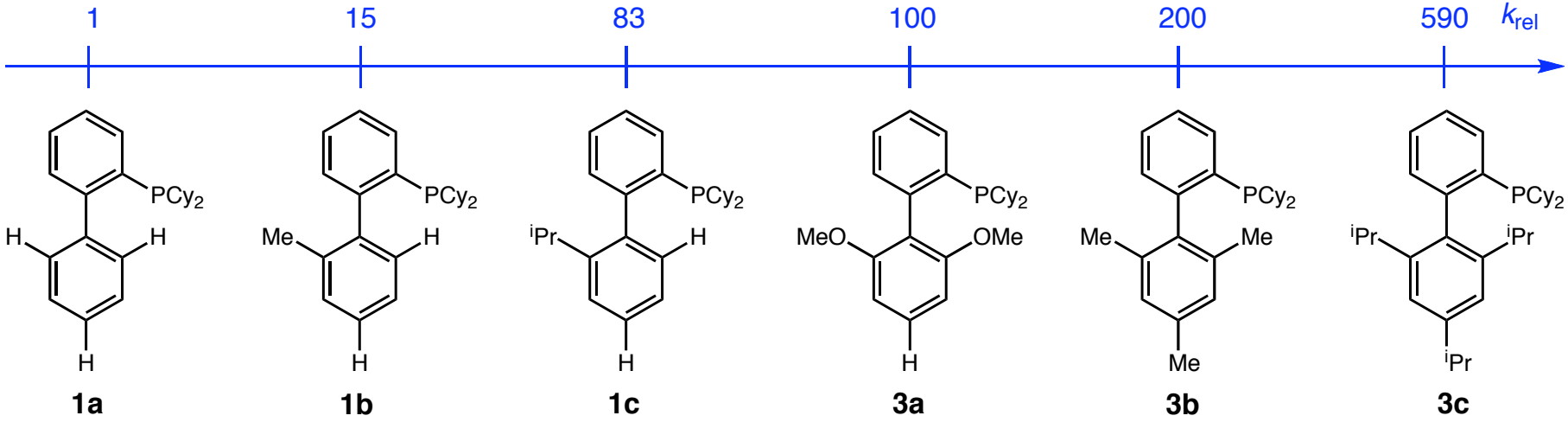


3c

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





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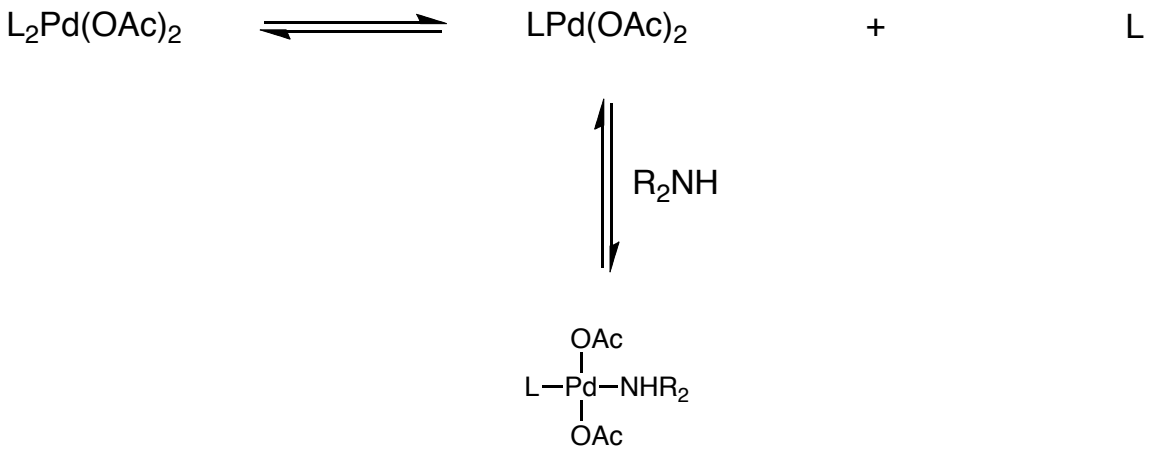

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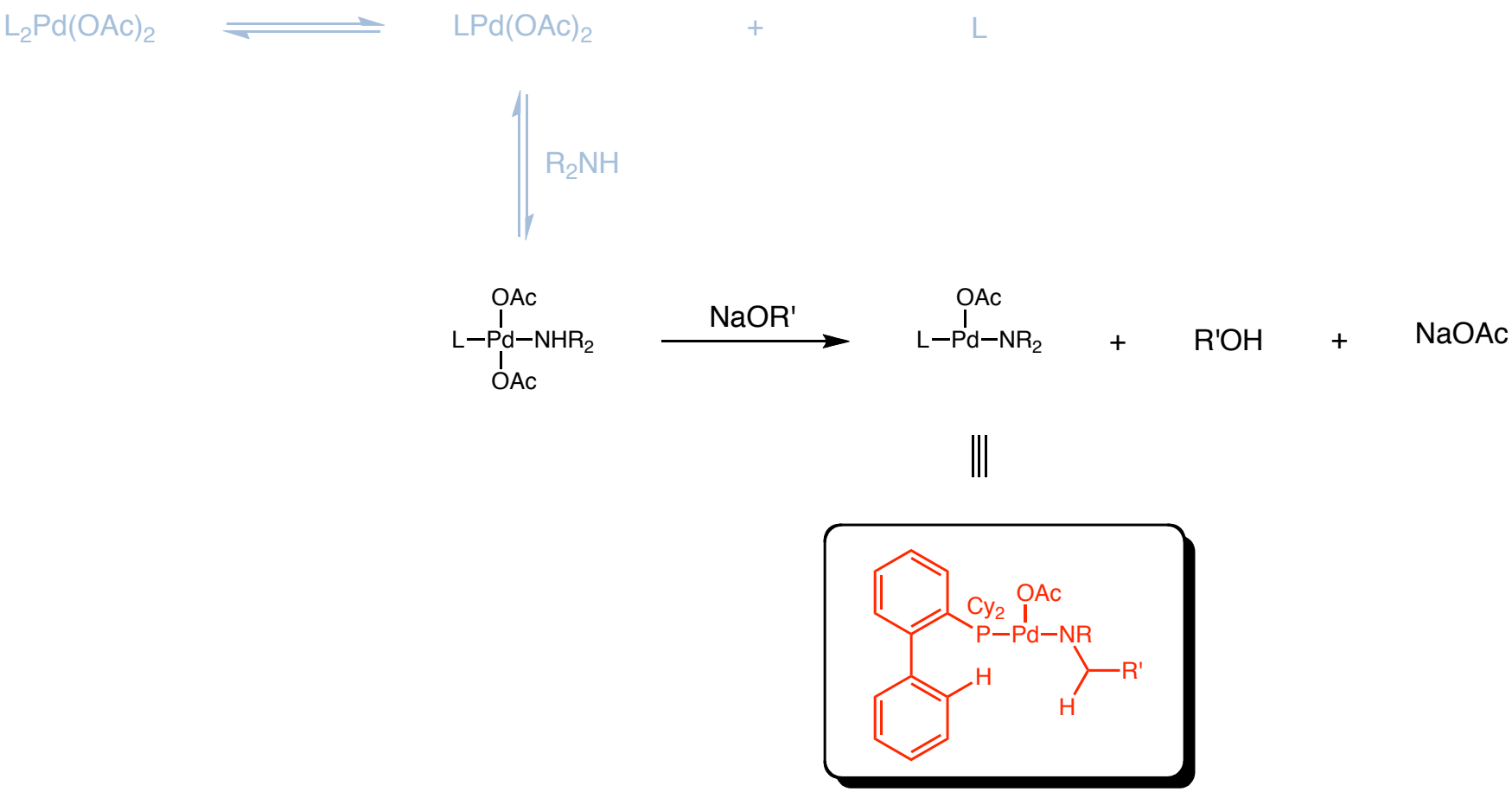

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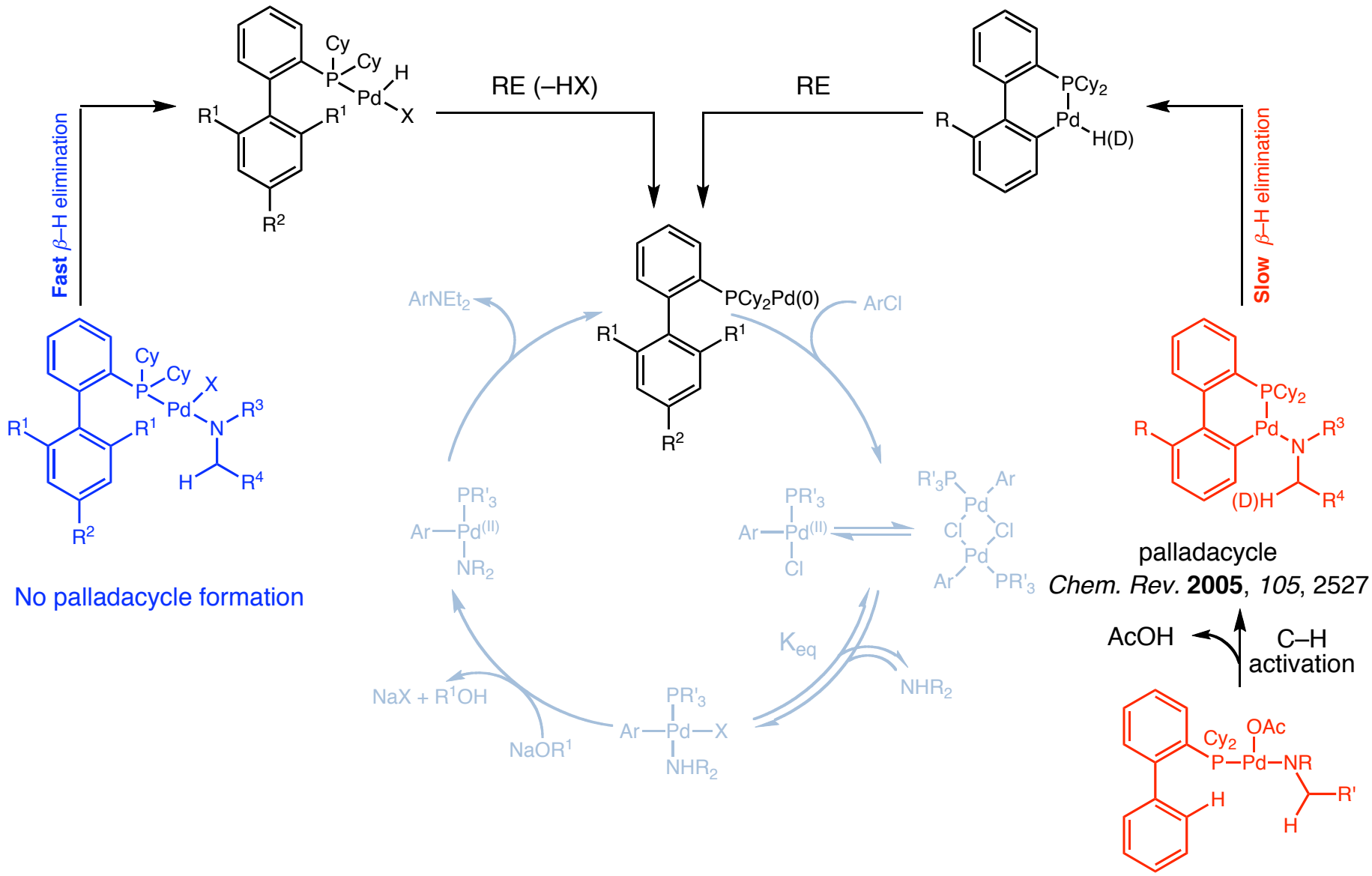

Buchwald, S. L. *et al JACS* **2003**, 125, 13978.
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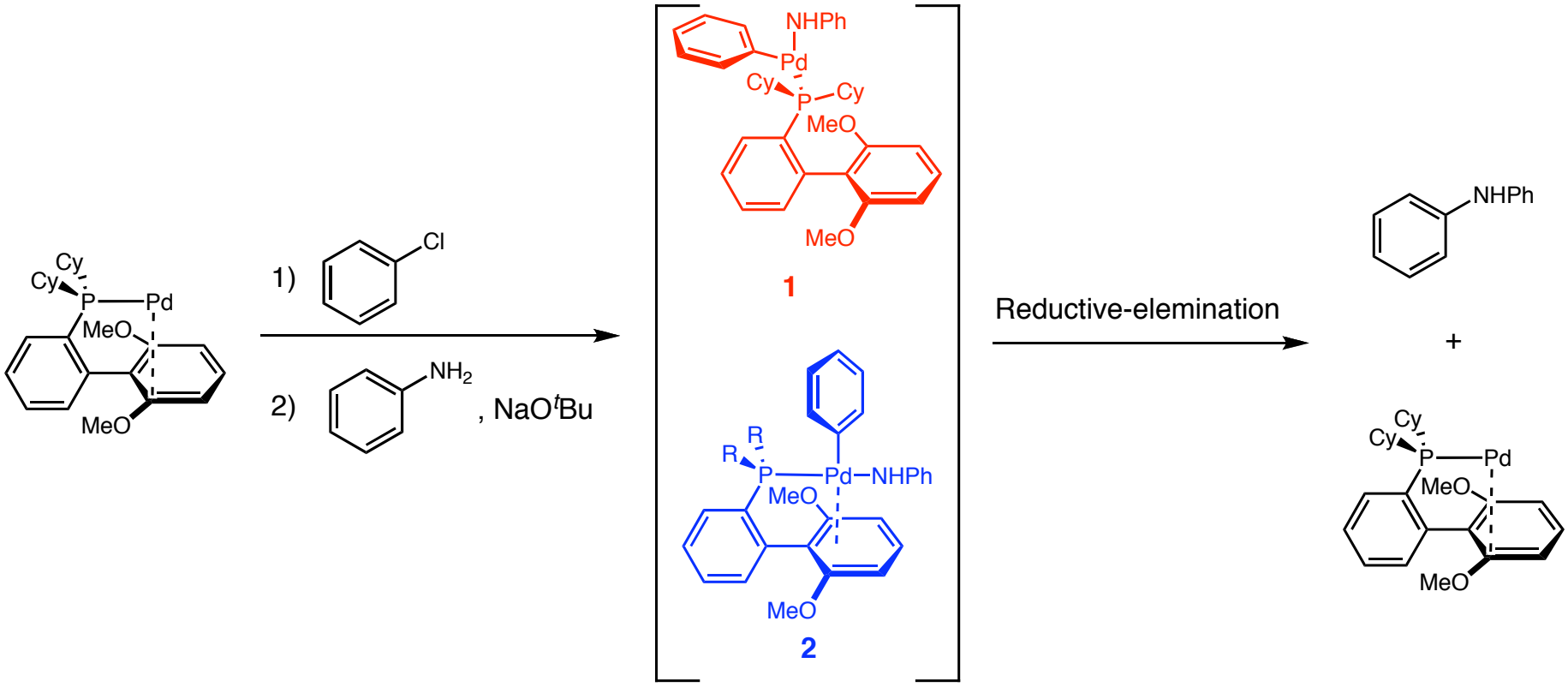
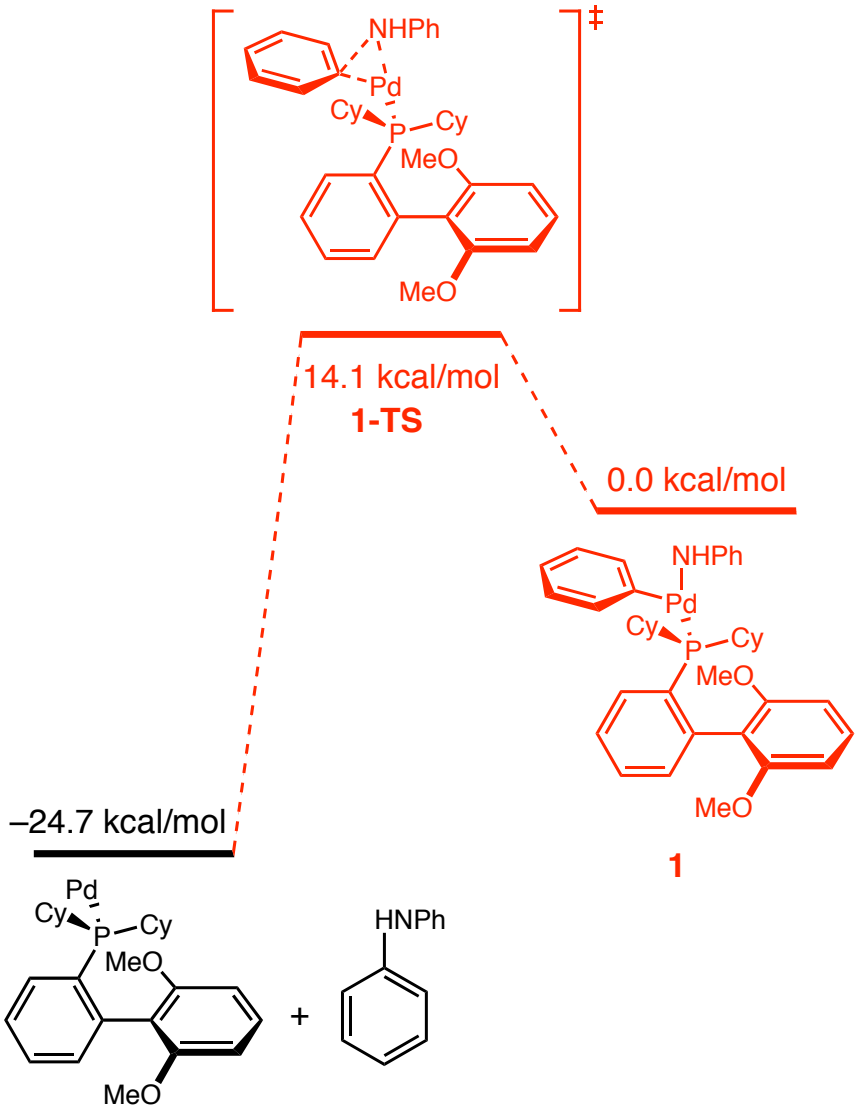
Biarylphosphine Ligands - Reductive Elimination via DFT Study



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

Biarylphosphine Ligands - Reductive Elimination via DFT Study



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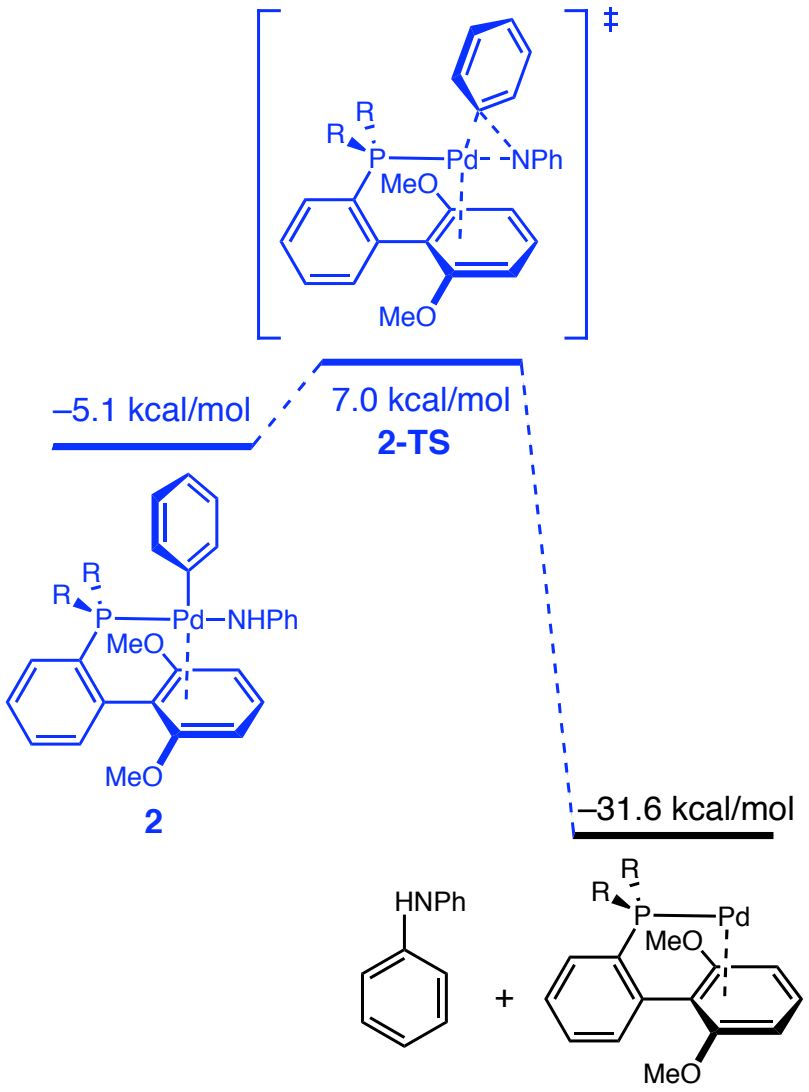

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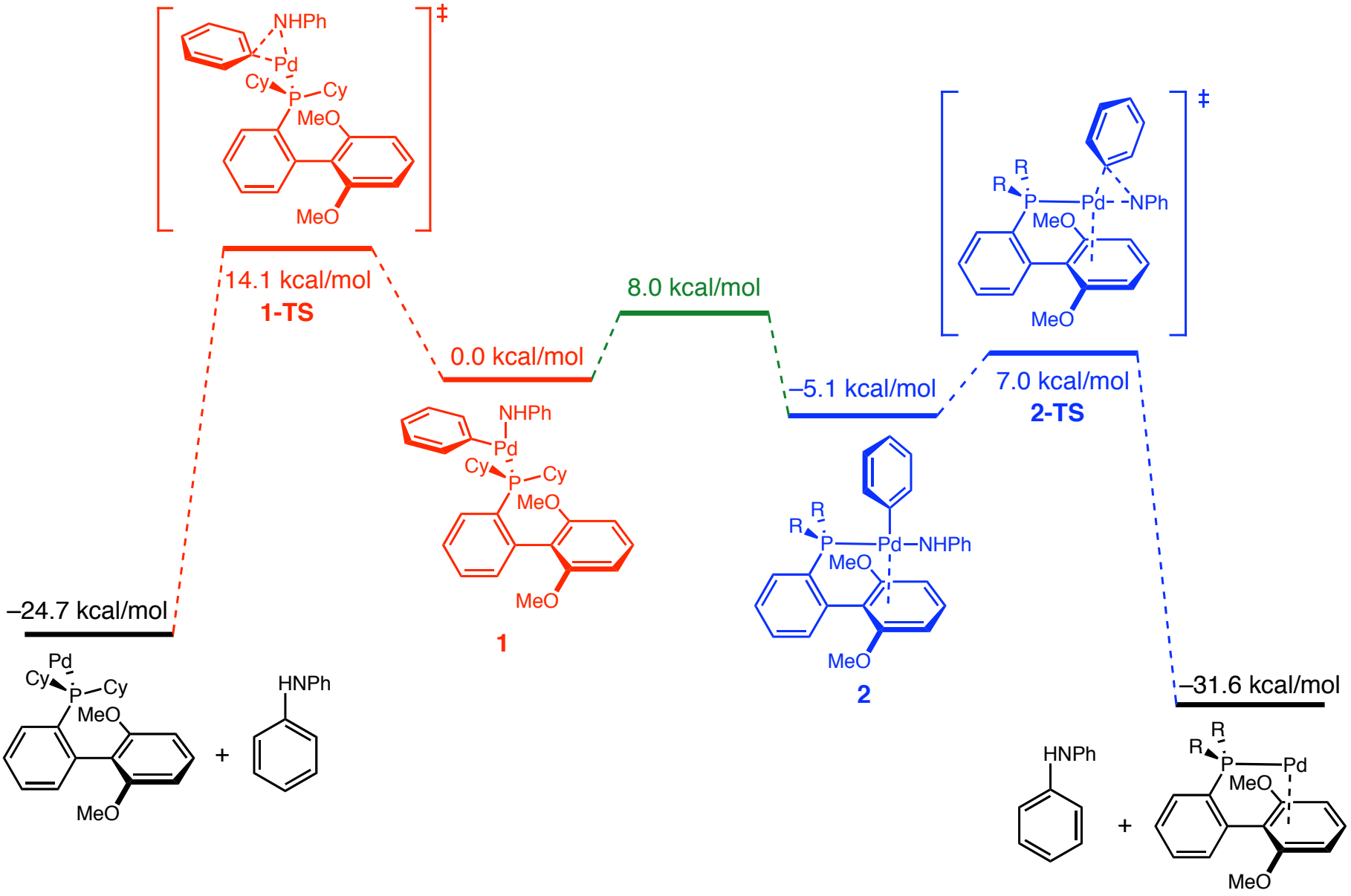
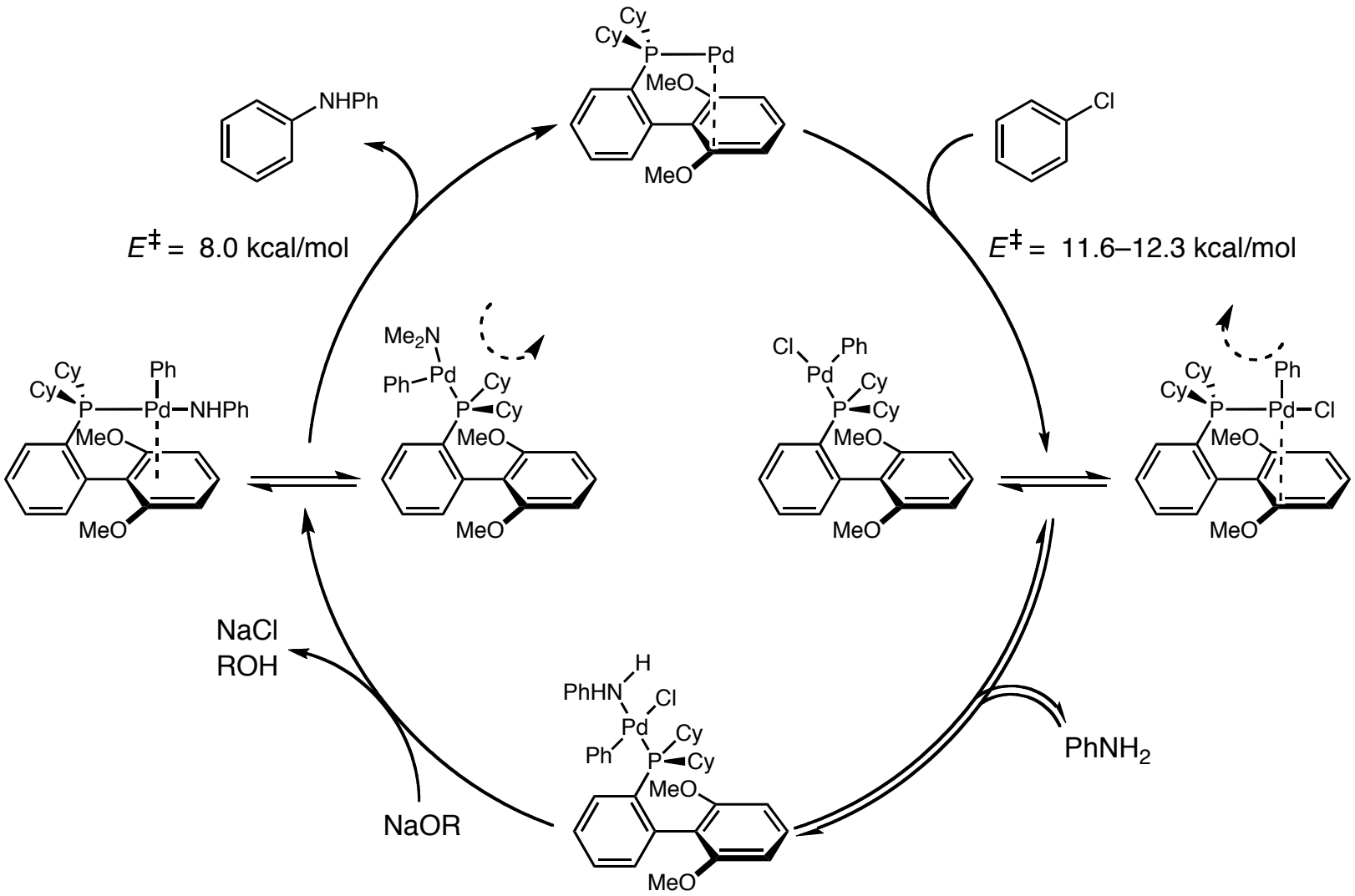


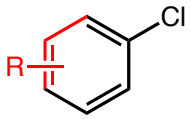
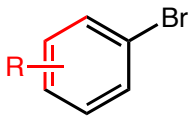
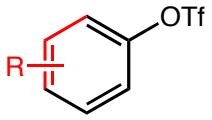
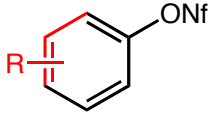
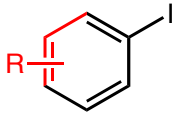
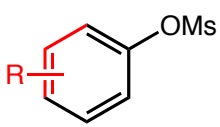
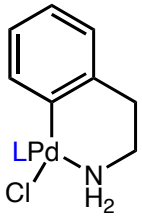
Barder, E. T. and Buchwald, S. L. *JACS* **2007**, *129*, 12003.

Biarylphosphine Ligands - Proposed Mechanism via DFT Study



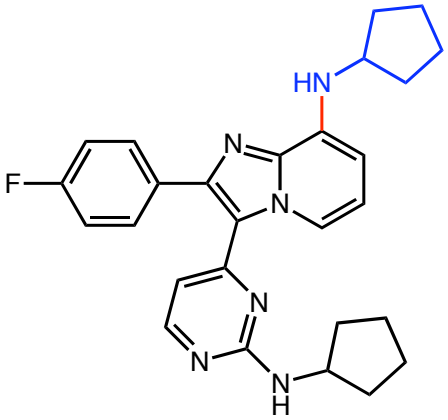
Barder, E. T. and Buchwald, S. L. *JACS* **2007**, *129*, 12003.

C–N Coupling with Biarylphosphine Ligands

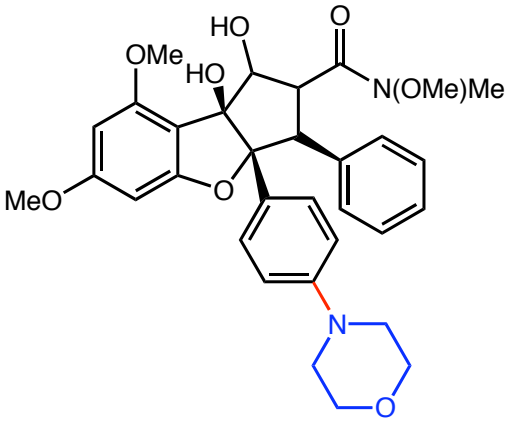
	$ArNR_2$	ArNHHet	$ArNH_2$	ArNHCOR	$ArNO_2$
		Ruphos, Xphos (^{t}Bu), Xphos (4Me^{t}Bu), *OL* **2005**, *7*, 3965; *ACIE* **2006**, *45*, 6523	Johnphos (Cy, ^{t}Bu) , Davephos (^{t}Bu), *OL* **2001**, *3*, 3417; *JACS* **2007**, *129*, 10354	Xphos (4Me^{t}Bu), *JACS* **2007**, *129*, 13001	Brettphos, *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

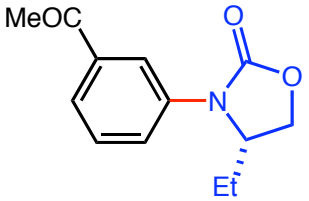
some examples in pharmaceutical synthesis



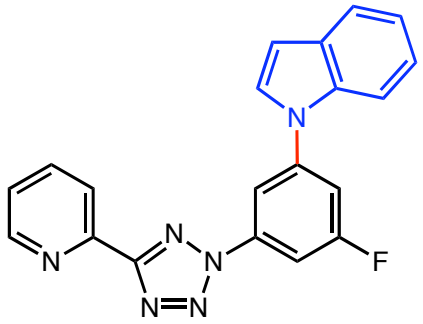
92% (Cl)
GalaxoSmithKline
synthesis of
antiherpes agents



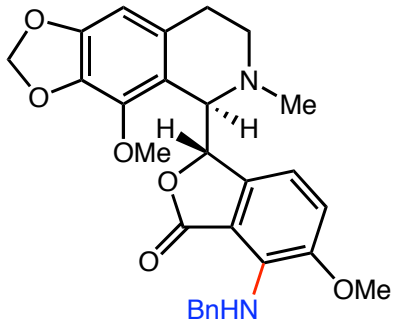
41% (Br)
Novartis synthesis of
rocaglamine analogs



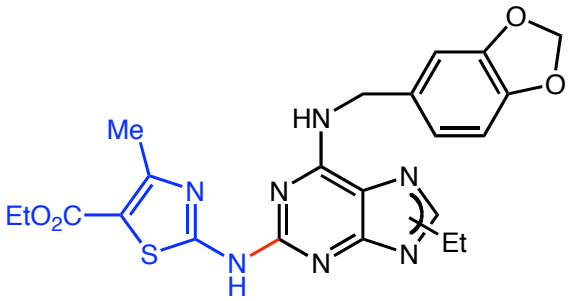
94% (Cl)
Pfizer synthesis of
N-Aryl oxazolidinones



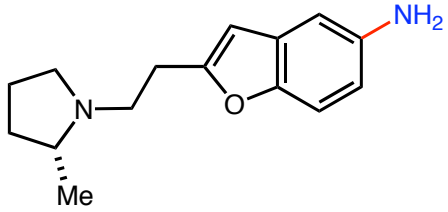
(I)
Merk synthesis of
mGlu5 receptor
antagonist



80% (OTf)
Athersys synthesis of
noscapine analogs



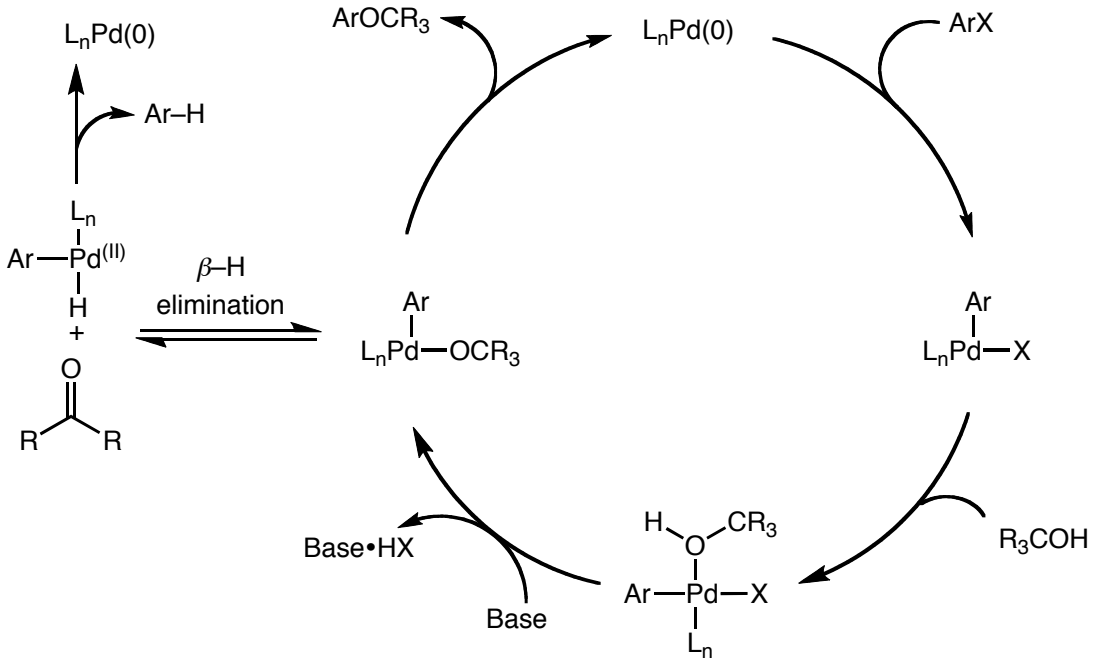
(Cl)
BMS synthesis of
phosphodiesterase 7
inhibitors



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

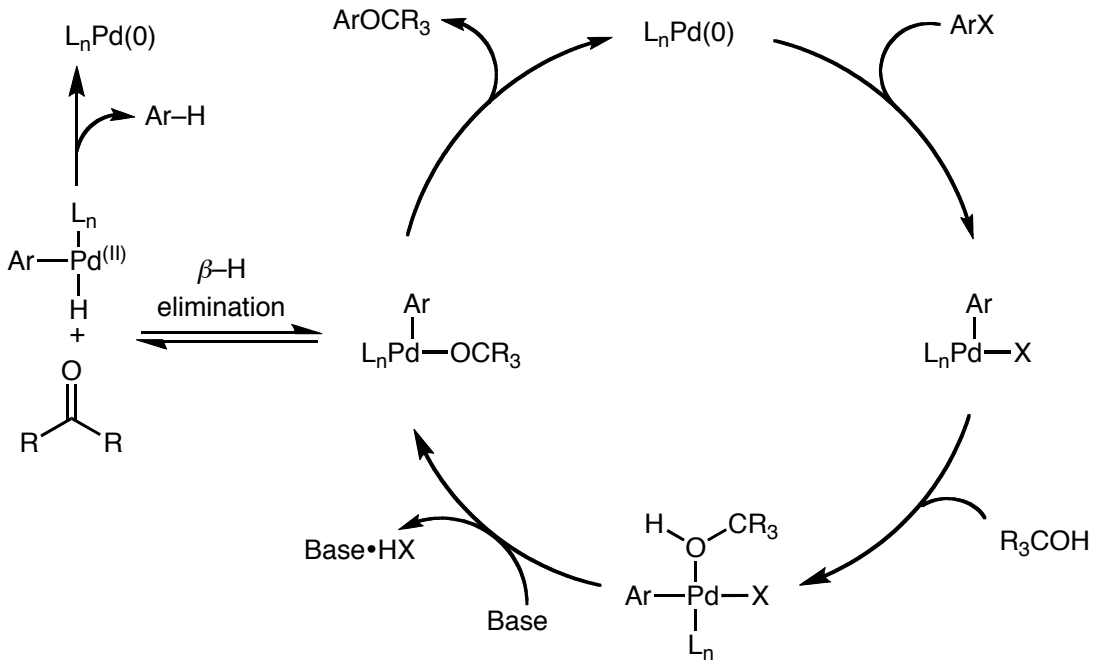
Surry, D. S. and Buchwald, S. L. *ACIE* **2008**, 4*7*, 6388.

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

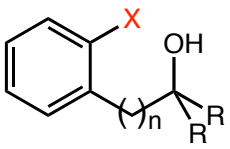


- The nucleophilicity of alcohols is much weaker than that of amines
- β–H elemination products are stable.

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

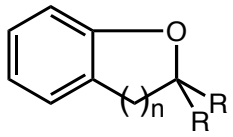


n = 1–3

X = Br, I
R = Me, alkyl

$(OAc)_2Pd$/Tol-BINAP
or DPPF, 5 mol%

K_2CO_3 or NaO^tBu/toluene
80–100 °C, ≤ 24 h

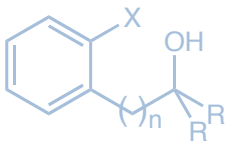


77–97% yield

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

C–O Coupling with Pd Complexes

scope limitation with bidentate phosphine ligands



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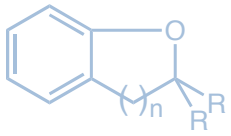
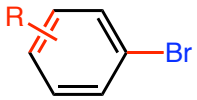
K_2CO_3 or NaO^{t}Bu/toluene
80–100 °C, ≤ 24 h



77–97% yield

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

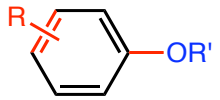
■ Intermolecular C–O coupling were successful with alkoxides



+ $R^1R^2R^3COH$

$(dba)_3Pd_2$/2.4Tol-BINAP
1.5 mol%

NaH/toluene, 50–100 °C

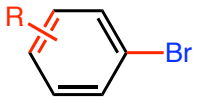


R = aryl, ^{t}Bu, CN, CF_3

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

48–81% yield

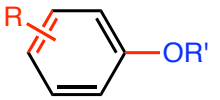
Buchwald, S. L. *et al JACS* **1997**, *119*, 3395.



+ $NaOR^1$

$(dba)_2Pd,Ni(COD)_2$/2DPPF
10–15 mol%

toluene, 95–120 °C, ≤ 18 h



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

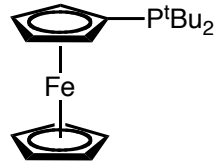
R^1 = ^{t}Bu, Me, TMDS

38–100% yield

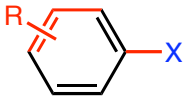
Mann, G. and Hartwig, J. F. *JACS* **1996**, *118*, 13109.
Mann, G. and Hartwig, J. F. *JACS* **1997**, *119*, 5413.

C–O Coupling with Pd Complexes

scope improvement with electron-rich bulky monodentate phosphine ligands

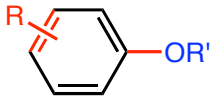


FcP^tBu_2



+ $NaOR^1$

$(dba)_2Pd/FcP^tBu_2$ or P^tBu_3
2–5 mol%
toluene, 95–110 °C, ≤ 24 h



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

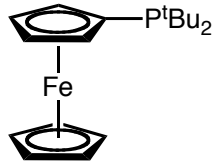
R^1 = ^{t}Bu, Me, Ar

62–85% yield

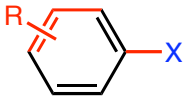
Hartwig, J. F. *et al JACS* **1999**, *121*, 3224.

C–O Coupling with Pd Complexes

scope improvement with electron-rich bulky monodentate phosphine ligands

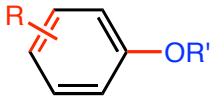


FcP^tBu_2



+ $NaOR^1$

$(dba)_2Pd/FcP^tBu_2$ or P^tBu_3
2–5 mol%
toluene, 95–110 °C, ≤ 24 h



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

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

62–85% yield

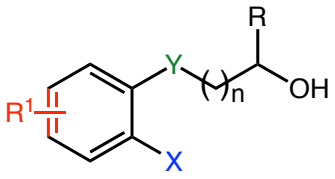
Hartwig, J. F. *et al JACS* **1999**, *121*, 3224.

♦ Sterically hindred 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



n = 0–2

X = Br, I

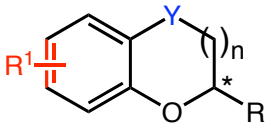
Y = CH_2, O, NMe(H)

R = Me, alkyl, ester, carbamate

R^1 = Me, CN, CO_2Me

$(OAc)_2Pd$/**L_2** or **L_1**
2–3 mol%

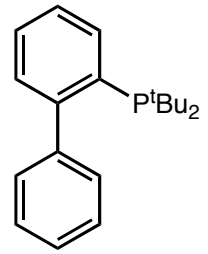
Cs_2CO_3 or K_3PO_4/toluene
50–80 °C, ≤ 28 h



65–95% yield

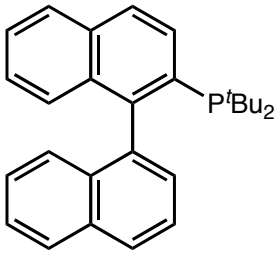
≥ 97% ee

L_1



JohnPhos

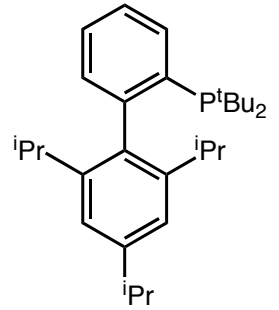
L_2

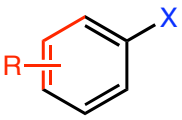


Buchwald, S. L. *et al JACS* **2000**, *122*, 12907.

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

L_3



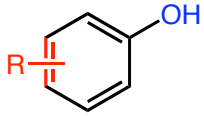


X = Cl, Br

R = alkyl, EWG, EDG

$(OAc)_2Pd$/**L_3** or **L_4**
0.5–2 mol%

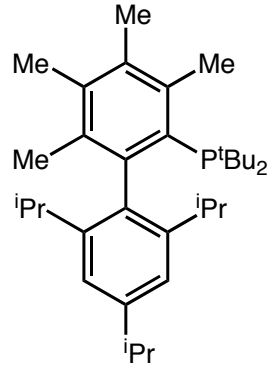
KOH/H_2O-dioxane
1000 °C, ≤ 18 h



80–98% yield

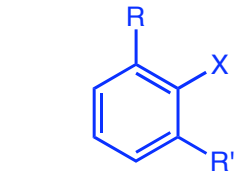
Buchwald, S. L. *et al JACS* **2008**, *128*, 10694.

L_4

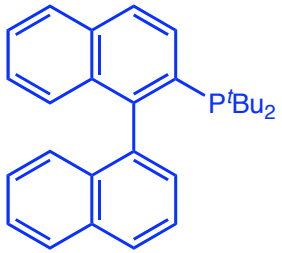


C–O Coupling with Pd Complexes

biarylphosphine ligand summary

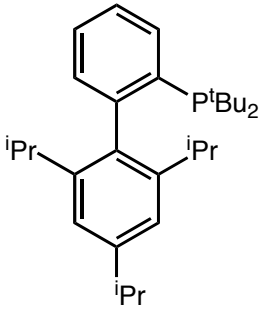


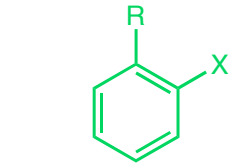
RCH_2OH

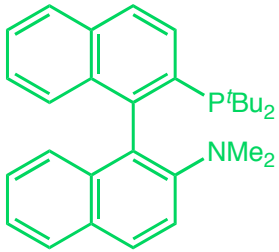


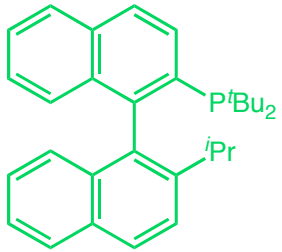
R_2CHOH

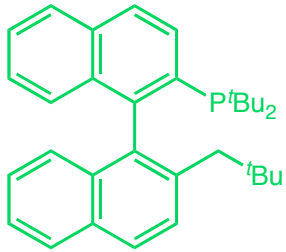
ArOH

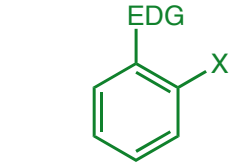


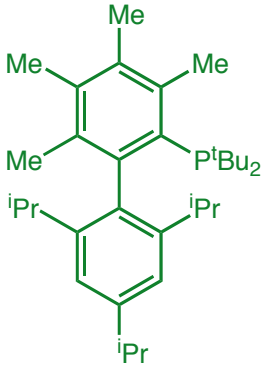


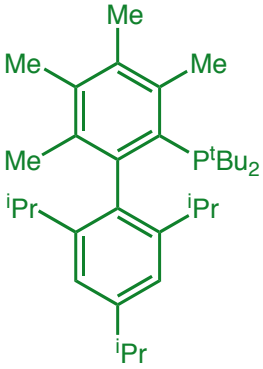


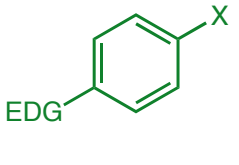












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