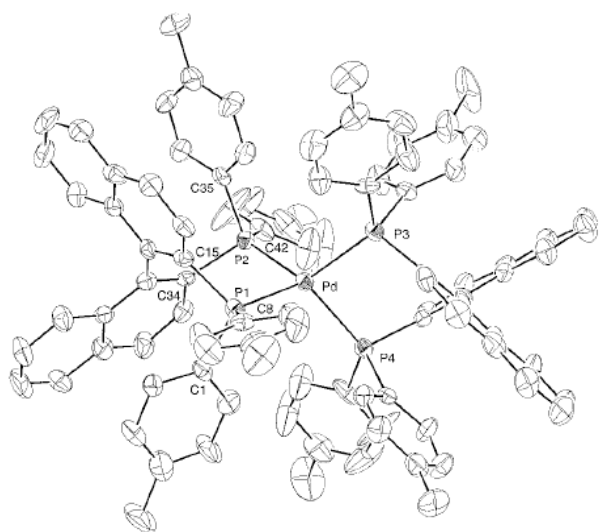
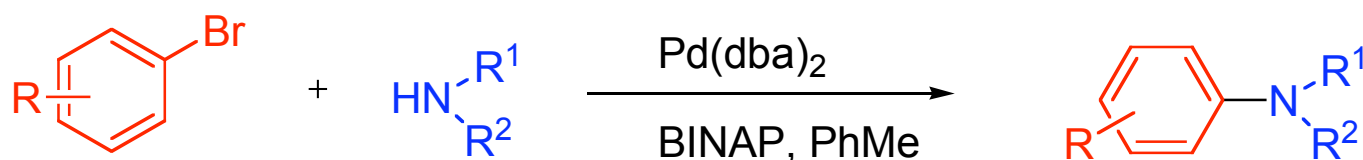
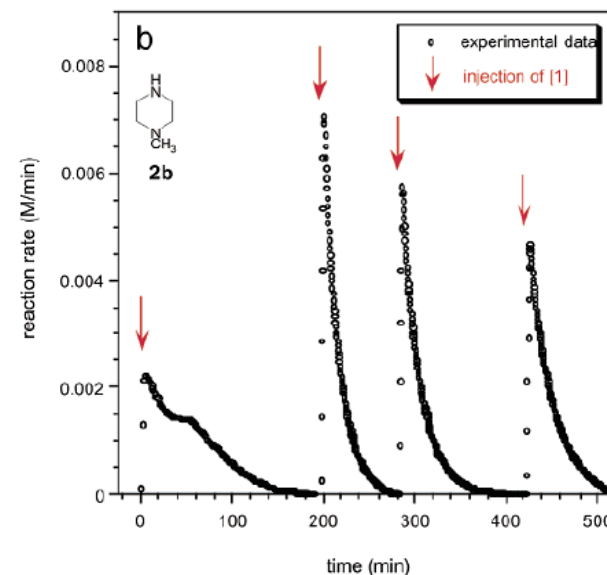


The Mechanism of Pd-Catalyzed Amination Controversy..... And Conclusion?

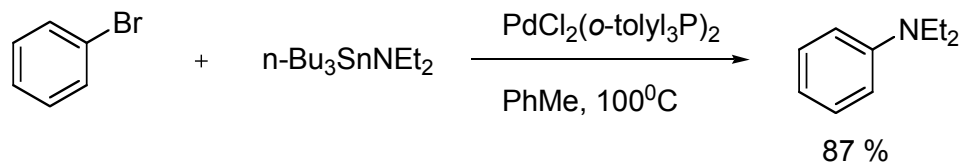


Steve Tymonko
SED Group Meeting
5/9/06

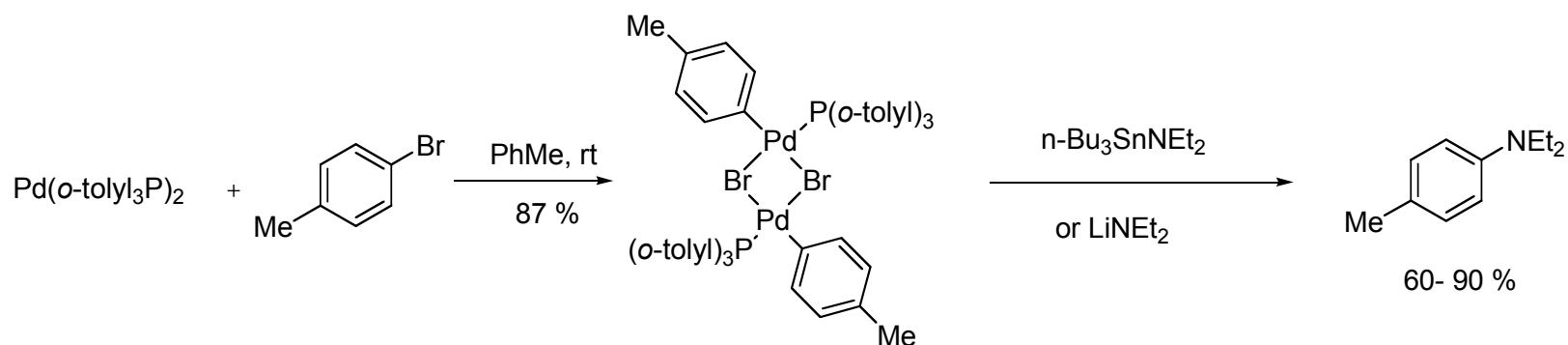


Pd-Catalyzed Amination- Tin

Initial Report- Kosugi, 1983



Hartwig, 1994

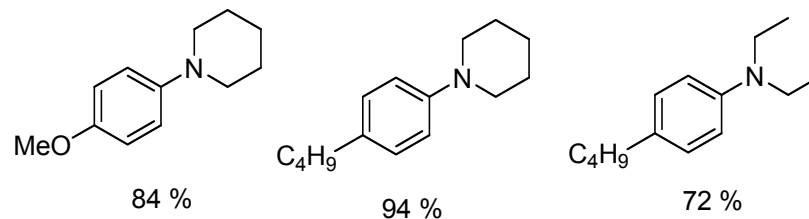
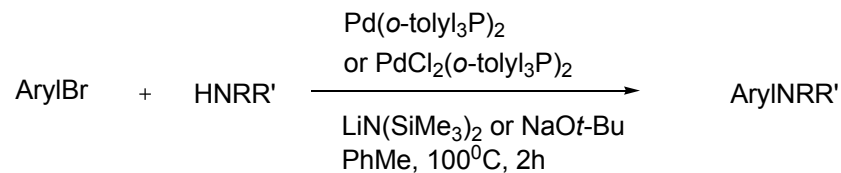
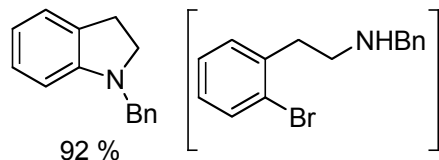
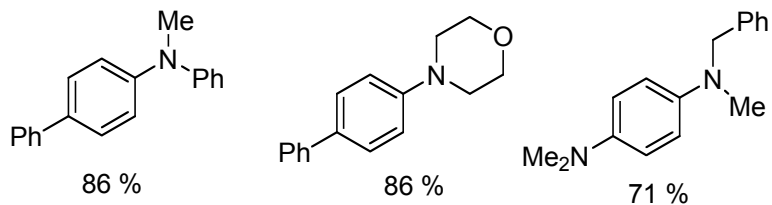
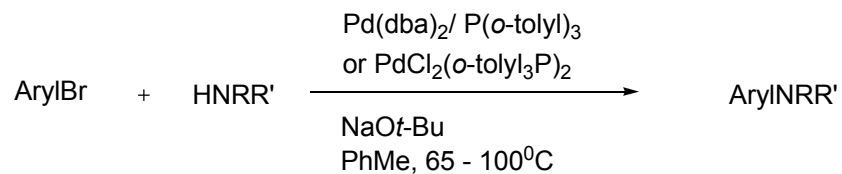


Tin mediated cross-couplings were rarely used due to poor substrate scope and toxicity

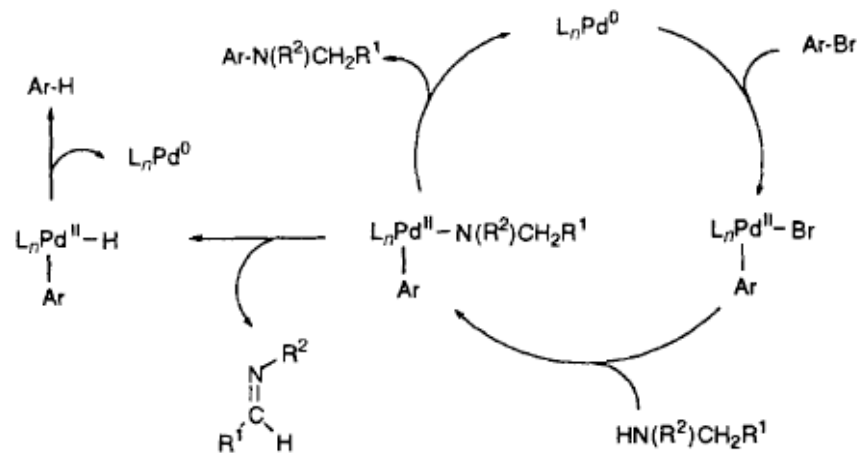
Kosugi, M. et al. *Chem. Lett.* **1983**, 927

Hartwig, J. et al. *J. Am. Chem. Soc.* **1994**, 116, 5969

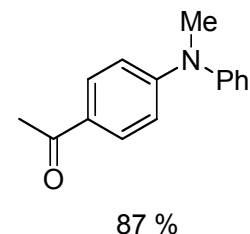
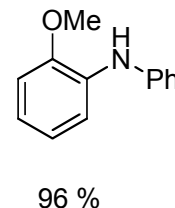
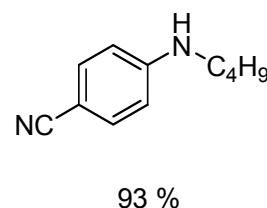
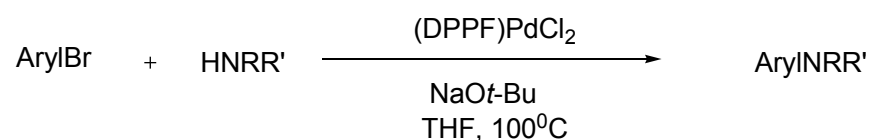
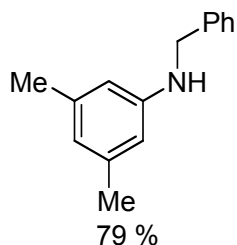
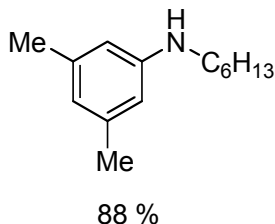
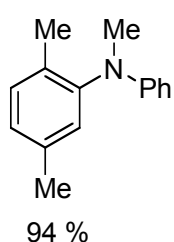
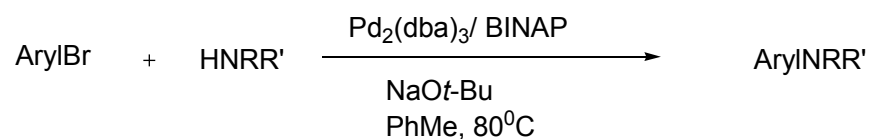
Moving Beyond Tin



Preparatively simple reactions with no need for Sn
Limited to secondary amines

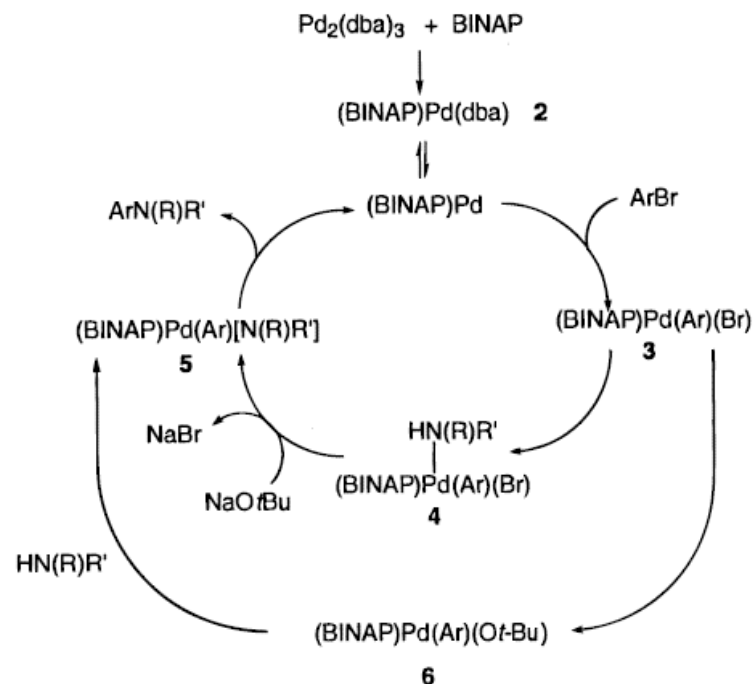
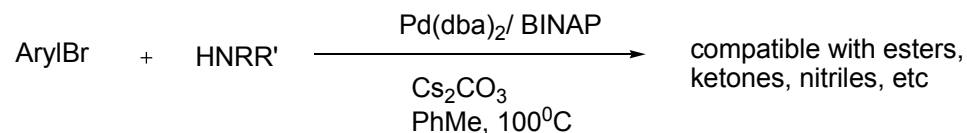
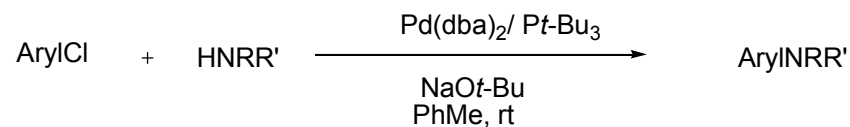
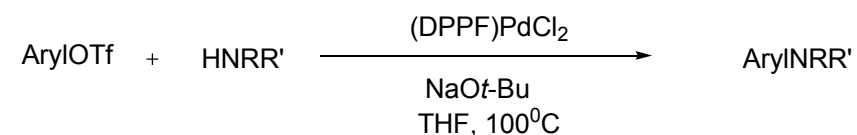
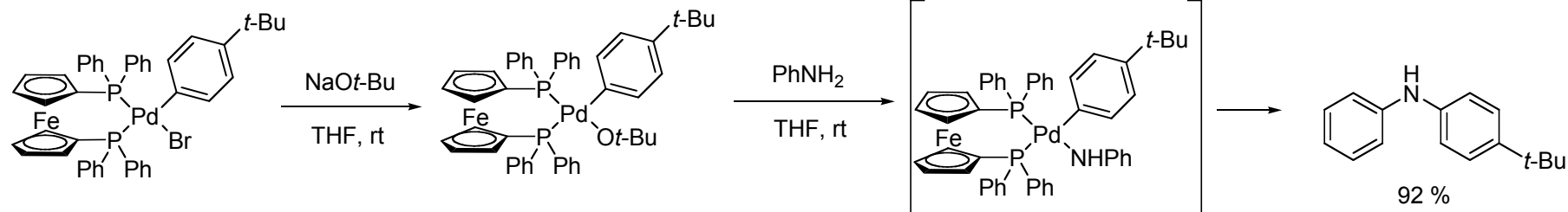


New Ligands, Better Generality



Bidentate ligands prevent β -hydride elimination

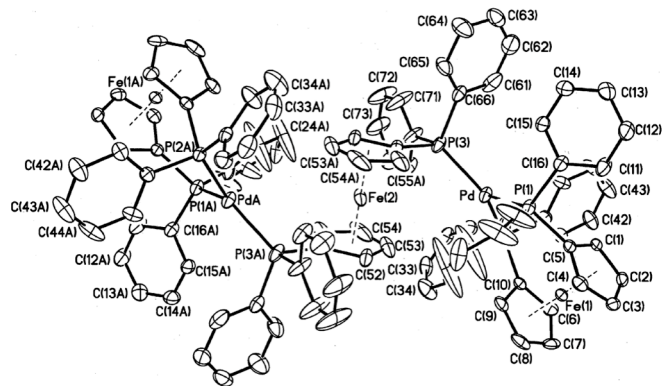
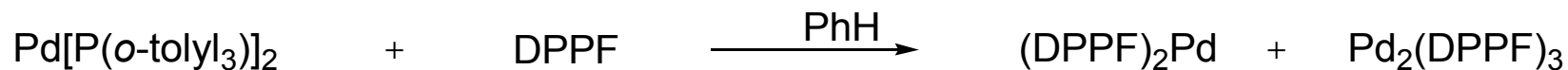
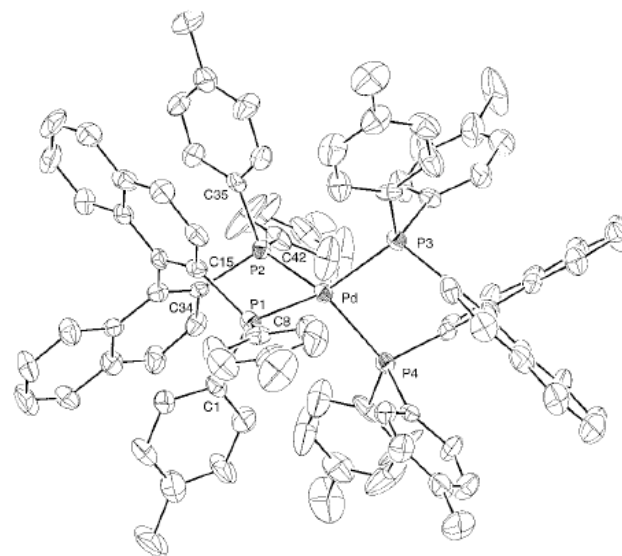
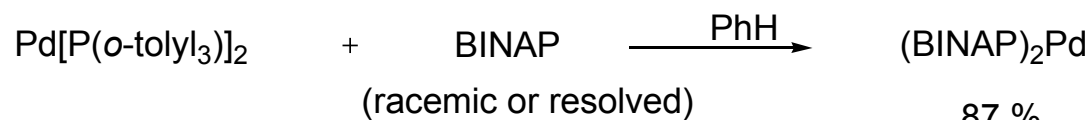
Other Early Observations and Advances



Greatly expanded substrate scope for both amine and halide coupling partners

Hartwig, J. et al. *J. Am. Chem. Soc.* **1996**, *118*, 13109
 Hartwig, J. et al. *Angew. Chem. Int. Ed.* **1998**, *37*, 2407
 Hartwig, J. et al. *J. Org. Chem.* **1999**, *64*, 5575
 Buchwald, S. et al. *J. Org. Chem.* **2000**, *65*, 1144

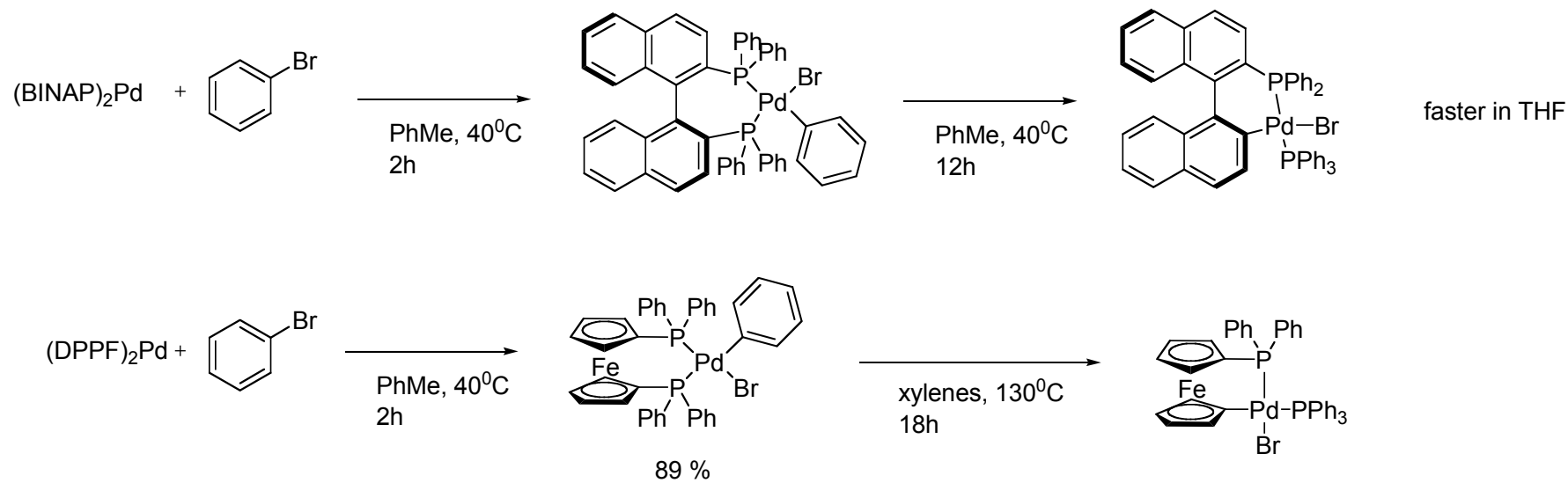
Hartwig- Pd(0) Catalyst Preparation



P-Pd-P angles: in BINAP complexes 90-91°
in DPPF complexes 98-101°

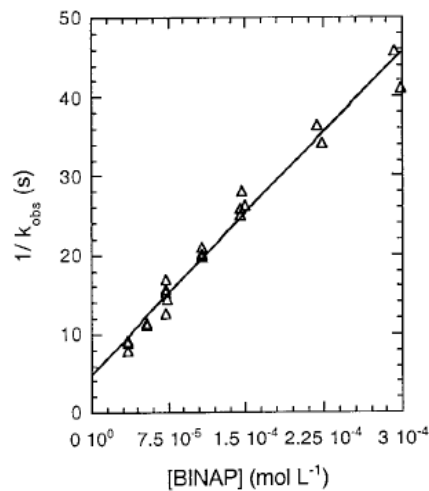
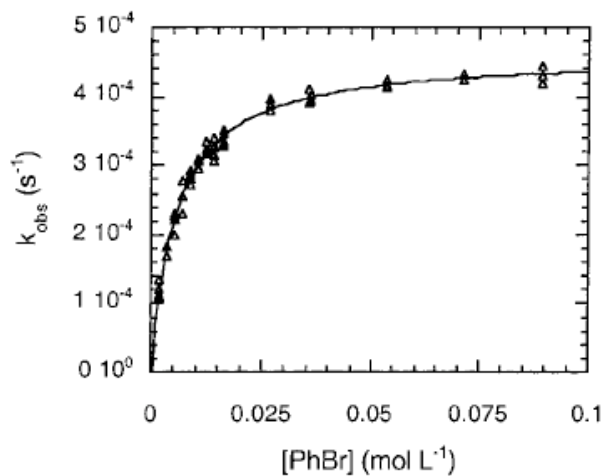
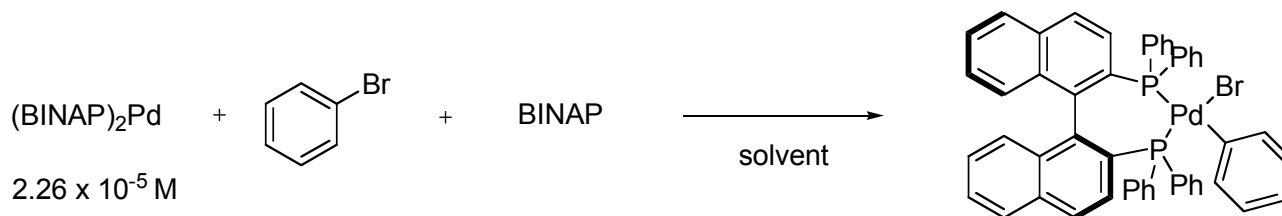
Ligated Pd(0) complexes will simplify kinetic analysis

Oxidative Addition



Oxidative addition products can decompose under the reaction conditions

Oxidative Addition



solvent	rate (x10 ⁻⁵ s ⁻¹)
---------	---

PhH	9.9
-----	-----

THF	7.3
-----	-----

PhMe	8.1
------	-----

bromide	rate (x10 ⁻⁴ s ⁻¹)
---------	---

2-OMe	3.9
-------	-----

2-Me	4.4
------	-----

H	4.3
---	-----

taken in saturation range

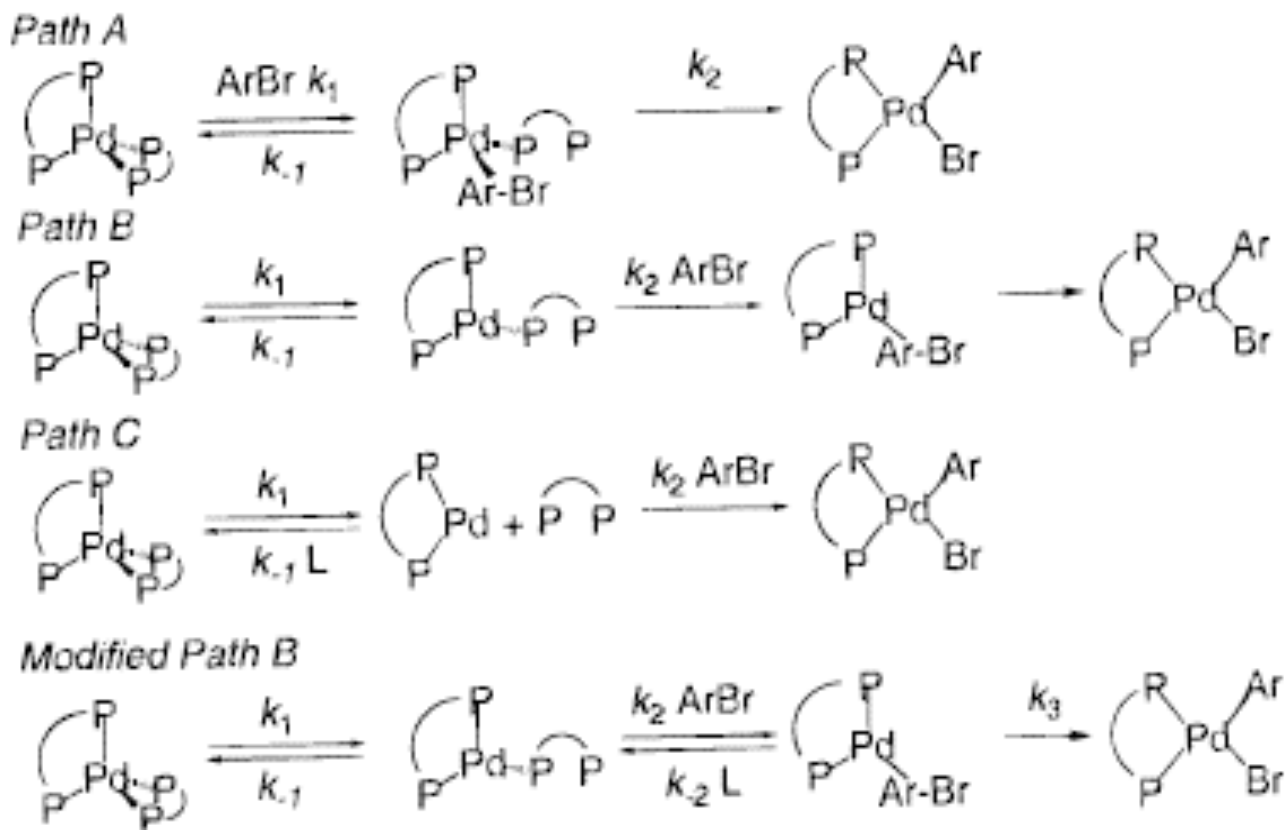
1st order in bromide under $1.78 \times 10^{-3} \text{ M}$
 0th order at high bromide concentration

-1st order in ligand

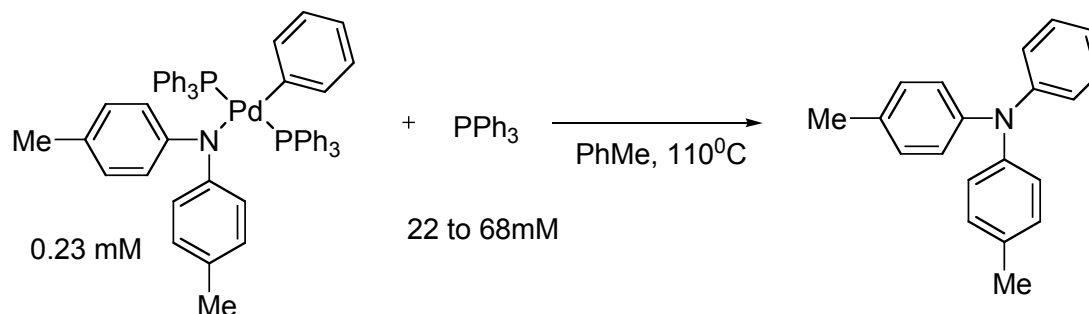
With DPPF all data matches except always 1st order in bromide

Oxidative Addition Mechanism

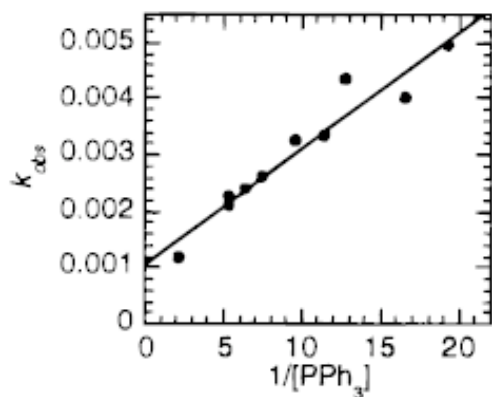
Given the previous data, which of the following mechanisms is operative?



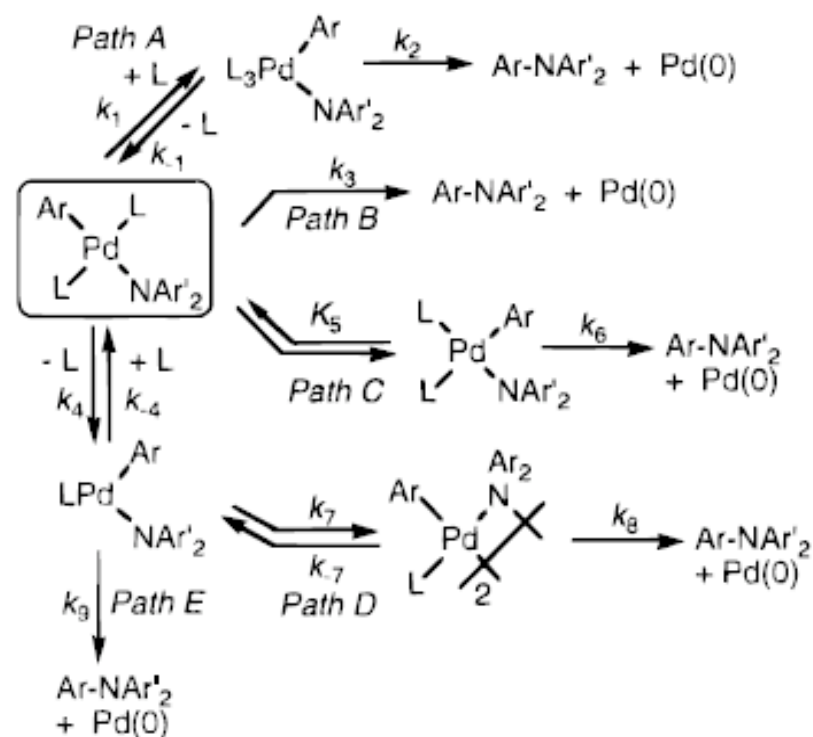
Reductive Elimination



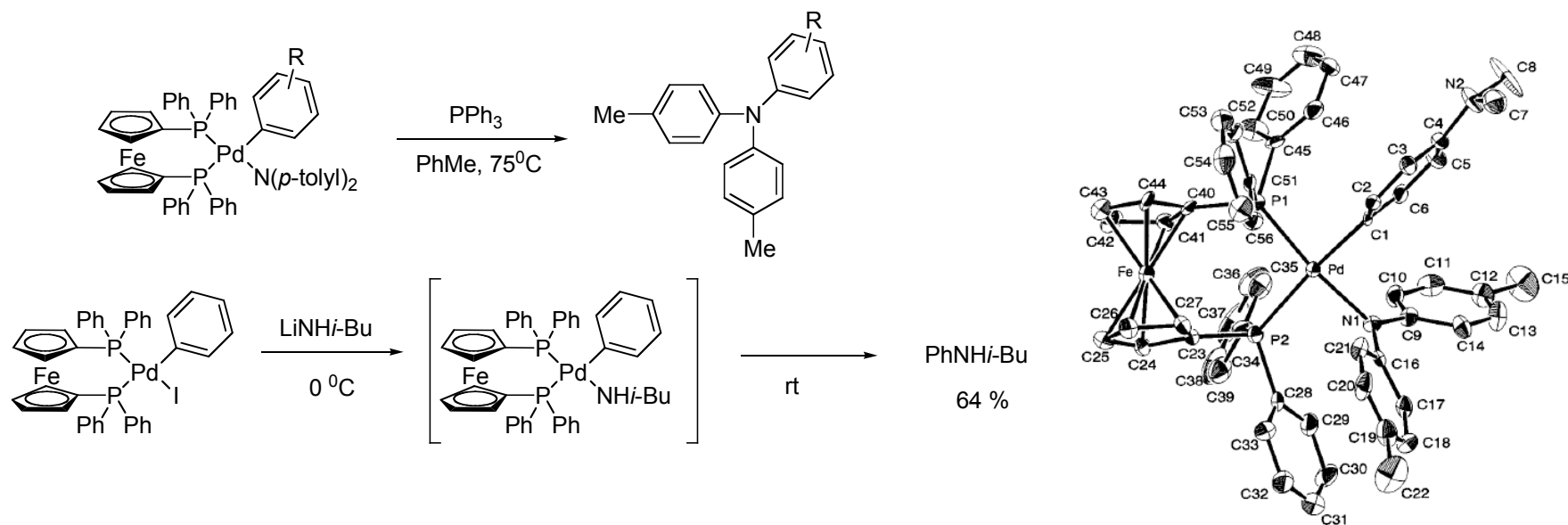
Rate between 0 and -1^{st} order in ligand
 1^{st} order in Pd



Paths C and E both operate



Reductive Elimination



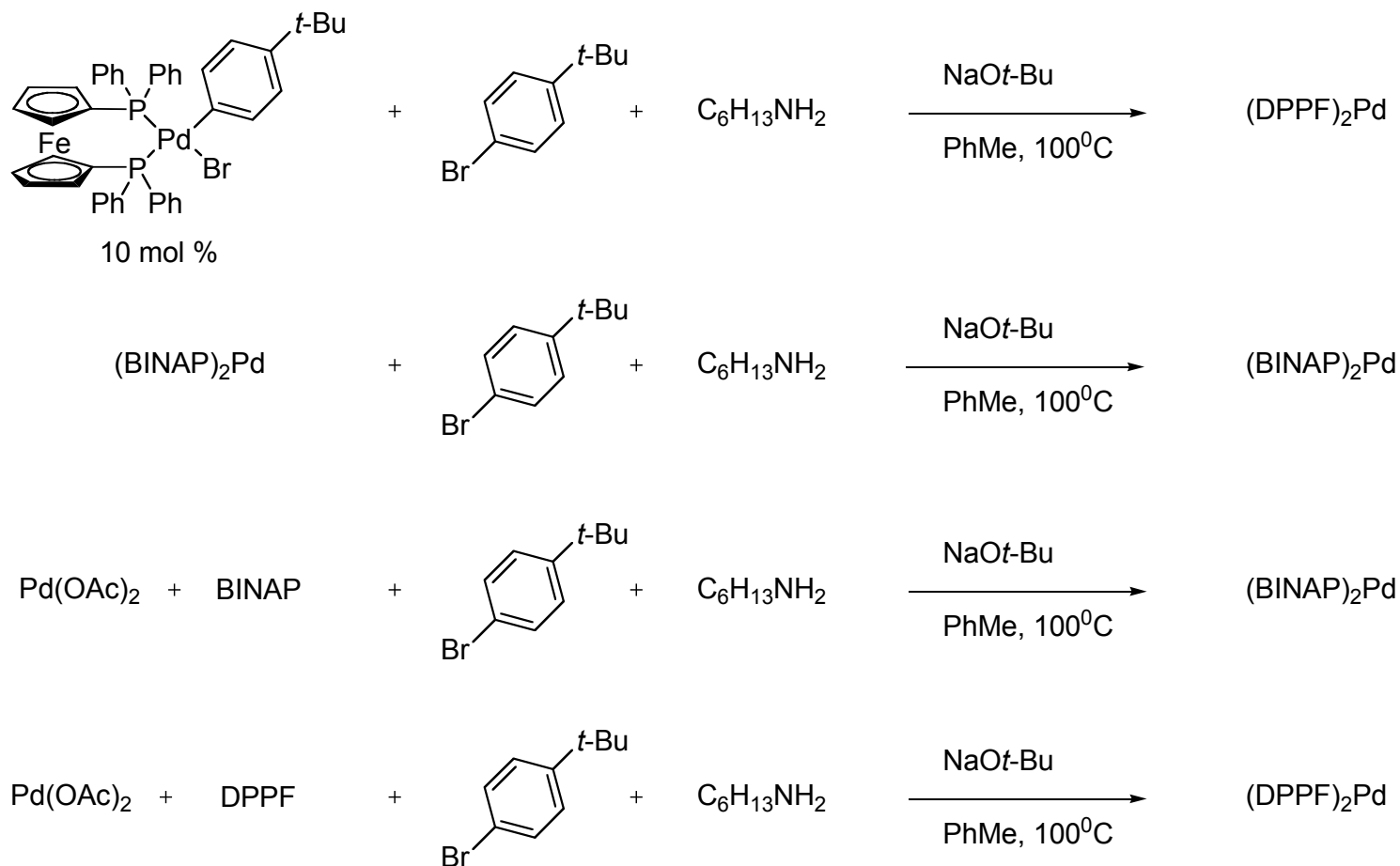
0th order in added ligand

P-Pd-P 100⁰

Rate= 4-Cl > H > 4-Me > 4NMe₂ > 4OMe

Direct reductive elimination from 4-coordinate Pd

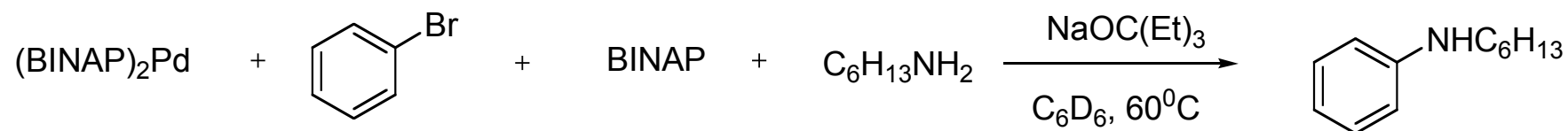
Catalyst Resting State



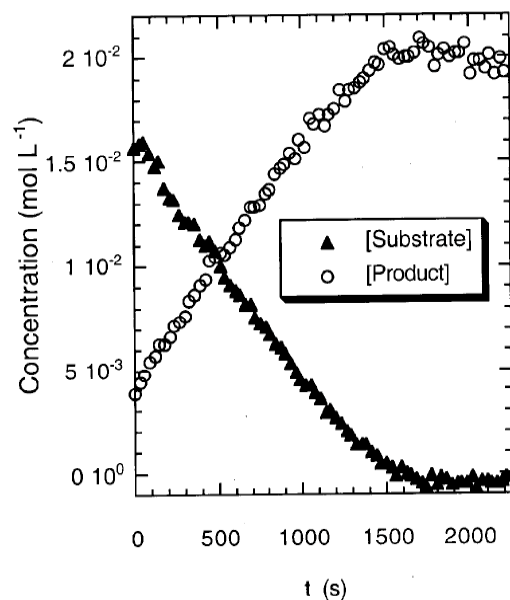
>85 % in all cases, no monooxide seen

^{31}P NMR shows only L_2Pd regardless of precatalyst or stoichiometry

Catalytic Conditions- Primary Amines



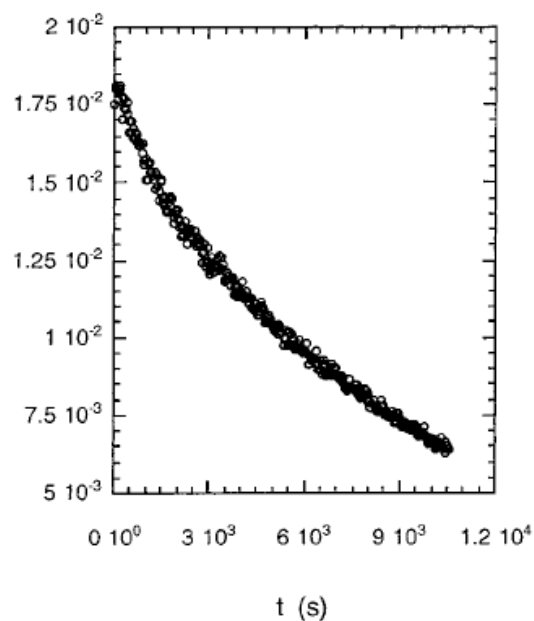
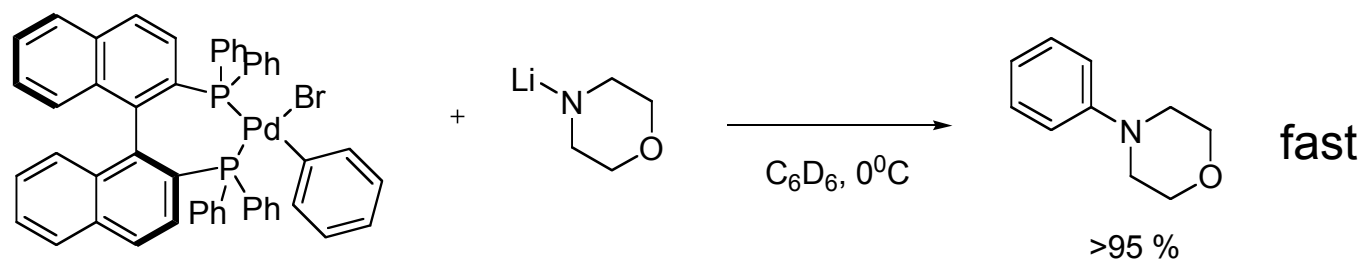
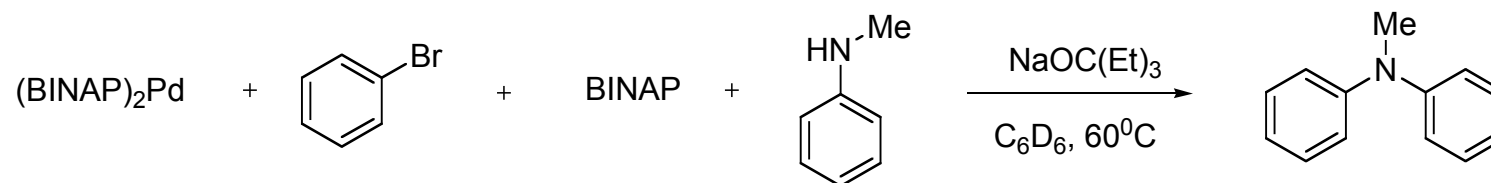
Reaction was zero order in BINAP, bromide, base, and amine



By ^{31}P NMR >85% catalyst remains after complete reaction

amine	$k_{\text{obs}} (\times 10^{-5} \text{ s}^{-1} \text{ mol}^{-1} \text{ L})$
hexylamine	3.2
<i>sec</i> -butylamine	3.1
benzylamine	2.8
<i>p</i> -anisidine	3.0
aniline	2.3

Catalytic Conditions- Secondary Amines

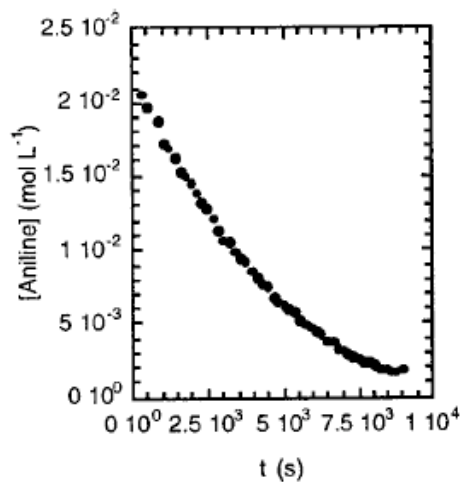
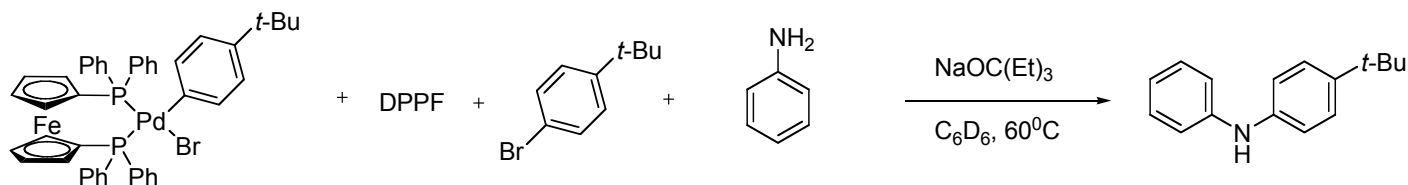


Zero order in BINAP, bromide, and base, appears 1st order in amine

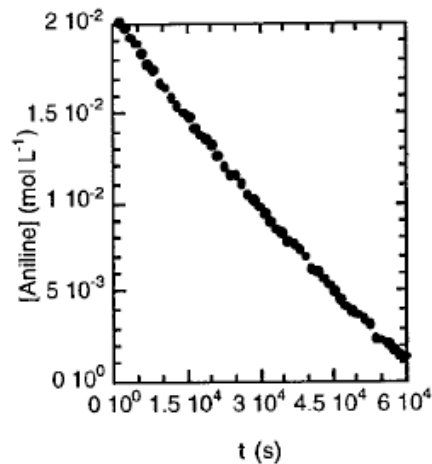
³¹P NMR monitoring of catalytic reactions shows loss of $(\text{BINAP})_2\text{Pd}$

Nonlinear behavior due to catalyst decomposition

Catalytic Conditions- DPPF



2 mM DPPF



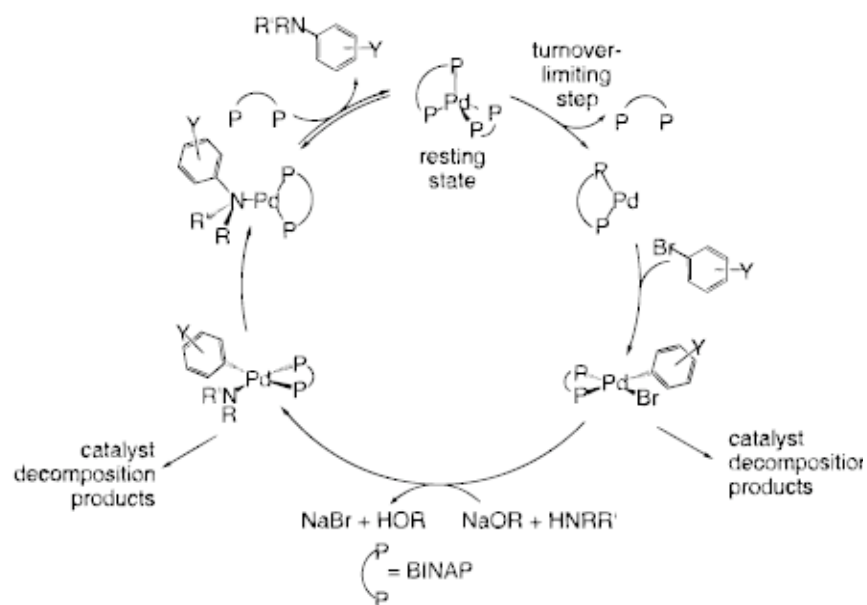
21.6 mM DPPF

1st order in bromide, -1st order in DPPF
Zero order in base, amine order complex

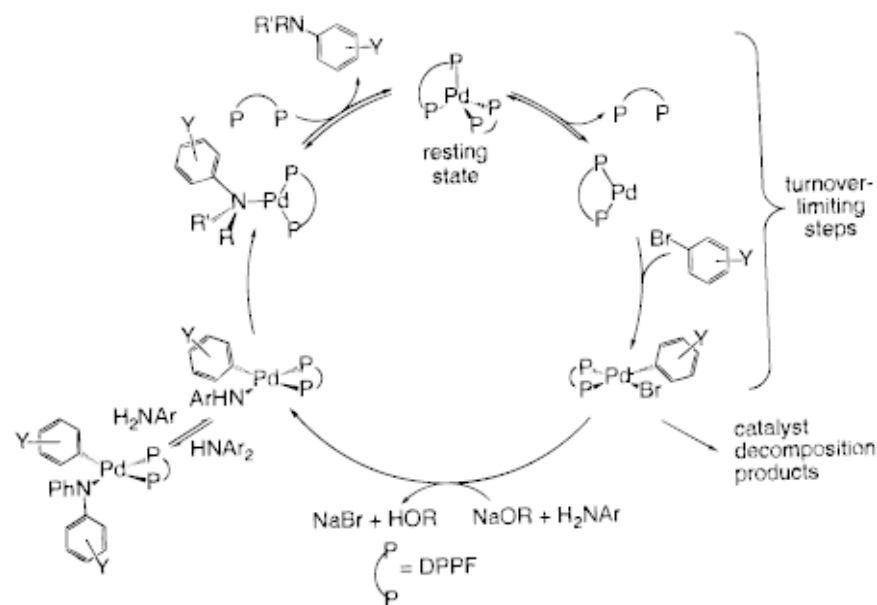
Product inhibition gives apparent first-order behavior in amine

Proposed Mechanism

For BINAP

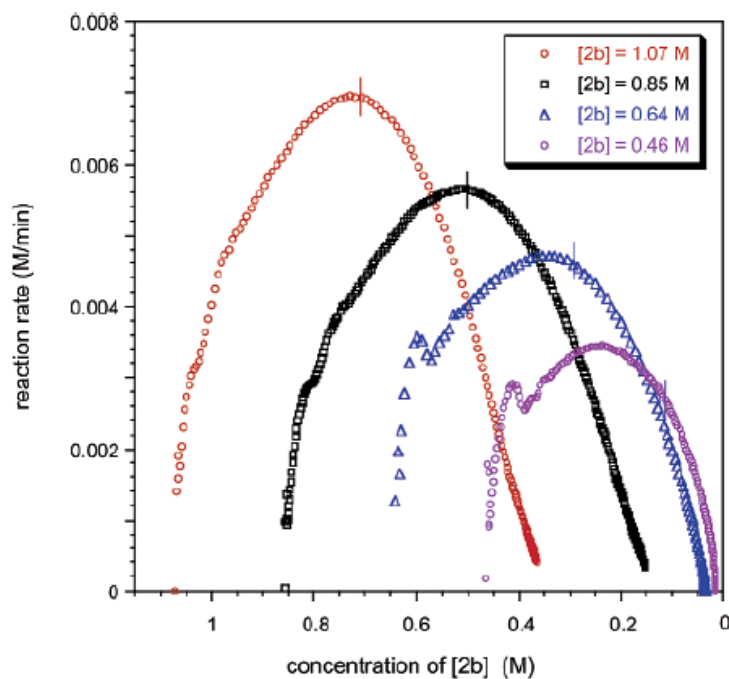
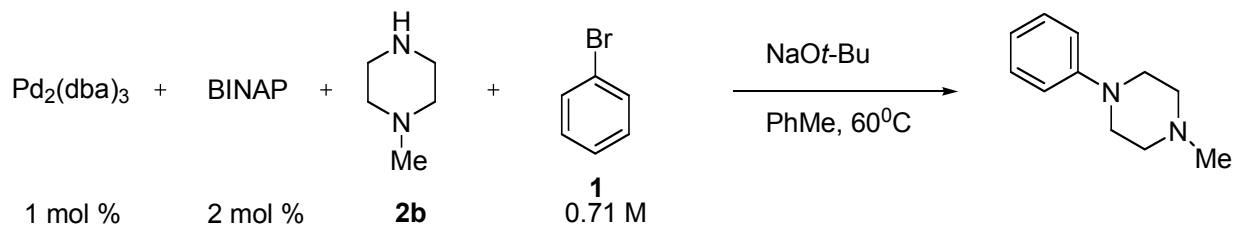


For DPPF

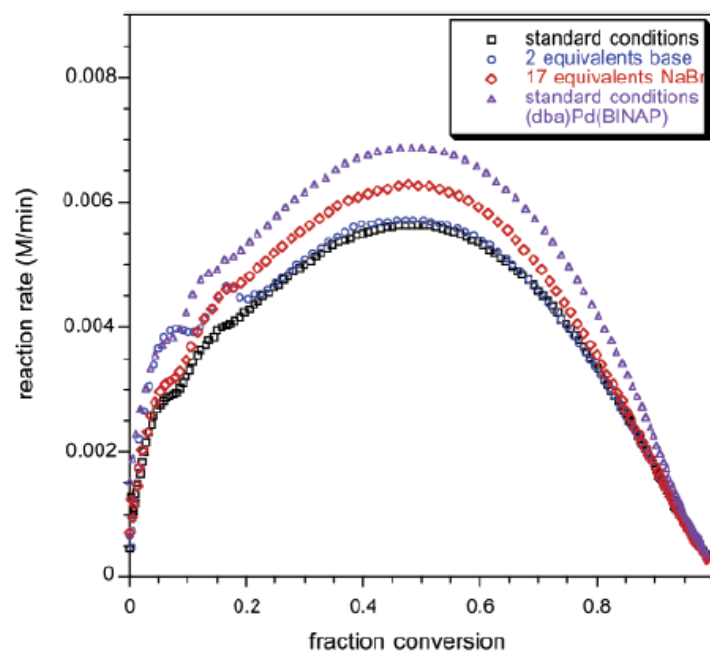


L_2Pd lies directly on the catalytic cycle; ligand dissociation/oxidative addition is rate determining

Reaction Calorimetry Kinetics

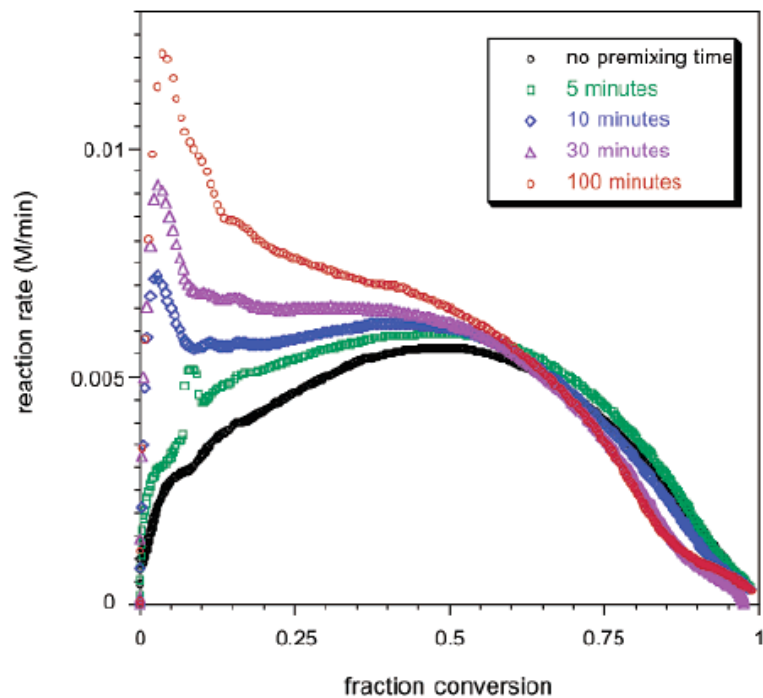
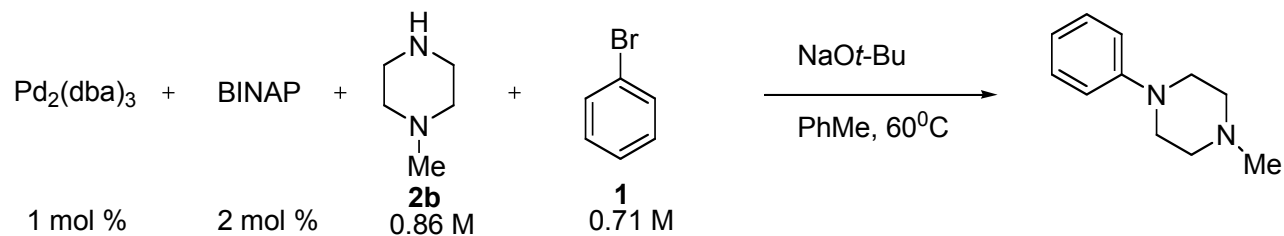


Hashes- 0.35 M in bromide



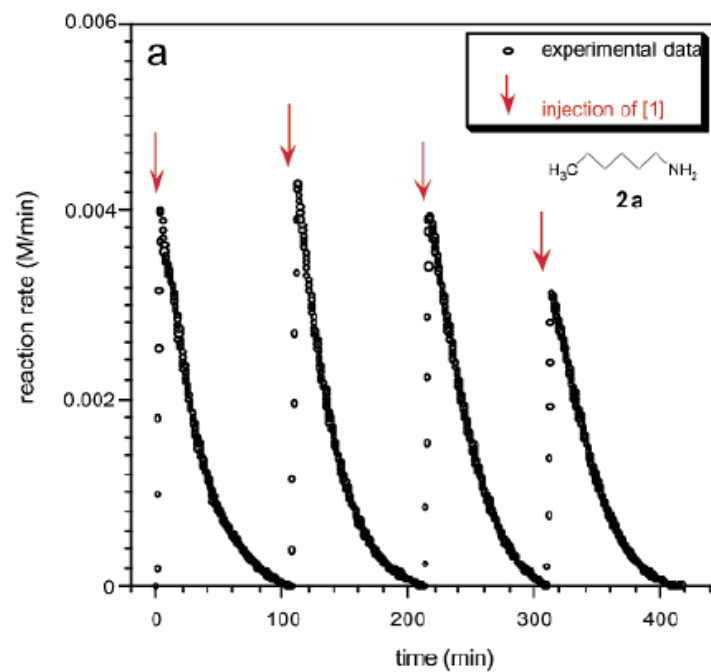
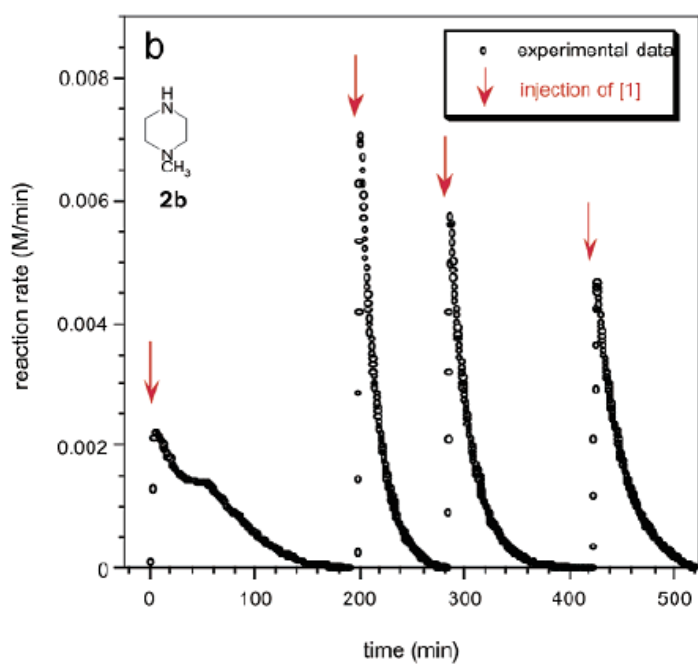
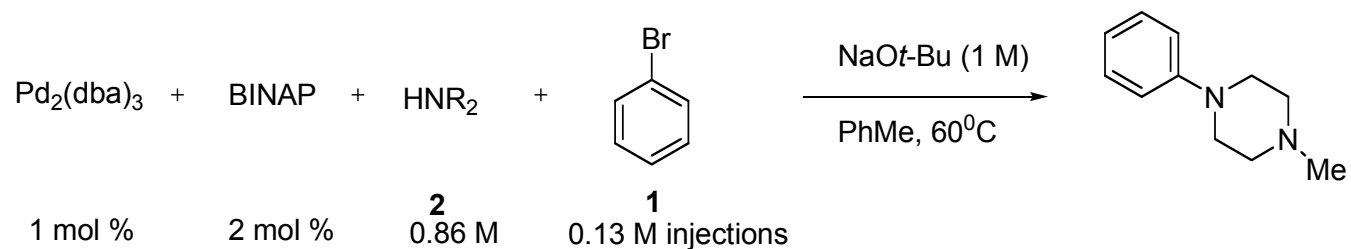
Induction period suggests changing Pd species: positive order in amine and bromide

Catalyst Premixing



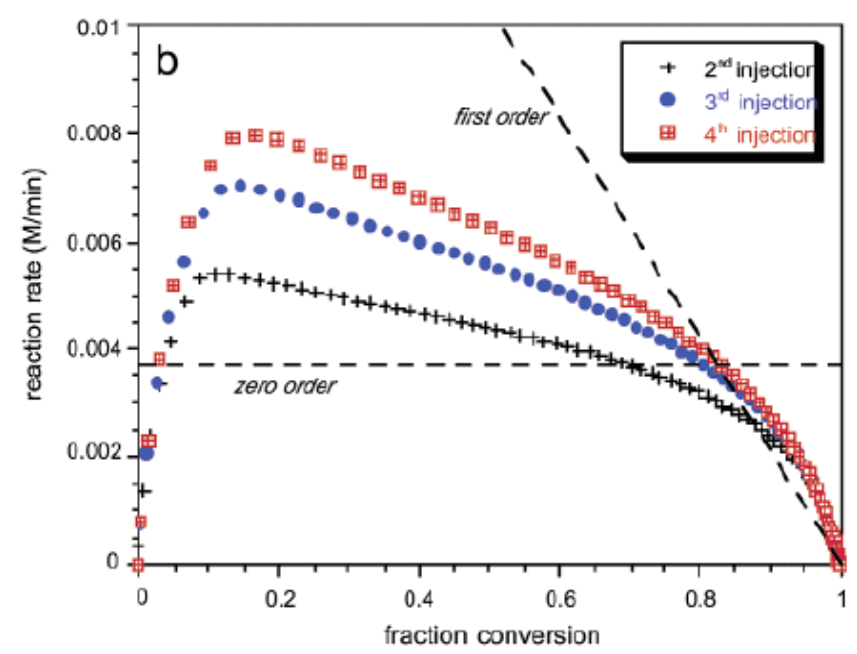
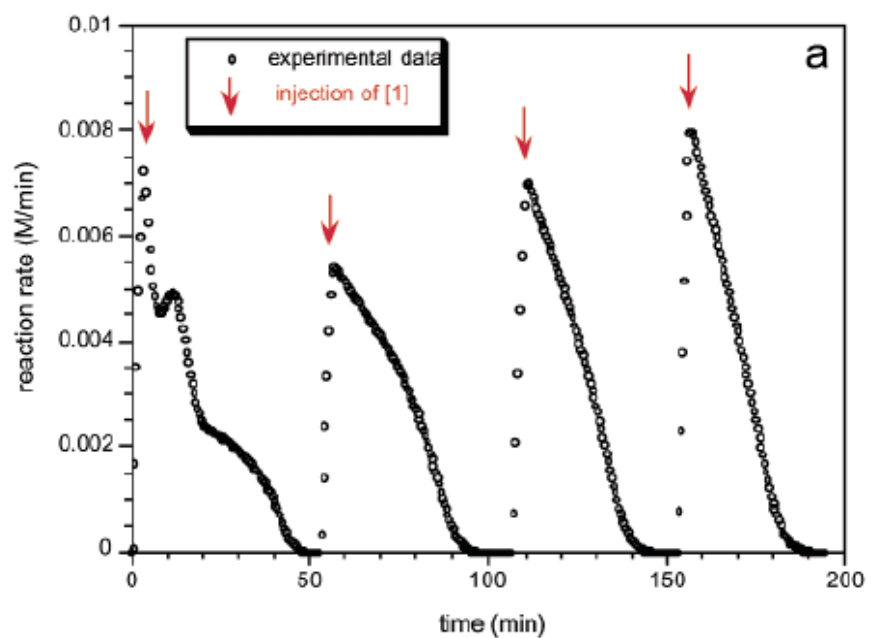
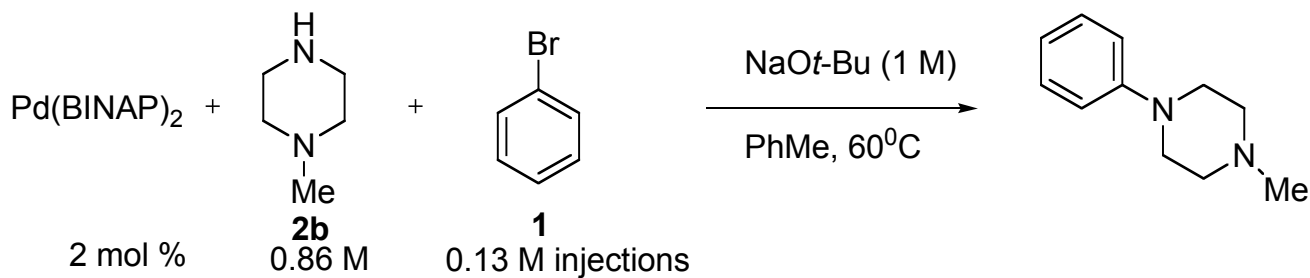
Premixing of all components except bromide gives greatly increased initial rates

Sequential Injections



Primary amines have much shorter induction periods

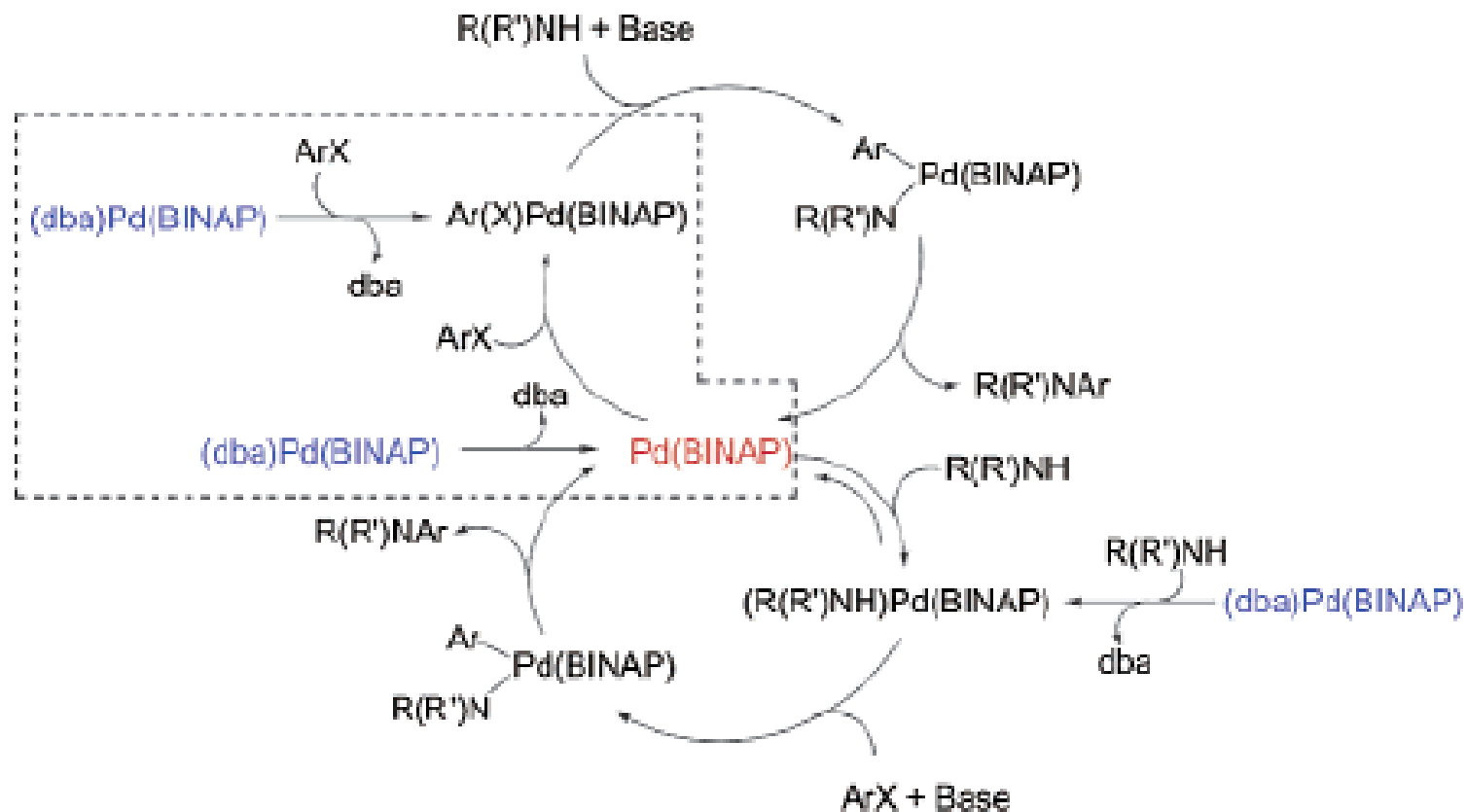
Sequential Injections



Apparent zero order due to increasing Pd linked with decreasing bromide

Most catalyst is inactive throughout the reaction: reaction never reaches full catalyst loading

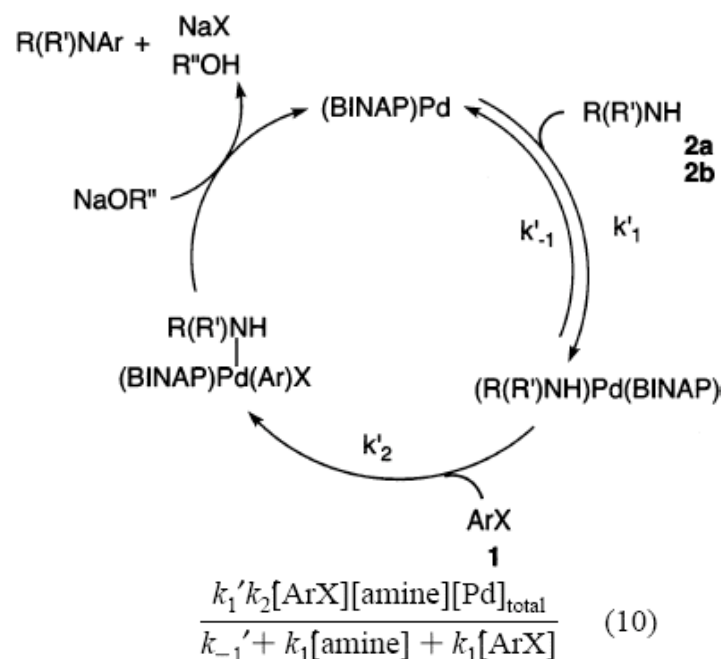
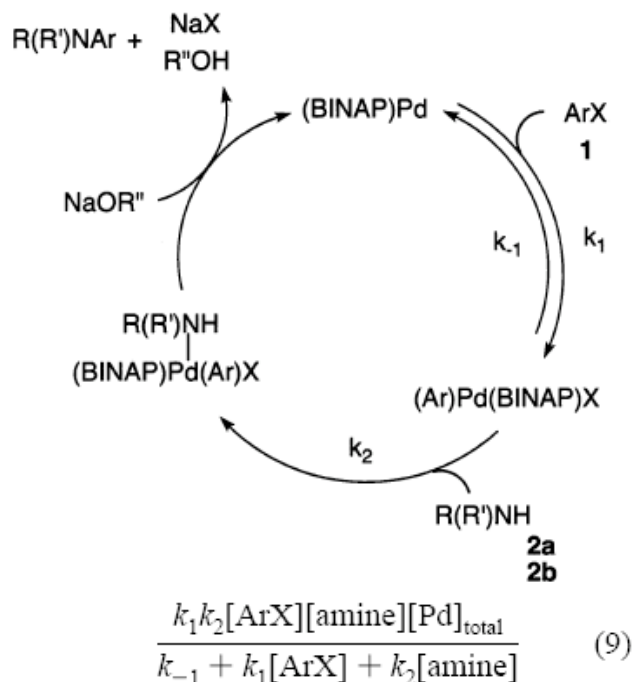
Catalyst Activation Mechanism



Amine displacement of dba during premixing gives higher initial rate
Easier displacement with primary amines explains reduced induction period

Steady-State Mechanism

Two possibilities for zero order in base, positive order in amine and bromide

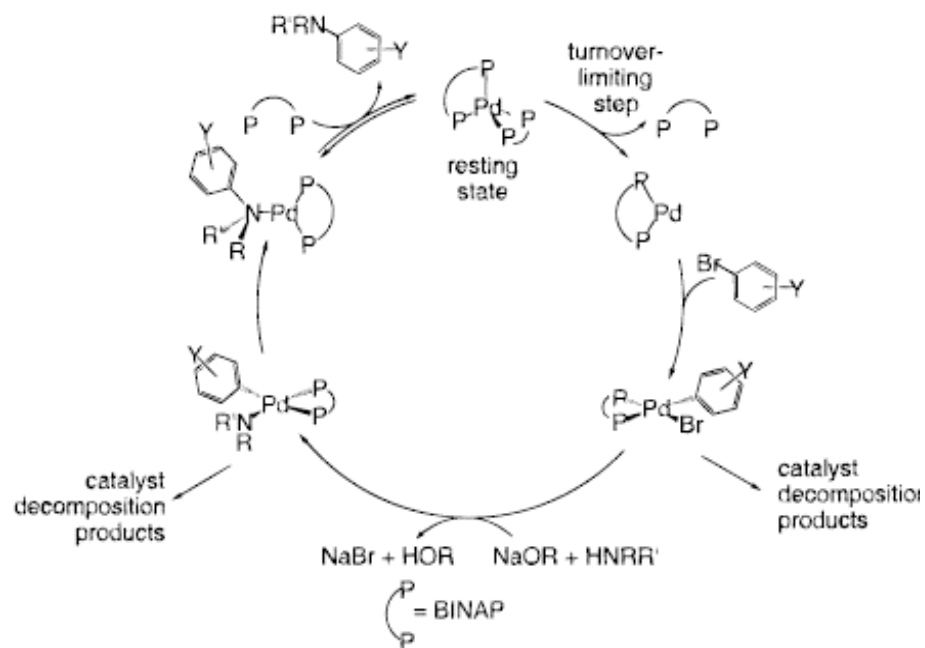


model parameter	primary amine <chem>CCCCCN</chem>		secondary amine <chem>CN1CCNCC1</chem>	
	Eq. (9) Scheme 3	Eq. (10) Scheme 4	Eq. (9) Scheme 3	Eq. (10) Scheme 4
k_1 (min.M ⁻¹)	4.43	1.06	37.00	2.88
k_{-1} (min ⁻¹)	0.05	0.05	11.88	11.88
k_2 (min.M ⁻¹)	1.06	4.43	2.88	37.00
(k_1/k_{-1}) (M ⁻¹)	85.96	20.62	3.11	0.24

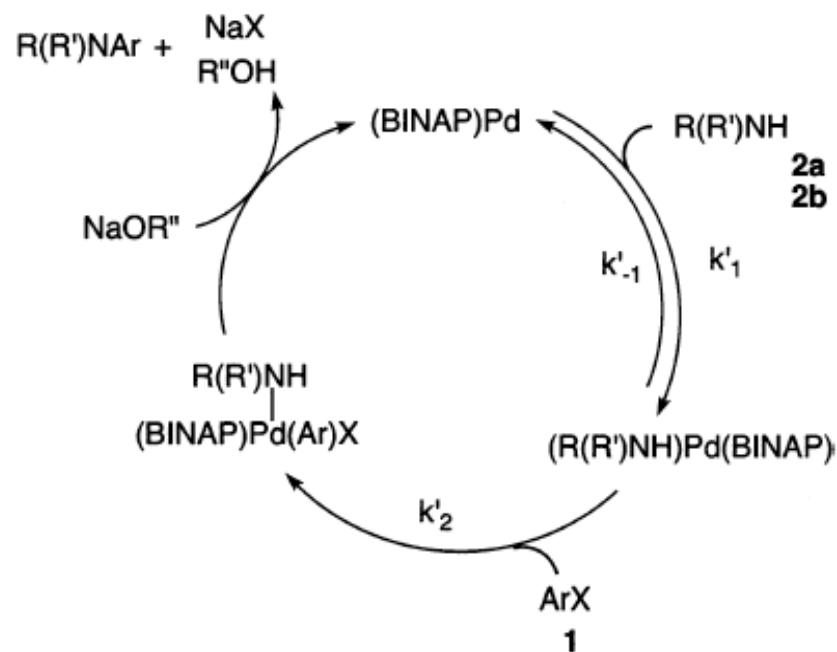
Data suggests amine binding prior to oxidative addition

Competing Proposals

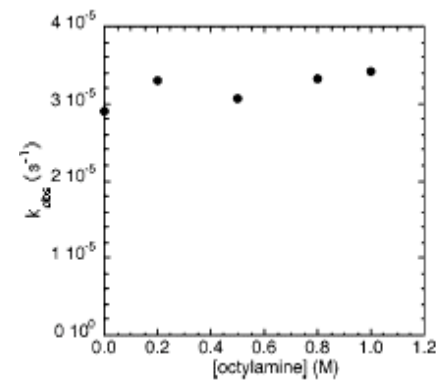
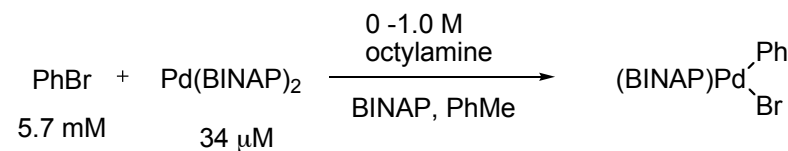
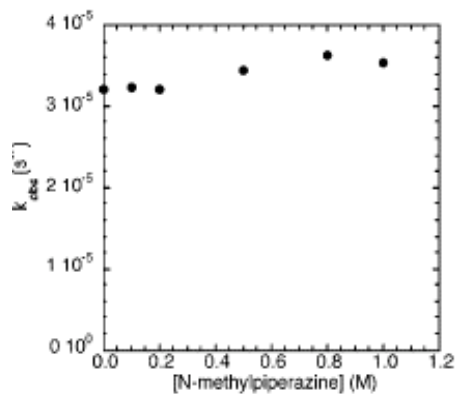
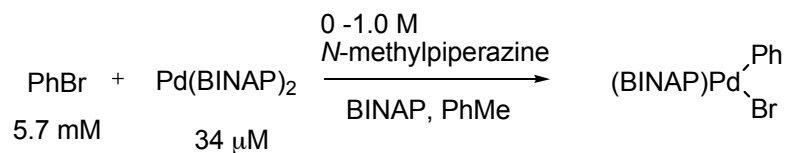
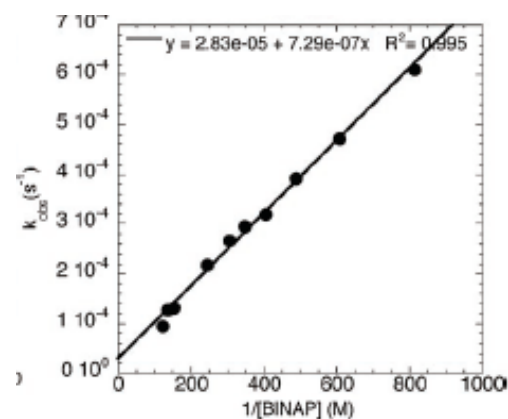
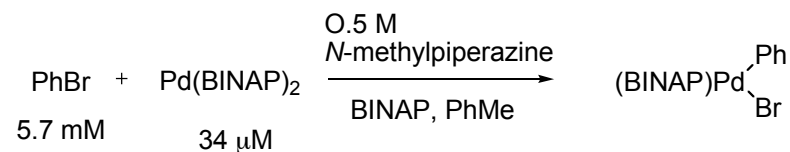
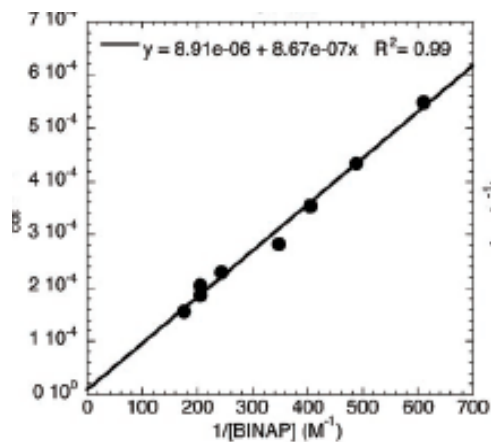
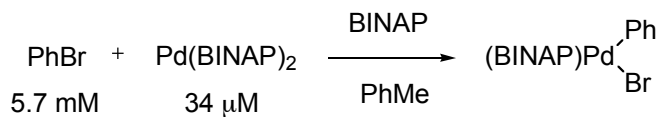
Hartwig



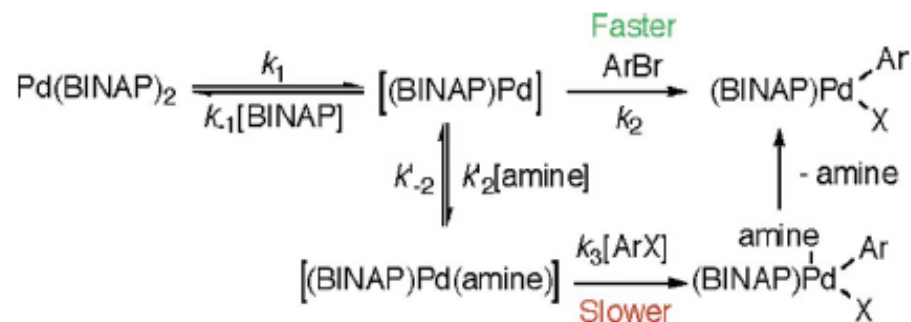
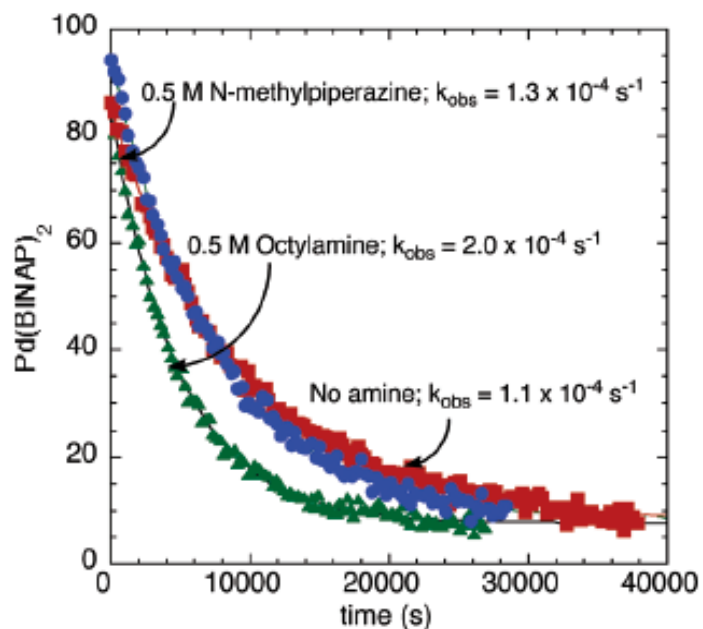
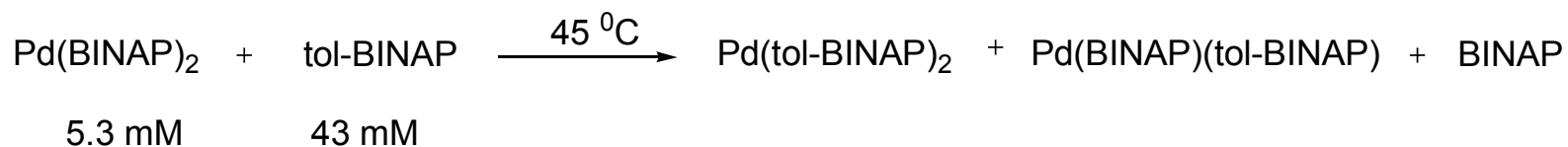
Blackmond and Buchwald



First Order in Amine Reconsidered

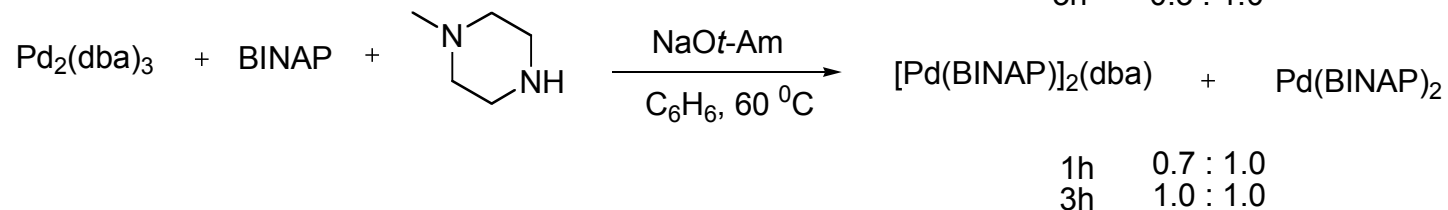
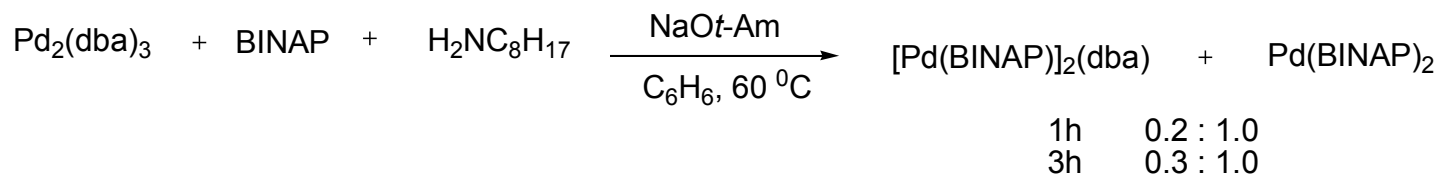
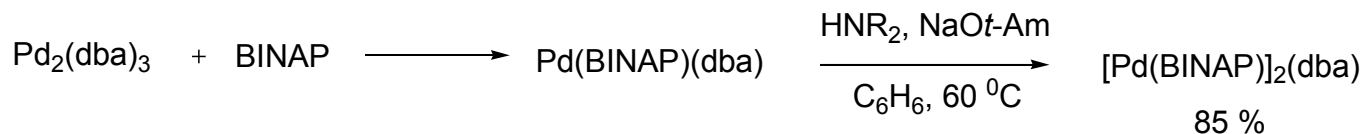


First Order in Amine Reconsidered

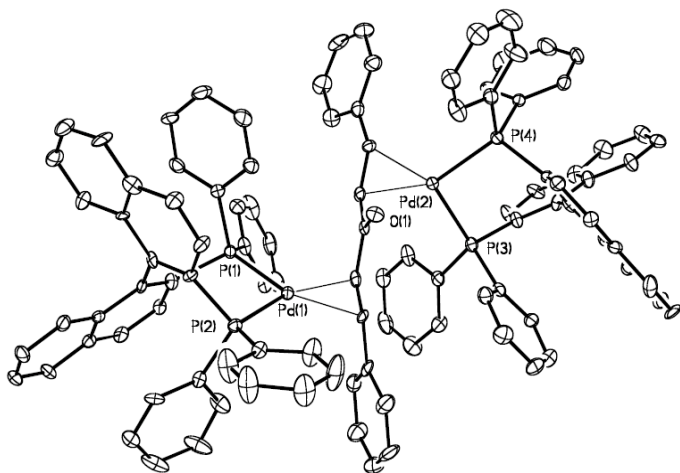


Amine has no effect on oxidative addition or catalyst composition

Toward A Revised Mechanism

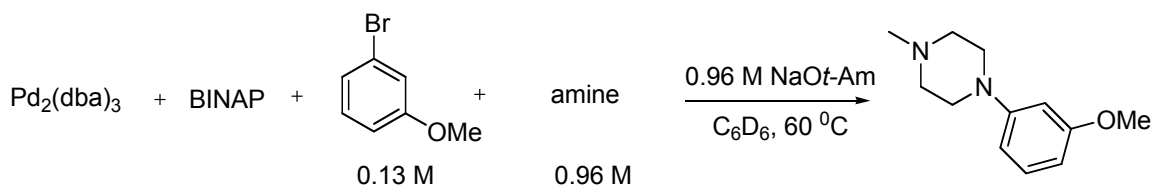
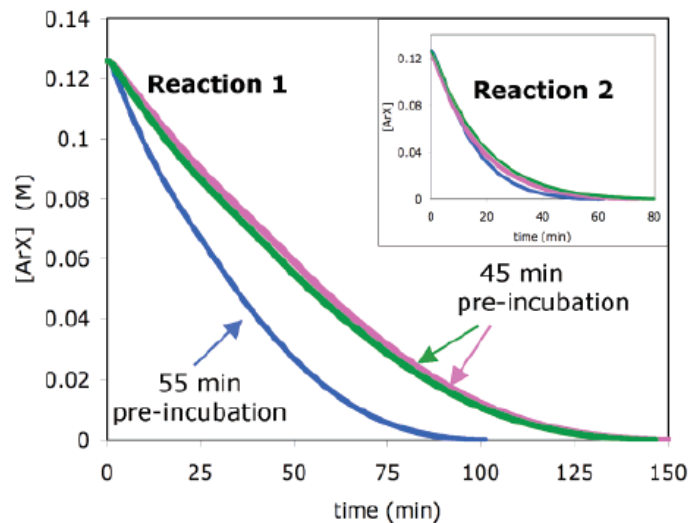
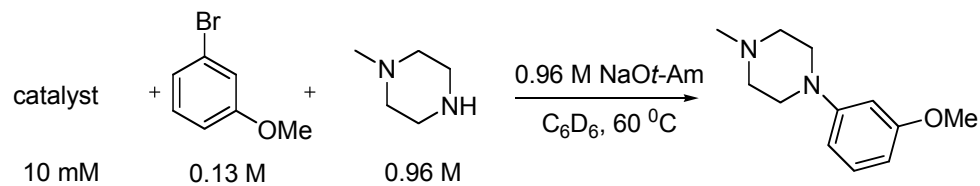
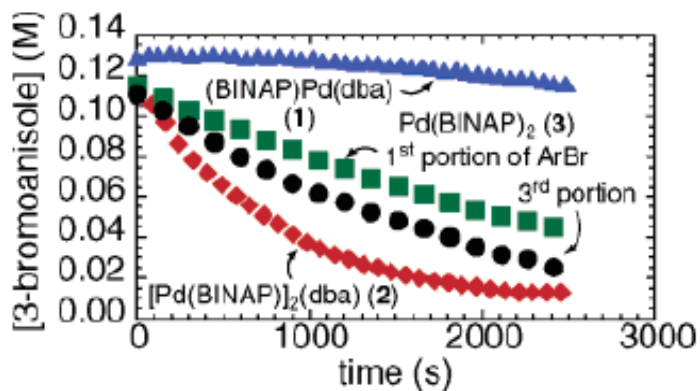


Identical observations during catalytic reactions, catalyst decomposes over time



Catalyst mixture is different for primary and secondary amines

Catalyst Composition Effects



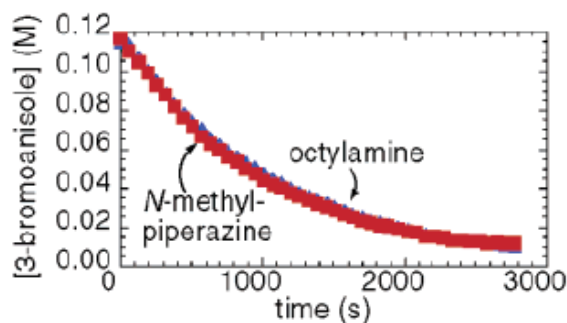
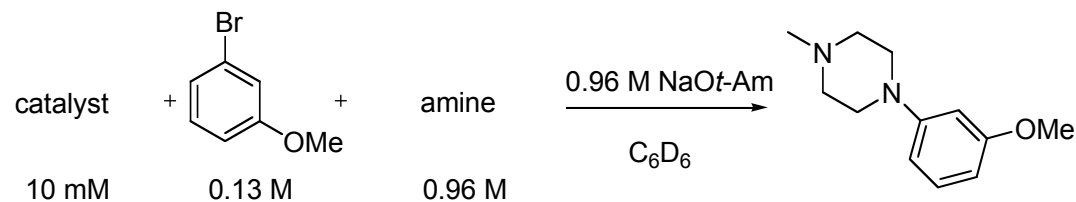
Differences between primary and secondary amines in 2002 paper due to sensitive incubation

Effects of incubation time

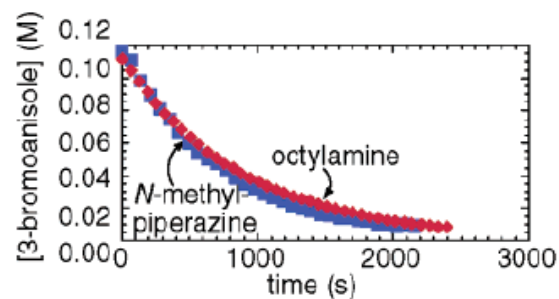
Pink, blue = *N*-methylpiperazine

Green = octylamine

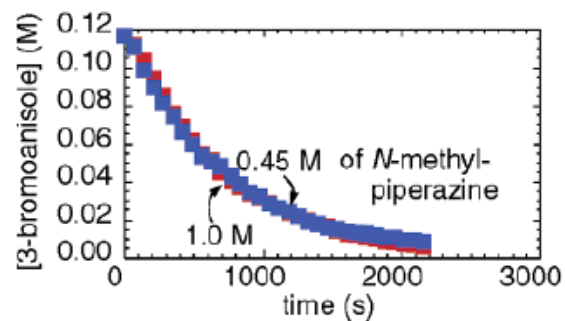
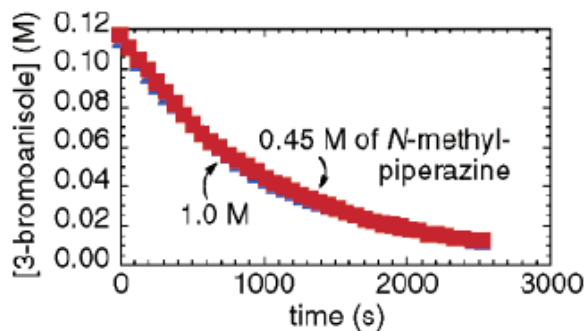
Amine and Catalyst Roles



With $[\text{Pd}(\text{BINAP})]_2(\text{dba})$, 50°C

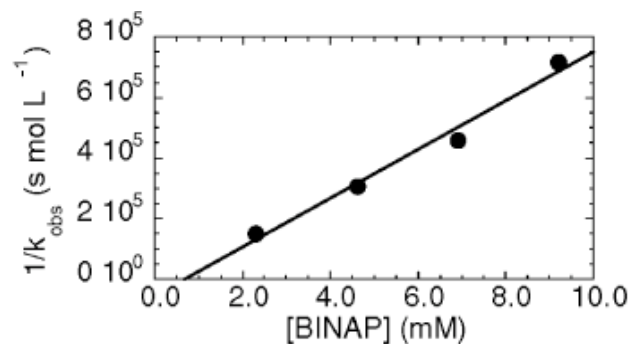
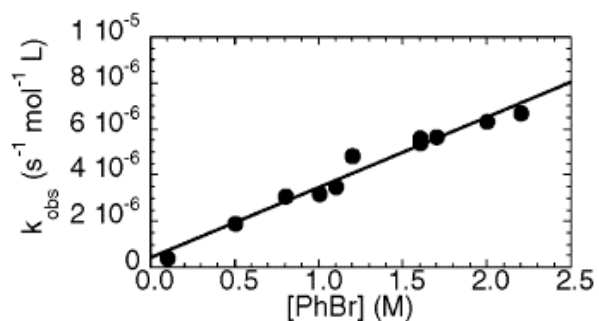


With $\text{Pd}(\text{BINAP})_2$, 70°C



$[\text{Pd}(\text{BINAP})]_2(\text{dba})$ is more active: amine is zero order

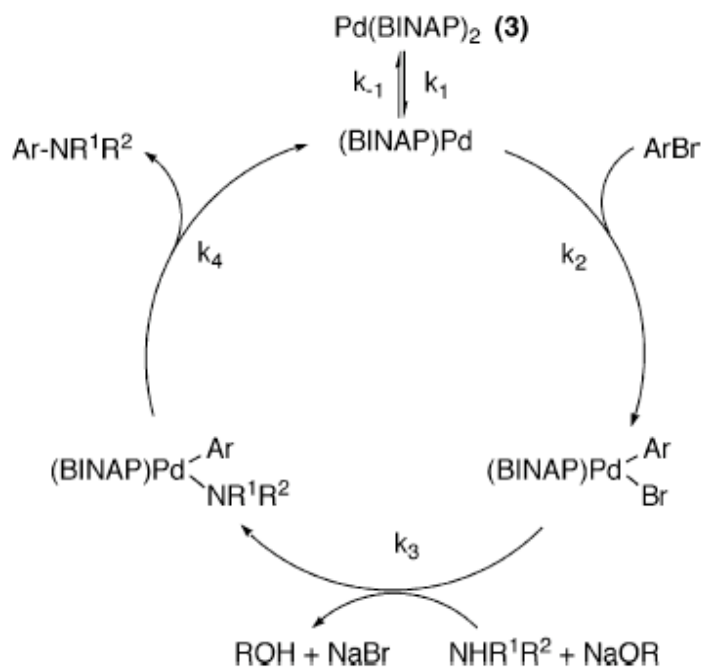
Bromide and Ligand



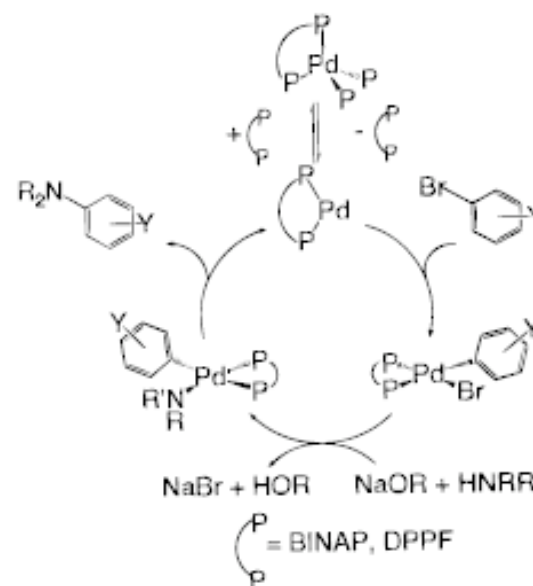
1st order in bromide, -1st order in ligand

Error was made in 2000 paper when determining order

Current Mechanism



Prior to 2000



$\text{Pd}(\text{BINAP})_2$ lies off the catalytic cycle: amine is not involved in oxidative addition

Conclusions

A combination of techniques was required to determine the mechanism of Pd-catalyzed amination [including](#):

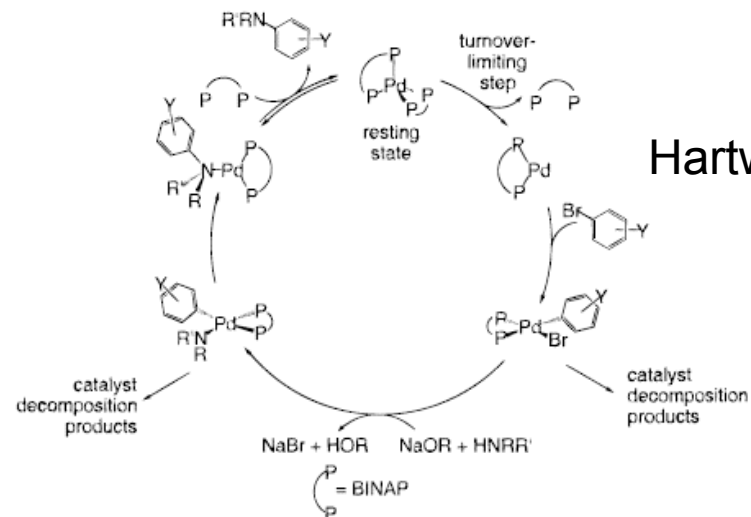
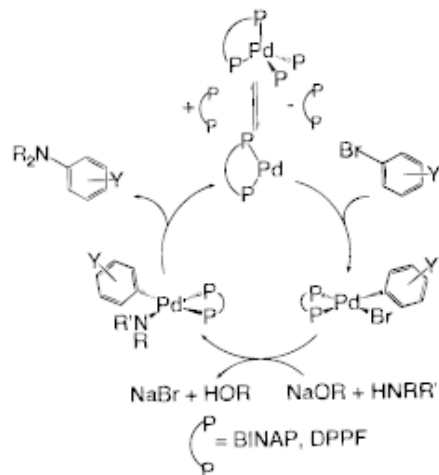
- stoichiometric analysis of individual steps of the catalytic cycle
- NMR analysis of catalyst composition under the reaction conditions
- in situ* monitoring under preparative conditions
- classical (initial rates) kinetics of both stoichiometric and catalytic systems

The amination proceeds through rate-limiting oxidative addition following dissociation of ligand from Pd(0)

Both stoichiometric and catalytic systems must be explored to identify the active mechanism under preparative conditions

Proposed Mechanisms

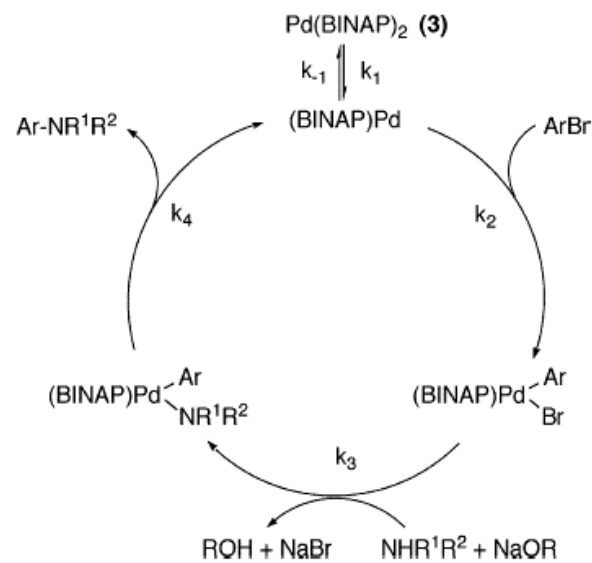
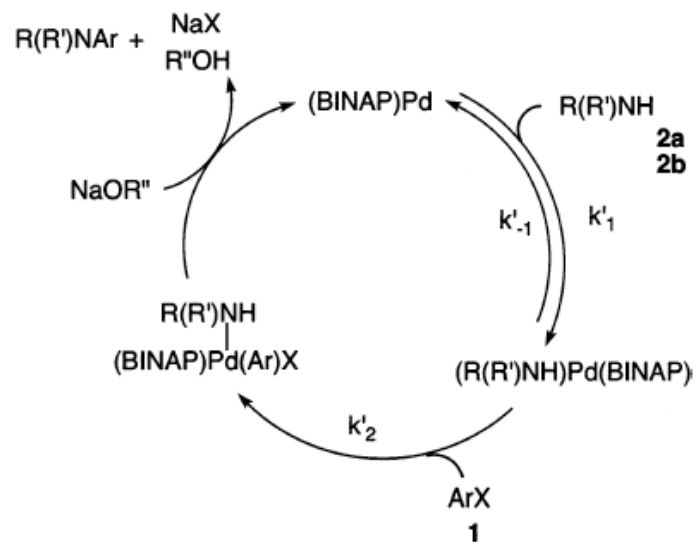
Early Proposal



Hartwig, 2000

Revised, 2006

Buchwald, Blackmond 2002



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