

# Tools and Observations in the Development of Catalytic Procedures

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*University of Strathclyde*

**Hot Topics in Organic Chemistry**  
**20<sup>th</sup> Annual Review Meeting**

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# Catalysis

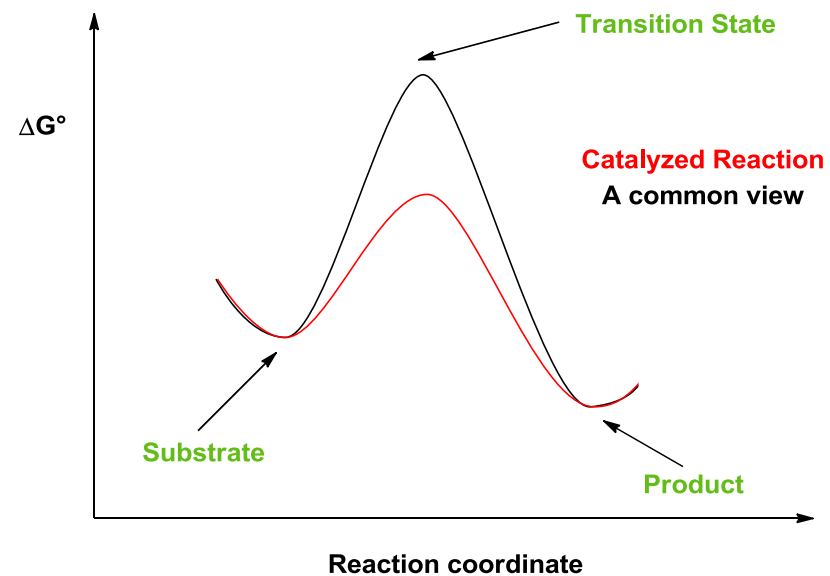
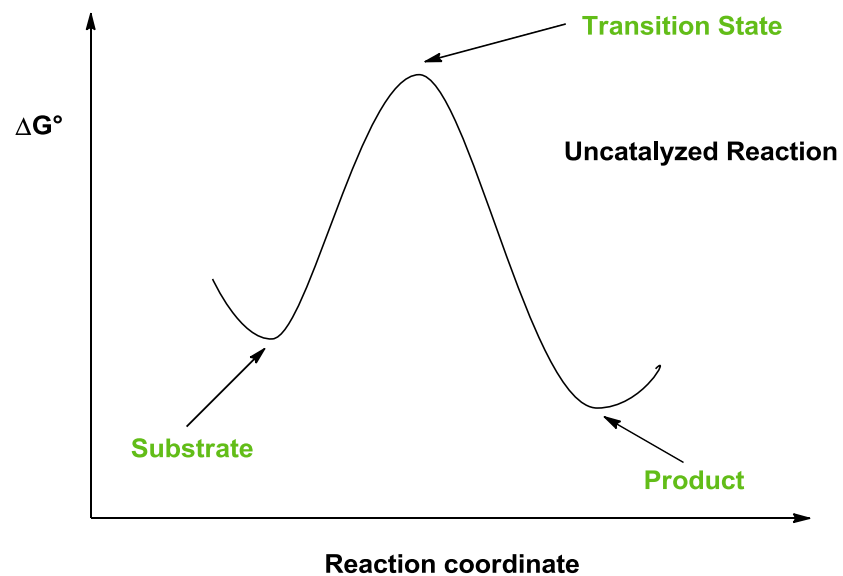
*A catalyst is a compound that takes part in a reaction, resulting in an increased rate for that reaction, but is not consumed in that reaction*

- >90% of all commercial chemical products involve catalysts in their production
- >\$30 billion industry
- >\$1000 billion of products worldwide

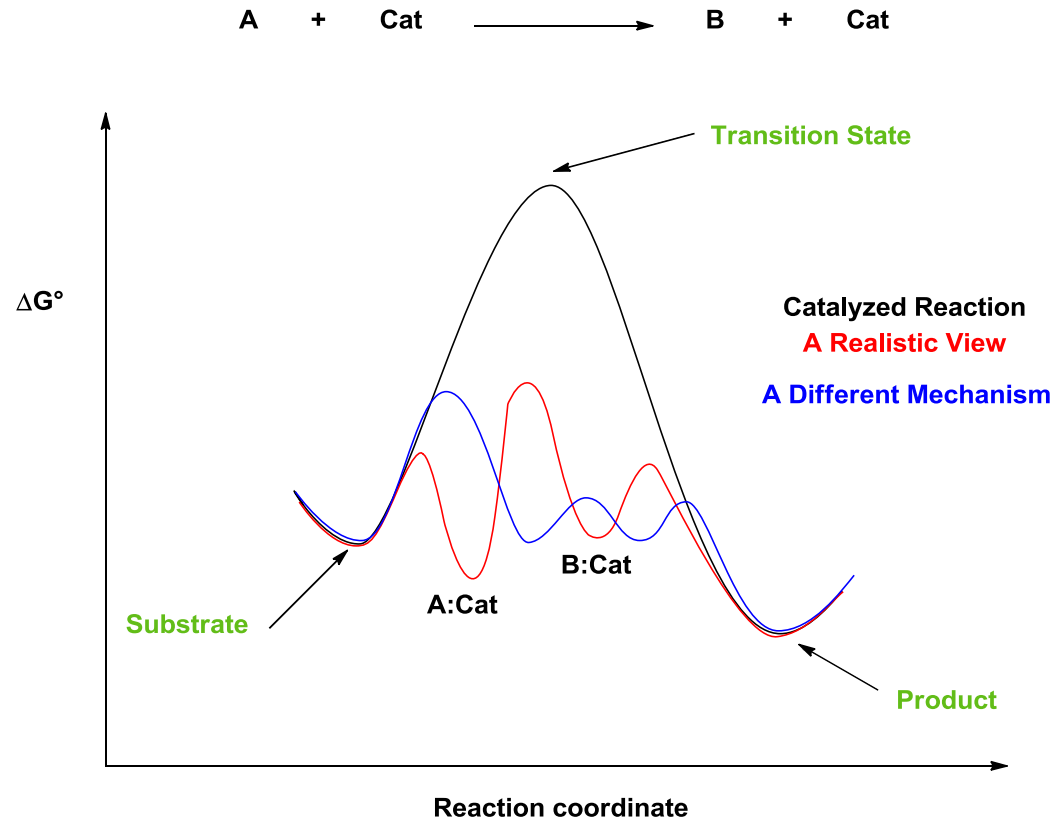
Term **catalysis** first used by Jons Jakob Berzelius in 1835



# Catalysis

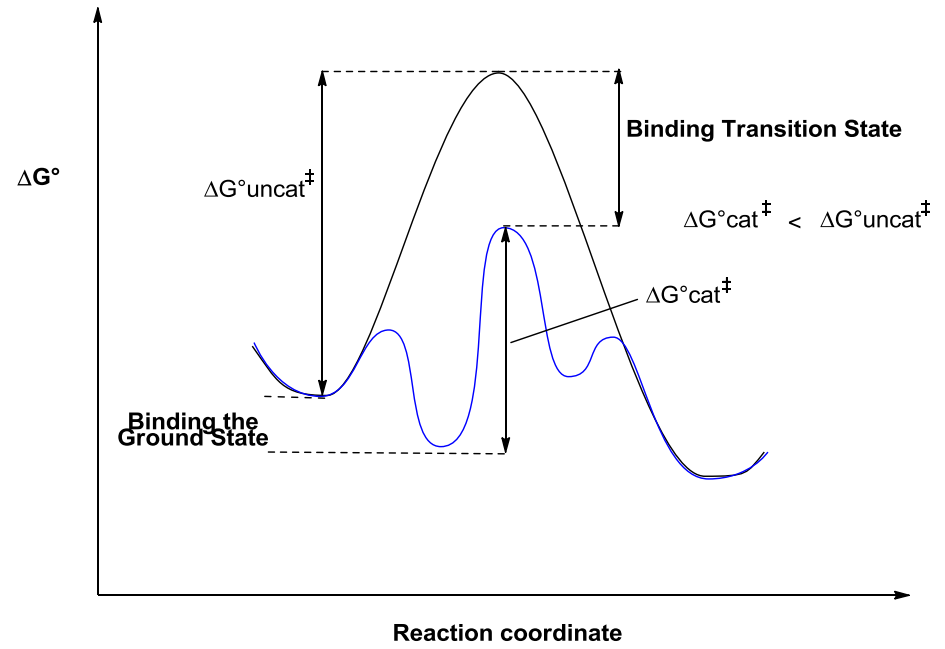
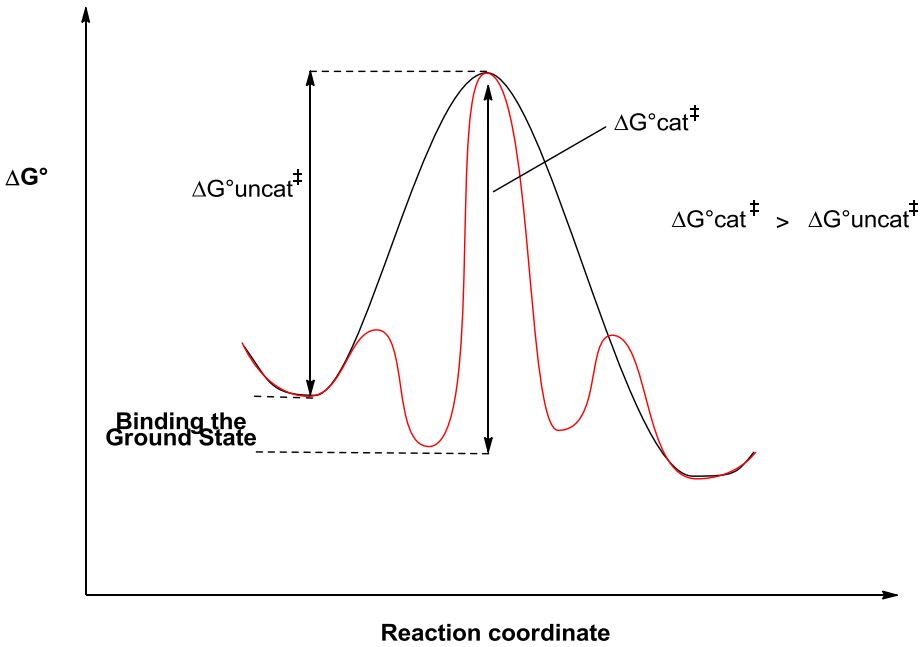


# Catalysis: A more realistic View

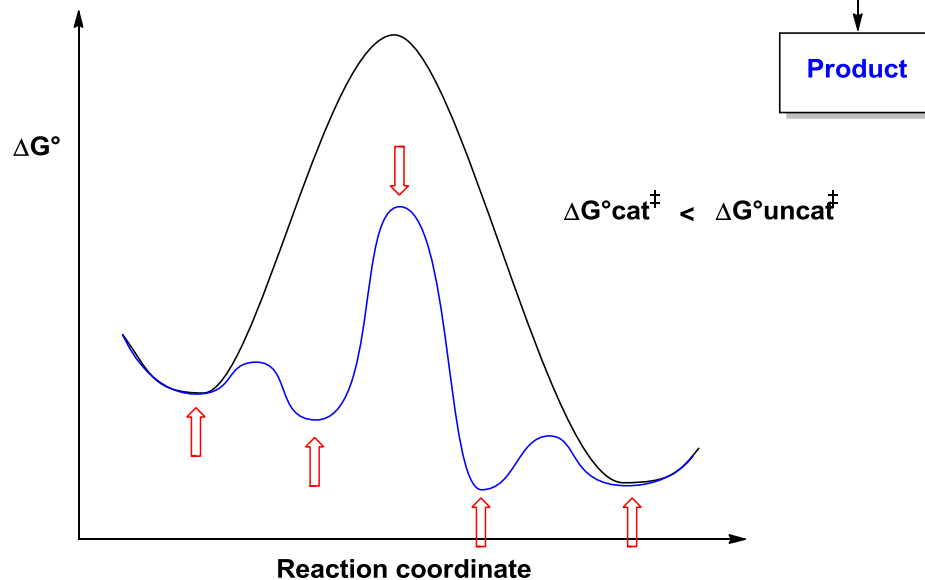
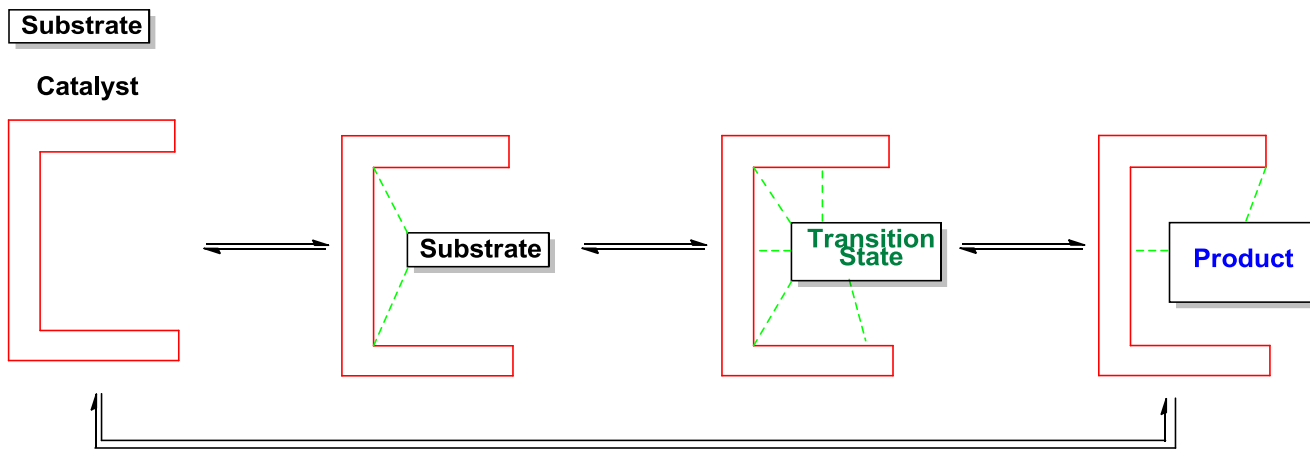


Bind transition state better than ground state

# Catalysis: Binding the Transition State

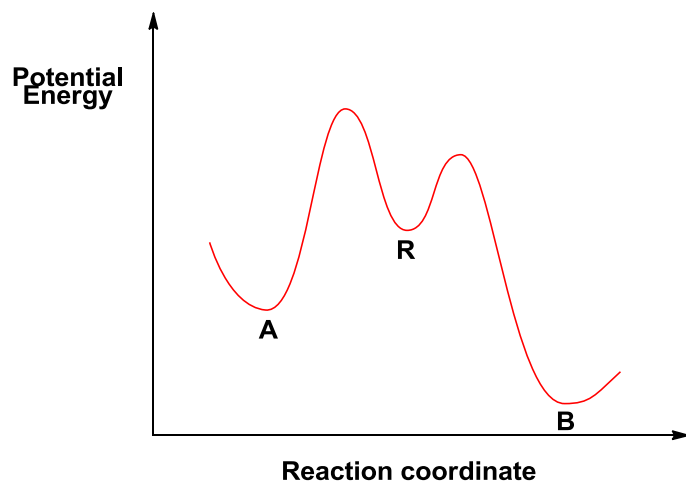


# Catalysis: Binding the Transition State

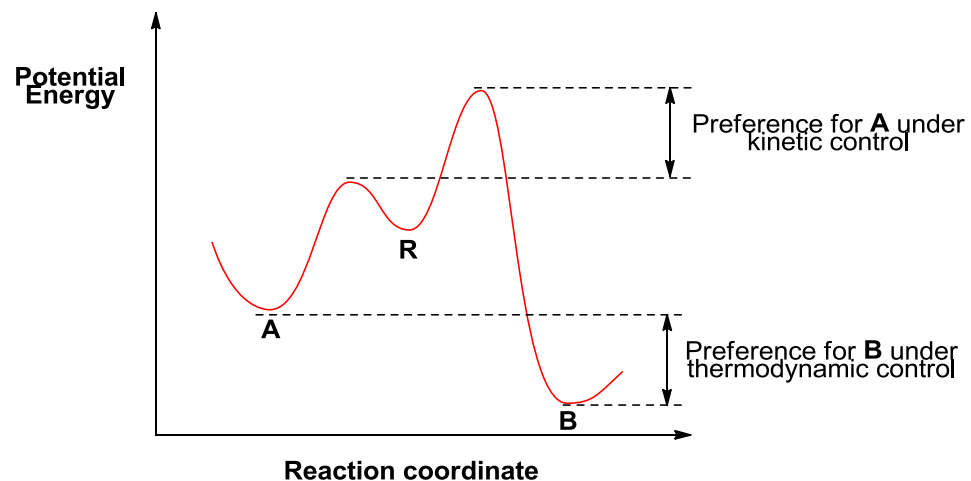


All principles hold for reactions operating *via* alternative mechanisms

# Kinetic Control vs Thermodynamic Control



Kinetic and thermodynamic product **B**

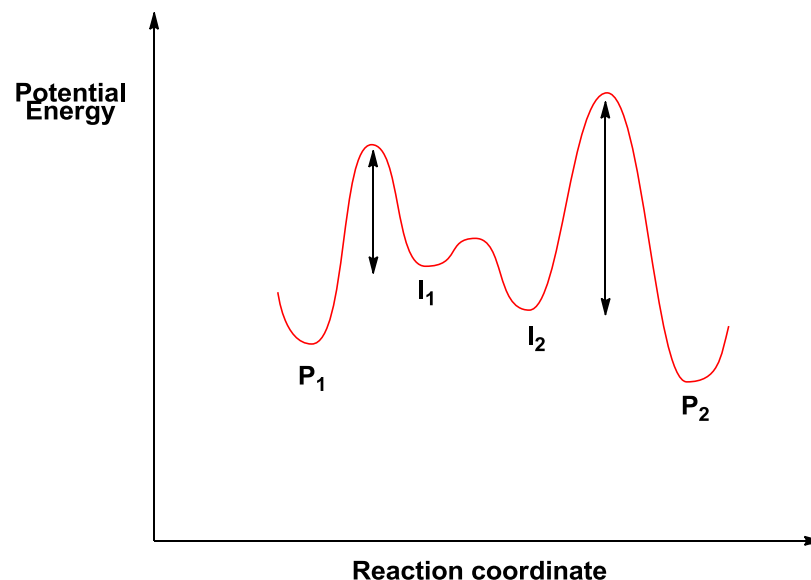


Kinetic product is **A**  
Thermodynamic product is **B**

**Kinetic control:** Ratio of products determined by relative energies of transition states

**Thermodynamic control:** Ratio of products determined by relative energies of products

# Curtin-Hammett Principle



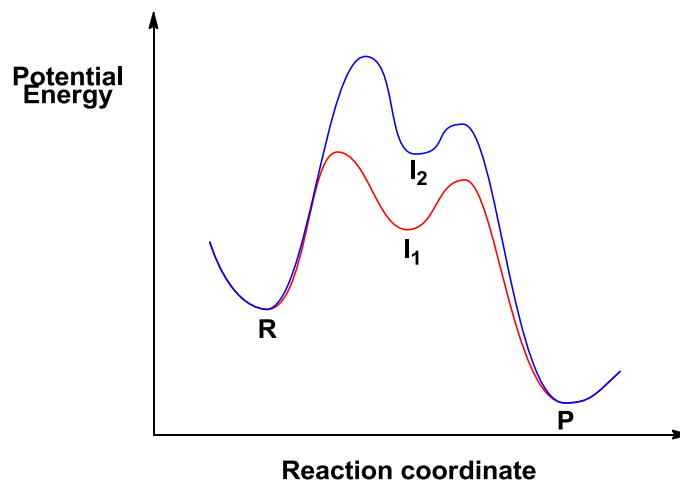
- $I_1$  and  $I_2$  are equilibrating intermediates (barrier small)
- Pathway to  $P_2$  derives from stable structure  $I_2$
- Pathway to  $P_1$  derives from less stable structure  $I_1$  but has lower transition state

Product ratio is determined by relative heights of barriers and **not** relative stability



# Microscopic Reversibility

The pathway for conversion of a product to a reactant is the exact microscopic reverse of the forward pathway



- **R** converted to **P** via **I<sub>1</sub>** or **I<sub>2</sub>**
- Two different pathways exist for **R** to **P** and **P** to **R**
- Ratio in forward and reverse direction depends upon relative barrier heights
- Transition state **I<sub>1</sub>** (or **I<sub>2</sub>**) is the same in both forwards and reverse direction

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# Monitoring a Reaction – Why?

**Deciphering a mechanism is the most enabling knowledge  
a chemist has to control the outcome of a reaction**

improve yield; improve efficiency; improve selectivity; reduce cost

**Well designed experiments central to interrogating,  
understanding and improving reactions**

**Spectroscopy**

**Chemical tools**

**Techniques**

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# Monitoring a Reaction: Spectroscopy

- Monitor a change in concentration over time
- Time scale of reaction pivotal

$T_{1/2} > \text{seconds}$ : Mix reactants and obtain realistic data

$T_{1/2} < \text{second}$  requires specialised equipment beyond humble bench chemist

## Chromatographic and Spectroscopic methods



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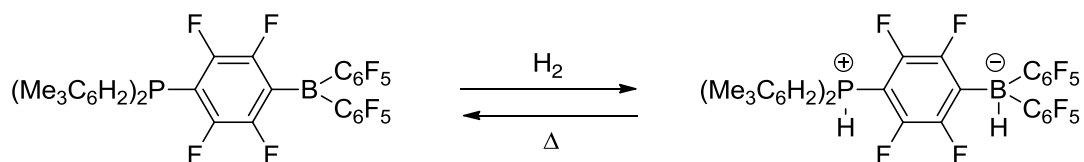
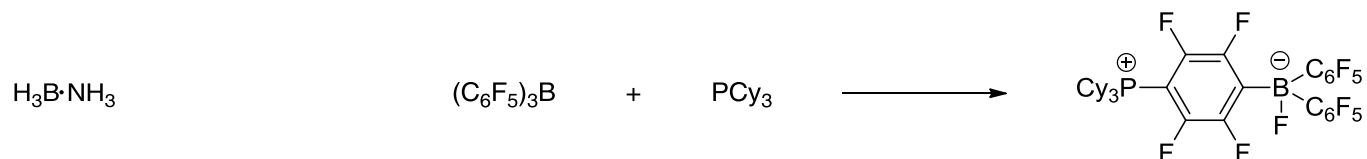
# Monitoring a Reaction: Chemical Tools

- Isotopic labelling
- Mechanistic probe *e.g.* Newcomb clock
- Intermediate isolation and reaction
- Structural analysis

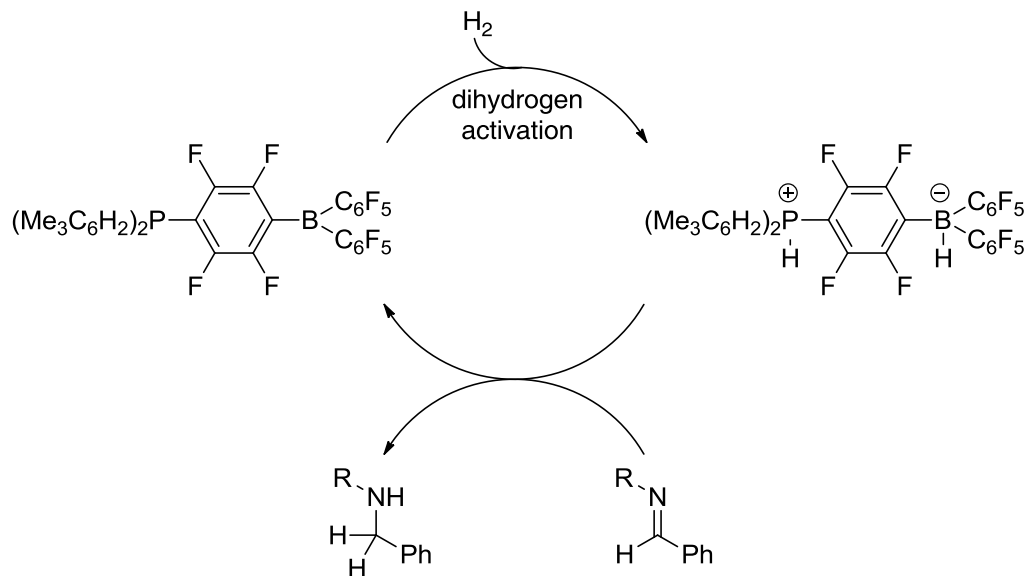
# Monitoring a Reaction: Techniques

- Kinetic analysis
  - Hammett analysis
  - Computational analysis
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# Frustrated Lewis Pairs: FLPs



Formation of an adduct  
is prevented by  
steric hindrance

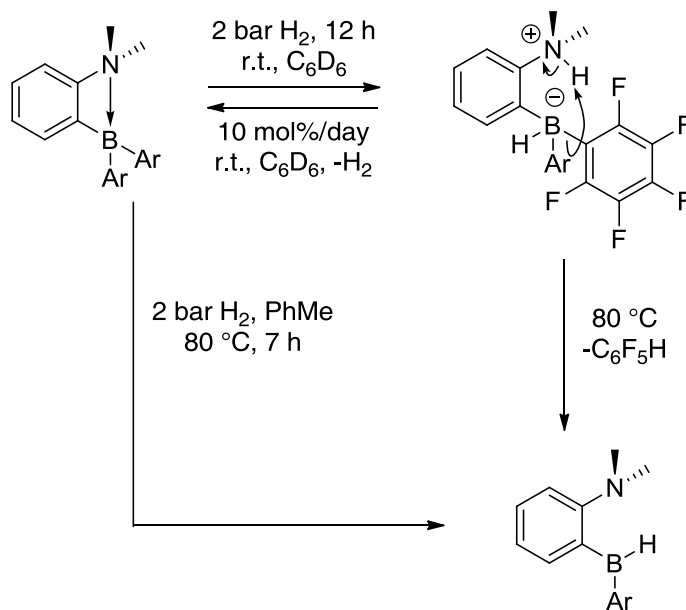


*Science* **2006**, 314, 1124

*Org. Biomol. Chem.* **2008**, 6, 1535

*Angew. Chem. Int. Ed.* **2010**, 49, 46

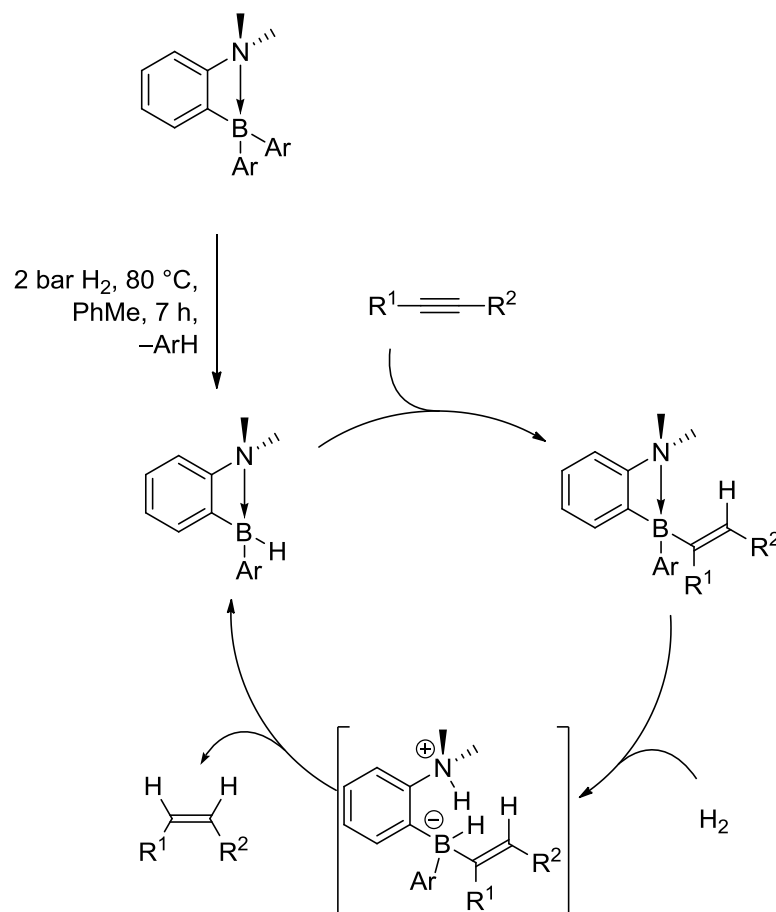
# FLP Catalytic Alkyne Reduction



*Dalton Trans.* **2012**, 41, 9029  
*Nature Chem.* **2013**, 5, 718

<sup>1</sup>H NMR  
<sup>19</sup>F NMR  
<sup>10</sup>B NMR

# FLP Catalytic Alkyne Reduction

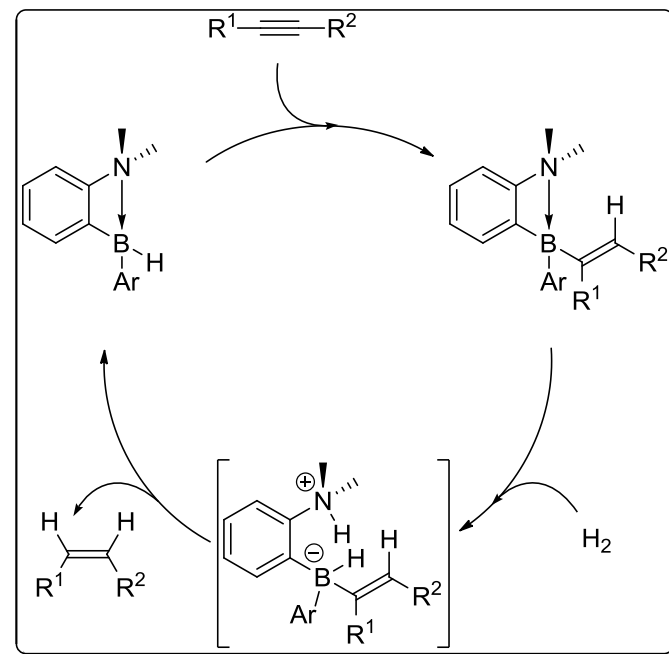
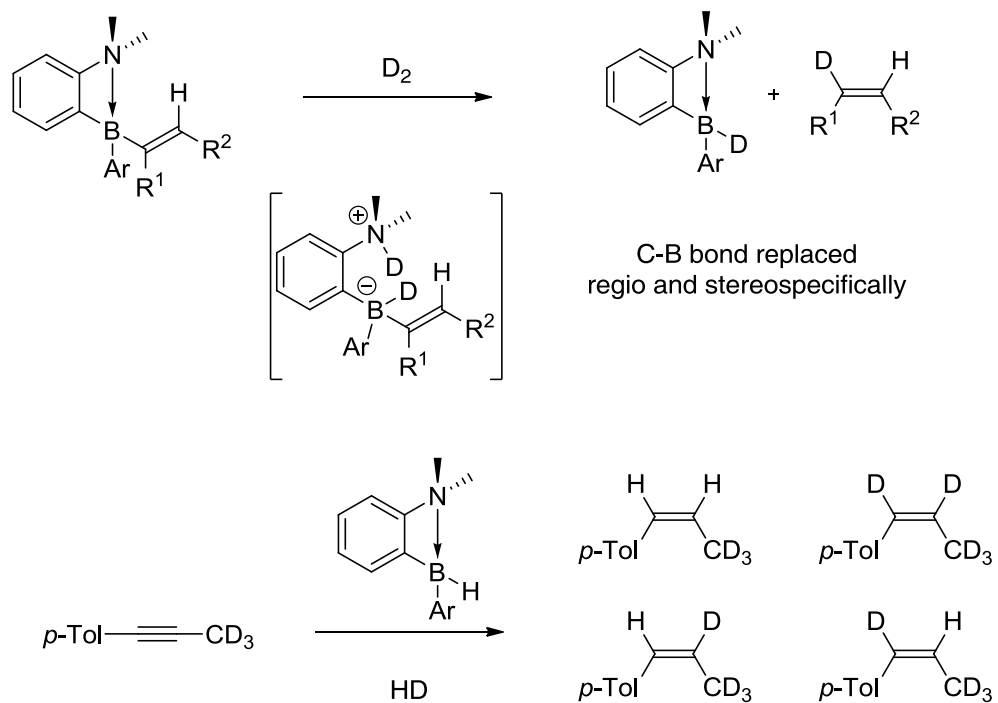


## Structure aminoborane directs

- Protodeborylation
- Electrostatic stabilisation
- Intramolecular protonation

NMR  
Intermediate isolation  
Computation  
Isotopic labelling

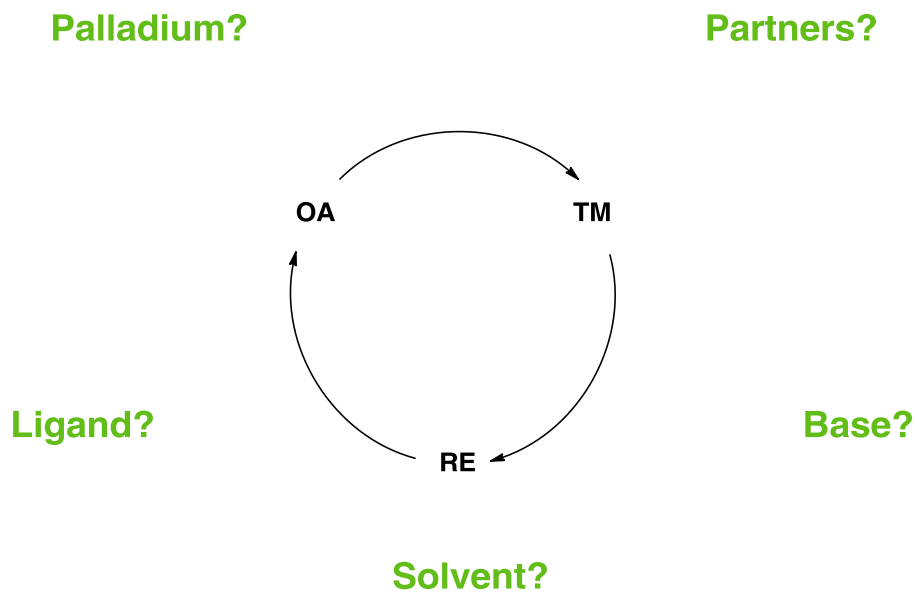
# FLP Catalytic Alkyne Reduction





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# Transition Metal Catalysed Cross Couplings



# Transition Metal Catalysed Cross Couplings



Richard F. Heck



Akira Suzuki



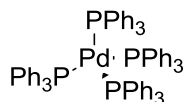
Ei-ichi Negishi

As the most important reactions developed in the last 50 years,  
cross coupling is relevant to the world

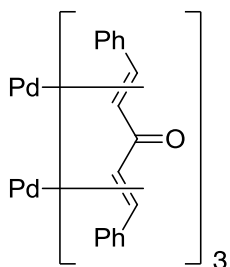
- 2010: 22% of all reactions in pharma are Pd-catalysed couplings
- 2012: Buchwald-Hartwig amination #1 reaction performed in pharma

# Transition Metal Catalysed Cross Couplings

Most common catalysts used are  $\text{Pd}(\text{PPh}_3)_4$  and  $\text{Pd}_2(\text{dba})_3$  derived systems



- Contains 2 extra ligands that inhibit reaction
- Quality often questionable

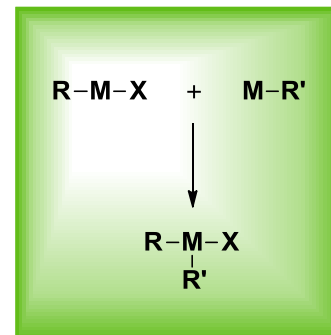
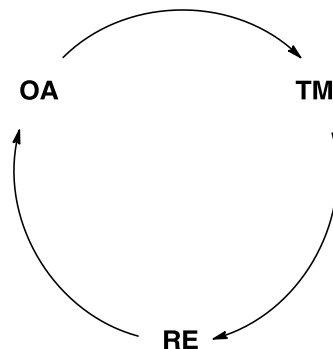


- Strong ligand that can require high temperature to dissociate
- Promotion of side reactions

- Mechanistic insights can lead to improved reaction design
- New catalysts will only be adopted if it is known why they are superior

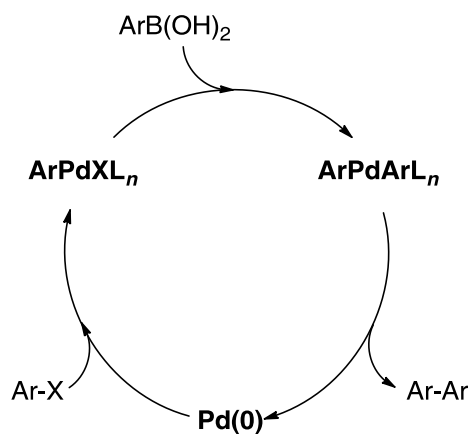
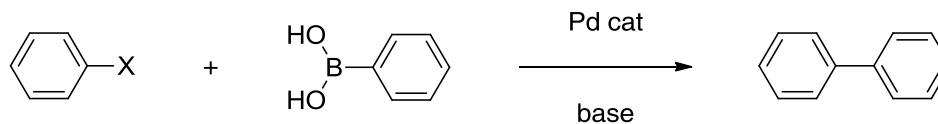
# Transition Metal Catalysed Cross Couplings

*Organometallics* **1990**, 9, 2276  
*J. Am. Chem. Soc.* **2009**, 131, 8141

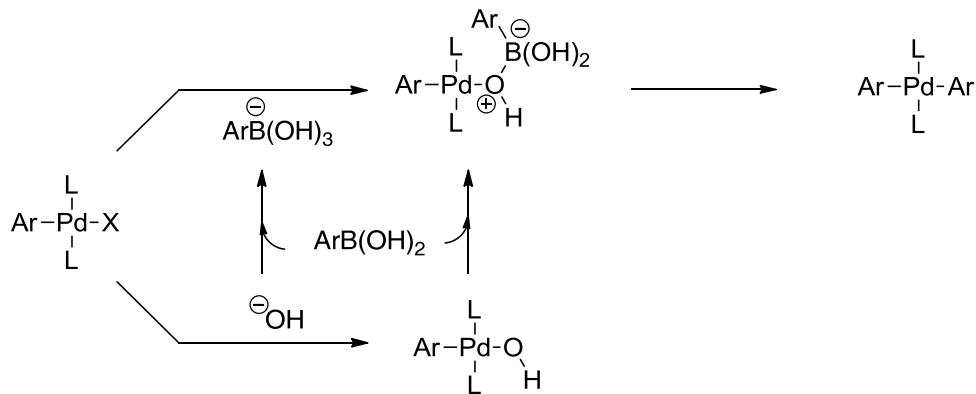


*J. Am. Chem. Soc.* **1980**, 102, 8321  
*J. Am. Chem. Soc.* **1984**, 106, 8321  
*Organometallics* **1991**, 10, 1431  
*Inorg. Chim. Acta* **1994**, 220, 249  
*J. Am. Chem. Soc.* **2009**, 131, 8141  
*J. Am. Chem. Soc.* **1982**, 104, 1310

# Suzuki-Miyura Cross Coupling



- Base required for all reactions
- No proton transfer in simplified mechanism
- NaOH,  $K_3PO_4$ ,  $Na_2CO_3$ ,  $NaHCO_3$ , NaOAc



*Chem. Rev.* **1995**, *95*, 2457

*Synlett* **1994**, 149

*J. Org. Chem.* **1994**, *59*, 8151

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# Suzuki-Miyaura Cross Coupling

- Borate coordinates to Pd prior to transfer

*J. Am. Chem. Soc.* **2005**, *127*, 11102

*J. Phys. Chem. A* **2006**, *110*, 1295

*J. Mol. Catal. A* **2010**, *324*, 39

*ACS Catal.* **2011**, *1*, 246

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# Suzuki-Miyura Cross Coupling

- $\Delta G^\ddagger$  only +0.6 kcal from PdOH species
- Problem: No transition state for formation of PdOH species located

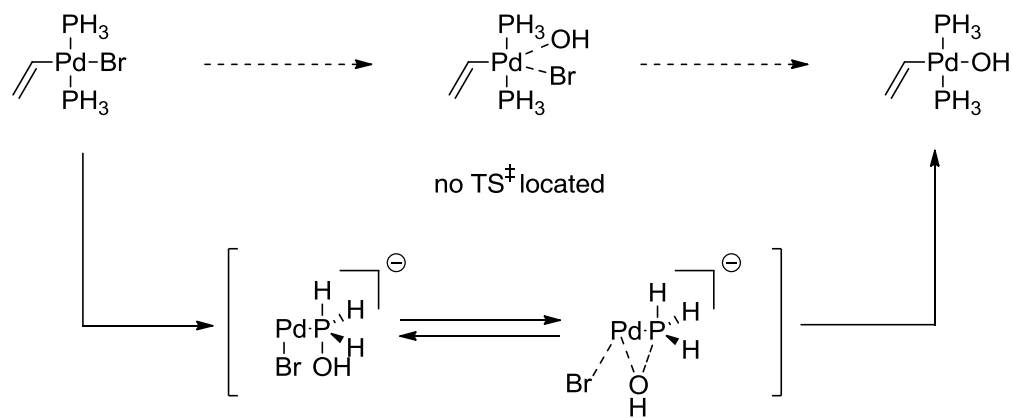
*J. Am. Chem. Soc.* **2005**, *127*, 9298

*J. Organomet. Chem.* **2006**, *691*, 4459

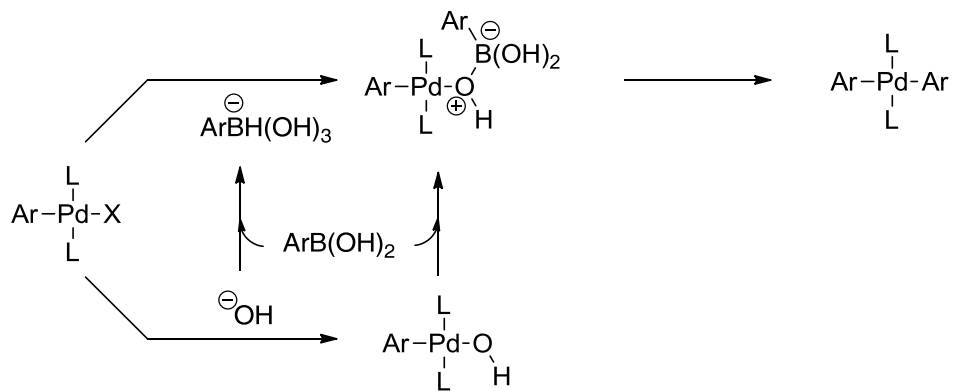
*Organometallics* **2006**, *25*, 3647

*Tetrahedron* **2008**, *64*, 7437

# Suzuki-Miyura Cross Coupling



- Consistent with observation that adding NaOH produces phosphine oxide



- Both pathways are accessible and dependent on concentrations and rates

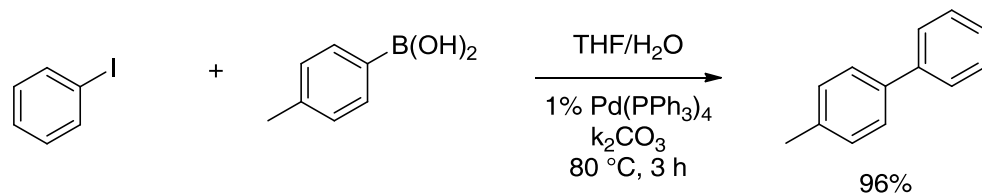
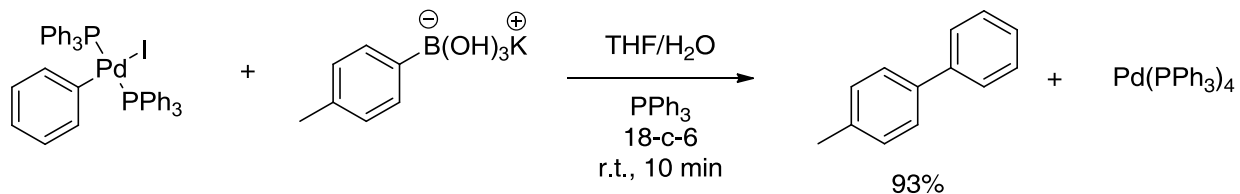
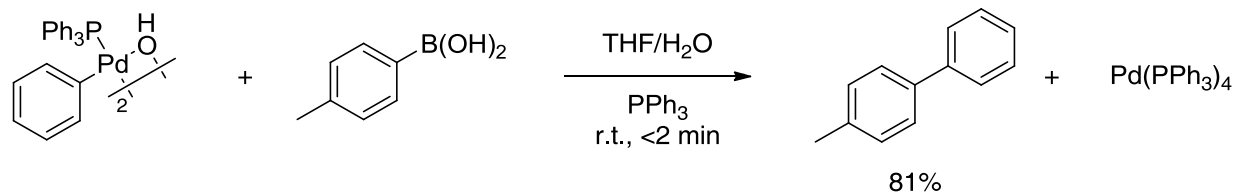
*J. Org. Chem.* **1998**, *63*, 461

*Angew. Chem. Int. Ed.* **2013**, *52*, 7362

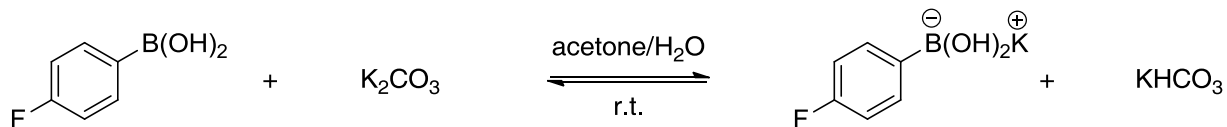
DFT Calculations



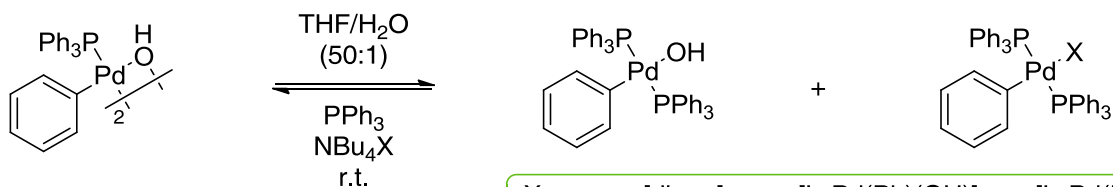
# Transmetalation Experimentally



# Transmetalation Experimentally



$[\text{K}_2\text{CO}_3]_0$	$[\text{ArB(OH)}_2]$	$[\text{ArBH(OH)}_3^-]$
0.15 M	0.017 M	0.043 M
0.10 M	0.020 M	0.040 M
0.03 M	0.030 M	0.030 M

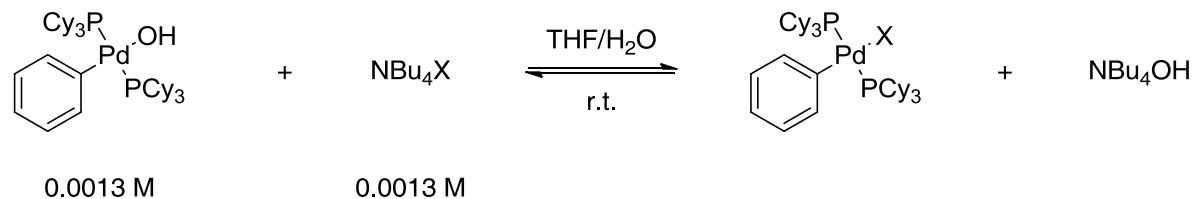


0.011 M

X	[dimer]	$[\text{L}_2\text{Pd(Ph)(OH)}]$	$[\text{L}_2\text{Pd(Ph)(X)}]$
I	0.0049 M	0.0028 M	0.0043 M
Br	0.0043 M	0.0038 M	0.0028 M
Cl	0.0032 M	0.0045 M	0.0031 M

Comparison of relative stabilities of hydroxo and halide complexes complicated by concurrent equilibrium between monomeric and dimeric palladium hydroxo complexes

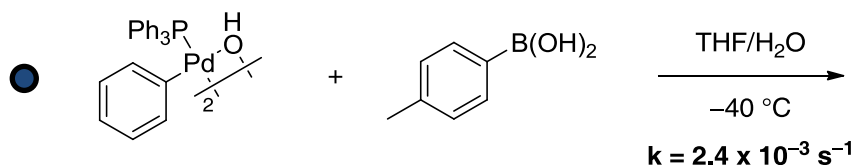
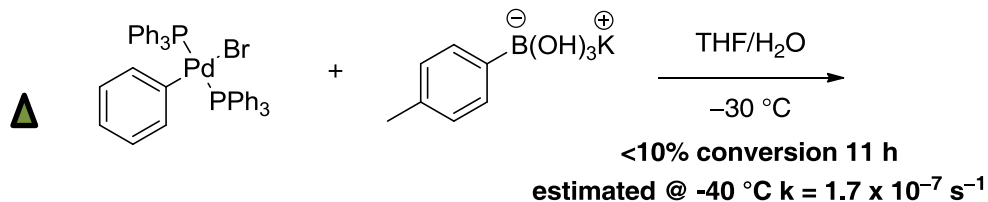
# Transmetalation Experimentally



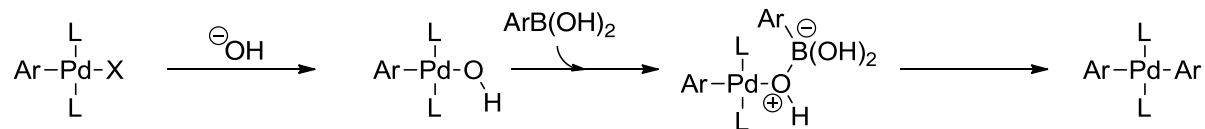
	25:1 THF/H <sub>2</sub> O	50:1 THF/H <sub>2</sub> O
X	<i>K</i>	<i>K</i>
I	1.1	0.17
Br	9.3	1.3
Cl	23	3.2

- Stability Pd-Cl > Pd-Br > Pd-I but equilibrium constants small
- Increasing amount of water decreases amount Pd-OH species
- Result of decreased hydration of free hydroxide ions
- Concentration of Pd-halide > Pd-OH under standard conditions

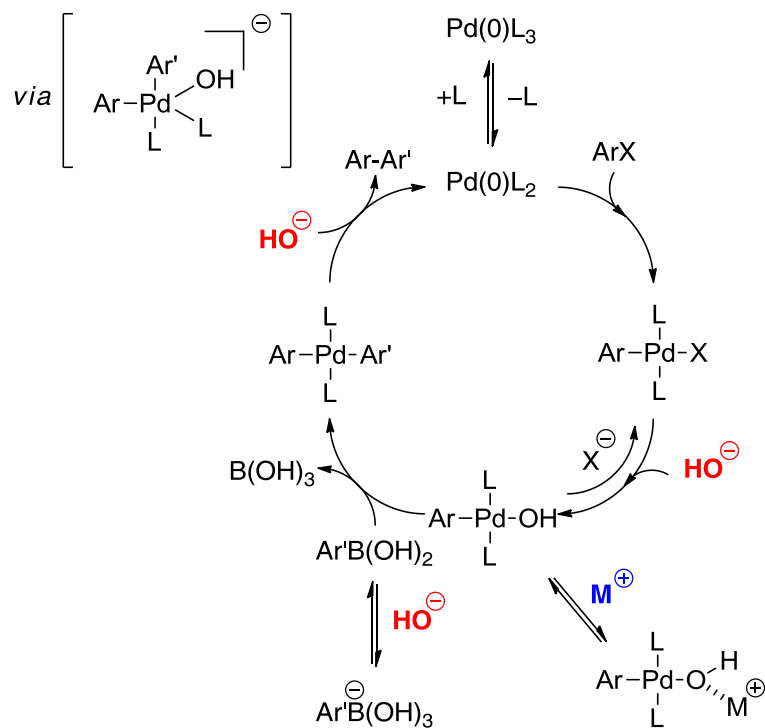
# Transmetalation Experimentally



- Reaction of hydroxo complex  $\sim 1.4 \times 10^4$  greater than bromo complex
- Implies hydroxy pathway accounts for transmetalation



# Role of Hydroxide, Counterions and Base



## Hydroxide ions:

- Enable formation of reactive Pd-OH
- Facilitate reductive elimination
- Slow reaction by forming  $\text{ArB(OH)}_3^-$

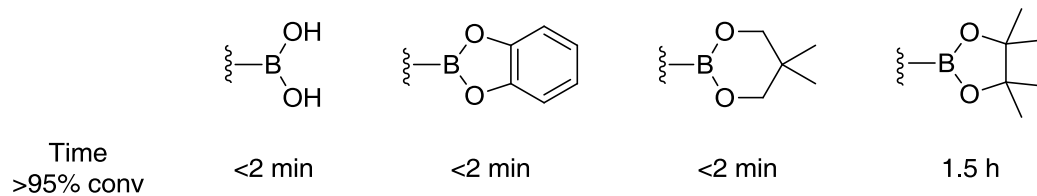
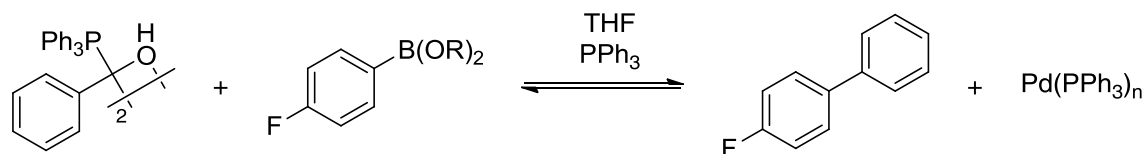
## Counteractions:

- Slow reaction through complexation of Pd-OH
- Decreasing reactivity  $n\text{Bu}_4\text{N}^+ > \text{k}^+ > \text{Cs}^+ > \text{Na}^+$

## Base:

- Acetate leads to  $\text{ArPd(OAc)}_2$  – does not TM
- Reaction tuned by ratio  $[\text{OH}^-]/[\text{Ar}'\text{B(OH)}_2]$

# Alternative Coupling Partners



- Trifluoroborates also couple through free boronic acid
- Boronic acids can also transfer to ArPdFL<sub>2</sub> species using fluoride ions

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# Suzuki-Miyaura Cross-Coupling: Caveats

- Data cannot be extrapolated to all metal-ligand systems
- Reactions with stronger bases will contain more trihydroxyborate
- Does not provide information on how aryl group transferred from B to Pd



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# Conclusions

- Deciphering a mechanism is the most enabling knowledge a chemist has to control the outcome of a reaction
- Well designed experiments central to interrogating, understanding and improving reactions

Spectroscopy

Chemical tools

Techniques

