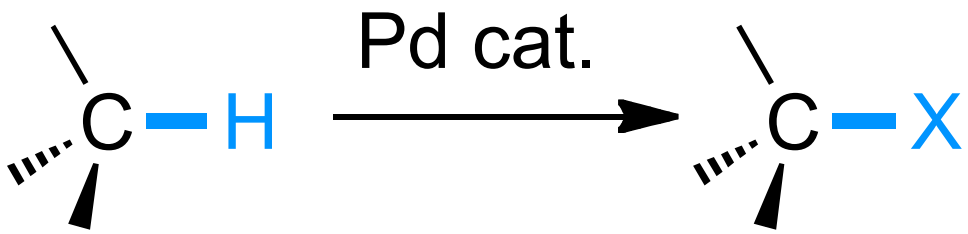
# Pd Catalyzed Functionalization of Non-Acidic C($sp^3$)-H Bonds




Lindsey Cullen

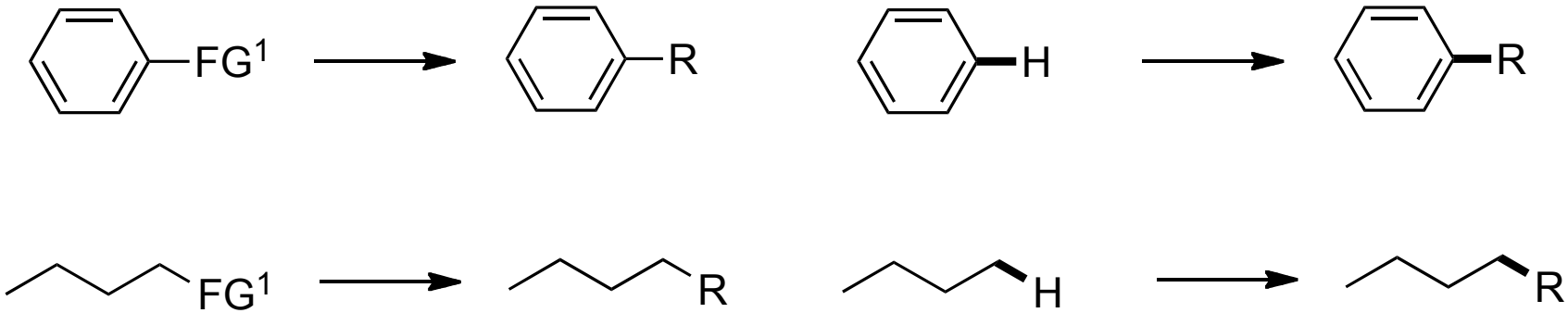
Denmark Group Meeting

Oct. 26, 2010

# Carbon-Carbon Bond Formation in Organic Molecules

Traditional:
Functional Group Transformation

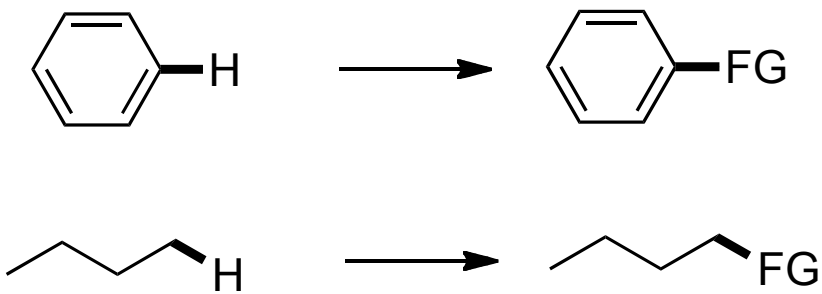
Alternative Approach:
C-H Functionalization




Why focus on C-H functionalization?

1. C-H bonds are common / could provide new disconnections
2. Atom economical
3. Cost effective

# Challenges to C-H Functionalization




1. Intrinsic low reactivity

   Large kinetic barrier to cleave C-H bond (104 kcal/mol)

2. Chemoselectivity

   Functionalized product may be more reactive

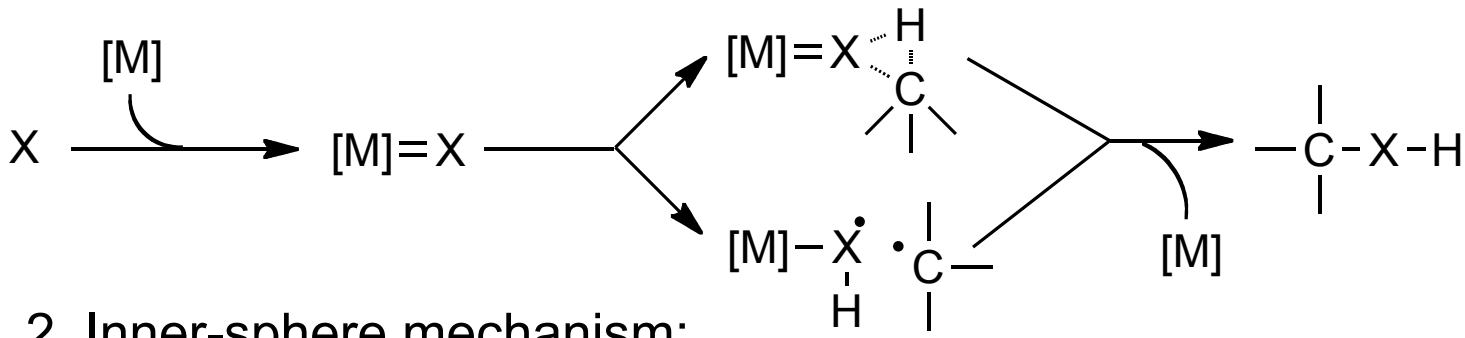
3. Regioselectivity

   $sp^2$ and $sp^3$ C-H bonds are ubiquitous

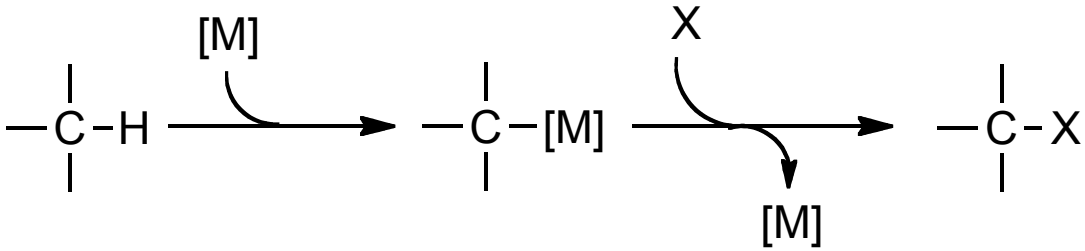
# C-H Functionalization: A Definition

Two general mechanisms:

1. Outer-sphere mechanism:




2. Inner-sphere mechanism:

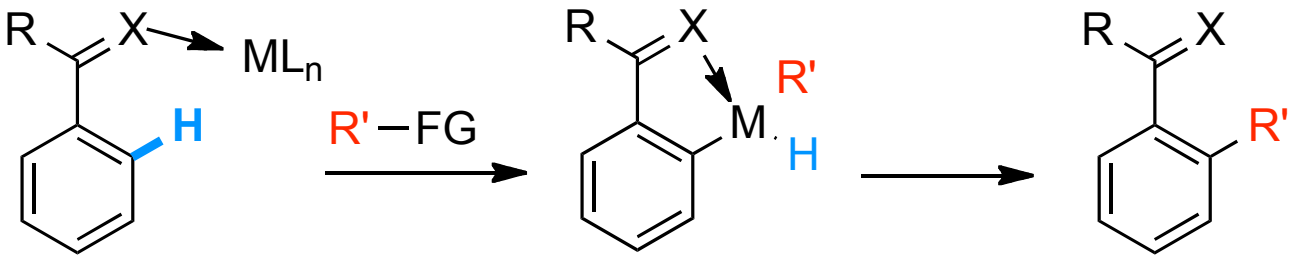



<u>C-H Functionalization</u> - formation of a C-M bond by cleavage of a C-H bond

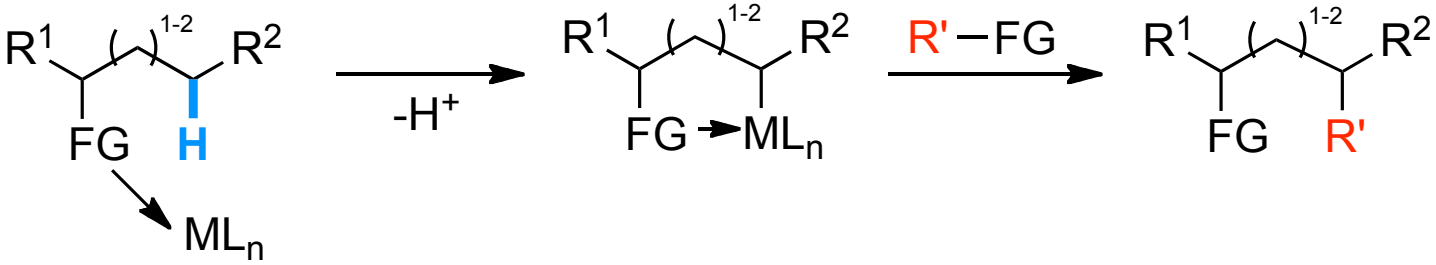

Baudoin, O. *et al. Chem. Eur. J.* **2010**, *16*, 2654.
Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507.

# Reactivity of nonacidic $sp^3$ C-H Bonds

C-H functionalization of $sp^2$ C-H bonds has been well studied:



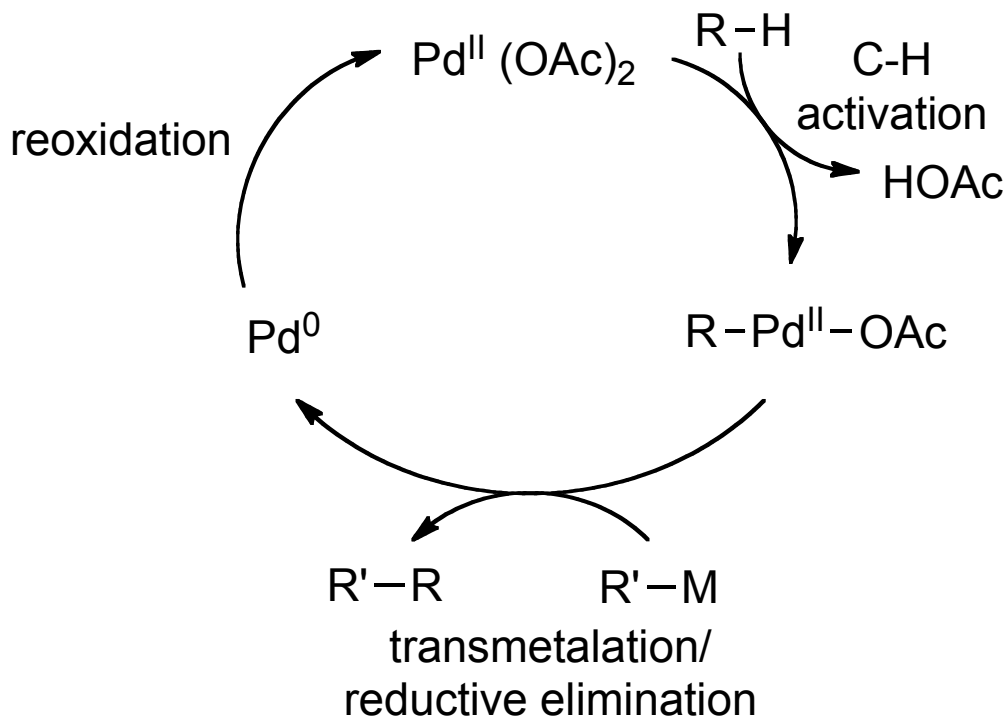

C-H functionalization of non-acidic $sp^3$ C-H bonds is less explored:




C($sp^3$)-H bonds lack $\pi$ orbitals to interact with metal center

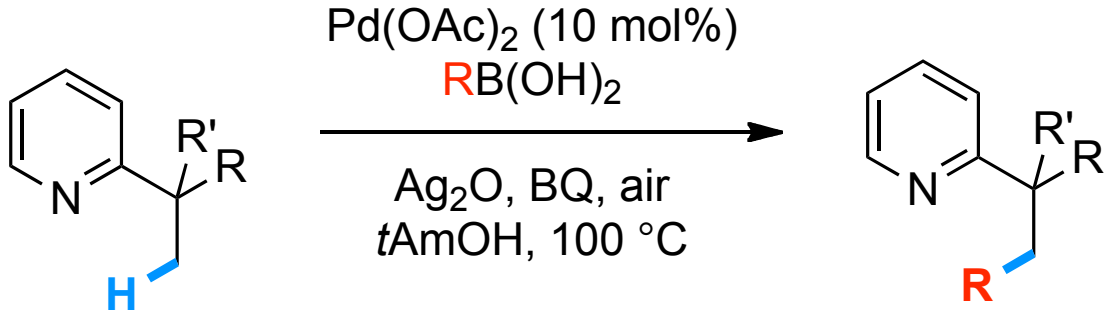
# Pd(II)/Pd(0) Systems for $sp^3$ C-H Activation

Pd(II)/Pd(0) Catalysis:



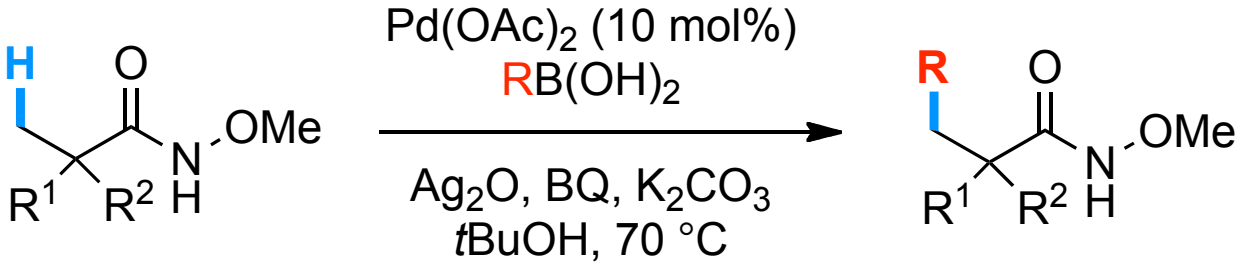

External oxidant is necessary to regenerate Pd(II) catalyst

# Pd(II)/Pd(0) sp$^3$ C-H Activation



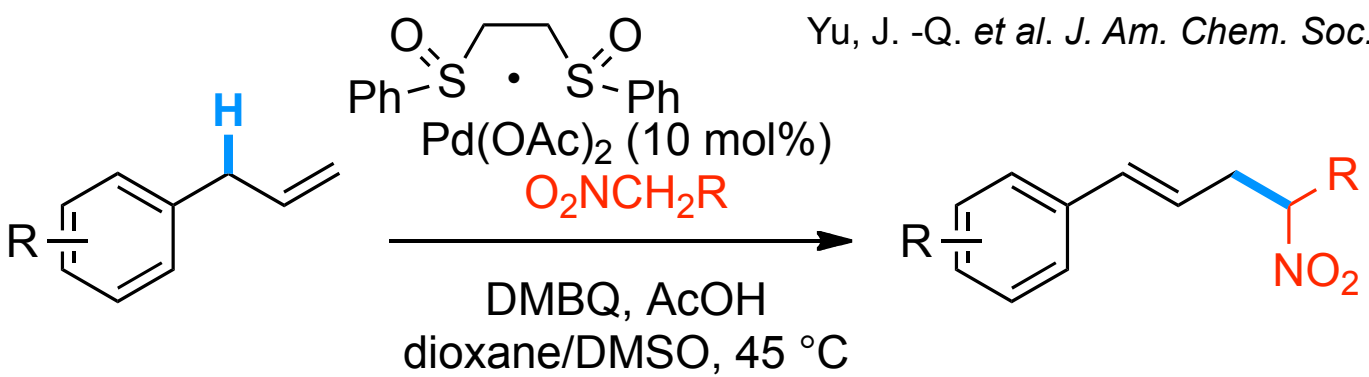

48-75%

Yu, J. -Q. *et al. J. Am. Chem. Soc.* **2006**, *128,* 12634.




41-85%

Yu, J. -Q. *et al. J. Am. Chem. Soc.* **2008**, *130,* 7190.

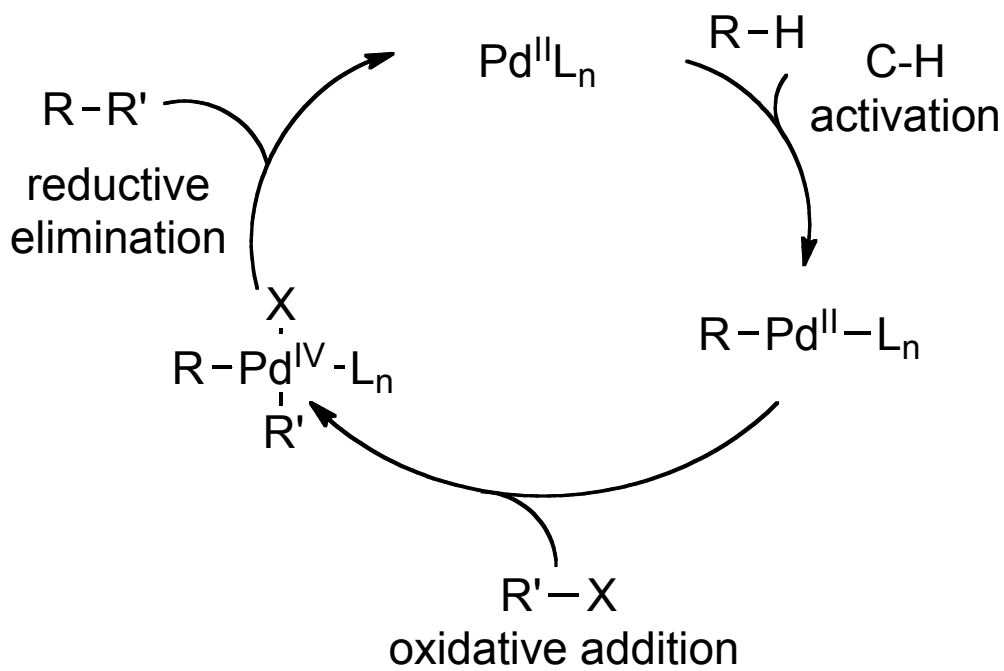



50-70%

White, M. C. *et al. J. Am. Chem. Soc.* **2008**, *130,* 14090.

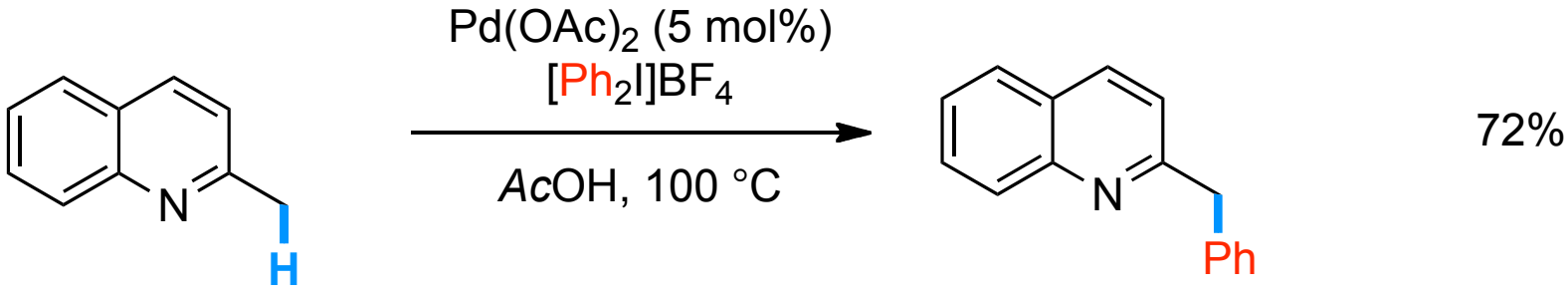
# Pd(II)/Pd(IV) Systems for $sp^3$ C-H Activation

Pd(IV)/Pd(II) Catalysis:

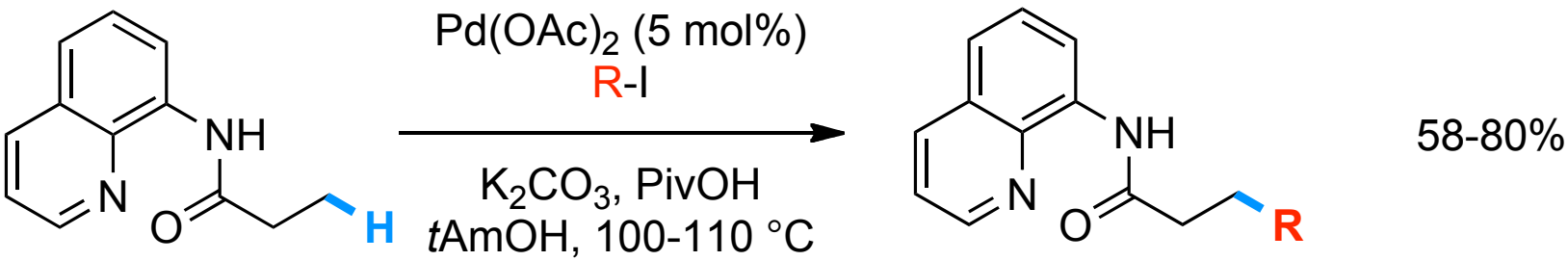



Additional oxidative addition step leads to Pd(IV) intermediates

# Pd(II)/Pd(IV) $sp^3$ C-H Activation



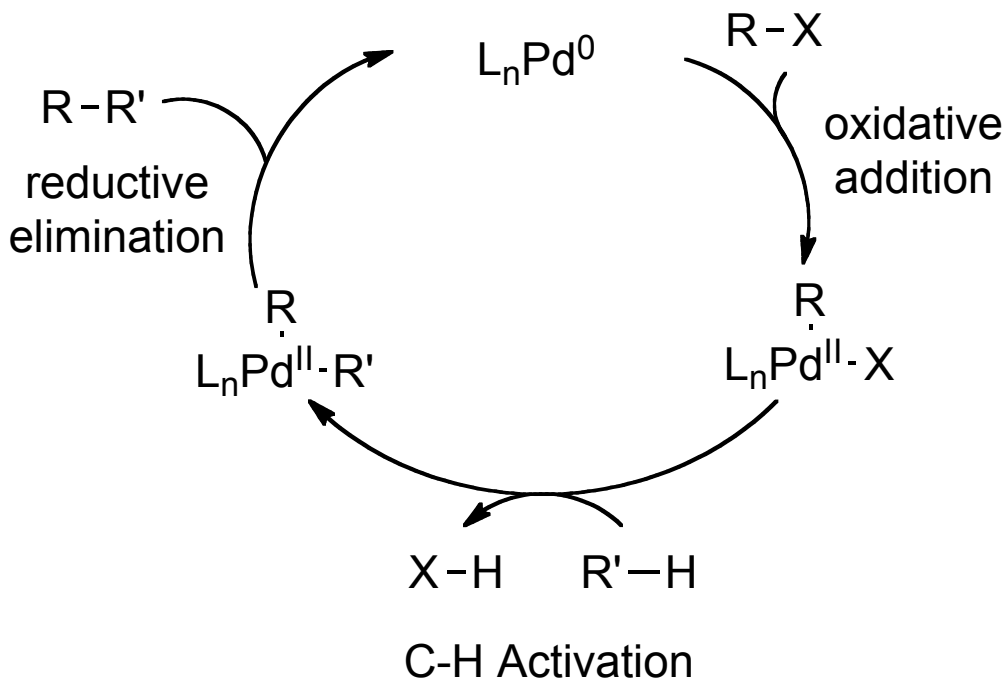

Sandford, M. S. *et al*. *J. Am. Chem. Soc.* **2005**, *127,* 7730.




Daugulis, O. *et al*. *J. Am. Chem. Soc.* **2010**, *132,* 3965.

# Pd(0)/Pd(II) Systems for $sp^3$ C-H Activation

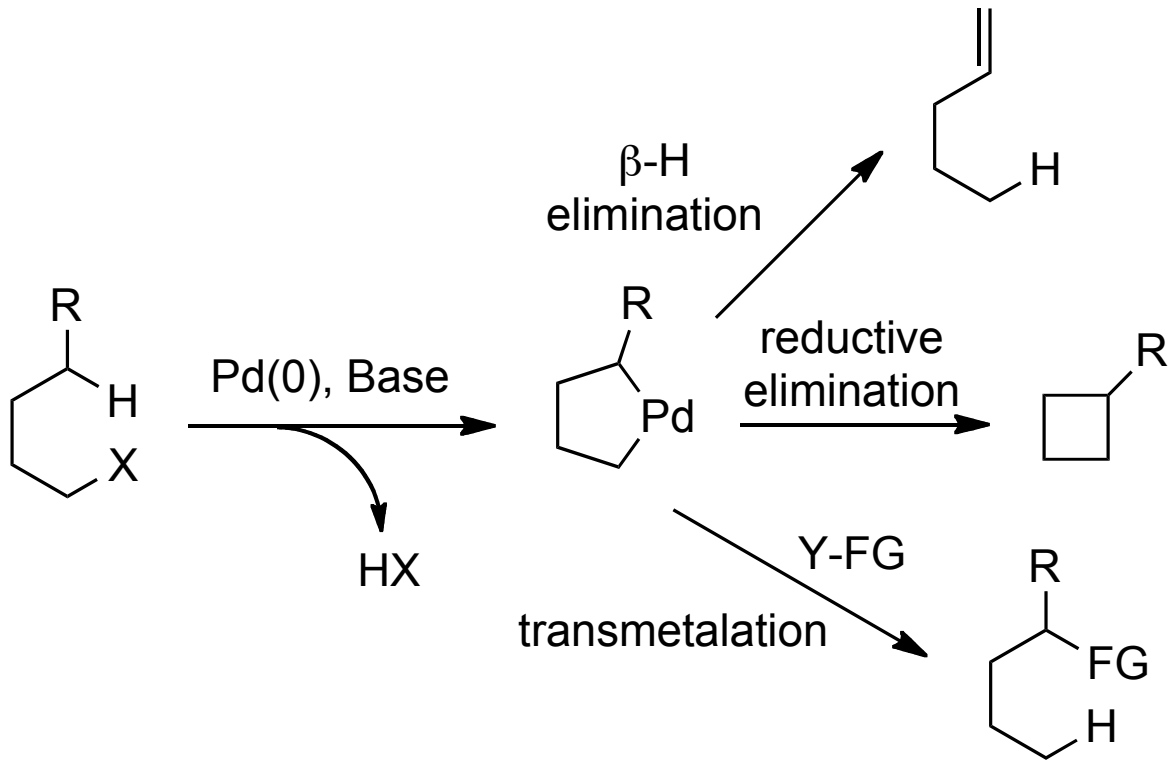
Pd(0)/Pd(II) Catalysis:




Oxidative addition to coupling partner gives Pd(II) intermediate

Most studied catalytic system for non-acidic $sp^3$ C-H functionalization

# Many Possible Reaction Pathways

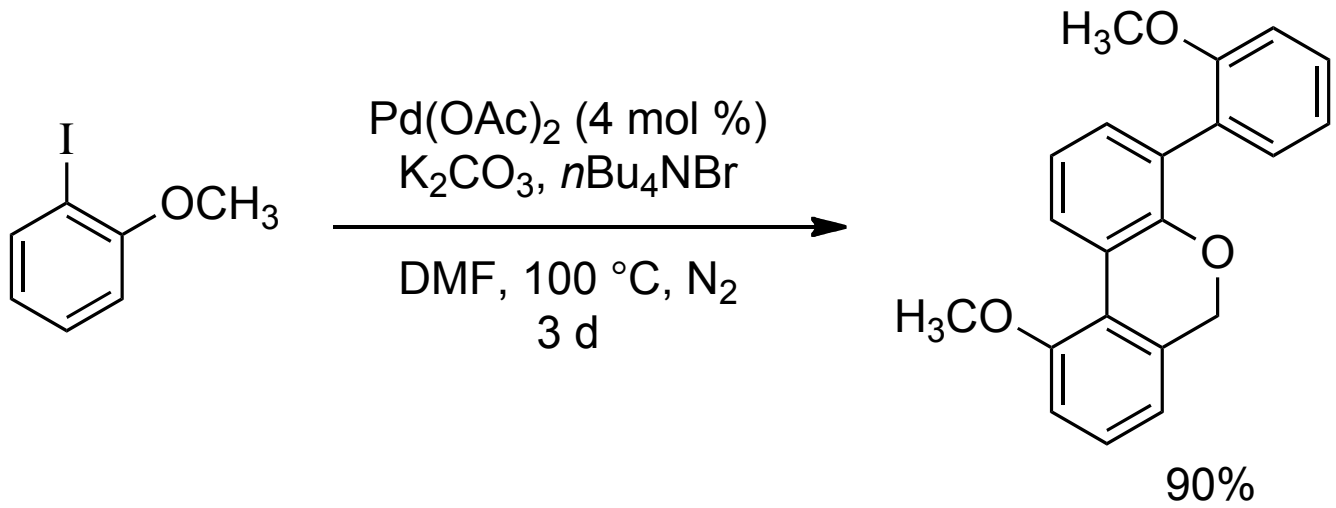


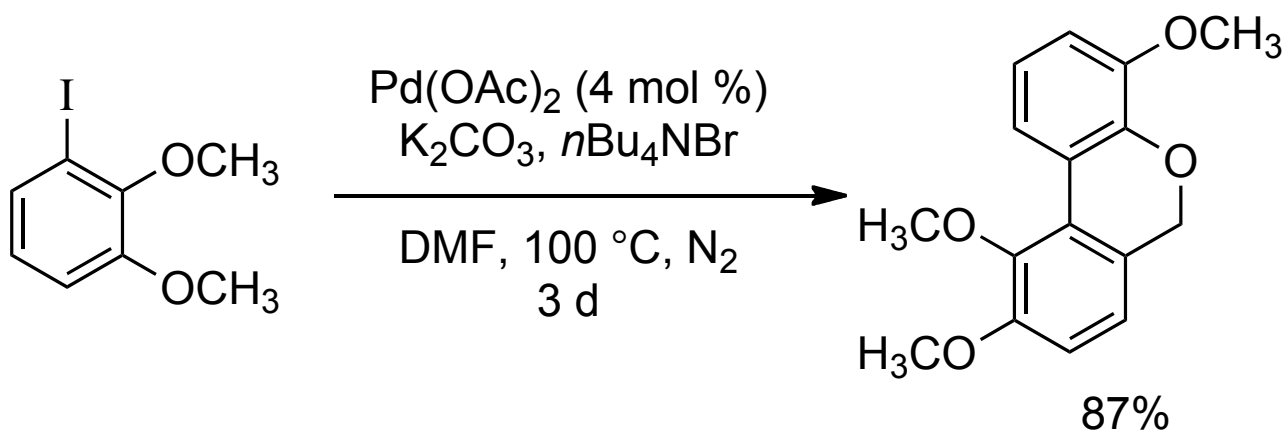

Two major challenges to $sp^3$ C-H activation:

1. Selective $sp^3$ C-H cleavage
2. Favoring one pathway over another

Dyker, G. *Angew. Chem. Int. Ed.* **1992**, *31*, 1023.

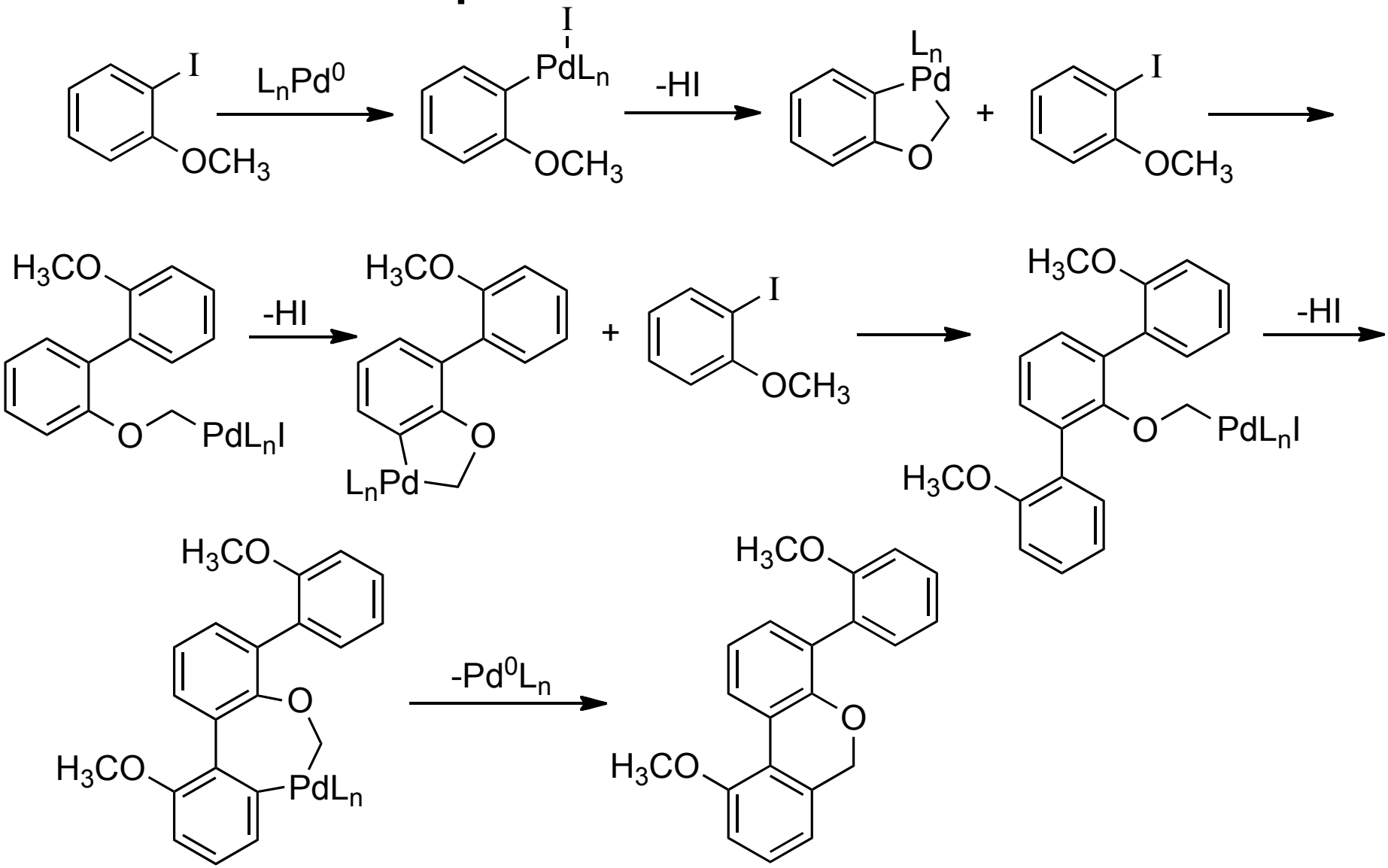
# C-H Activation of a Methoxy Group



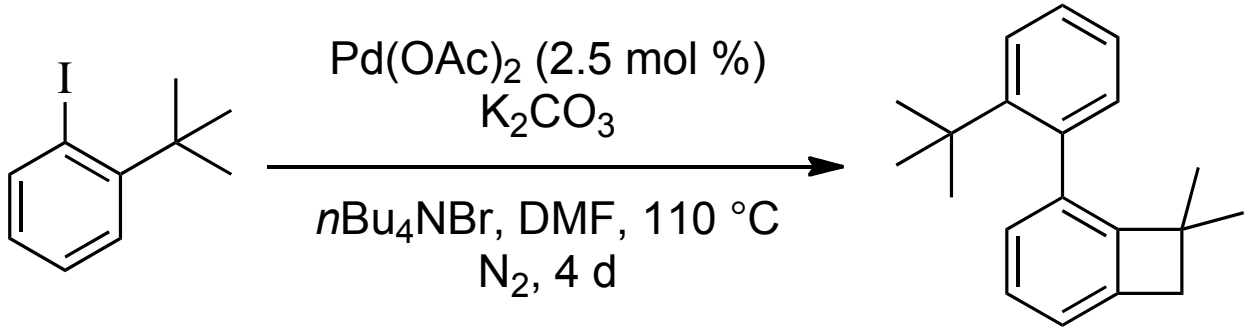

Dyker, G. *Angew. Chem. Int. Ed.* **1992**, *31*, 1023.

# Proposed Mechanism



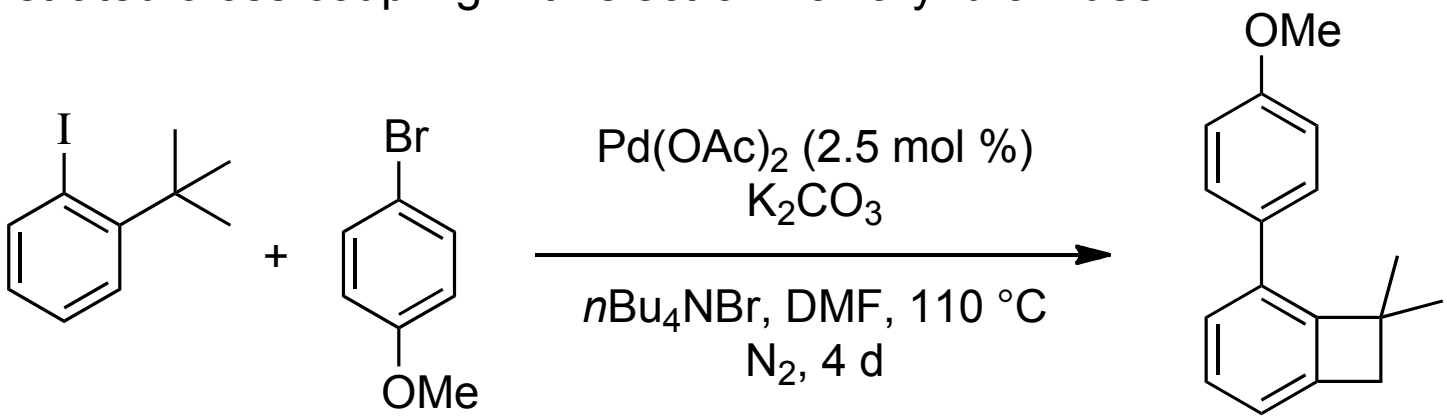

Dyker, G. *Angew. Chem. Int. Ed.* **1992**, *31*, 1023.

# C-H Activation of a *tert*-Butyl Group




75%

Demonstrated cross coupling with electron rich aryl bromides:



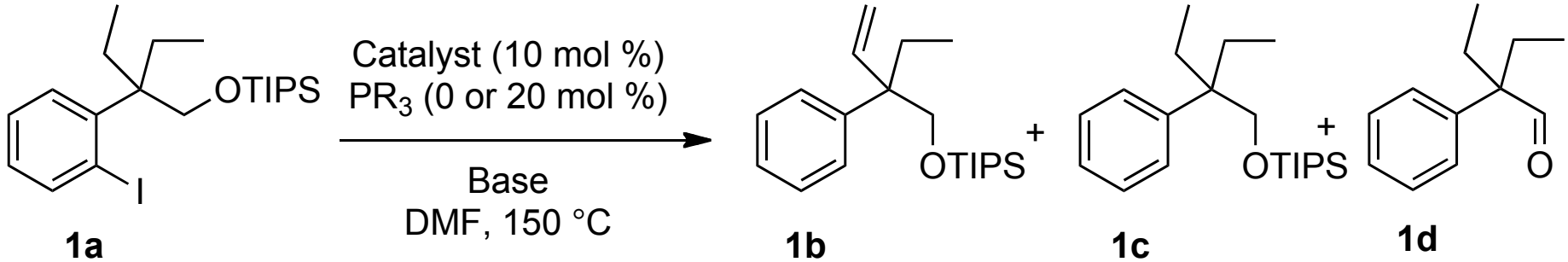

(5 equiv)

59%

C-H activation is not dependent on an adjacent heteroatom

Dyker, G. *Angew. Chem. Int. Ed.* **1994**, *33*, 103.

# C-H Activation of *gem*-Dialkyl Groups Gives β-Hydride Elimination

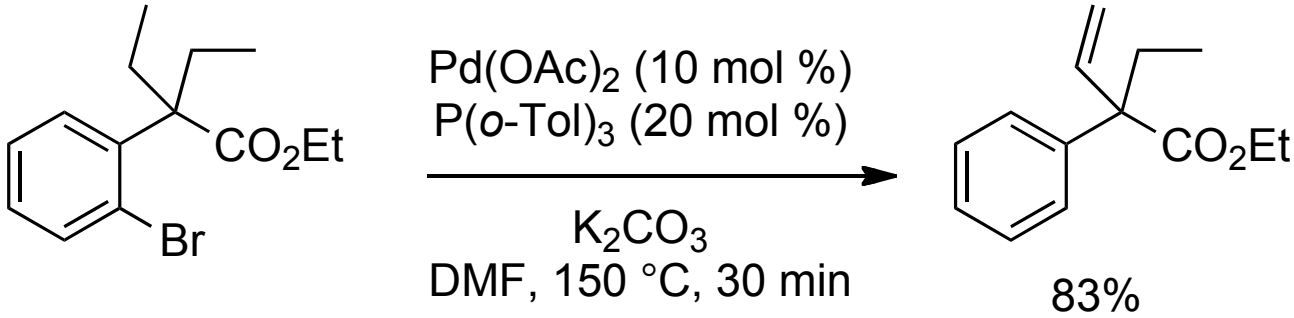



| Entry | Catalyst | $PR_3$ | Base | **1a** (%) | **1b** (%) | **1c** (%) | **1d** (%) |
|---|---|---|---|---|---|---|---|
| 1 | $Pd(OAc)_2$ | - | $Cs_2CO_3$ | 19 | 55 | 6 | <5% |
| 1 | $Pd(OAc)_2$ | $P(tBu)_3$ | $Cs_2CO_3$ | 0 | 58 | 6 | <5% |
| 3 | $Pd(OAc)_2$ | dppp | $Cs_2CO_3$ | 0 | 32 | 10 | 28% |
| 4 | $Pd(OAc)_2$ | $PPh_3$ | $Cs_2CO_3$ | 0 | 39 | 7 | 28% |
| 5 | $Pd(OAc)_2$ | $P(o\text{-Tol})_3$ | $Cs_2CO_3$ | 0 | 82 | 8 | <5% |
| 6 | $Pd(OAc)_2$ | $P(\text{mesityl})_3$ | $Cs_2CO_3$ | 0 | 75 | 6 | <5% |

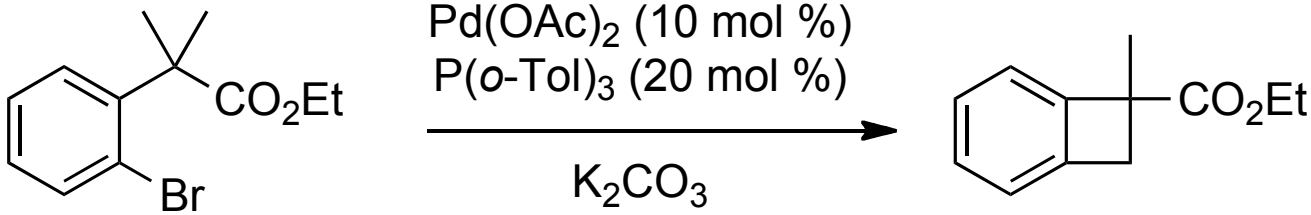
Addition of bulky triaryl phosphine ligands promotes C-H activation over protodehalogenation

Baudoin, O. *et. al. Angew. Chem. Int. Ed.* **2003**, *42*, 5736.

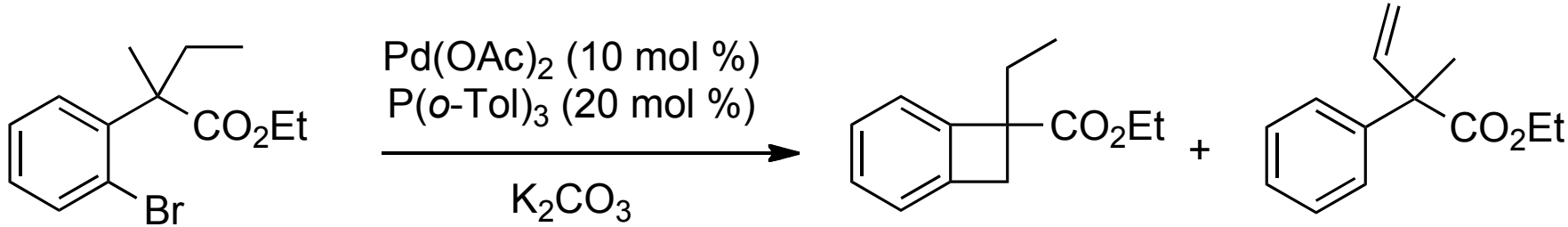
# Steric Differentiation in C-H Activation




83%




60%



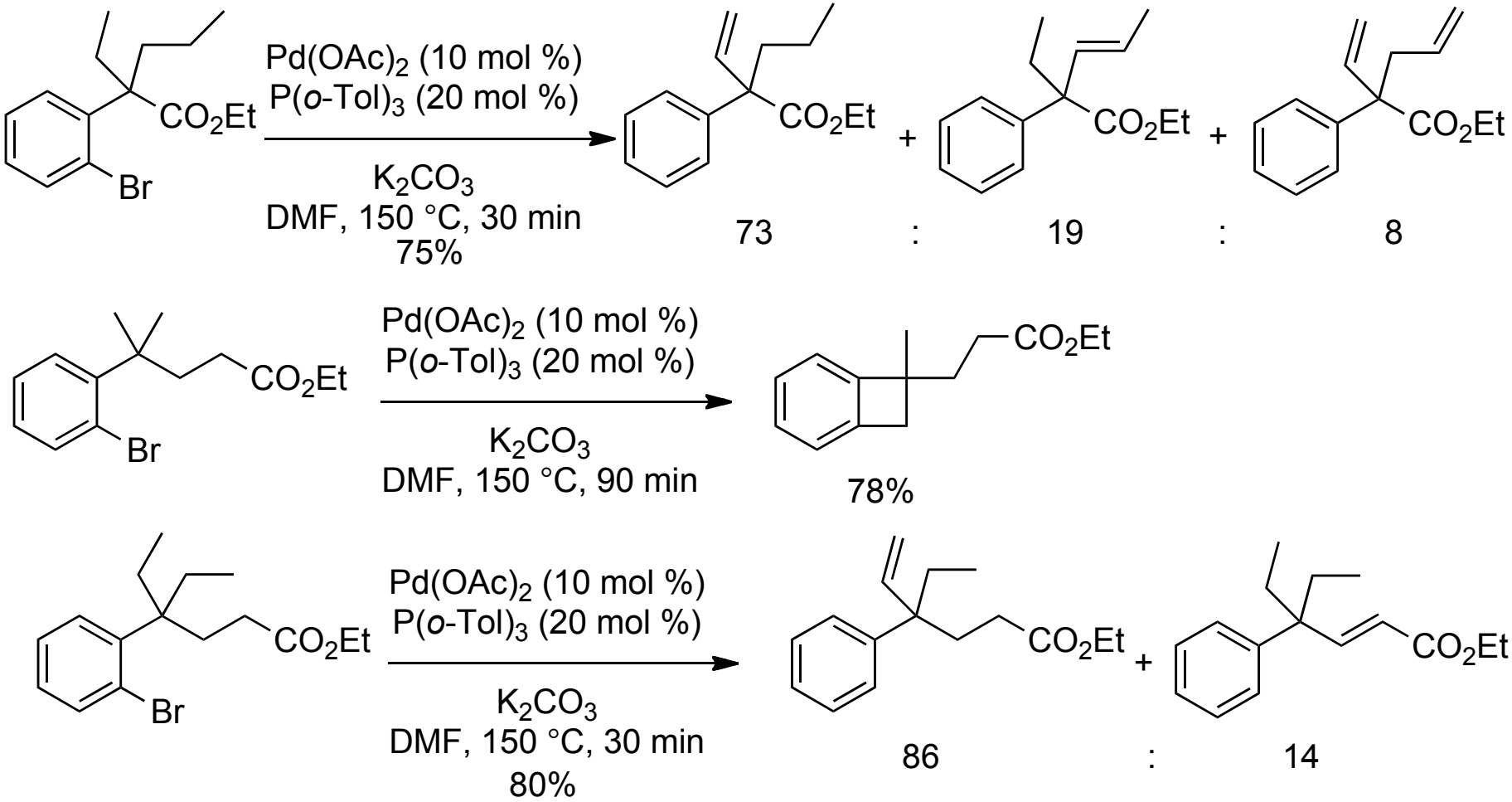

71%

95 : 5

C-H activation occurs preferentially at the less substituted alkyl group

Baudoin, O. *et. al. Angew. Chem. Int. Ed.* **2003**, *42*, 5736.

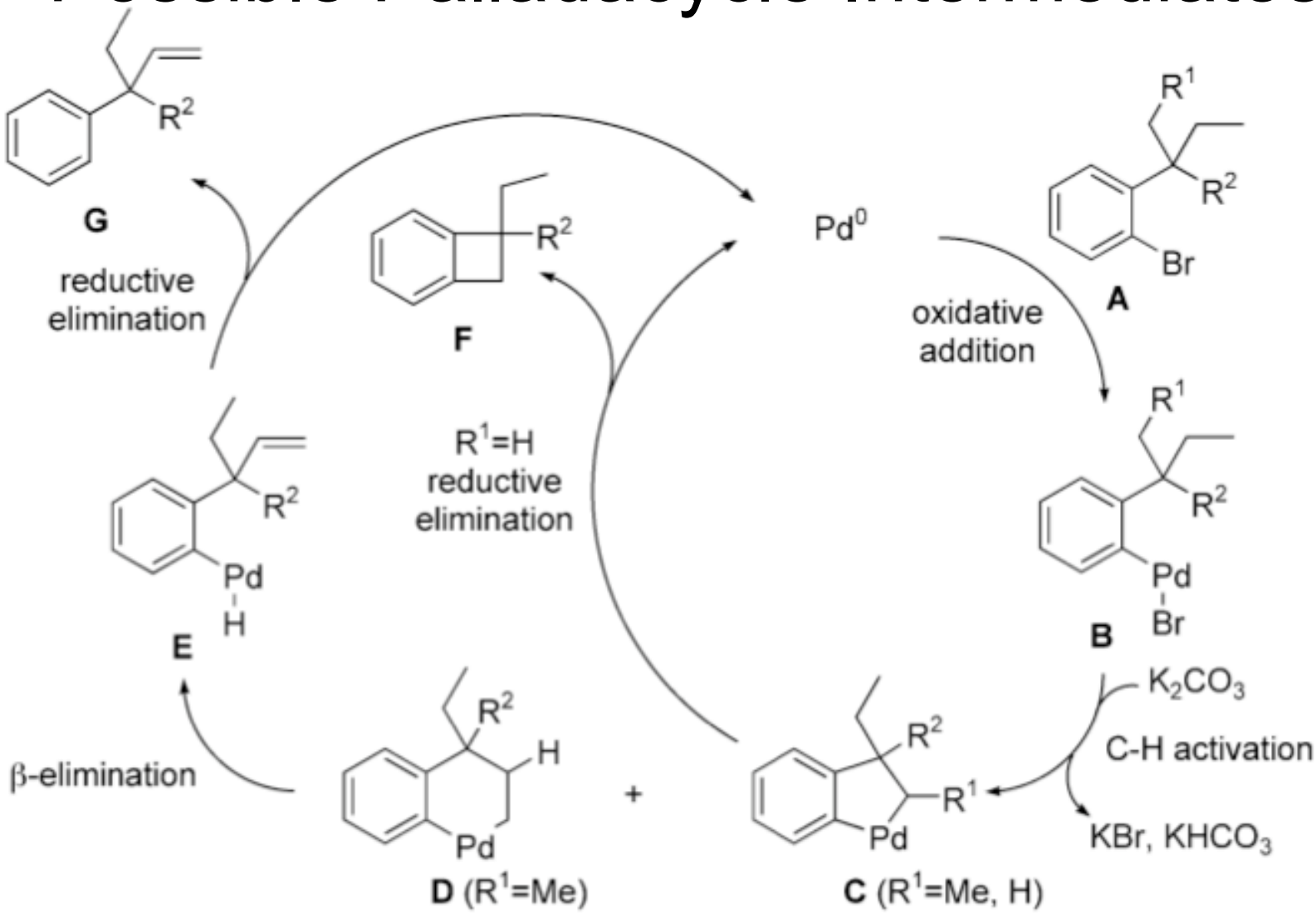
# Steric Factors Prevail over Conjugation




Steric factors prevail over formation of conjugated olefins

Baudoin, O. *et. al. Angew. Chem. Int. Ed.* **2003**, *42*, 5736.

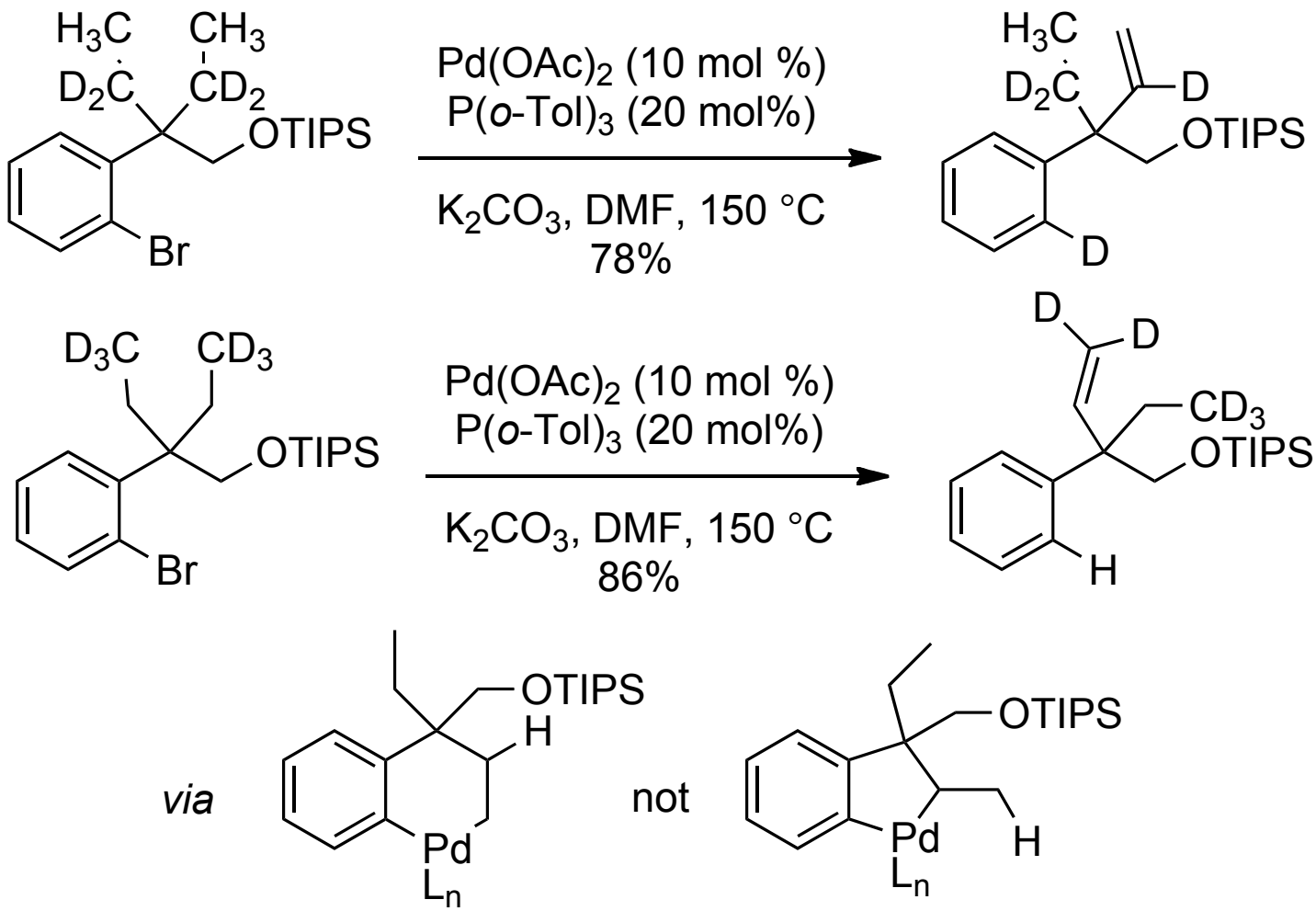
# Possible Palladacycle Intermediates




Olefin **E** could be formed through 5 or 6 membered palladcycle

Baudoin, O. *et. al. Angew. Chem. Int. Ed.* **2003**, *42*, 5736.

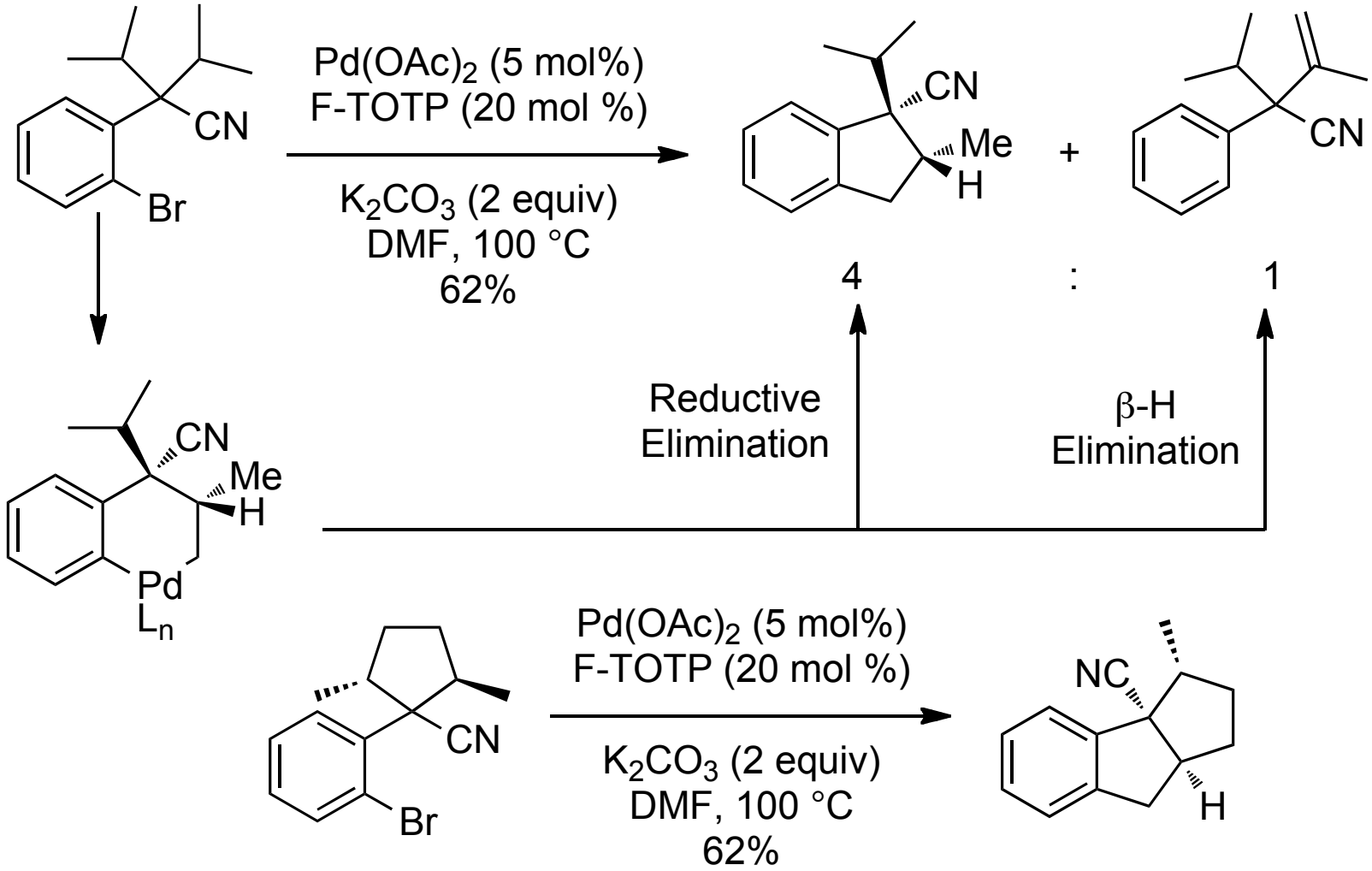
# Deuterium Labeling Studies




Reaction proceeds through a 6-membered palladacycle

Baudoin, O. *et. al. Angew. Chem. Int. Ed.* **2003**, *42*, 5736.

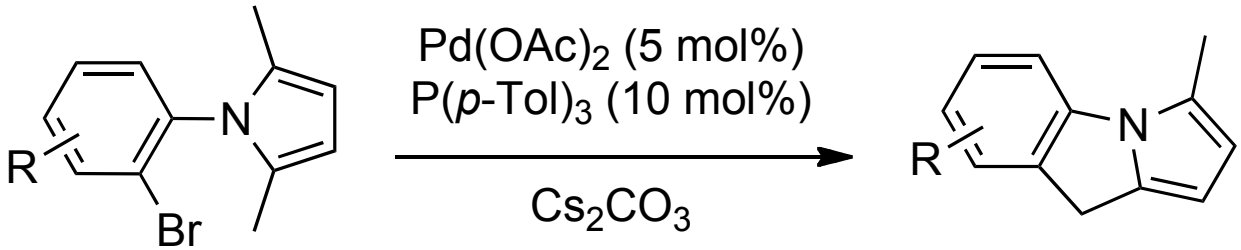
# Favoring Carbon-Carbon Bond Formation




Trisubstituted substrates favor reductive elimination

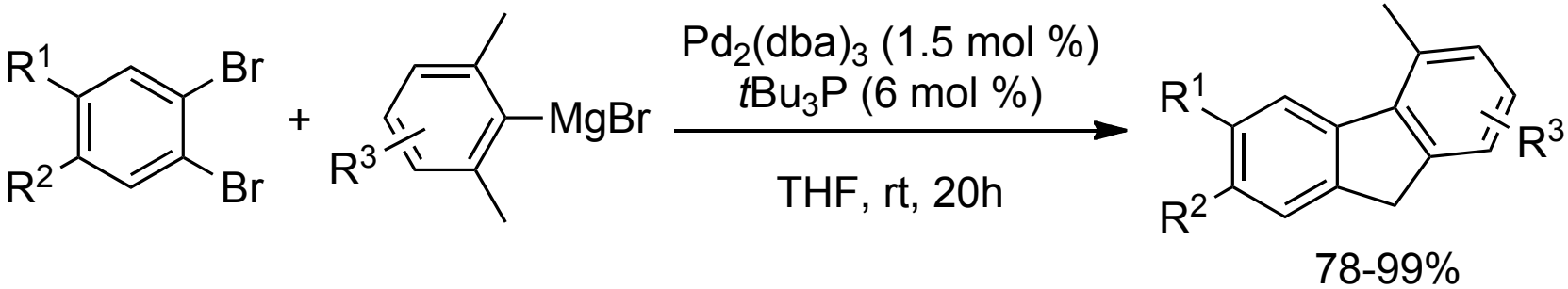
Baudoin, O. *et. al. Chem. Eur. J.* **2009**, *13,* 792.

# Intramolecular Arylation of Benzylic Methyl Groups




65-83%
Limited to R = EWG

Ren, H.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45,* 3462.

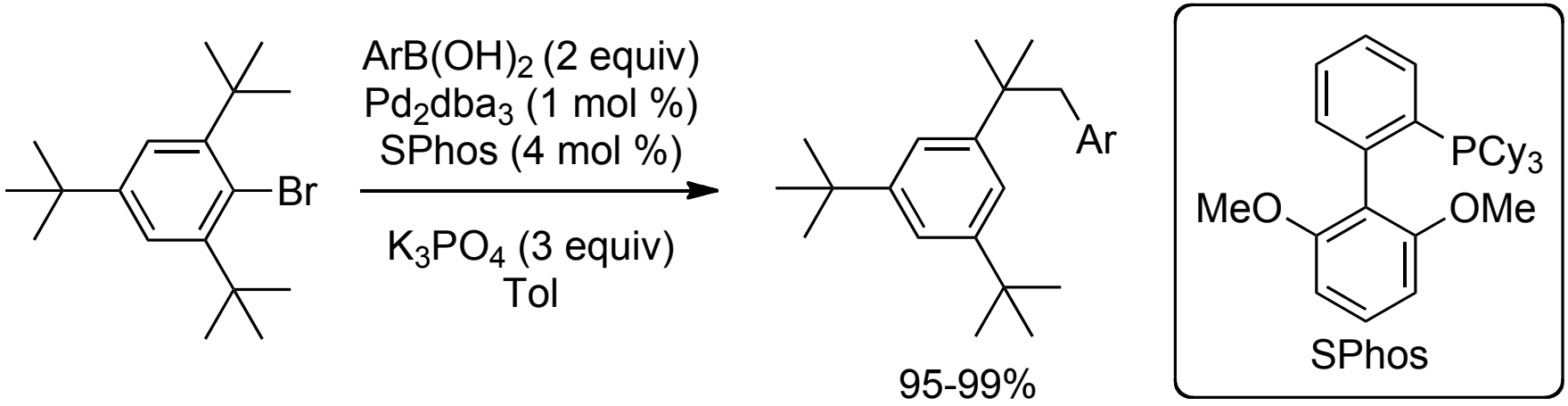



78-99%

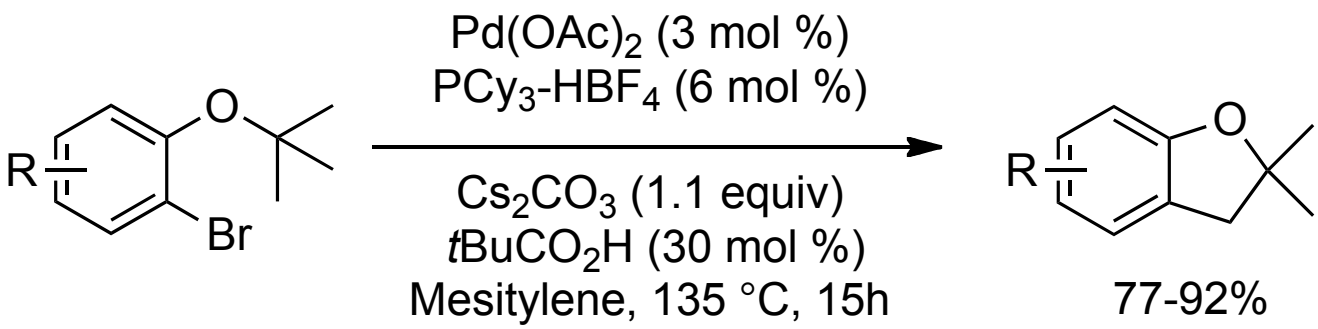
Dong, C. -G.; Hu, Q.-S. *Angew. Chem. Int. Ed.* **2006**, *45,* 2289.

Activation of benzylic methyl groups prevents β-hydride elimination

# Arylation of sp$^3$ C-H of *tert*-Butyl Groups



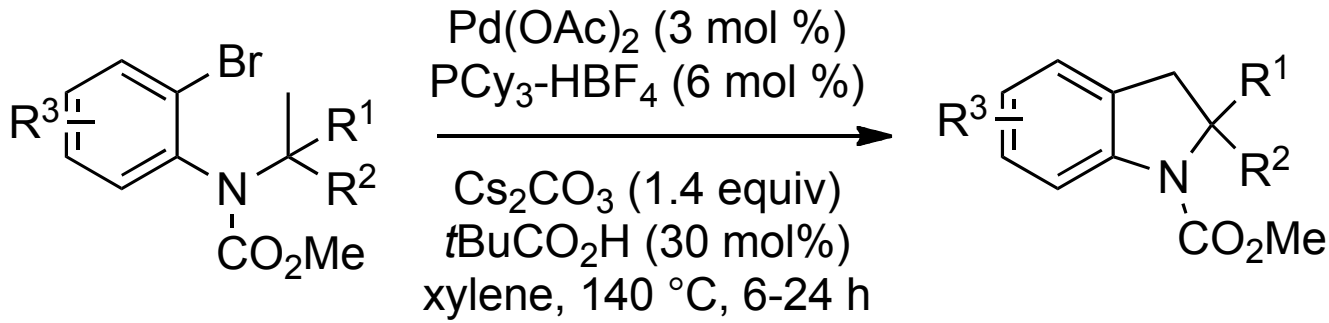

Buchwald, S.L. *et al*. *J. Am. Chem. Soc.* **2005**, *127,* 4685.

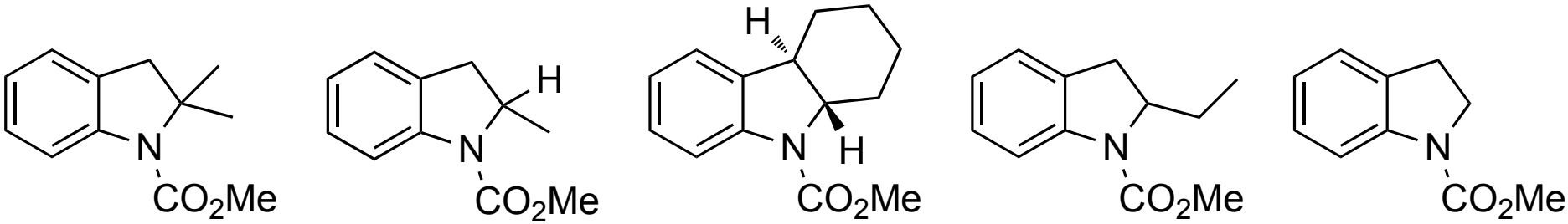



Fagnou, K, *et. al. J. Am. Chem. Soc.* **2007**, *129,* 14570.

Activation at quaternary carbons can also
Avoid β-hydride elimination

# Use of Substrates without Quaternary Carbons



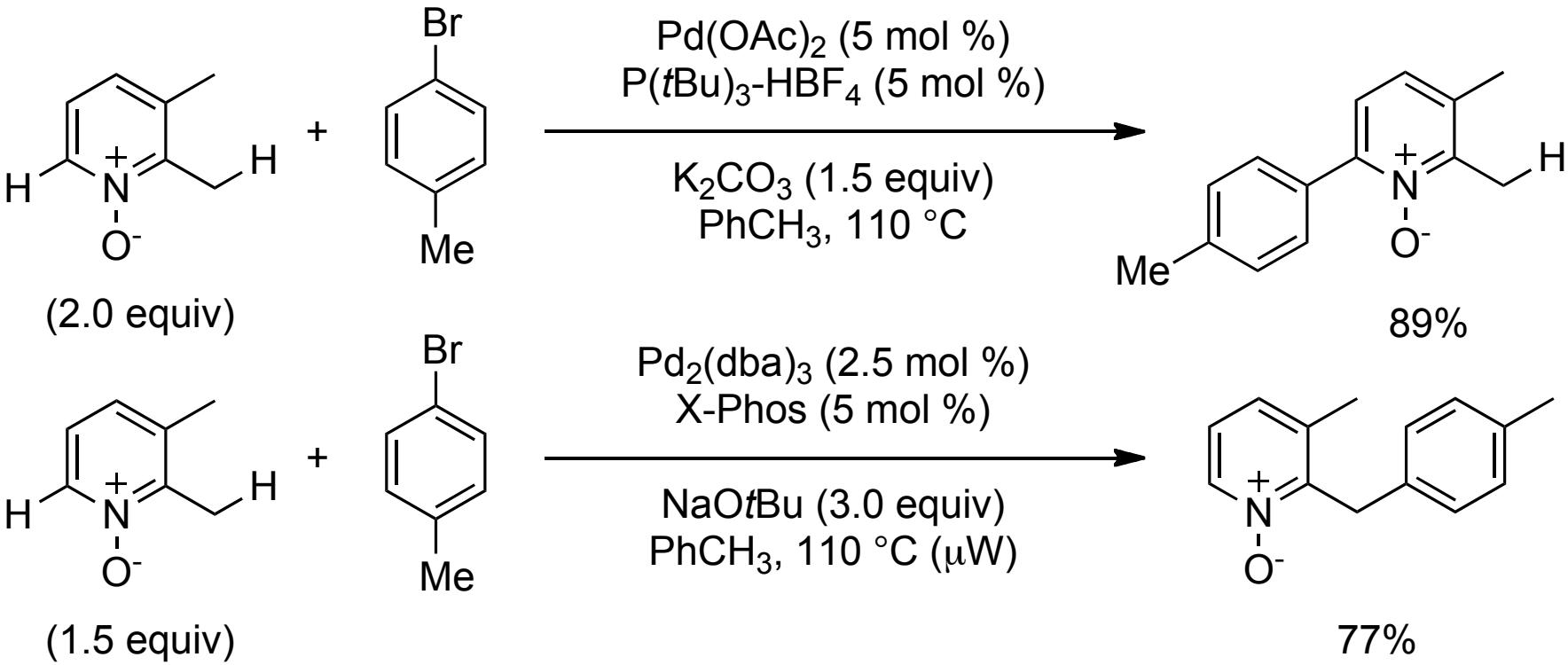



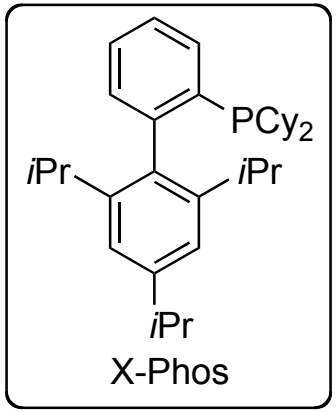

98% 80% 76% 89% 38%

Reductive elimination pathway can be competitive with β-H elimination

Fujii, N.; Ohno, H. *et. al. Org. Lett.* **2008**, *10,* 1759.

# Site-Selective $sp^3$ C-H Arylation

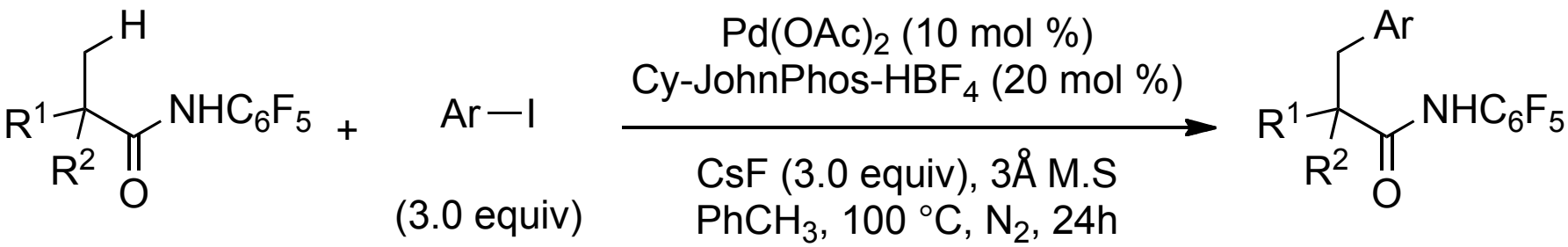


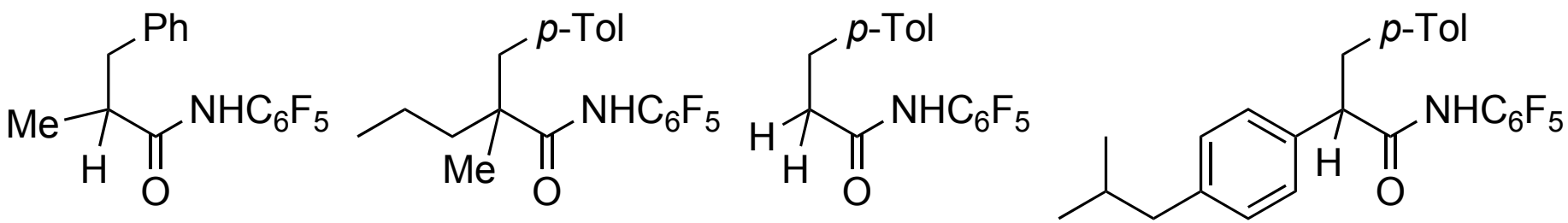




$sp^3$ C-H activation is favored over $sp^2$ C-H and β-hydride elimination

Fanou, K. *et. al. J. Am. Chem. Soc.* **2008**, *130,* 3266.

# Amide Directed Intermolecular Arylation




30% *mono*
53% *di*

78%

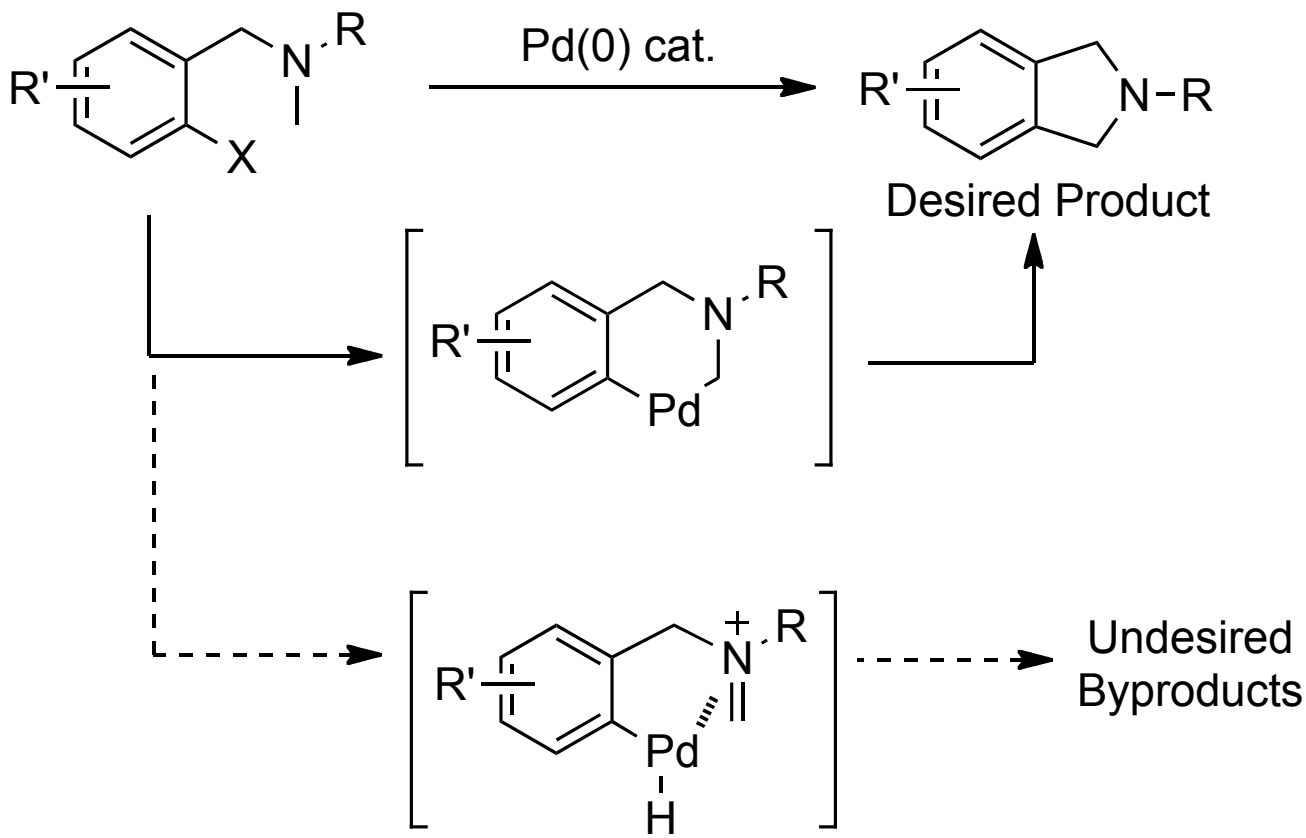
58%

80%

$sp^3$ C-H activation is favored over $sp^2$ C-H activation and β-hydride elimination

Yu, J.-Q. *et. al. J. Am. Chem. Soc.* **2009**, *131,* 9886.

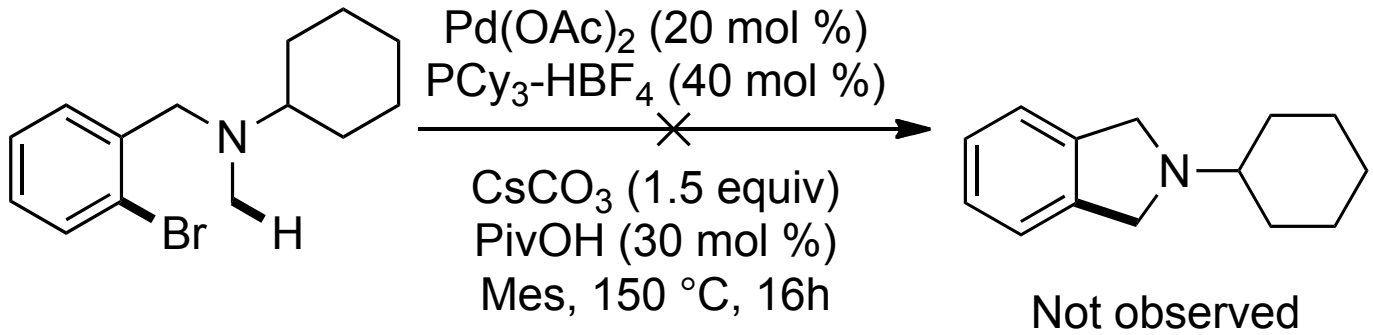
# $sp^3$ C-H Functionalization Adjacent to Nitrogen Atoms




β-Hydride elimination can lead to unproductive side reactions including dehalogenation of the starting material

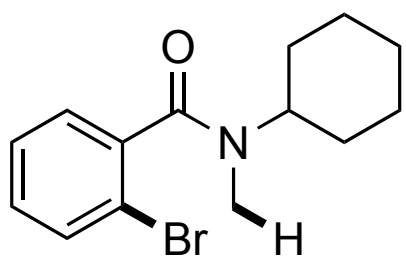
Rousseaux, S.; Fagnou, K. *et. al. J. Am. Chem. Soc.* **2010**, *132*, 10692.

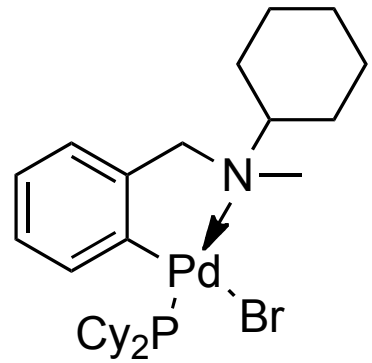
# Difficulty with Amine Substrates




Not observed

- Starting material recovered in 83% yield
- $^{31}$P NMR shows an unreactive Pd(II) intermediate
- Amide substrates lead to desired product



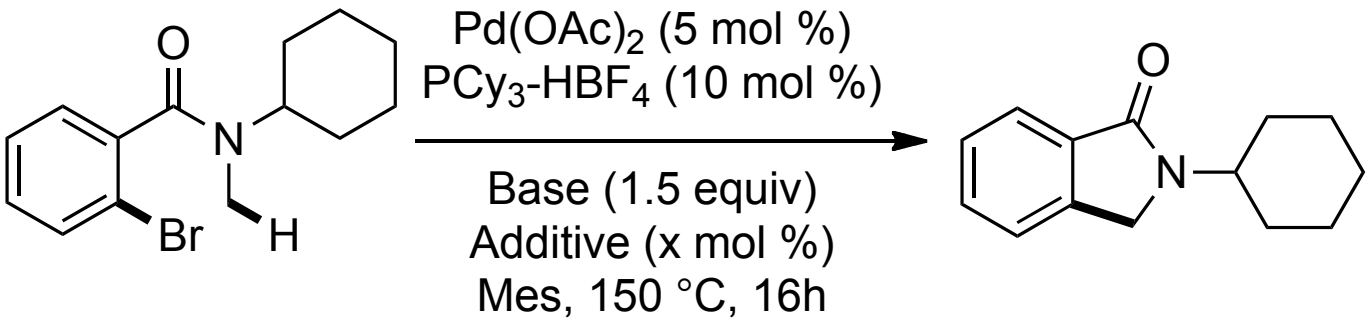




$^{31}$P NMR signal at 47 ppm

Lewis basicity of nitrogen has dramatic effect on the reaction outcome

Rousseaux, S.; Fagnou, K. *et. al. J. Am. Chem. Soc.* **2010**, *132*, 10692.

# Importance of Base and Additives




| Entry | Base | Additive | Yield (%) |
|---|---|---|---|
| 1 | $Cs_2CO_3$ | none | 14 |
| 2 | CsOPiv | none | 5 |
| 3 | $Cs_2CO_3$ | AcOH (30 mol%) | 27 |
| 4 | $Cs_2CO_3$ | PivOH (30 mol%) | 83 |
| 5 | $Cs_2CO_3$ | CsOPiv (110 mol%) | 88 |

Bulky pivalate additives greatly increase yield

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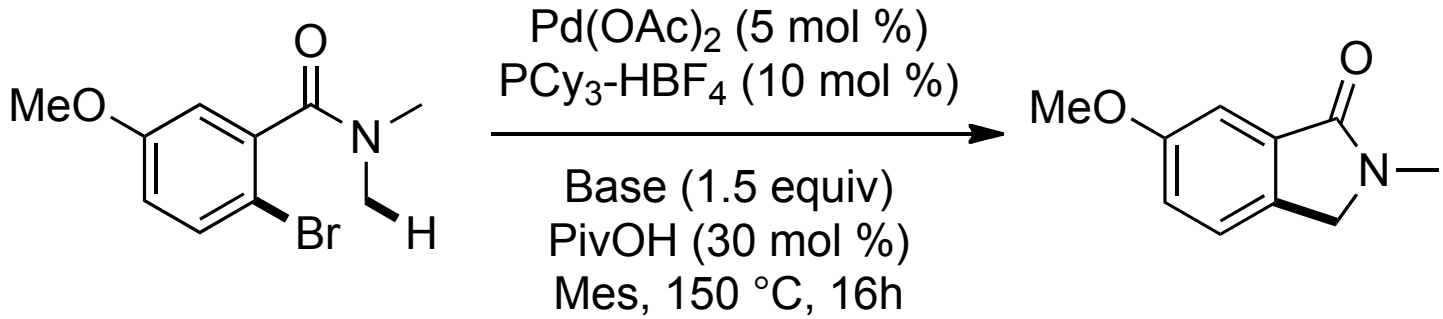
# Counterion Effect




| Entry | Base | Yield (%) |
|---|---|---|
| 1 | $Na_2CO_3$ | 0 |
| 2 | $K_2CO_3$ | 31 |
| 3 | $Rb_2CO_3$ | 56 |
| 4 | $Cs_3CO_3$ | 48 |

$Rb_2CO_3$ was optimal base for preventing dehalogenation of the starting material

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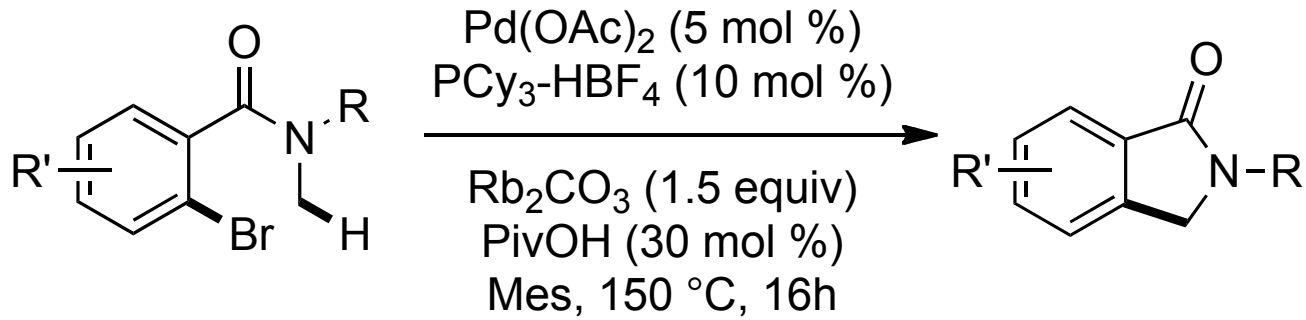
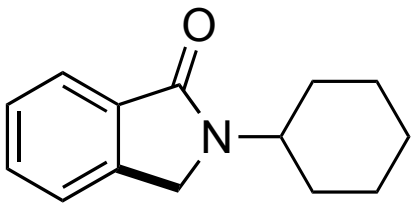
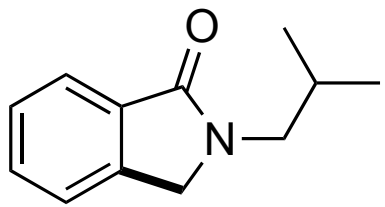
# Amide Scope

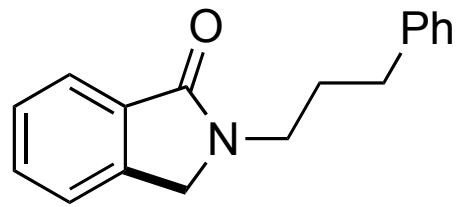


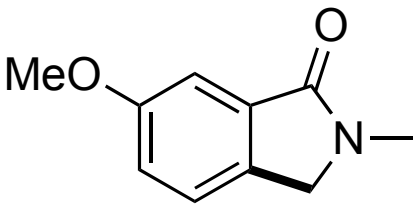
83%



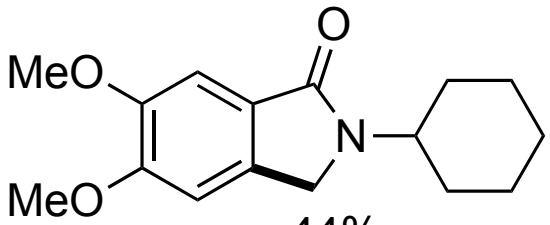
68%



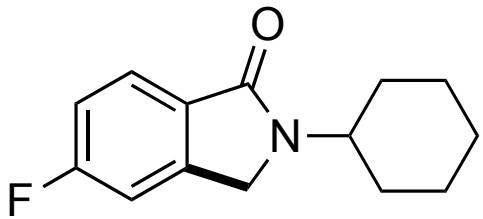
37%



56%



44%



70%

Selective for methyl C($sp^3$)-H and deactivated by electron rich aromatic rings

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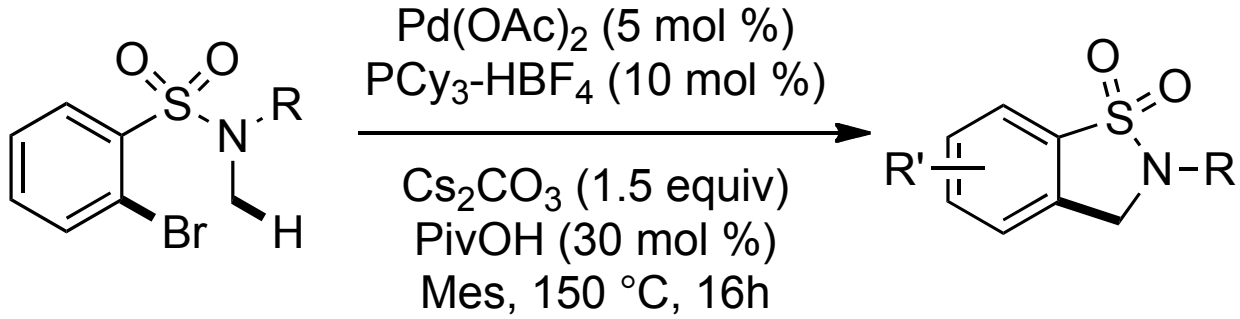
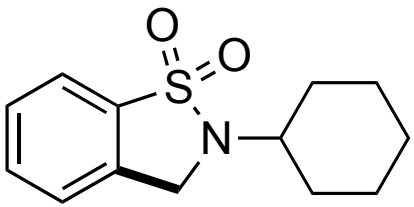
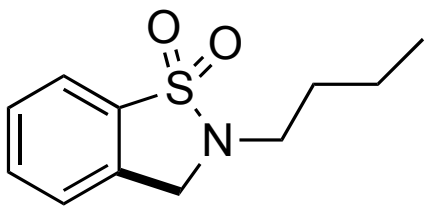
# Sulfonamide Scope

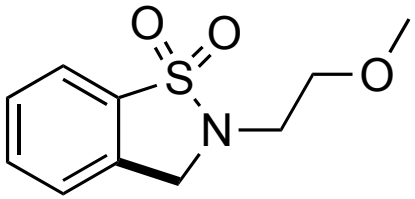


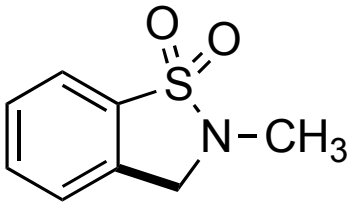
62%



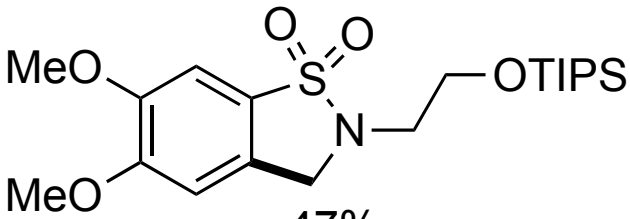
82%



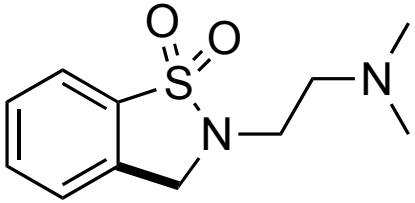
59%




52%




47%



71%

Sulfonamides gave similar results

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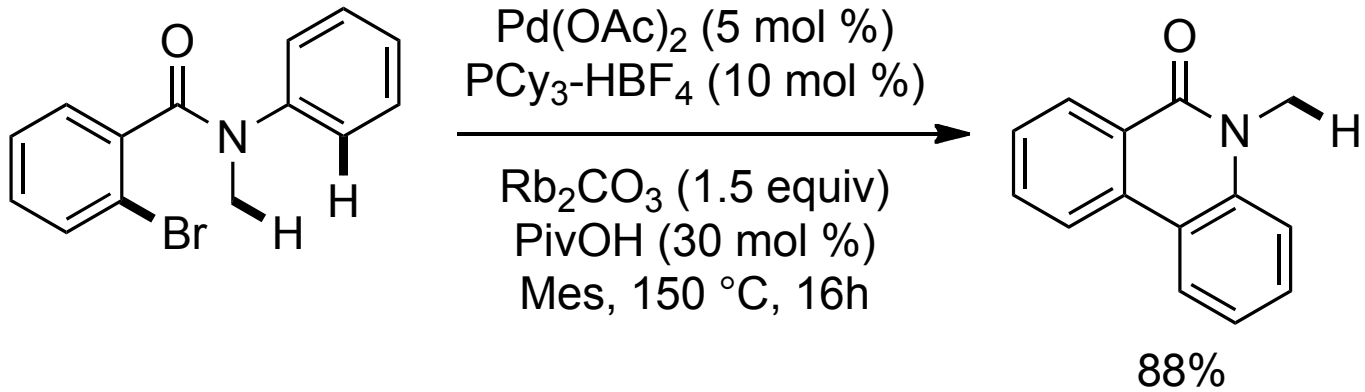
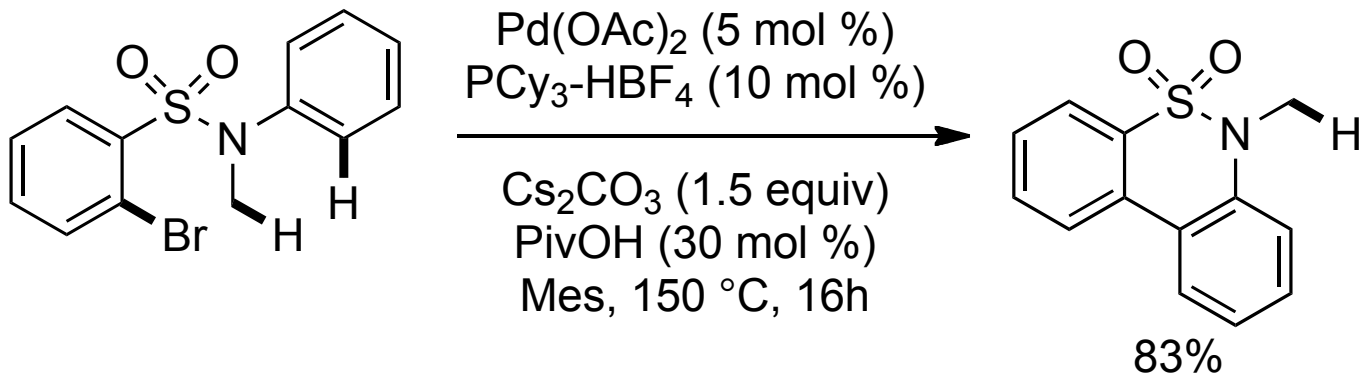
# Reactivity of $sp^2$ and $sp^3$ C-H Bonds




Complete selectivity for $sp^2$ C-H bond via a seven-membered palladacycle

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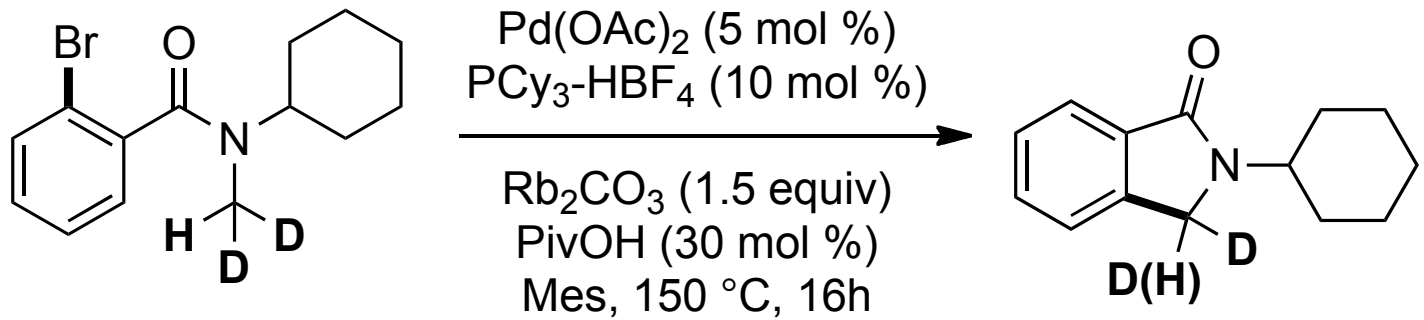
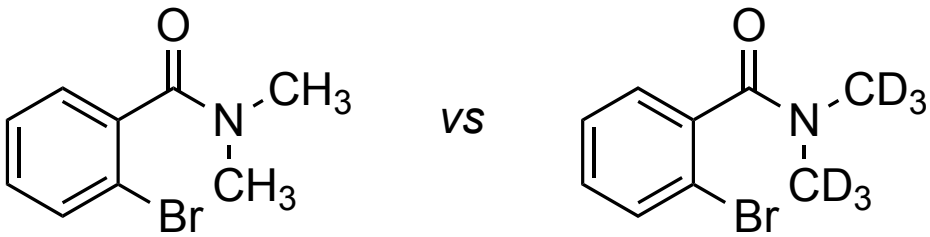
# KIE Effects




$k_H/k_D = 3.4$




$k_H/k_D = 6.5$

$k_H = 3.2 \times 10^{-6}$ M/s $\qquad$ $k_D = 4.9 \times 10^{-7}$ M/s

The observed KIE shows the the C-H(D) bond is cleaved in the rate determining step

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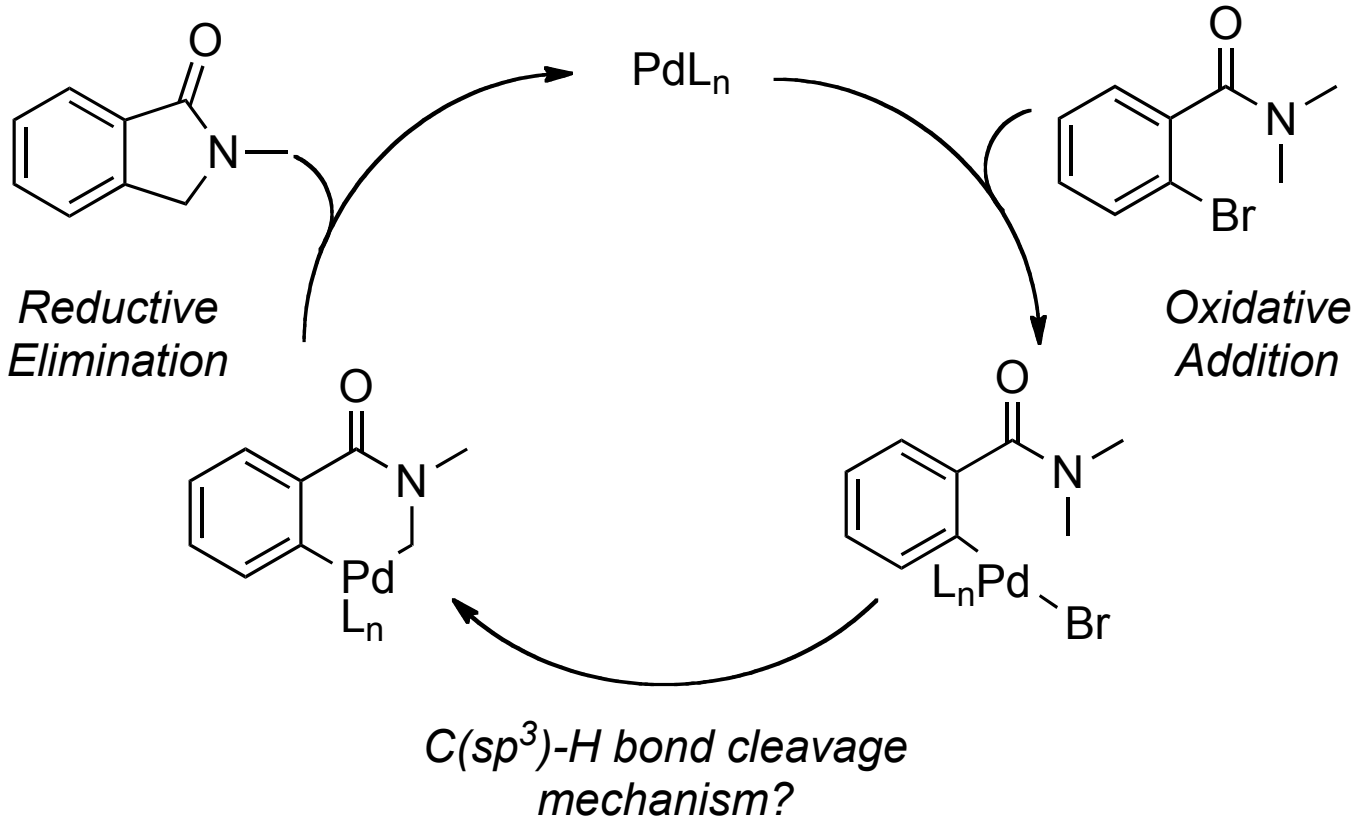
# Simple Catalytic Cycle




What is a mechanism of C-H cleavage? What is the role of the base additive?

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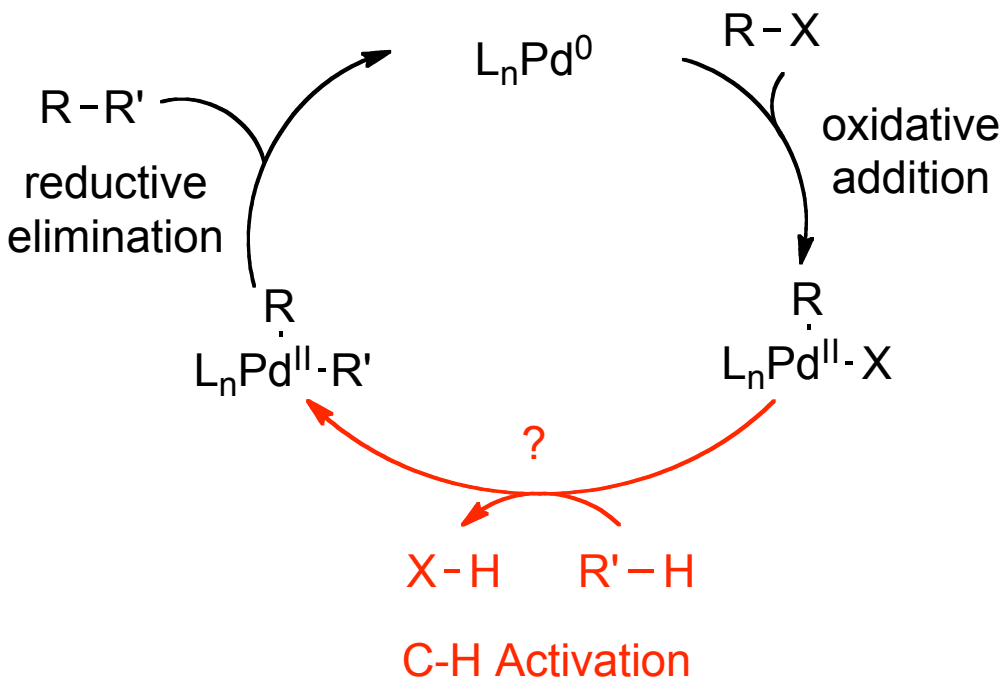
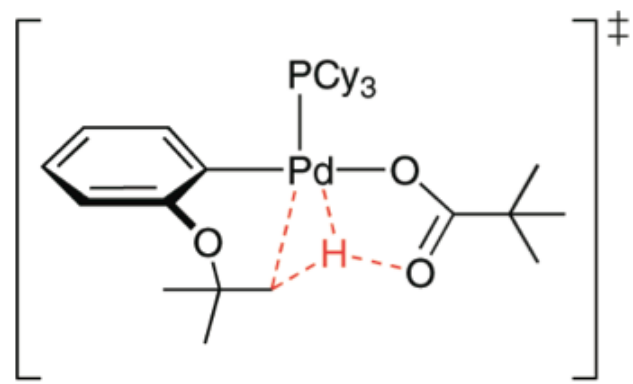
# Mechanism for $sp^3$ C-H Activation




*Inner-sphere Pivalate Assisted CMD*

Concerted metalation-deprotonation (CMD) pathway shown for $sp^2$ C-H bond activation may be operative

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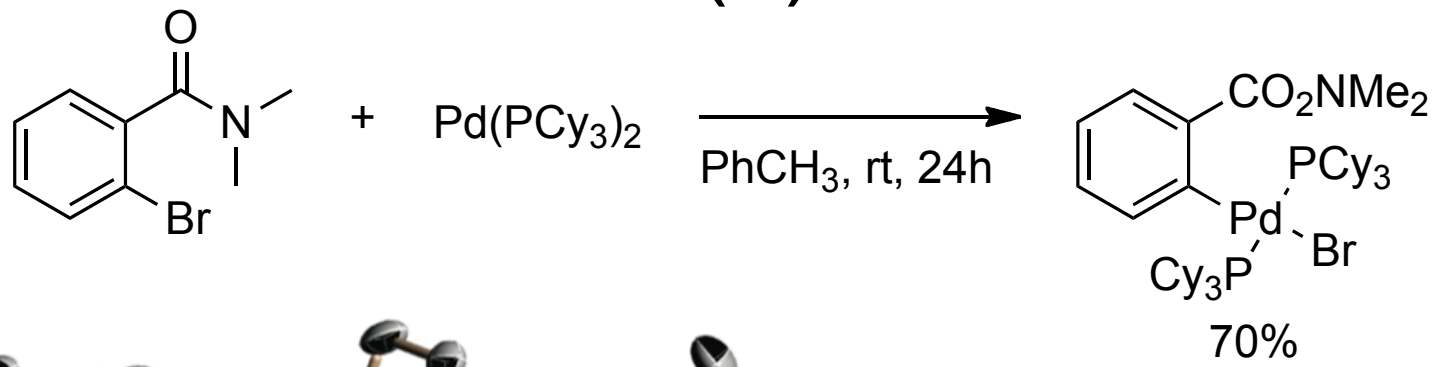
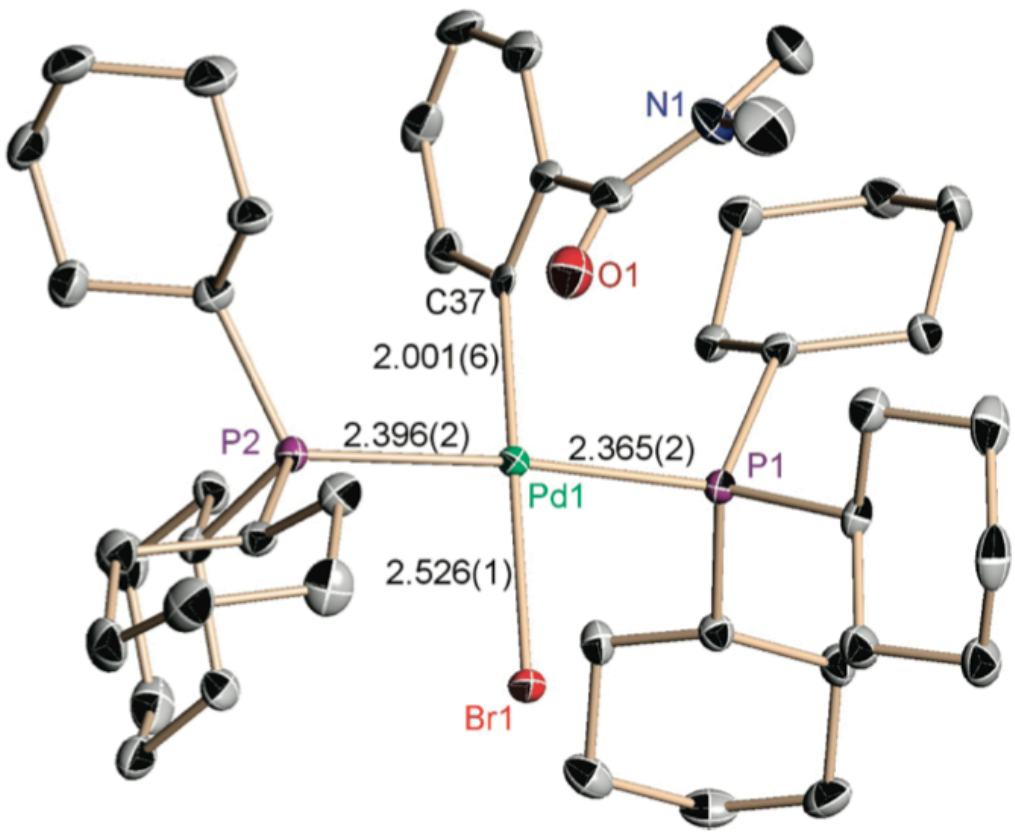
# Isolation of Pd(II) Intermediate




No significant Interactions between the amide and the Pd(II) center.

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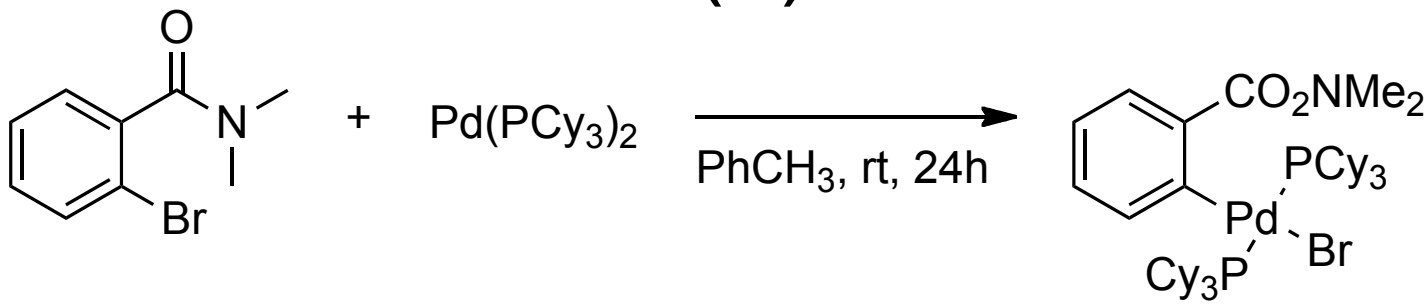
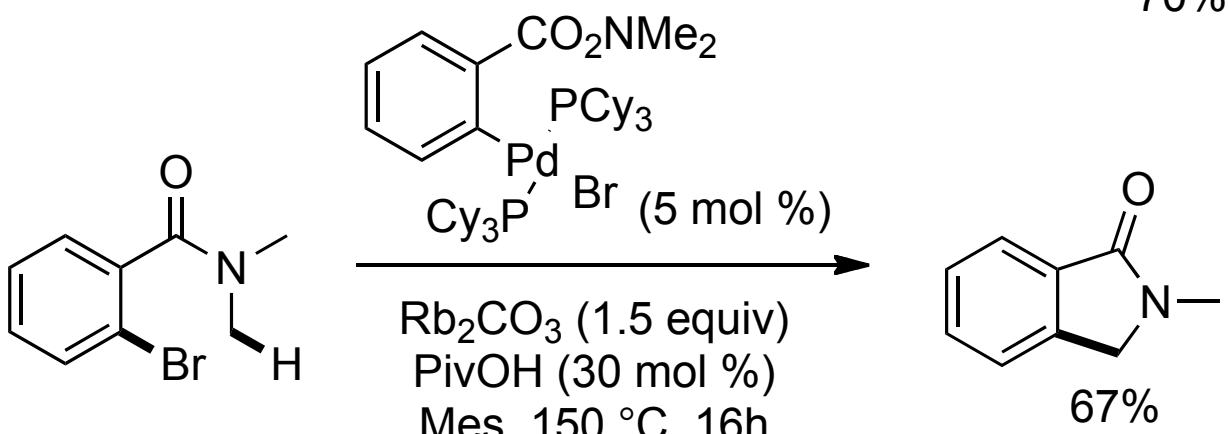
# Isolation of Pd(II) Intermediate




70%




67%
(76% standard conditions)

Isolated Pd(II) complex is a catalyst precursor for the reaction

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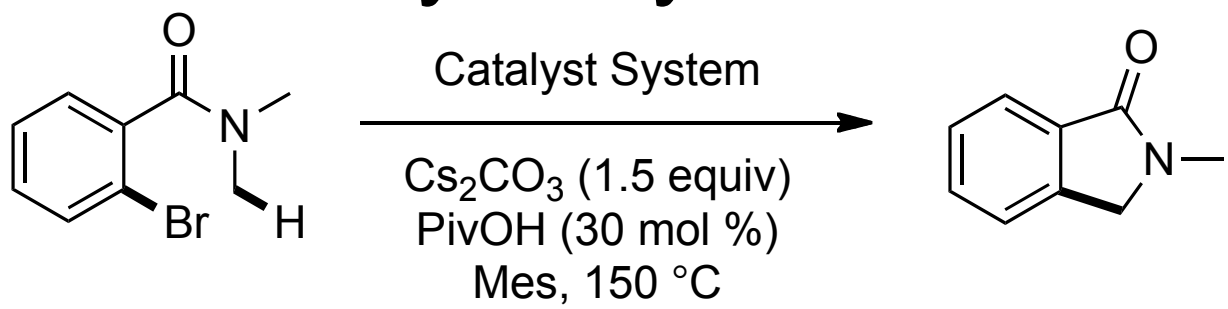
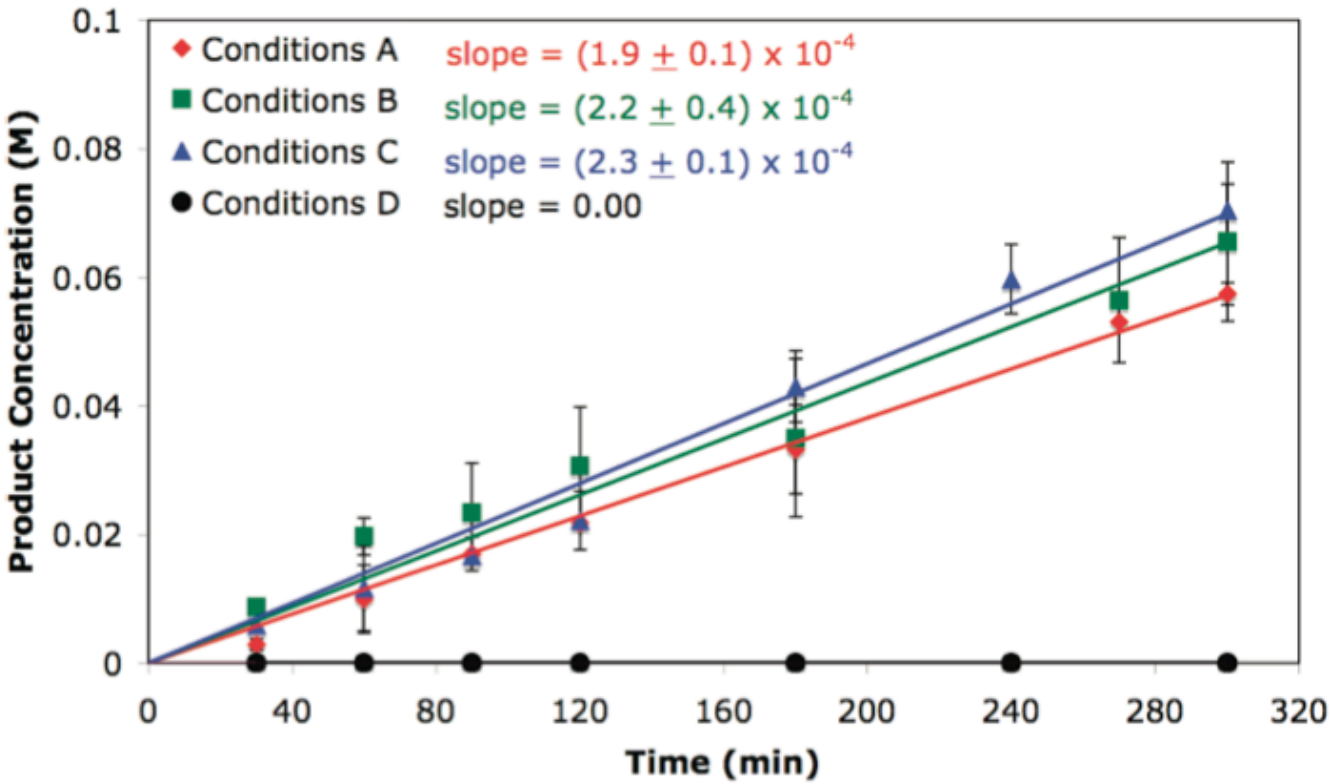
# Initial Product Formation with Different Catalytic Systems




◆ $Pd(OAc)_2$ (5 mol %) + $PCy_3$-$HBF_4$ (10 mol %)

■ $[(PCy_3)_2Pd(Ar)(Br)]$ (5 mol %)

▲ $Pd(PCy_3)_2$ (5 mol%)

● $Pd(PCy_3)_2$ (5 mol%) **without PivOH**

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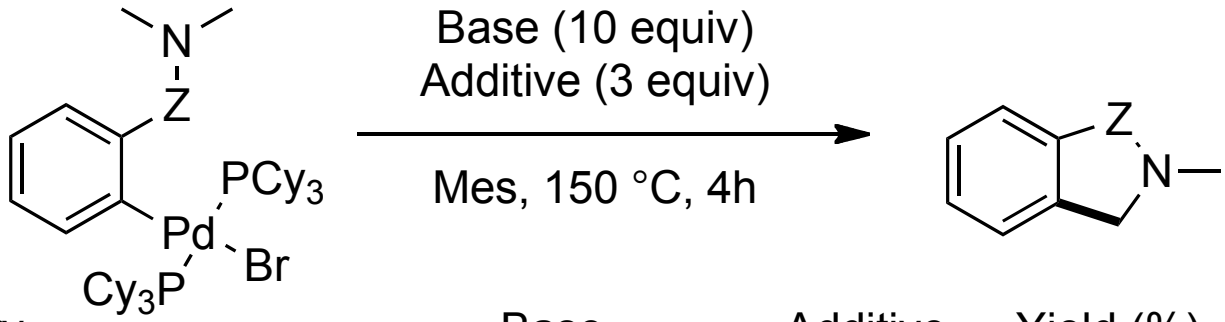
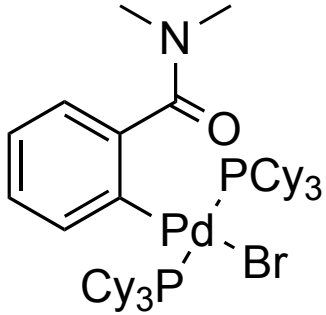
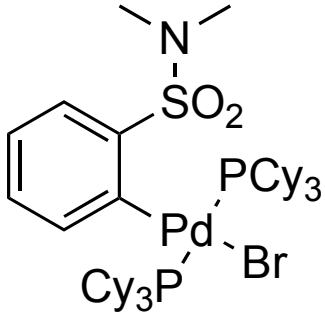
# Stoichiometric Studies to Probe Role of Base




| Entry | | Base | Additive | Yield (%) |
|---|---|---|---|---|
| 1 |  | none | none | 0 |
| 2 | | $Cs_2CO_3$ | none | 0 |
| 3 | | CsOPiv | none | 28 |
| 4 | | $Cs_2CO_3$ | CsOPiv | 96 |
| 5 |  | none | none | 0 |
| 6 | | $Cs_2CO_3$ | none | 6 |
| 7 | | CsOPiv | none | 35 |
| 8 | | $Cs_2CO_3$ | CsOPiv | 80 |

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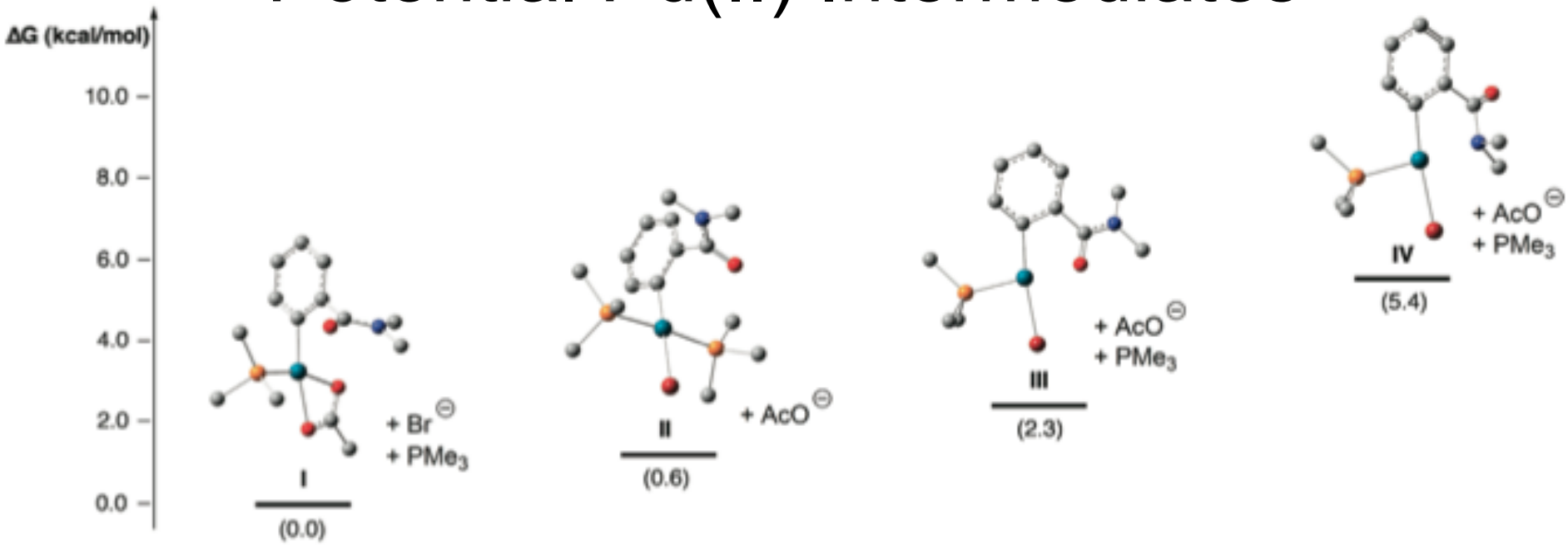
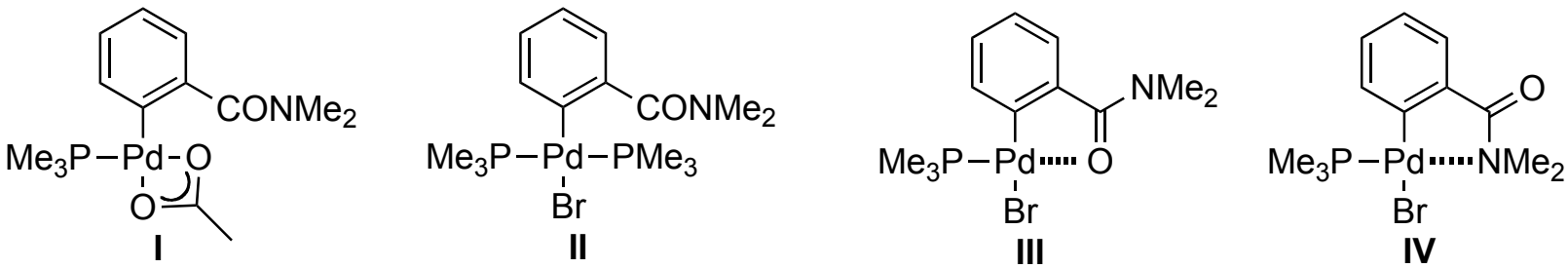
# Potential Pd(II) Intermediates




Coordination of amide does not promote dissociation of phosphine ligand

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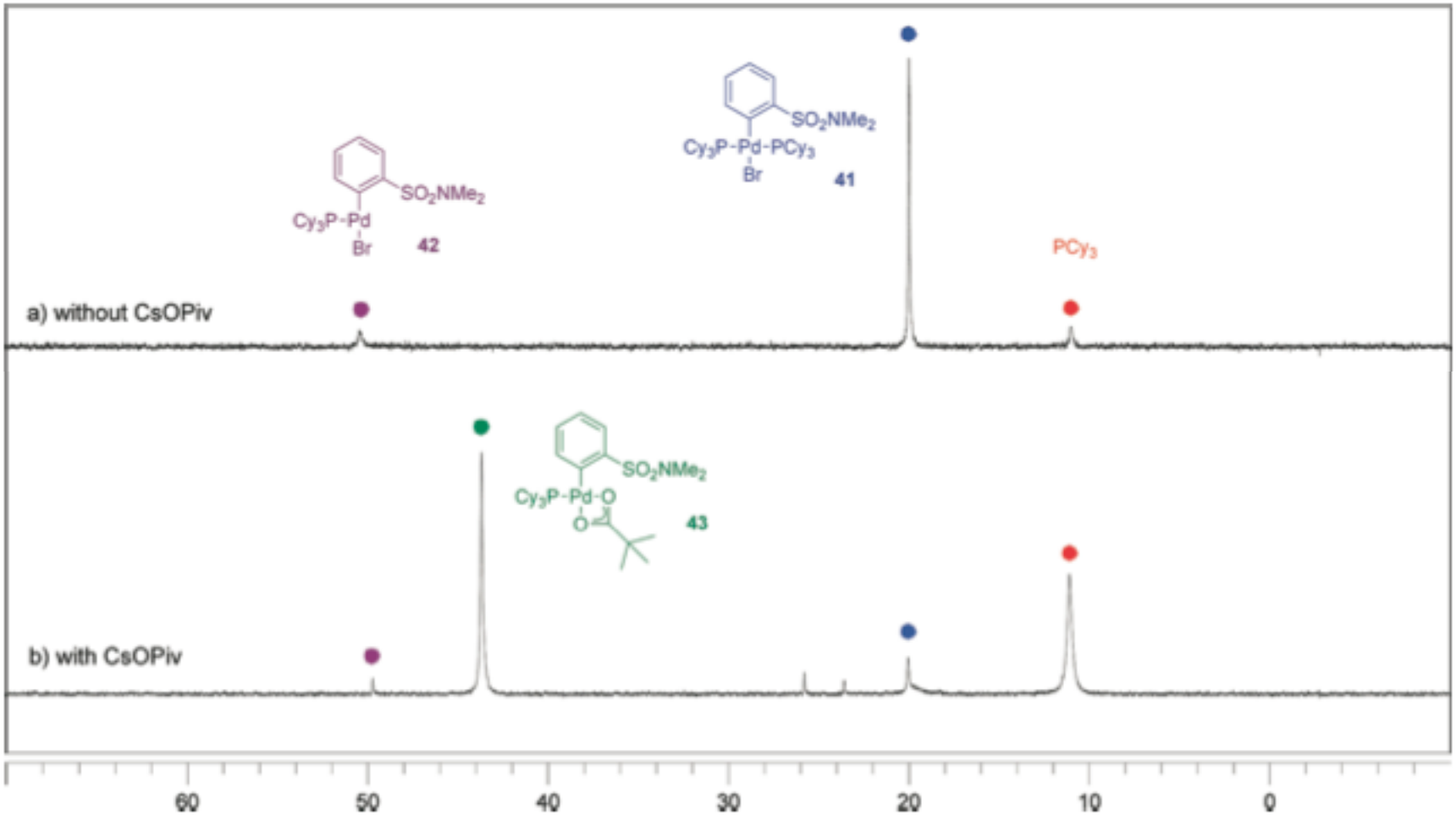
# Pivalate Promotes Phosphine Dissociation




Addition of CsOPiv (6 equiv) diminishes amount of Pd(II) intermediate **41** in solution

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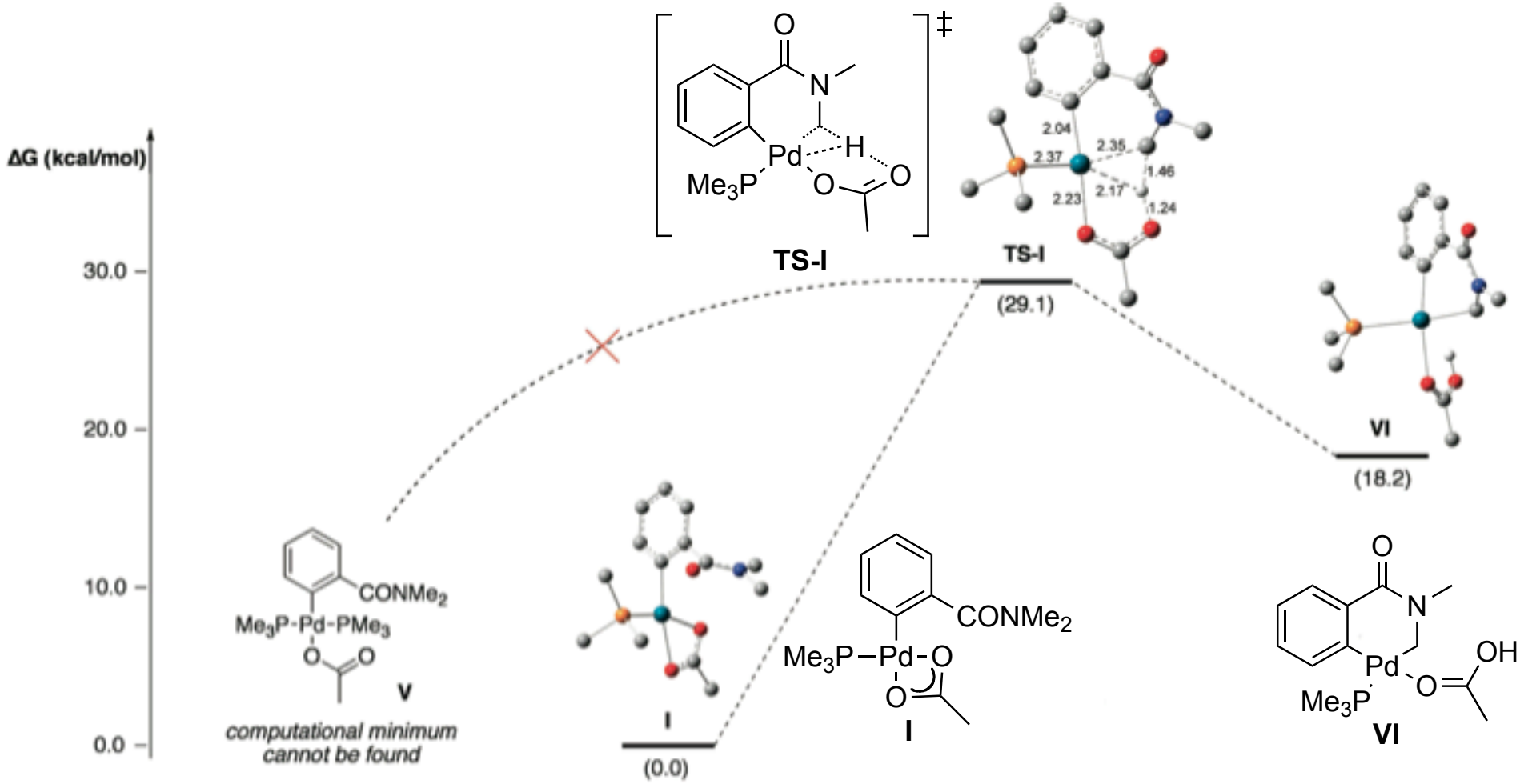
# Role of Carbonate Base




Rapid deprotonation of acid ligand is required to prevent **VI** from reverting to **I**

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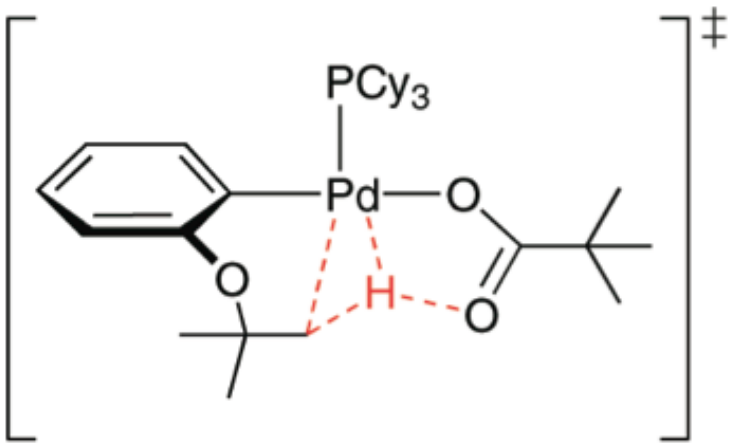
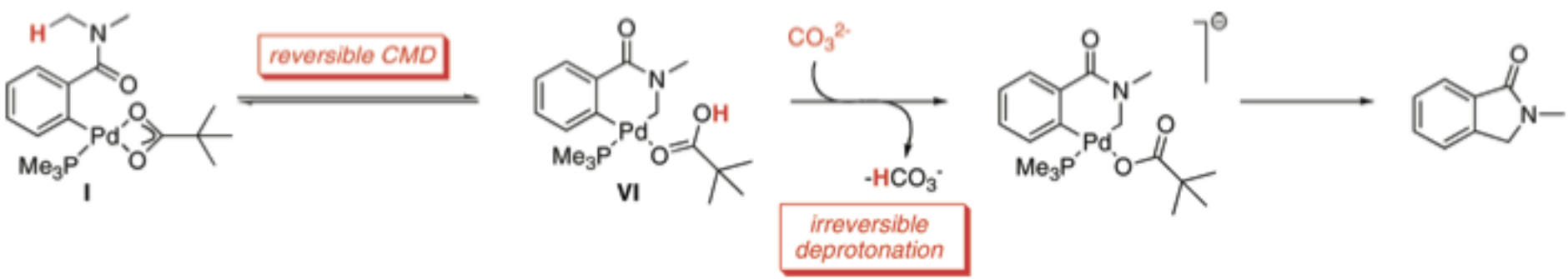
# Role of Pivalate and Base Additives

Proposed concerted metalation-deprotonation (CMD) transition state:




*Inner-sphere Pivalate Assisted CMD*

- Pivalate acts as the base to promote C-H cleavage
- Pivalate promotes phosphine dissociation
- Pivalate prevents catalyst inhibition by excess phosphine
- Carbonate is necessary for irreversible deprotonation of pivalate ligand after CMD

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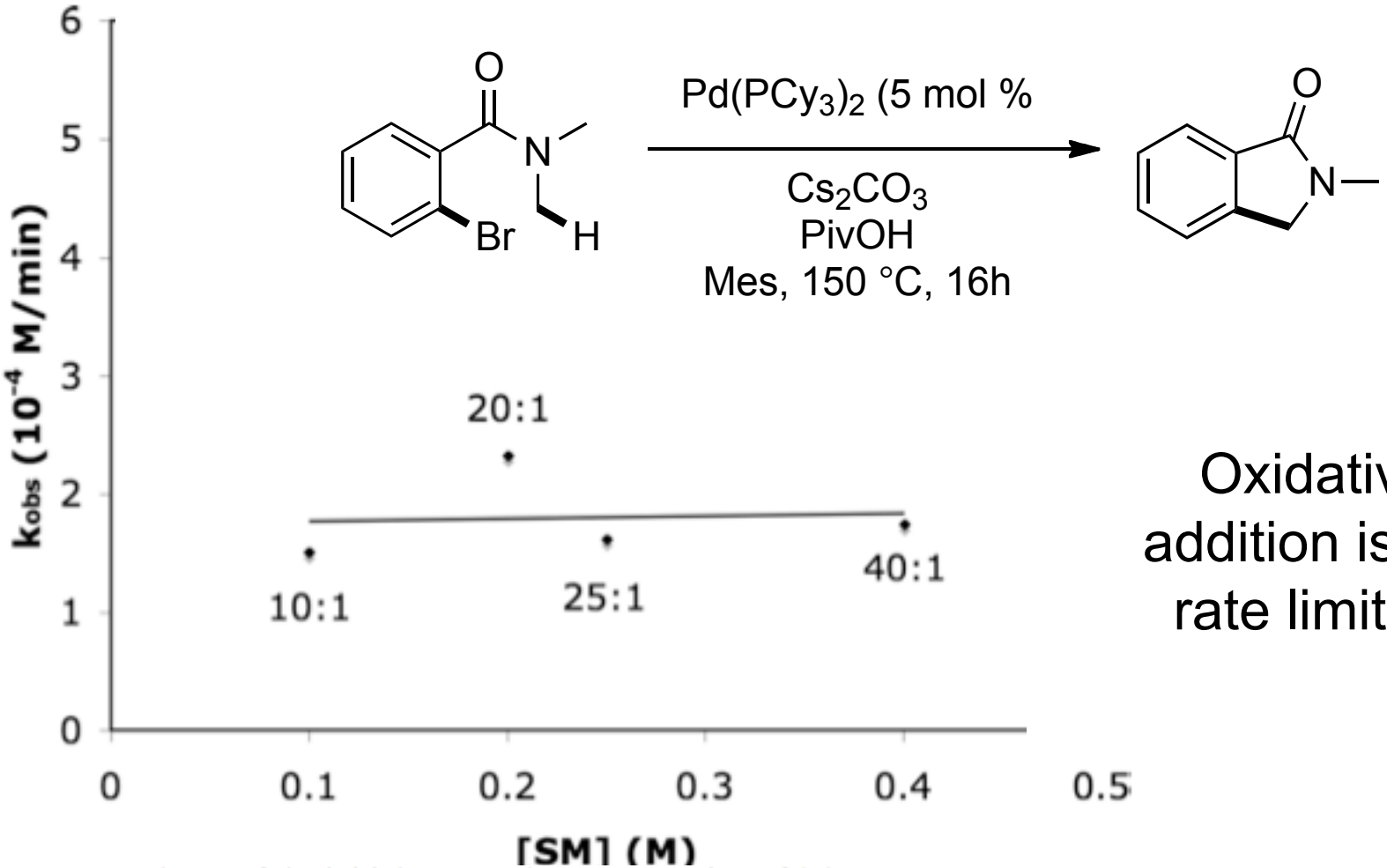
# Kinetic Studies: Zeroth-Order in Substrate




Oxidative addition is not rate limiting

***Figure 8.*** Dependence of the initial rate on the concentration of 2-bromo-*N*,*N*-dimethylbenzamide **12** (SM) (0.10−0.40 M). Conditions: $[Pd(PCy_3)_2] = 1.0 \times 10^{-2}$ M and $[PivOH] = 6.0 \times 10^{-2}$ M in 2.9 mL of mesitylene with 0.872 mmol of $Cs_2CO_3$ at 150 °C. Yields were determined by GC/MS using 1,3,5-trimethoxybenzene as an internal standard. Data labels represent **12**/palladium ratios.

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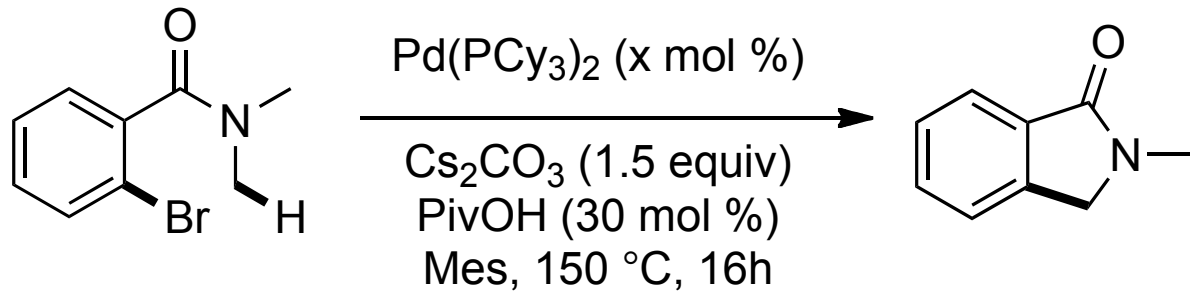
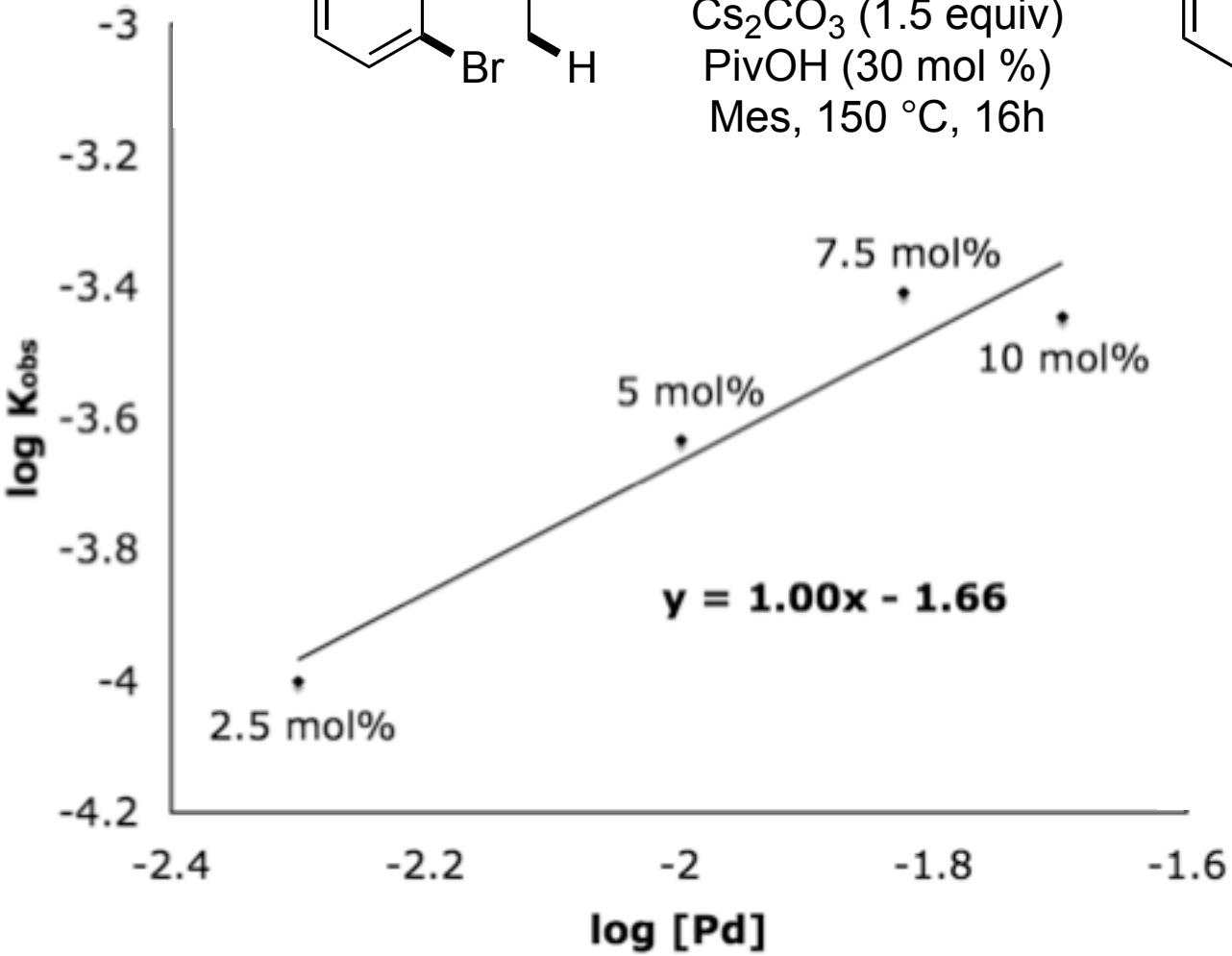
# Kinetic Studies: First-Order in Catalyst




Catalyst is present at the rate determining step

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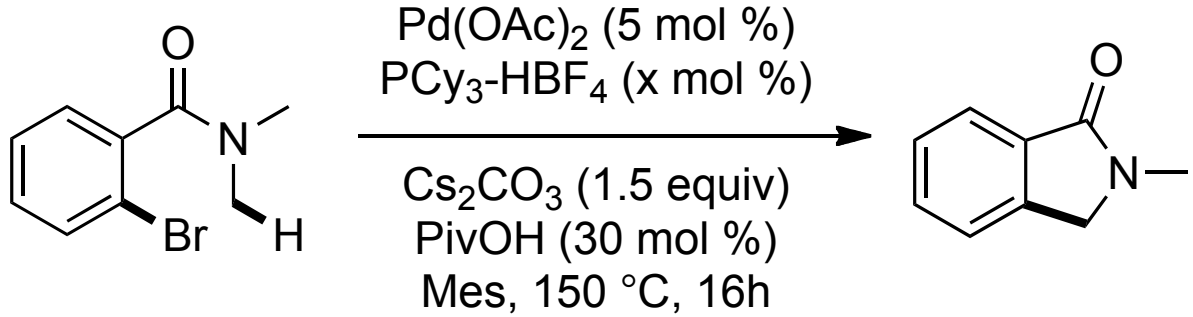
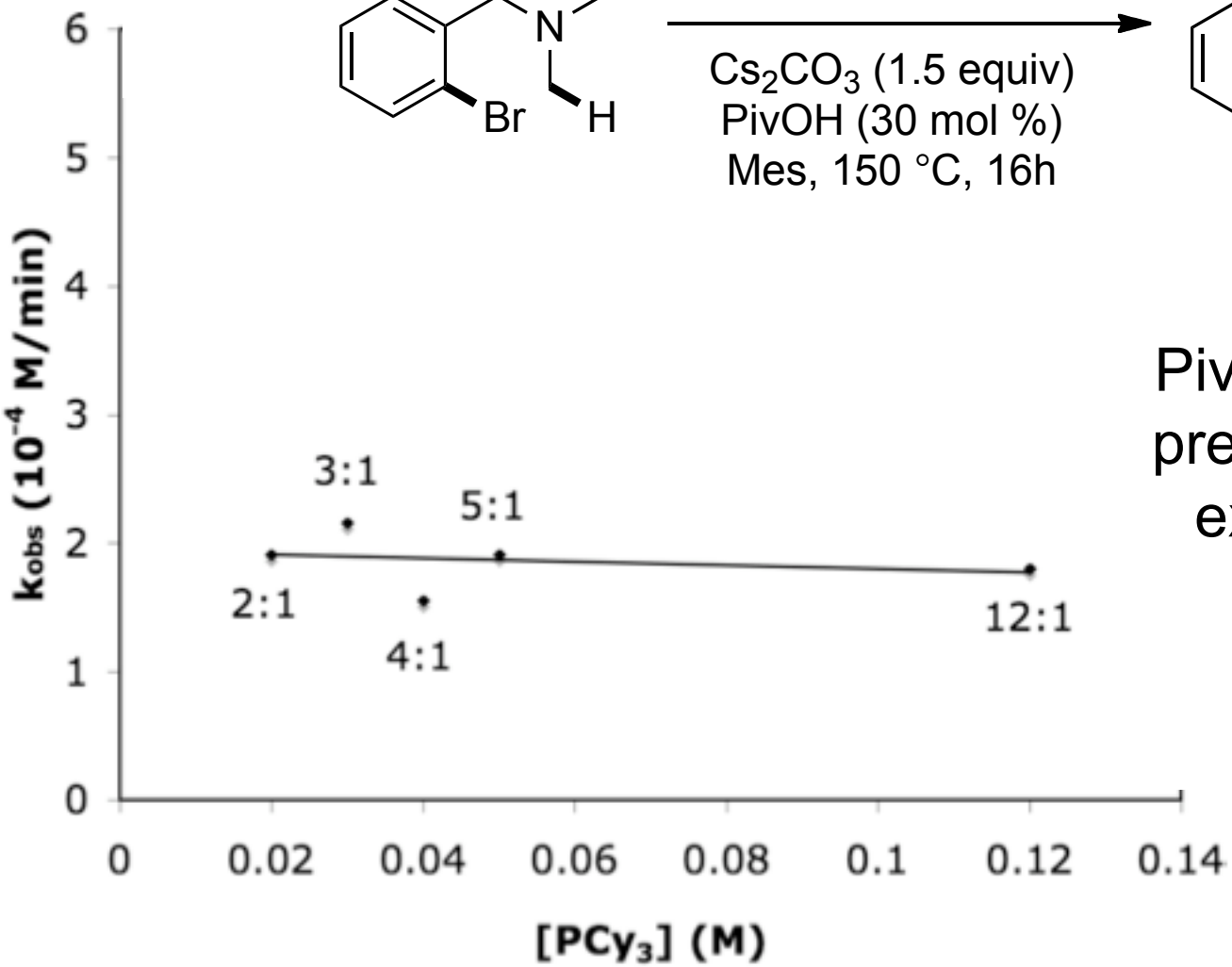
# Kinetic Studies: Excess Phosphine




Pivalate coordination prevents inhibition by excess phosphine

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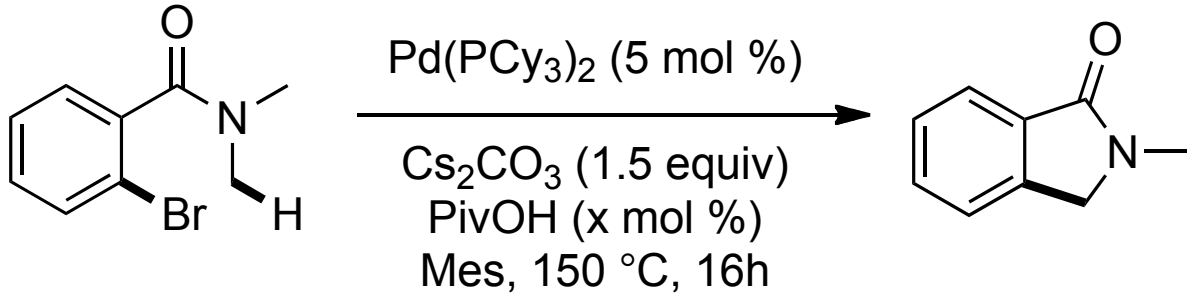
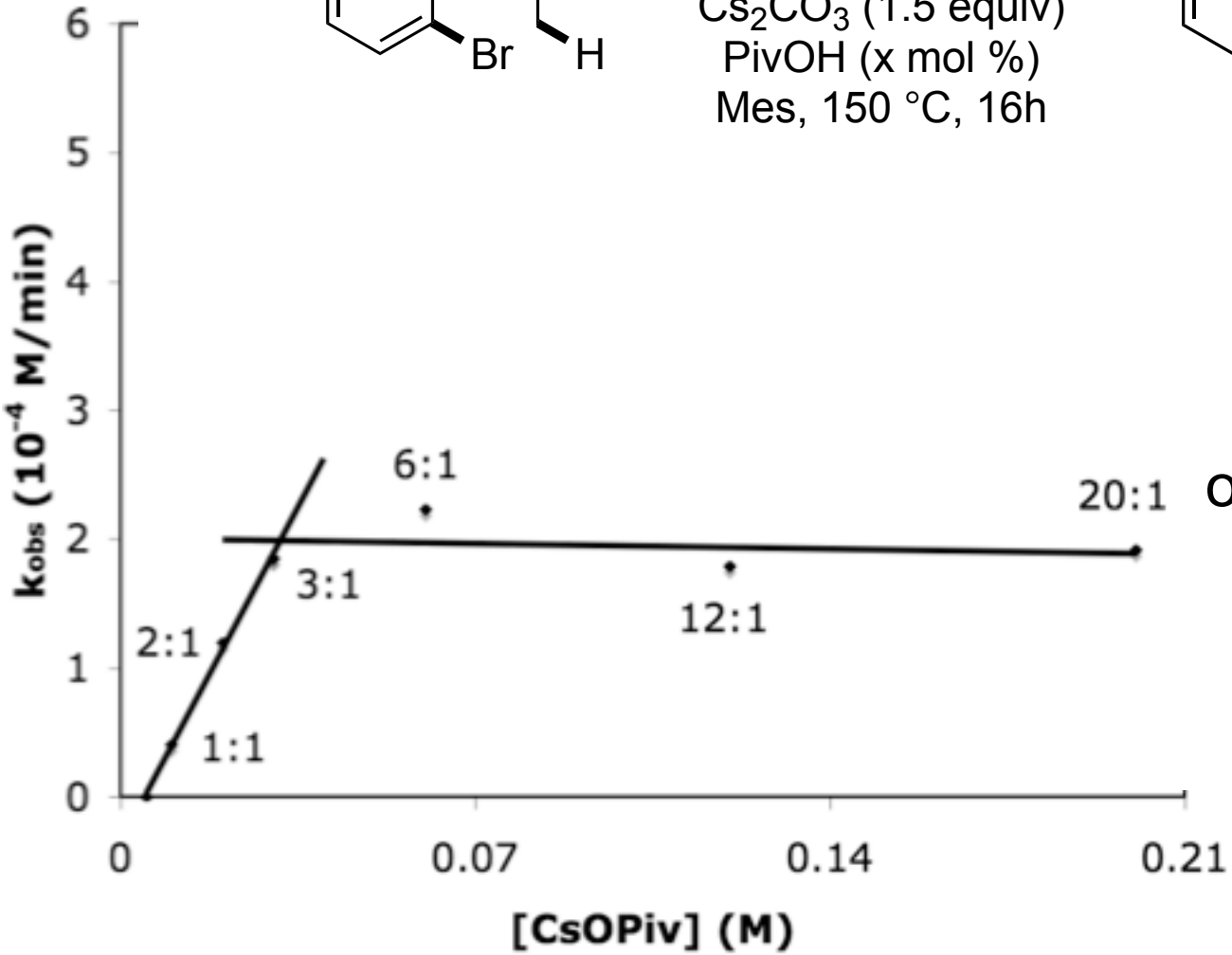
# Kinetic Studies: Pivalate Concentration

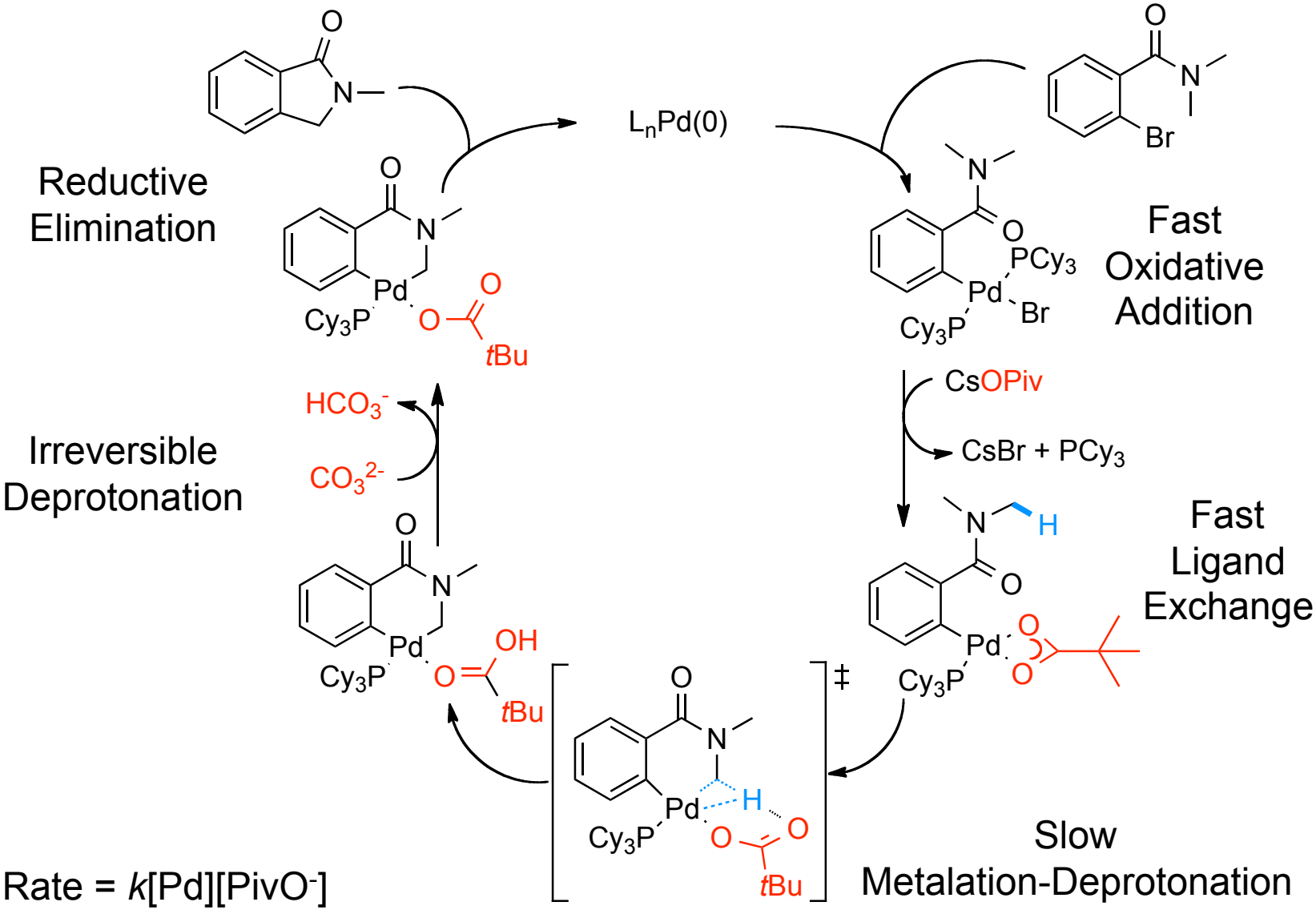



Saturation kinetics observed in ratios of pivalate/palladium > 3:1

Rousseaux, S.; Fagnou, K. *et. al. J. Am. Chem. Soc.* **2010**, *132*, 10692.

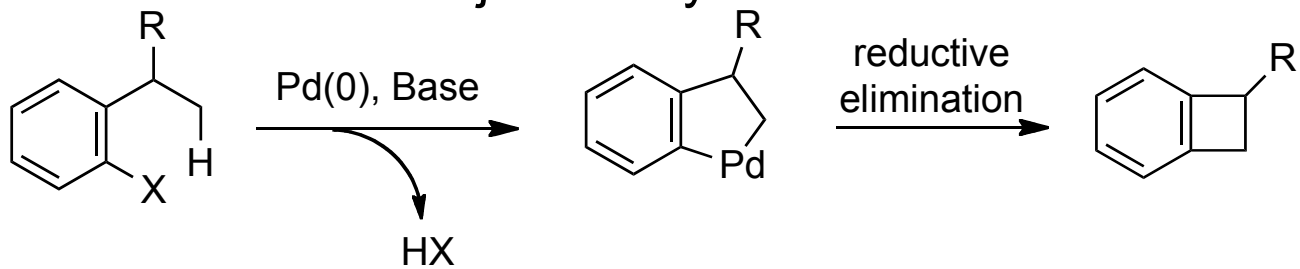
# Proposed Catalytic Cycle



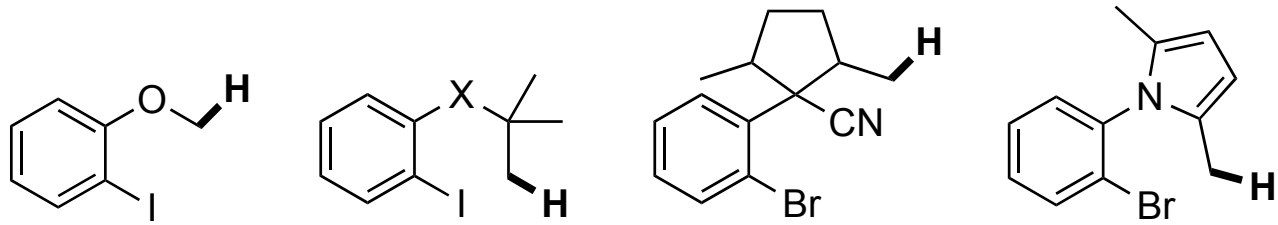

Rousseaux, S.; Fagnou, K. *et. al. J. Am. Chem. Soc.* **2010**, *132*, 10692.

# Conclusions & Future Directions

- Selective intramolecular $sp^3$ C-H functionalization can be achieved by oxidative addition into an adjacent aryl halide




- Most substrates to date are designed to prevent β-hydride elimination.




X=C, O, N

- The reaction proceeds through a concerted metalation-deprotonation mechanism with crucial involvement of base and additives.

- Further development using intermolecular coupling of aryl or alkyl halides with an appropriate directing group could great increase the synthetic utility of this process