Catalysis in the Pharmaceutical Industry :

Challenges and Approaches

Challenges in Catalysis for Pharmaceuticals and Fine Chemicals
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Bristol-Myers Squibb

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Outline

1. The power of Parallel Experimentation
2. Complex parameters and local optimization
3. The mechanism of catalyst activation and its impact on process robustness

Opportunities and Challenges of Catalytic Reactions

➢ Diversity of Transformations

- **Asymmetric hydrogenation, C–C cross-coupling, C–X couplings, Heck, reductive amination, epoxidation, allylic substitution, conjugate addition, cycloaddition, arylation, hydroxylation, amination**

➢ Sensitivity to Reaction Conditions

- **Effects of air and moisture, solvents, base/acid additives, catalyst ratios, pressure, temperature**

➢ There is No Magic Bullet!

- **>4000 phosphine ligands, along with thousands of other ligands, metal complexes, organocatalysts, enzymes**

To develop a robust catalytic process, large number of experiments are inevitable

A "Shotgun" HTP Screening Approach Will Fail

- **Significant parameters of a catalytic reaction:**
  - **Discrete parameters: Identity of pre-catalyst, ligand, base/additive, solvent**
  - **Continuous parameters: Loading of substrate, pre-catalyst, additive, solvent, water, L/M ratio, temperature, time**
  - **Total: 12 parameters (4 discrete, 8 continuous)**

- **If only two of each parameters are investigated:** $2^{12} = 4096$
- **Slightly expanding the number of ligands, additives and solvents:**

2^8 • 2 pre-catalysts • 20 ligands • 4 bases • 4 solvents = 163,840

HTP experimentation must be conducted in a RATIONAL manner!

Moseley et al, *Org. Process Res. Dev.* 2013, *17*, 40-46

Strategic and Iterative HTP Experiment Design

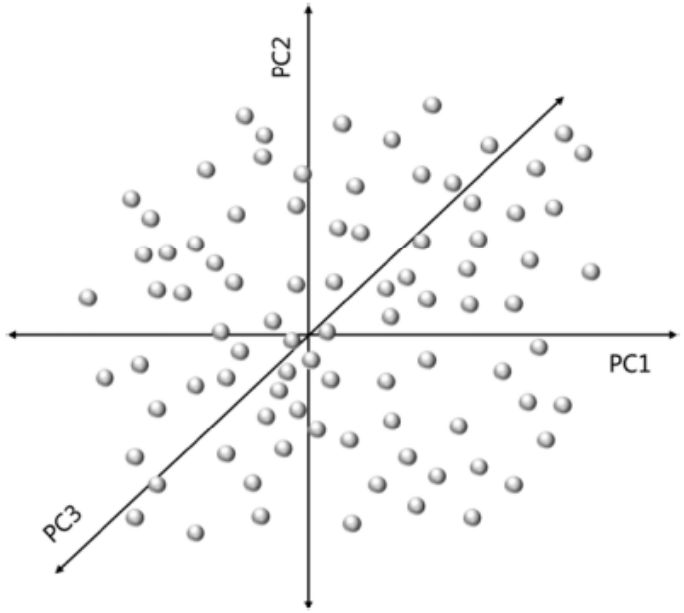


Figure 1. Uncharted chemical space: discrete parameters (e.g., ligands, solvents) mapped against three axes (principal components, PC1, PC2, PC3).

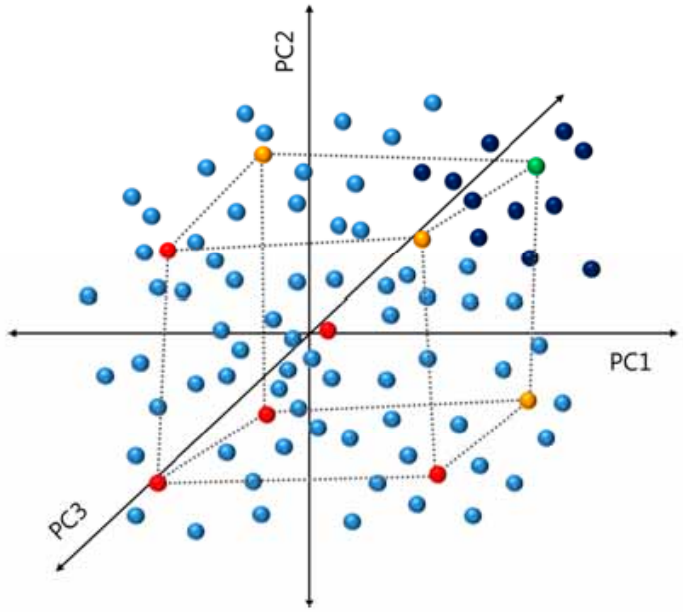
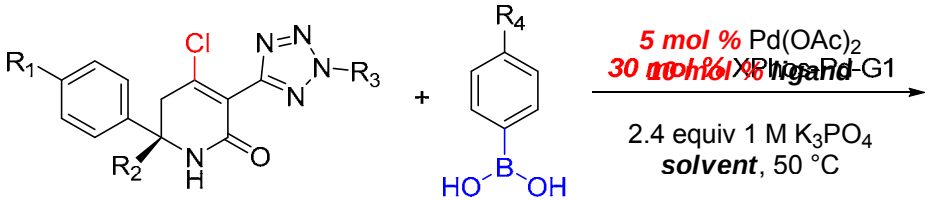


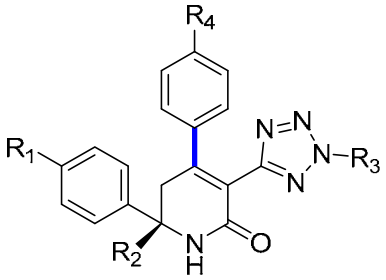
Figure 3. Results of an initial screening design (example only). Key: green = good; amber = moderate; red = poor; light blue = untested; dark blue = proposed for further study.

- **An initial round of HTP experiments should cover as much "chemical space" as possible (i.e., evaluating discrete variables); generally ligands and solvents have the most dramatic effects**
- **Subsequent rounds of experiments should explore the regions of chemical space around the top hits and then begin to asses the impact of continuous variables**

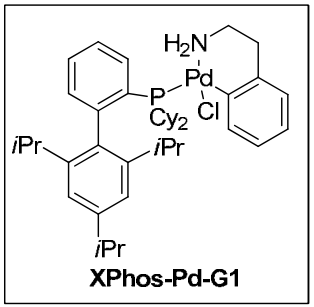
Moseley et al, *Org. Process Res. Dev.* 2013, *17*, 40-46

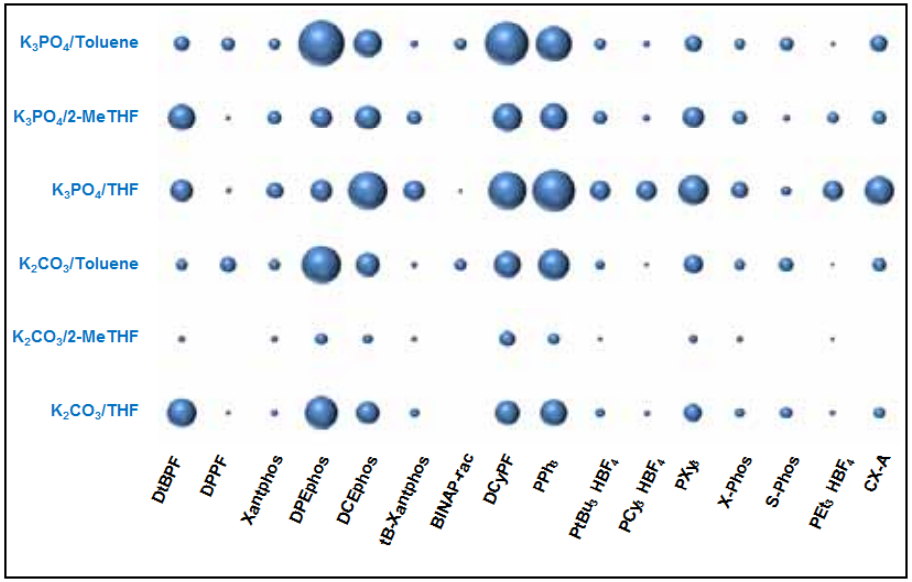
Substrate Specificity: There is No Magic Bullet!

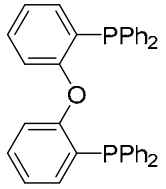




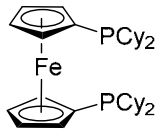
low yield



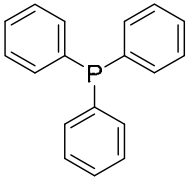




DPEphos
75AP (Toluene)



DCyPF
68AP (Toluene)



PPh_3
65AP (THF)

- **Challenge:** A key Suzuki coupling was low yielding, even with high cat. loading of XPhos-Pd-G1
- **Solution:** A single 96WP experiment identified three very different ligands that gave >60AP coupled product – under the same conditions, X-Phos gave <15AP regardless of base or solvent!

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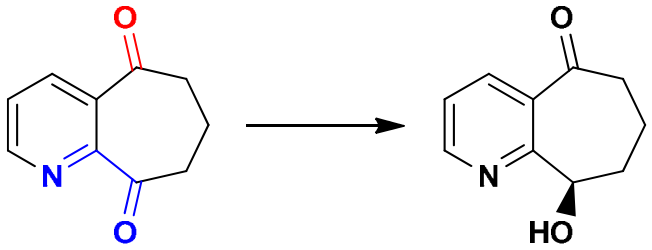
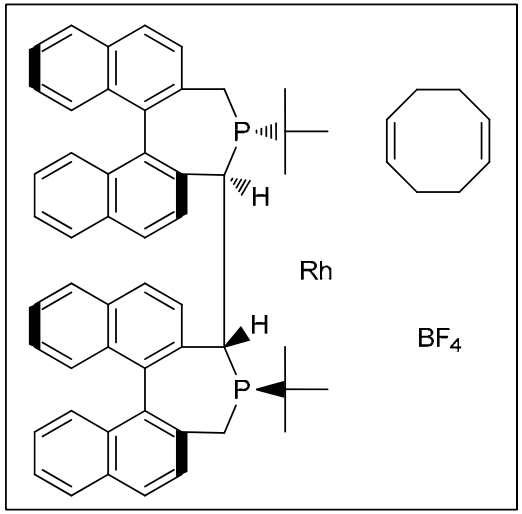
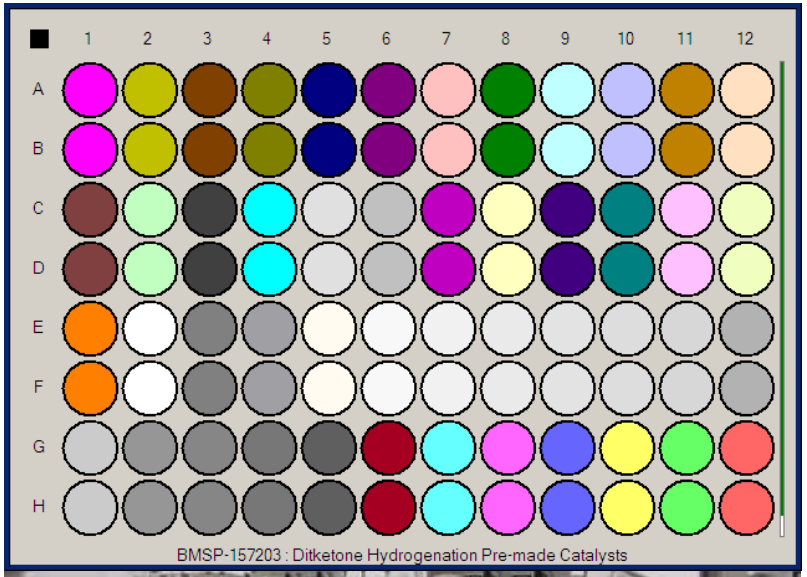
Asymmetric Hydrogenation of the Diketone





Rh(*R*-Binapine)(COD)BF_4



- ***Rh(R-binapine)(COD)BF_4 is the best from the 1st screening***
- ***>99.5%ee, 100% regioselectivity***
- ***Works best in DCM, as well as Methanol, EtOAc***

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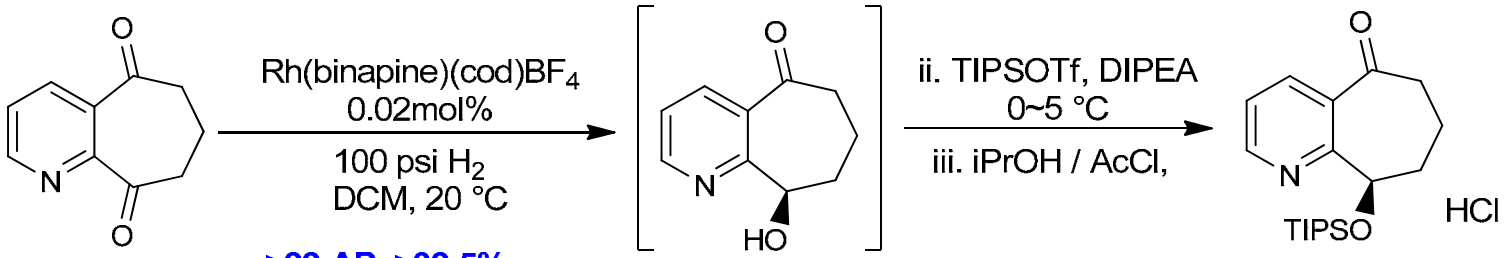
The Telescoped Process



80-85 % overall yield
~200 Kg prepared

Telescoped Process

- **Selected DCM for hydrogenation reaction, excellent selectivity**
- **Allows for direct telescope of TIPS-protection**
- **Considerably more cost effective than the enzymatic process**

- **Over 2000 catalytic conditions screened**
- **Primary metal included Rh, Ru, Pd, and Ir**
- **Rh showed complete conversion in many cases with excellent chemoselectivity**
  - ***Five Rh/ligand combinations showed >95% e.e.***

- **HTP screening is a powerful tool to avoid premature decisions and quickly identify a viable solution**

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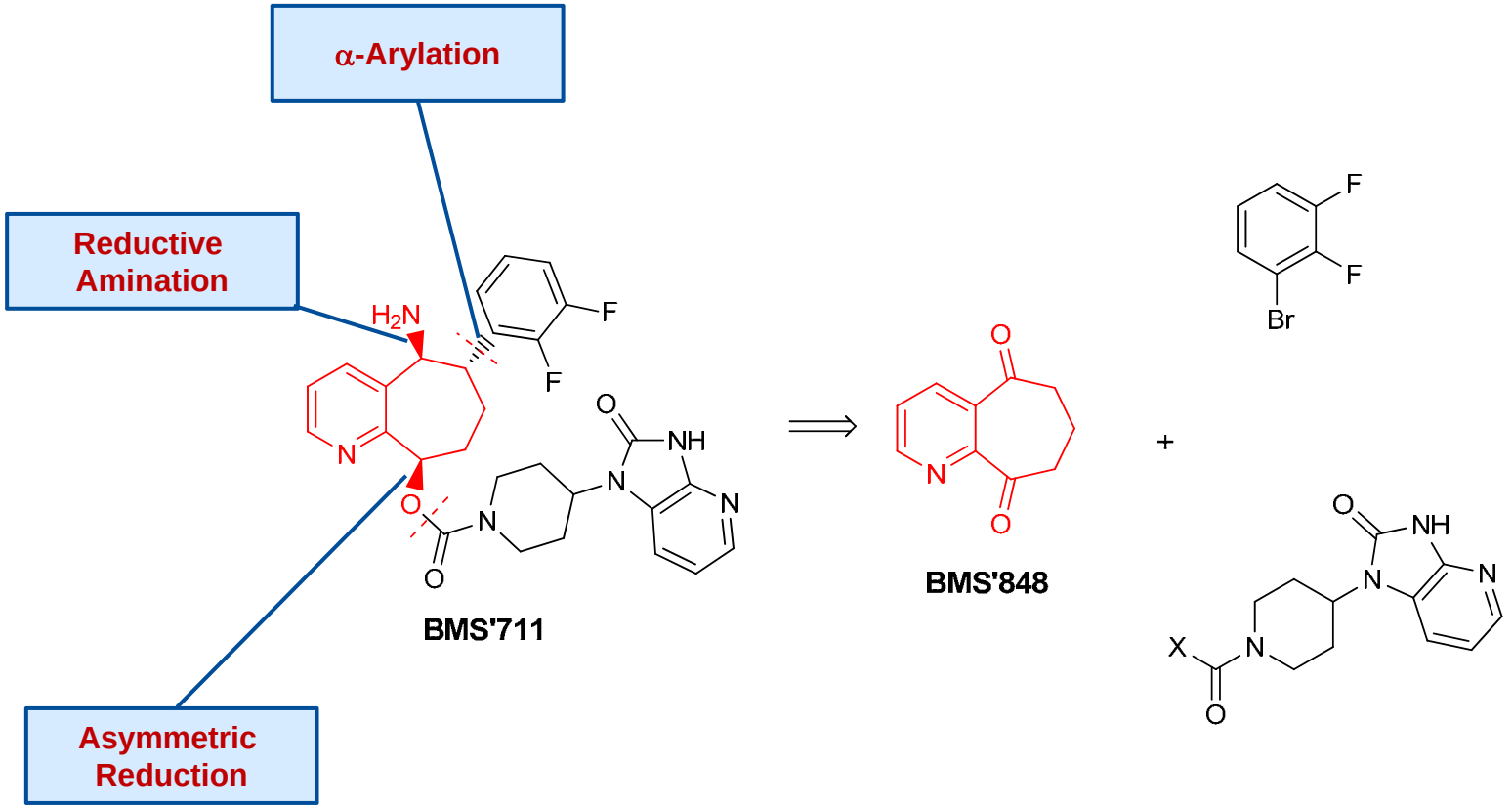
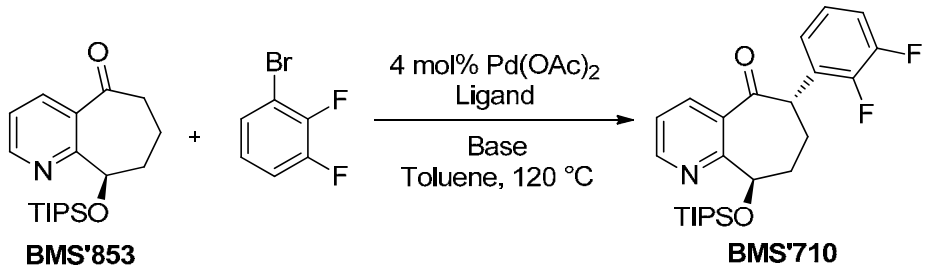
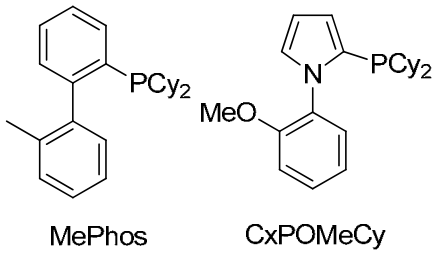
CGRP Antagonist Candidate



CGRP α-Arylation:Initial Catalyst Development

General Conditions:



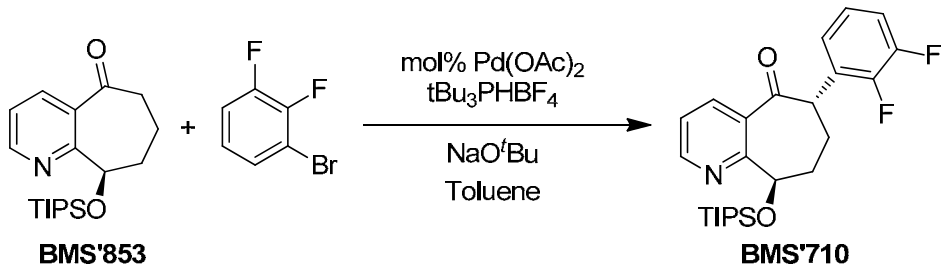


Key Findings

- Strong correlation between Ligand and Base
- Top ligands: tBu_3PHBF_4, MePhos, CxPOMeCy
- Moderate product yields

Ligand	Base	In Process Yield
DtBPF	NaOtBu	42%
DtBPF	K_3PO_4	9%
Binap	K_3PO_4	14%
XantPhos	K_3PO_4	5%
QPhos	NaOtBu	5%
S-Phos	NaOtBu	40%
S-Phos	Cs_2CO_3	27%
S-Phos	K_3PO_4	10%
MePhos	NaOtBu	50%
MePhos	K_3PO_4	6%
tBu_3PHBF_4	K_3PO_4	45%
tBu_3PHBF_4	NaOtBu	50%
CxPOMeCy	Cs_2CO_3	38%
CxPOMeCy	K_3PO_4	50%
CxPOMeCy	NaOtBu	40%

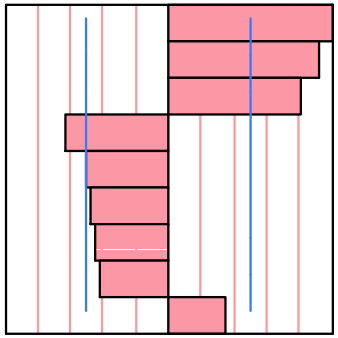
DoE Optimization of Pd/tBu_3PHBF_4

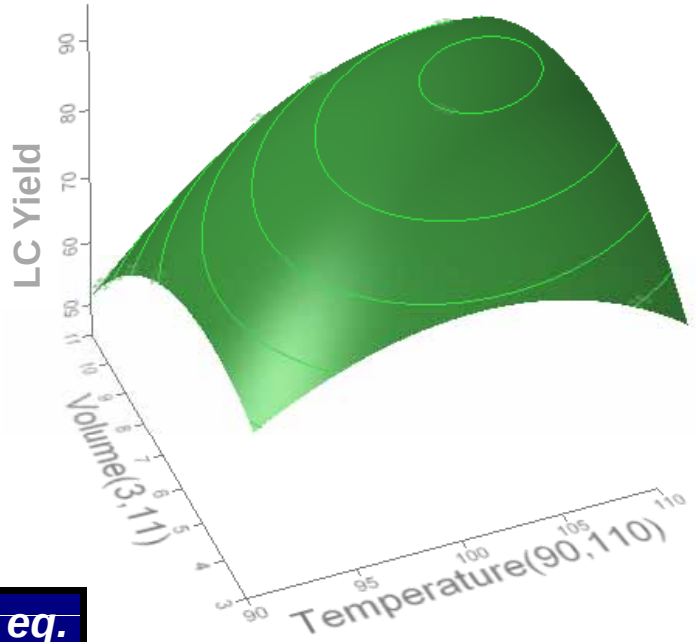


BMS'853 **BMS'710**

Sorted Parameter Estimates

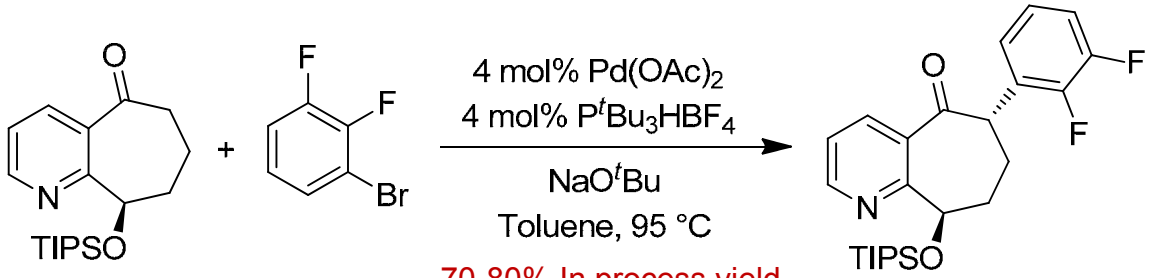
Term	Estimate	Prob>|t|
Catalyst Load(3.5,5.5)	9.450136	0.0004*
Temperature(90,110)	8.6668027	0.0010*
Temperature*Volume	8.156097	0.0028*
LM(1.5,2.5)	-5.888753	0.0165*
Volume*Volume	-10.28053	0.0481*
LM*Catalyst Load	-4.768903	0.0612
Temperature*Temperature	-9.280532	0.0720
Volume*Catalyst Load	-4.218903	0.0947
Volume(3,11)	3.300136	0.1590





	Temp °C	Vol	L/M	Cat mol%	Base eq.
Low	90	3	1.5	3.5	1.1
Mid	100	7	2	4.5	1.3
High	110	11	2.5	5.5	1.5

The Good News: Campaign Results

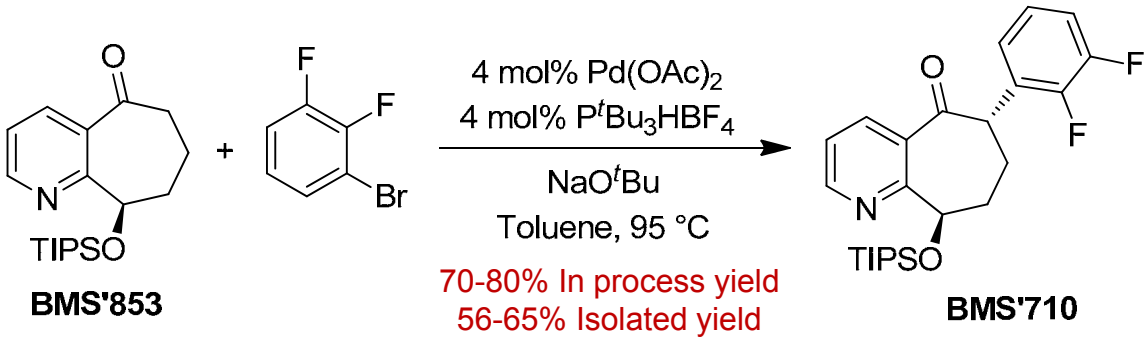


BMS'853 **BMS'710**

- **Campaign results**

Batch	Reactor (L)	BMS'853 (kg)	BMS'710 (kg)	Yield (%)	AP Purity
1	500	62.2	49	65.4	98.5
2	1000	85	57.2	55.9	98.6
3	1000	95	72	62.9	95

Looking Forward…7 Tons of Alumina?



Upcoming Campaigns:

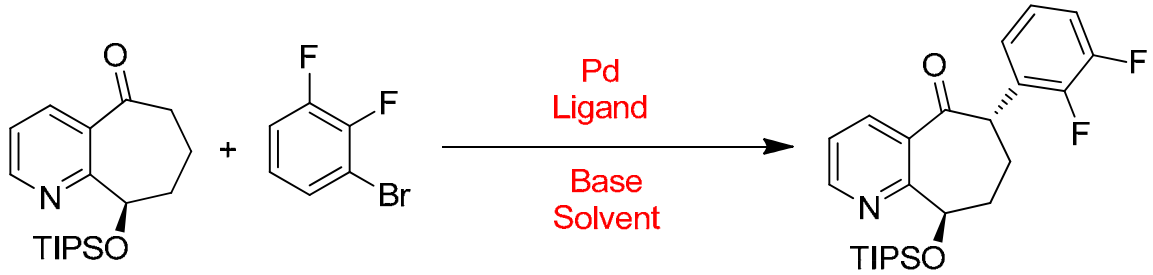
- Requirement of ~850 kg of **BMS'710**
- Another 400-900 kg needed soon after

Challenges to Address:

- Low isolated yields (56-65%)
- Strongly basic conditions lead to both **BMS'853** and **BMS'710** decomposition
- Tedious and time-consuming alumina treatment required (8 kg/kg)
- Cycle time per batch: 14 days

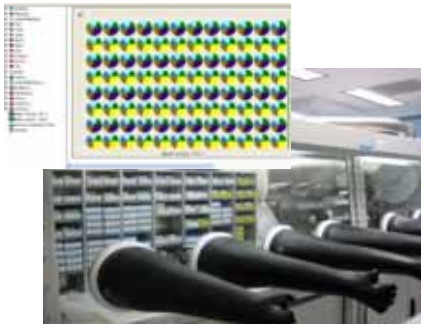
Need better catalytic conditions

Development of 2nd Generation Pd Catalyst



BMS'853 **BMS'710**

Initial Screening



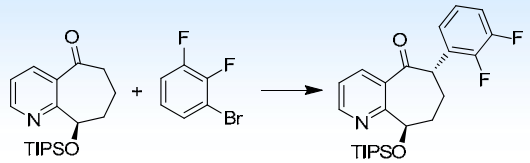
16 Catalysts
4 Bases
3 Solvents

Ligand	Base	Solvent	AP Conv	AP Prod	Prod/ Conv
tBu_3PHBF_4	NaO^tBu	Toluene	42	29	0.7
tBu_3PHBF_4	NaO^tBu	DME	20	4	0.2
tBu_3PHBF_4	NaO^tBu	t-amylOH	58	43	0.7
tBu_3PHBF_4	NaHMDS	Toluene	33	26	0.8
tBu_3PHBF_4	K_3PO_4	Toluene	3	1	0.3
tBu_3PHBF_4	K_3PO_4	DME	11	8	0.7
tBu_3PHBF_4	K_3PO_4	t-amylOH	31	27	**0.9**
tBu_3PHBF_4	Cs_2CO_3	t-amylOH	4	2	0.4

Key Findings

- Weak Bases: K_3PO_4 > Cs_2CO_3
- Solvent: *t*-amylOH > DME, toluene

Ligand Optimization



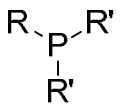
Standard conditions:
2.5 mol% Pd, 2.5 equiv K_3PO_4, *t*-amylOH
14 h, 80 °C

Ligand

Monodentate

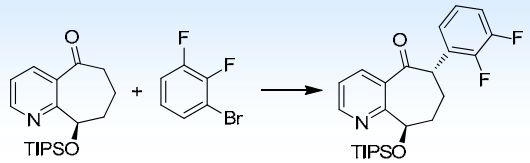
Bidentate

Simple



Ligand	AP Prod
PPh_3	0
Cy_3PHBF_4	0
$P(o\text{-}Anis)_3$	0
$^tBu_2MePHBF_4$	2
$P(Ad)_2{}^nBu$	5
tBu_3PHBF_4	34

Ligand Optimization



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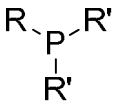
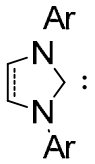
Ligand

Monodentate

Simple

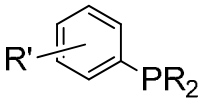


NHC

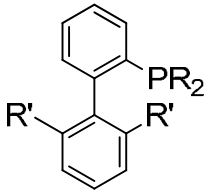


no Prod

Substituted

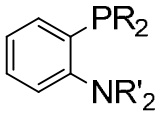


Biaryl



S-Phos
63 AP Prod

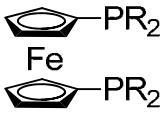
P-N,O Ligands



10-20 AP Prod

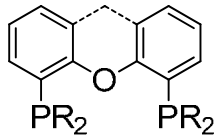
Bidentate

Ferrocene



R = Ph, Cy, tBu
<10 AP Prod

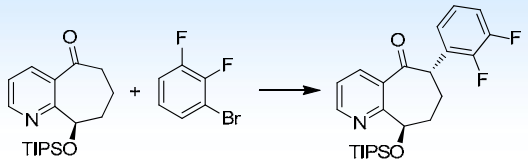
Bridged



R = Cy
<5 AP Prod

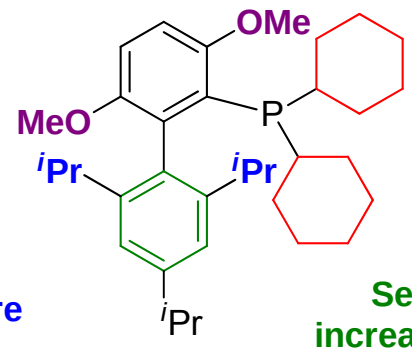
R = Ph
20-30 AP Prod

Ligand Optimization



General trend:
Biaryl mono-P (Buchwald) > Mono-P, Bi-P > NHC

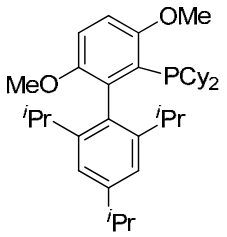
Methoxy groups lock orthogonal config and enhance reactivity



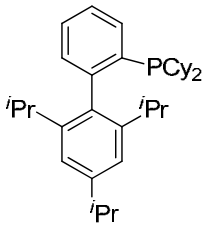
Cy > *t*-Bu, Ph e-rich, less bulky ligands encourage oxidative addition and transmetallation

Ortho-substituents prevent palladacycle formation and favors more active $L_1Pd(0)$ species

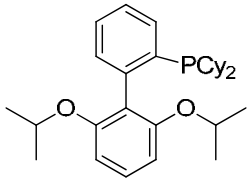
Secondary aryl ring increases catalyst stability and reactivity



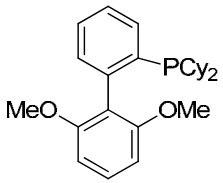
BrettPhos



X-Phos



RuPhos

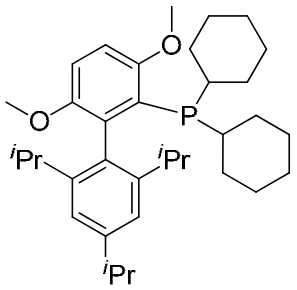


S-Phos

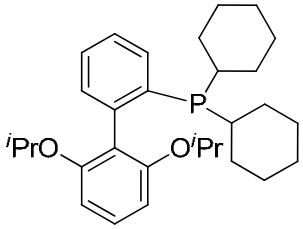
Ligand	Ortho R	AP Conv	AP Prod
BrettPhos	^{i}Pr (2)	98	87
X-Phos	^{i}Pr (2)	66	52
RuPhos	O^{i}Pr (2)	79	68
S-Phos	OMe (2)	76	65

Buchwald, S.L. *J. Am. Chem. Soc.* **2008**, *130*, 13552.
Buchwald, S.L. *Angew. Chem. Int. Ed.* **2006**, *45*, 6523.

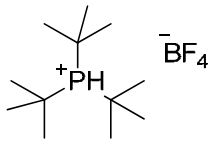
2nd Generation Process Comparison



BrettPhos



RuPhos



tBu_3PHBF_4

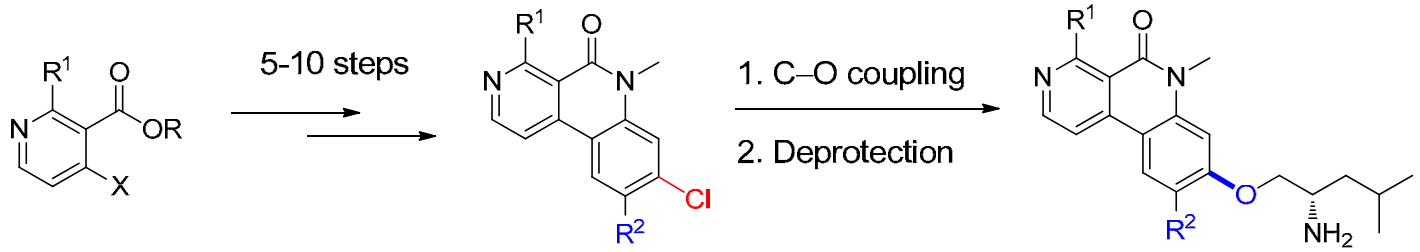
• Pd loading: 1.0 mol %	• Pd loading: 2.5 mol %	• Pd loading: 5 mol %
• In Process Yield: 93-97%	• In Process Yield : 86-91%	• In Process Yield: 79-86%
• Isolated Yield: 75-80%	• Isolated Yield: 65-70%	• Isolated Yield: 60-65%
• Direct crystallization from t-amylOH/IPA/H_2O	• Direct crystallization from t-amylOH/IPA/H_2O	
• No alumina required	• No alumina required	**• Alumina filtration required to remove impurities that inhibit next step**
• Proprietary ligand	**• Proprietary ligand**	• Non-proprietary ligand
• Limited availability	**• Limited availability**	• Wide availability

Be Aware of Local Optimization

Bristol-Myers Squibb

C–O Coupling with Aliphatic Alcohols

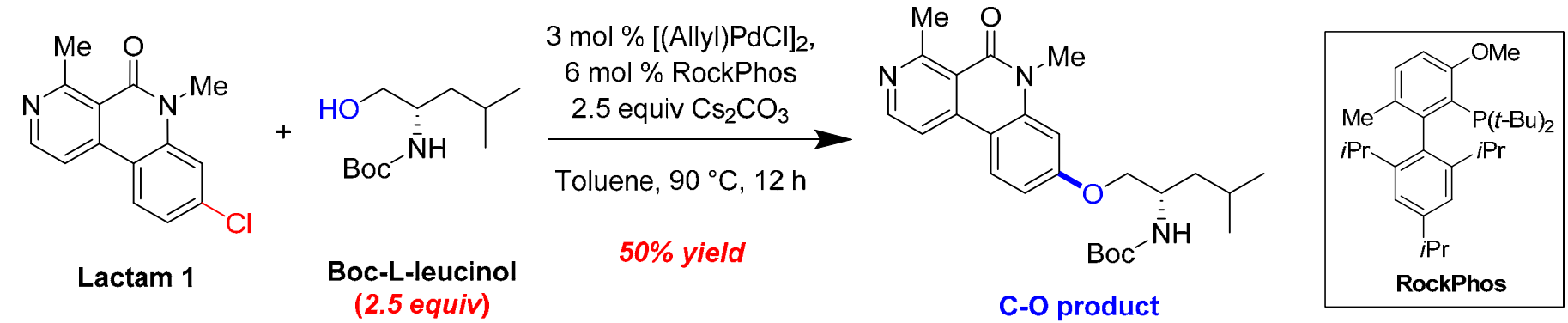
Lactam series - general synthetic route:



R^2 = H:
15-60% yield

R^2 = Me, OMe, Cl:
0-35% yield

Coupling of Lactam 1



Lactam 1

Boc-L-leucinol
(2.5 equiv)

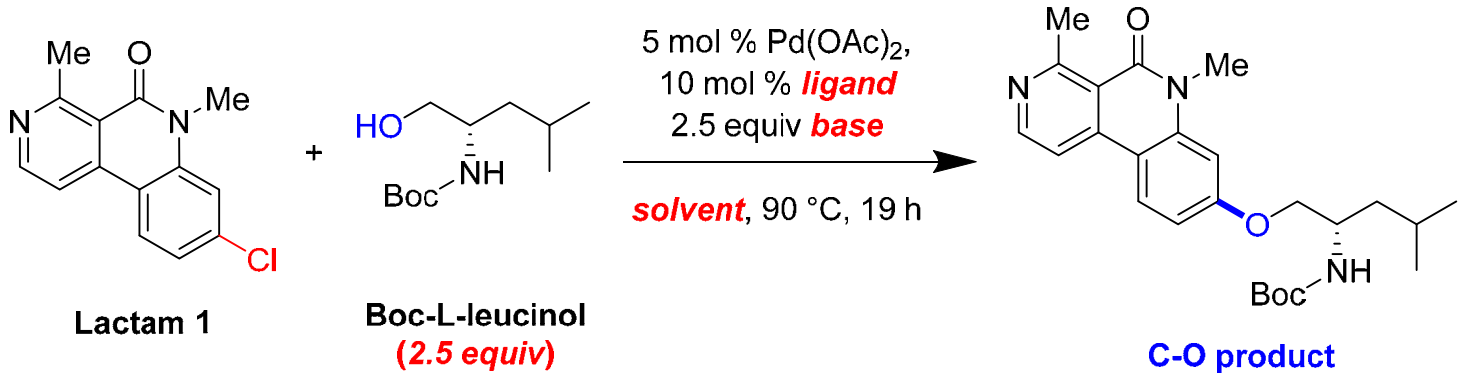
50% yield

C-O product

- **Challenges: Low yields at the end of the synthesis were non-ideal – *improved yield desired***
- **Cost and availability of RockPhos were both issues – *cheaper, more available ligand needed***
- **Large excess of Boc-leucinol made isolation challenging – *lower equiv of Boc-leucinol desired***

C–O Coupling : New Ligand Hits

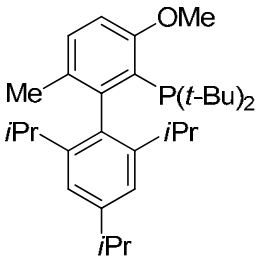
Ligand screen:



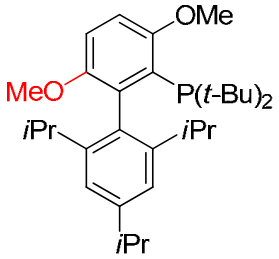
Lactam 1

Boc-L-leucinol
(2.5 equiv)

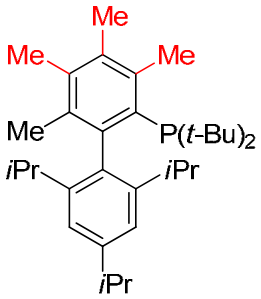
C-O product



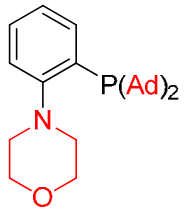
RockPhos
77AP



tB-BrettPhos
80-82AP



tB4Me-XPhos
80-81AP

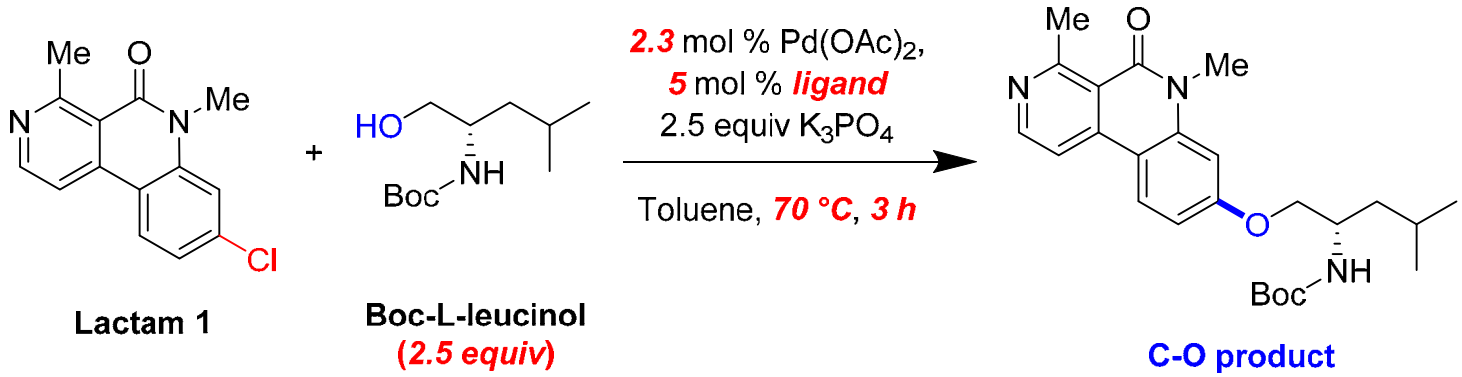


Mor-DalPhos
78-82AP

- **A single catalyst/ligand survey identified 3 new ligands that were effective for this coupling**
- **Cs_2CO_3 and K_3PO_4 were both found to be effective bases, and Toluene and CPME both gave good results**

Lactam Substrate: Comparison of Top Ligands

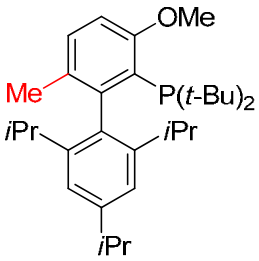
Comparison of top ligands:



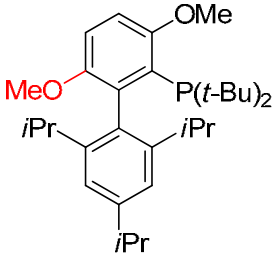
Lactam 1

Boc-L-leucinol
(2.5 equiv)

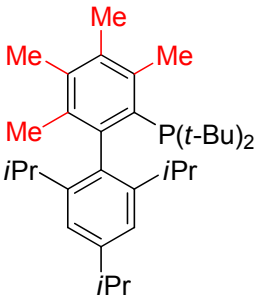
C-O product



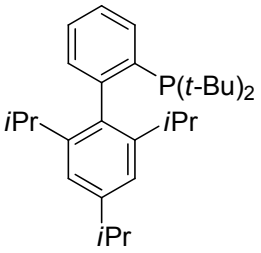
RockPhos
42AP



tB-BrettPhos
46AP



tB4Me-XPhos
89AP

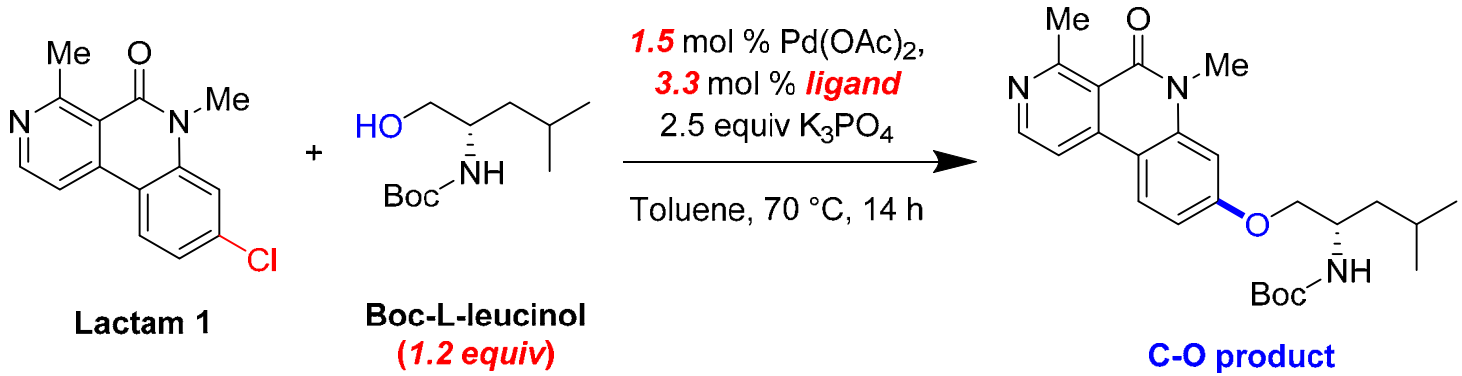


tB-XPhos
88AP

- **At lower temperature, lower catalyst loading and shorter reaction times, tB4Me-XPhos significantly outperforms RockPhos, tB-BrettPhos and Mor-DalPhos**
- **tB-XPhos, which was not part of the original ligand survey but has wide commercial availability, also gave excellent performance**

C–O Coupling : Reduction of Leucinol Loading

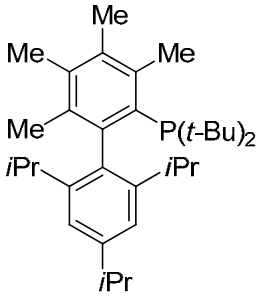
Optimization:



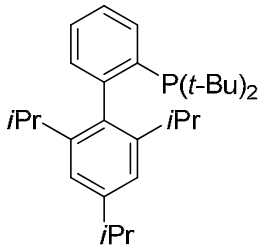
Lactam 1

Boc-L-leucinol
(1.2 equiv)

C-O product



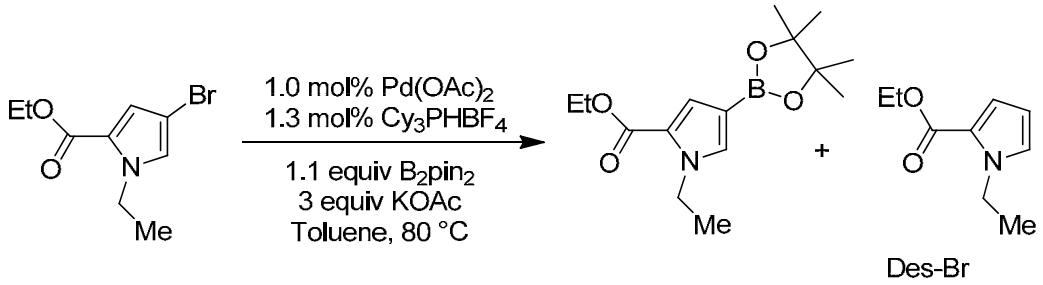
tB4Me-XPhos
89AP
(2.7AP des-Cl)



tB-XPhos
77AP
(12AP des-Cl)

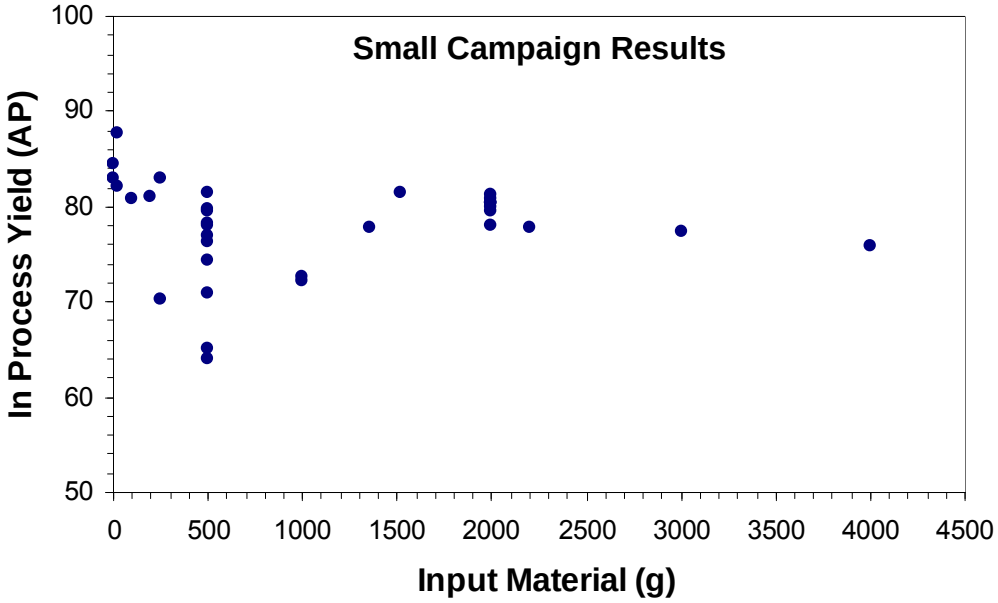
- **Boc-L-leucinol charge can be lowered to 1.2 equiv with tB4Me-XPhos or tB-XPhos while still giving high AP of the desired aryl ether, significantly facilitating the workup process**

Miyaura Borylation



Background

- Borylation conditions using $Pd(OAc)_2/Cy_3PHBF_4$ were identified and optimized by CRDG group
  - However, …

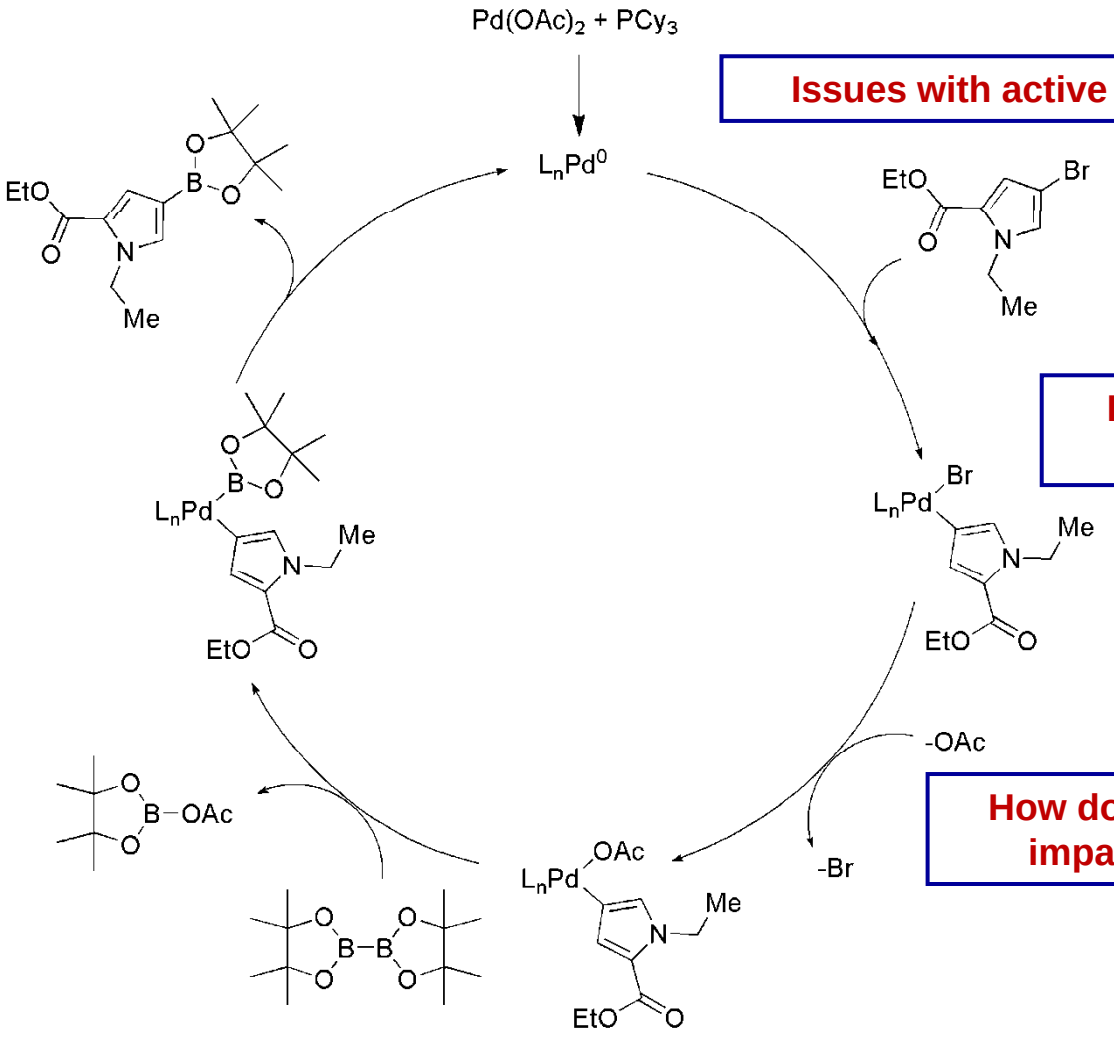


Reaction Issues

- ❑ Limited scalability (**?**)
- ❑ Poor reproducibility in yield
- ❑ Variable reaction times
- ❑ Low isolated yield (44-50%)
- ❑ ≥10 AP Des-Br formation

Mechanism-Driven Approach to Optimization

Proposed mechanism of Miyaura borylation:



Issues with active catalyst formation?

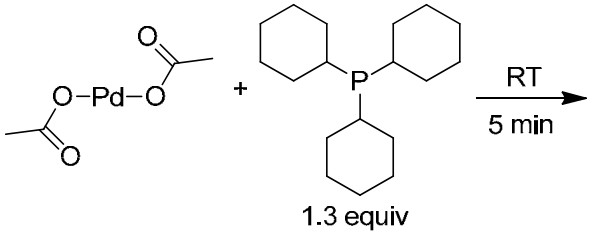
Is the catalyst stable during the reaction?

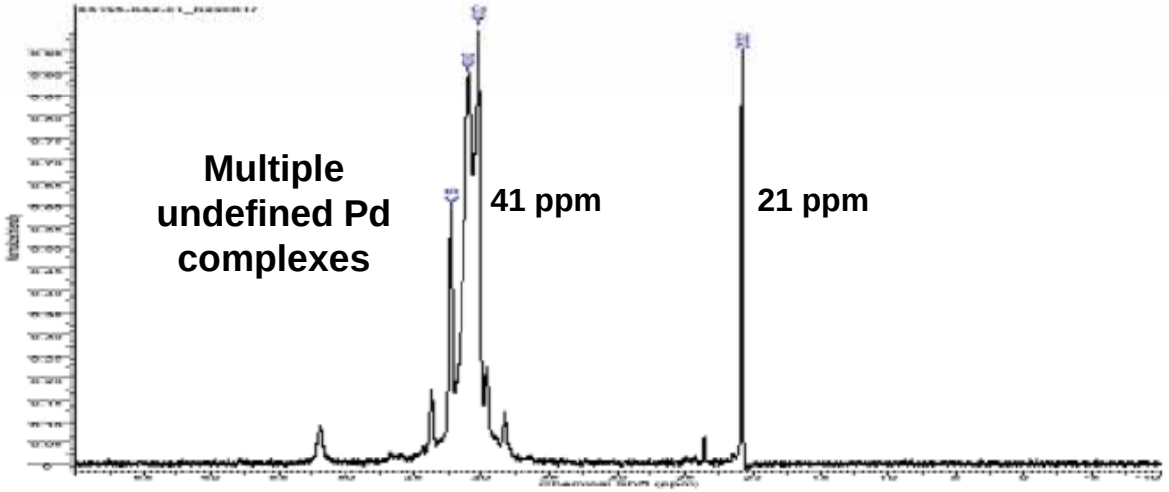
How does base solubility impact the reaction?

Miyaura *J. Org. Chem.* **1995**, *60*, 7508.

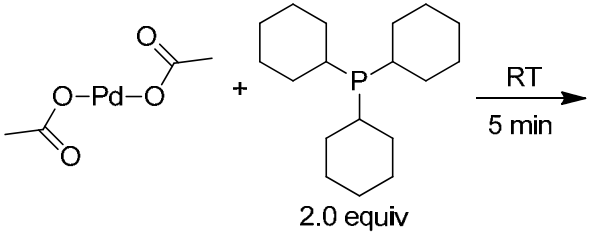
Step 1: Ligand Coordination to Pd

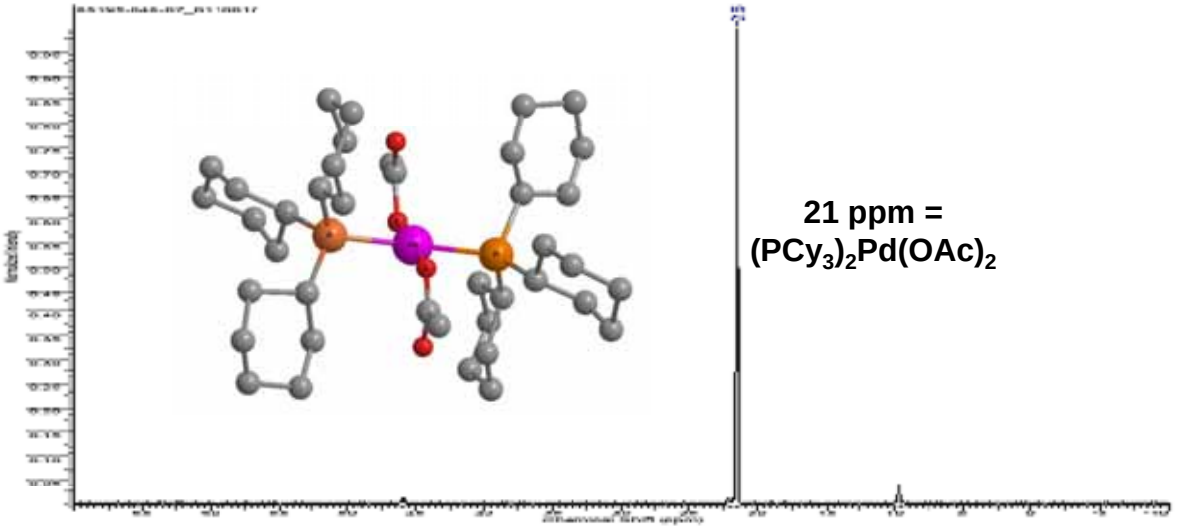
- **Scale-up conditions: 1.3:1 L/M**





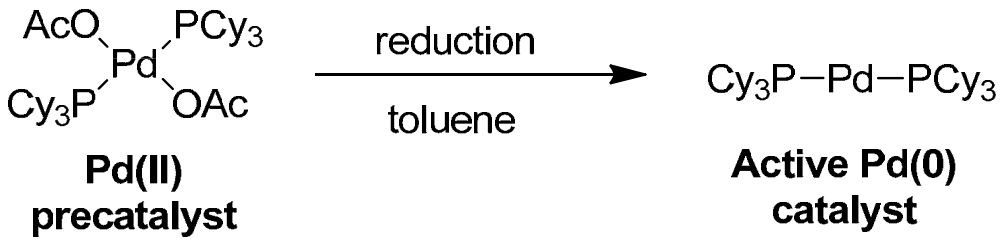
- **Standard conditions: 2:1 L/M**





Bristol-Myers Squibb

Step 2: Reduction of Pd(II) to Pd(0)

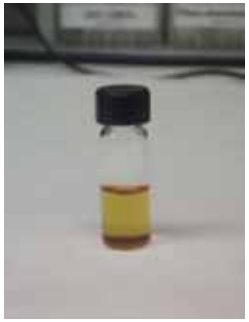


Pd(II) precatalyst

Active Pd(0) catalyst

entry	Reagent (equiv)	Temp (°C)	Time (h)	^{31}P NMR Observations
1	none	75	48	NR
2	PyrBr (10)	75	1	NR
3	PCy_3 (2)	75	1	NR
4	KOAc (10)	75	1	NR
5	H_2O (5)	70	1	NR
6	TBAOAc (10)	70	1	$Pd(PCy_3)_2$ w/ $O{=}PCy_3$ and Pd black
7	TBAOH (1)	70	1	$Pd(PCy_3)_2$ w/ $O{=}PCy_3$ and Pd black
8	$TBABF_4$ (10)	70	1	NR
9	TBABr (10)	70	1	Only $(PCy_3)_2PdBr_2$
10	B_2pin_2 (10)	70	5 min	Only $Pd(PCy_3)_2$

Step 2: Reduction of Pd(II) to Pd(0)



$Pd(OAc)_2$

PCy_3

RT

$(PCy_3)_2Pd(OAc)_2$

20 equiv B_2pin_2
5 min, 70 °C

fast

100% $Pd(PCy_3)_2$ + 2AcOBPin

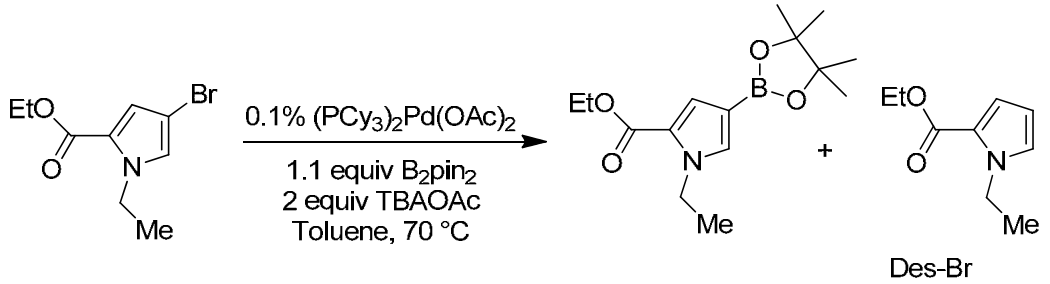
20 equiv TBAOAc
1 h, 70 °C

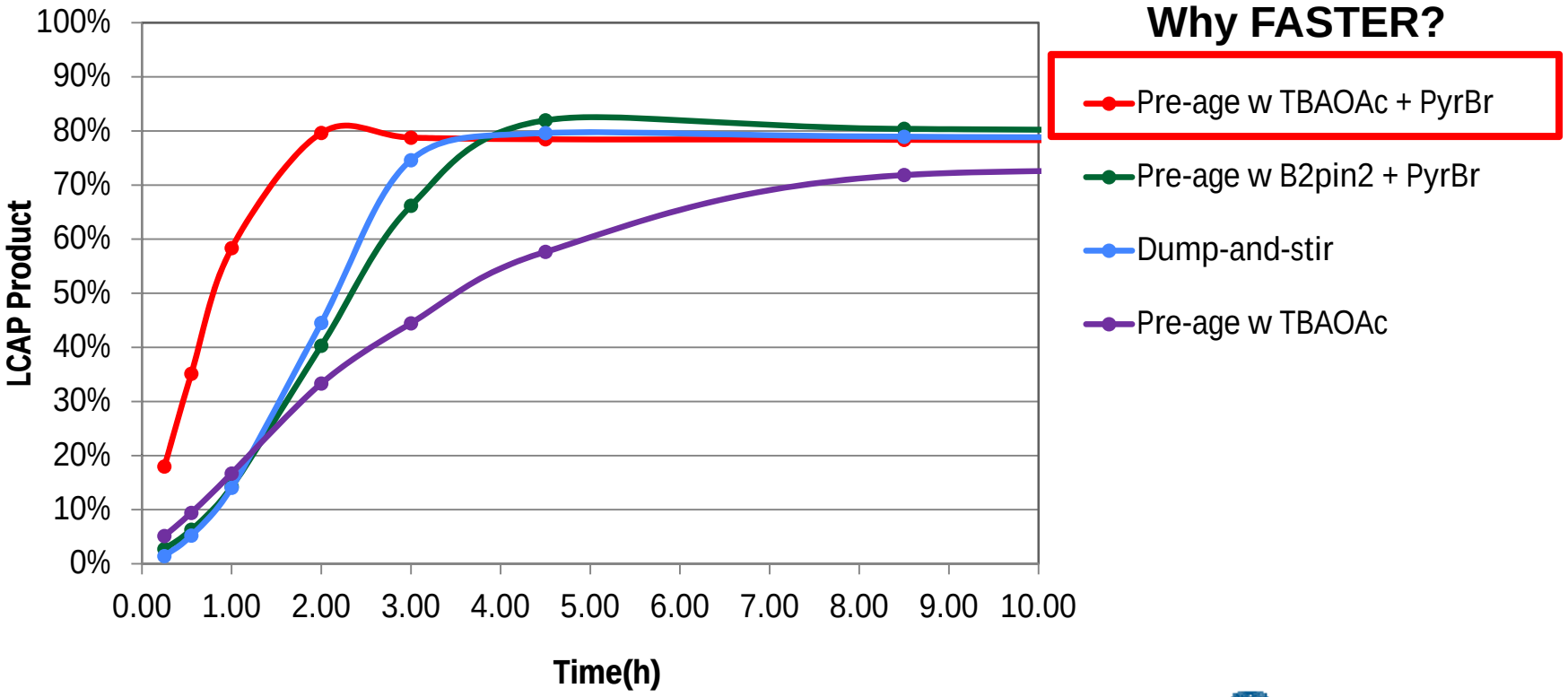
slow

O=PCy3 + $[Pd(0)PCy_3]$

O=PCy3 + 50% $Pd(PCy_3)_2$ +
50% Pd black

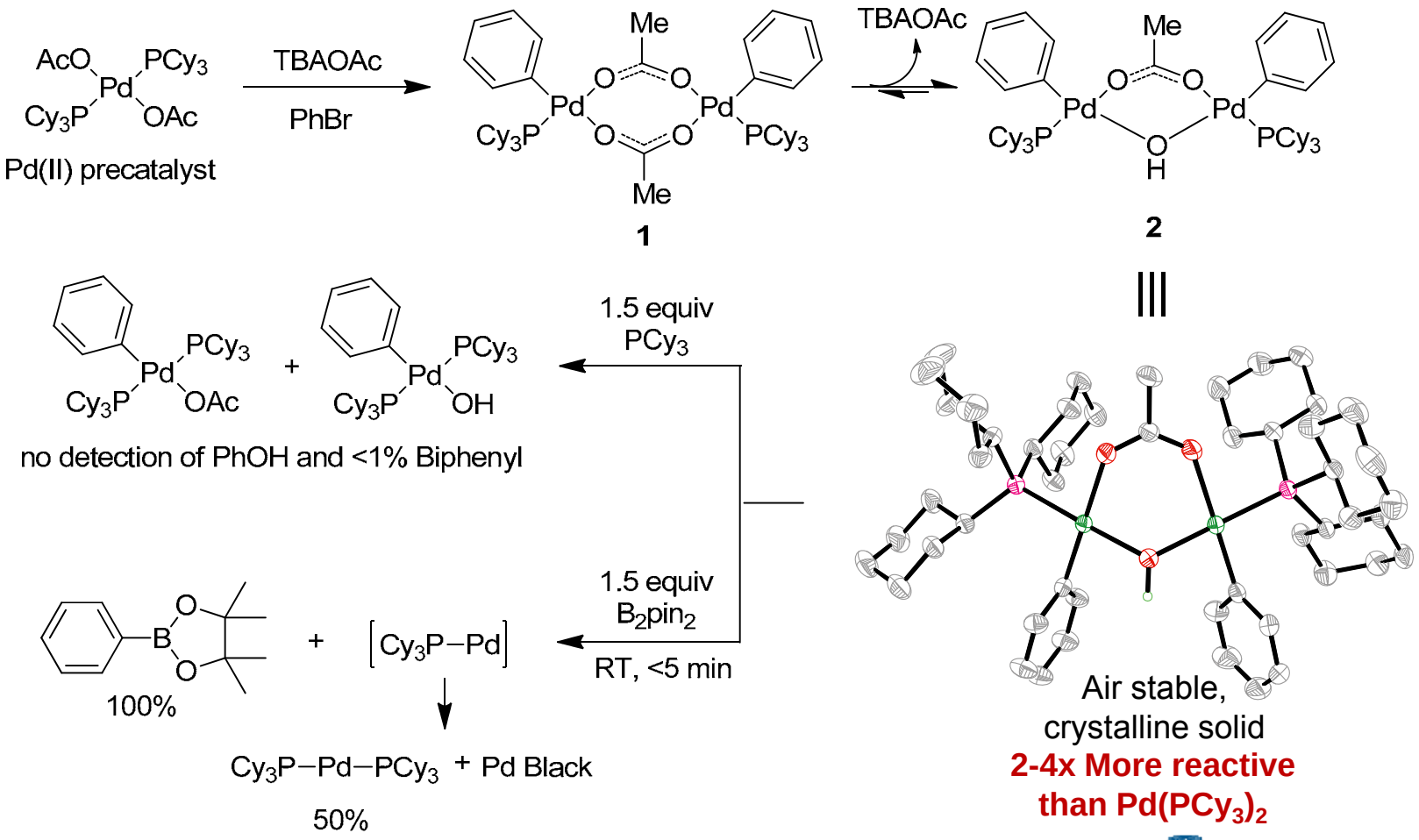
Step 3: Apply Catalyst Pre-Aging to Reaction





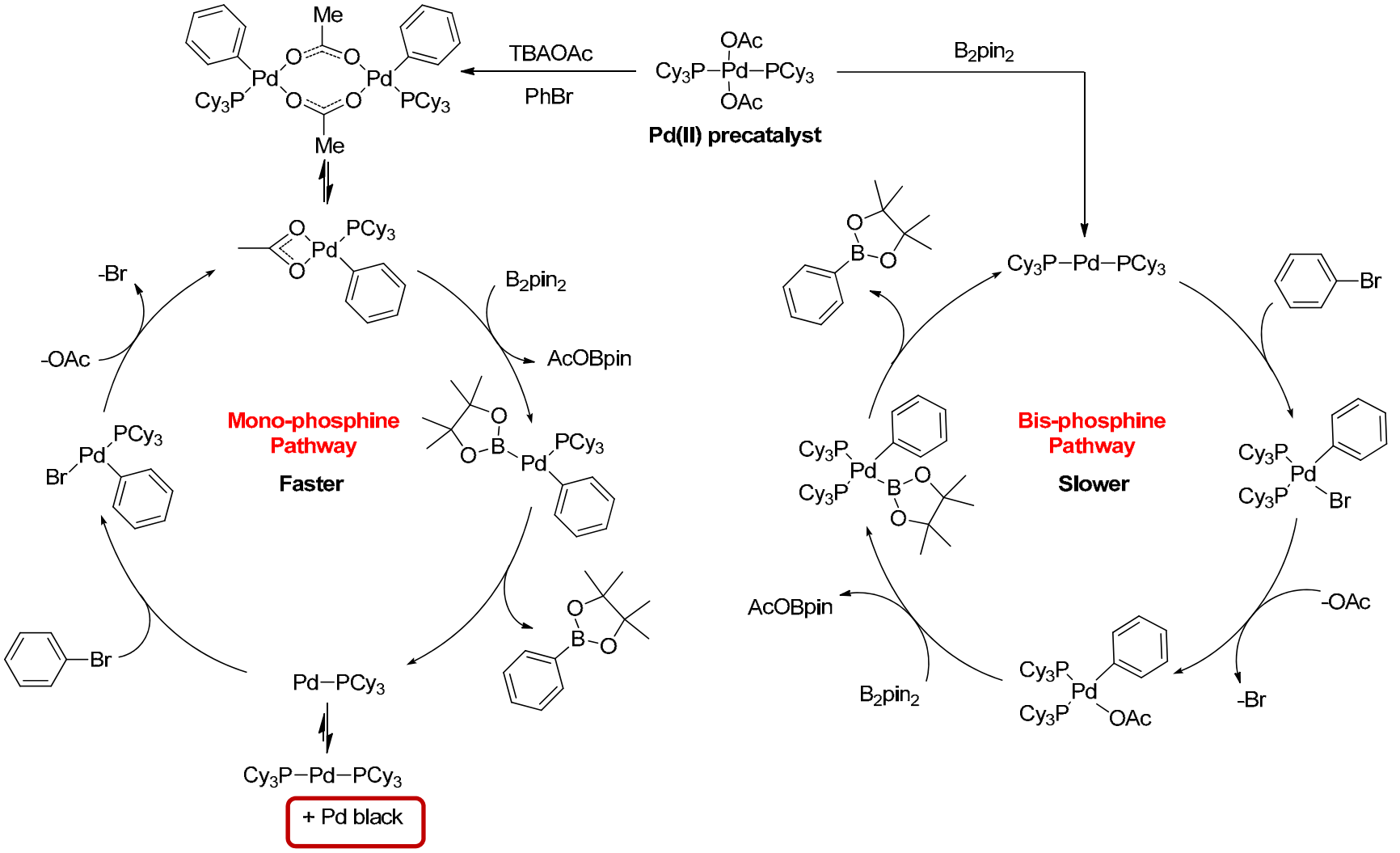
Isolation of Monoligated Pd(II) Complex

Pd(II) Reduction by Base in the Presence of ArBr :



Wei, C. S.; Davies, G. H. M.; Soltani, O.; Albrecht, J.; Gao, Q.; Pathirana, C.; Hsiao, Y.; Tummala, S.; Eastgate, M. D. *Angew. Chem. Int. Ed.* **2013**, *52*, 5822.

Catalytic Cycle Revised



Cause des-Br side reaciton

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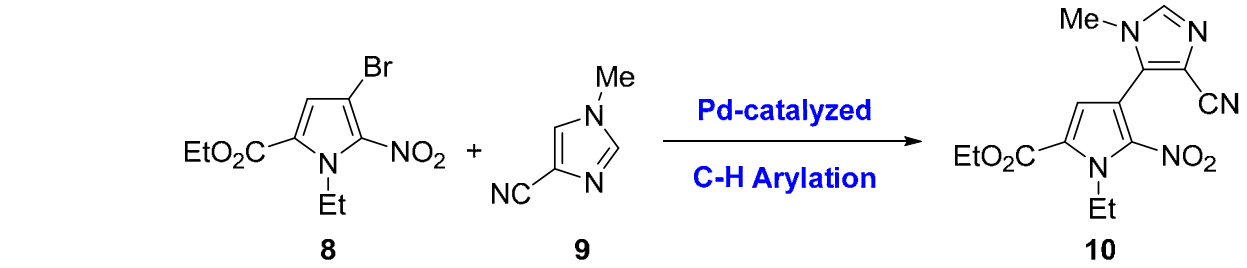
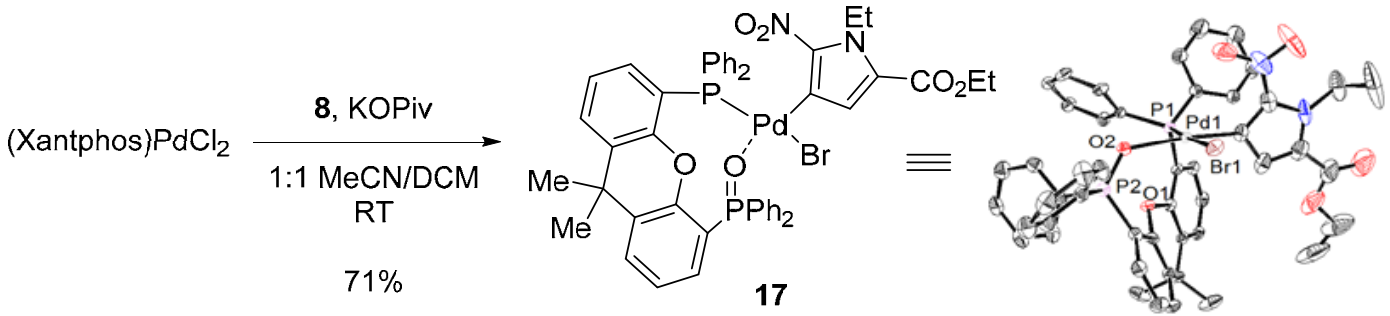
Catalyst Activation in C-H Arylation and Suzuki

Case of bidentate Ligands





Ji, Y.; Plata, R. E.; Regens, C. S.; Hay, M.; Schmidt, M.; Razler, T.; Qiu, Y.; Geng, P.; Hsiao, Y.; Rosner, T.; Eastgate, M. D.; Blackmond, D. G. *J. Am. Chem. Soc.* **2015**, *137*, 13272.

Summary

To effectively develop a robust catalytic process:

- **HTP screening is a powerful TOOL,**
- **To avoid local optimization, HTP screenings are best conducted in a parallel experimentation approach**
- **Mechanistic understanding is the key**

Bristol-Myers Squibb

Acknowledgements:

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T. Rosner

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Q. Gao

MVA COP

J. Bergum

V. Rosso

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M. Hay

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P. Lobben

O. Soltani

S. Tummala

B. Zheng

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