



WHAT STARTS HERE CHANGES THE WORLD
THE UNIVERSITY OF TEXAS AT AUSTIN



Department of
Chemistry and Biochemistry

Career in Review: John F. Hartwig*

Presentation in Guangbin's Lab

Apr 4th, 2013

Changxia Yuan

*Partial work of Prof. Hartwig

John F. Hartwig Biography Timeline

Selected People from Hartwig's Group in Academic:

Seth Herzon (Yale) Jianrong Zhou (Nanyang
Toshimichi Ohmura (Kyoto U.) Techological. U.)
Yasuhiro Yamashita (Tokyo U.) Qilong Shen (Shanghai I. of OC)
Jun Takaya (Tokyo Inst. of T.) Jing Zhao (Nanjing U.)
Makoto Yamashita (Kyoto U.) **~95% employed!!**



Selected Honor and Awards:

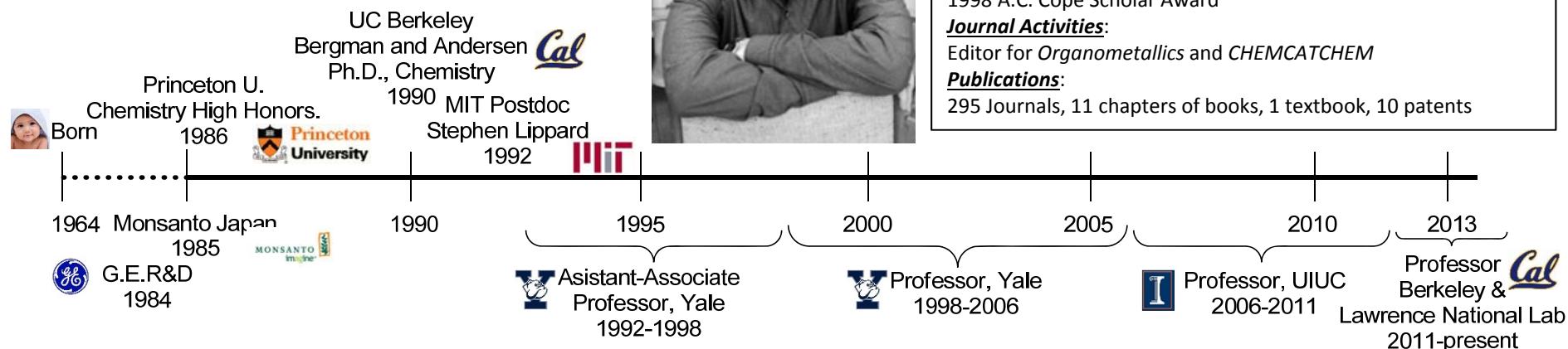
2013 Herbert C. Brown Award for Research in Synthetic Methods
2012 Member, National Academy of Sciences
2008 Mukaiyama Award from the Society of Synthetic Organic Chemistry, Japan
2007 Tetrahedron Young Investigator Award in Organic Synthesis
2004 Thieme-IUPAC Prize in Synthetic Organic Chemistry
1998 A.C. Cope Scholar Award

Journal Activities:

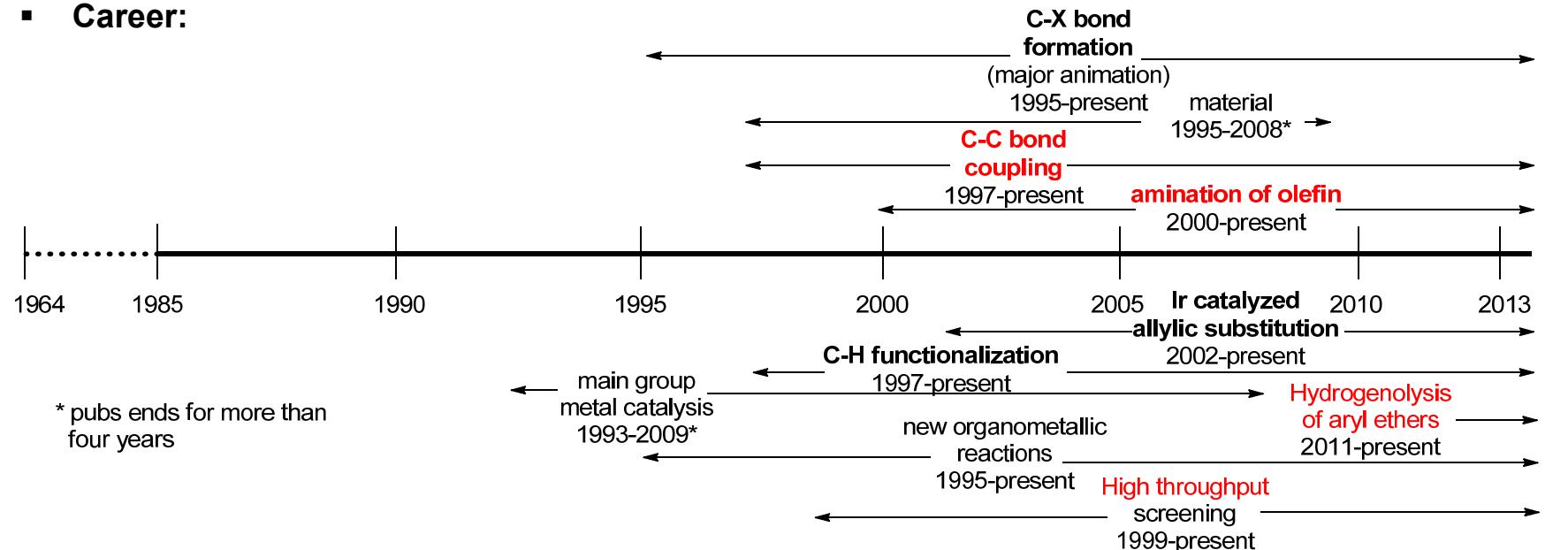
Editor for *Organometallics* and *CHEMCATCHEM*

Publications:

295 Journals, 11 chapters of books, 1 textbook, 10 patents



■ Career:



M1

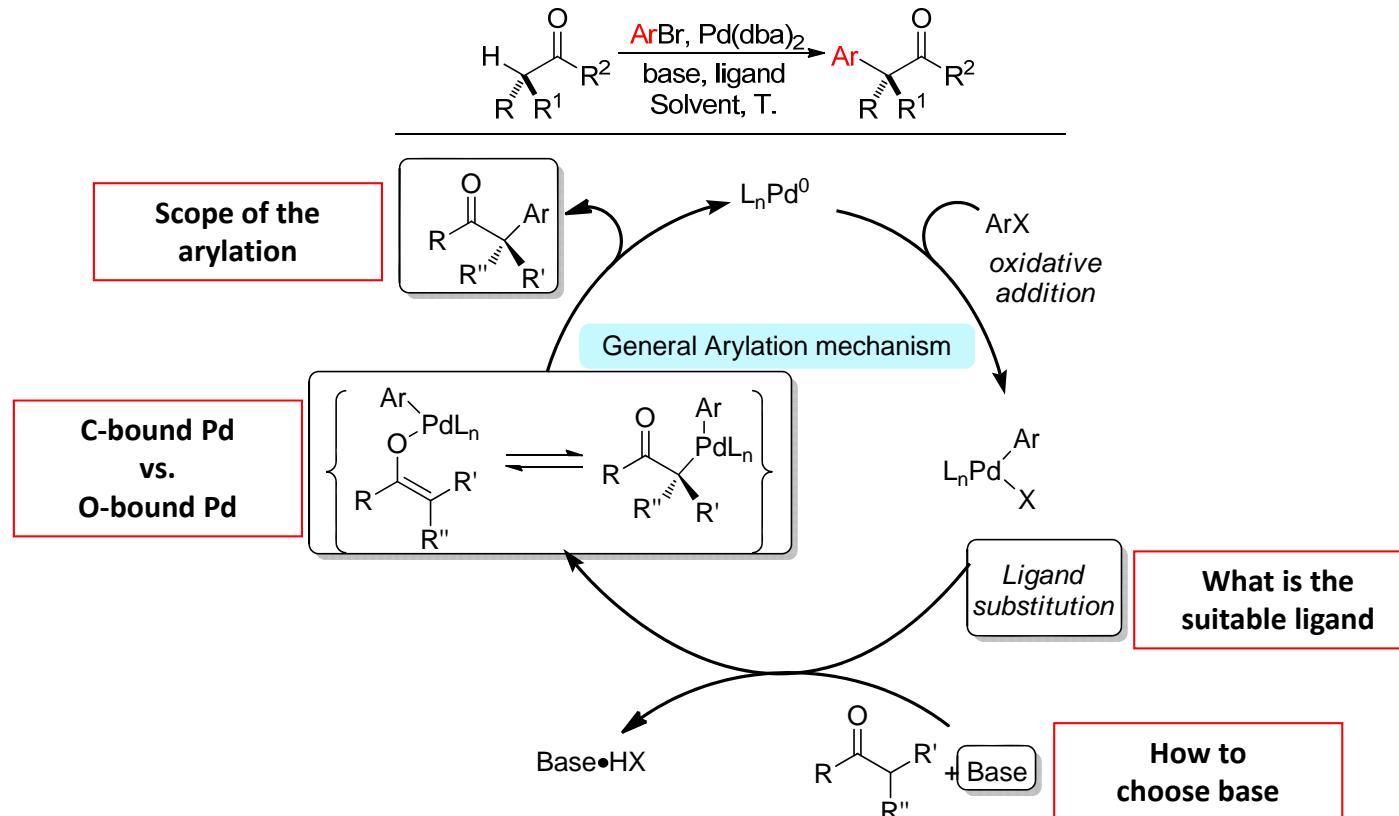
Honors

Honors are awarded at graduation by the departments of concentration. Departments determine honors on the basis of the grades received by the student in departmental studies in the sophomore, junior, and senior years (including junior independent work, the senior thesis, and, for students in the A.B. program, the senior departmental examination). Each department chooses the weight to be assigned to the various components in the honors calculation. The degree may be awarded with honors, high honors, or highest honors.

Moffat, 3/24/2013

Pd-Catalyzed Arylation of Carbonyl Compound

- Well-established mechanism:



D. A. Culkin J. F. Hartwig. *Acc. Chem. Res.* **2003**, 36, 234.

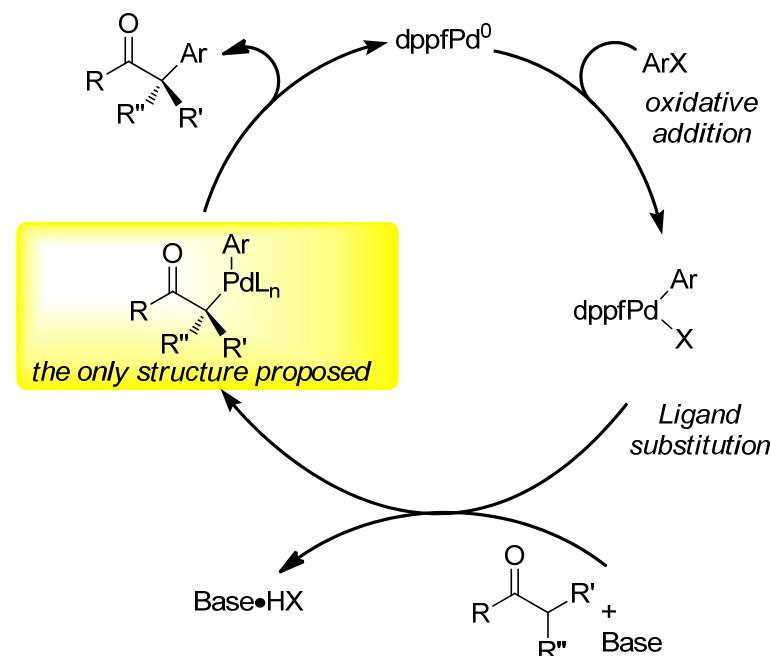
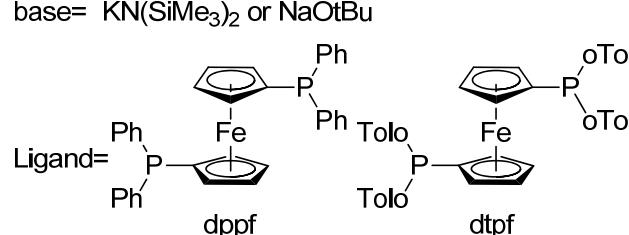
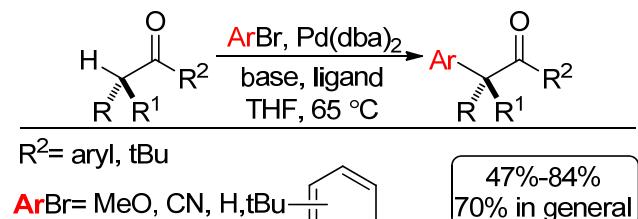
What I can learn from such a system?
How to extend the chemistry base on the existed chemistry?

- Pioneers (1997): Hartwig, Masahiro Miura, Buchwald.

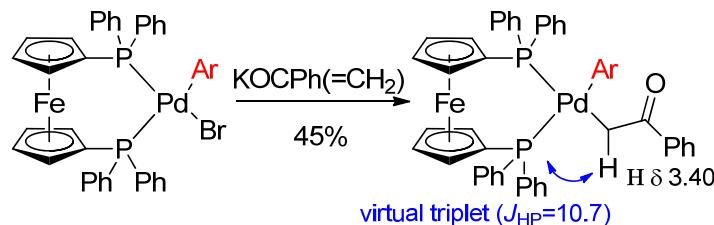
Pd-Catalyzed Arylation of Ketone

▪ Initial discover:

“Given the success of our recent palladium-catalyzed chemistry that produces aryl amines from aryl halides, amines, and an appropriate base, and the **similar pKa values of arylamines and ketones**, it seems likely that our amination procedures could be extended to the direct arylation of ketones.”



▪ Mechanistic observation:



Method to study the mechanism:

B.C. Hamann, J. F. Hartwig. *JACS*. **1997**, 119, 12383.

M2 discuss the P spectrum

Moffat, 3/24/2013

M4 Preparation of trans-[P(C₆

H₅)

3]

2

Pd(C₆

H₅)[N(p-CH₃

C₆

H₄)

2] (2).

Into a 20 mL vial was weighed 218 mg (0.261 mmol) of trans-(PPh₃)

2-

Pd(Ph)(I). The material was suspended in 15 mL of THF and 68 mg
(0.289 mmol) of KN(p-CH₃

C₆

H₄)

2

was added as a solid. The reaction

mixture was stirred for 1 h at room temperature and turned a deep red

color. The reaction mixture was filtered through a medium fritted

funnel. The resulting THF solution was concentrated by vacuum.

Crystalline material was obtained by addition of Et₂

O and cooling at

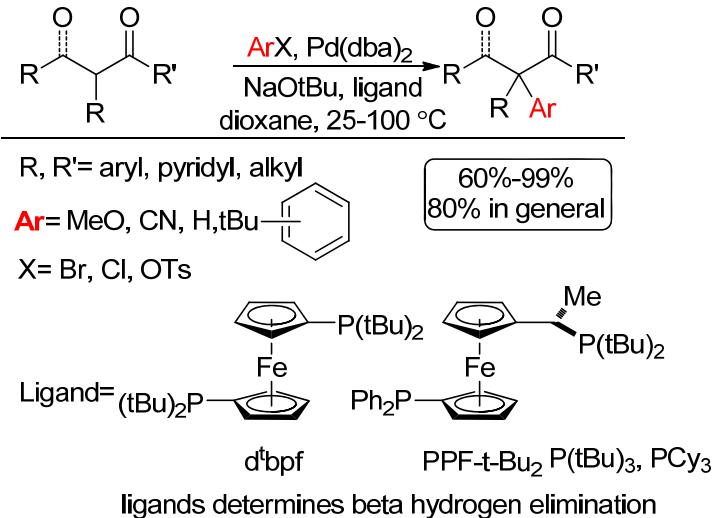
-35 °C for 12 h. The yield of red crystalline product was 184 mg

(78%)

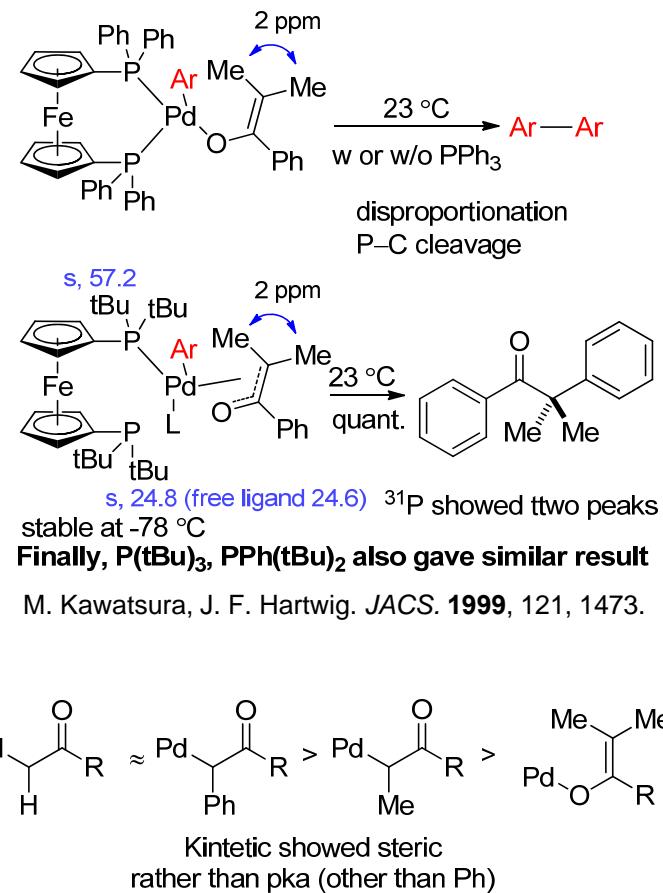
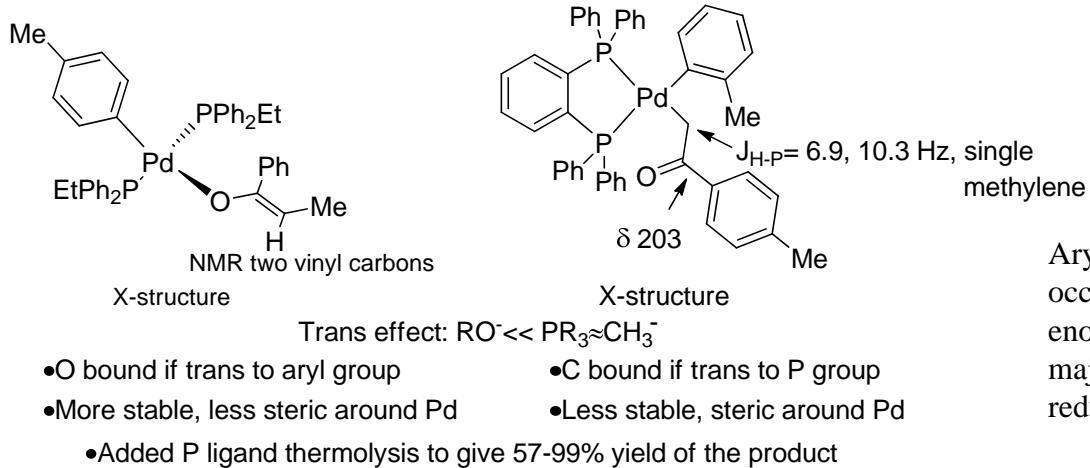
Moffat, 4/3/2013

Mechanism: Arylation of Carbonyl Compound

- Revised the enolate binding model:



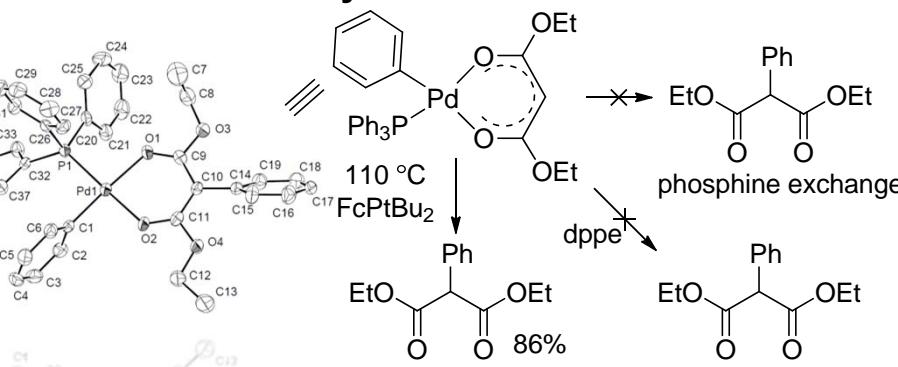
- Mechanism probe: study the reductive elimination



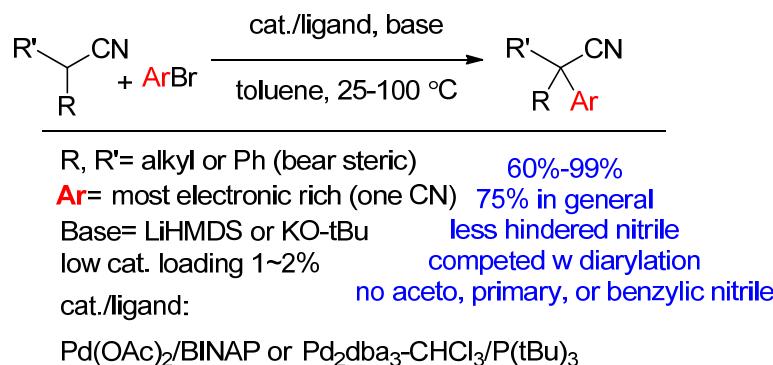
Arylation of the less hindered carbon of a dialkyl ketone occurs with high selectivity in the catalytic arylation of ketone enolates because the less hindered enolate complex is the major tautomer, not because of a large difference in rates for reductive elimination

Crystal Love

- First Malonate crystal:

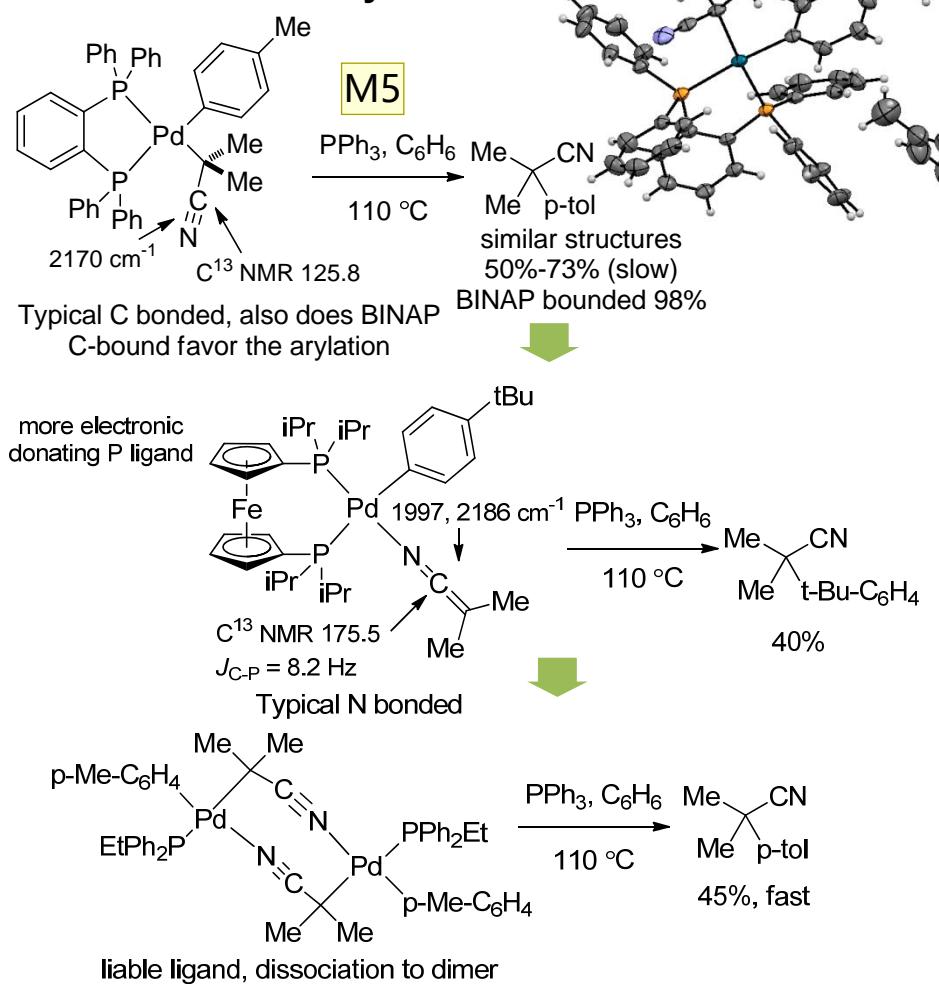


J. P. Wokkowsky, J. F. Hartwig. *Angew.* **2002**, *41*, 4289.



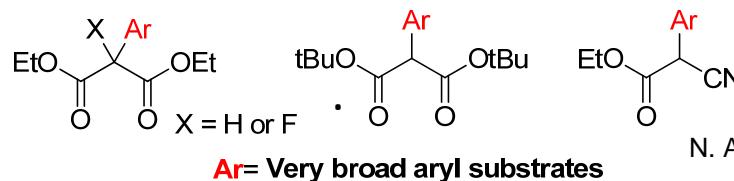
Question (binding model) -> get crystals -> get elimination product -> summarize reaction -> screen a good system -> get good result

- Nitrile Anion Crystal:



Uncommon research style

D. A. Culkin, J. F. Hartwig. *JACS*. **2002**, *124*, 9330; D. A. Culkin, J. F. Hartwig. *OM*. **2004**, *23*, 3398.



N. A. Beare, J. F. Hartwig. *JOC*. **2002**, *67*, 541.

幻灯片 6

M3 the greater steric hindrance of FcPtBu₂, relative to that of phenylphosphanes, induces reductive elimination from complexes of typically unreactive ligands derived from malonate and acetylacetone anions. This steric effect overrides the stabilizing effect of the h₂-O,O-coordination mode and the electron-withdrawing groups on the central carbon atom of the malonate anion.

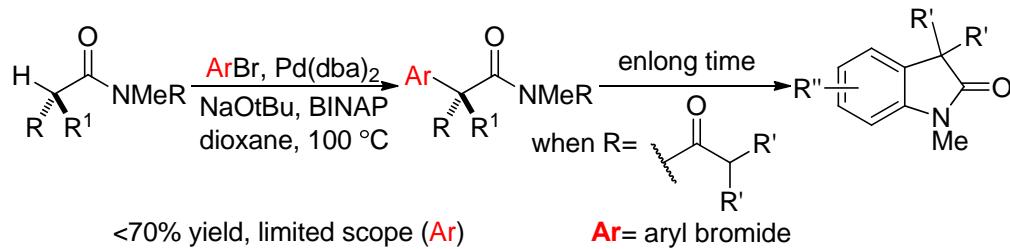
Moffat, 3/25/2013

M5 trap for the Pd(0) fragment induced the first reductive eliminations to form R-aryl nitriles

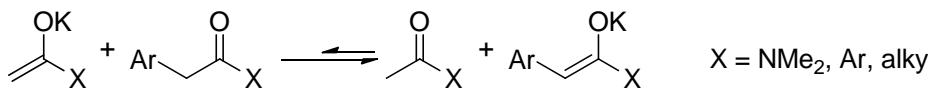
Moffat, 4/3/2013

Base Effect in Pd Arylation Chemistry

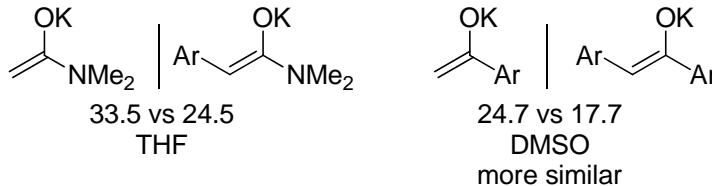
- Base effect on coupling reaction:



solve diarylation:



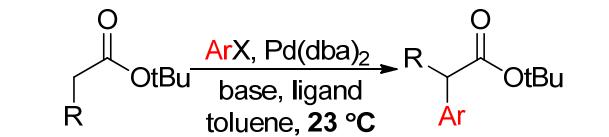
Limitation:



control the reaction selectivity for **monoarylation** and **rates**
pka dominates steric (Ar stabilize the anion, slow reaction)

K. H. Shaughnessy, J. F. Hartwig. *JOC*. **1998**, 63, 6546.

Pd-Catalyzed Arylation of Carbonyl Compound



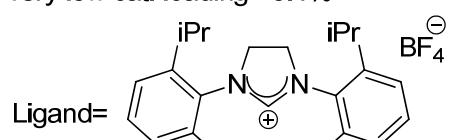
R, R'= H or alkyl

Ar= Very broad aryl substrates

Base= Na/KHMDS or LiNCy₂

very low cat. loading ~0.1%

60%-99%
80% in general



for R=alkyl

P(tBu)₃

tert-butyl acetate and the efficient arylation of R,R-disubstituted esters were developed

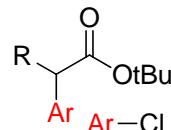
3 things matters: pKa, arylation faster than proton transfer

amine base crucial, ligand fast should be better

M. Jorgensen, J. F. Hartwig. *JACS.* **2002**, 124, 12557.

{[(PtBu)₃]PdBr}₂/Cy₂NLi improved the above rxn

T. Hama, J. F. Hartwig. *Org. Lett.* **2008**, 10, 1545.

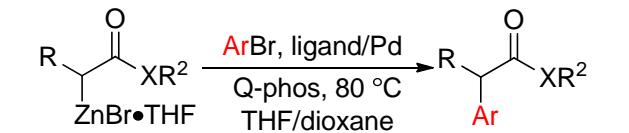


KHMDS, toluene
good yield
broad arene scope

T. Hama, J. F. Hartwig. *Org. Lett.* **2008**, 10, 1549.

Transmetallation in Arylation Chemistry

- Negishi type coupling:

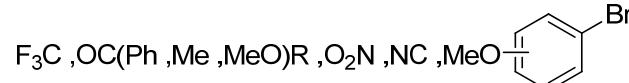
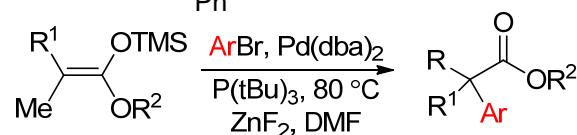
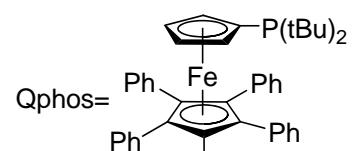


R, R' = H or alkyl

Ar = most electron deficient subs (3 new MeO-)

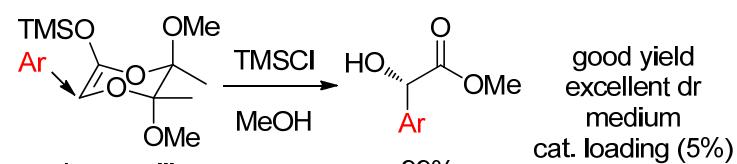
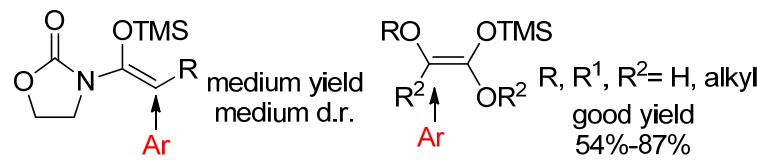
Base = Na/KHMDS or LiNCy₂
very low cat. loading ~0.1%

66%-99%
85% in general



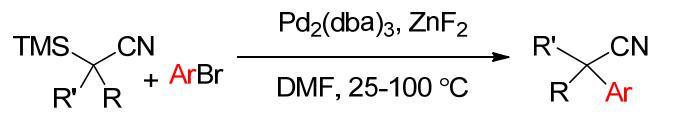
R' = Me, H Applied Evans Auxiliary moderate ee

T. Hama, J. F. Hartwig. JACS. 2003, 125, 11176.

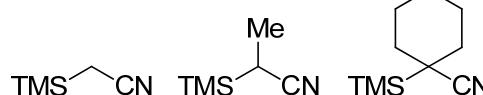


X, Liu, J. F. Hartwig. JACS. 2004, 126, 5182.

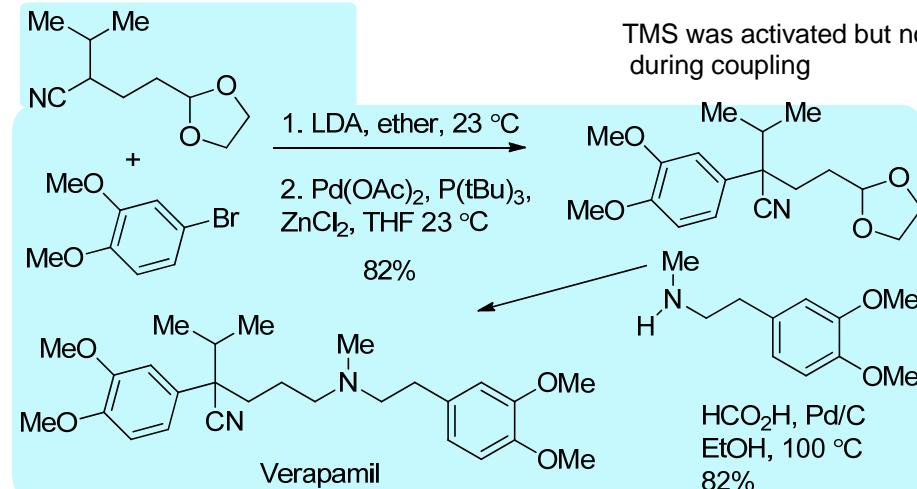
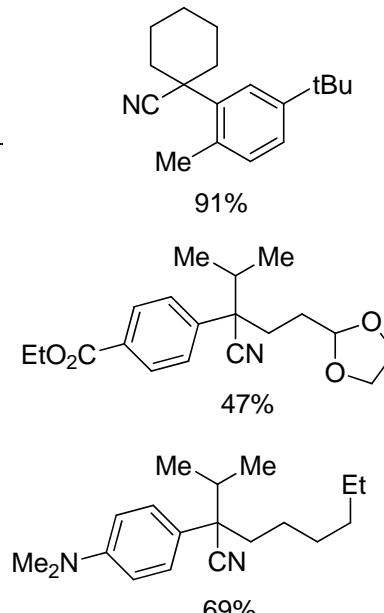
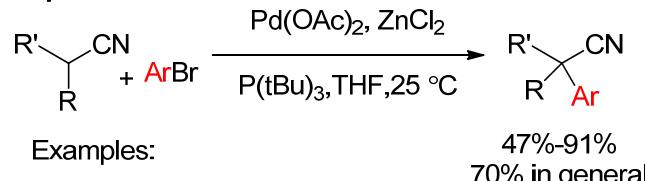
- Activate silyl group:



Ar = very broad aryl range
low cat. loading 1~2%
60%-99%
75% in general



Improved version:

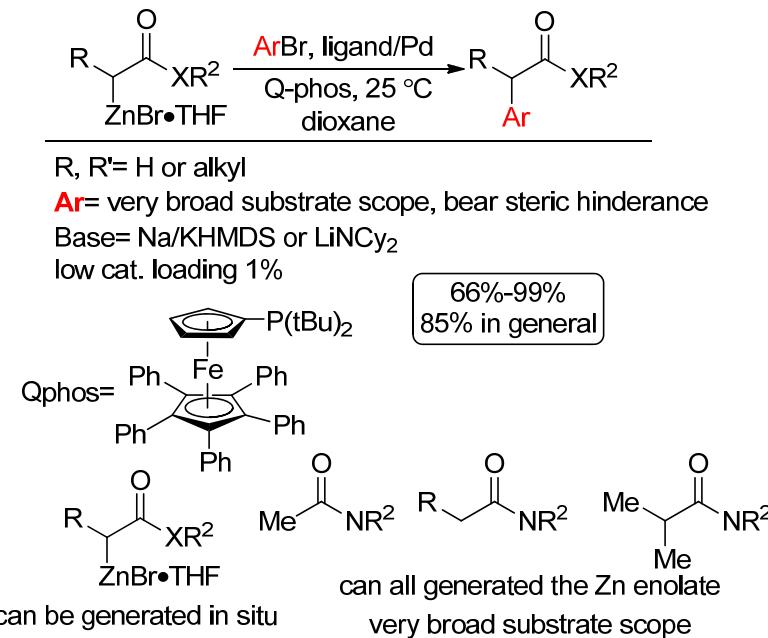


synthesis of Verapamil (hypertension)

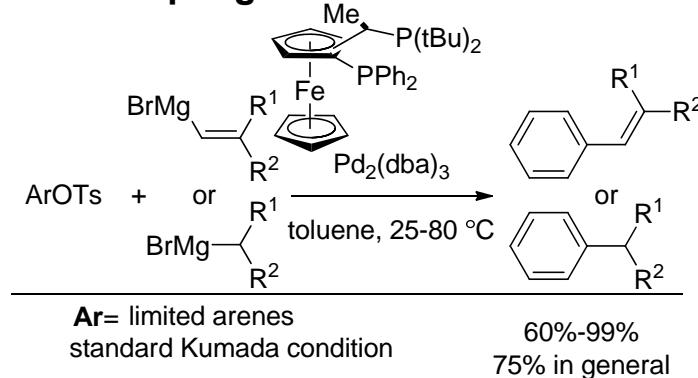
L, Wu, J. F. Hartwig. JACS. 2005, 126, 15824.

Tranmetallation continuation

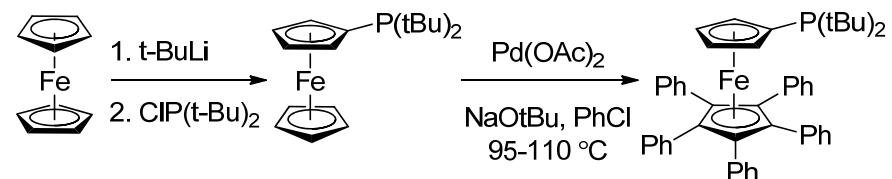
- More Negishi coupling:



- Kumada coupling:



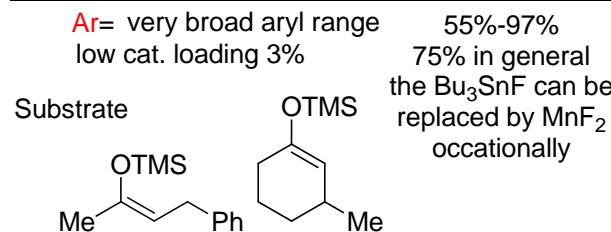
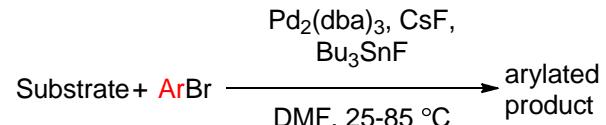
M. E. Limmert, J. F. Hartwig. *JOC*. **2005**, 70, 9364.



synthesis of Q-phos

N. Kataoka, J. F. Hartwig. *JOC*. **2006**, 67, 5553.

- Synergistic Effect assisted coupling:

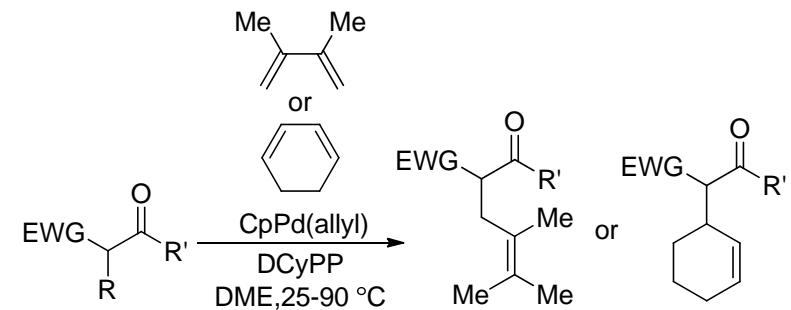


CsF alone gave poor yield and selectivity
mechanism unclear, any assumption?

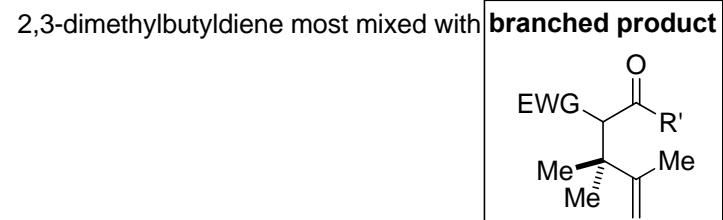
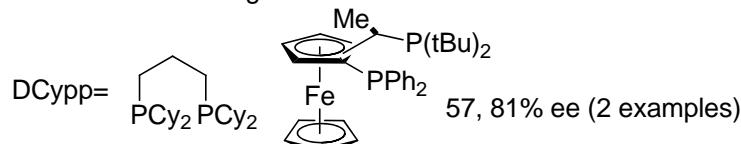
W. Su, J. F. Hartwig. *Angew*. **2006**, 45, 5852.

Miscellaneous Substrates

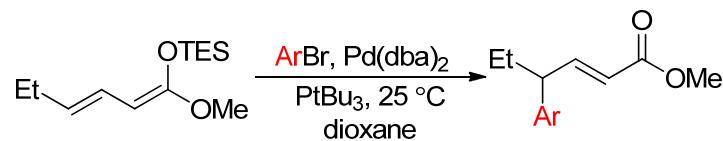
- Diene:



EWG= CN, ester, ketone, sulfone, aryl
2% to 5% Pd loading



A. Leitner, J. F. Hartwig. *JOC*. **2004**, 69, 7552.



R, R'= H or alkyl

Ar= very broad substrate scope, bear steric hindrance
Base= Na/KHMDS or LiNCy₂

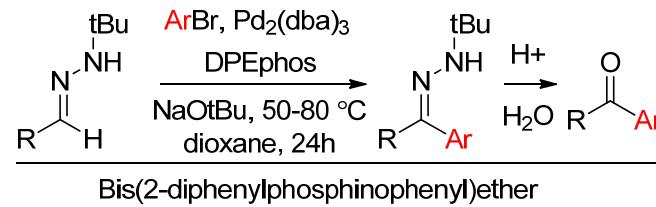
D. S. Huang, J. F. Hartwig. *Angew.* **2010**, 49, 5757.

- Aldehyde:



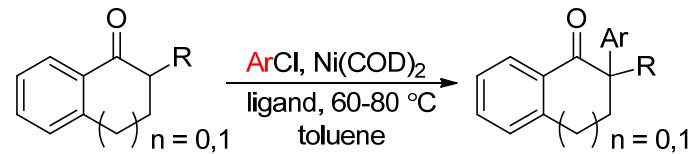
G. D. Vo, J. F. Hartwig. *Angew.* **2008**, 47, 2127.

- Hydrazine:



A. Takemiya, J. F. Hartwig. *JACS*. **2006**, 128, 14800.

- Ni(COD)₂ catalyzed arylation:



R, R'= H or Me

Ar= very broad substrate scope
can not bear steric hindrance

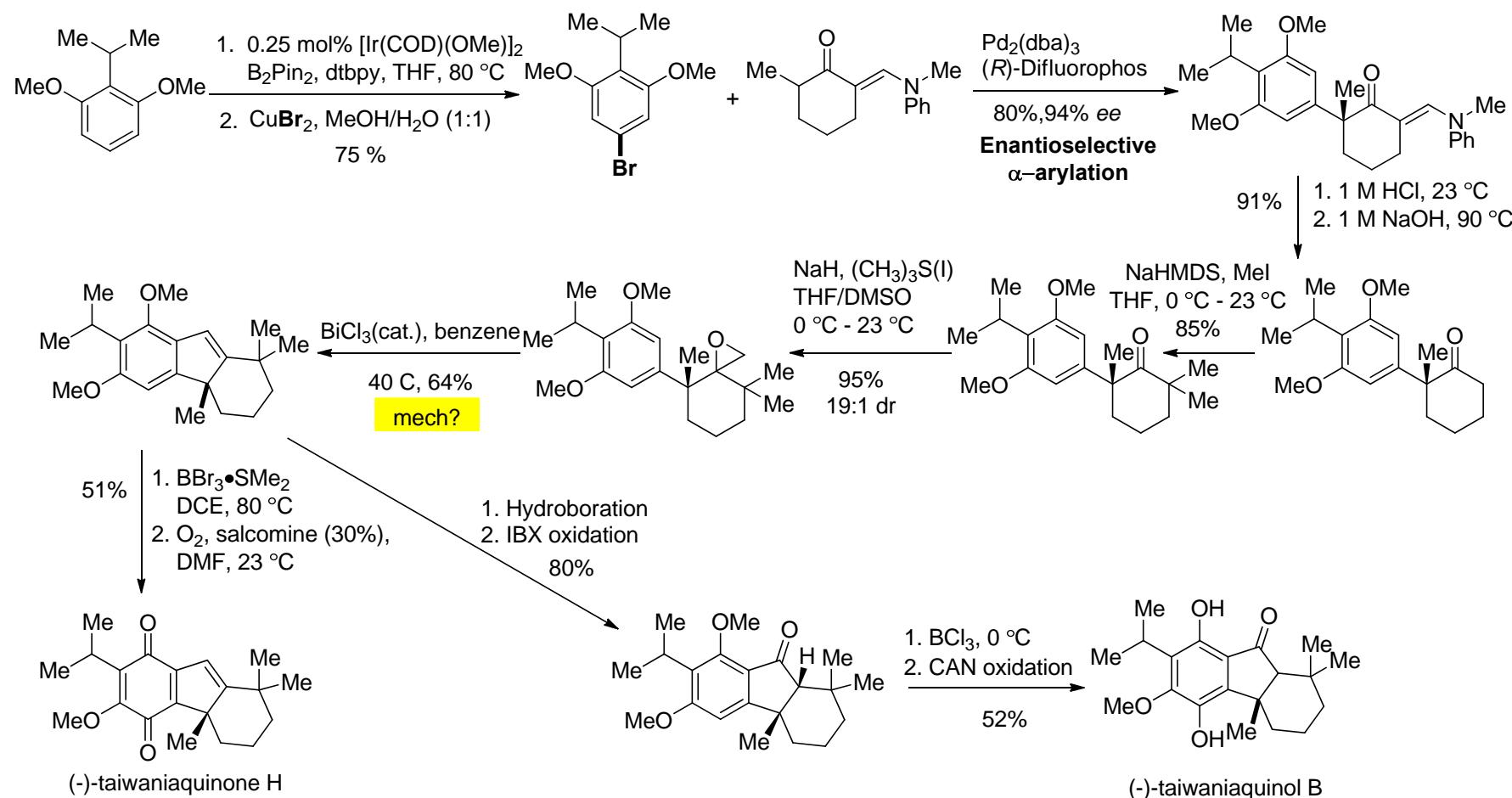
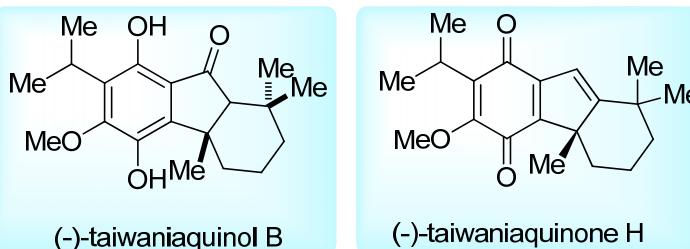
Base= NaOtBu sometimes diminished yield with bromoarenes

Ligand= (R)-BINAP or (R)-DIFLUORPHOS

ee= most >90%

S. Ge, J. F. Hartwig. *JACS*. **2011**, 133, 16330.

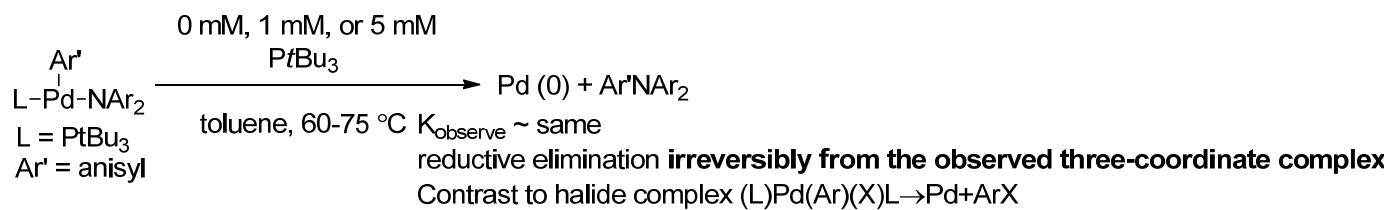
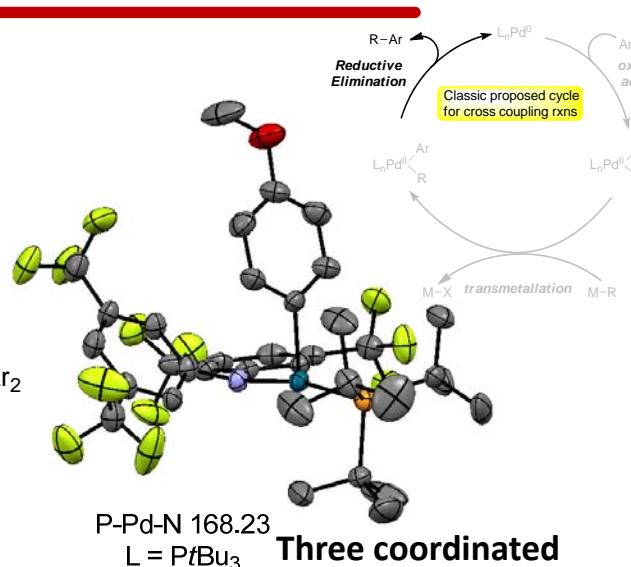
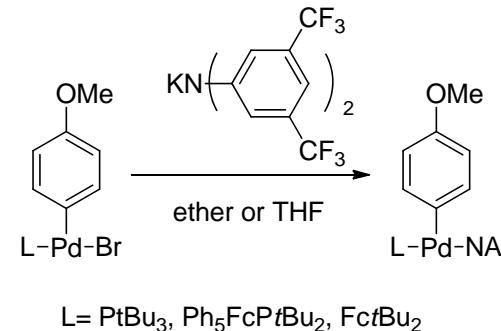
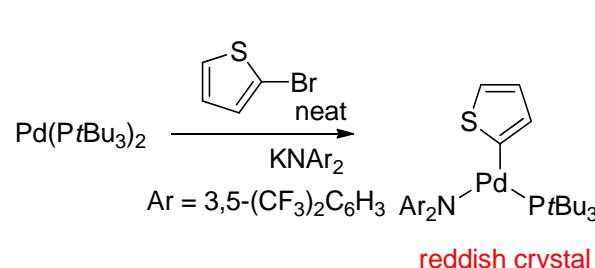
Application of Pd Arylation in Total Synthesis



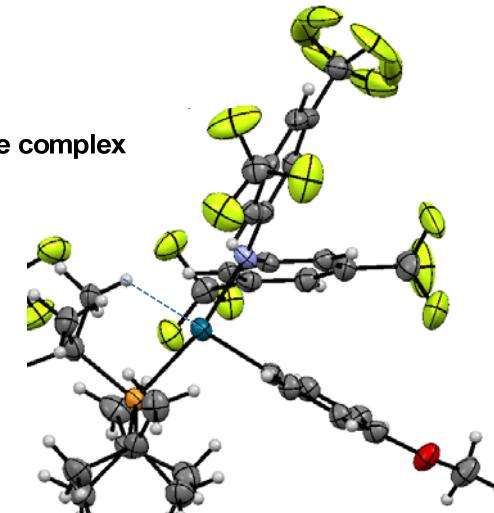
S.. Liao, J. F. Hartwig. *JACS*. **2011**, 133, 2088.

Part 2: First Three Coordinated Arylpalladium Complexes

- Crystal preparation:



Kinetic faster elimination than four coordinated complex



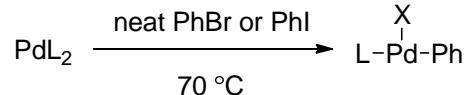
If interested, first arylpalladium cyanide complexes was made and studied in similar vein for the first time.

J. L. Klinkenberg, J. F. Hartwig. *JACS*. 2013, 134, 5758.

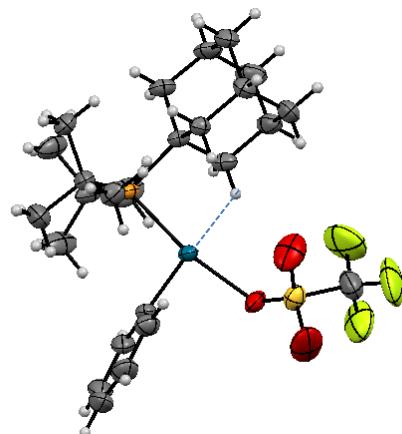
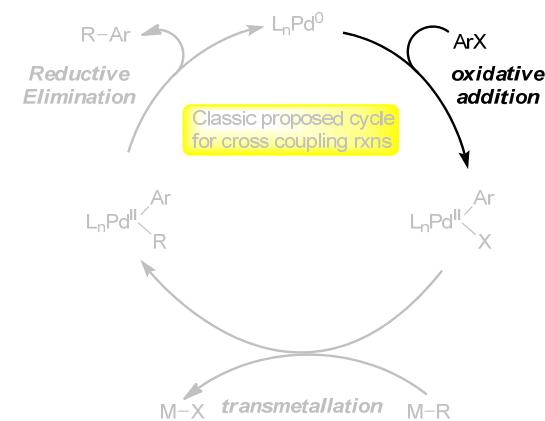
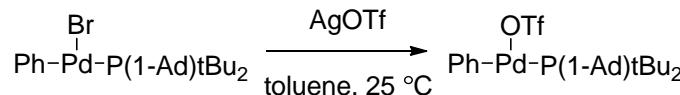
M. Yamashita, J. F. Hartwig. *JACS*. 2004, 126, 5344.

Further Study the Weak Agostic Interaction

- Study of arylpalladium halide complexes:



L = 1-AdPtBu₂, PtBu₃, Q-Phos
PhCl gave unstable intermediate
PhOTf gave unidentified metallic complexes



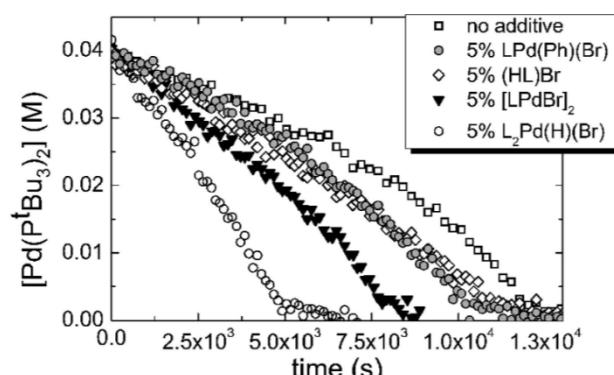
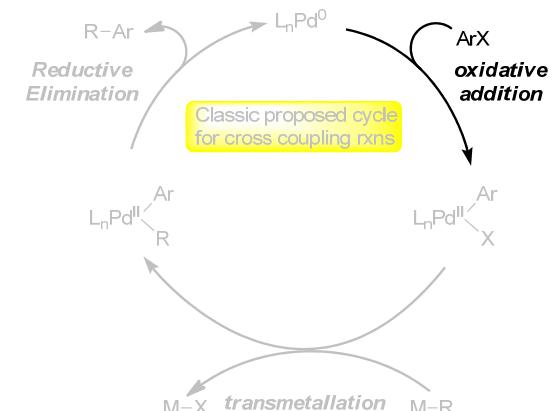
Complex: (1-AdPtBu₂)Pd(Ar)Br(OTf)

Major method: H/IR Spectrum comparison, Kinetic study, X-ray, bond angle analysis, DFT

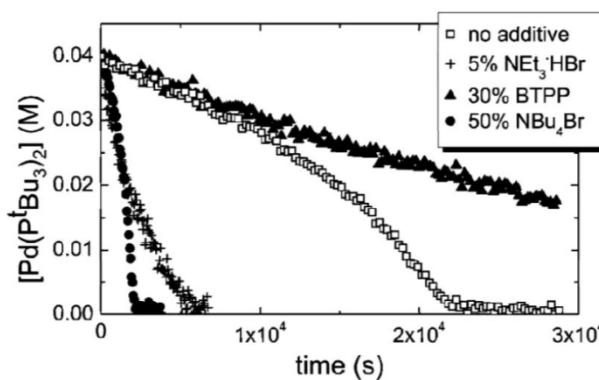
J. P. Stambuli, J. F. Hartwig. *JACS*. 2004, 126, 1184.

Palladium Hydride Acceleration on Oxidative Addition

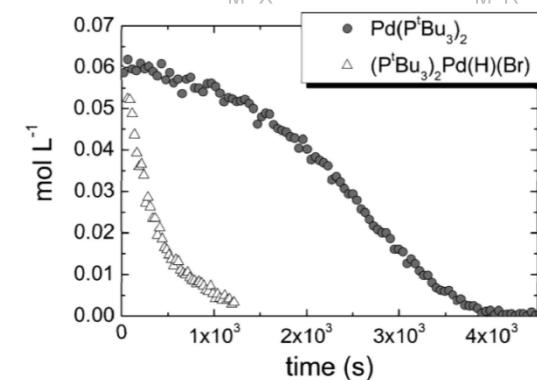
$(P^tBu_3)_2Pd$ (1)	$\xrightarrow[70\text{ }^\circ C]{\text{toluene or MEK}}$	$(P^tBu_3)Pd(\text{Ph})(\text{Br})$ (2)	toluene MEK	60%	98%
+ PhBr		$(P^tBu_3)_2Pd(\text{H})(\text{Br})$ (3)		10%	<2%
		$[(P^tBu_3)Pd(\mu\text{-Br})]_2$ (4)		13%	<2%
		$[\text{Pd}(P^tBu_2\text{C}(\text{CH}_3)_2\text{CH}_2)(\mu\text{-Br})]_2$ (5)		16%	<2%



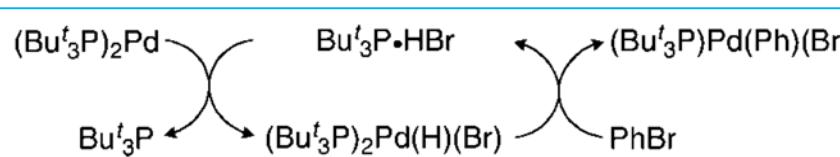
Decay of $Pd(PtBu_3)_2$ during the oxidative addition of PhBr in toluene at $70\text{ }^\circ C$ in the presence of additives ($L = PtBu_3$).



Decay of $Pd(PtBu_3)_2$ during the oxidative addition of PhBr in THF at $70\text{ }^\circ C$ in the presence of 5 mol % of $NEt_3 \cdot HBr$, 30 mol % (BTPP), or 50 mol % of NBu_4Br .



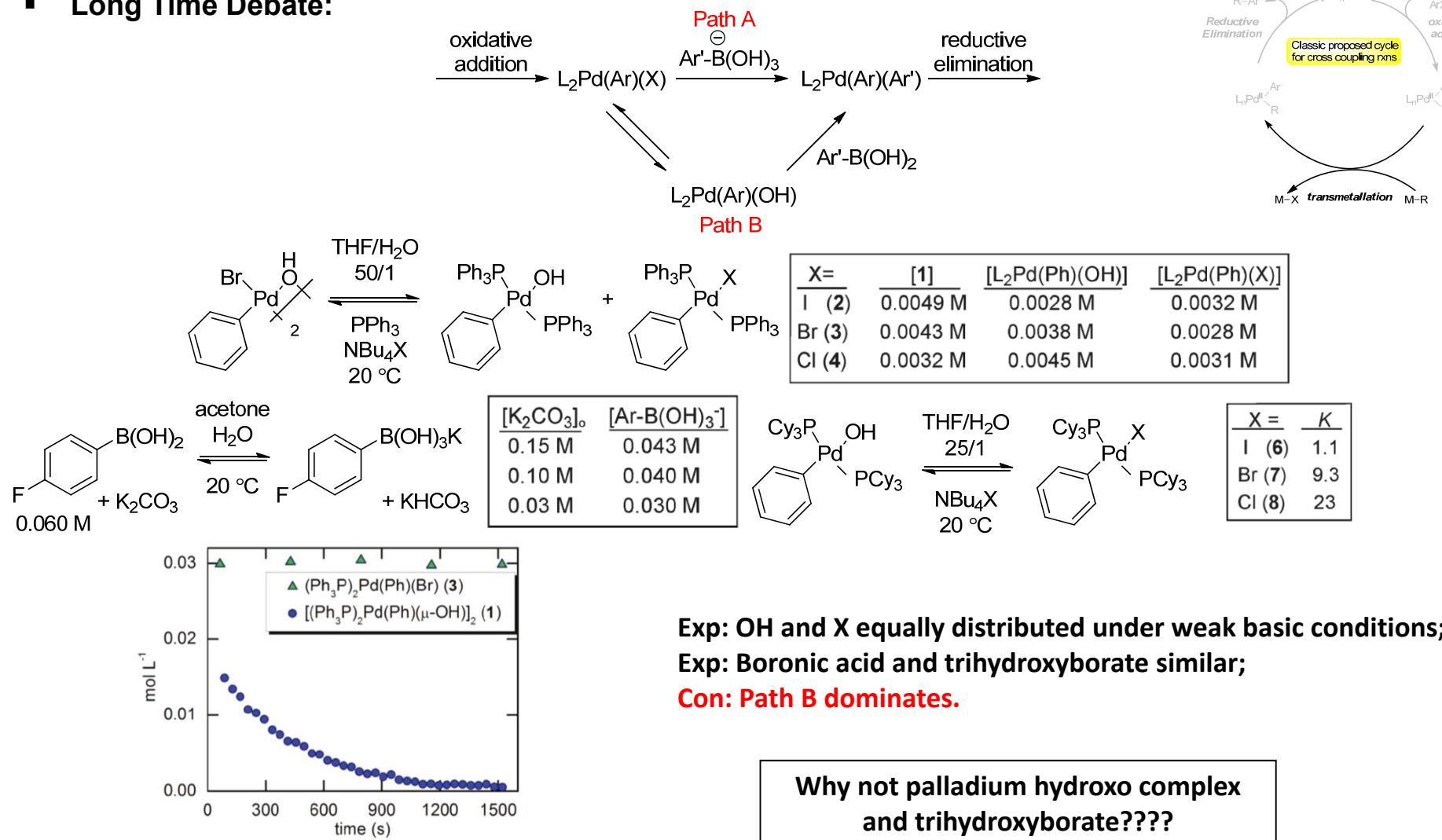
Relative decay of $Pd(PtBu_3)_2$ and $(P^tBu_3)_2Pd(H)(Br)$ during the oxidative addition of PhBr in 2-butanone at $70\text{ }^\circ C$.



Conclusion: bromobenzene reacts faster with $L_2Pd^{II}(\text{H})(\text{Br})$ than with the related $L_2Pd(0)$.
Proton Shuffle

Transmetallation in Suzuki-Miyaura Rxn (weak base)

- Long Time Debate:



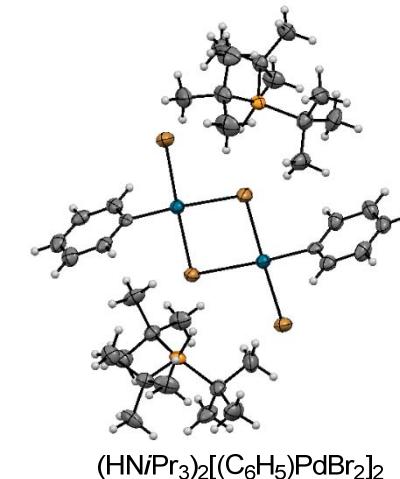
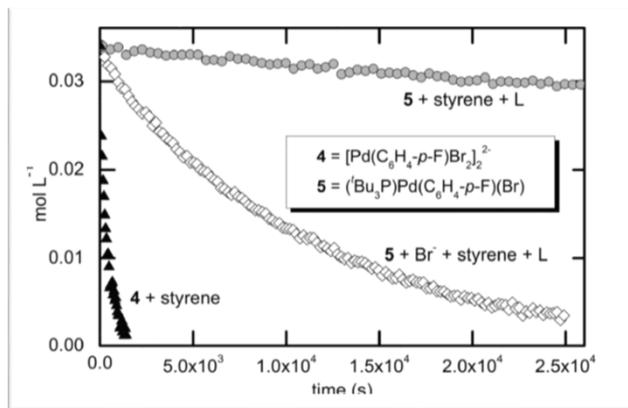
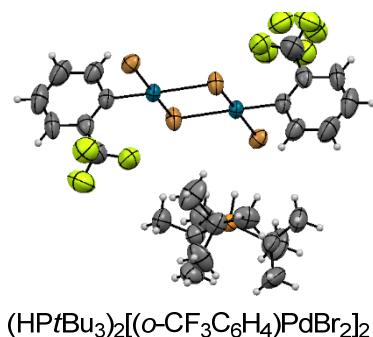
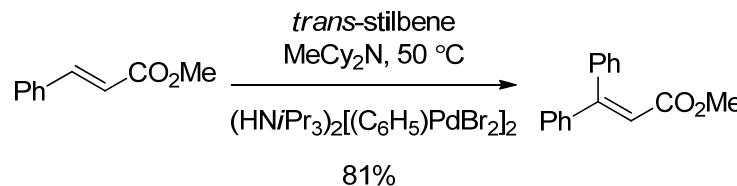
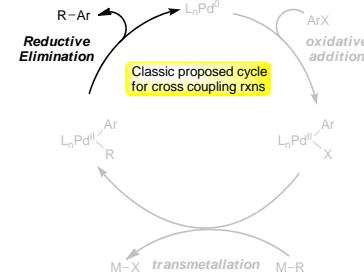
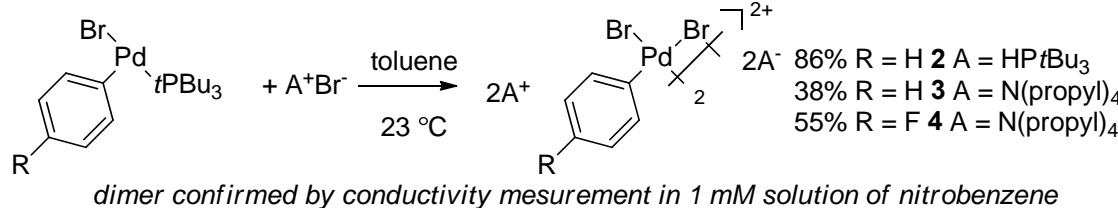
OH (0.015 M) & p-tolylboronic acid (0.15 M) and PPh₃ (0.15 M) at -40 °C

Br (0.030 M) & potassium p-tolyltrihydroxyborate (0.15 M), PPh₃ (0.15 M) and 18-crown-6 in THF/H₂O (50:1) at -30 °C as monitored by ³¹P NMR

B. Carrow, J. F. Hartwig. *JACS*. 2011, 133, 2116.

Study of Ligandless Arylpalladium Halide in Heck Rxn

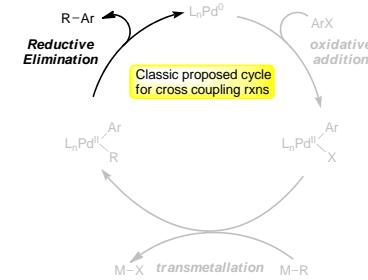
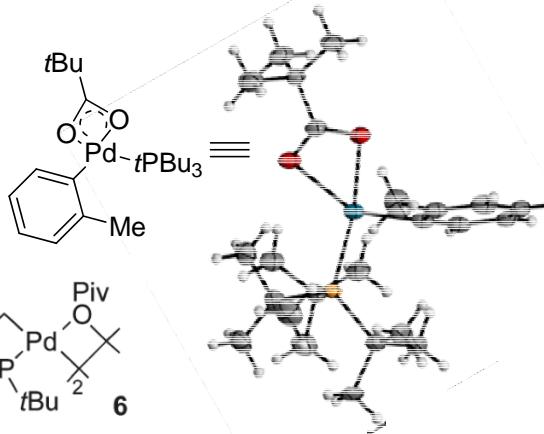
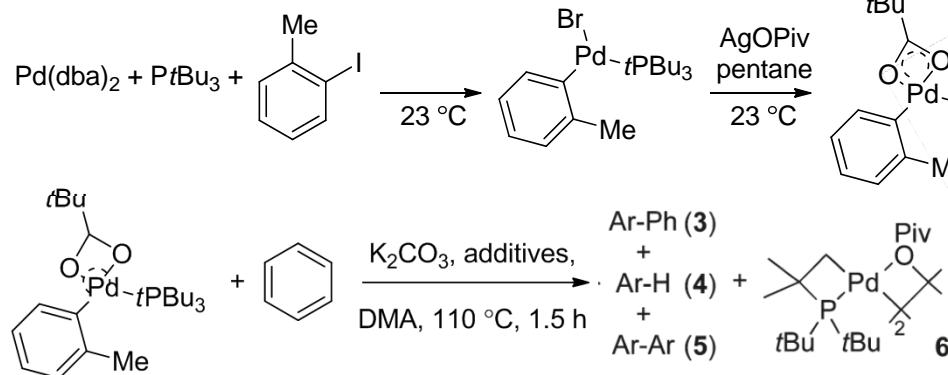
- Crystal preparation:



-anionic complexes in this work are more reactive than neutral,-
phosphine-ligated analogues because they are *less hindered*
-PtBu₃ bounded loose-mediocre selectivity-

C-H Bond Functionalization: by Ligandless Pd Complex

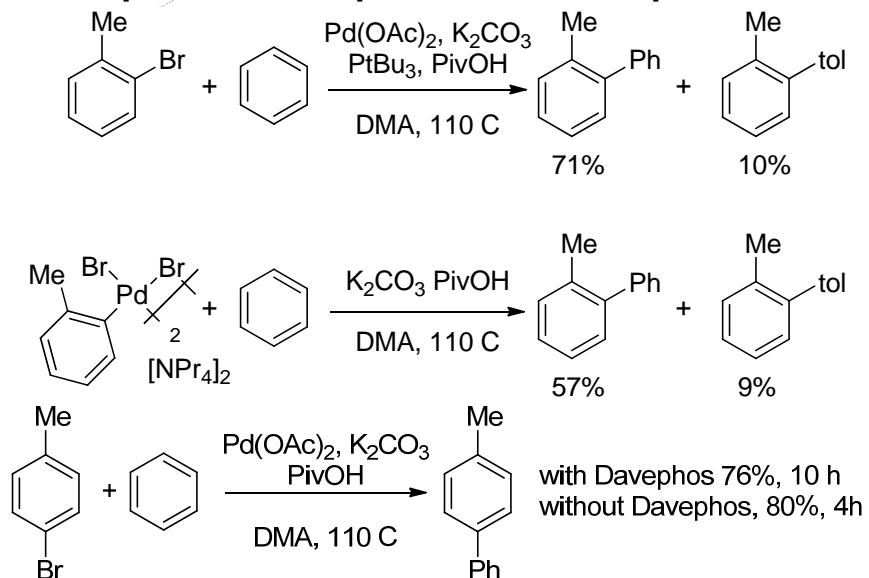
- Questioning an assumption:



entry	concn of 2	additives	yield of 3	yield of 4	yield of 5	3/5
1	0.04 M	—	trace	27%	32%	—
2	0.003 M	—	trace	33%	20%	—
3	0.003 M	PivOH (0.03 M)	trace	45%	25%	—
4	0.04 M	NHep ₄ Br (0.1 M)	30%	17%	23%	1.3
5	0.003 M	NHep ₄ Br (0.1 M)	51%	31%	7%	7.3
6	0.003 M	NHep ₄ OPiv (0.1 M)	49%	25%	5%	9.8
7	0.003 M	O ₂ (0.01 M)	63%	26%	<5%	>12

^a Yield by GC/MS with an internal standard.

- Experiments to prove the assumption:



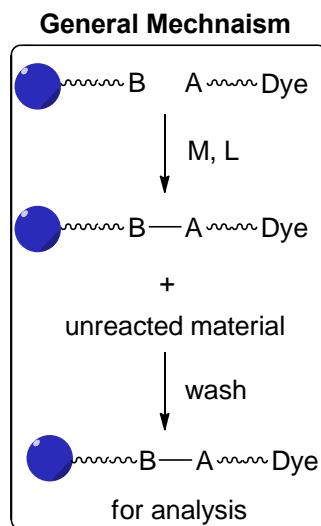
Isotope effect showed no change without P ligand
DFT also gave positive result

Part 3. High-Throughput Screening

What is high throughput screening?

High-throughput screening (HTS) is a method for scientific experimentation especially used in drug discovery and relevant to the fields of biology and chemistry. Using robotics, data processing and control software, liquid handling devices, and sensitive detectors. High-Throughput Screening allows a researcher to quickly conduct millions of chemical, genetic or pharmacological tests.

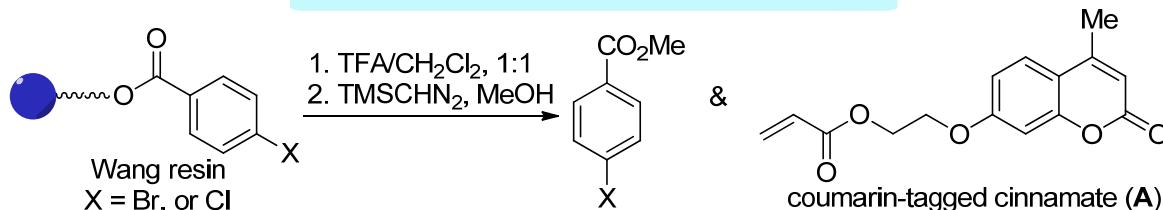
Fluorescence Resonance Energy Transfer



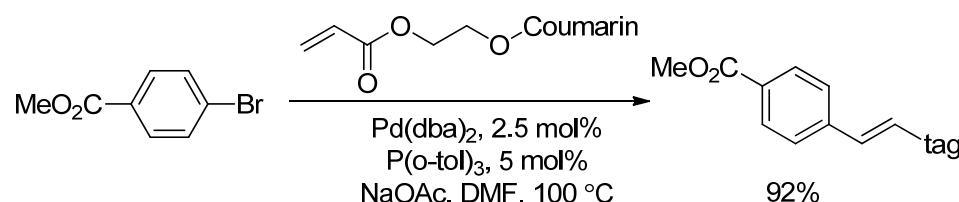
K. H. Shaughnessy, J. F. Hartwig. *JACS*. **1999**, 121, 2123.

Fluorescence-Based Assay for Heck Screening

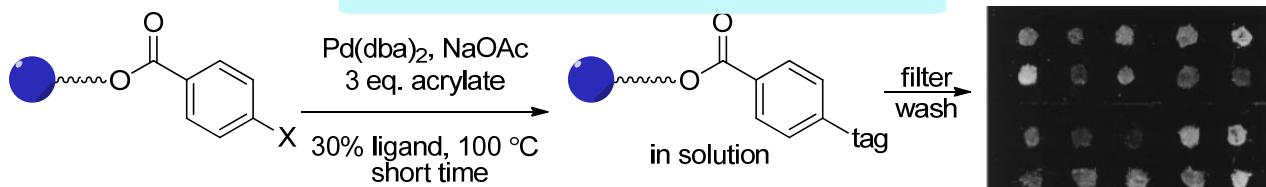
Step 1: Test the tags



Step 2: Setup benchmark reaction



Step 3: Setup benchmark reaction

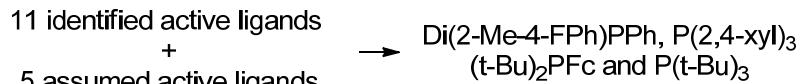


conclusion: sterically demanding orthosubstituted arylphosphines

reaction repeated in solution, monitored by GC
two "active" ligands showed negative result
all the "negative" ligands showed poor result

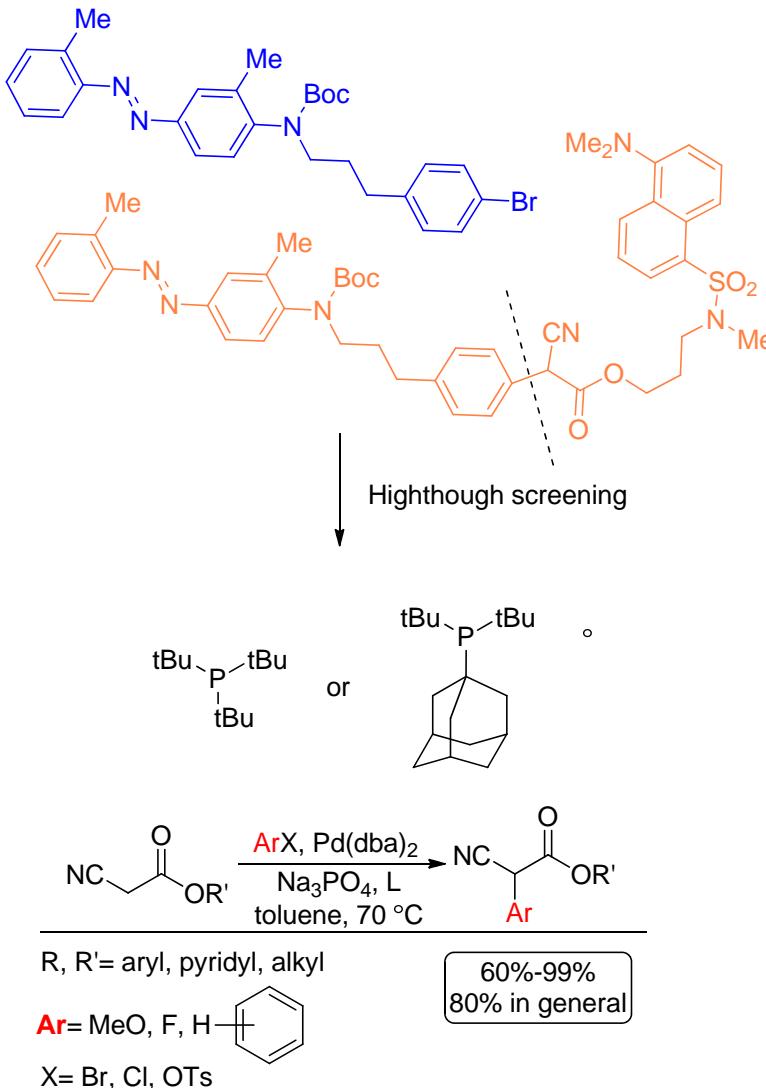
standard UV lamp
no fluorescent w/o cat.
40 P ligand tested

Step 4: Finalize conditions for application



screen real Heck coupling with the four ligands
the final conclusion, 4 ligands gave different result for different substrates...

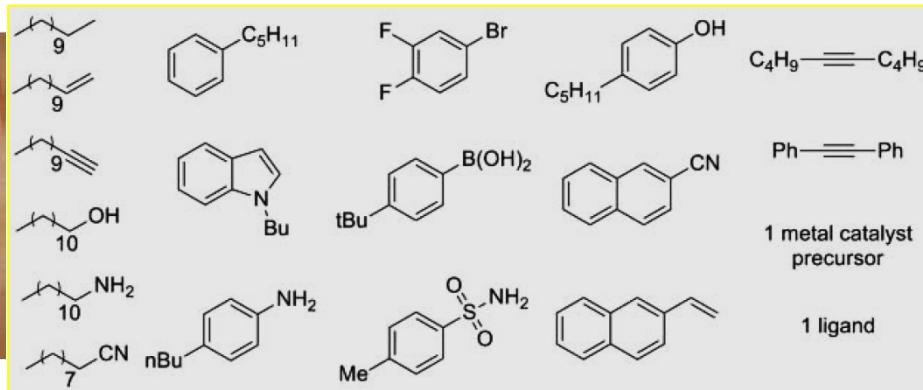
Fluorescence-Based Assay for Screening-2



Science Paper

Why Science

Two dimensional: many catalysts for many possible substrates
evaluate $>10^5$ reaction with less MS

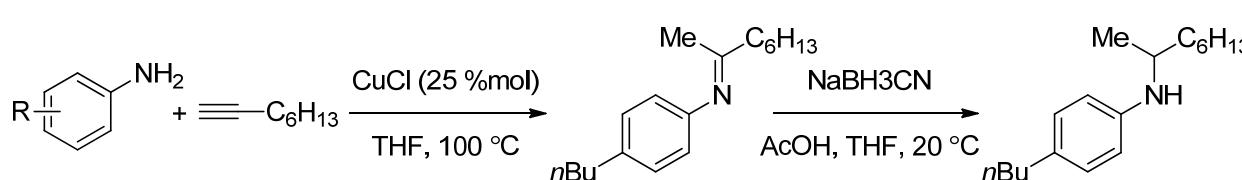


Method: 16 (15 metals + 1 control)*24 array = 16+24 mass spectroscopy
Three known reactions as positive controls; GC-MS also showed positive

If the interested trait was unambiguously found: specific GC-MS pattern & limited positive spots

Part 3: High Throughput Screening

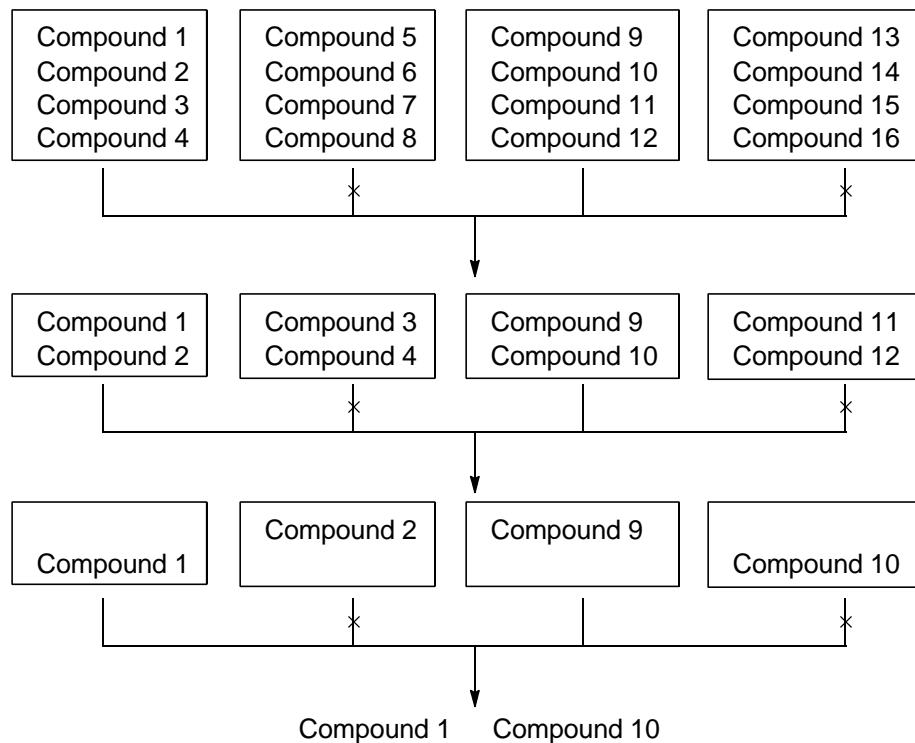
Result: Three spots showed positive with CuCl, and quick screening reveal the reaction without ligand



Entry	R	Catalyst Loading	Yield*
1	4-nBu	10 mol%	57%
2	4-OH	25 mol%	80%
3	4-CN	25 mol%	51%
4	4-CO2Me	25 mol%	68%
5	3-Br	25 mol%	84%
6	4-acetyl	25 mol%	60%
7	2,6-di-isopropyl	25 mol%	70%

* Yield determined by using gas chromatography with 1,3,5-trimethoxybenzene as an internal standard after hydrolysis with 1 M HCl at room temperature to 2-octanone

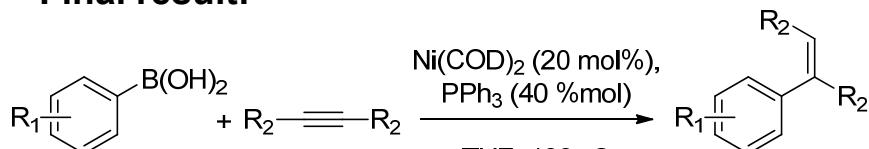
If the interested trait was found with suspicious identity: similar MW&GC patterns; multiple positive spots with two metals and several ligands



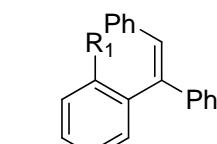
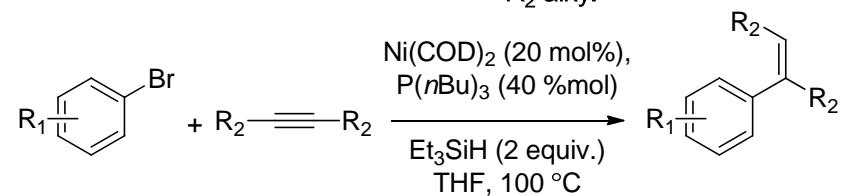
*consider the third compound as ligand
*consider they are in the same group

Great indication!

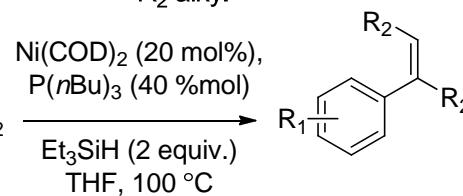
- Final result:



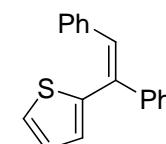
good to medium Z(major)/E
R₁ EWG groups
R₂ alkyl



R₁ = Me; 54%, 17.5:1
R₂ = CO₂Me, 53%; 1.2:1



69%, 1.1:1



38%, 5.4:1

Supporting Materials

More for high throughput screening reading:

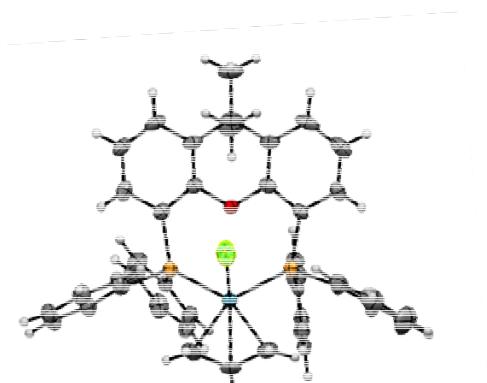
J. P. Stambuli, J. F. Hartwig. *Current Opinion in Chemical Biology* **2003**, 7, 420.
S. R. Stauffer, J. F. Hartwig. *JACS* **2003**, 125, 6977.

Part 4: Hydroamination of alkenes: Backgrounds

Initiated from the high-throughput screening!

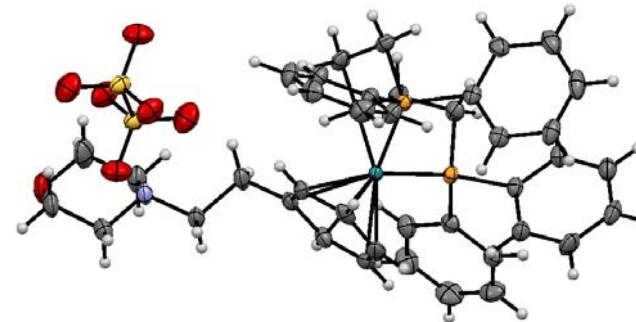
Development sequence: Palladium, Nickel, Iridium, Ruthenium, Tantalum*, Rhodium

Most first discovery in the synthesis Field



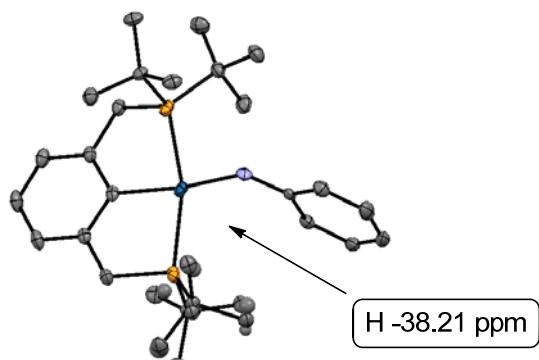
$[(\text{Xantphos})\text{Pd}(\eta^3\text{-allyl})]\text{Cl}$

Palladium mediated hydroamination



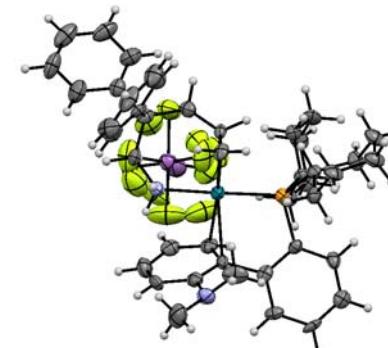
$[\text{Ru}(\eta^6\text{-arene})(\eta^3\text{-DPPPent})]\text{OTf}$

Ruthenium mediated hydroamination



$(\text{PCP})\text{IrH}(\text{NHPh})$

Ir mediated hydroamination



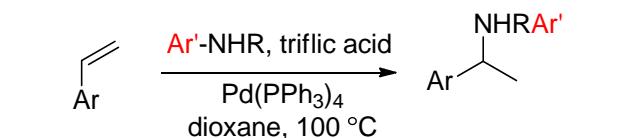
Rh complexed with Buchwald ligand and amido side chain

Ir mediated hydroamination

* It is hydroamidoalkylation of alkenes

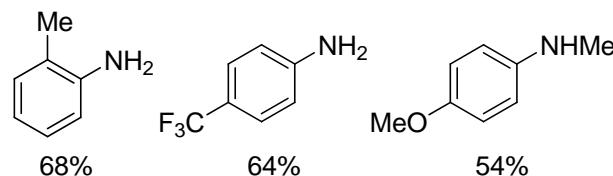
First Palladium Mediated Hydroamination

- Reaction:



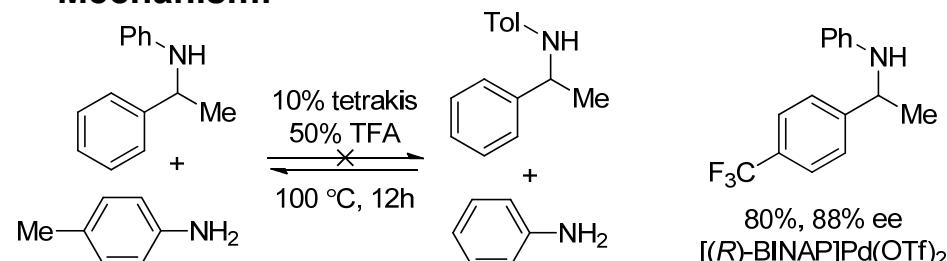
60%-99%
 80% in average

Notable subs:

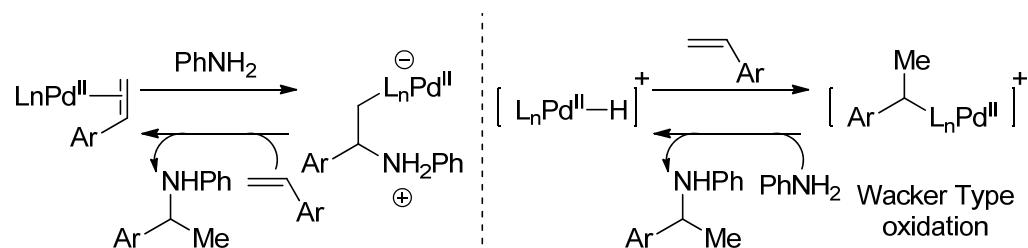


First Pd case; poor FG tolerance; poor subs scope

- Mechanism:

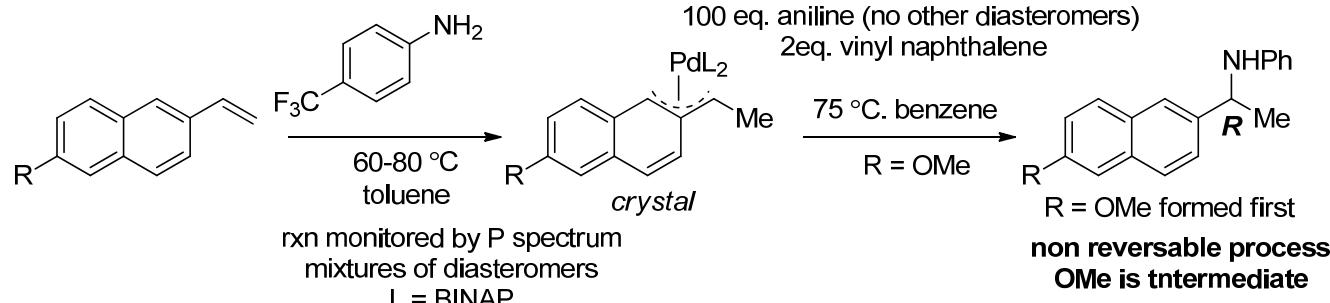


No alkyl exchange: enantioselective version possible



M. Kawatsura, J. F. Hartwig. *JACS* **2000**, 122, 9546..

- Further mechanism study:

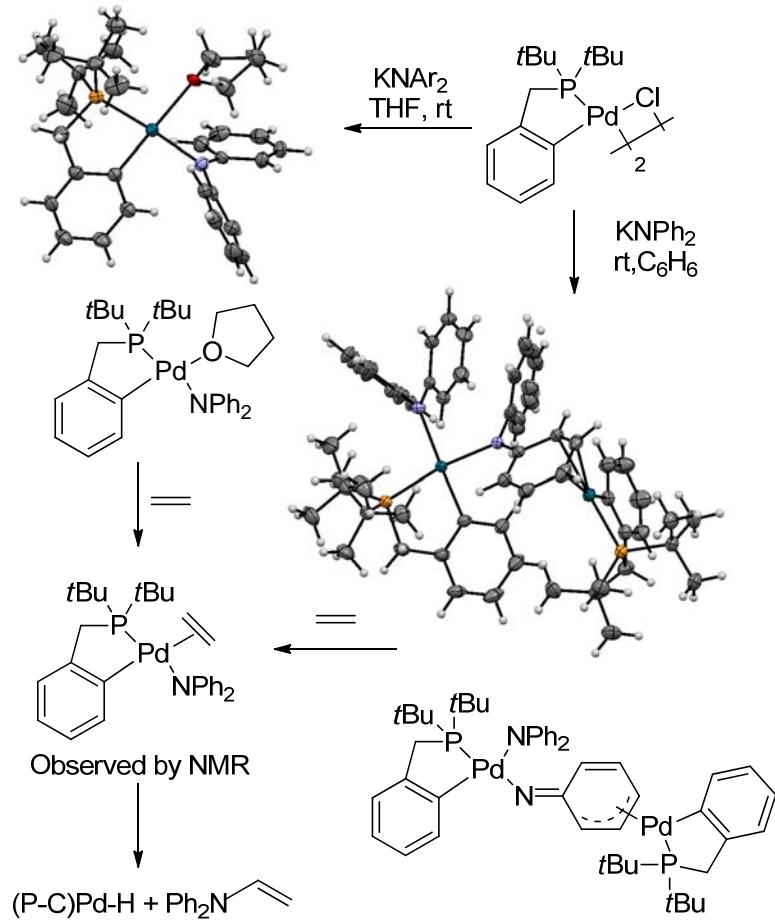
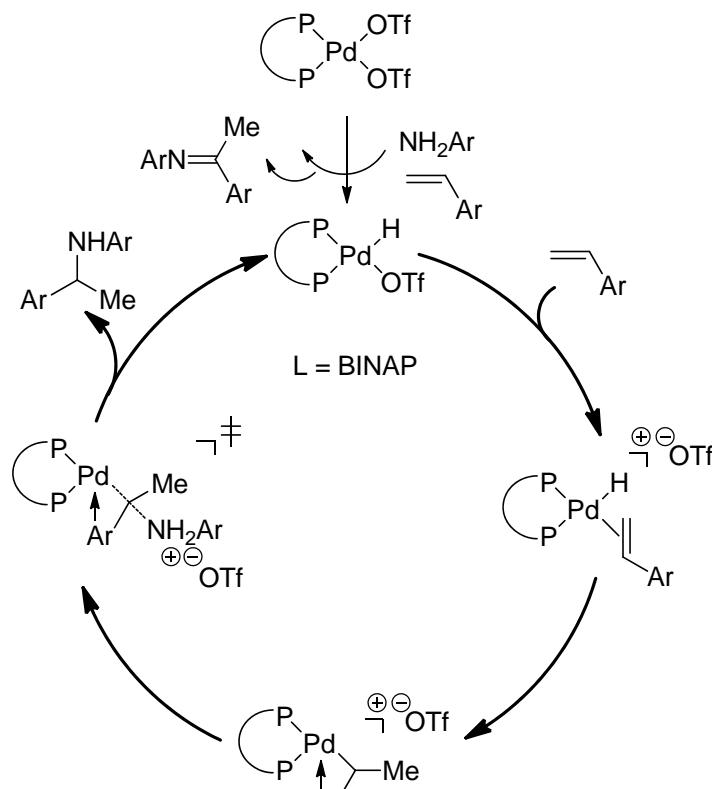


Final product R : stereo-inversion and external attack

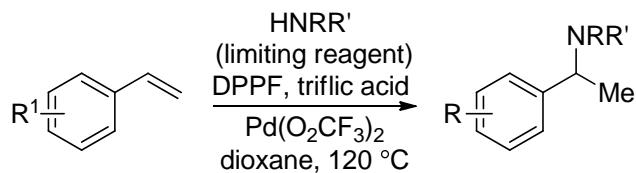
Kinetic measurement showed ergoneutral reaction which was exothermic but negative entropy

U. Nettekoven, J. F. Hartwig. *JACS* **2001**, 124, 1166;
 A. M. John, J. F. Hartwig. *JACS* **2006**, 128, 9306.

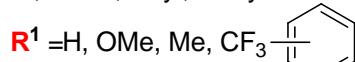
Mechanism Cycle



Intermolecular Hydroamination of Styrene and Dienes

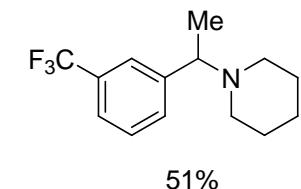
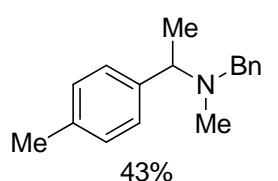
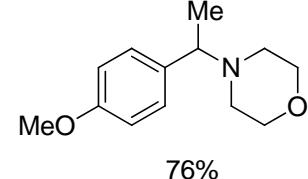
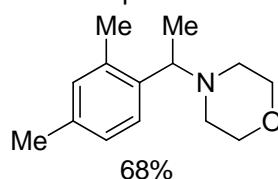


R, R'= H, alkyl,benzyl



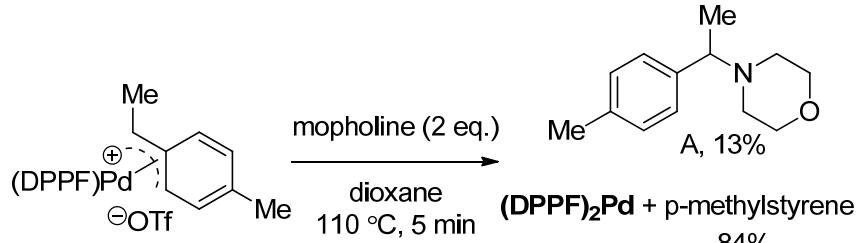
cat: Pd 10%, triflic acid 20%

Notable products:



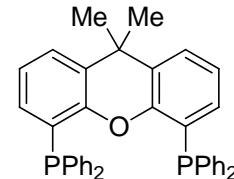
The first TS metal catalyzed alkylamine addition on alkene limited functional groups, limited amine source

Challenge: alkyl groups exchange between amine



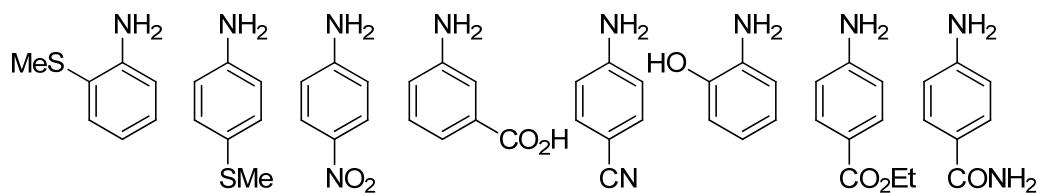
- added styrene, A still formed first- Pd complex in the cat. cycle
- reversible reaction, $(\text{DPPF})_2\text{Pd}$ is the true cat.

▪ Improvement:

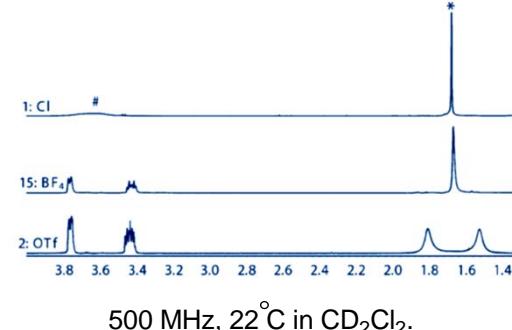
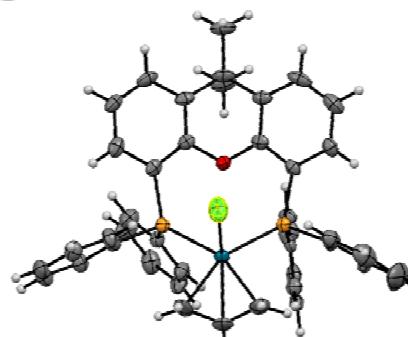


Improved condition: $[\text{Pd}(\eta^3\text{-allyl})\text{Cl}]_2$ 2% Xantphos

Representative amine: for both cyclohexadiene and styrene:



Advtg: Yield: 85% in average, impressive functional tolerance on EWG FG;
 Dsadvtg: only study cyclohexadiene and styrene.



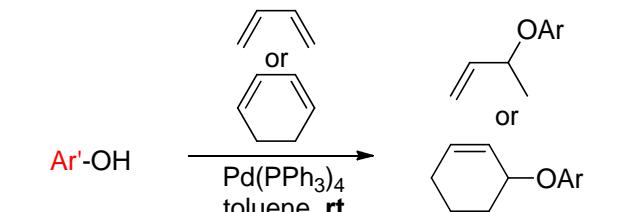
$[(\text{Xantphos})\text{Pd}(\eta^3\text{-allyl})]\text{Cl}$

Counterion effect

M. Utsunomiya, J. F. Hartwig. *JACS* **2003**, 125, 14286;
 A. M. Johns, J. F. Hartwig. *JACS* **2006**, 128, 1828.

Miscellaneous Reactions-1

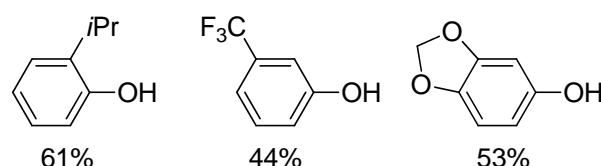
▪ **Dienes:**



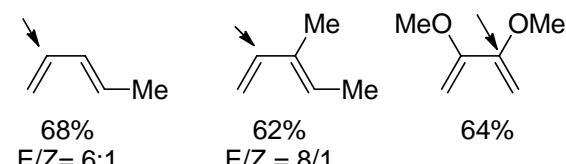
Ar = H, OMe, Me, Cl

tetrakis 1%

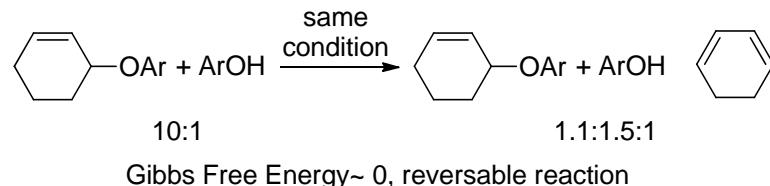
when cyclohexadiene:



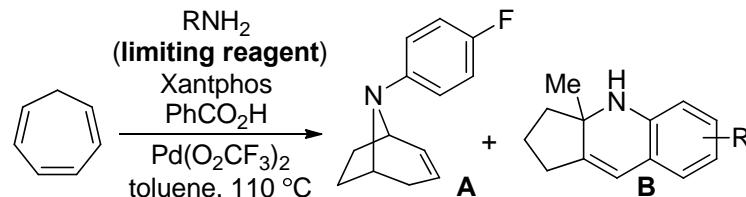
when 4-tertbutylphenol:



limited scope, mild condition, limited yield



▪ **Trienes:**



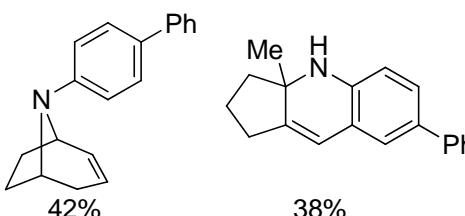
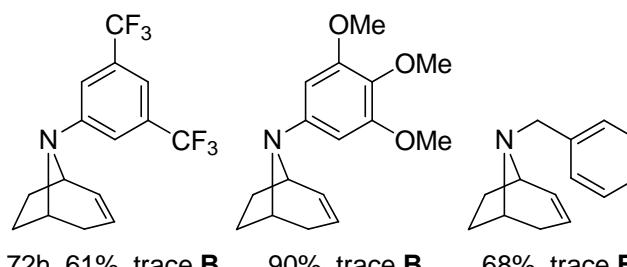
R' = CN, Me, OMe, F, CO₂Et, CF₃

cat: Pd 2%. Xantphos 4%

mechanism!

- A 60% in average
- B 20% in average

Notable subs:

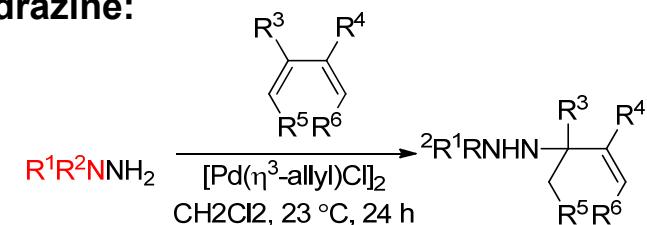


Limited triene scope, **A** cannot transfer to **B** under the condition

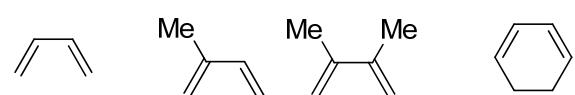
mechanism of the reaction

Miscellaneous Reactions-2

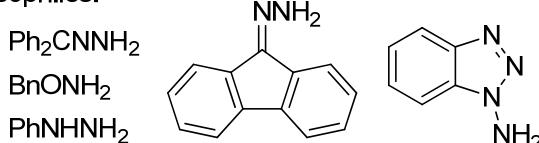
▪ Hydrazine:



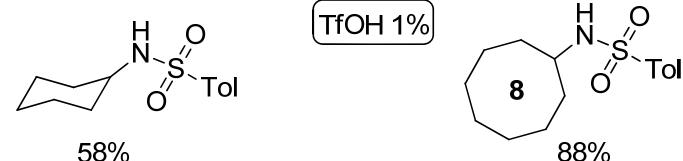
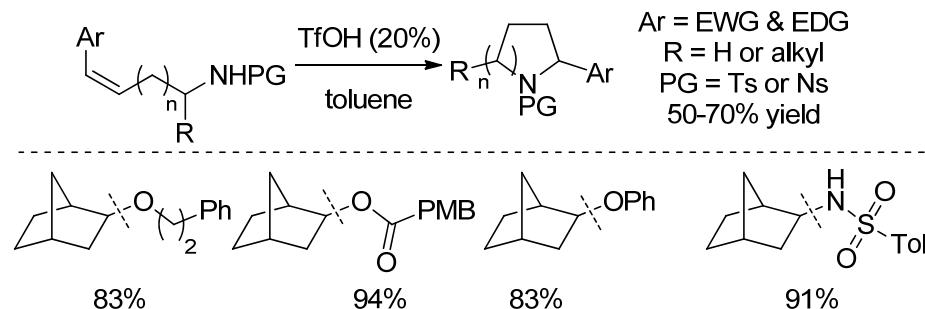
dienes:



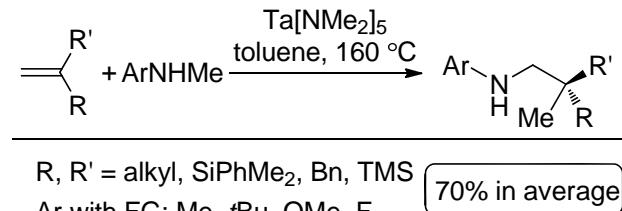
Nucleophiles:



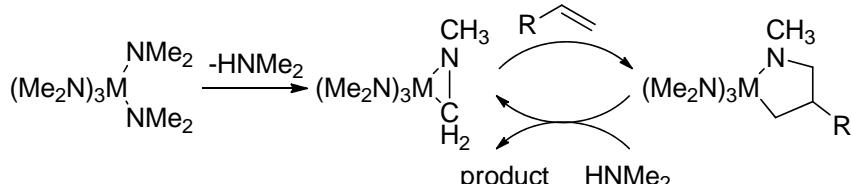
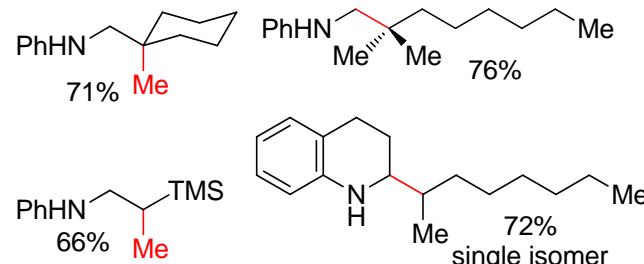
▪ Bronsted Acid catalyzed hydroamination:



▪ Amidoalkylation:

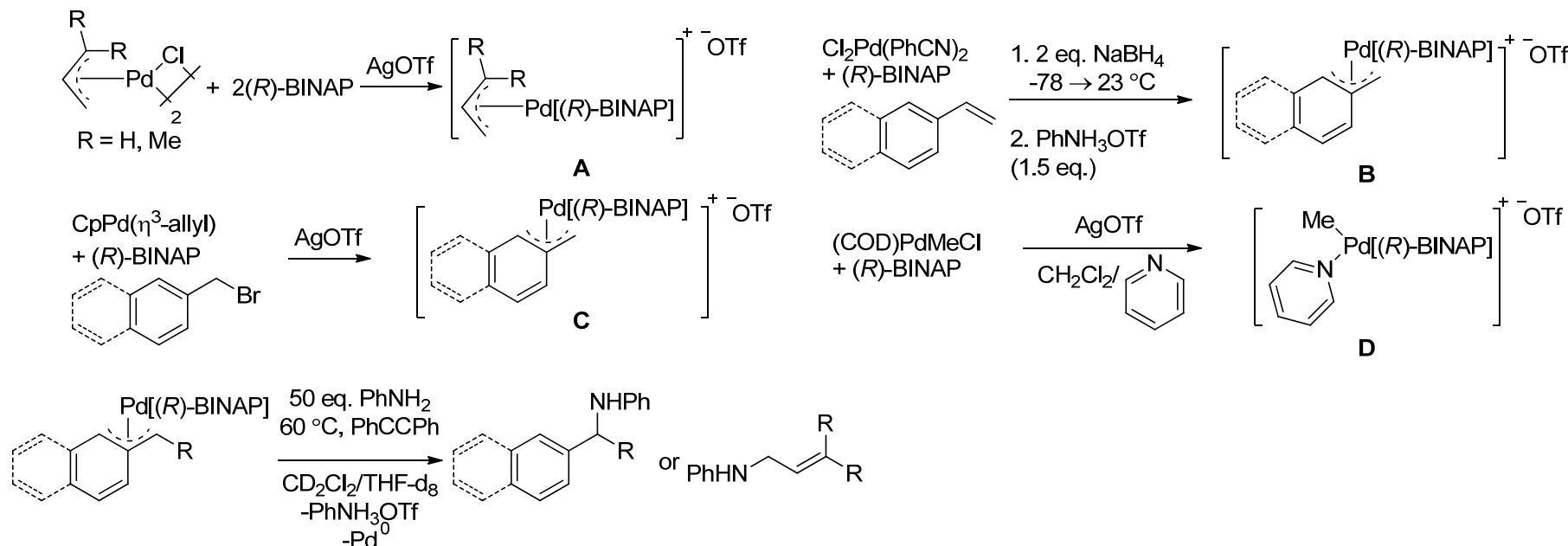


Representative products:



- A. M. Johns, J. F. Hartwig. *Angew* **2007**, 46, 7259.
B. Schlummer, J. F. Hartwig. *OL* **2002**, 4, 1471.
D. C. Rosenfeld, J. F. Hartwig. *OL* **2006**, 8, 4179.

Relative Rates for the Amination of Pd Complexes

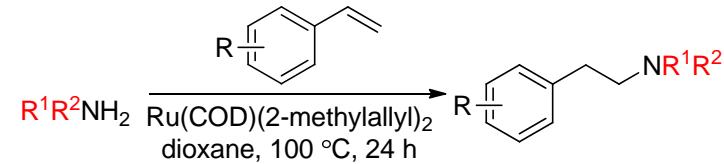


entry	η^3 electrophile	$t_{1/2}$ (min) ^b	$k_{\text{obs}} (\text{s}^{-1}) \times 10^3$ ^b
1		11	1.0
2		42 (15)	0.27 (0.79)
3		185 (159)	0.062 (0.072)
4		570 (7.1)	0.020 (1.63)
5		2200 (250)	0.0052 (0.046)

Conclusion: amine addition faster on η^3 -benzyl complex than η^3 -allyl complex

Ru Mediated Hydroamination of Alkenes

- First Anti Markovnikov hydroamination:

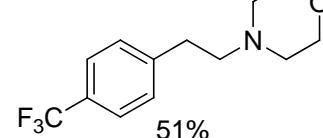
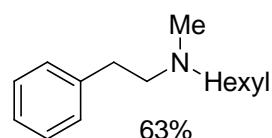
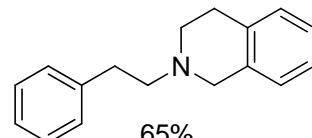
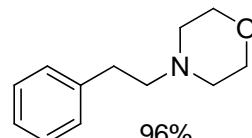


$\text{R}'\text{R}''\text{NH}_2$ = Most cyclic sec-amine

70% in general

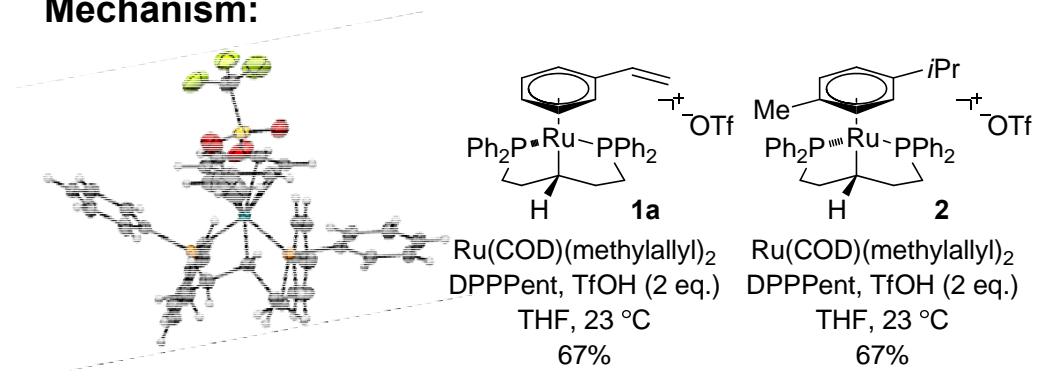
$\text{R} = \text{Me, OMe, CF}_3$

Representative results:

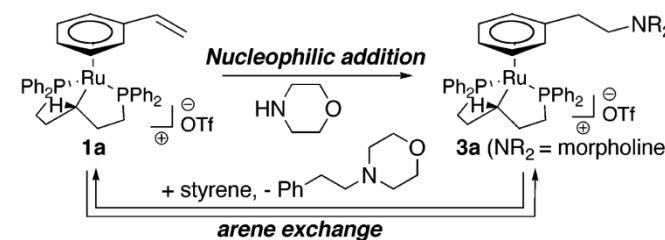


Ad: First Ru mediated hydroamination
Most for electron neutral and rich arenes;
yield was limited, most for sec-amine
Functional groups limitation
Only know the reaction was not reversible

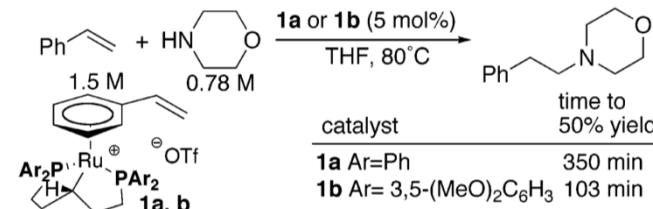
- Mechanism:



	1.5 M	0.78 M	catalyst	dioxane	100 °C	yield ^a	2h	5h
1a (5 mol%)						22%	40%	64%
2 (5 mol%)						10%	32%	56%
in situ ^b						9%	18%	40%



- Design:

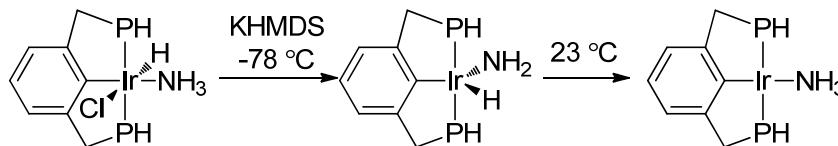


M. Utsunomiya, J. F. Hartwig. *JACS* **2004**, 126, 2702.

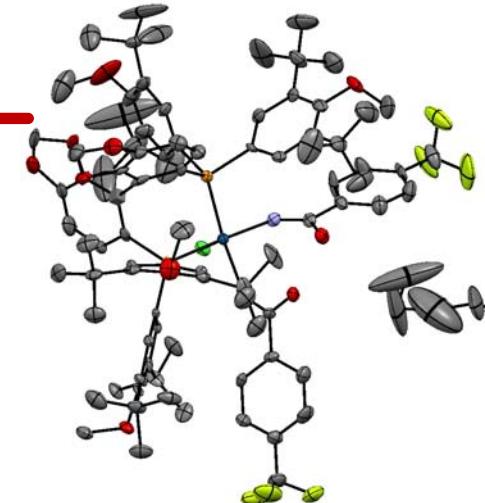
J. Takaya, J. F. Hartwig. *JACS* **2005**, 127, 5756.

Iridium Mediated Hydroamination

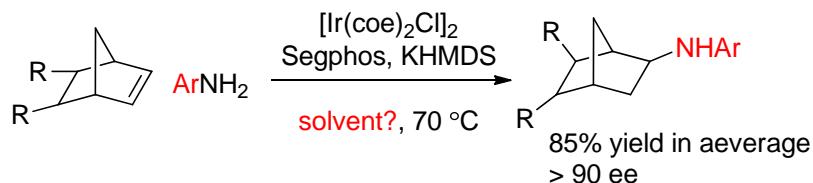
- Amazing observation:



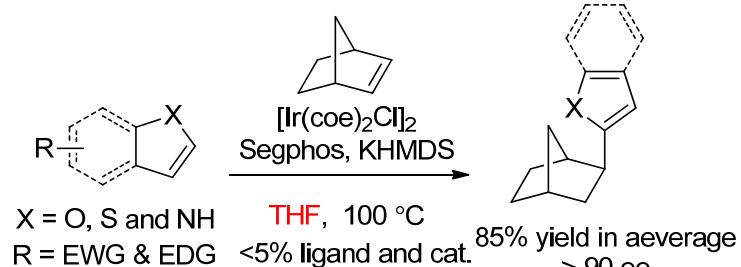
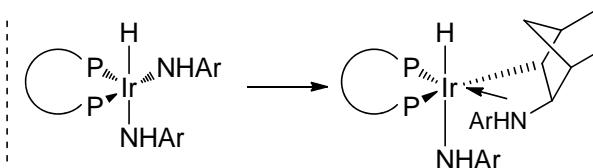
Stability of Iridium amido hydride complex



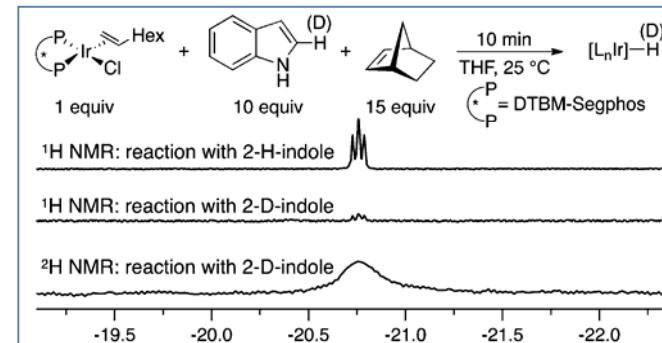
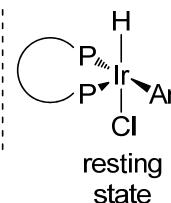
Stronger ionic component in Ir-N bond and to pπ-dπ bond (Just pKa)



very limited dienes
three dienes
8 examples
Ar with EDG & EWG

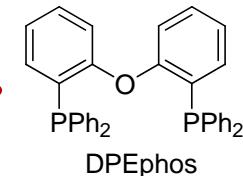


New type of reaction, still very limited on alkenes
broad scope and FG tolerance, good ee and yield

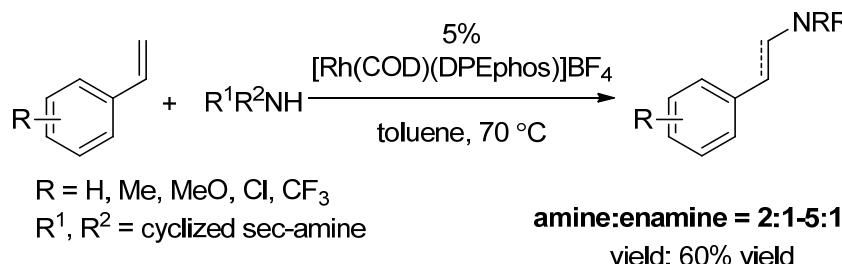


- M. Kanzelberger, J. F. Hartwig. *JACS* **2003**, 125, 13644.
 J. Zhou, J. F. Hartwig. *JACS* **2008**, 132, 12220;
 C. S. Sevov, J. F. Hartwig. *JACS* **2012**, 134, 11960.
 C. S. Sevov, J. F. Hartwig. *JACS* **2013**, 135, 2116.

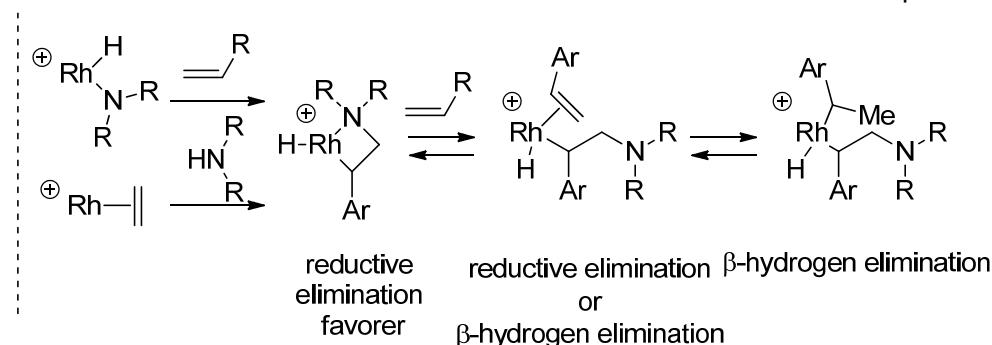
Rhodium Mediated Hydroamination of Alkenes



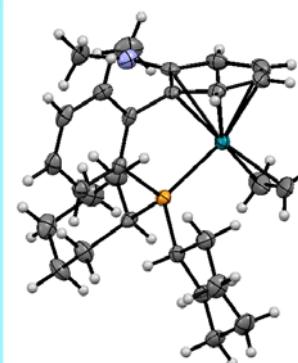
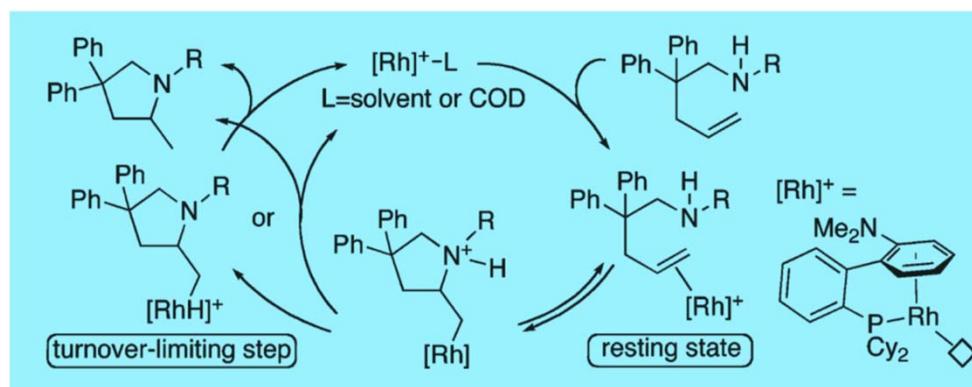
- Anti Markovnikov hydroamination:



Leshatelie principle: preadded enamine did not change the ratio
two product formed in parallel



Intramolecular hydroamination of terminal alkenes: with Buchwald's ligand

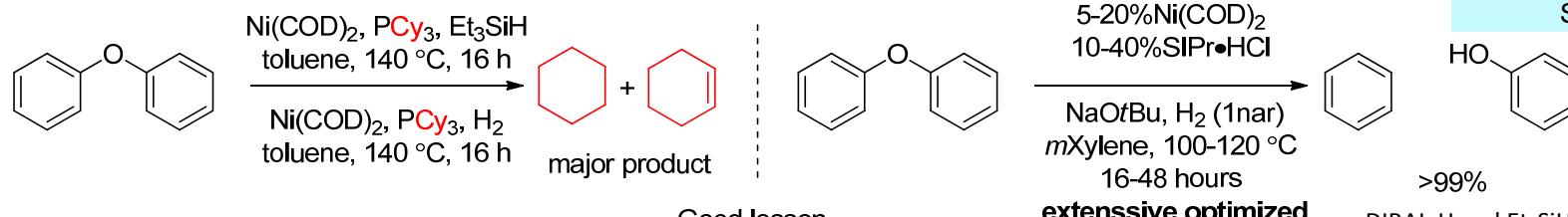


- M. Utsunomiya, J. F. Hartwig. *JACS* **2003**, 125, 5608.
Z. Liu, J. F. Hartwig. *JACS* **2008**, 130, 1570.
L. D. Julian, J. F. Hartwig. *JACS* **2010**, 132, 13813.
Z. Liu, J. F. Hartwig. *JACS* **2011**, 133, 2772.

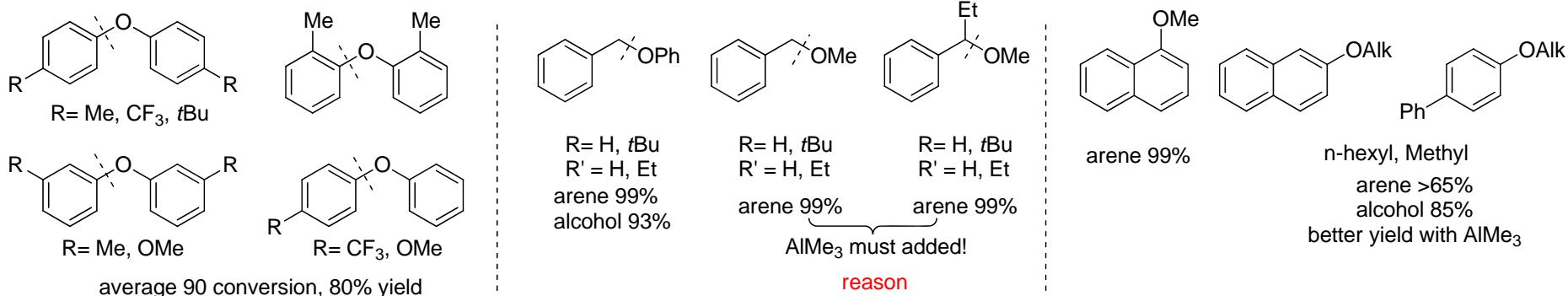
Part 5: Nickel-Catalyzed Hydrogenolysis of Aryl Ethers

- An existing problem to hydrolyze the ether bond:

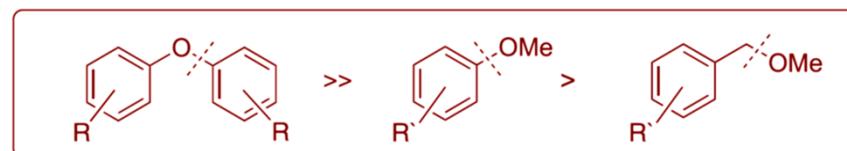
Idea from: Cleavage the C-O bond in brown coal for fuel



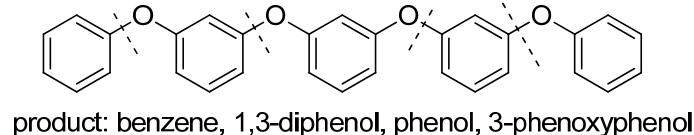
- Application:



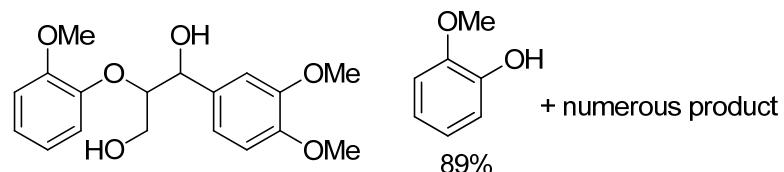
- Reactivity Comparison:



2012 JACS: Heterogeneous Ni cat. and lower loading
Advantage/Disadvantage?



product: benzene, 1,3-diphenol, phenol, 3-phenoxyphenol



A. G. Sergeev, J. F. Hartwig. *Science* **2011**, 332, 439;
A. G. Sergeev, J. F. Hartwig. *JACS*. **2012**, 134, 20226.

-End-

Fluorescence-Based Assay for Arylation Chemistry

