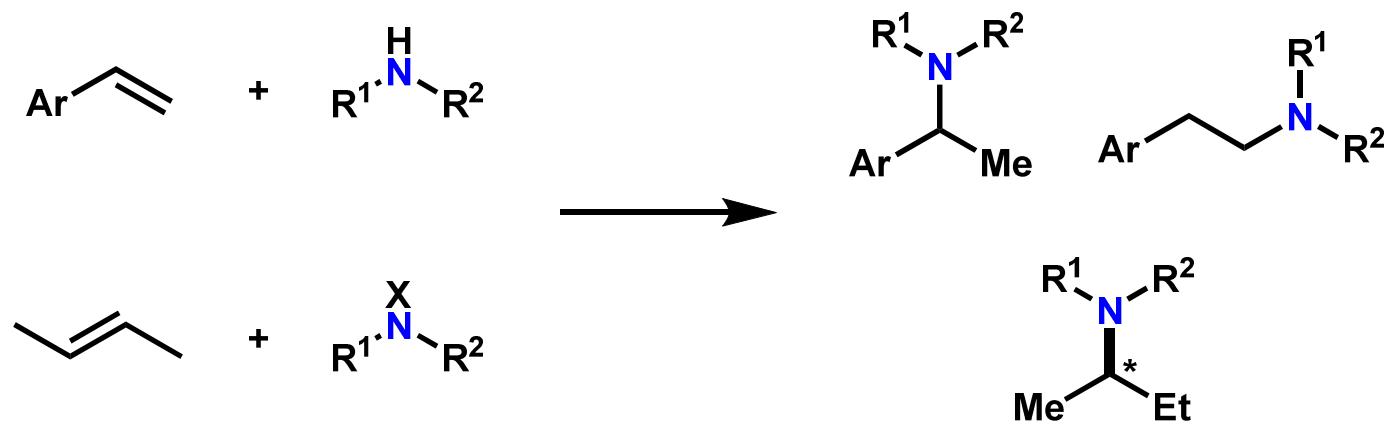


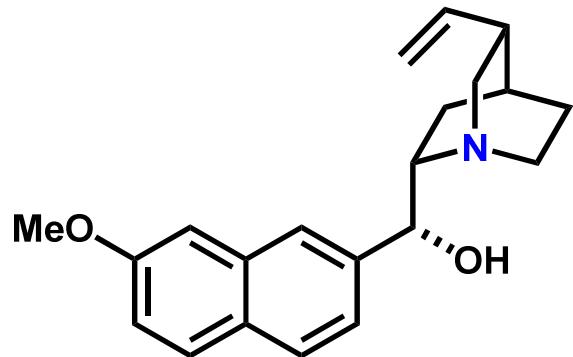
Hydroamination



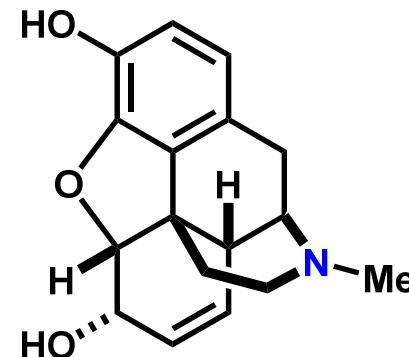
Literature Seminar 2016. 5. 14

Akinori Yamaguchi

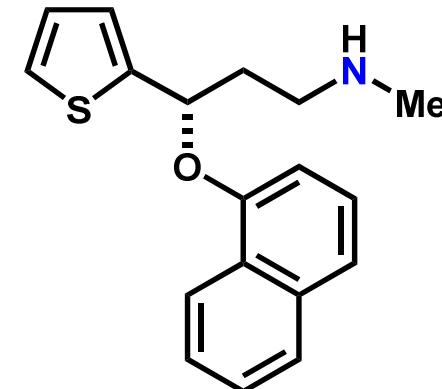
Amines in Biologically Active Molecules



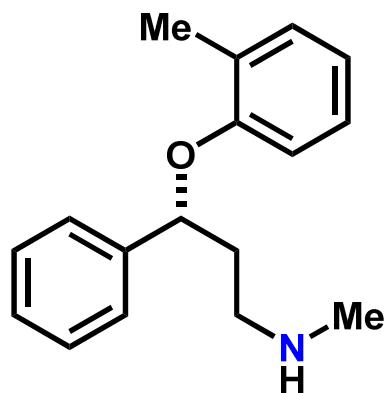
Quinine
(malaria)



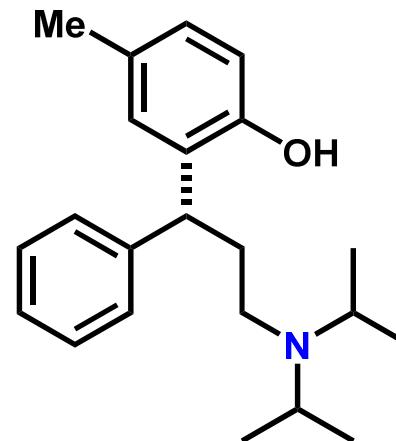
Morphine
(pain)



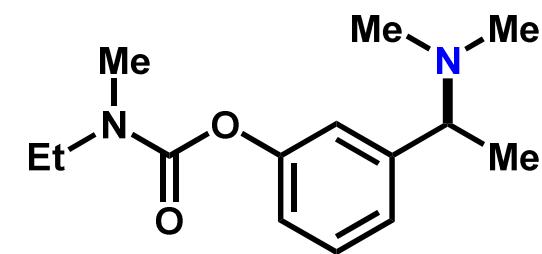
Duloxetine
(depression)



Atomoxetine
(depression)



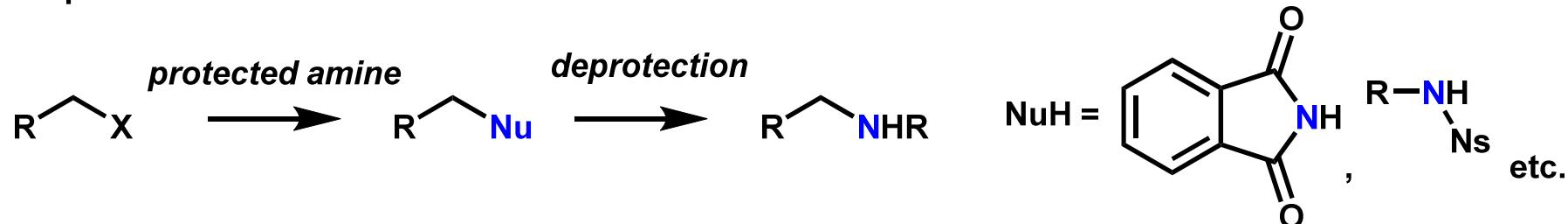
Tolterodine
(urinary disorders)



Rivastigmine
(dementia)

Strategies for Amine Synthesis

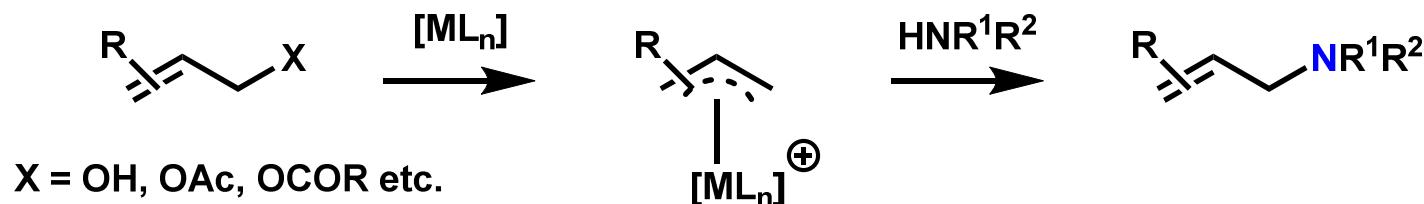
Nucleophilic substitution



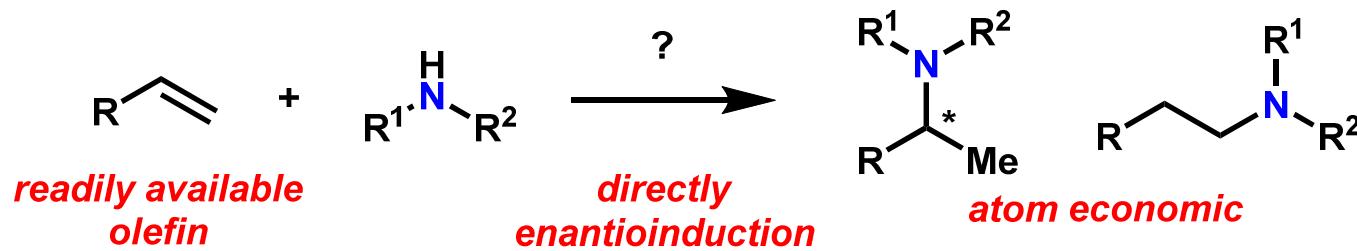
Reductive amination



Transition metal-catalyzed allylic substitution



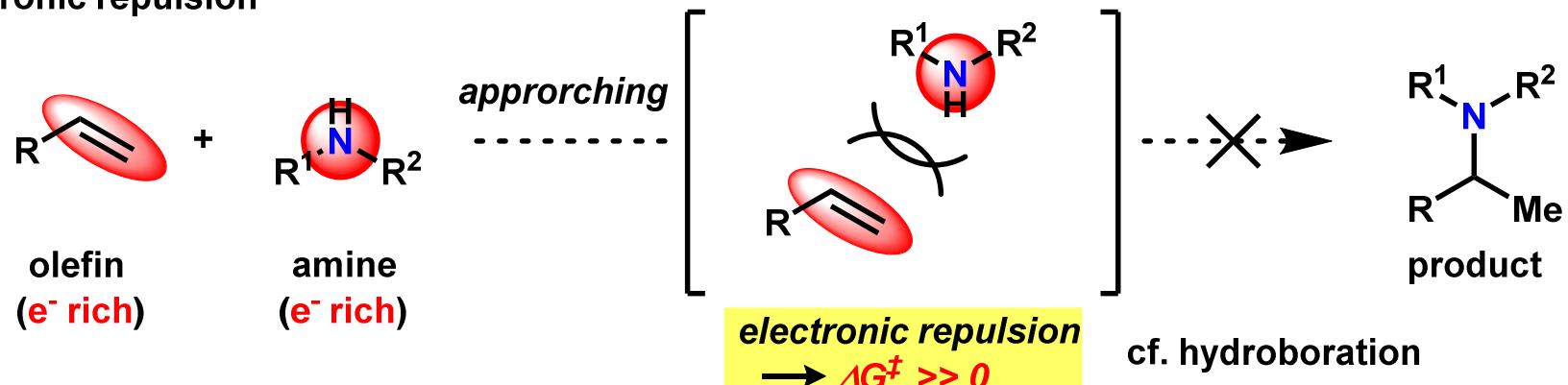
Hydroamination: direct addition of amines to alkenes



1) Kan, T.; Fukuyama, T. *Chem. Commun.* 2004, 353.

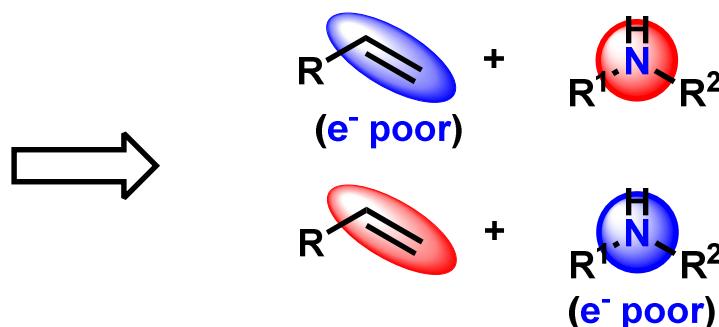
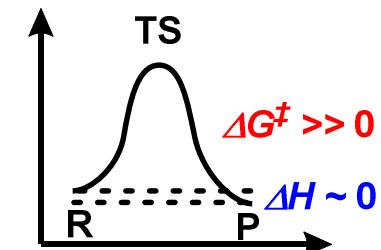
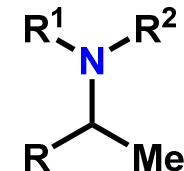
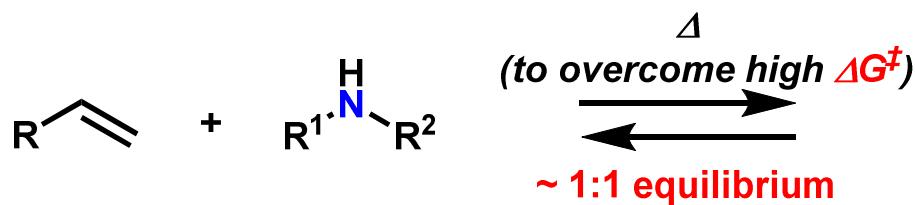
The Challenge for Hydroamination

Electronic repulsion

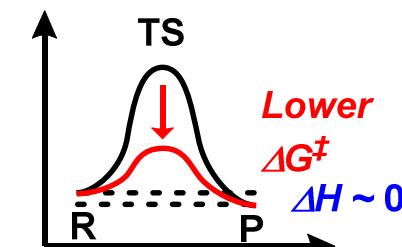


Dilemma in using high temperatures

for most hydroamination ... $\Delta H \sim 0$ kcal/mol



Reverse reactivity

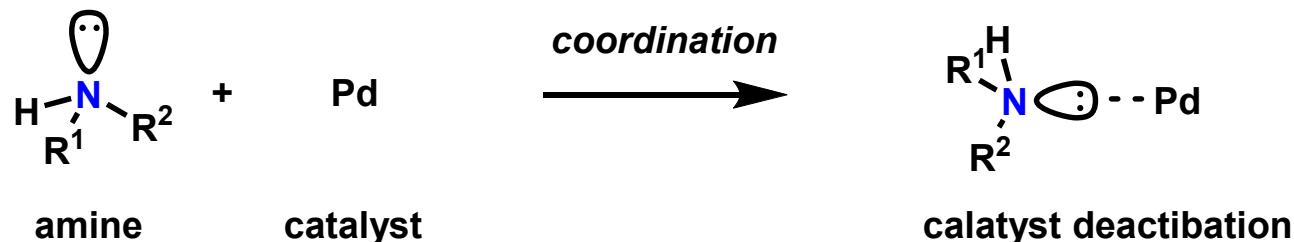


Efficient catalyst

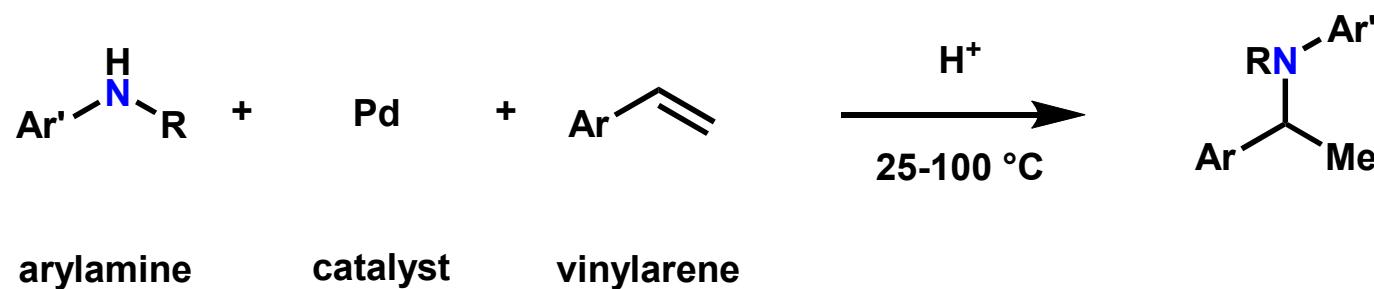
1) Brunet, J. J.; Neibecker, D.; Niedercorn, F. J. Mol. Catal. **1989**, 49, 235.

Late Transition Metal Catalysts

Catalyst deactivation

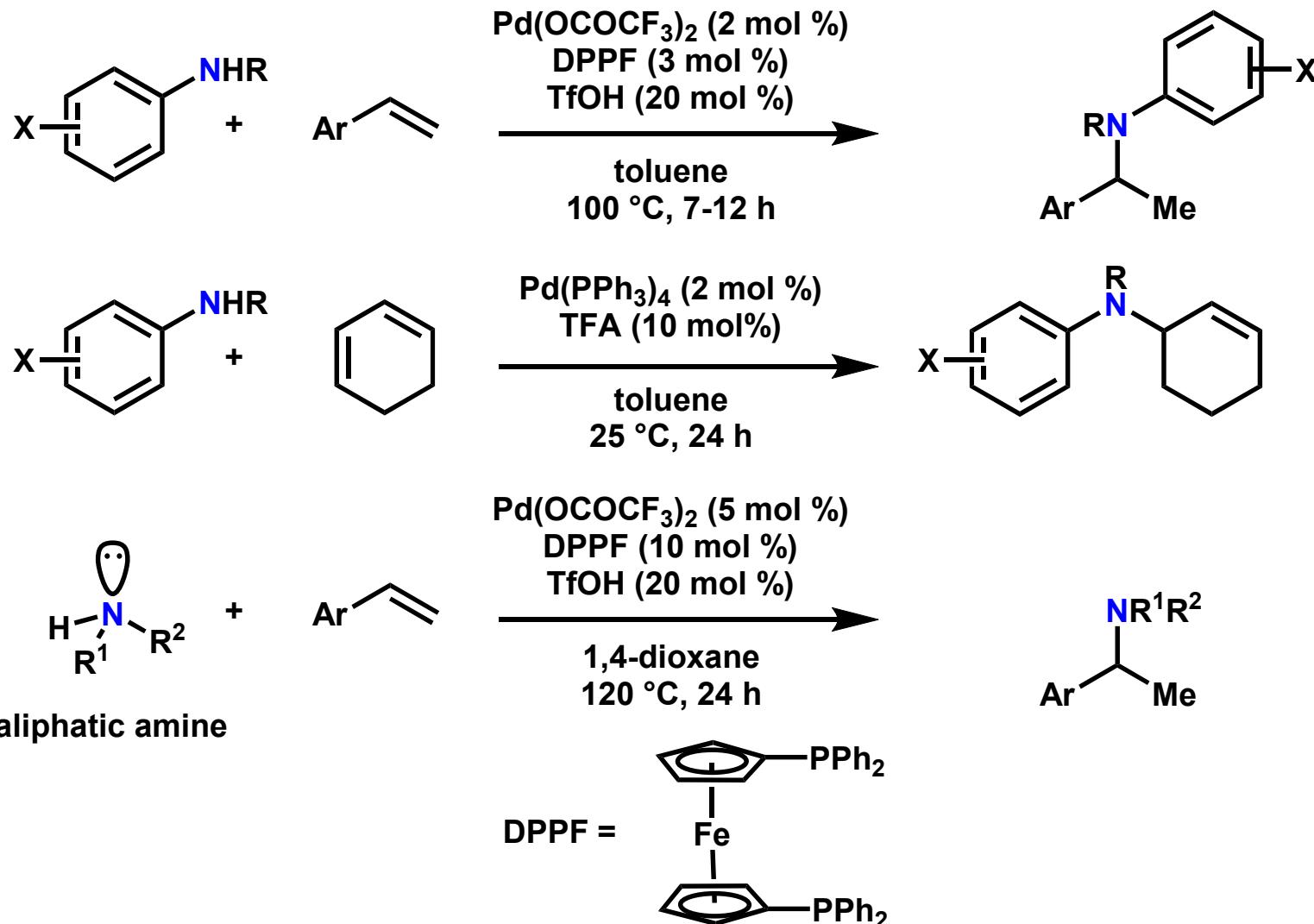


With Brønsted acid cocatalyst



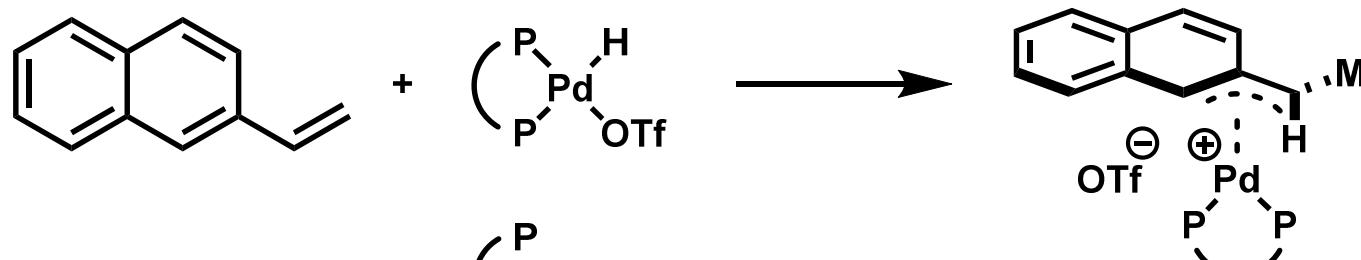
1) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 9546.

Intermolecular, Markovnikov Hydroamination



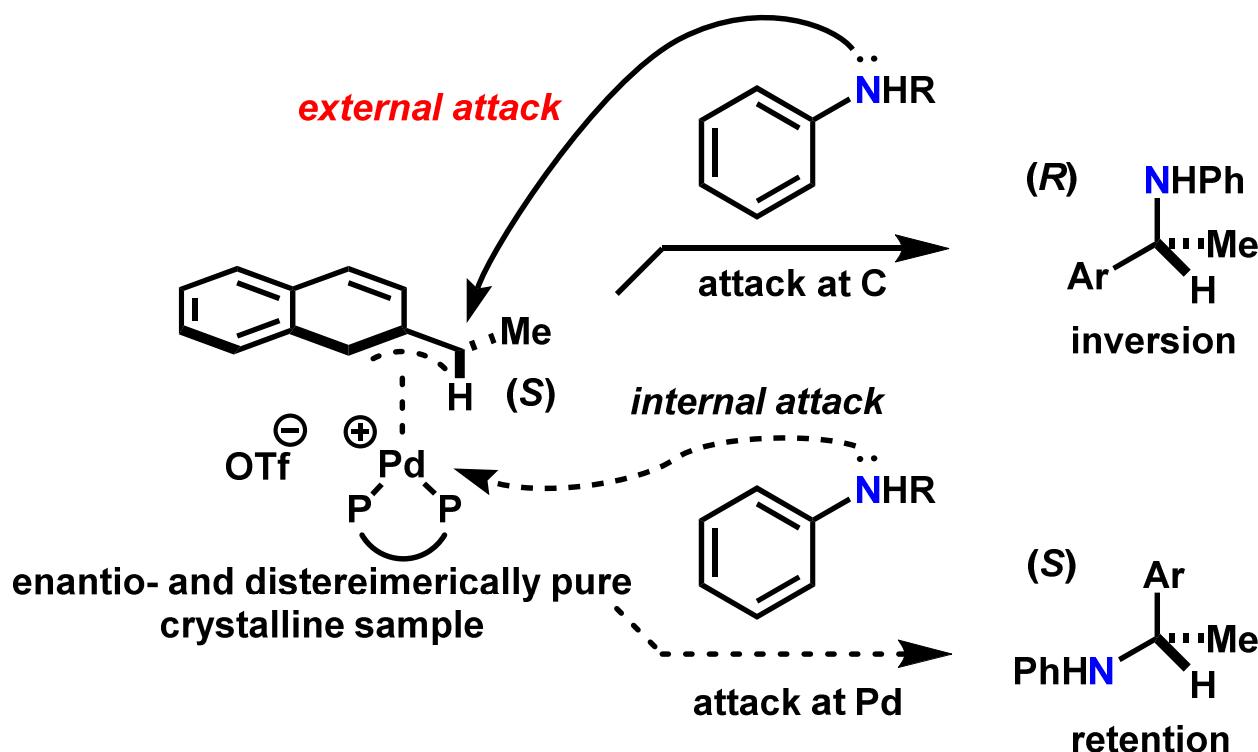
- 1) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 9546.
- 2) Lober, O.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 4366.
- 3) Pawlas, J.; Nakao, Y.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 3669.

Mechanistic Study



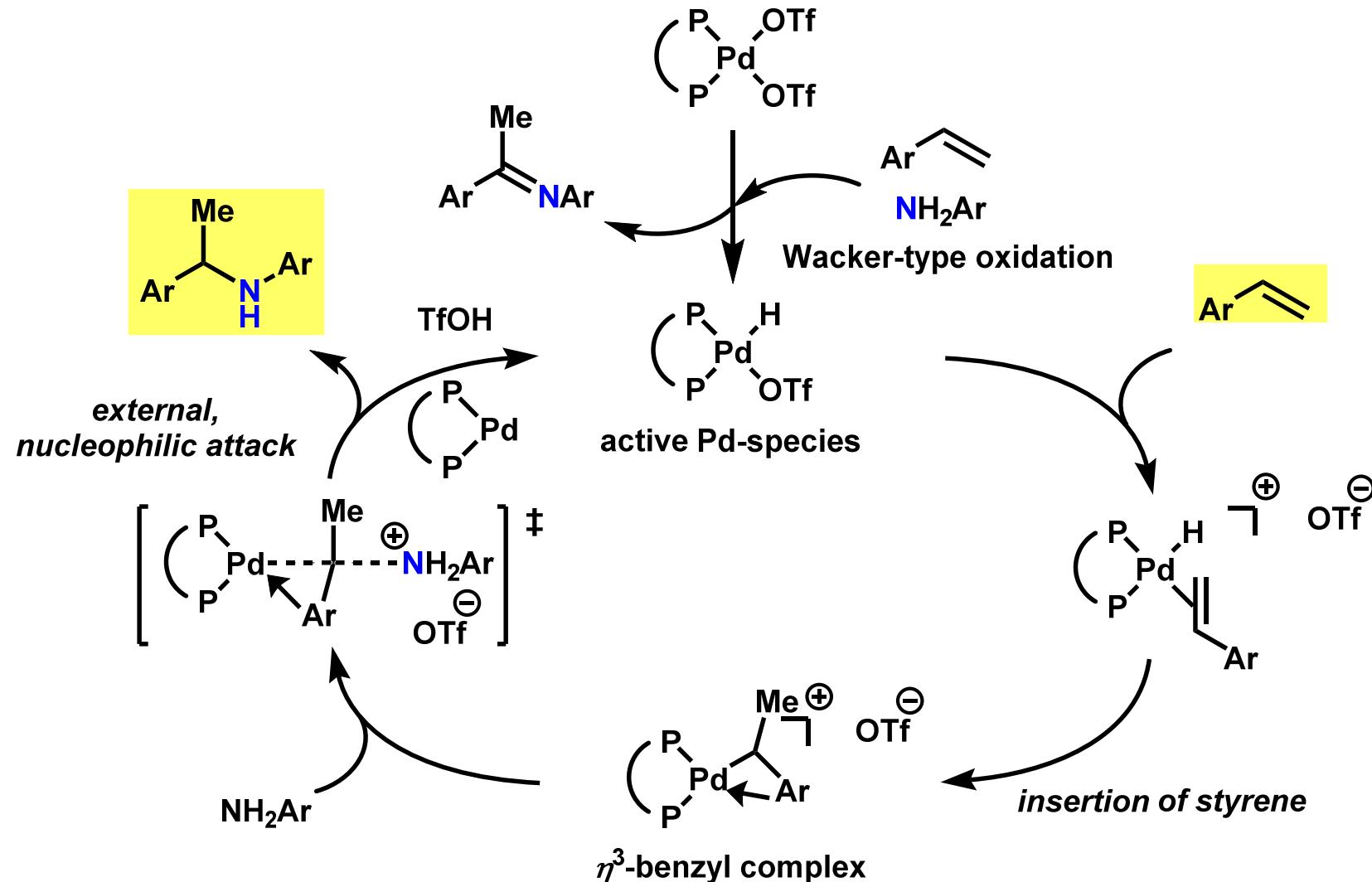
$\text{P} \quad \text{P}$
= *(R)*-tol-BINAP

isolated η^3 -benzyl complex
(one diastereomer)



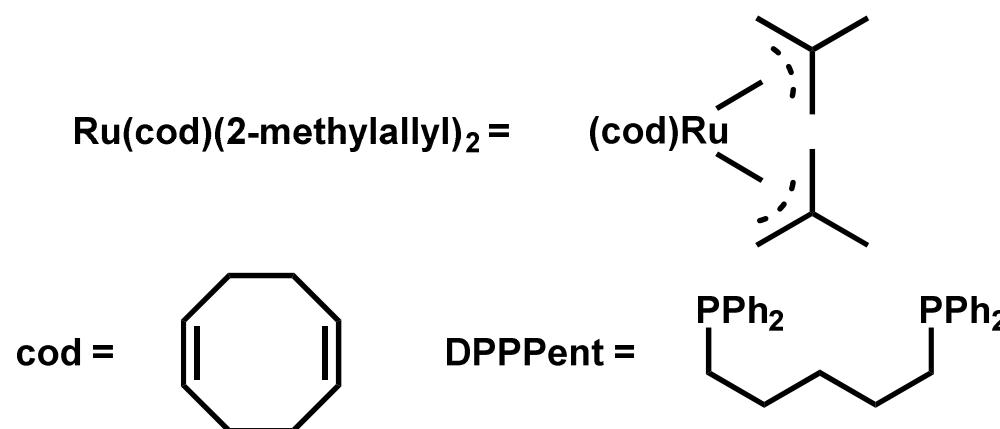
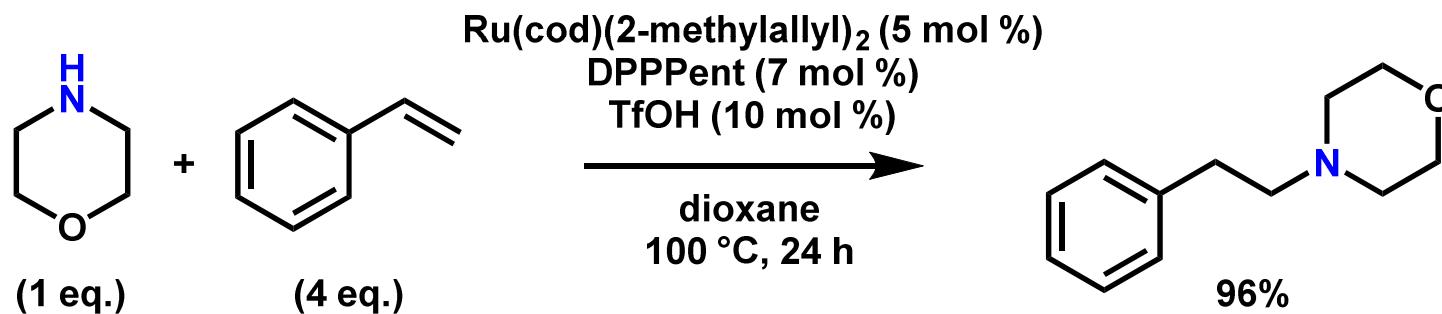
1) Nettekoven, U.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 1166.

Proposed Mechanism



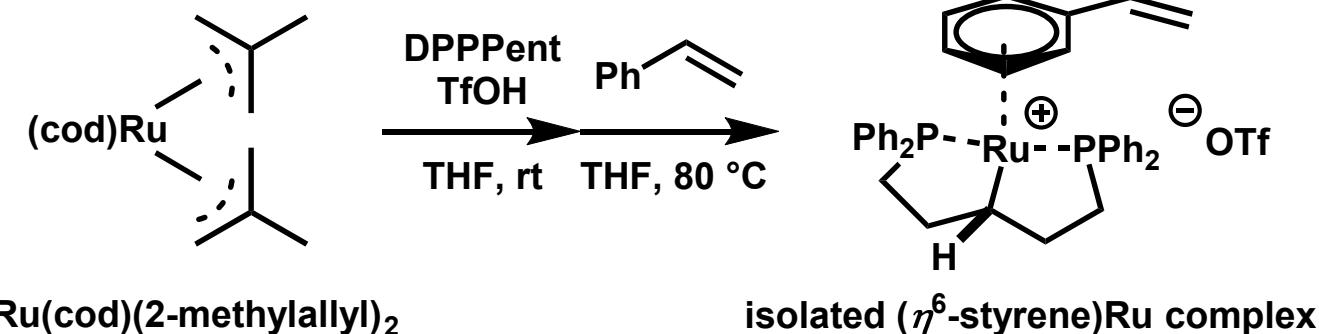
1) Nettekoven, U.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 1166.

Discovery of Anti-Markovnikov Hydroamination

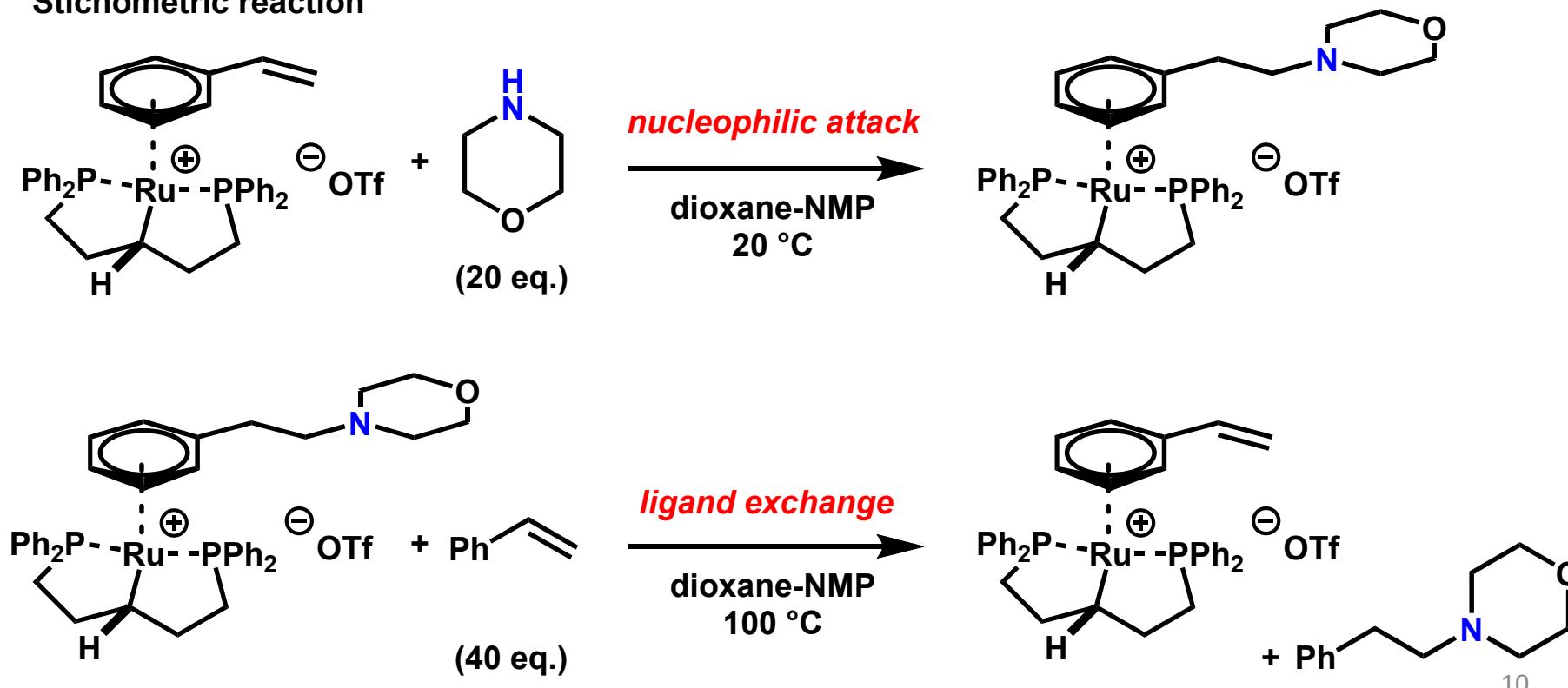


1) Utsunomiya, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *126*, 5608.

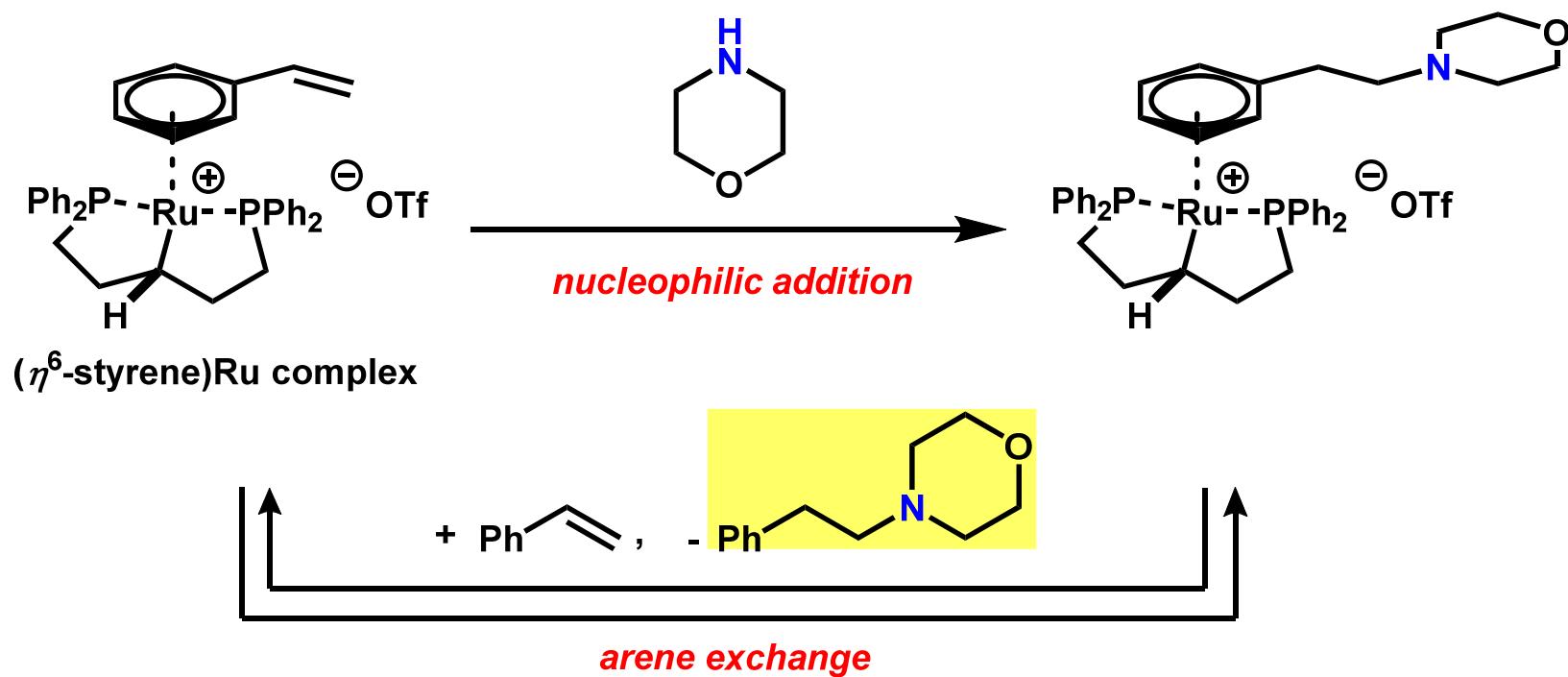
Mechanistic Study



Stichometric reaction

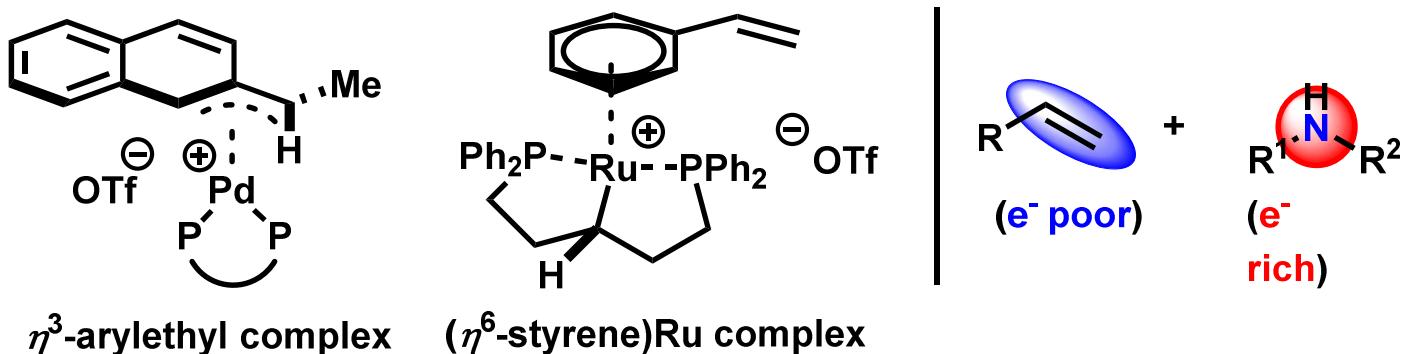


Proposed Reaction Mechanism



Limitation: Narrow Substrate Scope

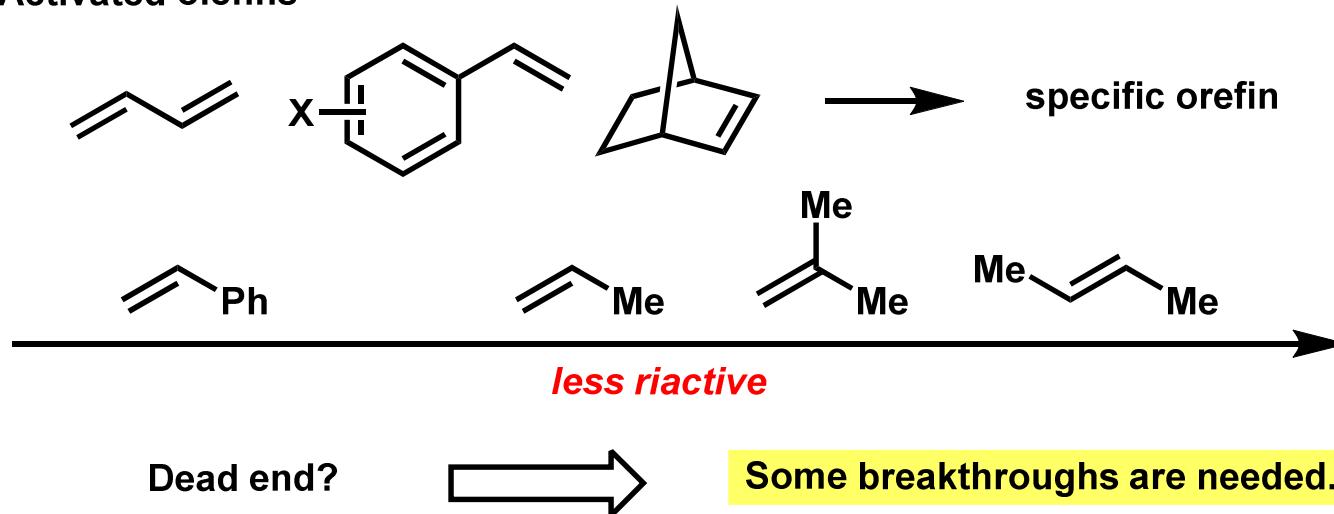
Powerful activation of activated olefin



- Late transition metals for activation

Pd, Ni, Ir, Ru, Rh ... \longrightarrow incompatibility

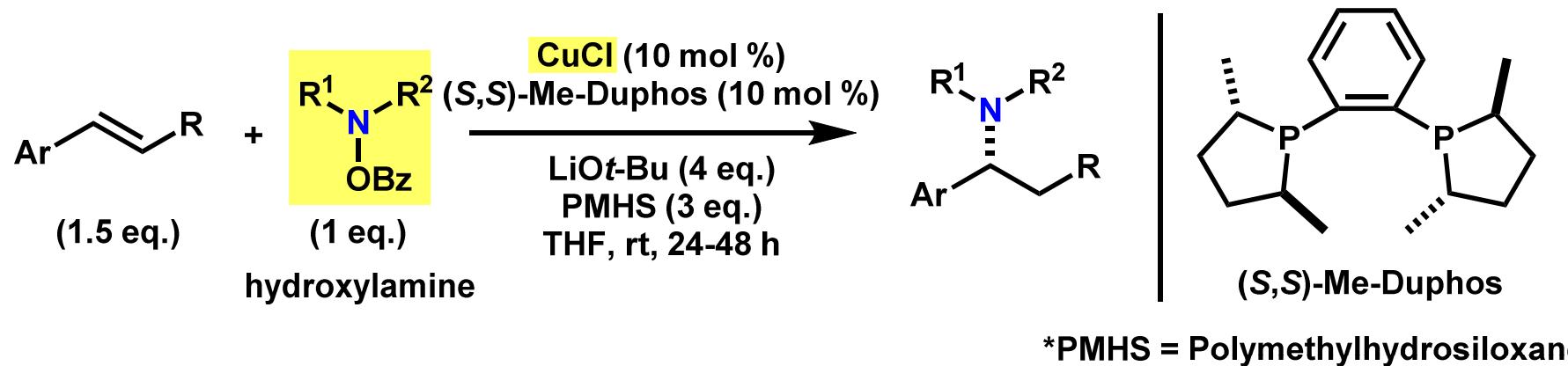
- Activated olefins



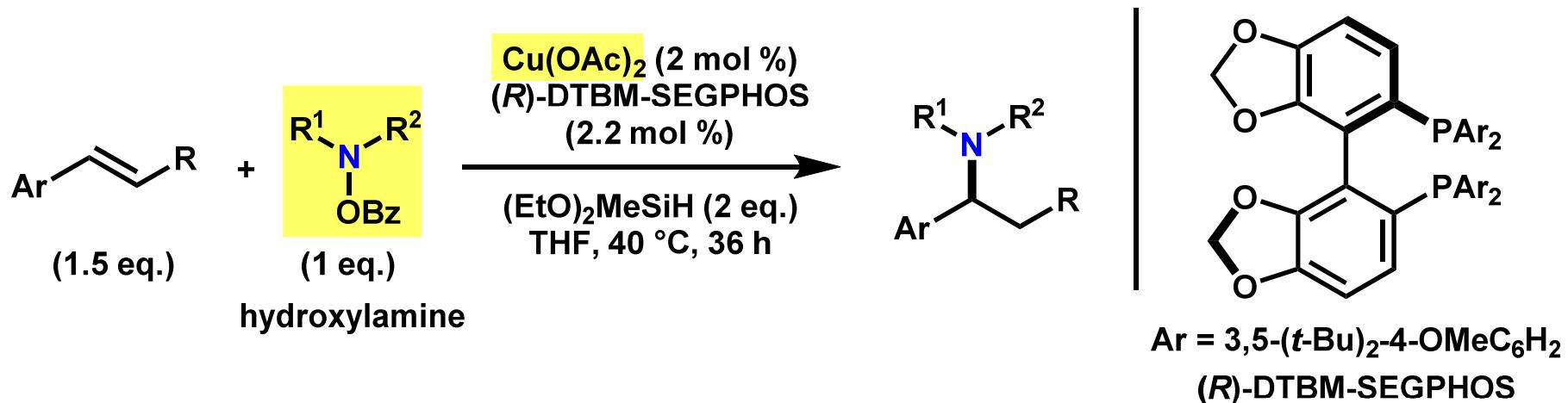
1) Hannedouche, J.; Schulz, E. *Chem. Eur. J.* **2013**, *19*, 4972.

Initial Discovery of CuH-Catalyzed Hydroamination

(a) Miki, Y.; Hirano, K.; Sato, T.; Miura, M. *Angew. Chem. Int. Ed.* **2013**, 52, 10830.

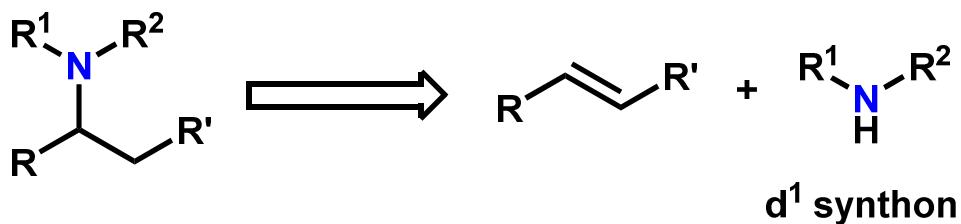


(b) Zhu, S.; NiljianSkul, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2013**, 135, 15746.

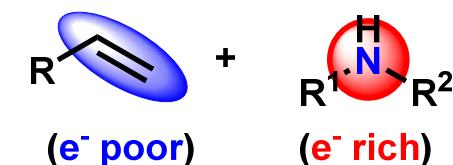


Novel Mechanistic Approach to Hydroamination

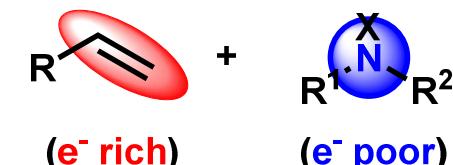
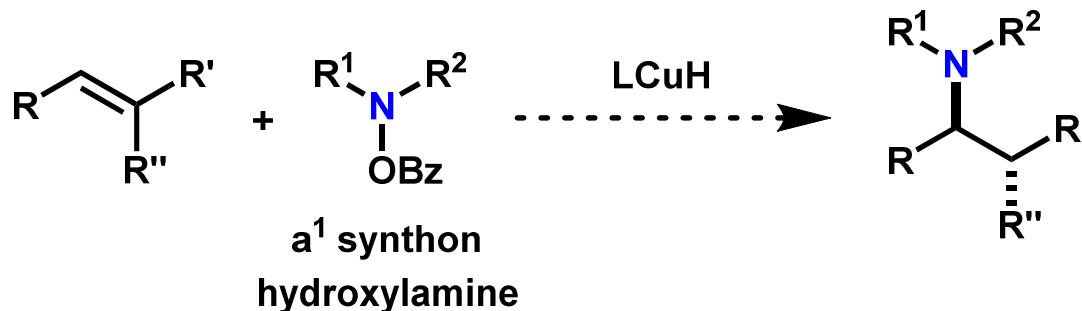
Traditional Approach



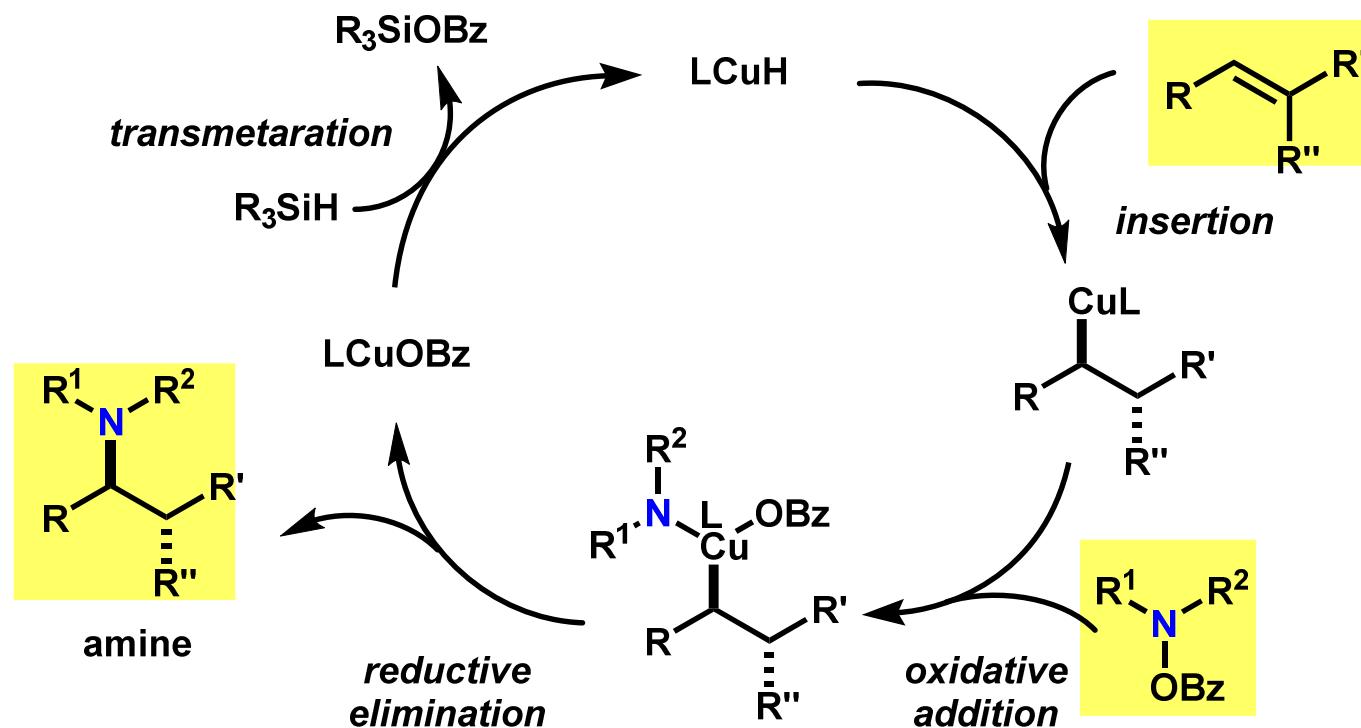
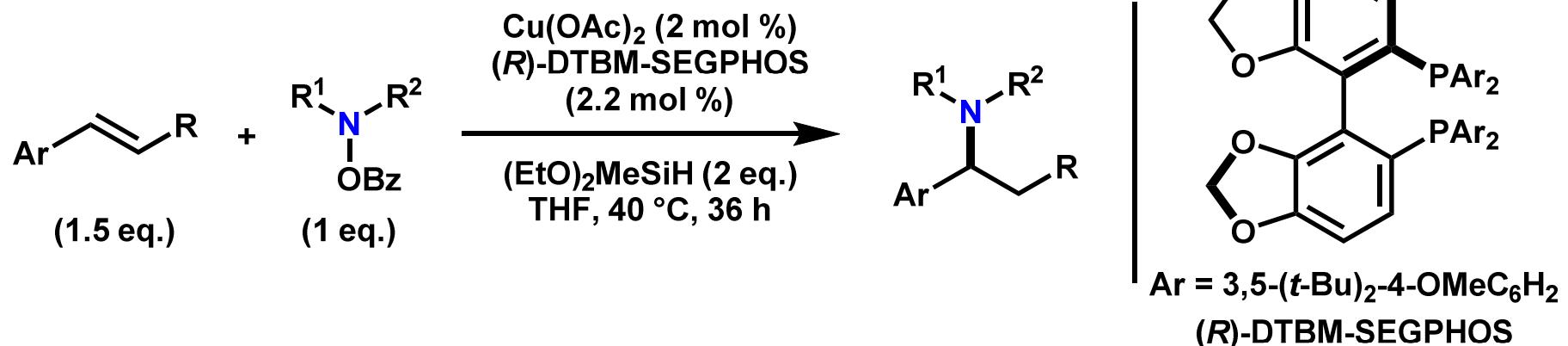
activation



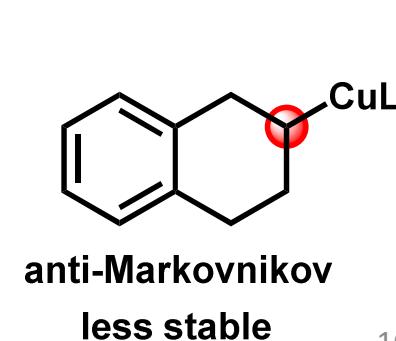
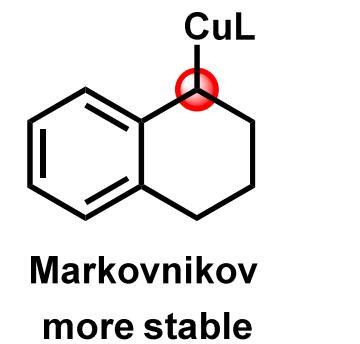
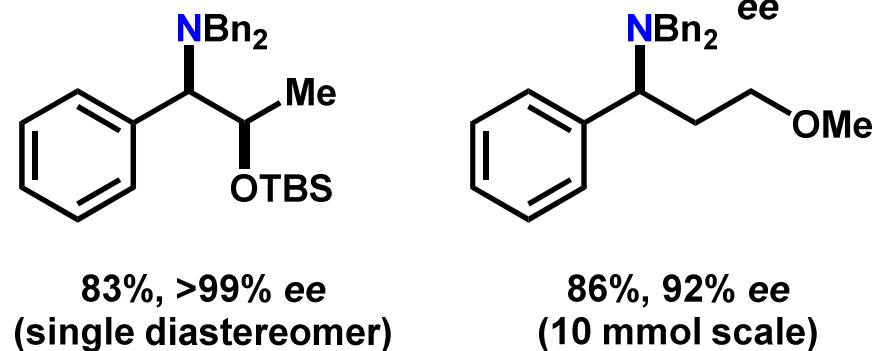
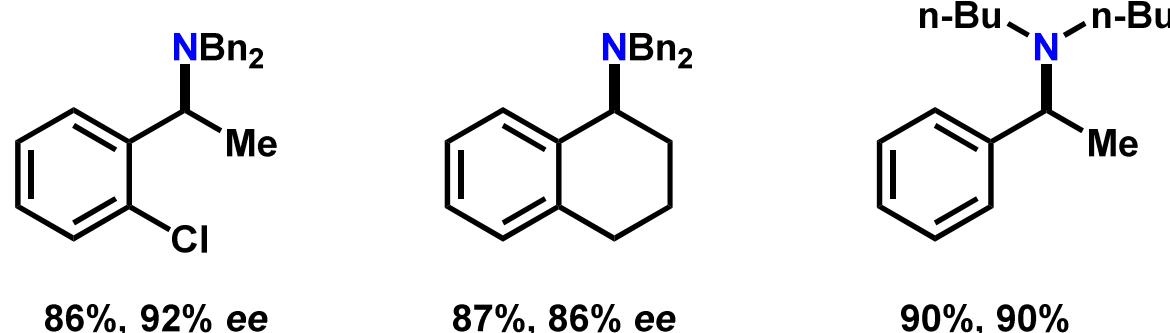
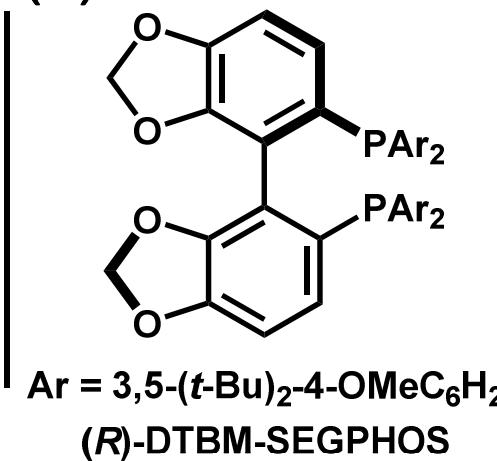
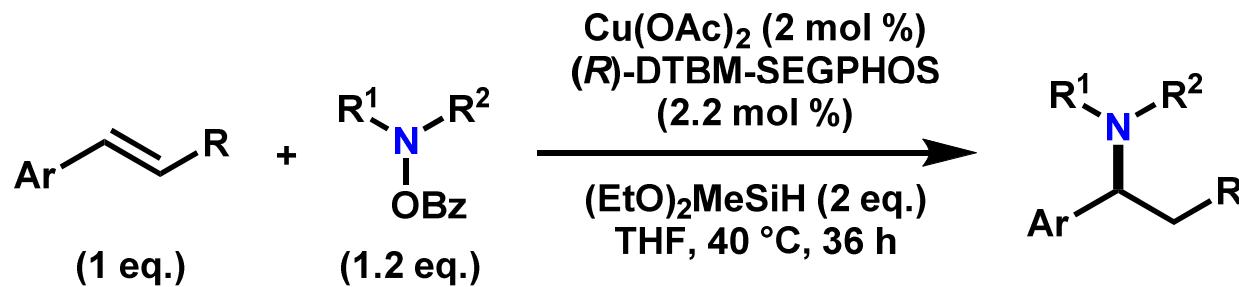
Novel Approach: CuH + electrophilic hydroxyamine



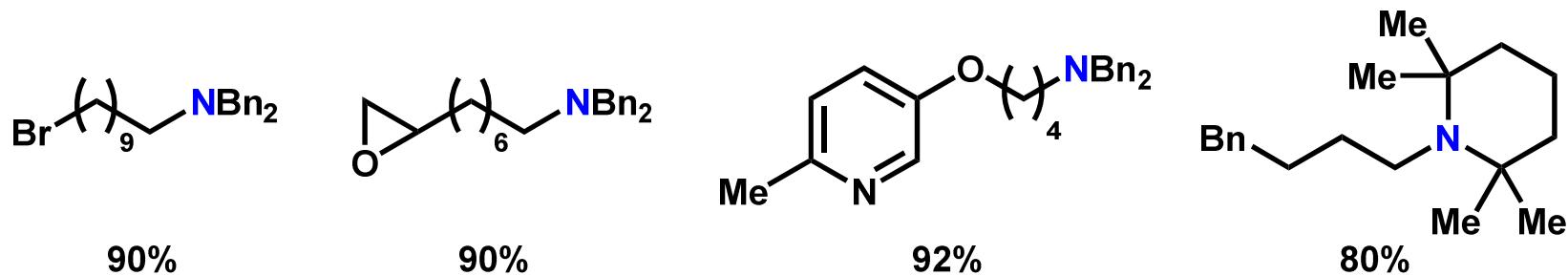
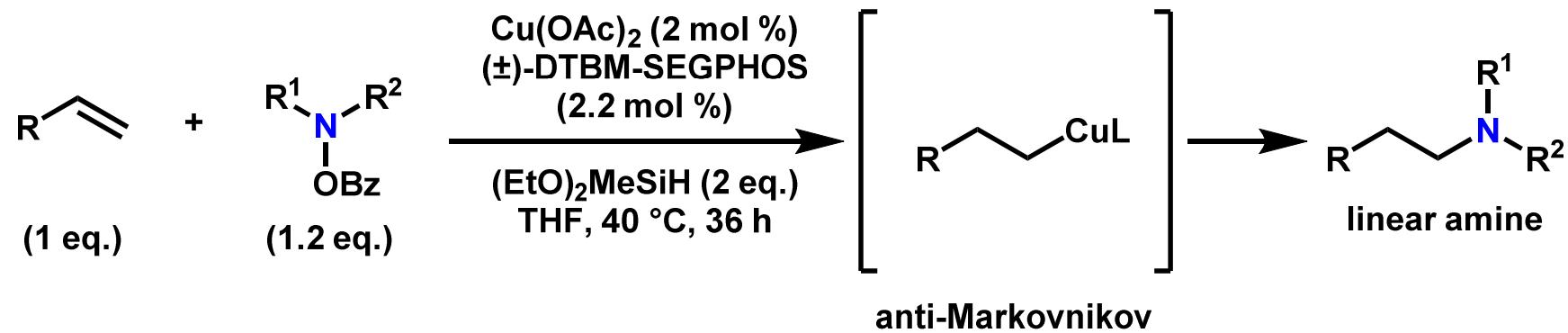
Proposed Reaction Mechanism



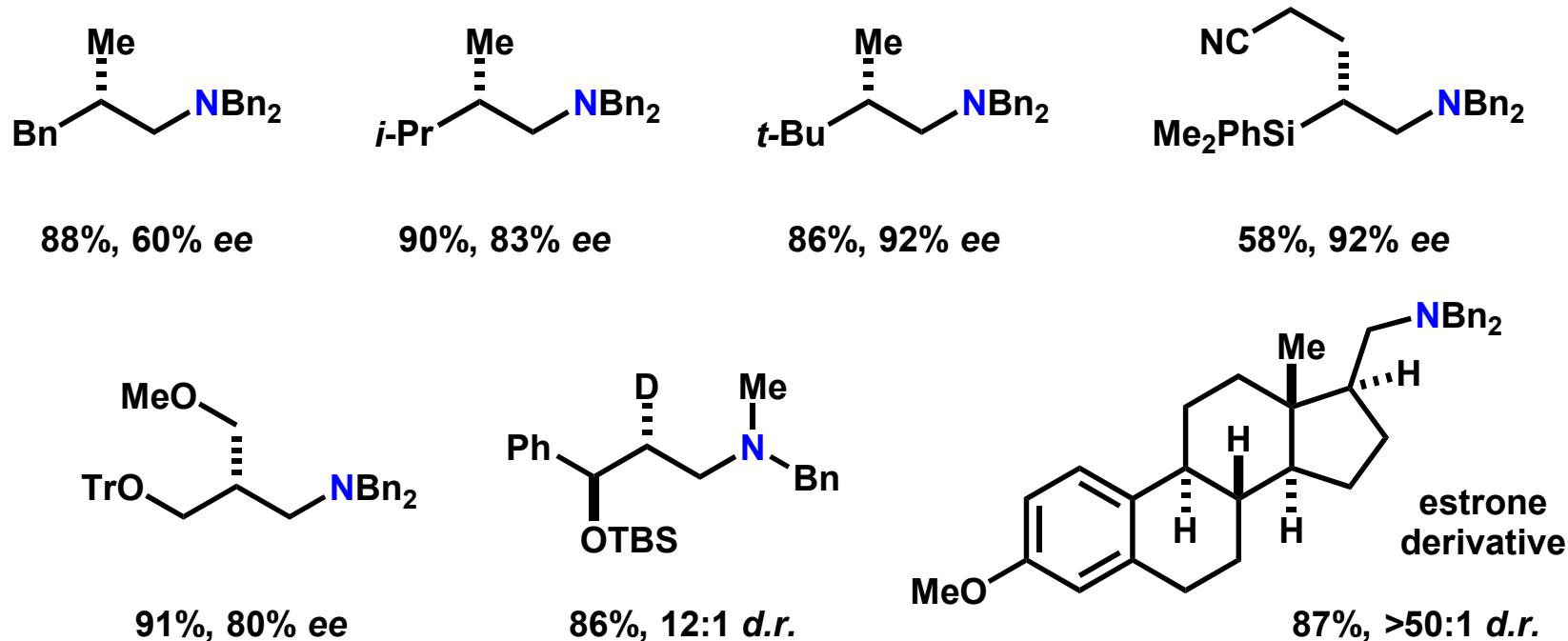
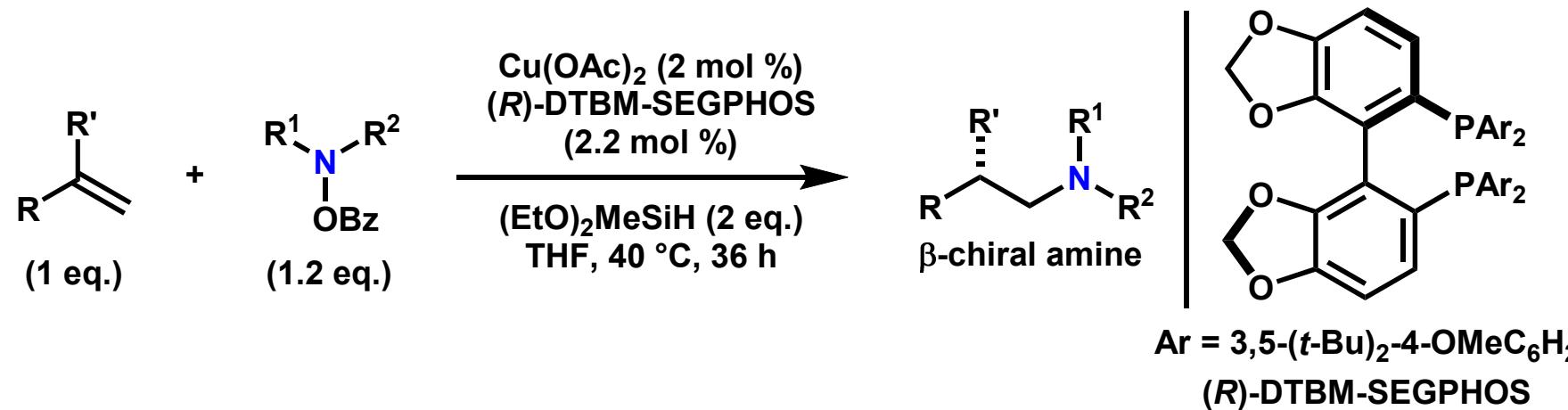
CuH-Catalyzed Hydroamination (1)



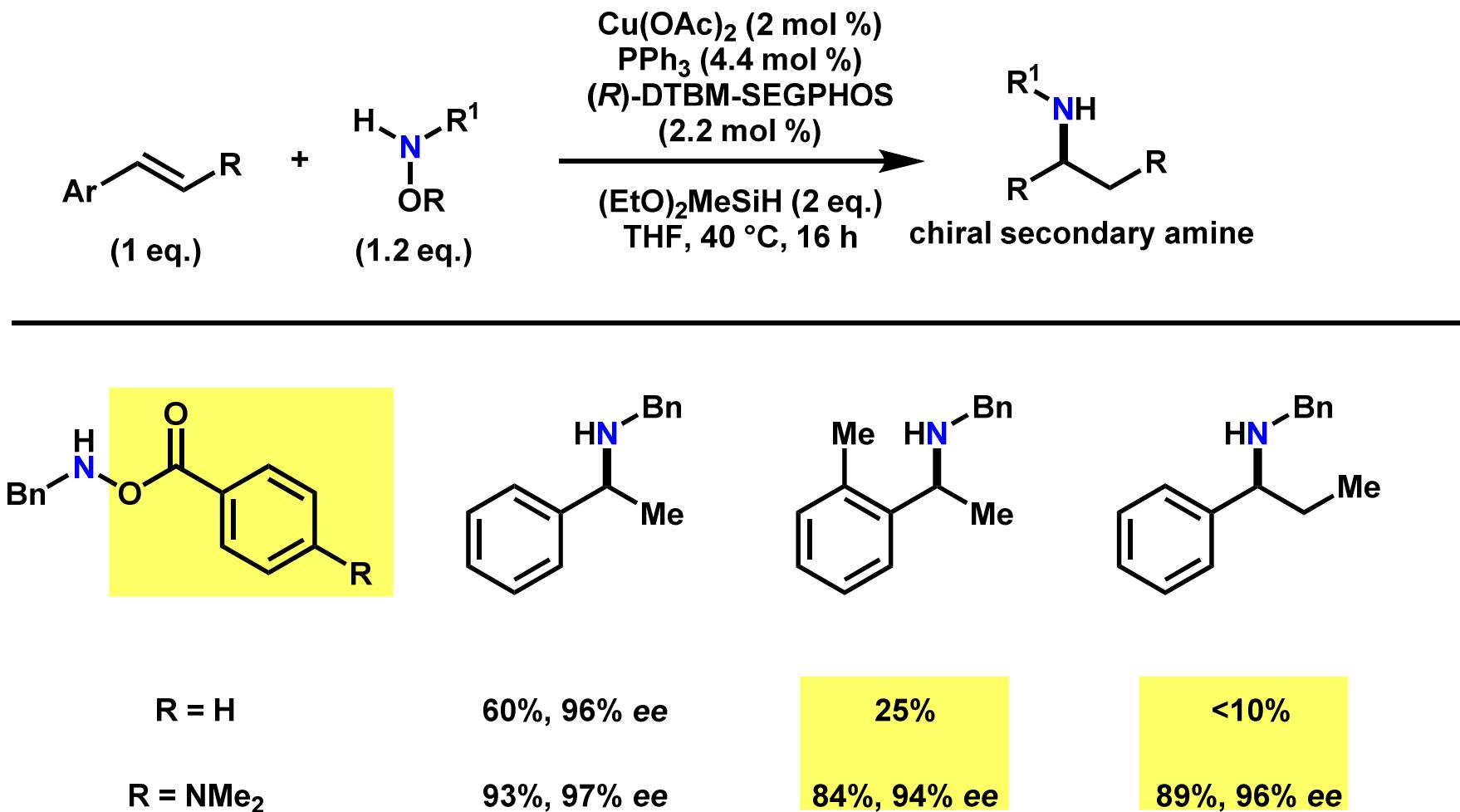
CuH-Catalyzed Hydroamination (2)



CuH-Catalyzed Hydroamination (3)

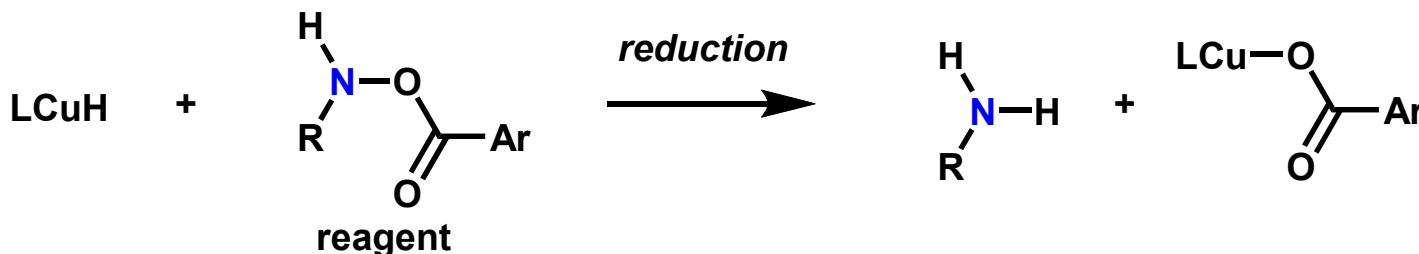


Synthesis of Chiral Secondary Amines

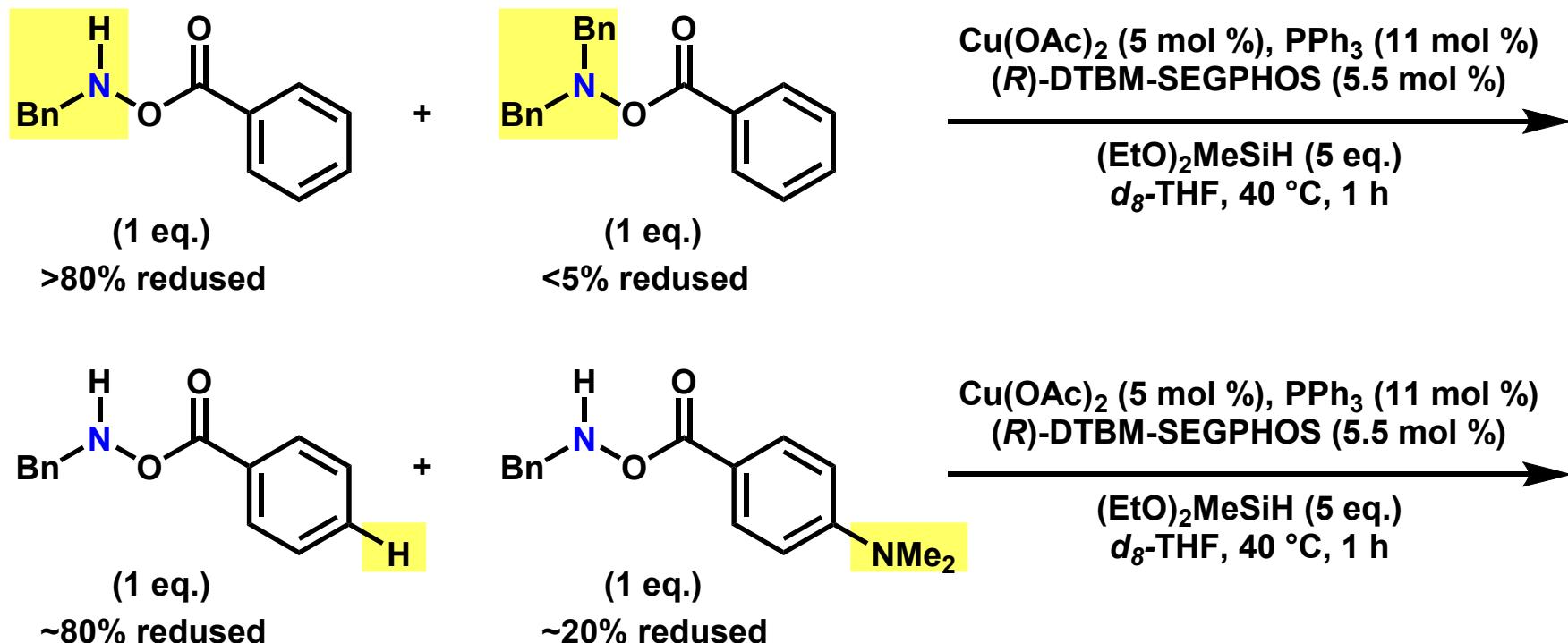


1) Niu, D.; Buchwald, S. L. *J. Am. Chem. Soc.* **2015**, 137, 9716.

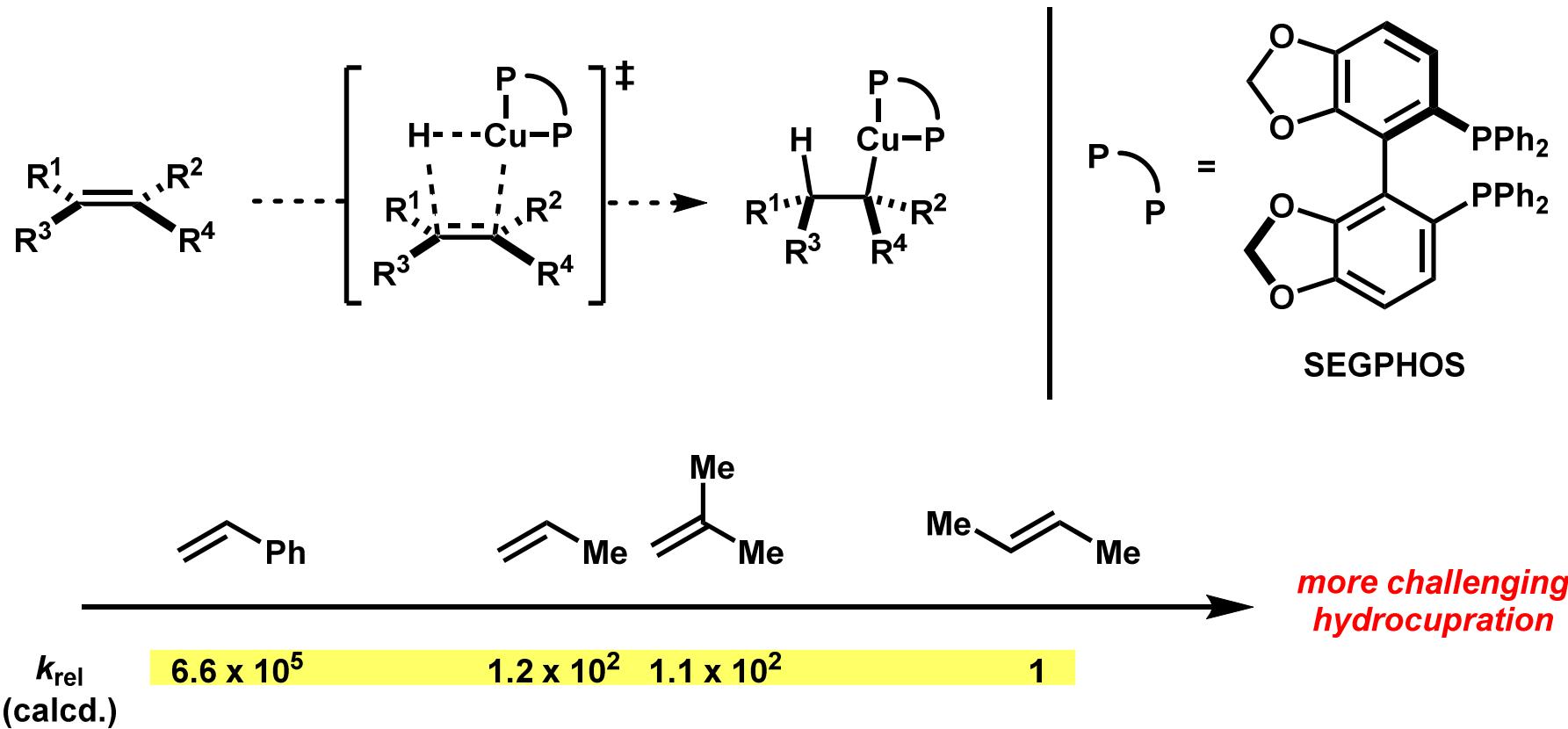
Unproductive Reduction of N-O Bond



NMR competition experiment

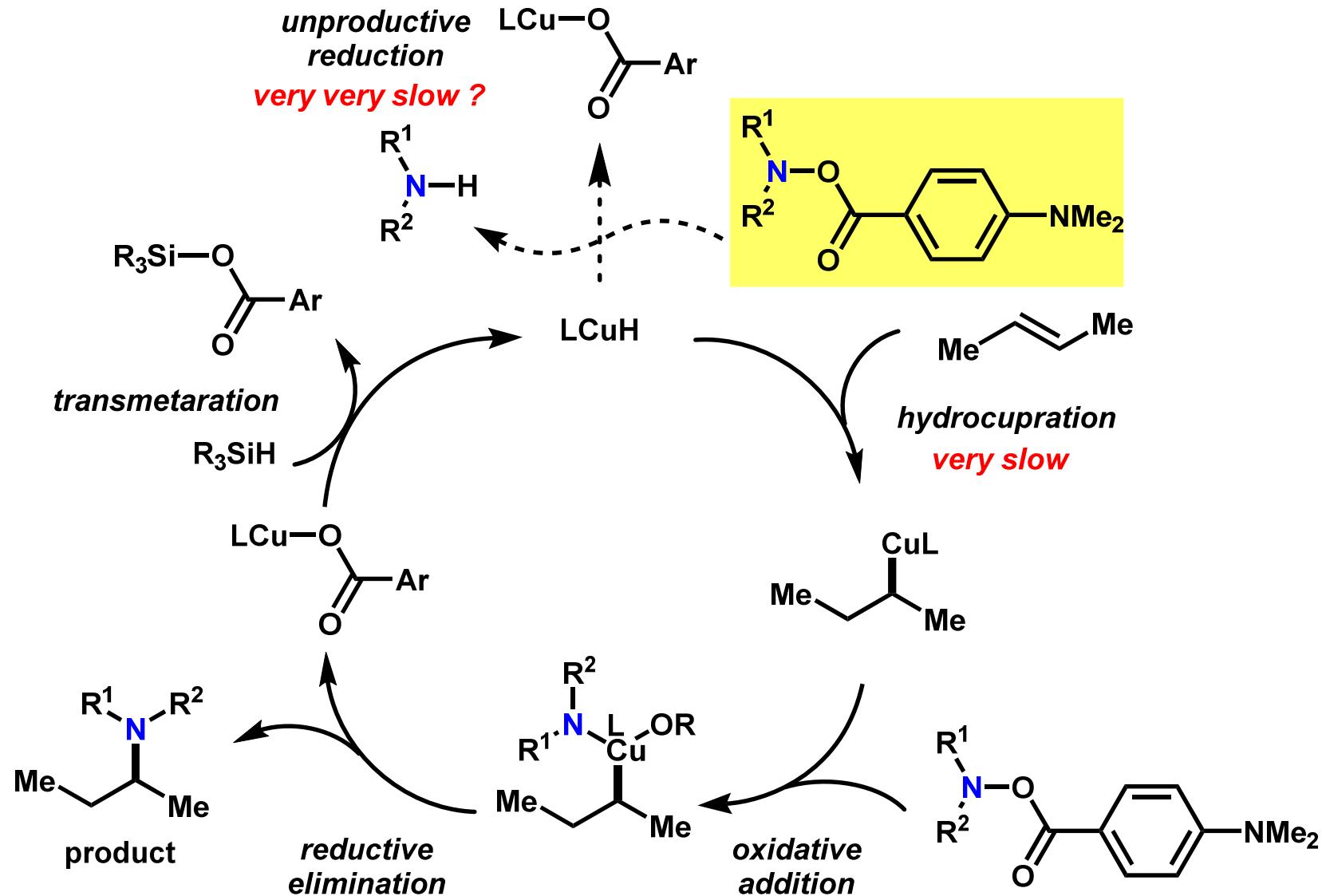


DFT Calculation for the Hydrocupration of Olefins

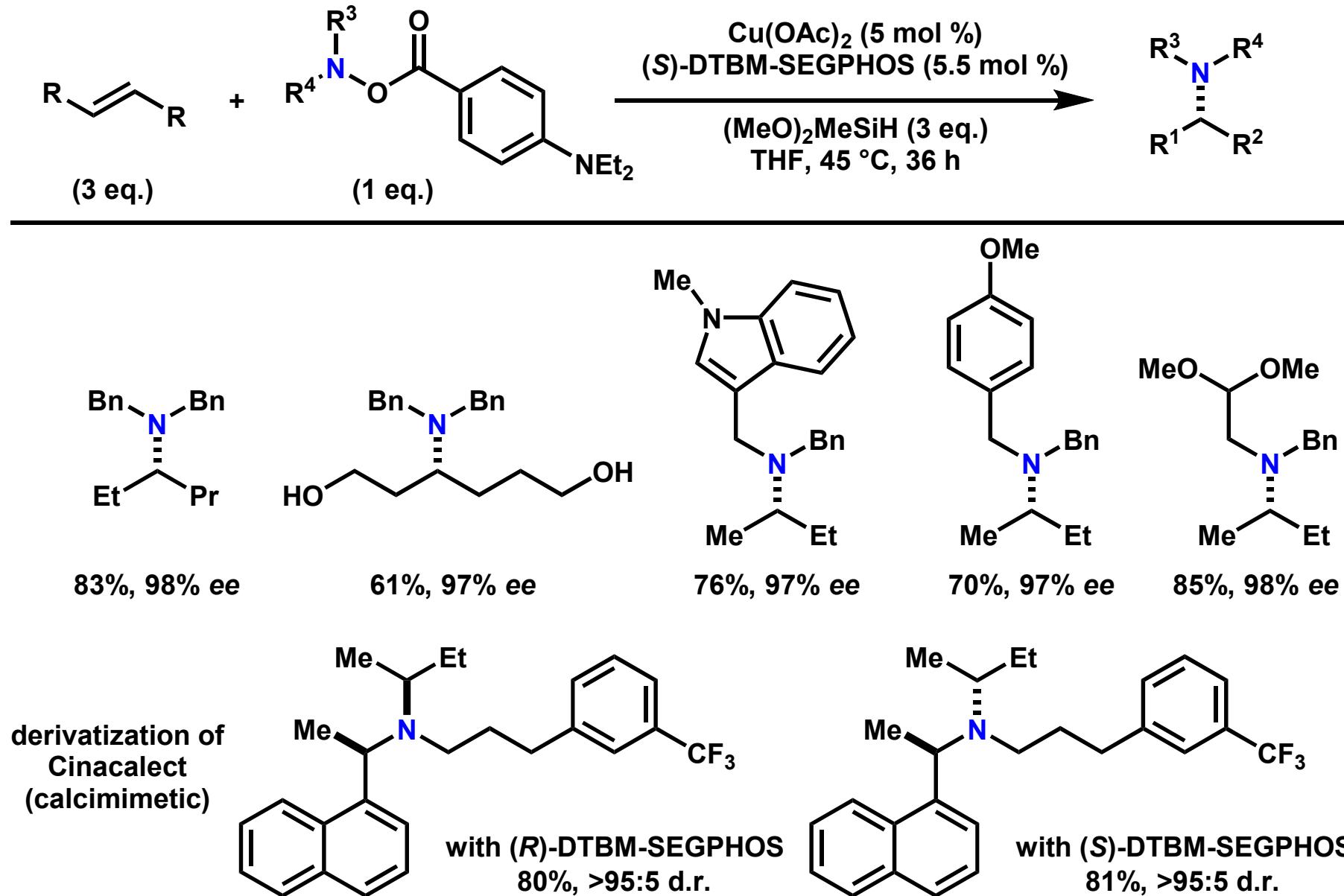


1) Yang, Y.; Shi, S.; Niu, D.; Liu, P.; Buchwald, S. L. *Science* **2015**, *349*, 62.

Proposed Catalytic Cycle

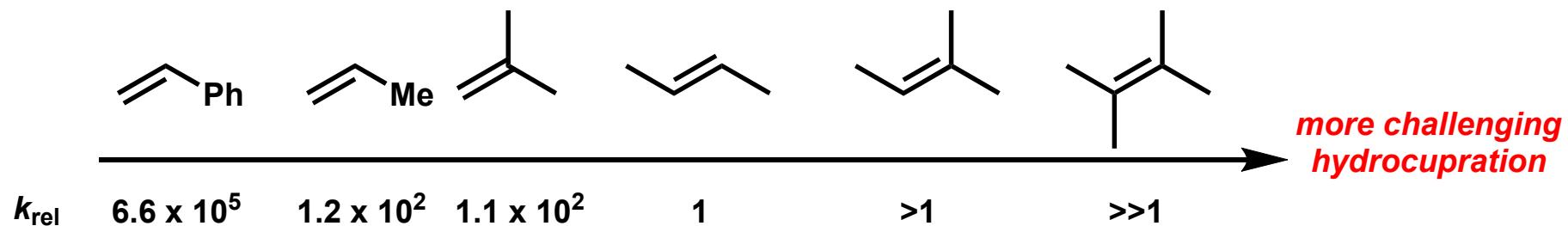


Hydrocupration of Unactivated Internal Olefins

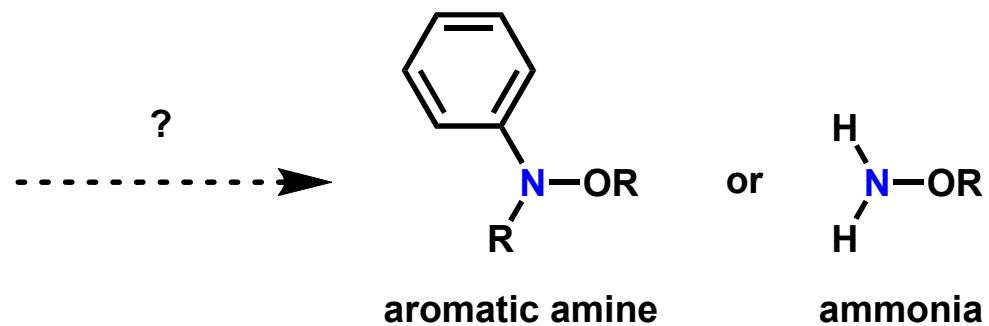


Outlook

Tri- and tertasubstituted alkenes

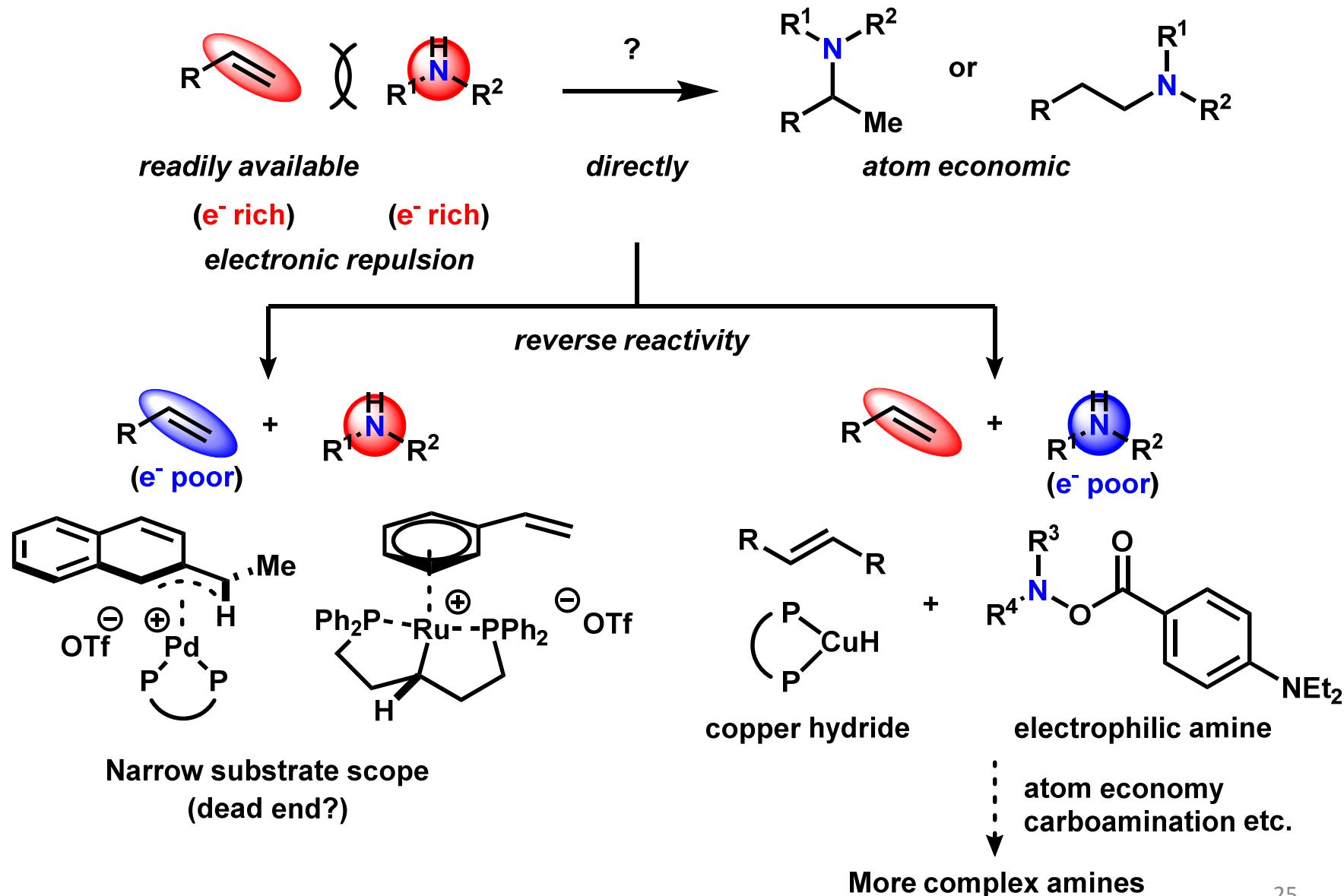


Aminating agents to transfer aromatic amines or ammonia



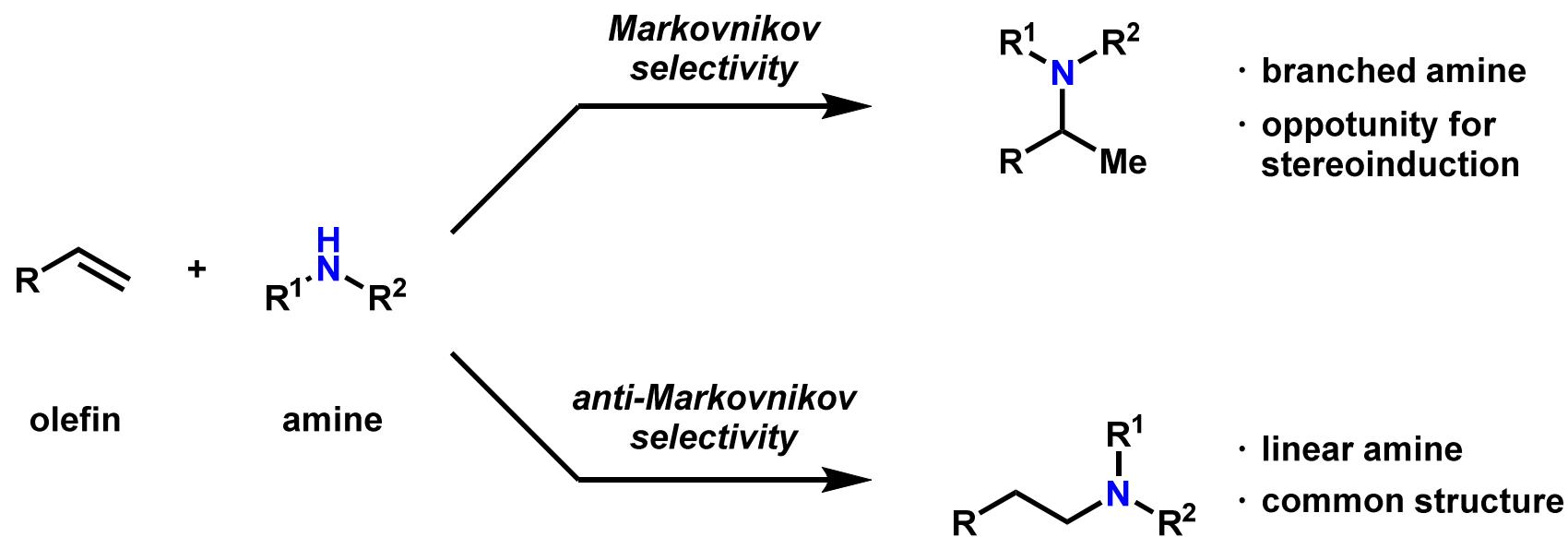
Summary

Hydroamination: direct addition of amines to alkenes



Appendix

Classification of Hydroamination: Regiochemical outcome



Pd-Catalyzed Markovnikov Hydroamination

Table 1. Effect of Catalyst Components and Acid on the Hydroamination of Styrene with Aniline^a

entry	catalyst	yield, % ^b
1	2% [Pd(PPh ₃) ₄]	0
2	2% Pd(OC(O)CF ₃) ₂ /8% PPh ₃	28
3	2% [Pd(PPh ₃) ₄]/20% TFA	67
4	2% [Pd(PPh ₃) ₄]/20% TfOH	83
5	2% Pd(OC(O)CF ₃) ₂ /8% PPh ₃ /20% TFA	68
6	2% [Pd(OC(O)CF ₃) ₂]/3% DPPF	78
7	2% [Pd(OC(O)CF ₃) ₂]/3% DPPF/20% TfOH	>99
8	2% [(DPPF)Pd(OTf) ₂]	96

^a Reactions were run for 6 h in toluene solvent at 100 °C. Reactions with lower yields did not show complete conversion. ^b Yields are for isolated material and are an average of two runs.

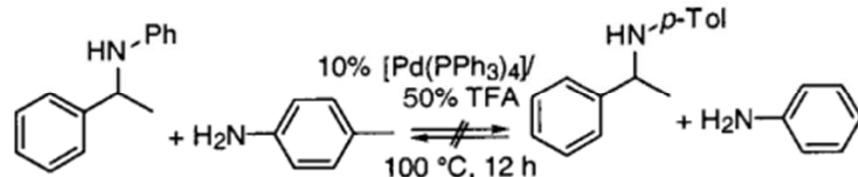


Table 2. Palladium-Catalyzed Hydroamination of Styrene^a

	Amine	Olefin	Cond.	time	Yield ^b
1			A	12 h	83%
2			B	7 h	>99%
3			A	12 h	93%
4			B	7 h	78%
5			A	12 h	64%
6			B	7 h	88%
7			B	7 h	68%
8			B	7 h	99%
9			B	7 h	85%
10			B	7 h	98%
11			C	72 h	98%
12			B	12 h	55%
13			A	12 h	65%
14			B ^c	12 h	54%

^a Reaction conditions: A, 2% Pd(PPh₃)₄/20 triflic acid, 100 °C; B, 2% Pd(TFA)₂/3% DPPF, 20% TfOH, 100 °C; C, 5% (DPPF)Pd(OTf)₂, generated from (DPPF)Pd(OTf)₂ and AgOTf, 25 °C. ^b Yields are for pure, isolated material and are an average of two runs. ^c 5 mol % catalyst used.

Pd-Catalyzed Markovnikov Hydroamination

Table 1. Pd-Catalyzed Addition of Arylamines to Cyclohexadiene^a

Entry	Amine	Yield ^b (%)	Entry	Amine	Yield ^b (%)
1		99	9		80
2		85	10		95
3		89	11		96
4		88	12		97
5 ^c		91	13 ^d		79
6 ^c		96	14 ^d		88
7		78	15		97
8		95	16		98

^a Reaction conditions: 0.5 mmol amine, 2 mmol cyclohexadiene, 2 mol % Pd(PPh₃)₄, 10 mol % TFA, toluene, 25 °C, 24 h. ^bYields are for pure, isolated compounds and are an average of two runs. ^cReaction time: 48 h. ^dReaction conditions: 2.5 mol % [Pd(π -allyl)Cl]₂, 10 mol % PPh₃, toluene, 100 °C, 24 h.

Table 2. Reactions of Arylamines with Various Dienes

Entry	Diene	Amine	Yield ^a (%)	Entry	Diene	Amine	Yield ^a (%)
1 ^b		PhNH ₂	71	4 ^e		PhNH ₂	73
2 ^c		PhNH ₂	89 ^d	5 ^b		PhNHMe	84
3 ^c		PhNHMe	84				

^a Yields are for pure, isolated compounds and are an average of two runs. ^bReaction conditions: 0.5 mmol amine, 2 mmol diene, 1 mol % Pd(PPh₃)₄, 50 mol % acetic acid. ^cSame reaction conditions except 2 mol % Pd(PPh₃)₄, 10 mol % TFA. ^d6% of diallylamine obtained for this reaction with excess diene. ^eFour-fold excess of aniline used.

Pd-Catalyzed Markovnikov Hydroamination

Table 1. Effects of Catalyst, Acid, and Solvent on the Hydro-amination of Styrene with Morpholine at 120 °C^a

entry	catalyst	solvent	yield ^b
1	5% Pd(O ₂ CF ₃) ₂ /10% DPPF/20% TfOH	dioxane	79
2	5% Pd(O ₂ CF ₃) ₂ /10% DPPF/20% TfOH	toluene	25
3	5% Pd(O ₂ CF ₃) ₂ /5% DPPF/20% TfOH	dioxane	2
4	5% Pd(DPPF)(OTf) ₂	dioxane	1
5	5% Pd(DPPF)(OTf) ₂ /5% DPPF/10% TfOH	dioxane	74
6	5% Pd(Ph ₃) ₄ /20% TfOH	dioxane	6
7	20% TfOH	dioxane	1
8	5% Pd(O ₂ CF ₃) ₂ /20% TfOH	dioxane	1
9	5% Pd(O ₂ CF ₃) ₂ /10% DPPF	dioxane	2
10	5% Pd(O ₂ CF ₃) ₂ /10% DPPF/20% TFA	dioxane	19
11	5% Pd(O ₂ CF ₃) ₂ /10% DPPF/20% NFA ^c	toluene	72
12	5% Pd(O ₂ CF ₃) ₂ /10% DPPF/20% NFA ^c	dioxane	67

^a Reaction conditions: 0.4 mmol morpholine, 0.8 mmol styrene, 0.2 mL dioxane, 24 h. ^b GC yields, in percent. ^c NFA = nonafluorobutane sulfonic acid.

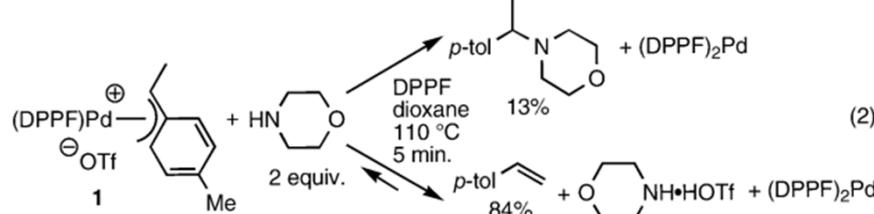
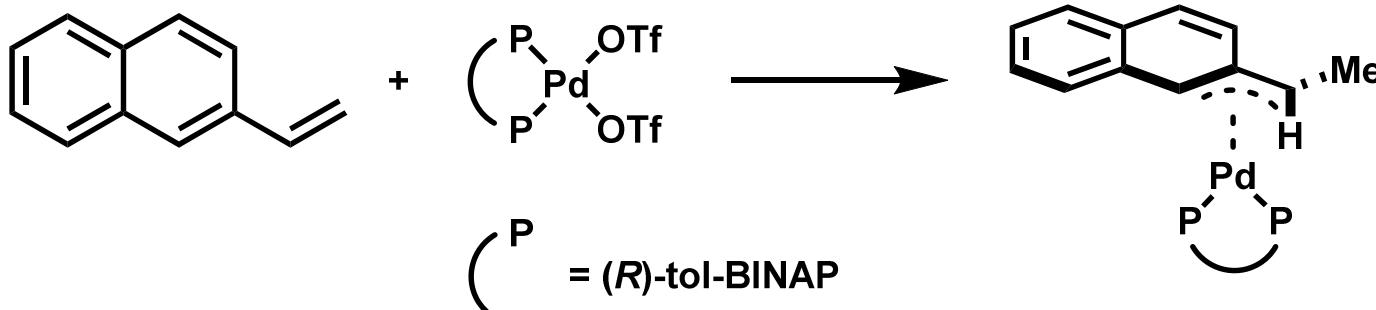


Table 2. Pd-Catalyzed Hydroamination of Alkylamines with Vinylarenes

entry	product	yield ^b	entry	product	yield ^b
1		75%	8 ^g		63%
2 ^c		51%	9 ^e		71%
3		76%	10		58%
4 ^d		79%	11 ^g		52%
5 ^{e,f}		51%	12 ^h		63%
6 ^{e,f}		48%	13 ^{e,f,g}		43% ⁱ
7		72%	14 ^{g,j}		53%

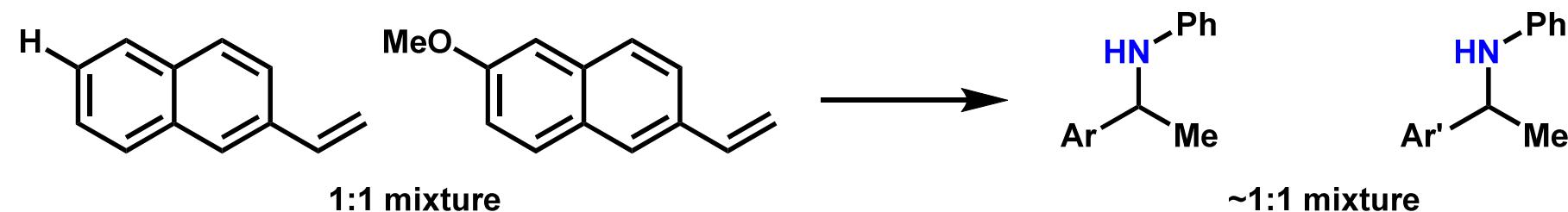
^a Amine/vinylarene/Pd(TFA)₂/DPPF/TfOH = 1:2:0.05:0.10:0.20 (1 mmol of amine) in 0.50 mL of dioxane. ^b Isolated yield. ^c 48 h. ^d 100 °C. ^e 4.0 mmol of vinylarene was used. ^f 0.20 mL of dioxane. ^g 110 °C. ^h 80 °C. ⁱ 10% of dibenzylmethylamine was obtained as side product. ^j 18 h.

Competition Experiment

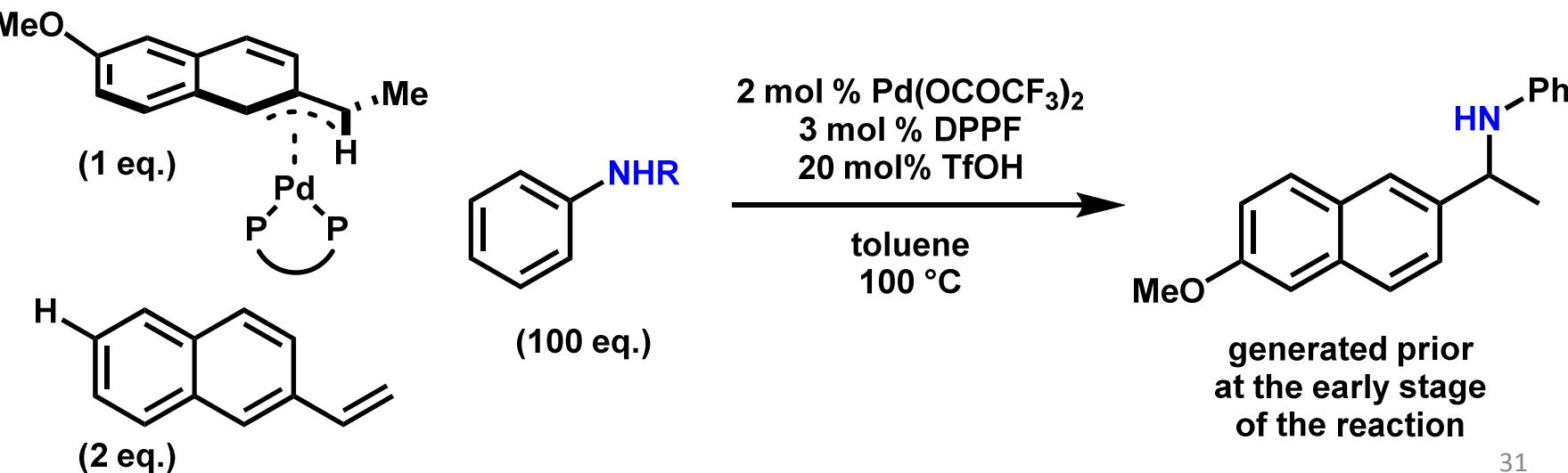


The two olefins have comparable reactivity.

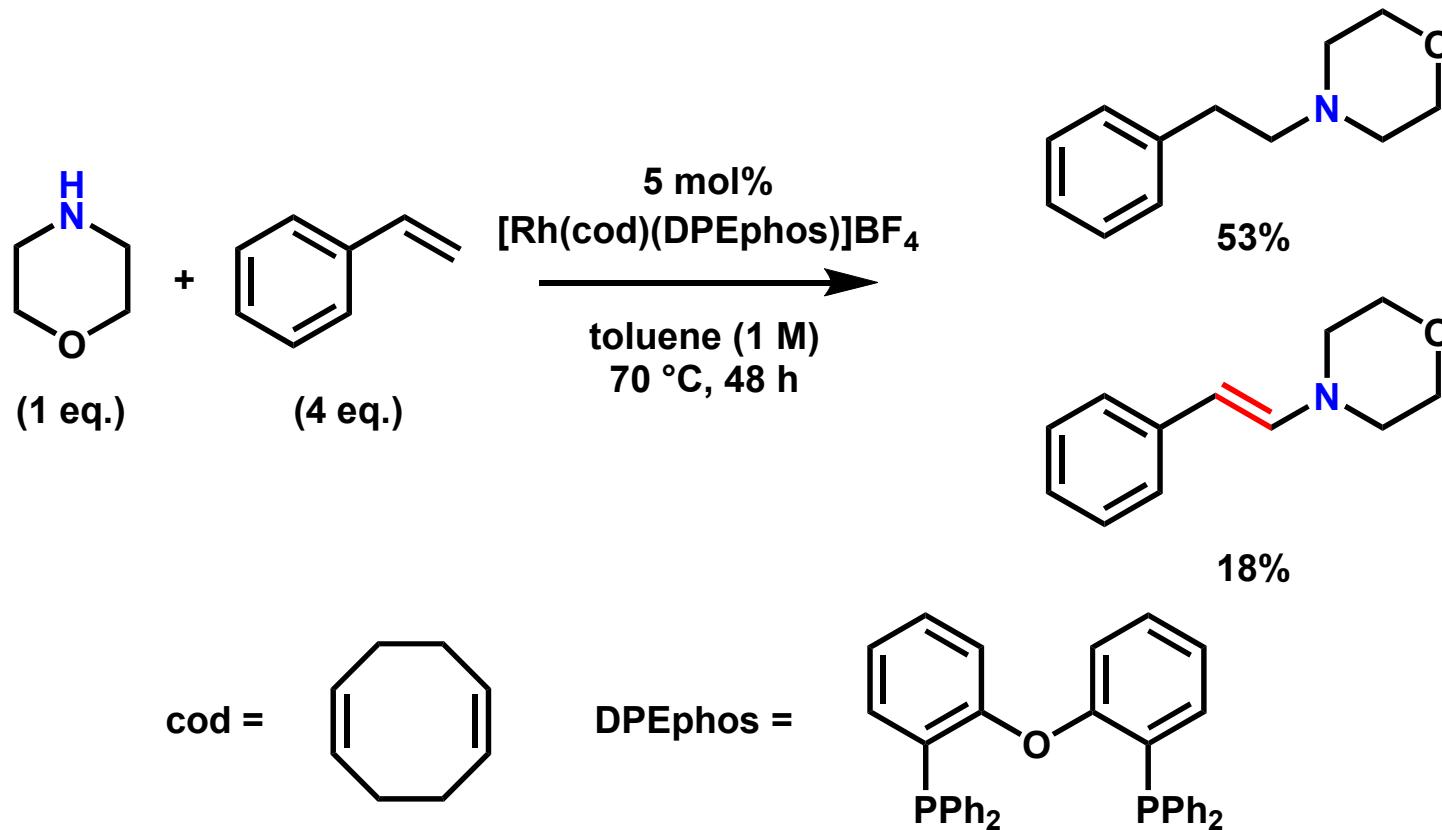
isolated η^3 -arylethyl complex
(one diastereomer)



Competition experiment



Rhodium-Catalyzed Anti-Markovnikov Hydroamination



Ru-Catalyzed Anti-Markovnikov Hydroamination

Table 1. Effects of Catalyst Components on the Hydroamination of Styrene and Morpholine in Dioxane at 100 °C^a

entry	Ru (%)	ligand	acid	yields: 1 ^b (%)	2 ^b (%)
1	5	7% DPPPent	10% TfOH	96	<1
2	5	—	10% TfOH	0	<1
3	5	7% DPPPent	—	0	0
4	5	7% DPPPent	10% TFA	8	0
5	2	3% DPPPent	5% TfOH	90	<1
6	5	14% PPh ₃	10% TfOH	36	9
7	5	14% PEtPh ₂	10% TfOH	61	3
8	5	7% DPPB ^c	10% TfOH	54	12
9	5	7% DPPHEx ^d	10% TfOH	33	2
10	5	7% DPPF ^e	10% TfOH	55	44
11	5	7% DPEphos ^f	10% TfOH	19	2

^a Reaction conditions: morpholine 0.4 mmol, styrene 0.8 mmol, dioxane 0.2 mL, 100 °C, 24 h. ^b GC yields. ^c 1,4-Bis(diphenylphosphino)butane. ^d 1,6-Bis(diphenylphosphino)hexane. ^e 1,1'-Bis(diphenylphosphino)ferrocene. ^f Bis(2-diphenylphosphinophenyl)ether.

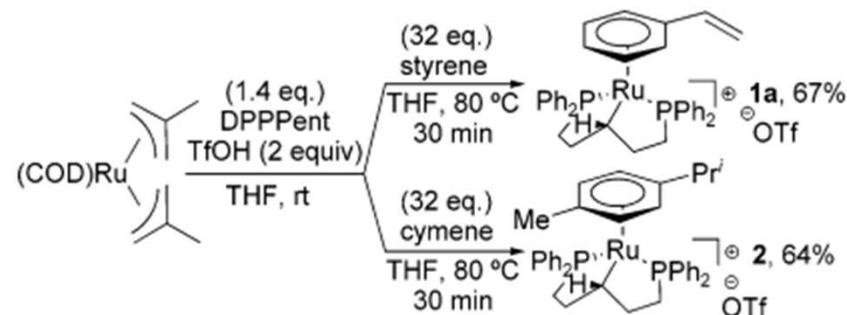
Table 2. Ruthenium-Catalyzed Hydroamination of Vinylarenes with Alkylamines^a

entry	product	yield ^b	entry	product	yield ^b
1		96%	8 ^{c, d, e}		50%
2		91%	9		81%
3 ^c		64%	10		72%
4		90%	11 ^{e, f, g}		91%
5		82%	12 ^{f, g, h}		71%
6 ^c		65%	13 ^h		51%
7 ^{c, d, e}		63%	14 ^{d, i, j}		40%

^a Amine/vinylarene/Ru/DPPPent/TfOH = 1:2:0.05:0.07:0.10 (1 mmol of amine) in 0.50 mL of dioxane. ^b Isolated yield. ^c 4 mmol of vinylarene was used. ^d 80 °C. ^e 48 h. ^f 0.25 mL of dioxane. ^g 110 °C. ^h DiPPF was used as ligand. ⁱ 1.5 mmol of vinylarene was used. ^j 72 h.

Ru-Catalyzed Anti-Markovnikov Hydroamination

Scheme 1

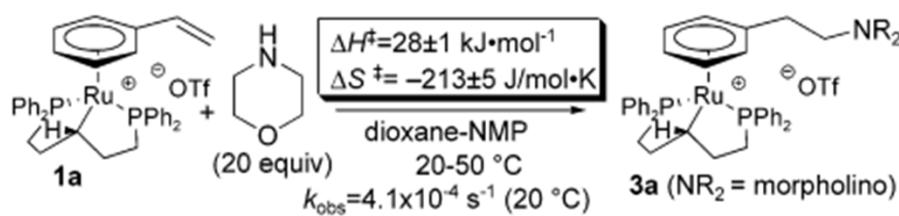


Scheme 2

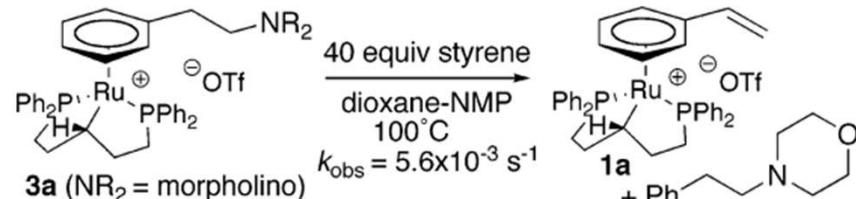
	1.5 M	0.78 M	catalyst	dioxane	yield ^a
				100 °C	2h
1a (5 mol%)			cat.	15min	22%
2 (5 mol%)				30min	10%
<i>in situ</i> ^b				1h	9%
					40%
					63%
					87%
					96%
					94%
					92%

^a Yield by GC. ^bRu(COD)(2-methylallyl)₂ (5 mol %), DPPPent (7 mol %), TfOH (10 mol %).

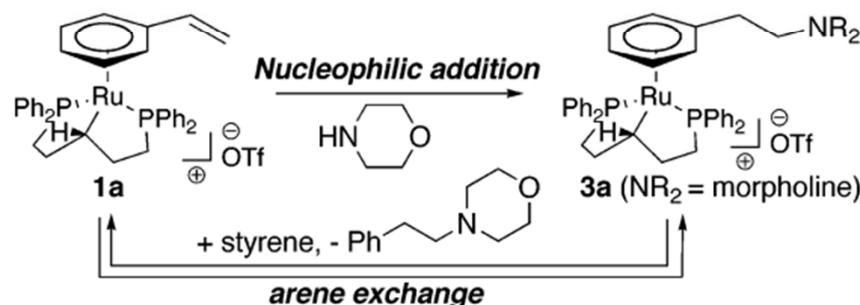
Scheme 3



Scheme 4



Scheme 5

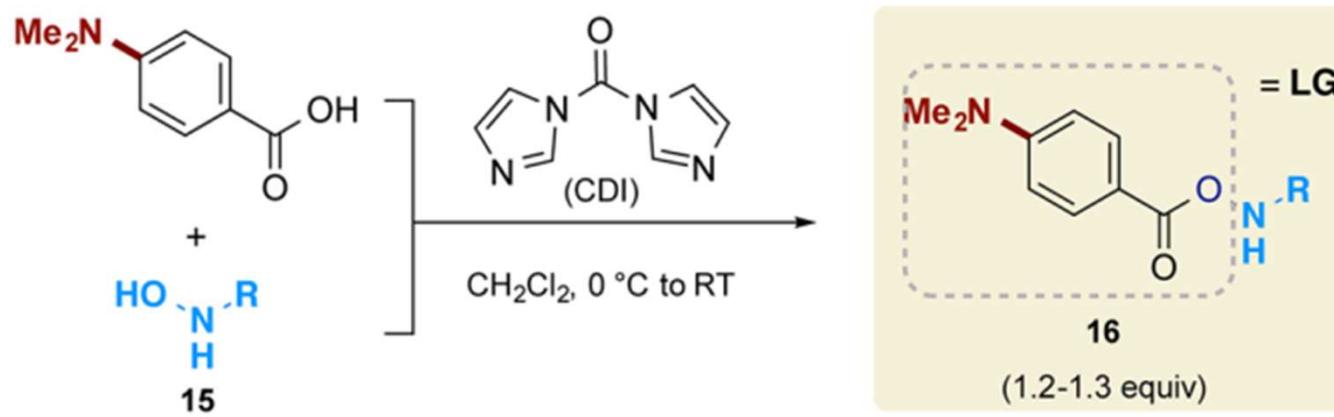


Scheme 6

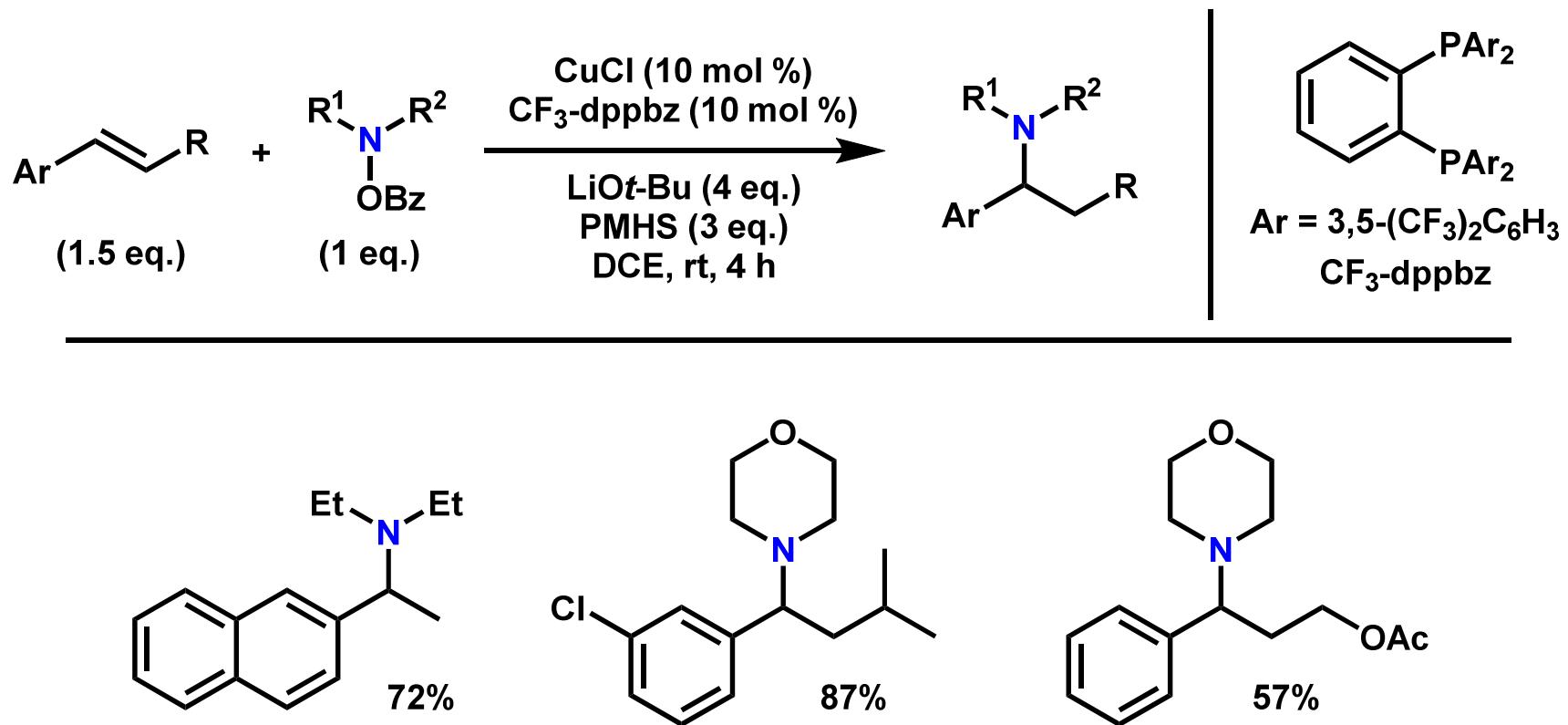
	1.5 M	0.78 M	1a or 1b (5 mol%)	time to 50% yield
catalyst				
1a Ar=Ph				350 min
1b Ar= 3,5-(MeO) ₂ C ₆ H ₃				103 min

1) Utsunomiya, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, 126, 5608.

Synthesis of Amine Transfer Reagents



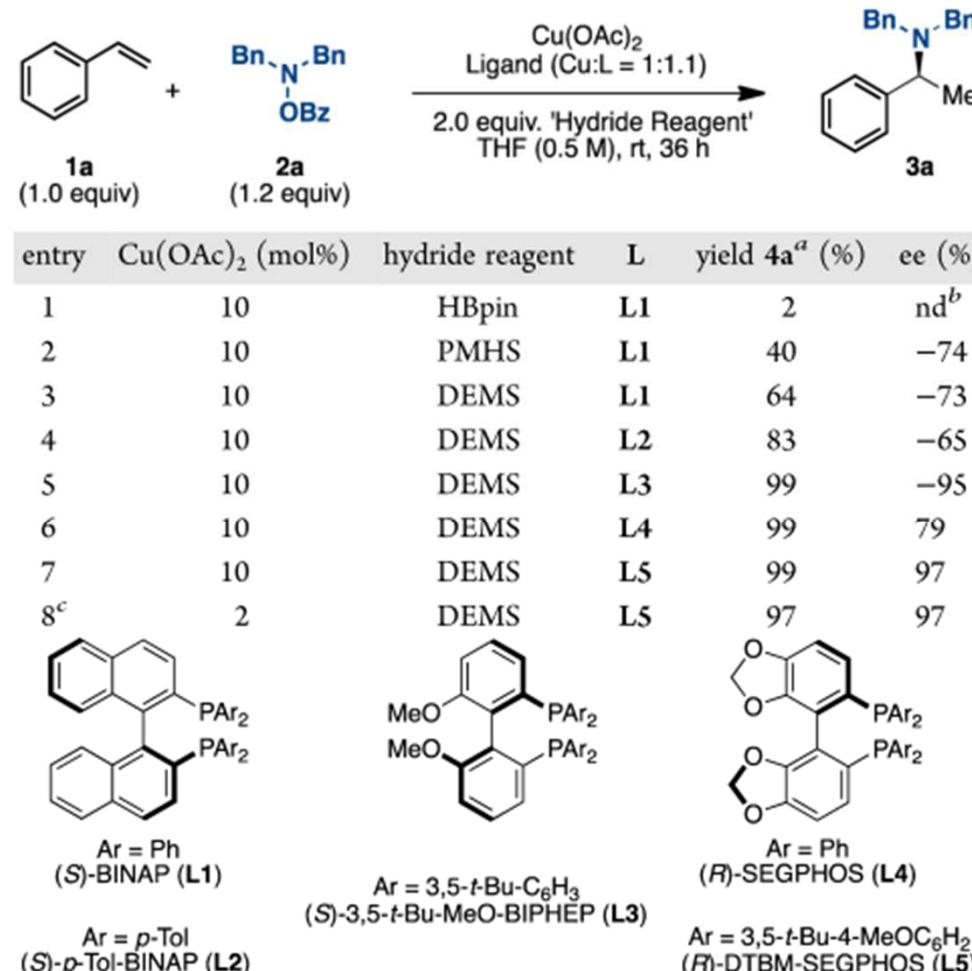
CuH-Catalyzed Hydroamination by Miura et al.



1) Miki, Y.; Hirano, K.; Sato, T.; Miura, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 10830.

CuH-Catalyzed Hydroamination

Table 1. Reaction Optimization

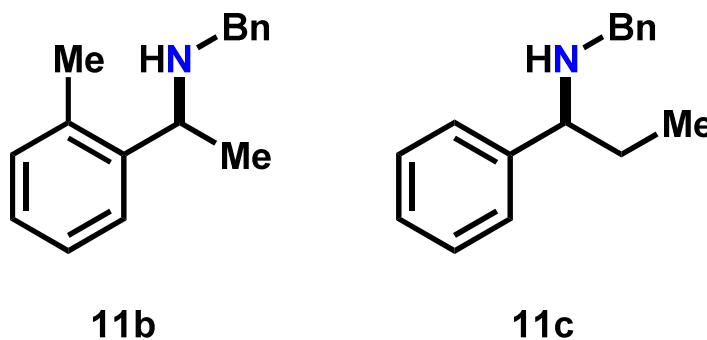
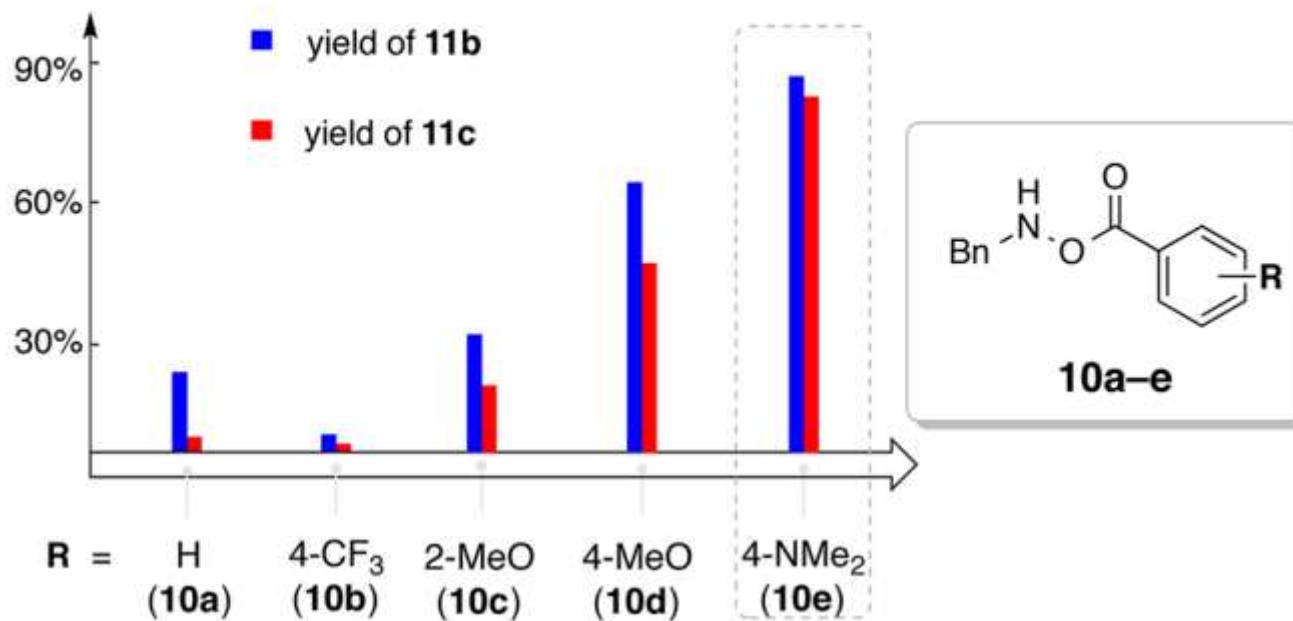


^aGC yields with dodecane as the internal standard. ^bNot determined.

^cReaction was carried out at 40 °C.

Hydroamination Using Modified Amine Transfer Reagents

c) Hydroamination^a of **9b** and **9c** using modified amine transfer reagents **10a–e**



Unproductive Reduction of N-O Bond

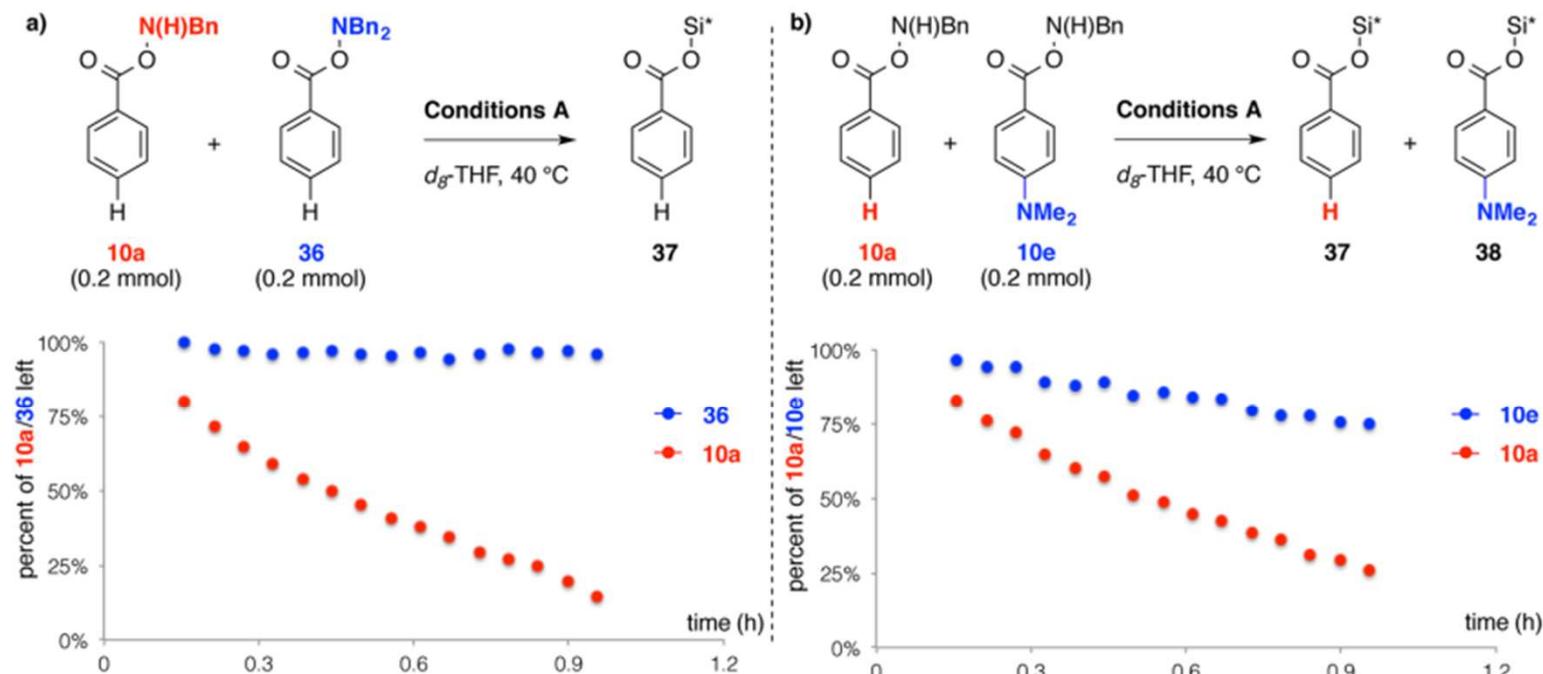
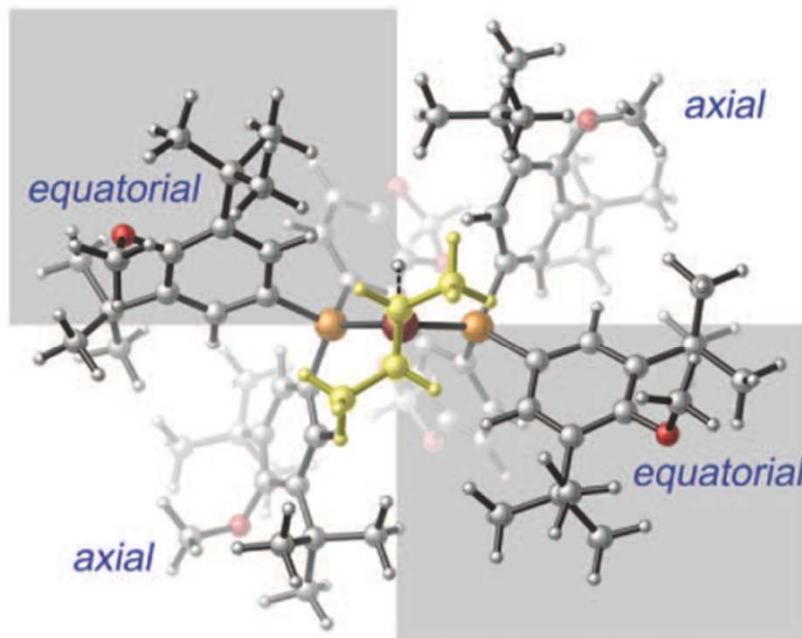
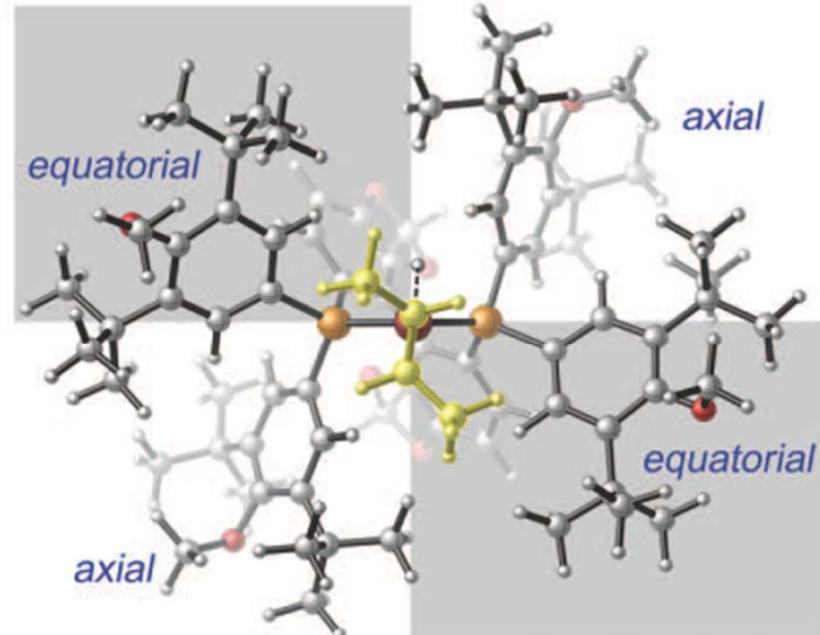


Figure 4. Relative rates of the reactions between LCuH and different amine transfer agents. $\text{Si}^* = \text{Si}(\text{OEt})_2\text{Me}$. **Conditions A:** a 0.6 mL of a stock solution made from $\text{Cu}(\text{OAc})_2$ (3.6 mg), (*R*)-DTBM-SEGPHOS (26 mg), PPh_3 (11.6 mg), $\text{HSi}(\text{OEt})_2\text{Me}$ (0.32 mL, 2.0 mmol), and THF-d_8 (1.0 mL) is used. The progress of these experiments was monitored by ^1H NMR.

Transition-State Structures of the Hydrocupration



TS2a-favored
(Re)-face attack
 $\Delta G^\ddagger = 23.3$ kcal/mol
 $\Delta H^\ddagger = 8.6$ kcal/mol



TS2b-disfavored
(Si)-face attack
 $\Delta G^\ddagger = 26.6$ kcal/mol
 $\Delta H^\ddagger = 10.9$ kcal/mol

Fig. 4. Transition-state structures of the enantioselectivity-determining hydrocupration step with **(R)-DTBM-SEGPHOS.** Energies are computed at the M06/SDD-6-311+G(d,p)/SMD(THF) level, with geometries optimized at the B3LYP/SDD-6-31G(d) level.