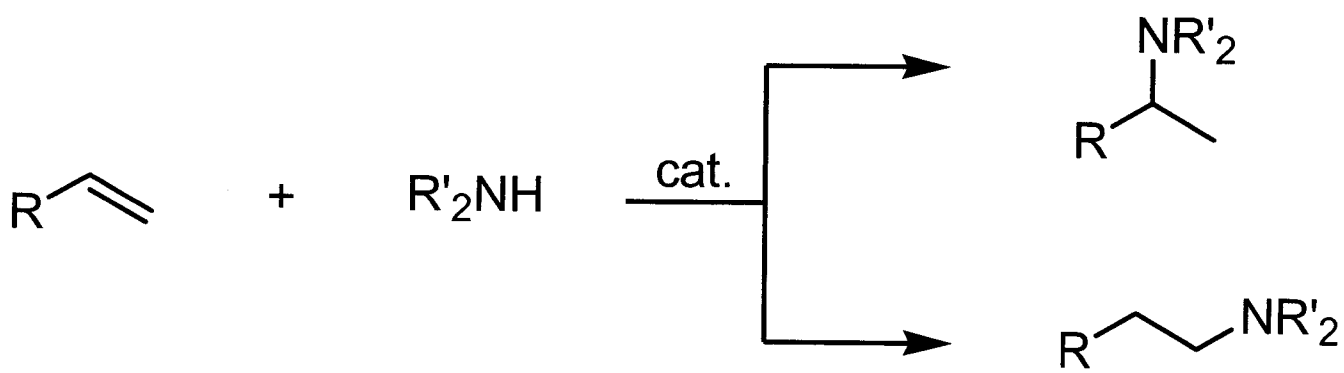
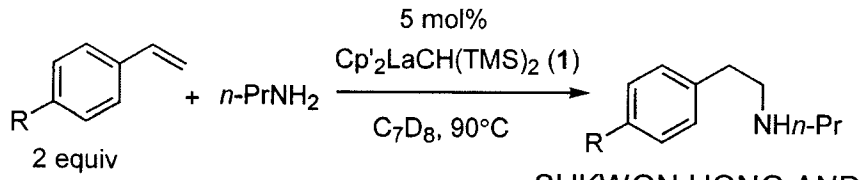
Late Transition Metal Catalyzed Intermolecular Hydroamination of Alkenes



Min Xie

Feb. 8th, 2005

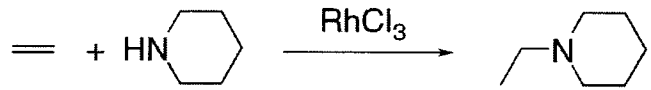
Catalytic Intermolecular Hydroamination of Alkenes



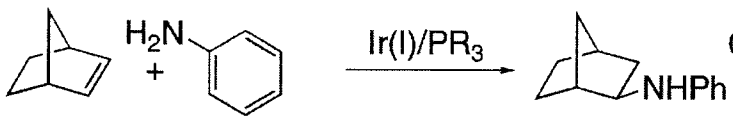
SUKWON HONG AND TOBIN J. MARKS* *Acc. Chem. Res.* **2004,** 37, *673-686*

•High Temperature Intermolecular

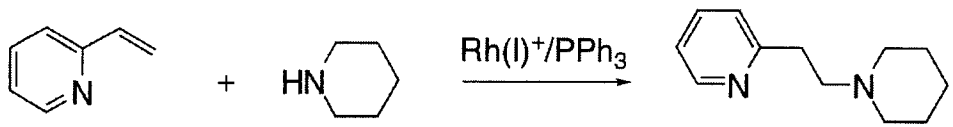
Coulson



•Activated Olefins



Casalnuovo (original system)
Togni (asymmetric system)



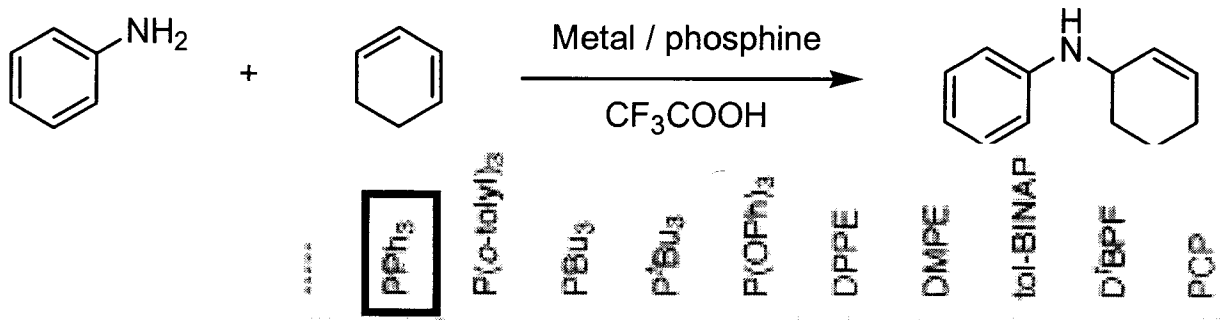
Beller

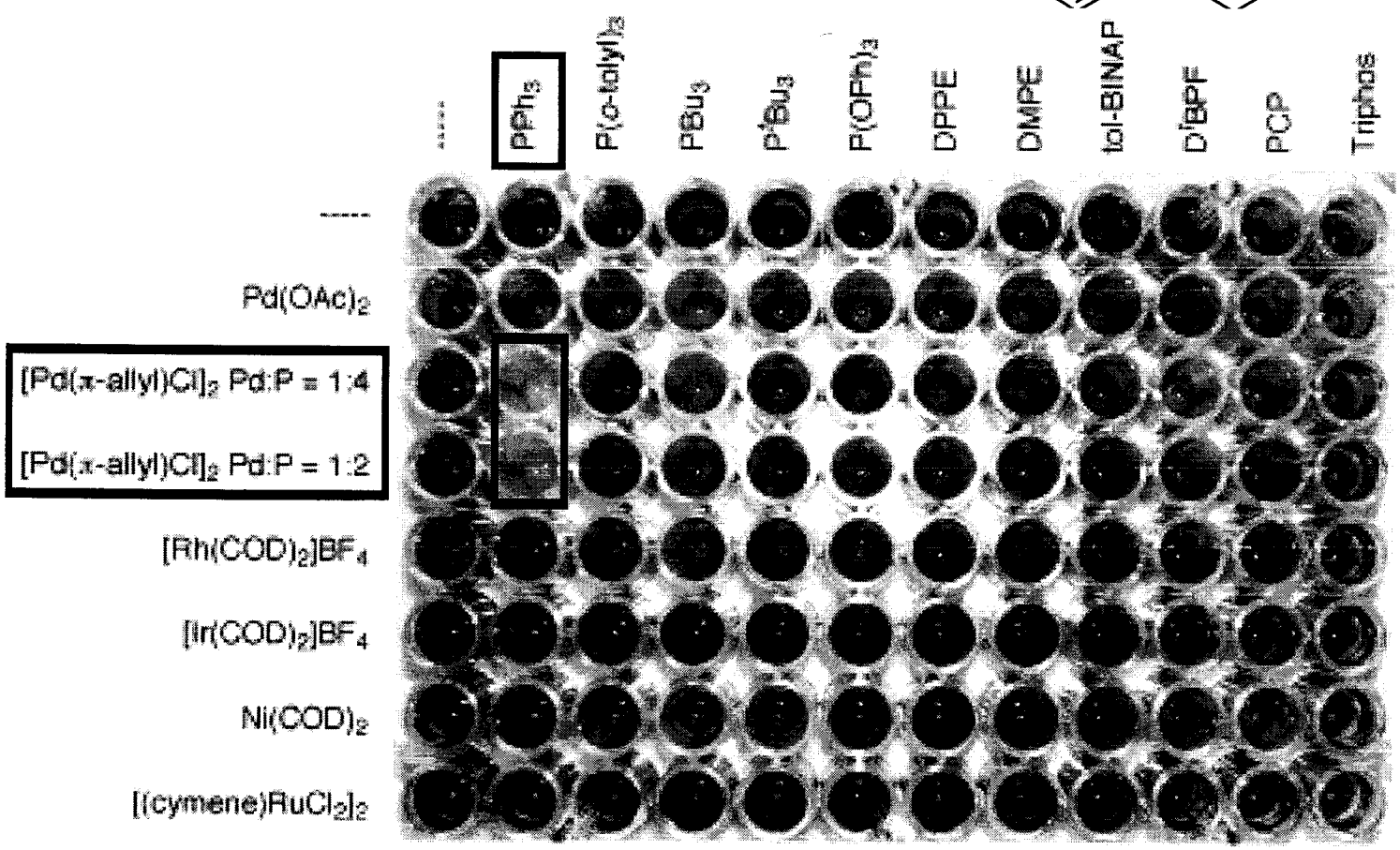
John F. Hartwig, *Pure Appl. Chem.* **2004**, *76*, 507-516

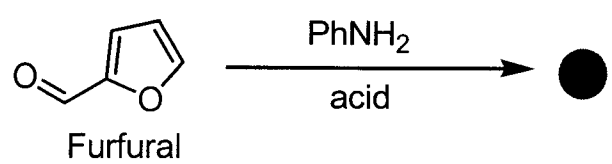
Li, Na, K base catalyst developed by Beller

Jayasree Seayad, Annegret Tillack, Christian G. Hartung, Matthias Beller* *Adv. Synth. Catal.* **2002**, *344*, 795 - 813

Simple Spot Test to Screen Catalysts



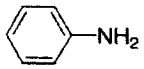
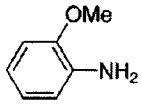
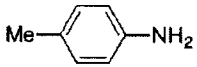
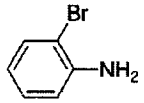
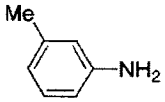
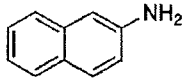
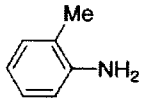
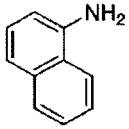
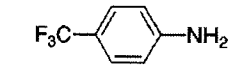
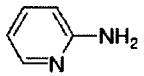
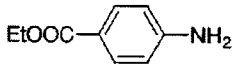
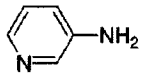
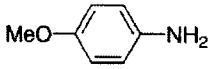
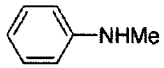
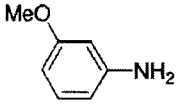
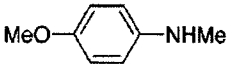




Oliver Lober, Motoi Kawatsura, and John F. Hartwig*, *J. Am. Chem. Soc.* **2001,** *123,* 4366-4367

Pd Catalyzed Hydroamination of 1,3-Dienes with Arylamines

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 % $Pd(PPh_3)_4$, 10 mol % TFA, toluene, 25 °C, 24 h. [b]Yields are for pure, isolated compounds and are an average of two runs. [c]Reaction time: 48 h. [d]Reaction conditions: 2.5 mol % $[Pd(\pi\text{-allyl})Cl]_2$, 10 mol % PPh_3, toluene, 100 °C, 24 h.

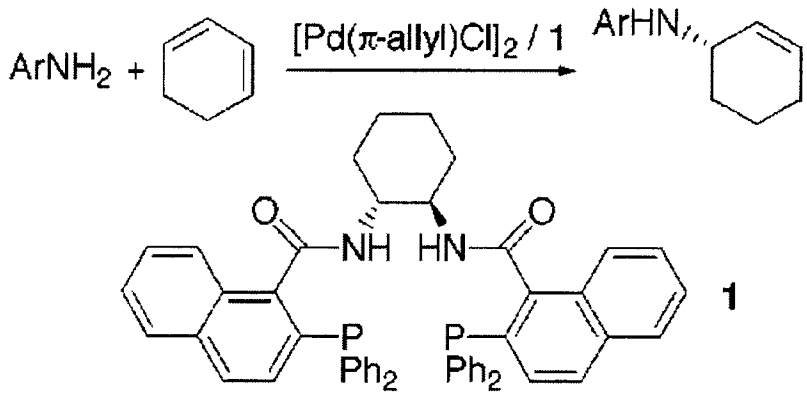
Table 2. Reactions of Arylamines with Various Dienes

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. [b]Reaction conditions: 0.5 mmol amine, 2 mmol diene, 1 mol % $Pd(PPh_3)_4$, 50 mol % acetic acid. [c]Same reaction conditions except 2 mol % $Pd(PPh_3)_4$, 10 mol % TFA. [d]6% of diallylamine obtained for this reaction with excess diene. [e]Four-fold excess of aniline used.

Oliver Lober, Motoi Kawatsura, and John F. Hartwig*, *J. Am. Chem. Soc.* **2001,** *123,* 4366-4367

Enantioselective Hydroamination of 1,3-Dienes with Arylamines



amine	ligand	M	time (h)	yield[a](%)	ee[b](%)
$PhNH_2$	(*R*,*R*)-**1**	neat	72	94	50 (*S*)
$PhNH_2$	(*R*,*R*)-**1**	1.2	120	87	89 (*S*)
$PhNH_2$	(*R*,*R*)-**1**	0.6	120	63	92 (*S*)
p-$MeC_6H_4NH_2$	(*R*,*R*)-**1**	1.2	120	78	86 (*S*)
o-$MeC_6H_4NH_2$	(*R*,*R*)-**1**	1.2	120	59	90 (*S*)
p-$EtO_2CC_6H_4NH_2$	(*R*,*R*)-**1**	1.2	120	83	95 (*S*)
p-$F_3CC_6H_4NH_2$	(*R*,*R*)-**1**	1.2	120	73	95 (*S*)

Oliver Lober, Motoi Kawatsura, and John F. Hartwig*, *J. Am. Chem. Soc.* **2001,** *123,* 4366-4367

Pd Catalyzed Hydroamination of Vinylarenes with Arylamines

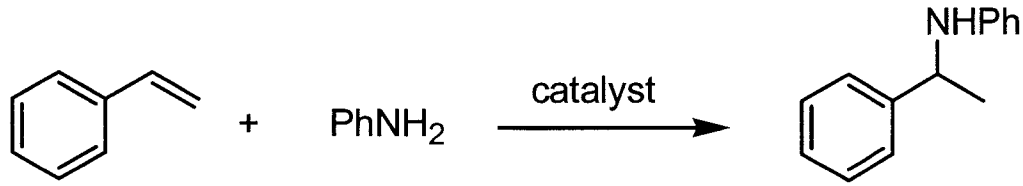


Table 1. Effect of Catalyst Components and Acid on the Hydroamination of Styrene with Aniline[a]

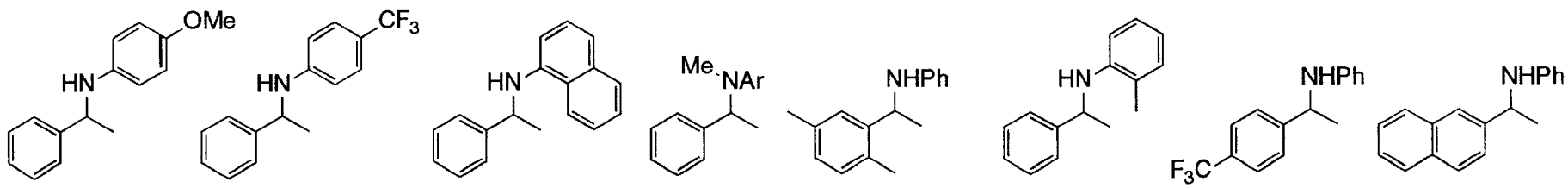
entry	catalyst	yield, %[b]
1	2% $[Pd(PPh_3)_4]$	0
2	2% $Pd(OC(O)CF_3)_2$/8% PPh_3	28
3	2% $[Pd(PPh_3)_4]$/20% TFA	67
4	2% $[Pd(PPh_3)_4]$/20% TfOH	83
5	2% $Pd(OC(O)CF_3)_2$/8% PPh_3/20% TFA	68
6	2% $[Pd(OC(O)CF_3)_2]$/3% DPPF	78
7	2% $[Pd(OC(O)CF_3)_2]$/3% DPPF/20% TfOH	>99
8	2% $[(DPPF)Pd(OTf)_2]$	96

[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.

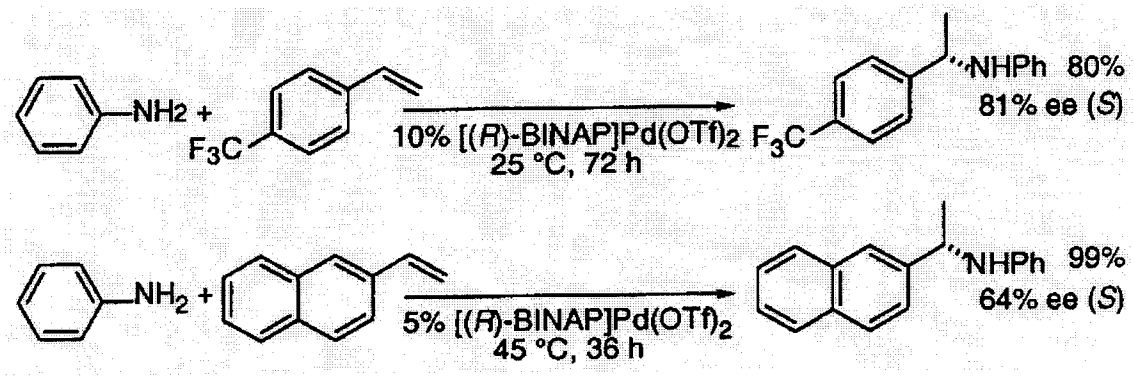
Key components: Pd(II), ligands and counter ion.

M. Kawatsura and John F. Hartwig*, *J. Am. Chem. Soc.* **2000,** *122,* 9546-9547

Pd Catalyzed Hydroamination of Vinylarenes with Arylamines



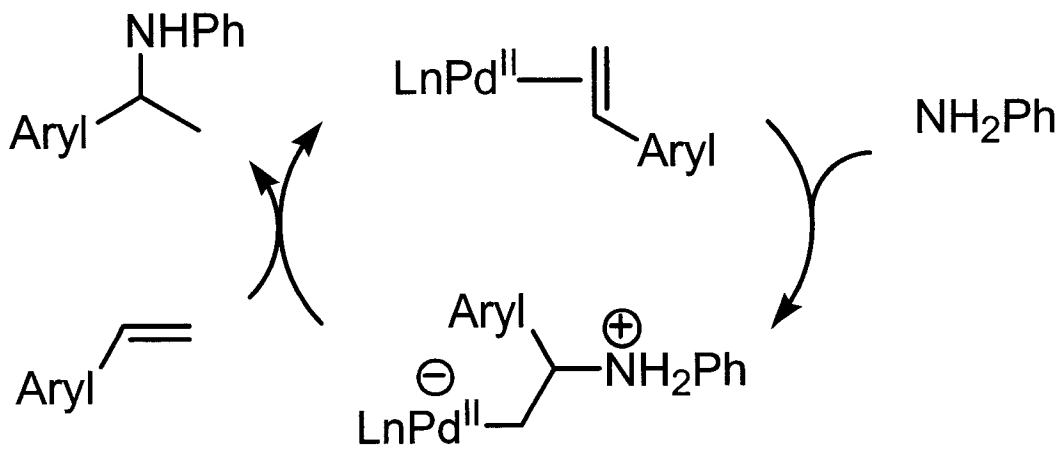
93 %	64 %	94 %	65 %	94 %	64 %	99 %	98 %
2 % $Pd(PPh_3)_4$	2 % $Pd(PPh_3)_4$	2 % $Pd(TFA)_2$	2 % $Pd(TFA)_2$	2 % $Pd(TFA)_2$	2 % $Pd(TFA)_2$	2 % $Pd(TFA)_2$	2 % $Pd(TFA)_2$
20 mol % HOTf	20 mol % HOTf	DPPF	DPPF	DPPF	DPPF	DPPF	DPPF
100 °C 12 h	100 °C 12 h	20 mol % HOTf	20 mol % HOTf	20 mol % HOTf	20 mol % HOTf	20 mol % HOTf	20 mol % HOTf
		100 °C 12 h	100 °C 7 h	100 °C 12 h	100 °C 72 h	25 °C 72 h	25 °C 72 h

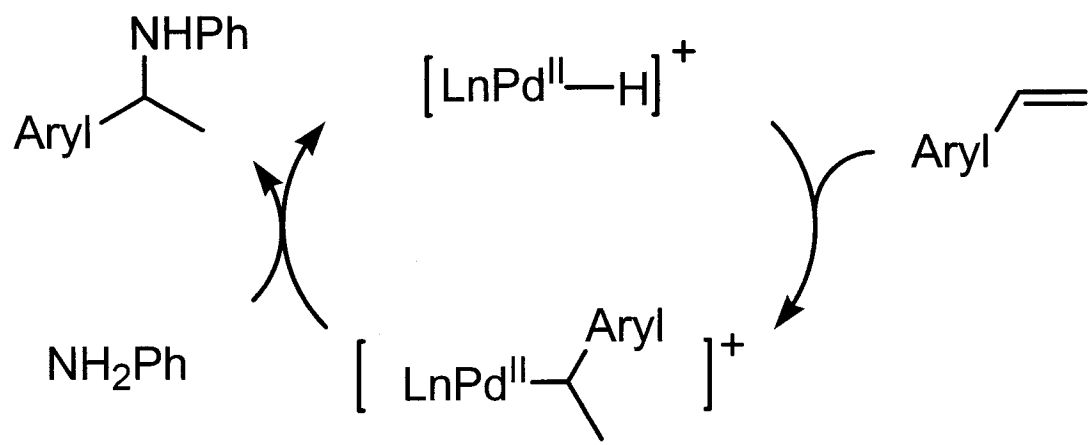


M. Kawatsura and John F. Hartwig*, *J. Am. Chem. Soc.* **2000,** *122,* 9546-9547

John F. Hartwig, *Pure Appl. Chem.* **2004**, *76*, 507-516

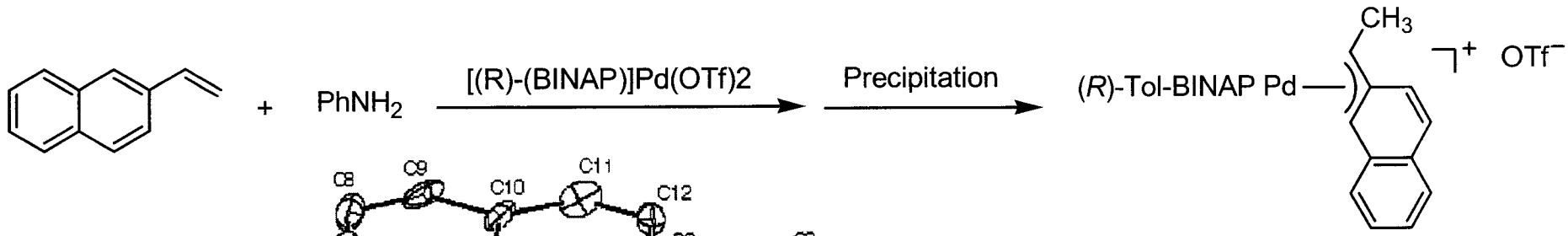
Potential Mechanisms

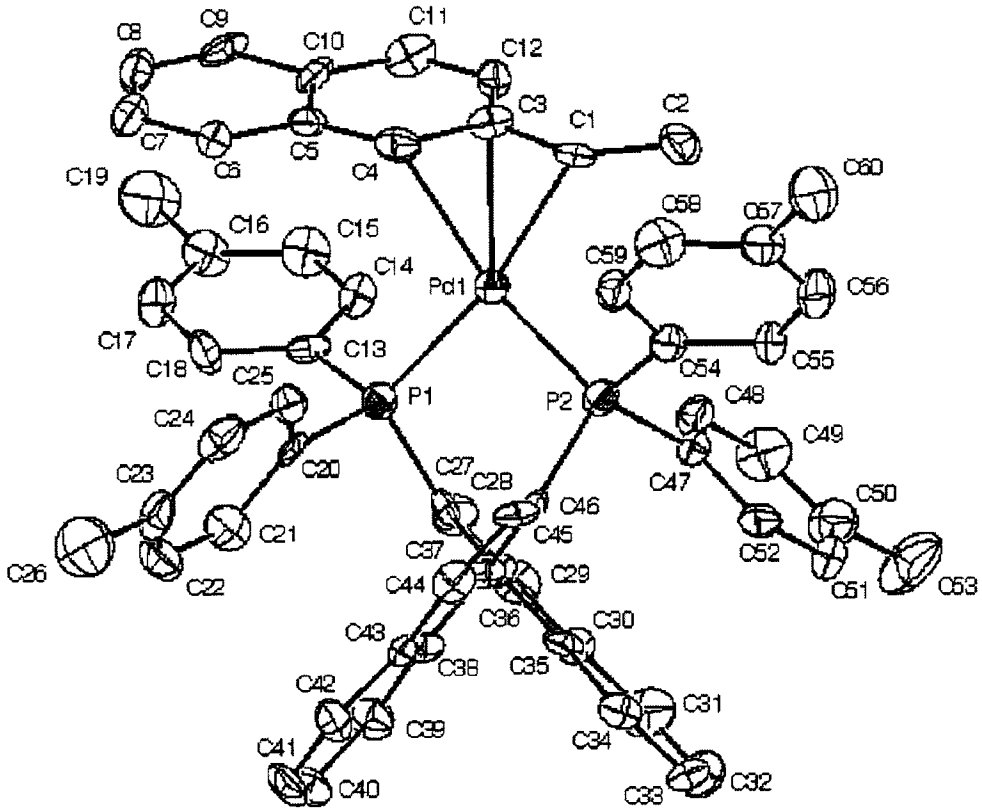




M. Kawatsura and John F. Hartwig*, *J. Am. Chem. Soc.* **2000,** *122,* 9546-9547

Isolated Intermediate: η^3-Arylethyl Complex





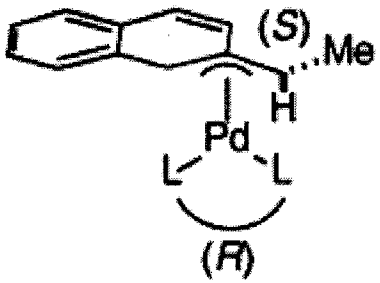
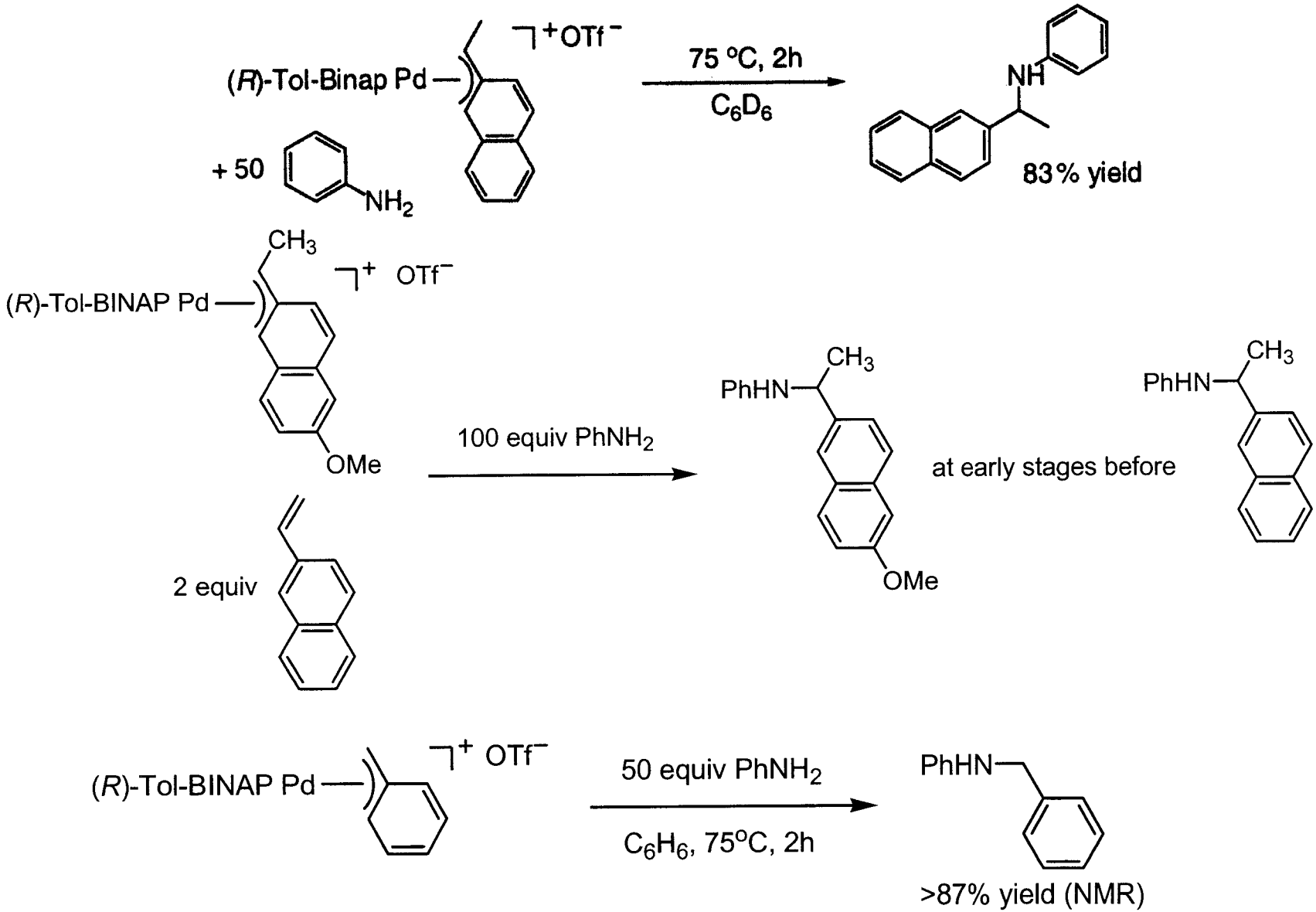


Figure 1. ORTEP plot of **1a** at 50% probability level (hydrogen atoms, triflate anion, and solvent molecules are omitted for clarity). Selected bond lengths: Pd−C1 = 2.157(9) Å; Pd−C4 = 2.323(10) Å; Pd−P1 = 2.329-(3) Å; Pd−P2 = 2.285(2) Å.

Ulrike Nettekoven and John F. Hartwig*, *J. Am. Chem. Soc.* **2002,** *124,* 1166-1167

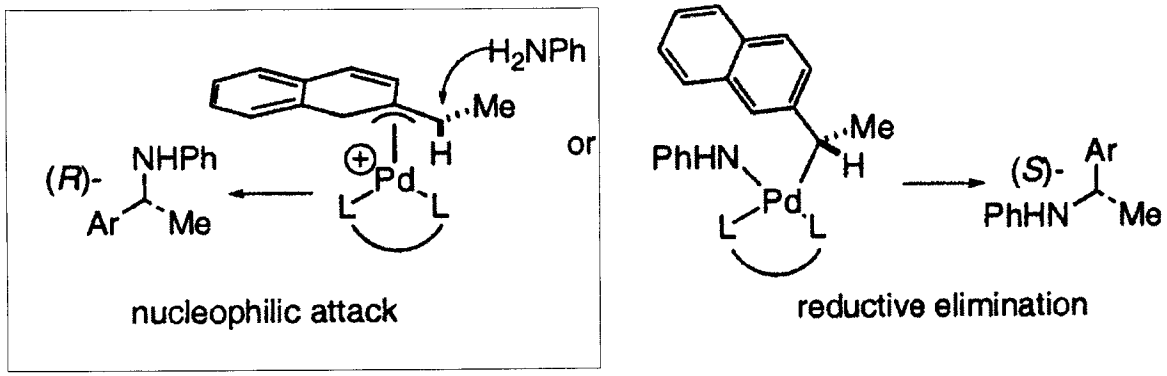
η^3-Arylethyl Complex as Intermediate

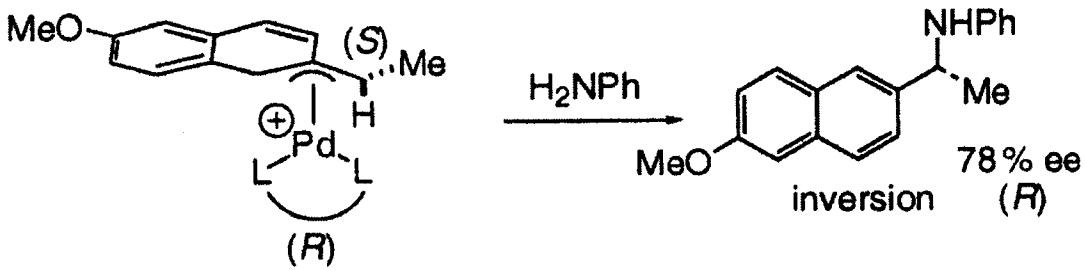


M. Kawatsura and John F. Hartwig*, *J. Am. Chem. Soc.* **2000**, *122*, 9546-9547

John F. Hartwig, *Pure Appl. Chem.* **2004**, *76*, 507-516

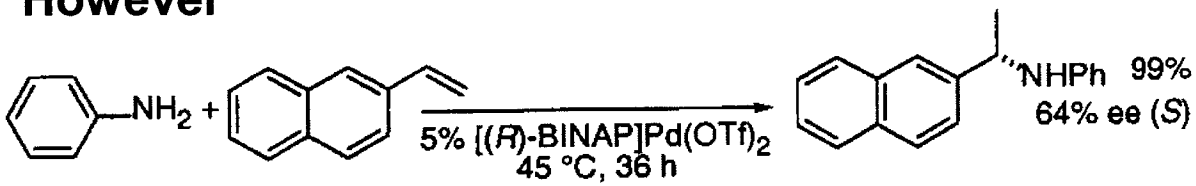
Formation of C-N Bond:





$k = 2.3 \times 10^{-5}\ M^{-1}s^{-1}$

However

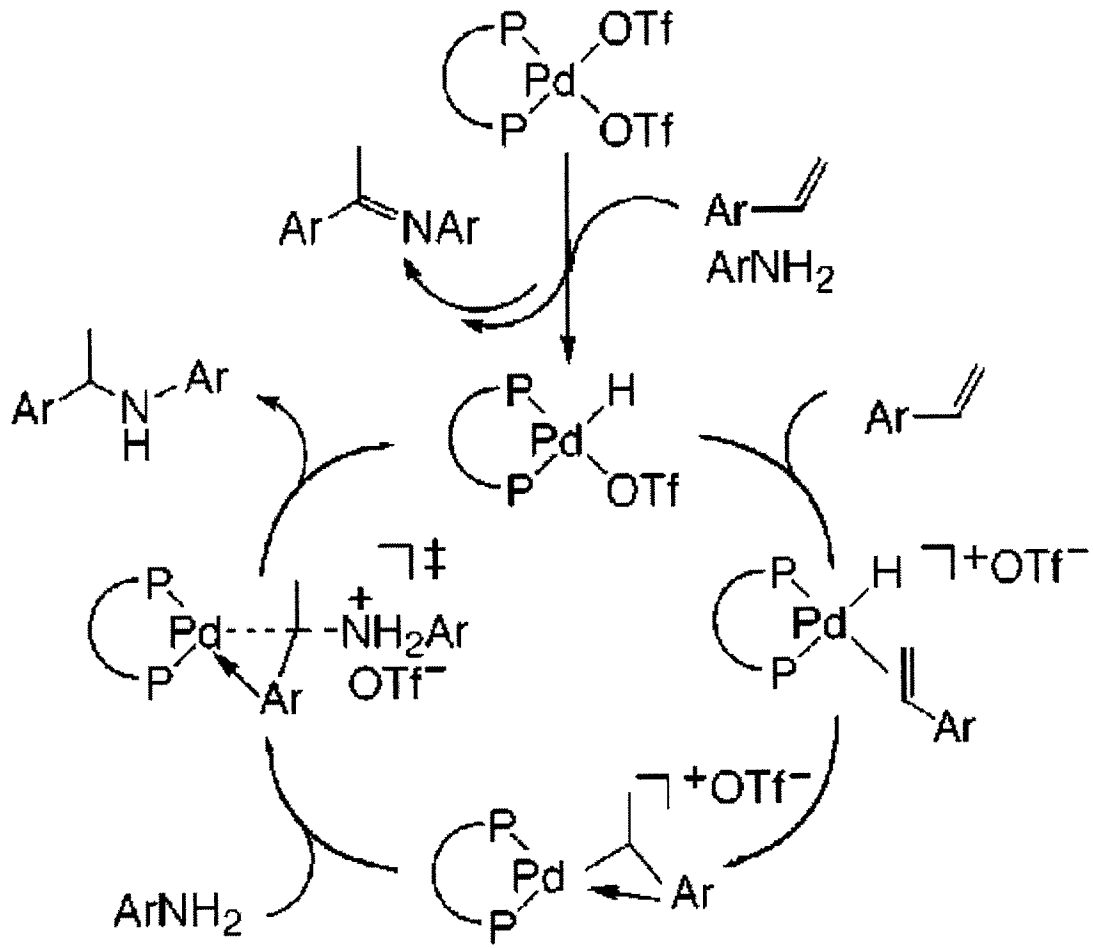


$k = 7.7 \times 10^{-5}\ M^{-1}s^{-1}$

Minor diastereomeric intermediate produces the major enantiomeric product.

John F. Hartwig, *Pure Appl. Chem.* **2004**, *76*, 507-516

Catalytic Cycle



Ulrike Nettekoven and John F. Hartwig*, *J. Am. Chem. Soc.* **2002,** *124,* 1166-1167

Pd Catalyzed Hydroamination with Alkylamines: Catalyst Components

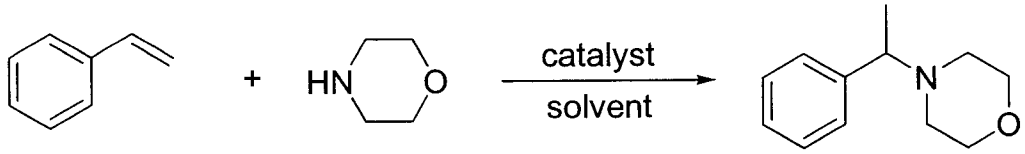


Table 1. Effects of Catalyst, Acid, and Solvent on the Hydroamination of Styrene with Morpholine at 120 °C[a]

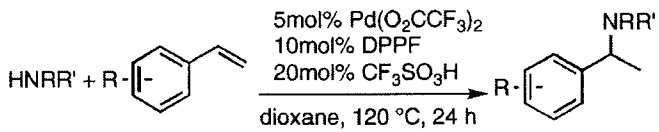
entry	catalyst	solvent	yield[b]
1	5% $Pd(O_2CF_3)_2$/10% DPPF/20% TfOH	dioxane	79
2	5% $Pd(O_2CF_3)_2$/10% DPPF/20% TfOH	toluene	25
3	5% $Pd(O_2CF_3)_2$/5% DPPF/20% TfOH	dioxane	2
4	5% $Pd(DPPF)(OTf)_2$	dioxane	1
5	5% $Pd(DPPF)(OTf)_2$/5% DPPF/10% TfOH	dioxane	74
6	5% $Pd(PPh_3)_4$/20% TfOH	dioxane	6
7	20% TfOH	dioxane	1
8	5% $Pd(O_2CF_3)_2$/20% TfOH	dioxane	1
9	5% $Pd(O_2CF_3)_2$/10% DPPF	dioxane	2
10	5% $Pd(O_2CF_3)_2$/10% DPPF/20% TFA	dioxane	19
11	5% $Pd(O_2CF_3)_2$/10% DPPF/20% NFA[c]	toluene	72
12	5% $Pd(O_2CF_3)_2$/10% DPPF/20% NFA[c]	dioxane	67

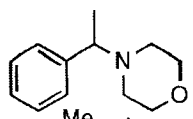
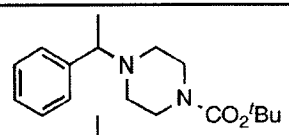
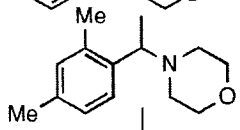
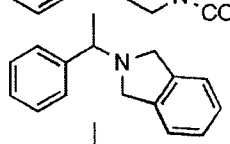
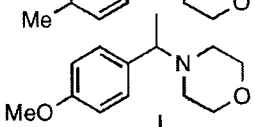
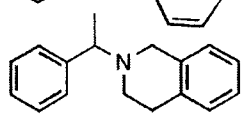
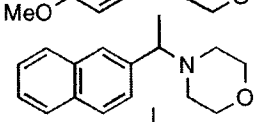
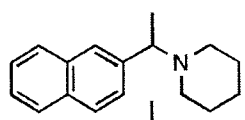
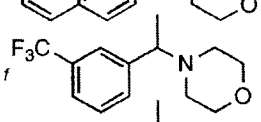
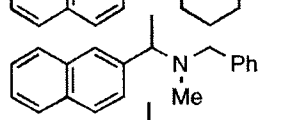
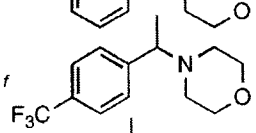
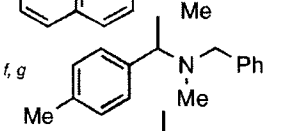
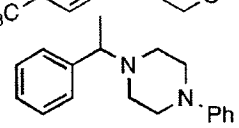
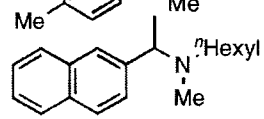
[a] Reaction conditions: 0.4 mmol morpholine, 0.8 mmol styrene, 0.2 mL dioxane, 24 h. [b] GC yields, in percent. [c] NFA = nonafluorobutane sulfonic acid.

Pd(II), ligand and acid cocatalyst are each required.

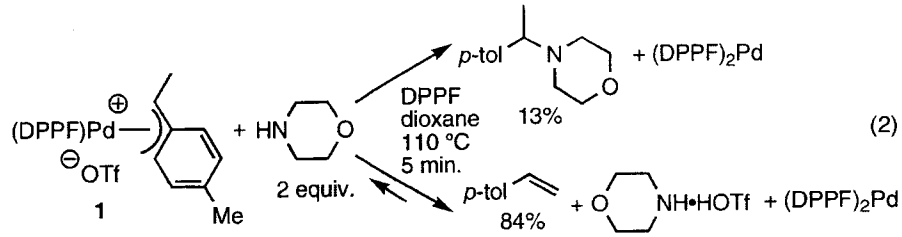
Masaru Utsunomiya and John F. Hartwig*, *J. Am. Chem. Soc.* **2003,** *125,* 14286-14287

Pd Catalyzed Hydroamination with Alkylamines: Scope, Mechanism and Selectivity

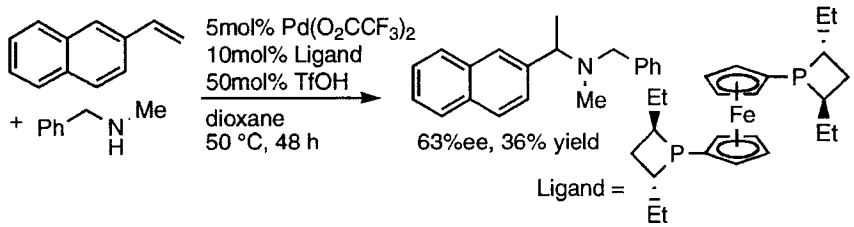


entry	product	yield [b]	entry	product	yield [b]
1		75%	8 [g]		63%
2 [c]		51%	9 [e]		71%
3		76%	10		58%
4 [d]		79%	11 [g]		52%
5 [e, f]		51%	12 [h]		63%
6 [e, f]		48%	13 [e, f, g]		43% [i]
7		72%	14 [g, j]		53%

[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.



(2)



Masaru Utsunomiya and John F. Hartwig*, *J. Am. Chem. Soc.* **2003,** *125,* 14286-14287

Hydroamination of 1,3-Diene with Alkylamines

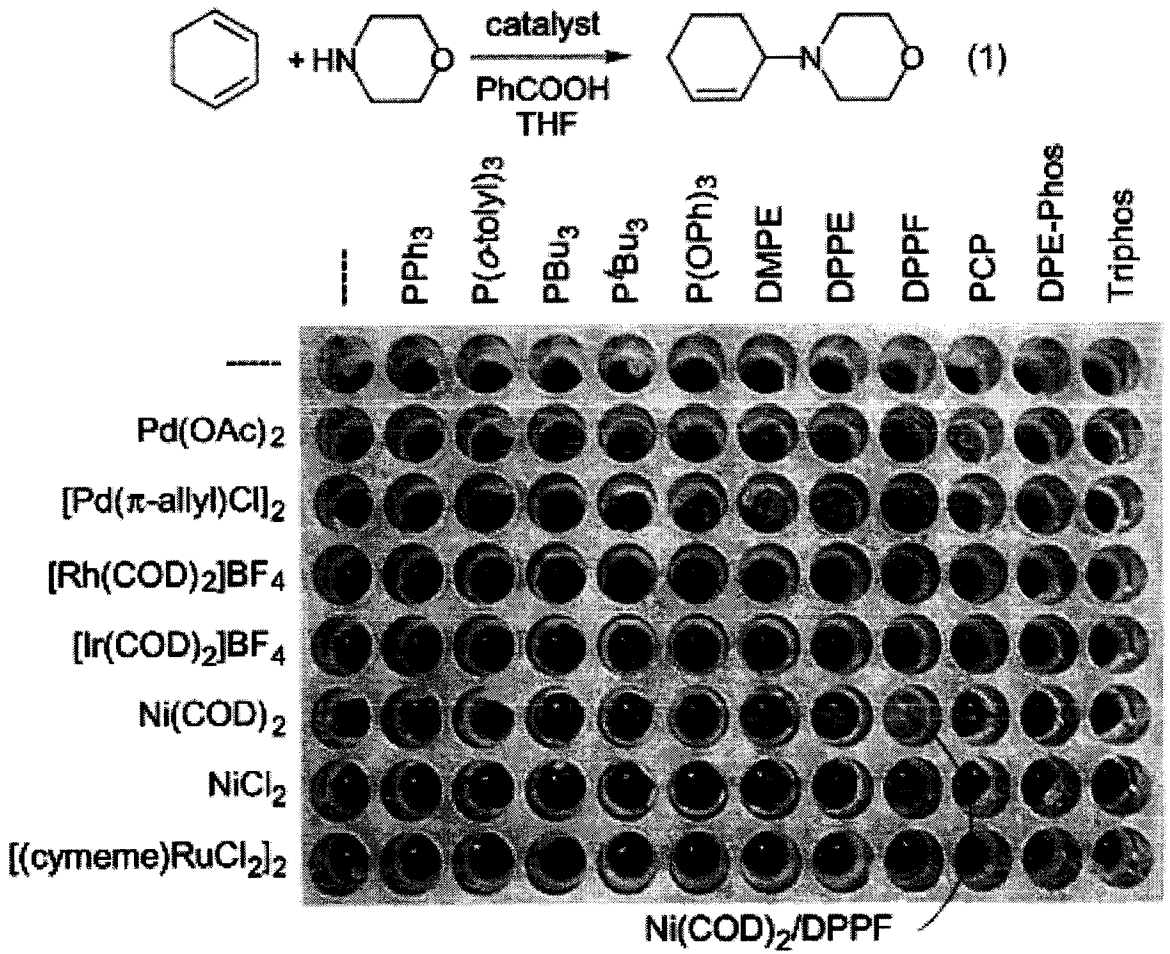
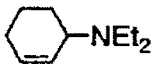
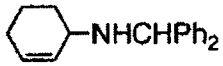
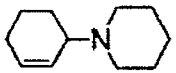
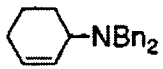
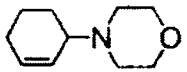
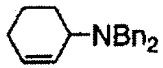
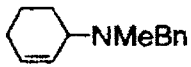
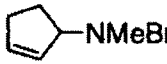
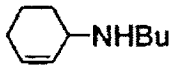
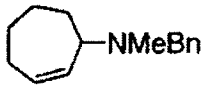
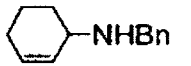
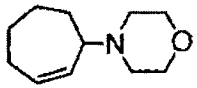
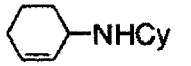
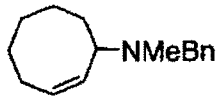
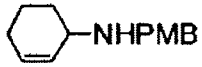


Figure 1. Evaluation of catalysts for eq 1, visualized by the combination of acetaldehyde, sodium nitroferricyanide(III) dihydrate ($Na_2Fe(CN)_5NO \cdot 2H_2O$), and NaOH. DPPF = 1,1′-bis(diphenylphosphino)ferrocene.

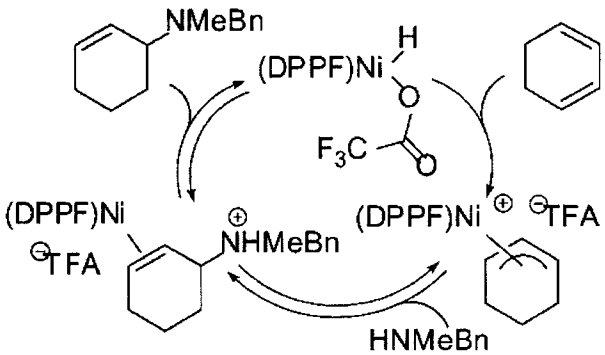
Jan Pawlas, Yoshiaki Nakao, Motoi Kawatsura, and John F. Hartwig* *J. Am. Chem. Soc.* **2002**, 124, 3669-3679

Ni Catalyzed Hydroamination of 1,3-Diene with Alkylamines

Table 1. Nickel-Catalyzed Hydroamination of 1,3-Dienes

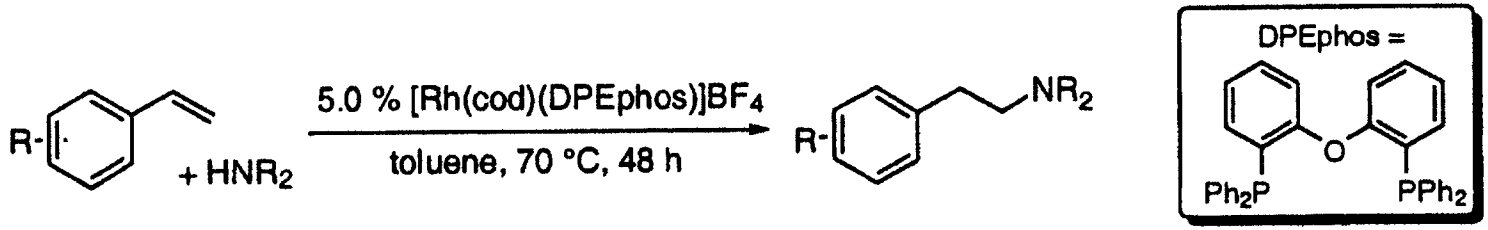
Entry	Product	Time (h)	Yield (%)	Entry	Product	Time (h)	Yield (%)
1		20	78	9		60	85
2		20	82	10		113	56
3		20	80	11		72[b]	71
4		20	89	12		43	91
5		7	89	13		60	94
6		6	93	14		60	83
7		37	82	15		84[b]	38[c]
8		30	87	16		0.5	83[d]

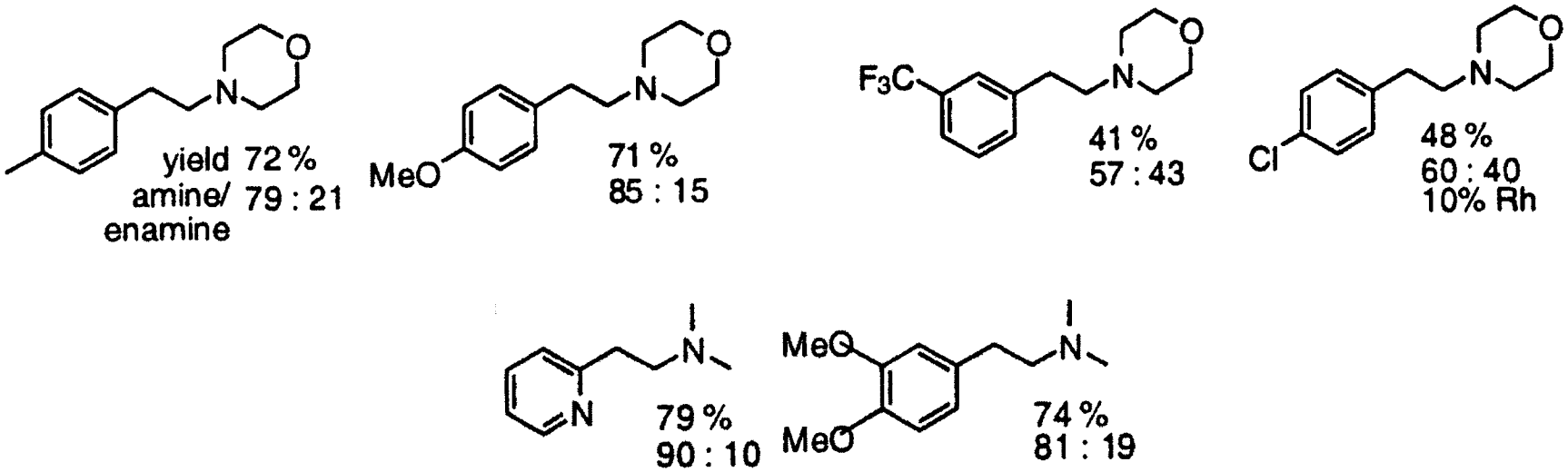
[a] Reaction conditions: 2.0 mmol amine, 4.0 mmol diene, 5.0 mol % DPPF, 5.0 mol % $Ni(COD)_2$, 20 mol % TFA, toluene, 25 °C. [b] At 60 °C. [c] Three regioisomers (GC/MS 14:4:7). [d] Isomer ratio by GC/MS: 27:2:2.



Jan Pawlas, Yoshiaki Nakao, Motoi Kawatsura, and John F. Hartwig* *J. Am. Chem. Soc.* **2002**, 124, 3669-3679

Rh Catalyzed Anti-Markovnikov Hydroamination





John F. Hartwig, *Pure Appl. Chem.* **2004**, *76*, 507-516

Hydroamination vs Oxidative Amination

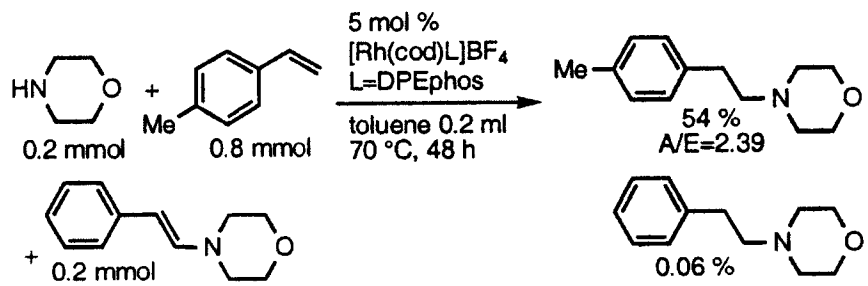
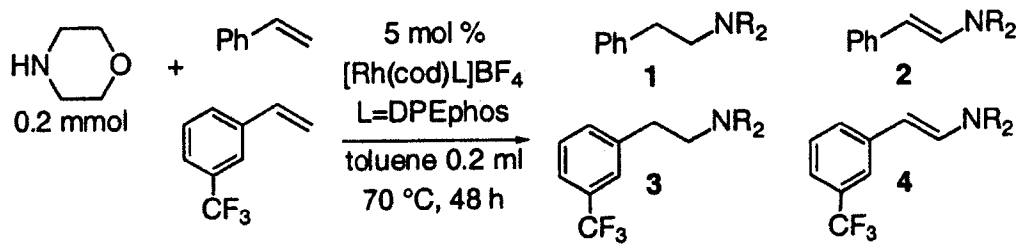


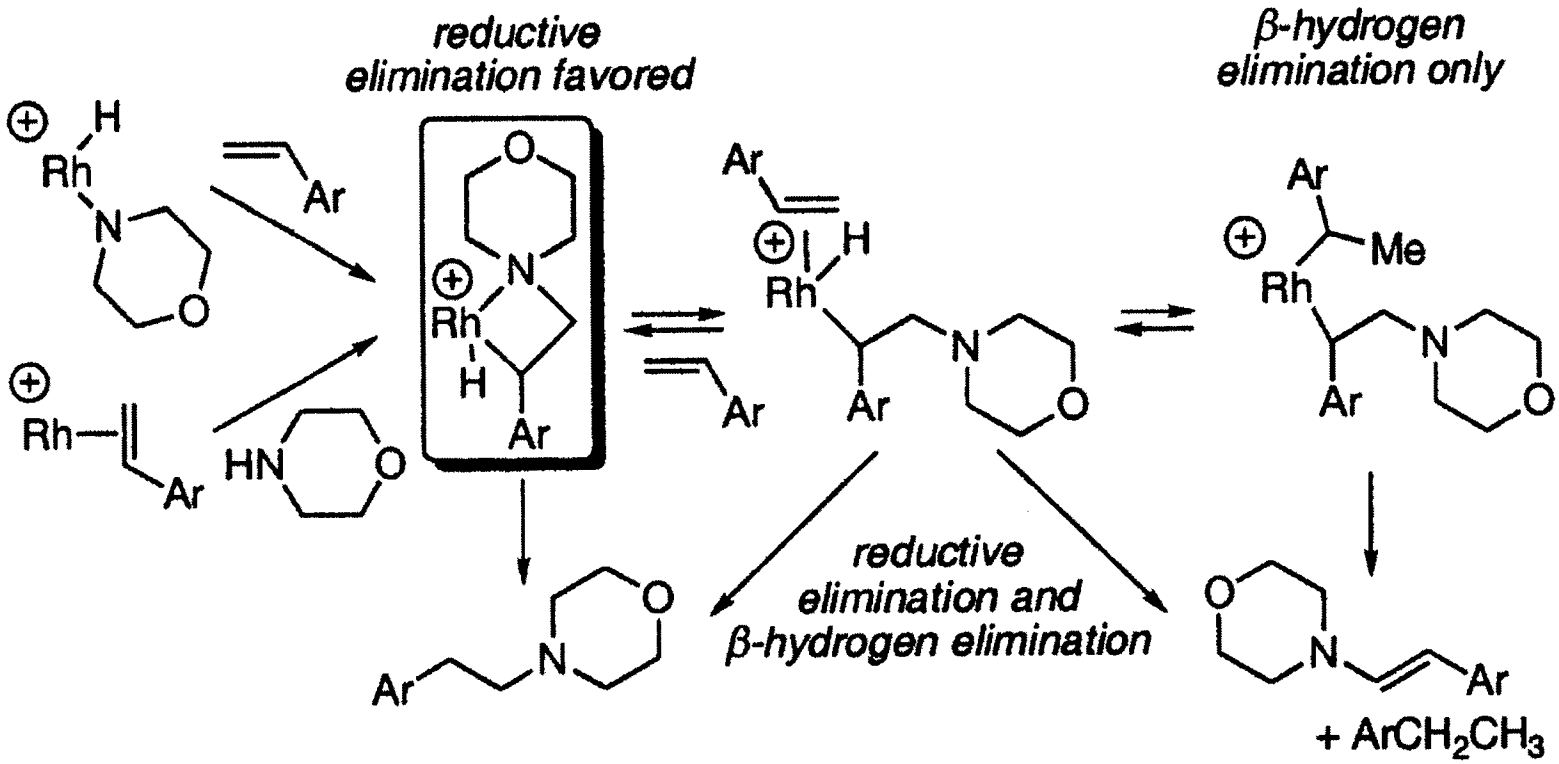
Table 3 Effect of one vinylarene on the hydroamination of another vinylarene.



Ph	F_3C	amine **1** : enamine **2**[a]	amine **3** : enamine **4**[a]
0.8 mmol	-	72 : 28	–
-	0.8 mmol	–	38 : 62
0.4 mmol	0.4 mmol	50 : 50	47 : 53

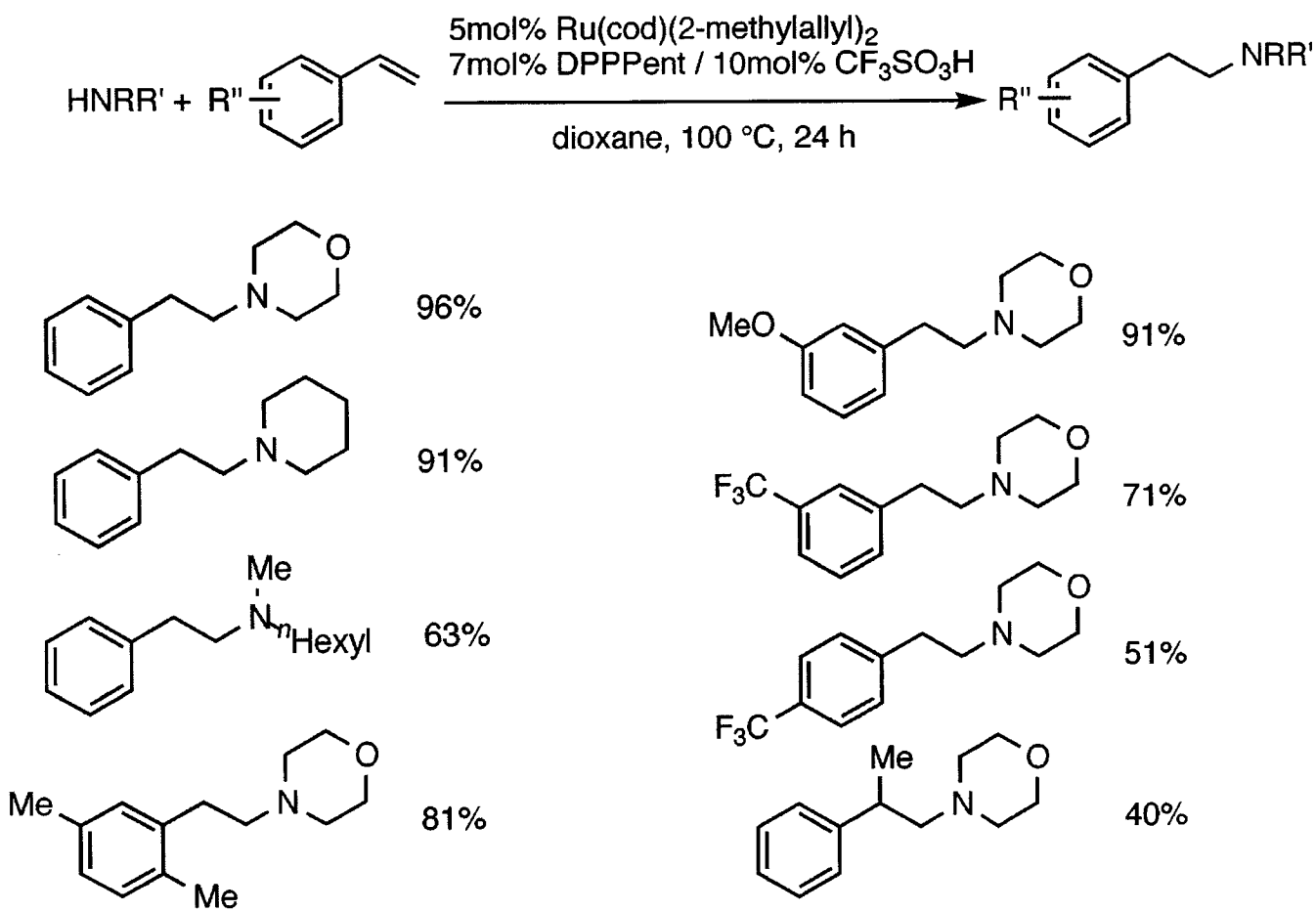
John F. Hartwig, *Pure Appl. Chem.* **2004**, *76*, 507-516

Possible Mechanism



John F. Hartwig, *Pure Appl. Chem.* **2004**, *76*, 507-516

Ru Catalyzed Anti-Markovnikov Hydroamination



Exquisite chemo- and regioselectivity of Ru catalyst.

Masaru Utsunomiya and John F. Hartwig* *J. Am. Chem. Soc.* **2004**, *126*, 2702-2703

Summary

Pd

aryl amines to1,3-dienes and vinyl arenes, alkyl amines to vinyl arenes
Markovnikov
moderate (but promising) enantioselectivity

Ni

alkyl amines to 1,3-dienes

Rh

anti-Markovnikov
competitive oxidative amination

Ru

excellent chemo- and regio (anti-Markovnikov) selectivity.