

Recent Advances in Catalytic Hydroamination Reactions

As countless examples of nitrogen-containing organic molecules can be found in pharmaceutical, agricultural, and industrial areas, the synthesis of carbon-nitrogen bonds is of fundamental interest in organic chemistry. Amongst the numerous methods developed for the synthesis of nitrogen-containing building blocks such as amines, imines, and enamines, the most efficient and atom-economical method is the direct addition of amines to carbon-carbon double and triple bonds—the so called *hydroamination* (Fig. 1).

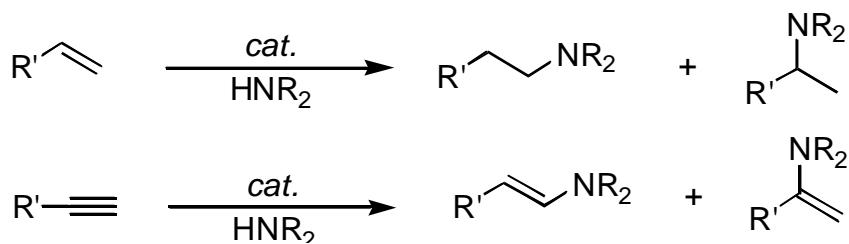


Figure 1: Hydroamination of alkenes and alkynes

Although a general hydroamination procedure applicable to a wide variety of substrates remains elusive, tremendous strides have been made towards the achievement of this challenging goal.¹ Increasing interest in hydroamination has been sparked over the last 3 years as several new catalytic systems for the hydroamination of alkenes and alkynes have been discovered. These catalytic systems and select mechanistic investigations will be described.

¹ Nobis, M., Drießen-Hölscher, B., *Angew. Chem. Int. Ed. Engl.* **2001**, *40*, 3983.

Ricci, A., *Modern Amination Methods*, **2000**, Wiley-VCH, Weinheim.

Müller, T., Beller, M., *Chem. Rev.* **1998**, *98*, 675.

Recent advances in Catalytic Hydroamination Reactions



Ernest Lee

May 27, 2002

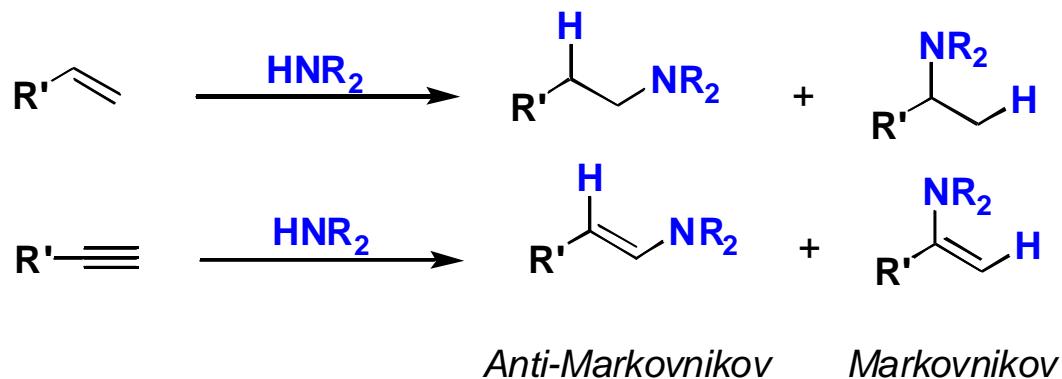
Dept. of Chemistry
University of Toronto

Overview

- Introduction to Hydroamination
- Early Examples
- Intramolecular Hydroamination
 - Alkynes
 - Alkenes
- Intermolecular Hydroamination
 - Alkynes
 - Alkenes
 - Allenes/Dienes
- Concluding Remarks

Introduction

- C-N bond formation is of fundamental interest in organic chemistry
 - Examples of nitrogen-containing compounds can be found in Pharmaceutical, Agricultural, and Industrial fields
- **Hydroamination** - addition of HNR_2 across C-C double/triple bonds
- Most efficient route to amines, imines, enamines
 - no byproducts - 100% atom economy



Ricci, A., *Modern Amination Methods*. Wiley VCH, Weinheim, 2000

Thermodynamics

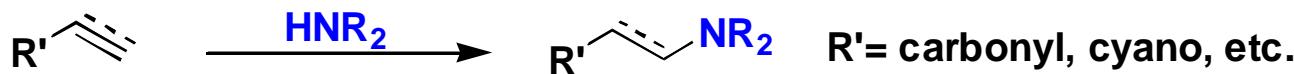


Amine	$D_R G^q$ (kJ/mol)	$D_R H^q$ (kJ/mol)	$D_R S^q$ (J/mol·K)
NH_3	-14.7	-52.7	-127.3
EtNH_2	-33.4	-78.7	-152.2
Et_2NH	-30.0	-79.5	-166.3

- Thermodynamically favourable
- Entropically disfavoured
- Catalysis is essential for overcoming high activation energy

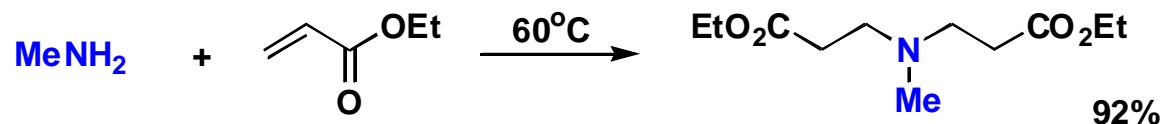
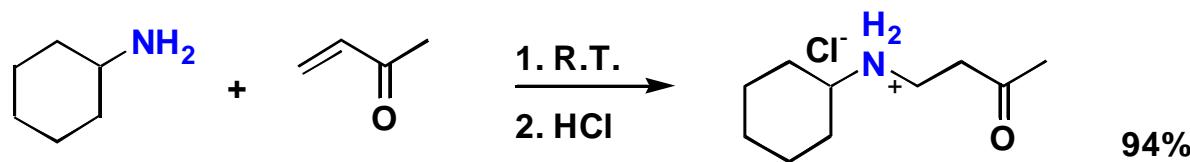
Cornils, B., Herrmann, W. A., *Applied Homogeneous Catalysis with Organometallic Compounds*. Wiley VCH, Weinheim, **2000**

Activated Alkenes/Alkynes



Anti-Markovnikov

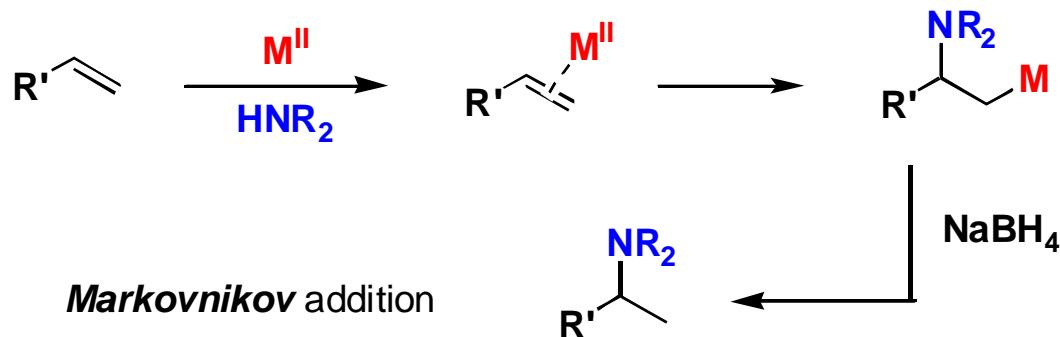
- Examples of additions to activated olefins/alkynes



Jung, M., in Trost, B.M., Fleming, I. *Comp. Org. Synth.* **1991**, 4, 1

Unactivated Alkenes/Alkynes

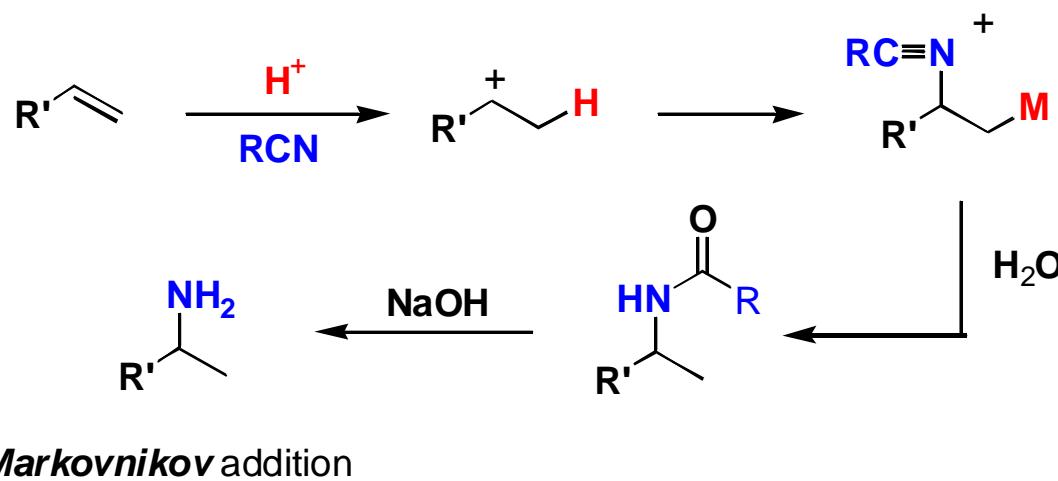
- Requires activation of alkene/alkyne
- Early examples involved stoichiometric additions of metal(II) salts
- M = Hg(II), Fe(II), Zr(II), Ti(II), Pt(II), Mo(II), W(II), etc...



- Problems with polymerization and catalyst poisoning

Hegedus, L., in Trost, B.M., Fleming, I. *Comp. Org. Synth.* **1991**, 4, 551

Ritter Reaction



Markovnikov addition

- Requires strong acid
- Harsh conditions for amide hydrolysis

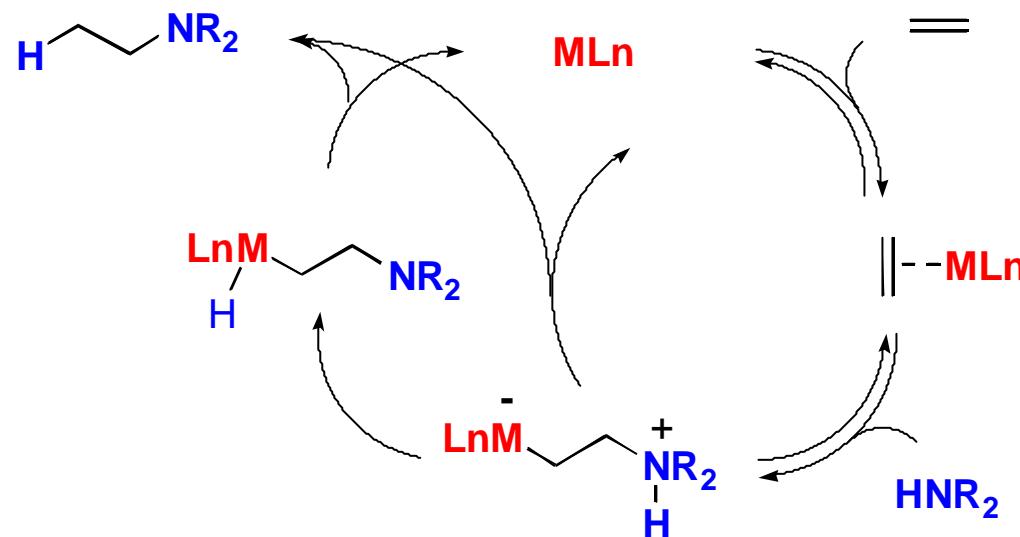
Larock, R., in Trost, B.M., Fleming, I. *Comp. Org. Synth.* **1991**, 4, 269

Activation and Catalysis

3 General methods for metal activation towards hydroamination :

1. Olefin Activation - π coordination
2. Amine Activation - deprotonation
3. Amine Activation - oxidative addition

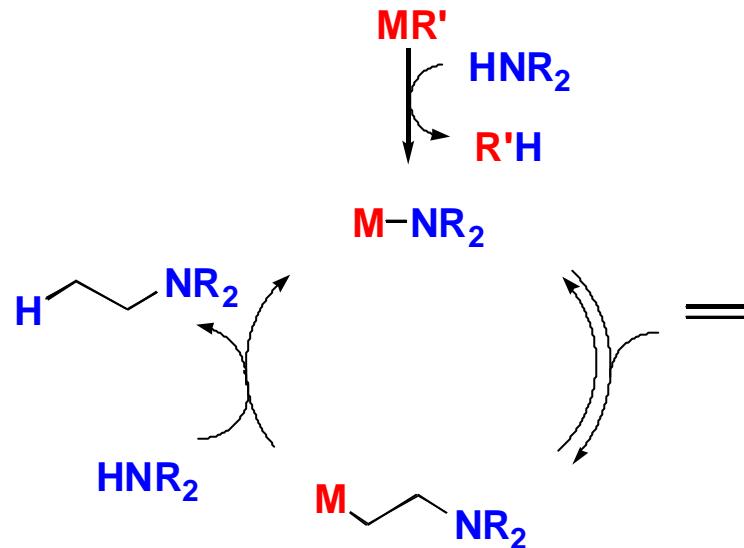
1. Olefin Activation



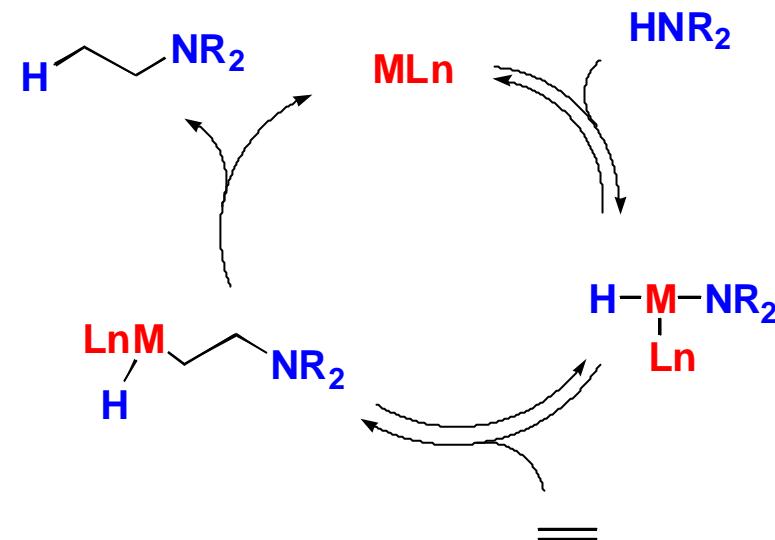
Cornils, B., Herrmann, W. A., *Applied Homogeneous Catalysis with Organometallic Compounds*. Wiley VCH, Weinheim, 2000

Activation and Catalysis (2)

2. Amine Activation - deprotonation

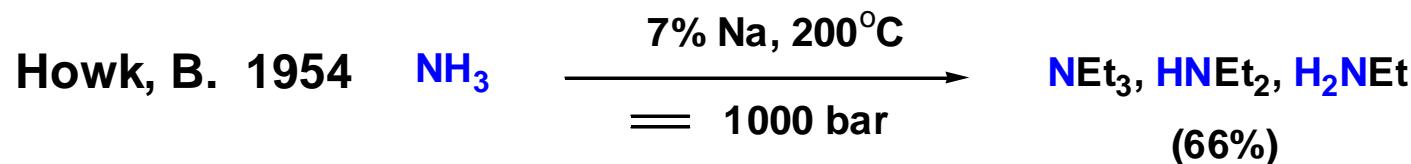


3. Amine Activation - oxidative addition



Cornils, B., Herrmann, W. A., *Applied Homogeneous Catalysis with Organometallic Compounds*. Wiley VCH, Weinheim, 2000

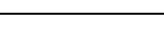
Alkali Metal Catalysis



1954 - 1980

Catalyst : Li, Na, BuLi, EtLi/TMEDA, Et₂NLi, NaNH₂, CsNH₂...

Amines : NH_3 , HNEt_2 , PrNH_2 , BuNH_2 , PhNH_2

	Pressure	Temp	Yield
=	11-1000 bar	80-250°C	24-100%
	-	50-200°C	18-95%
/ \ 	800-1000 bar	200-250°C	3-20%

Müller, T., Beller, M., *Chem. Rev.* **1998**, 675

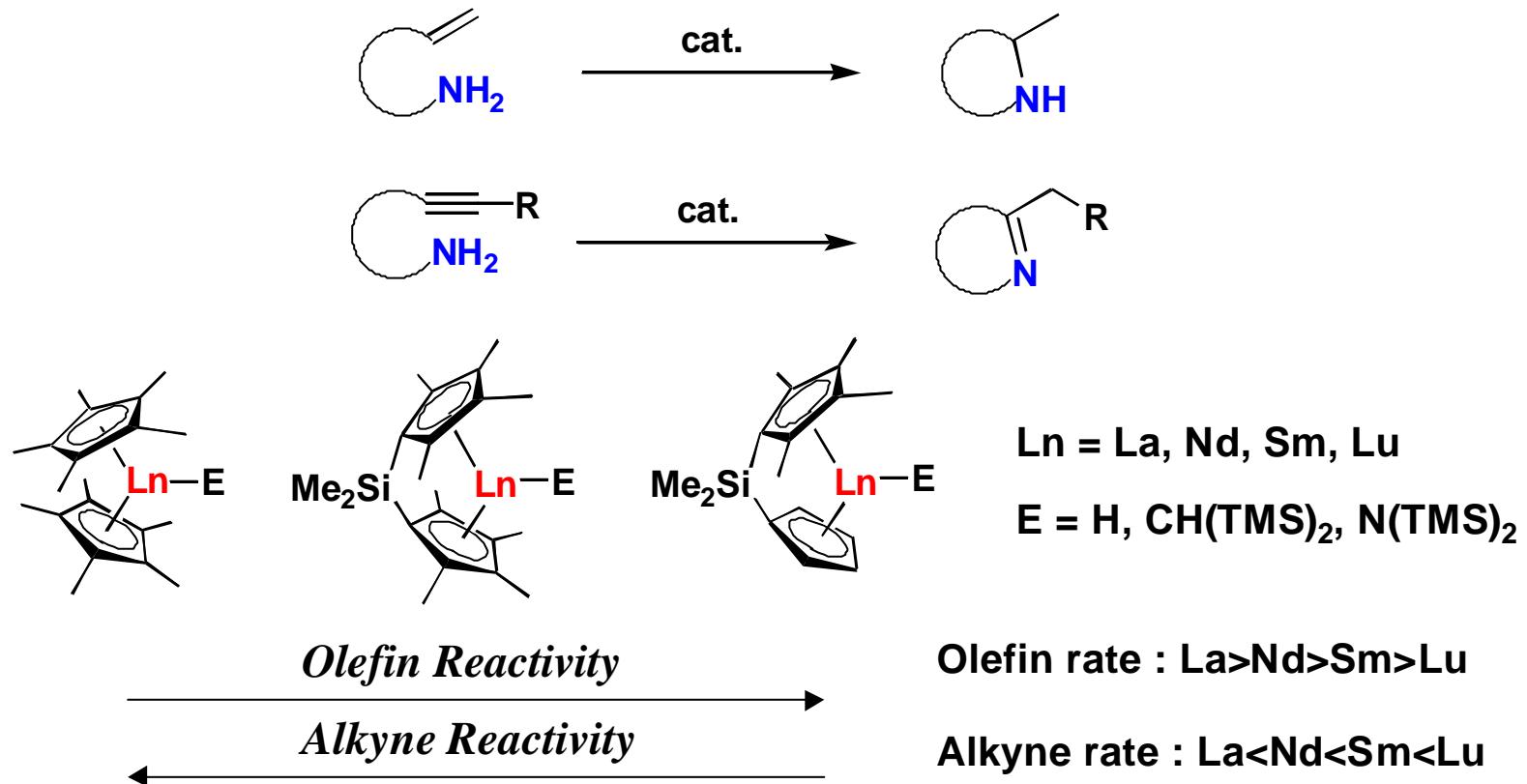
Early Titanium Catalysis



Substrate	Product	Temp	Yield	Substrate	Product	Temp	Yield				
		R.T.	94%			80	88%				
		R.T.	94%			80	89%				
		R.T.	92%	20 mol% CpTiCl ₃ , 40 mol% iPr ₂ EtN 30min, R.T.=THF 80°C=Tol							

Livinghouse, T., et al., J. Am. Chem. Soc. 1992, 5459

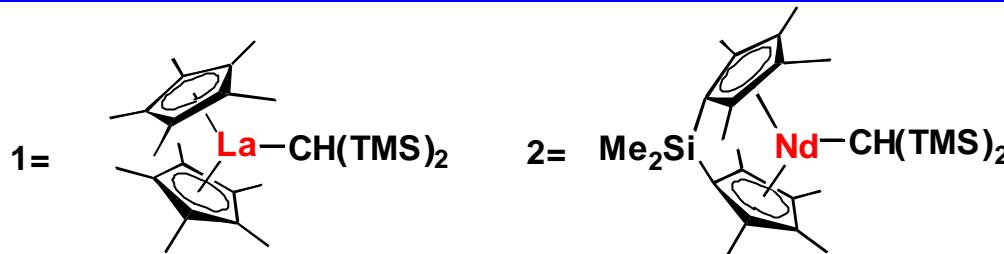
Lanthanide Catalysis

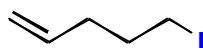
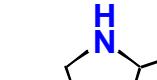
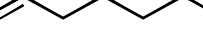
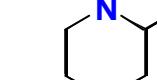
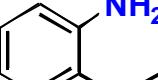
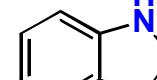
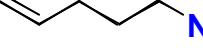
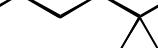
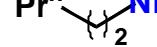


Marks, T., et al., *J. Am. Chem. Soc.* **1992**, 275; **1994**, 10241

Marks, T., Li, Y., *J. Am. Chem. Soc.* **1996**, 9295

Lanthanides (Amino-Olefins)



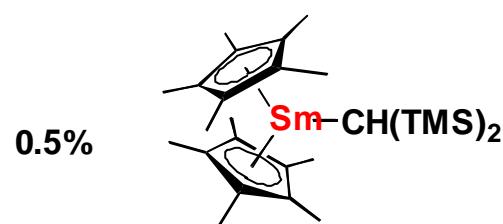
Catalyst	Amino Olefin	Product	N_t/h	Temp	Catalyst	Amino Olefin	Product	N_t/h	Temp
1	 NH_2		140	60	2	 NHMe		11	25
1	 NH_2		5	60	1	 NH_2		12	80
1	 NH_2		45	25	2	 NH_2		0.3	60
1	 NH_2		95	25	2	$n\text{PrNH}_2$		0.4	60

Solvent = d_8 Toluene

Marks, T., et al., J. Am. Chem. Soc. 1992, 275

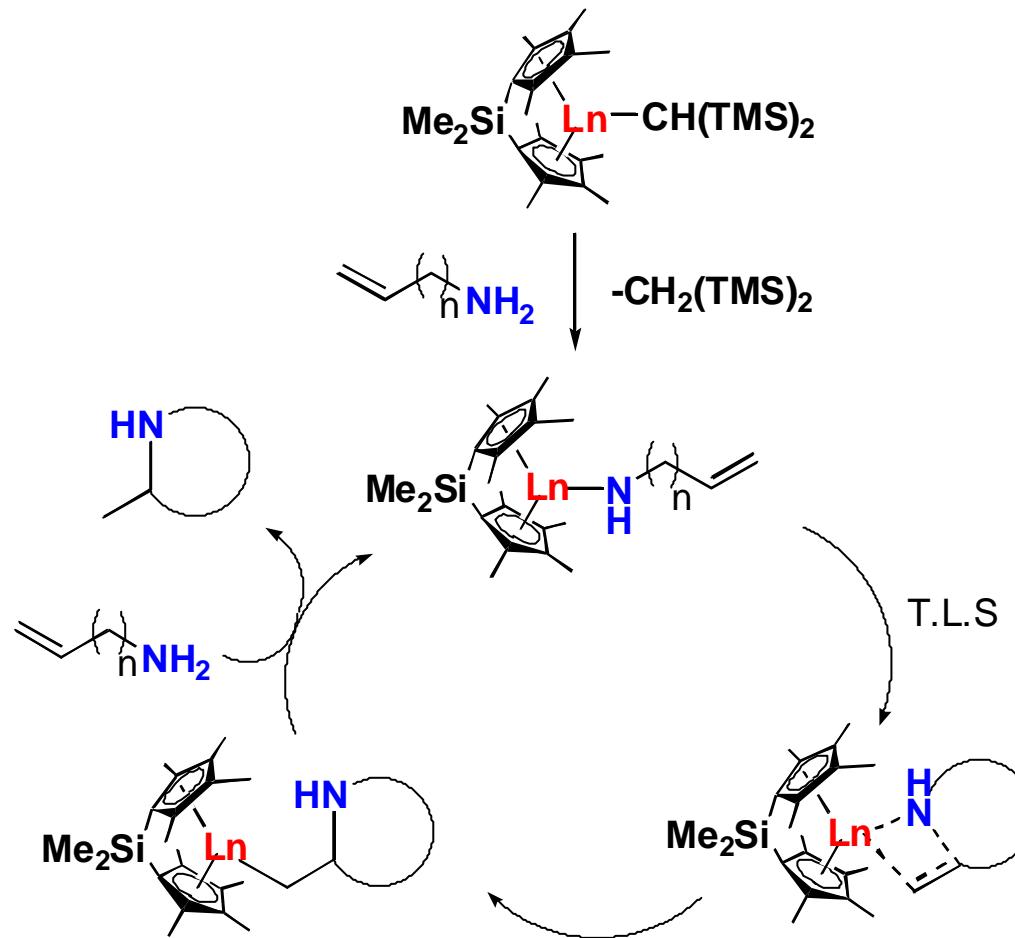
Lanthanides (Amino-Alkynes)

Substrate	Product	N _t /h	Yield	Substrate	Product	N _t /h	Yield
		77	95			4	95
		96	95			129	90
		580	90			47	85
		7600	95			2	85



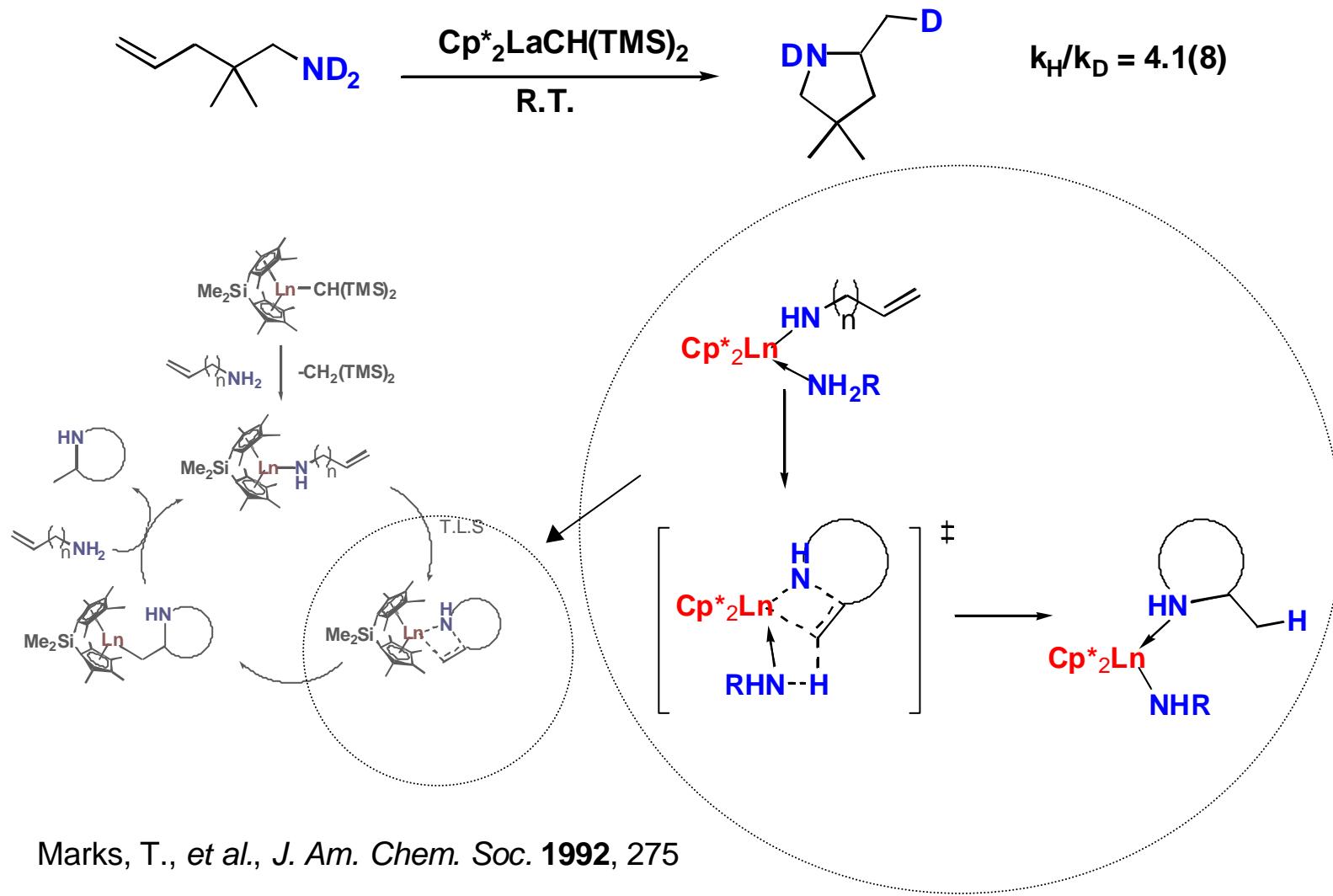
Marks, T., Li, Y., J. Am. Chem. Soc. **1996**, 9295

Lanthanide Mechanism



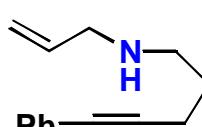
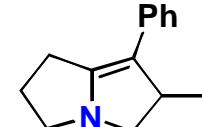
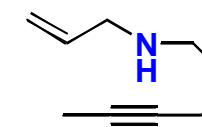
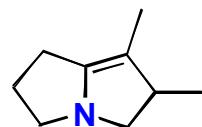
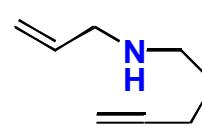
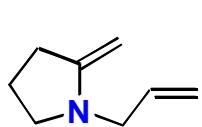
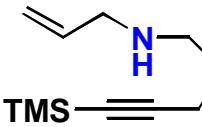
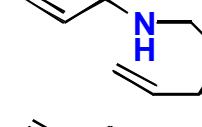
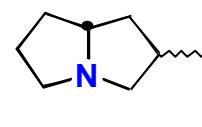
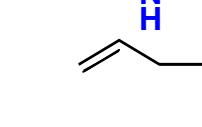
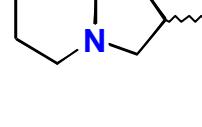
Marks, T., et al., *J. Am. Chem. Soc.* **1992**, 275; **1994**, 10241

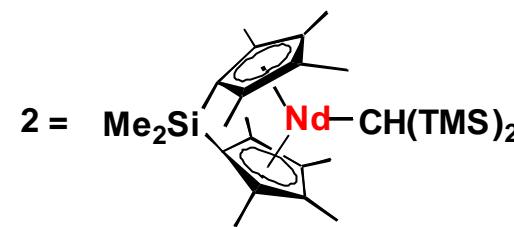
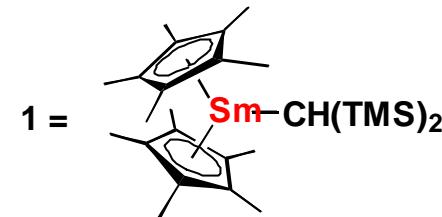
Lanthanide Mechanism Revised



Marks, T., et al., *J. Am. Chem. Soc.* **1992**, 275

Tandem Hydroamination/Cyclization

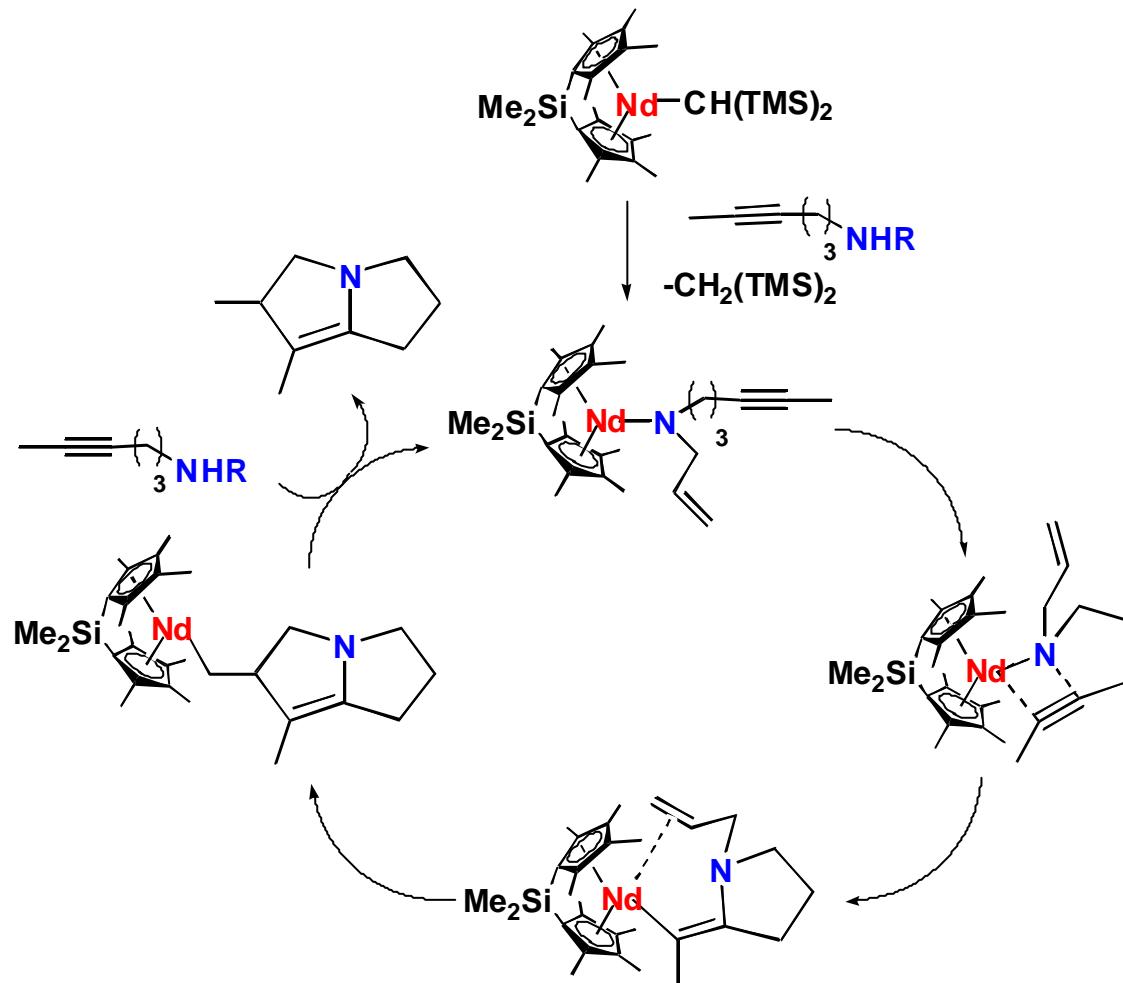
Cat	Substrate	Product	N _f /h	Yield
1			17	85
1			124	75
2*			27	52
1			1.7	91
2			55	93
2			5	88



2% Catalyst, R.T., Benzene

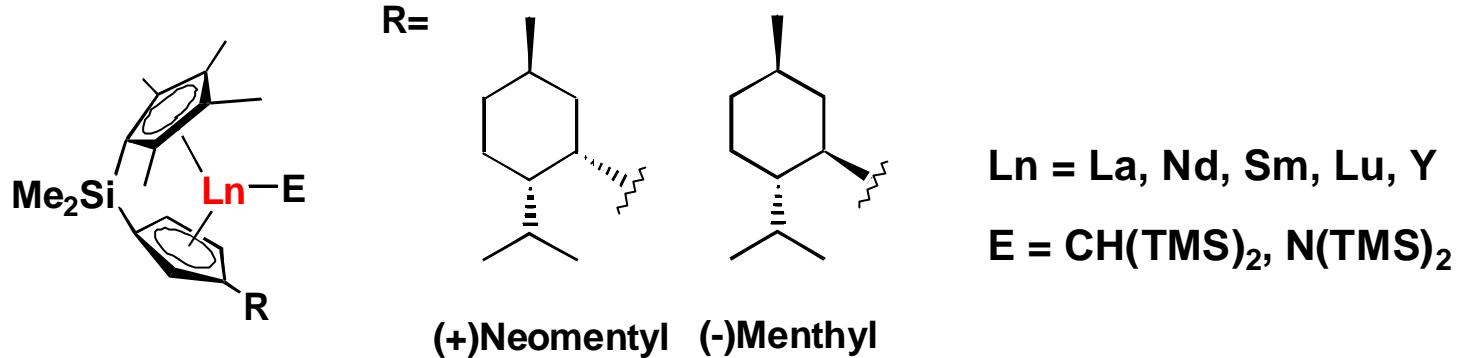
Marks, T., Li, Y., J. Am. Chem. Soc. 1998, 1757

Tandem Hydroamination/Cyclization Mechanism



Marks, T., Li, Y., *J. Am. Chem. Soc.* **1998**, 1757

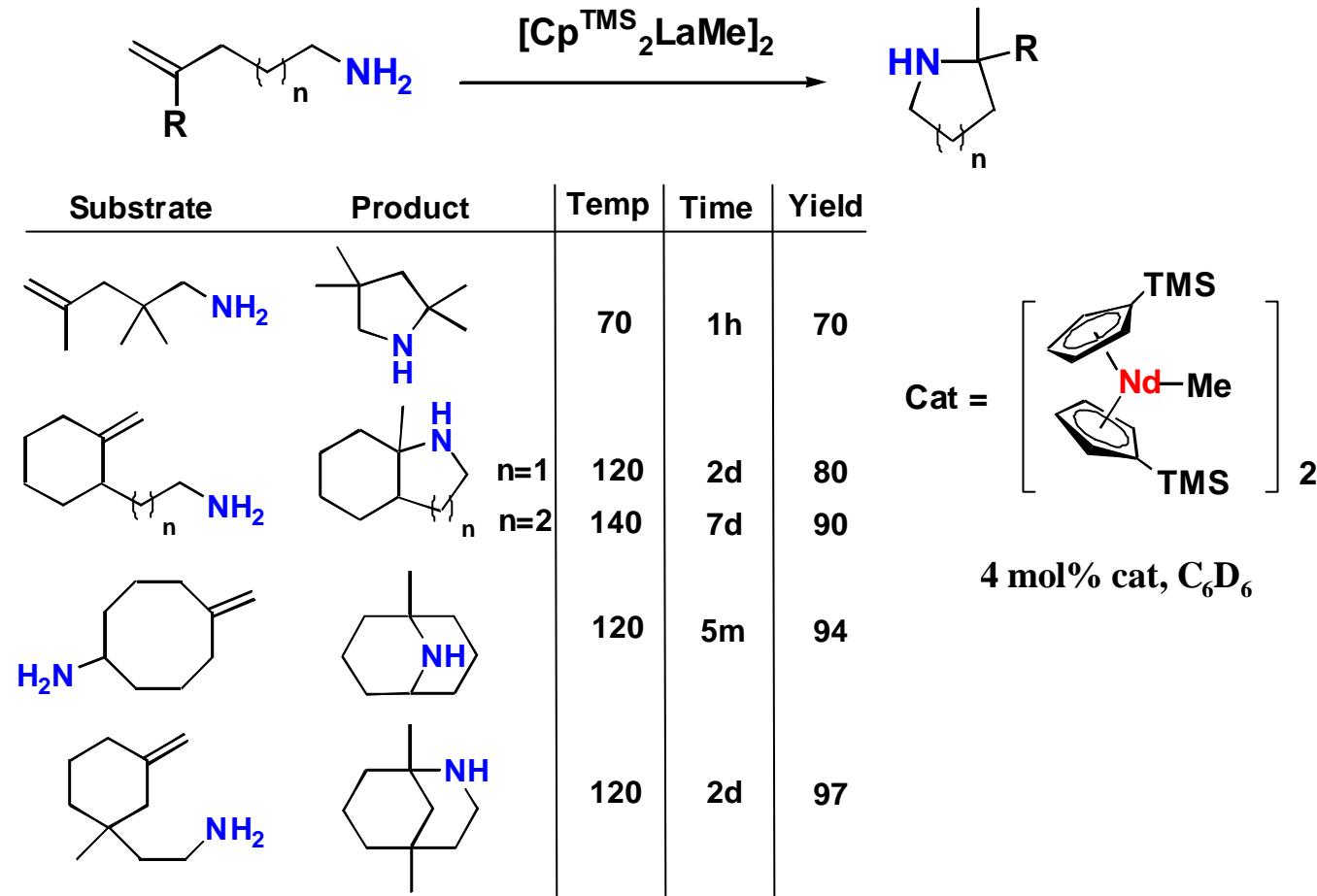
Asymmetric Lanthanide Catalysis



Amino Olefin	Product	Catalyst	ee	N _f /h	Temp
		NmCp ₂ Nd CH(TMS) ₂	64	93	0
		MtCp ₂ Sm CH(TMS) ₂	72	11	0
		NmCp ₂ Sm CH(TMS) ₂	58	33	0
		NmCp ₂ La CH(TMS) ₂	31	-	25
		MtCp ₂ Sm CH(TMS) ₂	15	2	25
		NmCp ₂ Sm CH(TMS) ₂	17	2	25

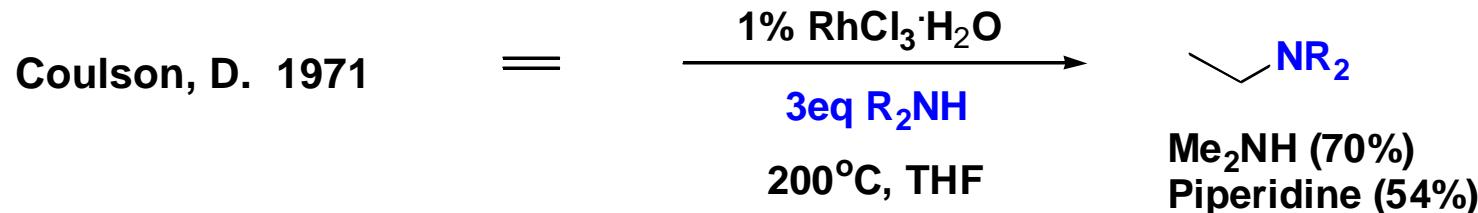
Marks, T., et al., *J. Am. Chem. Soc.* **1994**, 10241

Further Lanthanide Catalysis

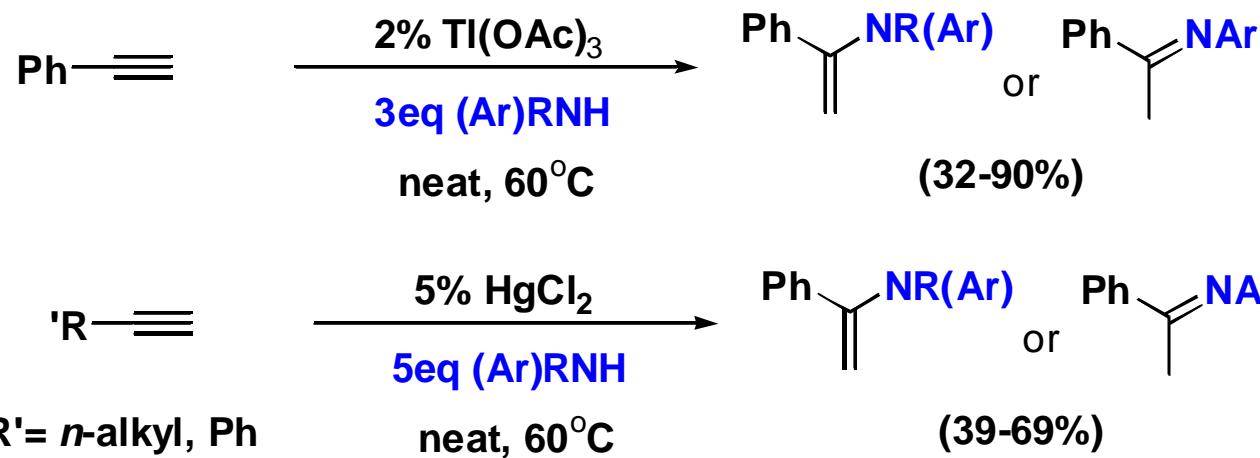


Molander, G., Dowdy, E., *J. Org. Chem.* **1998**, 8983

Early Intermolecular Hydroaminations

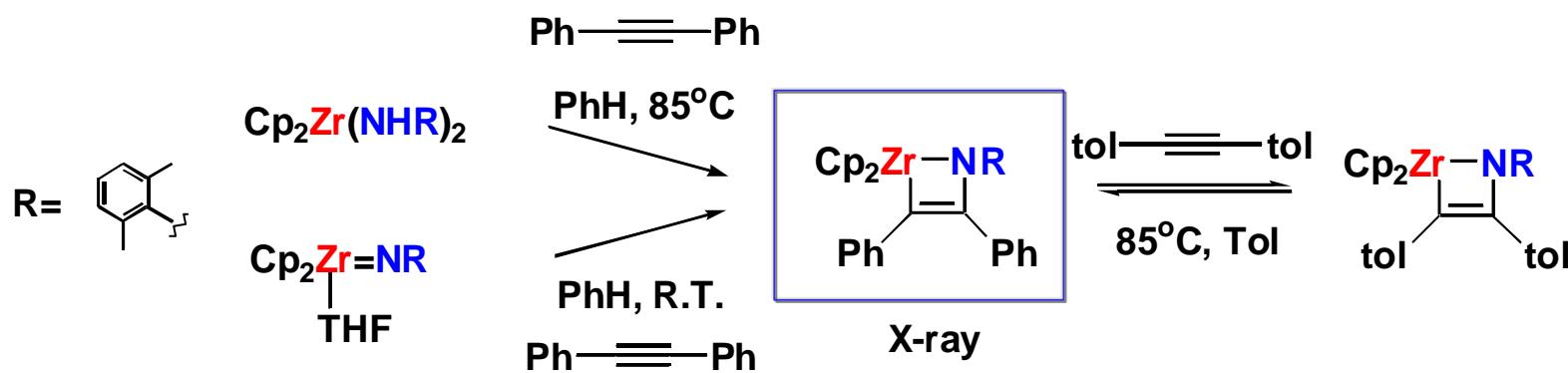
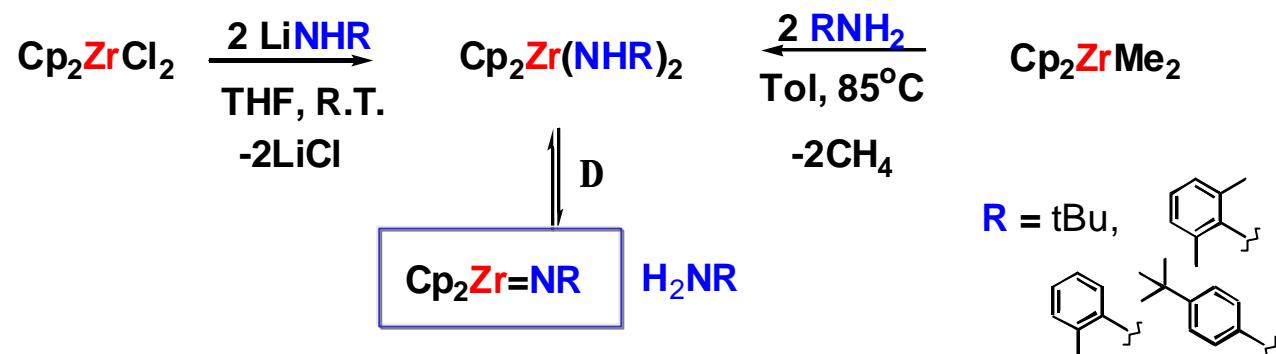


Barluenga, J. 1975, 1980



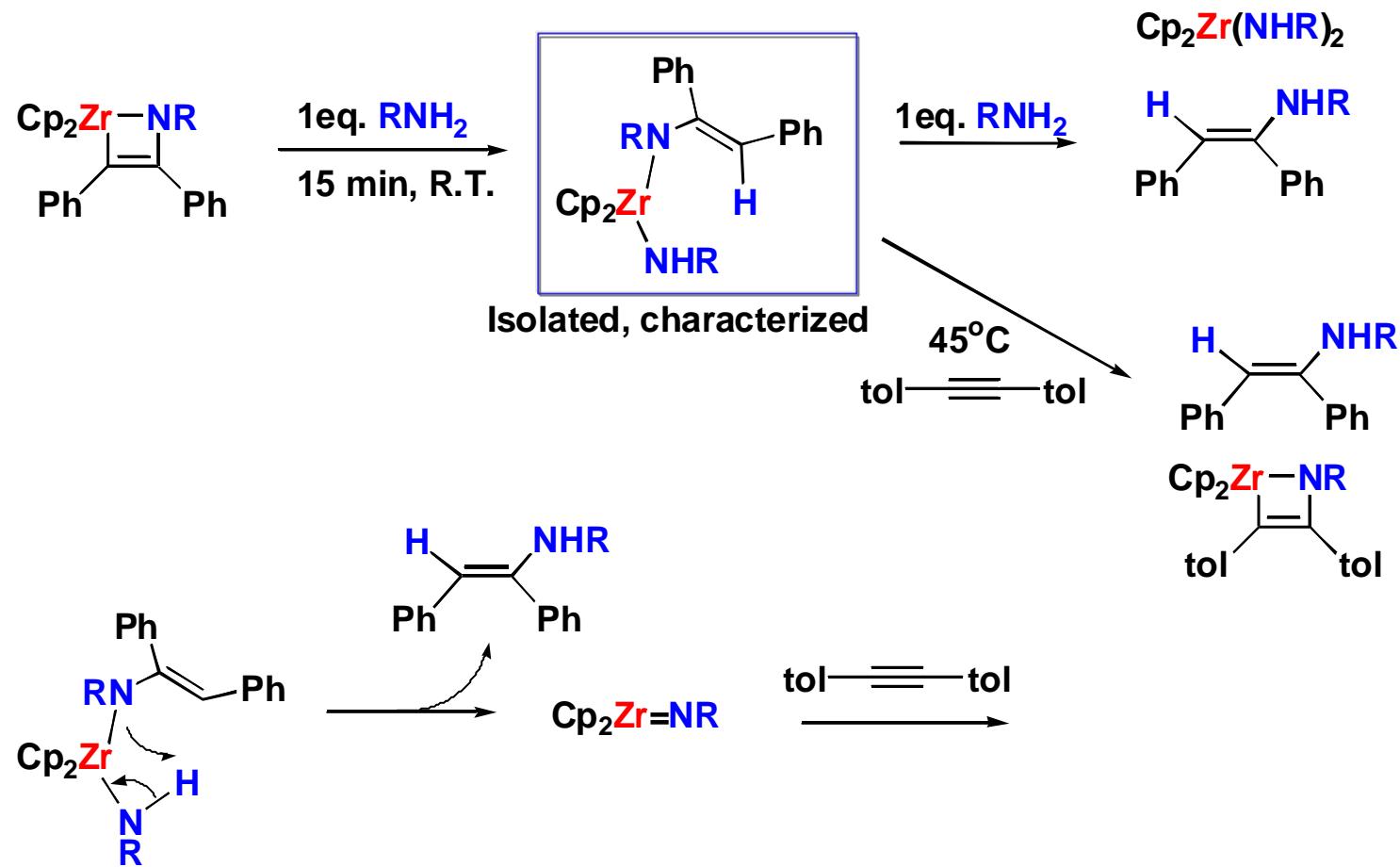
Müller, T., Beller, M., *Chem. Rev.* **1998**, 675

Zirconium Catalysis



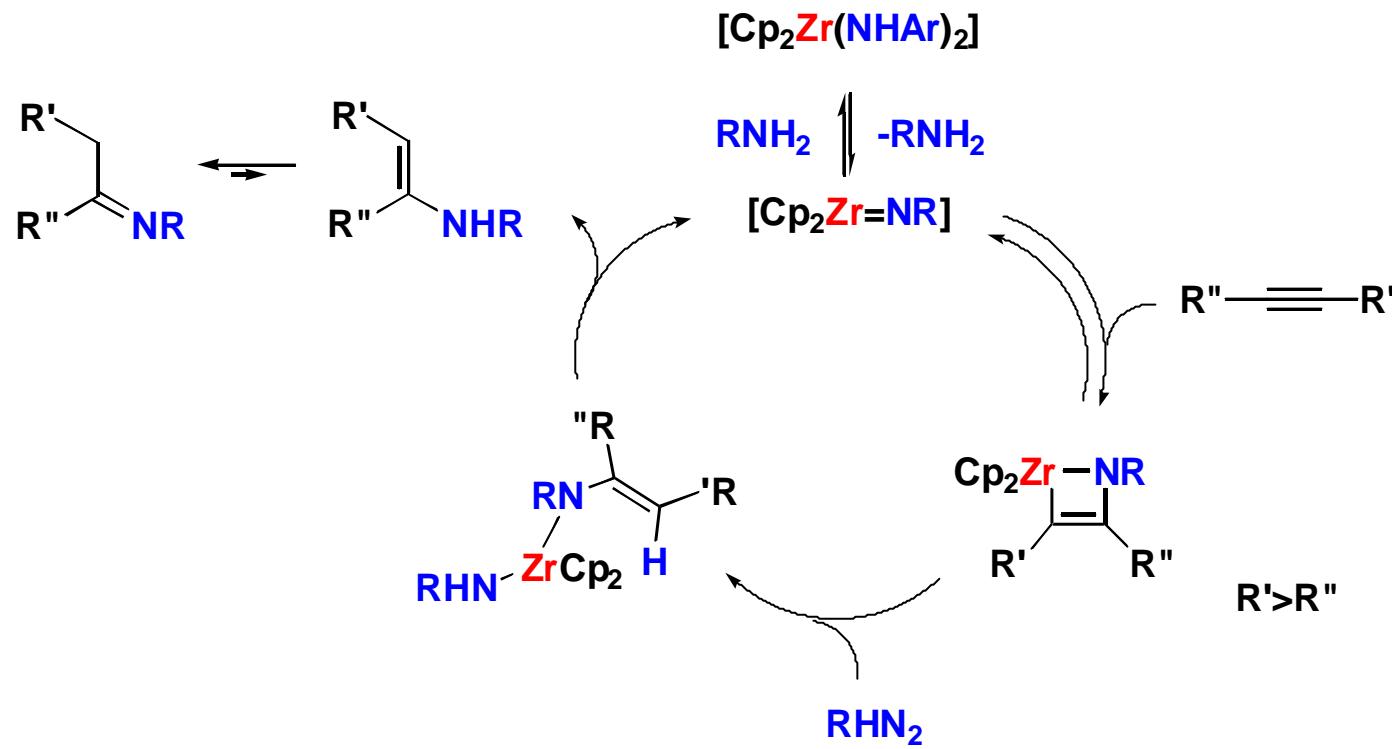
Bergman, R.G., et al., J. Am. Chem. Soc. 1992, 1708

Zirconium Catalysis (2)



Bergman, R.G., et al., *J. Am. Chem. Soc.* 1993, 2753

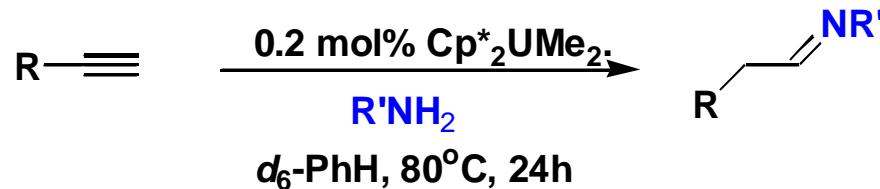
Zirconium Mechanism



R=Ph, Me, tBu : 3 mol% cat., 100°C, N_f/h=0.2-0.04

Bergman, R.G., et al., J. Am. Chem. Soc. 1992, 1708

Actinide Catalysis

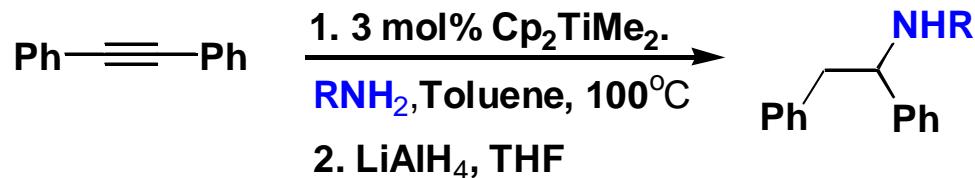


R	R'	Yield	R	R'	Yield
TMS	Me	95%	t-Bu	Me	95%
TMS	Et	95%	t-Bu	Et	95%
n-Bu	Me	70%	Ph	Et	50%
n-Bu	Et	95%			

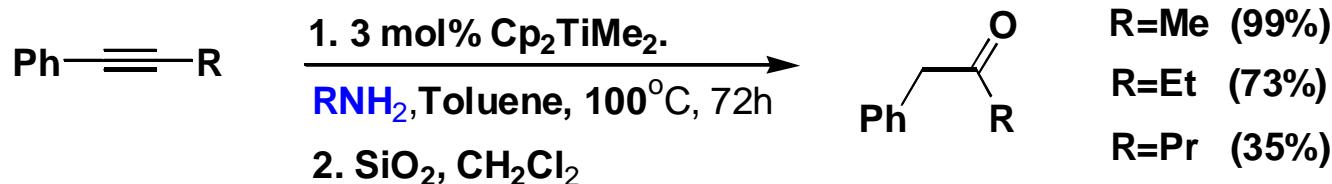
- Excellent yields for alkyl terminal alkynes
- Anti-Markovnikov regiochemistry
- Low catalyst loading

Eisen, M., *et al.*, *Organometallics*. **1996**, 3773

Titanium Catalysis



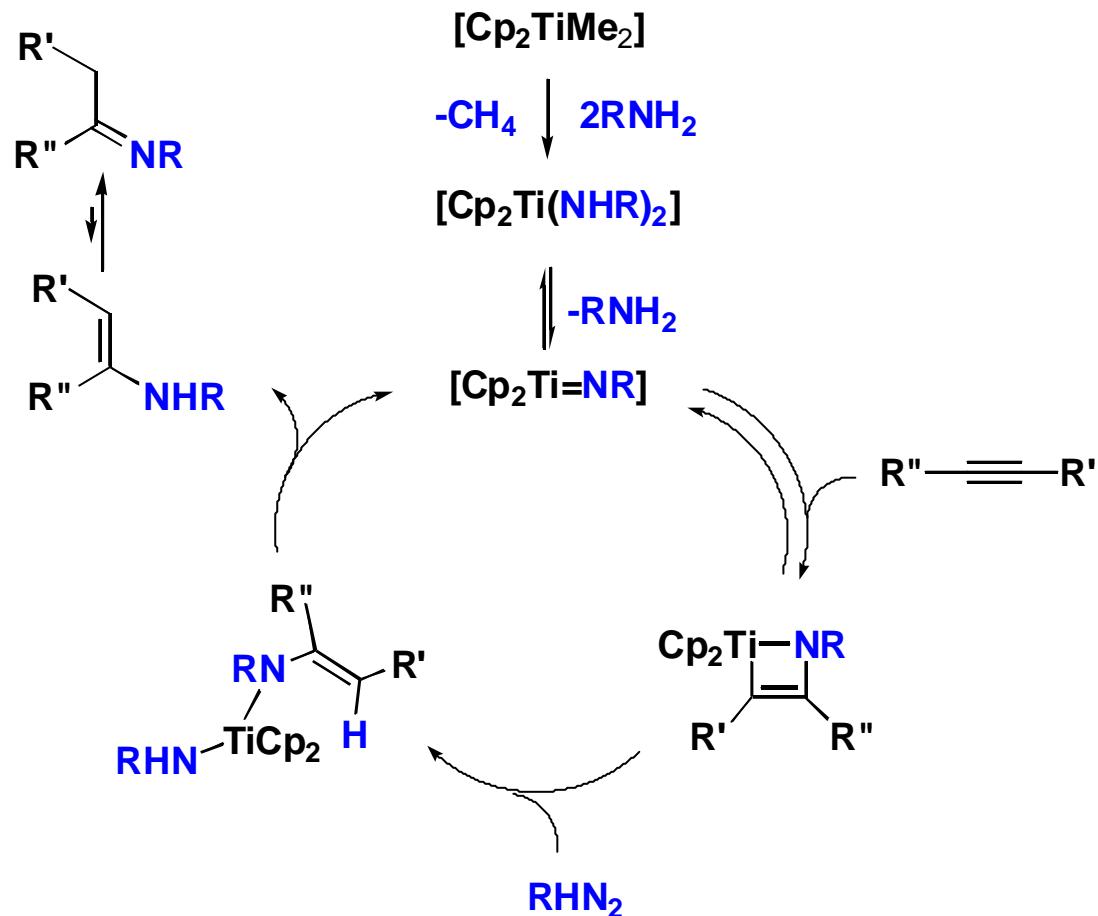
R	Yield	SiO ₂	R	Yield	SiO ₂
Ph	62%	92%	t-Bu	86%	91%
2,6-Me ₂ C ₆ H ₃	68%	89%	Cy	86%	65%
4-F-C ₆ H ₄	63%	93%	Bn	3%	5%



- High temperatures required
- Problems with unhindered alkyl amines
- No terminal alkynes

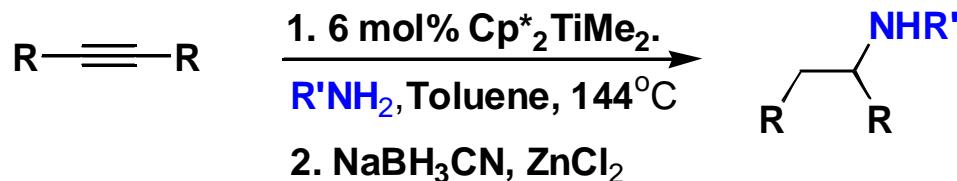
Doye, S., et al., *Angew. Chem. Int. Ed. Engl.* **1999**, 3389

Titanium Catalysis Mechanism



Doye, S., et al., *Angew. Chem. Int. Ed. Engl.* **1999**, 3389

Titanium Catalysis (2)

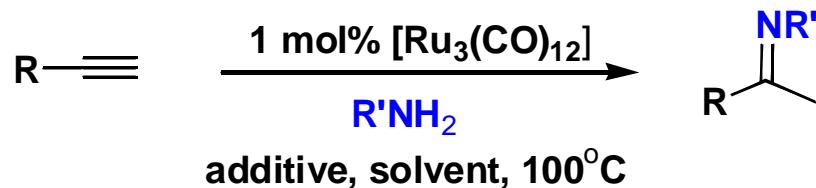


R	R'	Time	Yield	R	R'	Time	Yield	
Ph	<i>n</i> -Pr	4	86%		Et	Bn	24	87%
Ph	PMB	6	97%		Et	BnCH ₂	24	78%
Ph	<i>n</i> -Hex	5	89%		<i>n</i> -Pr	BnCH ₂	24	82%
Et	PMB	24	91%					

- Improved yields over Cp_2TiMe_2 for *n*-alkyl and benzylamines
- High temperatures still required
- No hydroamination products isolated for any terminal alkynes

Doye, S., Heutling, A., *J. Org. Chem.* **2002**, 1961

Ruthenium Catalysis

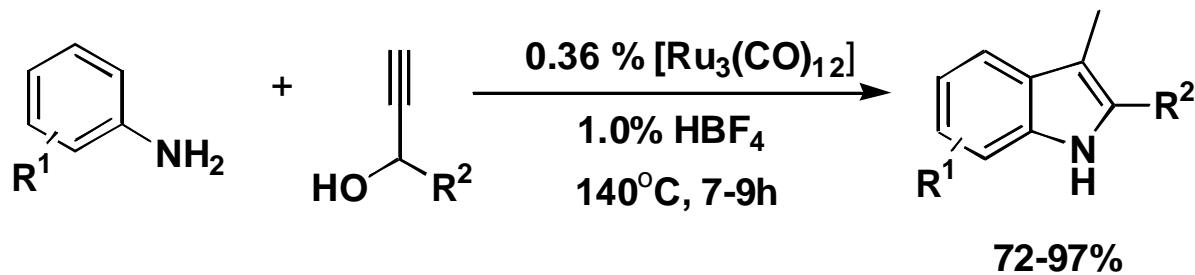
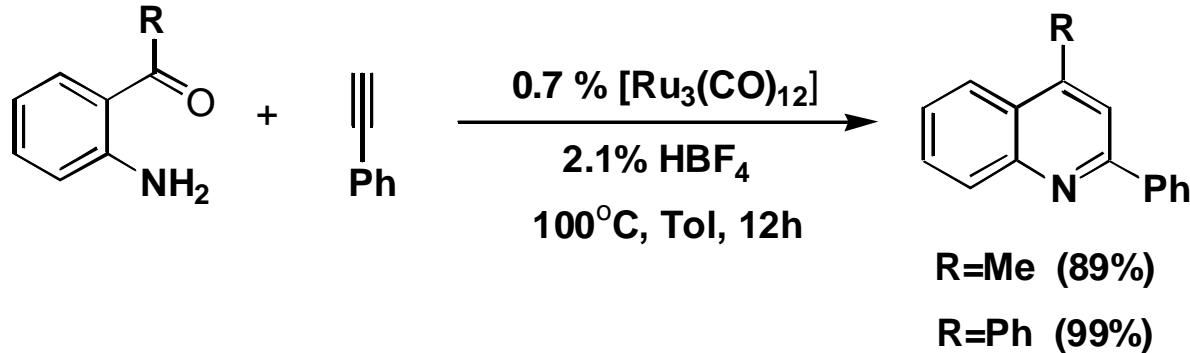


R	R'	additive	solvent	Time	Yield
C ₆ H ₅	4-Me-C ₆ H ₄	NH ₄ PF ₆ (0.3)	-	3h	95%
C ₆ H ₅	2-Me-(6-Et)-C ₆ H ₄	HBF ₄ /OEt ₂ (2.1)	-	12h	89%
C ₆ H ₅	4-Cl-C ₆ H ₄	NH ₄ PF ₆ (0.6)	-	3h	88%
C ₆ H ₅	4-MeCO-C ₆ H ₄	HBF ₄ /OEt ₂ (3.0)	-	12h	80%
n-hexyl	C ₆ H ₄	NH ₄ PF ₆ (1.5)	MeOH	12h	63%
CH ₂ OMe	2-Me-(6-Et)-C ₆ H ₄	HBF ₄ /OEt ₂ (3.0)	Tol	12h	41%

- Excellent yields for aryl terminal alkynes (50g scale)
- Unexplained additive effect
- No special precautions (atmosphere, water)

Wakatsuki, Y., et al., *Angew. Chem. Int. Ed. Engl.* **1999**, 3222

Ruthenium Catalysis



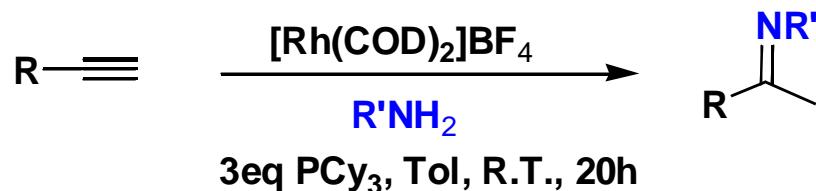
$\text{R}^1=\text{H, } p\text{-Me, } p\text{-MeO, } o\text{-CH}_3, p\text{-Cl, } o\text{-CO}_2\text{Me}$

$\text{R}^2=\text{Me, Et, } n\text{-pentyl, Ph}$

Wakatsuki, Y., et al., *Angew. Chem. Int. Ed. Engl.* **1999**, 3222

Wakatsuki, Y., et al., *Riken Rev.* **2001**, 53

Rhodium Catalysis

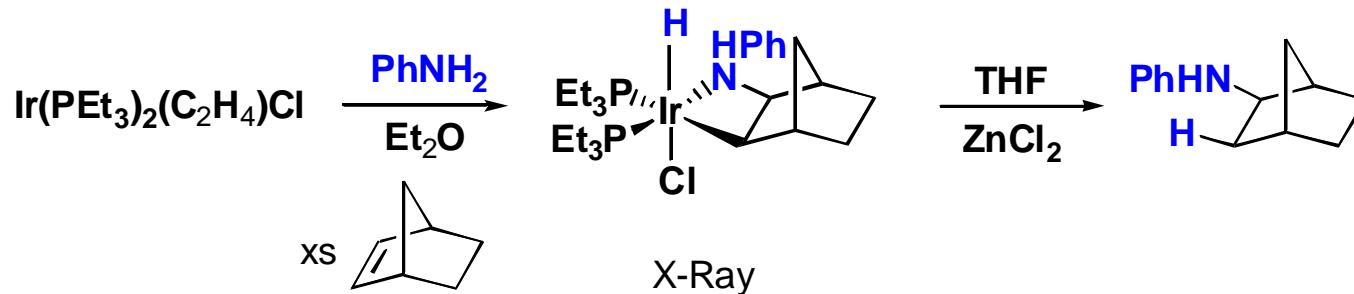
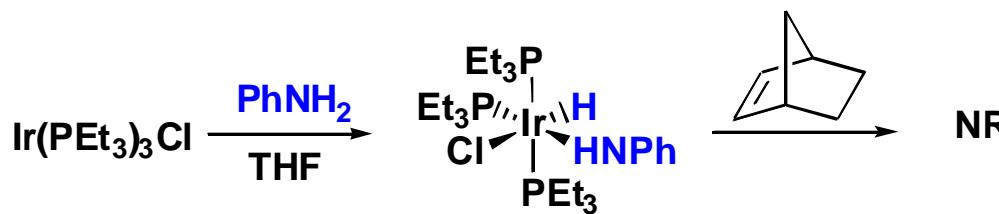
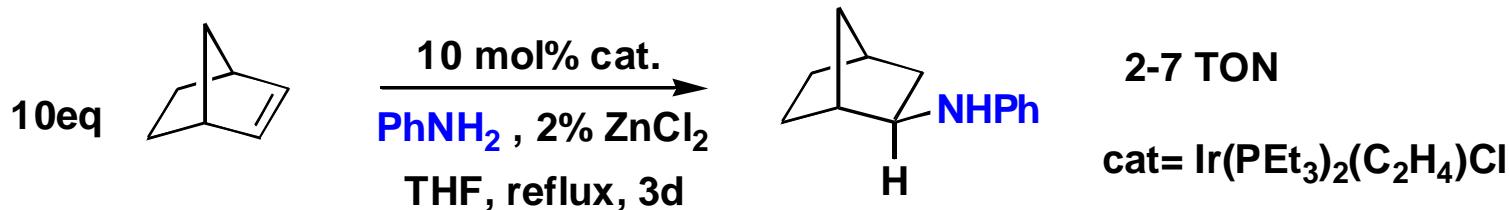


R	R'	cat %	Yield
n-hexyl	C ₆ H ₄	1.5	79%
n-butyl	C ₆ H ₄	1.5	83%
n-butyl	2-Me-C ₆ H ₄	1.5	55%
n-hexyl	4-Me-C ₆ H ₄	1.5	73%
n-hexyl	4-MeO-C ₆ H ₄	1.5	63%
n-hexyl	4-Cl-C ₆ H ₄	1.0	99%
Ph	C ₆ H ₄	2.5	10%

- Excellent yields for alkyl terminal alkynes
- Markovnikov regiochemistry
- Room temperature reaction

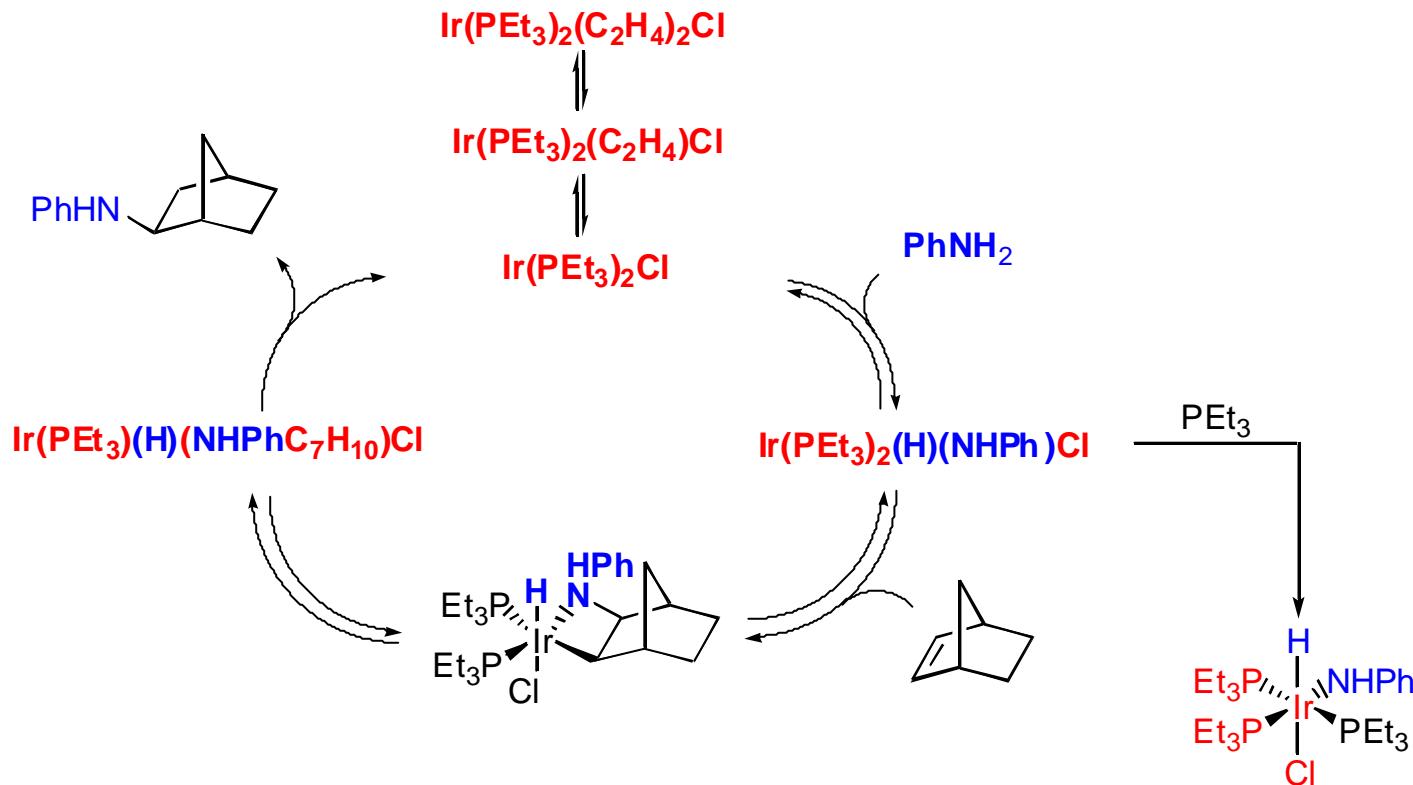
Beller, M., et al., *J. Org. Chem.* **2001**, 6339

Iridium Catalysis



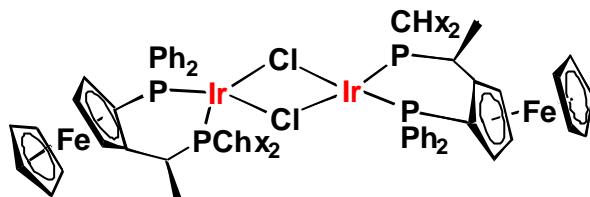
Casalnuovo, A., et al., *J. Am. Chem. Soc.* **1988**, 6738

Iridium Mechanism

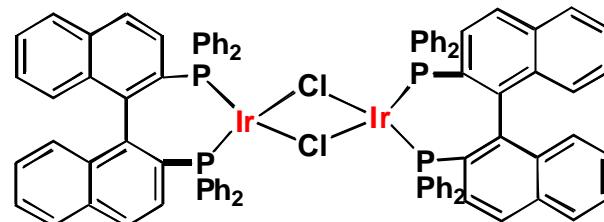


Casalnuovo, A., et al., *J. Am. Chem. Soc.* **1988**, 6738

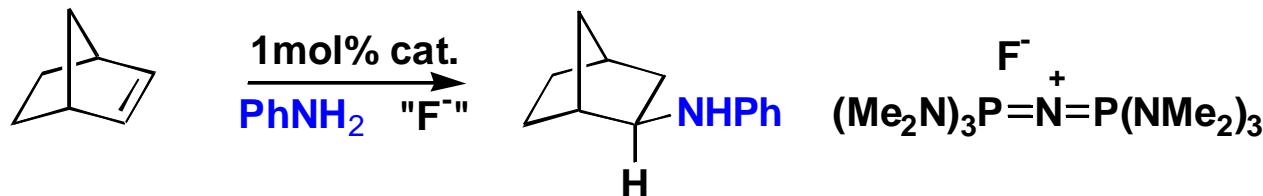
Asymmetric Hydroamination



1



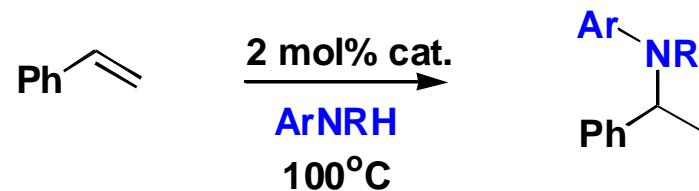
2



Catalyst	T (°C)	F ⁻ (eq)	Yield(%)	ee(%)
1	50	0	12	51 (S)
1	50	1	81	31 (R)
1	25	1	12	60 (R)
1	50	4	51	16 (R)
2	75	2	45	78 (R)
2	75	4	22	95 (R)

Togni, A., et al., J. Am. Chem. Soc. 1997, 10857

Palladium Catalysis

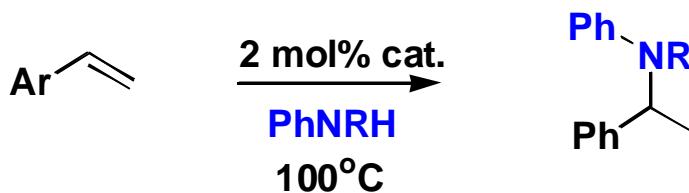


cat = 2%Pd(OC(O)CF₃)₂ / 3%DPPF / 20%TfOH

Amine	Time	Yield	Amine	Time	Yield
	7h	99%		7h	88%
	7h	78%		7h	68%
	12h	64%		12h	54%

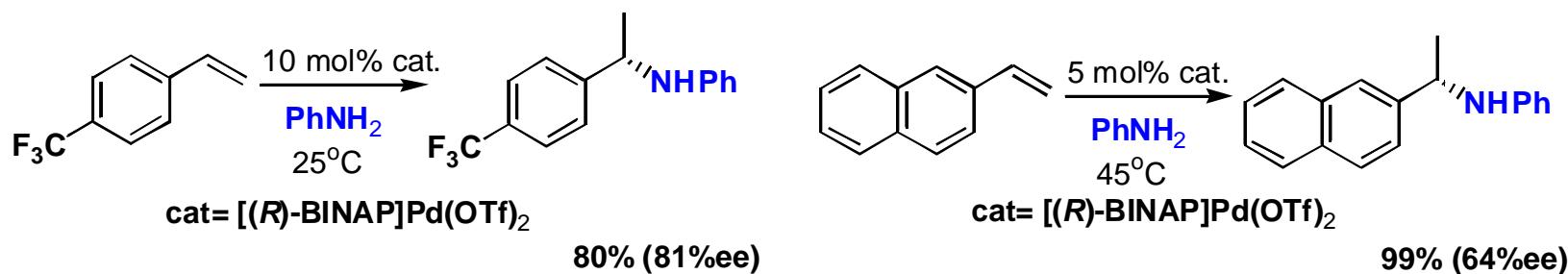
Hartwig, J., Kawatsura, M., *J. Am. Chem. Soc.* **2000**, 9546

Palladium Catalysis (2)



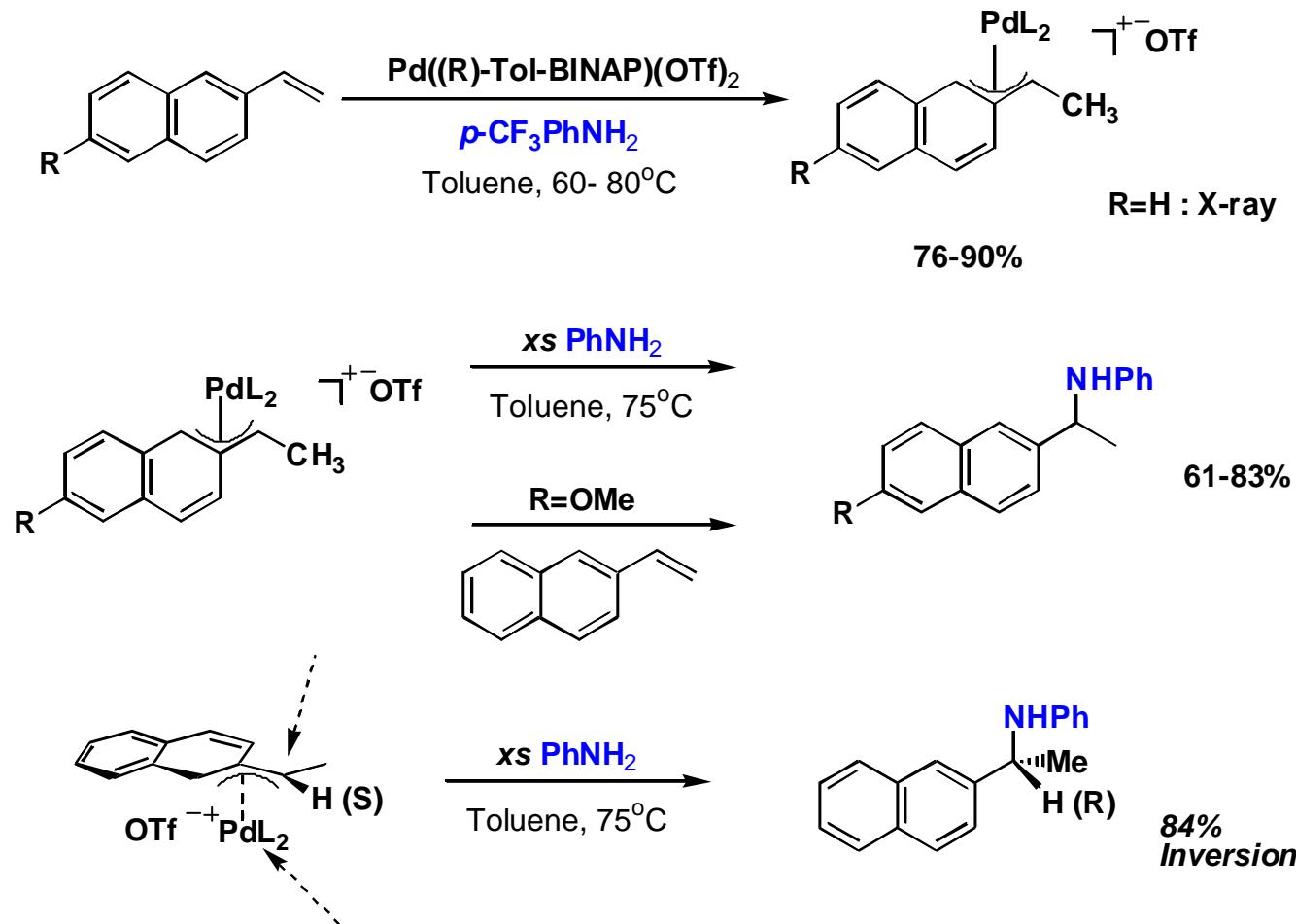
cat = 2%Pd(OC(O)CF₃)₂ / 3%DPPF / 20%TfOH

	Time	Yield		Time	Yield		Time	Yield
	7h	99%		7h	98%		7h	85%



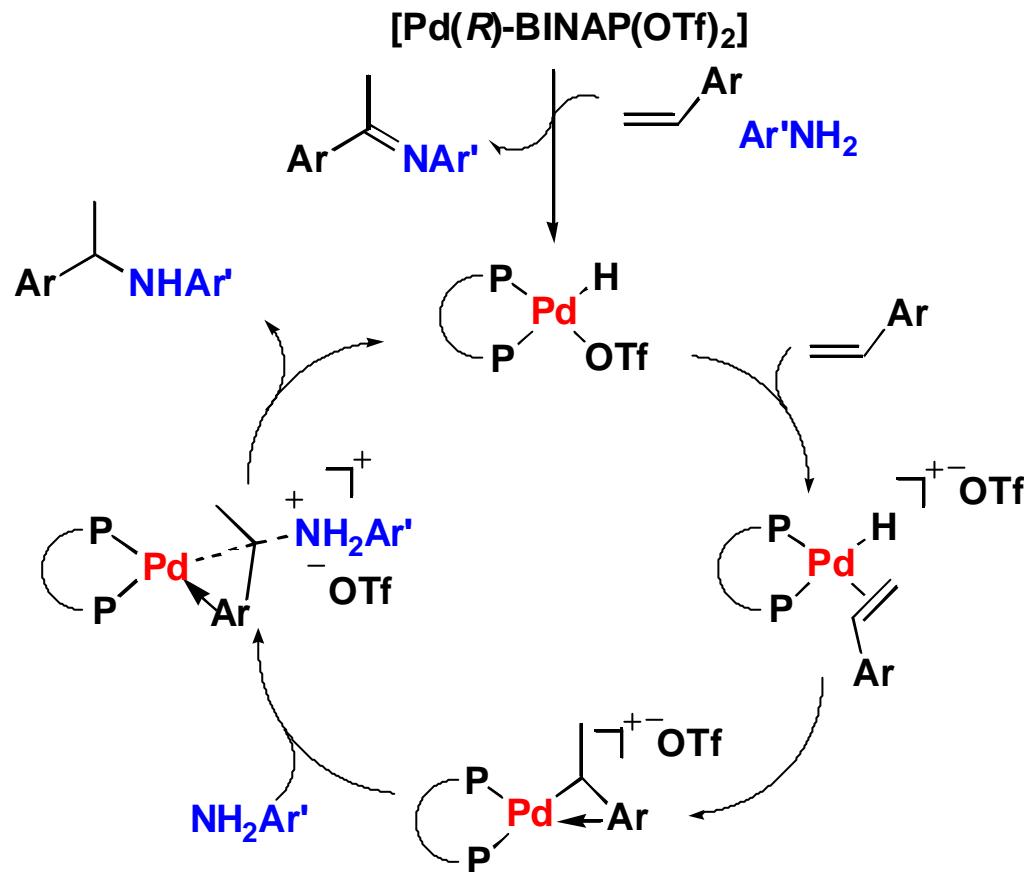
Hartwig, J., Kawatsura,M., *J. Am. Chem. Soc.* **2000**, 9546

Palladium Mechanism



Hartwig, J., Nettekoven, U., *J. Am. Chem. Soc.* **2002**, 1167

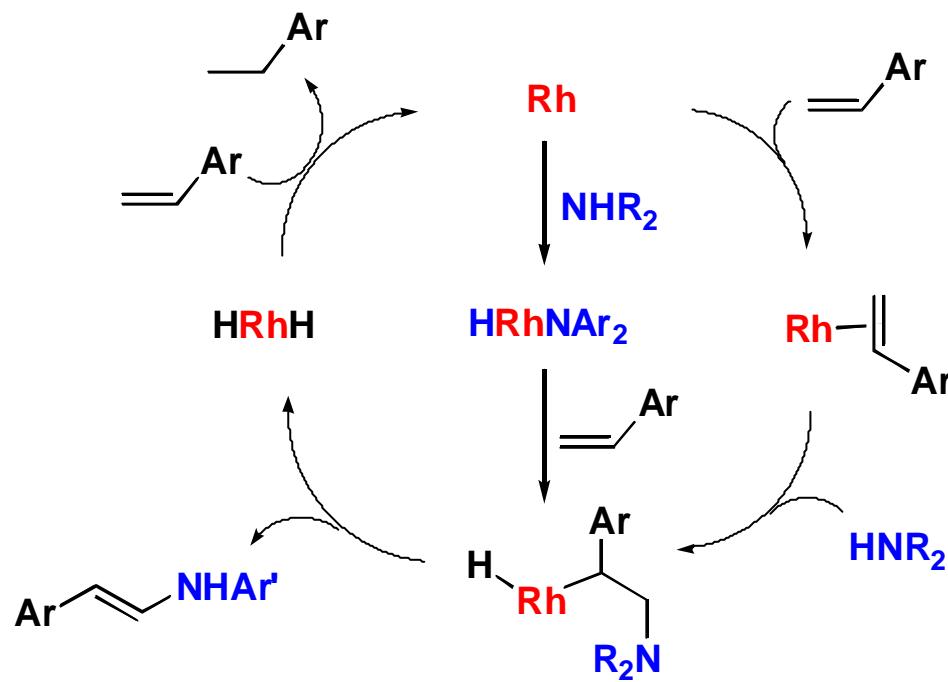
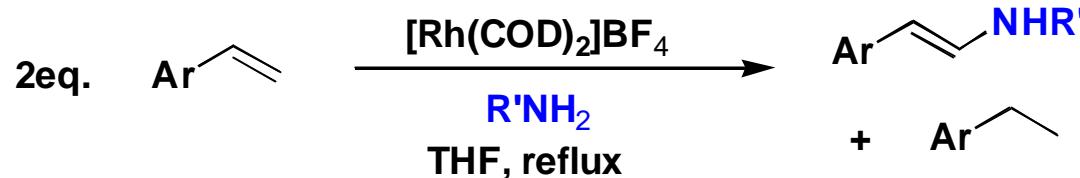
Palladium Mechanism (2)



Hartwig, J., Nettekoven, U., *J. Am. Chem. Soc.* **2002**, 1167

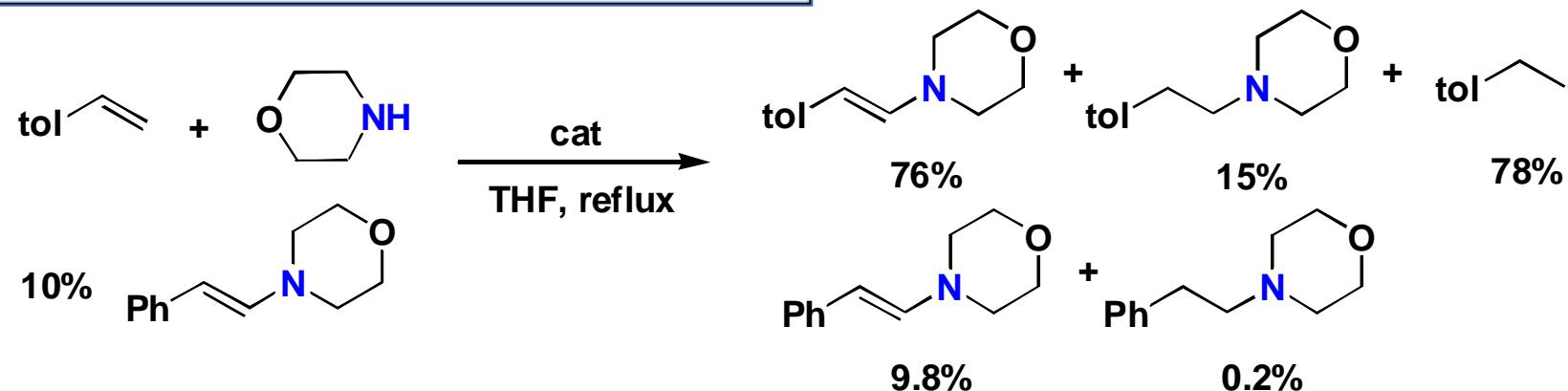
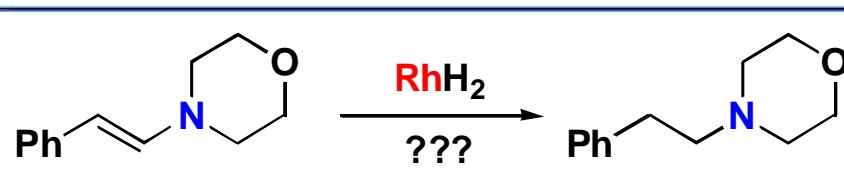
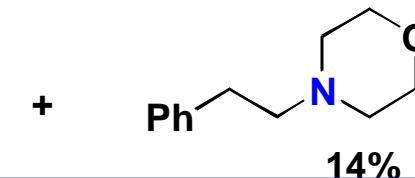
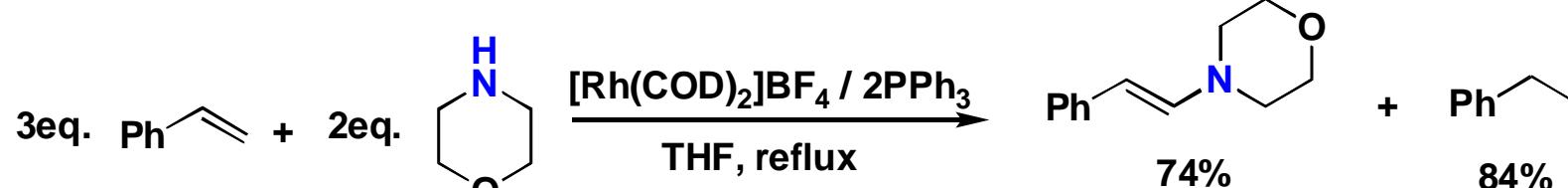
Oxidative Amination

Oxidative
Amination



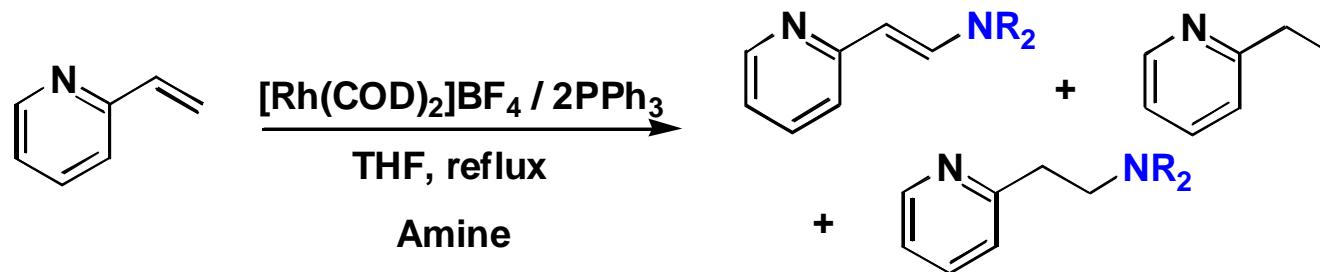
Beller, M., et al., *Chem. Eur. J.* 1999, 1306

Oxidative/Hydroamination



Beller, M., et al., *Chem. Eur. J.* 1999, 1306

Oxidative/Hydroamination



Starting Amine	Amine	Enamine	Ethyl-Py
Pyrrolidine	54%	21%	56%
Piperidine	47%	53%	42%
Morpholine	98%	2%	2%
Thio-Morpholine	98%	1%	1%
N-Phenyl Piperazine	91%	8%	6%
Et_2NH	<1	<1	-
$n\text{BuNH}_2$	<1	<1	-

Conclusions

- Tremendous progress towards an efficient catalytic hydroamination reaction
- Intramolecular systems more easily developed
- Intermolecular hydroaminations of olefins still a challenge (especially anti-markovnikov additions)
- Still no effective general catalyst (alkynes, alkenes, allenes, etc...)
- Many more interesting results to come...

Elements of Hydroamination

Alkali Metals

Late T-Metals

III A	IV A	V A	VI A	VII A		
S B	S C	N P	O S	F Cl	Ne Ar	
13 Al	14 Si	15 P	16 S	17 Cl	18 Ar	
31 Ga	32 Ge	33 As	34 Se	35 Br	36 Kr	
49 In	50 Sn	51 Sb	52 Te	53 I	54 Xe	
81 Tl	82 Pb	83 Bi	84 Po	85 At	86 Rn	

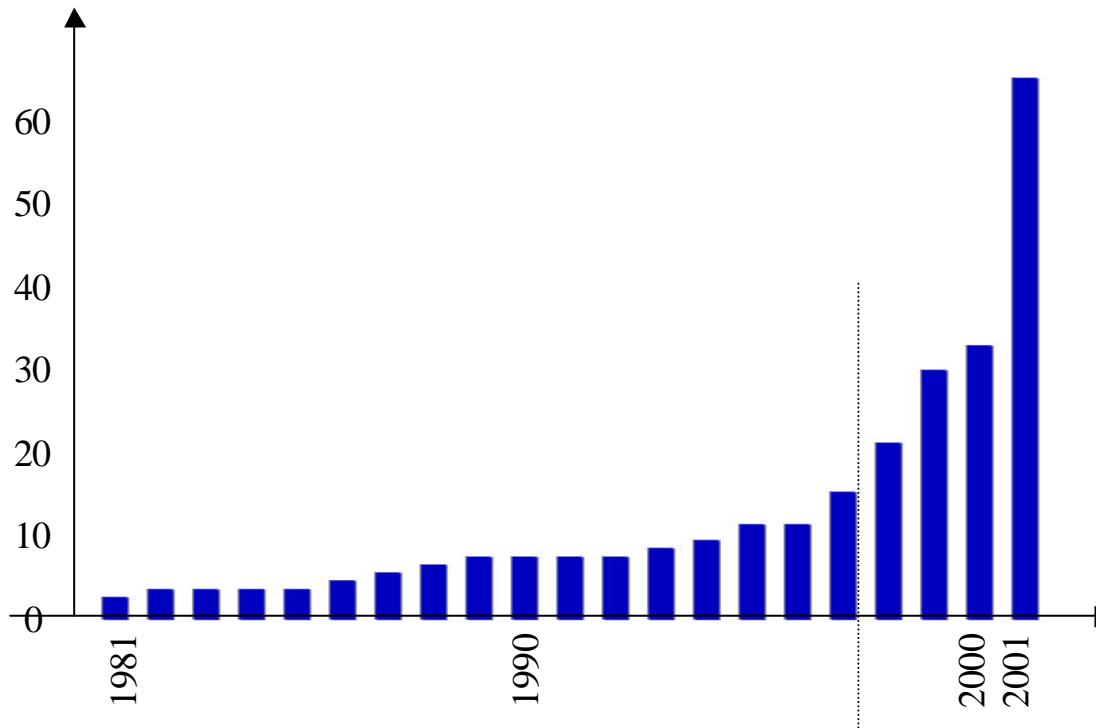
Early T-Metals

- | | | | | | | | | | | | | | | |
|---------------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| * Lanthanide Series | Ce | Pr | Nd | Pm | Sm | Eu | Gd | Tb | Dy | Ho | Er | Tm | Yb | Lu |
| + Actinide Series | Th | Pa | U | Np | Pu | Am | Cm | Bk | Cf | Es | Fm | Md | No | Lr |

Lanthanides/Actinides

- No widely applicable catalyst developed yet

Hydroamination Publications



- Review of work prior to 1998
 - Müller, T., Beller, M., *Chem. Rev.* **1998**, 98, 675