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).

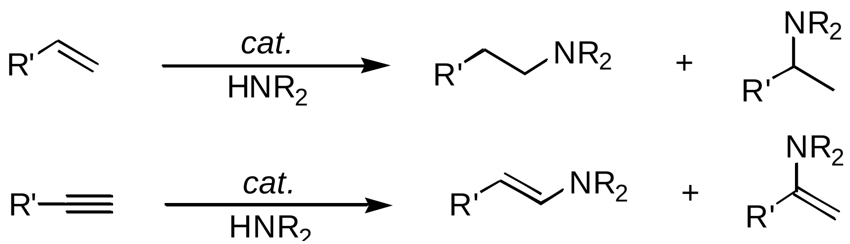

Figure 1: Hydroamination of alkenes and alkynes

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., Drieβen-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

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May 27, 2002

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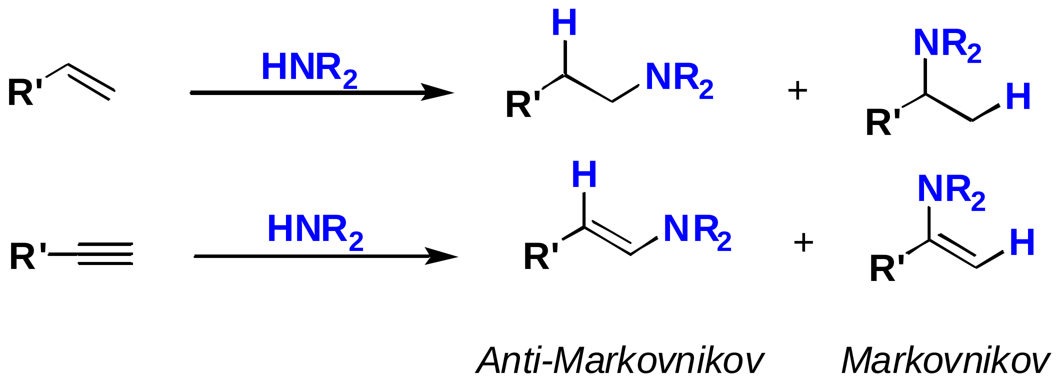
Overview

- 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**

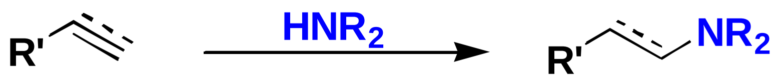
Thermodynamics

Amine	D_RG^q (kJ/mol)	D_RH^q (kJ/mol)	D_RS^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**

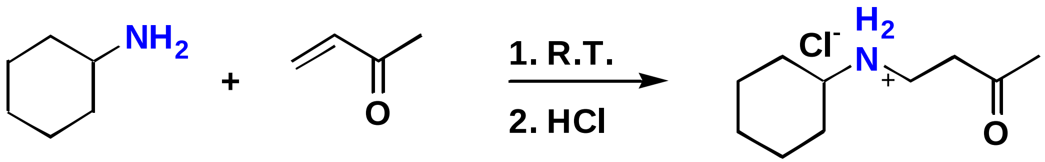
Activated Alkenes/Alkynes



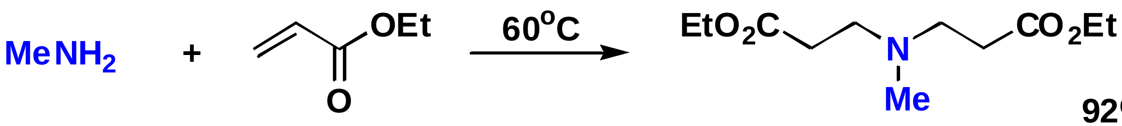
R'= carbonyl, cyano, etc.

Anti-Markovnikov

- Examples of additions to activated olefins/alkynes



94%

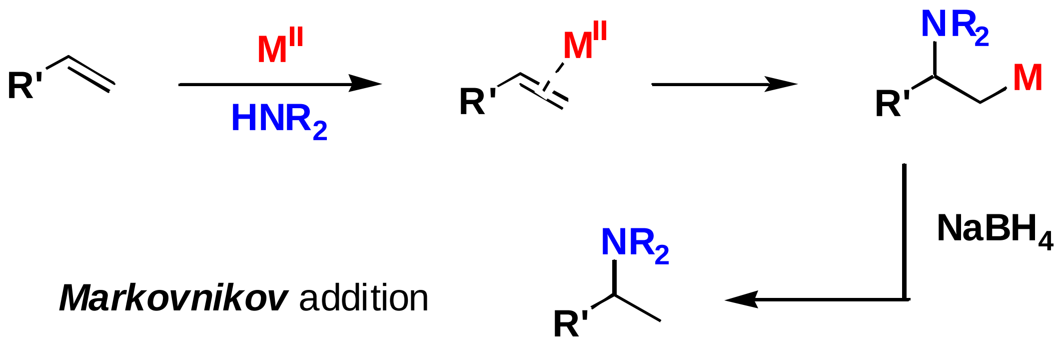


92%

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

Unactivated Alkenes/Alkynes

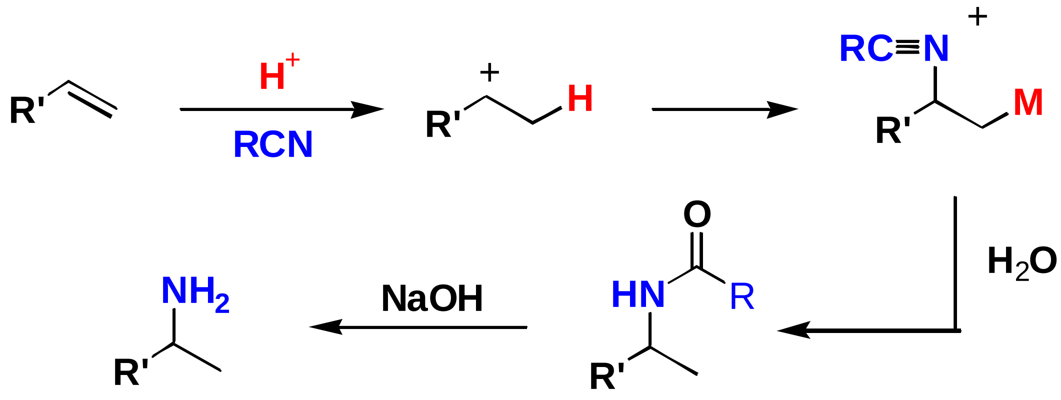
- Requires activation of alkene/alkyne
- Early examples involved stoichiometric additions of metal(II) salts
- M = Hg(II), Fe(II), Zr(II), Ti(II), Pt(II), Mo(II), W(II), etc...



- 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

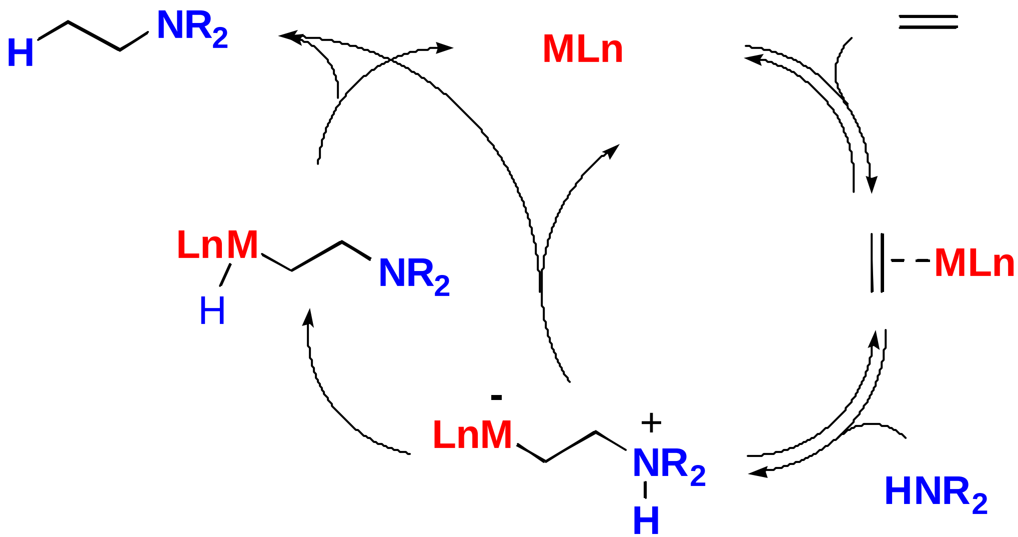
Larock, R., in Trost, B.M., Fleming, I. *Comp. Org. Synth.* **1991**, 4, 269

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

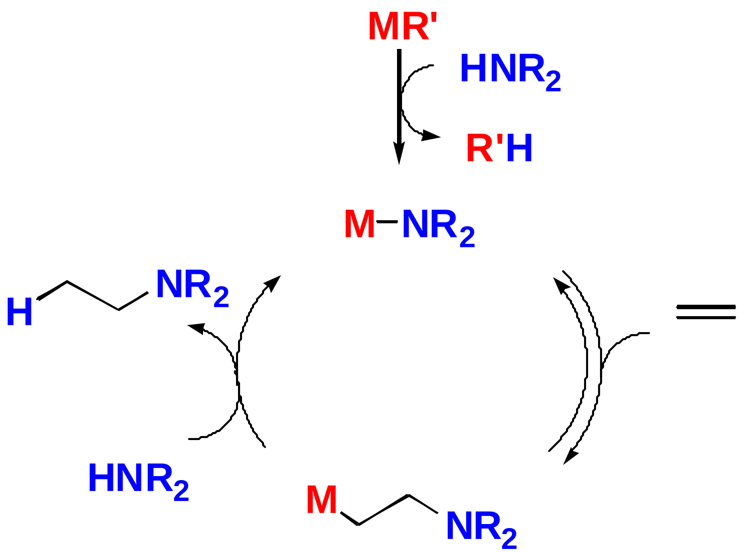
1. Olefin Activation



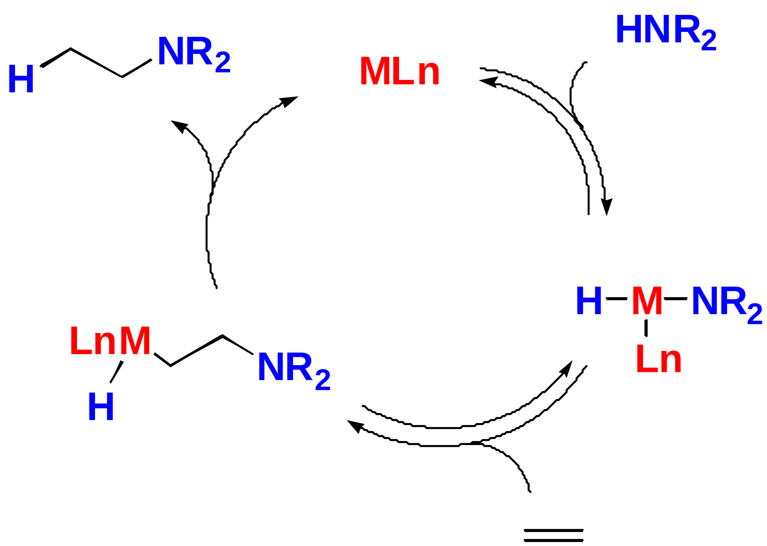
Cornils, B., Herrmann, W. A., *Applied Homogeneous Catalysis with Organometallic Compounds*. Wiley VCH, Weinheim, **2000**

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**

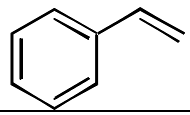
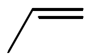
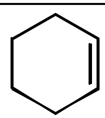
Alkali Metal Catalysis

Howk, B. 1954 NH_3 +  → (7% Na, 200 °C; 1000 bar) NEt_3, $HNEt_2$, H_2NEt (66%)

1954 - 1980

Catalyst : Li, Na, BuLi, EtLi/TMEDA, Et_2NLi, $NaNH_2$, $CsNH_2$…

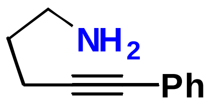
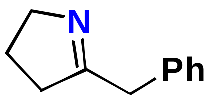
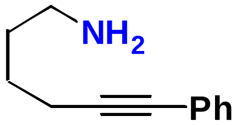
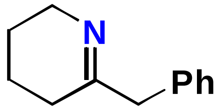
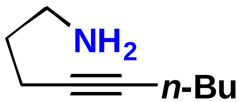
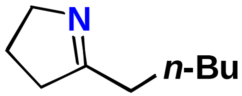
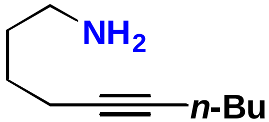
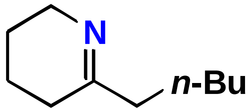
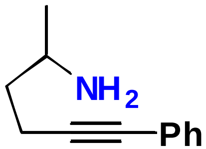
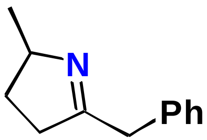
Amines : NH_3, $HNEt_2$, $PrNH_2$, $BuNH_2$, $PhNH_2$

	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

$CpTiCl_3$ —(2 RNH_2; THF, R.T.; -2HCl)→ **$CpClTi{=}NR$** ←(2 RNH_2; THF, R.T.; $-2CH_4$)— $CpTi(Me)_2Cl$

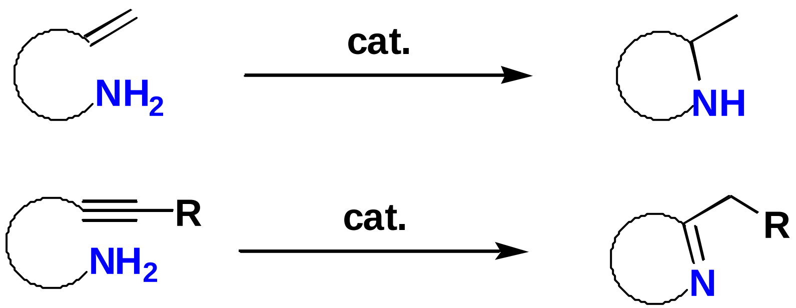
Substrate	Product	Temp	Yield	Substrate	Product	Temp	Yield
		R.T.	94%			80	88%
		R.T.	94%			80	89%
		R.T.	92%				

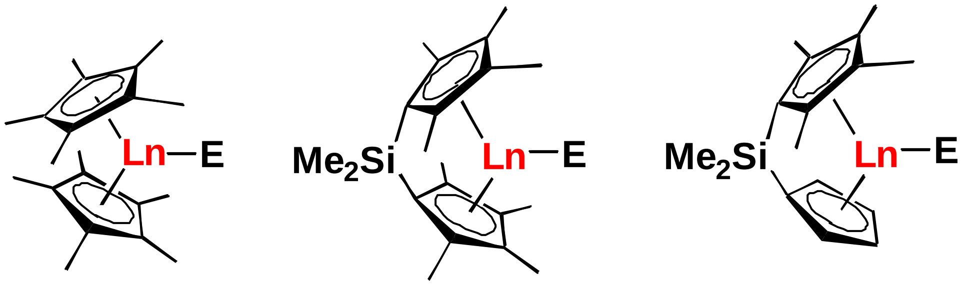
20 mol% $CpTiCl_3$, 40 mol% $i Pr_2EtN$

30min, R.T.=THF 80^{o}C=Tol

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

Lanthanide Catalysis





Ln = La, Nd, Sm, Lu

E = H, CH(TMS)$_2$, N(TMS)$_2$

Olefin Reactivity →

← ***Alkyne Reactivity***

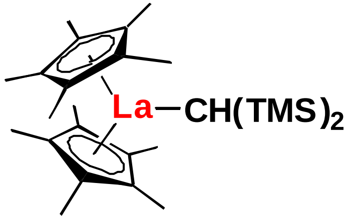
Olefin rate : La>Nd>Sm>Lu

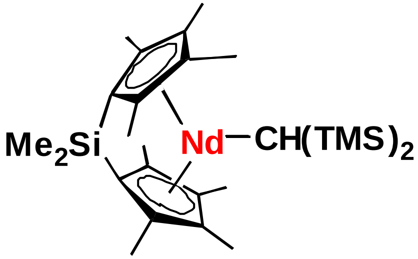
Alkyne rate : La<Nd<Sm<Lu

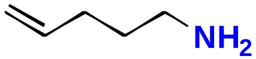
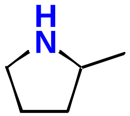
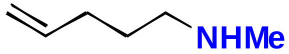
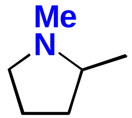
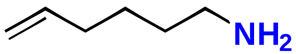
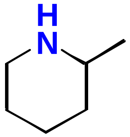
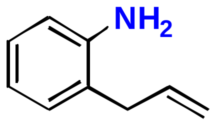
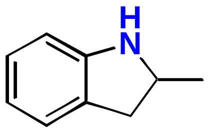
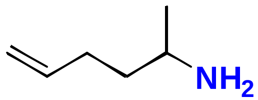
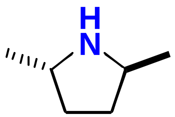
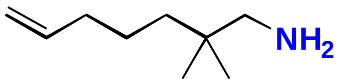
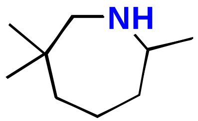
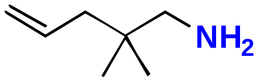
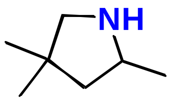
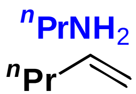
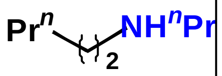
Marks, T., *et al.*, *J. Am. Chem. Soc.* **1992**, 275; **1994**, 10241

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

Lanthanides (Amino-Olefins)

1= 

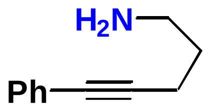
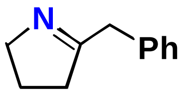
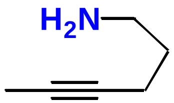
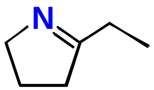
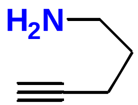
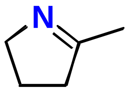
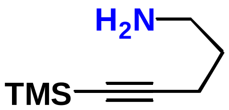
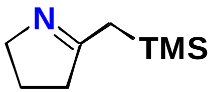
2= 

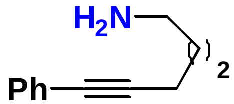
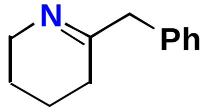
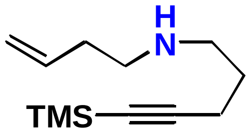
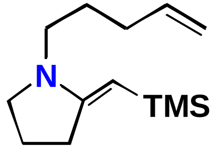
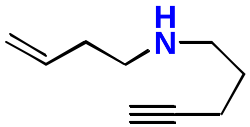
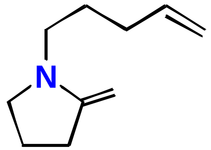
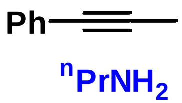
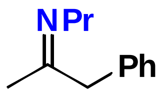
Catalyst	Amino Olefin	Product	N_t/h	Temp	Catalyst	Amino Olefin	Product	N_t/h	Temp
1			140	60	2			11	25
1			5	60	1			12	80
1			45	25	2			0.3	60
1			95	25	2			0.4	60

Solvent = d_8 Toluene

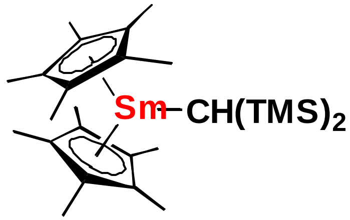
Marks, T., *et al.*, *J. Am. Chem. Soc.* **1992**, 275

Lanthanides (Amino-Alkynes)

Substrate	Product	N_t/h	Yield
		77	95
		96	95
		580	90
		7600	95

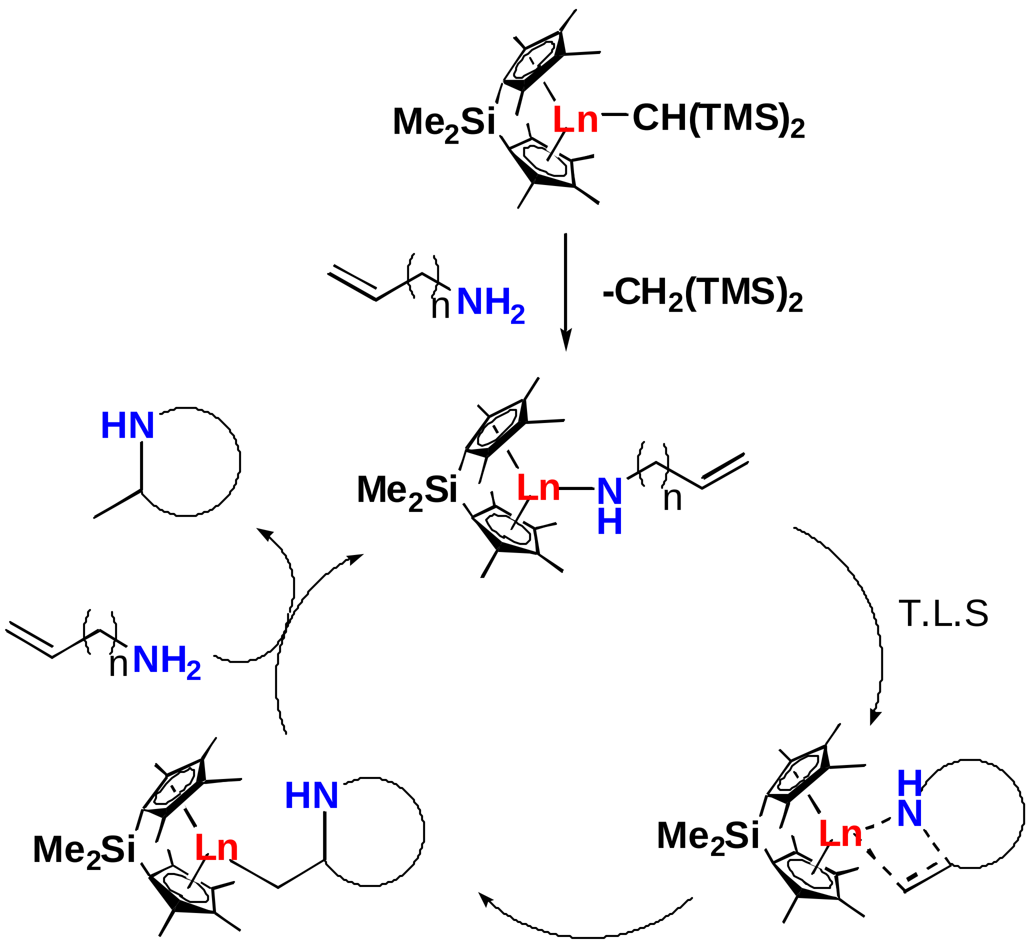
Substrate	Product	N_t/h	Yield
		4	95
		129	90
		47	85
		2	85

0.5%



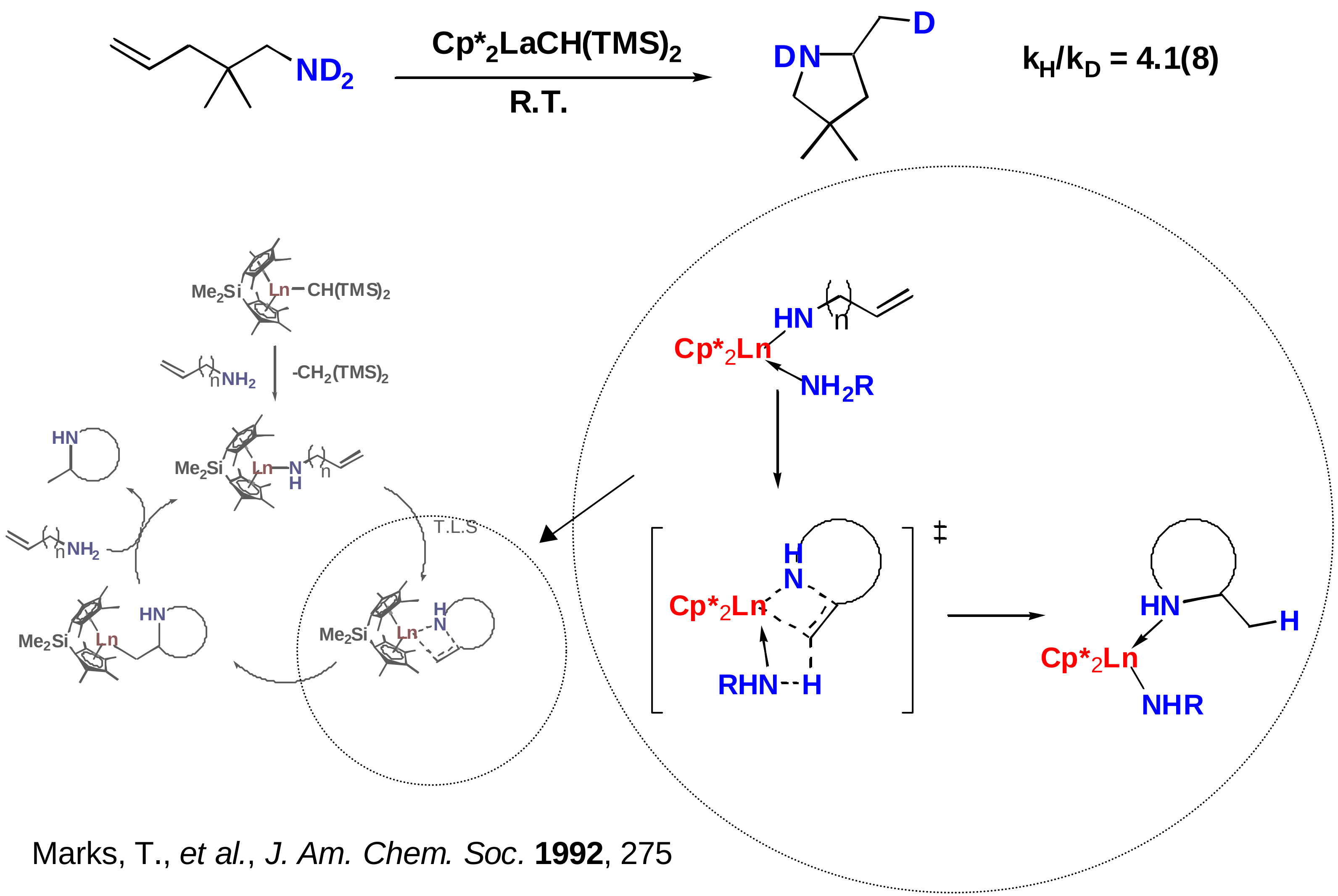
Marks, T., Li, Y., *J. Am. Chem. Soc.* **1996**, 9295

Lanthanide Mechanism



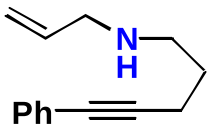
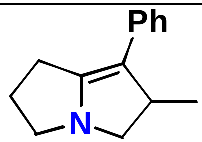
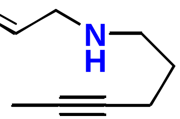
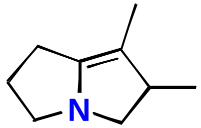
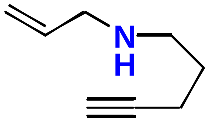
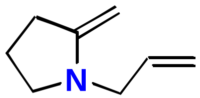
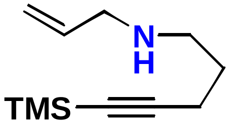
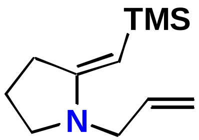
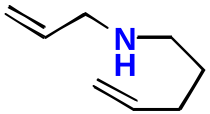
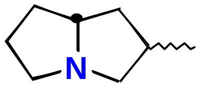
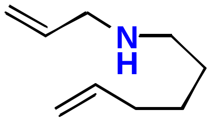
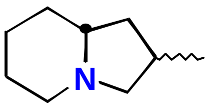
Marks, T., *et al.*, *J. Am. Chem. Soc.* **1992**, 275; **1994**, 10241

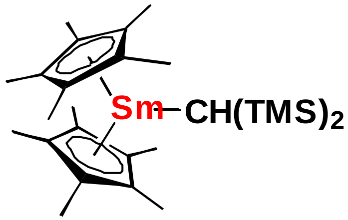
Lanthanide Mechanism Revised

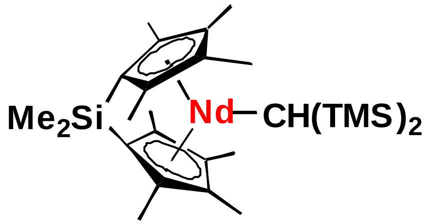


Marks, T., *et al.*, *J. Am. Chem. Soc.* **1992**, 275

Tandem Hydroamination/Cylization

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

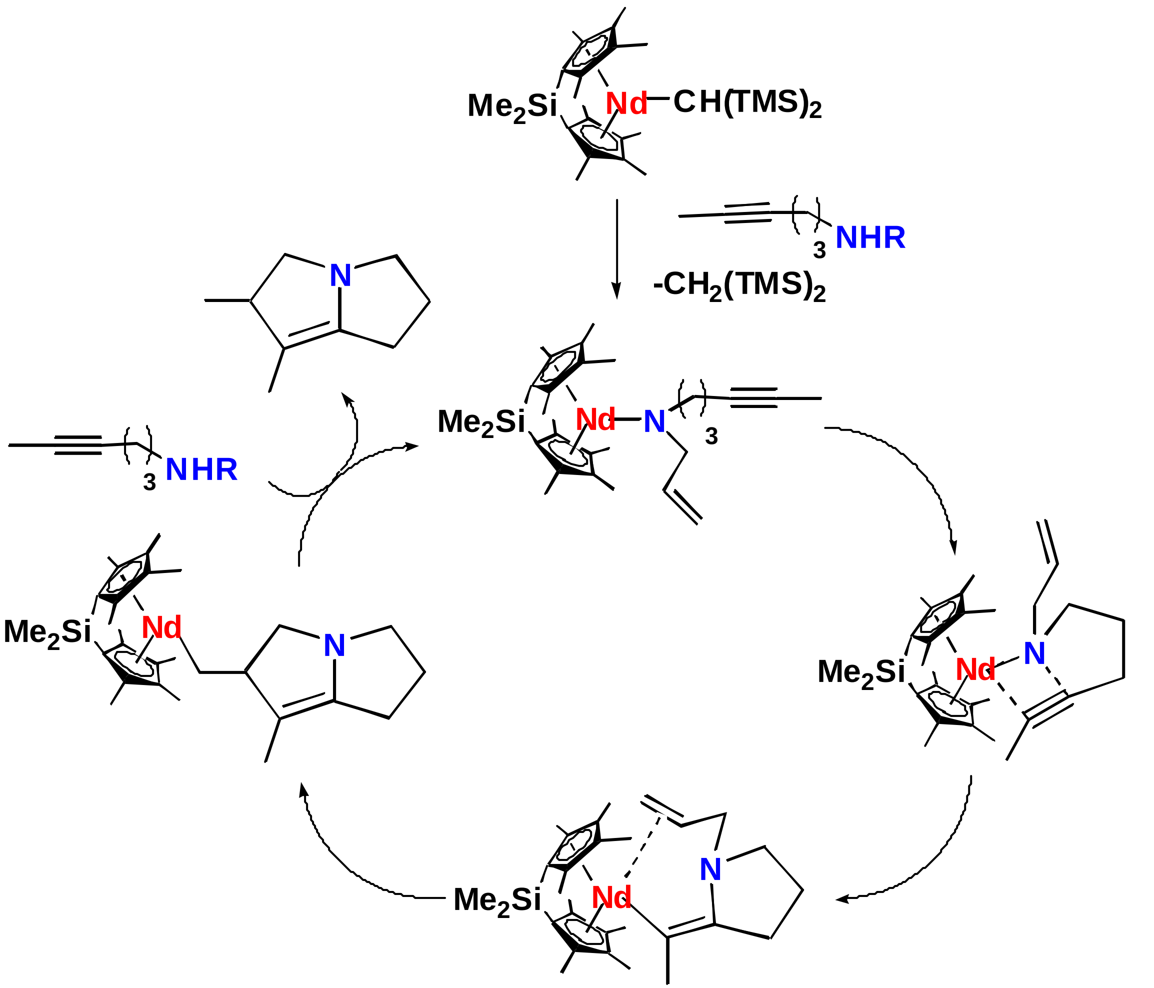
1 = 

2 = 

2% Catalyst, R.T., Benzene

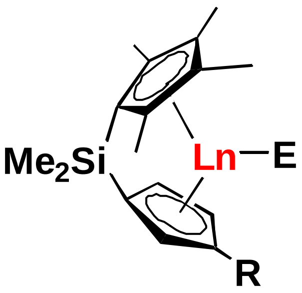
Marks, T., Li, Y., *J. Am. Chem. Soc.* **1998**, 1757

Tandem Hydroamination/Cylization Mechanism

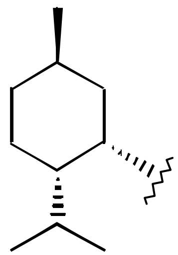


Marks, T., Li, Y., *J. Am. Chem. Soc.* **1998**, 1757

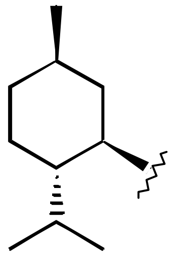
Asymmetric Lanthanide Catalysis



R=



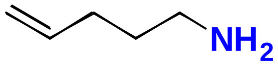
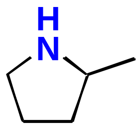
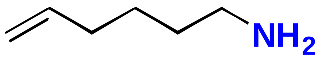
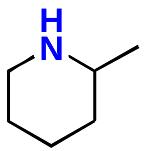
(+)Neomentyl



(-)Menthyl

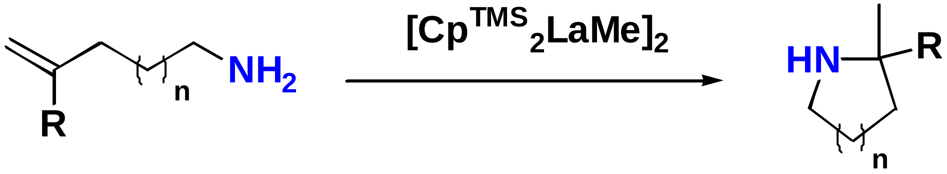
Ln = La, Nd, Sm, Lu, Y

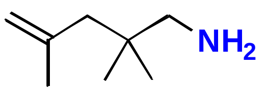
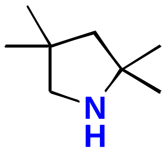
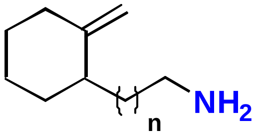
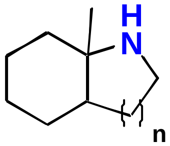
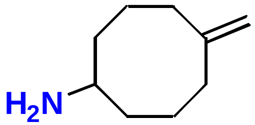
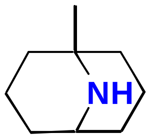
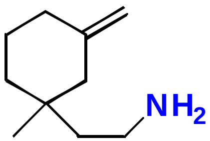
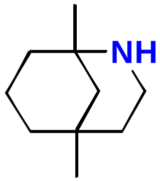
E = $CH(TMS)_2$, $N(TMS)_2$

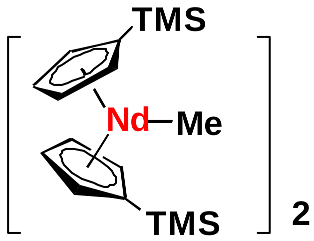
Amino Olefin	Product	Catalyst	ee	N_t/h	Temp
		$NmCp_2$**Nd**$CH(TMS)_2$	64	93	0
		$MtCp_2$**Sm**$CH(TMS)_2$	72	11	0
		$NmCp_2$**Sm**$CH(TMS)_2$	58	33	0
		$NmCp_2$**La**$CH(TMS)_2$	31	-	25
		$MtCp_2$**Sm**$CH(TMS)_2$	15	2	25
		$NmCp_2$**Sm**$CH(TMS)_2$	17	2	25

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

Further Lanthanide Catalysis



Substrate	Product		Temp	Time	Yield
			70	1h	70
		n=1	120	2d	80
		n=2	140	7d	90
			120	5m	94
			120	2d	97

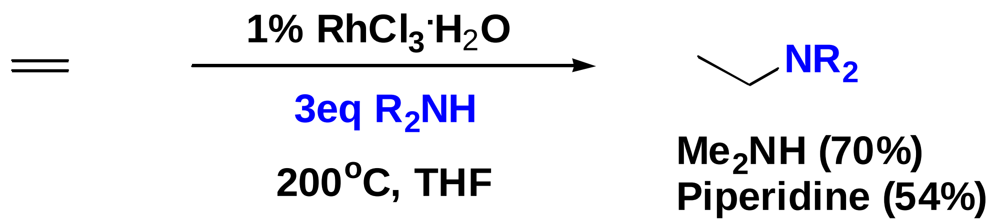
Cat = 

4 mol% cat, C_6D_6

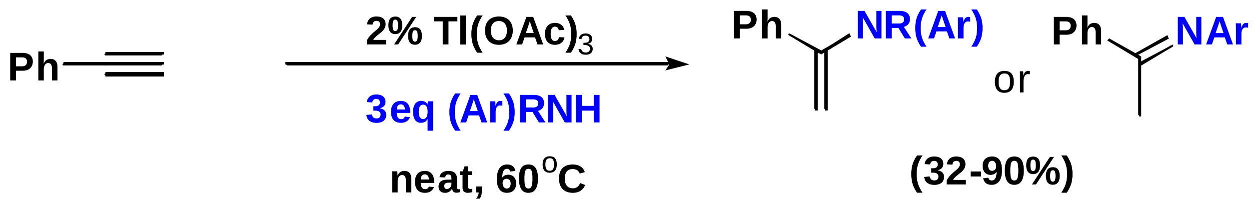
Molander, G., Dowdy, E., *J. Org. Chem.* **1998**, 8983

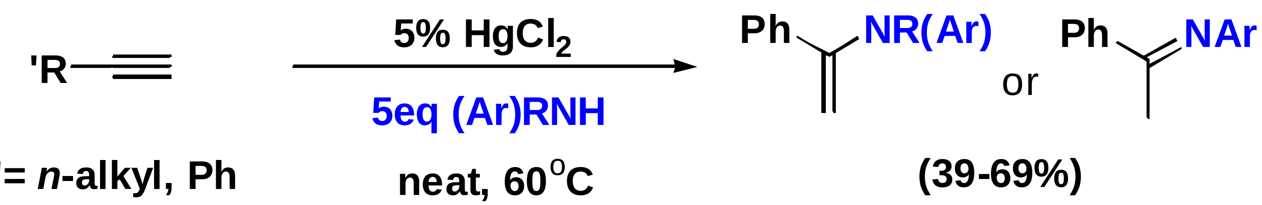
Early Intermolecular Hydroaminations

Coulson, D. 1971



Barluenga, J. 1975, 1980

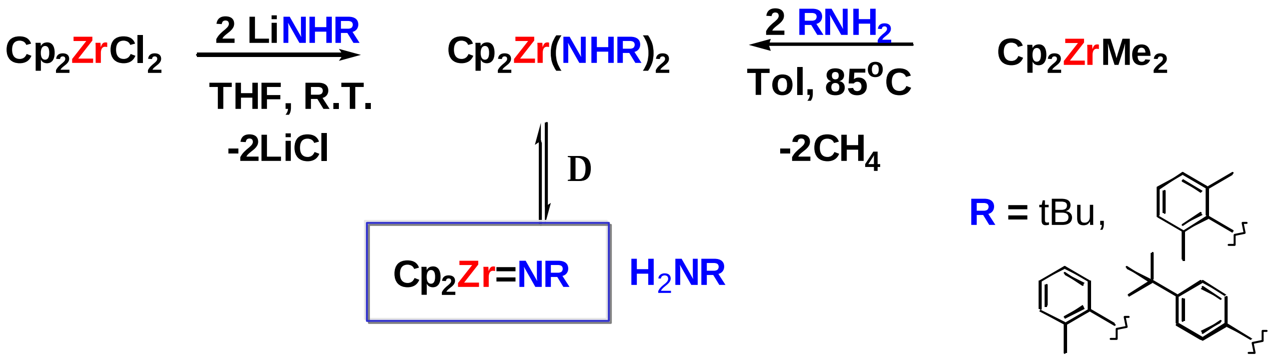


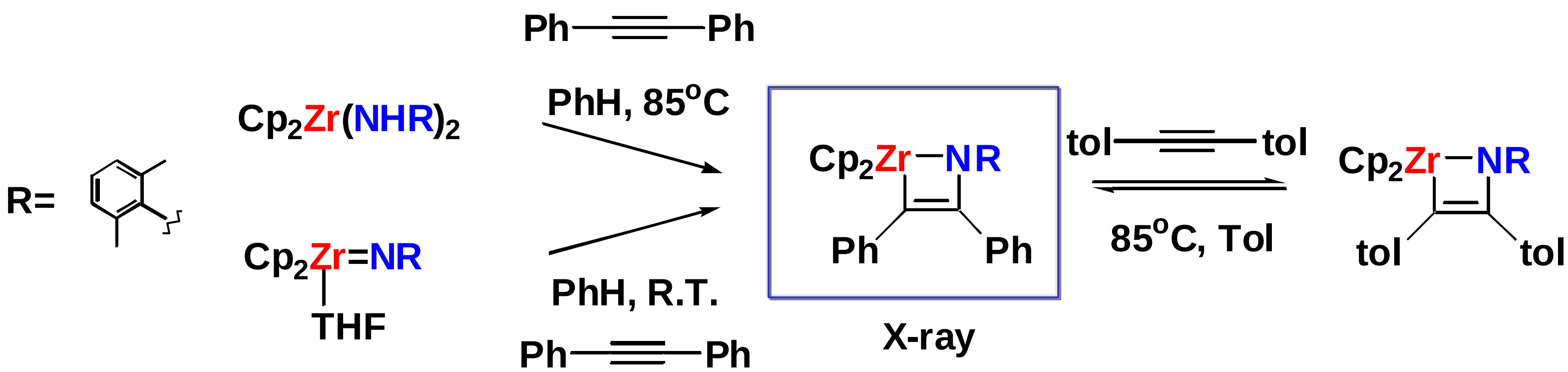


R'= *n*-alkyl, Ph

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

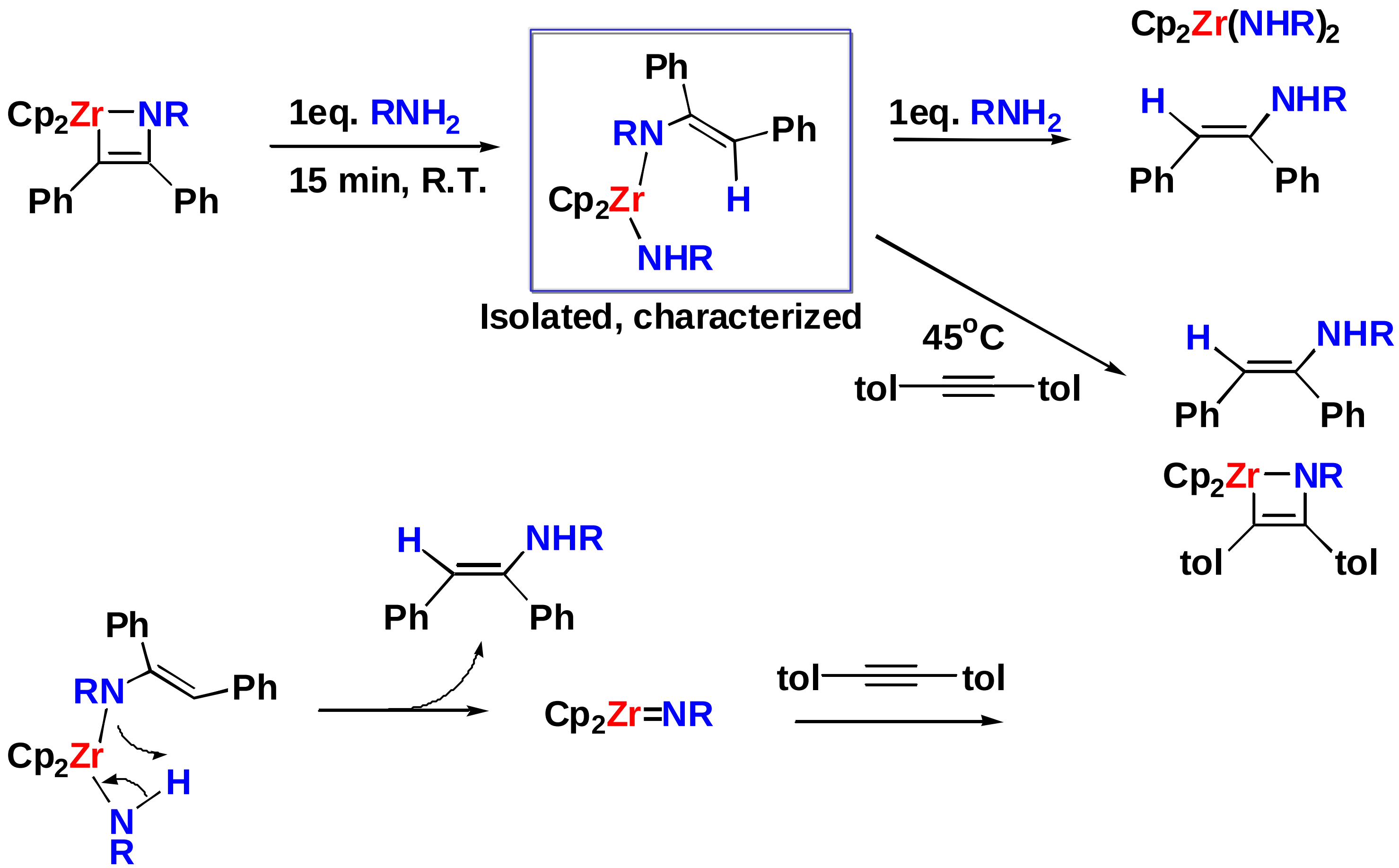
Zirconium Catalysis





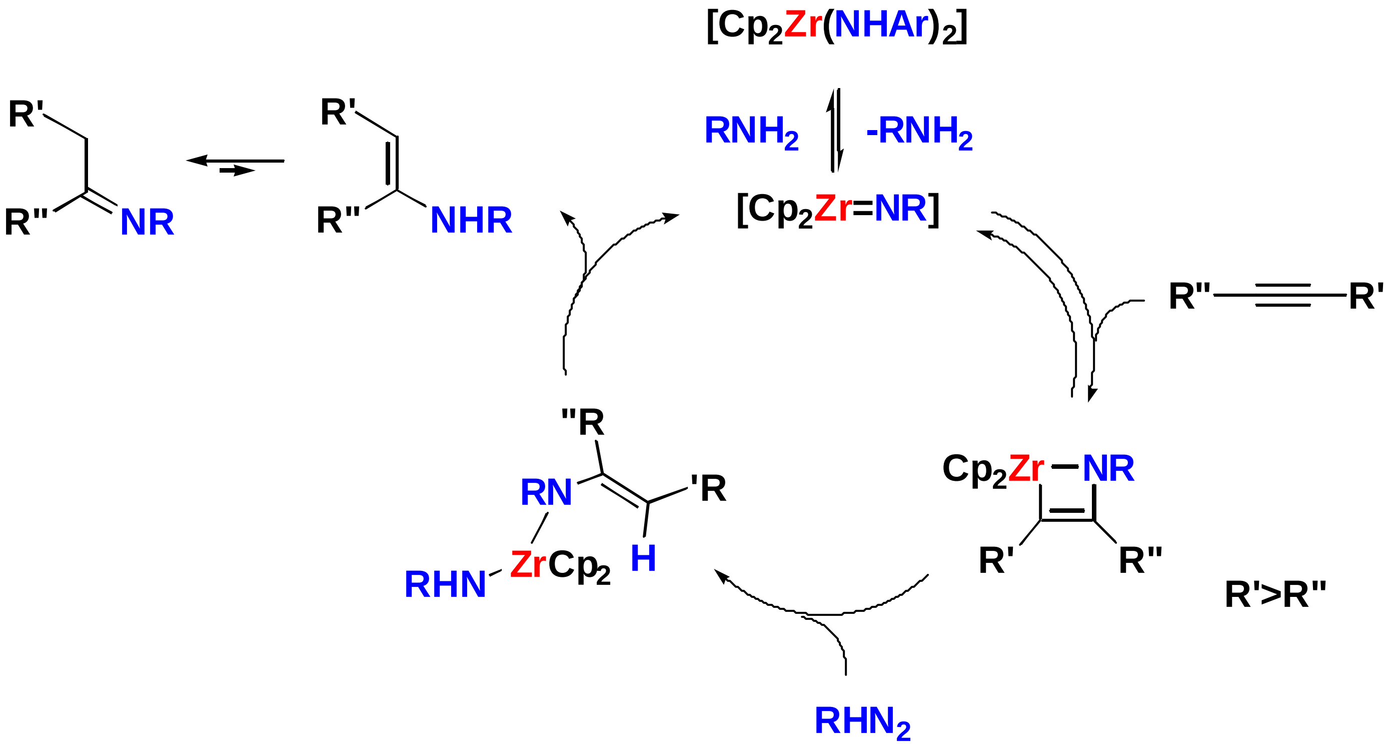
Bergman, R.G., *et al*., *J. Am. Chem. Soc.* **1992**, 1708

Zirconium Catalysis (2)



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

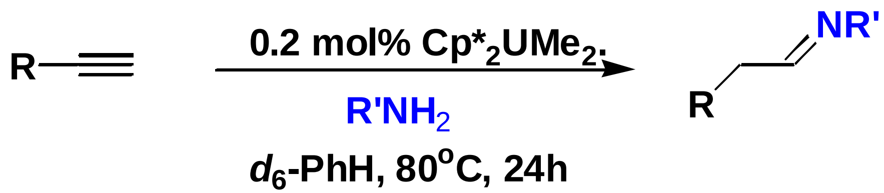
Zirconium Mechanism



R=Ph, Me, tBu : 3 mol% cat., 100ºC, N_t/h=0.2-0.04

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

Actinide Catalysis

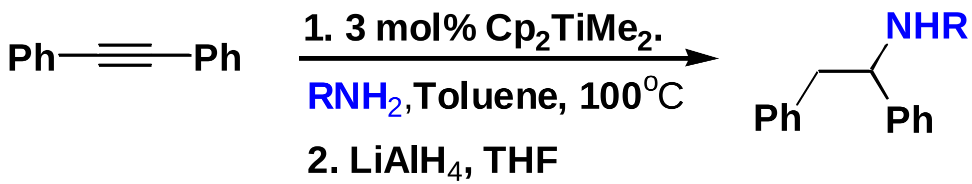


R	R'	Yield	R	R'	Yield
TMS	Me	95%	t-Bu	Me	95%
TMS	Et	95%	t-Bu	Et	95%
n-Bu	Me	70%	Ph	Et	50%
n-Bu	Et	95%			

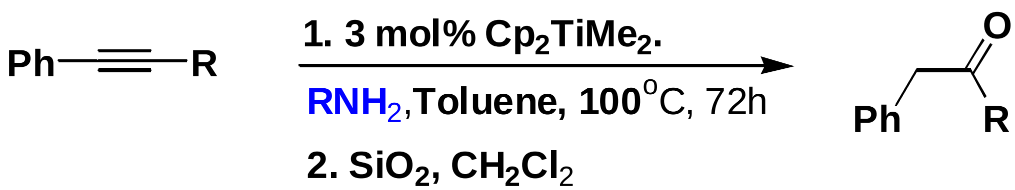
- Excellent yields for alkyl terminal alkynes
- Anti-Markovnikov regiochemistry
- Low catalyst loading

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-$Me_2C_6H_3$	68%	89%		Cy	86%	65%
4-F-C_6H_4	63%	93%		Bn	3%	5%

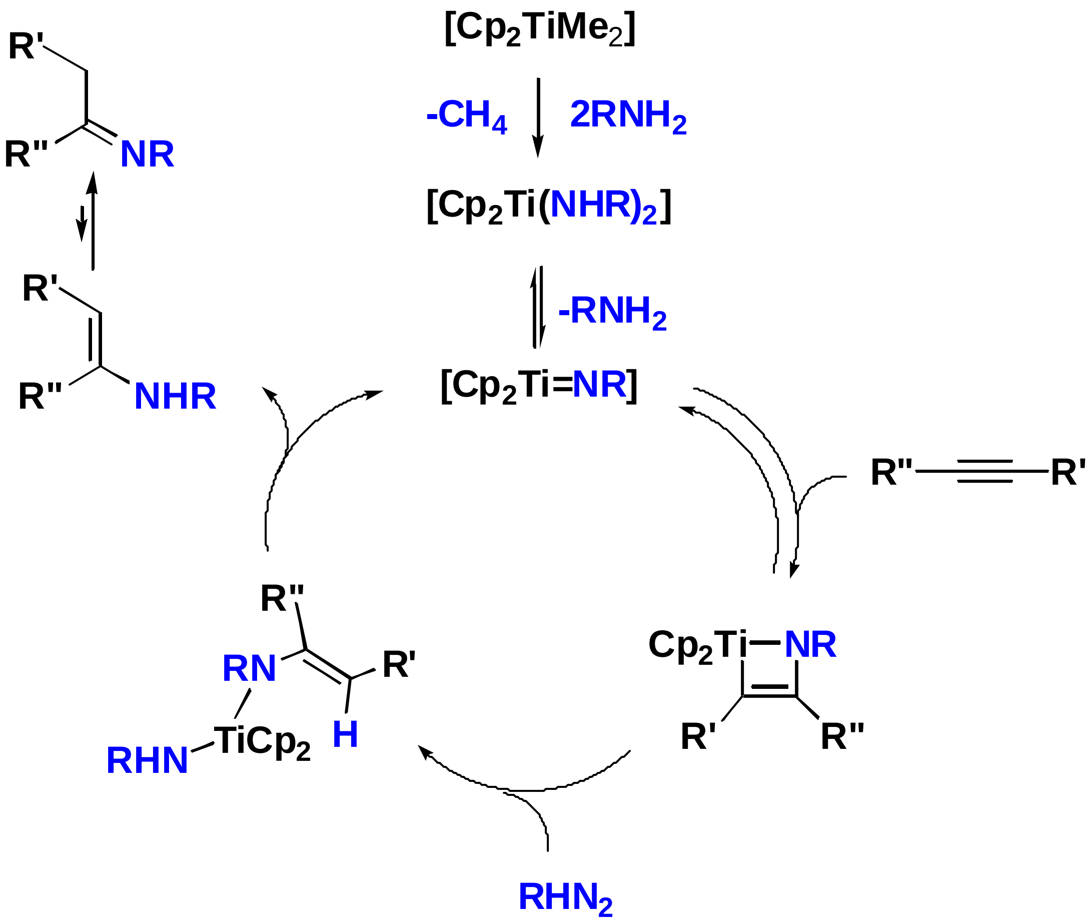


R=Me (99%)
R=Et (73%)
R=Pr (35%)

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

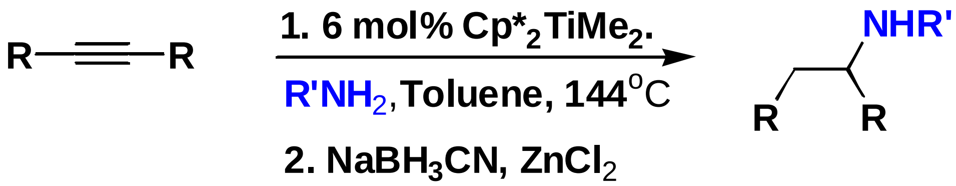
Doye, S., et al., *Angew. Chem. Int. Ed. Engl.* **1999**, 3389

Titanium Catalysis Mechanism



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

Titanium Catalysis (2)

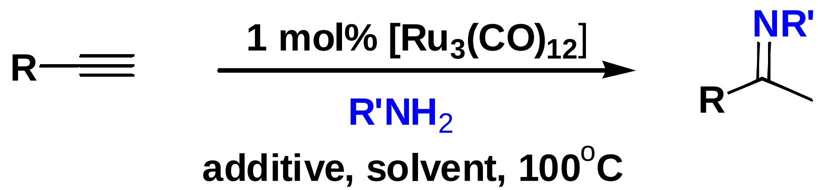


R	R'	Time	Yield	R	R'	Time	Yield
Ph	*n*-Pr	4	86%	Et	Bn	24	87%
Ph	PMB	6	97%	Et	$BnCH_2$	24	78%
Ph	*n*-Hex	5	89%	*n*-Pr	$BnCH_2$	24	82%
Et	PMB	24	91%				

- 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

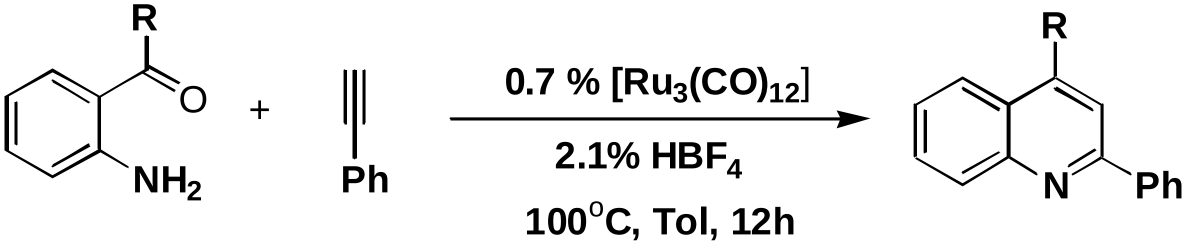


R	R'	additive	solvent	Time	Yield
C_6H_5	4-Me-C_6H_4	NH_4PF_6 (0.3)	-	3h	95%
C_6H_5	2-Me-(6-Et)-C_6H_4	HBF_4/OEt_2 (2.1)	-	12h	89%
C_6H_5	4-Cl-C_6H_4	NH_4PF_6 (0.6)	-	3h	88%
C_6H_5	4-MeCO-C_6H_4	HBF_4/OEt_2 (3.0)	-	12h	80%
n-hexyl	C_6H_4	NH_4PF_6 (1.5)	MeOH	12h	63%
CH_2OMe	2-Me-(6-Et)-C_6H_4	HBF_4/OEt_2 (3.0)	Tol	12h	41%

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

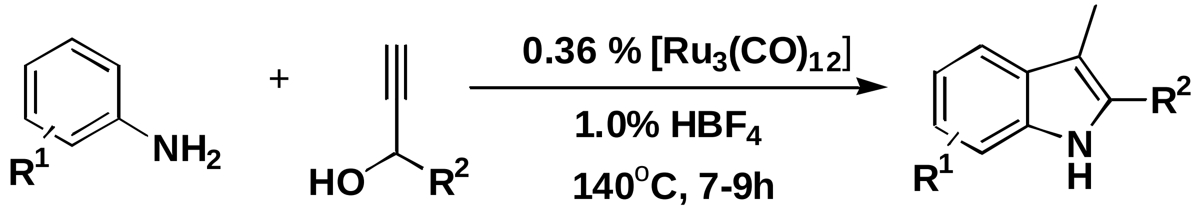
Wakatsuki, Y., *et al*., *Angew. Chem. Int. Ed. Engl.* **1999**, 3222

Ruthenium Catalysis



R=Me (89%)

R=Ph (99%)



72-97%

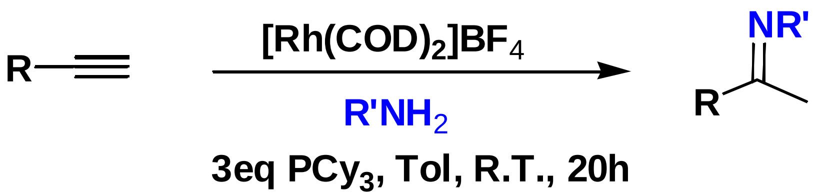
R^1=H, *p*-Me, *p*-MeO, *o*-CH_3, *p*-Cl, *o*-CO_2Me

R^2=Me, Et, *n*-pentyl, Ph

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

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

Rhodium Catalysis

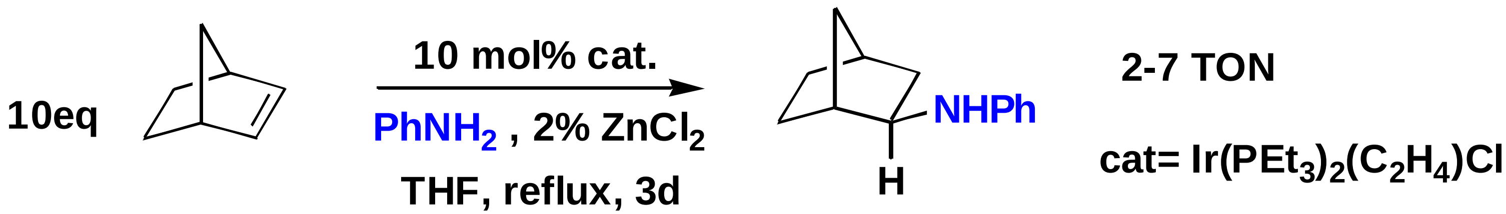


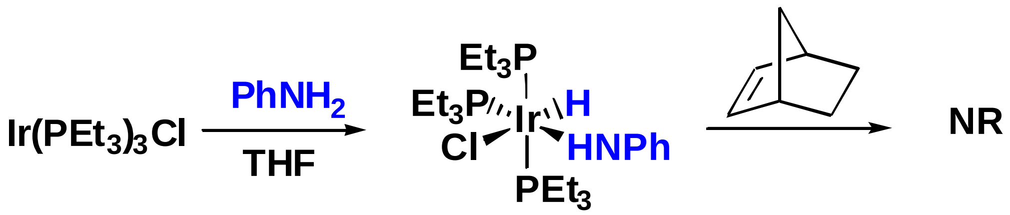
R	R'	cat %	Yield
n-hexyl	C_6H_4	1.5	79%
n-butyl	C_6H_4	1.5	83%
n-butyl	2-Me-C_6H_4	1.5	55%
n-hexyl	4-Me-C_6H_4	1.5	73%
n-hexyl	4-MeO-C_6H_4	1.5	63%
n-hexyl	4-Cl-C_6H_4	1.0	99%
Ph	C_6H_4	2.5	10%

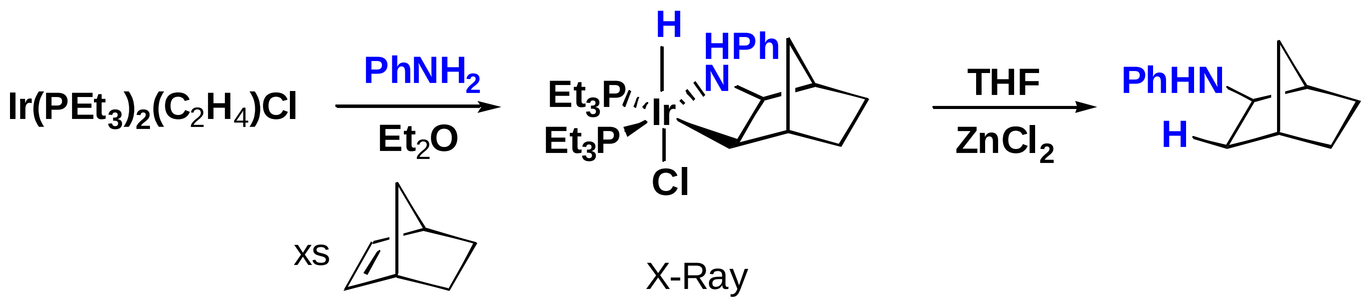
- Excellent yields for alkyl terminal alkynes
- Markovnikov regiochemistry
- Room temperature reaction

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

Iridium Catalysis

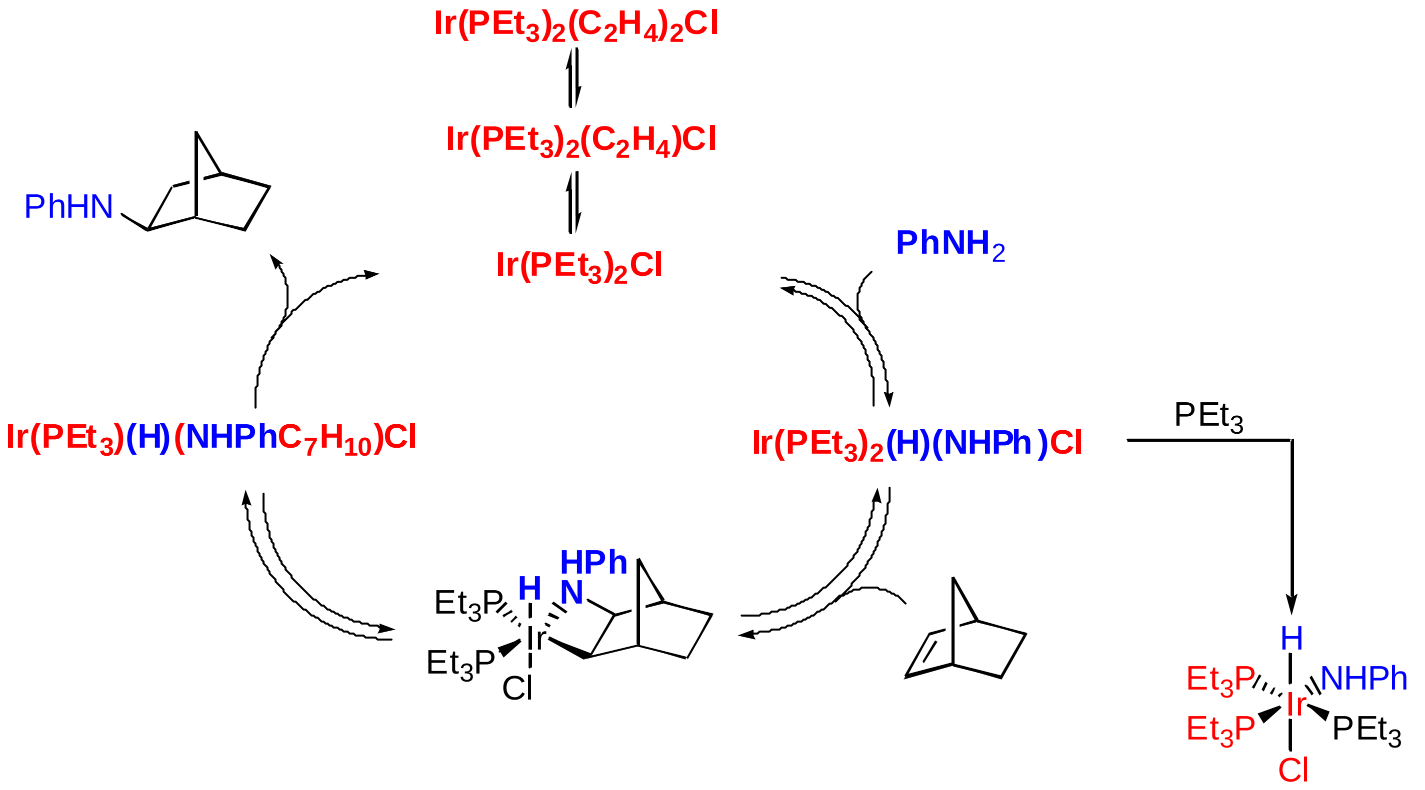






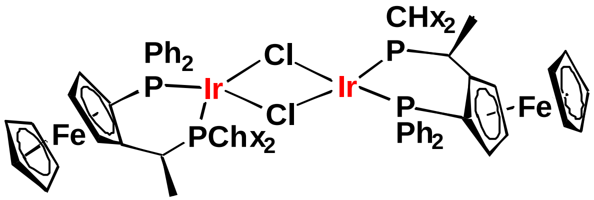
Casalnuovo, A., *et al.*, *J. Am. Chem. Soc.* **1988**, 6738

Iridium Mechanism



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

Asymmetric Hydroamination



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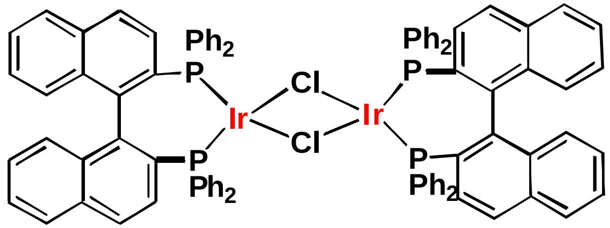

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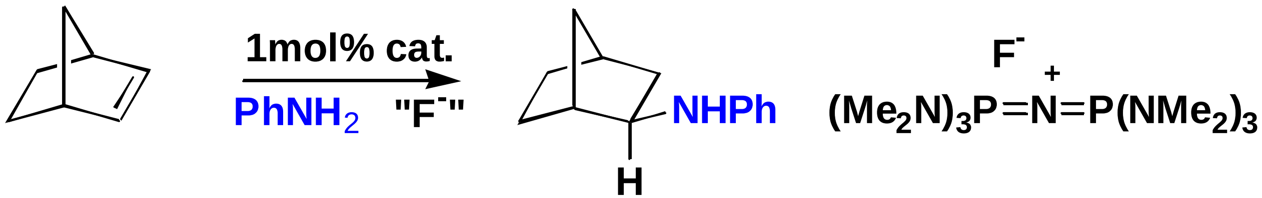
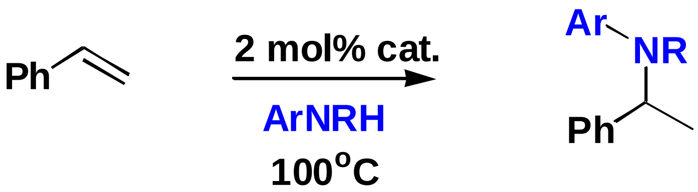


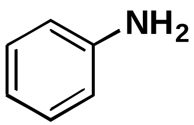
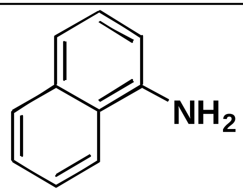
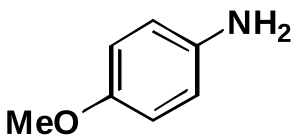
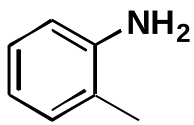
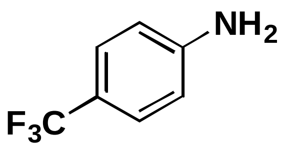
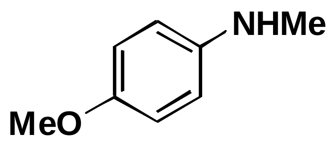
Catalyst	T (°C)	F⁻ (eq)	Yield(%)	ee(%)
1	50	0	12	51 (S)
1	50	1	81	31 (R)
1	25	1	12	60 (R)
1	50	4	51	16 (R)
2	75	2	45	78 (R)
2	75	4	22	95 (R)

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

Palladium Catalysis

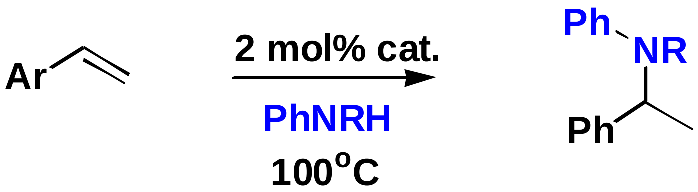


cat= 2%Pd(OC(O)CF_3)$_2$ / 3%DPPF / 20%TfOH

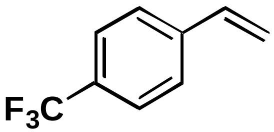
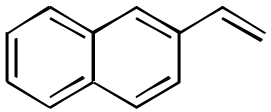
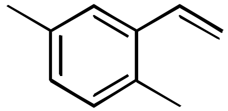
Amine	Time	Yield	Amine	Time	Yield
	7h	99%		7h	88%
	7h	78%		7h	68%
	12h	64%		12h	54%

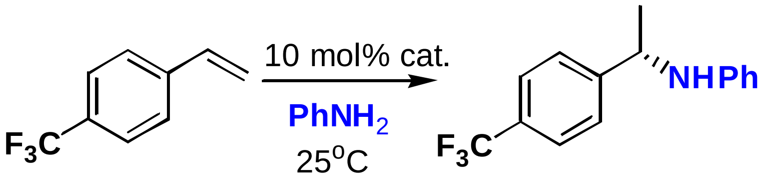
Hartwig, J., Kawatsura,M., *J. Am. Chem. Soc.* **2000**, 9546

Palladium Catalysis (2)



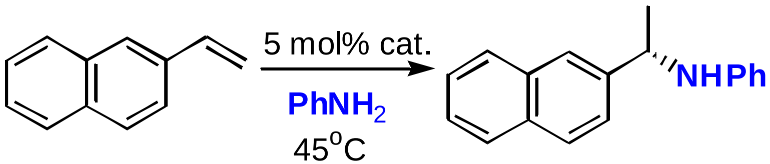
cat= 2%Pd(OC(O)$CF_3)_2$ / 3%DPPF / 20%TfOH

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



cat= [(*R*)-BINAP]Pd$(OTf)_2$

80% (81%ee)

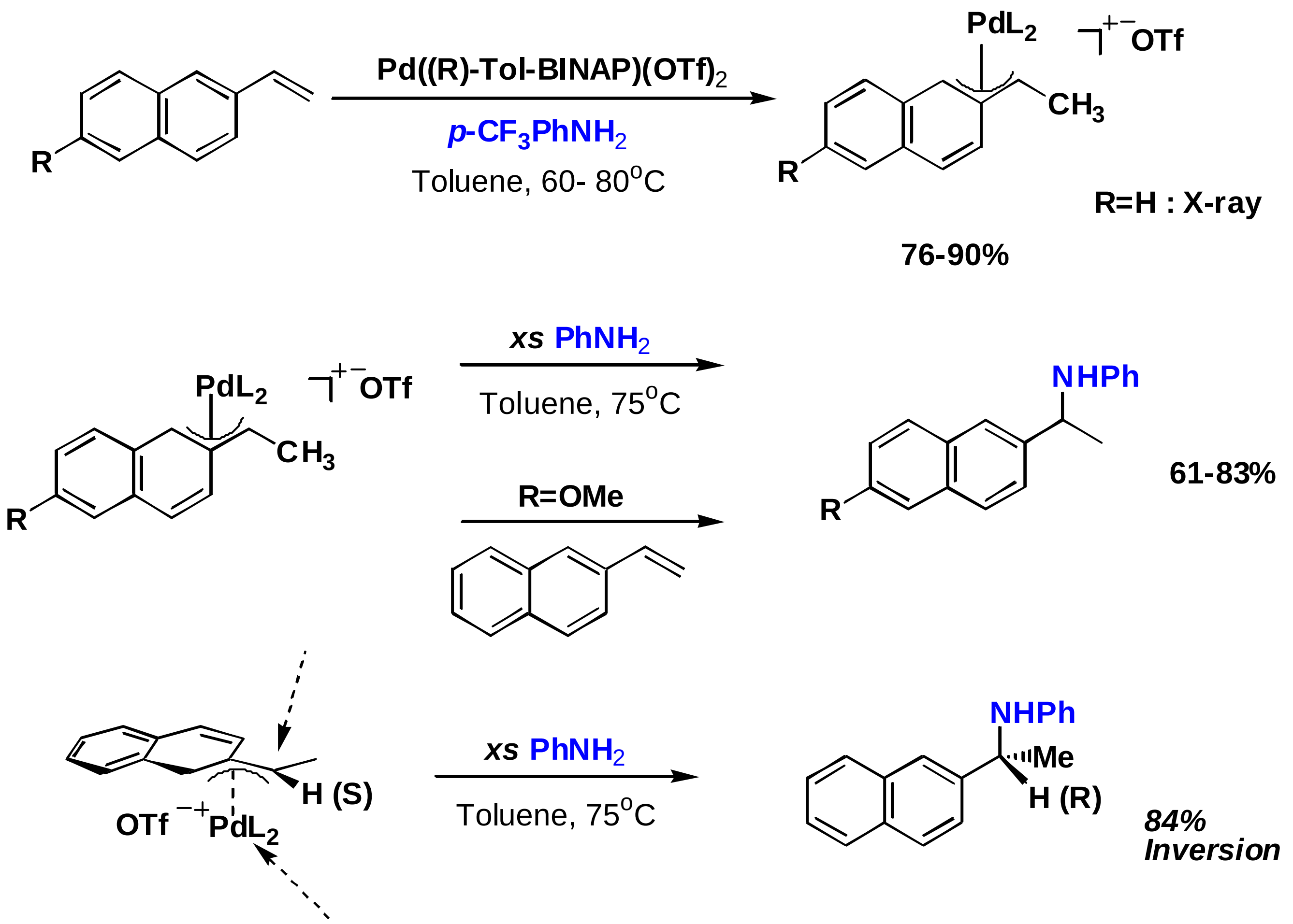


cat= [(*R*)-BINAP]Pd$(OTf)_2$

99% (64%ee)

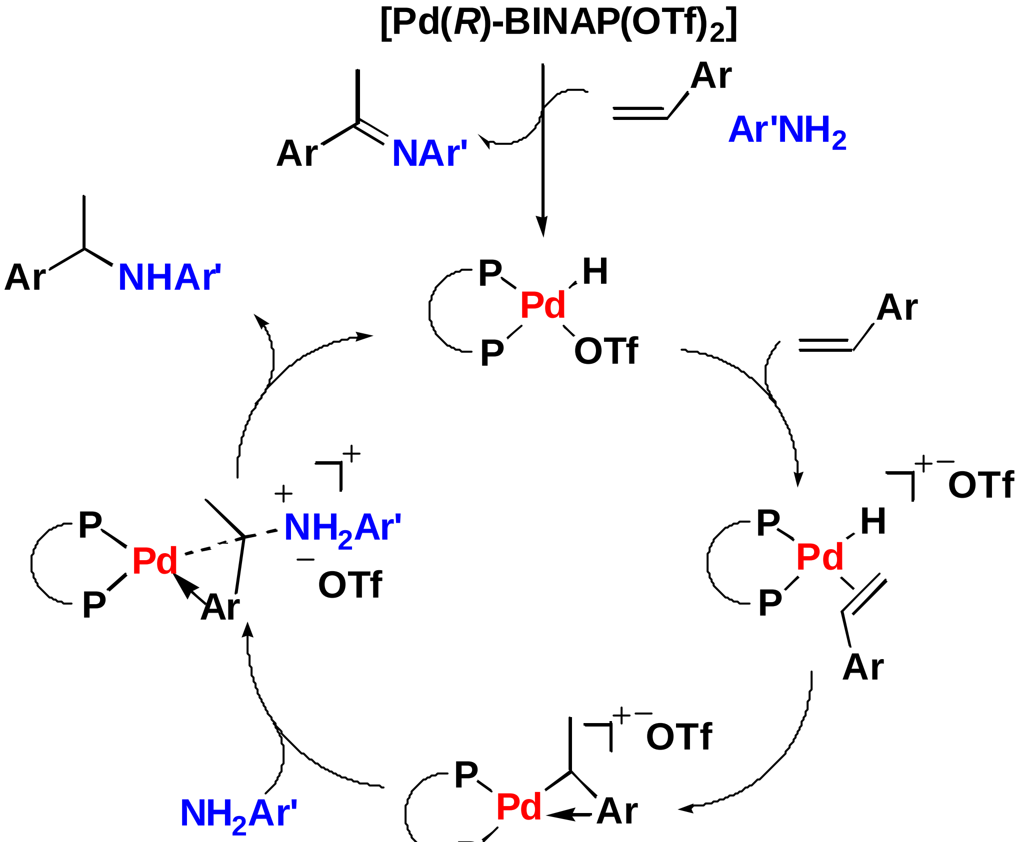
Hartwig, J., Kawatsura,M., *J. Am. Chem. Soc.* **2000**, 9546

Palladium Mechanism



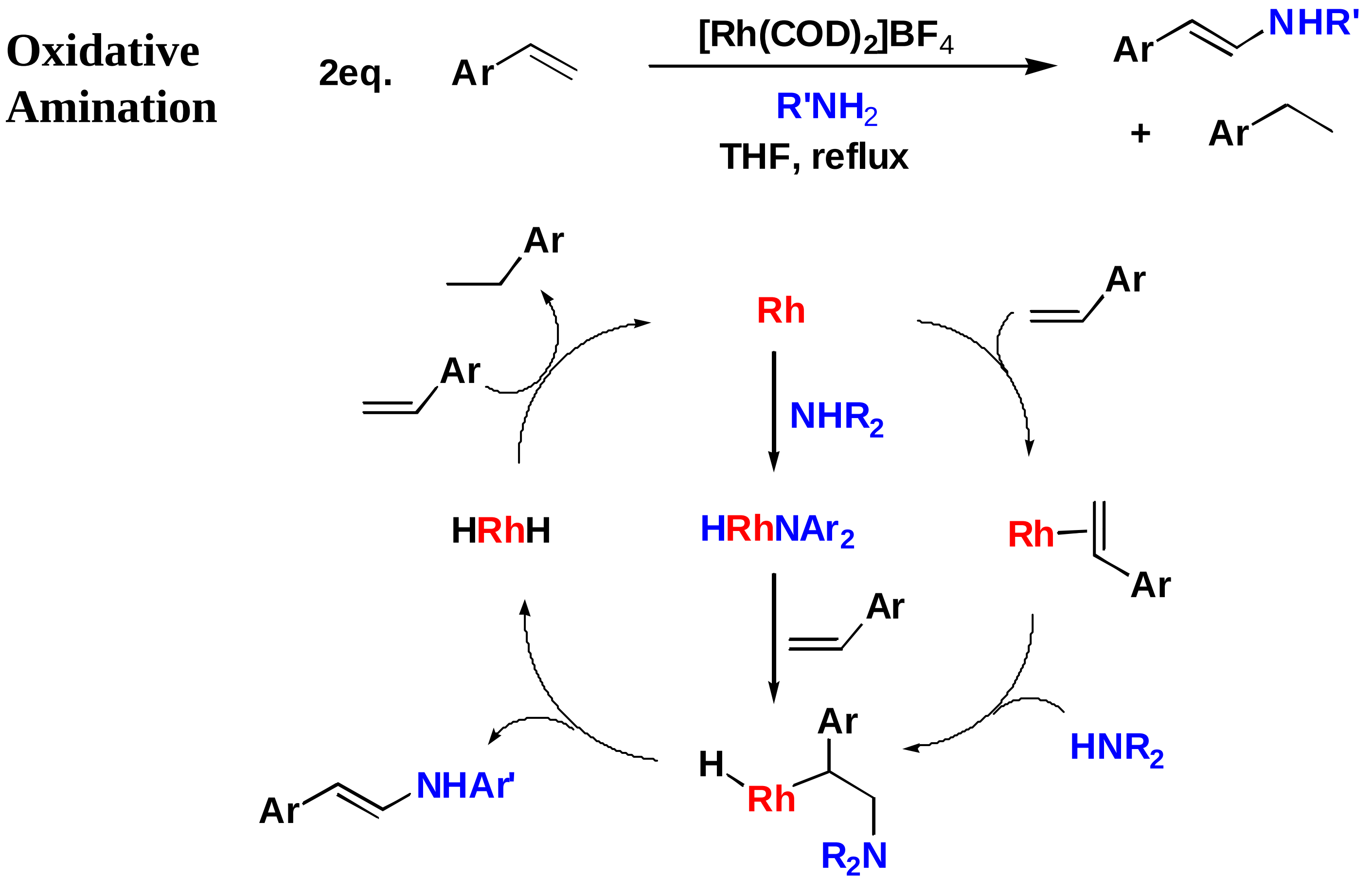
Hartwig, J., Nettekoven, U., *J. Am. Chem. Soc.* **2002**, 1167

Palladium Mechanism (2)



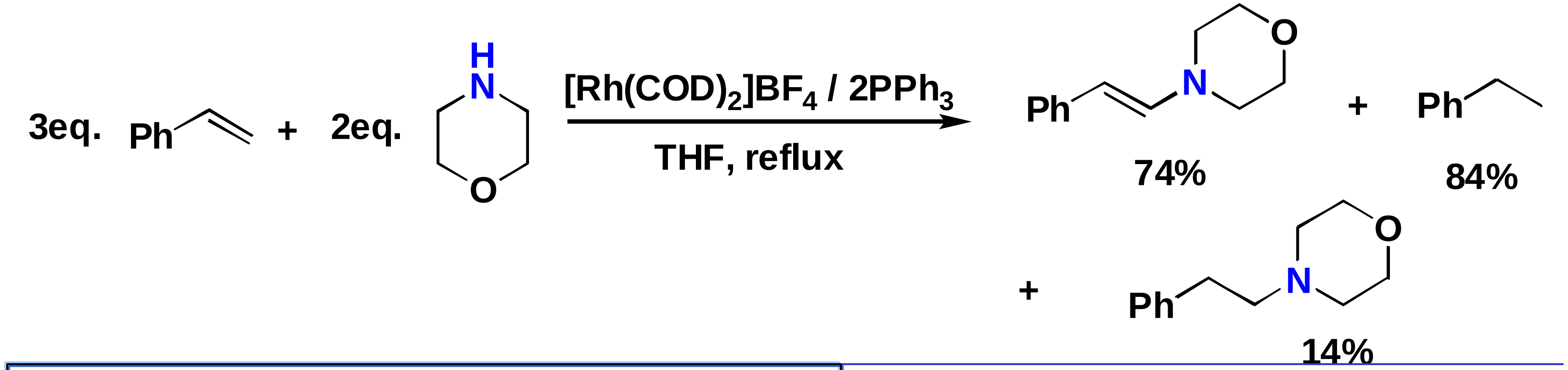
Hartwig, J., Nettekoven, U., *J. Am. Chem. Soc.* **2002**, 1167

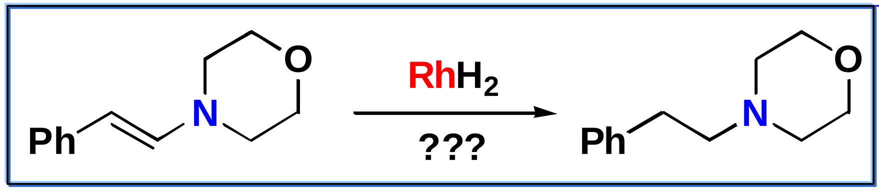
Oxidative Amination

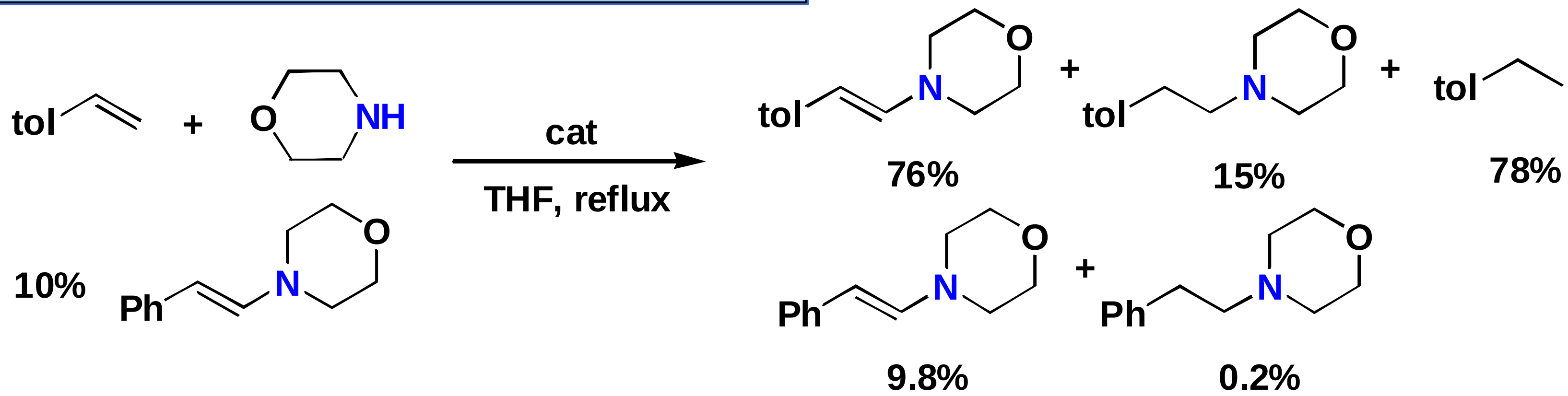


Beller, M., et al., *Chem. Eur. J.* **1999**, 1306

Oxidative/Hydroamination

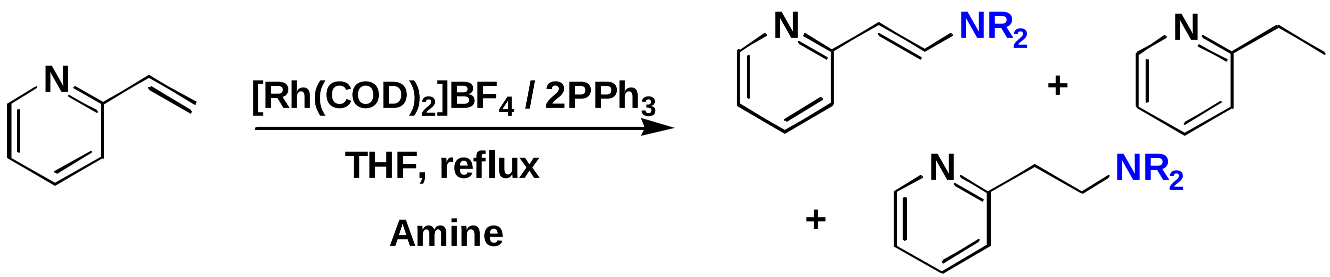






Beller, M., et al., *Chem. Eur. J.* **1999**, 1306

Oxidative/Hydroamination



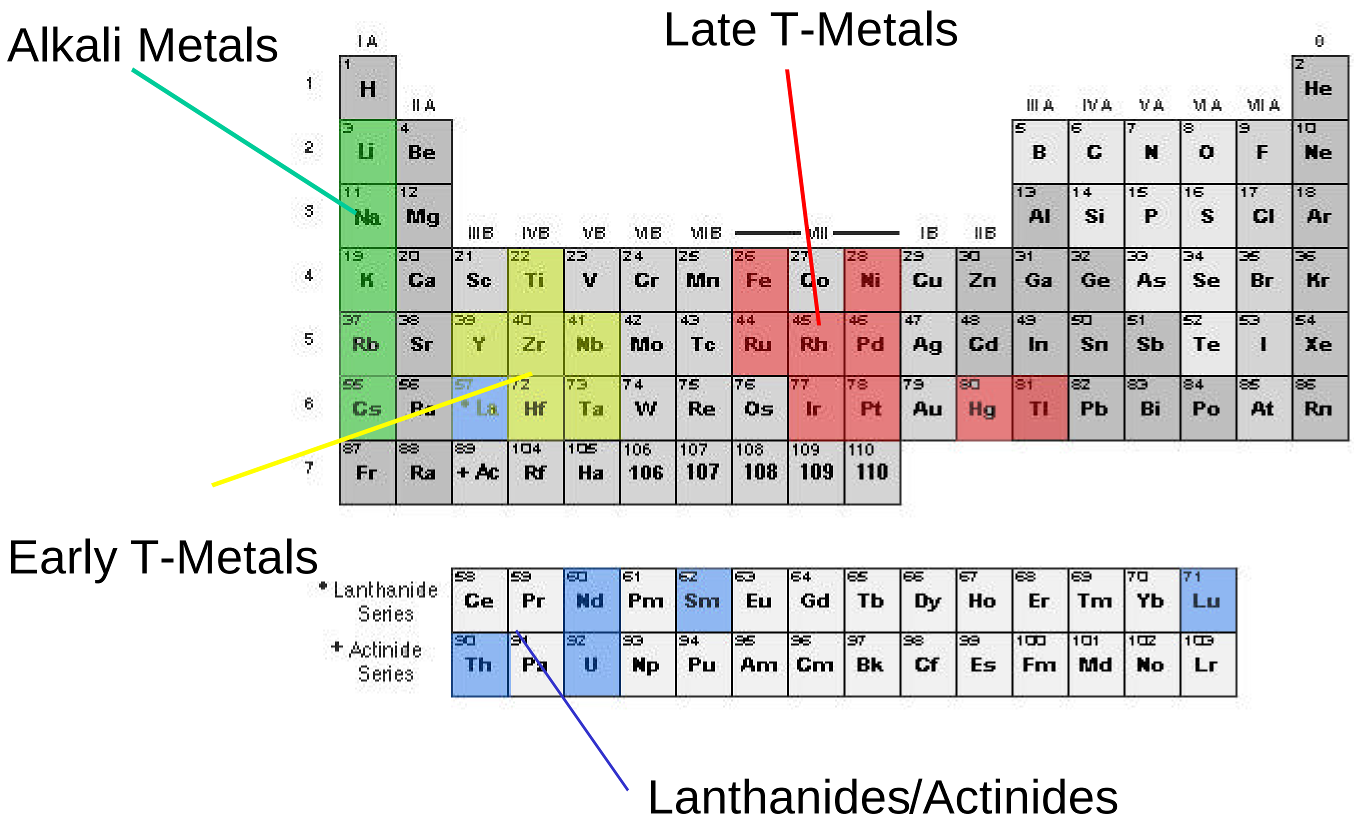
Starting Amine	Amine	Enamine	Ethyl-Py
Pyrrolidine	54%	21%	56%
Piperidine	47%	53%	42%
Morpholine	98%	2%	2%
Thio-Morpholine	98%	1%	1%
N-Phenyl Piperazine	91%	8%	6%
Et_2NH	<1	<1	-
n$BuNH_2$	<1	<1	-

Beller, M., et al., *Eur. J. Inorg. Chem.* **1999**, 1111

Conclusions

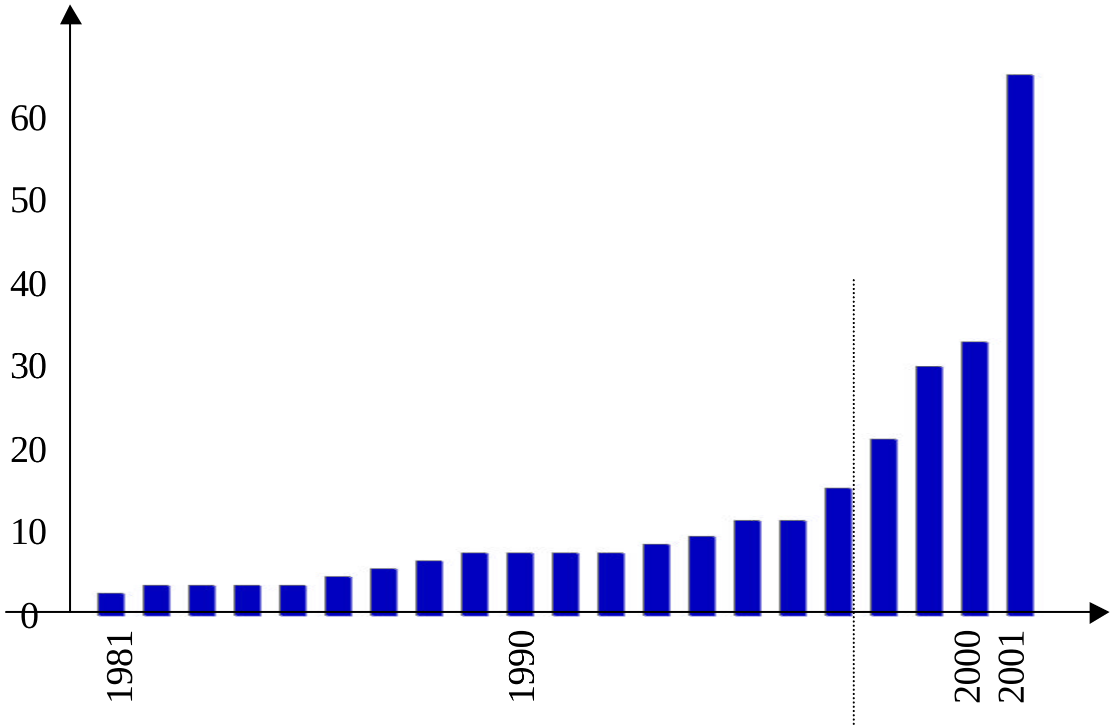
- Tremendous progress towards an efficient catalytic hydroamination reaction
- Intramolecular systems more easily developed
- Intermolecular hydroaminations of olefins still a challenge (especially anti-markovnikov additions)
- Still no effective general catalyst (alkynes, alkenes, allenes, etc...)
-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

Elements of Hydroamination



•No widely applicable catalyst developed yet

Hydroamination Publications



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