Most Recent Advances in Hydroamination:

A Little Supplement to CEM852

Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, ASAP

He, C.; Zhang, J. *J. Am. Chem. Soc.* **2006**, ASAP

Shibasaki, M.; Qin, H. *J. Am. Chem. Soc.* **2006**, ASAP

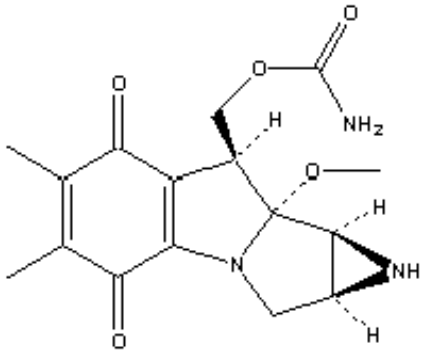
Ackermann, L. *Angew. Chem. Int. Ed.* **2005**, *44*, 5972-4

Roesky, P. *Angew. Chem. Int. Ed.* **2005**, *44*, 7794-8

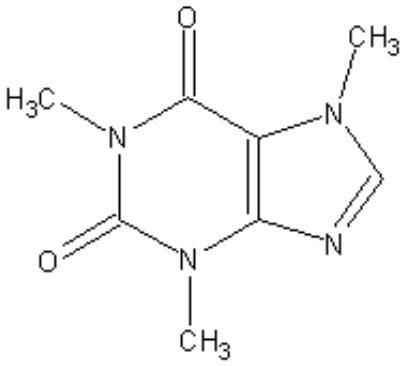
Seminar Outline

- Introduction of hydroaminations
- History of hydroaminations
- New catalysts for hydroaminations
- Conclusions

Organonitrogen Compounds in Industry



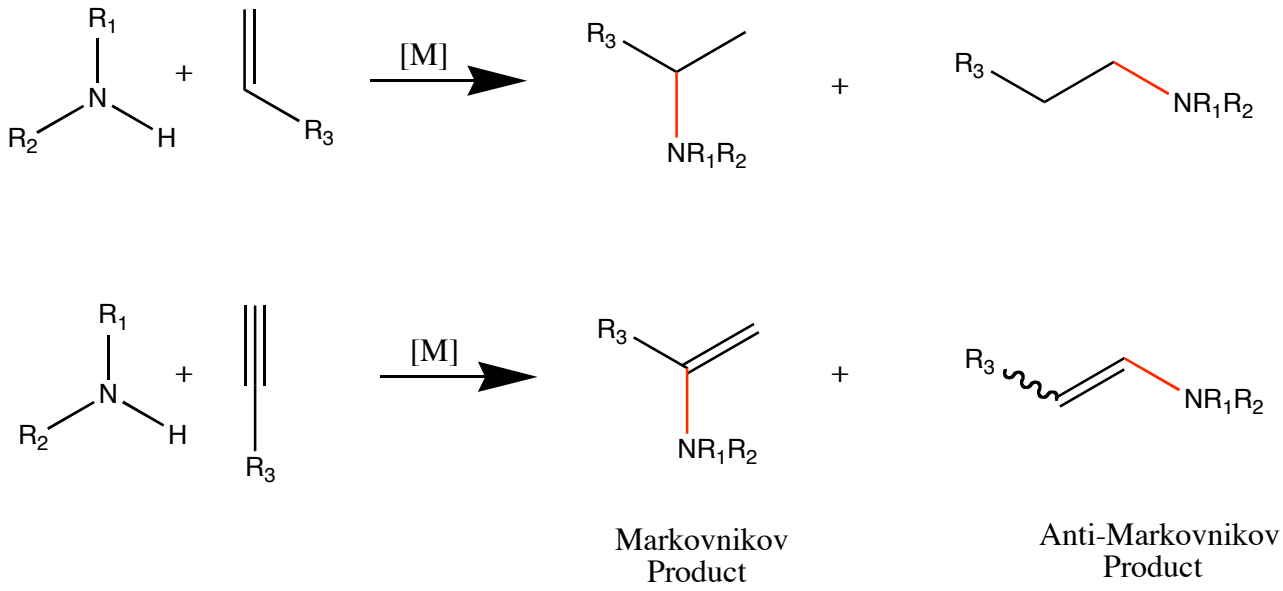
Mitomycin (antibiotic)



caffeine

- **Bactericides, herbicides, corrosion inhibitors,extraction agent in the production of penicillin,softening agents, wetting agents, dye fixers,asphalt emulsifiers, pigment dispersing agents,petroleum additives, a polymer in paper making,textile finishing**

Hydroamination of Alkenes and Alkynes

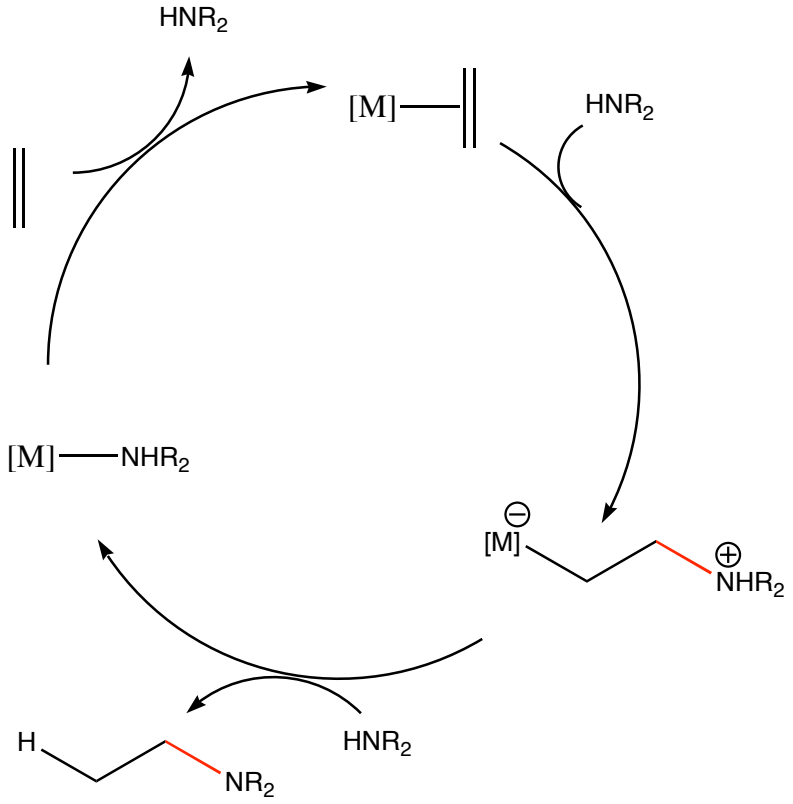


- **Overall reaction is thermodynamically favorable with negative reaction entropy, which means high temperature is not able to overcome high activation barrier.**

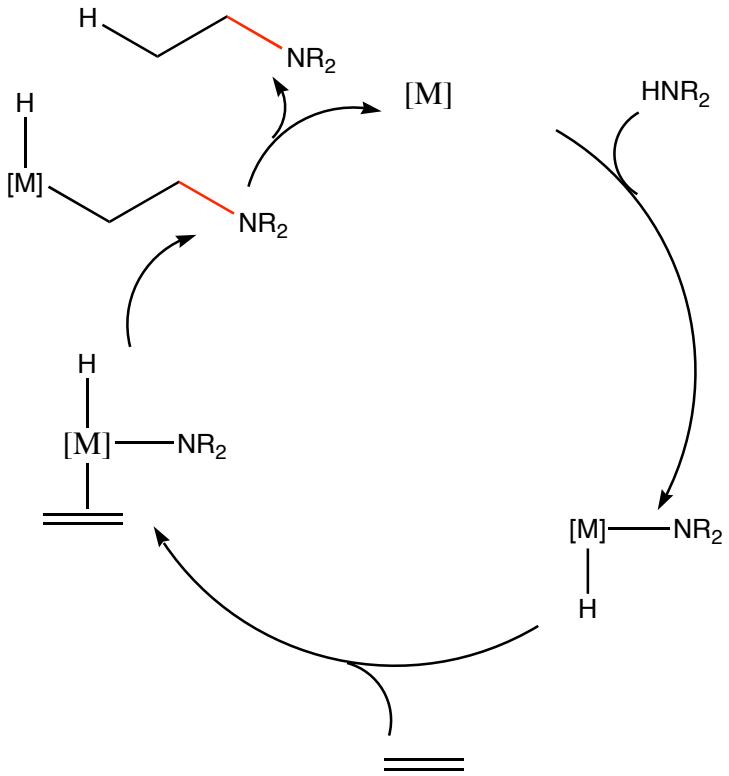
Steinborn, D.; Taube, R. Z. *Chem.* **1986**, *26*, 349

Two General Catalytic Cycles

Olefin Activation

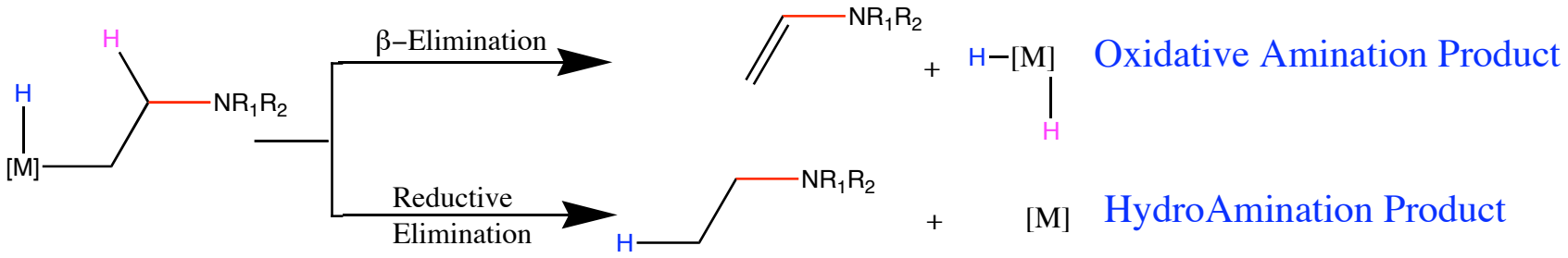


Amine Activation



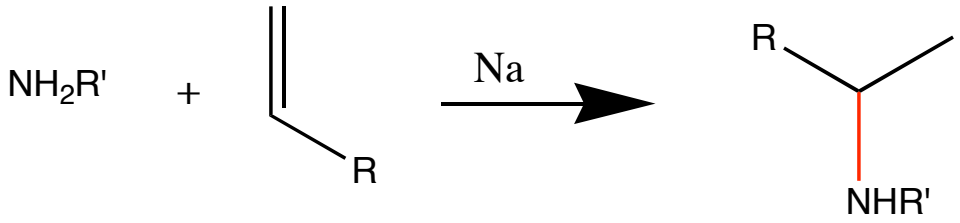
Togni, A. *J. Am. Chem. Soc.* **2000**, *122*, 4098

Two Pathways for Breaking the Metal Alky Bond



Muller, T. E. *Chem. Rev.* **1998**, *98*, 675

First Example of Hydroamination



R= H,CH_3,$(CH_2)_nCH_3$
R'= H, Et

Condtions: 200°C and 1000atm
Yields were generally poor with polymeric side-products

Howk, A. et al *J. Am. Chem. Soc.* **1954**, *76*, 1899

Other Metals Used for Hydroamination

- Stoichiometric Hg

  Barluenga, J. et al *Synthesis* **1975**, 116
- Ca compounds

  Crimmin, M. R. et al *J. Am. Chem. Soc.* **2005**, *127*, 2042
- Lanthanide: La, Sm, Nd…

  Marks, T. J. et al *J. Am. Chem. Soc.* **1989**, *111*, 4108
- Late-transition-metal complex: Ir, Rh, Ni, Pd, Pt, and Ru

  Coulson, D. R. *Tetrahedron Lett.* **1971**, *5*, 429

  Casalnuovo, A. L. et al *J. Am. Chem. Soc.* **1988**, *110*, 6738
- Group 4 metal: Ti, Zr, and Hf

  Bergman, R.G. et al *J. Am. Chem. Soc.* **1992**, *114*, 1708
- Actinide metal catalyst: U and Th

  Haskel, A. et al *Organometallics* **1996**, *15*, 3773

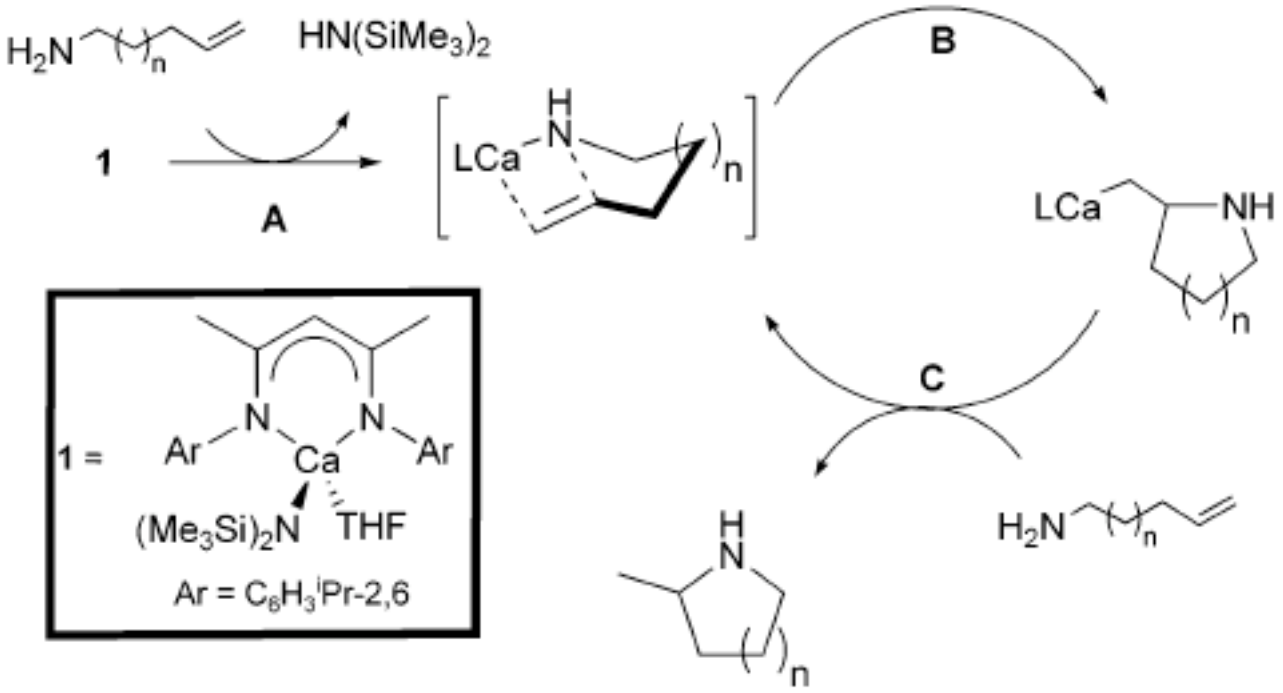
Disadvantages of These Catalysts…

- Toxic: Hg
- Highly sensitive to moisture and air: Ln, Ti, Zr and Hf.
- Bad polar-functional-groups tolerance: Ln, group 4 metals
- Expensive: late transition metals
- Modest selectivity, sluggish rates, sometimes requiring stabilizing ligands or additives: late transition metals

What to do?

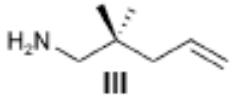
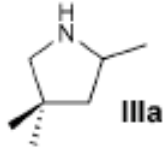
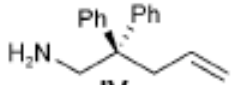
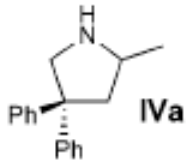
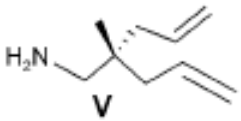
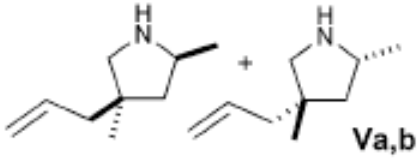
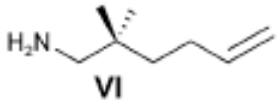
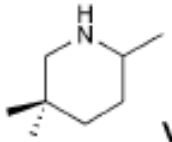
- Explore more (metal) catalysts
- Optimization of conditions by detailed study of mechanisms
- Do NOT use any metals:Proton-catalyzed hydroamination
  Bergman, R. G. et al *J. Am. Chem. Soc.* **2005**, *127*, 14542

Calcium-Mediated Hydroamination Catalyst



Crimmin, M. R. et al *J. Am. Chem. Soc.* **2005**, *127*, 2042

Calcium-Mediated Hydroamination Catalyst

Entry[a]	aminoalkene	product(s)	time(h)	temp (°C)	% Conv.[b]
1	 III	 IIIa	0.25	25	>99
2	 IV	 IVa	0.25	25	>99
3	 V	 Va,b	0.25	25	>99
4	 VI	 VIa	6	60	86

[a] Entries 1−3, 10 mol % cat. loading. Entry 4, 20 mol % (10 mol % required 72 h to produce 85% conversion). [b] Determined by ^{1}H NMR in C_6D_6.

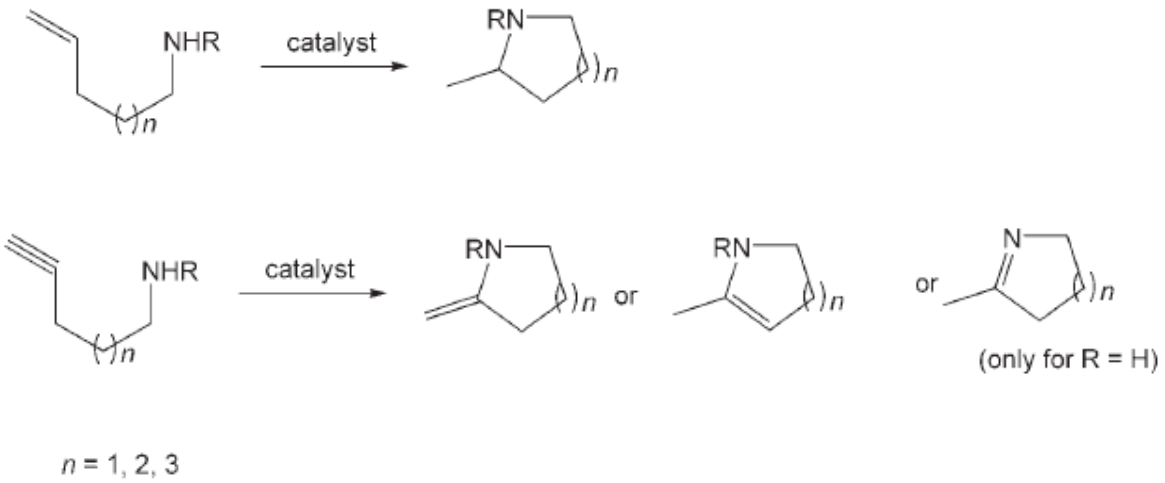
Crimmin, M. R. et al *J. Am. Chem. Soc.* **2005**, *127*, 2042

Calcium-Mediated Hydroamination: Scope

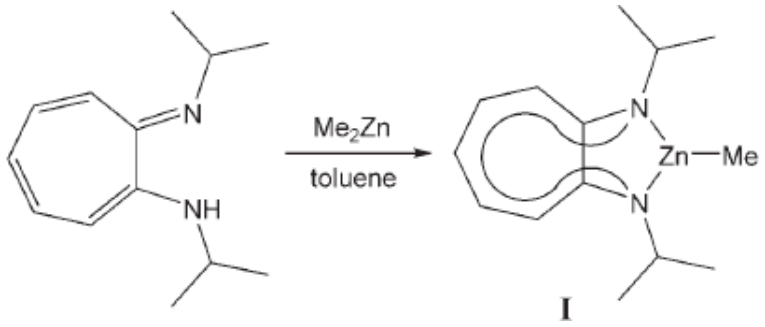
- Commensurate with some Ln catalyst (cationic Sc species)
- Low cost and easily available
- Environmentally benign
- Catalyst is not stale
- Functional group tolerance? Not known yet.

Crimmin, M. R. et al *J. Am. Chem. Soc.* **2005**, *127*, 2042

Zinc-Mediated Hydroamination

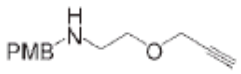
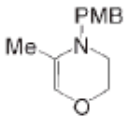
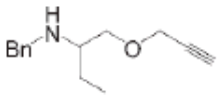
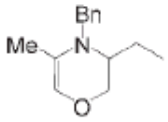
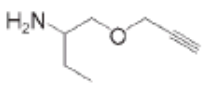
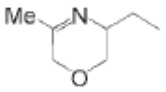
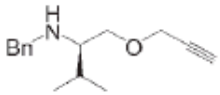
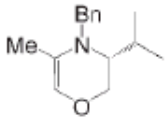
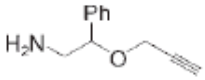
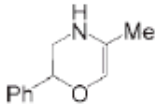
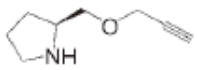
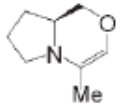
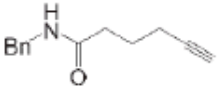
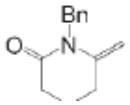


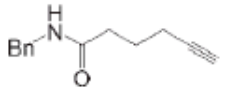
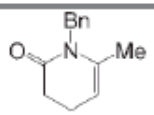
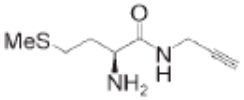
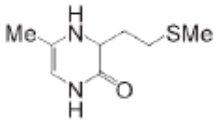
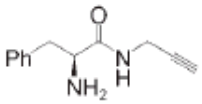
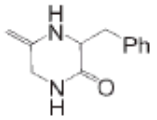
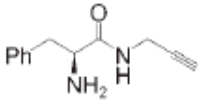
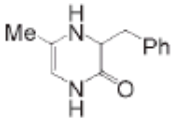
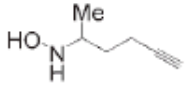
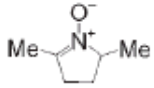
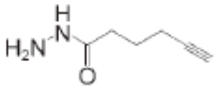
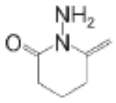
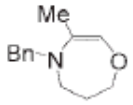
Catalyst



Roesky, P. *Angew. Chem. Int. Ed.* **2005**, *44*, 7794-8

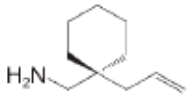
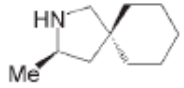
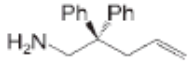
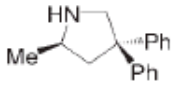
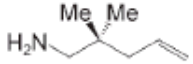
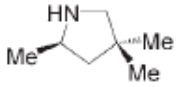
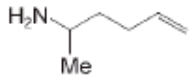
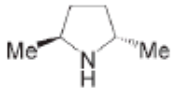
Zinc-Mediated Hydroamination

Entry	Substrate		Product		cat. **I** [mol %]	Activ.[b] [mol %]	*t* [h]	Conv. [%][c]
1		**1a**		**1b**	1 1	– 1	144 39	>99[d] >99[d]
2		**2a**		**2b**	1 0.1 1	– 0.1 1	72 8 45	>99 >99, (91)[e] >99[d]
3		**3a**		**3b**	10 2	– 2	144 14	>99 >99, (70)[e]
4		**4a**		**4b**	1 10 1	– 10 1	96 1.5 144	19 >99 94
5		**5a**		**5b**	10 2	– 2	6 14	>99 >99
6		**6a**		**6b**	1 0.1	– 0.1	4 8	95 >99
7		**7a**		**7b**	10	–	60	25

Entry	Substrate		Product		cat. **I** [mol%]	Activ.[b] [mol%]	*t* [h]	Conv. [%][c]
8		**7a**		**8b**	10	10	60	> 99[f]
9		**9a**		**9b**	10	–	15	92
10		**10a**		**10b**	5	–	72	51
11		**10a**		**11b**	10	–	15	> 99
12		**12a**		**12b**	1 0.5	– 0.5	5 4	98[d] > 99[d]
13		**13a**		**13b**	10	–	14	> 99
14		**14a**		**14b**	5	–	312	> 99

[a] Reaction conditions: amine (430 μmol), catalyst **I**, benzene (0.5 mL), 120 °C. [b] Activator: $[PhNMe_2H][B(C_6F_5)_4]$. [c] Determined by ^1H NMR spectroscopy. [d] The reaction was carried out at 60 °C. [e] Yield of isolated product; the reaction was performed on a 2-mmol scale. [f] **8b**/**7b** = 6:1.

Zinc-Mediated Hydroamination of Alkene

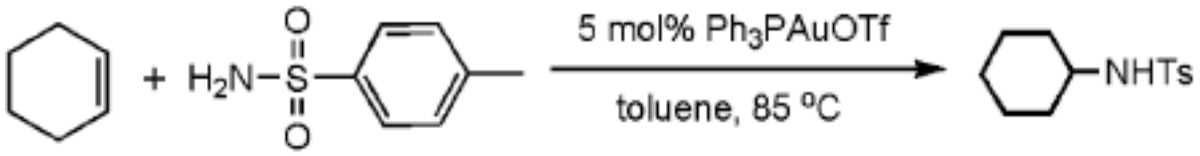
Entry	Substrate		Product		cat. **I** [mol%]	Activ.[b] [mol%]	*t* [h]	Conv. [%][c]
1		**15a**		**15b**	10	–	30	87[d]
					5	–	28	>99
					5	5	8	80
2		**16a**		**16b**	10	–	12	>99
					10	–	24	69[d]
					5	5	5	>99
3		**17a**		**17b**	13.3	–	72	>99
					5	5	52	46
4		**18a**		**18b**	10	10	36	19

[a] Reaction conditions: amine (430 µmol), catalyst **I**, benzene (0.5 mL), 120°C. [b] Activator: $[PhNMe_2H][B(C_6F_5)_4]$. [c] Determined by ^1H NMR spectroscopy. [d] Yield of isolated product; the reaction was carried out at 100°C in toluene.

- Good functional tolerance
- Cocatalyst repuired to speed the reaction
- Ring size has a larger influence than electronic effects
- Slower for alkenes

Roesky, P. *Angew. Chem. Int. Ed.* **2005**, *44*, 7794-8

Gold-Mediated Hydroamination of Alkene



Entry	Olefin	Nucleophile	Time(h)	Product	Yield(%)[b]
1	(**1a**)	$TsNH_2$ (**1b**)	15	TsHN (**1c**)	90(91)[c]
2[d]	**1a**	$TsNHCH_3$ (**2b**)	44	Ts(Me)N (**2c**)	56
3[e]	**1a**	RSO_2NH_2 (**3b**)	15	RSO_2NH (**3c**)	89
4	(**3a**)	**1b**	20	TsHN (**4c**)	83
5	Ph (**4a**)	**1b**	14	NHTs, Ph, Me (**5c**)	51
6	Ph (**5a**)	**1b**	16	NHTs, Ph (**6c**)	56
7	MeO (**6a**)	**1b**	14	TsHN, MeO (**7c**)	95(93)[c]

[a] Reactions were conducted with 1 mmol of nucleophiles, 4 mmol of olefins (2.0−2.8 mmol could be recovered after the reaction in most cases), and 5 mol % of $Ph_3PAuCl/AgOTf$ in 2 mL of toluene at 85 °C. [b] Isolated yield. [c] The yield in parentheses refers to a reaction performed without solvent. [d] At 95 °C. [e] R = $MeOC_6H_4$. [f] **9c**:**9c′** = 2:1. [g] A 1:1 ratio of $TsNH_2$ and norbornene was used.

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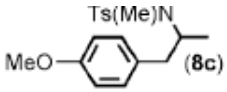
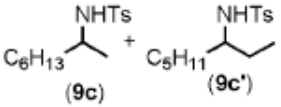
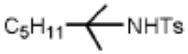
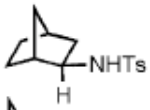
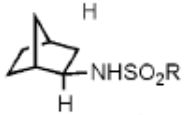
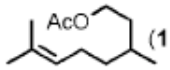
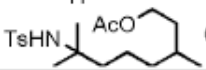
Gold-Mediated Hydroamination of Alkene

Entry	Olefin	Nucleophile	Time(h)	Product	Yield(%)[b]
8	**6a**	**2b**	48	 (**8c**)	55
9	 (**8a**)	**1b**	14	 (**9c**) + (**9c'**)	85[f]
10	 (**9a**)	**1b**	38	 (**10c**)	51
11[g]	 (**10a**)	**1b**	15	 (**11c**)	89
12[g]	**10a**	**3b**	15	 (**12c**)[e]	80
13	 (**11a**)	**1b**	48	 (**13c**)	44

[a] Reactions were conducted with 1 mmol of nucleophiles, 4 mmol of olefins (2.0−2.8 mmol could be recovered after the reaction in most cases), and 5 mol % of $Ph_3PAuCl/AgOTf$ in 2 mL of toluene at 85 °C. [b] Isolated yield. [c] The yield in parentheses refers to a reaction performed without solvent. [d] At 95 °C. [e] R = $MeOC_6H_4$. [f] **9c**:**9c'** = 2:1. [g] A 1:1 ratio of $TsNH_2$ and norbornene was used.

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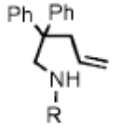
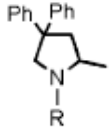
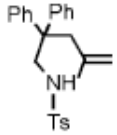
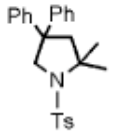
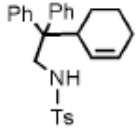
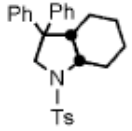
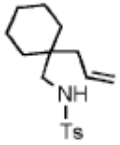
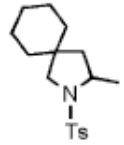
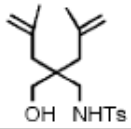
Gold-Mediated Hydroamination of Alkene

Entry	Substrate	Time(h)	Product	Yield(%)[b]
1	 R = Ts, **1d**	17	 R = Ts, **1e**	96
2[c]	R = Ns, **2d**	48	R = Ns, **2e**	99
3	R = Ac, **3d**	48	R = Ac, **3e**	0
4	 (**4d**)	15	 (**4e**)	91
5	 (**5d**)	15	 (**5e**)	95
6	 (**6d**)	15	 (**6e**)	99
7	 (**7d**)	10	 (**7e**)	97

[a] Reactions were conducted with 0.5 mmol of substrate and 5 mol % of $Ph_3PAuCl/AgOTf$ in 2 mL of toluene at 85 °C. [b] Isolated yield. [c] Ns= 2-nitrobenzenesulfonate.

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Gold-Mediated Hydroamination of Alkene: Facts

- Unactivated olefins can work to give Markovnikov product
- Nucleophiles: olefins = 1:4
- No b-elimination doesn't occur
- Mechanism study based on NMR shows gold(I) activates olefin, but not $TsNH_2$, which attacks from the oppsite face of gold
- The reaction is inhibited by alkylamines or aniline

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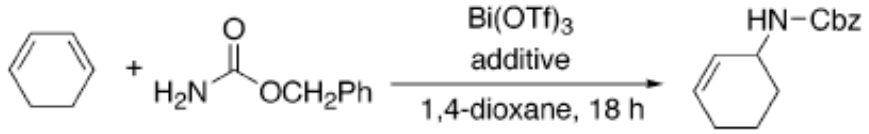
Bismuth-Mediated Hydroamination: Catalyst



1a **2a** **3aa**

entry	$Bi(OTf)_3$ (*x* mol %)	additive (*y* mol %)	**1a** (equiv)	temp (°C)	yield (%)
1	10	0	4	25	17
2	10	$Cu(CH_3CN)_4PF_6$ **4** (10)	4	25	79
3	10	$Cu(OTf)(C_6H_6)_{1/2}$ **5** (10)	4	25	24
4	10	KPF_6 **6** (10)	4	25	79
5	10	NH_4PF_6 **7** (10)	4	25	74
6	0	**4** (10)	4	25	0
7	10	**4** (10)	2	25	71
8	10	**4** (10)	2	50	66
9	10	**4** (10) + dppe (4)	2	50	80
10	10	**6** (10)	2	50	73
11	10	**6** (10) + dppe (4)	2	50	42

- Catalyst: Bi
- Cocatalyst repuired: PF_6 ligand
- Cu is not needed

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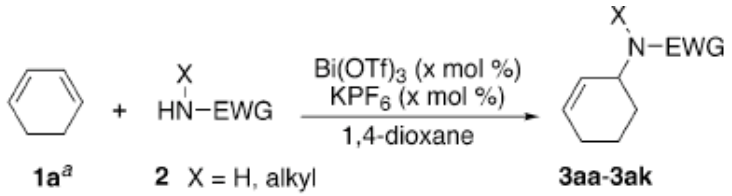
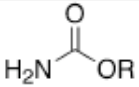
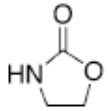
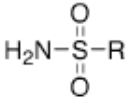
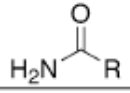
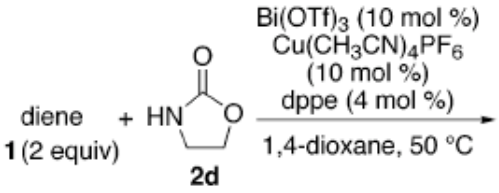
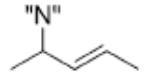
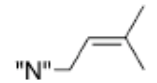
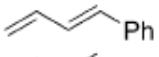
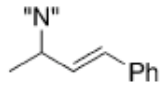
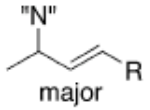
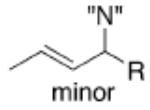
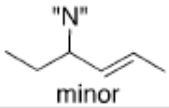
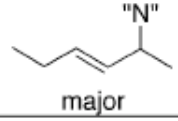
Bismuth-Mediated Hydroamination: Scope



1a[a] **2** X = H, alkyl **3aa-3ak**

entry	nucleophile			cat. (x mol %)	temp (°C)	time (h)	yield[b] (%)
1		R = CH_2Ph	**2a**	10	50	18	72
2		R = CH_3	**2b**	10	50	18	94
3		R = *n*-Bu	**2c**	10	50	18	72
4			**2d**	10	50	18	88
5		R = Ph	**2e**	5	25	5	73
6		R = *p*-tol	**2f**	5	25	3	83
7		R = *p*-MeO-C_6H_4	**2g**	5	25	5	84
8		R = *p*-CF_3-C_6H_4	**2h**	5	50	5	79
9		R = *o*-NO_2-C_6H_4	**2i**	10	25	24	62
10		R = Ph	**2j**	10	100	12	69
11		R = *p*-CF_3-C_6H_4	**2k**	10	90	17	60



entry	diene	time (h)	product	yield[a] (%)
1		**1b** 18		**3bd** 94
2		**1c** 18		**3cd** 60
3		**1d** 18		**3dd** 77
4[b]	R = $(CH_2)_7CH_3$	**1e** 18	 major	73 (3:1)
5[b]	R = $(CH_2)_2Ph$	**1f** 18	 minor	74 (3:1)
6[b]		**1g** 18	 minor  major	76 (1:2)

- Not sensitive to electronic properties of the nucleophiles
- Acyclic dienes can work; isomers were produced

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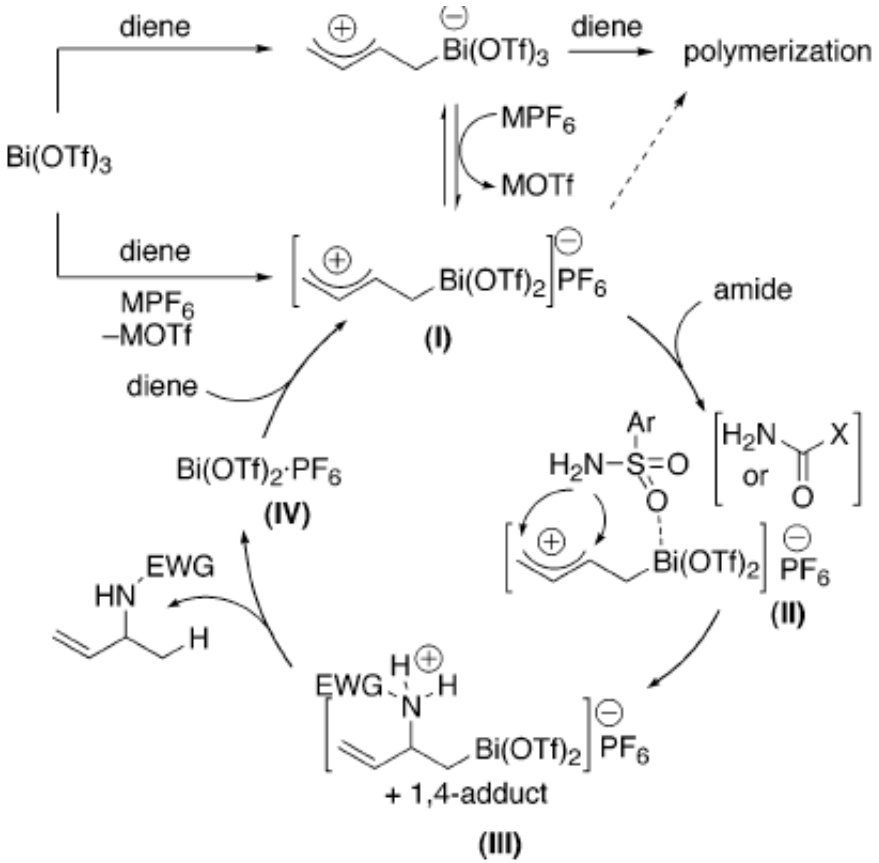
Bismuth -Mediated Hydroamination: Mechanism



• Couneranion exchange with PF_6^- , the coordination site of Bi will be available

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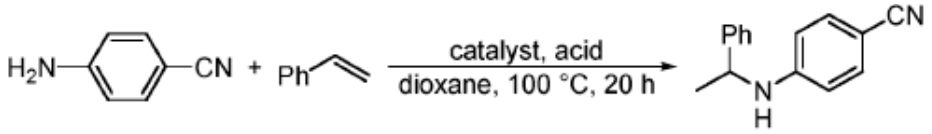
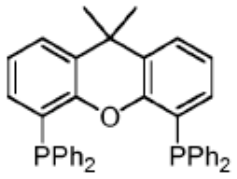
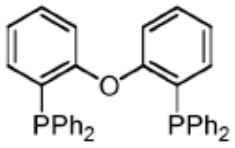
Pd-Mediated Hydroamination of Alkene



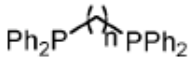
entry	Pd precursor	ligand	acid	yield[b]
1	2% (Xantphos)Pd(OTf)$_2$	-	-	81 (93)
2	2% (Xantphos)PdCl$_2$	-	-	0
3	2% (DPPF)Pd(OTf)$_2$	-	-	7 (13)
4	2% [(Xantphos)Pd(CH$_3$CN)$_2$](OTf)$_2$	-	-	76 (91)
5	2% (DPPF)Pd(CH$_3$CN)$_2$(OTf)$_2$	-	-	9 (16)
6	2% Pd(TFA)$_2$	3% Xantphos	5% TfOH	66
7	2% Pd(TFA)$_2$	2% DPPPent	20% TfOH	11
8	2% Pd(TFA)$_2$	3% BINAP	5% TfOH	2
9	2% Pd(TFA)$_2$	3% DPEphos	5% TfOH	10
10	2% Pd(TFA)$_2$	3% D^{i}PrPF	20% TfOH	0
11	2% Pd(PPh$_3$)$_4$	-	5% TfOH	2
12	2% [Pd(COD)(η^3-allyl)]OTf	2% Xantphos	-	86 (36)
13	2% [Pd(COD)(η^3-allyl)]OTf	2% DPPF	-	2 (13)
14	2% [Pd(COD)(η^3-allyl)]OTf	2% DPEphos	-	3 (14)
15	2% [Pd(COD)(η^3-allyl)]OTf	2% BINAP	-	0 (16)
16	2% [Pd(COD)(η^3-allyl)]OTf	2% DPPPent	-	2 (10)
17	2% [Pd(COD)(η^3-allyl)]OTf	2% DPPE	-	0 (9)
18	-	-	10% TfOH	0
19	-	-	10% HBF$_4$[c]	0



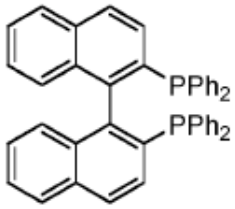
Xantphos



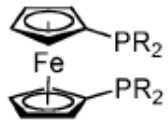
DPEphos



n = 2, DPPE
n = 5, DPPPent



Binap



R = ^{i}Pr, D^{i}PrPF
R = Ph, DPPF

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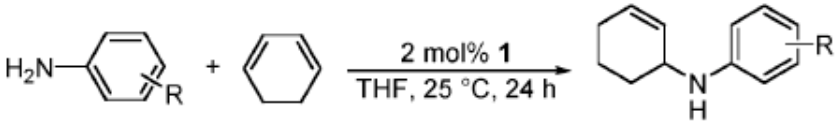
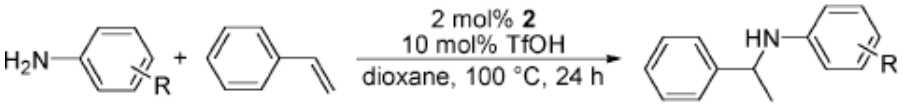
Pd-Mediated Hydroamination of Alkene



entry	amine	yield[b]	entry	amine	yield[b]
1	R = 3-NO_2	96	8[d]	R = 2-CN	98
2[c]	R = 4-NO_2	99	9	R = 3-CN	99
3	R = 3-COOH	81	10	R = 4-CN	97
4	R = 3-$COCH_3$	93	11	R = 2-CO_2Et	88
5	R = 4-$COCH_3$	99	12	R = 3-CO_2Et	82
6	R = 2-SMe	98	13	R = 4-CO_2Et	95
7	R = 4-SMe	99	14[d]	R = 2-OH	57

[a] Reaction conditions: 1.0 mmol of amine, 2.0 mmol of 1,3-cyclohexadiene, 2.0 mL of THF. [b] Isolated yield (average of two runs), in percent. [c] 50 °C. [d] 4.0 mmol of diene, 1.0 mL of THF, 50 °C.



entry	amine	yield[b]	entry	amine	yield[b]
1	R = 2-OH	80	8	R = C-CN	71
2	R = 4-CH_2CH_2OH	89	9	R = 3-CN	90
3	R = 3-COOH	92	10	R = 4-CN	72
4[c]	R = 3-$COCH_3$	81	11	R = 2-CO_2Et	99
5	R = 4-$COCH_3$	71	12	R = 3-CO_2Et	92
6	R = 2-SMe	59	13[d]	R = 4-CO_2Et	89
7[d]	R = 4-SMe	88	14[d]	R = 3-$NHCOCH_3$	91
			15[d]	R = 4-$CONH_2$	86

[a] Reaction conditions: 1.0 mmol of amine, 2.0 mmol of styrene, 1.0 mL of dioxane. [b] Isolated yield (average of two runs), in percent. [c] Reaction catalyzed by 2 mol % Xantphos, and 2 mol % $[Pd(CH_3CN)_4](BF_4)_2$. [d] Reaction run without TfOH cocatalyst.

1: XantphosPd(η^3-allyl)Cl

1: XantphosPd(η^3-allyl)OTf

- Good functional tolerance
- Excellent yields
- More factors influecing the reaction were studied in the paper: bite angle of the ligand, acid effect and counterion effect

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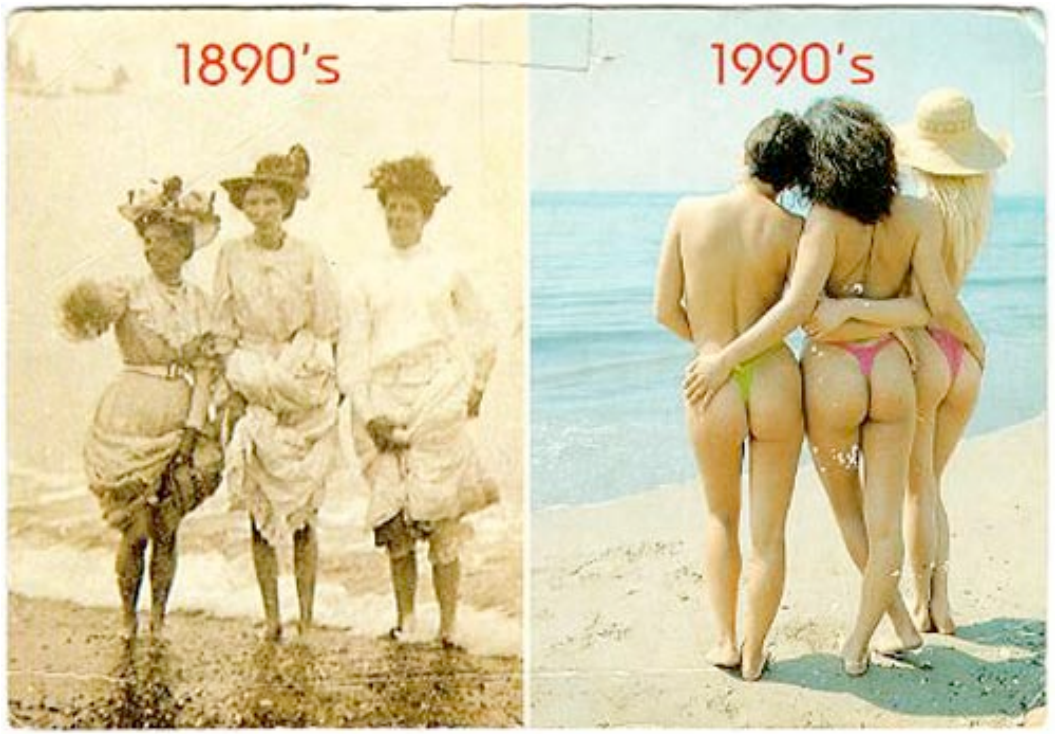
Conclusions

1. New metal-catalyzed hydroaminations were established in 4 months
2. More effient
3. Better functional group tolerance
4. Cheap, readily available and robust to moisture and air

Happy Chinese New Year

Dog's Year, I'll be 30…

A Lot Things Changed…



But My Life Is Still Crappy...

I Planned a Lot of Things Done Before 30…

But Still Not Decided Which First...

Thank You! Questions?