

Catalytic Asymmetric Hydroaminations

(And Hydroalkoxylations, But Mostly Hydroaminations)

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MacMillan Group Meeting

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Hydroamination (and Hydroalkoxylation): An Outline

Brief Introduction to Hydroaminations

Rare Earth Metal-Catalyzed Asymmetric Hydroaminations

Intramolecular reactions

Intermolecular reactions

Group 4 Metal-Catalyzed Asymmetric Hydroaminations

Cationic metal catalysts

Neutral metal catalysts

Late Transition Metal-Catalyzed Asymmetric Hydroaminations

Iridium-catalyzed reactions

Palladium-catalyzed reactions

Gold-catalyzed reactions

Rhodium-catalyzed reactions

Base-Catalyzed Asymmetric Hydroaminations

Brønsted Acid-Catalyzed Asymmetric Hydroaminations

Muller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795.

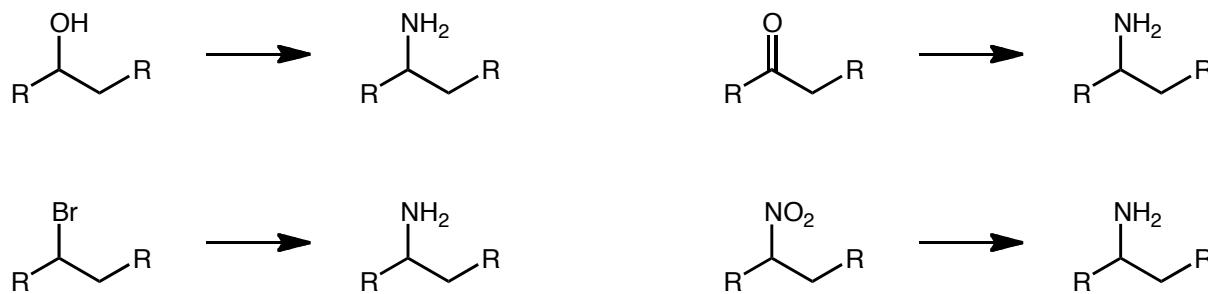
Aillaud, I.; Collin, J.; Hannedouche, J.; Schulz, E. *Dalton Trans.* **2007**, 5105.

Hultzsch, K. C. *Adv. Synth. Catal.* **2005**, *347*, 367.

Hydroamination Reactions

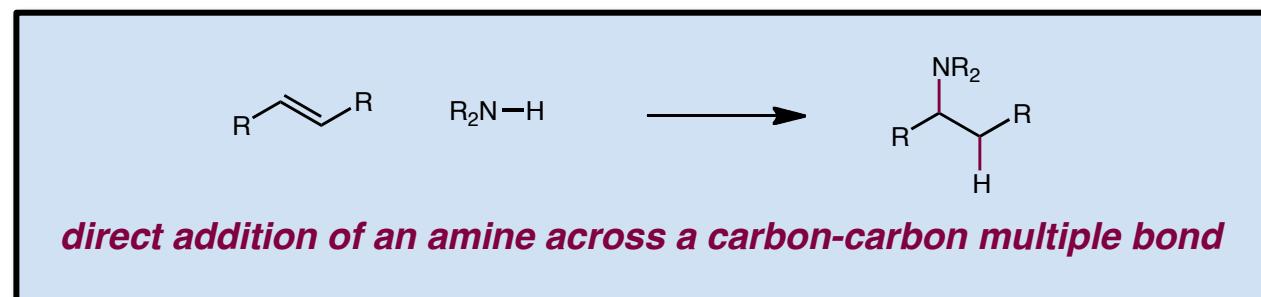
- Amines are a valuable and commercially important class of compounds used for bulk chemicals specialty chemicals and pharmaceuticals

synthesis of amines:



- Most classical methods require refined starting materials and generate unwanted byproducts

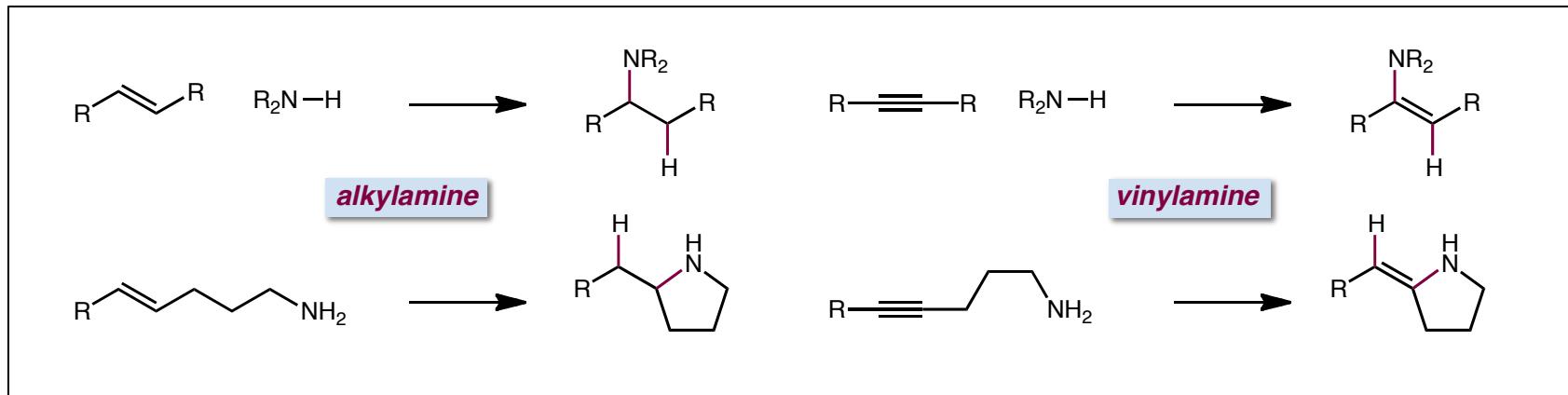
hydroamination reaction:



- Hydroaminations are 100% atom economical and use simple and inexpensive starting materials

Hydroamination Reactions

hydroamination reaction: direct addition of an amine across a carbon-carbon multiple bond



Why are hydroamination reactions not used more?

Challenges: thermodynamically feasible (slightly exothermal) but entropically negative
⇒ **high reaction barrier**

repulsion between the nitrogen lone pair and the olefin/alkyne π-system

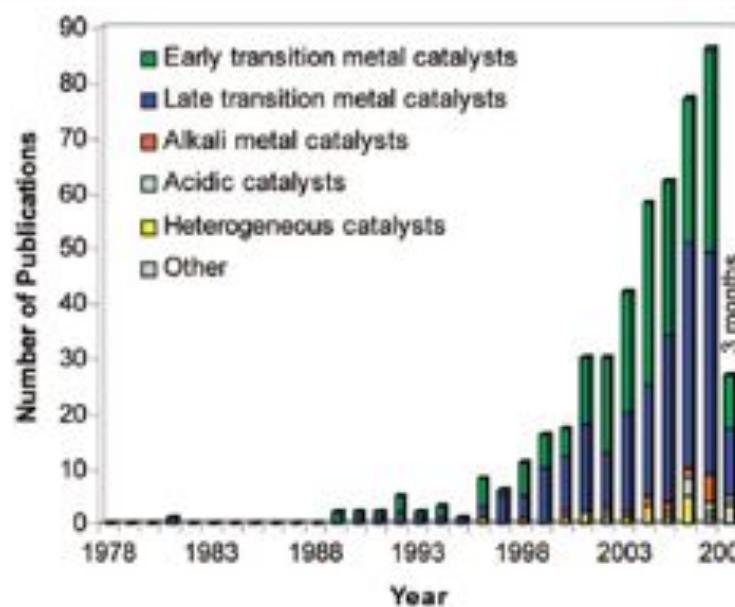
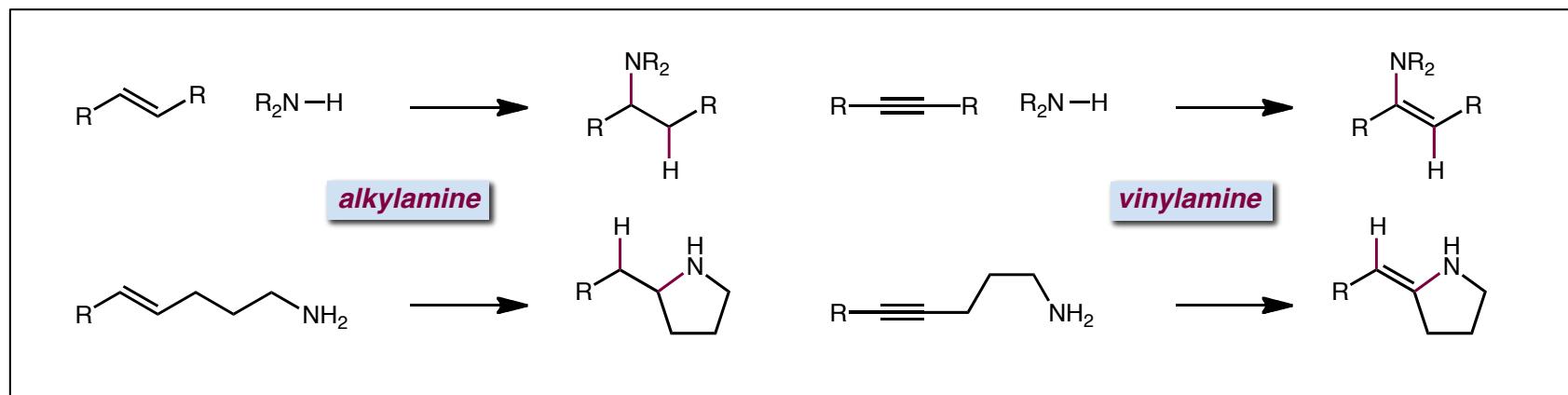
regioselectivity (markovnikov vs. anti-markovnikov) for intermolecular reactions
⇒ **anti-markovnikov on the "Top 10 Challenges for Catalysis" in 1993**

Haggins, J. Chem. Eng. News **1993**, 71, 23.

Muller, T. E.; Hultsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. Chem. Rev. **2008**, 108, 3795.

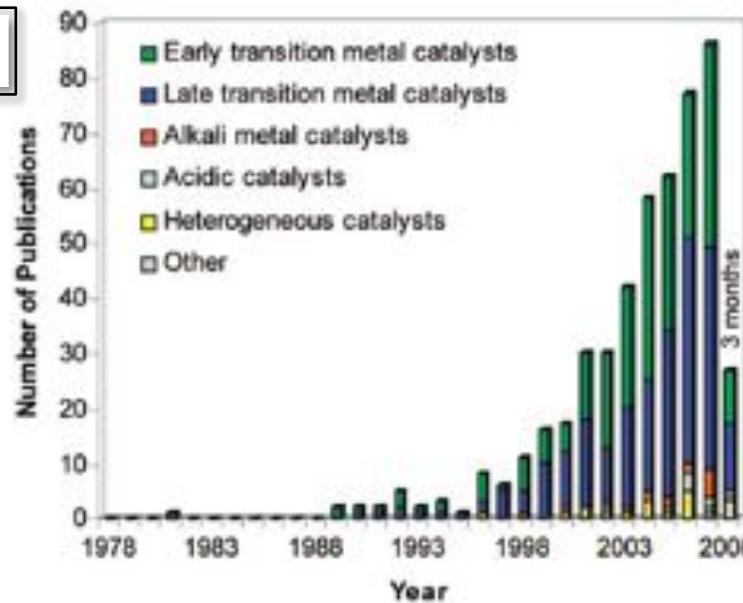
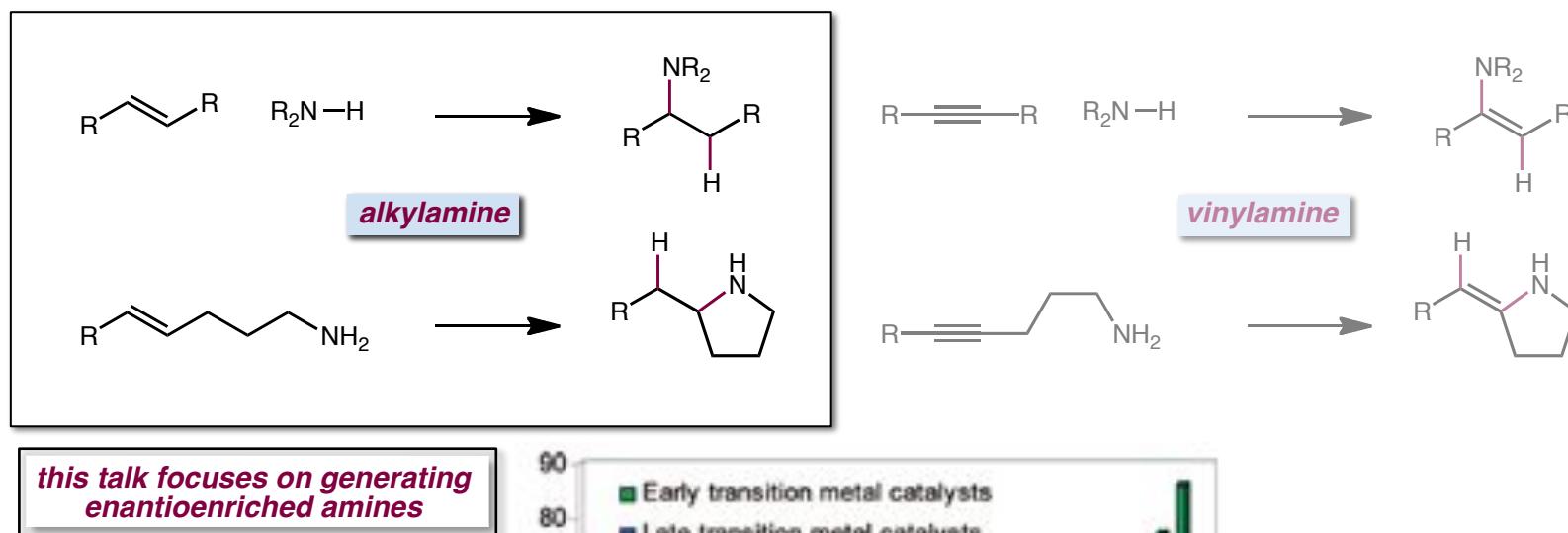
Hydroamination Reactions

hydroamination reaction: direct addition of an amine across a carbon-carbon multiple bond



Hydroamination Reactions

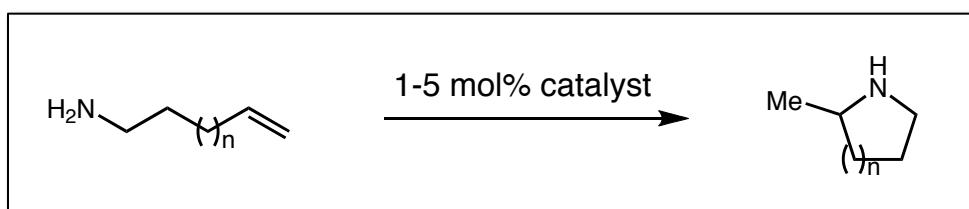
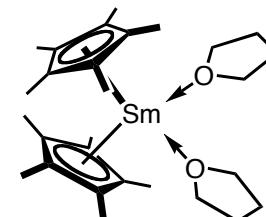
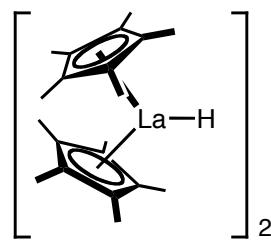
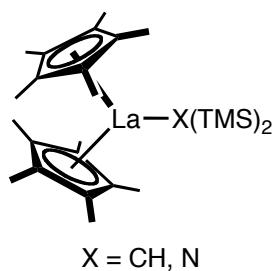
hydroamination reaction: direct addition of an amine across a carbon-carbon multiple bond



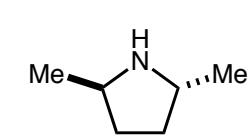
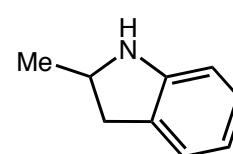
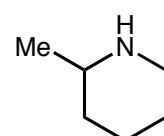
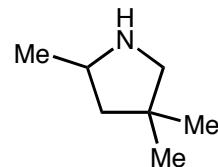
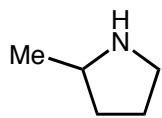
Rare Earth Metal Catalyzed Hydroaminations

Rare Earth Metal-Catalyzed Intramolecular Hydroaminations: Seminal Work

- Seminal work of lanthanide-catalyzed hydroamination reaction was reported in 1989 by Marks using metallocene-based catalysts



generally produces the exocyclic hydroamination product



TOF:
(h⁻¹) 13 (25 °C)
 140 (60 °C)

125 (25 °C)

5 (60 °C)

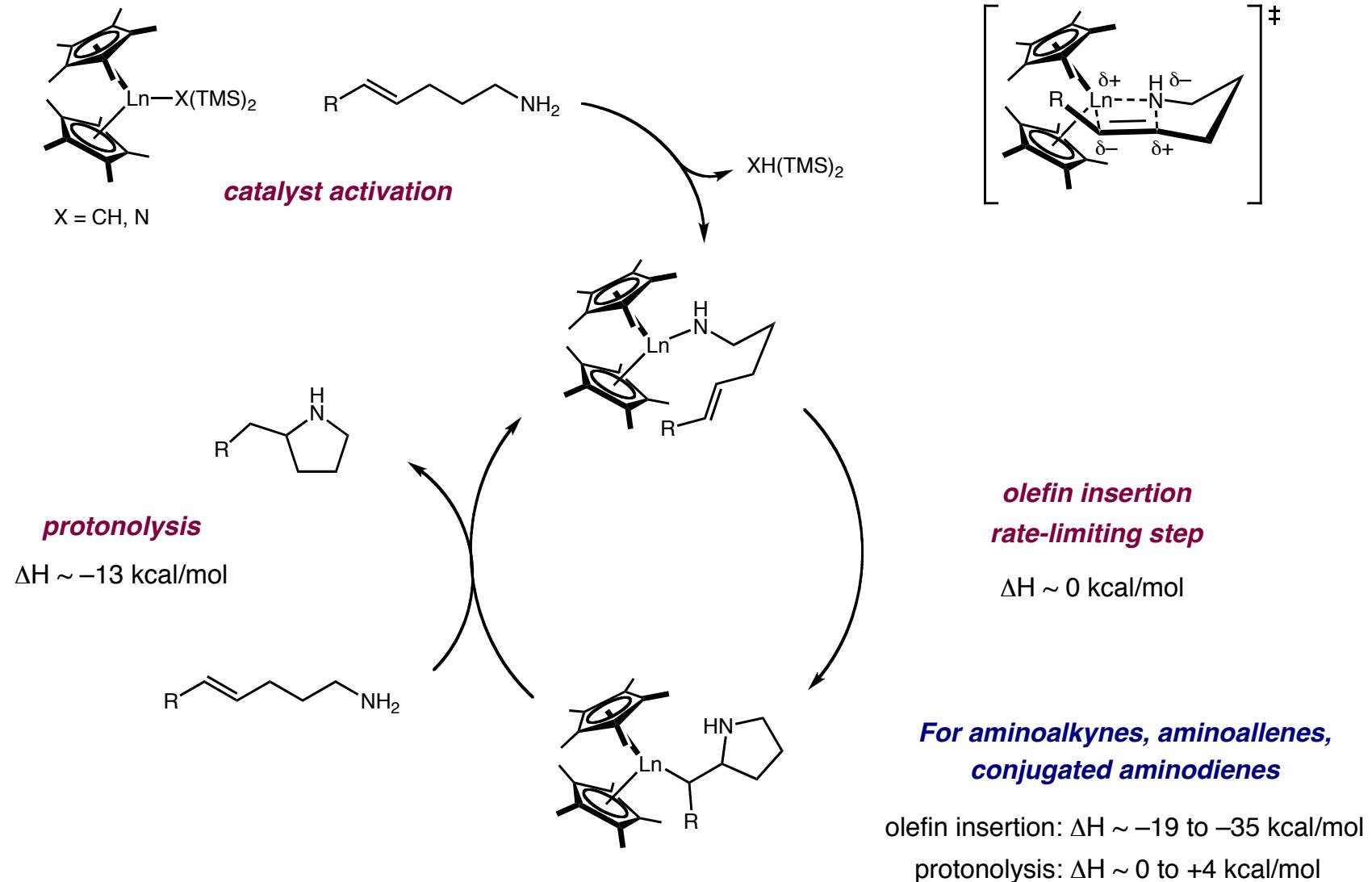
13 (80 °C)

84 (25 °C)

Gagné, M. R.; Marks, T. J. *J. Am. Chem. Soc.* **1989**, *111*, 4108.
Gagné, M. R.; Nolan, S. P.; Marks, T. J. *Organometallics* **1990**, *9*, 1716.

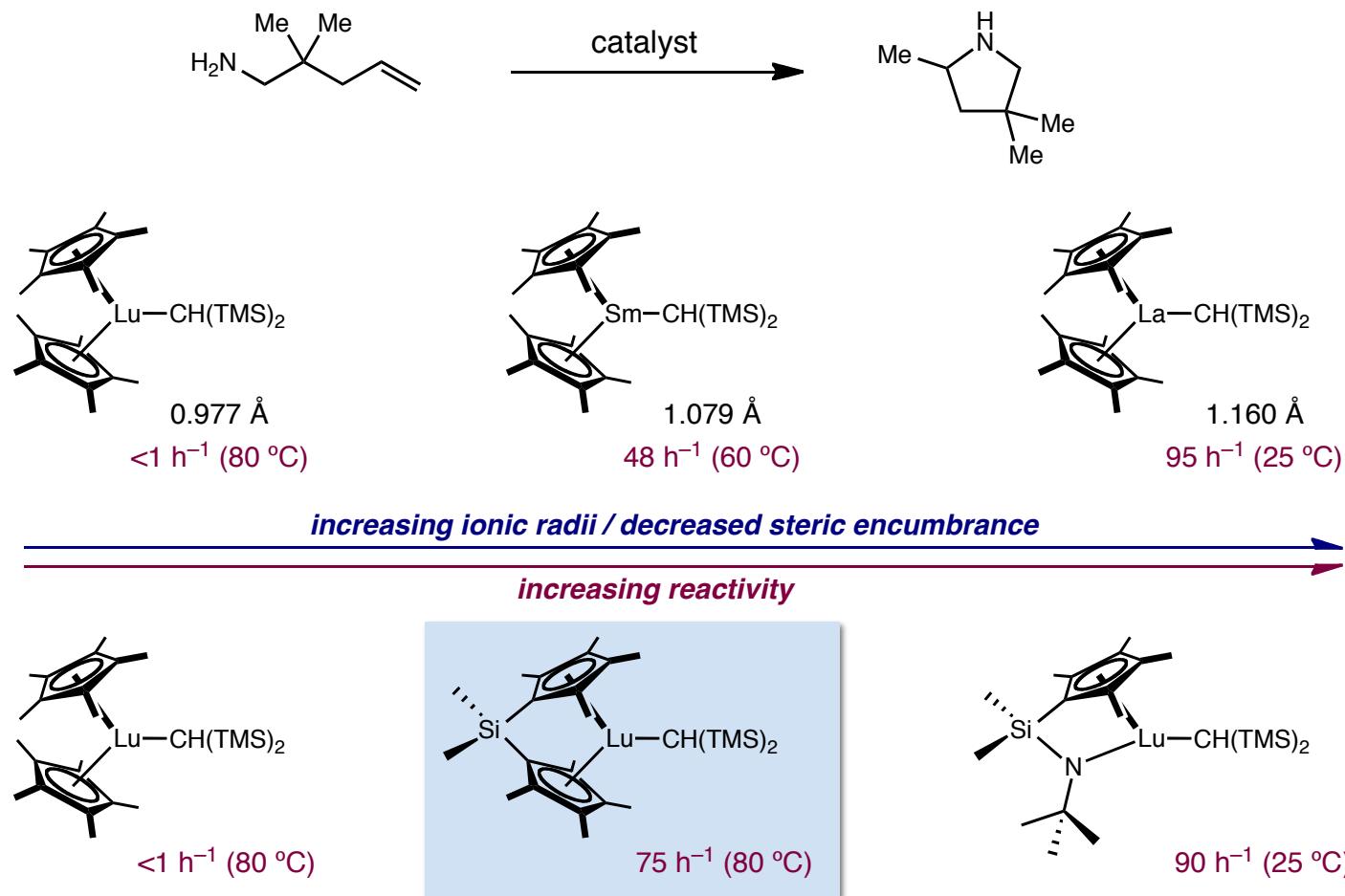
Mechanism for Rare Earth Metal-Catalyzed Hydroaminations

- Transformation proceeds through a rare earth metal amido species



Rare Earth Metal Catalysts for Intramolecular Hydroamination

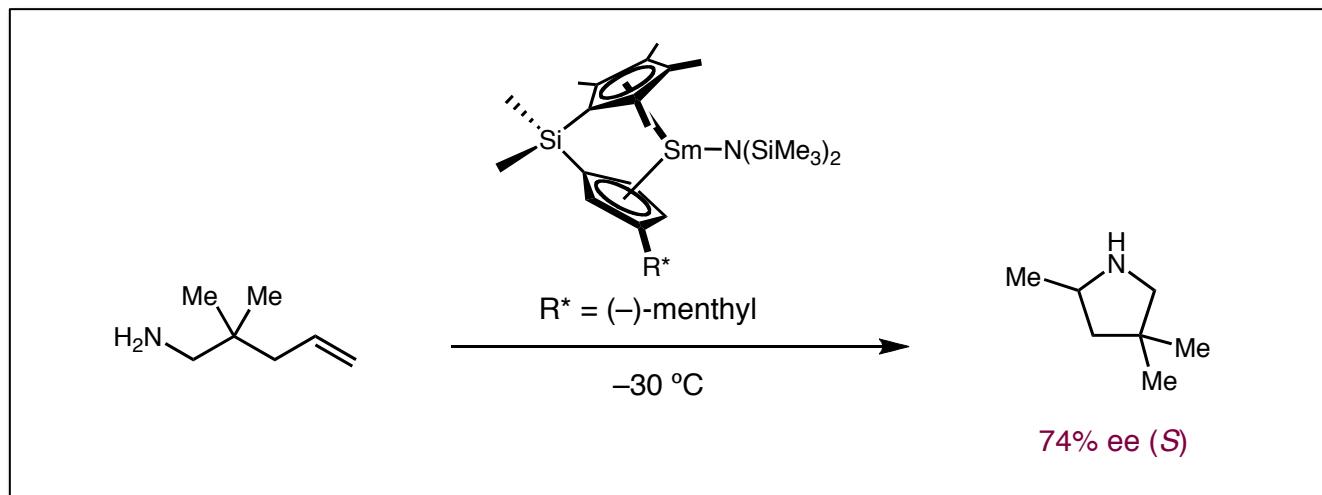
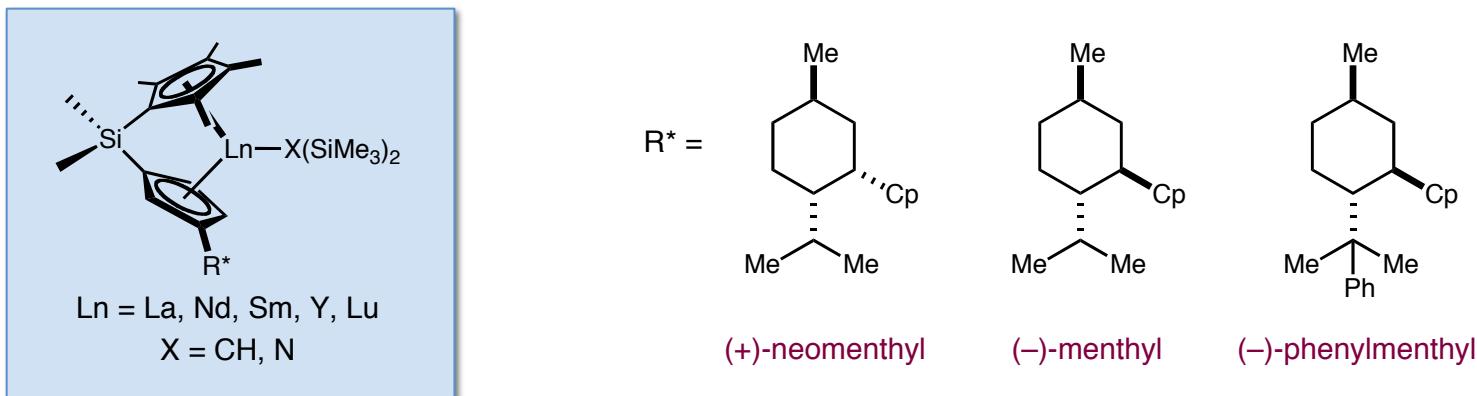
- Catalytic activity in rare earth metal-catalyzed hydroamination of aminoalkenes generally increase with increased accessibility to the metal center



- Trend usually holds for alkenes using metallocene catalysts, but alkynes often show reverse trend

Rare Earth Metal-Catalyzed Asymmetric Hydroamination: Seminal Work

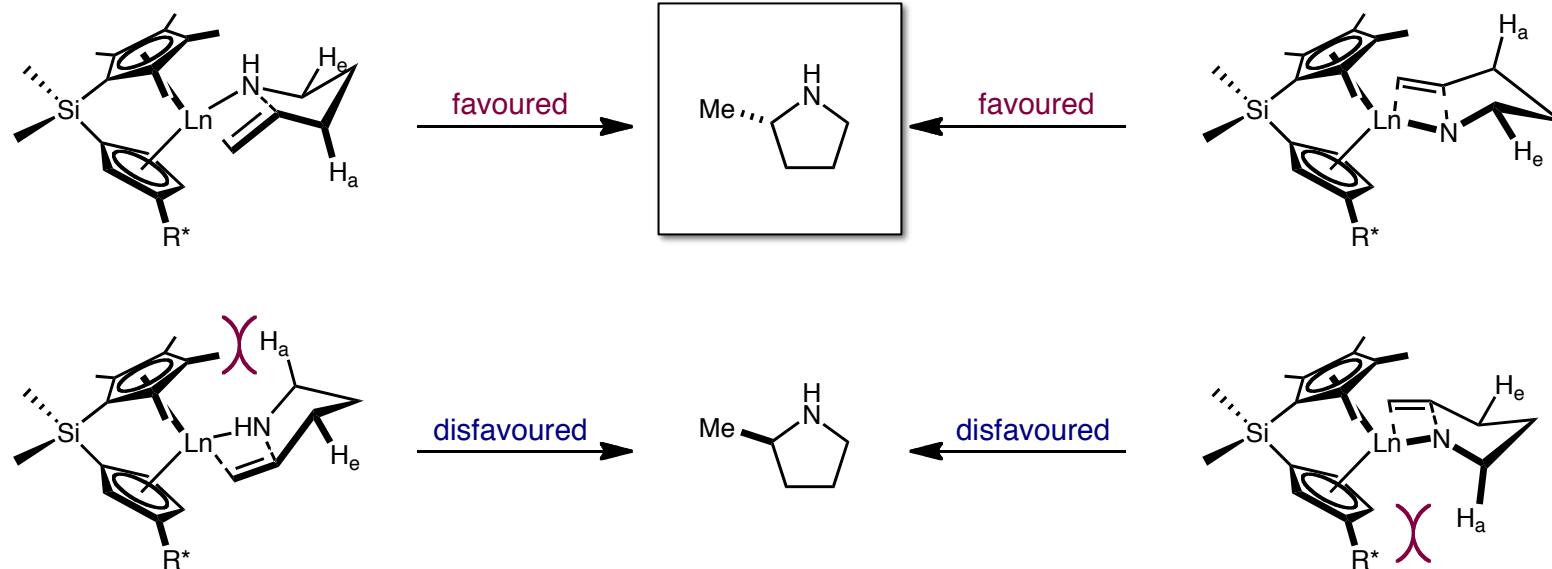
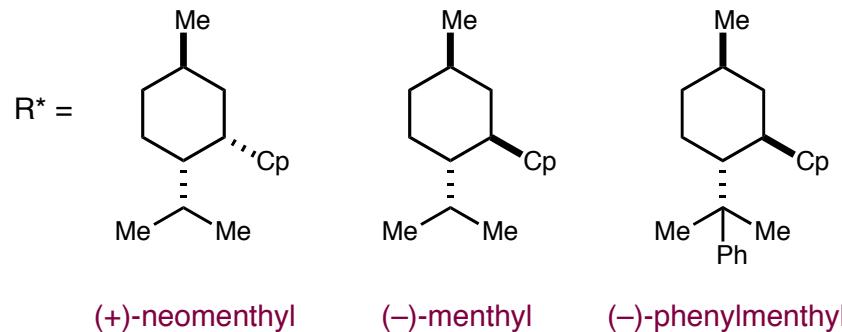
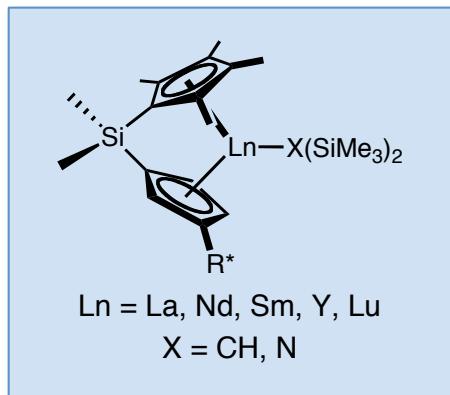
- The first chiral lanthanocene catalysts were reported by Marks in 1992



Gagné, M. R.; Brard, L.; Conticello, V. P.; Giardello, M. A.; Marks, T. J.; Stern, C. L. *Organometallics*, **1992**, *11*, 2003.

Rare Earth Metal-Catalyzed Asymmetric Hydroamination: Seminal Work

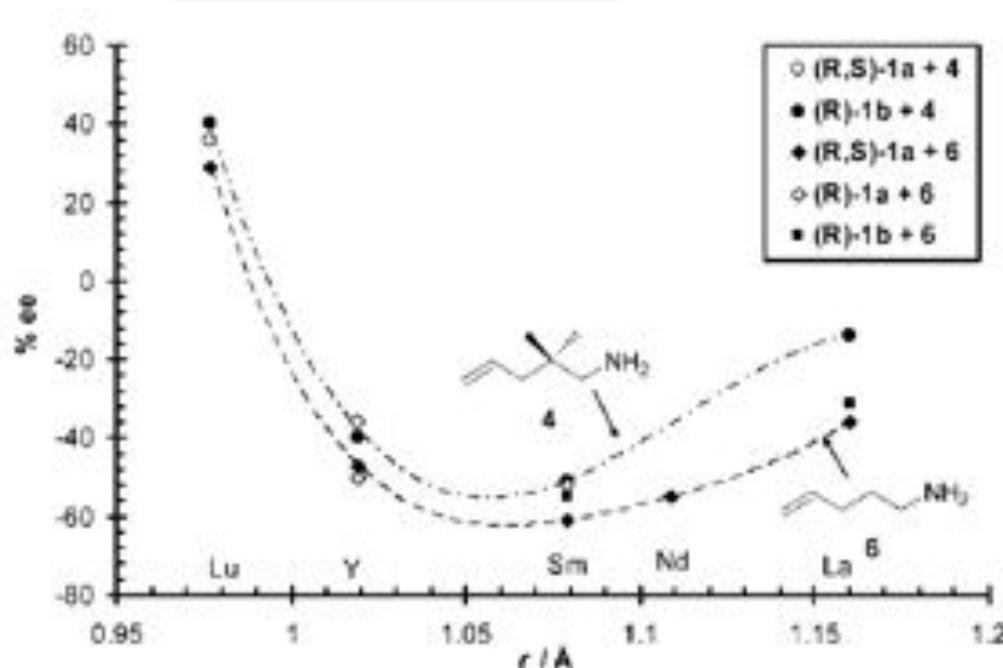
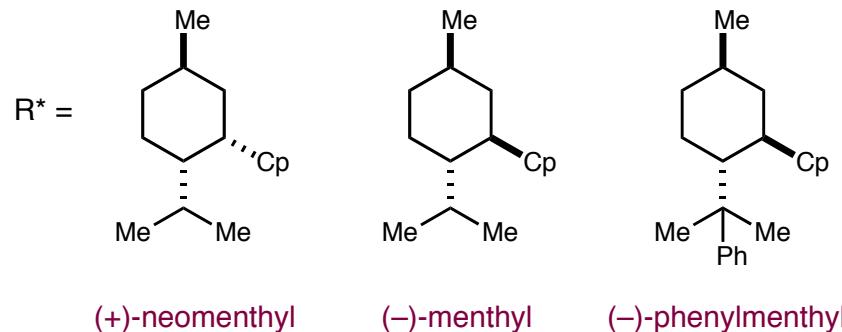
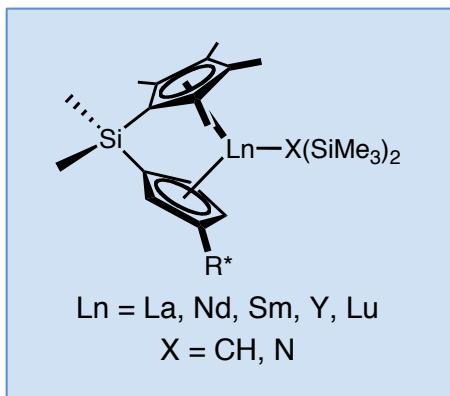
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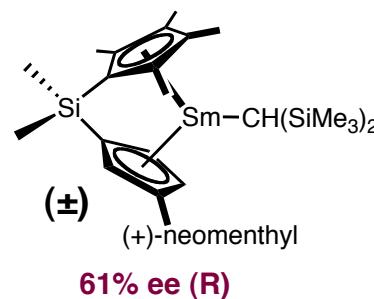
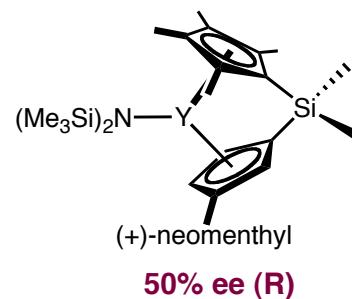
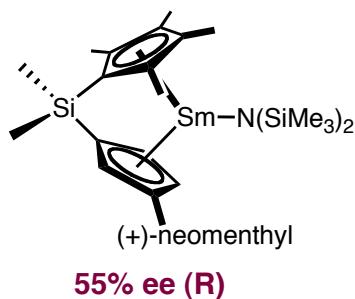
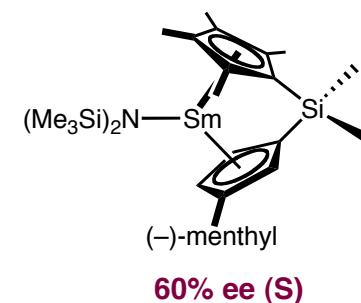
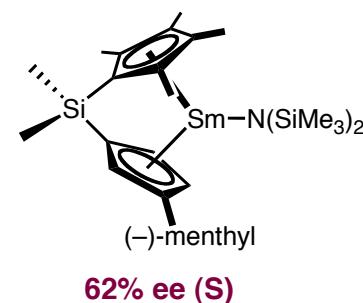
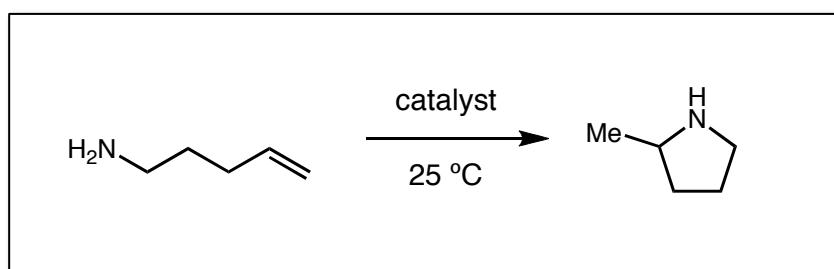
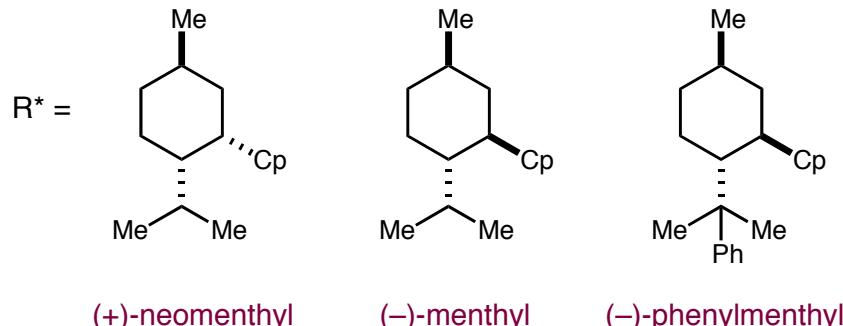
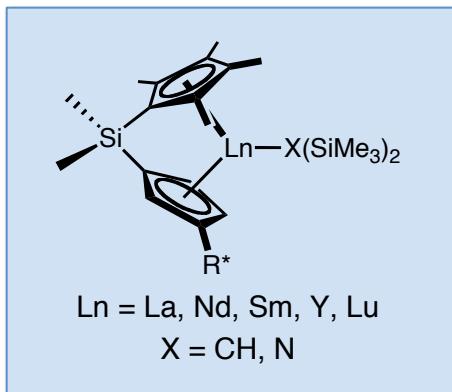
- The first chiral lanthanocene catalysts were reported by Marks in 1992



*ionic radii of rare earth metal effects the enantioselectivity
maximum enantioselectivity observed with samarocene*

Rare Earth Metal-Catalyzed Asymmetric Hydroamination: Seminal Work

- The first chiral lanthanocene catalysts were reported by Marks in 1992

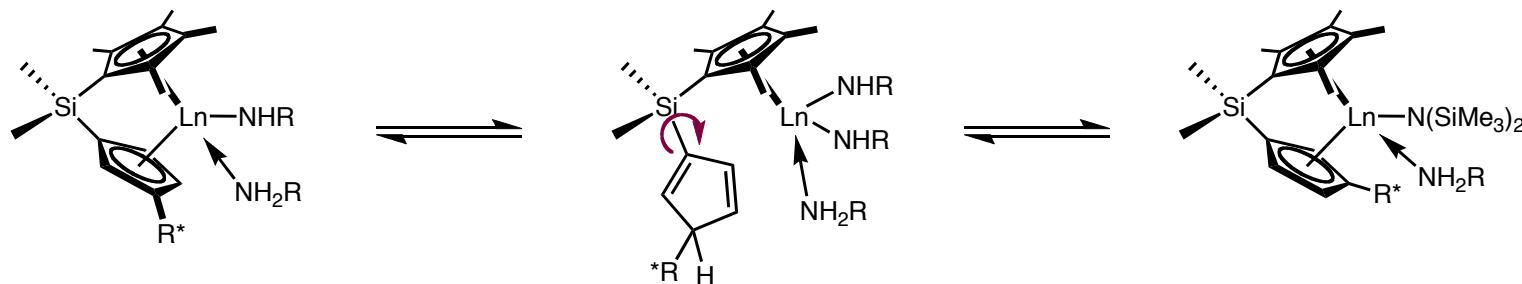


you can obtain 61% ee from a racemic precatalyst

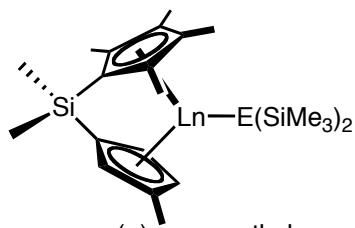
ee of product is independent of ee of precatalyst

Epimerization of Chiral Lanthanocene Complexes

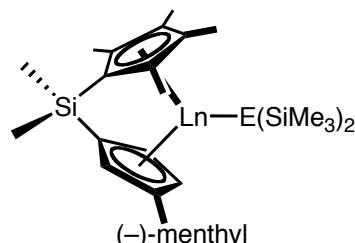
- Marks' chiral lanthanocene complexes were found to epimerize under hydroamination conditions



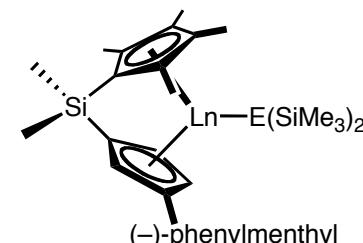
But why does racemic catalyst give enantioenriched product?



80:20 (R):(S)



>95:5 (S):(R)



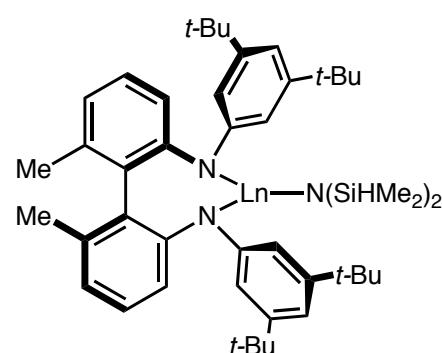
90:10 (S):(R)

equilibrium ratio are independent of the epimer ratio of the precatalyst

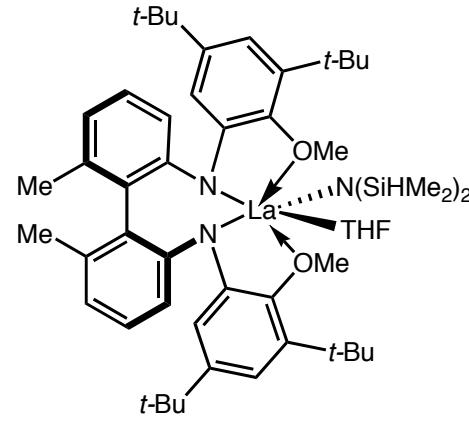
Chiral Rare Earth Metal Catalysts Based on Non-Cyclopentadienyl Ligands

- In 2003, new chiral hydroamination catalysts based on non-metallocene ligands were reported

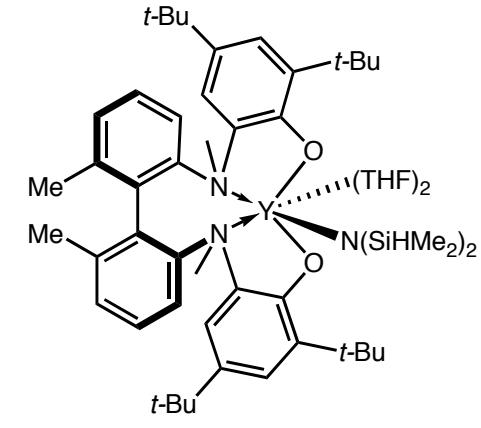
Chiral Bisaryl amido and Aminophenolate Catalysts



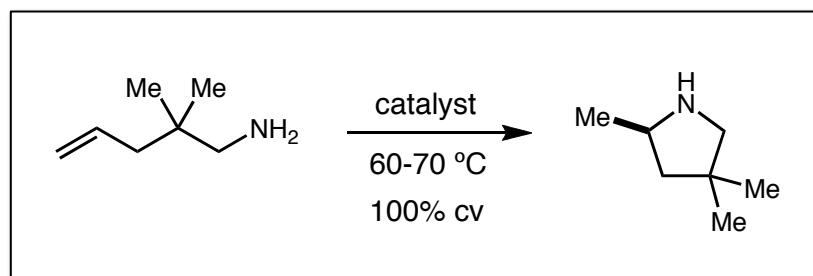
Y 336 h, 50% ee
Sm 168 h, 33% ee
La 168 h, 18% ee



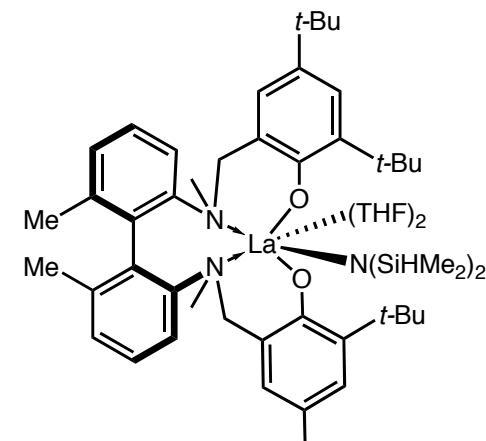
192 h, 21% ee



24 h, 11% ee



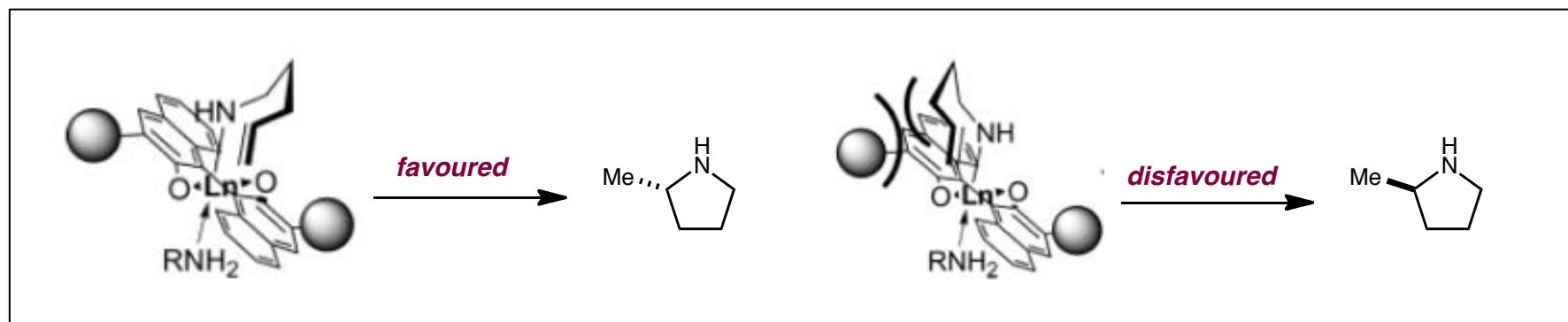
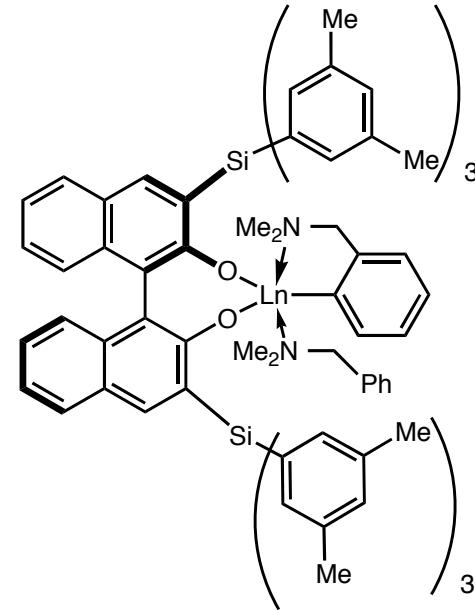
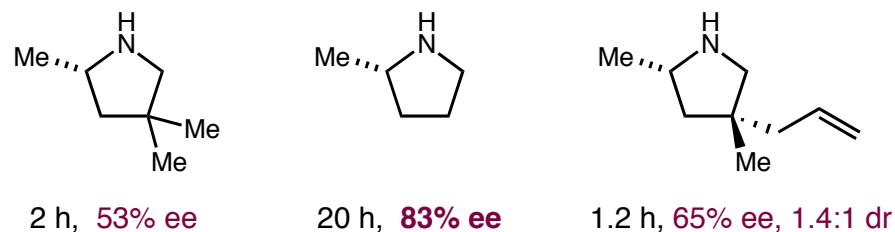
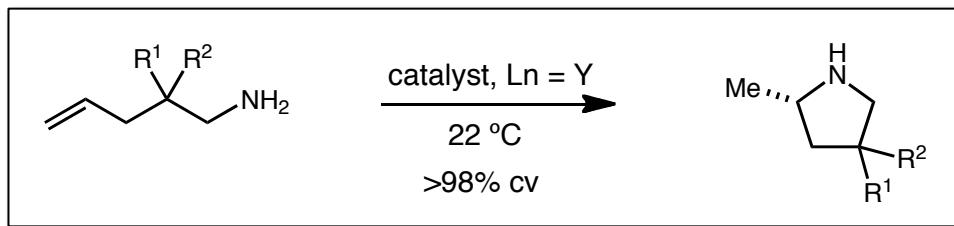
Complexes were shown to be configurationally stable under hydroamination conditions



40 h, 61% ee

Chiral Rare Earth Metal Catalysts Based on Non-Cyclopentadienyl Ligands

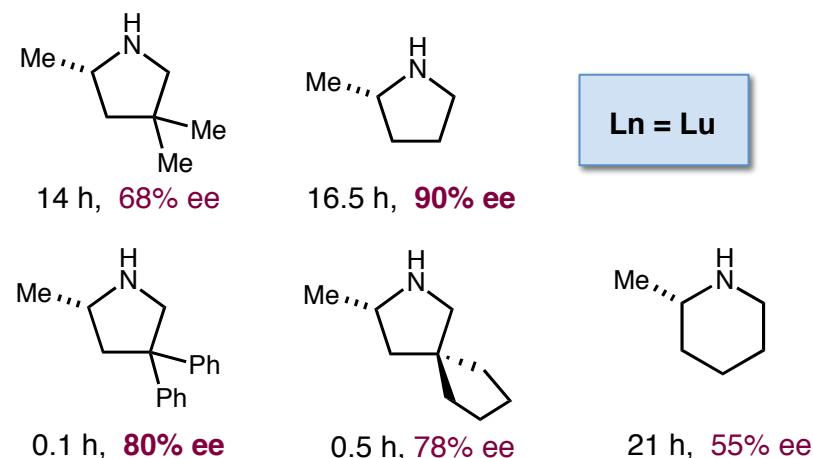
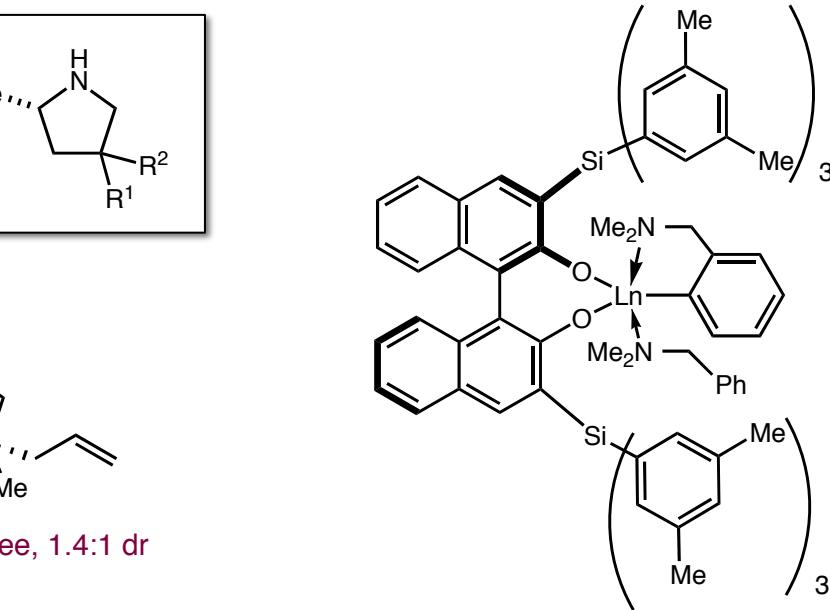
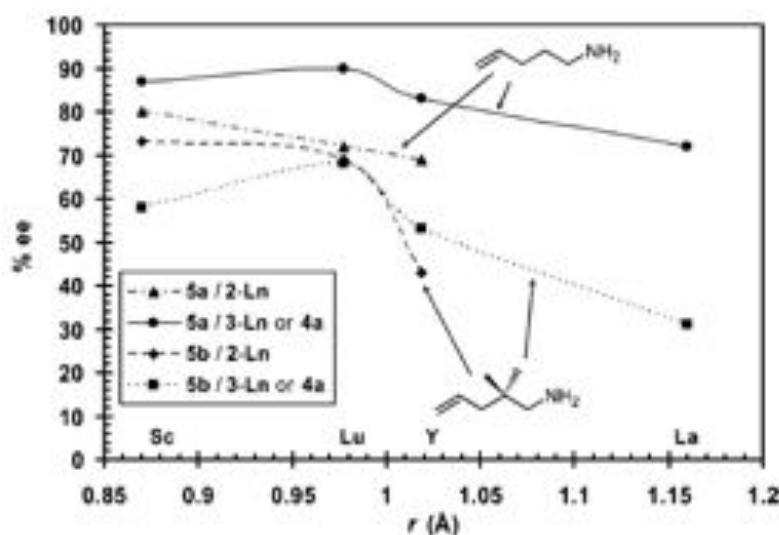
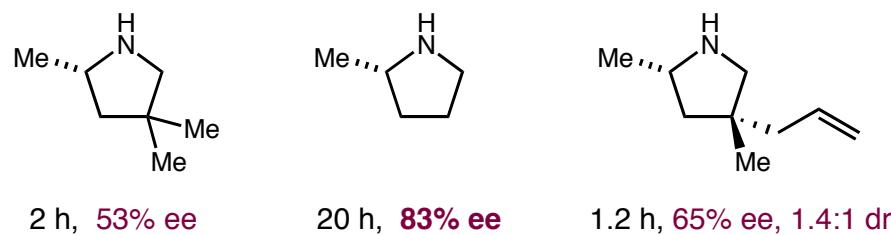
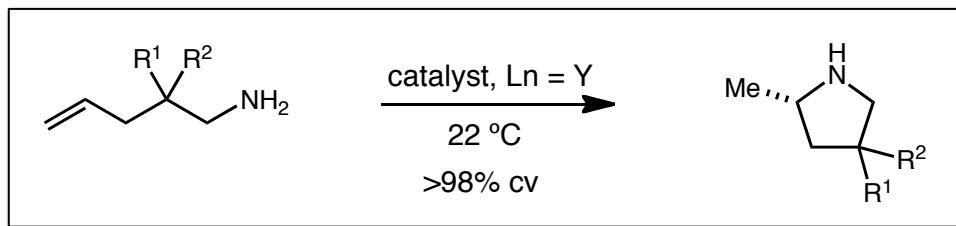
- Hultzsch's 3,3'-bis(trisaryl)silyl binaphtholate catalyst can allow for higher enantioselectivity



Gribkov, D. V.; Hultzsch, K. C.; Hampel, F. *J. Am. Chem. Soc.* **2006**, *128*, 3748.
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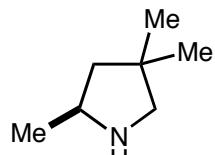
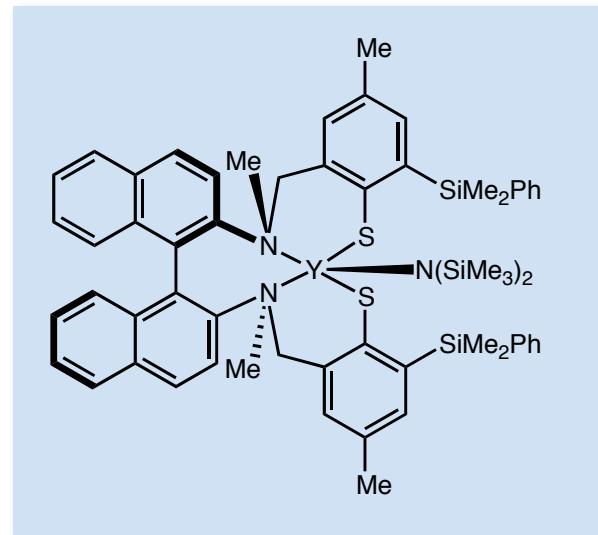
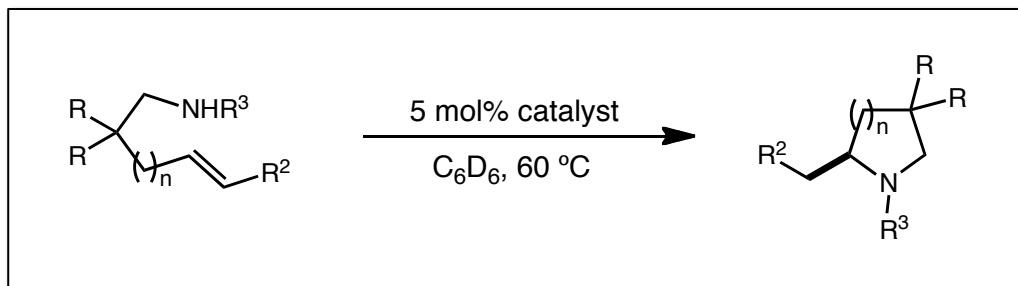
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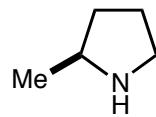
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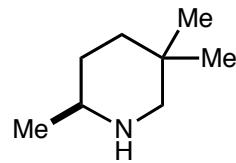
- Livinghouse reported a bisthiolate yttrium complex showing less substrate dependence



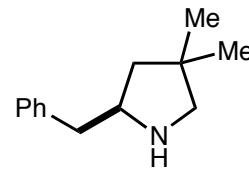
9h, 87% ee



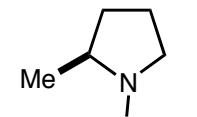
8h, 81% ee



3h, 80% ee
 (75°C)



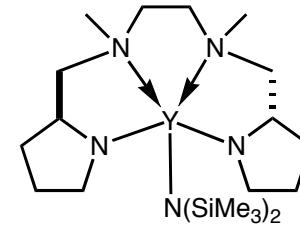
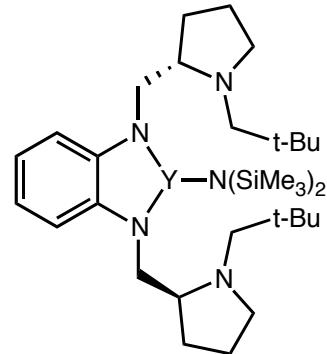
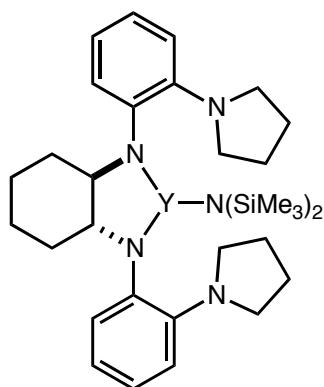
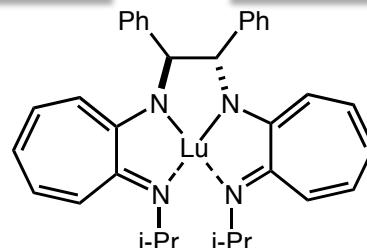
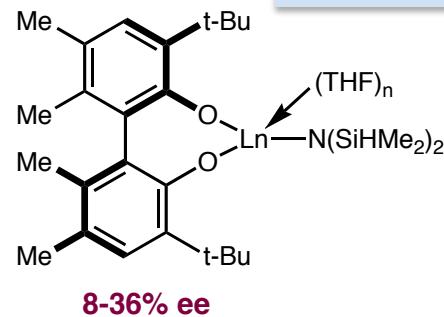
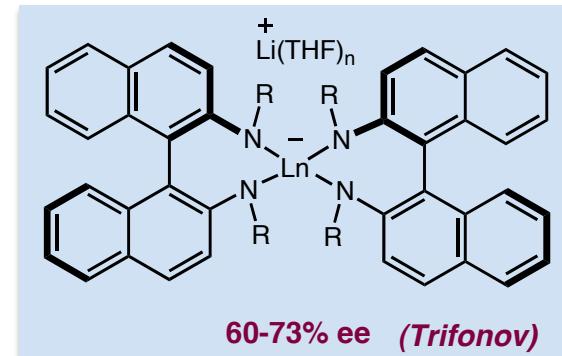
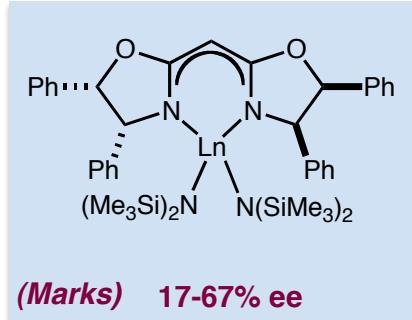
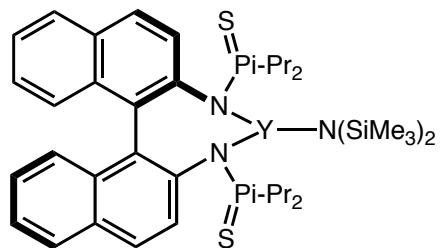
3h, 82% ee



30h, 69% ee

Other Chiral Rare Earth Metal Catalysts for Intramolecular Hydroamination

- There are still more chiral catalysts for intramolecular hydroamination....



Intermolecular Hydroamination Catalyzed by Rare Earth Metal Catalysts

- Only a very limited number of reports of rare earth catalyzed intermolecular reactions, both racemically and enantioselectively

Primary Challenge: inefficient competition between strongly binding amines and weakly binding alkenes for vacant coordination sites

$$\text{rate} = k[\text{amine}]^0[\text{alkene}]^1[\text{catalyst}]^1$$

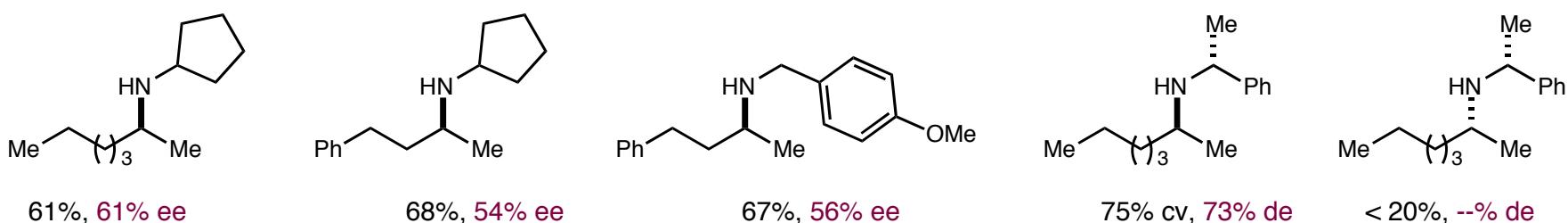
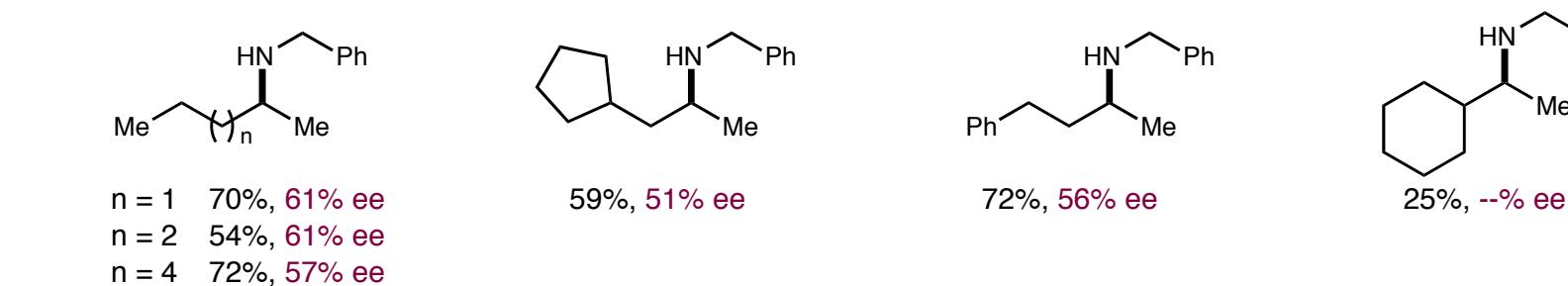
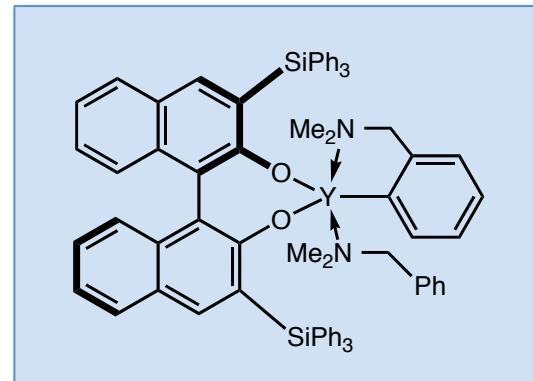
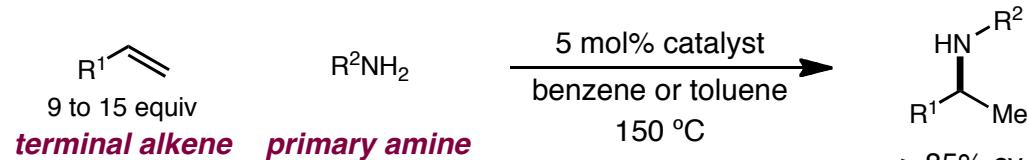
large excess of alkene is generally required, contradicting the atom economical aspect of hydroaminations

New Consideration: regioselectivity (Markovnikov vs. *anti*-Markovnikov)



Asymmetric Intermolecular Hydroamination Catalyzed by Rare Earth Metals

- In 2010 Hultszsch reports the first (and to date the only) asymmetric intermolecular hydroamination using a chiral binaphtholate yttrium catalyst



Rare Earth Metal Catalyzed Hydroaminations: Summary

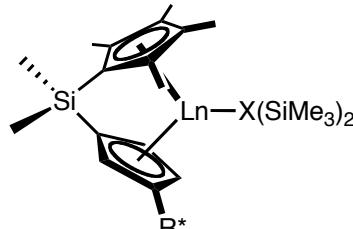
- Rare earth metal catalyzed hydroaminations are almost exclusively restricted to intramolecular

PROS No protecting groups

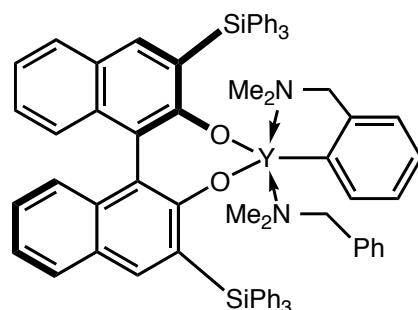
Non-activated alkenes and simple amines

CONS Very low functional group tolerance

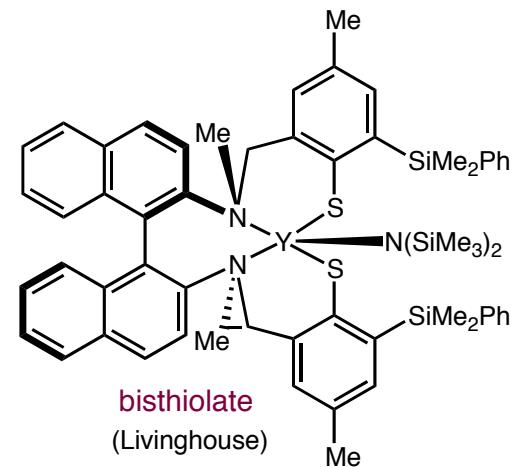
Air and moisture sensitive - GLOVEBOX



ansa-Metallocene
(Marks)

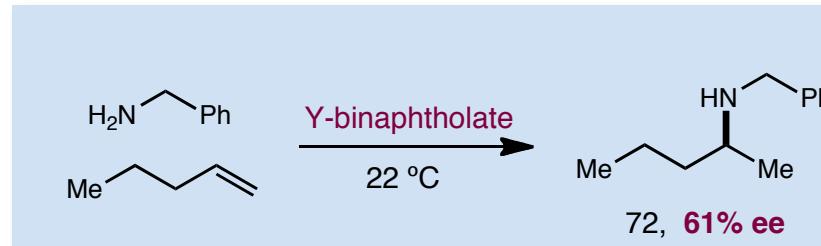


binaphtholate/biphenolate
(Marks, Hultzsch, Scott)



bisthiolate
(Livinghouse)

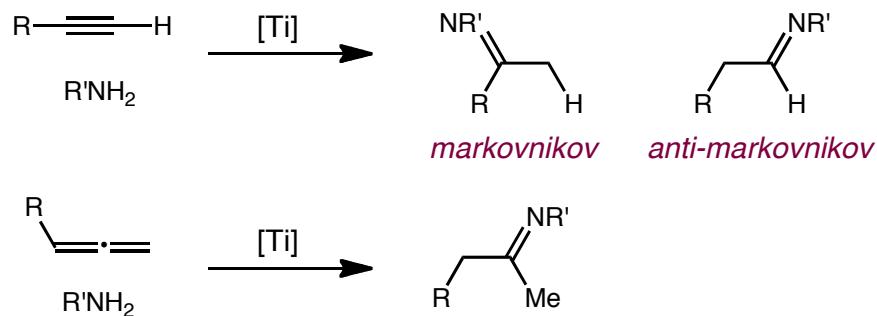
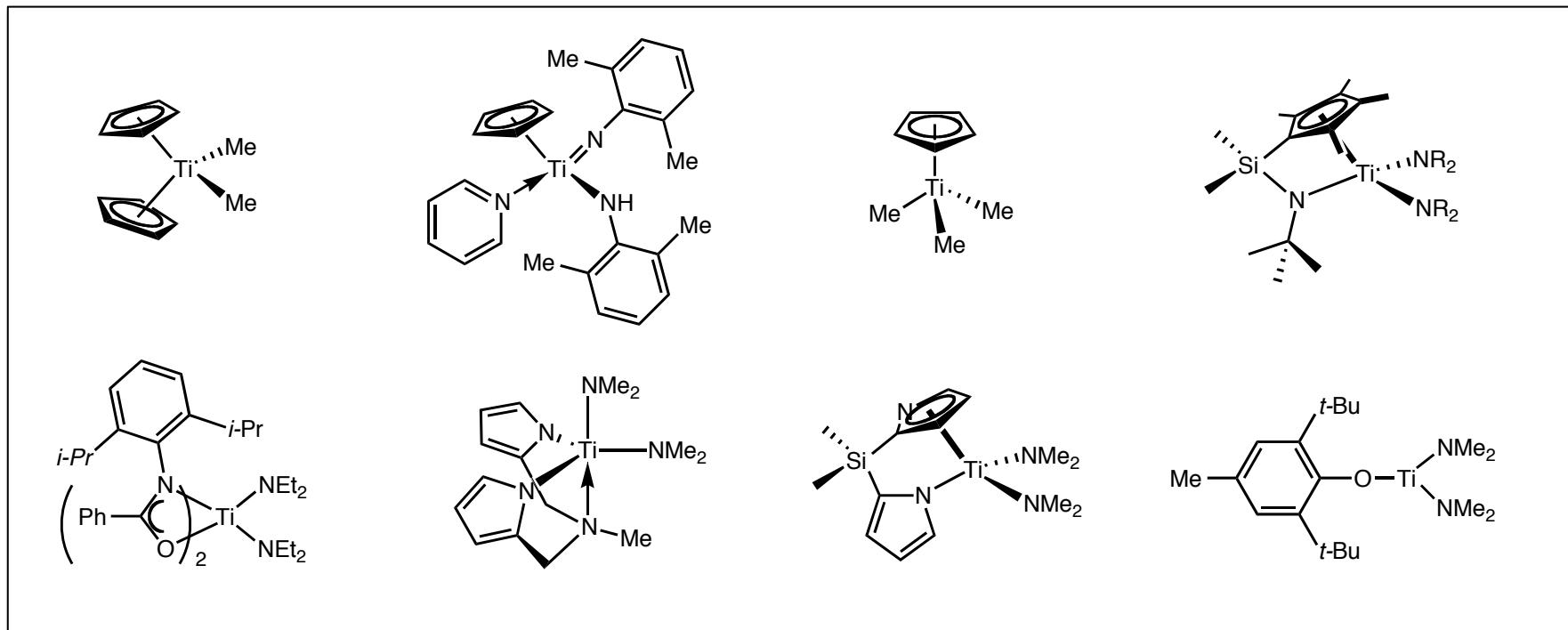
- Current Asymmetric *State of the Art* - Livinghouse's bisthiolate and Hultzsch's binaphtholate catalysts



Group 4 Metal-Catalyzed Hydroaminations

Group 4 Metal-Catalyzed Hydroamination

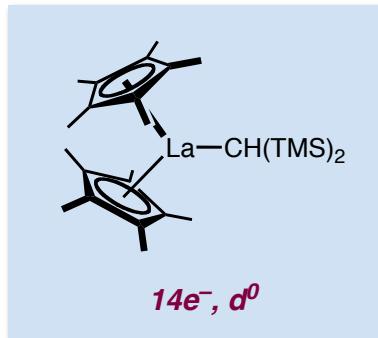
■ Early studies of group 4 metals as catalysts for hydroamination restricted scope to alkynes and allenes



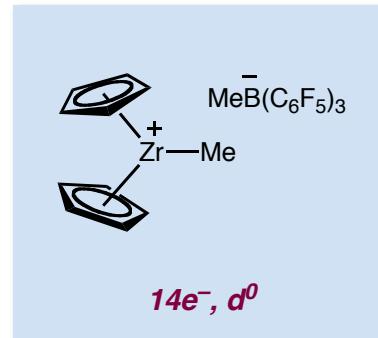
Effective for both inter- and intramolecular
Less air and moisture sensitive
Better functional group tolerance
Many precatalysts commercially available

Group 4 Metal-Catalyzed Hydroamination of Alkenes

- Cationic group 4 metal complexes are isoelectronic to lanthanocene complexes so should have similar reactivity



$14e^-$, d^0

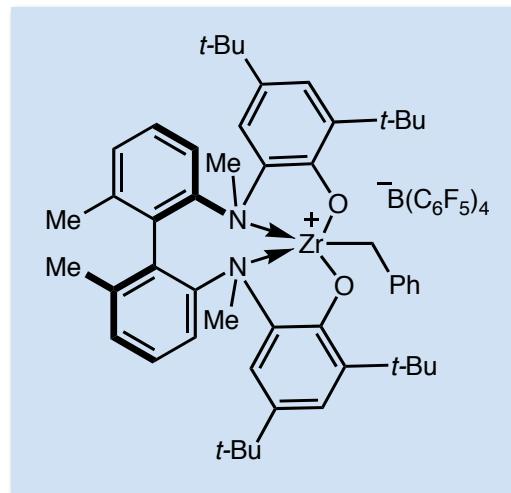
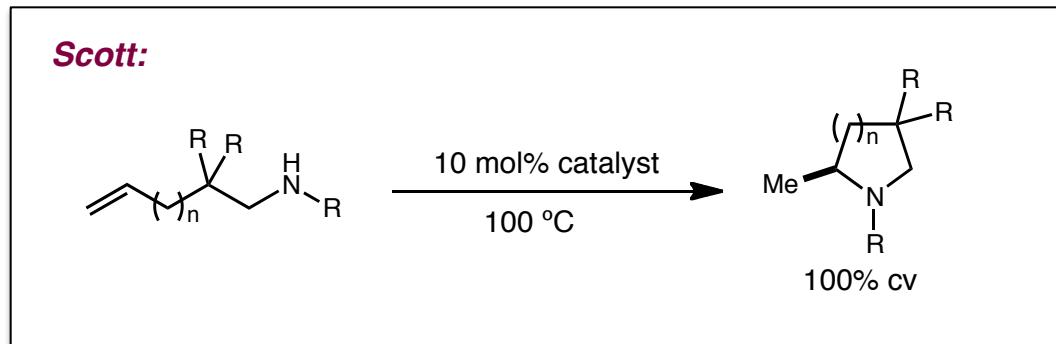


$14e^-$, d^0

- Scope of group 4 metal-catalyzed hydroaminations should be able to include aminoalkenes

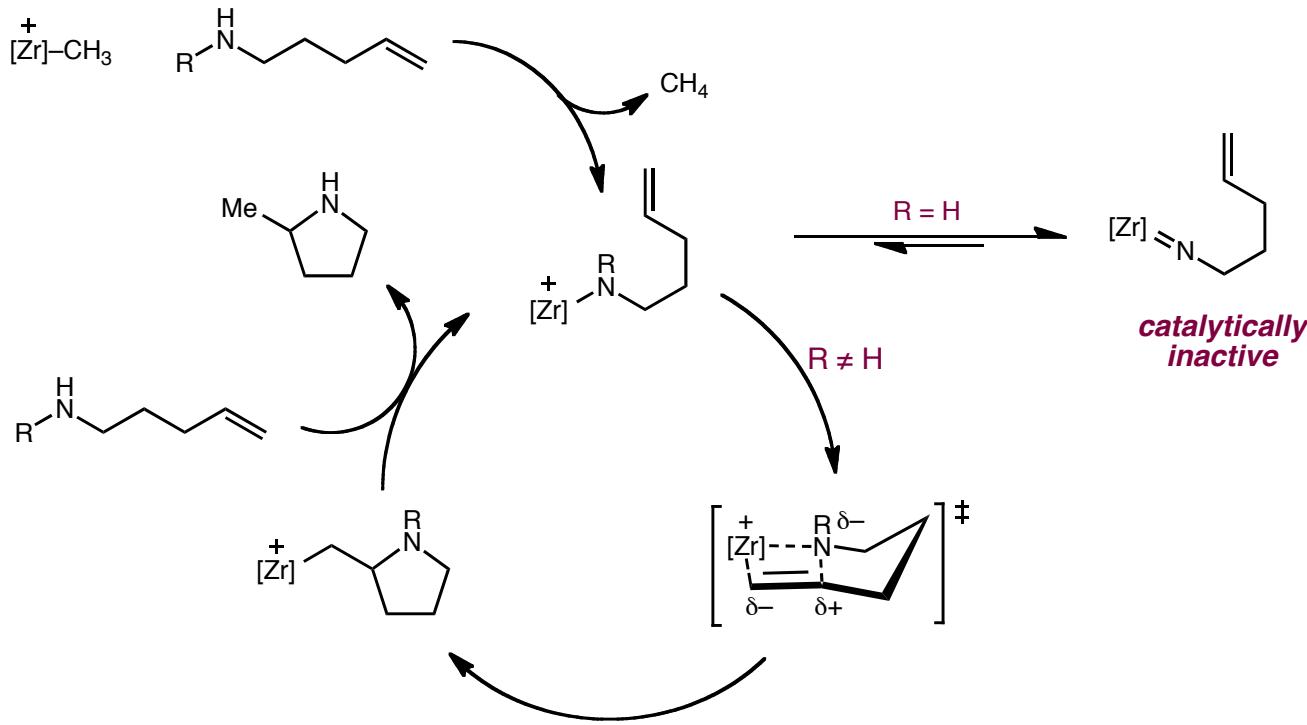
Group 4 Metal-Catalyzed Hydroamination of Alkenes

- Cationic group 4 metal complexes are isoelectronic to lanthanocene complexes so should have similar reactivity
- In 2004 both Hultzsch (racemic) and Scott (enantioselective) reported cationic zirconium catalysts for the intramolecular hydroamination of alkenes using secondary amines



Mechanism of Cationic Group 4 Metal-Catalyzed Hydroamination

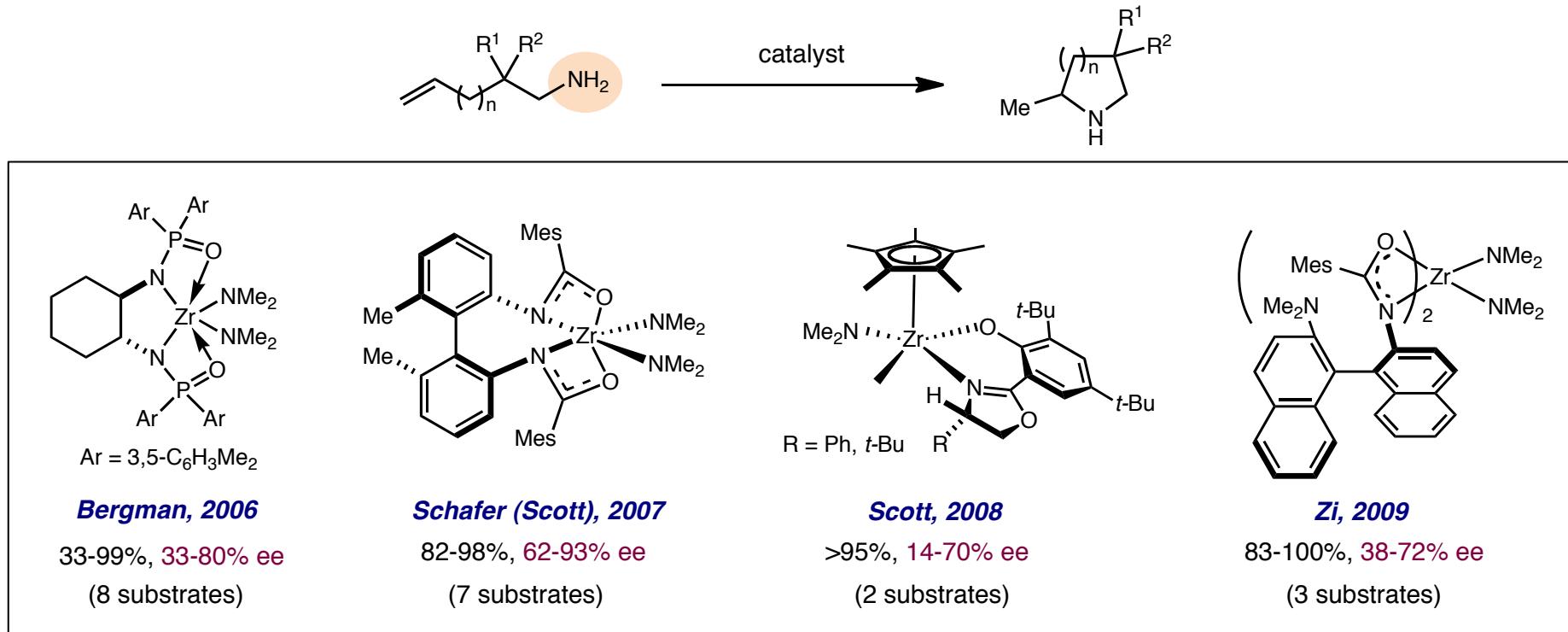
- Hydroamination reactions with cationic group 4 metal complexes proceed through an analogous mechanism to the rare earth metal catalysts



- Primary aminoalkenes result in no reaction because cationic zirconium amido species are readily deprotonated to yield catalytically inactive zirconium imido species
- Neutral metal imido species operate by a different mechanism and are unreactive towards non-activated alkenes using these catalysts

Asymmetric Neutral Group 4 Metal-Catalyzed Hydroamination

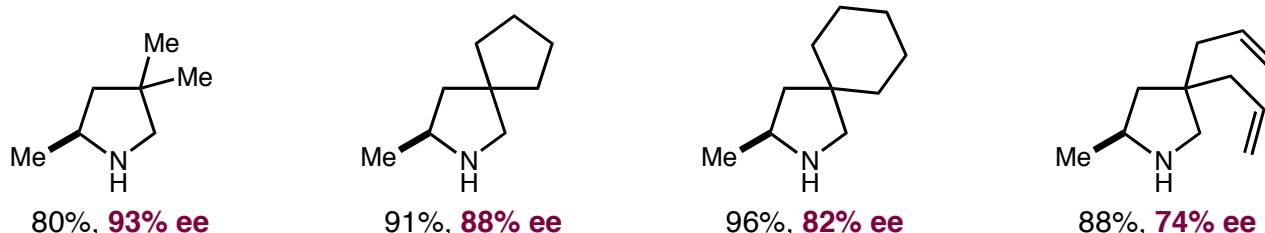
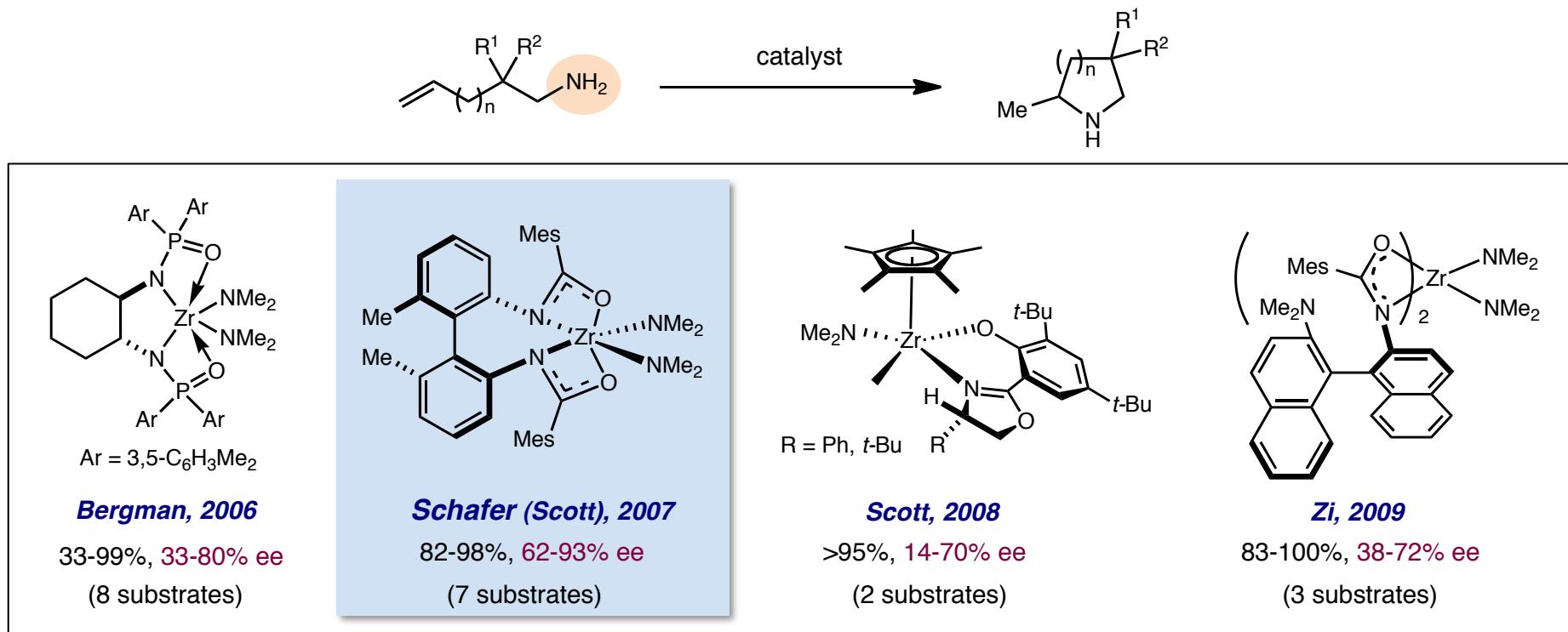
- In recent years, several groups have developed chiral neutral zirconium catalysts for primary amines



Watson, D. A.; Chiu, M.; Bergman, R. G. *Organometallics* **2006**, *25*, 4731.
Bexrud, J. A.; Beard, J. D.; Leitch, D. C.; Schafer, L. L. *Angew. Chem. Int. Ed.* **2007**, *46*, 354.
Gott, A. L.; Clarke, A. J.; Clarkson, G. J.; Scott, P. *Chem. Commun.* **2008**, 1422.
Zi, G.; Liu, X.; Xiang, L.; Song, H. *Organometallics* **2009**, *28*, 1127.

Asymmetric Neutral Group 4 Metal-Catalyzed Hydroamination

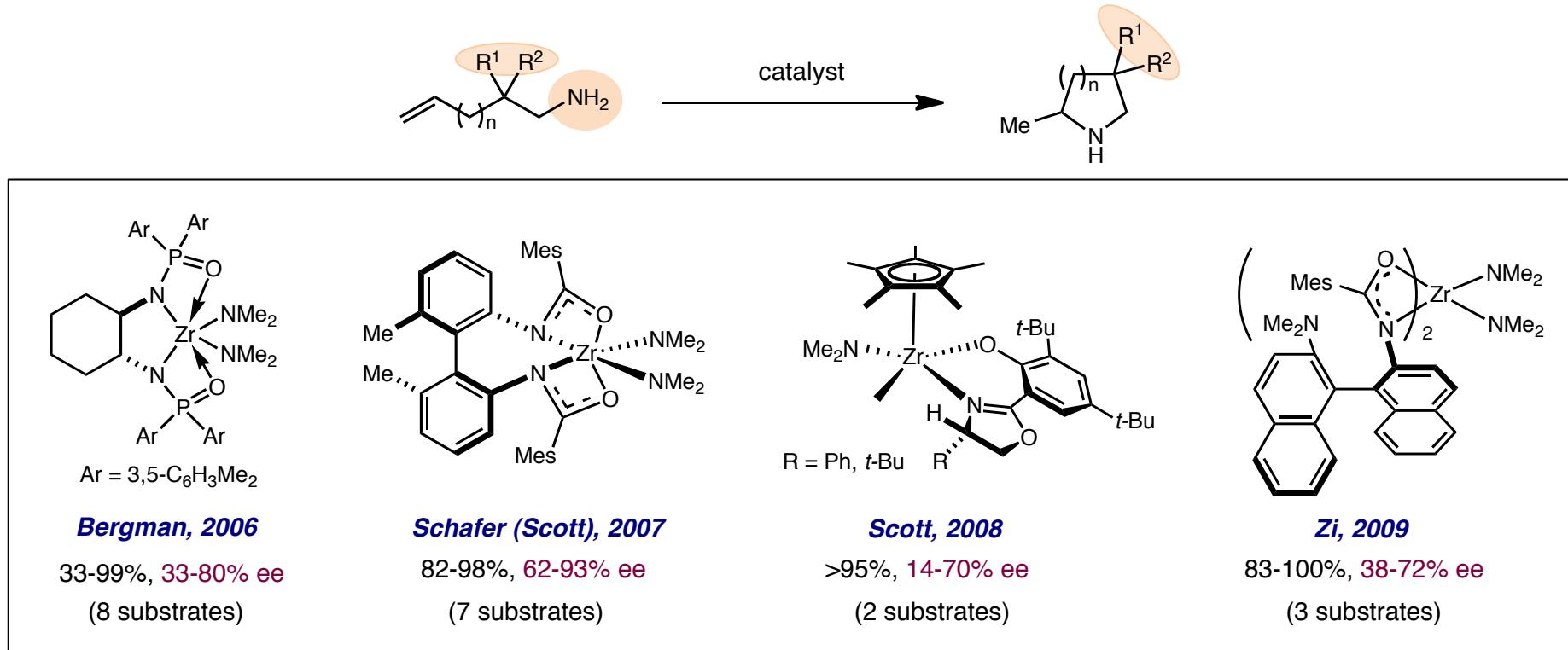
- In recent years, several groups have developed chiral neutral zirconium catalysts for primary amines



Watson, D. A.; Chiu, M.; Bergman, R. G. *Organometallics* **2006**, *25*, 4731.
 Bexrud, J. A.; Beard, J. D.; Leitch, D. C.; Schafer, L. L. *Angew. Chem. Int. Ed.* **2007**, *46*, 354.
 Gott, A. L.; Clarke, A. J.; Clarkson, G. J.; Scott, P. *Chem. Commun.* **2008**, 1422.
 Zi, G.; Liu, X.; Xiang, L.; Song, H. *Organometallics* **2009**, *28*, 1127.

Asymmetric Neutral Group 4 Metal-Catalyzed Hydroamination

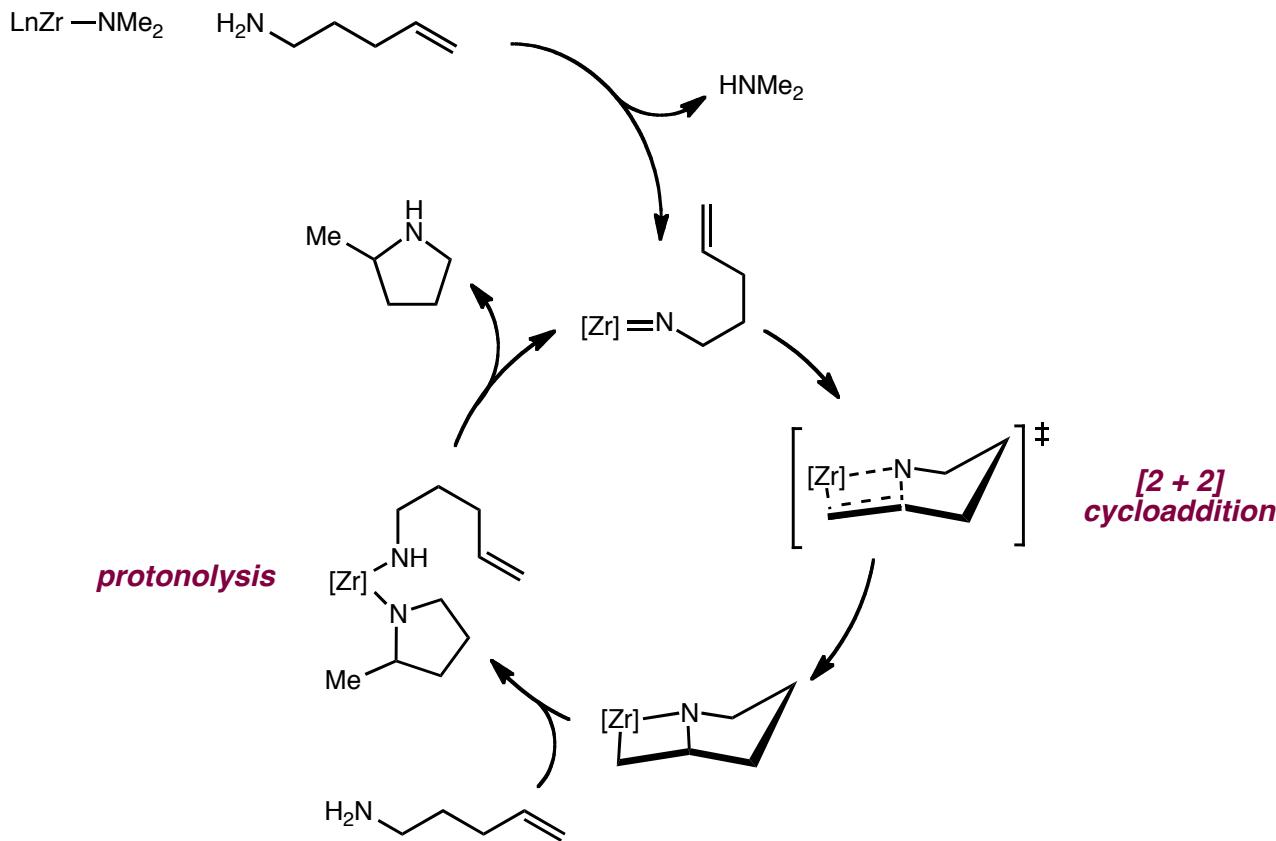
- In recent years, several groups have developed chiral neutral zirconium catalysts for primary amines



**substrates require β -geminal substitution
generally restricted to pyrrolidines**

Mechanism of Neutral Group 4 Metal-Catalyzed Hydroamination

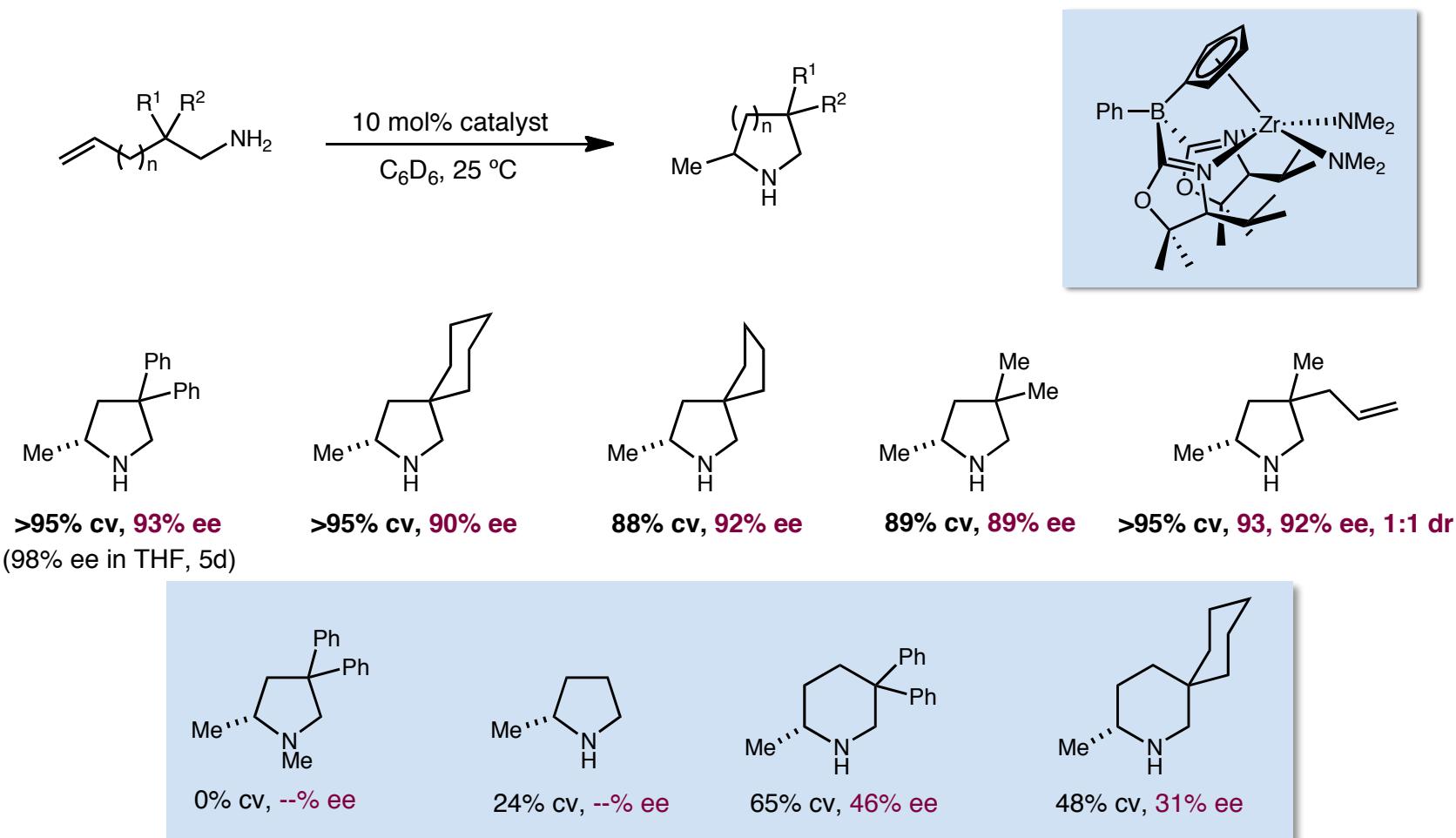
- Hydroamination reactions with neutral group 4 metal complexes proceed through a [2 + 2] cycloaddition of a metal imido species and the alkene



Bexrud, J. A.; Bear, J. D.; Leitch, D. C.; Schafer, L. L. *Org. Lett.* **2005**, *7*, 1959.
Muller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795.

Asymmetric Neutral Group 4 Metal-Catalyzed Hydroamination

■ This year (Jan 2011) Sadow reported a highly enantioselective intramolecular hydroamination



generally restricted to β -geminal substituted pyrrolidines

Group 4 Hydroaminations: Summary

- Group 4 metal-catalyzed asymmetric hydroaminations are exclusively intramolecular for alkenes
- Numerous examples of inter- and intramolecular hydroaminations for alkynes and allenes

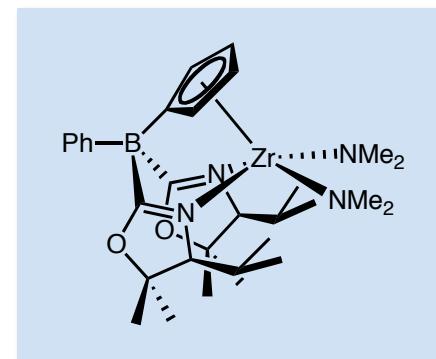
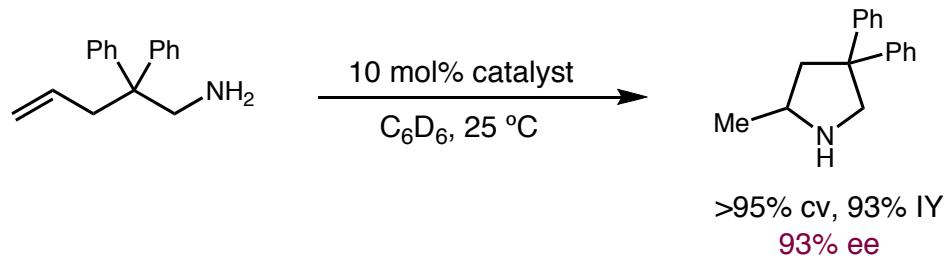
PROS

No protecting groups
Less air and moisture sensitive
More functional group tolerance
(halides, ethers, nitriles)

CONS

Intramolecular only for alkenes (non-strained)
Scope limited (ie, pyrrolidines with β -substitution)

- Current Asymmetric *State of the Art* - Sadow's neutral zirconium catalyst for primary aminoalkenes



Late Transition Metal-Catalyzed Hydroaminations

Late Transition Metal-Catalyzed Asymmetric Hydroamination

- Late transition metals are highly attractive and desirable for asymmetric hydroaminations

Higher functional group tolerance Lowest air and moisture sensitivity																		
Hydrogen	1	H	Helium	2	He													
lithium	3	Li	boron	4	Be	nitrogen	5	B	carbon	6	C	oxygen	7	N	fluorine	8	F	
8.41	9.0122	11	12	9.3122	12	10.81	13	14	15	16	17	18.998	19	20.190	19	20.988		
10.890	11.999	11	12	12.000	12	13.127	13	14.007	15.000	16.000	17.000	18.000	19	20.000	18	20.948		
potassium	19	K	calcium	20	Ca	nitrogen	21	Sc	carbon	22	Ti	oxygen	23	Al	fluorine	24	Ne	
30.065	31.998	19	20	31.998	20	10.81	21	44.955	32	11.996	22	12.011	33	13.011	34	14.000		
rubidium	37	Rb	silicon	38	Sr	nitrogen	39	Y	carbon	40	V	oxygen	41	Si	fluorine	42	Ar	
35.455	36.950	37	38	36.950	38	10.81	39	47.967	43	11.996	40	12.011	44	13.011	45	14.000		
cesium	55	Cs	silicon	56	Ba	nitrogen	71	Zr	carbon	72	Nb	oxygen	73	Cr	fluorine	74	Ca	
54.938	55.982	55	56	55.982	56	10.81	71	88.906	50	90.906	72	91.906	73	92.906	74	101.906		
barium	72	*	silicon	73	*	nitrogen	74	Y	carbon	75	Mo	oxygen	76	Cr	fluorine	77	Ca	
132.91	137.30	*	silicon	73	*	nitrogen	74	89.906	51	90.906	75	91.906	76	92.906	77	101.906		
lanthanum	87	Fr	silicon	88	Ra	nitrogen	103	Lu	carbon	104	Rf	oxygen	105	Db	fluorine	106	Uuu	
138.91	139.954	87	88	139.954	89	10.81	103	138.91	52	139.954	104	139.954	105	140.954	106	141.954		
cerium	140.954	*	silicon	141.954	*	nitrogen	142.954	Pr	carbon	143.954	Nd	oxygen	144.954	Pm	fluorine	145.954	Uun	
140.954	141.954	*	silicon	141.954	*	nitrogen	142.954	140.954	53	141.954	143.954	54	144.954	145.954	55	146.954		
neodymium	144.954	La	silicon	145.954	Ce	nitrogen	146.954	140.954	55	145.954	147.954	56	148.954	149.954	57	150.954		
144.954	145.954	La	silicon	145.954	Ce	nitrogen	146.954	140.954	55	145.954	147.954	56	148.954	149.954	57	150.954		
praseodymium	147.954	Pr	silicon	148.954	Nd	nitrogen	149.954	140.954	56	147.954	150.954	57	151.954	152.954	58	153.954		
147.954	148.954	Pr	silicon	148.954	Nd	nitrogen	149.954	140.954	56	147.954	150.954	57	151.954	152.954	58	153.954		
neodymium	151.954	Sm	silicon	152.954	Eu	nitrogen	153.954	140.954	57	151.954	152.954	58	154.954	155.954	59	156.954		
151.954	152.954	Sm	silicon	152.954	Eu	nitrogen	153.954	140.954	57	151.954	152.954	58	154.954	155.954	59	156.954		
europium	154.954	Gd	silicon	155.954	Tb	nitrogen	156.954	140.954	58	154.954	155.954	59	157.954	158.954	60	159.954		
154.954	155.954	Gd	silicon	155.954	Tb	nitrogen	156.954	140.954	58	154.954	155.954	59	157.954	158.954	60	159.954		
gadolinium	157.954	Dy	silicon	158.954	Ho	nitrogen	159.954	140.954	59	157.954	158.954	60	160.954	161.954	61	162.954		
157.954	158.954	Dy	silicon	158.954	Ho	nitrogen	159.954	140.954	59	157.954	158.954	60	160.954	161.954	61	162.954		
thulium	160.954	Tb	silicon	161.954	Tm	nitrogen	162.954	140.954	60	160.954	161.954	61	163.954	164.954	62	165.954		
160.954	161.954	Tb	silicon	161.954	Tm	nitrogen	162.954	140.954	60	160.954	161.954	61	163.954	164.954	62	165.954		
ytterbium	164.954	Dy	silicon	165.954	Er	nitrogen	166.954	140.954	61	164.954	165.954	62	167.954	168.954	63	169.954		
164.954	165.954	Dy	silicon	165.954	Er	nitrogen	166.954	140.954	61	164.954	165.954	62	167.954	168.954	63	169.954		
ytterbium	167.954	Ho	silicon	168.954	Tm	nitrogen	169.954	140.954	62	167.954	168.954	63	170.954	171.954	64	172.954		
167.954	168.954	Ho	silicon	168.954	Tm	nitrogen	169.954	140.954	62	167.954	168.954	63	170.954	171.954	64	172.954		
ytterbium	170.954	Tb	silicon	171.954	Yb	nitrogen	172.954	140.954	63	170.954	171.954	64	173.954	174.954	65	175.954		
170.954	171.954	Tb	silicon	171.954	Yb	nitrogen	172.954	140.954	63	170.954	171.954	64	173.954	174.954	65	175.954		
ytterbium	173.954	Dy	silicon	174.954	Er	nitrogen	175.954	140.954	64	173.954	174.954	65	176.954	177.954	66	178.954		
173.954	174.954	Dy	silicon	174.954	Er	nitrogen	175.954	140.954	64	173.954	174.954	65	176.954	177.954	66	178.954		
ytterbium	176.954	Ho	silicon	177.954	Tm	nitrogen	178.954	140.954	65	176.954	177.954	66	179.954	180.954	67	181.954		
176.954	177.954	Ho	silicon	177.954	Tm	nitrogen	178.954	140.954	65	176.954	177.954	66	179.954	180.954	67	181.954		
ytterbium	180.954	Tb	silicon	181.954	Yb	nitrogen	182.954	140.954	66	180.954	181.954	67	183.954	184.954	68	185.954		
180.954	181.954	Tb	silicon	181.954	Yb	nitrogen	182.954	140.954	66	180.954	181.954	67	183.954	184.954	68	185.954		
ytterbium	183.954	Dy	silicon	184.954	Er	nitrogen	185.954	140.954	67	183.954	184.954	68	186.954	187.954	69	188.954		
183.954	184.954	Dy	silicon	184.954	Er	nitrogen	185.954	140.954	67	183.954	184.954	68	186.954	187.954	69	188.954		
ytterbium	186.954	Ho	silicon	187.954	Tm	nitrogen	188.954	140.954	68	186.954	187.954	69	189.954	190.954	70	191.954		
186.954	187.954	Ho	silicon	187.954	Tm	nitrogen	188.954	140.954	68	186.954	187.954	69	189.954	190.954	70	191.954		
ytterbium	190.954	Tb	silicon	191.954	Yb	nitrogen	192.954	140.954	69	190.954	191.954	70	193.954	194.954	71	195.954		
190.954	191.954	Tb	silicon	191.954	Yb	nitrogen	192.954	140.954	69	190.954	191.954	70	193.954	194.954	71	195.954		
ytterbium	193.954	Dy	silicon	194.954	Er	nitrogen	195.954	140.954	70	193.954	194.954	71	196.954	197.954	72	198.954		
193.954	194.954	Dy	silicon	194.954	Er	nitrogen	195.954	140.954	70	193.954	194.954	71	196.954	197.954	72	198.954		
ytterbium	196.954	Ho	silicon	197.954	Tm	nitrogen	198.954	140.954	71	196.954	197.954	72	199.954	200.954	73	201.954		
196.954	197.954	Ho	silicon	197.954	Tm	nitrogen	198.954	140.954	71	196.954	197.954	72	199.954	200.954	73	201.954		
ytterbium	199.954	Tb	silicon	200.954	Yb	nitrogen	201.954	140.954	72	199.954	200.954	73	202.954	203.954	74	204.954		
199.954	200.954	Tb	silicon	200.954	Yb	nitrogen	201.954	140.954	72	199.954	200.954	73	202.954	203.954	74	204.954		
ytterbium	202.954	Dy	silicon	203.954	Er	nitrogen	204.954	140.954	73	202.954	203.954	74	205.954	206.954	75	207.954		
202.954	203.954	Dy	silicon	203.954	Er	nitrogen	204.954	140.954	73	202.954	203.954	74	205.954	206.954	75	207.954		
ytterbium	205.954	Ho	silicon	206.954	Tm	nitrogen	207.954	140.954	74	205.954	206.954	75	208.954	209.954	76	210.954		
205.954	206.954	Ho	silicon	206.954	Tm	nitrogen	207.954	140.954	74	205.954	206.954	75	208.954	209.954	76	210.954		
ytterbium	208.954	Tb	silicon	209.954	Yb	nitrogen	210.954	140.954	75	208.954	209.954	76	211.954	212.954	77	213.954		
208.954	209.954	Tb	silicon	209.954	Yb	nitrogen	210.954	140.954	75	208.954	209.954	76	211.954	212.954	77	213.954		
ytterbium	211.954	Dy	silicon	212.954	Er	nitrogen	213.954	140.954	76	211.954	212.954	77	214.954	215.954	78	216.954		
211.954	212.954	Ho	silicon	212.954	Tm	nitrogen	213.954	140.954	77	211.954	212.954	78	214.954	215.954	79	216.954		
ytterbium	214.954	Tb	silicon	215.954	Yb	nitrogen	216.954	140.954	78	214.954	215.954	79	217.954	218.954	80	219.954		
214.954	215.954	Tb	silicon	215.954	Yb	nitrogen	216.954	140.954	78	214.954	215.954	79	217.954	218.954	80	219.954		
ytterbium	217.954	Dy	silicon	218.954	Er	nitrogen	219.954	140.954	79	217.954	218.954	80	220.954	221.954	81	222.954		
217.954	218.954	Ho	silicon	218.954	Tm	nitrogen	219.954	140.954	79	217.954	218.954	80	220.954	221.954	81	222.954		
ytterbium	220.954	Tb	silicon	221.954	Yb	nitrogen	222.954	140.954	80	220.954	221.954	81	223.954	224.954	82	225.954		
220.954	221.954	Tb	silicon	221.954	Yb	nitrogen	222.954	140.954	80	220.954	221.954	81	223.954	224.954	82	225.954		
ytterbium	223.954	Dy	silicon	224.954	Er	nitrogen	225.954	140.954										

Late Transition Metal-Catalyzed Asymmetric Hydroamination

- Late transition metals are highly attractive and desirable for asymmetric hydroaminations

Higher functional group tolerance
Lowest air and moisture sensitivity

hydrogen	1 H 1.0079	helium	2 He 4.0026
lithium	3 Li 6.941	boron	5 B 10.81
beryllium	4 Be 9.0122	carbon	6 C 12.011
magnesium	12 Mg 24.302	nitrogen	7 N 14.007
sodium	11 Na 22.990	oxygen	8 O 16.000
magnesium	12 Mg 24.302	fluorine	9 F 18.000
potassium	19 K 39.098	nitrogen	10 Ne 20.180
calcium	20 Ca 40.078	oxygen	11 Ar 39.948
rubidium	37 Rb 85.460	phosphorus	15 P 31.008
strontium	38 Sr 87.62	sulfur	16 S 32.065
cesium	55 Cs 132.91	chlorine	17 Cl 35.453
barium	56 Ba 137.33	silicon	14 Si 28.086
lanthanum	57-70 Lu 174.97	gallium	31 Ga 69.779
cerium	58 Ce 140.119	germanium	32 Ge 72.045
neodymium	59 Nd 144.960	arsenic	33 As 74.932
praseodymium	60 Pr 144.960	selenium	34 Se 78.96
europium	61 Eu 151.960	tellurium	35 Te 127.904
thulium	62 Tm 160.95	iodine	53 I 126.90
ytterbium	63 Yb 173.95	astatine	54 Xe 126.90
lutetium	64 Lu 174.97	radon	86 Rn 222.000
lanthanum	57-70 Lu 174.97	neptunium	93 Np 237.000
cerium	58 Ce 140.119	plutonium	94 Pu 244.000
neodymium	59 Nd 144.960	americium	95 Am 243.000
praseodymium	60 Pr 144.960	curium	96 Cm 247.000
europium	61 Eu 151.960	berkelium	97 Bk 249.000
thulium	62 Tm 160.95	californium	98 Cf 251.000
ytterbium	63 Yb 173.95	curium	99 Cm 252.000
lutetium	64 Lu 174.97	neptunium	100 Np 253.000
lanthanum	57-70 Lu 174.97	plutonium	101 Pu 254.000
cerium	58 Ce 140.119	americium	102 Am 255.000
neodymium	59 Nd 144.960	curium	103 Cm 256.000
praseodymium	60 Pr 144.960	berkelium	104 Bk 257.000
europium	61 Eu 151.960	californium	105 Cf 258.000
thulium	62 Tm 160.95	curium	106 Cm 259.000
ytterbium	63 Yb 173.95	neptunium	107 Np 260.000
lutetium	64 Lu 174.97	plutonium	108 Pu 261.000
lanthanum	57-70 Lu 174.97	americium	109 Am 262.000
cerium	58 Ce 140.119	curium	110 Cm 263.000
neodymium	59 Nd 144.960	berkelium	111 Bk 264.000
praseodymium	60 Pr 144.960	californium	112 Cf 265.000
europium	61 Eu 151.960	curium	113 Cm 266.000
thulium	62 Tm 160.95	neptunium	114 Np 267.000
ytterbium	63 Yb 173.95	plutonium	115 Pu 268.000
lutetium	64 Lu 174.97	americium	116 Am 269.000
lanthanum	57-70 Lu 174.97	curium	117 Cm 270.000
cerium	58 Ce 140.119	berkelium	118 Bk 271.000
neodymium	59 Nd 144.960	californium	119 Cf 272.000
praseodymium	60 Pr 144.960	curium	120 Cm 273.000
europium	61 Eu 151.960	neptunium	121 Np 274.000
thulium	62 Tm 160.95	plutonium	122 Pu 275.000
ytterbium	63 Yb 173.95	americium	123 Am 276.000
lutetium	64 Lu 174.97	curium	124 Cm 277.000
lanthanum	57-70 Lu 174.97	berkelium	125 Bk 278.000
cerium	58 Ce 140.119	californium	126 Cf 279.000
neodymium	59 Nd 144.960	curium	127 Cm 280.000
praseodymium	60 Pr 144.960	neptunium	128 Np 281.000
europium	61 Eu 151.960	plutonium	129 Pu 282.000
thulium	62 Tm 160.95	americium	130 Am 283.000
ytterbium	63 Yb 173.95	curium	131 Cm 284.000
lutetium	64 Lu 174.97	berkelium	132 Bk 285.000
lanthanum	57-70 Lu 174.97	californium	133 Cf 286.000
cerium	58 Ce 140.119	curium	134 Cm 287.000
neodymium	59 Nd 144.960	neptunium	135 Np 288.000
praseodymium	60 Pr 144.960	plutonium	136 Pu 289.000
europium	61 Eu 151.960	americium	137 Am 290.000
thulium	62 Tm 160.95	curium	138 Cm 291.000
ytterbium	63 Yb 173.95	berkelium	139 Bk 292.000
lutetium	64 Lu 174.97	californium	140 Cf 293.000
lanthanum	57-70 Lu 174.97	curium	141 Cm 294.000
cerium	58 Ce 140.119	neptunium	142 Np 295.000
neodymium	59 Nd 144.960	plutonium	143 Pu 296.000
praseodymium	60 Pr 144.960	americium	144 Am 297.000
europium	61 Eu 151.960	curium	145 Cm 298.000
thulium	62 Tm 160.95	berkelium	146 Bk 299.000
ytterbium	63 Yb 173.95	californium	147 Cf 300.000
lutetium	64 Lu 174.97	curium	148 Cm 301.000
lanthanum	57-70 Lu 174.97	neptunium	149 Np 302.000
cerium	58 Ce 140.119	plutonium	150 Pu 303.000
neodymium	59 Nd 144.960	americium	151 Am 304.000
praseodymium	60 Pr 144.960	curium	152 Cm 305.000
europium	61 Eu 151.960	berkelium	153 Bk 306.000
thulium	62 Tm 160.95	californium	154 Cf 307.000
ytterbium	63 Yb 173.95	curium	155 Cm 308.000
lutetium	64 Lu 174.97	neptunium	156 Np 309.000
lanthanum	57-70 Lu 174.97	plutonium	157 Pu 310.000
cerium	58 Ce 140.119	americium	158 Am 311.000
neodymium	59 Nd 144.960	curium	159 Cm 312.000
praseodymium	60 Pr 144.960	berkelium	160 Bk 313.000
europium	61 Eu 151.960	californium	161 Cf 314.000
thulium	62 Tm 160.95	curium	162 Cm 315.000
ytterbium	63 Yb 173.95	neptunium	163 Np 316.000
lutetium	64 Lu 174.97	plutonium	164 Pu 317.000
lanthanum	57-70 Lu 174.97	americium	165 Am 318.000
cerium	58 Ce 140.119	curium	166 Cm 319.000
neodymium	59 Nd 144.960	berkelium	167 Bk 320.000
praseodymium	60 Pr 144.960	californium	168 Cf 321.000
europium	61 Eu 151.960	curium	169 Cm 322.000
thulium	62 Tm 160.95	neptunium	170 Np 323.000
ytterbium	63 Yb 173.95	plutonium	171 Pu 324.000
lutetium	64 Lu 174.97	americium	172 Am 325.000
lanthanum	57-70 Lu 174.97	curium	173 Cm 326.000
cerium	58 Ce 140.119	berkelium	174 Bk 327.000
neodymium	59 Nd 144.960	californium	175 Cf 328.000
praseodymium	60 Pr 144.960	curium	176 Cm 329.000
europium	61 Eu 151.960	neptunium	177 Np 330.000
thulium	62 Tm 160.95	plutonium	178 Pu 331.000
ytterbium	63 Yb 173.95	americium	179 Am 332.000
lutetium	64 Lu 174.97	curium	180 Cm 333.000
lanthanum	57-70 Lu 174.97	berkelium	181 Bk 334.000
cerium	58 Ce 140.119	californium	182 Cf 335.000
neodymium	59 Nd 144.960	curium	183 Cm 336.000
praseodymium	60 Pr 144.960	neptunium	184 Np 337.000
europium	61 Eu 151.960	plutonium	185 Pu 338.000
thulium	62 Tm 160.95	americium	186 Am 339.000
ytterbium	63 Yb 173.95	curium	187 Cm 340.000
lutetium	64 Lu 174.97	berkelium	188 Bk 341.000
lanthanum	57-70 Lu 174.97	californium	189 Cf 342.000
cerium	58 Ce 140.119	curium	190 Cm 343.000
neodymium	59 Nd 144.960	neptunium	191 Np 344.000
praseodymium	60 Pr 144.960	plutonium	192 Pu 345.000
europium	61 Eu 151.960	americium	193 Am 346.000
thulium	62 Tm 160.95	curium	194 Cm 347.000
ytterbium	63 Yb 173.95	berkelium	195 Bk 348.000
lutetium	64 Lu 174.97	californium	196 Cf 349.000
lanthanum	57-70 Lu 174.97	curium	197 Cm 350.000
cerium	58 Ce 140.119	neptunium	198 Np 351.000
neodymium	59 Nd 144.960	plutonium	199 Pu 352.000
praseodymium	60 Pr 144.960	americium	200 Am 353.000
europium	61 Eu 151.960	curium	201 Cm 354.000
thulium	62 Tm 160.95	berkelium	202 Bk 355.000
ytterbium	63 Yb 173.95	californium	203 Cf 356.000
lutetium	64 Lu 174.97	curium	204 Cm 357.000
lanthanum	57-70 Lu 174.97	neptunium	205 Np 358.000
cerium	58 Ce 140.119	plutonium	206 Pu 359.000
neodymium	59 Nd 144.960	americium	207 Am 360.000
praseodymium	60 Pr 144.960	curium	208 Cm 361.000
europium	61 Eu 151.960	berkelium	209 Bk 362.000
thulium	62 Tm 160.95	californium	210 Cf 363.000
ytterbium	63 Yb 173.95	curium	211 Cm 364.000
lutetium	64 Lu 174.97	neptunium	212 Np 365.000
lanthanum	57-70 Lu 174.97	plutonium	213 Pu 366.000
cerium	58 Ce 140.119	americium	214 Am 367.000
neodymium	59 Nd 144.960	curium	215 Cm 368.000
praseodymium	60 Pr 144.960	berkelium	216 Bk 369.000
europium	61 Eu 151.960	californium	217 Cf 370.000
thulium	62 Tm 160.95	curium	218 Cm 371.000
ytterbium	63 Yb 173.95	neptunium	219 Np 372.000
lutetium	64 Lu 174.97	plutonium	220 Pu 373.000
lanthanum	57-70 Lu 174.97	americium	221 Am 374.000
cerium	58 Ce 140.119	curium	222 Cm 375.000
neodymium	59 Nd 144.960	berkelium	223 Bk 376.000
praseodymium	60 Pr 144.960	californium	224 Cf 377.000
europium	61 Eu 151.960	curium	225 Cm 378.000
thulium	62 Tm 160.95	neptunium	226 Np 379.000
ytterbium	63 Yb 173.95	plutonium	227 Pu 380.000
lutetium	64 Lu 174.97	americium	228 Am 381.000
lanthanum	57-70 Lu 174.97	curium	229 Cm 382.000
cerium	58 Ce 140.119	berkelium	230 Bk 383.000
neodymium	59 Nd 144.960	californium	231 Cf 384.000
praseodymium	60 Pr 144.960	curium	232 Cm 385.000
europium	61 Eu 151.960	neptunium	233 Np 386.000
thulium	62 Tm 160.95	plutonium	234 Pu 387.000
ytterbium	63 Yb 173.95	americium	235 Am 388.000
lutetium	64 Lu 174.97	curium	236 Cm 389.000
lanthanum	57-70 Lu 174.97	berkelium	237 Bk 390.000
cerium	58 Ce 140.119	californium	238 Cf 391.000
neodymium	59 Nd 144.960	curium	239 Cm 392.000
praseodymium	60 Pr 144.960	neptunium	240 Np 393.000
europium	61 Eu 151.960	plutonium	241 Pu 394.000
thulium	62 Tm 160.95	americium	242 Am 395.000
ytterbium	63 Yb 173.95	curium	243 Cm 396.000
lutetium	64 Lu 174.97	berkelium	244 Bk 397.000
lanthanum	57-70 Lu 174.97	californium	245 Cf 398.000
cerium	58 Ce 140.119	curium	246 Cm 399.000
neodymium	59 Nd 144.960	neptunium	247 Np 400.000
praseodymium	60 Pr 144.960	plutonium	248 Pu 401.000
europium	61 Eu 151.960	americium	249 Am 402.000
thulium	62 Tm 160.95	curium	250 Cm 403.000
ytterbium	63 Yb 173.95	berkelium	251 Bk 404.000
lutetium	64 Lu 174.97	californium	252 Cf 405.000
lanthanum	57-70 Lu 174.97	curium	253 Cm 406.000
cerium	58 Ce 140.119	neptunium	254 Np 407.000
neodymium	59 Nd 144.960	plutonium	255 Pu 408.000
praseodymium	60 Pr 144.960	americium	256 Am 409.000
europium	61 Eu 151.960	curium	257 Cm 410.000
thulium	62 Tm 160.95	berkelium	258 Bk 411.000
ytterbium	63 Yb 173.95	californium	259 Cf 412.000
lutetium	64 Lu 174.97	curium	260 Cm 413.000
lanthanum	57-70 Lu 174.97	neptunium	261 Np 414.000
cerium	58 Ce 140.119	plutonium	262 Pu 415.000
neodymium	59 Nd 144.960	americium	263 Am 416.000
praseodymium	60 Pr 144.960	curium	264 Cm 417.000
europium	61 Eu 151.960	berkelium	265 Bk 418.000
thulium	62 Tm 160.95	californium	266 Cf 419.000
ytterbium	63 Yb 173.95	curium	267 Cm 420.000
lutetium	64 Lu 174.97	neptunium	268 Np 421.000
lanthanum	57-70 Lu 174.97	plutonium	269 Pu 422.000
cerium	58 Ce 140.119	americium	270 Am 423.000
neodymium	59 Nd 144.960	curium	271 Cm 424.000
praseodymium	60 Pr 144.960	berkelium	272 Bk 425.000
europium	61 Eu 151.960	californium	273 Cf 426.000
thulium	62 Tm 160.95	curium	274 Cm 427.000
ytterbium	63 Yb 173.95	neptunium	275 Np 428.000
lutetium	64 Lu 174.97	plutonium	276 Pu 429.000
lanthanum	57-70 Lu 174.97	americium	2

*Lanthanide series

lutetium	neptunium	pesium	neobromium	promethium	seaborgium	technetium	gadolinium	berkelium	dysprosium	neptunium	curium	thulium	ytterbium
57	58	59	60	61	62	63	64	65	66	67	68	69	70
La	Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb
138.91	140.52	141.91	144.24	145.91	150.36	151.96	152.25	158.93	160.50	164.93	167.26	169.93	173.66
actinium	protactinium	thorium	rutherfordium	meitnerium	ununhexium	curium	berkelium	californium	curium	berkelium	curium	thorium	protactinium
89	90	91	92	93	94	95	96	97	98	99	100	101	102
Ac	Th	Pa	U	Np	Pu	Am	Cm	Bk	Cf	Es	Fm	Md	No
227.0	232.04	231.04	238.05	239.05	240.04	241.04	247.04	248.04	250.04	252.05	253.05	256.04	258.04

* * Actinide series

Late Transition Metal-Catalyzed Asymmetric Hydroamination

- Late transition metals are highly attractive and desirable for asymmetric hydroaminations

Higher functional group tolerance
Lowest air and moisture sensitivity

hydrogen 1 H 1.0079	helium 2 He 4.003
lithium 3 Li 6.941	boron 5 B 10.81
beryllium 4 Be 9.012	carbon 6 C 12.011
magnesium 12 Mg 24.305	nitrogen 7 N 14.007
sodium 11 Na 22.990	oxygen 8 O 16.000
potassium 19 K 39.098	fluorine 9 F 18.998
calcium 20 Ca 40.078	neon 10 Ne 20.180
rubidium 37 Rb 85.460	lithium 3 Li 6.941
strontium 38 Sr 87.62	beryllium 4 Be 9.012
cesium 55 Cs 132.91	magnesium 12 Mg 24.305
barium 56 Ba 137.33	aluminum 13 Al 26.982
lanthanum 57-70 * 131.91	silicon 14 Si 28.086
cerium 71 Lu 174.97	phosphorus 15 P 30.988
holmium 72 Hf 178.49	sulfur 16 S 32.065
erbium 73 Ta 180.95	chlorine 17 Cl 35.453
dysprosium 74 W 183.84	nitrogen 18 Ar 39.948
ytterbium 75 Re 186.21	oxygen 19 Ar 39.948
thulium 76 Os 190.23	fluorine 20 Ar 39.948
lutetium 77 Ir 196.97	lithium 3 Li 6.941
neptunium 78 Pt 198.19	beryllium 4 Be 9.012
curium 79 Au 198.97	magnesium 12 Mg 24.305
plutonium 80 Hg 200.59	aluminum 13 Al 26.982
neptunium 81 Tl 201.98	silicon 14 Si 28.086
curium 82 Pb 204.38	phosphorus 15 P 30.988
plutonium 83 Bi 206.98	sulfur 16 S 32.065
neptunium 84 Po 209.98	chlorine 17 Cl 35.453
curium 85 At 211.93	nitrogen 18 Ar 39.948
neptunium 86 Rn 222.03	oxygen 19 Ar 39.948
curium 87 Fr 223.03	fluorine 20 Ar 39.948
neptunium 88 Ra 226.03	lithium 3 Li 6.941
curium 89-102 * 229.03	beryllium 4 Be 9.012
neptunium 103 Lr 230.03	magnesium 12 Mg 24.305
curium 104 Rf 232.03	aluminum 13 Al 26.982
curium 105 Db 233.03	silicon 14 Si 28.086
curium 106 Sg 234.03	phosphorus 15 P 30.988
curium 107 Bh 235.03	sulfur 16 S 32.065
curium 108 Hs 236.03	chlorine 17 Cl 35.453
curium 109 Mt 237.03	nitrogen 18 Ar 39.948
curium 110 Uun 238.03	oxygen 19 Ar 39.948
curium 111 Uuu 239.03	fluorine 20 Ar 39.948
curium 112 Uub 240.03	lithium 3 Li 6.941
curium 114 Uuq 241.03	beryllium 4 Be 9.012

* Lanthanide series

**** Actinide series**

Late Transition Metal-Catalyzed Asymmetric Hydroamination

- Late transition metals are highly attractive and desirable for asymmetric hydroaminations

*Higher functional group tolerance
Lowest air and moisture sensitivity*

* Lanthanide series

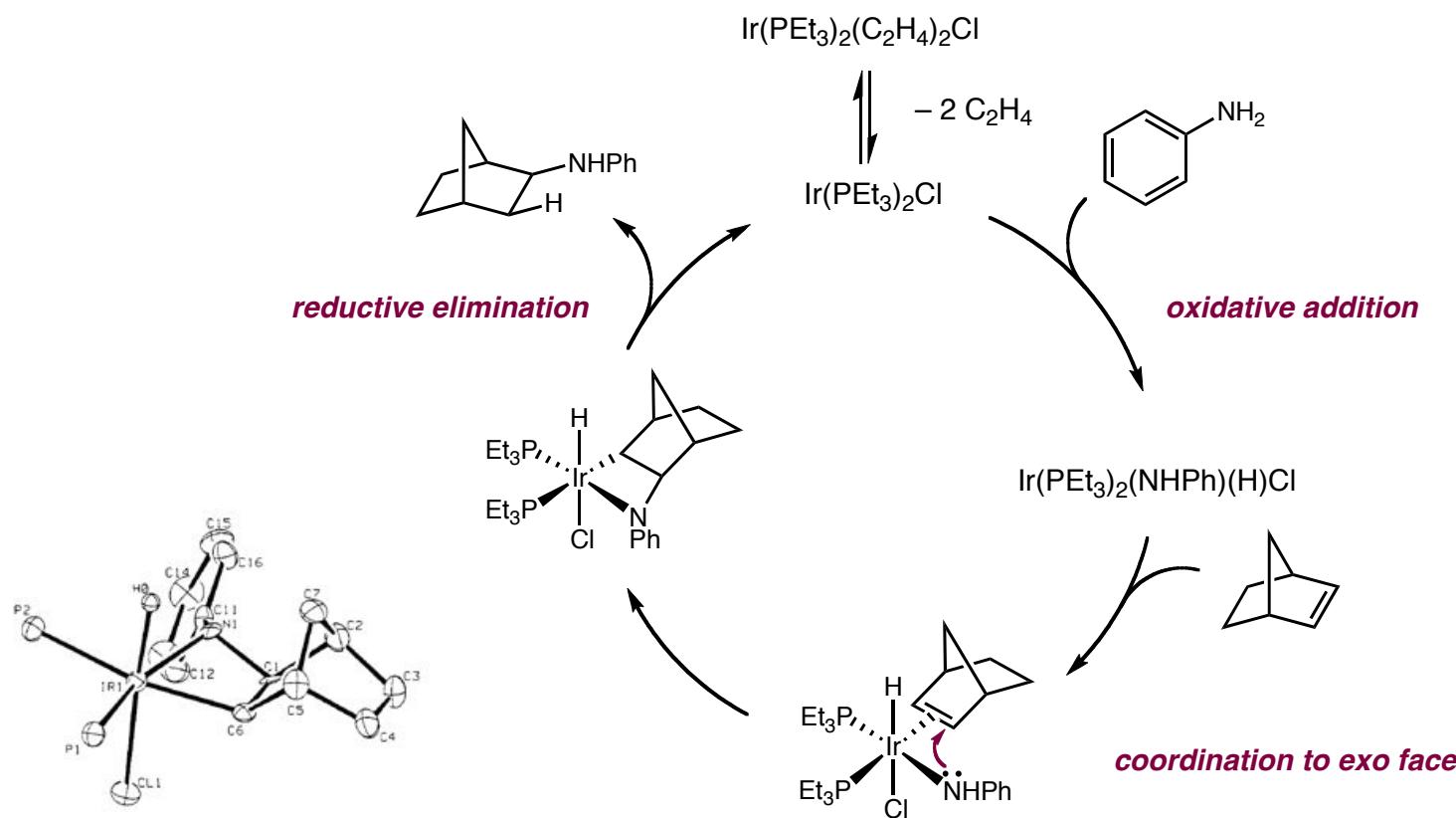
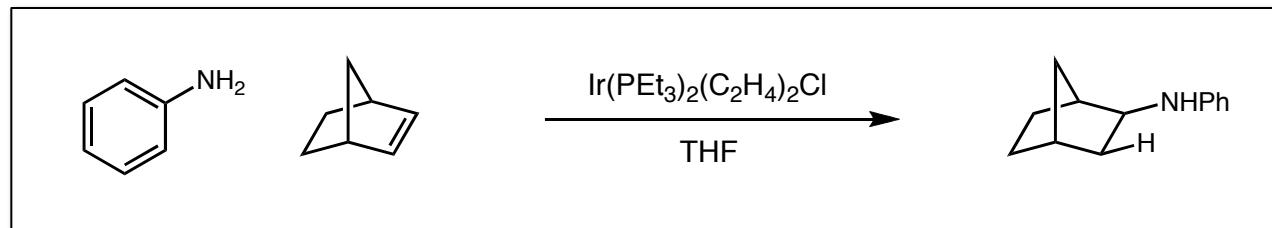
Lanthanum	57	cerium	58	praseodymium	59	neodymium	60	promethium	61	samarium	62	europium	63	gadolinium	64	terbium	65	dysprosium	66	holmium	67	erbium	68	thulium	69	ytterbium	70
La	138.91	Ce	140.12	Pr	141.91	Nd	144.24	Pm	147.91	Sm	150.36	Eu	151.96	Gd	157.25	Tb	160.93	Dy	162.93	Ho	167.26	Er	169.93	Tm	173.06	Yb	
Ac	132.91	Th	132.94	Pa	131.04	U	134.03	Np	134.93	Pu	139.90	Am	140.91	Cm	142.93	Bk	147.93	Cf	150.93	Es	152.93	Fm	154.93	Md	156.93	No	
Ra	226.02																										

** Actinide series

- Most substrates are restricted to activated substrates, such as strained olefins, styrenes, dienes, alkynes

Iridium-Catalyzed Intermolecular Hydroamination

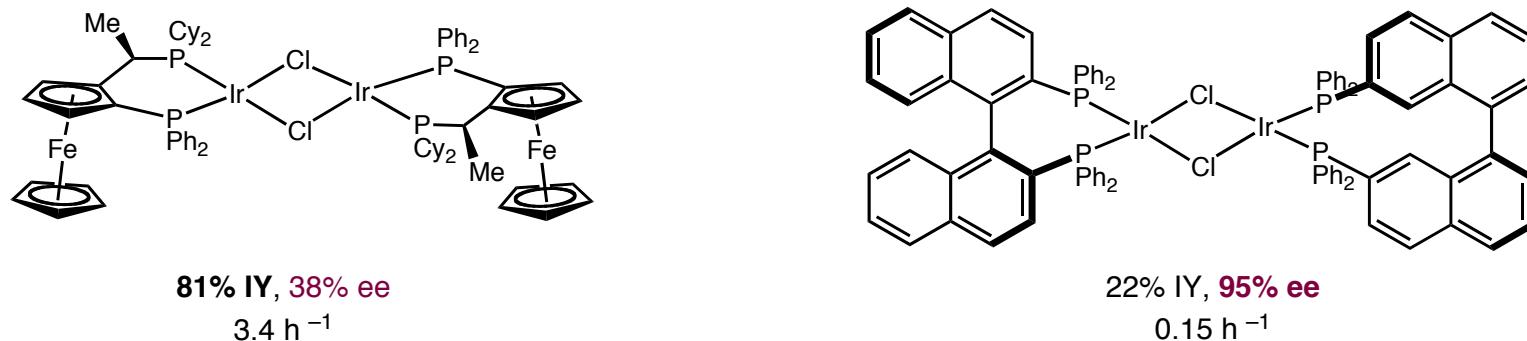
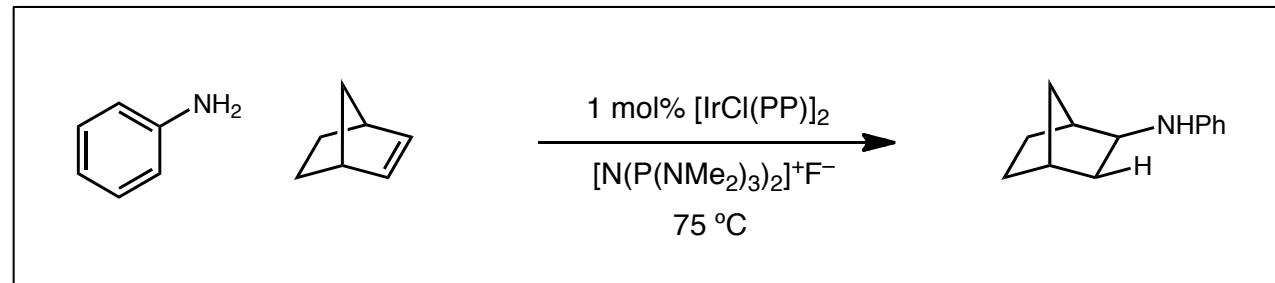
■ The first iridium-catalyzed hydromation was reported in 1989 by Milstein



Casalnuovo, A. L.; Calabrese, J. C.; Milstein, D. *J. Am. Chem. Soc.* **1989**, *110*, 6738.

Iridium-Catalyzed Intermolecular Hydroamination

■ Inspired by Milstein, Togni and coworkers developed an asymmetric version in 1997



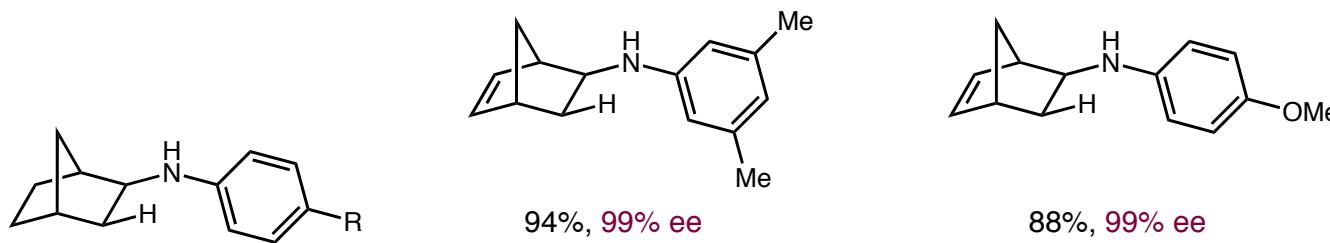
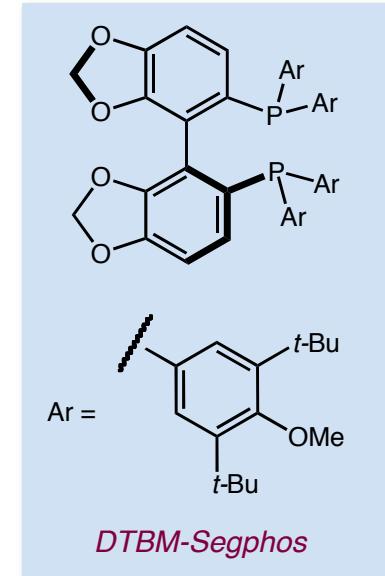
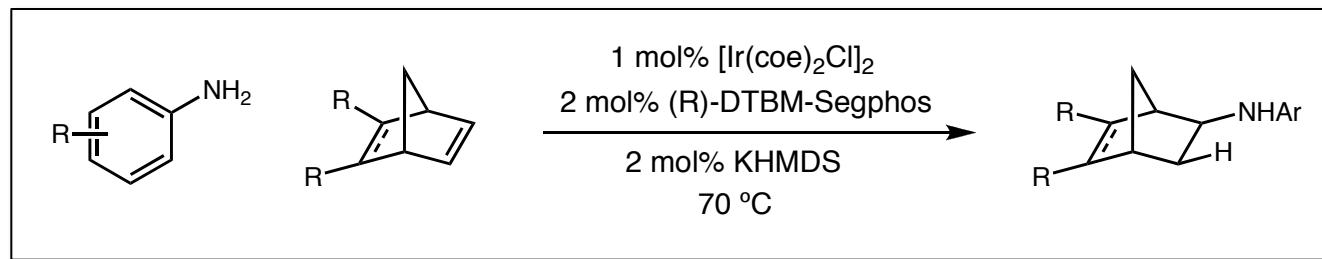
Fluoride required for yield and enantioselectivity

Possible roles: acts as a good π -donating ligand on iridium

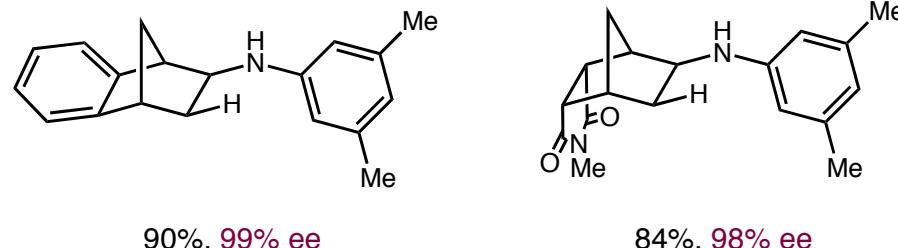
deprotonates aniline to generate anilide

Iridium-Catalyzed Intermolecular Hydroamination

- In 2008, Hartwig and coworkers improved the iridium catalyzed hydroamination to provide high yields and enantioselectivities for a wider scope of bicyclic alkenes

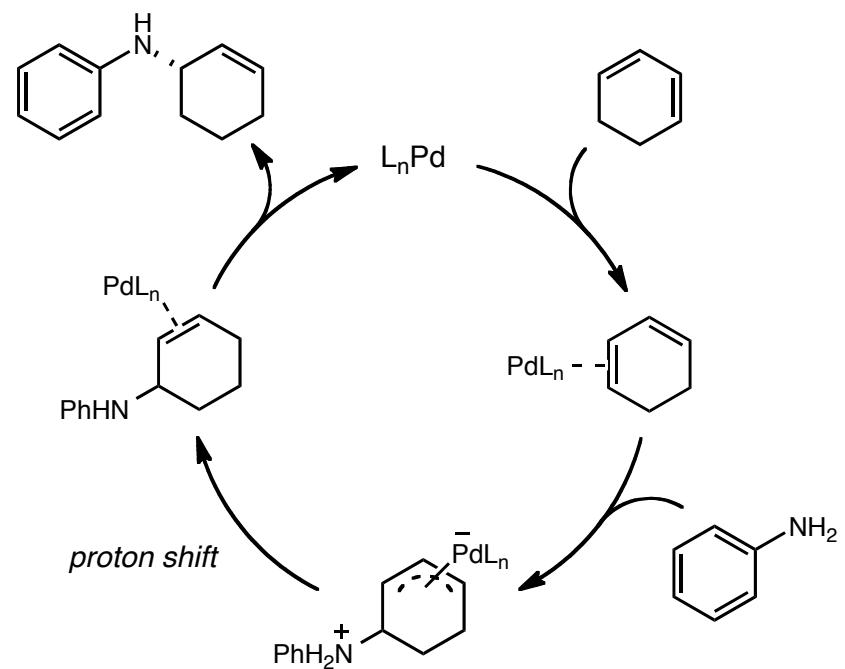
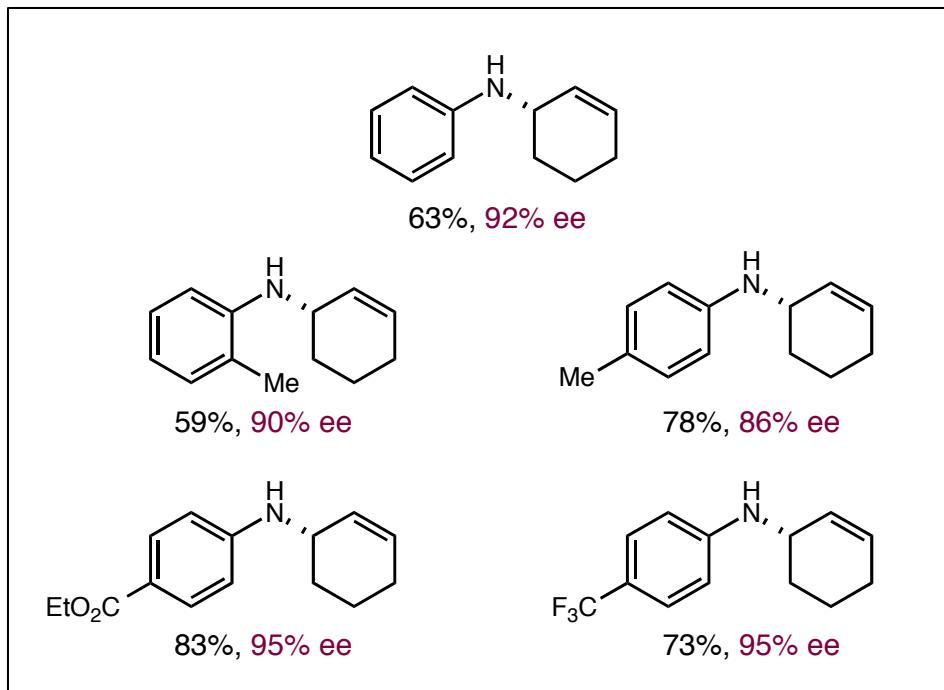
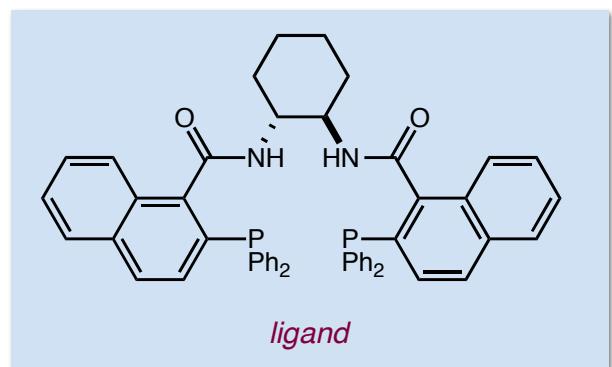
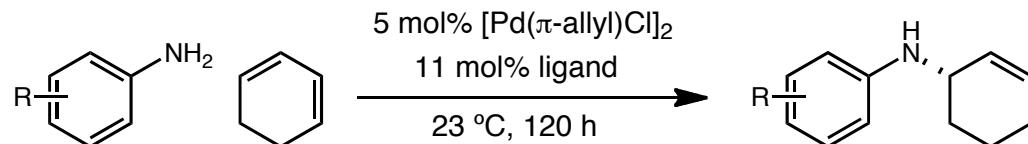


$\text{R} = t\text{-Bu}$ 85%, 92% ee
 Br 91%, 96% ee
 OMe 75%, 98% ee
 CF_3 77%, 91% ee



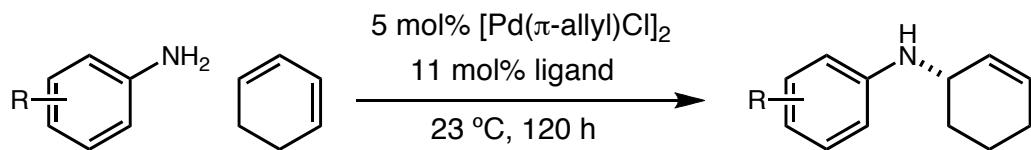
Palladium-Catalyzed Asymmetric Intermolecular Hydroamination

■ In 2001, Hartwig reported the first enantioselective palladium-catalyzed hydroamination of dienes

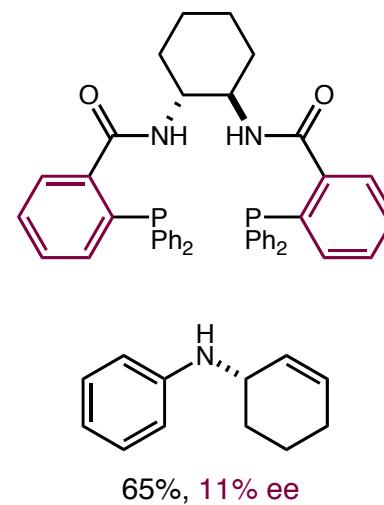
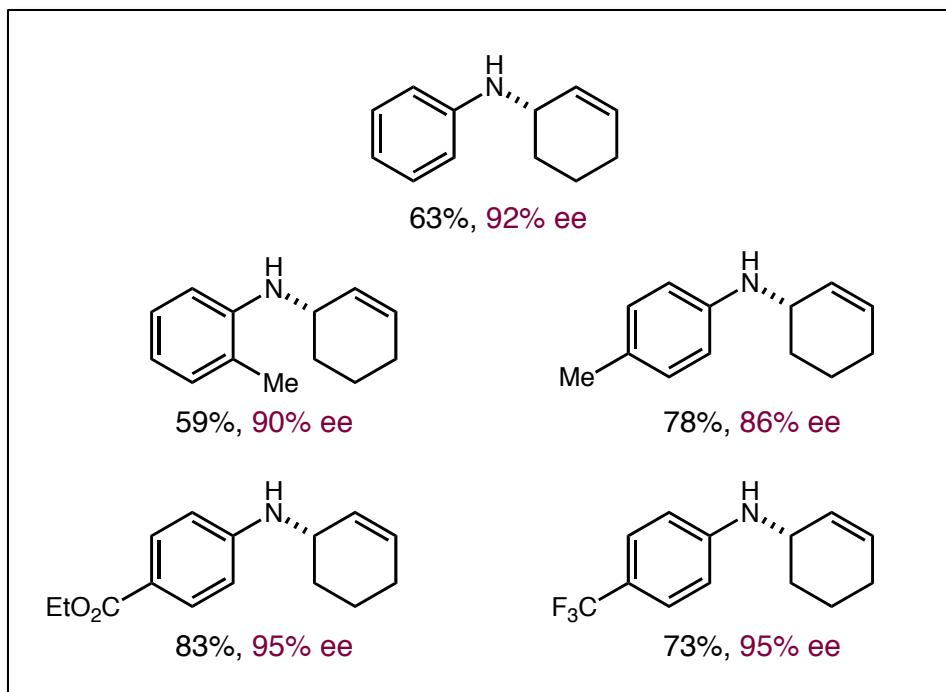


Palladium-Catalyzed Asymmetric Intermolecular Hydroamination

- In 2001, Hartwig reported the first enantioselective palladium-catalyzed hydroamination of dienes

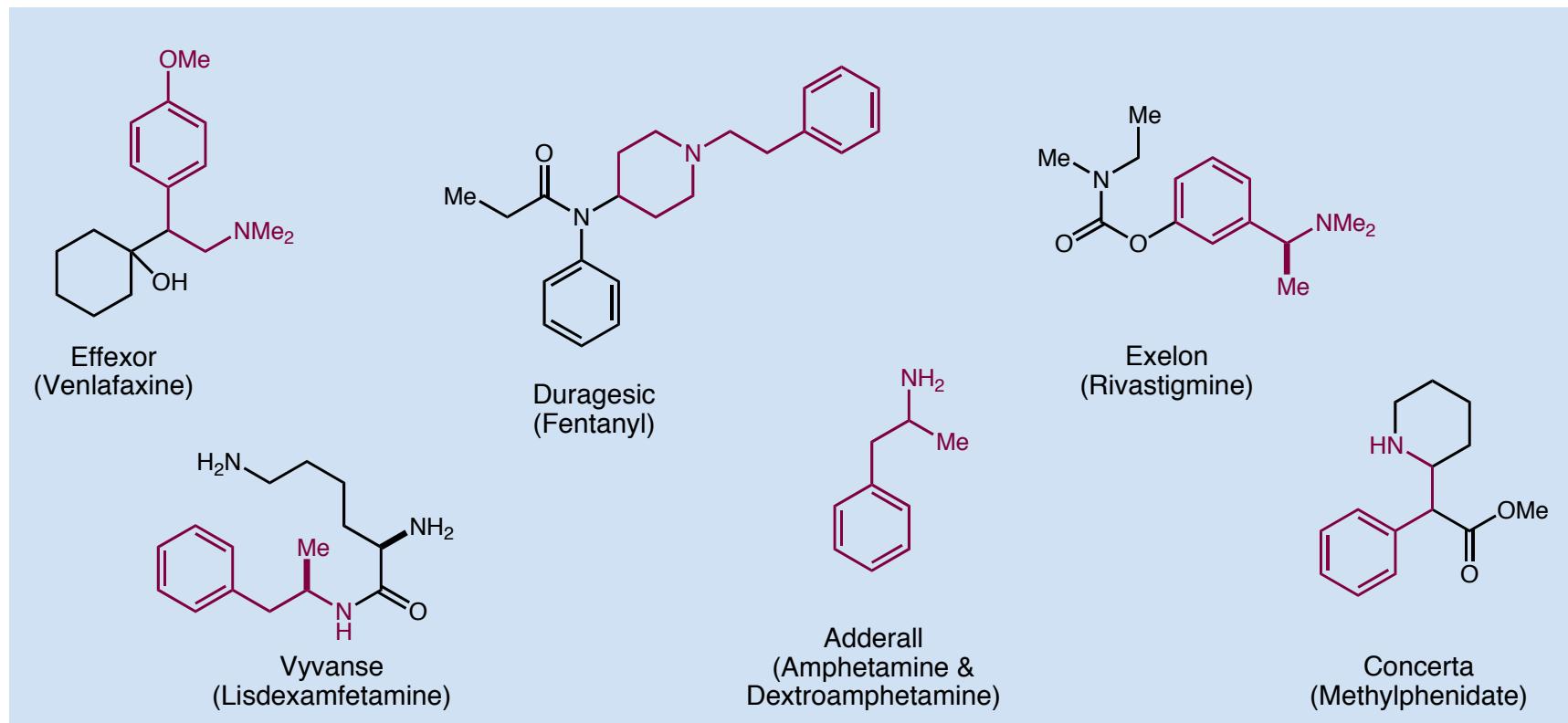
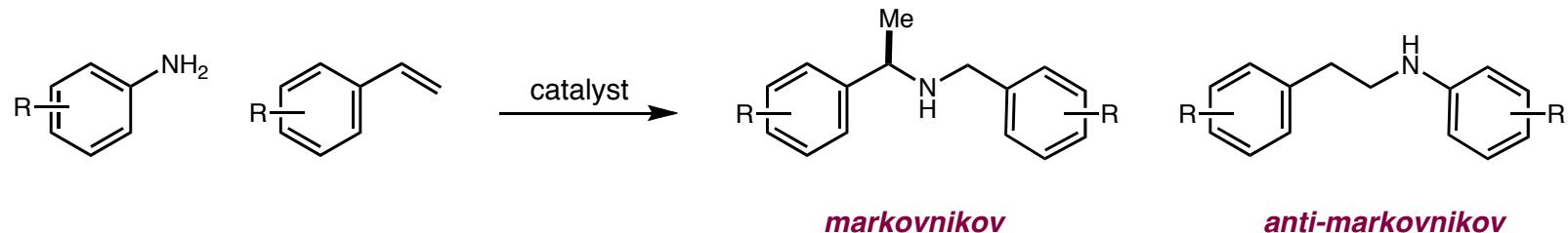


naphthyl units extremely important for enantioselectivity



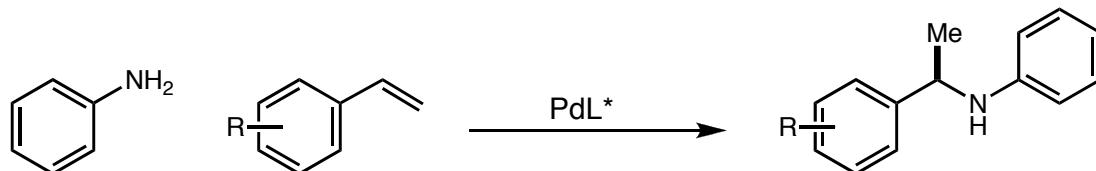
Palladium-Catalyzed Asymmetric Intermolecular Hydroamination of Styrenes

- Hydroamination of styrenes is a powerful synthetic transformation for benzylic or homobenzylic amines

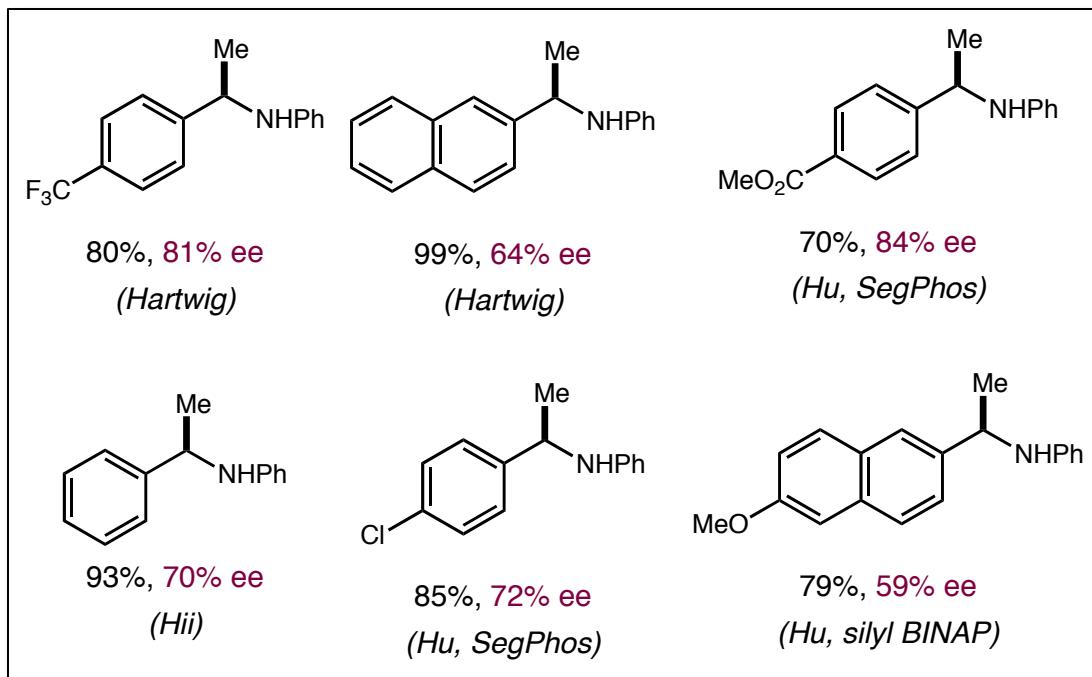


Palladium-Catalyzed Asymmetric Intermolecular Hydroamination

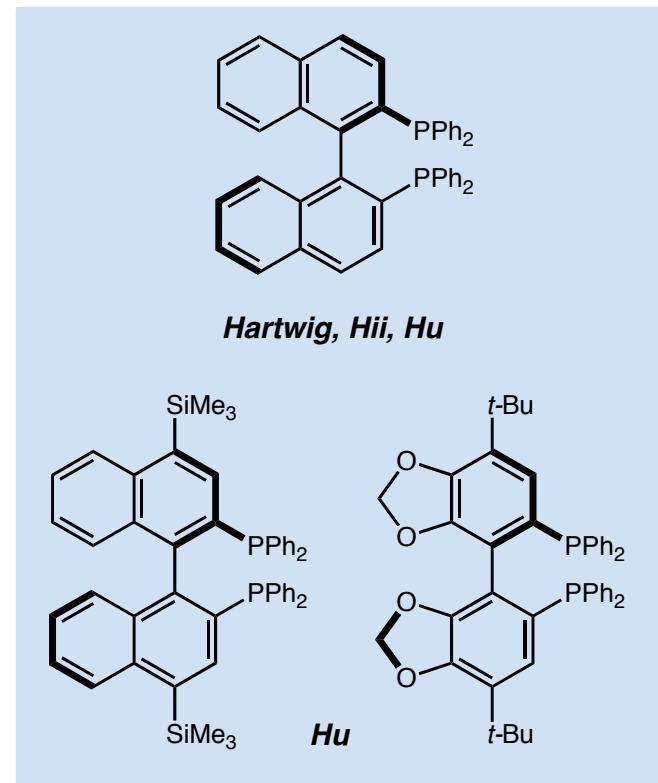
- Several groups have developed hydroaminations of styrenes using aryl amines



Pd-catalyzed reaction generally gives markovnikov products



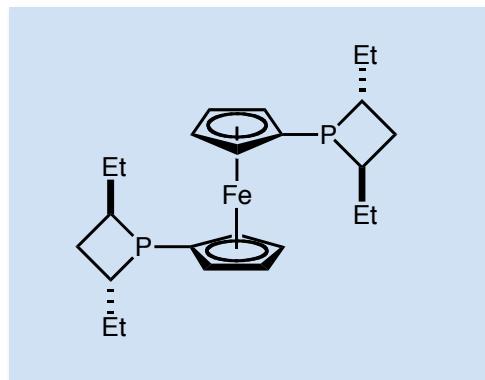
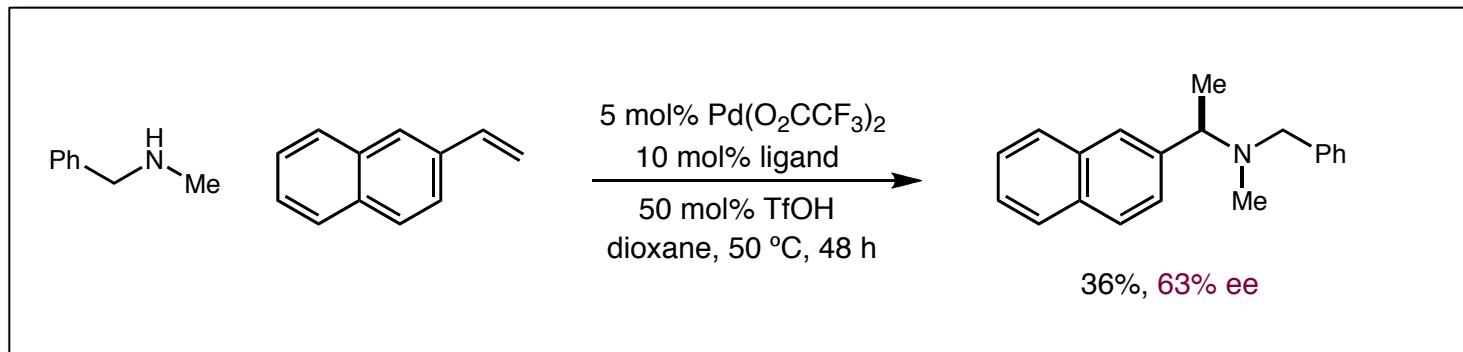
Limited to the addition of aryl amines



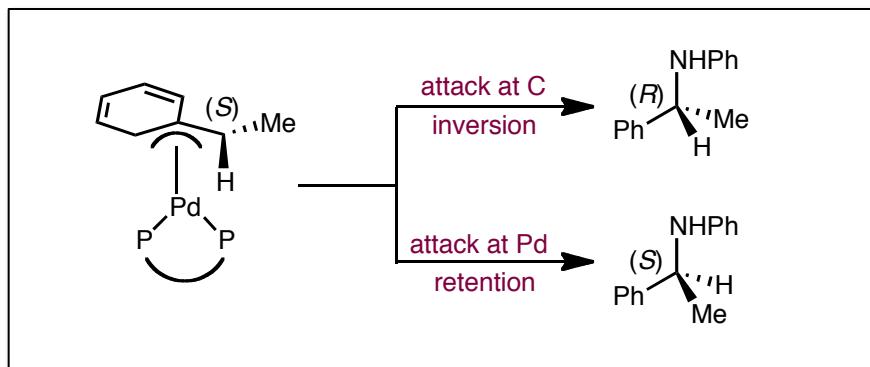
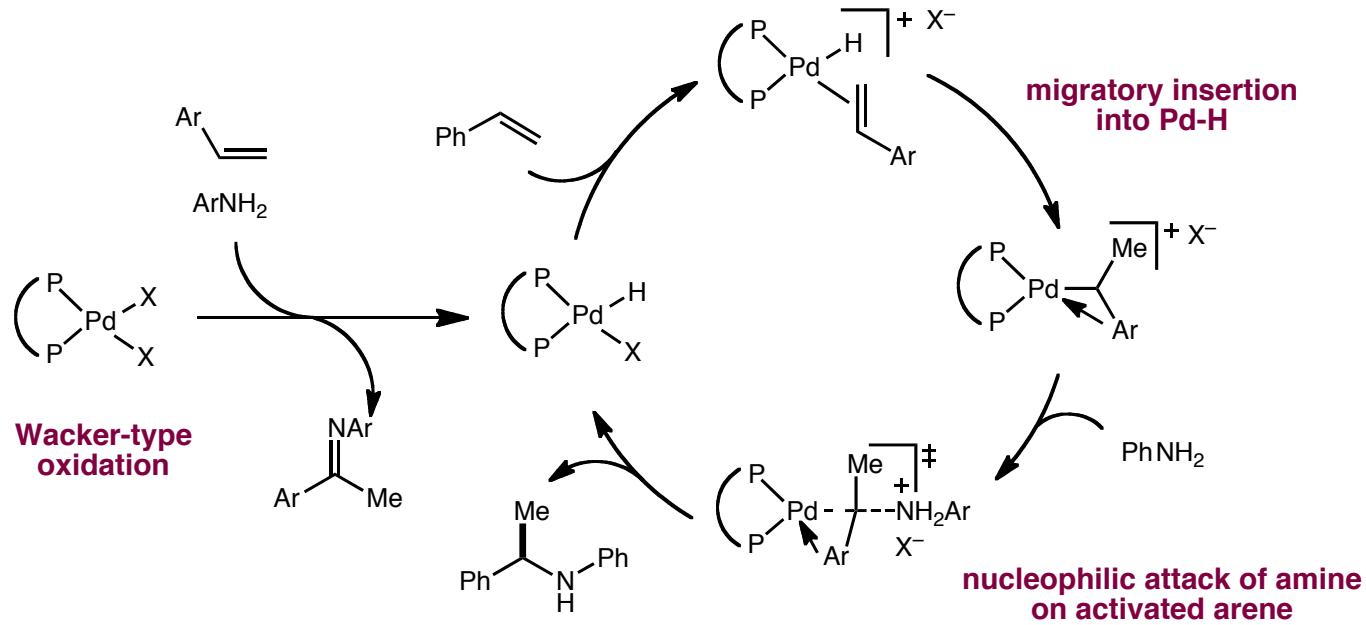
Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, 122, 9546.
Li, K.; Horton, P. N.; Hursthouse, M. B.; Hii, K. K. *J. Organomet. Chem.* **2003**, 665, 250.
Hu, A.; Ogasawara, M.; Sakamoto, T.; Okada, A.; Nakajima, K.; Takahashi, T.; Lin, W. *Adv. Synth. Catal.* **2006**, 348, 2051.

Palladium-Catalyzed Asymmetric Intermolecular Hydroamination

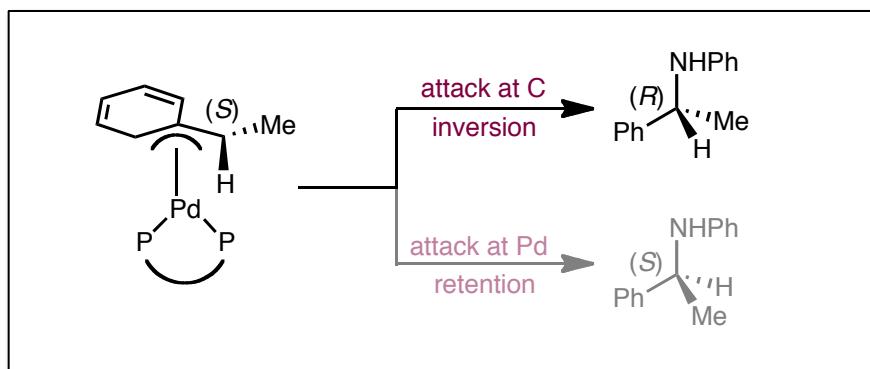
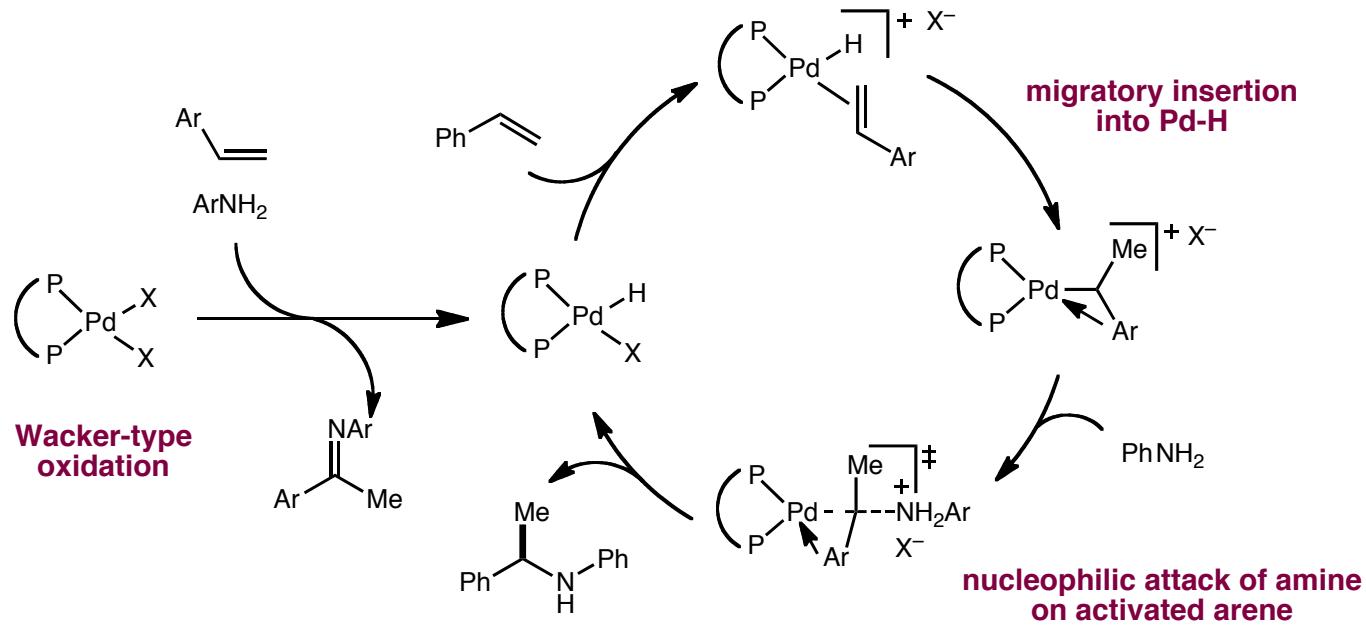
- Hartwig reoptimized the reaction to be successful with secondary alkylamines
- Only one asymmetric example was reported with lower yield than the racemic variant



Palladium-Catalyzed Hydroamination of Styrenes: Mechanism

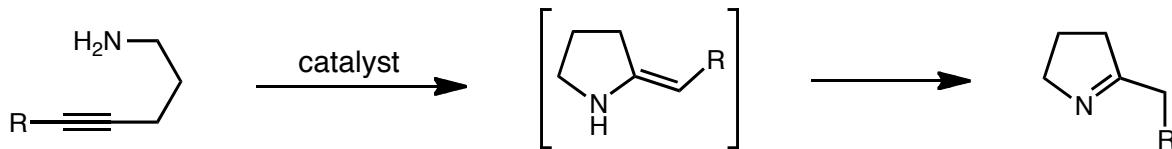


Palladium-Catalyzed Hydroamination of Styrenes: Mechanism

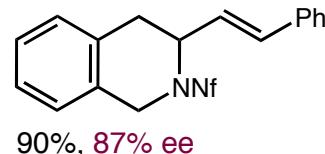
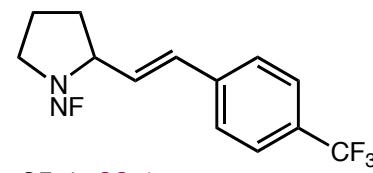
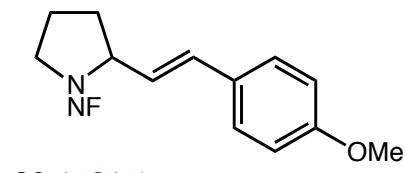
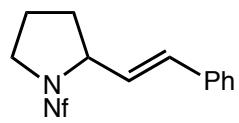
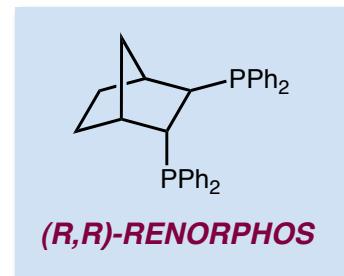
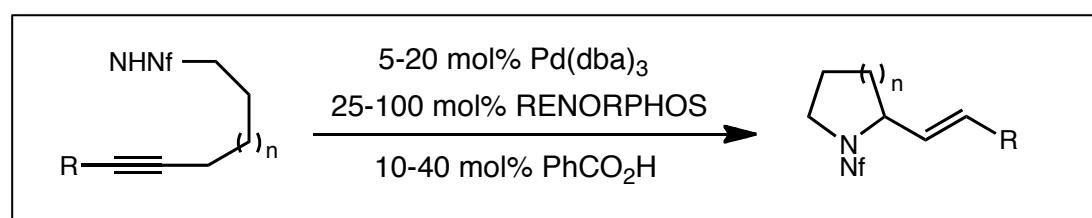


Palladium-Catalyzed Intramolecular Asymmetric Hydroamination of Alkynes

- Hydroamination of alkynes usually does not introduce a new stereocenter

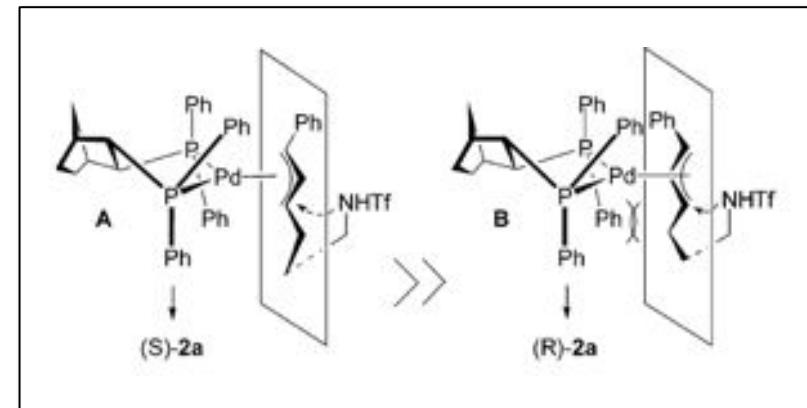
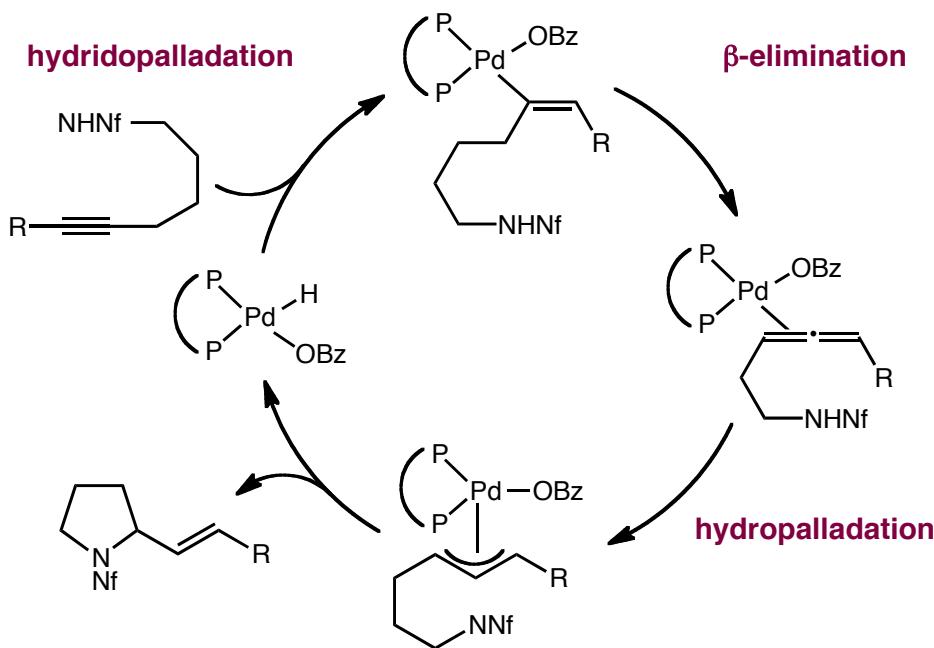
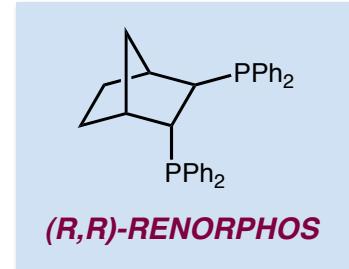
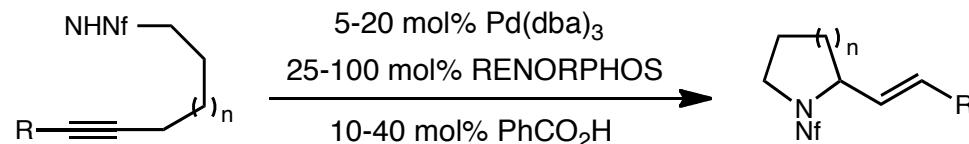


- Palladium-catalyzed hydroamination of alkynes proceeds through a different mechanism and creates a stereocenter



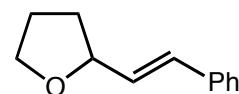
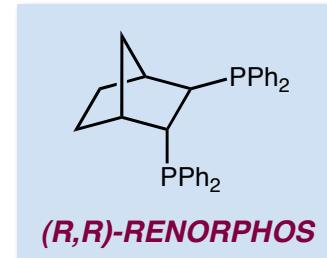
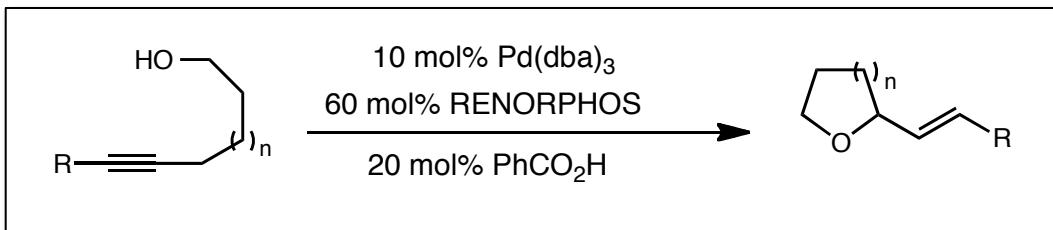
Palladium-Catalyzed Intramolecular Asymmetric Hydroamination of Alkynes

- The palladium-catalyzed hydroamination of aminoalkynes proceeds through an allene

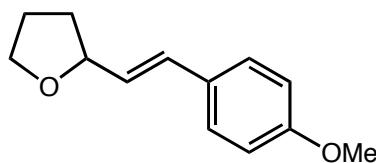


Palladium-Catalyzed Intramolecular Asymmetric Hydroalkoxylation of Alkynes

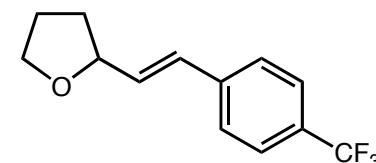
- Yamamoto was able to extend this methodology to the *first asymmetric hydroalkoxylation*, although with lower yield and selectivity



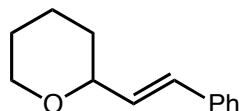
52%, 80% ee



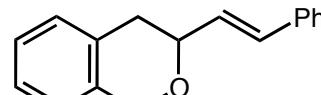
48%, 40% ee



60%, 82% ee



61%, 78% ee



57%, 86% ee

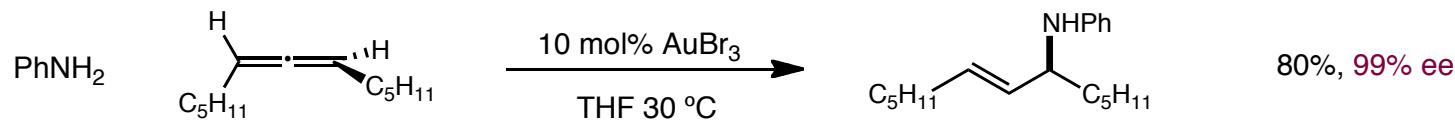
Why do we not see hydroalkoxylation as often as hydroamination?

- diminished nucleophilicity and weaker Lewis base character of oxygen
- high thermodynamic stability of O-H σ-bonds (111 kcal vs 93 kcal for N-H)

Gold-Catalyzed Asymmetric Hydroamination Reactions

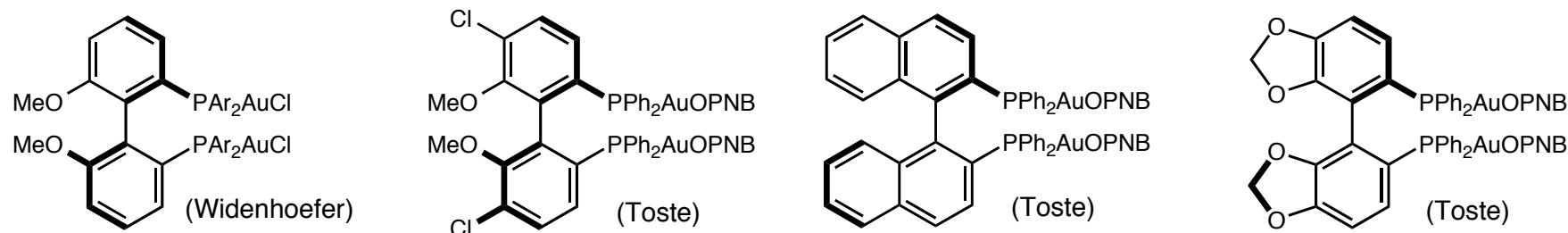
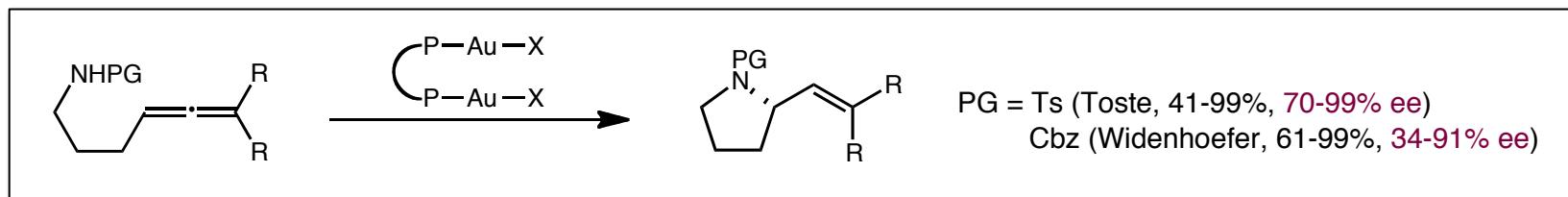
- The ability of gold complexes to activate carbon-carbon multiple bonds make them attractive candidates for hydroamination catalysts
- However, to date there are only a few reports of enantioselective hydroamination reactions

Yamamoto's chirality transfer (2006):

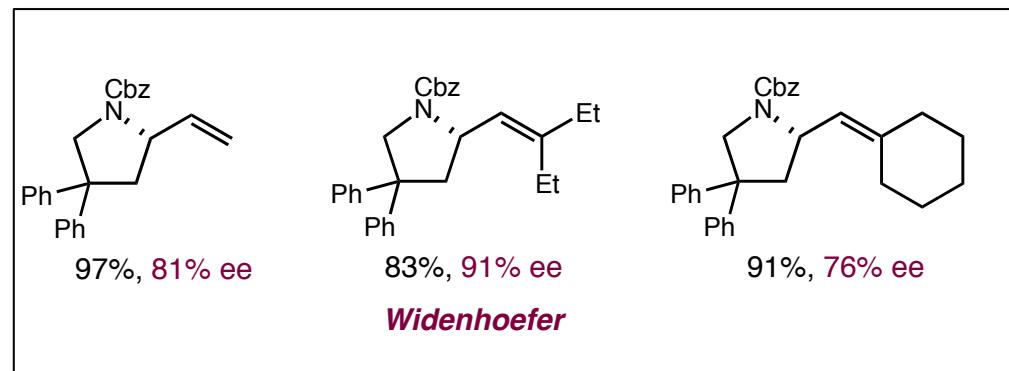
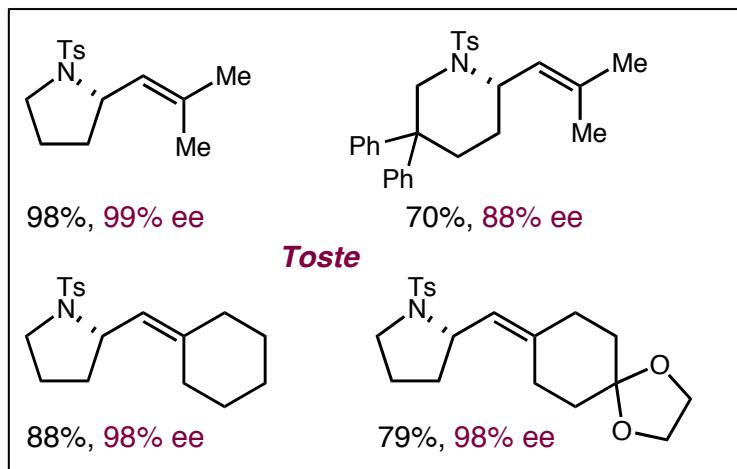


Gold(I)-Catalyzed Asymmetric Hydroamination of Aminoallenes

- The first enantioselective gold-catalyzed hydroaminations were by Toste and Widenhoefer in 2007 using dinuclear gold(I)-phosphine complexes with biaryl-based backbone



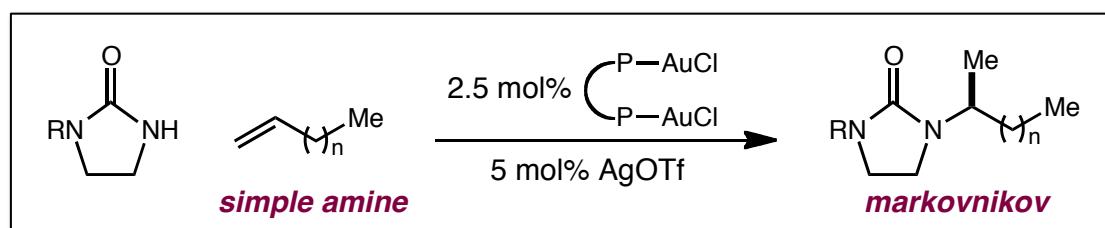
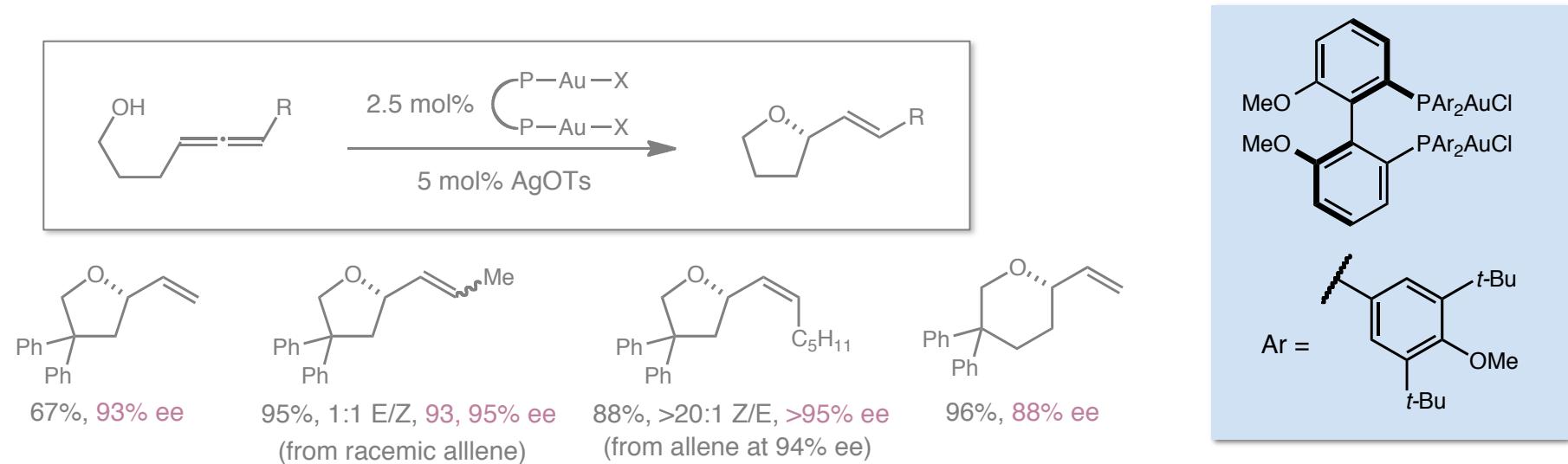
- Scope of the reaction is limited to terminal and trisubstituted allenes



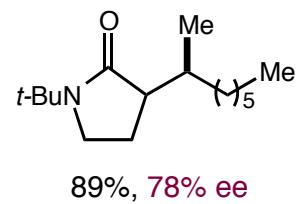
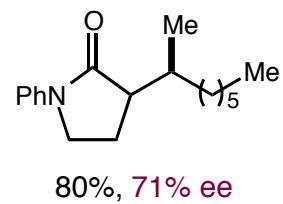
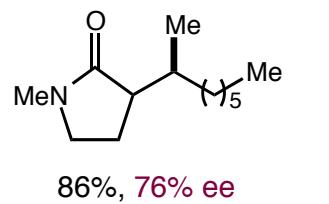
LaLonde, R. L.; Sherry, B. D.; Kang, E. J.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 2452.
Zhang, Z.; Bender, C. F.; Widenhoefer, R. A. *Org. Lett.* **2007**, *9*, 2887.

Gold(I)-Catalyzed Asymmetric Hydroamination and Hydroalkoxylation

■ Widenhoefer's general protocol can be extended to other substrate classes



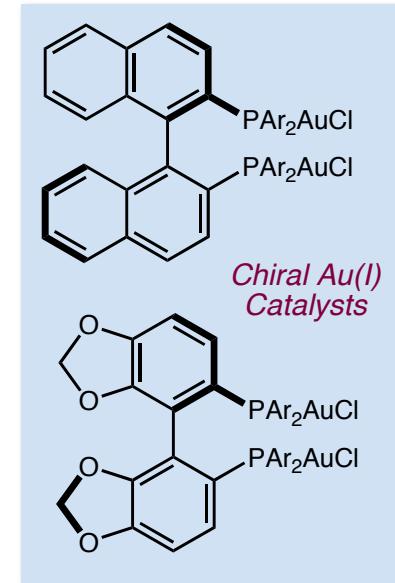
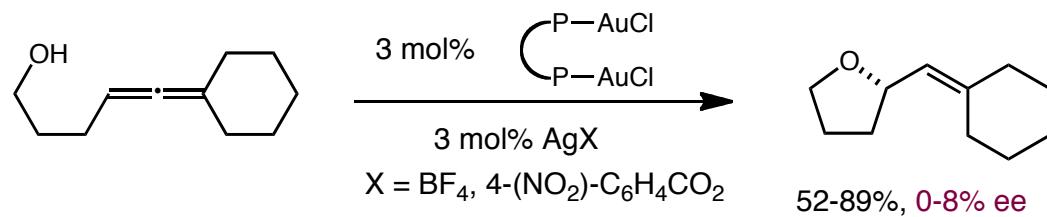
First intermolecular asymmetric hydroamination catalyzed by gold(I)
substrate scope demonstrated for the asymmetric variant is very limited



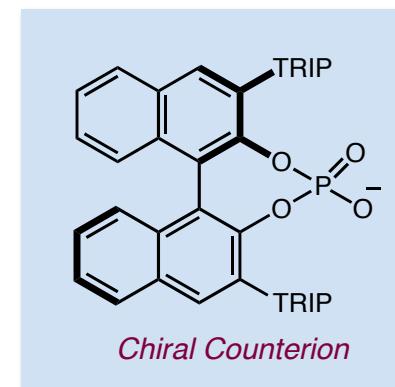
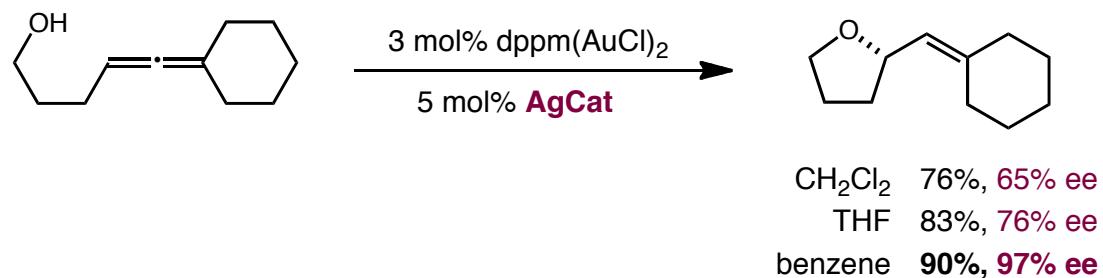
Zhang, Z.; Lee, S. D.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2009**, *131*, 5373.
Zhang, Z.; Widenhoefer, R. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 283.

Gold(I)-Catalyzed Asymmetric Hydroamination and Hydroalkoxylation

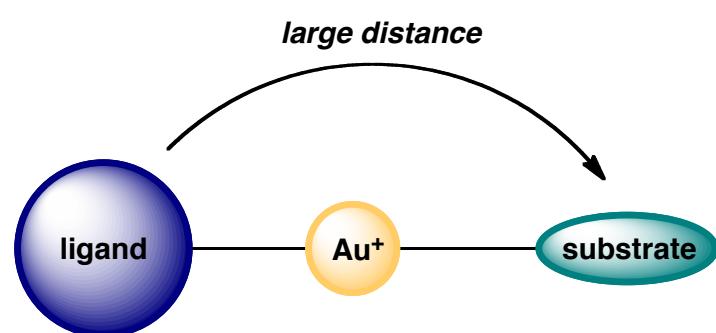
- Toste also wanted to expand the scope of the hydroamination protocol, but with poor results



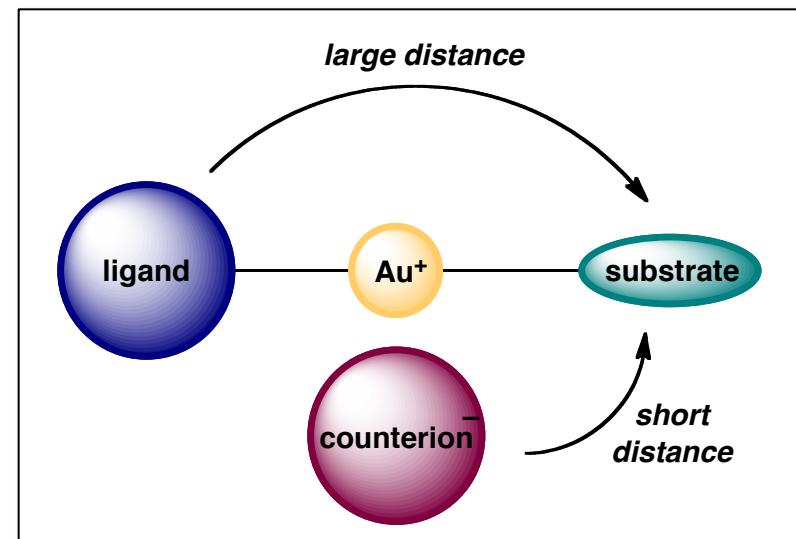
- Employing a chiral counterion gave significantly better results



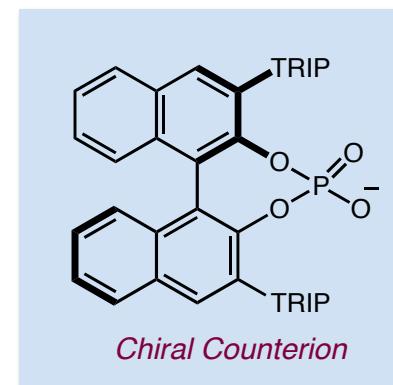
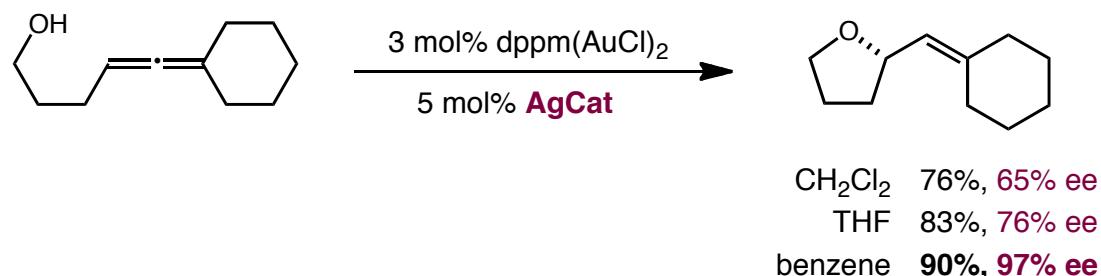
Gold(I)-Catalyzed Asymmetric Hydroamination and Hydroalkoxylation



Au(I) complexes have linear coordination geometry

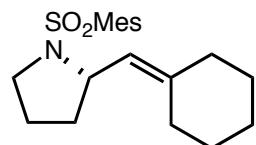
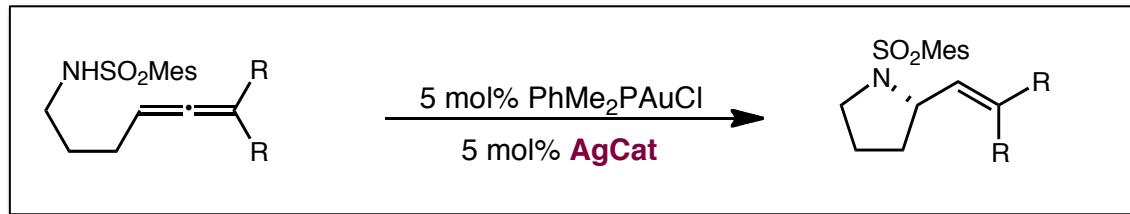


- Employing a chiral counterion gave significantly better results



Gold(I)-Catalyzed Asymmetric Hydroamination and Hydroalkoxylation

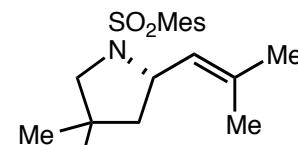
- Chiral counterion strategy allows for both hydroamination and hydroalkoxylation with high selectivity



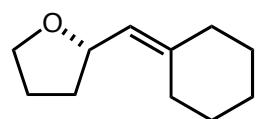
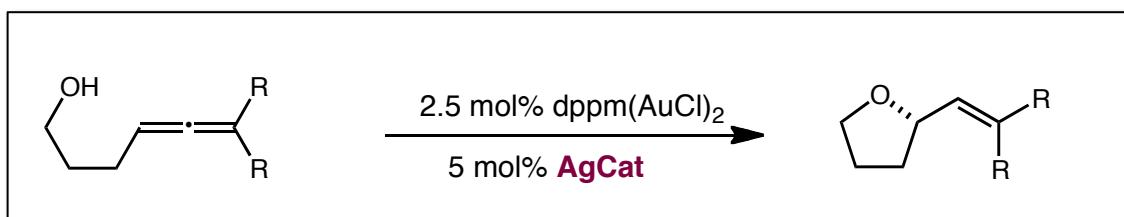
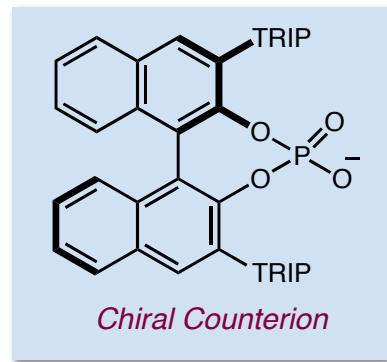
97%, 96% ee



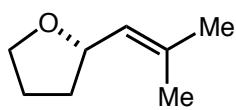
88%, 98% ee



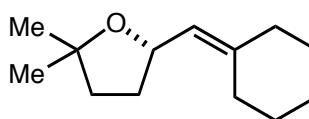
84%, 99% ee



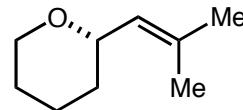
90%, 97% ee



91%, 95% ee



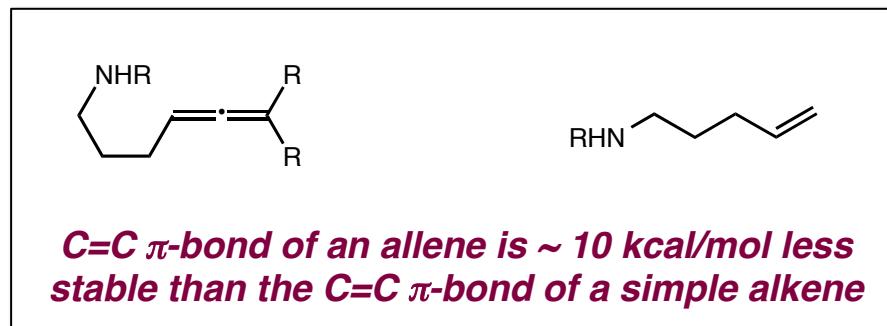
79%, 99% ee



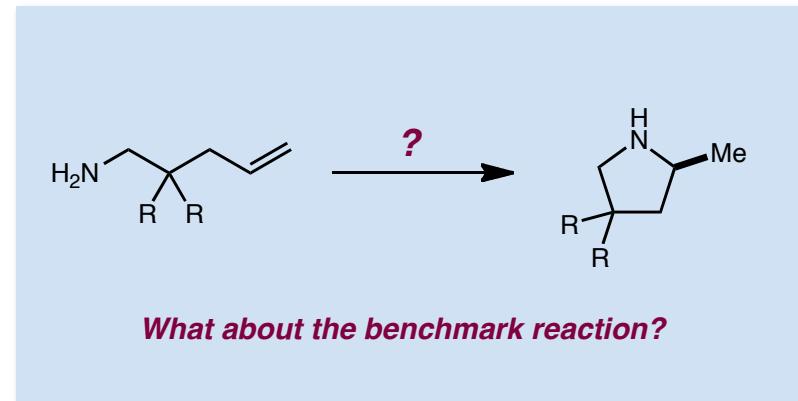
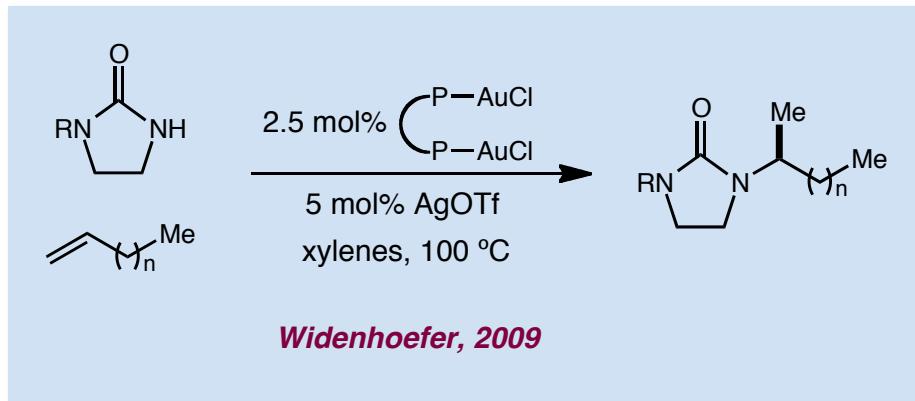
81%, 90% ee

Rhodium-Catalyzed Asymmetric Hydroamination of Aminoalkenes

- Late-transition metal catalyzed asymmetric hydroaminations generally require activated substrates (allenes, strained alkenes, dienes, styrenes) or alkynes

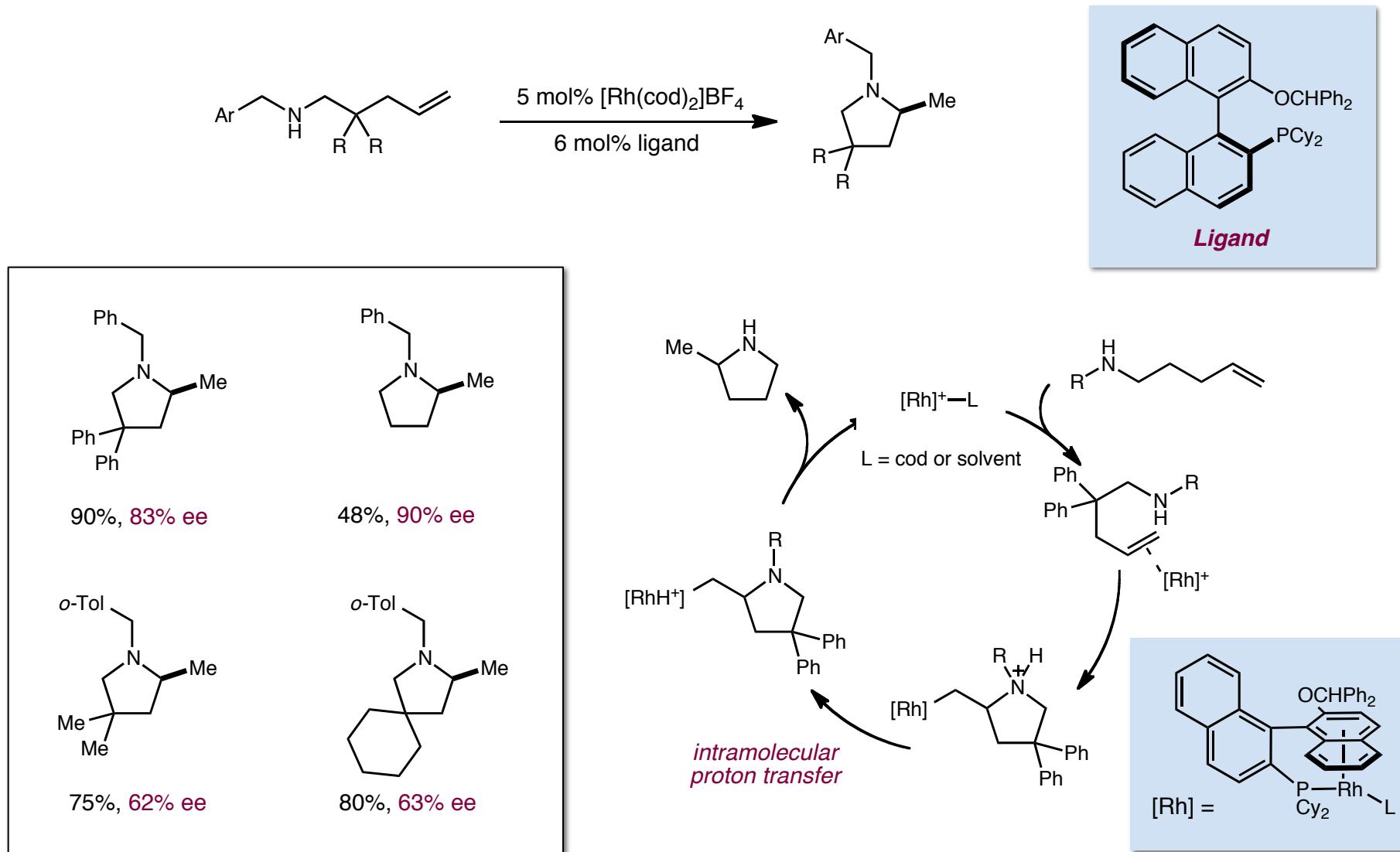


- We've only seen one example of a simple alkene participating in a late transition metal-catalyzed hydroamination



Rhodium-Catalyzed Asymmetric Hydroamination of Aminoalkenes

- In 2010, Buchwald introduced the first rhodium enantioselective hydroamination of aminoalkenes



Late Transition Metal-Catalyzed Hydroaminations: Summary

- Late transition metal-catalyzed hydroaminations (and hydroalkoxylations) are almost exclusively with activated alkenes and alkynes
- Enantioselective reactions have been developed using Ir, Pd, Au, Rh

PROS Good functional group tolerance

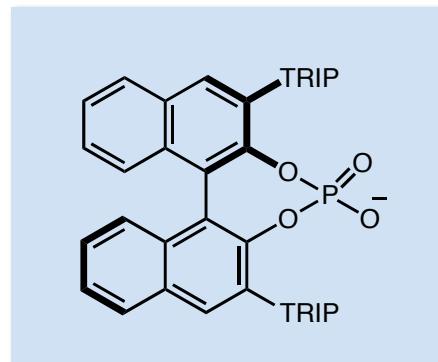
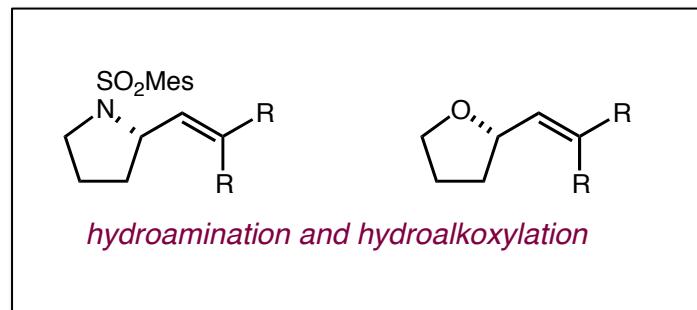
Least air and moisture sensitive

Both inter- and intramolecular examples

Higher enantioselectivities

CONS Limited examples for simple alkenes

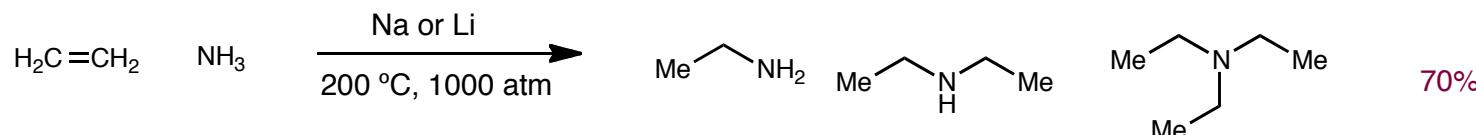
- Current Asymmetric *State of the Art* - Toste's asymmetric counterion



Base-Catalyzed Hydroaminations

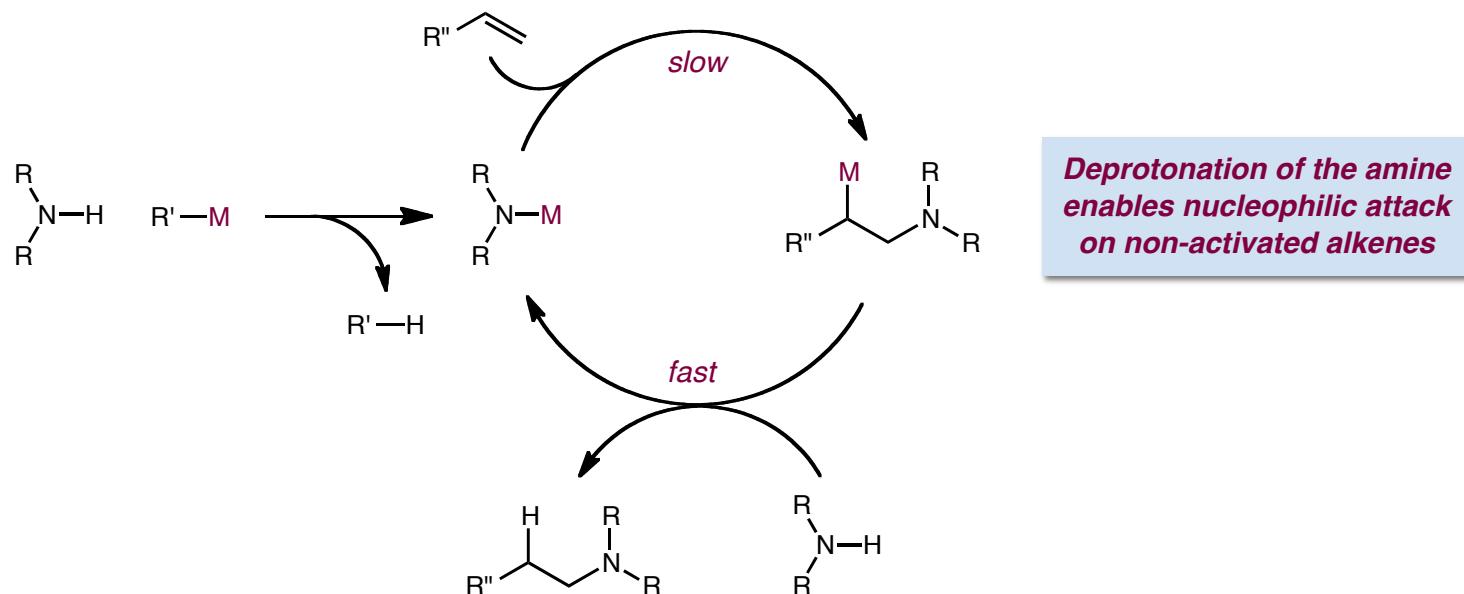
Main Group Metals: Base-Catalyzed Asymmetric Hydroamination

- Recent interest has focused on early and late transition metal catalysts but alkali metals have been known catalysts for over 50 years



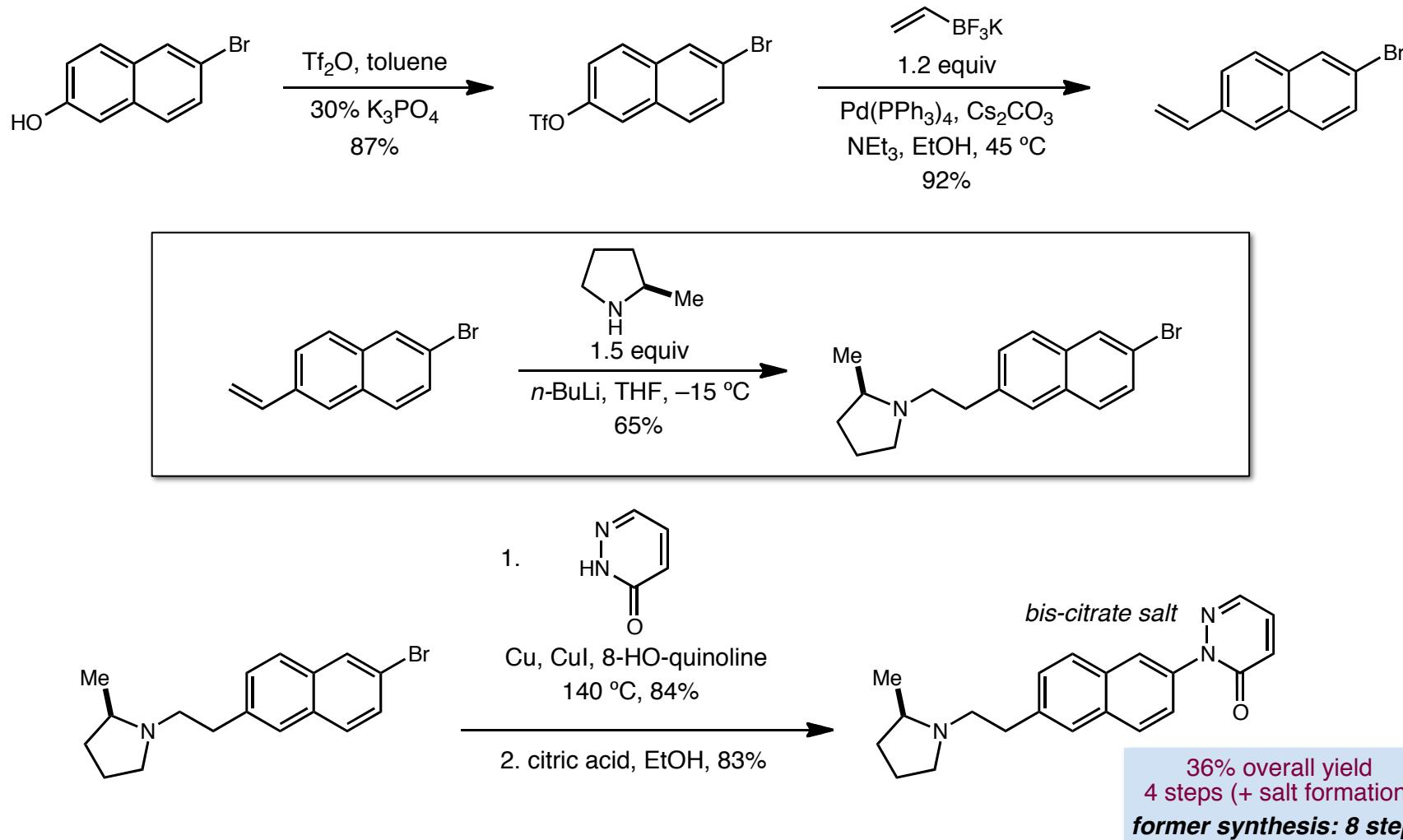
Hawk, B. W.; Little, E. L.; Scott, S. L.; Whitman, G. M. *J. Am. Chem. Soc.* **1954**, *76*, 1899.

- Reaction proceeds through the highly nucleophilic alkali metal amide



Main Group Metals: Base-Catalyzed Asymmetric Hydroamination

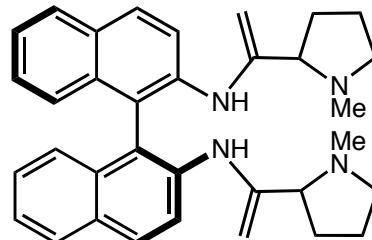
- A base-catalyzed hydroamination has been used by Abbott Laboratories for a scalable synthesis of a histamine-3-inhibitor



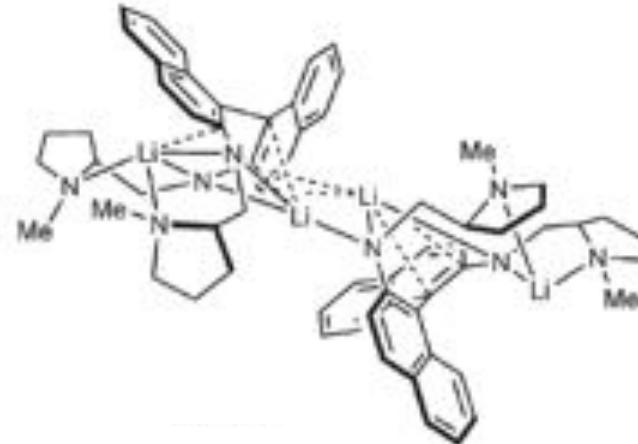
Main Group Metals: Base-Catalyzed Asymmetric Hydroamination

- Despite being known for over 50 years, there is very limited reports of asymmetric variants

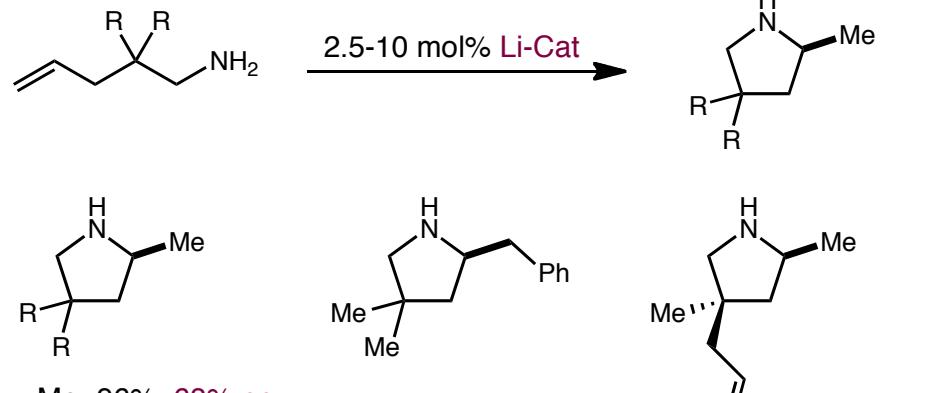
Hultzsch, 2006:



2 equiv *n*-BuLi

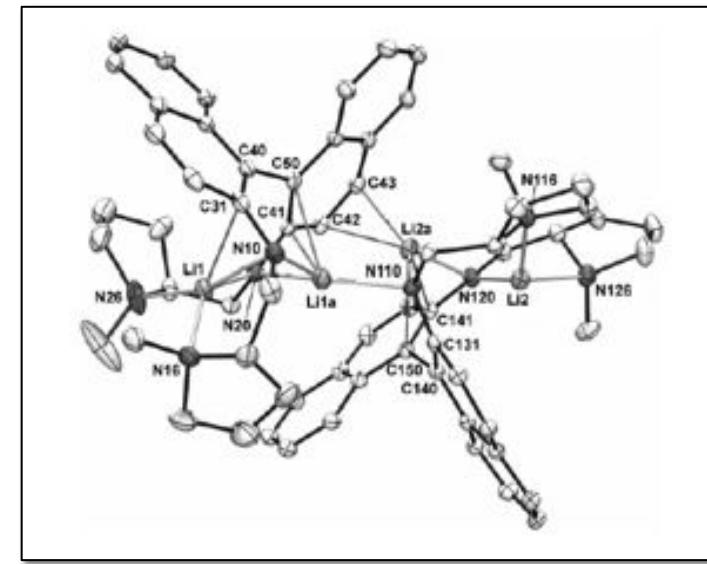


- Cyclization proceeds with high yields and moderate selectivity



R = Me 96%, 68% ee
Ph 97%, 31% ee
-(CH₂)₄- 98%, 74% ee

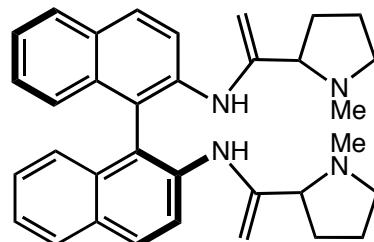
98%, 17% ee 98%, 1.2:1 dr, 64, 72% ee



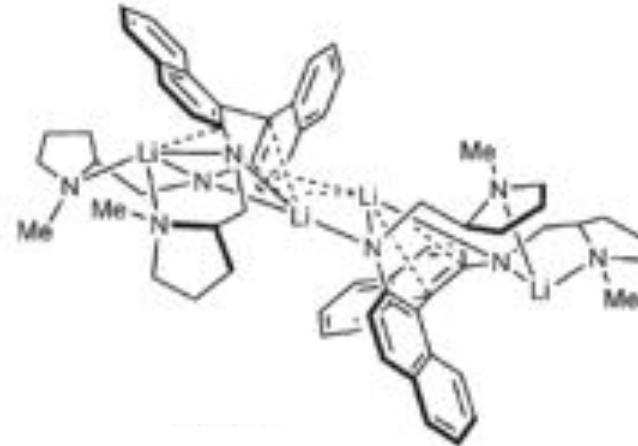
Main Group Metals: Base-Catalyzed Asymmetric Hydroamination

- Despite being known for over 50 years, there is very limited reports of asymmetric variants

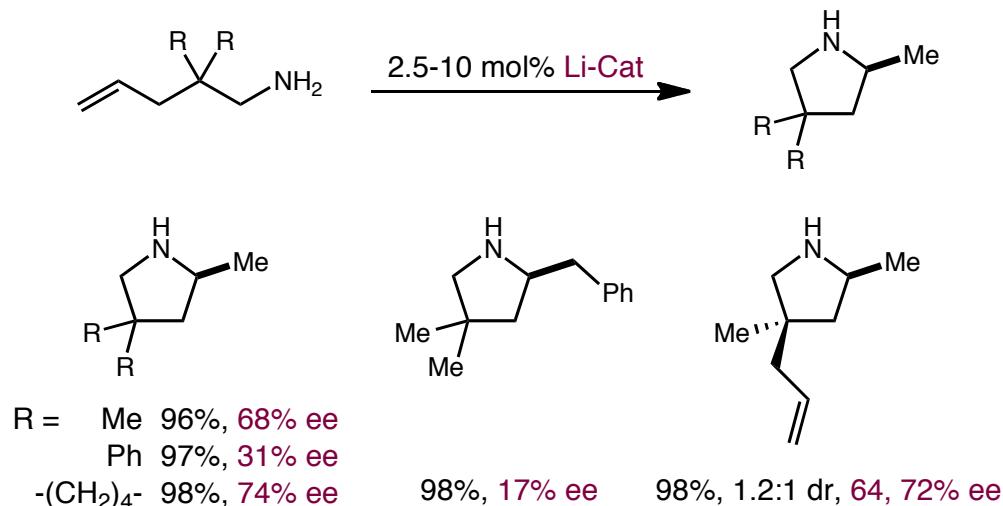
Hultzsch, 2006:



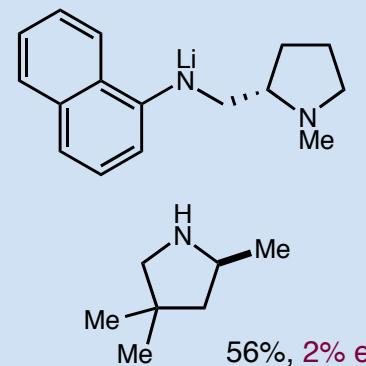
2 equiv *n*-BuLi



- Cyclization proceeds with high yields and moderate selectivity



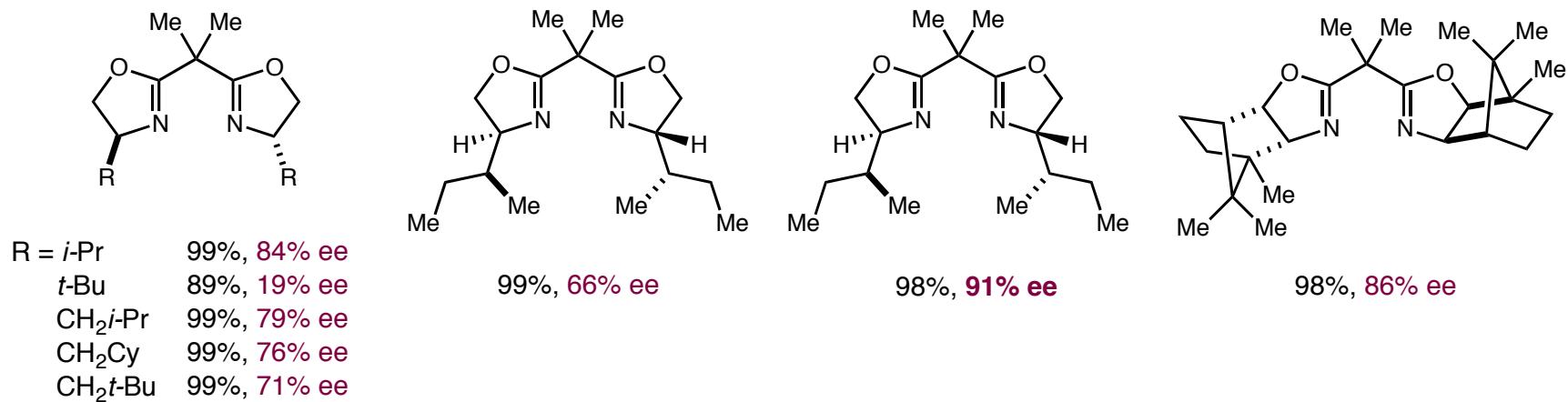
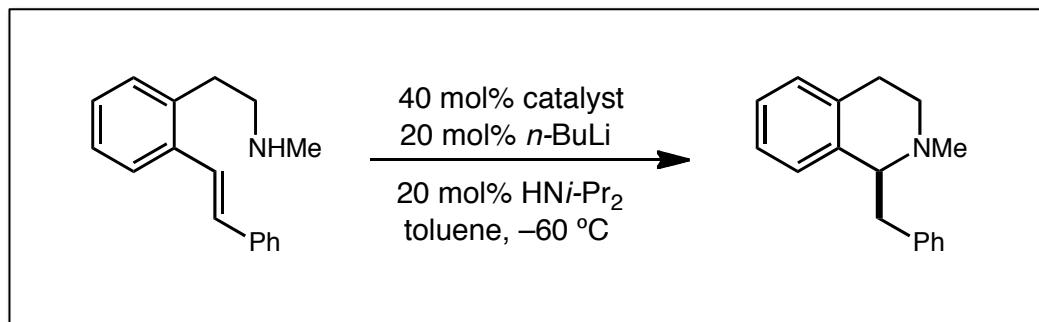
*close proximity of the lithium atoms
is essential for catalyst performance*



Main Group Metals: Base-Catalyzed Asymmetric Hydroamination

- Asymmetric intramolecular hydroaminations can be carried out with catalytic *n*-BuLi and bisoxazolines

Tomioka, 2007:

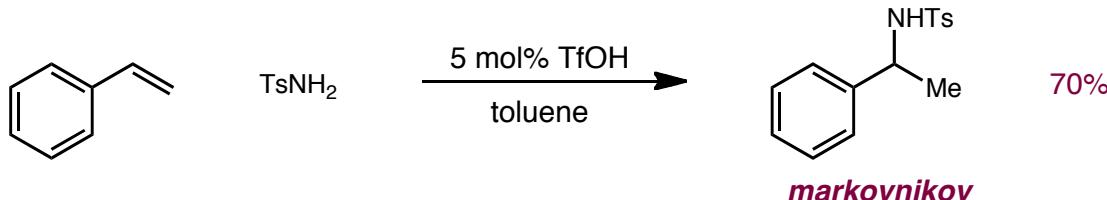


diisopropylamine acts as an external protonating agent

Acid-Catalyzed Hydroaminations

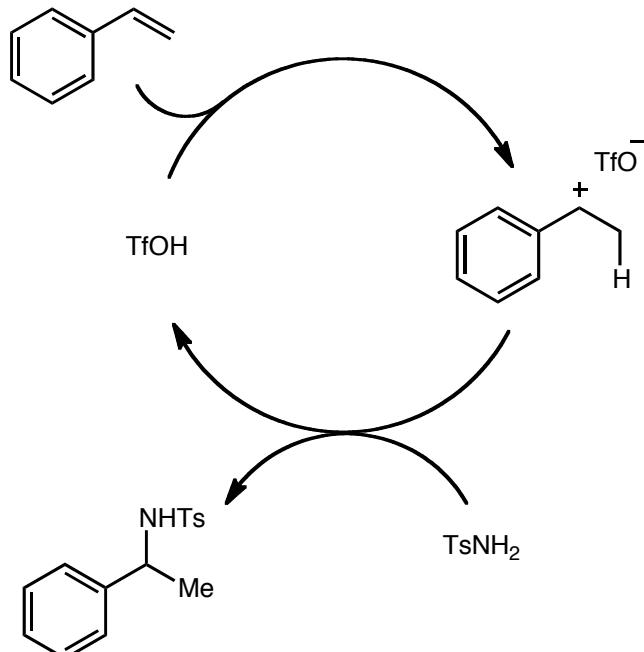
Non-Metal Catalysts: Acid-Catalyzed Asymmetric Hydroamination

- Brønsted acids have not been used extensively as catalysts in hydroamination reactions



Li, Z.; Zhang, J.; Brouwer, C.; Yang, C.-G.; Reich, N. W.; He, C. *Org. Lett.* **2006**, *8*, 4175.

- Reaction proceeds through the generation of a carbenium ion followed by attack of the amine



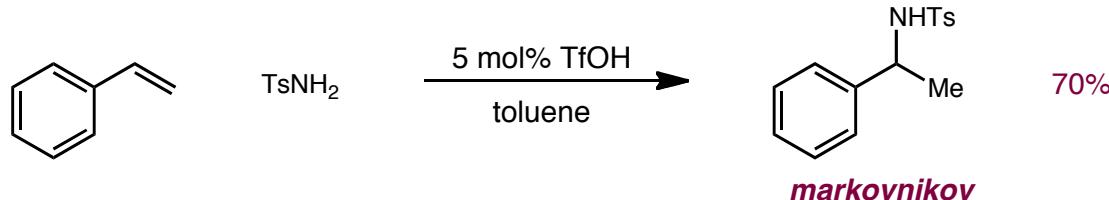
Acid-Catalysis Challenge:

amine is more basic than the π -system of the alkene/alkyne

formation of ammonium salts destroys nucleophilicity and avoids activation of the π -system

Non-Metal Catalysts: Acid-Catalyzed Asymmetric Hydroamination

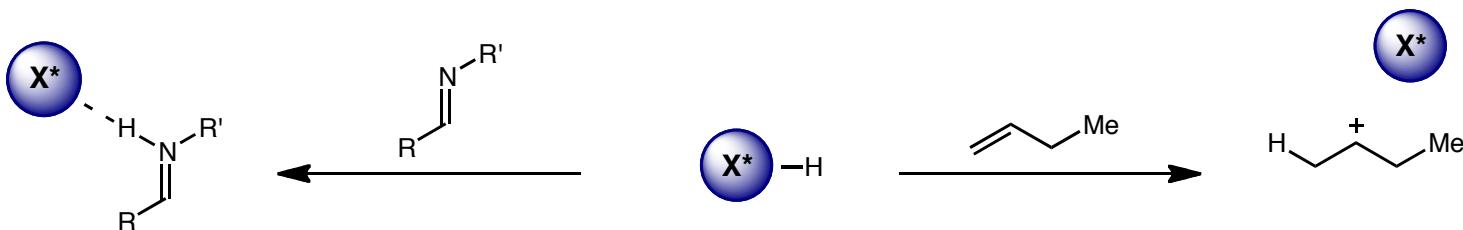
- Brønsted acids have not been used extensively as catalysts in hydroamination reactions



Li, Z.; Zhang, J.; Brouwer, C.; Yang, C.-G.; Reich, N. W.; He, C. *Org. Lett.* **2006**, *8*, 4175.

- There is an additional challenge that comes with enantioselective acid-catalyzed hydroaminations:

Proximity and Organization of Chiral Information



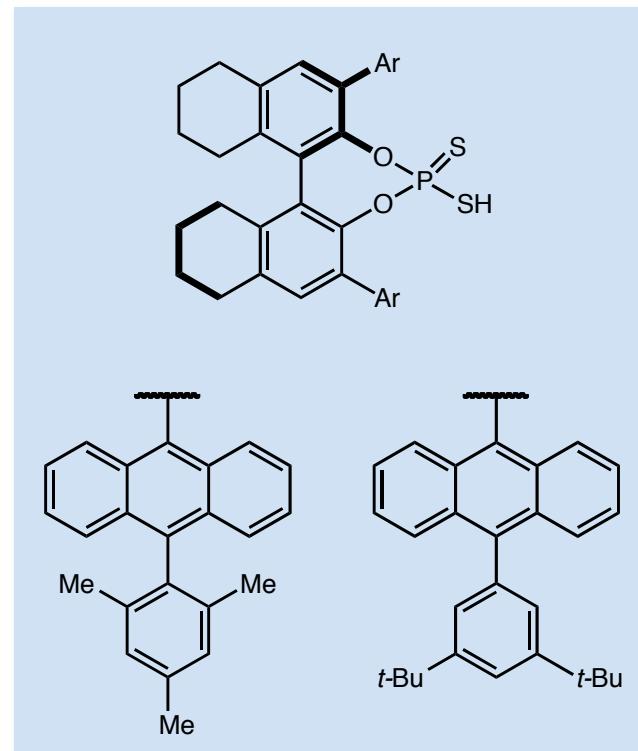
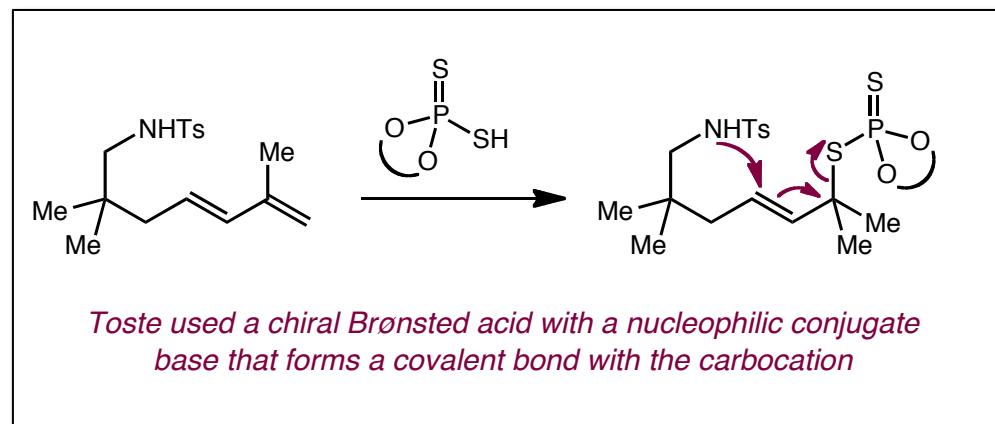
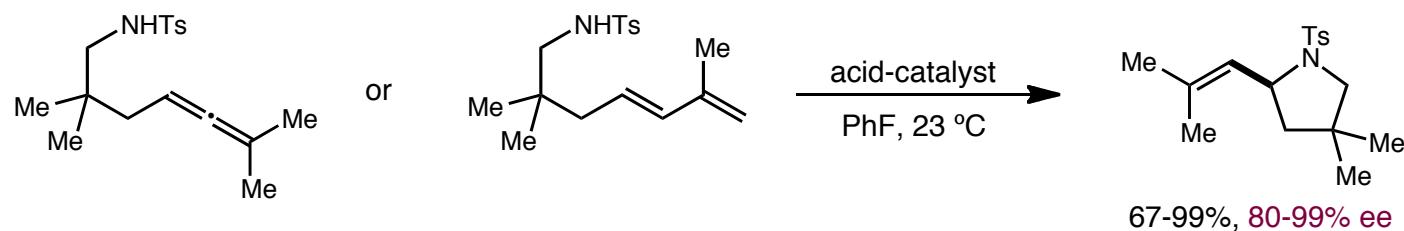
hydrogen bonding anchors chiral information close to the electrophile and contributes to molecular organization

chiral bronsted acid

Electrostatic forces can hold conjugate base in proximity to the carbocation but will lack rigidity and poor enantiotopic discrimination

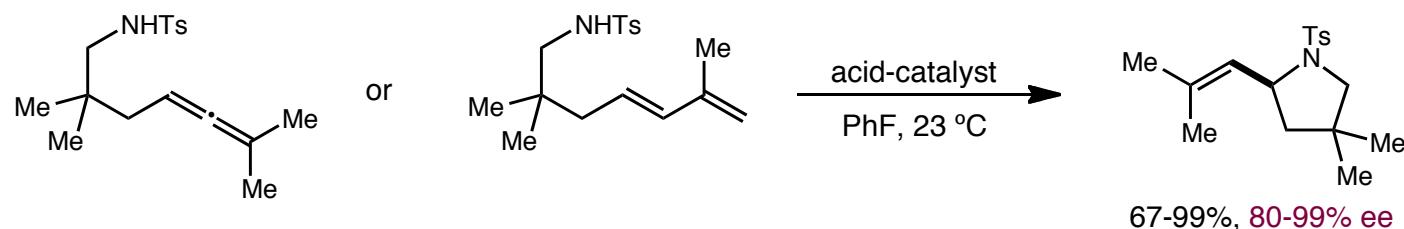
Non-Metal Catalysts: Acid-Catalyzed Asymmetric Hydroamination

- Recently (February 2011) Toste reported the first asymmetric acid-catalyzed hydroamination

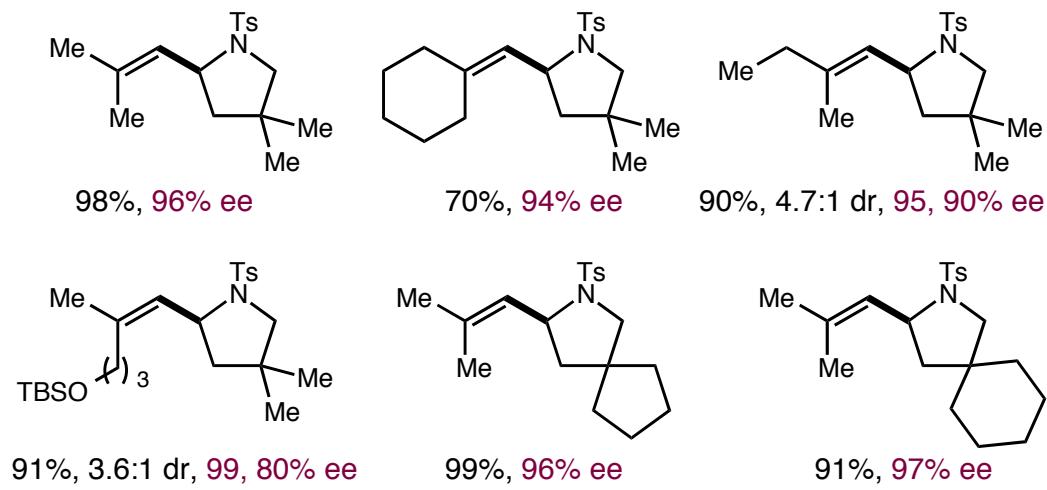


Non-Metal Catalysts: Acid-Catalyzed Asymmetric Hydroamination

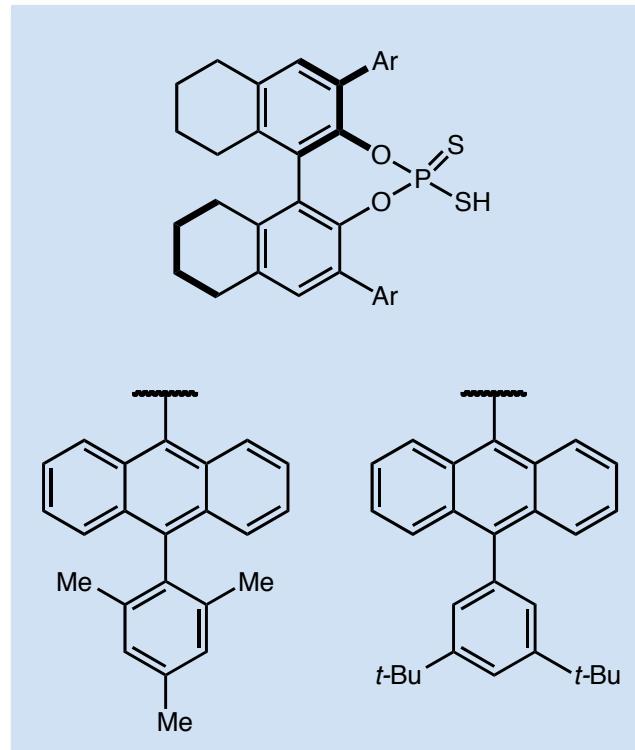
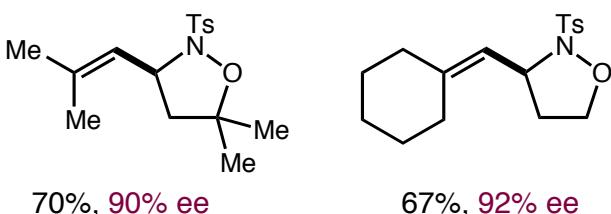
■ Recently (February 2011) Toste reported the first asymmetric acid-catalyzed hydroamination



via dienes:



via allenes



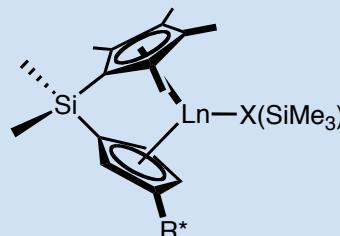
Shapiro, N. D.; Rauniyar, V.; Hamilton, G. L.; Wu, J.; Toste, F. D. *Nature* 2011, 470, 245.

Catalytic Asymmetric Hydroamination (and Alkoxylation)

- Five main catalytic pathways for asymmetric hydroamination reactions

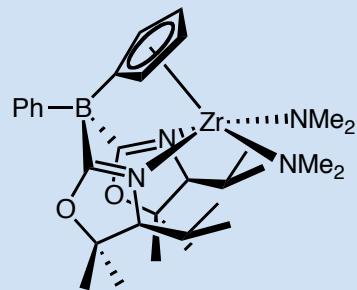
Rare Earth Metal Catalysis

intramolecular aminoalkenes
intermolecular simple alkenes



Group 4 Metal Catalysis

intramolecular aminoalkenes

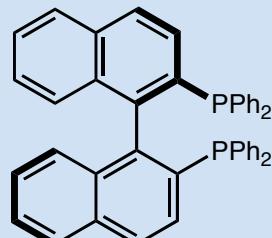


Late Transition Metal Catalysis

intermolecular strained alkenes,
styrenes, conjugated dienes

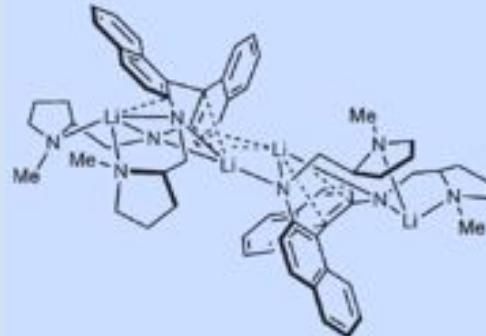
intramolecular aminoalkene,
aminoallene, aminoalkyne

Ir Pd
Au Rh



Base Catalysis

intramolecular aminoalkenes



Acid Catalysis

intramolecular aminodienes/allenes

