Catalytic Asymmetric Hydroaminations

(And Hydroalkoxylations, But Mostly Hydroaminations)

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MacMillan Group Meeting

February 16, 2011

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.

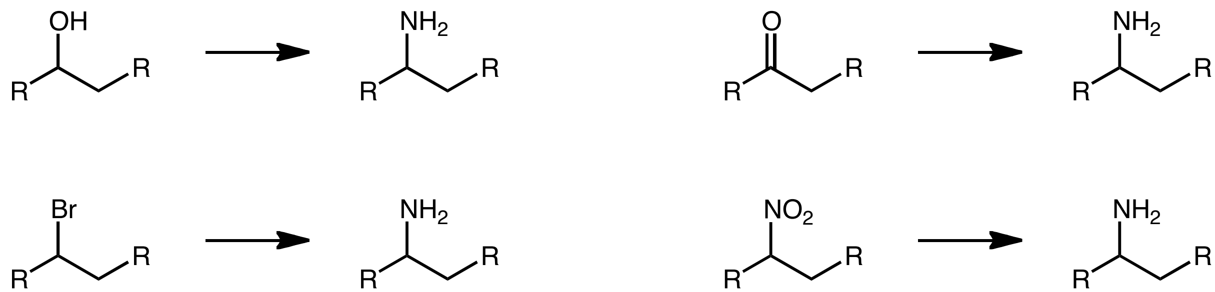
Aillaud, I.; Collin, J.; Hannedouche, J.; Schulz, E. *Dalton Trans.* **2007**, 5105.

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

Hydroamination Reactions

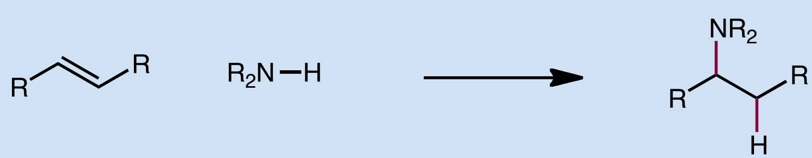
- Amines are a valuable and commercially important class of compounds used for bulk chemicals specialty chemicals and pharmaceuticals

synthesis of amines:



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

hydroamination reaction:

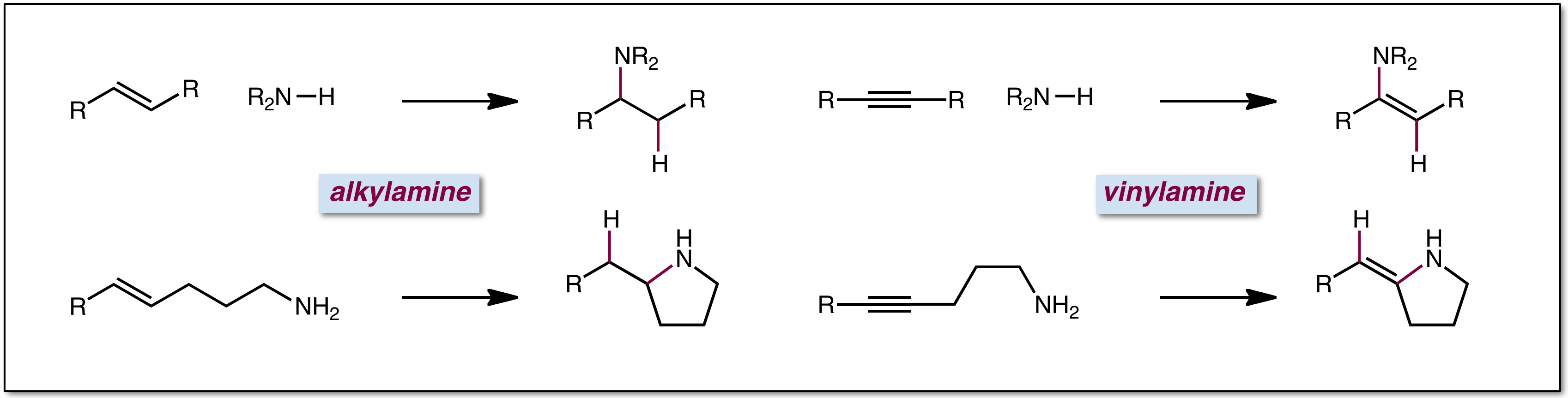


direct addition of an amine across a carbon-carbon multiple bond

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

Hydroamination Reactions

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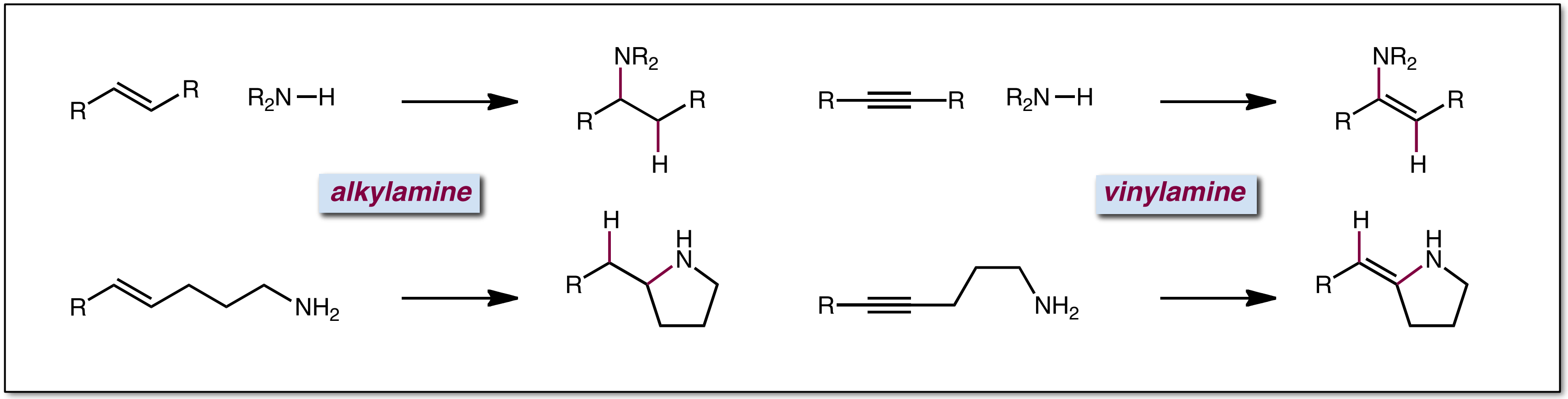

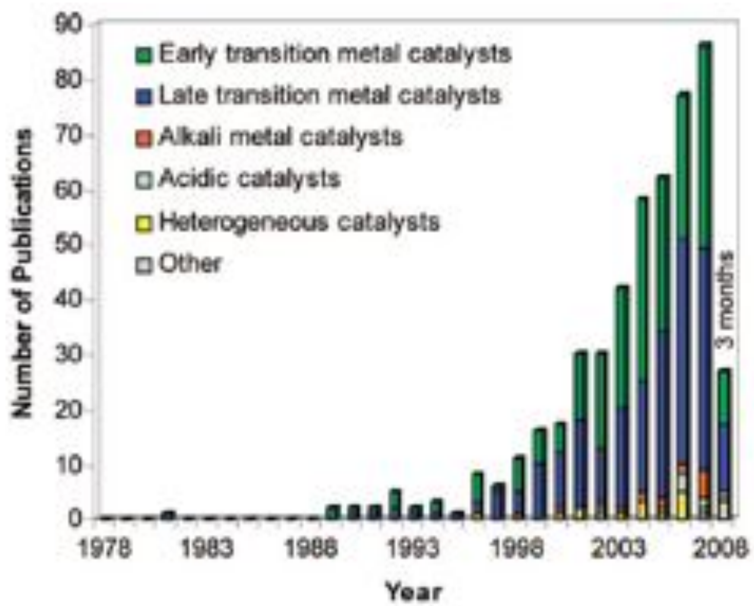

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Hydroamination Reactions

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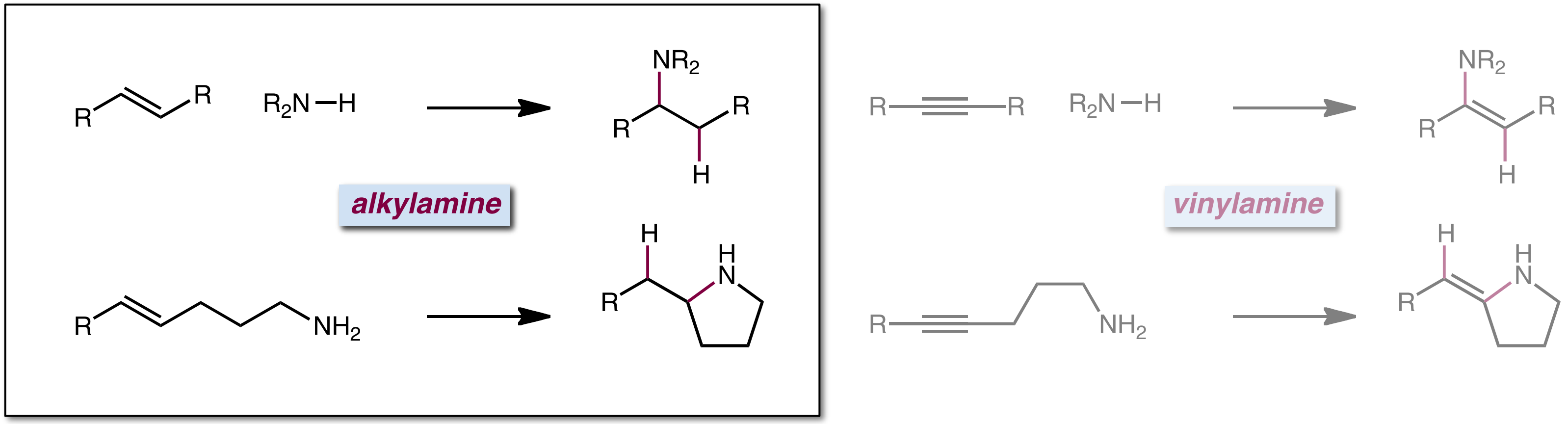
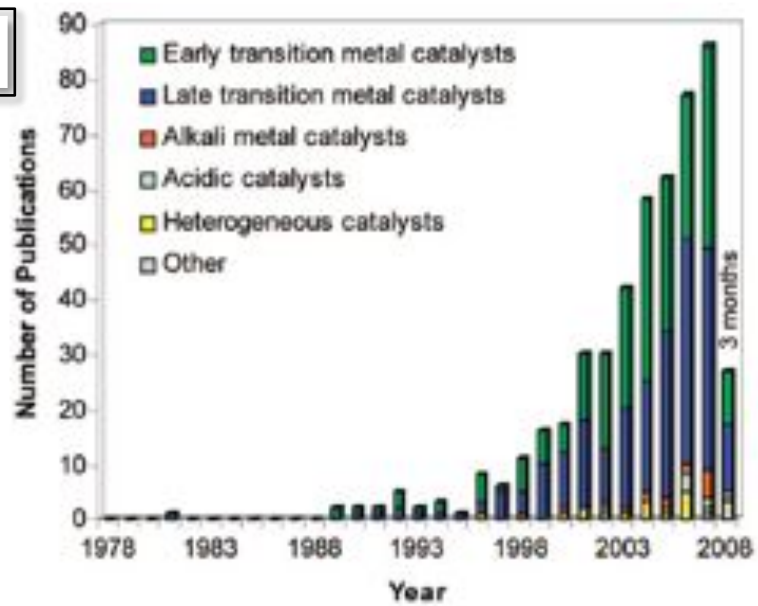


this talk focuses on generating enantioenriched amines



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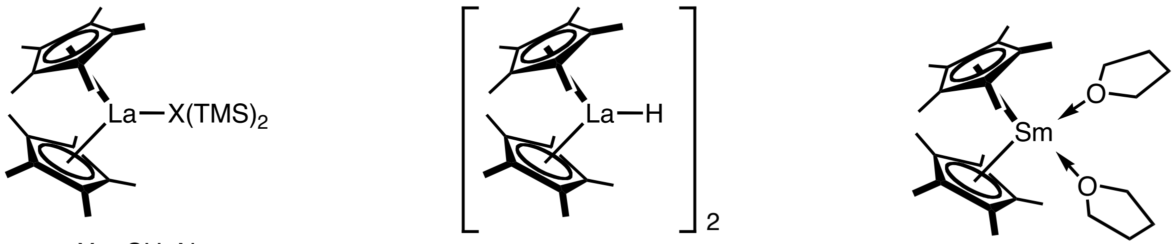
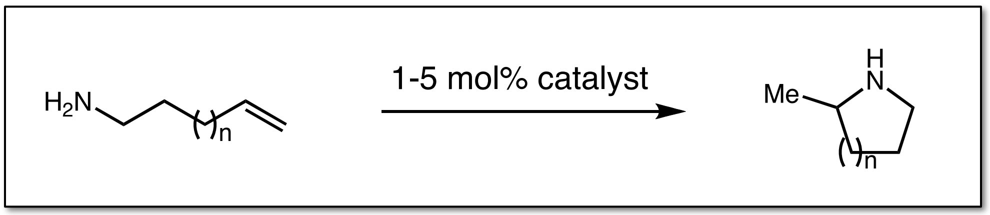
Rare Earth Metal Catalyzed Hydroaminations

Rare Earth Metal-Catalyzed Intramolecular Hydroaminations: Seminal Work

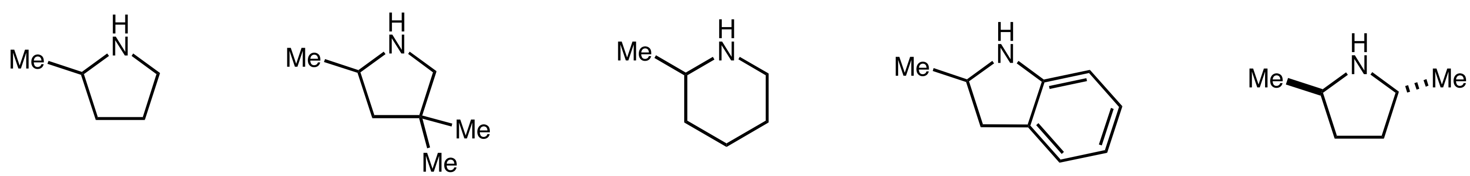
- Seminal work of lanthanide-catalyzed hydroamination reaction was reported in 1989 by Marks using metallocene-based catalysts



X = CH, N



generally produces the exocyclic hydroamination product

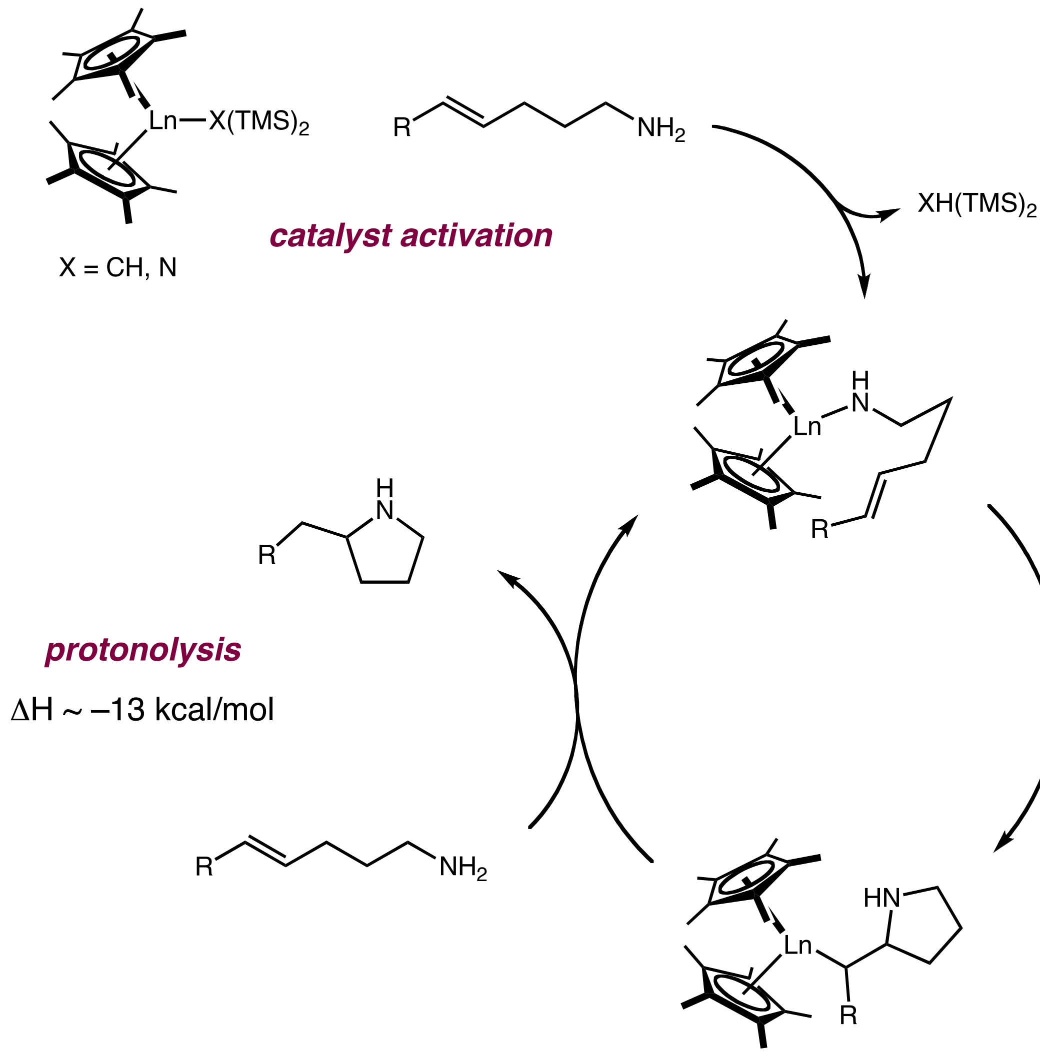


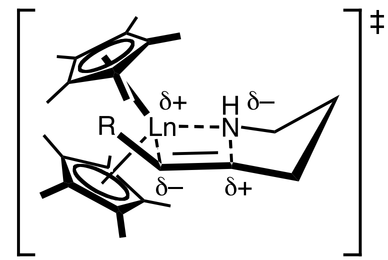
TOF: (h^{-1})	13 (25 °C) 140 (60 °C)	125 (25 °C)	5 (60 °C)	13 (80 °C)	84 (25 °C)

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





olefin insertion
rate-limiting step

ΔH ~ 0 kcal/mol

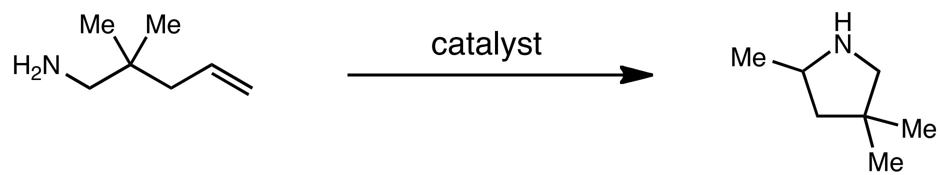
For aminoalkynes, aminoallenes, conjugated aminodienes

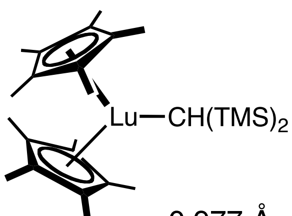
olefin insertion: ΔH ~ –19 to –35 kcal/mol

protonolysis: ΔH ~ 0 to +4 kcal/mol

Rare Earth Metal Catalysts for Intramolecular Hydroamination

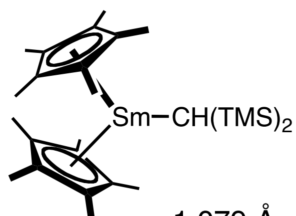
- Catalytic activity in rare earth metal-catalyzed hydroamination of aminoalkenes generally increase with increased accessibility to the metal center





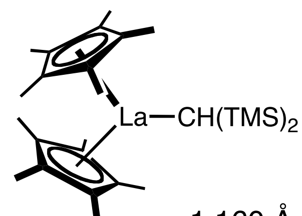
0.977 Å

<1 h^{-1} (80 °C)



1.079 Å

48 h^{-1} (60 °C)

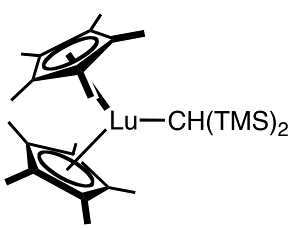


1.160 Å

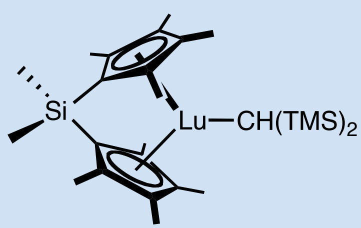
95 h^{-1} (25 °C)

increasing ionic radii / decreased steric encumbrance

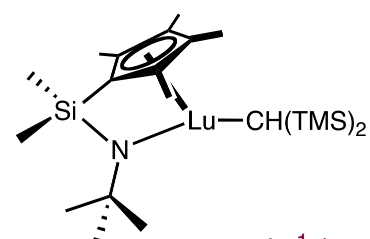
increasing reactivity



<1 h^{-1} (80 °C)



75 h^{-1} (80 °C)



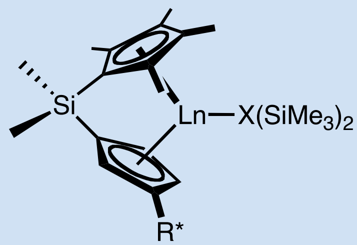
90 h^{-1} (25 °C)

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

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

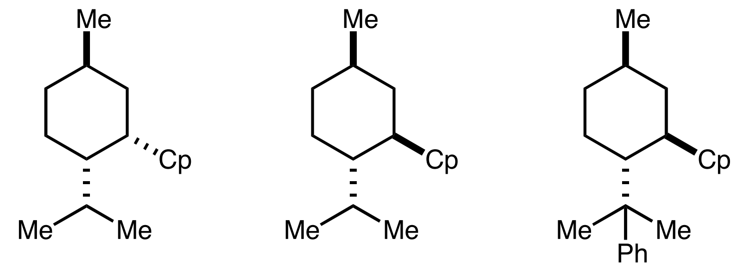
Rare Earth Metal-Catalyzed Asymmetric Hydroamination: Seminal Work

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

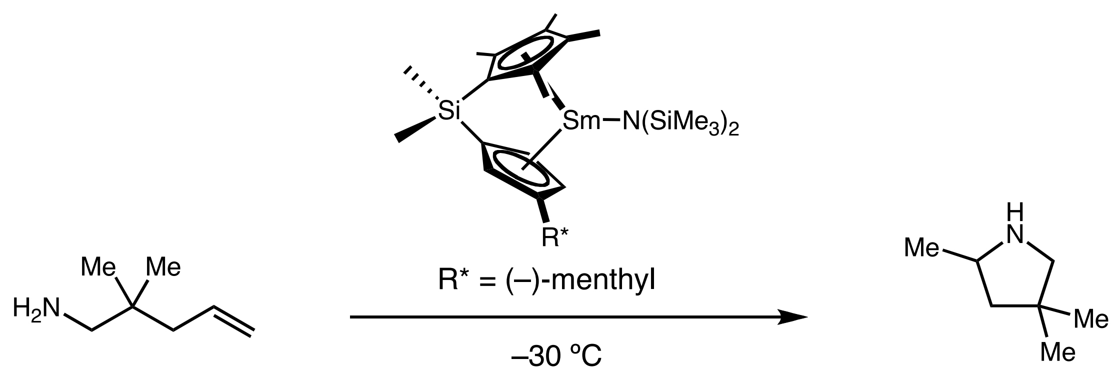


Ln = La, Nd, Sm, Y, Lu
X = CH, N

R* =



(+)-neomenthyl (–)-menthyl (–)-phenylmenthyl



74% ee (*S*)

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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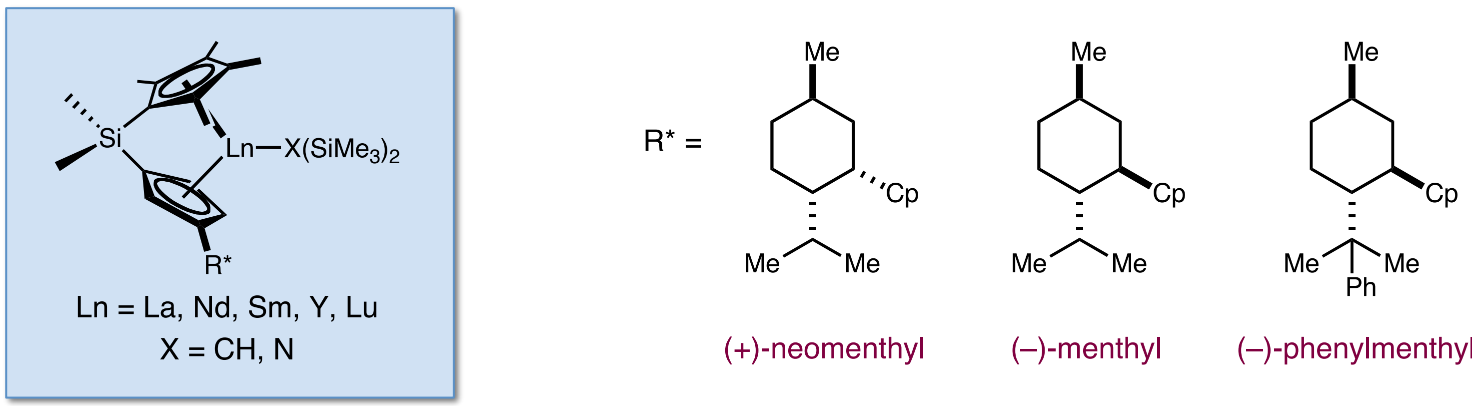

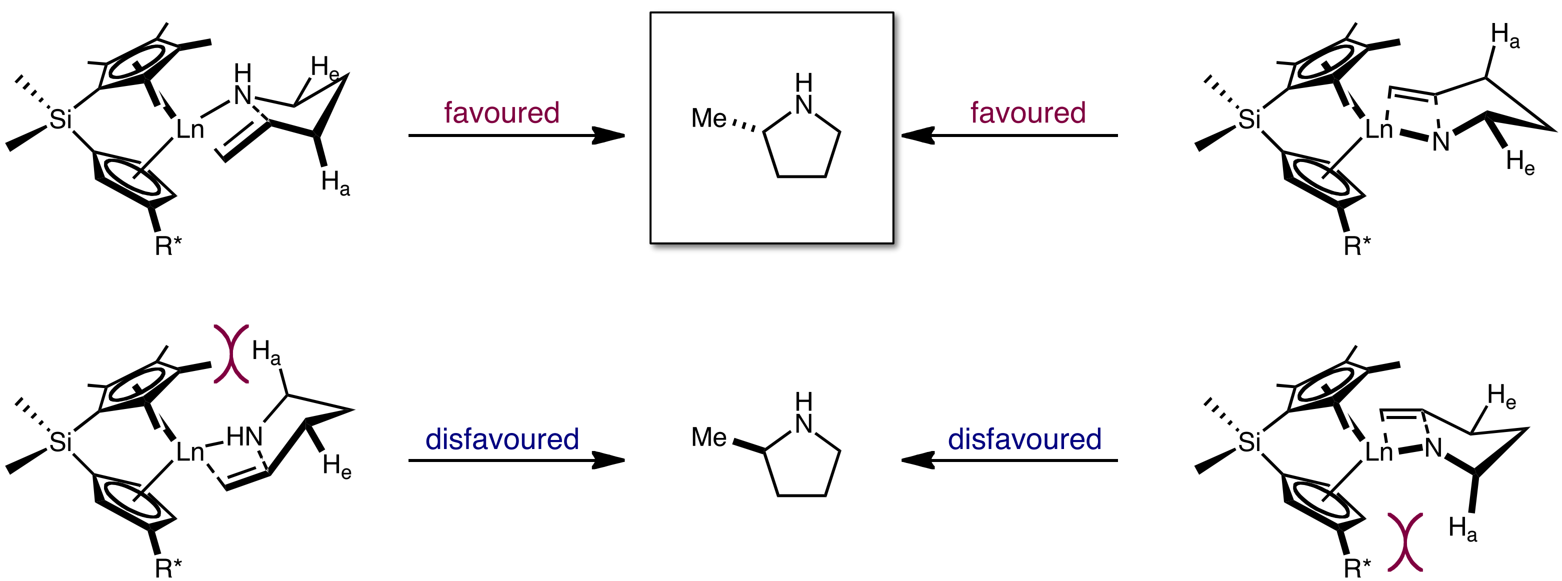

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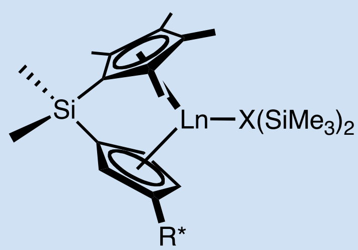

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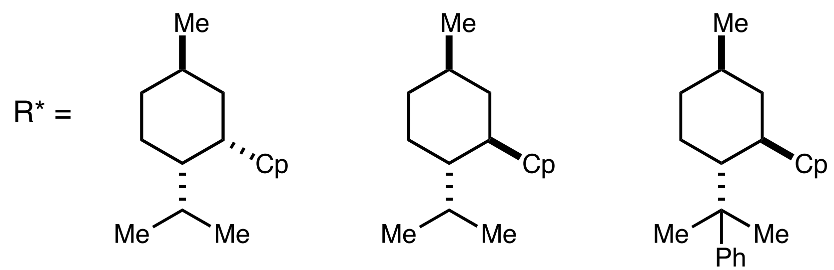
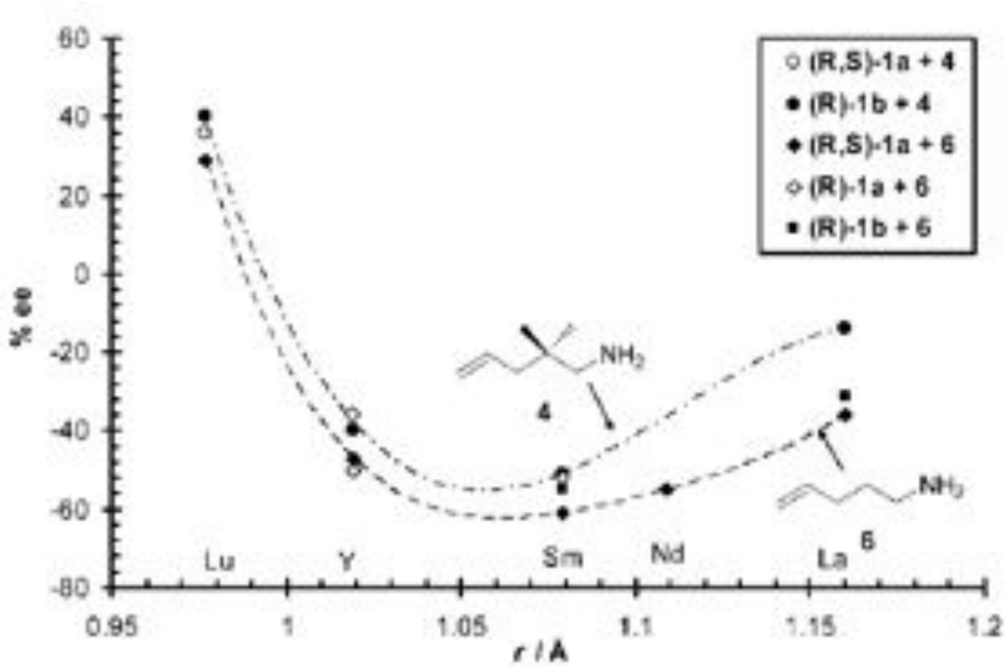
X = CH, N



(+)-neomenthyl (–)-menthyl (–)-phenylmenthyl



ionic radii of rare earth metal effects the enantioselectivity

maximum enantioseletivity observed with samarocene

Hultzsch, K.C. *Adv. Synth. Catal*, **2005**, *347,* 367.
Gagné, M. R.; Brard, L.; Conticello, V. P.; Giardello, M. A.; Marks, T. J.; Stern, C. L. *Organometallics*, **1992**, *11*, 2003.

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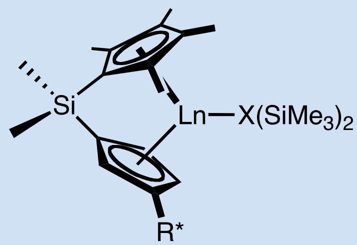

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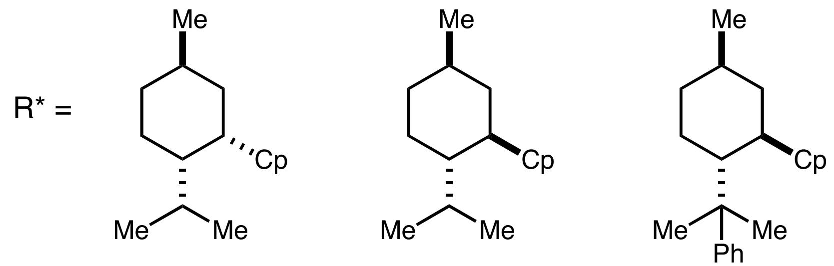

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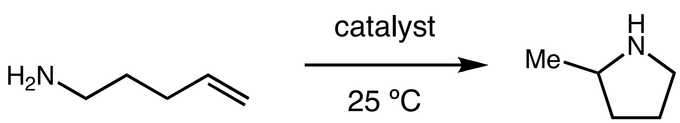
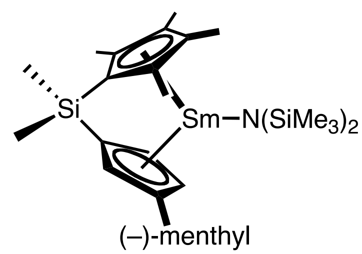
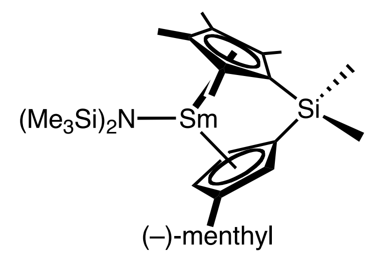
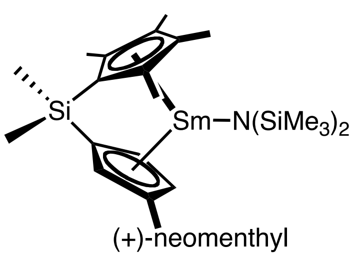




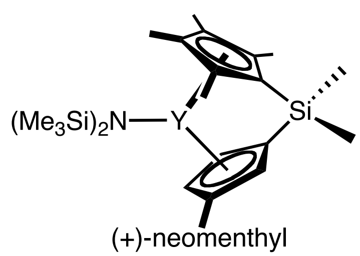
62% ee (S)



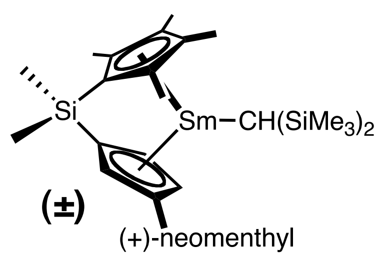
60% ee (S)



55% ee (R)



50% ee (R)



61% ee (R)

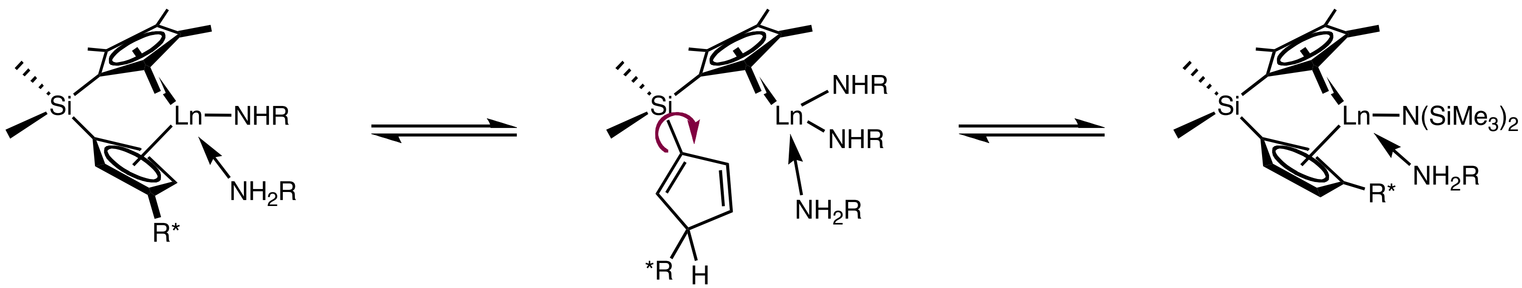
you can obtain 61% ee from a racemic precatalyst

ee of product is independent of ee of precatalyst

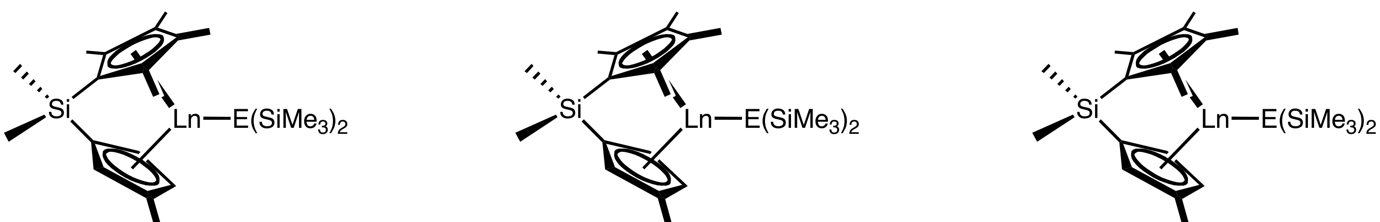
Hong, S.; Marks, T. J.; *Acc. Chem. Res.* **2004**, *37*, 673.
Gagné, M. R.; Brard, L.; Conticello, V. P.; Giardello, M. A.; Marks, T. J.; Stern, C. L. *Organometallics*, **1992**, *11*, 2003.

Epimerization of Chiral Lanthanocene Complexes

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



But why does racemic catalyst give enantioenriched product?



(+)-neomenthyl	(–)-menthyl	(–)-phenylmenthyl
80:20 (R):(S)	**>95:5 (S):(R)**	**90:10 (S):(R)**

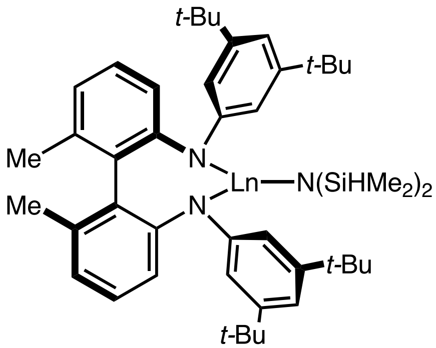
equilbrium ratio are independent of the epimer ratio of the precatalyst

Hong, S.; Marks, T. J. *Acc. Chem. Res.* **2004**, *37*, 673.

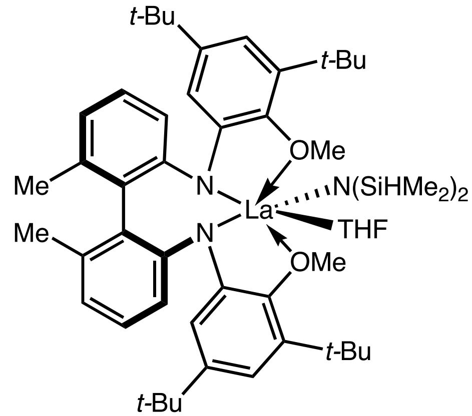
Chiral Rare Earth Metal Catalysts Based on Non-Cyclopentadienyl Ligands

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

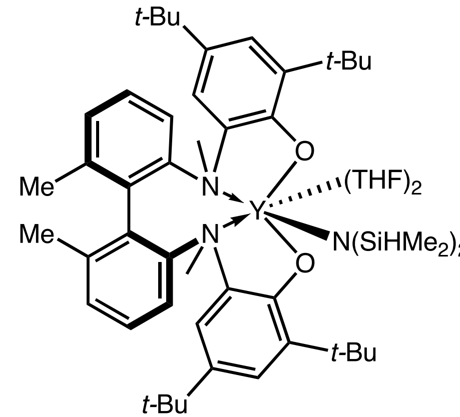
Chiral Bisarylamido and Aminophenolate Catalysts



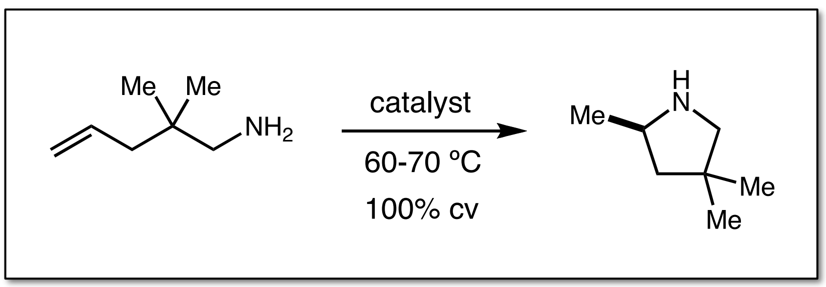
Y	336 h, 50% ee
Sm	168 h, 33% ee
La	168 h, 18% ee



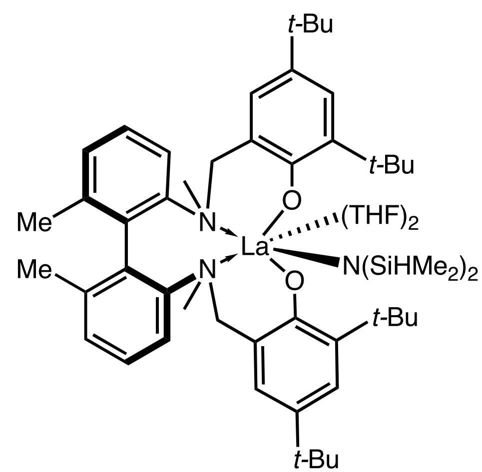
192 h, 21% ee



24 h, 11% ee



Complexes were shown to be configurationally stable under hydroamination conditions

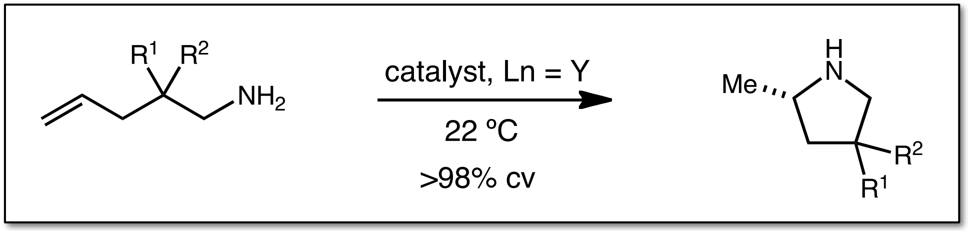


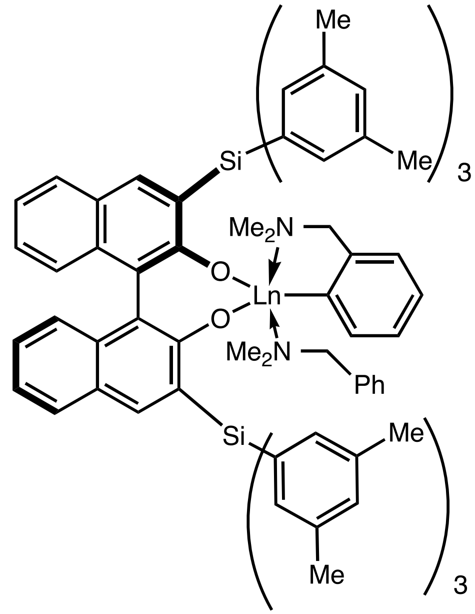
40 h, 61% ee

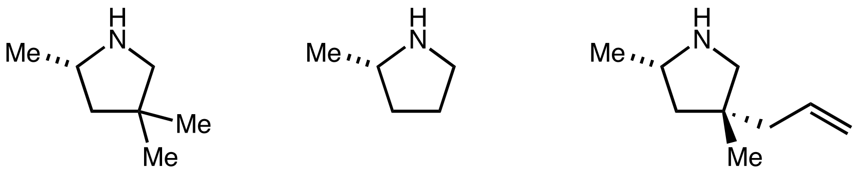
O'Shaughnessy, P. N.; Scott, P. *Tetrahedron: Asymmetry* **2003**, *14*, 1979

Chiral Rare Earth Metal Catalysts Based on Non-Cyclopentadienyl Ligands

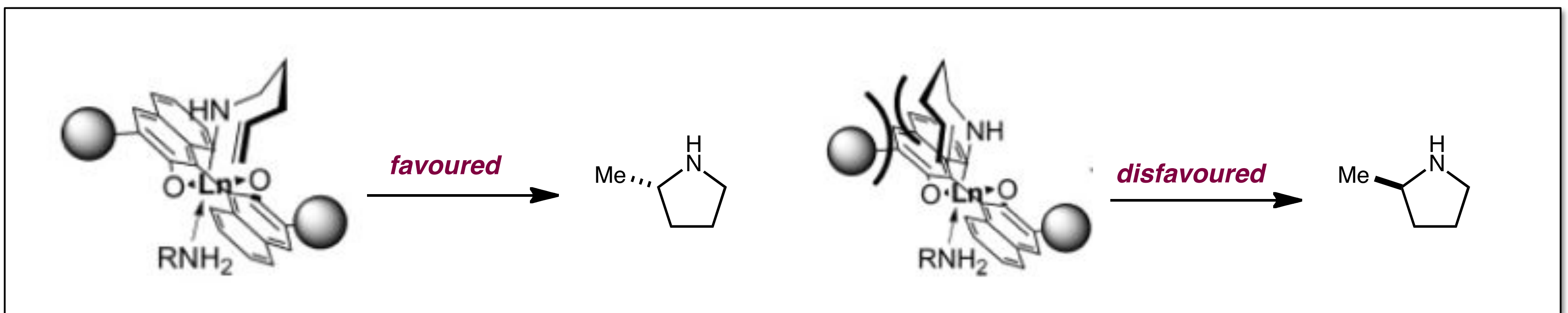
- Hultzsch's 3,3'-bis(trisarylsilyl)binaphtholate catalyst can allow for higher enantioselectivity







2 h, 53% ee | 20 h, **83% ee** | 1.2 h, 65% ee, 1.4:1 dr



Gribkov, D. V.; Hultzsch, K. C.; Hampel, F. *J. Am. Chem. Soc.* **2006**, *128*, 3748.
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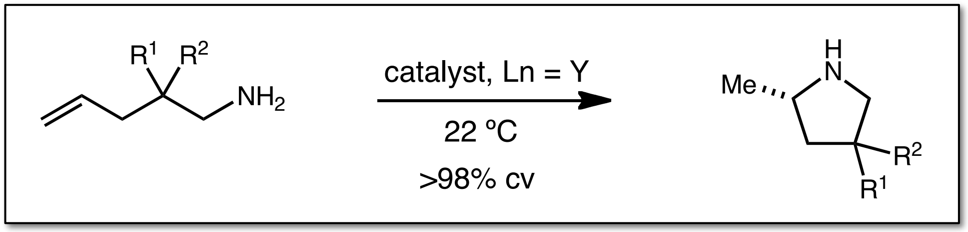
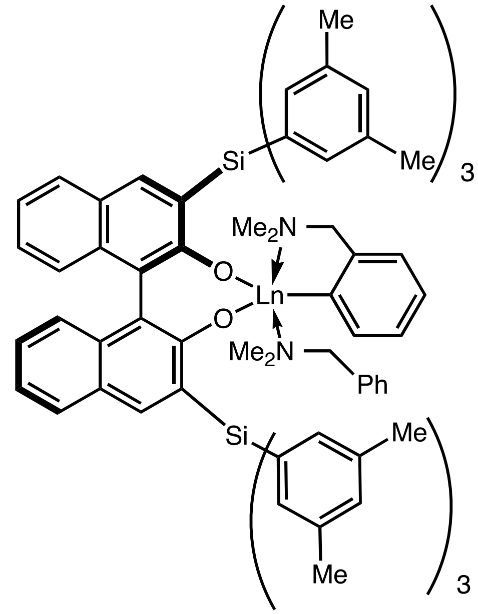
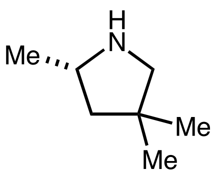
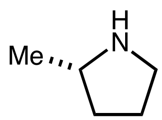


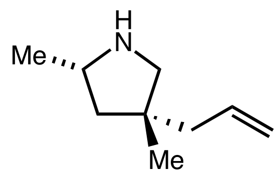




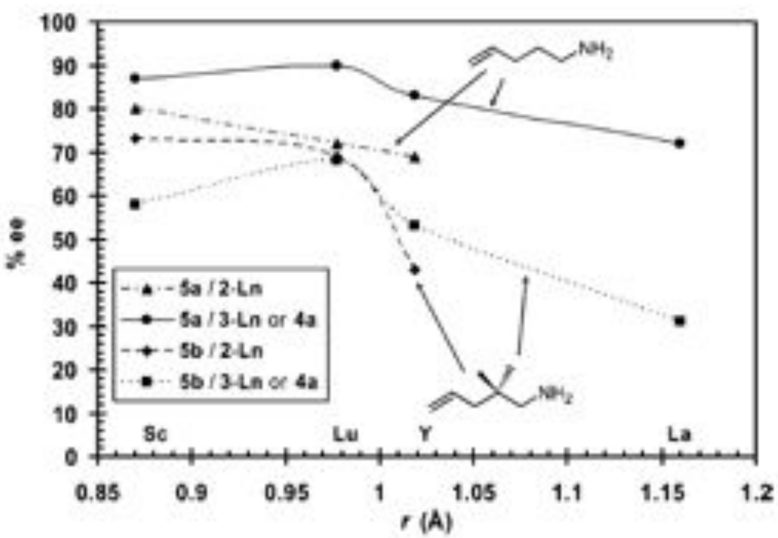
2 h, 53% ee

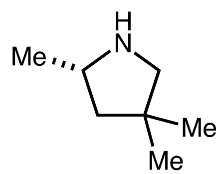


20 h, **83% ee**

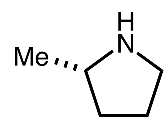


1.2 h, 65% ee, 1.4:1 dr



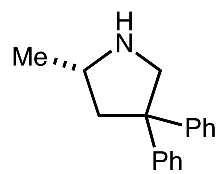


14 h, 68% ee

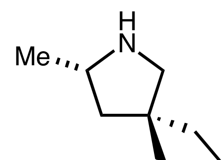


16.5 h, **90% ee**

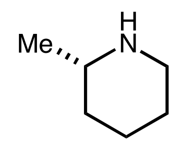
Ln = Lu



0.1 h, **80% ee**



0.5 h, 78% ee

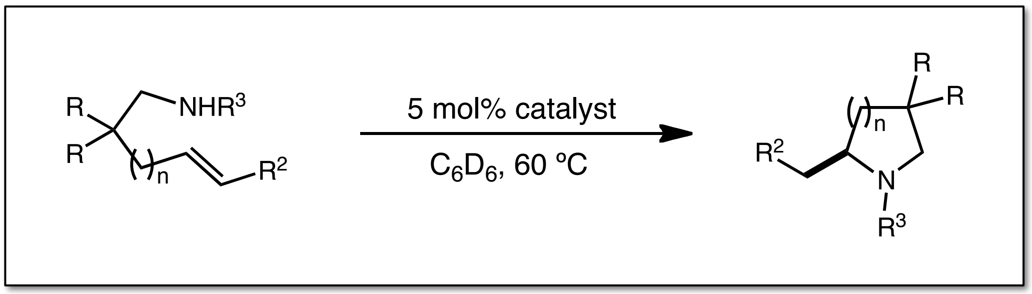


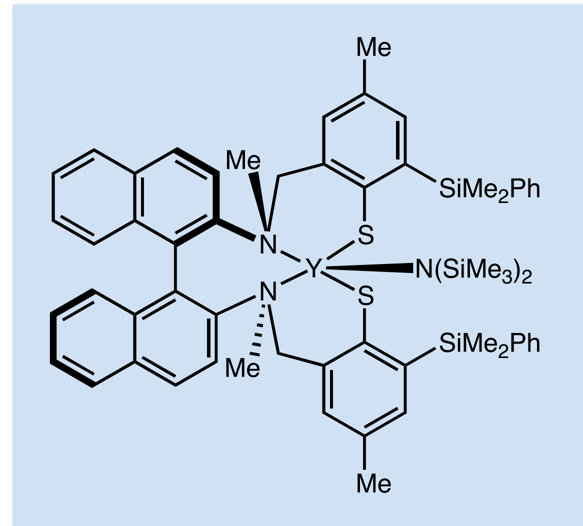
21 h, 55% ee

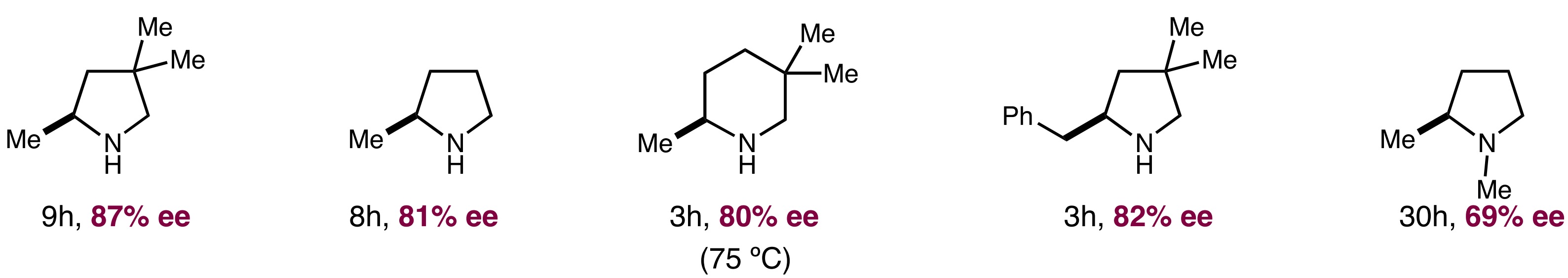
Gribkov, D. V.; Hultzsch, K. C.; Hampel, F. *J. Am. Chem. Soc.* **2006**, *128*, 3748.
Gribkov, D. V.; Hultzsch, K. C. *Chem. Commun.* **2004**, 730.

Chiral Rare Earth Metal Catalysts Based on Non-Cyclopentadienyl Ligands

- Livinghouse reported a bisthiolate yttrium complex showing less substrate dependence



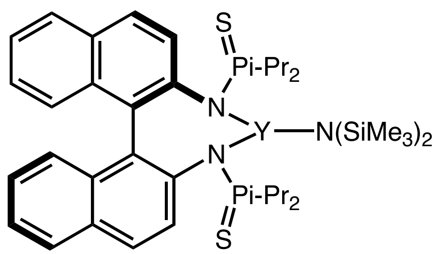




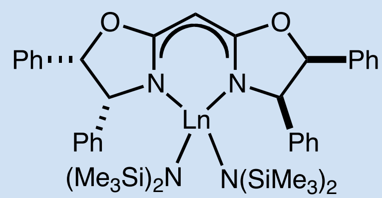
Kim, J. Y.; Livinghouse, T. *Org. Lett.* **2005**, *7*, 1737.

Other Chiral Rare Earth Metal Catalysts for Intramolecular Hydroamination

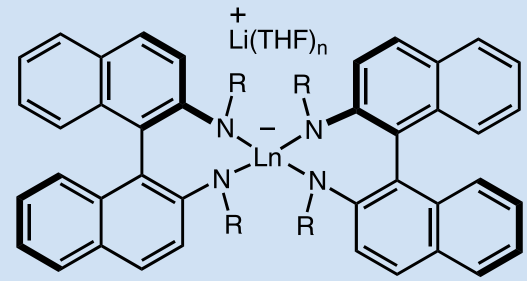
- There are still more chiral catalysts for intramolecular hydroamination....



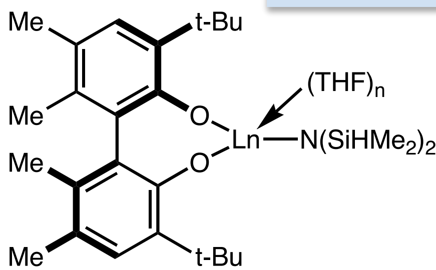
61% ee



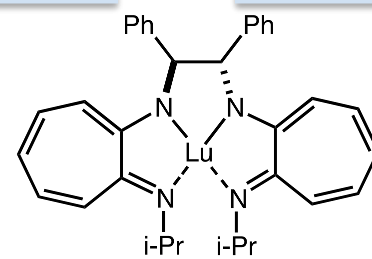
(Marks) **17-67% ee**



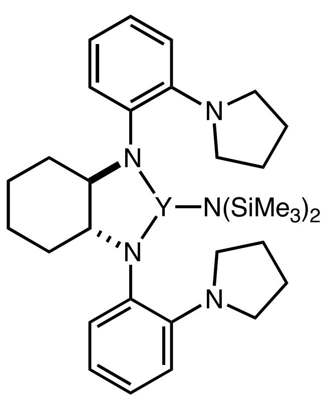
60-73% ee ***(Trifonov)***



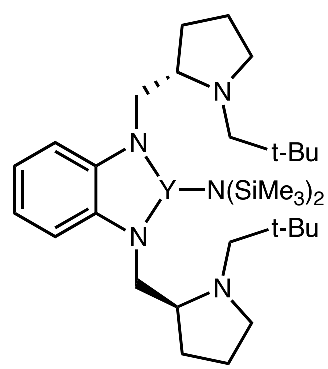
8-36% ee



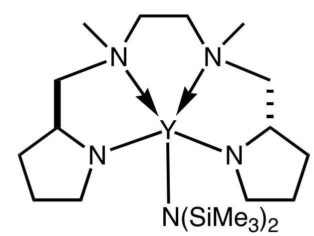
9-44% ee



17% ee



5% ee



11% ee

Intermolecular Hydroamination Catalyzed by Rare Earth Metal Catalysts

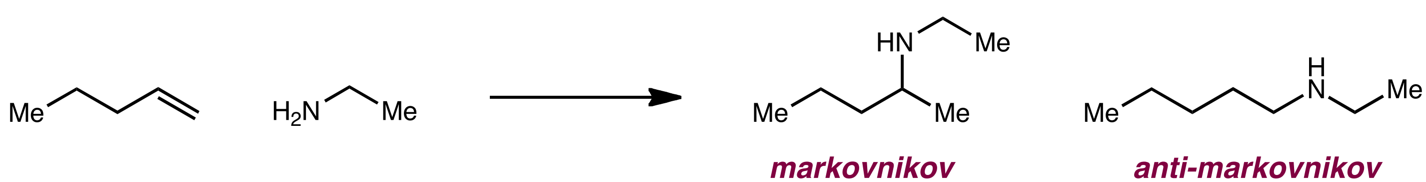
- Only a very limited number of reports of of rare earth catalyzed intermolecular reactions, both racemically and enantioselectively

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

$$rate = k[amine]^0[alkene]^1[catalyst]^1$$

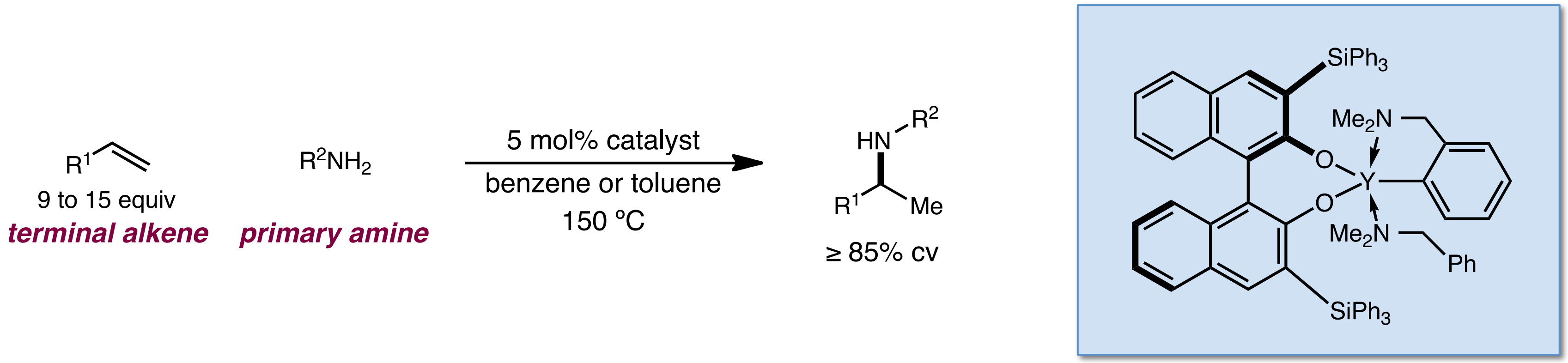
large excess of alkene is generaly required, contradicting the atom economical aspect of hydroaminations

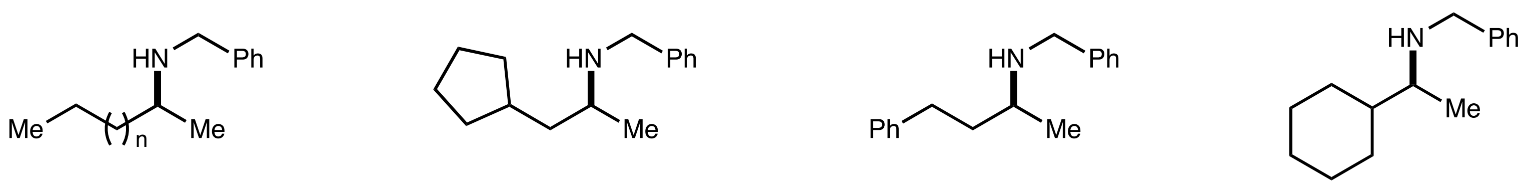
New Consideration: regioselectivity (Markovnikov vs. *anti*-Markovnikov)



Asymmetric Intermolecular Hydroamination Catalyzed by Rare Earth Metals

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



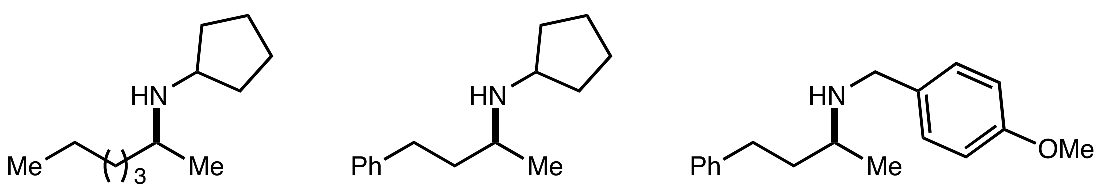


n = 1 70%, 61% ee
n = 2 54%, 61% ee
n = 4 72%, 57% ee

59%, 51% ee

72%, 56% ee

25%, --% ee



61%, 61% ee

68%, 54% ee

67%, 56% ee

75% cv, 73% de

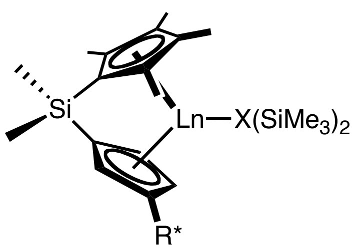
< 20%, --% de

Reznichenko, A. L.; Nguyen, H.N.; Hultzsch, K. C. *Angew. Chem. Int. Ed.* **2010**, *49*, 8984.

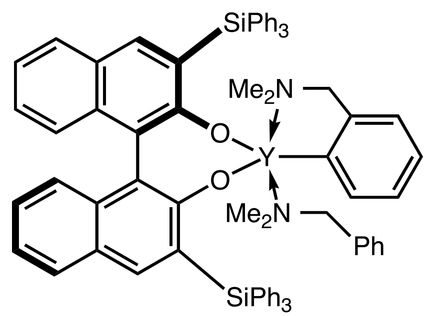
Rare Earth Metal Catalyzed Hydroaminations: Summary

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

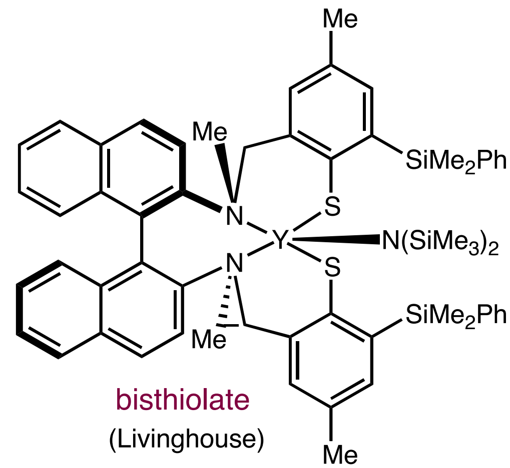
PROS	No protecting groups	***CONS***	Very low functional group tolerance
	Non-activated alkenes and simple amines		Air and moisture sensitive - GLOVEBOX



ansa-Metallocene
(Marks)

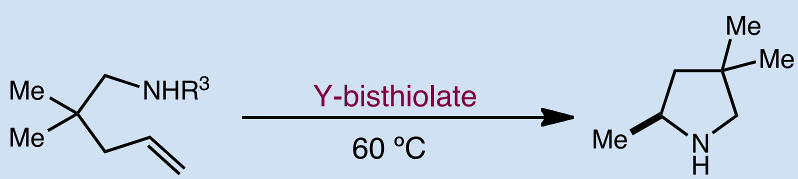


binaphtholate/biphenolate
(Marks, Hultzsch, Scott)

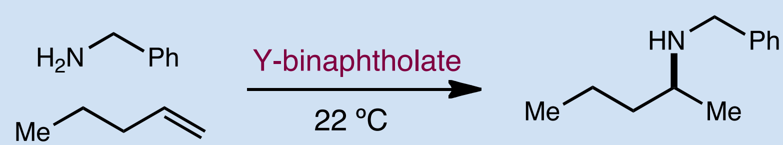


bisthiolate
(Livinghouse)

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



9 h, **87% ee**

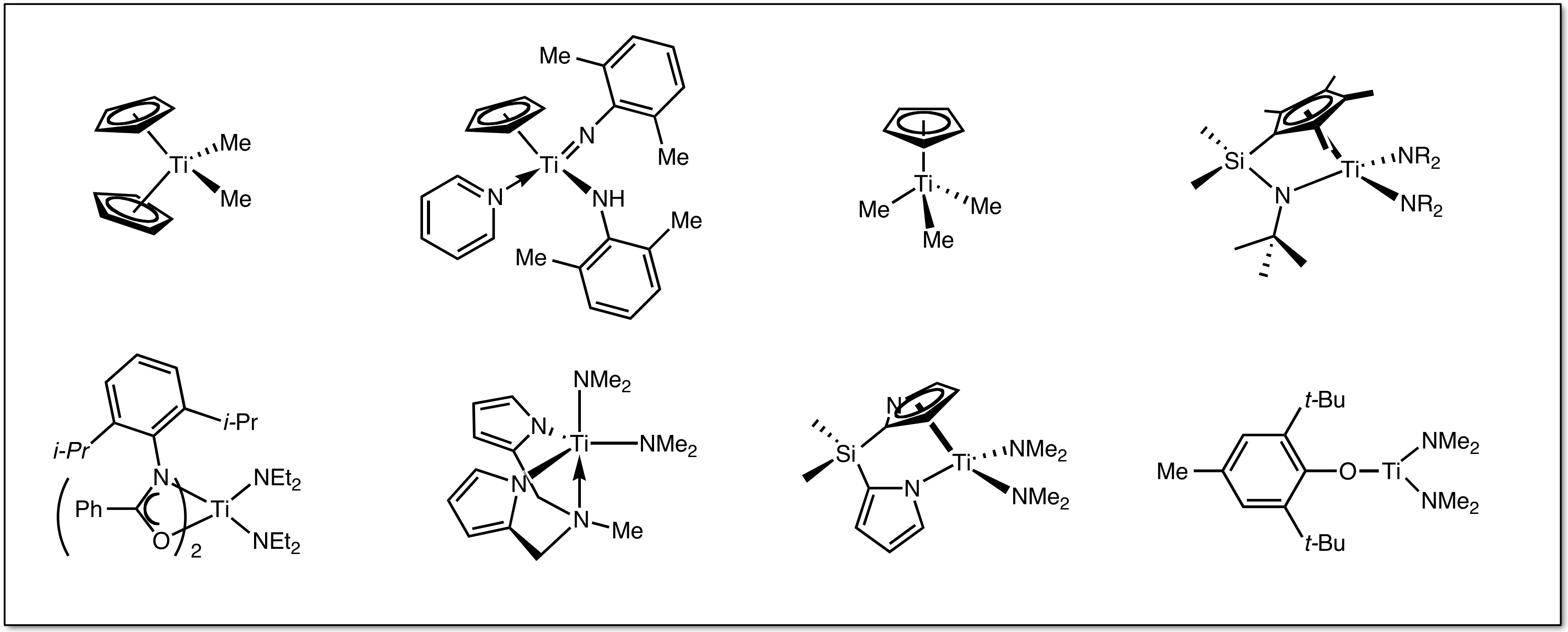


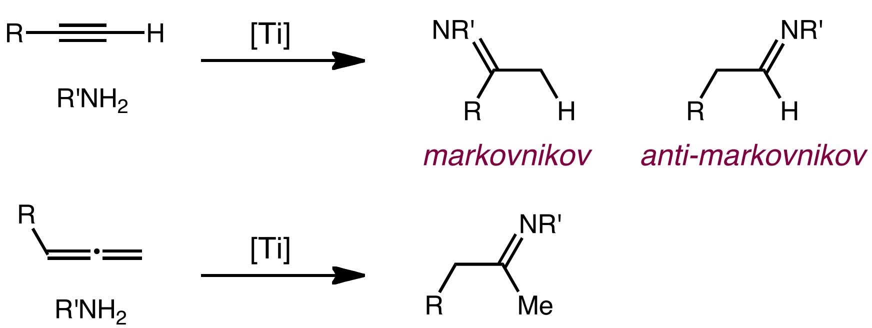
72, **61% ee**

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

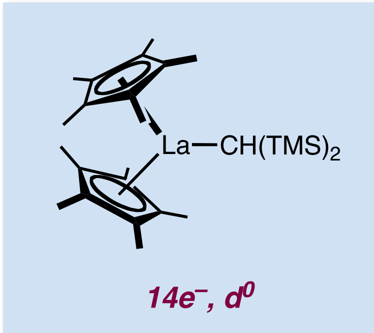
Better functional group tolerance

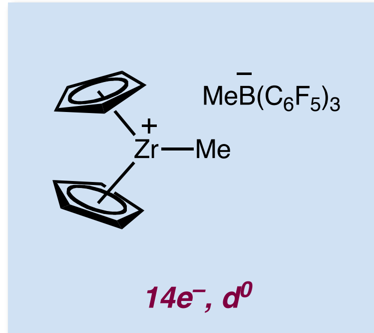
Many precatalysts commercially available

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

Group 4 Metal-Catalyzed Hydroamination of Alkenes

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





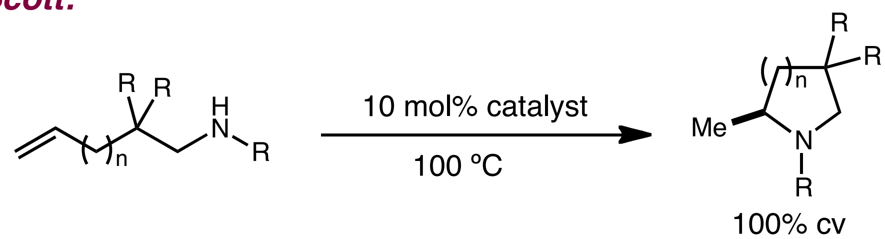
- Scope of group 4 metal-catalyzed hydroaminations should be able to include aminoalkenes

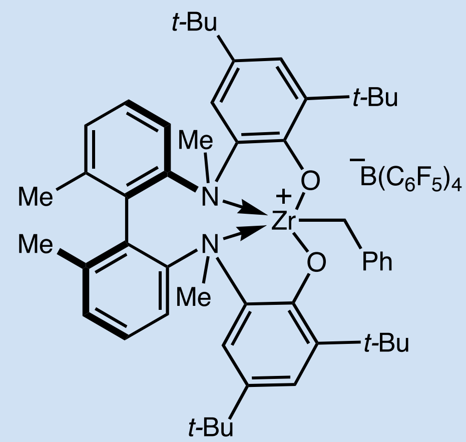
Gribkov, D. V.; Hultzsch, K.C. *Angew. Chem. Int. Ed.* **2004**,*43*, 5452.
Knight, P. D.; Munslow, P. N.; O'Shaughnessy, Scott, P. *Chem. Commun.* **2004**, 894.

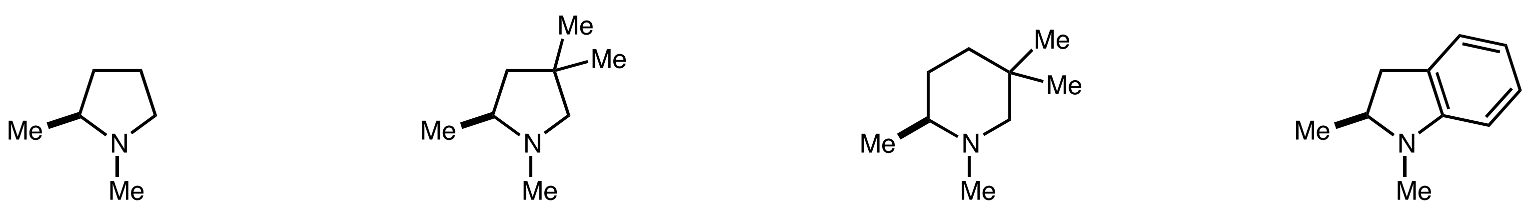
Group 4 Metal-Catalyzed Hydroamination of Alkenes

- 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

Scott:





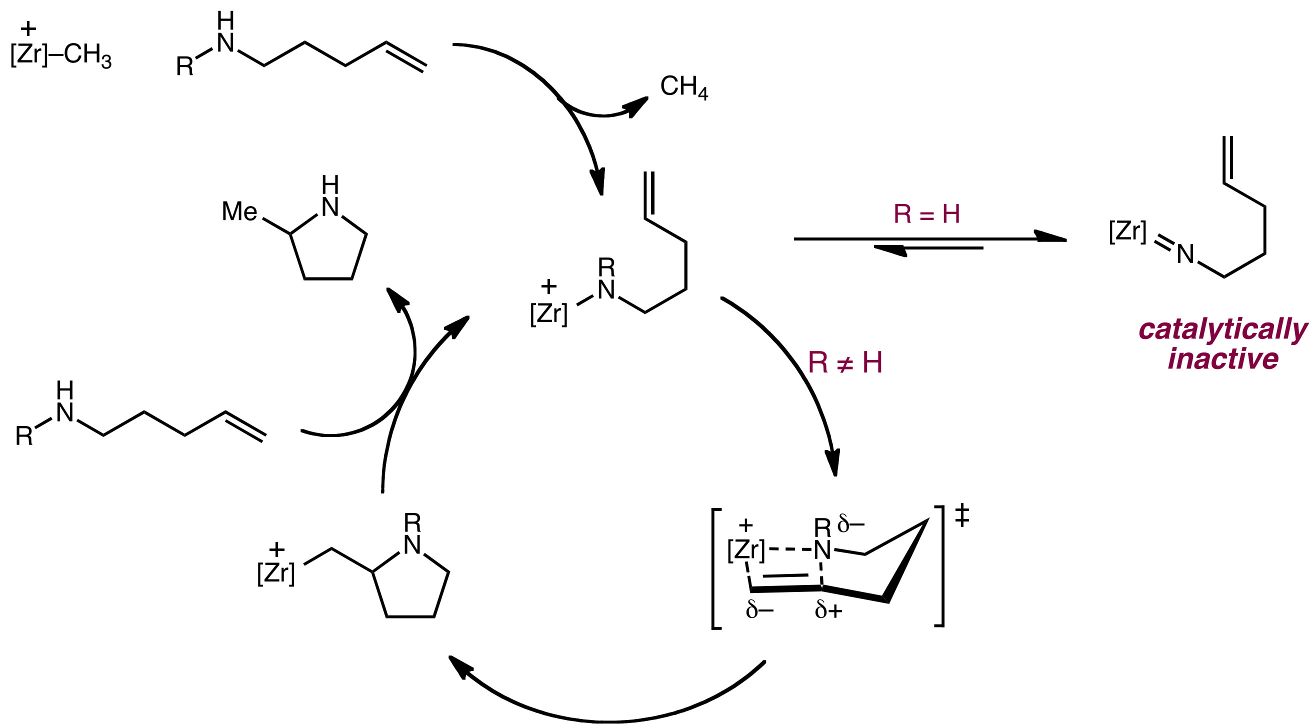


64% ee, 4 h | 14% ee, 48 h | **82% ee**, 3 h | 20% ee, 3 h

Gribkov, D. V.; Hultzsch, K.C. *Angew. Chem. Int. Ed.* **2004**,*43*, 5452.
Knight, P. D.; Munslow, P. N.; O'Shaughnessy, Scott, P. *Chem. Commun.* **2004**, 894.

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



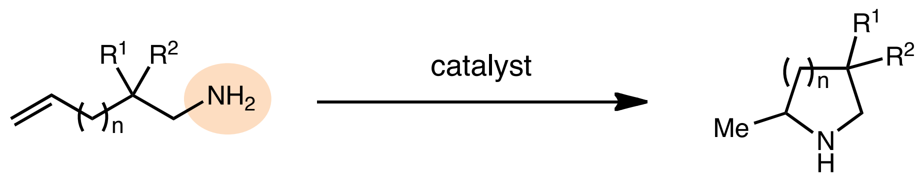
- Primary aminoalkenes result in no reaction because cationic zirconium amido species are readily deprotonated to yield catalytically inactive zirconium imido species

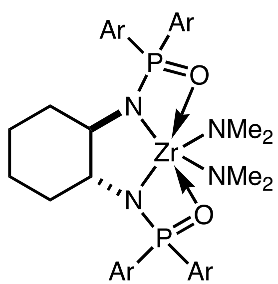
- Neutral metal imido species operate by a different mechanism and are unreactive towards non-activated alkenes using these catalysts

Gribkov, D. V.; Hultzsch, K.C. *Angew. Chem. Int. Ed.* **2004**,*43*, 5452.
Knight, P. D.; Munslow, P. N.; O'Shaughnessy, Scott, P. *Chem. Commun.* **2004**, 894.

Asymmetric Neutral Group 4 Metal-Catalyzed Hydroamination

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



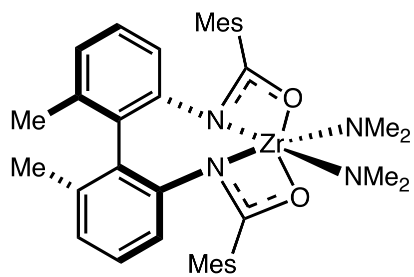


Ar = 3,5-$C_6H_3Me_2$

Bergman, 2006

33-99%, 33-80% ee

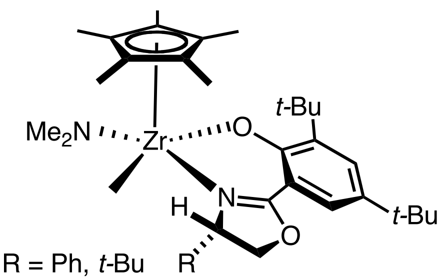
(8 substrates)



Schafer (Scott), 2007

82-98%, 62-93% ee

(7 substrates)

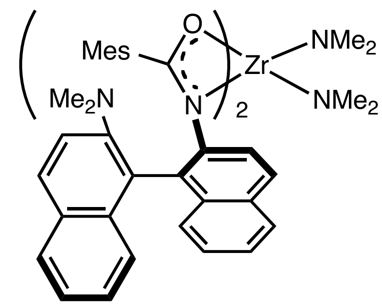


R = Ph, *t*-Bu

Scott, 2008

>95%, 14-70% ee

(2 substrates)



Zi, 2009

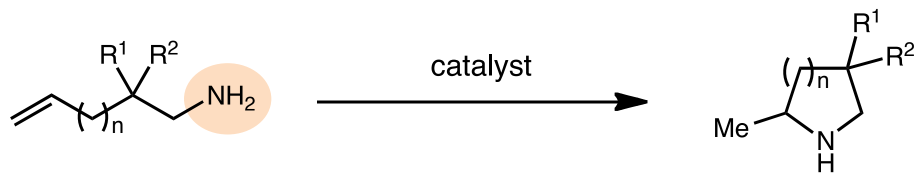
83-100%, 38-72% ee

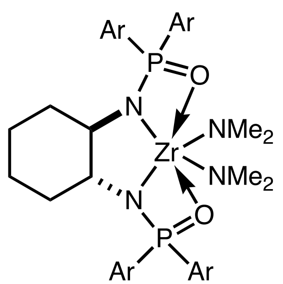
(3 substrates)

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





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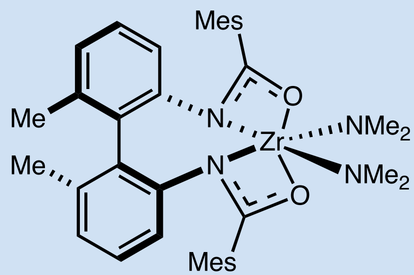
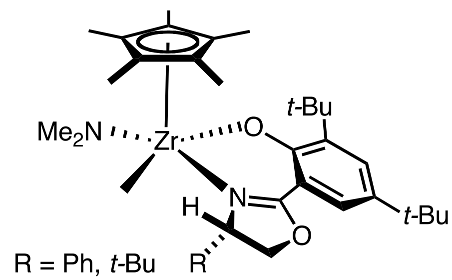


Schafer (Scott), 2007

82-98%, 62-93% ee

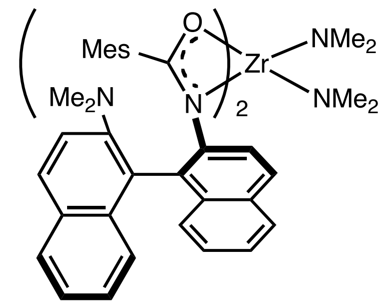
(7 substrates)



Scott, 2008

>95%, 14-70% ee

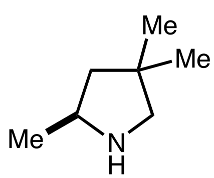
(2 substrates)



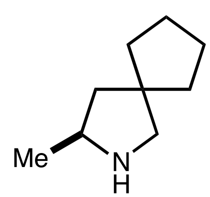
Zi, 2009

83-100%, 38-72% ee

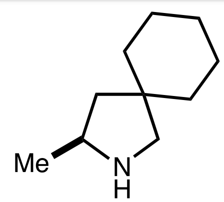
(3 substrates)



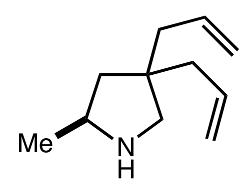
80%, **93% ee**



91%, **88% ee**



96%, **82% ee**

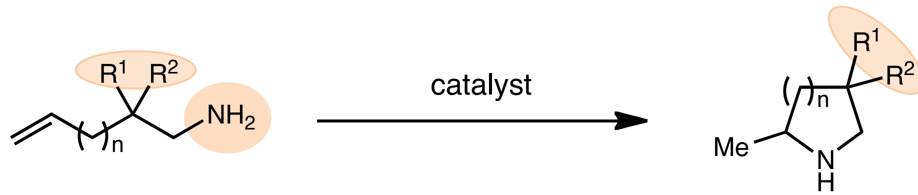


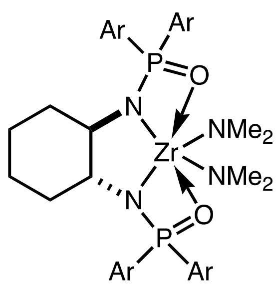
88%, **74% ee**

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



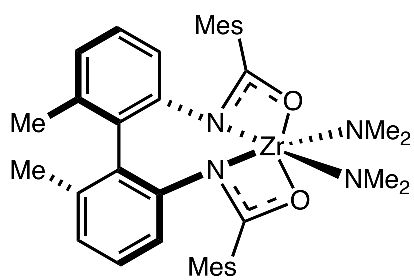


Ar = 3,5-$C_6H_3Me_2$

Bergman, 2006

33-99%, 33-80% ee

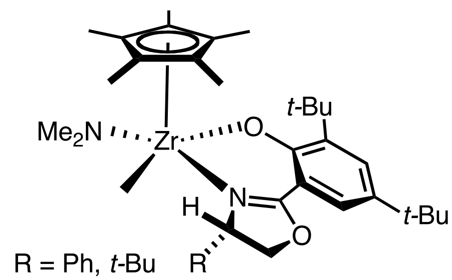
(8 substrates)



Schafer (Scott), 2007

82-98%, 62-93% ee

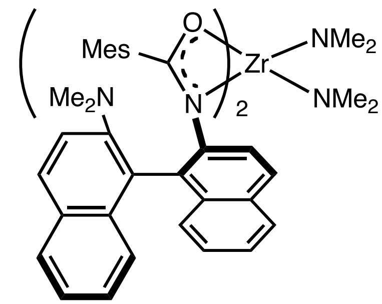
(7 substrates)



Scott, 2008

>95%, 14-70% ee

(2 substrates)



Zi, 2009

83-100%, 38-72% ee

(3 substrates)

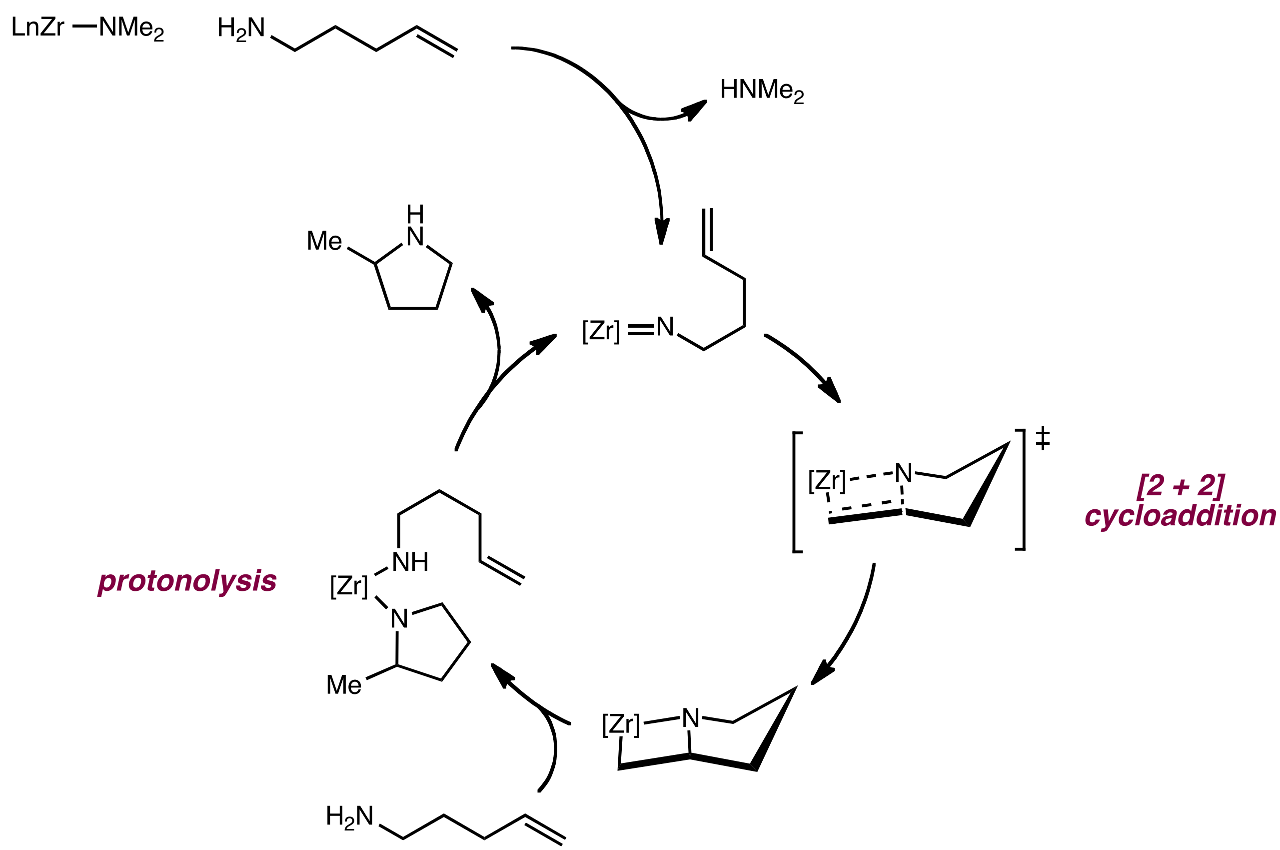
substrates require β-geminal substitution

generally restricted to pyrrolidines

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.

Mechanism of Neutral Group 4 Metal-Catalyzed Hydroamination

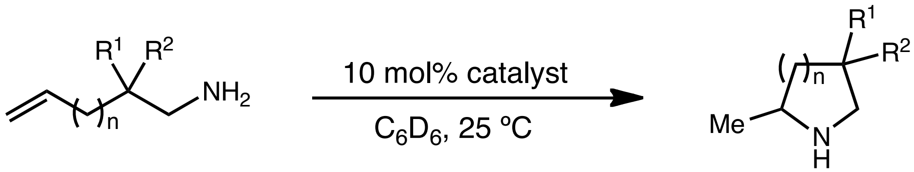
- Hydroamination reactions with neutral group 4 metal complexes proceed through a [2 + 2] cycloaddition of a metal imido species and the alkene

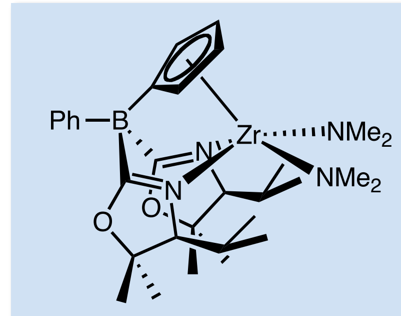


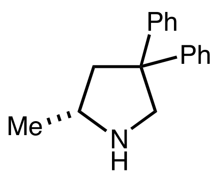
Bexrud, J. A.; Bear, J. D.; Leitch, D. C.; Schafer, L. L. *Org. Lett.* **2005**, *7*, 1959.
Muller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795.

Asymmetric Neutral Group 4 Metal-Catalyzed Hydroamination

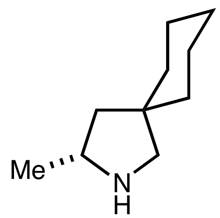
- This year (Jan 2011) Sadow reported a highly enantioselective intramolecular hydroamination



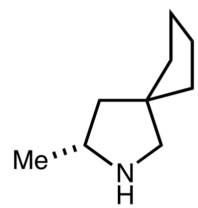




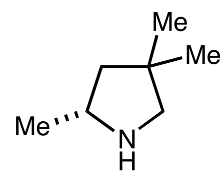
>95% cv, 93% ee
(98% ee in THF, 5d)



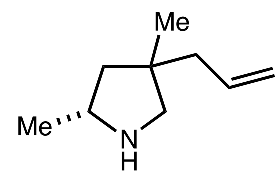
>95% cv, 90% ee



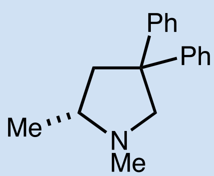
88% cv, 92% ee



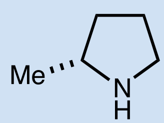
89% cv, 89% ee



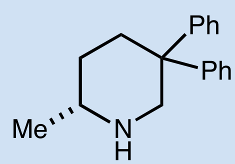
>95% cv, 93, 92% ee, 1:1 dr



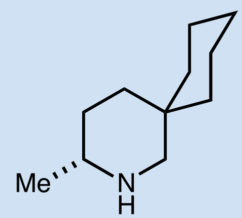
0% cv, --% ee



24% cv, --% ee



65% cv, 46% ee



48% cv, 31% ee

generally restricted to β-geminal substituted pyrrolidines

Manna, K.; Xu, S.; Sadow, A. D. *Angew. Chem. Int. Ed.* **2011**, *50*, ASAP.

Group 4 Hydroaminations: Summary

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

PROS

No protecting groups

Less air and moisture sensitive

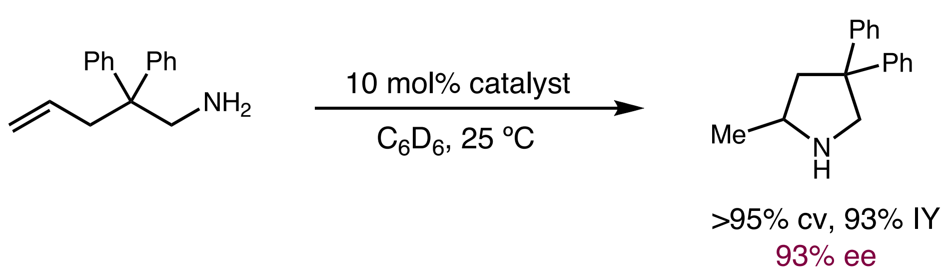
More functional group tolerance
(halides, ethers, nitriles)

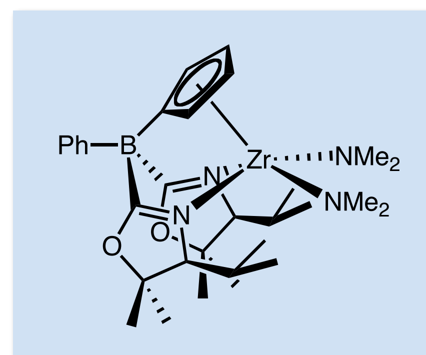
CONS

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

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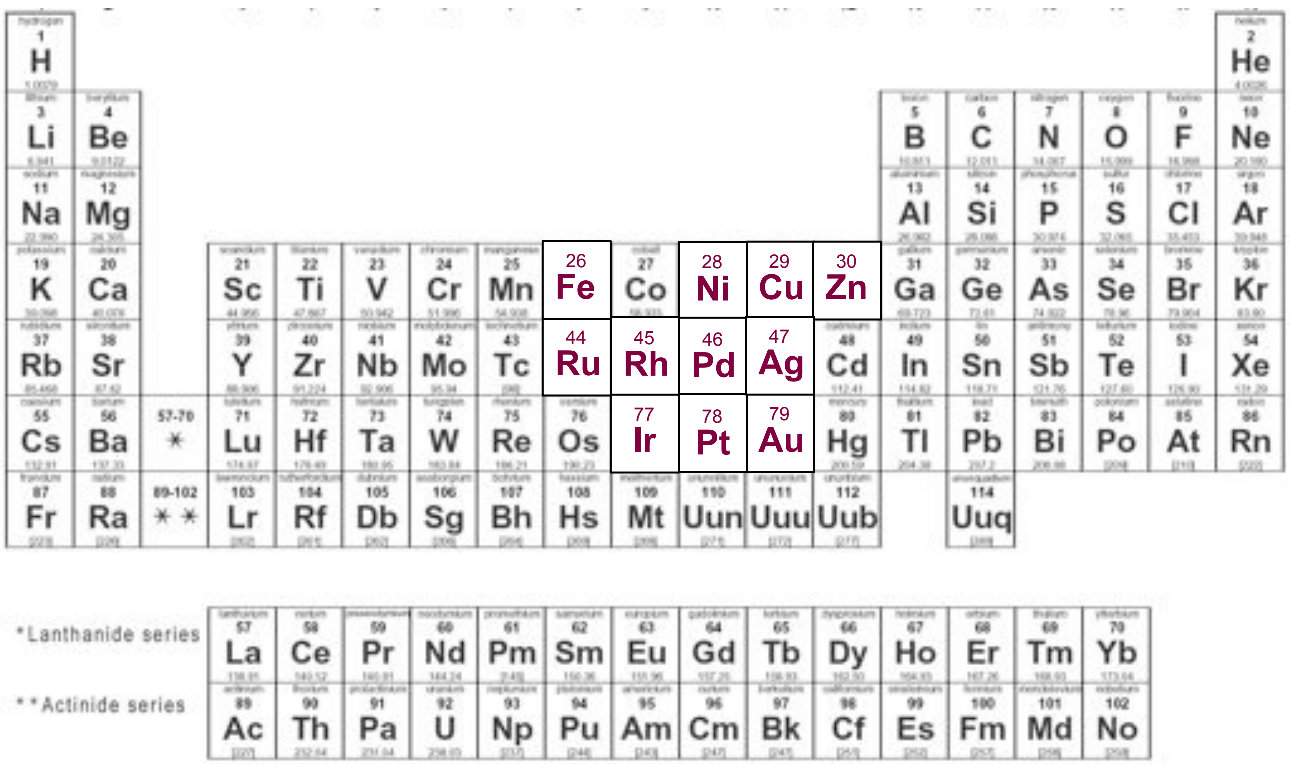

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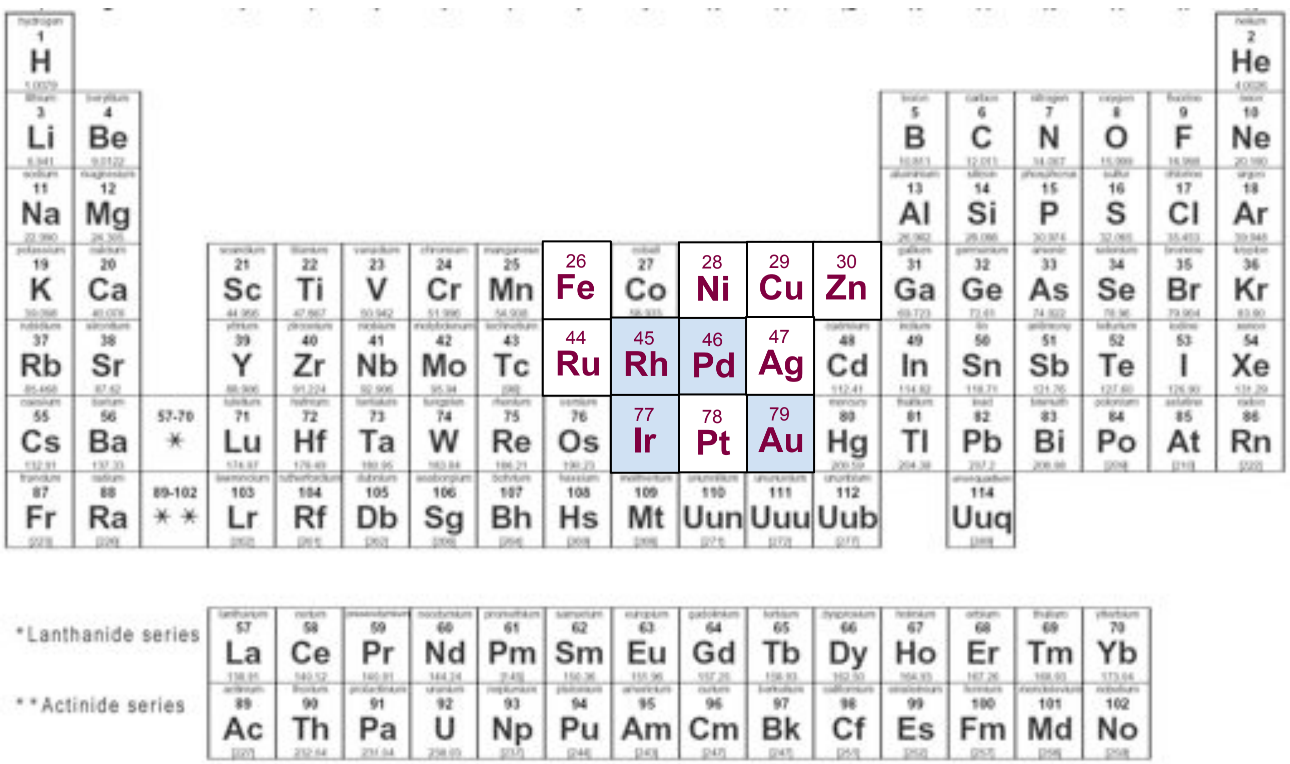

Late Transition Metal-Catalyzed Asymmetric Hydroamination

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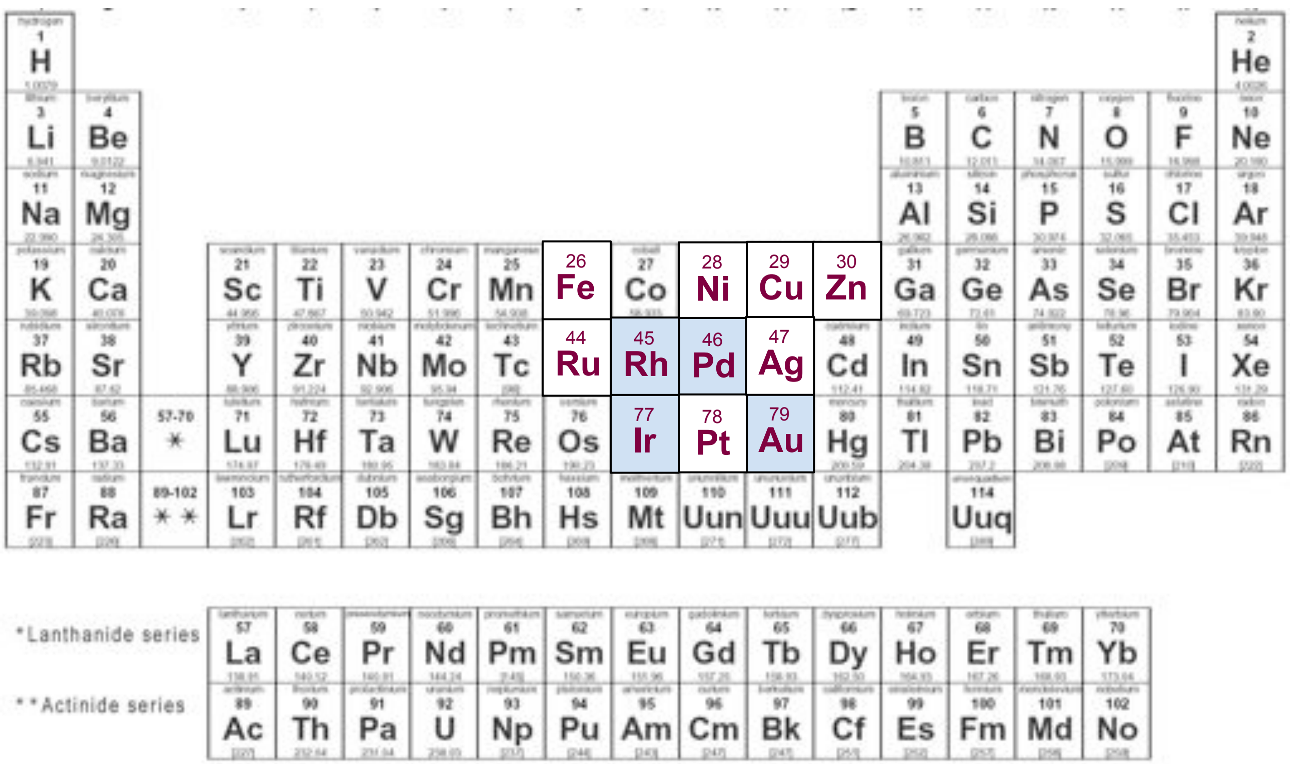
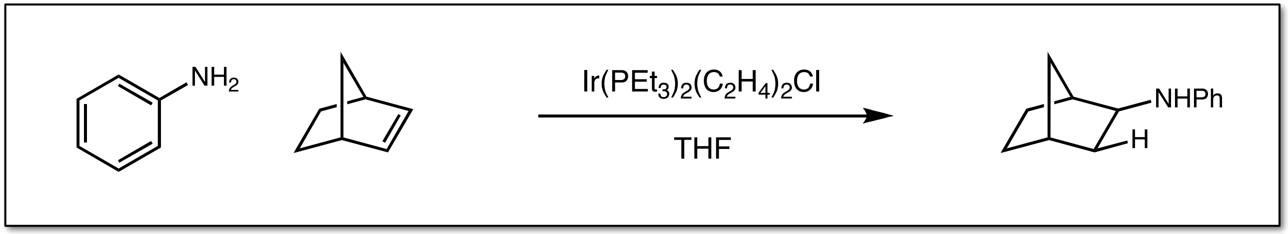
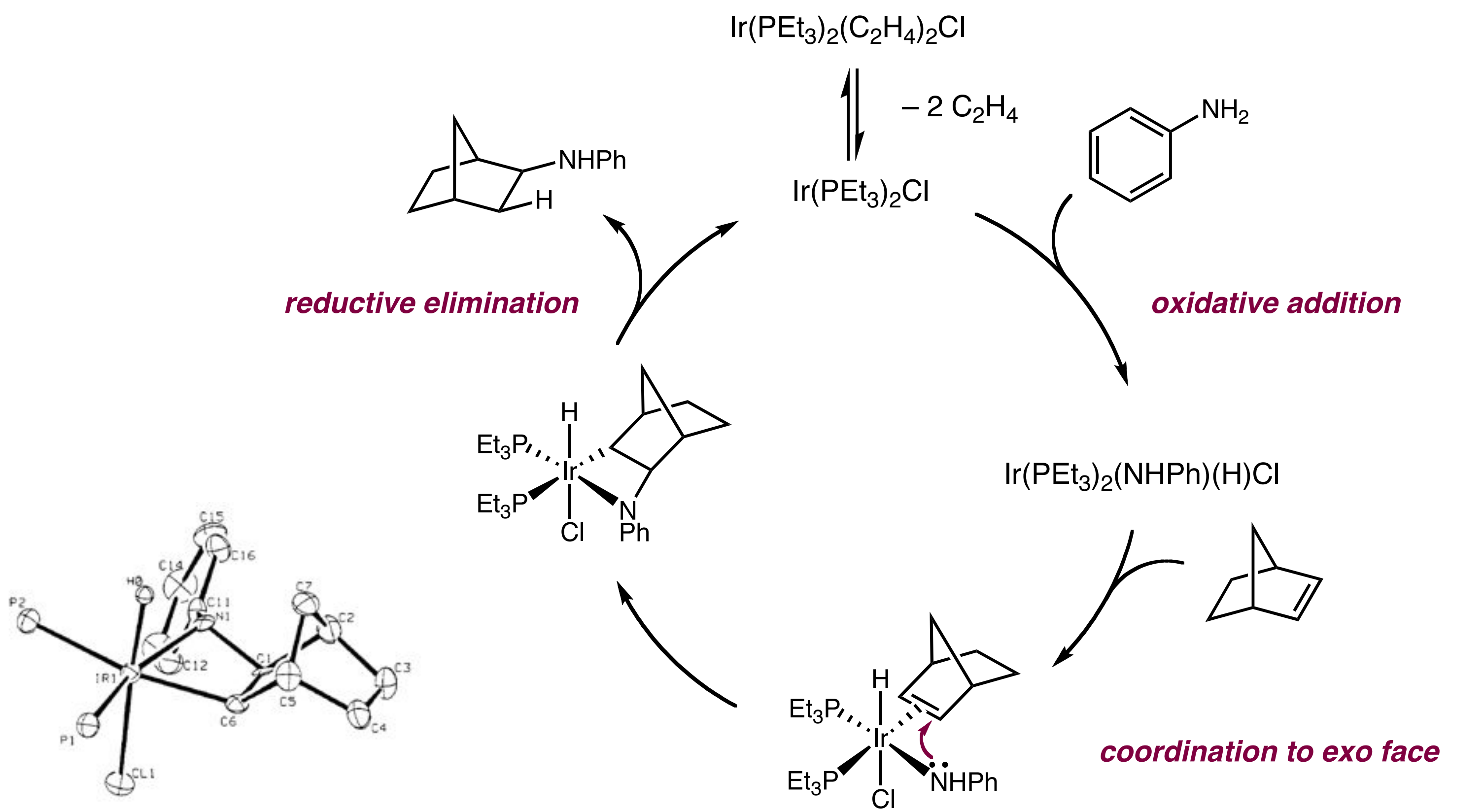


- Most substrates are restricted to activated substrates, such as strained olefins, styrenes, dienes, alkynes

Iridium-Catalyzed Intermolecular Hydroamination

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

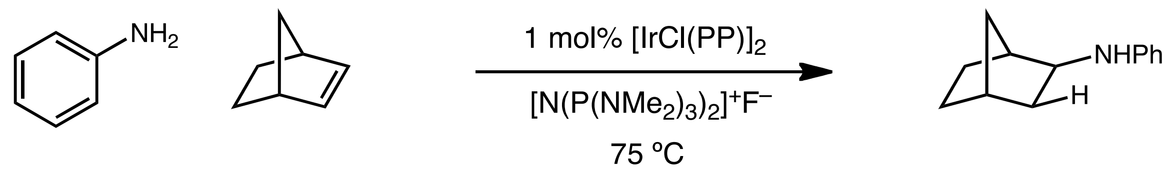


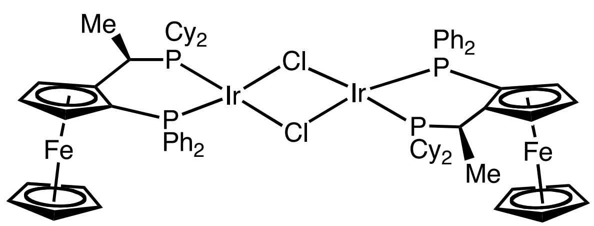


Casalnuovo, A. L.; Calabrese, J. C.; Milstein, D. *J. Am. Chem. Soc.* **1989**, *110*, 6738.

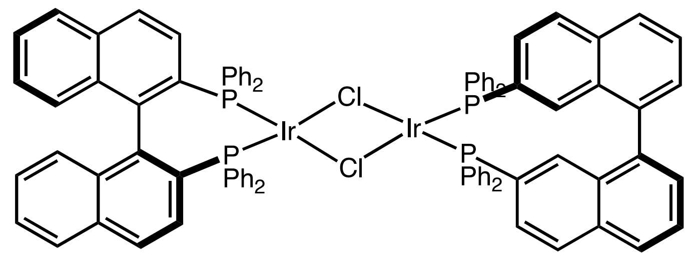
Iridium-Catalyzed Intermolecular Hydroamination

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





81% IY, 38% ee
3.4 h $^{-1}$



22% IY, **95% ee**
0.15 h $^{-1}$

Fluoride required for yield and enatioselectivity

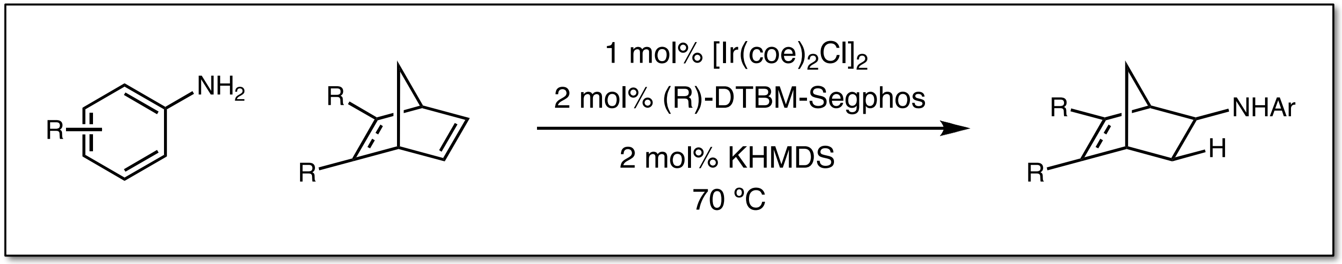
Possible roles: acts as a good π-donating ligand on iridium

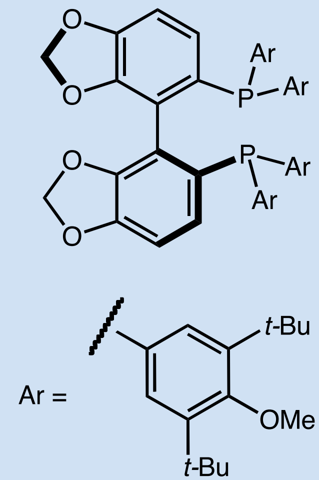
deprotonates aniline to generate anilide

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

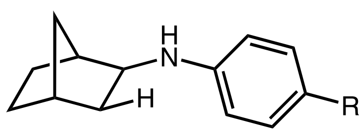
Iridium-Catalyzed Intermolecular Hydroamination

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

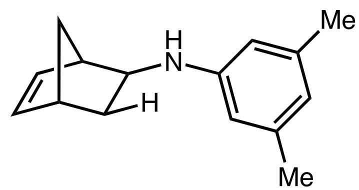




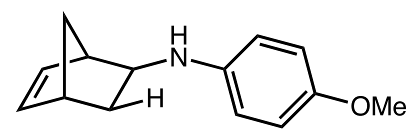
DTBM-Segphos



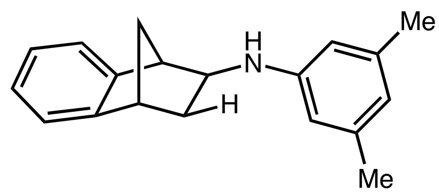
R =	
t-Bu	85%, 92% ee
Br	91%, 96% ee
OMe	75%, 98% ee
CF_3	77%, 91% ee



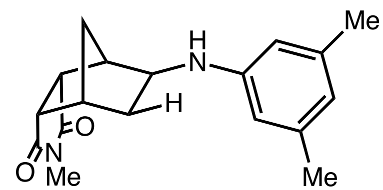
94%, 99% ee



88%, 99% ee



90%, 99% ee

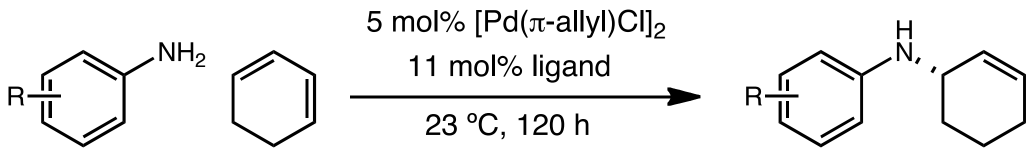


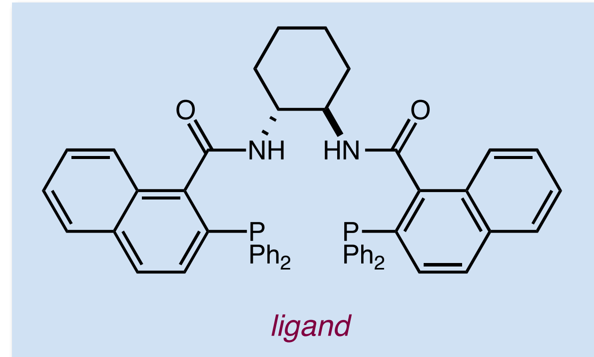
84%, 98% ee

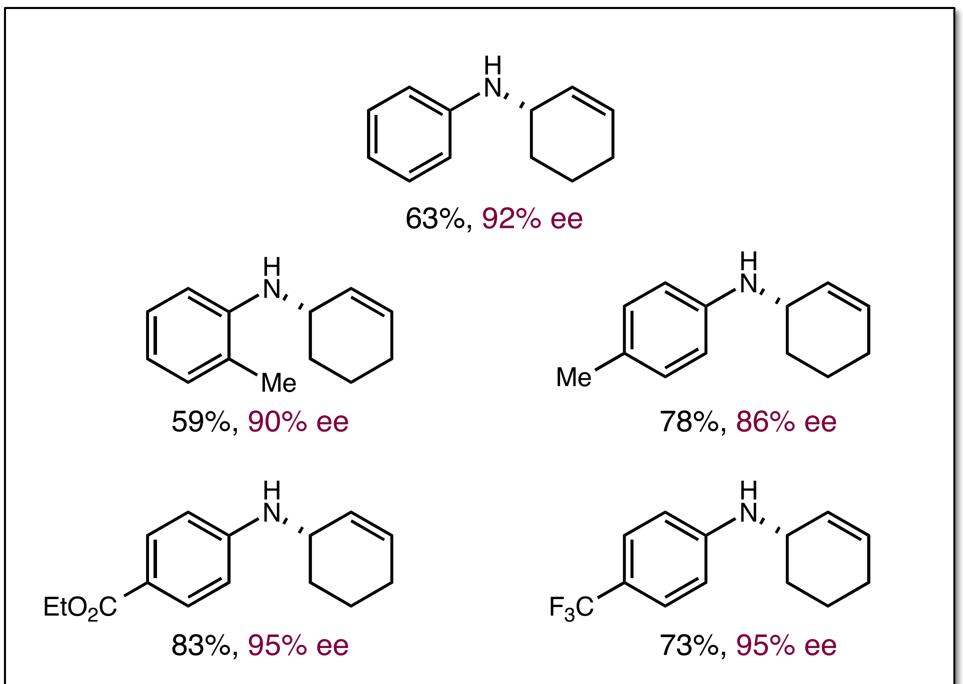
Zhou, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 12220.

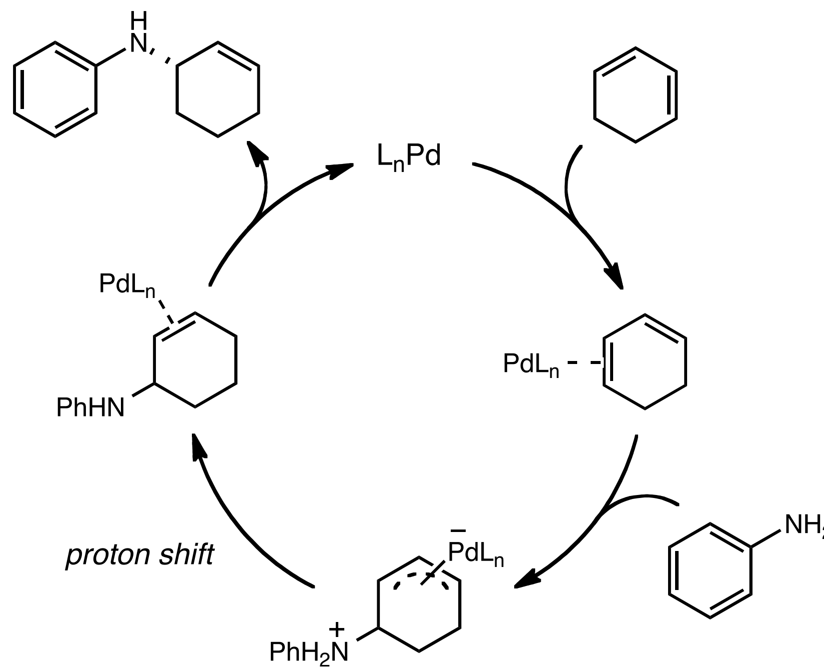
Palladium-Catalyzed Asymmetric Intermolecular Hydroamination

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









Lober, O.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 4366

Palladium-Catalyzed Asymmetric Intermolecular Hydroamination

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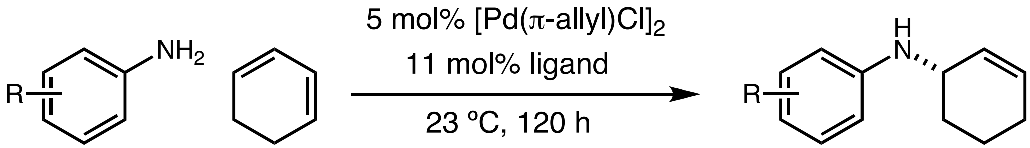
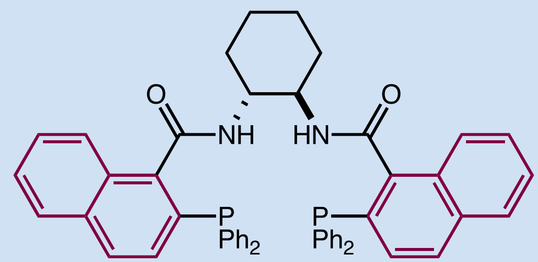
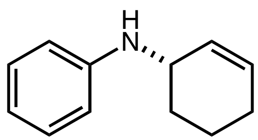
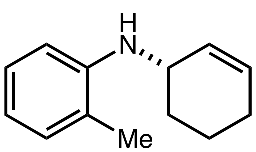




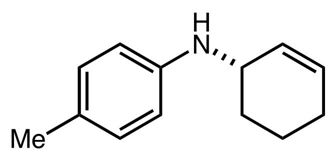
ligand



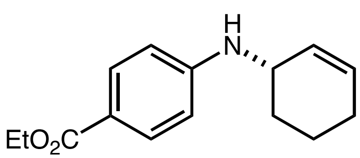
63%, 92% ee



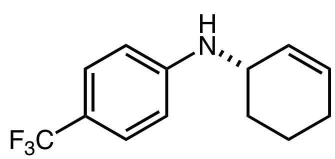
59%, 90% ee



78%, 86% ee

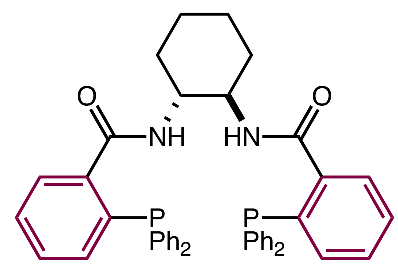


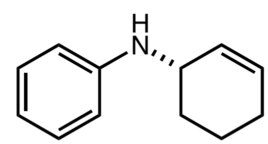
83%, 95% ee



73%, 95% ee

naphthyl units extremely important for enantioselectivity



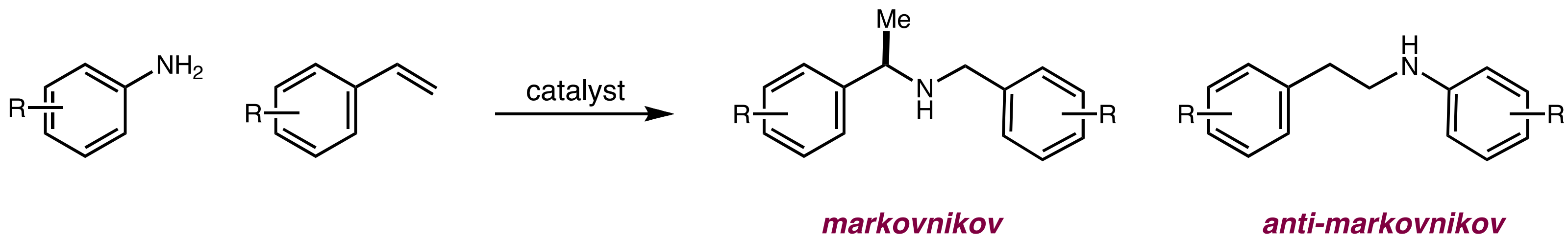


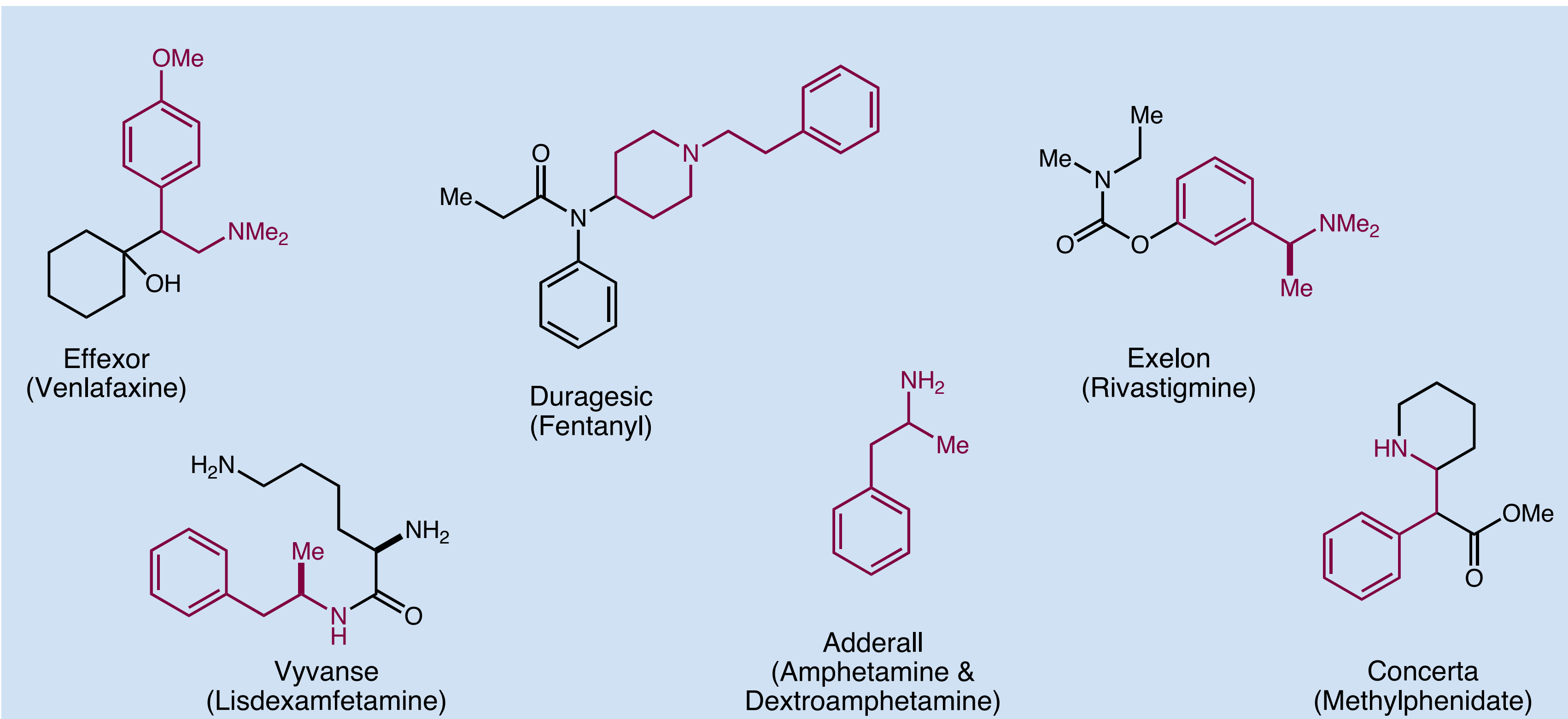
65%, 11% ee

Lober, O.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 4366

Palladium-Catalyzed Asymmetric Intermolecular Hydroamination of Styrenes

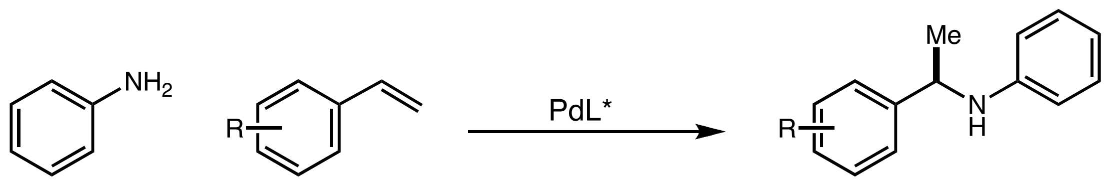
- Hydroamination of styrenes is a powerful synthetic transformation for benzylic or homobenzylic amines



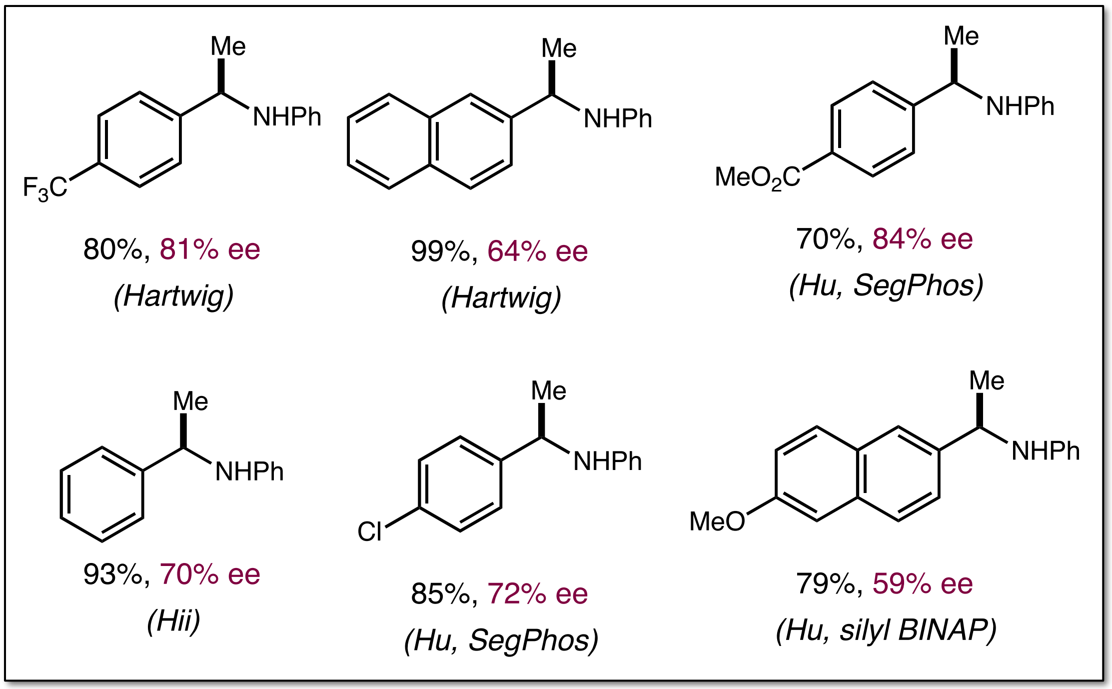


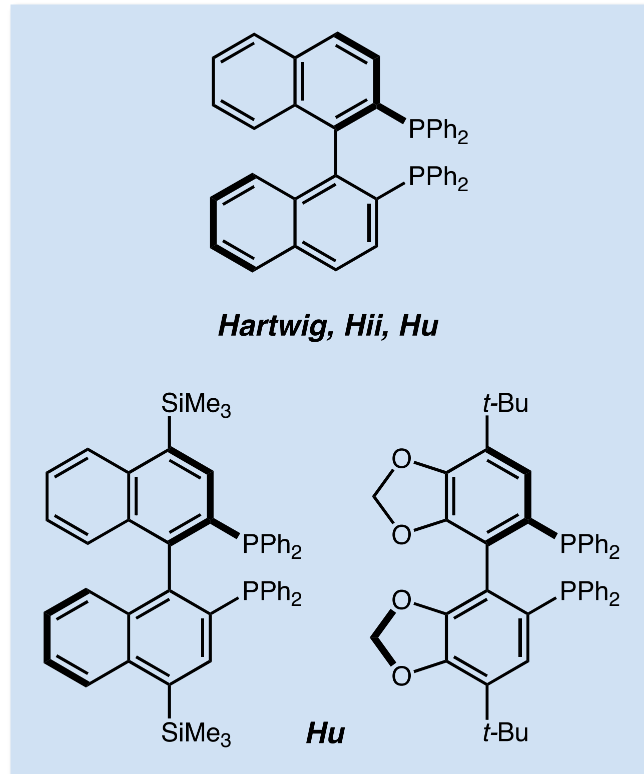
Palladium-Catalyzed Asymmetric Intermolecular Hydroamination

- Several groups have developed hydroaminations of styrenes using aryl amines



Pd-catalyzed reaction generally gives markovnikov products



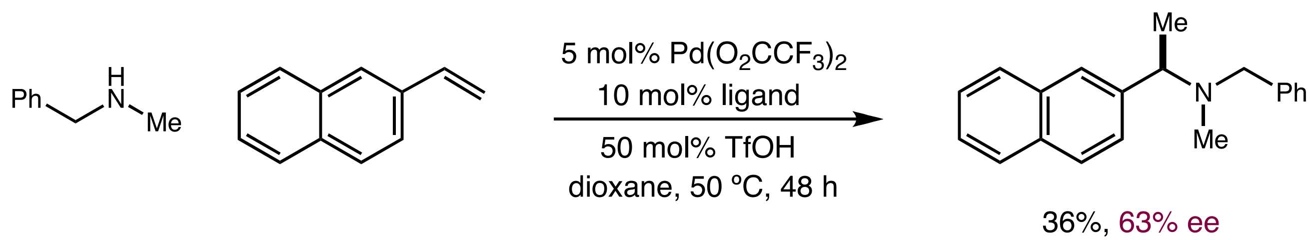


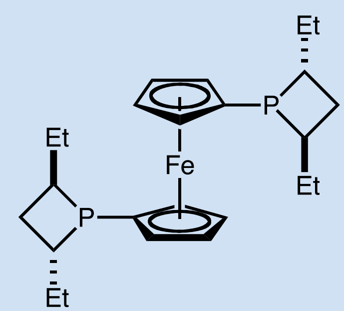
Limited to the addition of aryl amines

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

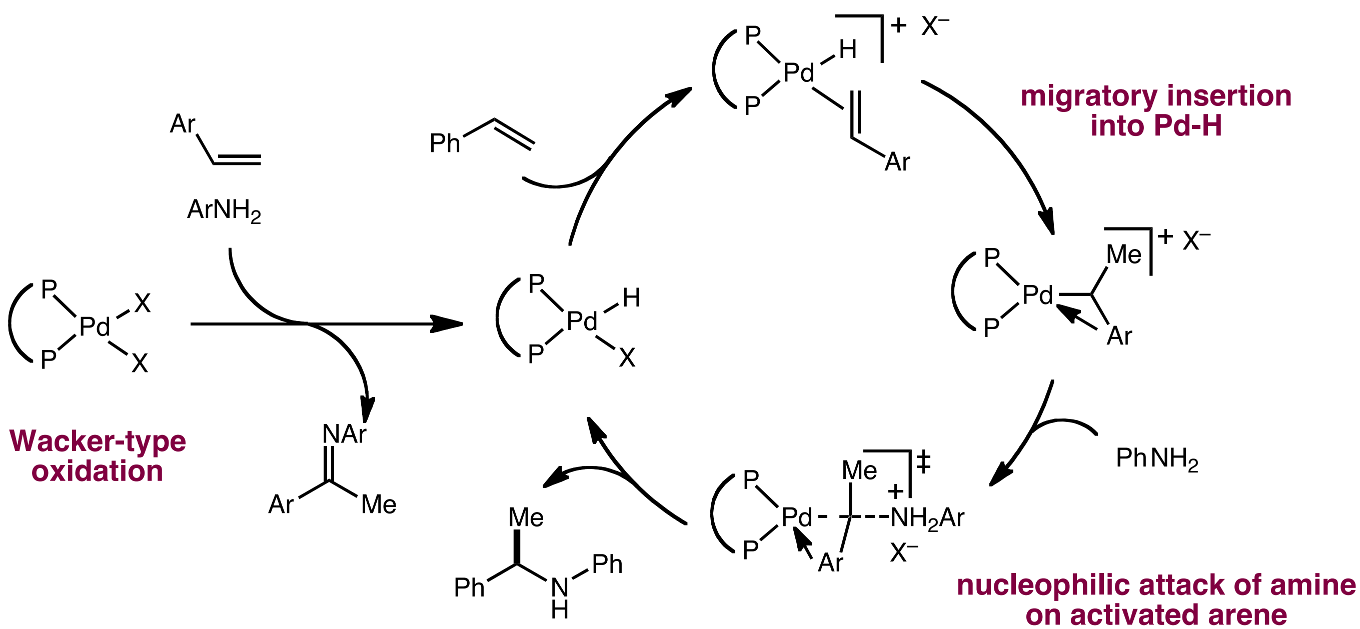
- Hartwig reoptimized the reaction to be successful with secondary alkylamines
- Only one asymmetric example was reported with lower yield than the racemic variant

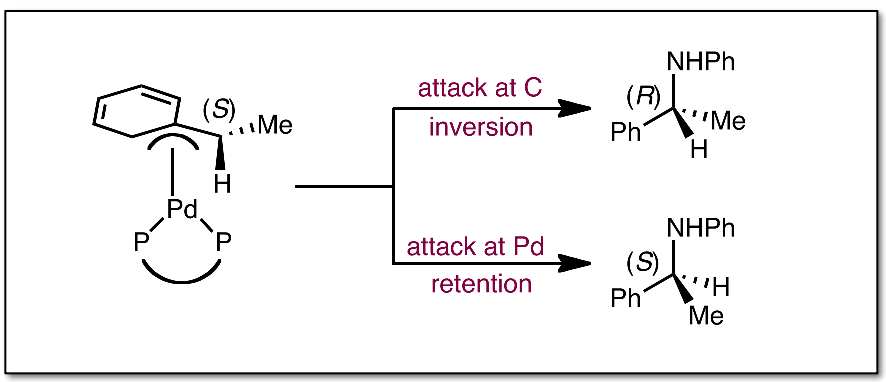




Utsunomiya, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 14286.

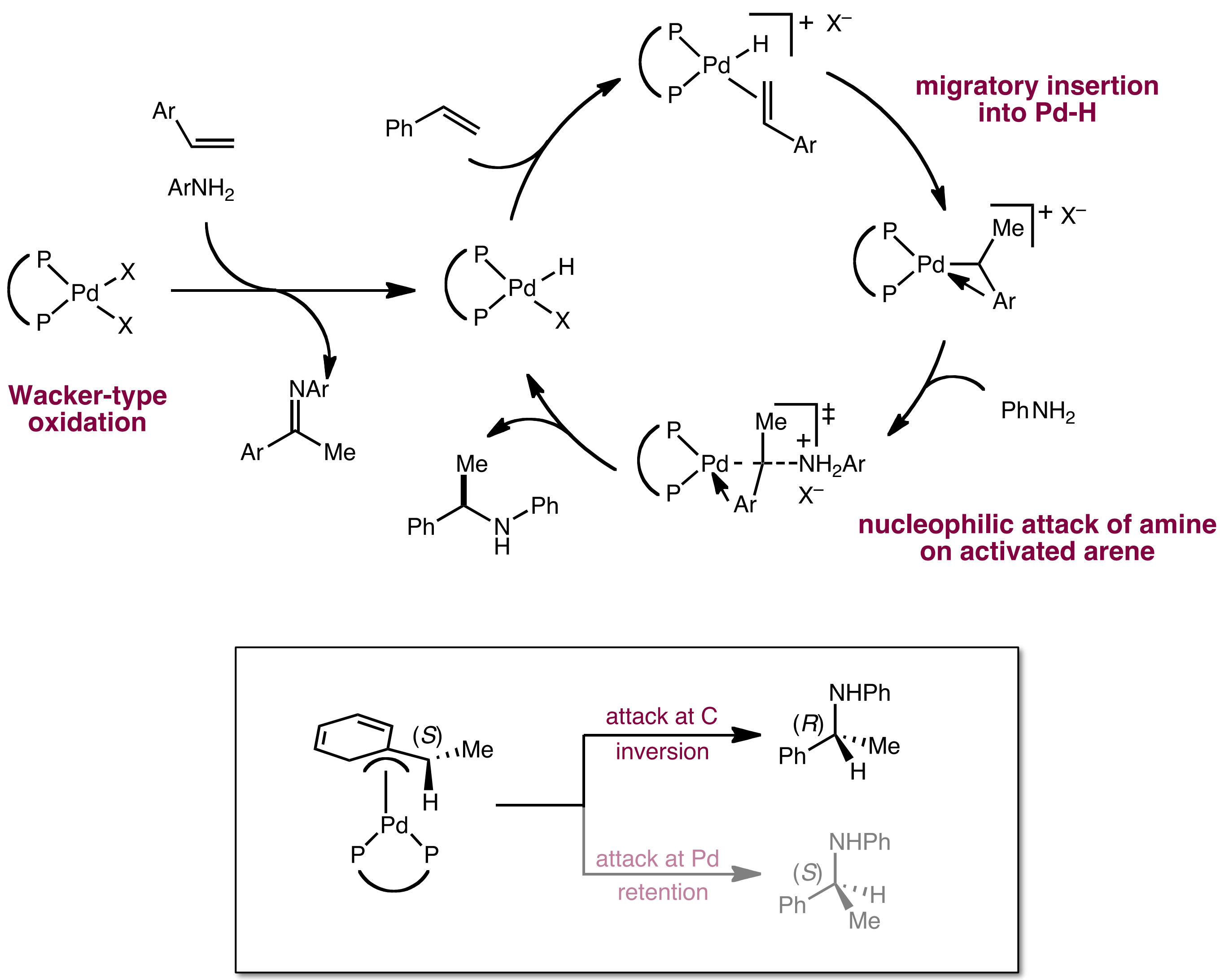
Palladium-Catalyzed Hydroamination of Styrenes: Mechanism





Nettekoven, U.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124,* 1166.

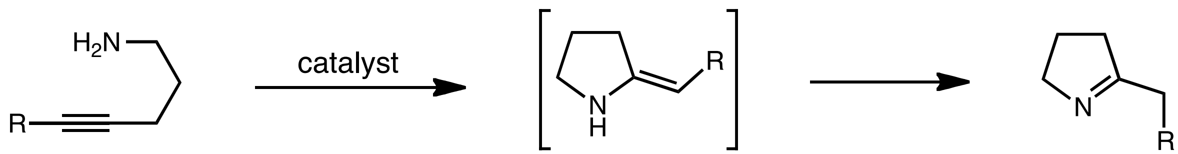
Palladium-Catalyzed Hydroamination of Styrenes: Mechanism



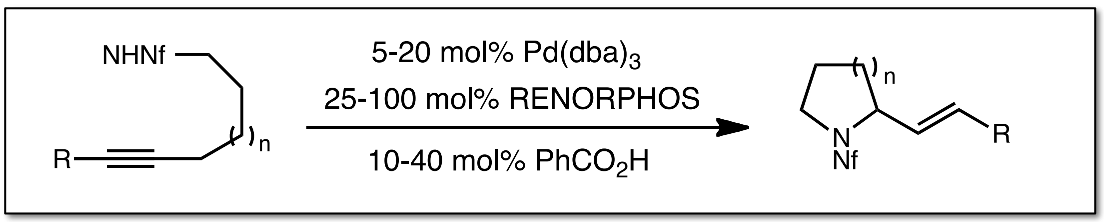
Nettekoven, U.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124,* 1166.

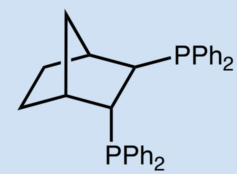
Palladium-Catalyzed Intramolecular Asymmetric Hydroamination of Alkynes

- Hydroamination of alkynes usually does not introduce a new stereocenter

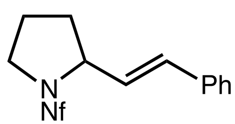


- Palladium-catalyzed hydroamination of alkynes proceeds through a different mechanism and creates a stereocenter

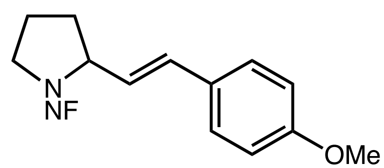




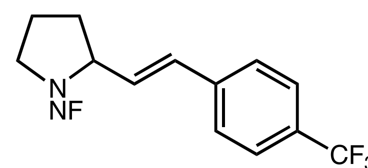
(R,R)-RENORPHOS



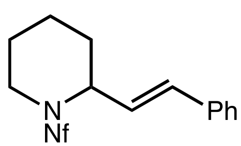
93%, 91% ee



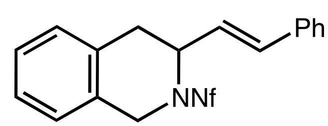
90%, 81% ee



85%, 88% ee



92%, 90% ee

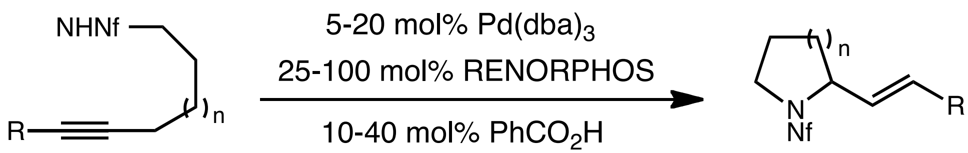


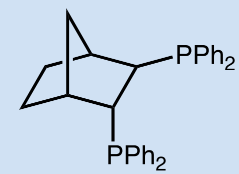
90%, 87% ee

Lutete, L. M.; Kadota, I.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 1622.

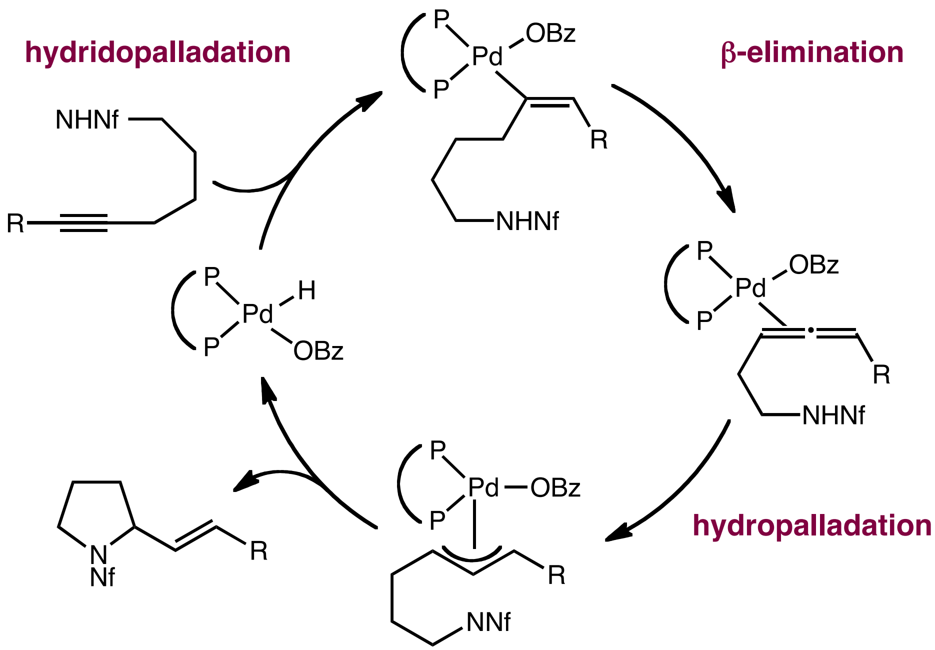
Palladium-Catalyzed Intramolecular Asymmetric Hydroamination of Alkynes

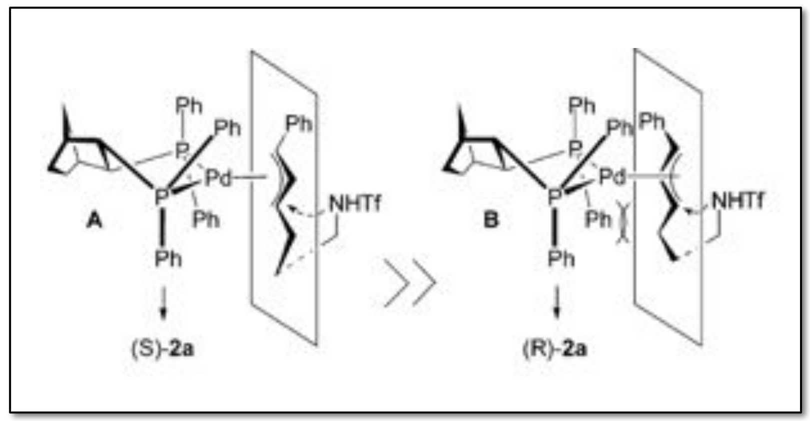
- The palladium-catalyzed hydroamination of aminoalkynes proceeds through an allene





(R,R)-RENORPHOS

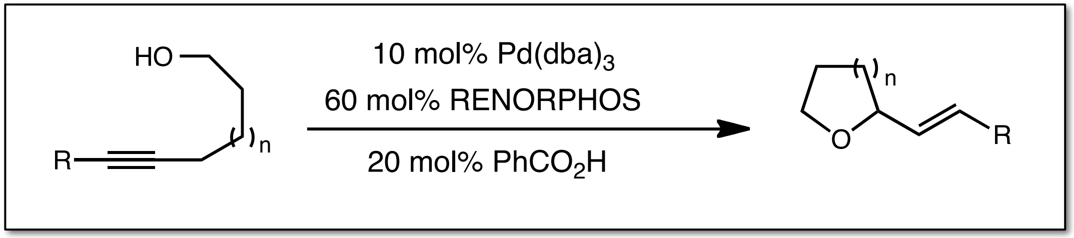


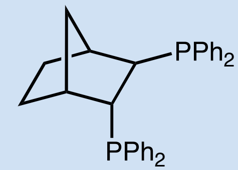


Lutete, L. M.; Kadota, I.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 1622.

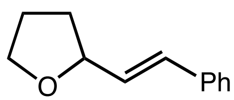
Palladium-Catalyzed Intramolecular Asymmetric Hydroalkoxylation of Alkynes

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

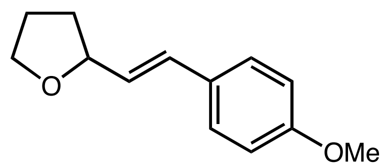




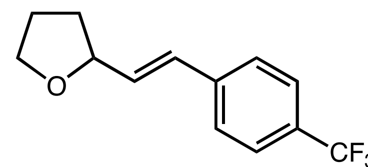
(R,R)-RENORPHOS



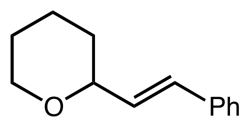
52%, 80% ee



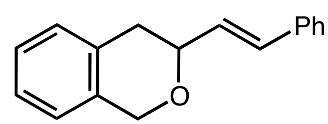
48%, 40% ee



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)

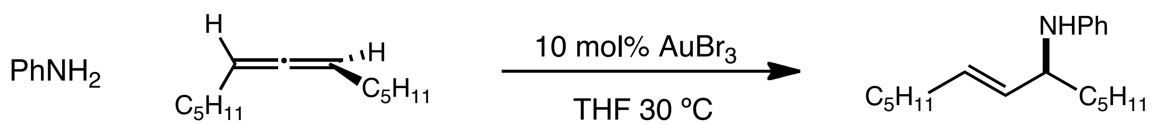
Patil, N. T.; Lutete, L. M.; Wu, H.; Pahadi, N. K.; Gridnev, I. D.; Yamamoto, Y. *J. Org. Chem.* **2006**, *71*, 4270.

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):

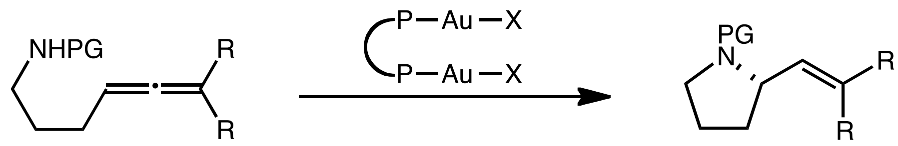


80%, 99% ee

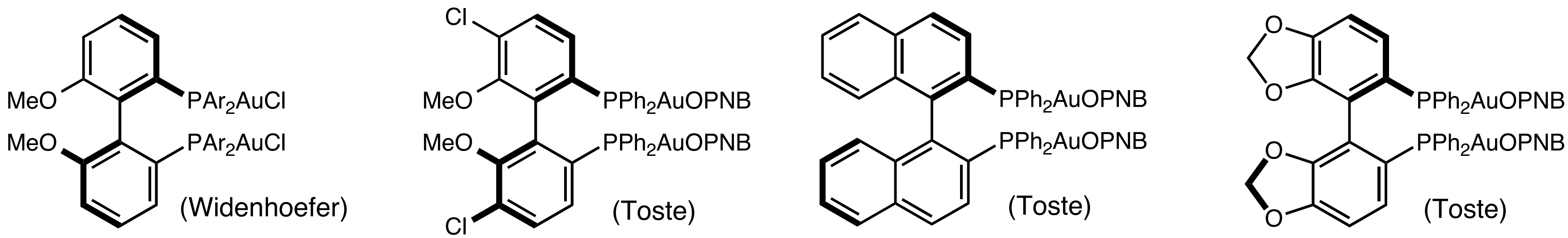
Nishina, N.; Yamamoto, Y. *Angew. Chem. Int. Ed.* **2006**, *45*, 3314.

Gold(I)-Catalyzed Asymmetric Hydroamination of Aminoallenes

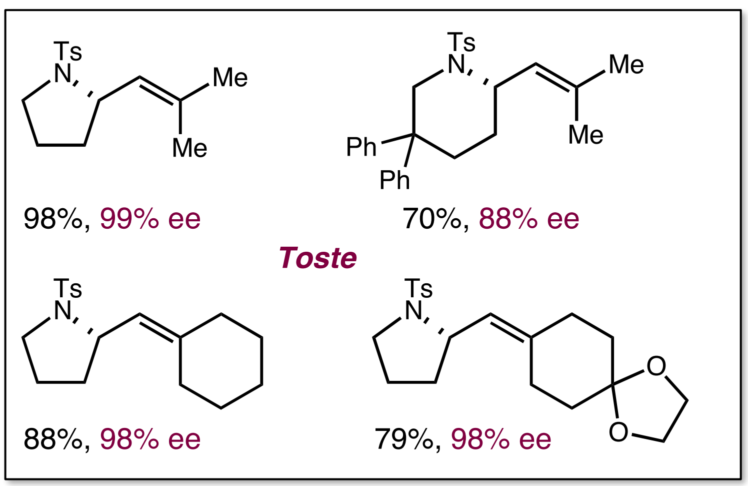
- The first enantioselective gold-catalyzed hydroaminations were by Toste and Widenhoefer in 2007 using dinuclear gold(I)-phosphine complexes with biaryl-based backbone

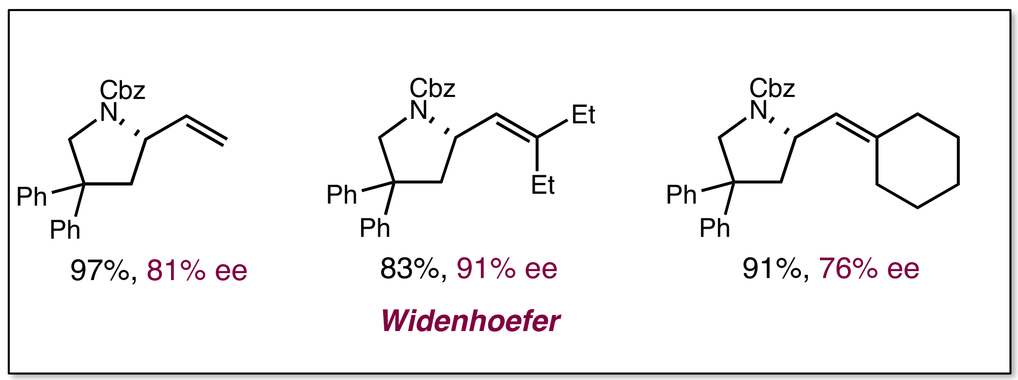


PG = Ts (Toste, 41-99%, 70-99% ee)
Cbz (Widenhoefer, 61-99%, 34-91% ee)



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

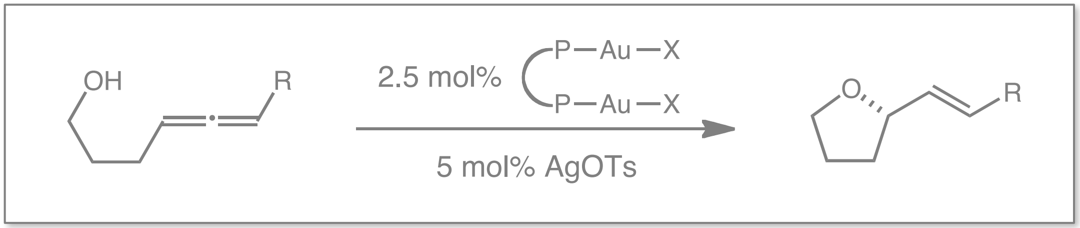


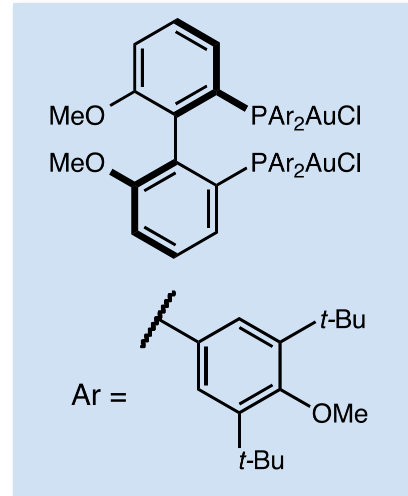


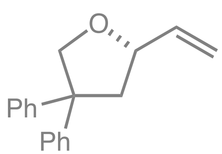
LaLonde, R. L.; Sherry, B. D.; Kang, E. J.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 2452.
Zhang, Z.; Bender, C. F.; Widenhoefer, R. A. *Org. Lett.* **2007**, *9*, 2887.

Gold(I)-Catalyzed Asymmetric Hydroamination and Hydroalkoxylation

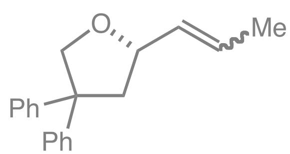
■ Widenhoefer's general protocol can be extended to other substrate classes



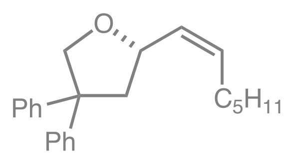




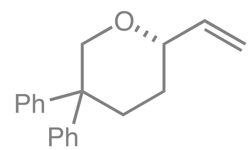
67%, 93% ee



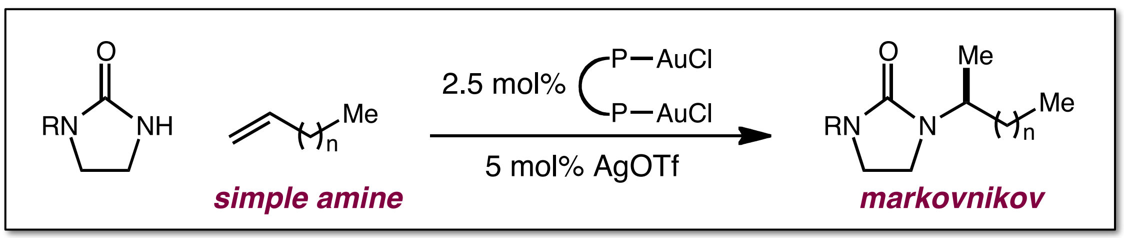
95%, 1:1 E/Z, 93, 95% ee
(from racemic alllene)



88%, >20:1 Z/E, >95% ee
(from allene at 94% ee)

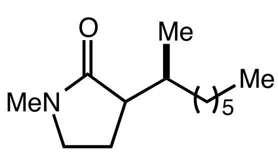


96%, 88% ee

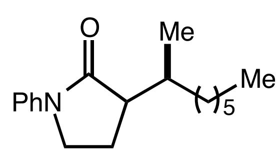


First intermolecular asymmetric hydroamination catalyzed by gold(I)

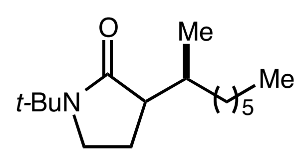
substrate scope demonstrated for the asymmetric variant is very limited



86%, 76% ee



80%, 71% ee

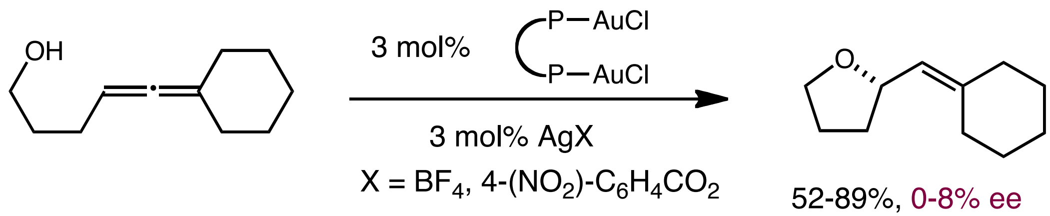


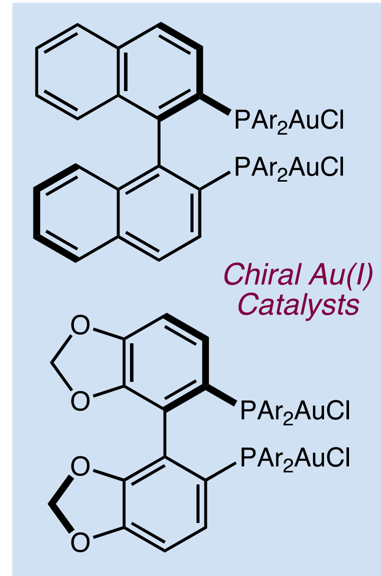
89%, 78% ee

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.

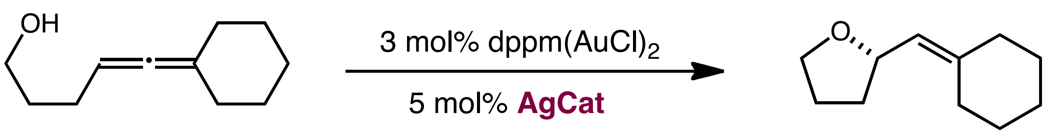
Gold(I)-Catalyzed Asymmetric Hydroamination and Hydroalkoxylation

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

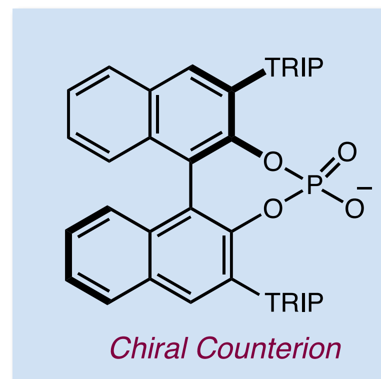




- Employing a chiral counterion gave significantly better results

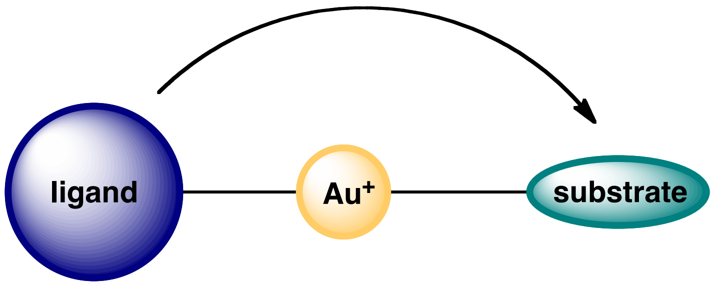


CH_2Cl_2	76%, 65% ee
THF	83%, 76% ee
benzene	**90%, 97% ee**

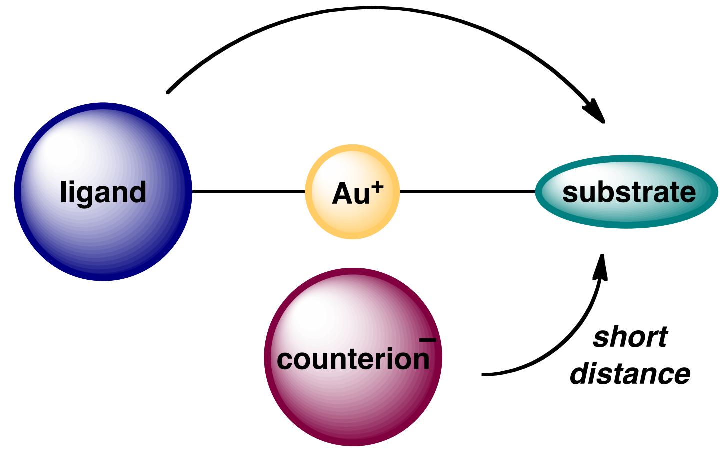


Hamilton, G. L.; Kang, E. J.; Mba, M.; Toste, F. D. *Science* **2007**, *317*, 496.

Gold(I)-Catalyzed Asymmetric Hydroamination and Hydroalkoxylation



Au(I) complexes have linear coordination geometry



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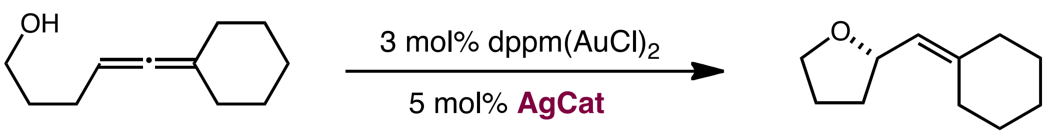
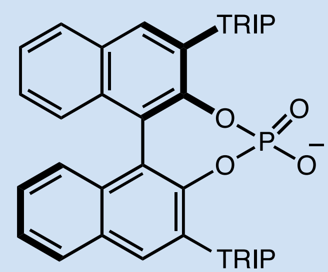


CH_2Cl_2	76%, 65% ee
THF	83%, 76% ee
benzene	**90%, 97% ee**

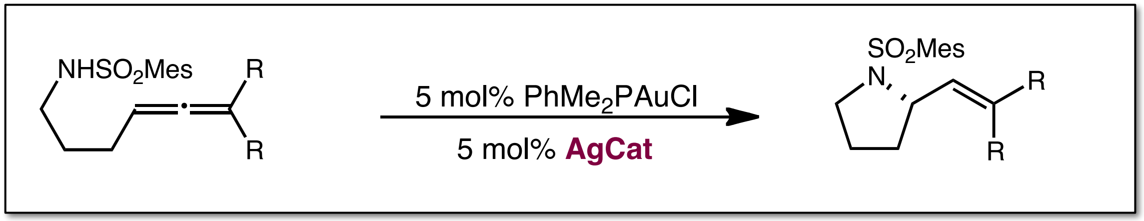


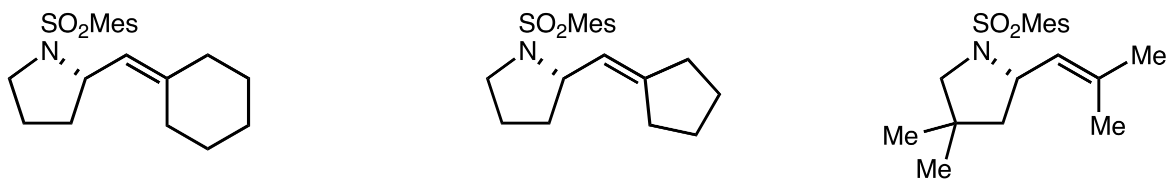
Chiral Counterion

Hamilton, G. L.; Kang, E. J.; Mba, M.; Toste, F. D. *Science* **2007**, *317*, 496.

Gold(I)-Catalyzed Asymmetric Hydroamination and Hydroalkoxylation

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

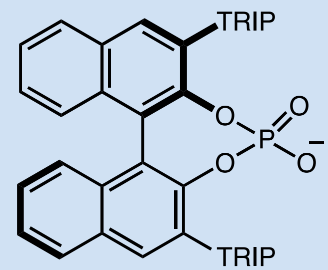




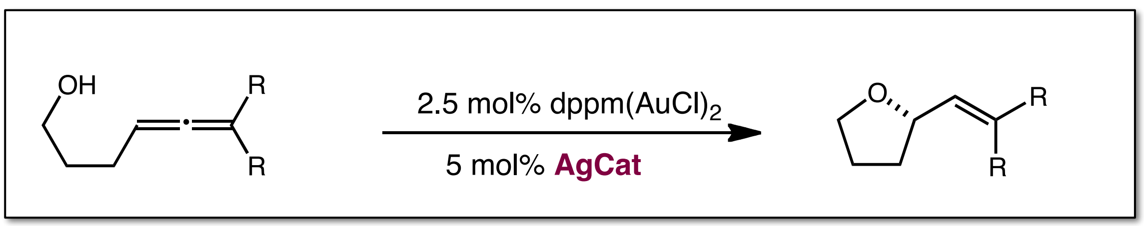
97%, 96% ee

88%, 98% ee

84%, 99% ee



Chiral Counterion



90%, 97% ee

91%, 95% ee

79%, 99% ee

81%, 90% ee

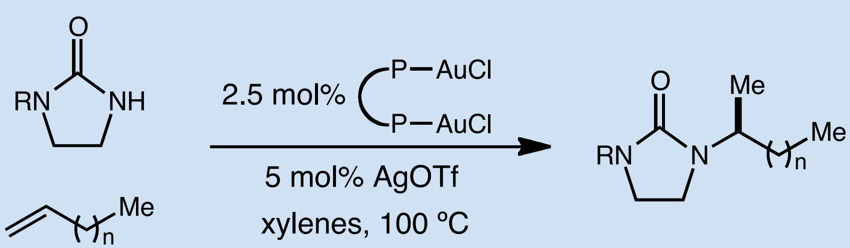
Hamilton, G. L.; Kang, E. J.; Mba, M.; Toste, F. D. *Science* **2007**, *317*, 496.

Rhodium-Catalyzed Asymmetric Hydroamination of Aminoalkenes

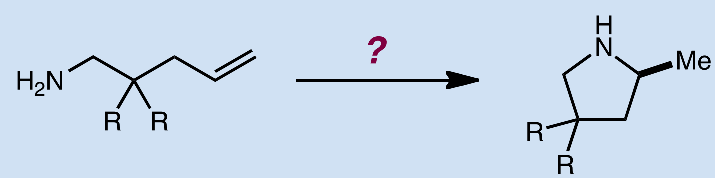
- Late-transition metal catalyzed asymmetric hydroaminations generally require activated substrates (allenes, strained alkenes, dienes, styrenes) or alkynes

C=C π-bond of an allene is ~ 10 kcal/mol less stable than the C=C π-bond of a simple alkene

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



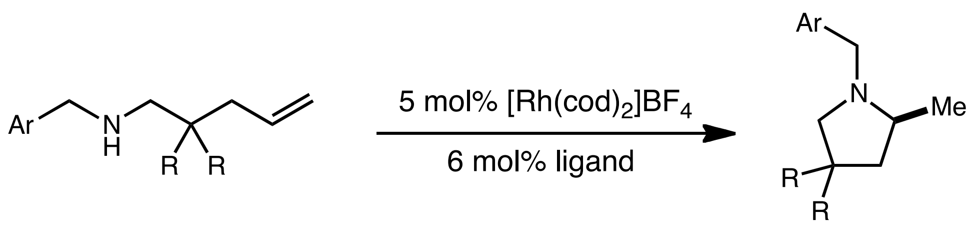
Widenhoefer, 2009

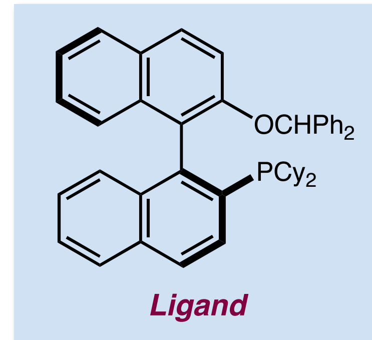


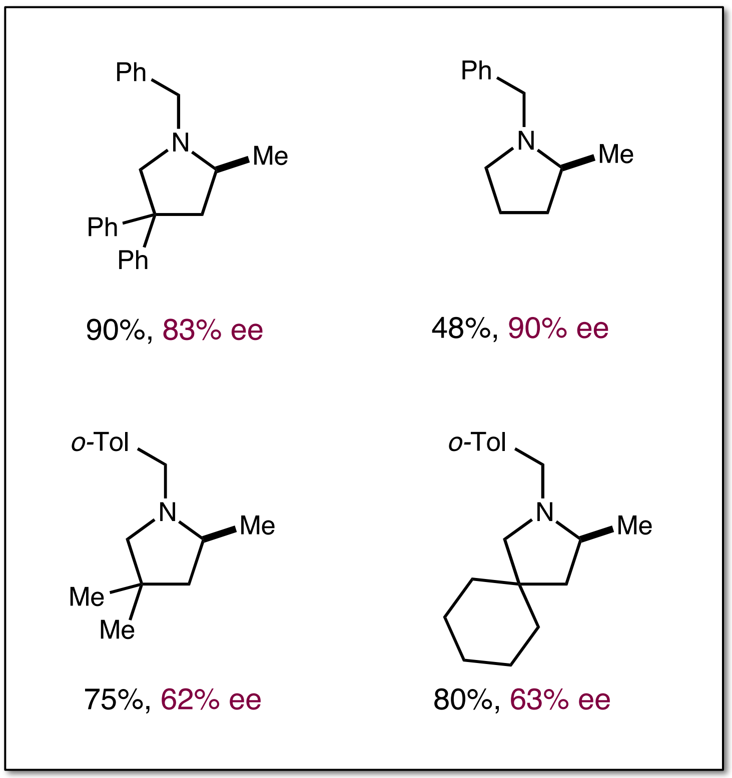
What about the benchmark reaction?

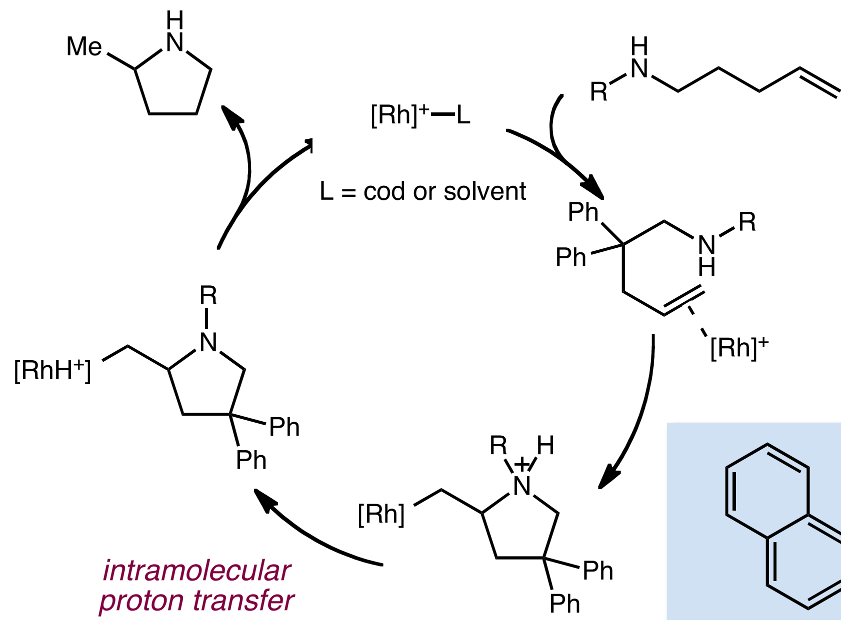
Rhodium-Catalyzed Asymmetric Hydroamination of Aminoalkenes

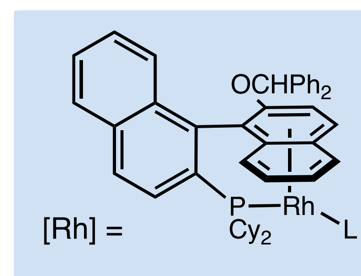
- In 2010, Buchwald introduced the first rhodium enantioselective hydroamination of aminoalkenes











Shen, X.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2010**, *49*, 564.

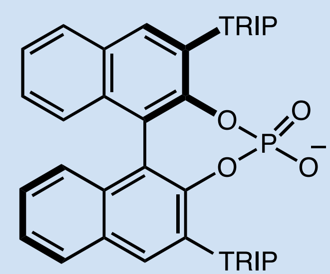
Late Transition Metal-Catalyzed Hydroaminations: Summary

- 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	***CONS***	Limited examples for simple alkenes
	Least air and moisture sensitive		
	Both inter- and intramolecular examples		
	Higher enantioselectivities		

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

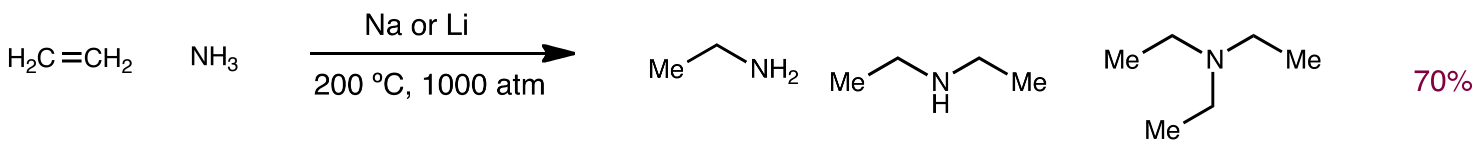
hydroamination and hydroalkoxylation



Base-Catalyzed Hydroaminations

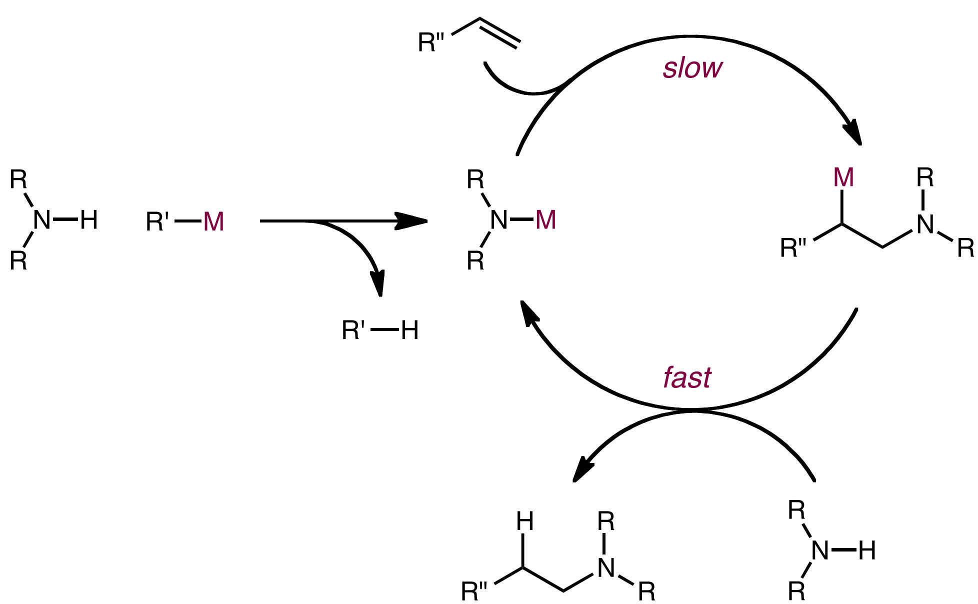
Main Group Metals: Base-Catalyzed Asymmetric Hydroamination

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



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

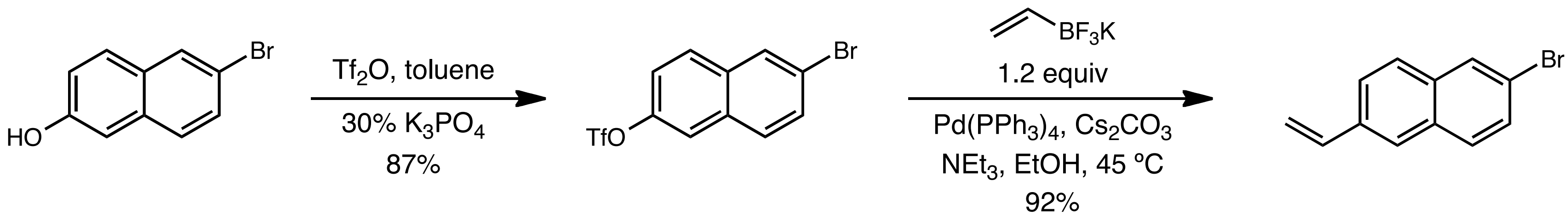
- Reaction proceeds through the highly nucleophilic alkali metal amide

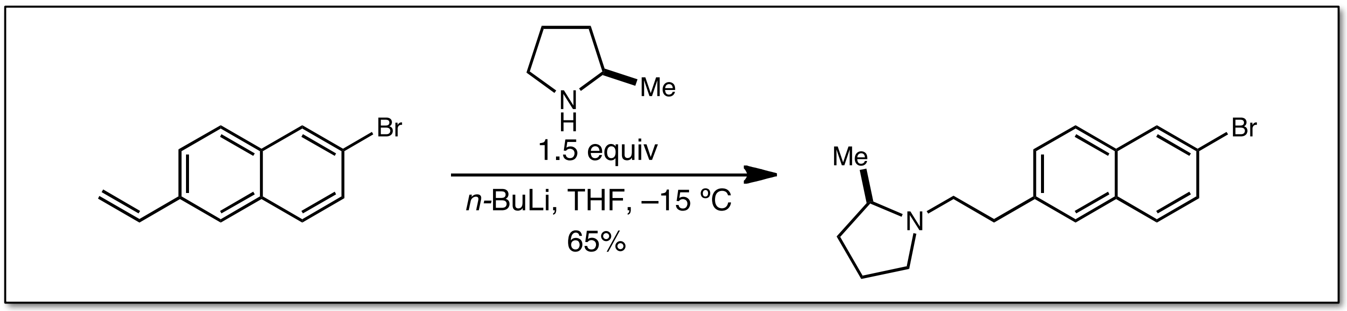


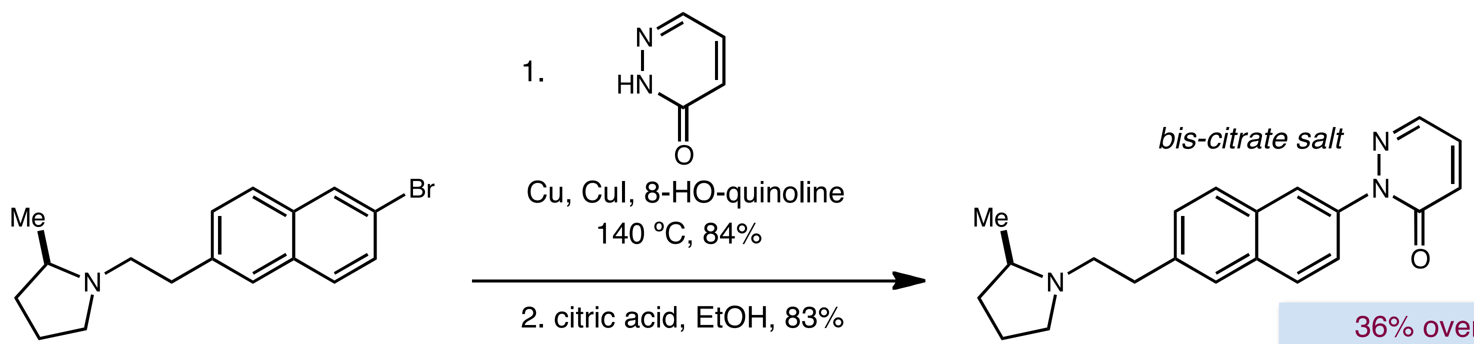
Deprotonation of the amine enables nucleophilic attack on non-activated alkenes

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-inhibior







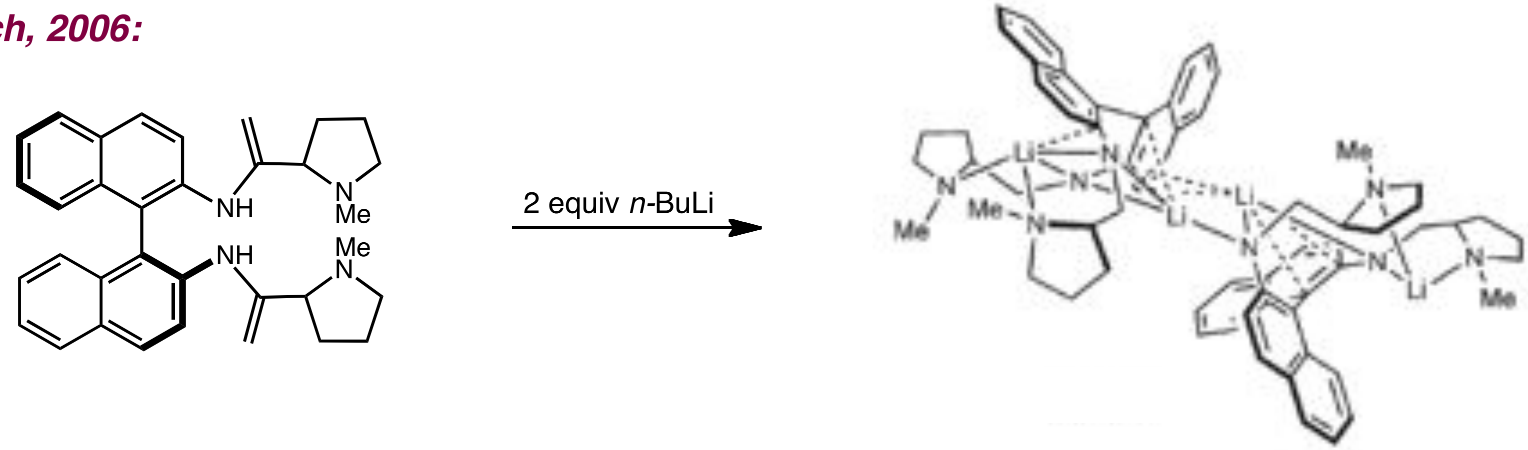
36% overall yield
4 steps (+ salt formation)
former synthesis: 8 steps

Ku, Y.-Y.; Grieme, T.; Pu, Y.-M.; Bhatia, A. V. *Adv. Synth. Catal.* **2009**, *351*, 2024.

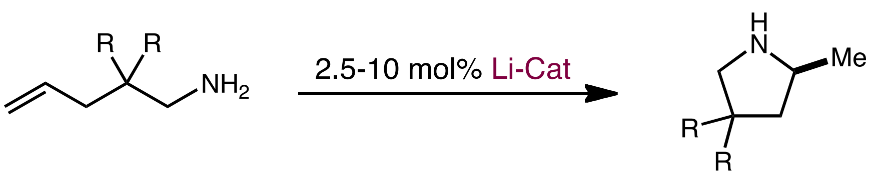
Main Group Metals: Base-Catalyzed Asymmetric Hydroamination

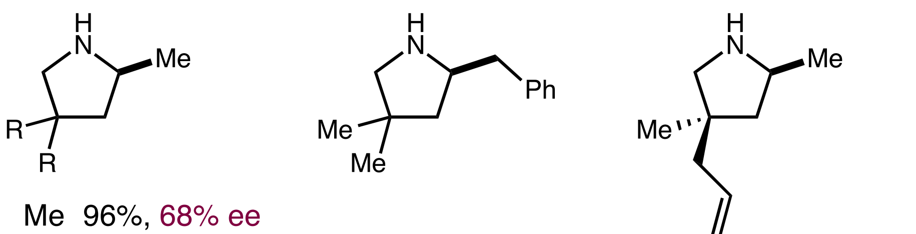
- Despite being known for over 50 years, there is very limited reports of asymmetric variants

Hultzsch, 2006:



- Cyclization proceeds with high yields and moderate selectivity

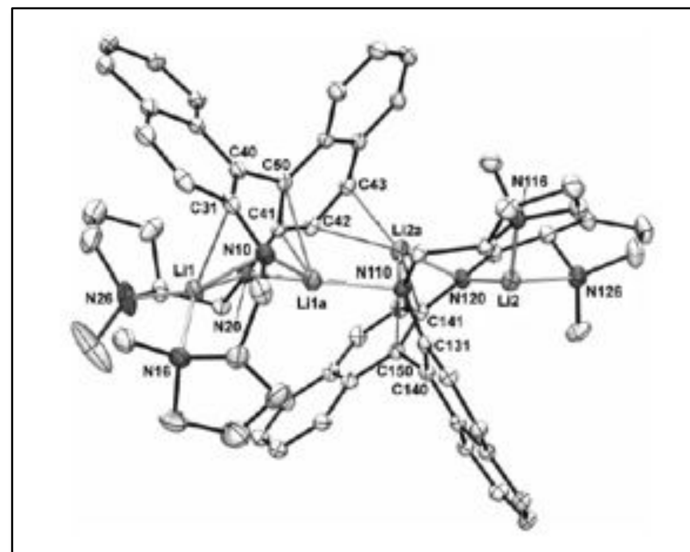




R = Me 96%, 68% ee
Ph 97%, 31% ee
-$(CH_2)_4$- 98%, 74% ee

98%, 17% ee

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



Horrillo Martinez, P.; Hultzsch, K. C.; Hampel, F. *Chem. Commun.* **2006**, 2221.

Main Group Metals: Base-Catalyzed Asymmetric Hydroamination

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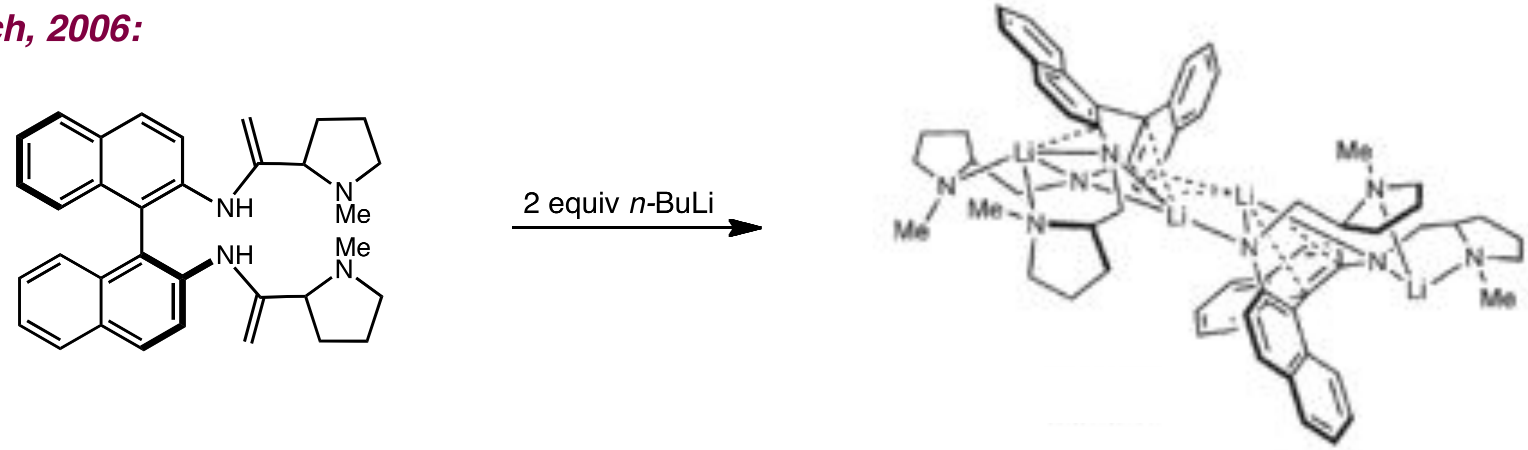

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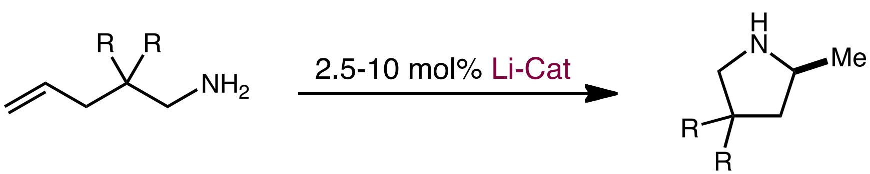
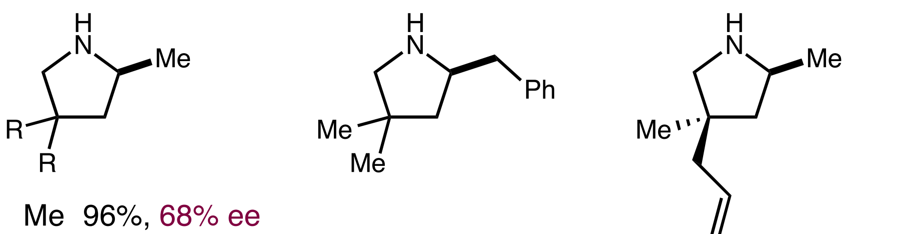


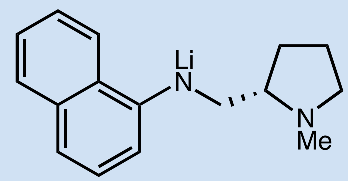


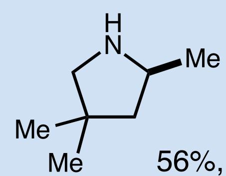
R = Me 96%, 68% ee
Ph 97%, 31% ee
$-(CH_2)_4-$ 98%, 74% ee

98%, 17% ee

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

close proximity of the lithium atoms is essential for catalyst performance





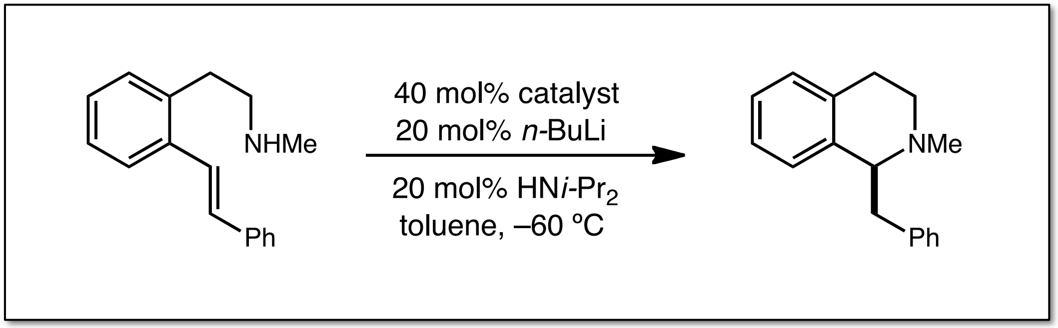
56%, 2% ee

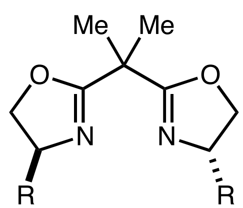
Horrillo Martinez, P.; Hultzsch, K. C.; Hampel, F. *Chem. Commun.* **2006**, 2221.

Main Group Metals: Base-Catalyzed Asymmetric Hydroamination

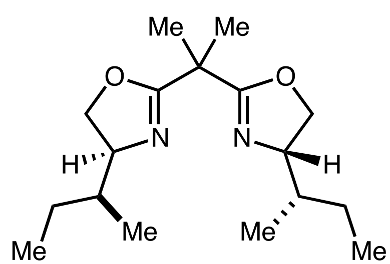
- Asymmetric intramolecular hydroaminations can be carried out with catalytic *n*-BuLi and bisoxazolines

Tomioka, 2007:

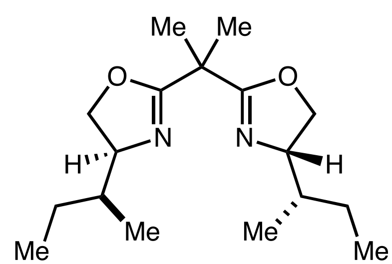




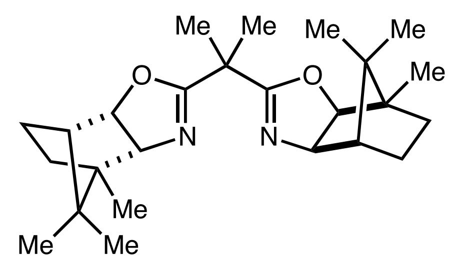
R = *i*-Pr	99%, 84% ee
t-Bu	89%, 19% ee
CH_2*i*-Pr	99%, 79% ee
CH_2Cy	99%, 76% ee
CH_2*t*-Bu	99%, 71% ee



99%, 66% ee



98%, **91% ee**



98%, 86% ee

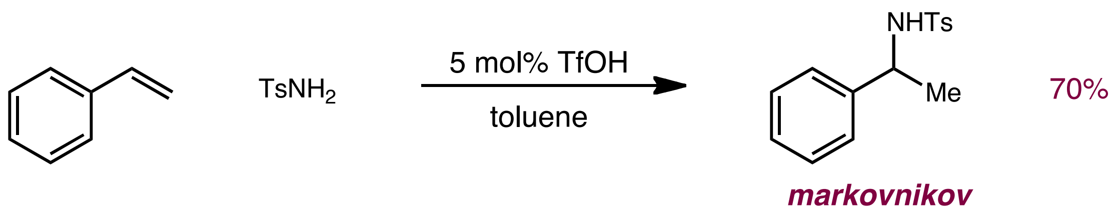
diisopropylamine acts as an external protonating agent

Ogata, T.; Ujihara, A.; Tsuchida, S.; Shimizu, T.; Kaneshige, A.; Tomioka, K. *Tetrahedron Lett.* **2007**, *48*, 6648.

Acid-Catalyzed Hydroaminations

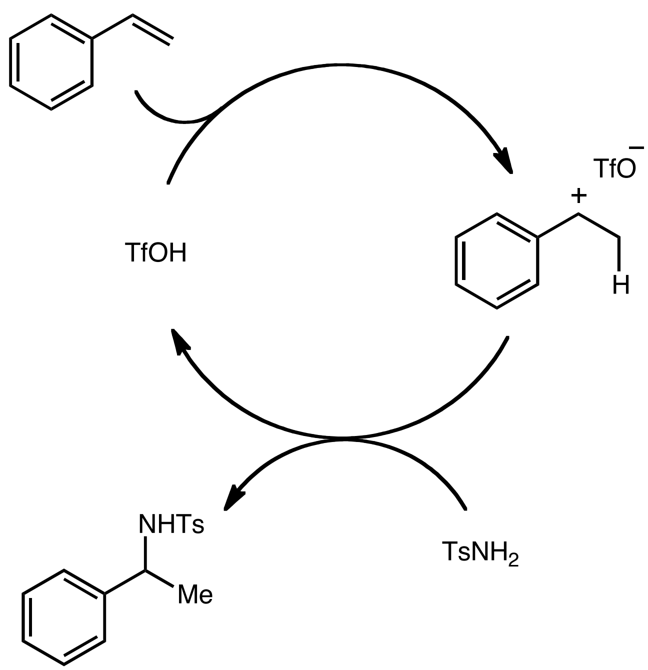
Non-Metal Catalysts: Acid-Catalyzed Asymmetric Hydroamination

- 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



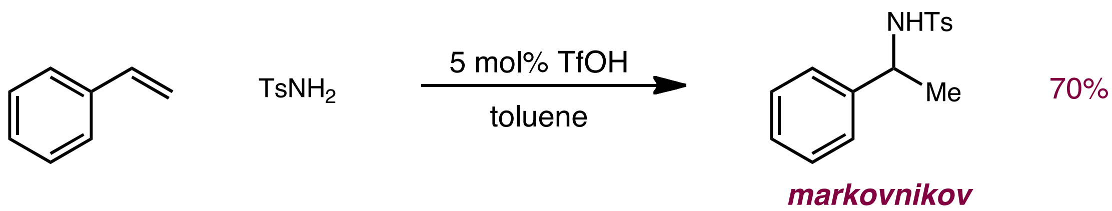
Acid-Catalysis Challenge:

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

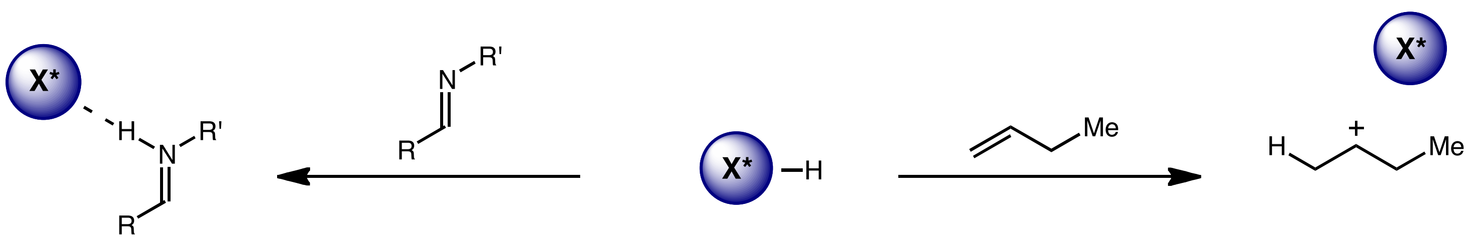
- Brønsted acids have not been used extensively as catalysts in hydroamination reactions



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



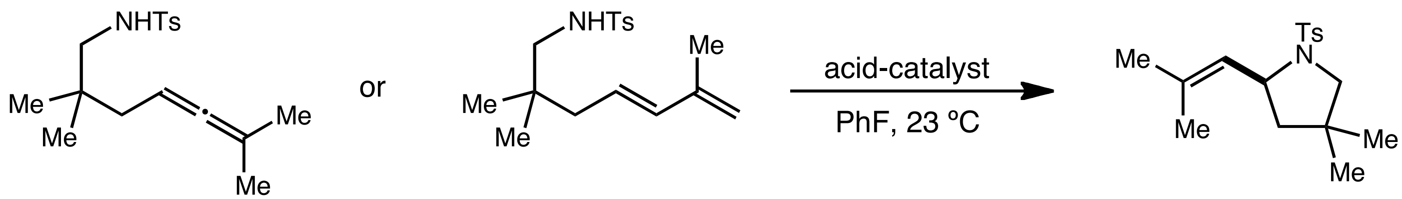
chiral bronsted acid

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

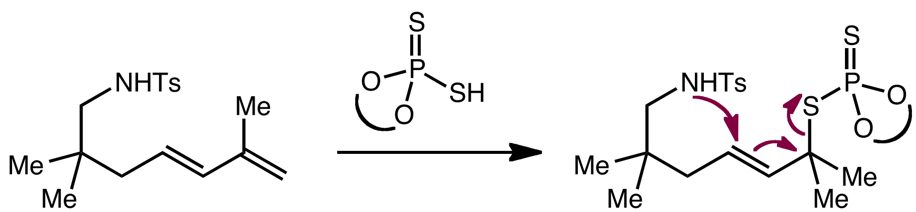
Electrostatic forces can hold conjugate base in proximity to the carbocation but will lack rigidity and poor enantiotopic discrimination

Non-Metal Catalysts: Acid-Catalyzed Asymmetric Hydroamination

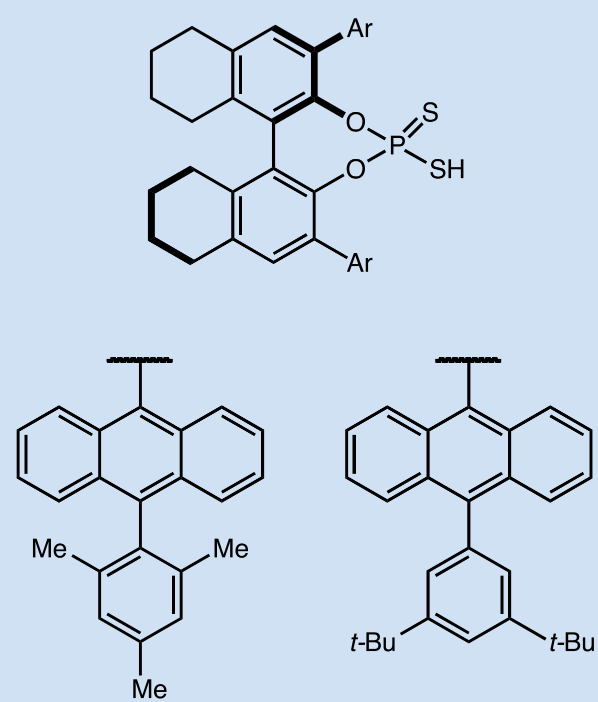
- Recently (February 2011) Toste reported the first asymmetric acid-catalyzed hydroamination



67-99%, 80-99% ee



Toste used a chiral Brønsted acid with a nucleophilic conjugate base that forms a covalent bond with the carbocation



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

Non-Metal Catalysts: Acid-Catalyzed Asymmetric Hydroamination

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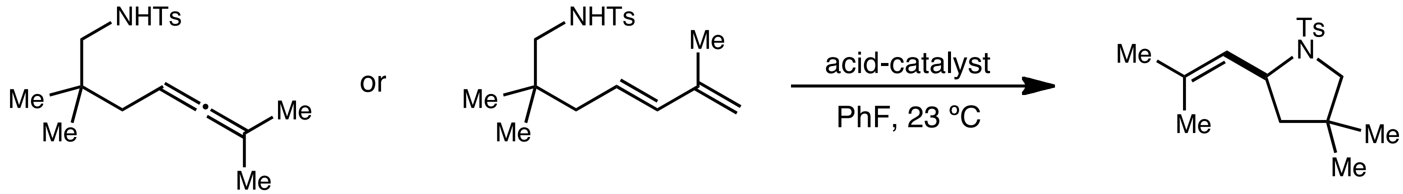
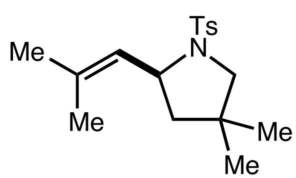
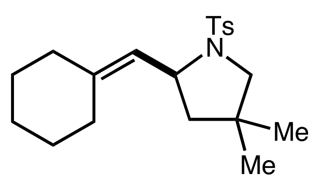


67-99%, 80-99% ee

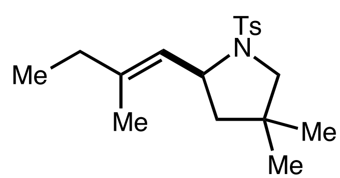
via dienes:



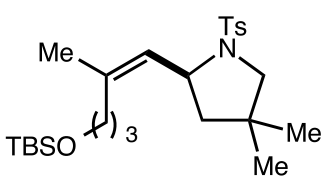
98%, 96% ee



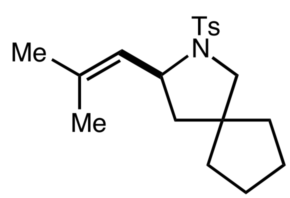
70%, 94% ee



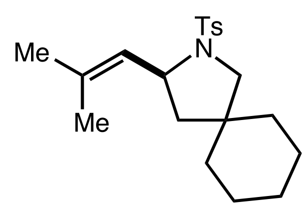
90%, 4.7:1 dr, 95, 90% ee



91%, 3.6:1 dr, 99, 80% ee

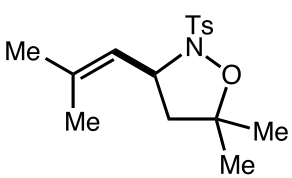


99%, 96% ee

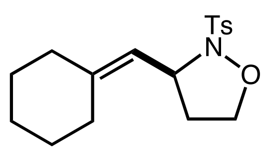


91%, 97% ee

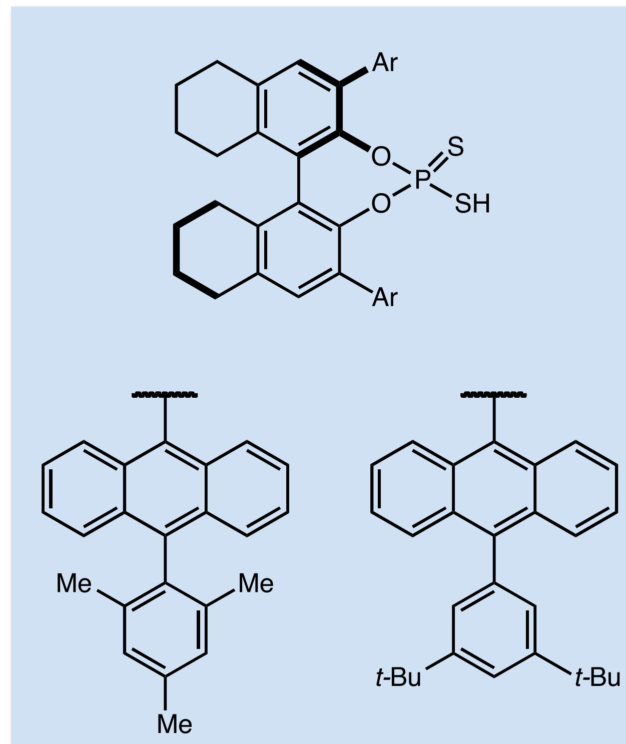
via allenes



70%, 90% ee



67%, 92% ee



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

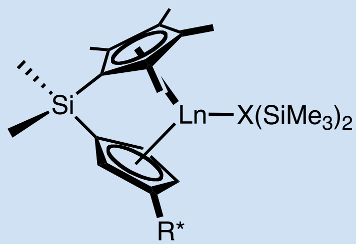
Catalytic Asymmetric Hydroamination (and Alkoxylation)

■ Five main catalytic pathways for asymmetric hydroamination reactions

Rare Earth Metal Catalysis

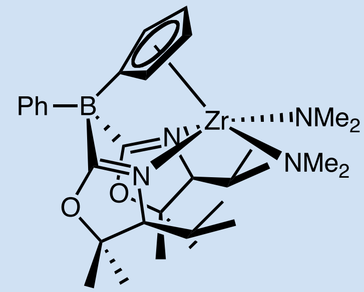
intramolecular aminoalkenes

intermolecular simple alkenes



Group 4 Metal Catalysis

intramolecular aminoalkenes



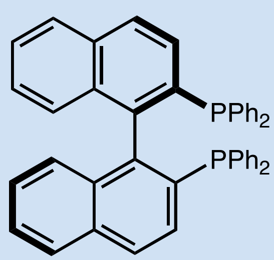
Late Transition Metal Catalysis

intermolecular strained alkenes, styrenes, conjugated dienes

intramolecular aminoalkene, aminoallene, aminoalkyne

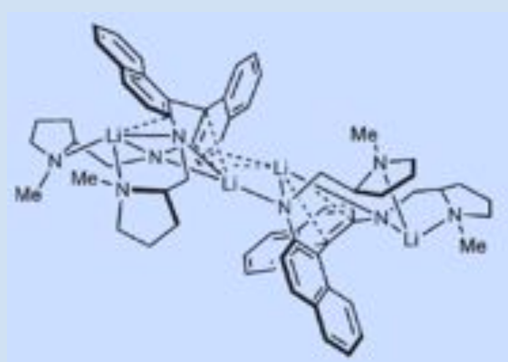
Ir Pd

Au Rh



Base Catalysis

intramolecular aminoalkenes



Acid Catalysis

intramolecular aminodienes/allenes