Catalytic Asymmetric Hydroaminations
(And Hydroalkoxylation, But Mostly Hydroaminations)

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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

Hydroamination Reactions

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

  synthesis of amines:

  \[ \text{OH} \quad \text{\rightarrow} \quad \text{NH}_2 \]
  \[ \text{Br} \quad \text{\rightarrow} \quad \text{NH}_2 \]
  \[ \text{O} \quad \text{\rightarrow} \quad \text{NH}_2 \]
  \[ \text{NO}_2 \quad \text{\rightarrow} \quad \text{NH}_2 \]

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

  hydroamination reaction:

  \[ \text{direct addition of an amine across a carbon-carbon multiple bond} \]

- 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 \( \pi \)-system
  regioselectivity (markovnikov vs. anti-markovnikov) for intermolecular reactions
  ➔ anti-markovnikov on the "Top 10 Challenges for Catalysis" in 1993

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*

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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 metalloocene-based catalysts

\[ \text{H}_2\text{N}-\text{CH}_2-\text{CH}_2-\text{CH}-(\text{CH}_2)_n-\text{CH}-(\text{CH}_2)_m-\text{NH}_2 \]  
1-5 mol% catalyst  
\[ \text{Me}_2\text{NCH}_2\text{CH}_2\text{CH}-(\text{CH}_2)_n\text{CH}-(\text{CH}_2)_m\text{CH}_2\text{NHMe} \]

TOF:  
- 13 (25 °C)  
- 125 (25 °C)  
- 5 (60 °C)  
- 13 (80 °C)  
- 84 (25 °C)

Mechanism for Rare Earth Metal-Catalyzed Hydroaminations

- Transformation proceeds through a rare earth metal amido species

\[ X = \text{CH, N} \]

**catalyst activation**

**protonolysis**
\[ \Delta H \sim -13 \text{ kcal/mol} \]

**olefin insertion**
rate-limiting step
\[ \Delta H \sim 0 \text{ kcal/mol} \]

For aminoalkynes, aminoallenes, conjugated aminodienes

olefin insertion: \( \Delta H \sim -19 \) to \(-35 \) kcal/mol
protonolysis: \( \Delta H \sim 0 \) 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.

\[
\text{H}_2\text{N}-\text{Me}-\text{Me} \xrightarrow{\text{catalyst}} \text{Me}-\text{N}\text{Me}
\]

Lu–CH(TMS)_2
0.977 Å
<1 h\(^{-1}\) (80 °C)

Sm–CH(TMS)_2
1.079 Å
48 h\(^{-1}\) (60 °C)

La–CH(TMS)_2
1.160 Å
95 h\(^{-1}\) (25 °C)

increasing ionic radii / decreased steric encumbrance

increasing reactivity

Lu–CH(TMS)_2
<1 h\(^{-1}\) (80 °C)

\[
\text{Si} \quad \text{Lu–CH(TMS)}_2
\]

75 h\(^{-1}\) (80 °C)

Si–N–Lu–CH(TMS)_2
90 h\(^{-1}\) (25 °C)

- Trend usually holds for alkenes using metalloocene 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

![Diagram of lanthanocene catalysts and chiral ligands](image)

- R* = (+)-neomethyl
- R* = (-)-menthyl
- R* = (-)-phenylmenthyl

![Diagram of reaction mechanism](image)

- R* = (-)-menthyl
- 74% ee (S)

Rare Earth Metal-Catalyzed Asymmetric Hydroamination: Seminal Work

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

\[
R^* = \begin{cases} 
(+)-\text{neomenthyl} & \\
(-)-\text{menthyl} & \\
(-)-\text{phenylmenthyl} & 
\end{cases}
\]

Rare Earth Metal-Catalyzed Asymmetric Hydroamination: Seminal Work

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

\[ R^* = \begin{align*}
& \text{Me} \quad \text{Me} \\
& \text{Me} \quad \text{Me} \\
& \text{Me} \quad \text{Ph} \\
\end{align*} \]

(+)-neomenthyl \quad (-)-menthyl \quad (-)-phenylmenthyl

*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

![Catalyst Structure](image)

\[
R^* = \begin{align*}
\text{H}_{2}N & \xrightarrow{\text{catalyst}} \text{Me} \\
\text{H}_{2}N & \xrightarrow{25 \degree C} \text{Me} \\
\text{H}_{2}N & \xrightarrow{\text{catalyst}} \text{Me}
\end{align*}
\]

- **ee of product is independent of ee of precatalyst**

**References**

Epimerization of Chiral Lanthanocene Complexes

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

But why does racemic catalyst give enantioenriched product?

- 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-metalloocene ligands were reported

Chiral Bisarylamido and Aminophenolate Catalysts

 Complexes were shown to be configurationally stable under hydroamination conditions

**Chiral Rare Earth Metal Catalysts Based on Non-Cyclopentadienyl Ligands**

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

![Chemical diagram showing the reaction of a catalyst with a substrate, followed by the formation of a product with specified enantiomeric excess (ee) and diastereomeric ratio (dr).]

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

Chiral Rare Earth Metal Catalysts Based on Non-Cyclopentadienyl Ligands

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

![Catalyst Structure]

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

![Graph]

Chiral Rare Earth Metal Catalysts Based on Non-Cyclopentadienyl Ligands

- Livinghouse reported a bisthiolate yttrium complex showing less substrate dependence

\[
\text{C}_{6}	ext{D}_{6}, 60 \degree \text{C}
\]

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....

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 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

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

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

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

\[\text{Me-}\text{CH=CH} \quad \text{H}_2\text{N-}\text{Me} \rightarrow \begin{array}{c}
\text{Me} \quad \text{H}_2\text{N} \quad \text{Me} \\
\text{Me}\end{array} \quad \begin{array}{c}
\text{Me} \quad \text{H}_2\text{N} \quad \text{Me} \\
\text{Me}\end{array}
\]

*markovnikov*  *anti-markovnikov*
Asymmetric Intermolecular Hydroamination Catalyzed by Rare Earth Metals

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

\[ R^1\text{C} \quad 5 \text{ mol\% catalyst} \quad 150 \degree \text{C} \quad 85\% \text{ ee} \]

\[ R^1 \text{Me} \quad \text{benzene or toluene} \quad R^2 \text{NH}_2 \]

9 to 15 equiv \( \text{terminal alkene primary amine} \)

\[ \text{Me} \quad \text{Me} \quad \text{HN} \quad \text{Ph} \]
\[ \text{Me} \quad \text{HN} \quad \text{Ph} \]
\[ \text{Me} \quad \text{HN} \quad \text{Ph} \]
\[ \text{Me} \quad \text{HN} \quad \text{Ph} \]

\[ n = 1 \quad 70\%, \ 61\% \text{ ee} \]
\[ n = 2 \quad 54\%, \ 61\% \text{ ee} \]
\[ n = 4 \quad 72\%, \ 57\% \text{ ee} \]

\[ \text{Me} \quad \text{Me} \quad \text{HN} \quad \text{C}_{\text{cyclo}} \]
\[ \text{Ph} \quad \text{HN} \quad \text{Me} \]
\[ \text{Ph} \quad \text{HN} \quad \text{Me} \]
\[ \text{Me} \quad \text{Me} \quad \text{HN} \quad \text{Ph} \]
\[ \text{Me} \quad \text{Me} \quad \text{HN} \quad \text{Ph} \]
\[ \text{Me} \quad \text{Me} \quad \text{HN} \quad \text{Ph} \]

\[ 61\%, \ 61\% \text{ ee} \]
\[ 68\%, \ 54\% \text{ ee} \]
\[ 67\%, \ 56\% \text{ ee} \]
\[ 75\% \text{ cv}, \ 73\% \text{ de} \]
\[ < 20\%, \ --\% \text{ de} \]

**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

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

![ansa-Metallocene](Marks)

![binaphtholate/biphenolate](Marks, Hultsch, Scott)

![bisthiolate](Livinghouse)

![Y-bisthiolate](Me, Me, NHR³) → ![9 h, 87% ee](Me, Me, Me)

![Y-binaphtholate](H₂N-Ph) → ![72, 61% ee](Me, Me, Me)
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

- 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

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**Scott:**

![Reactions and structures](image)

- 64% ee, 4 h
- 14% ee, 48 h
- 82% ee, 3 h
- 20% ee, 3 h

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**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.

![Mechanism diagram]

- 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

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Year</th>
<th>Yield</th>
<th>ee (%)</th>
<th>Substrates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bergman, 2006</td>
<td></td>
<td>33-99%</td>
<td>33-80%</td>
<td>(8 substrates)</td>
</tr>
<tr>
<td>Schaefer (Scott), 2007</td>
<td>82-98%</td>
<td>62-93%</td>
<td>ee</td>
<td>(7 substrates)</td>
</tr>
<tr>
<td>Scott, 2008</td>
<td></td>
<td>&gt;95%</td>
<td>14-70%</td>
<td>(2 substrates)</td>
</tr>
<tr>
<td>Zl, 2009</td>
<td></td>
<td>83-100%</td>
<td>38-72%</td>
<td>(3 substrates)</td>
</tr>
</tbody>
</table>

Asymmetric Neutral Group 4 Metal-Catalyzed Hydroamination

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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)

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Gott, A. L.; Clarke, A. J.; Clarkson, G. J.; Scott, P. *Chem. Commun.* **2008**, *1422.*

Asymmetric Neutral Group 4 Metal-Catalyzed Hydroamination

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![Catalyst Diagram]

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33-99%, 33-80% ee
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**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

---

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.

Asymmetric Neutral Group 4 Metal-Catalyzed Hydroamination

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

\[
\text{R}^1 \text{R}^2 \quad \xrightarrow{10 \text{ mol}\% \text{ catalyst}} \quad \text{Me} \quad \text{Me}
\]

\[\text{C}_6\text{D}_6, 25 \degree \text{C}\]

>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

In general, restricted to \(\beta\)-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 (e.g., pyrrolidines with β-substitution)

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

\[ \text{Ph} \equiv \text{Ph} \equiv \text{NH}_2 \quad \xrightarrow{10 \text{ mol\% catalyst}} \quad \text{Ph} \equiv \text{Ph} \equiv \text{Me} \equiv \text{N} \equiv \text{Ph} \equiv \text{Ph} \equiv \text{NH}_2 \quad \text{C}_6\text{D}_6, \ 25 \ ^\circ\text{C} \]

>95% cv, 93% IY
93% ee
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**
Late Transition Metal-Catalyzed Asymmetric Hydroamination

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Lowest air and moisture sensitivity
Late Transition Metal-Catalyzed Asymmetric Hydroamination

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Lowest air and moisture sensitivity
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

- 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

Chemical reaction:

\[
\text{NH}_2 \text{C}_6\text{H}_5 + \text{Ir(PEt}_3)_2(\text{C}_2\text{H}_4)_2\text{Cl} \rightarrow \text{NPhC}_8\text{H}_7 \text{H}
\]

Catalyst: \(\text{Ir(PEt}_3)_2(\text{C}_2\text{H}_4)_2\text{Cl}\)

Product: \(\text{NPhC}_8\text{H}_7\text{H}\)

THF solvent

Chemical steps:
- **Reductive elimination**
- **Oxidative addition**
- **Coordination to exo face**

References:
Iridium-Catalyzed Intermolecular Hydroamination

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

\[
\begin{align*}
\text{Cyclohexaneamine} & \quad \xrightarrow{1 \text{ mol\% } [\text{IrCl}((\text{PP})_2], [N(\text{P}(\text{NMe}_2)_3)_2]^+\text{F}^-} \\
& \quad \quad \text{75 °C} \quad \text{Naphthylcyclopenteneamine}
\end{align*}
\]

- **81\% IY, 38\% ee**
  - 3.4 h\(^{-1}\)

- **22\% IY, 95\% ee**
  - 0.15 h\(^{-1}\)

**Fluoride required for yield and enantioselectivity**

Possible roles: acts as a good \(\pi\)-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.

$$\text{1 mol}\% \text{[Ir(coe)$_2$Cl]$_2$} \rightarrow \text{2 mol}\% \text{(R)-DTBM-Segphos} \rightarrow \text{2 mol}\% \text{KHMDS} \rightarrow 70 \degree\text{C}$$

<table>
<thead>
<tr>
<th>R</th>
<th>Yield</th>
<th>Enantiomeric Excess</th>
</tr>
</thead>
<tbody>
<tr>
<td>t-Bu</td>
<td>85%</td>
<td>92% ee</td>
</tr>
<tr>
<td>Br</td>
<td>91%</td>
<td>96% ee</td>
</tr>
<tr>
<td>OMe</td>
<td>75%</td>
<td>98% ee</td>
</tr>
<tr>
<td>CF$_3$</td>
<td>77%</td>
<td>91% ee</td>
</tr>
</tbody>
</table>

94%, 99% ee

88%, 99% ee

90%, 99% ee

84%, 98% ee

Palladium-Catalyzed Asymmetric Intermolecular Hydroamination

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

\[
\text{R} - \text{NH}_2 + \text{Cy} \rightarrow \text{R} - \text{NH} - \text{Cy}
\]

5 mol% \([\text{Pd}(\pi\text{-allyl})\text{Cl}]_2\)
11 mol% ligand
23 °C, 120 h

![ligand]

<table>
<thead>
<tr>
<th>Product</th>
<th>Yield</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me (\pi\text{-allyl}-\text{Pd})</td>
<td>63%</td>
<td>92% ee</td>
</tr>
<tr>
<td>Me (\pi\text{-allyl}-\text{MePd})</td>
<td>59%</td>
<td>90% ee</td>
</tr>
<tr>
<td>(\text{EtO}_2\text{C} - \pi\text{-allyl}-\text{Pd})</td>
<td>83%</td>
<td>95% ee</td>
</tr>
<tr>
<td>(\text{F}_3\text{C} - \pi\text{-allyl}-\text{Pd})</td>
<td>73%</td>
<td>95% ee</td>
</tr>
</tbody>
</table>

Palladium-Catalyzed Asymmetric Intermolecular Hydroamination

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

\[
\begin{array}{c}
\text{R-NH} \quad \text{R-NH} \\
\text{Ph} \quad \text{Ph}
\end{array}
\]

5 mol% [Pd(η-allyl)Cl]_2
11 mol% ligand
23 °C, 120 h

\[
\begin{array}{c}
\text{R-NH} \quad \text{R-NH} \\
\text{Ph} \quad \text{Ph}
\end{array}
\]

Palladium-Catalyzed Asymmetric Intermolecular Hydroamination of Styrenes

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

![Chemical structures and reactions](attachment:Chemical_Structures.png)
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

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

Wacker-type oxidation

Migratory insertion into Pd-H

Nucleophilic attack of amine on activated arene

Palladium-Catalyzed Hydroamination of Styrenes: Mechanism

Wacker-type oxidation

migratory insertion into Pd-H

nucleophilic attack of amine on activated arene

attack at C inversion

attack at Pd retention

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.

\[
\begin{align*}
&\text{HO} & \text{10 mol}\% \text{ Pd(dba)}_3 \\
&\text{R} = \equiv & \text{60 mol}\% \text{ RENORPHOS} \\
&\text{n} & \text{20 mol}\% \text{ PhCO}_2\text{H} \\
\end{align*}
\]

\[
\begin{align*}
\text{Cyclic product} & \text{Ph} & \text{52\%, 80\% ee} \\
\text{Cyclic product} & \text{Ph} & \text{48\%, 40\% ee} \\
\text{Cyclic product} & \text{Ph} & \text{60\%, 82\% ee} \\
\text{Cyclic product} & \text{Ph} & \text{61\%, 78\% ee} \\
\text{Cyclic product} & \text{Ph} & \text{57\%, 86\% ee} \\
\end{align*}
\]

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 α-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):

\[
\text{PhNH}_2 + \text{H} \overset{10 \text{ mol}\% \text{ AuBr}_3, \text{THF} 30 ^\circ \text{C}}{\text{\rightarrow}} \text{NHPh} \]

80\%, 99\% ee

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

\[
\text{NHPG} \xrightarrow{\text{P-Au-X}} \text{PG} \\
\text{PG} = \text{Ts (Toste, 41-99\%, 70-99\% ee)} \\
\text{Cbz (Widenhoefer, 61-99\%, 34-91\% ee)}
\]

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

Gold(I)-Catalyzed Asymmetric Hydroamination and Hydroalkoxylation

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

![Chemical structures and reactions]

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

- 67%, 93% ee
- 95%, 1:1 E/Z, 93%, 95% ee (from racemic allene)
- 88%, >20:1 Z/E, >95% ee (from allene at 94% ee)
- 96%, 88% ee

- 86%, 76% ee
- 80%, 71% ee
- 89%, 78% ee

Gold(I)-Catalyzed Asymmetric Hydroamination and Hydroalkoxylation

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

\[
\text{OH} \quad \xrightarrow{3 \text{ mol\% } P-\text{AuCl}} \quad \xrightarrow{3 \text{ mol\% } AgX, X = BF_4, 4-(NO_2)-C_6H_4CO_2} \quad 52-89\%, 0-8\% \text{ ee}
\]

- Employing a chiral counterion gave significantly better results

\[
\text{OH} \quad \xrightarrow{3 \text{ mol\% dpmm(AuCl)_2}, 5 \text{ mol\% AgCat}} \quad \text{76\%, 65\% ee, 83\%, 76\% ee, 90\%, 97\% ee}
\]

Gold(I)-Catalyzed Asymmetric Hydroamination and Hydroalkoxylation

Employing a chiral counterion gave significantly better results

\[
\text{OH} \quad \text{3 mol\% dpdm(AuCl)}_2 \quad \text{5 mol\% AgCat} \\
\rightarrow \\
\text{76\%, 65\% ee} \quad \text{83\%, 76\% ee} \quad \text{90\%, 97\% ee}
\]

Gold(I)-Catalyzed Asymmetric Hydroamination and Hydroalkoxylation

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

\[
\begin{align*}
\text{NHSO}_2\text{Mes} & \quad \text{R} \\
\text{SO}_2\text{Mes} & \quad \text{N}_2 \quad \text{C} \\
\text{SO}_2\text{Mes} & \quad \text{R} \\
\text{SO}_2\text{Mes} & \quad \text{N}_2 \quad \text{C} \\
\text{SO}_2\text{Mes} & \quad \text{R} \\
\end{align*}
\]

97\%, 96\% ee

88\%, 98\% ee

84\%, 99\% ee

**Rhodium-Catalyzed Asymmetric Hydroamination of Aminoalkenes**

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

\[ \text{C=C } \pi\text{-bond of an allene is } \sim 10 \text{ kcal/mol less stable than the C=C } \pi\text{-bond of a simple alkene} \]

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

\[ \text{Widenhoefer, 2009} \]

*What about the benchmark reaction?*
Rhodium-Catalyzed Asymmetric Hydroamination of Aminoalkenes

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

\[
\text{ArH}_{\text{N}}\text{N}_{\text{R}}\rightarrow\text{Ar}\text{N}\text{Me}
\]

\[
\text{5 mol\% [Rh(cod)\textsubscript{2}]BF\textsubscript{4}}
\]

\[
6 \text{ mol\% ligand}
\]

**Late Transition Metal-Catalyzed Hydroaminations: Summary**

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

<table>
<thead>
<tr>
<th><strong>PROS</strong></th>
<th><strong>CONS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Good functional group tolerance</td>
<td>Limited examples for simple alkenes</td>
</tr>
<tr>
<td>Least air and moisture sensitive</td>
<td></td>
</tr>
<tr>
<td>Both inter- and intramolecular examples</td>
<td></td>
</tr>
<tr>
<td>Higher enantioselectivities</td>
<td></td>
</tr>
</tbody>
</table>

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

![Diagram of hydroamination and hydroalkoxylation](image-url)
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

\[ \text{H}_2\text{C}=\text{CH}_2 + \text{NH}_3 \xrightarrow{\text{Na or Li}} \text{Me-}\text{NH}_2 + \text{Me-}\text{NMe}_2 \text{Me} \quad 70\% \]


- 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-inhibitor.

\[
\text{HO} \underset{\text{Tf}_2\text{O, toluene}}{\xrightarrow{30\% K_3\text{PO}_4}} \text{Br} \quad \text{BF}_3\text{K} \quad \xrightarrow{\text{1.2 equiv}} \quad \text{Me} \\
\text{Br} \quad \text{Pd(PPH}_3)_4, \text{Cs}_2\text{CO}_3 \quad \text{NET}_3, \text{EtOH, 45} \degree \text{C}} \\
\text{1.5 equiv} \quad \xrightarrow{n-\text{BuLi, THF, } -15 \degree \text{C}} \quad \text{65%} \\
\text{Me} \\
\text{N} \\
\text{H} \\
\text{Me} \\
\text{Br} \\
\begin{array}{c}
\text{Cu, Cul, 8-HO-quinoline} \\
\text{140} \degree \text{C}, \text{84%} \\
\text{2. citric acid, EtOH, 83%}
\end{array}
\]

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

Main Group Metals: Base-Catalyzed Asymmetric Hydroamination

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

Hultsch, 2006:

Cyclization proceeds with high yields and moderate selectivity

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
- -(CH₂)₄ 98%, 74% ee
- 98%, 17% ee
- 98%, 1.2:1 dr, 64, 72% ee

Main Group Metals: Base-Catalyzed Asymmetric Hydroamination

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

**Tomioka, 2007:**

\[
\text{R} = \text{i-Pr} \quad 99\%, \; 84\% \; \text{ee} \\
\text{t-Bu} \quad 89\%, \; 19\% \; \text{ee} \\
\text{CH}_2\text{i-Pr} \quad 99\%, \; 79\% \; \text{ee} \\
\text{CH}_2\text{Cy} \quad 99\%, \; 76\% \; \text{ee} \\
\text{CH}_2\text{t-Bu} \quad 99\%, \; 71\% \; \text{ee}
\]

*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

\[
\text{TsNH}_2 + \text{E} \xrightarrow{5\ \text{mol}\% \text{ TfOH}} \text{NHTsMe} \quad 70\%
\]


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

**Acid-Catalysis Challenge:**

*amine is more basic than the \(\pi\)-system of the alkene/alkyne*

*formation of ammonium salts destroys nucleophilicity and avoids activation of the \(\pi\)-system*
Non-Metal Catalysts: Acid-Catalyzed Asymmetric Hydroamination

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

\[ \text{TsNH}_2 + \text{toluene} \xrightarrow{5 \text{ mol}\% \text{TfOH}} \text{MeNH}_2 \rightarrow 70\% \]

*markovnikov*


- 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 Brønsted 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

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

Non-Metal Catalysts: Acid-Catalyzed Asymmetric Hydroamination

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

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

**Base Catalysis**
- intramolecular aminoalkenes

**Acid Catalysis**
- intramolecular aminodienes/allenes