Asymmetric Aminohydroxylation of Alkenes

\[
\begin{align*}
\text{R} & \quad \text{XNCINa} \quad (X=\text{Ts, Ms, CBz, Boc, Teoc}) \\
\text{OR} & \quad \text{XNBrLi} \quad (X=\text{Ac}) \\
& \quad \begin{array}{c}
4 \text{ mol}\% \ K_2\text{OsO}_2(\text{OH})_4 \\
5 \text{ mol}\% \ (\text{DHQ})_2\text{PHAL} \\
1:1 \ \text{ROH:} \text{H}_2\text{O}
\end{array}
\end{align*}
\]

- originally developed with chloramine T \((\text{Na}^+\text{ClNTs}^-)\), as for a racemic protocol developed by Sharpless in the 1980s

- found that the reaction works better with smaller N-substituents, (eg MeSO_2^-), and even better still with salts of N-halocarbamates \((\text{NC(O)OR}; \text{ease of deprotection!})\) or N-haloamides

- regiocontrol is a problem, particularly with electronically unbiased alkene substituents

- in most respects the reaction is similar to the AD, including the model for asymmetric induction
  (note that, for a given olefin, the HO/NHR are delivered to the same face in both regioisomeric products)

chloramine-T: Angew., 1996, 35, 451
Scope of the asymmetric aminohydroxylation
(all reactions shown carried out with (DHQ)$_2$-PHAL; figure shown is ee)

**Symmetrical trans-alkenes:**

![Chemical structure of symmetrical trans-alkenes]

- R = Ts: 62
- R = Ms: 75
- R = Cbz: 91
- R = Ac: 94

**Symmetrical cis-alkenes:**

![Chemical structure of symmetrical cis-alkenes]

- R = Ts: 77
- R = Ms: 95
- R = Cbz: 84
- R = Ac: --

**Styrenes:**

![Chemical structure of styrenes]

- R = Ts: 50 2:1
- R = Ms: --
- R = Cbz: 93 1:1
- R = Ac: 88 1:6

**Cinnamates (electronically distinguished):**

![Chemical structure of cinnamates]

- R = Ts: 81 5:1
- R = Ms: 95 9:1
- R = Cbz: 94 10:1
- R = Ac*: 99 20:1

* - iPr ester

regiochemistry
Regiochemical control by adjustment of aromatic linking group

\[
\begin{align*}
\text{MeO} & \quad \text{O} \\
\text{Et} & \quad \text{N} \\
\text{MeO} & \quad \text{O} \\
\text{Et} & \quad \text{N} \\
\text{MeO} & \quad \text{O} \\
\text{Et} & \quad \text{N} \\
\end{align*}
\]

\[
\text{(DHQ)₂PHAL} \quad \text{or} \quad \text{(DHQ)₂AQN}
\]

- (DHQ)₂PHAL (94% ee) > 10 : 1
- (DHQ)₂AQN (95% ee)
- 21 : 79

\[
\begin{align*}
\text{Ph} & \quad \text{H} \\
\text{NHCbz} & \quad \text{Et} \\
\text{Ph} & \quad \text{H} \\
\text{NHCbz} & \quad \text{Et} \\
\text{Ph} & \quad \text{H} \\
\text{NHCbz} & \quad \text{Et} \\
\end{align*}
\]

\[
\text{(DHQ)₂PHAL} \quad \text{or} \quad \text{(DHQ)₂AQN}
\]

- (DHQ)₂PHAL (93% ee) ca. 1 : 1
- (DHQ)₂AQN 1 : 13
- (88% ee)

Asymmetric Hydrogenation of Alkenes

• H₂ is cheap and reduction is atom efficient! Can generate two asymmetric centres simultaneously

• Homogeneous catalysts based on Rh (I) or Ru (II) with chiral phosphine ligands

For Rh catalysts, general substrate structure:

\[ \text{e.g. Aminoacrylates (X=NH, E=CO}_2\text{R)} \]

Also (usually Ru catalysts):
• Enamides
• Acrylic acids
• Allylic alcohols
Asymmetric Homogeneous Hydrogenation with Chiral Diphosphines: Monsanto synthesis of L-DOPA

\[
\begin{align*}
\text{MeO} & \quad \text{CO}_2\text{Me} \\
\text{OMe} & \quad \text{NHAc}
\end{align*}
\]

\[0.1\% [(R,R)-(\text{dipamp})\text{Rh(COD)}]^+\text{BF}_4\]

\[3 \text{ atm } \text{H}_2, 50^\circ\text{C}, \text{H}_2\text{O} / \text{iPrOH}\]

\[94\% \text{ ee}\]

\[\begin{align*}
\text{MeO} & \quad \text{CO}_2\text{Me} \\
\text{OMe} & \quad \text{NHAc}
\end{align*}\]

\[\text{HBr}\]

\[\text{L-DOPA} \quad \text{(anti-Parkinson's)}\]

- First large-scale application of asymmetric hydrogenation, but the ligand lacks generality.
Mechanism of hydrogenation with Rh(I)dipamp

But...recent work suggests that this does not operate in all cases (e.g. electron-rich phosphines)... See commentary in Angew. Chem. Int. Ed. 2001, 40, 4611.
**Rh(I)-BINAP Complexes**

- Axially chiral binaphthyl diphosphine ligands offer improved ee's and wider substrate tolerance in aminoacrylate reduction.

![Diagram of Rh(I)-BINAP complex showing axial and equatorial coordination.](image-url)

Simplified by removing backbone:

Chiral environment has 4 quadrants, two "blocked" and two "open":

For alternative pictures, see Figure 8 in: Noyori, *J. Am. Chem. Soc.* **2002**, *124*, 6649
Rh(I)-BINAP-catalysed hydrogenation of aminoacrylates


Note that for a given ligand enantiomer, the sense of asymmetric induction is determined by acrylate geometry (hence need geometrically pure starting materials):

\[
\text{Ph} = \text{CO}_2R \quad \rightarrow \quad \text{Ph} = \text{CO}_2R
\]

\[
\text{H}_2, \text{MeOH} \quad \rightarrow \quad \text{H}_2, \text{MeOH}
\]

One drawback is that chirality transfer from chiral backbone to coordinating PPh\textsubscript{2} groups is not always efficient.
Also, no bis(diarylphosphine) ligand gives >99% ee for a range of acylaminoacrylates
**Rhodium (I)-diphosphole complexes:**
electron rich, sterically demanding ligand systems


- electron rich alkylphosphines allow increased back-bonding to alkene substrates - more tightly held
- flexible backbone in BPE leads to two ligand environments, one less selective than the other:

\[
\begin{align*}
\text{R groups held away} & \quad \text{from coordination sites} \\
\text{R groups held towards} & \quad \text{coordination sites}
\end{align*}
\]

...so rigid DuPHOS generally better (although BPE can still be useful with VERY hindered substrates)

DuPHOS and BPE are outstanding ligands for Rh catalysed hydrogenation of aminoacrylates

- unlike BINAP, the sense of enantioselectivity is independent of acrylamide geometry - mixtures can be used!

\[
\text{CO}_2\text{Me} \quad \text{R}_1 = \text{R}_2 = \text{H} \quad 99.8\% \text{ ee} \\
\text{Et} \quad \text{R}_1 = \text{H}, \text{R}_2 = \text{Me} \quad 99.6\% \text{ ee} \\
\text{Et} \quad \text{R}_1 = \text{Me}, \text{R}_2 = \text{H} \quad 99.4\% \text{ ee}
\]

- also works for N-Cbz aminoacrylates - direct access to usefully protected amino acids

- very substrate tolerant - the following all give >99% ee with Et-DuPHOS

\[
\text{Et} \quad \text{CO}_2\text{Me} \quad \text{R} = \text{H}, \text{Me}, \text{Et}, \text{i-Pr}, \text{Ph}, 1\text{-naph}, 2\text{-naph}, 2\text{-thiophenyl}, \text{ferrocenyl}, 4\text{-}(X)\text{-Ph}, 3\text{-}(X)\text{-Ph}, 3,5\text{-di}(X)\text{-Ph} \ (X = \text{F}, \text{Br}, \text{OMe}, \text{CF}_3)
\]

- even works for tetrasubstituted aminoacrylates - other ligands give <70% ee and are slow

\[
\text{Ph} \quad \text{Et} \quad \text{CO}_2\text{Me} \quad 88\% \text{ ee}
\]

Asymmetric reduction of enamides

ruthenium BINAP mediated reduction of cyclic enamides

\[
\text{[Ru(R-BINAP)(COD)]^+ TfO^-} \quad 4 \text{ atm. H}_2, \text{EtOH/DCM}
\]

(rhodium BINAP gives 70% ee)

N-acetyl-tetrahydropapaverine


rhodium DuPHOS mediated reduction of acyclic enamides

\[
0.2\% [\text{Rh((S,S)-Me-DuPHOS)(COD)]^+ TfO^-} \quad 60 \text{ psi H}_2, \text{MeOH}
\]

96% ee

Ru-diphosphine catalysed reduction of acrylic acids

\[ \text{R}_3\text{CO}_2\text{H} \quad \xrightarrow{(\text{BINAP})\text{Ru(OAc)}_2} \quad \text{R}_3\text{CO}_2\text{H} \]

\[ \text{R}_3\text{CO}_2\text{H} \quad \xrightarrow{1\% (S-\text{BINAP})\text{Ru(OAc)}_2} \quad \text{R}_3\text{CO}_2\text{H} \]


- Corresponding methyl esters are inert to this catalyst
Mechanism of hydrogenation with Ru BINAP complexes is different from Rh

- Like the rhodium counterpart, the hydrogenation is stereospecifically syn; but unlike the rhodium reaction, the α-hydrogen is incorporated from the gas source, the β-hydrogen from protonolysis by solvent

- Ruthenium (II) prefers to form monohydrides, whereas rhodium (I) prefers to form dihydrides (G. Wilkinson, Nature, 1965, 208, 1203)

Ru-BINAP catalysed reduction of allylic alcohols

• Sense of induction depends on alkene geometry: